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Proposed Brighton Collaboration process for developing a standard case definition for study of new clinical syndrome X, as applied to Thrombosis with Thrombocytopenia Syndrome (TTS)

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1. Since at least mid-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). There is no standard case definition (CD) for TTS accepted for use by all countries yet. On Apr. 3, 2021, the British Societyof Haemotology published its Updated Guidance on Management. Version 1.0 with CD for possible, probable, and definite cases of TTS.(4) This document is oriented towards identification and treatment of cases rather than being designed for epidemiologic studies, especially initial case finding, however. Therefore, there is an urgent need for the latter a draft of which is included in 4 below
2. Since its inception in 1999, the Brighton Collaboration has sought to advance the science of vaccine safety by developing standard CD for adverse events following immunizations (AEFI's).(5) To date, >60 CD's have been developed, such as fever, seizure, anaphylaxis, intussusception, narcolepsy, etc., including individual CD for thrombosis (6) and for thrombocytopenia (7).
   2.1. Based on this experience, we propose a two-step process (see 3.0) to develop both:
      2.1.1.a "draft interim case finding definition" to facilitate identifying a cohort of individuals with this clinical entity (see 3.1 for process; 4.0 for draft); who could then be studied using a common study protocol and assessment tools.
         2.1.1.1.While others have called this new syndrome Vaccine-induced immune thrombotic thrombocytopenia (VITT) (1,2); but this assumes a causal mechanism, so we have elected to use 'thrombosis with thrombocytopenia syndrome' (TTS) (3) for this initial case finding purpose.
         2.1.1.2.To this end, vaccination with a SARS-2-CoV vaccine would not be required to enter this cohort but clearly vaccine exposure information would be collected on

these individuals along with other variables and laboratory tests which have yet to be fully identified (see 3.2).

2.1.2. a final Brighton case definition eventually (see 3.2).

2.2. When new clinical syndromes or diseases are first identified, standard CD are needed for both clinical (e.g., appropriate diagnosis, treatment) and public health (e.g., epidemiologic studies, and data harmonization) purposes. This is especially true for rare events where any misclassification will hinder scientific progress. The process for developing a final standard CD for a new illness usually takes some time; however, requiring serial improvement of working or interim CD as full knowledge accumulates. The US CDC CD for what came to be called Acquired Immuno-Deficiency Syndrome (AIDS) for example was initially developed in 1981 and revised in 1985, 1987, and 1993 (4). The Chinese CD for COVID-19 changed seven times from Jan. 15 to Mar. 30, 2020 (5).

2.3. The Brighton CD's are usually tiered into three levels of available evidence, high, medium, and low. This gradient in evidence might be acquired from clinical trials (high) or routine passive surveillance (low); or alternatively, tertiary referral hospital (high) vs. basic rural clinic (low).

2.4. Because Brighton's overall interest is in accurate understanding of whether the vaccine exposure causes the AEFI or not; and because most AEFI's lack an unique clinical or laboratory marker to establish a causal link, therefore, the only way of demonstrating this causal link is by showing that vaccinated persons have a higher rate of the AEFI than unvaccinated persons in an unbiased manner (either from clinical trials or epidemiologic studies). Process-wise, the data for this rate comparison is usually best attained by first finding all possible cases of the specific AEFI or adverse event of special interest (AESI), then separatelyascertaining their vaccine exposure status in a blinded manner, before linking the two. As Brighton CD are designed to find all possible cases of meaning the CD in an unbiased manner relative to vaccine exposure, they do not include vaccine exposure as part of the CD.

3. Proposed process:

3.1. For interim/working CD for TTS: We initially proposed identifying a small number (e.g. 3) hematologists familiar with the recent cases of TTS in UK/Europe to join a similar number of Brighton Thrombosis Case Definition (CD) WG members. In practice, however, we found it too challenging to get busy clinicians together across multiple time zones in a hurry on short notice. Alternatively, we used a pre-organized meeting of the International Network of Special Immunization Services (INSIS) on this topic on Apr. 6, 2021 (and subsequent days via email) to draft the interim version and are now sharing it for broad peer review. We hope to finalize the interim CD within 1-2 weeks. Our initial focus is on cases with both thrombocytopenia and thrombosis. We recognize that it is possible that some individuals may experience either thrombosis or thrombocytopenia alone, but evaluation of this will separately.

3.2. For a final CD: we will:

3.2.1. review as complete a description as possible of identified TTS cases;

3.2.2. create a list of variables we wish to collect on them; we are merging questionnaires from UK, EMA, Canada, and others and will then develop a consensus document based upon peer review.

3.2.3. organize and distribute the work to collect this information on each possible TTS case in a timely manner. For this process, we can create a distributed database file, merging all the de-identified data from each country, protecting confidentiality yet allowing for needed analyses.

3.2.4. analyze the data to refine the Working CD with the goal of developing a formal final Brighton CD as swiftly as possible.

N.B.: While this case finding definition focuses on identifying cases that have both thrombocytopenia and thrombosis, it is possible that patients with this condition are part of a spectrum which may include thrombocytopenia alone as well as patients with thrombosis without thrombocytopenia. The existing Brighton Case Definitions can be used to identify and classify those patients for further study.

