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COVID-19: Vaccine-induced immune thrombotic thrombocytopenia

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Abstract

In late February 2021, a prothrombotic syndrome was encountered for the first time in some of the recipients of ChAdOx1 CoV-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India). Since the hallmark of this syndrome is the development of thrombocytopenia and/or thrombosis between 4 and 42 days after receiving a COVID-19 vaccine, it was named vaccine-induced immune thrombotic thrombocytopenia (VITT). Other names include "vaccine-induced prothrombotic immune thrombocytopenia" and "thrombosis with thrombocytopenia syndrome" by the Centers for Disease Control and the Food and Drug Administration (FDA). VITT appears similar to heparin-induced thrombocytopenia in that "platelet activating" autoantibodies are produced in both these conditions due to prior exposure of COVID-19 vaccine and heparin respectively, in turn causing thrombotic complications and consumptive thrombocytopenia. In this article, recent advances in the understanding of pathobiology, clinical features, investigative work-up, and management of VITT are reviewed.

KEYWORDS
cerebral venous thrombosis, COVID-19, VITT

1 | INTRODUCTION

In late February 2021, a prothrombotic syndrome was encountered for the first time in some of the recipients of ChAdOx1 CoV-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India). Since the hallmark of this syndrome is the development of thrombocytopenia and/or thrombosis between 4 and 42 days after receiving a COVID-19 vaccine, it was named vaccine-induced immune thrombotic thrombocytopenia (VITT). Other names include "vaccine-induced prothrombotic immune thrombocytopenia" and "thrombosis with thrombocytopenia syndrome" by the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA). VITT appears similar to heparin-induced thrombocytopenia (HIT) in that "platelet activating" autoantibodies are produced in both these conditions due to prior exposure of COVID-19 vaccine and heparin respectively, in turn causing thrombotic complications and consumptive thrombocytopenia. In this article, recent advances in the understanding of pathobiology, clinical features, investigative work-up, and management of VITT are reviewed.

2 | METHOD

A comprehensive search of PubMed and EMBASE from March 2020 to June 2022 was made using three search items: COVID-19, cerebral venous thrombosis (CVT), and VITT. The search items were combined using the Boolean operator. Societal guidelines reviewed at the time of writing this article include: American Society of Hematology, International Society on Thrombosis and Hemostasis, American College of Cardiology, American Heart Association/American Stroke Association, and National Institute for Health and Care Excellence (NICE) in the United Kingdom.

3 | DISCUSSION

3.1 | Incriminated vaccines

After the initial reports of VITT in some of the recipients of ChAdOx1 CoV-19 vaccine, VITT was also reported in a small minority of Ad26.COV2.S vaccine (Janssen; Johnson & Johnson) recipients. Both AZ & JJ vaccines utilize recombinant adenoviral vectors (chimpanzee for AZ and human for JJ). Apart from ChAdOx1 CoV-19 and Ad26.COV2.S vaccines, VITT is not reported with other adenoviral vector-based vaccines like Gam-COVID-Vac/Sputnik V (Gamaleya Institute), Ad5-based COVID-19 vaccine (CanSino Biologics), and Ad26.ZEBOV-GP (recombinant) Ebola vaccine (Janssen Biologics). The UK regulatory agency has reported 15 cases of major thrombosis with concurrent thrombocytopenia with Pfizer and two cases with Moderna vaccines (whether these are cases of VITT has not been confirmed). Elsewhere, a single possible VITT case related to mRNA-1273 (Moderna) vaccine has been published.[1,2] No confirmed case is reported with BNT162b2 (Pfizer-BioNTech) yet. Compared to recombinant adenoviral vector vaccines, the risk of VITT however appears far lower with mRNA vaccines. It is unknown whether the differences in VITT incidence with different vaccines may be attributable to differences in vaccine constituents.

3.2 | Incidence of VITT

Whereas the previse incidence of VITT is unknown, the highest incidence was reported from Norway, in which five cases developed VITT with AstraZeneca vaccine among approximately 130 000 individuals vaccinated. This suggests an incidence of 1 in 26 000.[3] On the flip-side, there have been some speculations of underestimates due to decreased recognition and underreporting of the cases, especially with regards to an initial report from the CDC in the United States, which suggested an incidence of 1 in 533 333.[4] As per CDC review, the updated incidence for JJ vaccine was two per million (based on a total of 15 cases reported following 7.98 million doses administered). For AstraZeneca vaccine, the incidence appears to be 20.3 per million doses in those aged 18 to 49 years compared to 10.9 per million doses in those aged 50 years and older.

Whereas initial reports suggested that most VITT cases were young (<55 or 60 years), on retrospection, this probably simply reflects the age of the initially vaccinated populations, as cases in older individuals >60 years are now increasingly emerging and being reported.[5,6] Whereas reports are conflicting,[3,5–7] there may be a female predominance in VITT cases. If this is indeed true, it would be consistent with the incidence of other immune disorders, which often exhibit a female preponderance, including HIT.[8]

3.3 | Pathobiological basis of VITT

VITT is caused by autoimmune IgG antibodies against platelet-factor 4 (PF4) (also called CXCL4) bound to platelets. These antibodies activate platelets via low affinity platelet FcγIIa receptors (receptors on the platelet surface that bind the Fc portion of IgG) in turn causing "pancellular" activation. This implies that besides activating platelets, anti-PF4 antibodies activate monocytes (leading to tissue factor expression), neutrophils (leading to NETosis), and endothelial cells (leading to tissue factor expression).[9] The net result is marked stimulation of the coagulation system, thromboembolic complications, and consumptive thrombocytopenia.

Whereas the precise mechanism by which the implicated vaccines induce anti-PF4 antibodies genesis is unknown, an evolving model suggests the possibility of a two-hit process.[9] The first-hit refers to vaccine component/s binding with PF4, altering its conformation and thus generating a "neoantigen."[7] The second-hit refers to induction of a systemic inflammatory response. It appears that the two-hits together lead to production of anti-PF4 antibodies. PF4 is a positively-charged tetrameric protein. Whereas the presence of the positive charge ordinarily causes PF4 molecules to repel each other, when negatively charged (polyanionic) molecules such as heparin, viral DNA/RNA, or endogenous polyphosphates come in contact, the conformation of PF4 is altered thus facilitating the formation of higher order structures that act as neoantigens.[10–13] Whereas it is not yet known which of the >1000 protein components in the incriminated COVID-19 vaccines induce neoantigen formation, preliminary studies suggest that a complex of adenoviral hexon proteins ("hexon" is the major adenoviral surface protein), proteins from the HEK3 cell line, and free DNA bound to PF4 may be responsible.[7,9,14]

There is case series-based evidence that VITT antibodies are often transient. In one series of 65 confirmed VITT cases, serial functional assays became negative in 48 (74%), at a median of 15.5 weeks (range, 5–28 weeks).[15] None of the 29 individuals who subsequently received an mRNA COVID-19 vaccine (mostly while still receiving anticoagulant therapy for initial VITT episode) developed increases in enzyme-linked immunosorbent assay (ELISA) titre or new thromboses; two individuals developed mild thrombocytopenia with declining ELISA titres and no recurrence of platelet-activating antibodies. In another series of 35 confirmed VITT cases, serial functional assays became negative in 11 weeks in 23 of the 35 (66%) and after 12 weeks in 14 of 15 evaluable individuals (93%).[16] Whereas ELISA assay titres demonstrated a decline, in most instances they did not become negative. None of the five individuals who subsequently received an mRNA COVID-19 vaccine (mostly while still receiving anticoagulant therapy for initial VITT episode) developed new thromboses. This data supports the safety and permissibility of giving second or booster doses of mRNA vaccine in VITT patients. On the contrary, given the persistence of VITT antibodies for protracted periods in some individuals ("long VITT"), avoidance of future adenoviral vectored COVID-19 vaccines seems sensible.[17,18]

