

Recommendations for the diagnosis and management of persons with suspected vaccine-induced immune thrombotic thrombocytopenia (VITT)

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Abstract

In recent months, rare cases of thrombosis at unusual sites associated with thrombocytopenia, occurring within a typical risk window (i.e., 4-28 days) after receiving SARS CoV2 vaccines, have been reported. Healthcare professionals should be prepared to detect these cases on time. The Expert Panel of the Knowledge Management and Transfer Network conducted a free search of the related literature. With the available information and the clinical expertise of the working group, we formulated, reviewed, and endorsed recommendations for the timely suspicion, diagnosis (case definitions, the use of initial laboratory and imaging tests, specific tests), and management of these thrombotic conditions. This document is considered a living document that will be updated as new evidence emerges, and recommendations may change over time.

Keywords: Thrombocytopenia; COVID-19 Vaccines; Thrombosis

Recomendaciones para diagnóstico y manejo de personas con trombocitopenia trombotica inmune inducida por vacunas (VITT)

Resumen

En meses recientes se han reportado casos raros de trombocitopenia y trombosis en sitios inusuales, que ocurren dentro de una ventana de riesgo típica (por ejemplo de 4 a 28 días) luego de recibir vacunas de SARS CoV 2. Los profesionales de la salud deben estar preparados para detectar estos casos a tiempo. Un panel de expertos y una red de transferencia de conocimiento realizó una búsqueda libre de literatura seleccionada. Con la información disponible y la experiencia clínica del grupo de trabajo revisamos y dimos recomendaciones para la sospecha temprana, el diagnóstico (definición de caso, el uso de pruebas de laboratorio específicas y de imágenes diagnósticas) para el manejo de estas condiciones tromboticas. Este documento es considerado un documento vivo que debe ser actualizado a medida que surja nueva evidencia y las recomendaciones vayan cambiando con el tiempo

Palabras clave: trombocitopenia; COVID 19; vacunas; trombosis

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Introduction

On April 7, 2021, the European Medicines Agency (EMA) Safety Committee stated a review of cases of thrombosis associated with thrombocytopenia and, in some cases, hemorrhage in people who received the ChAdOx1 nCoV-19 vaccine (Vaxzevria, formerly COVID-19 AstraZeneca vaccine) and concluded that these events should be included as infrequent side effects of Vaxzevria.

On April 20, 2021, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that a warning about "unusual blood clots with low blood platelets" should be added to the product information for the COVID-19 Janssen vaccine. The PRAC also concluded that these events should be included as infrequent side effects of the vaccine.

These cases of thrombosis with thrombocytopenia included venous thrombosis events at unusual sites, such as cerebral venous sinus thrombosis (VST) and splanchnic vein thrombosis (SVT), as well as arterial thrombosis. Most of the cases reported so far have occurred in women under 60 years of age, within two weeks after the first dose. There is limited information about the second dose.

Healthcare professionals should be alert to signs and symptoms of thrombosis in unusual sites such as cerebral venous sinus, splanchnic veins, multi-site arterial thrombosis, or usual venous thrombosis or pulmonary thromboembolism associated with thrombocytopenia, in order to seek timely diagnosis and treatment, according to the recommendations presented in this document.

Health care professionals should inform vaccine recipients that they should seek medical attention if they experience any of the following symptoms:

- Neurologic: sudden onset of severe or persistent worsening headaches, blurred vision, focal neurologic manifestations, or seizures
- Persistent abdominal pain, nausea, vomiting
- Dyspnea, precordial pain, tachycardia, or arrhythmias
- Edema, redness in an extremity, or pallor and coldness in a limb; pain or functional limitation.
- Petechiae and ecchymosis away from the vaccination site

In terms of mechanism, it is believed that the vaccine may trigger an immune response leading to an atypical heparin-induced thrombocytopenia-like disorder mediated by antibodies directed against platelet factor 4 (PF4)¹. At this time, it is not possible to identify specific risk factors.

