Guidelines: Diagnosis and Management of Thrombosis with Thrombocytopenia Syndrome (TTS) following Adenovirus Vectored COVID-19 Vaccinations

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Introduction

Rare cases of blood clots with low platelets after receipt of adenovirus vector COVID-19 vaccines (AstraZeneca (AZ) and Johnson & Johnson (J&J) COVID-19 vaccines) have been reported and are referred to as Thrombosis with Thrombocytopenia Syndrome (TTS).

Although initial media reports described older females to be at higher risk of developing this condition, at present there is no clear signal of risk factors that would predispose an individual to TTS. This document provides guidance to UN medical staff globally on the diagnosis, management and reporting of TTS. **UN medical staff need to be alert for this syndrome and arrange for early referral to local hospitals or consultation with hematologists and/or consider early medical evacuation for further confirmation (lab, imaging) and treatment of this condition if capacity does not exist at their local duty station.**

Note that this is a living document which will be updated as more information emerges. For any questions, contact DHMOSH Public Health at dos-dhmosh-public-health@un.org More information from the WHO is available here.

Current Situation Update

At the time of writing, the AZ vaccine is currently authorized for use in several other countries globally though some have restricted or limited it's use despite evidence that this is a rare event. The J&J vaccine is also given in some countries around the world. Based on a multinational Phase 3 trial, the AZ vaccine has around 70% efficacy in preventing symptomatic COVID-19 at/after 14 days post second dose. Although there is some concern about vaccine efficacy against certain COVID-19 variants, the WHO continues to recommend use of this vaccine even in countries where variants are circulating[1,2].

TTS is a condition of blood clots associated with low platelet counts, that occurs following receipt of the vaccine. The likely mechanism is antibodies that induce massive platelet activation against platelet factor 4 (PF4), reducing platelet count and causing thrombosis although the full mechanism remains to be elucidated. This syndrome is thought to clinically mimic "heparin-induced thrombocytopenia" (HIT) but does not require heparin itself as a trigger. Most cases occurred 3 to 30 days[3,4,5] after receipt of

[1] https://www.who.int/news-room/feature-stories/detail/the-effects-of-virus-variants-on-covid-19-vaccines
[2] AstraZeneca ChAdOx1-S/nCoV-19 [recombinant]. COVID-19 vaccine (who.int)
[3] https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf
[4] Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield) (who.int)
[5] https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

the AZ vaccine, and in women[6] under 60 years old[7]. Some cases have also occurred after receipt of the J&J vaccine 3 to 15 days following receipt of this vaccine[8].

Available evidence so far, at the time of writing, continues to suggest that **this syndrome is extremely rare**[9] though information continues to evolve.

Because of the rarity of events and potential severity of COVID-19, the European Medicines Agency (EMA) concluded that the overall benefits of the vaccine continue to outweigh the risk. The WHO has also stated that the very rare incidence should be weighed against the risk of morbidity from COVID-19. See WHO statement here. The WHO has stated that a causal relationship, while plausible, has still yet to be confirmed.

A recent study[10] out of Denmark and Norway observed increased rates of venous thromboembolic events with the AZ vaccine, however the absolute risk was small.

Clinical Presentation of TTS

Patients with TTS may present with cerebral sinus vein thrombosis (CSVT), or with other arterial or venous clots.

Mild to moderate constitutional symptoms such as fever, fatigue, headache, or muscle aches are common in the first 24 – 48 hours following vaccination and are not suggestive of TTS. However, patients with the following symptoms **30 days** following AZ or J&J vaccine should make you suspect TTS:

- **Persistent, severe and intense headache**
- **signs of low platelets such as petechiae, purpura or easy bruising or bleeding**
- **focal neurological symptoms**
- **seizures, or blurred or double vision (suggesting CSVT or arterial stroke)**
- **shortness of breath or chest pain (suggesting pulmonary embolism or acute coronary syndrome)**
- **abdominal pain (suggesting portal vein thrombosis)**
- **limb swelling, redness, pallor, or coldness (suggesting deep vein thrombosis or acute limb ischemia)**
- **back pain**

[6] Note that additional studies needed on this since many vaccine recipients are women as they fall under the high priority first responders groups such as teachers and healthcare workers being prioritized early for vaccination.
[7] https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood
[8] https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Ad26.COV2.S-2021.1

[9]There appears to be geographic variation in terms of reported incidence of TTS with very few cases reported from non-EU countries. Norway has reported a rate of 1 in every 25,000 doses, Germany reported 1 in 100,000 doses, while Europe's overall figures are 1 in 210,000. The UK has reported about 1 in 500,000 doses. Specifically, 169 reported cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis were reported in 34 million vaccine recipients in the UK and European Economic Area as of time of writing this document.
[10] Reference: Arterial events, venous thromboembolism, thrombocytopenia after vaccination with Oxford-AstraZeneva ChAdOx1-@ in Denmark and Norway: population-based cohort study. BMR 2021; 373 Pottegard A et al.
[9]Reference: "Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19). WHO 2021

TTS can occur within 30 days of AZ or J&J vaccine, (peak time period for initial symptoms between days 6 to 14 after vaccination), so the above symptoms occurring within this time frame should raise clinical suspicion of TTS[9].

