

Treatment of drug-induced immune thrombocytopenias

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Abstract

Several therapeutic agents can cause thrombocytopenia by either immune-mediated or non-immune-mediated mechanisms. Non-immune-mediated thrombocytopenia is due to direct toxicity of drug molecules to platelets or megakaryocytes. Immune-mediated thrombocytopenia, on the other hand, involves the formation of antibodies that react to platelet-specific glycoprotein complexes, as in classic drug-induced immune thrombocytopenia (DITP), or to platelet factor 4, as in heparin-induced thrombocytopenia (HIT) and vaccine-induced immune thrombotic thrombocytopenia (VITT). Clinical signs include a rapid drop in platelet count, bleeding or thrombosis. Since the patient's condition can deteriorate rapidly, prompt diagnosis and management are critical. However, the necessary diagnostic tests are only available in specialized laboratories. Therefore, the most demanding step in treatment is to identify the agent responsible for thrombocytopenia, which often proves difficult because many patients are taking multiple medications and have comorbidities that can themselves also cause thrombocytopenia. While DITP is commonly associated with an increased risk of bleeding, HIT and VITT have a high mortality rate due to the high incidence of thromboembolic complications. A structured approach to drug-associated thrombocytopenia/thrombosis can lead to successful treatment and a lower mortality rate. In addition to describing the treatment of DITP, HIT, VITT, and vaccine-associated immune thrombocytopenia, this review also provides the pathophysiological and clinical information necessary for correct patient management.

Introduction

Thrombocytopenia may develop in patients receiving several therapeutic agents. According to the pathogenesis of the thrombocytopenia, two categories can be distinguished: immune-mediated and non-immune-mediated thrombocytopenia.¹ In the latter, direct cytotoxic effects of the drug molecules on the megakaryocytes may impair megakaryopoiesis or, more rarely, cause an accelerated platelet elimination by directly stimulating platelet apoptosis.² In contrast, in drug-induced immune thrombocytopenia (DITP) a humoral immune response against platelet antigens causes increased platelet destruction/consumption and/or impaired platelet production.³ Platelet specific glycoprotein (GP) complexes such as GPIIb/IIIa and GPIb/IX are most common target antigens in cases of DITP. As in primary immune thrombocytopenia (ITP), these antibodies may be associated to severe thrombocytopenia and bleeding while life-threatening thromboembolic complications are common in heparin-induced thrombocytopenia⁴ (HIT) and vaccine induced-

thrombotic thrombocytopenia (VITT).⁵ The identification of the compound responsible for the reduced platelet count is essential to define the correct therapeutic approach in these patients. However, this is often challenging in many patients who are taking multiple medications and have comorbidities that can by themselves lead to thrombocytopenia. In this review, we will provide an update on treatment of DITP, HIT, VITT and vaccine-associated immune thrombocytopenia. Since the therapeutic approach must take into account both the pathophysiological mechanisms and the clinical characteristics of the individual patient, these aspects will also be briefly dealt with.

Drug-induced immune thrombocytopenia

Thrombocytopenia with a definite or probable causal relation to drug administration has been reported for many drugs. A freely available data bank called “Platelets on the

Web” (<https://www.ouhsc.edu/platelets/ditp.html>) contains more than 300 drugs with at least one confirmed/suspected case of DITP.

Pathophysiology of drug-induced immune thrombocytopenia

In DITP, IgG (less commonly IgM/A) antibodies bind to platelets leading to their destruction via either complement activation^{6,7} and/or phagocytosis^{8,9} (Figure 1). According to their binding mechanisms, at least six types of antibodies have been identified³ (Table 1): 1) quinine-type drug-dependent antibodies (DDAbs); 2) hapten-dependent DDAbs; 3) fiban-type DDAbs; 4) drug-specific DDAbs (against chimeric antibodies); 5) autoantibody; and 6) immune complexes (see below; sections on HIT/VITT).