After using the Bradford-Hill criteria, the EMA found several arguments to support that a causal relationship between vaccination with Vaxzevria and adverse events is at least a reasonable possibility^{2,3}. There are enough alarm signals to consider those episodes, occurring mainly in women under 55 years of age and with a time of onset within two weeks

after vaccination, could be associated with the biologic. Atypical heparin-induced thrombocytopenia (aHIT) is the most plausible disorder given the similarities observed in the serologic profile and clinical presentation of the affected patients. It is considered extremely likely that the syndrome, which resembles aHIT, is related to a severe autoantibody against PF4 with high binding affinity. It was hypothesized that the antibody itself is changing the structure of PF4, similar to what has been shown for aHIT. Greinacher et al¹ found high titers of anti-PF4 antibody in all patients with serological studies, supporting this hypothesis. The same authors suggested naming this disorder as vaccine-induced prothrombotic immune thrombocytopenia and, based on this, an algorithm was proposed by the German Society for Thrombosis and Hemostasis Research (GTH)⁴.

Subsequently, the name of the entity has been changed to Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)^{5,6}. In addition, the scientific advisory board at COVID-19 in Ontario⁷ and the British Society of Haematology published guidelines for thrombosis syndrome and thrombocytopenia after coronavirus vaccination, including a classification of cases⁸. However, there is no consensus regarding the case definition, since not all specific presentations of thromboembolic events have been defined. Therefore, the EMA report recommended that the definition should not be limited to those cases of cerebral VST with thrombocytopenia and could be broadened to include all thrombotic events².

The importance of immediate specialized medical treatment is emphasized. By recognizing the signs of blood clots and low blood platelets and treating them early, health professionals can help recovery and avoid complications in those affected. Thrombosis in combination with thrombocytopenia requires specialized clinical management. Healthcare professionals should consult applicable guidance and consult specialists (e.g., hematologists, coagulation specialists) to diagnose and treat this condition.

Given the current timing of the pandemic and the morbidity and mortality impact of SARS CoV2/COVID-19 infection, the positive effects of vaccination outweigh the risks. However, under the precautionary principle, we should keep close surveillance of the evidence, and strengthen the processes of pharmacovigilance, identification, and timely management of cases, as well as community literacy programs and standardization of clinical practice.

Health professionals and vaccine recipients should be aware of the possibility of very rare cases of thrombosis associated with thrombocytopenia occurring within two weeks of vaccination. However, COVID-19 is associated with a relevant risk of thrombotic events associated with infection and a high risk of hospitalization and death, so the overall benefits of these vaccines far outweigh the risk of adverse events from the vaccines.

For all of the above, the panel of experts of the Colombian Consensus for the diagnosis and management of persons with suspected vaccine-induced immune thrombotic thrombocytopenia generates recommendations within the framework of a person-centered care model, which guarantees clear and transparent information to persons regarding the risks and benefits of vaccination, as well as guidelines that allow them to suspect, detect and manage these thrombotic conditions promptly.

Methodology

We developed evidence-based and evidence-informed recommendations following the Manual for the Development of Clinical Practice Guidelines and the methodology proposed by NICE for generating guidelines in response to health and social care emergencies, agreed with clinical experts. From the EMA reports published up to April 7, 2021, about the occurrence of VITT, in April 2021 the work team performed a free search in Google Scholar in the first ten pages of results with free terms including "vaccine," "AstraZeneca," "Janssen," "Johnson & Johnson", "thromboembolic", "events," from which relevant documents were selected. Subsequently and in a complementary manner, we consulted the web pages of governmental agencies, national and international scientific societies, and guideline development sites, which allowed the narrative synthesis of information of clinical interest on cases of patients with VITT, which revealed the absence of sufficient information regarding pathophysiological mechanisms, diagnostic standards, and specific management.