3.4 | Similarity to spontaneous HIT

VITT belongs to a spectrum of platelet-activating anti-PF4/heparin disorders, which include classic HIT, Autoimmune HIT (aHIT), and Spontaneous HIT.[19]

3.4.1 | Classic HIT

In the classic HIT, 5 to 10 days after exposure to unfractionated heparin (UFH) or low molecular weight heparin (LMWH), patients develop thrombocytopenia, often with thrombosis. It is a rare disorder affecting <0.1% to 5% of individuals and is caused by formation of heparin-dependent antibodies (called "HIT antibodies" or "PF4/heparin antibodies").[20] Heparin-dependency implies that platelet counts fall as long as the individual is receiving heparin and typically recover within 4–5 days of stopping it. In cases of VITT, however, the epitope on PF4 differs from the epitope recognized by HIT antibodies. Consequently, unlike HIT, VITT autoantibodies are heparin-independent, that is, these are neither induced by prior exposure to UFH or LMVH nor do they require heparin for detection in in-vitro platelet activation assays. Since PF4 on platelet surface is located within the heparin binding site,[20] contrary to HIT, one study suggests that VITT antibody binding can possibly be blocked with heparin.[21] Therapeutic role of heparin to treat VITT is evolving.

3.4.2 | Autoimmune HIT

Whereas in aHIT, similar to the classic HIT, thrombocytopenia may ensue within the 5–10 days window following heparin exposure, the antibodies produced are both heparin-dependent and heparin-independent. This implies that thrombocytopenia sometimes may only develop *after* stopping heparin (delayed-onset HIT), or persist for days to weeks (or even progress) after stopping heparin (persisting or refractory HIT). For heparin-independent antibodies, heparin is not required to produce a strongly positive result in a functional assay such as the serotonin-release assay (SRA).[7] In aHIT cases, the sole heparin exposure may have been heparin flushes (heparin-flush HIT) or fondaparinux (fondaparinux-associated HIT).

3.4.3 | Spontaneous HIT

As the name suggests, in this syndrome the development of thrombocytopenia is spontaneous and does not require proximate heparin exposure to explain the clinical and serologic picture. The usual precipitants include: (a) Orthopedic surgery (like total knee replacement); (b) viral or bacterial infection, and (c) in association with a monoclonal gammopathy in which the IgG has anti-PF4 platelet-activating properties.[22]

In its pathobiology, VITT most strongly resembles spontaneous HIT as it develops in the absence of proximate heparin exposure and is triggered by an adenoviral vectored COVID-19 vaccine. Additionally, similar to spontaneous HIT in which monoclonal anti-PF4 antibodies are seen, VITT is caused by monoclonal or oligoclonal anti-PF4 antibodies. This is in contrast to the classic HIT in which polyclonal antibodies are generated. In a recent study, all five VITT patients yielded strong positive results in solid-phase ELISAs, but results from SRA (performed in the presence of low concentrations of heparin)

were variably positive between patients and within the same patient over time.[23] All five patients tested positive in an assay that used PF4-treated platelets, the PF4-dependent P-Selectin Expression Assay (PEA: 48%, 68%, 61%, 68%, and 73% in VITT Patients 1 through 5, respectively. Negative control PEA values ranged from 1% to 8%).[23] These findings are consistent with the possibility that given the very limited epitope specificity of VITT antibodies within the heparin-binding domain of PF4, in VITT patients single or very few clones producing anti-PF4 antibodies are more active or persistent than multiple clones producing polyclonal antibodies in classical HIT.[20] Given the small sample size, based on this study alone, it appears premature to proclaim with confidence whether λ light chain restriction seen with all five patients tested is characteristic of VITT antibodies. The study also demonstrated persistent platelet-activating and strongly ELISA-binding antibodies in both native sera and isolated anti-PF4 antibody fractions obtained from two patients at ∼1.5 months (Patient 4) and ∼2.5 months (Patient 1) after initial presentation. This is consistent with other studies demonstrating significantly longer persistence of anti-PF4 antibodies in VITT patients compared to HIT.[15,24,25]

3.4.4 | Spontaneous HIT disorders versus ITP

The key distinguishing feature between VITT (and related HIT disorders) and immune thrombocytopenia (ITP) is that whereas in VITT antiplatelet-antibodies *activate* platelets thus inducing thrombosis, in ITP antiplatelet-antibodies do not cause platelets activation.

3.5 | Diagnostic criterial of VITT

For a definitive diagnosis, all of the following five criteria must be met:

1. COVID vaccination 4–42 days prior to symptom onset (the peak time period for initial symptoms is 6–14 days). VITT has not been reported to occur immediately (within 1–2 days) or beyond 7 weeks post-vaccination. Accordingly, in suspected VITT cases, the first thing to clarify is the date of COVID-19 vaccination.
2. Any venous or arterial thrombosis (often cerebral or abdominal).
3. Thrombocytopenia (platelet count <150 000/μl). Whereas the median platelet count in VITT cases is 20 000 to 25 000/μl, presence of thrombosis with normal platelet count post-vaccination might be in an early stage of VITT. Peripheral smear must be requested along with full blood count (FBC) as former is needed to confirm true thrombocytopenia and rule out pseudothrombocytopenia from platelet clumping.
4. Raised D-dimer >4 times upper limit of normal. Whereas there may be differences in the reference ranges used by individual laboratories, thresholds for "very high" and "high" D-dimer values include: very high = >4000 ug/L FEU or DDU; high = >2000 ug/L up to 4000 ug/L FEU or DDU.[26] (FEU = fibrinogen-equivalent units, DDU = D-dimer units) (4000 ug/L = 4 ug/ml).

5. Positive anti-PF4 antibodies testing by ELISA.

Since not all the above may be present/found simultaneously, gray zone probable or possible VITT diagnosis must be entertained during the post-vaccine period. In patients with low platelet counts, high D-dimer, and presence of symptoms concerning of thrombosis and/or positive imaging can be considered to have VITT and should be started on empirical treatment (see below) while awaiting PF4 ELISA results (take 1 to 2 days to return as sample often needs to be sent off-site for analysis).[27] Presence of severe thrombocytopenia (<30 000 μl) and/or intracranial hemorrhage are particularly concerning as associated with highest mortality.

3.6 | Clinical presentations of VITT

3.6.1 | Thrombosis

Thrombosis is the usual presenting symptom in most VITT cases.[3,7,26,28] CVT, which may in turn cause and thus present as intracerebral hemorrhage (ICH), is reported as the commonest site of thrombosis in some case series.[26,28,29] NICE guideline identified CVT in 147 cases among 405 VITT cases (25%).[29] Nonetheless, thrombosis in VITT has been reported at multiple other sites involving both venous and arterial vasculatures at both typical and atypical sites (mostly atypical).