Clinical features of drug-induced immune thrombocytopenia

Thrombocytopenia usually occurs approximately 5-10 days after initial drug administration and the median nadir platelet count is $<20 \times 10^9/L$. An exception is thrombocytopenia

induced by chimeric GPIIb/IIIa antagonists. In this case, DITP may present within hours of exposure (early onset) due to already preformed naturally occurring antibodies against murine compounds of the therapeutic monoclonal antibodies. Bleeding is a frequent complication of DITP. Incidence rates of 9% and 0.8% have been reported for major and fatal bleeding in patients with DITP, respectively.¹⁰

Diagnosis of drug-induced immune thrombocytopenia

Five clinical criteria have been proposed to help physicians to determine the diagnosis of DITP¹: 1) exposure to new drugs 5-10 days before onset of thrombocytopenia; 2) recovery from thrombocytopenia after discontinuing the candidate drug; 3) other drugs were continued or reintroduced after discontinuation of the candidate drug with a sustained normal platelet count; 4) other causes for thrombocytopenia were excluded; and 5) re-exposure to the candidate drug (a practice that may cause unwarranted risk) resulted in recurrent thrombocytopenia.¹¹ Nevertheless, considering that acquired thrombocytopenia

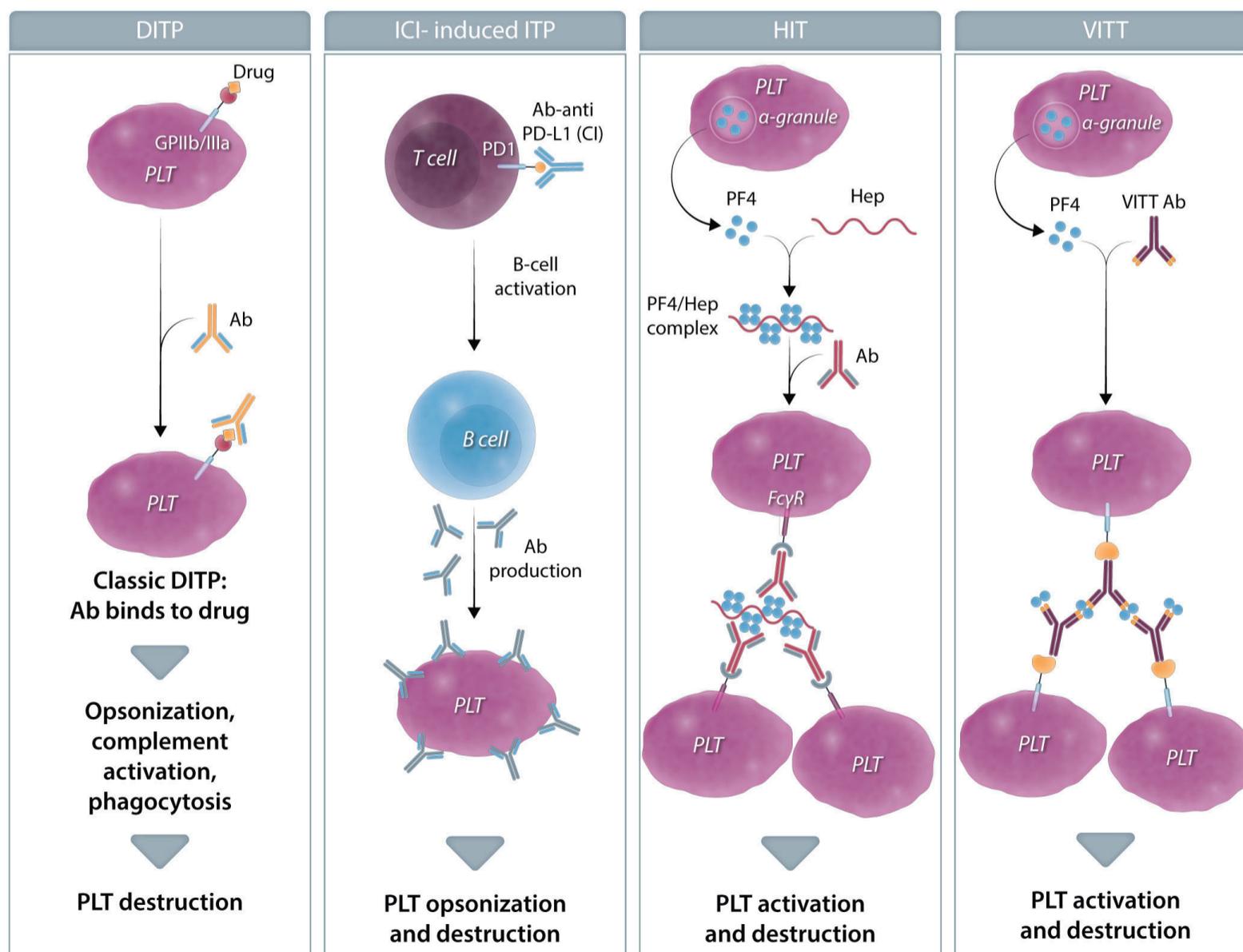


Figure 1. Schematic representation of the pathophysiology of drug-induced thrombocytopenia (DITP), immune checkpoint inhibitor-induced thrombocytopenia (ICI-induced ITP), heparin-induced thrombocytopenia (HIT), and vaccine-induced immune thrombotic thrombocytopenia (VITT). Ab: antibody; PLT: platelet; GP: glycoprotein; Hep: heparin; PF4: platelet factor 4; CI: checkpoint inhibitor; PD-L1: like programmed death-ligand 1.

Table 1. Binding mechanisms of antibodies in drug-induced immune thrombocytopenia (DITP).

	Mechanism	Example of drugs
Quinine-type	Drug binds DDAb and subsequently to platelet integrin	Quinine, sulfonamide antibiotics, non-steroidal anti-inflammatory drugs
Hapten-dependent	Drug links covalently to membrane protein and induces drug-specific binding by DDAb	Penicillin, some cephalosporin antibiotics
Fiban-type	Drug reacts with GPIIb/IIIa and induces neoepitope(s) for the DDAb	Tirofiban, Eptifibatide
Drug-specific	DDAb recognize murine component of chimeric Fab fragment specific for GPIIIa	Abciximab
Autoantibody	Drug induces antibody that reacts with autologous platelets in absence of drug	Gold salts, procainamide
Immune complexes	Antibodies form immune complexes with their target antigens	Heparin, an as yet unidentified component of adenoviral vector-based vaccine against COVID-19

