COVID-19: MANAGEMENT OF VACCINE-ASSOCIATED THROMBOTIC SYNDROMES

A Rapid Guidance Summary from the Penn Medicine Center for Evidence-based Practice
Last updated May 20, 2021. All links rechecked May 20 unless otherwise noted.

This Rapid Guidance Summary is a description of existing guidance and evidence reviews from a variety of sources that was in effect at the time of publication. It should not be used or interpreted as a clinical practice guideline, but instead can be used in development of local recommendations and policies.

Key questions answered in this summary

- How should patients with possible thrombotic adverse events following SARS-CoV-2 coronavirus vaccination be managed?

CEP NOTE: Several different names have been used for the thrombotic syndromes that are the subject of this report: Authorities in the United States are calling it "thrombosis with thrombocytopenia syndrome" (TTS) while some foreign agencies refer to it as "vaccine-induced thrombotic thrombocytopenia" (VITT) or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT).

Summary of major recommendations

- We present a concordance table of recommendations from eight different professional societies. There is consensus on most components of the diagnostic pathway and on many aspects of treatment.
- All guidelines recommend that CBC with platelet count should be obtained immediately for patients with suspected TTS. If the platelet count is below 150,000/µl, D-dimer and PF4 antibody (HIT ELISA) tests should be done and imaging examinations should be performed if warranted by the patient's individual symptoms. Treatment should not be delayed while waiting for PF4 results if imaging findings are positive for thrombosis or the patient's symptoms are worrisome.
- A hematology specialist should be consulted if TTS is suspected or confirmed.
- All guidelines recommend that direct thrombin inhibitors (either argatroban or bivalirudin, not dabigatran) or direct oral anticoagulants should be used for treatment of suspected thrombosis patients with TTS. Heparin and low molecular weight heparin should be avoided. Platelet transfusion should be avoided unless there is severe bleeding or a need for surgical intervention.
- Most guidelines recommend that intravenous immune globulin should be given, especially if the patient's condition is severe. There is not yet consensus on second-line treatment for patients with persistent or worsening TTS.
- Some guidelines have recommended that anticoagulant treatment continue for at least three months.

Government agency guidance on identification of possible TTS

Source	Recommendations
FDA April 23	Reports of adverse events following use of the Janssen COVID-19 vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination. Most cases of thrombosis with thrombocytopenia reported following the Janssen COVID-19 vaccine have occurred in females ages 18 through 49 years; some have been fatal. The clinical course of these events shares features with autoimmune heparin-induced thrombocytopenia. [HIT]
EMA April 22	Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. CEP NOTE: This information is the same for both AstraZeneca and Janssen vaccines.
Health Canada April 16	Healthcare professionals should be alert to the signs and symptoms of thromboembolism and thrombocytopenia so that they can promptly treat these conditions according to available evidence and clinical guidelines. Healthcare professionals should tell people receiving the vaccine to seek medical attention if they develop symptoms of blood clots such as shortness of breath, chest pain, leg swelling, persistent abdominal pain; neurological symptoms such as severe and persistent worsening headaches or blurred vision; or skin bruising or petechiae beyond the site of vaccination after a few days.
CDC April 13	Maintain a high index of suspicion for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J COVID-19 vaccine, including severe headache, backache, new neurologic symptoms, severe abdominal pain, shortness of breath, leg swelling, petechiae (tiny red spots on the skin), or new or easy bruising. Obtain platelet counts and screen for evidence of immune thrombotic thrombocytopenia. CEP NOTE: Slide presentations from the CDC Advisory Committee on Immunization Practices meeting of April 23 can be downloaded from https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html
JCVI April 7	Anyone who has symptoms four days or more after vaccination is advised to seek prompt medical advice, such as a new onset of severe or persistent headache, blurred vision, confusion or seizures, shortness of breath, chest pain, leg swelling or persistent abdominal pain

Government agency guidance on management of possible TTS

Source	Recommendations
FDA April 23	In individuals with suspected thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine, the use of heparin may be harmful and alternative treatments may be needed. Consultation with hematology specialists is strongly recommended. See guidance from the American Society of Hematology.
CDC April 13	In patients with a thrombotic event and thrombocytopenia after the J&J COVID-19 vaccine, evaluate initially with a screening PF4 enzyme-linked immunosorbent (ELISA) assay as would be performed for autoimmune HIT. Consultation with a hematologist is strongly recommended. Do not treat patients with thrombotic events and thrombocytopenia following receipt of J&J COVID-19 vaccine with heparin, unless HIT testing is negative. If HIT testing is positive or unable to be performed in patient with thrombotic events and thrombocytopenia following receipt of J&J COVID-19 vaccine, non-heparin anticoagulants and high-dose intravenous immune globulin should be strongly considered.

