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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). These is no standard case definition (CD) for TTS accepted for use by all countries yet. On Apr. 3, 2021, the British Society of 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 (**see 4. below for Draft Interim CD needing peer review**).
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 1) Brighton's overall interest is in accurate understanding of whether the vaccine exposure causes the AEFI or not; and because 2) most AEFI's lack an unique clinical or laboratory marker to establish a causal link; 3) 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 separately ascertaining 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: 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.

3.2. For a final CD: we will:

3.2.1. review as complete a line listing of possible 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.

4. Draft Interim Case Finding Definition for Review (for 3.1); Please submit comments here:

Any patient presenting with acute venous or arterial thrombosis **AND** new onset thrombocytopenia (as confirmed by both the Brighton Case Definitions for thrombocytopenia and thrombosis (6,7) (with the presence of PF4 platelet-activating antibodies) (NOTE: there is controversy as to whether to require this at this point or to collect all cases regardless of PF4 antibody status and then evaluate the presence of these antibodies to confirm the association)---and no known exposure to heparin or any other underlying condition or explanation for the condition.

- The Brighton Collaboration case definition for thrombocytopenia (7) is quite simple: a platelet count of less than 150,000/ *u*l. There is only one level of certainty.
- 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 findings as follows

  Imaging study 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

  - Ultrasound – Doppler
  - Computed Tomography (CT scan) – contrast/angiography
  - Magnetic resonance venography (MRV) or arteriography (*MRA*)
  - Echocardiogram
  - Perfusion V/Q scan
  - Conventional angiography/Digital substraction angiography

  OR

  - Procedure that confirms the presence of a thrombus (eg. Thrombectomy)

  OR

  - Pathology consistent with thrombosis/thromboembolism including biopsy or autopsy

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

  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

5. 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.
6. References:

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