DDAbs: drug dependent antibodies; GP: glycoprotein.

is common in patients who are taking multiple medications and have comorbidities that can lead to thrombocytopenia, identifying the drug responsible for thrombocytopenia based uniquely on clinical information may prove very difficult. Therefore, *in vitro* confirmation of DDabs is recommended, even if the available tests do not always allow a laboratory to confirm the diagnostic suspicion.

Laboratory assays have been developed to detect antibodies that bind to platelets in the presence of drugs or a drug metabolite. These assays have moderate sensitivity due to the insolubility of some drugs, and are not always feasible since some antibodies are specific for drug metabolites that are not available for testing.^{10,12}

Treatment of patients suspected of having drug-induced immune thrombocytopenia

Immediate discontinuation of the drug responsible is the initial step for the treatment of DITP. In patients receiving multiple medications, if feasible, all compounds started within the last 5-10 days should be stopped and replaced. Discontinuation of the drugs could also be done sequentially, possibly depending on the *a priori* probability that a specific drug is incriminated. It is important to consider testing for drug-dependent antibodies before any therapeutic initiative is taken; therefore, a serum sample should be collected before DITP-treatment to subsequently confirm the clinical suspicion. In this context, it should be noted that intravenous immunoglobulin (IVIg) interferes with immunoassays that are commonly used to DDAb. In our experience, blood samples should be collected either before or at least 48 hours after IVIg administration in case the patient received this treatment (see below).

Generally, after 4-5 half-lives of the offending drug or drug metabolite, the platelet count begins to recover once

treatment has been stopped. Notably, as long as the drug or its metabolite(s) are present in plasma, transfusion of platelets is unsuccessful.¹³ Administration of high doses of IVIG (1 g/kg body weight) can be used to accelerate platelet recovery under two circumstances: in patients with severe thrombocytopenia and bleeding or in those at high risk of bleeding.^{14,15} A suggested approach to manage cases of suspected DITP is reported in Figure 2.

Of note, well-documented reports indicate that folk medicines, herbal preparations, and even foods occasionally trigger acute thrombocytopenia.¹⁶ However, it is not clear whether immune mechanisms are responsible for the decrease in platelet count in all these cases.