With the available information and the clinical expertise of the working group, the members of the Knowledge Management and Transfer Network (RGTC for its Spanish initials) listed below, formulated, reviewed, and endorsed the recommendations contained in this document:

- Global Institute of Clinical Excellence
- Colombian Association of Hematology and Oncology
- Latin American Cooperative Group of Hemostasis and Thrombosis
- Colombian Association of Neurology
- Colombian Association of Internal Medicine
- Colombian Association of Critical Medicine
- Colombian Association of Gastroenterology
- Colombian Association of Pneumology and Thoracic Surgery
- National University of Colombia
- Colombian Association of Nephrology and Arterial Hypertension
- Simon Bolivar University
- Colombian Society of Family Medicine
- Colombian Association of Emergency Medicine Specialists
- Los Andes University
- Colombian Society of Cardiology and Cardiovascular Surgery Association
- Colombian Association of Organ Transplantation
- Colombian Association of Infectology
- Sanitas University Foundation

- Colombian Association of Scientific Societies
- University Foundation of Health Sciences

Part of the recommendations we consulted are derived from evidence of similar conditions such as heparin-induced thrombocytopenia. Therefore, we would like to clarify that:

1. This document is considered a living document that will be updated as new evidence emerges, and recommendations may change over time. However, patient management should be individualized to specific circumstances.
2. Under person-centered care guidelines, all necessary, clear, and truthful information regarding the risks and the benefits of vaccination should be provided.
3. A literacy plan should be included for the community and for emergency, specialized and primary care teams to identify and manage cases on time.
4. These recommendations should be included in the pharmacovigilance guidelines.

Recommendations

The following are the recommendations endorsed by RGTC, including guidelines for diagnosis, approach to special conditions such as venous sinus thrombosis and splanchnic thrombosis, and treatment recommendations.

1. Diagnosis

Even though we found insufficient data to support a commonly agreed diagnostic strategy or a standard case definition for VITT, characteristic findings in patients are:

- Reduced platelet count.
- Venous or arterial thrombotic events occurring within a typical risk window (i.e., 4-28 days post-vaccination)
- Thrombotic complications including, but not limited to VST, and even thrombotic events at multiple sites.
- High titers of anti-PF4 antibodies which may be requested, when available, after Hematology expert evaluation.
- Exclusion of other etiologies of venous thrombosis and thrombocytopenia.

The need for and characterization of the most appropriate functional tests remains to be established.

When to suspect VITT?

VITT should be suspected in persons who previously received vaccination against SARS CoV2 between 4 and 28 days.

Flu-like symptoms such as: arthralgias, osteomyalgias, and mild to moderate headache in the first 2 to 3 days of vaccine administration are common side effects of all currently available vaccines and are not a cause for concern.

The following manifestations should arouse suspicion, and lead to evaluation for thrombosis and thrombocytopenia^{8,9,10}:

- Neurologic symptoms: sudden onset of severe headache; or persistent, progressive, worsening headache, blurred

vision, focal neurologic manifestations, seizures

- Persistent abdominal pain, nausea, vomiting
- Dyspnea, precordial pain, tachycardia, or arrhythmias
- Edema, redness in an extremity; or pallor and coldness in a limb; pain or functional limitation.
- Petechiae and ecchymosis away from the vaccination site.

As a good practice tip, always rule out SARS-CoV2/ COVID-19 infection through SARS CoV2 rt-PCR testing.

VITT Case Definitions

The Expert Panel of the British Society of Haematology⁸ has proposed case definitions adapted as described below. It is essential to point out that there is no unanimity among the scientific societies of other countries in recommending these definitions.

Definite case

- Usually occur between 5 and 28 days after vaccination (it should be noted that most cases report onset of symptoms in the first 16 days after vaccine administration).
- Rapidly progressive thrombosis (with a high preponderance of cerebral VST, but splanchnic thrombosis, pulmonary embolism, and arterial ischemia may also occur).
- Typical laboratory findings:
 - platelet count $<150 \times 10^9/L$,
 - very raised D-dimer levels ($> 4000\text{ng/mL}$, above the level expected for venous thromboembolism),
 - many develop low fibrinogen levels.
- Antibodies to platelet factor 4 have similarities to heparin-induced thrombocytopenia (HIT), but in the absence of patient exposure to heparin treatment. Antibodies are detected by ELISA assay (when available) but not usually by other HIT assay methods.
- Emphasize that other common causes of thrombosis and thrombocytopenia such as: atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, antiphospholipid syndromes, hematologic malignancies, heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria have been ruled out.
- Verify that the patient has not received previous heparin therapy.

Suspected cases can be classified as follows:

Possible case

- Any patient presenting with acute thrombosis or new onset thrombocytopenia within 28 days of receiving the SARS CoV2 vaccine. Based on further evaluation, possible cases are reclassified as unlikely or probable.