Examples of venous thrombosis in decreasing order of frequency include:

- CVT: Headache is by far the commonest (89%), usually the first, and may be the only symptom of CVT.[30] It may precede other symptoms and signs by days to weeks.[31]
- Splanchnic vein thrombosis (includes mesenteric vein, splenic vein, portal vein, hepatic vein): It may present with severe new abdominal or back pain
- Adrenal vein thrombosis: It may present as adrenal hemorrhage and can induce acute adrenal failure if bilateral
- Pulmonary embolism: It may present as shortness of breath and pleuritic-type chest pain
- Deep venous thrombosis: It may present as calf swelling, pain, and tenderness
- Ophthalmic vein thrombosis: It may present as visual obscurations.[28,32,33]

Arterial thrombosis is seen both in cerebral vasculature (as ischemic stroke most often involving middle cerebral artery territory), myocardial infarction, and acute limb ischemia. Where the pathophysiologic explanation for thrombosis at atypical sites is not known, the distribution appears similar to what is seen with other unusual thrombophilias such as paroxysmal nocturnal hemoglobinuria (PNH) and thromboembolic complications associated with a *JAK2* mutation.[34]

Clinical presentations of CVT: can be divided into three major syndromes:

1. Intracranial hypertension: most often presents as new-onset headache with or without nausea, vomiting, and visual disturbance.[35] As alluded above, headache is by far the commonest (89%), usually the first, and may be the only symptom of CVT.[30] CVT-related headaches may be diffuse or localized. They often have a gradual onset, are persistent and progressive over days to weeks.[36] In a minority of CVT patients, sudden-onset thunderclap headache mimicking subarachnoid hemorrhage has been reported.[37,38] Intermittent headaches with variable severity is yet another reported presentation. Visual obscurations may occur, coinciding with bouts of increased headache mimicking migraine.[35] These obscurations may develop due to papilledema and/or sixth nerve palsies, which could be either unilateral or bilateral. Visual loss from optic nerve damage is also reported in some cases. Unlike migraine, CVT-related headaches often worsen with recumbency and with Valsalva maneuvres, as is typical with increased intracranial pressure, and are often refractory to analgesics. On rare occasions, dilated orbital or scalp veins and/or scalp oedema may be visible. In one study, 17 (14%) of 123 consecutive patients with CVT presented with "isolated headache" with no other symptoms.[39] This implies observing a high index of suspicion in the right clinical context (i.e., new-onset headache AND recent history of COVID vaccination in the past 4–42 days).

2. Focal deficits: such as monoparesis or hemiparesis (sometimes even asymmetric bilateral weakness) ± expressive dysphasia, especially with thrombosis of left lateral sinus (37%)[30] and/or seizures (focal, generalized, or even status epilepticus) (39%).[40] Focal deficits depend on the area of the brain affected. Superior sagittal sinus (which drains both hemispheres) is the commonest venous sinus affected (62%)[30] and typically presents with bilateral symptoms – an important distinction from the more commonly encountered unilateral focal deficits from ischemic/hemorrhagic stroke. Also, unlike ischemic stroke (arterial occlusion) patients in whom the deficits tend to be maximal at onset, in CVT, deficits are progressive. In one study, deficits onset was <48 h in about 1/3 of patients, 48 h to 30 days in just over half of patients, and >30 days in almost 10% of patients.[30] Seizures also tend to develop more frequently in CVT cases (39%) than with other stroke subtypes.

3. Subacute encephalopathy (mental status changes, stupor, or coma)[41]: may develop due to oedema of bilateral thalami, basal ganglia, or other deep structures drained by thrombosed deep cerebral veins; if not promptly diagnosed and treated, the syndrome can progress to coma and death. Encephalopathy with mental state changes is more likely to be the presenting feature (than headache or focal deficit) in elderly patients.[42] Encephalopathy however can develop in a younger patient, and indeed would suggest severe disease, if encountered (significant cerebral oedema, large venous infarction, and hemorrhagic venous infarction).

In suspected CVT cases, either magnetic resonance imaging with venogram or computed tomography with venogram can accurately detect CVT.[43] A conventional angiogram is rarely needed. There is some suggestion that neuroimaging findings of CVT may lag behind

clinical symptoms.[44] In patients with high suspicion for VITT and CVT (severe headache between 4 and 42 days after receiving an implicated vaccine, thrombocytopenia, high D-dimer, positive PF4 antibody testing) in whom initial neuroimaging is negative, initiation of empirical VITT treatment with full-dose anticoagulation and repeat interval neuroimaging is therefore recommended.[44]

3.6.2 | Thrombocytopenia

As the name alludes, besides thrombosis, the other hallmark feature of VITT is thrombocytopenia. It is often encountered as an incidental finding on FBC test or can present clinically with new unexplained pinprick bruising or mucosal bleeding. Clinically serious hemorrhage, especially intracranial hemorrhage is often encountered as a complication of CVT (due to venous congestion) rather than thrombocytopenia.[3,7] Conversely, bleeding complications can develop due to severe isolated thrombocytopenia without thrombosis.[26] The typical platelet count range in VITT patients is between 10 000 and 100 000/μl (median of 20 000 to 25 000/μl).[7] Just like neuroimaging for CVT, which may be unremarkable initially, platelet count may be higher than 100 000/μl in VITT patients initially and thus may require linear monitoring.

3.6.3 | Lab confirmation and initiation of VITT empirical treatment

If VITT is suspected, immediate FBC (to look for thrombocytopenia) and appropriate imaging (to look for thrombosis) should be requested. VITT patients often develop disseminated intravascular coagulation (DIC), which manifests as thrombocytopenia, significantly raised D-dimer level, low or low-normal fibrinogen level (normal = 2 to 4 g/L; low = <2 g/L), and normal or mildly raised prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). Finding thrombocytopenia in the right clinical context (4–42 days after COVID-19 vaccination) should therefore prompt (a) peripheral smear (to rule out pseudothrombocytopenia from platelet clumping) and (b) further lab tests (to rule out DIC).

Given the clinical context, if VITT remains a possibility after appropriate imaging and FBC, anti-PF4 antibodies testing should be requested next and empirical treatment commenced. Blood sampling for PF4-ELISA (HIT assay) must be sent prior to initiation of any therapies. Pending PF4 ELISA results, empirical combination therapy with non-heparin anticoagulation (therapeutic dose) and intravenous immunoglobin (IVIG) should be commenced if:

1. Thrombosis AND at least one of the following are confirmed: thrombocytopenia OR markedly raised D-dimer OR both.
2. Both thrombocytopenia and markedly raised D-dimer are present but initial imaging fails to find thrombosis, especially when the clinical presentation is that of new-onset headache, which is severe, progressive and not responding to simple painkillers (i.e., when CVT is suspected).

Prospectively, VITT is ruled out if PF4 ELISA returns negative AND there is no thrombocytopenia. Thrombosis if present in such cases should be treated in the standard way.

Anti-PF4 antibodies testing is either done by ELISA (first choice) or functional assay (like SRA, or PF4-enhanced SRA, or other PF4-dependent functional assay). A positive anti-PF4 antibodies result, typically with an optical density (OD) >2.00, in the right setting should be considered confirmatory for the diagnosis of VITT. Heparin use must be avoided until VITT has been ruled out or until an alternative other plausible diagnosis has been made.

A study evaluating multiple ELISA assays demonstrated some false-negative results with PF4/heparin and PF4/platelet lysate ELISA tests.[45] It seems that no single ELISA method detects all cases of VITT. Therefore, if VITT is strongly suspected and ELISA is negative or equivocal, either a second ELISA or a functional assay should be considered. Functional assays are generally not required for VITT diagnosis if ELISA is strongly positive (high OD readings in the range of 2.00 to 3.00 OD units or higher). In patients with high OD, functional assay (like SRA), though not required, may still be considered for mechanistic understanding and case reporting purposes. Owing to poor sensitivity, rapid HIT assays are generally negative in VITT and therefore should not be used to confirm or exclude VITT diagnosis.[26,45–47] Given concerns about accuracy of HIT testing for diagnosing VITT, many investigational assays are currently under study like washed platelet functional assay, referred to as PF4-induced platelet activation, and a flow cytometry assay, referred to as PF4-induced flow cytometry-based platelet activation.[48] Initial data has reported very high sensitivity and specificity of these assays when tested on 16 VITT samples and 20 vaccinated controls without VITT.