Professional society guidance on identification of possible TTS

Source	Recommendations
BSH May 14	Symptoms start 5 or more days after COVID-19 vaccination and often occur at unusual sites in the body. Headaches are common and unusually severe and persistent, and may be worse on lying down or bending forward. The headache may occur with changes in vision, feeling or being sick. Fits (seizures) can occur, or weakness on one side of the body or a drop in consciousness. Other symptoms can include: • Persistent abdominal pain • Blood in the stools • Chest pain, shortness of breath • Leg swelling
ASH April 29	Urgent medical evaluation for TTS is indicated if any of the following develop 4 to 30 days after vaccination: severe headache, visual changes, abdominal pain, nausea and vomiting, back pain, shortness of breath, leg pain or swelling; petechiae, easy bruising, or bleeding. Diagnostic criteria (all four must be met): • COVID vaccine (J&J/Janssen or AstraZeneca only) within previous 4 to 30 days • Venous or arterial thrombosis (often cerebral or abdominal) • Thrombocytopenia* • Positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA Note: A patient who presents with thrombosis and a normal platelet count post-vaccination might be in an early stage of TTS. Continued assessment for development of thrombocytopenia/TTS required. Use of non-heparin anticoagulant may be indicated if patient is 4 to 30 days post-Johnson & Johnson or AstraZeneca vaccine. CEP NOTE: ASH and CDC held a recorded webinar April 20 on diagnosis and management of TTS

Professional society guidance on management of suspected or confirmed TTS

Source	**ASH**	**UCSF**	**THANZ**	**Ontario**
Country	USA	USA	Australia/NZ	Canada
Latest update	April 29	April 26	May 13	May 7
Testing				
Date window	4-30 days	4-30 days	4-30 days	4-28 days
CBC with platelet count	First	First	First	First
Platelet count threshold	150	150	150, or falling	150
Blood smear	Yes	NR	NR	Second
Fibrinogen	Second	First, also aPTT	First	NR
D-dimer (threshold)	Second	First	First (5 X ULN)	Second
PF4 antibody/HIT	Second (Note 1)	Second (Note 1)	Second	Third
HIPA or SRA (functional test)	NR		Second, if thrombosis or positive PF4	Third
Imaging	First, if symptomatic	First, as indicated by symptoms	Second, as indicated by symptoms	Second, if clinical suspicion of thrombosis
Anticoagulation			(Note 3)	
Direct thrombin inhibitors	Yes	Yes	Yes	Alternate
Direct oral anticoagulants	Yes	Yes	Yes	First choice
Fondaparinux	Yes	Yes	Yes	NR
Danaparoid	Yes	NR	Yes	NR
Heparin	Avoid	Avoid	Avoid	Avoid
Comment	Continue at least 3 months.		Continue 3-6 months Ensure tests normal before discontinuing.	NR
Treatment	(Note 2)	(Note 2)	(Note 2, Note 4)	(Note 2)
IVIG	1 g/kg daily, 2 days	1 g/kg daily, 2 days	0.5-1 g/kg daily, 2 days	1 g/kg daily, 2 days
Platelet transfusion	Avoid	Avoid except for serious bleeding	Avoid	Avoid
Plasma exchange	Not recommended unless initial treatment unsuccessful	NR	If signs of new or progressive thrombosis	NR
Rituximab	NR	NR	NR	NR
Eculizumab	Reported	NR	NR	NR
Corticosteroids	No consensus yet	NR	If signs of new or progressive thrombosis	NR

HIPA–heparin-induced platelet activation assay; SRA–serotonin-release assay; ULN–upper limit of normal

Note 1: Draw blood prior to any therapies.

Note 2: Do not delay treatment while waiting for PF4 results if patient has worrisome symptoms or positive imaging findings.

Note 3: If patient has low platelet count and elevated D-dimer, but no thrombosis, consider prophylactic anticoagulation using a non-heparin medication.