Risk factors for TTS

Some data suggest that there is a higher risk in younger adults compared with older adults. No additional risk factors have yet been identified[11].

Although pregnancy is associated with higher rates of thrombosis, thrombocytopenic and hemorrhage, it is not known if pregnancy is associated with higher risk of TTS.

It is not known if TTS is a risk following the second dose (reports to date have been with first dose).

What To Do When An Individual Presents with the Above Symptoms

1. Ask patient about their COVID-19 vaccine history and note the date that they received the doses, if any
2. Draw a complete blood count (CBC) from the patient, with platelet count and peripheral smear.
3. If platelet count is equal ^{or} less than 150 x 10^9 /L[10], **AND** their symptoms occur within 30 days after COVID-19 vaccination, such patients are considered a **suspect case of TTS**.
4. Suspect TTS patients should be further evaluated for TTS through:
    a. **Imaging for thrombosis** based on symptoms, focused on detection of CSVT with CT or MRI venogram, splanchnic thrombosis, pulmonary emboli, and/or DVT
    b. **D-dimers**: majority of TTS patients have markedly elevated values (>4000 mcg/L)
    c. **Fibrinogen**: some TTS patients are reported to have low values
    d. **PF4-heparin ELISA**: almost 100% of cases reported had positive assays.
        i. *Note that in those with normal platelets and normal d-dimer it is unlikely that the diagnosis is TTS and other differential diagnoses should be pursued*
        ii. *If platelets are >150 and d-dimer is elevated or there is a particular suspicion for TTS, repeat blood work is recommended in 24 hours.*
5. **If such lab tests and services in #3 are not available in your clinic, you need to urgently organize a referral to a local hospital/lab with these services, or medically evacuate to diagnose, rule out and/or treat TTS.** Routine empiric administration of IVIG and anticoagulation before proper diagnosis is not recommended.

An algorithm of these steps is found in Annex 1.

Treatment of TTS

Treatment of suspect or confirmed TTS requires consultation with a specialist hematologist. However, please bear in mind the following principles for treating such patients:

1. DO NOT give heparin (both unfractionated heparin and low molecular weight heparins)
2. Avoid platelet transfusions
3. Consult a hematologist (in person, virtually, by phone)

[11] https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

4. If you have the therapies available, **initiate therapy with intravenous immunoglobulin and non-heparin anticoagulation pending PF4 ELISA results only if:**

    a. **Patient has signs/symptoms of serious thrombosis AND at least one of the following:**
        i. **Low platelets OR**
        ii. **Positive imagine OR**
        iii. **Both**

    OR

    b. **Patient has no signs, symptoms or imaging documenting thrombosis BUT there is low platelets AND very high/rising D-dimer.**

- Note: IVIG dose is 1 g/kg daily for 2 days for severe or life-threatening clots, if available. Further IVIG may require balancing bleeding and thrombotic risk
- Note: Use first line anticoagulants: direct oral anti-Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban)

Further information concerning specialized guidance on how to confirm TTS diagnosis and its clinical management is available at UK: Guidance Produced from the Expert Haematology Panel (EHP) focused on Covid-19 Vaccine induced Thrombosis and Thrombocytopenia (VITT)
and American Society of Haematology: TTS Guidance

Reporting TTS

Prompt reporting of such cases amongst UN personnel is mandatory to learn more about this rare but serious thrombotic phenomenon.

All cases of thrombosis, thrombocytopenia occurring within 30 days of COVID-19 vaccinations must be reported immediately to DHMOSH Public Health at dos-dhmosh-public-health@un.org

Additional considerations

Those who have had TTS post-vaccination should not receive a second dose of AZ vaccine[12].

Recommendations for those who require a second dose of vaccine and whether or not in this situation, a different type of vaccine (for example mRNA or other) can be used are still under development.

New Update

On June 11, 201 the EMA's safety committee has indicated that those with capillary leak syndrome should not be vaccinated with the AZ vaccine. Symptoms include feeling faint, rapid swelling of arms and legs or sudden weight gain in the days following vaccination. Six cases have been reviewed and

[12] https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

most occurred in women and within 4 days of vaccination. The WHO has not yet released guidance on this matter.

References

- UK: Guidance Produced from the Expert Haematology Panel (EHP) focused on Covid-19 Vaccine induced Thrombosis and Thrombocytopenia (VITT)
- Ontario: Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) Following AstraZeneca COVID-19 Vaccination
- Interim statement of the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety on AstraZeneca COVID-19 vaccine
- https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood
- https://www.uptodate.com/contents/covid-19-vaccine-induced-immune-thrombotic-thrombocytopenia-vitt?topicRef=129849&source=see_link
- NEJM: Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination (9 April 2021)
- WHO: Guidance for clinical case management of thrombosis with thrombocytopenia syndrome(TTS) following vaccination to prevent coronavirus disease (COVID-19) (who.int)

Annex 1: Summary of Algorithm for TTS