Immune thrombocytopenia induced by immune checkpoint inhibitors

Immune checkpoint inhibitors (ICI) were developed as a novel treatment approach for cancer and are currently used as immune therapy. ICI are monoclonal antibodies against proteins (PD-L1 and CTLA4¹⁷) used by tumor cells to escape the immunosurveillance system. Complications during immune therapy with ICI are primarily inflammatory conditions and autoimmune disorders. However, ICI-induced ITP has been observed in some cases.¹⁸ This condition is rare, with an incidence between 0.2% to 2.8%, and is almost never severe or fatal.¹⁹

Pathophysiology of ICI-induced immune thrombocytopenia

Immune-induced adverse events are thought to be triggered by a revival of exhausted T cells that can be induced on ICI administration (Figure 1). Whereas the exact pathomechanism of ICI-induced ITP is still unclear, it is likely

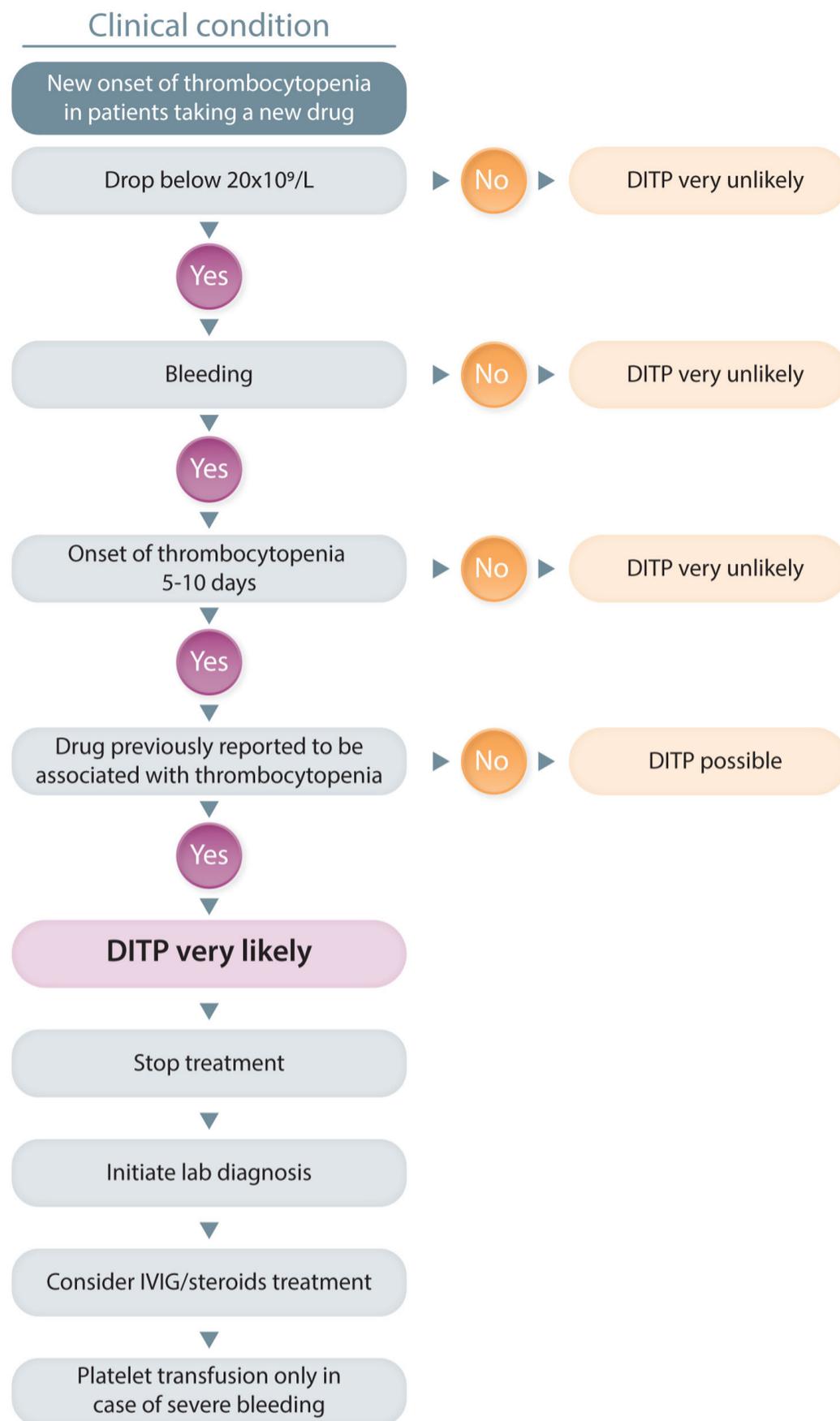


Figure 2. Suggested algorithm to manage cases with suspected drug-induced thrombocytopenia (DITP). (Adapted from Arnold *et al.*⁸⁰).

