






## RECOMMENDATIONS AND GUIDELINES

# Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: Communication from the ISTH SSC Subcommittee on Platelet Immunology

Ishac Nazy<sup>1,2</sup>   | Ulrich J. Sachs<sup>3</sup> | Donald M. Arnold<sup>1,2</sup> | Steven E. McKenzie<sup>4</sup> | Phil Choi<sup>5,6</sup> | Karina Althaus<sup>7,8</sup> | Maria Therese Ahlen<sup>9</sup>  | Ruchika Sharma<sup>10</sup> | Rachael F. Grace<sup>11</sup>  | Tamam Bakchoul<sup>12</sup> 

<sup>1</sup>Department of Medicine, Michael G. DeGroot School of Medicine, McMaster University, Hamilton, ON, Canada

<sup>2</sup>McMaster Centre for Transfusion Research, Hamilton, ON, Canada

<sup>3</sup>Department of Thrombosis and Haemostasis, Giessen University Hospital, Giessen, Germany

<sup>4</sup>Cardeza Foundation for Hematological Research, Thomas Jefferson University, Philadelphia, PA, USA

<sup>5</sup>Haematology Department, The Canberra Hospital, Canberra, ACT, Australia

<sup>6</sup>John Curtin School of Medical Research, ANU, Canberra, ACT, Australia

<sup>7</sup>Transfusion Medicine, Medical Faculty of Tuebingen, University of Tuebingen, Tuebingen, Germany

<sup>8</sup>Centre for Clinical Transfusion Medicine Tuebingen ZKT gGmbH, Tuebingen, Germany

<sup>9</sup>Norwegian National Unit for Platelet Immunology, University Hospital of North Norway, Tromsø, Norway

<sup>10</sup>Versiti BloodCenter of Wisconsin Pediatric Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI, USA

<sup>11</sup>Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA

<sup>12</sup>Institute for Clinical and Experimental Transfusion Medicine, Medical Faculty of Tuebingen, University Hospital of Tuebingen, Tuebingen, Germany

### Correspondence

Ishac Nazy, Department of Medicine, Michael G. DeGroot School of Medicine, McMaster University, HSC 3H53, 1280 Main Street West, L8S 4K1 Hamilton, ON, Canada.  
Email: nazyi@mcmaster.ca

Tamam Bakchoul, Universitätsklinikum Tübingen, Transfusion Medicine, Otfried-Müller, 72076 Tübingen, Germany.  
Emails: tamam.bakchoul@med.uni-tuebingen.de, tamambakchoul@yahoo.com

### Abstract

Vaccine administration is under way worldwide to combat the current COVID-19 pandemic. The newly developed vaccines are highly effective with minimal adverse effects. Recently, the AstraZeneca ChadOx1 nCov-19 vaccine has raised public alarm with concerns regarding the rare, but serious, development of thrombotic events, now known as vaccine-induced immune thrombotic thrombocytopenia (VITT). These thrombotic events appear similar to heparin-induced thrombocytopenia, both clinically and pathologically. In this manuscript, the ISTH SSC Subcommittee on Platelet Immunology outlines guidelines on how to recognize, diagnose and manage patients with VITT.

### KEYWORDS

AstraZeneca ChadOx1 nCov-19 vaccine, COVID-19, platelet activation, thrombocytopenia, thrombosis

## 1 | INTRODUCTION

The COVID-19 pandemic has resulted in significant morbidity and mortality worldwide.<sup>1,2</sup> Clinically, critically ill COVID-19 patients develop coagulation abnormalities, leading to significant thrombosis and death.<sup>3-6</sup> Recent studies by Althaus *et al.* and Nazy *et al.* indicate that platelet activation by immunoglobulin G-immune complexes can activate platelets in critically ill COVID-19 patients via platelet FcγRIIa.<sup>7,8</sup>

COVID-19 vaccination campaigns with several vaccine types are currently under way. Europe have described patients who developed thrombosis and thrombocytopenia 5 to 28 days after administration of AstraZeneca ChadOx1 nCov-19 vaccine.<sup>9,10</sup> These include rare thrombotic events such as cerebral sinus vein and splanchnic vein thrombosis.<sup>9,10</sup> This rare syndrome is known as vaccine-induced immune thrombotic thrombocytopenia (VITT).<sup>9,10</sup> Although data on VITT is limited, some clinical and laboratory features of VITT have similarities to those observed in patients with severe COVID-19 infection and in patients with autoimmune heparin-induced thrombocytopenia (HIT). The SSC Platelet Immunology felt that a brief communication paper could help physicians and laboratory staff manage these cases.