Multiple recent studies have demonstrated that anti-PF4 antibodies from both Ad26.COV2.S and ChAdOx1 nCoV-19-associated VITT patients recognize un-complexed PF4.[7,49,50] Leveraging this information, a recent study reported that a novel un-complexed PF4 ELISA specifically differentiates VITT (secondary to both Ad26.COV2.S and ChAdOx1 nCoV-19) with high sensitivity and specificity from related disorders like classic HIT, delayed-onset HIT, spontaneous HIT, and commonly-encountered HIT-suspected patients who are PF4/polyanion ELISA-positive but functional assays negative.[25] In order to inform COVID-19 booster vaccinations strategies, it is indeed imperative to first make a reliable lab distinction between these overlapping pathologic entities. The study also demonstrated that while Ad26.COV2.S-associated VITT patients are uniformly strongly positive in PF4-polyanion ELISAs, they are frequently negative in the SRA. The PF4-dependent PEA that uses platelets treated with PF4 rather than heparin consistently diagnosed Ad26.COV2.S-associated VITT. Most Ad26.COV2.S-associated VITT antibodies persisted for >5 months in PF4-polyanion ELISAs, while the PEA became negative earlier.

3.6.4 | Differential diagnosis

Especially in individuals with negative PF4 antibody testing, alternative diagnoses to explain the presence of thrombocytopenia and/or
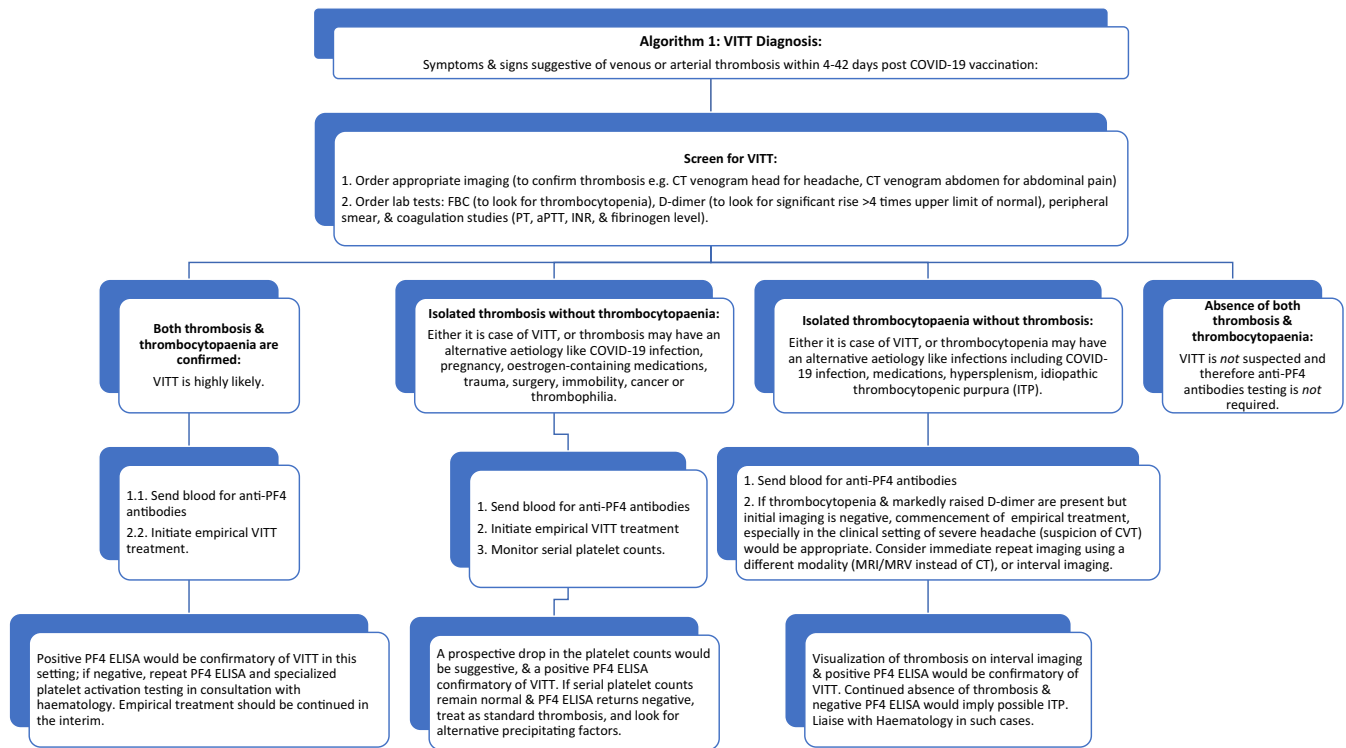
Algorithm 1: VITT Diagnosis:

Symptoms & signs suggestive of venous or arterial thrombosis within 4-42 days post COVID-19 vaccination:

Screen for VITT:

1. Order appropriate imaging (to confirm thrombosis e.g. CT venogram head for headache, CT venogram abdomen for abdominal pain)

2. Order lab tests: FBC (to look for thrombocytopenia), D-dimer (to look for significant rise >4 times upper limit of normal), peripheral smear, & coagulation studies (PT, aPTT, INR, & fibrinogen level).

Both thrombosis & thrombocytopenia are confirmed:

VITT is highly likely.

Isolated thrombosis without thrombocytopaenia:

Either it is case of VITT, or thrombosis may have an alternative aetiology like COVID-19 infection, pregnancy, oestrogen-containing medications, trauma, surgery, immobility, cancer or thrombophilia.

Isolated thrombocytopaenia without thrombosis:

Either it is case of VITT, or thrombocytopenia may have an alternative aetiology like infections including COVID-19 infection, medications, hypersplenism, idiopathic thrombocytopenic purpura (ITP).

Absence of both thrombosis & thrombocytopaenia:

VITT is *not* suspected and therefore anti-PF4 antibodies testing is *not* required.

1.1. Send blood for anti-PF4 antibodies

2.2. Initiate empirical VITT treatment.

1. Send blood for anti-PF4 antibodies

2. Initiate empirical VITT treatment.

3. Monitor serial platelet counts.

1. Send blood for anti-PF4 antibodies

2. If thrombocytopenia & markedly raised D-dimer are present but initial imaging is negative, commencement of empirical treatment, especially in the clinical setting of severe headache (suspicion of CVT) would be appropriate. Consider immediate repeat imaging using a different modality (MRI/MRV instead of CT), or interval imaging.

Positive PF4 ELISA would be confirmatory of VITT in this setting; if negative, repeat PF4 ELISA and specialized platelet activation testing in consultation with haematology. Empirical treatment should be continued in the interim.

A prospective drop in the platelet counts would be suggestive, & a positive PF4 ELISA confirmatory of VITT. If serial platelet counts remain normal & PF4 ELISA returns negative, treat as standard thrombosis, and look for alternative precipitating factors.

Visualization of thrombosis on interval imaging & positive PF4 ELISA would be confirmatory of VITT. Continued absence of thrombosis & negative PF4 ELISA would imply possible ITP. Liaise with Haematology in such cases.