that ICI trigger the expression of antiplatelet antibodies similarly to primary ITP.²⁰

Clinical manifestations of ICI-induced immune thrombocytopenia

Patients who develop ICI-induced ITP show symptoms common to other types of thrombocytopenia, such as petechiae, easy bruising, spontaneous bleeding, and hematuria.²⁰ However, more severe manifestations, such as cerebral hemorrhage with subsequent neurological deficits, have been also reported in some rare fatal cases.²¹

Diagnosis of ICI-induced immune thrombocytopenia

Obtaining a clear diagnosis of ICI-induced ITP is complex for several reasons. First, it is characterized by symptoms similar to all immune thrombocytopenias. Moreover, the absence of specific diagnostic tests and/or biomarkers represents a critical limitation. Consequently, the diagnosis can only be made by a process of exclusion. In addition, it must be remembered that the onset of the majority of the symptoms appears within the first 12 weeks of treatment, which is an identical time-frame to other more common types of acquired thrombocytopenias.²²

Risk management of patients with ICI-induced immune thrombocytopenia

Due to the uncertainties of a laboratory or clinical diagnosis, there is no reliable strategy to lower the risk of this condition. However, the search for autoantibodies in patients with a personal or family history of autoimmune diseases is recommended.²⁰

Treatment of ICI-induced immune thrombocytopenia

There is neither a general or a specific treatment for ICI-induced ITP. However, the American Society of Clinical Oncology published a guideline for the management of ICI-induced ITP depending on platelet count.²³ In this, Grade 1 thrombocytopenia (platelets $<100 \times 10^9/L$) should be managed by continuation of the immune therapy with a tightly scheduled follow up and laboratory evaluation. Restarting therapy is possible after recovery of a normal platelet count. In cases of Grade 2 thrombocytopenia ($<75 \times 10^9/L$), maintain treatment but monitor for improvement; if not resolved, interrupt ICI. When the platelet count decreases to below $50 \times 10^9/L$ (Grades 3 and 4), the advice of a consultant hematologist should be sought. Usually, in cases of Grades 3 and 4, the ICI treatment should be withheld and the use of high-dose corticosteroids and/or IVIG over at least four weeks is suggested. If symptoms and platelet count do not improve within 48–72 hours of high-dose corticosteroid therapy, administration of infliximab (a chimeric monoclonal antibody neutralizing TNF- α) is recommended. In the absence of any recovery to Grade 1, the immune therapy must be definitively discontinued. There are other treatments, (e.g., rituximab or thrombopoietin receptor agonists) which can be considered in cases of patients refractory to initial therapy.

Heparin-induced thrombocytopenia

Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) binds to platelet factor 4 (PF4) and forms immunogenic complexes that induce the production of antibodies specific for PF4/heparin complexes in a subgroup of treated patients. A minority of these immunized patients could develop HIT type II (hereafter referred to as HIT), which is characterized by a drop in platelet count starting between days 5–10 of heparin therapy, with or without thromboembolic events.⁴ The use of LMWH instead of UFH is associated with a lower risk of HIT. In contrast to HIT, non-immune thrombocytopenia (HIT type I) can also occur in 10–30% of patients treated with heparin due to direct binding to platelets resulting in mild platelet activation. In fact, it has been shown that binding of UFH, LMWH or fondaparinux to the GPIIb/IIIa complex potentiates outside-in platelet signaling resulting in HIT type I,¹ which typically occurs within the first few days (earlier than day 5) of heparin therapy, and is usually mild and without major clinical consequences.

Platelet count often remains above $80\text{--}100 \times 10^9/L$ and returns to basal levels spontaneously within a few days despite continuous heparin treatment.