## 2 | POSSIBLE MECHANISMS

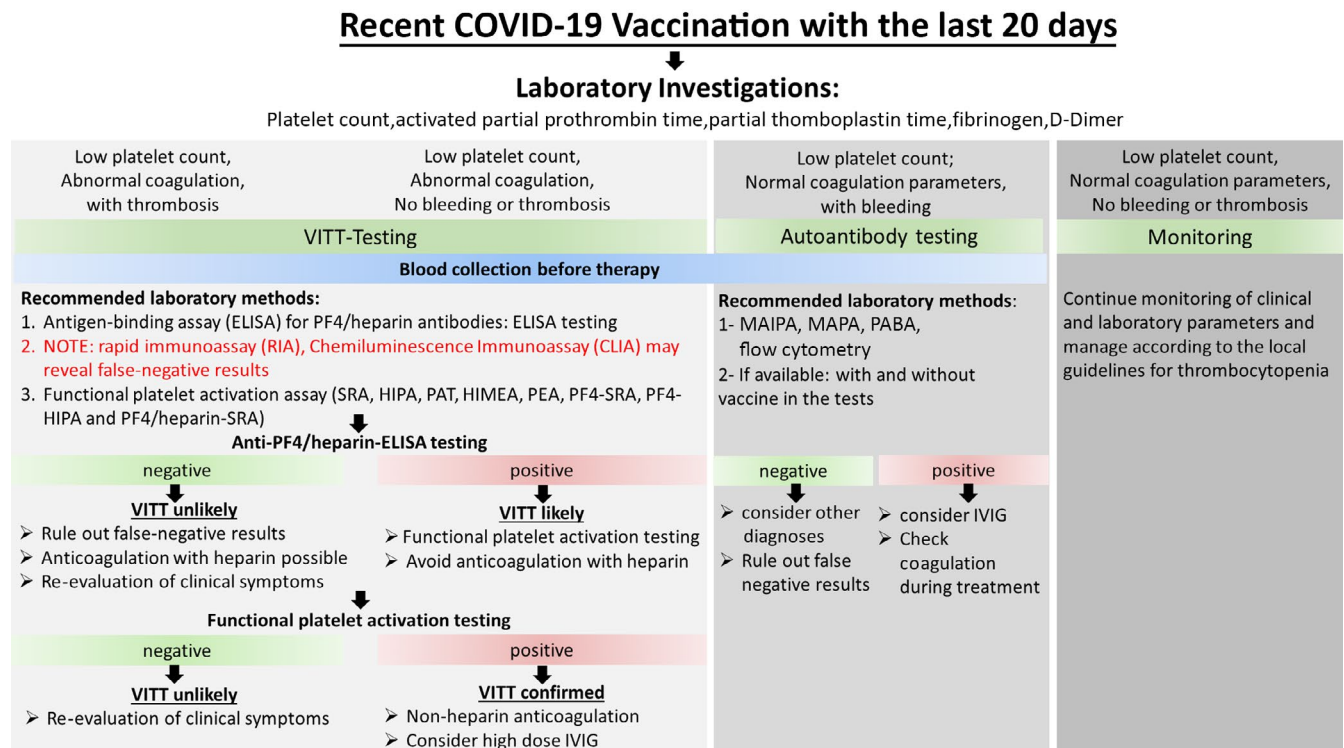
Preliminary data suggests that VITT after AstraZeneca vaccination has some clinical and serological similarities to HIT such as the

presence of high-titer anti-PF4/heparin antibodies that cause platelet activation in functional assays. In addition, mRNA vaccines for COVID-19 have been associated with severe thrombocytopenia and bleeding.<sup>11</sup> Recent studies have implicated an antibody-mediated platelet activation as the mechanism of the clotting events.<sup>9,10</sup> This requires immediate clinical recognition followed by confirmatory laboratory diagnosis, using specialized tests (Figure 1).

## 3 | RECOMMENDATIONS FOR LABORATORY INVESTIGATION

Besides complete blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer testing, the following actions should be considered:

1. All samples for VITT testing should be collected into serum or plasma tubes based on the requirement of the testing facility, before the administration of any treatment, especially intravenous immunoglobulin (IVIG) and danaparoid. In addition, these samples should be conserved for future testing and to be used for improving testing and validation of these newly developed assays.
2. A negative rapid immunoassay against PF4 such as particle centrifugation assay and chemiluminescence immunoassay may reveal false-negative results. Once again, samples for VITT testing should be conserved until modified test methods are validated.