Unlikely case

- Thrombocytopenia without thrombosis with D dimer at or near normal and normal fibrinogen
- Thrombosis with normal platelet count, with D-dimer $<2000 \text{ ng/mL}$ and normal fibrinogen
- Intermediate or high probability of heparin-induced thrombocytopenia.

Likely case

- The patient has not received heparins or has a low probability of HIT.
- D-dimer $> 4000 \text{ ng/mL}$ (or D-dimer 2000-4000 ng/mL with strong clinical suspicion)

Diagnostic approach

The RGTC has agreed on the following recommendations for the diagnostic approach^{5,7,8,9,11,12,13}:

- If there is clinical suspicion or a possible case, we suggest requesting the following laboratory tests:
 - Hemogram and manual platelet count in a citrated tube, reticulocyte count, peripheral blood smear (in search of differential diagnoses).
 - D-dimer
 - Fibrinogen
 - Prothrombin time and activated partial thromboplastin time.
 - According to the clinical presentation, consider RT-PCR test for SARS-CoV2 to diagnose COVID-19.
- In case of clinical suspicion of thrombotic phenomena, consider, according to previously established guidelines, the request for confirmatory diagnostic imaging (Fig. 1), and the concept of the corresponding specialties (e.g., Internal Medicine, Hematology, Neurology, or Gastroenterology):
 - Cerebral VST: computed axial tomography (CT) with angiography in arterial and venous phase, or cerebral magnetic resonance angiography with venography.
 - Splanchnic venous thrombosis (SVT): ultrasound with Doppler (for the diagnosis of portal venous thrombosis and Budd-Chiari syndrome), or CT angiography, or magnetic resonance venography (diagnosis of all types of SVT and differential diagnoses).
 - Pulmonary thromboembolism: pulmonary scintigraphy (when there is normal or near-normal chest X-ray), or CT angiography.
 - Deep venous or arterial thrombosis: venous or arterial Doppler or CT angiography depending on the clinical condition.
- In patients with previous exposure to heparin, consider differential diagnosis with heparin-induced thrombocytopenia (HIT). The 4T score is used¹⁴. Prior exposure to heparin makes it more likely that it is the cause, but the treatment of VITT and HIT is similar.
- In probable cases (acute thrombosis, thrombocytopenia, and high D-dimer elevation between 4 and 28 days after receiving the vaccine):
 - Request concept of Internal Medicine, or Hematology.
 - Request evaluation by Neurology, Gastroenterology, or General Surgery depending on the location of the thrombosis.
 - When available, consider ELISA test to detect antibodies against platelet factor 4 or save serum sample for further processing. Those who test positive should have a confirmatory HIPA (heparin-induced platelet activation) or SRA (serotonin-release assay)