FIGURE 1   Although VITT is a rare condition, it can cause potentially life-threatening venous and arterial thromboses at both typical and atypical sites (like cerebral venous sinus thrombosis [CVST], splanchnic venous thrombosis). In a patient who has developed thrombocytopenia and/or thrombosis between 4-42 days after receiving an incriminated COVID-19 vaccine, the VITT diagnosis is made by demonstrating anti-PF4 antibodies by ELISA or functional assay. The mainstay of VITT treatment is anticoagulation and IVIG. aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; FBC, full blood count; ITP, immune thrombocytopenia; IVG, intravenous immune globulin; PT, prothrombin time; VITT, vaccine-induced thrombotic thrombocytopenia

thrombosis should be considered. Depending upon the presence or absence of thrombosis and/or thrombocytopenia, the diagnostic possibilities can be grouped into four categories (see Figure 1):

1. Presence of both thrombosis and thrombocytopenia: plus, high or very high D-dimer level and low or normal fibrinogen level would imply that VITT is highly likely thus warranting sending blood for anti-PF4 antibodies and initiation of empirical treatment forthwith without waiting for anti-PF4 antibodies test results. Appropriate empirical treatment in this setting would include a combination therapy of a non-heparin anticoagulant (e.g., DOAC) and IVIG. Prospectively, positive PF4 ELISA would confirm VITT; if negative (could be falsely negative), repeat PF4 ELISA and specialized platelet activation testing in consultation with hematology should be considered. Empirical treatment should probably be continued after multidisciplinary team (MDT) consultation in the interim. MDT members should relook the full clinical picture at this point to decide whether an alternative diagnosis is a possibility. Other than VITT, the differential diagnosis of thrombosis with thrombocytopenia include cancer, HIT, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, and PNH.

2. Isolated thrombosis without thrombocytopenia: implies that either it is case of VITT, or thrombosis may have an alternative etiology like COVID-19 infection, pregnancy, estrogen-containing

medications, trauma, surgery, immobility, cancer or thrombophilia. An estimated 5% of VITT cases do not have thrombocytopenia at the time of clinical presentation.[27] VITT, however, is less likely in isolated thrombosis without thrombocytopenia, if D-dimer level is raised (but not the high and very high levels seen in VITT) and normal fibrinogen. Conversely, unlike VITT, COVID-19-associated thrombosis is generally not expected to induce positive anti-PF4 antibodies test result. In the right clinical context, a safe management approach in this clinical setting appears to involve testing for anti-PF4 antibodies, interim empirical initiation of VITT treatment, and serial monitoring of platelet counts; a prospective drop in the platelet counts would be suggestive, and a positive anti-PF4 antibodies test confirmatory. Empirical treatment pending anti-PF4 antibodies testing in such cases may include combination therapy (anticoagulation plus IVIG) if the suspicion of VITT is high; otherwise, IVIG therapy may be delayed until the result of anti-PF4 antibodies testing becomes available. Patients presenting with VTE in the post-vaccine window should best be treated with a non-heparin anticoagulant pending PF4 ELISA and following the platelet count. Unlike VITT-associated thrombosis which merits initiation of non-heparin anticoagulant therapy (like DOAC), therapeutic anticoagulation for COVID-19-associated thrombosis typically involves using low molecular weight (LMW) heparin during inpatient stay.

3. Isolated thrombocytopenia without thrombosis: implies that either it is case of VITT, or thrombocytopenia may have an alternative etiology like infections including COVID-19 infection, medications, hypersplenism, idiopathic thrombocytopenic purpura (ITP), etc. VITT is less likely if isolated thrombocytopenia without thrombosis is associated with normal or near-normal D-dimer and normal fibrinogen levels. In the right clinical context, a safe management approach in this clinical setting appears to involve testing for anti-PF4 antibodies and revisiting clinical manifestations in greater detail while maintaining low threshold to request appropriate imaging (or interval imaging) to look for thrombosis. Initiation of empirical treatment would depend upon the degree of relative suspicion for VITT vs other causes of thrombocytopenia. If thrombocytopenia and markedly raised D-dimer are present but imaging comes back negative, initiation of empirical treatment, especially in the clinical setting of severe headache (suspicion of CVT) is appropriate. In such cases, either immediate repeat imaging using a different modality (MRI/MRV instead of CT head) or interval imaging would be sensible. Empirical treatment should include combination therapy (anticoagulation plus IVIG) in suspected CVT cases; otherwise, non-heparin anticoagulation, with IVIG reserved in those with platelet counts <25 000/µl (as this degree of thrombocytopenia is very suggestive of consumptive coagulopathy). Patients with isolated thrombocytopenia and continued absence of thrombosis and negative PF4 ELISA are likely ITP (and not VITT).

4. Absence of both thrombosis and thrombocytopenia: implies that VITT is not suspected and therefore anti-PF4 antibodies testing is not required. In a series of 492 health care workers vaccinated with AstraZeneca vaccine, six had positive anti-PF4 antibody testing, despite being clinically well and without any evidence of thrombosis and thrombocytopenia.[51] Notably, their sera did not cause platelet activation in in-vitro functional assay. Another study found anti-PF4 antibodies in 7% of AstraZeneca vaccine recipients and 8% of BioNTech/Pfizer vaccine recipients.[52] Retrospective testing in individuals who had sera available from prior to vaccination showed that some were positive even before vaccination. Based on these observations, a positive anti-PF4 antibody test alone without concurrent thrombosis and/or thrombocytopenia cannot be considered sufficient to make the diagnosis of VITT.

Given above, any assessment of the likelihood of VITT versus other conditions must involve formal input from consulting hematologist and other related specialists like stroke physicians/neurologists.

Every confirmed case must be reported to the regulators. A referral to tertiary care center should be considered if VITT is confirmed.

3.6.5 | Therapeutic considerations in VITT

Given that prospective clinical treatment studies do not exist and proposed therapeutic considerations in VITT (often extrapolated from "HIT") are rapidly evolving, clinicians involved in the care of a suspected VITT case are highly recommended to review one of the regularly updated online resources to know the most up-to-date diagnostic pathways and treatment algorithms.

3.6.6 | Hospitalization

With the possible exception of a VITT case presenting with isolated thrombocytopenia without thrombosis (who may be managed on outpatient basis using a DOAC and very close follow-up), all VITT cases should be hospitalized. Since CVT patients may experience rapid deterioration after appearing clinically well, VITT-related CVT patients should best be pre-emptively hospitalized in an advanced neuroscience center where neurosurgical facilities are available locally. This expectantly would enable urgent neurosurgical intervention should rapid deterioration develops.

3.6.7 | Therapeutic anticoagulation

Concerning management, unless contraindicated (e.g., in expanding ICH), standard full-therapeutic dose anticoagulation with appropriate adjustments for body weight and kidney function remains the primary treatment modality in all VITT cases even in the absence of thrombosis. Individuals who are strongly suspected on clinical grounds to have developed VITT and are awaiting confirmatory testing should be empirically commenced on therapeutic anticoagulation.

DOACs and fondaparinux

Direct oral anticoagulants (DOACs) including factor Xa inhibitors (apixaban, edoxaban, or rivaroxaban) and direct thrombin inhibitor (dabigatran) remain the therapeutic agents of choice in many VITT cases (Dabigatran is the least studied DOAC in this setting). As per NICE guideline, in July 2021, the marketing authorization for edoxaban or dabigatran specified the need for 5 days of parenteral anticoagulation before commencing DOAC therapy. Subcutaneous Fondaparinux (an indirect factor Xa inhibitor) is the usual parenteral agent of choice in this setting, although argatroban or bivalirudin may be preferable in certain instances (see below). Edoxaban or dabigatran commencement without first completing 5 days of parenteral anticoagulation would be an "off-label use" of these agents. For longer term use, DOACs are generally preferable because of greater experience and better safety profile (fondaparinux can uncommonly cause in vivo cross-reactivity, that is, antibody-enhanced platelet activation). Whereas the safety of DOACs in pregnancy is unknown, fondaparinux can be used in pregnancy.