Note 4: Repeat ELISA and functional testing at 6 weeks, 3 months, and 6 months. See guideline for additional follow-up.

Professional society guidance on management of suspected or confirmed TTS (continued)

Source	ISTH	BSH	RCP	GTH (update)
Country	International	UK	UK	Germany
Latest update	April 20	April 20	April 10	April 1
Testing	**(see Figure 1)**			
Date window	4-28 days	5-28 days	4-28 days	4-16 days
CBC with platelet count	First	First	First	First
Platelet count threshold	150	150	150	NR
Blood smear	NR	First	NR	First
Fibrinogen	Second, also aPTT	First	Second	NR
D-dimer (threshold)	Second	First (4,000, Note 5)	Second (2,000)	First
PF4 antibody/HIT	Second	Second	NR	Second (Note 1)
HIPA or SRA (functional test)	Third, if available	NR	—	If PF4 positive (Note 6)
Imaging	First, as indicated by symptoms	Second (Note 7)	Neuroimaging if headache symptoms	First, if indicated
Anticoagulation				
Direct thrombin inhib.	Yes	Yes	—	Yes
Direct oral anticoag.	Yes	Yes	—	Yes
Fondaparinux	Yes	Yes	—	Discouraged
Danaparoid	Avoid	Yes	—	Yes
Heparin	Avoid	Avoid	—	Avoid
Comment		Continue at least 3 months Ensure tests normal before discontinuing.	—	Include non-pharmaceutical prophylaxis
Treatment	(Note 2)			
IVIG	Give immediately 0.5-1 g/kg daily, 2 days	Give urgently: 1 g/kg, divide over 2 days if needed	—	1 g/kg daily, 2 days
Platelet transfusion	Avoid	Evidence is unclear	—	NR
Plasma exchange	Consider if platelets remain depressed.	If very severe or resistant case	—	NR
Rituximab	NR	If IVIg unsuccessful	—	NR
Eculizumab	NR	NR	—	NR
Corticosteroids	Consider if platelets remain < 50 per nl	May be helpful, but benefits uncertain	—	NR

HIPA–heparin-induced platelet activation assay; SRA–serotonin-release assay

Note 1: Draw blood prior to any therapies

Note 2: Do not delay treatment while waiting for PF4 results if patient has worrisome symptoms or positive imaging findings.

Note 5: Threshold 2,000 if clinical suspicion is strong

Note 6: Modified HIPA if HIPA or SRA negative

Note 7: Ultrasound of abdomen to diagnose possible portal and splanchnic vein thrombosis, neuroimaging for possible CVST

Guidance sources

BSH–British Society for Haematology
EMA–European Medicines Agency
FDA–US Food and Drug Administration
GTH– Society of Thrombosis and Haemostasis Research (Germany)
ISTH–International Society for Thrombosis and Haemostasis
JCVI–Joint Committee on Vaccination and Immunisation (UK)
MHRA–Medicines and Healthcare products Regulatory Agency (UK)
Ontario–Ontario COVID-19 Science Advisory Table
RCP–Royal College of Physicians (UK)
THANZ–Thrombosis and Haemostasis Society of Australia and New Zealand
UCSF–University of California, San Francisco
WHO–World Health Organization

Sources with no relevant guidance at this time

American College of Physicians
Canadian Agency for Drugs and Technologies in Health
Cochrane COVID Review Bank
ECRI Guidelines Trust
European Hematology Association
Evidence Aid
FLARE (Massachusetts General Hospital)
Health Information and Quality Authority (Ireland)
Infectious Diseases Society of America
National COVID-19 Clinical Evidence Taskforce (Australia)
National Institute for Health and Care Excellence (NICE, UK)
Oxford COVID-19 Evidence Service

Update history (key additions and changes only)

May 10: Initial report.
May 13: Expanded summary points
May 20: Updated guidance from THANZ

About this report

A Rapid Guidance Summary is a focused synopsis of recommendations from selected guideline issuers and health care systems, intended to provide guidance to Penn Medicine providers and administrators during times when latest guidance is urgently needed. It is not based on a complete systematic review of the evidence. Please see the CEP web site (http://www.uphs.upenn.edu/cep) for further details on the methods for developing these reports.

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Figure 1. ISTH flowchart