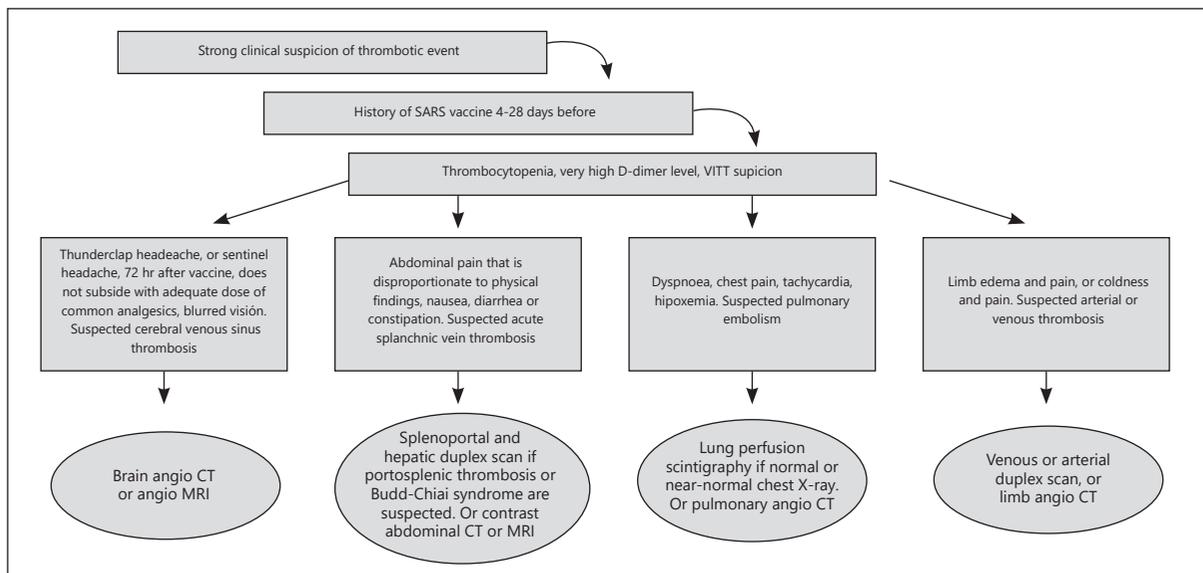


Figure 1. Diagnostic imaging in the diagnosis of VITT

test. Ideally, a modified test (no heparin, free PF4 FP4) should be available for atypical cases. This is important because patients who do not have antibodies by ELISA can be treated with heparin.

2. Addressing specific conditions

Since some of the thrombotic manifestations of VITT can be difficult to diagnose, some diagnostic clues are summarized below.

Cerebral venous sinus thromboses (VST)

Cerebral VST is an uncommon form of cerebrovascular attack (CVA)¹⁵. Unlike arterial stroke, which is more prevalent in the elderly, VST generally affects young people. Eighty percent of cases occur under 50 years of age, and 75% in women^{16,17}.

Risk factors for VST are associated with acquired and inherited events, including central nervous system events such as neoplasms and intracranial infections, procedures such as surgery and lumbar puncture, and systemic risk factors for thrombotic events, e.g., nephrotic, vasculitis, oral contraceptives, pregnancy and puerperium¹⁸. Oral contraceptive use is by far the most common risk factor, and is associated with an approximately 6-fold increased risk for VST^{19,20}.

Cerebral venous sinus thrombosis, along with other paradoxical thromboembolic events, occurs in other immune thrombocytopenic states such as immune thrombocytopenia and HIT. Although viral infections rarely cause VST, SARS CoV2/ COVID-19 infection is associated with stroke involving arterial and venous vessels, producing stroke directly with thrombosis in situ or indirectly through systemic inflammation and endotheliopathy.

The diagnosis of VST is often delayed by about seven days from the onset of clinical manifestations. The most frequent symptoms are headache (89%), seizures (39%), paresis (37%), papilledema (28%), and mental status changes (22%), with

specificities depending on the sinus involved. Large sinuses are the most frequently affected, such as the superior longitudinal and lateral (transverse) sinus. The pain is usually bilateral, global, anterior or posterior of mild onset with progression to a severe picture, or of subacute course that increases with Valsalva maneuvers. The type of headache of vascular origin is called thunderclap headache, characterized by sudden pain of greater severity in the first minute, intensity greater than 7/10 on the analogous functional scale, of rapid recovery or may be manifested by mild dull pain. Another pain is sentinel headache, characterized by the second peak of pain 3 to 14 days after the initial one, moderate to severe, with symptoms and signs of focalization of other neurological areas²¹. On physical examination, papilledema, involvement of the lateral rectus muscles, increased tone and reflexes, as well as changes in heart rate, blood pressure, and respiratory rate, up to profound compromise of consciousness are characteristic.

The manifestations according to the main venous sinuses involved are:

- The superior sagittal sinus drains most of the cerebral cortex. The clinical manifestation is the characteristic headache of endocranial hypertension in 70% of cases. Patients usually present with focal neurological symptoms, seizures, and papillary edema. The lateral sinus drains blood from the sagittal sinus, cerebellum, brainstem, and posterior cerebral hemispheres. Isolated occlusion is rare; patients usually have thrombosis of multiple sinuses or cerebral veins. Manifestations are similar to those of superior sagittal sinus. The cavernous sinuses lie on either side of the sella turcica. They drain blood from the orbits and from the anterior part of the base of the brain. Patients usually present with headache, chemosis, proptosis, red-eye, and painful ophthalmoplegia. The presentation may be more insidious, with only sixth-pair palsy, mild chemosis, and proptosis.

