RECOMMENDATIONS FOR THE DIAGNOSIS AND TREATMENT OF THROMBOTIC EVENTS FOLLOWING VACCINATION AGAINST COVID-19

Date: 9 June 2021 (version 5 revised)

- Healthcare professionals must be alert to signs and symptoms of thrombosis and thrombocytopaenia in patients with recent history (3-21 days) of inoculation with adenoviral vector vaccines (AstraZeneca and Janssen).

- The adverse reaction known as thrombosis with thrombocytopaenia syndrome (STT), formerly known as vaccine-induced thrombotic thrombocytopaenia (VITT),[1] is characterised by **severe thrombosis** (cerebral venous sinus thrombosis, splanchnic vein thrombosis, arterial thrombosis), **frequently associated with thrombocytopaenia** and sometimes haemorrhage, following administration of adenoviral vector vaccines (the AstraZeneca and Janssen vaccines).[2]

- This adverse reaction is rare (frequency < 1/10 000), and manifests 3-21 days after vaccination in the majority of cases. The younger population appears to present the greatest risk: most cases have affected individuals aged < 60 years, and the majority of patients have been women (estimated incidence rates in our setting: 12 cases per million population < 60 years vs 2 cases per million population > 60 years). Recent data from the United Kingdom indicate an estimated incidence rate of 18 cases per million population < 50 years and 10 cases per million population > 50 years, following the first dose of the vaccine.[3] After the second dose, incidence is 1.4 cases per million population aged under 50 years. Given the lower number of second doses administered among individuals younger than 50 years, and the short time interval since administration, we currently lack reliable data for this age group. According to current evidence, these events are triggered by an immune response against platelets.

- Administration of a second dose of these vaccines is contraindicated in individuals presenting thrombotic events with thrombocytopaenia (TTS) after the first dose of an adenoviral vector vaccine.[4]

As a precaution, we advise against administering a second dose of adenoviral vector vaccine in individuals whose symptoms give rise to strong suspicion of TTS (even if unconfirmed): thrombocytopaenia or thrombosis appearing in the 21 days following administration of the first dose.

Due to pathogenic similarities, we also advise against administering these vaccines to individuals with history of heparin-induced thrombocytopaenia.

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[1] Recomendaciones diagnóstico-terapéuticas del grupo de trabajo de expertos de FACME ad-hoc sobre el manejo de la trombosis venosa cerebral relacionada con la vacunación frente a COVID-19. Neurología 2021. https://doi.org/doi:10.1016/j.nrl.2021.05.001

[2] AEMPS (7/5/2021). 5º Informe de Farmacovigilancia sobre Vacunas COVID-19. https://www.aemps.gob.es/laAEMPS/docs/informe-farmacovigilancia-mayo-2021.pdf?x74586

[3] MHRA Coronavirus vaccine - weekly summary of Yellow Card reporting (June 1st 2021). https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

[4] EMA/AEMPS. Ficha técnica de Vaxzevria actualizada a 26 de mayo de 2021. https://cima.aemps.es/cima/pdfs/ft/1211529001/FT_1211529001.pdf

- Given the immune nature of this thrombotic thrombocytopaenia, **restricting the use of these vaccines in patients with conventional thrombotic risk factors is not currently under consideration.** We must also consider the benefits of vaccination for these patients, given that COVID-19 itself is associated with increased incidence of thrombotic events.
- FACME **considers it essential to continue monitoring this adverse reaction** and to ensure the detection of potential cases, to assist physicians in starting appropriate treatment, and to guarantee that all cases are duly documented and reported to the Spanish Pharmacovigilance System. Shown below are our detailed recommendations on the diagnosis, management algorithm, treatment, documentation, and notification of cases.