Parenteral direct thrombin inhibitors (argatroban or bivalirudin)

Are other options though less preferable due to cost and possibility of treatment failure due to a phenomenon called "aPTT confounding." Both argatroban and bivalirudin prolong aPTT, PT, and INR. aPTT monitoring is therefore necessary in every patient receiving IV

infusion therapy with argatroban or bivalirudin. Since aPTT is additionally prolonged due to acquired DIC in VITT patients, DIC-induced aPTT-prolongation confounds aPTT monitoring. This may result in underdosing of argatroban/bivalirudin and possible treatment failure. Conversely, parenteral direct thrombin inhibitors have their advantages as well. For example, both agents are short-acting (argatroban half-life: ~40 to 50 min; bivalirudin half-life: 25 min). This implies that the anticoagulant effect is rapidly reversed upon discontinuation of IV infusion. Use of parenteral direct thrombin inhibitors is therefore worthwhile in the subset of patients who are deemed at a higher risk of bleeding or who may need surgical interventions. NICE guideline however recommends that if argatroban is commenced, owing to high-bleeding risk or need for surgical intervention, it should be switched to fondaparinux or DOAC as soon as the bleeding risk has reduced.[27] Both argatroban and bivalirudin can be used in pregnancy. Argatroban is hepatically eliminated and therefore no dose adjustment is needed in renal impairment. Bivalirudin is renally eliminated and therefore no dose adjustment is needed in hepatic impairment.

UFH and LMWH

It may be reasonable to avoid UFH, LMWH, and heparin flushing solution in cases of diagnostic uncertainty when delayed or spontaneous HIT remains a valid differential diagnosis. Since it is not yet known whether or not heparin exacerbates VITT, given availability of safer alternative anticoagulation regimens, avoidance of UFH and LMWH seems a sensible approach anyway.[27]

Warfarin

Similar to HIT, Warfarin should generally be avoided in VITT patients. Exceptions may include VITT patients with concurrent severe renal or hepatic impairment, or mechanical heart valves. In either case, Warfarin cannot be immediately used until platelet counts have normalized or returned to the baseline (due to lack of efficacy during ongoing hemostatic activation). Once thrombocytopenia has resolved, any consideration for initiation of Warfarin therapy would require at least five consecutive days of overlapping non-heparin anticoagulant therapy until INR becomes therapeutic. Being a known teratogenic agent, Warfarin is avoided in first trimester of pregnancy unless benefits outweigh risks (e.g., concurrent mechanical heart valve). In the rare instance when argatroban is transitioned to Warfarin, frequent INR monitoring would be paramount as both agents prolong INR.

Duration of therapeutic anticoagulation therapy

The natural history of VITT is not well understood and as such there is no data to guide decision-making regarding the timescale for monitoring and duration of anticoagulant therapy. Similar to any patient with provoked VTE, in VITT patients with evident thrombosis, it seems reasonable to continue anticoagulation for 3 months after platelet count recovery, as long as no further thrombosis occurs. For VITT without thrombosis, it seems sensible to continue anticoagulation till (a) platelet count recovery, or (b) by analogy with the duration of anticoagulation in classic HIT, for 4–6 weeks after platelet count recovery. Unless contraindicated, patients who were taking a

parenteral anticoagulant in the hospital can be switched to a DOAC at the time of discharge. If DOAC therapy is contraindicated, either continuation of parenteral therapy (like fondaparinux) long-term, or switch to oral Warfarin therapy with appropriate bridging (provided thrombocytopenia has already resolved) may be considered.

3.7 | Immunomodulatory agents: IVIG and Steroids

Similar to therapeutic anticoagulation, unless contraindicated, high-dose IVIG is recommended in all VITT patients. Individuals who are strongly suspected on clinical grounds to have developed VITT and are awaiting confirmatory testing should receive IVIG empirically. A suggested dose is 1 g/kg intravenously once per day for 2 days, based on actual body weight. Similar to its use in other forms of aHIT, the rationale of using IVIG in VITT is expectant interruption of VITT antibody-induced platelet activation and secondary consumptive thrombocytopenia. IVIG thus helps correct thrombocytopenia.[5,53] It appears that Ig binds to platelet FcγIIa receptors, blocking platelet activation (it does not seem to disrupt autoantibody binding to PF4 however).[5]

If serial platelet counts fail to rise to an acceptable level and/or there is progression of thrombosis despite IVIG therapy, an add-on short course of steroid therapy may be considered. Corticosteroids have also been tried as an adjunct to IVIG in some cases, especially in the acute management of CVT.[54] A suggested regimen would be methylprednisolone 1 g for 3 days or dexamethasone 20 to 40 mg for 4 days. Whereas the effectiveness of steroid use in these particular clinical settings is unknown, corticosteroids are commonly used and are generally known to be effective in many immune disorders.

Given that IVIG induced interruption of platelet activation in VITT is sometimes transient, clinicians need to remain heedful and observant of recurrent or progressive bleeding as well as thrombotic complications after the effects of IVIG wear off. For example, in one series of five individuals with VITT and various thrombotic manifestations treated with IVIG, after a rapid but transient platelet count recovery, one patient developed recurrent thrombocytopenia and new CVT.[53] It is thus imperative to continue to monitor serial platelet counts post-IVIG therapy both while inpatient (daily) and following discharge from the hospital.

3.8 | Therapeutic considerations in special situations

3.8.1 | Cerebral venous thrombosis

Extrapolating the HIT guidelines, therapeutic anticoagulation should be promptly instituted in CVT patients even in the presence of secondary intracranial hemorrhage (ICH). As ICH in this setting is attributable to increased venous back pressure, it is necessary to prevent progressive venous thrombosis to control this bleeding. In CVT with secondary ICH and concurrent severe thrombocytopenia (<20 000/μl)

or low fibrinogen level, dosing strategy may however require alteration. In severely ill patients, parenteral agents with short half-life may be preferable; after full platelet count recovery, most patients can be transitioned to an oral anticoagulant (DOAC preferred over vitamin K antagonist). In addition to therapeutic anticoagulation, IVIG after laboratory testing for PF4 antibodies has been sent is also recommended in CVT patients.[7,55,56] Some experts even recommend administration of steroids. Platelet transfusion should be avoided (see below).

3.8.2 | Pregnancy

Whereas ordinarily LMWH and UFH are considered safer than other anticoagulants during pregnancy, until further evidence becomes available, their use is generally not recommended in female VITT patients who are pregnant. In such cases, alternative anticoagulant options that appear reasonable include fondaparinux or danaparoid (if available).[57] Whereas Danaparoid (an indirect parenteral inhibitor of thrombin and factor Xa) does not have a reversal agent, fondaparinux can possibly be reversed using andexanet alfa. In practice, unless a patient is likely to undergo urgent invasive procedure, the often readily available subcutaneous fondaparinux is preferred. Nonetheless, owing to a long half-life of 17 to 21 h, subcutaneous fondaparinux is not suitable if a patient is likely to undergo urgent invasive procedure. Since danaparoid can be administered both subcutaneously and intravenously, it seems the preferred option if an urgent invasive procedure is anticipated. Ordinarily, danaparoid is administered subcutaneously following an initial intravenous bolus, however, it can be given as an intravenous infusion if needed. Though expensive, intravenous argatroban or bivalirudin can also be used in pregnancy if an invasive procedure is likely. For long-term use, subcutaneous fondaparinux, or in exceptional circumstances even Warfarin may be used (when benefits outweigh risks, e.g., concurrent mechanical heart valve). NICE recommends avoiding DOACs in pregnant ladies.[27]

3.8.3 | Refractory disease or multiple thromboses

Refractory disease, that is, persistent thrombocytopenia and ongoing thrombosis despite institution of combination therapy (anticoagulation + IVIG), multiple thromboses (with evidence of excessive platelet activation [platelet count <30 000/μl]) and CVT are special instances that may necessitate rescue therapy with therapeutic plasma exchange (TPE) and immunosuppression.[6,58] Daily TPE can done by using fresh frozen plasma (1 volume exchange a day), or plasma plus albumin (as the replacement fluid). TPE may be needed daily for up to 5 days, or until platelet count recovery. Since TPE is much more invasive and not as widely available, it's use is reserved in refractory cases who have failed anticoagulation/IVIG combination therapy. Provided not pregnant, refractory VITT patients who fail TPE therapy as well may be considered for intravenous rituximab therapy

next (dose: 375 mg/m^2 of body surface area given once a week for 4 weeks; it is the licensed dose for cancer indications). The suggestion to consider rituximab (as a last resort) comes from its known efficacy when used (as an off-label treatment) in other autoimmune conditions such as ITP. Complement inhibition with eculizumab has also been tried in some patients requiring rescue therapy with evidence for improvement.