- If VST is suspected, a computed tomography (CT) scan with angiography in arterial and venous phase or cerebral magnetic resonance angiography should be performed.

Splanchnic venous thrombosis (SVT)

The concept of SVT includes mesenteric venous thrombosis, portal vein thrombosis, splenic vein thrombosis, and Budd-Chiari syndrome. Thrombosis may co-occur in several of these beds^{22,23}. The clinical manifestations of acute SVT are nonspecific and sometimes present without causing acute symptoms. The most common symptom is abdominal pain in about half of the patients, followed by gastrointestinal tract bleeding and ascites. Pain disproportionate to the findings on physical examination is usually striking. Other symptoms include nausea, vomiting, anorexia, diarrhea or constipation, and fever. In addition, each site of thrombosis may manifest differentially. The manifestations of sub-acute and chronic SVT may be different, but they are of less interest for VITT diagnosis.

Acute mesenteric venous thrombosis is manifested by significant abdominal pain and may be associated with diarrhea, nausea, vomiting, and lower gastrointestinal tract bleeding. When the proximal venous arches are involved, abdominal pain is more severe and spread to the dorsum, and ileus occurs due to ischemia. Intestinal infarction occurs in one third of patients and should be suspected when there is hematochezia, ascites, metabolic acidosis, acute renal injury, or respiratory failure. Acute portal vein thrombosis may be manifested by abdominal pain of sudden onset, with fever, nausea, vomiting, and diarrhea. Acute splenic venous thrombosis presents with abdominal pain, gastrointestinal bleeding, and nausea. Acute Budd-Chiari syndrome is manifested by abdominal pain, ascites, hepatomegaly, and hepatic necroinflammation, leading to liver failure in severe cases.

3. Treatment

Since this is a newly described syndrome, whose disease mechanisms remain to be elucidated, all recommendations are based on extrapolations from previously known conditions, such as HIT and non-heparin-dependent autoimmune thrombocytopenic thrombocytopenias, and analysis of clinical features in reported cases.

In patients presenting with new-onset thrombocytopenia and documented thrombosis between 4 and 28 days post-vaccination, several international societies have generated documents that include treatment recommendations similar to that for severe HIT^{4,8-10}. This treatment should be initiated promptly in the presence of a high clinical suspicion of VITT, even in the absence of a report of antibodies to PF4. Recommended treatment includes intravenous human immunoglobulin (IVIg), and anticoagulation without heparin. Anticoagulation is selected according to the patient's clinical status; direct oral anticoagulants (with a preference for factor Xa inhibitors), parenteral direct thrombin inhibitors (argatroban or bivalirudin), and fondaparinux have been mentioned

among the options. Greater caution is required for the use of anticoagulation when platelets are less than $50 \times 10^9/L$ or when there is severe bleeding. However, VITT is associated with fibrinogen consumption and bleeding, which should not absolutely contraindicate anticoagulation, particularly if the platelet count is greater than $20 \times 10^9/L$ and rising after initiation of IVIG^{9,10}. While so far there is no evidence that heparin products worsen immune thrombotic thrombocytopenia, the syndrome's similarities to HIT suggest avoiding unfractionated or low-molecular-weight heparin.

Also based on similarities with HIT, it is recommended to avoid platelet transfusions. However, risk/benefit assessment in individual patients with severe bleeding and need for surgical intervention may favor platelet transfusion, following initiation of IVIG, non-heparin anticoagulation and fibrinogen replacement (if deficient).