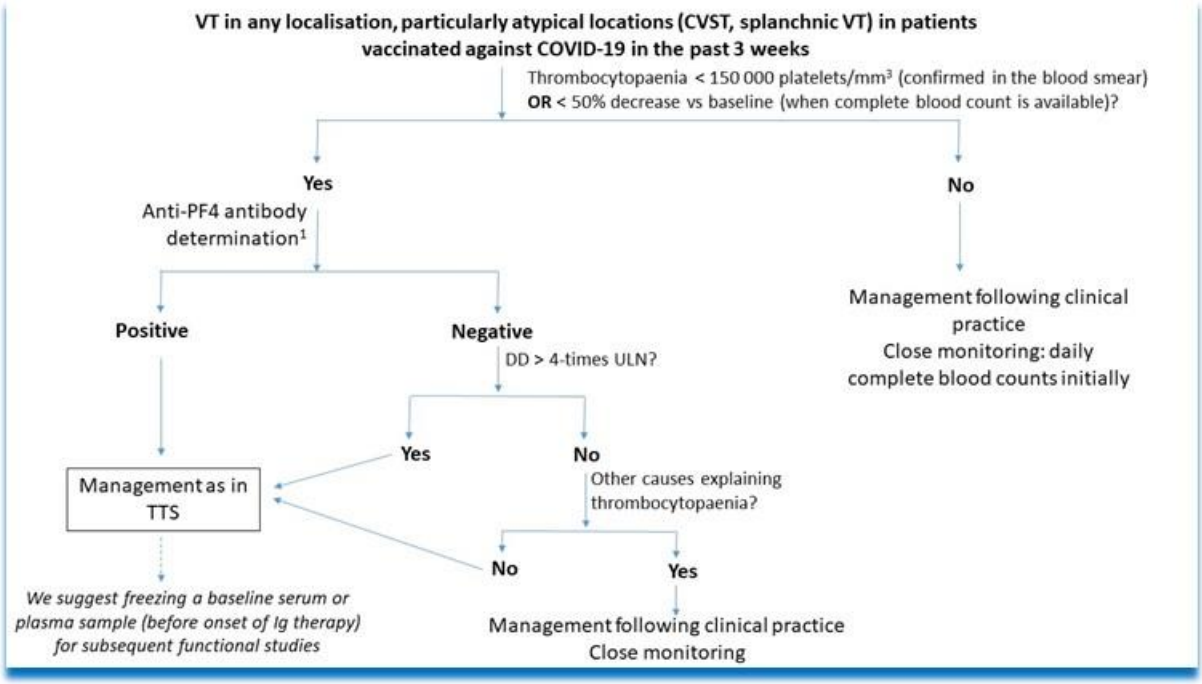
1. RED FLAGS

Patients with **recent history (3-21 days) of inoculation with adenoviral vector vaccines (AstraZeneca and Janssen vaccines)** and presenting alert signs and/or symptoms of suspected thromboembolism:

Localisation	**Signs and symptoms**	**EMERGENCY diagnostic test**
Cerebral venous sinus thrombosis (CVST)	HEADACHE characterised by: Rapidly progressive or sudden onset, strict unilateral or bilateral localisation, exacerbation with decubitus position, interrupted sleep, exacerbation with Valsalva manoeuvres or exercise, resistance to symptomatic treatment, progressive worsening, and/or repeated medical consultation due to headache. Headache may be accompanied by: Alarm symptoms: repeated vomiting, seizures, behavioural alterations, confusional episodes, persistent visual symptoms, gait alterations, loss of strength or sensitivity. Alarm signs: optic disc swelling, hemiparesis, hemibody hypoaesthesia, oculomotor alterations, dysmetria or ataxia, aphasia or dysarthria, impaired level of consciousness.	CT venography or MRI angiography Normal findings in non-contrast MRI or CT studies **do not rule out** CVST.
Splanchnic vein thrombosis	ABDOMINAL PAIN, typically with subacute (but also acute) progression, diffuse or colic, possibly accompanied by nausea, vomiting and diarrhoea, or fever. Abdominal examination typically detects no abnormalities, and peritonism usually does not manifest until progression to tissue involvement/infarction. There are no specific laboratory findings. Patients may present haemoconcentration due to abdominal fluid sequestration; therefore, thrombocytopaenia may not be observed. Patients usually do not present metabolic acidosis, leukocytosis, or elevated levels of lactate, CK, amylase, or other markers until progression to tissue involvement/infarction.	Contrast CT Abdominal CT angiography in the event of suspicion.