The evidence-base for above recommendations come from a series of three patients with refractory VITT in whom daily TPE resulted in improvement in platelet counts and cessation of thrombosis.[59] In one case, IVIG was given after each TPE procedure. In another case, a single dose of rituximab was given after the fifth TPE procedure. In another larger series of 220 patients with severe thrombocytopenia plus CVT, or severe thrombocytopenia plus extensive thrombosis, rescue TPE therapy demonstrated a survival rate of 90%.[6] In comparison, the overall mortality in patients with platelet count <30 000/μl is estimated to be 41%. The study thus strongly suggested considering rescue TPE therapy in severe thrombocytopenia plus CVT, or thrombocytopenia plus extensive thrombosis. Concurrent bleeding complications may however make catheter placement and prolonged apheresis challenging.

3.8.4 | Patients in need of surgery

Since both VITT-related thrombocytopenia and therapeutic anticoagulation can predispose to hemorrhagic complications, pre-emptive fibrinogen replacement therapy may be considered in some patients to balance the relative risks of thrombosis and bleeding. While this is an off-label indication, maintaining a fibrinogen level of at least 1.5 g/L may be particularly desirable in patients at a higher risk of bleeding like those in need of surgical intervention. There are however no hard pre-op platelet and fibrinogen target levels recommended because any reduction in surgery-related additional-bleeding-risk would be deemed advantageous. This implies that surgery should not be delayed solely because a particular platelet and fibrinogen target level has not been achieved pre-operatively.

3.8.5 | Bleeding in VITT patients

Whereas platelet transfusion can theoretically improve platelet counts, such transfusions can worsen thrombosis. Given the competing goals of stopping bleeding and preventing thrombosis, managing bleeding in VITT cases is very challenging. As a general rule, platelet transfusions should be reserved for (a) life-threatening bleeding causing hemodynamic or respiratory compromise, (b) bleeding into a critical anatomical site (like ICH), or (c) patients requiring imminent surgery. Depending on the platelet count and fibrinogen level, it may be reasonable to transfuse platelets and/or a source of fibrinogen (fibrinogen concentrate, plasma, or cryoprecipitate) (target fibrinogen level is >1 g/L) in such cases. Patients already receiving therapeutic

anticoagulation may also need a reversal agent. Andexanet alfa can be used to reverse factor Xa inhibitors (apixaban, edoxaban, rivaroxaban, and possibly fondaparinux), and idarucizumab to reverse direct thrombin inhibitor (dabigatran). Whereas no reversal agents are available for argatroban and bivalirudin, as previously mentioned, their anticoagulant effect is rapidly reversed upon discontinuation of IV infusion. Warfarin can be reversed using vitamin K and prothrombin complex concentrate.

As a general rule, presence of bleeding but absence of aforementioned indications, should not absolutely preclude anticoagulation, particularly if platelets are >20 000/μl or rising following IVIG initiation. To mitigate the potential risk of hemorrhagic complications in patients with very low platelet counts (<20 000/μl), there has been a suggestion to preferentially consider IV argatroban for initial anticoagulation till platelet counts start to rise following IVIG initiation. There are two possible dosage regimens for IV argatroban: a lower critical-illness-dose, or therapeutic-dose.[27] Whereas the lower critical-illness-dose may be subtherapeutic to treat thrombosis in VITT patients, the therapeutic-dose may unacceptably increase the risk of hemorrhagic complications. As a trade-off, therapeutic-dose IV argatroban, plus platelet transfusion has also been suggested,[27] although it may unacceptably increase the risk of thrombotic complications. It appears that not enough is currently known about the natural history of VITT to advise clinicians the relative merits and risks of these two dosage regimens.

3.8.6 | Bleeding in ITP patients after COVID vaccination

As mentioned above, post–COVID vaccine patients with isolated thrombocytopenia and continued absence of thrombosis and negative PF4 ELISA are likely ITP (and not VITT). Over 100 cases of new-onset ITP have been reported following AZ and JJ as well as Moderna & Pfizer vaccines (a rare complication with incidence estimates of 1 in 100 000 to 1 in 1 000 000). In post–COVID vaccine ITP patients, the platelet count at presentation is often <10 000/μl, somewhat lower than the median platelet count in VITT (i.e., 20 000/μl), and the commonest presentation is bleeding. The mainstay of treatment is IVIG and/or steroids, with platelet transfusions reserved for critical bleeding. In refractory cases, thrombopoietin agents and possibly a single dose of vincristine may be useful. Rituximab should, however, be avoided in ITP cases because it can blunt post-vaccination immune response, plus would preclude second dose/booster dose administration by more than 6 months.

In patients presenting with isolated thrombocytopenia without thrombosis 4 to 42 days post-vaccination, IVIG should be commenced empirically pending PF4 ELISA (IVIG use is recommended in both VITT and ITP). In a patient with pre-existing ITP, if platelet count drops during the relevant timeframe post-vaccination without new thrombosis, it seems sensible to send PF4 ELISA to make a distinction between ITP and VITT.

3.8.7 | Cadaveric liver transplantation

If an individual with VITT dies and their liver is transplanted to another individual, there is theoretical possibility of transmitting VITT antibody-producing cells in the donor liver. The transplant physicians should therefore inform potential recipients about this risk.

3.9 | Discharge criteria in VITT

Hospitalized VITT patients can only be considered safe for discharge if all of these conditions are met: (a) platelet count is demonstrated to have been improving for at least 2 to 3 days and is now >50 000/μl, (b) patient is already fully anticoagulated with no evidence of any new or progressive thrombosis, and (c) no evidence of bleeding for at least 2 to 3 days. Appropriate post-discharge follow-up must include twice weekly monitoring for (a) clinical status, (b) serial platelet count, and (c) serial coagulation studies (PT, aPTT, fibrinogen, D-dimer), especially if abnormal while inpatient.

3.10 | VITT prevention

3.10.1 | Choice of COVID-19 vaccines as a preventative strategy against VITT

Since there is no RCT data available of relative efficacies and safety profiles of different vaccines, the primary criterion for selection of a COVID-19 vaccine remains "availability." However, for individuals with access to more than one vaccine, an mRNA vaccine may be selected if avoidance of VITT is a priority. Likewise, individuals with a prior history of HIT or thrombosis may like to avoid adenoviral COVID-19 vaccines and receive a different type of COVID-19 vaccine. As is still the case in some countries, if the choice is between an adenoviral vaccine and no vaccine, an adenoviral vaccine is still a safer option given the aforementioned over 100-fold higher incidence of thrombotic complications of COVID-19 illness versus VITT.

Given lack of suggestive data, a prior history of VTE, or predisposition to VTE (due to recent surgery, obesity, factor V Leiden (FVL) or other inherited thrombophilia, etc) is not considered a contraindication to vaccination.