Based on the publications reviewed^{4,7-13} and experience with other entities with similar presentations, the RGTC reached consensus on a management algorithm (Fig. 2) and the following treatment recommendations:

1. In likely or definite cases of VITT, we recommend to initiate in-patient treatment as a priority while awaiting confirmation of the diagnosis.
2. Administer IVIG at a dose of 1 gram/kg/day for two consecutive days.
3. In patients with thrombosis in connection with VITT, we suggest to initiate anticoagulant therapy without delay.
 - Consider platelet count, age, comorbidities, and bleeding risk to individualize the appropriate anticoagulant type and dose.
 - In particular cases, consider using adjusted doses of anticoagulants.
 - Apply greater caution for the use of anticoagulation when platelets are less than $50 \times 10^9/L$ or when there is severe bleeding. Even though, decreased fibrinogen and bleeding do not absolutely contraindicate anticoagulation, mainly if the platelet count is greater than $20 \times 10^9/L$ and rising after initiation of IVIG.
 - In all cases, the platelet count and overall clinical course should be assessed daily or more frequently to define appropriate management changes.
4. Even with thrombocytopenia, these patients require anticoagulation, ideally with the accompaniment of a hematologist in the multidisciplinary management team. If not available, the patient should be urgently referred to a third or fourth-level institution.
5. We recommend anticoagulants (other than heparin) such as those used to treat heparin-induced thrombocytopenia. These include direct anticoagulants and fondaparinux.
6. We recommend following the general recommendations to start therapy with direct oral anticoagulants, without using heparins in the first days, considerations related to the risk of bleeding due to the association with thrombocytopenia:
 - Prefer low anticoagulant doses until the platelet count is in a safe range (greater than $50 \times 10^9/L$), e.g.,