	Signs of portal hypertension and abdominal distension will be observed in the event of portal or splenic vein involvement.	
Lower limb deep vein thrombosis (LL-DVT)	PAINFUL TUMEFACTION of the limb (unilateral or bilateral).	Venous ultrasound of the affected leg (or both legs)
Pulmonary thromboembolism (PTE)	DYSPNOEA, typically with sudden onset, pleuritic CHEST PAIN, haemoptoic sputum.	Chest CT angiography

2. MANAGEMENT ALGORITHM FOR PATIENTS WITH SUSPECTED TTS



[1] ELISA is the most reliable technique. In the event of positive results for anti-PF4 antibodies, with any technique, a baseline serum or plasma sample should be frozen prior to immunoglobulin therapy in order to perform subsequent studies into the capacity of the patient's antibodies to activate platelets in vitro.

Abbreviations: CVST: cerebral venous sinus thrombosis; DD: D-dimer; TTS: thrombosis with thrombocytopaenia syndrome; ULN: upper limit of normality; VT: venous thrombosis.

NOTE: The periodic review of notified cases, conducted in collaboration with AEMPS, found a greater-than-expected number of cases of **CVST without thrombocytopaenia** in the vaccinated population, even in the age-stratified analysis. It is currently unclear whether this is a distinct entity, whether thrombocytopaenia may not have been detected correctly, or whether the platelet count in these patients had decreased from elevated baseline levels, without reaching the pathological range. Therefore, we recommend close clinical monitoring and daily laboratory analyses.

3. TREATMENT OF THROMBOTIC EVENTS WITH THROMBOCYTOPAENIA SUSPECTED TO BE AN ADVERSE REACTION TO VACCINATION (TTS)

1. **Hospitalisation** with close monitoring and control of platelet count. Follow-up by a haematologist with experience managing heparin-induced thrombocytopaenia.

2. In the absence of clinically relevant active bleeding* (with the exception of cerebral haemorrhage secondary to venous infarction), start **anticoagulant treatment with alternatives to low-molecular-weight heparin or unfractionated heparin**:

   - IV argatroban (first choice if CrCl < 30mL/min)[1,2]: requires partial thromboplastin time (PTT) monitoring (therapeutic range: 1.5-3.0)
   - IV bivalirudin[1,2]: requires PTT monitoring (therapeutic range: 1.5-3.0)
   - SC fondaparinux[3]
   - Oral rivaroxaban or apixaban[4]

   [1] Treatment of choice in patients with severe thrombosis: CVST, splanchnic VT, extensive PTE or PTE involving main pulmonary branches, extensive LL-DVT.
   [2] In patients with platelet count < 30 000/mm^3 or haemorrhagic infarction secondary to CVST, the lower limits of the therapeutic range of PTT should initially be targeted.
   [3] In patients with platelet count < 30 000/mm^3, assess reducing to 50% of the corresponding dose according to weight.
   [4] May be considered in patients with initially less severe thrombosis, no active bleeding, and with a platelet count > 50 000/mm^3.

   ** In the event of clinically relevant active bleeding other than cerebral haemorrhage secondary to venous infarction, the risk/benefit balance of anticoagulation treatment should be assessed on an individual basis.*

3. **Platelet transfusion is contraindicated** except in patients with clinically relevant active bleeding or requiring invasive procedures with high haemorrhagic risk.