Indications for delaying vaccination for at least 3 months include patients who have undergone hematopoietic cell transplantation or engineered cellular therapy (e.g., chimeric antigen receptor [CAR] T-cells).[60] The expectation is that such a delay would help maximize vaccine efficacy. Vaccination should also be delayed in cancer patients receiving intensive cytotoxic chemotherapy (e.g., cytarabine/ anthracycline-based induction regimens for acute myeloid leukemia) until absolute neutrophil count recovery.[60]

Given improved efficacy, individuals who have previously received one dose of ChAdOx1 nCoV-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India) without any untoward thrombotic complications should receive the second dose. Conversely, those who developed VITT after first dose should preferably switch to an mRNA vaccine for the second dose of a two-dose series or a booster dose.

3.10.2 | Choice of booster vaccinations as a preventative strategy against VITT

Multiple observational studies have demonstrated that whereas protection against severe COVID-19 infection and hospitalization remains high, vaccine protection against SARS-CoV-2 infection generally wanes over time in both adults and children. Both because of waning effectiveness and emergence of new viral variants, several countries have initiated booster vaccination schedules. In US, CDC recommends booster dosage in all individuals who received a primary Pfizer or Moderna COVID-19 vaccine series at least 5 months after the last dose.[61] In Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine) recipients, the CDC recommends a booster dose at least 2 months after the dose.[61] The CDC also recommends that in individuals who are >50 years old or are ≥12 years old and have certain immunocompromising conditions, a second booster dose of an mRNA vaccine be given at least 4 months after the first booster.[61]

Evolving evidence suggests that in the context of several SARS-CoV-2 variants that are concerning for their potential for immune escape, administration of a booster vaccine helps augment vaccine efficacy at least in the short term. In an observational study, receipt of a booster dose was associated with a 10-times lower rate of infection in all age groups, and among individuals 60 years or older, an 18-times lower rate of severe illness (absolute difference 5.4 cases per 100 000 days).[62] In another retrospective study, individuals ≥60 years old who had received a primary series and an initial booster dose with BNT162b2, receipt of a *second* booster dose (i.e., fourth dose of BNT162b2) at least 4 months after the last was associated with a 3.5-fold lower risk of severe infection.[63]

With regards to Omicron variant and its sublineages (BA.1, BA.2, BA.2.12.1, BA.4, and BA.5), several observation studies have consistently reported that COVID-19 vaccines remain effective in preventing severe disease (as reflected by hospitalization), especially among those who have received a booster dose.[64–70] Conversely, COVID-19 vaccines effectiveness in preventing symptomatic infection appears lower compared with other variants. In vitro neutralization data on sublineages BA.4 and BA.5 suggest that vaccine effectiveness may be further eroded with these sublineages compared with BA.1 and BA.2. Worryingly, the majority of *infection-naïve individuals* who received a primary vaccine series have demonstrated no detectable neutralizing activity against Omicron compared with the original Wuhan strain virus and the Delta variant.[71–73] Conversely, in *previously infected individuals*, who received a primary series and booster vaccination retain adequate neutralizing titres against Omicron sublineages BA.1 and BA.2; neutralizing titres against sublineages BA.4 and BA.5 however are often low.[74–77] A future ray of hope is administration of booster doses with *investigational formulations* of currently available mRNA vaccines (both bivalent vaccines that include spike proteins from the original viral strain and the Omicron variants and a monovalent vaccine that includes the spike protein from the Omicron variant). According to the unpublished data, compared with booster dosages with the original vaccines, booster dosages with *investigational formulations* appears to elicit broadly neutralizing activity against other variants (including the Omicron sublineages B.4 and B.5).[78,79]

Concerning the safety of the booster vaccination, multiple studies have demonstrated that the frequency and severity of side effects following booster doses are similar to those reported following a primary series. In fact, for mRNA vaccines, local and systemic reactions including myocarditis were reported slightly less frequently after the booster dose than the second dose.[80] No studies have demonstrated an increased likelihood of VITT (or other thrombotic complications) following vaccination in individuals with prior thrombosis. Even in patients with increased thrombotic risk such as due to FVL, other inherited thrombophilia, high body mass index, or recent surgery, the likelihood of VITT (or other thrombotic complications) does not seem to rise following COVID-19 vaccination. In other words, past medical history (PMH) of VTE or predisposition to VTE, is *not* considered a contraindication to COVID-19 vaccination. Some organizations have recommended that individuals with PMH of HIT should avoid adenoviral COVID-19 vaccines and instead receive a different type of COVID-19 vaccine.[81] Likewise, in individuals who developed VITT with an adenoviral vectored vaccine, another dose of an adenoviral vectored vaccine should be avoided.[82] In such instances, it seems safe to instead switch to an mRNA vaccine for the second dose of a two-dose series or a booster dose.

Given the updated risk-benefit analysis, the most recent CDC recommendation is to prefer mRNA COVID-19 vaccines over the Janssen COVID-19 vaccine in *all* vaccine-eligible people, and to restrict Janssen COVID-19 vaccine usage to only those individuals with a *contraindication* to mRNA COVID-19 vaccines (e.g., severe allergic reaction) or when an individual would otherwise remain unvaccinated due to limited access to mRNA COVID-19 vaccines.[81]

3.10.3 | Role of prophylactic aspirin as a preventative strategy against VITT

There is in vitro evidence that aspirin does not prevent platelet activation by PF4 antibodies. Hence whereas Individuals already taking aspirin for another reason can continue taking it, there is no suggestive data to support prophylactic aspirin pre- or post-vaccination as a strategy to reduce thrombotic risk. In addition to suggested therapeutic inefficacy, initiation of prophylactic aspirin runs an extra (purely theoretical and non-documented) risk of causing a lower antibody immune response post-vaccination. This assumptive theoretical risk stems from data from several other vaccines that has suggested a blunted immune response with prophylactic acetaminophen.[83,84]

3.11 | Balancing the anti-vax trends

3.11.1 | Thrombotic complications of COVID-19 vaccination versus COVID-19 illness

In one study, the rate of CVT in individuals hospitalized with COVID-19 was estimated to be 207 per million.[85] In comparison, the same study estimated CVT rate post-vaccination to be 0.9 to 3.6 per million. One meta-analysis demonstrated the rate of thrombosis to be

8% in individuals hospitalized for COVID-19 and 23% in ICU patients.[86] With the mortality rate for COVID-19 infection as high as 1%, it is imperative to emphasize the need for COVID-19 vaccination. Unfortunately, despite clear evidence of thrombotic complications of COVID-19 illness exceeding VITT-induced thrombosis and/or thrombocytopenia rates by over 100-fold, vaccine hesitancy around COVID-19 is significant. Both WHO and UN have, therefore, warned against these anti-vax trends.

4 | CONCLUSION

Since COVID-19 vaccination remains the most important measure to prevent COVID-19 infection, there is broad consensus among regulatory agencies that the benefits of vaccination significantly outweigh the risks. Since much about COVID-19 complications remains unknown, there is a considerable risk to patients if scientific data are taken out of context and without paying due deliberation to all possible caveats. For example, since vaccinated asymptomatic individuals have not been tested, whether an association exists between COVID-19 vaccines and PF4 antibody, thrombocytopenia, and thrombosis is not definitively clear. Likewise, the true relative prevalence and risk of anti-PF4 antibody post-vaccination and VITT patients are unknown. Since spurious associations are always possible in rare disease research, case selection bias affecting current knowledge is readily conceivable. Further research must concern delineating the molecular and cellular mechanisms underpinning venous thrombosis in COVID-19 illness as well as VITT patients.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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