**FIGURE 1** Recommendations for laboratory diagnosis and patient management following bleeding and/or thrombosis after vaccination with the AstraZeneca Vaccine for COVID-19

3. The clinical picture should guide management and laboratory investigation:
  - a. Thrombocytopenia, bleeding, and normal coagulation parameters (normal PT, APTT, PT, fibrinogen, and D-dimer levels) may indicate an immunization-associated immune thrombocytopenia (ITP), and depending on bleeding risk, strong consideration is recommended for high dose IVIG without anticoagulation.
    - (i) Autoantibody testing against platelet glycoproteins using MAIPA,<sup>12</sup> MACE,<sup>13</sup> PABA,<sup>14</sup> or flow cytometry<sup>15</sup> including the presence of vaccine (where available).
  - b. Thrombocytopenia and thrombosis: this may indicate a HIT-like syndrome (VITT), and management should be initiated with non-heparin anticoagulation upon suspicion, PF4-ELISA and SRA confirmation as per HIT syndrome. Testing should follow the algorithm below (where available): if VITT testing is positive and diagnosis is confirmed, continue nonheparin anticoagulation with consideration for high-dose IVIG.
  - c. Thrombocytopenia without bleeding or thrombosis but abnormal coagulation parameters (at least one of: PT, APTT, fibrinogen, and D-dimer, especially with dynamic change): this may indicate an early VITT syndrome and consideration should be given to initiate thromboprophylaxis with non-heparin anticoagulation until the results of confirmatory testing are available.
  - d. Thrombocytopenia without bleeding or thrombosis and normal coagulation parameters: there is a potential for vaccine associated isolated thrombocytopenia. It is currently unclear whether these cases are induced by the vaccine such as drug-induced thrombocytopenia or by primary ITP. Monitor and manage as per local guidelines for thrombocytopenia, based on bleeding risk.

## 4 | VITT TESTING ALGORITHM

Testing for VITT should begin with a binding assay (such as platelet factor 4 [PF4] ELISA) to identify the presence of anti-PF4/polyanion antibodies (Figure 1).

1. If the PF4 binding assay is negative, this patient does not have HIT or HIT-like VITT.
2. If the PF4 binding assay is positive (or not available), the sample should be tested in one or multiple HIT functional assays as available, such as the serotonin release assay (SRA),<sup>16</sup> heparin-induced platelet activation assay,<sup>17</sup> platelet aggregation test,<sup>18</sup> heparin-induced multiple electrode aggregometry,<sup>19</sup> PF4-dependant P-selectin expression assay,<sup>20</sup> PF4-SRA,<sup>21</sup> and PF4/heparin-SRA.<sup>22</sup> A positive result strongly suggests this person has VITT in the appropriate clinical context.

## 5 | CONCLUSION AND FUTURE ASPECTS

Although VITT is an extremely rare event in the context of COVID-19-specific vaccinations, it can be associated with severe morbidity and mortality. Data is emerging regarding details on the clinical presentation and mechanism(s) leading to the disease, including PF4/heparin associated antibodies and potentially other immune complexes related to platelet activation. To ensure these cases are recognized, diagnosed, and properly treated, the recommendations proposed here provide direction to allow clinicians and laboratories to perform initial testing currently known to aid in the diagnosis of VITT. It is important to mention that recommendations provided in this letter are made based on expert consensus based on limited data on the pathophysiology of VITT. It is almost certain that an update will be needed once more data is available. Thus, it is important that samples are conserved for future testing once the pathophysiology of VITT is fully understood and novel assays are developed.

Future directions will focus on correlating clinical presentations with laboratory findings including an international surveillance registry for all VITT due to the various COVID-19 vaccines.

### CONFLICT OF INTEREST

The authors declare no competing financial interests.

### AUTHOR CONTRIBUTION

All the authors designed the study, wrote the manuscript, and revised the intellectual content of the manuscript. All authors approved the final version of the manuscript.

### ORCID

Ishac Nazy  <https://orcid.org/0000-0002-5695-4343>

Maria Therese Ahlen  <https://orcid.org/0000-0002-3104-3818>

Rachael F. Grace  <https://orcid.org/0000-0001-7302-0449>

Tamam Bakchoul  <https://orcid.org/0000-0002-6797-6812>

### TWITTER

Ishac Nazy  @ishacgaby

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**How to cite this article:** Nazy I, Sachs UJ, Arnold DM, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: Communication from the ISTH SSC Subcommittee on Platelet Immunology. *J Thromb Haemost.* 2021;00:1-4. <https://doi.org/10.1111/jth.15341>