4. Combination treatment with:
   - IV immunoglobulins: 1 g/kg/day for 2 days (preferable) or 0.4 g/kg/day for 5 days. Prior immunoglobulin determination is not necessary.

     or:

     Plasmapheresis (with albumin replacement): in patients with contraindications for immunoglobulin therapy.

5. In patients with active bleeding and hypofibrinogenaemia, fibrinogen concentrate should be administered to keep levels > 150 mg/dL.

4. RECOMMENDATIONS FOR PRECISE DOCUMENTATION AND RECORDING OF CASES OF THROMBOSIS ASSOCIATED WITH THROMBOCYTOPAENIA

Suspected cases should be reported as quickly as possible to **https://www.notificaram.es**.

We also recommend collecting complete data on the case and participating in the specific registries run by Spanish and European scientific societies.

In order to notify cases as completely as possible, we recommend providing the following data, where available:

Patient data:

- **Date of birth (if unknown: age _____)**
- **Sex: woman / man**

Hospital admission: No / Yes; date:

Medication data:

- **Vaccine:**
  - **Name; doses administered; administration date; batch.**
    - **Pfizer / Moderna / AstraZeneca / Janssen**
    - **Date 1st dose: Date 2nd dose:**
  - **History of COVID-19:**
    - **No / Yes If yes:**
      - **date of diagnosis (date of diagnostic test):**
      - **diagnostic technique: PCR / antigen / serology**
- **Concomitant medications when thrombosis diagnosed:** contraceptives (specify), anticoagulants (specify), anti-platelets (specify)

Adverse events:

- **Description, start date, end date, and outcome.**
- **Further observations:**
  - Date of symptom onset:
  - Date of diagnosis of thrombotic complication:
  - Localisation of thrombosis
    - CVST / splanchnic VT / pulmonary embolism / LL-DVT / other localisation
  - Diagnostic imaging technique used
    - CT angiography / MRI angiography / CT / MRI / Doppler ultrasound / other technique
  - Platelet count and D-dimer level (at diagnosis and follow-up, if available). Baseline platelet count, if available.
    - Platelets: ____ × 10^3/µL, date _____
    - Platelets: ____ × 10^3/µL, date _____
    - Platelets: ____ × 10^3/µL, date _____
    - Platelets: ____ × 10^3/µL, date _____
    - D-dimer: _____ ng/mL, date _____
    - D-dimer: _____ ng/mL, date _____
  - Anti-PF4 antibody determination and technique used
    - Not performed

        - If performed:
            - Date
            - Technique/commercial brand
            - Conclusions: negative / positive; quantification: ____
    - Any other relevant test performed to rule out alternative diagnoses
    - Relevant personal or family history (considered potentially relevant to the event): No / Yes
        - Venous thromboembolism (family/personal): No / Yes
        - Ischaemic events: myocardial infarction, stroke, other (family/personal): No / Yes
        - Thrombocytopaenia (family/personal): No / Yes
        - Other treatments (eg, migraine, cancer): No / Yes

    - Treatment administered (anticoagulation, immunoglobulin, other): onset, duration, and dosage
        - Anticoagulation: No / Yes If yes:
            - IV argatroban; date of onset:
            - IV bivalirudin; date of onset:
            - SC fondaparinux; date of onset:
            - Oral rivaroxaban or apixaban; date of onset:
            - Heparin: low-molecular-weight / unfractionated; date of onset:
            - Acenocoumarol; date of onset:
        - Immunoglobulins: No / Yes If yes:
            - Date of 1st administration
            - Dose: 1 g/kg/day for 2 days / 0.4 g/kg/día for 5 days / other dosage
        - Platelet transfusion: No / Yes If yes:
            - Date(s):
            - Platelet concentrate: ____ units
            - Plateletpheresis (units):
            - Fibrinogen: No / Yes If yes:
                - Date:
                - Dose:
        - Plasmapheresis: No / Yes If yes:
            - Date(s):
            - Substitution with: albumin / plasma