4. Draft Case Finding Definition Thrombosis Thrombocytopenia Syndrome

Any patient presenting with both acute venous or arterial thrombosis **AND** new onset thrombocytopenia[1] (as confirmed by both the Brighton Case Definitions for thrombocytopenia and thrombosis (6,7)[2]) and no known recent exposure to heparin .[3]

- The Brighton Collaboration case definition for thrombocytopenia (7) is quite simple: a plateletcount of less than 150,000/ *u*l. A smear should also be evaluated to rule out platelet clumping.[4]
- The Brighton Collaboration case definition for thrombosis (6) is still undergoing final review. Currently the criteria for meeting the definition with level one certainty require confirmation by imaging, surgical, or pathology findings as specified below. Level two and three criteria are for a possible case and follow this to allow inclusion of cases from countries that may not have access to more sophisticated diagnostic studies.
- TTS cases will be classified regarding level of certainty based upon the Brighton level achieved for thrombosis.

LEVEL ONE BC THROMBOSIS CRITERIA

Imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism in the absence of an alternative diagnosis for the reported event to account for the combination of symptoms

- Imaging studies include any of the following, depending on the location of the lesion[5]
  - Ultrasound – Doppler
  - Computed Tomography (CT scan) – contrast/angiography
  - Magnetic resonance venography (MRV) or arteriography (*MRA*)
  - Echocardiogram
  - Perfusion V/Q scan
  - Conventional angiography/Digital subtraction angiography

  OR
- Procedure that confirms the presence of a thrombus (e.g. Thrombectomy)

  OR
- Pathology consistent with thrombosis/thromboembolism including biopsy or autopsy

Most appropriate imaging test depends on the location of the lesion. Any of the tests listed may be used as available. Based on radiologist/expert interpretation.

Beyond the presence of thrombocytopenia, additional abnormal laboratory clotting study results are not required for confirmation as they can be normal in presence of thrombotic/thromboembolic events. When present, they can be supportive of the diagnosis, including:

- D-dimer elevated above the upper limit of normal for age
- Shortened PT, PTT– below the lower limit of normal for age

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[1] Wise, Robert P., et al. "Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data*Vaccine* 25.31 (2007): 5717-5724.

[2] Note: Anti-PF-4 antibodies have been included in clinical case definitions designed to identify patients for treatment. Since our goal here is to provide a case finding definition to further our understanding of the syndrome via epidemiologic studies, these tests have not been included is the case finding definition, but this information will be collected on the cases identified.

[3] Note: The entity of TTS has been described as similar to HIT observed following heparin administration. Therefore we would want to exclude cases with recent heparin exposure

[4] The definition also required evidence of bleeding. This is not included in this case finding definition.

[5] Imaging will depend on location and whether venous or arterial thrombosis is present. With venogram for venous thrombosis and head CT or CT angiogram or MRI/MRI angiogram for arterial lesions.

LEVEL TWO BC THROMBOSIS CRITERIA (modified) - Probable Case

Clinical Presentation Consistent with Thrombosis or Thromboembolism Event, including

- **Specific clinical syndromes including any of the following**
    - Deep vein thrombosis (DVT) – symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intraabdominal thrombosis
    - Pulmonary thromboembolism (PE) - sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest [Wells criteria for scoring –based on clinical findings]
    - Stroke
    - Myocardial infarction

AND

- **Supporting Imaging or laboratory (D-dimer) findings suggestive but not definitive of thrombosis/thromboembolism including any of the following**

    - Chest radiograph
    - Echocardiogram
    - Computed tomography without contrast

OR

    - D-dimer - elevated above the upper limit of normal for age

LEVEL THREE BC THROMBOSIS CRITERIA- Possible Case (Modified)

Clinical Presentation Consistent with Thrombosis or Thromboembolism Event, including

Specific clinical syndromes (see full list in the flow diagram below):

- Deep vein thrombosis (DVT) – symptoms will depend on the location of the thrombosis, for example: swelling, pain, redness, or warmth of an extremity; headache, visual disturbance, seizures for sinus vein thrombosis; abdominal pain for intraabdominal thrombosis
- Pulmonary thromboembolism (PE) - sudden onset shortness of breath, pleuritic chest pain, sudden death/pulseless electrical activity arrest [Wells criteria for scoring –based on clinical findings]
- *Stroke*
- *Myocardial infarction*

5. **Decision tree algorithm for case-finding of Thrombocytopenia Thrombosis Syndrome (TTS)**

A. Is the platelet count <150 X 10^9/L with a confirmatory peripheral smear showing reduced platelets with no evidence of clumping (that could indicate a falsely low platelet count)

No → **Level 5: NOT a case of TTS**

YES

B. Was presence of thrombosis/thromboembolism confirmed by ≥ 1 of the following (check all that apply)?

- ☐ **Imaging Study**
  - — Ultrasound – Doppler
  - — CT scan – contrast / angiography
  - — Magnetic resonance venography or arteriography
  - — Echocardiogram
  - — Perfusion V/Q scan
  - — Conventional angiography / digital substraction angiography
- ☐ **Surgical procedure** - that confirmed presence of a thrombus (e.g. thrombectomy)
- ☐ **Pathologic examination** – including biopsy or autopsy

YES → **Level 1 (Definite case) TTS**

No

No

C. Did the clinical presentation suggest 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 but not all 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; focal cerebral dysfunction; encephalopathy; seizure)*
- ☐ **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 including asystole, cyanosis)*

YES

D. Were imaging &/or lab findings supportive of diagnosis of thrombosis / thromboembolism? (Check all that apply)

- ☐ **Chest radiograph**
- ☐ **Echocardiogram**
- ☐ **Computed tomography without contrast**

YES → **Level 2 (Probable case TTS)**

No → **Level 3 (Possible case TTS)**

Level 4: EXCLUDED: Reported as TTS but insufficient evidence to meet any level of the case

6. Acknowledgement: We thank in advance the voluntary contributions of all the colleagues who make development of Brighton Collaboration CDs possible. We hope to post a list such contributors for TTS CD when ready.

7. References:

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