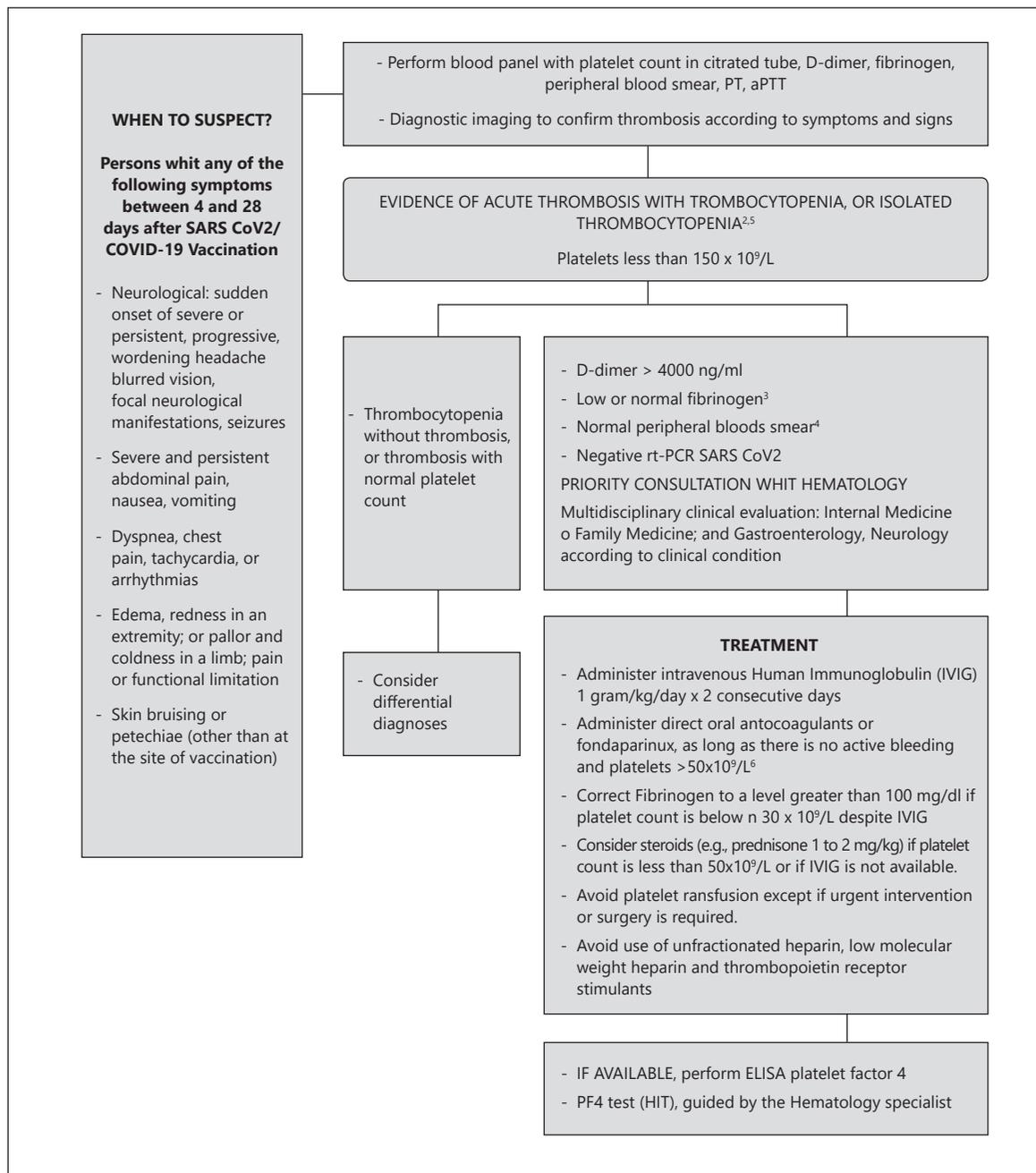


Figure 2. Algorithm for the diagnosis and management of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)¹

Notes: 1. Also referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT). 2. A patient presenting with thrombosis and a normal platelet count after vaccination requires ongoing evaluation for the development of thrombocytopenia/VITT. 3. Low fibrinogen and extremely high D-dimer levels suggest the diagnosis of disseminated intravascular coagulation, which is included in the VITT syndrome. 4. Microangiopathy with red cell fragmentation and hemolysis has not been a feature of the reported cases. 5. Patients who develop isolated thrombocytopenia may be in the early stage of VITT, but in the continued absence of thrombosis should be considered immune thrombocytopenic purpura associated with vaccination, which is not included in the VITT syndrome. 6. In the presence of documented thrombosis, the use of anticoagulants is indicated. Caution should be used with platelet counts below $50 \times 10^9/L$ or in patients with active bleeding.

Modified from: Scully M, Singh D, Lown R, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. *Science Briefs of the Ontario COVID-19 Science Advisory Table*. 2021 Mar;1(17) online ahead of print, 2021 Apr 16. *N Engl J Med* 2021;10.1056/NEIMoa2105385. Pai M, Grill A, Ivers et al. Vaccine induced prothrombotic immune thrombocytopenia VPIIT following AstraZeneca <https://doi.org/10.47326/ocsat.2021.02.17.1.0>. American Society of Hematology. Vaccine-induced Immune Thrombotic Thrombocytopenia: Frequently Asked Questions. (Version 1.1; last updated April 19, 2021). <https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia>. British Society of Haematology. Guidance produced by the Expert Haematology Panel (EPH) focussed on Vaccine induced Thrombosis and Thrombocytopenia (VITT). Version 1.3.7 April 2021 https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf <file:///C:/Users/nyomayusa/Downloads/ISTH%20VITT%20Guidance%202.pdf>

- rivaroxaban 10 mg PO once a day, or apixaban 2.5 mg PO every 12 hours.
- Take into account the availability of anticoagulation reversal agents.
7. If fondaparinux is preferred, consider weight adjusted dosing.
 8. **We recommend NOT to use unfractionated heparin, low molecular weight heparin, or vitamin K antagonists.** Avoid use of heparin in catheters.
 9. We suggest NOT to use routine platelet transfusion. It should be reserved for life-threatening bleeding or before invasive procedures. In such a case, this should preferably be done after initiating IVIG, anticoagulation without heparin, and fibrinogen replacement (when deficient).
 10. Avoid use of thrombopoietin receptor stimulants (eltrombopag/ romiplostim).
 11. Consider steroids (e.g., prednisone 1 to 2 mg/kg) if the platelet count is less than $50 \times 10^9/L$ or if IVIG is not available.
 12. Correct fibrinogen to levels greater than 100 mg/dl if platelet count remains less than $30 \times 10^9 / L$ despite IVIG and steroid therapy.
 13. The use of plasma exchange (when available) could be considered, if agreed in a medical board.

Ethical disclosures

Protection of human and animal subjects. No experiments in humans or animals were done for this work.

Right to privacy and informed consent. The authors declare that no data that enables identification of the patients appears in this article.

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Conflict of interest. None declared

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