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Updated Brighton Collaboration Case Definition for Thrombosis with Thrombocytopenia Syndrome (TTS)

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Beginning in February, 2021, multiple European countries (e.g., Austria, Denmark, Norway, Germany, UK) and Australia have reported cases of thrombosis with thrombocytopenia syndrome (TTS) in persons who received the Astra-Zeneca (AZ) COVID-19 vaccine (1-3, 10) and more recently in the US with the Janssen vaccine (11). In May 2021, a draft interim case definition was proposed by the Brighton Collaboration. Since that time, understanding of this condition and its relationship to vaccines has evolved. Recent work by Andreas Greinacher and others now allow revision of the original case definition and level of certainty algorithm.¹ The goal of this case definition is to facilitate harmonized studies of this outcome. This supplements guidelines published by WHO provided information on case identification for treatment.

The Case Definition (CD) Level of Certainty (LOC) is determined based on a series of clinical conditions defined below.

Condition A: **Platelet count <150 X 10⁹/L and of new onset with no known recent exposure to heparin (within the last 30 days)**

Condition B1: **Presence of thrombosis/thromboembolism confirmed by ≥ 1 of the following (Check all that apply below)**

Imaging Study

- Ultrasound – Doppler
- CT scan – contrast / angiography
- Magnetic resonance venography or arteriography
- Echocardiogram
- Perfusion V/Q scan
- Conventional angiography / digital subtraction angiography

Surgical procedure - that confirmed presence of a thrombus (e.g. thrombectomy)

¹ Greinacher, A., Langer, F., Makris, M., Pai, M., Pavord, S., Tran, H., & Warkentin, T. E. (2021). Vaccine-induced immune thrombotic thrombocytopenia (VITT)-update on diagnosis and management considering different resources. *Journal of Thrombosis and Haemostasis*.

Pathologic examination – including biopsy or autopsy

Condition B2: **Severe and persistent headache onset ≥ 5 d post vaccination with elevated D-DIMER >8 x ULN (Upper limits of normal)**

Condition C: **Clinical presentation suggests one of the specific clinical syndromes below? (Check the most appropriate) NOTE: the italicized signs/symptoms in brackets after each are suggestive of the syndrome but not an exhaustive list; some of them should be present. Diagnosis of the syndrome by a clinical specialist is also acceptable**

Cerebral venous sinus thrombosis / other Cerebral venous thrombosis (*new onset of unexplained headache, often severe, typically persisting; focal cerebral dysfunction; encephalopathy; seizure; blurred vision; double vision*)

Deep vein thrombosis (*new onset swelling usually but not always in lower extremities; localized swelling accompanied by pain [may be crampy in nature] and tenderness; reddened/discoloured/warm skin; pitting edema*)

Pulmonary thromboembolism (*sudden onset: shortness of breath[at rest or on exertion], pleuritic chest pain [sudden, intense, sharp, stabbing or burning in nature, made worse by breathing/coughing/sneezing/laughing], cough +/- hemoptysis), tachypnea, tachycardia, arrhythmia, cyanosis, hypotension*)

Intra-abdominal thrombosis. (*abdominal pain [may be out of proportion to physical exam findings], bloating, nausea, vomiting, diarrhea, bloody stools, ascites, hepatomegaly if hepatic vein location*)

Ischemic Stroke (*sudden onset of focal neurologic deficits such as difficulty with speech [dysphasia or dysarthria], hemiparesis, ataxic gait abnormal eye movements, facial paresis*)

Myocardial infarction (*chest pain [often crushing in nature], shortness of breath, arrhythmias, cyanosis, sudden death*)

Arterial Thrombosis

Condition D: **One or more of these imaging or lab findings supportive of the diagnosis of thrombosis / thromboembolism? (Check all that apply)**

Echocardiogram or doppler ultrasound

Computed tomography without contrast or MRI

D-dimer (Elevated above upper limit of normal for age)

Condition E: **At least one of these Lab findings that are strongly supportive of the diagnosis of platelet-activating antibody mediated thrombosis? (Check all that apply)**

D-dimer ≥ 4 times ULN for age

Positive anti-platelet factor 4 (PF4) assay: specific anti-PF4 ELISA (note: rapid tests are insensitive for these antibodies) or functional test with addition of PF4

TTS Case Definition Level of Certainty Determination

If yes to (A and B1) or yes to (A and B2): then is Level 1

If no to (B1 and B2)_and_[If yes to A plus yes to (C and E)] then is level 1

If no to (B1 and B2)_and_[If yes to A plus yes to (C and D)] then is level 2

If no to (B1 and B2)_and_[If yes to A plus [(yes to C) and (no to D and E)] then is level 3

If there is insufficient information to determine the conditions needed to a level of certainty of 1, 2 or 3 then the level of certainty is level 4

If there is sufficient information to determine the conditions A, B, C, D, and E but the aggregate of the conditions do not meet the LOC 1, 2, or 3 then the LOC is Level 5; Not a Case of TTS.