Pathophysiology of heparin-induced thrombocytopenia

A subset of anti-PF4/heparin antibodies binds with their Fc-domains to Fc gamma Receptor IIA (Fc γ RIIA) on platelets,²⁴ leading to platelet activation (Figure 1). Subsequently, the activated platelets release their granular contents, generate microparticles, promote thrombin formation, and finally aggregate.^{25,26} The activation of endothelium and monocytes, together with the expression of tissue factor, contributes to the pathophysiology of HIT.²⁷ In addition, there is increasing evidence to suggest that neutrophils are also involved in thrombus formation. In fact, they are activated by P-selectin²⁸ on platelets and via Fc γ RIIA by anti-PF4/heparin antibodies²⁹ leading to neutrophil extracellular trap (NET) formation and release of their prothrombotic molecules (NETosis).

Clinical manifestations of heparin-induced thrombocytopenia

The key clinical feature of HIT is a drop in platelet count of $>50\%$ (from the highest value upon the first heparin administration), usually starting 5–10 days after beginning heparin treatment. However, HIT can be observed earlier in patients who are re-exposed to heparin after receiving it in the previous 100 days (rapid onset HIT).^{30,31} In a subgroup of HIT patients, characterized by disseminated intravascular coagulation (DIC), a bigger drop in platelet count ($<20 \times 10^9/L$) might be observed.^{25,30}

Thrombosis represents the most severe complication of HIT and contributes to disease-related morbidity and mortality. A new thrombotic complication is observed in almost 50% of patients with acute HIT;³² deep-vein thrombosis (DVT) is the most common. Notably, patients with HIT may develop asymptomatic thrombosis in veins in the lower and upper extremities, highlighting the importance of examining all four extremities in HIT.³³ Rare complications of HIT include thrombosis in cerebral and splanchnic veins, as well as catheter-associated thrombosis. Although less frequent, arterial thrombosis has also been reported and usually involves lower-limb, cerebral, coronary, mesenteric and brachial arteries.²⁶ In a few cases, severe HIT-associated DIC triggers microthrombosis and critical limb ischemia. Finally, skin necrosis at the heparin injection sites and adrenal hemorrhagic necrosis are rare clinical manifestations of HIT.⁴

Diagnosis of heparin-induced thrombocytopenia

The diagnosis of HIT can be challenging. The most commonly used scoring system is the 4Ts system,³⁴ which includes four typical clinical peculiarities of HIT: (i) thrombocytopenia; (ii) timing of onset of thrombocytopenia;

Table 2. The 4Ts scoring system to evaluate the pretest risk for heparin-induced thrombocytopenia (HIT).

4Ts	2 points	1 point	0 point
Thrombocytopenia	Platelet count falls >50% and platelet nadir $\geq 20 \times 10^9/L$	Platelet count falls 30-50% or platelet nadir $10-19 \times 10^9/L$	Platelet count falls <30% or platelet nadir $< 10 \times 10^9/L$
Timing of fall in platelet count	Clear onset between days 5-10 or falls ≤ 1 day*	Onset after day 10 or falls ≤ 1 day**	Platelet count falls <4 days or >14 days after exposure
Thrombosis or other sequelae	New thrombosis*** (confirmed)	Suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

The resulting clinical probability score is divided into high (6–8 points), intermediate (4–5 points), and low (≤ 3 points). *In case of prior heparin exposure during the last 30 days. **In case of prior heparin exposure within 30-100 days previously. ***Also skin necrosis, acute systemic reaction post-intravenous unfractionated heparin (UFH) bolus, progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions.

(iii) thrombosis or other clinical sequelae; and (iv) the likelihood of other causes of thrombocytopenia (Table 2). The 4Ts system has modest positive predictive values and high negative predictive values.³⁵

The laboratory diagnosis of HIT is based on the demonstration of the presence of anti-PF4/heparin antibodies and their ability to activate platelets in the presence of heparin. Several enzyme-linked immunosorbent assays (ELISA) and particle-based immunoassays are commercially available to detect antibody binding. Recent data showed high negative predictive values of these assays, and therefore they are effective for excluding HIT, while their low specificity makes a positive test result of little use in confirming a clinical suspicion.³⁶

The presence of platelet-activating antibodies can be determined only by using functional assays that combine both high sensitivity and specificity for clinically-relevant HIT antibodies. The Heparin-Induced Platelet Activation³⁷ assay and Serotonin Release Assay³⁸ are currently considered the “gold standard”.

Management of patients with suspected heparin-induced thrombocytopenia

The first step in the management of patients with suspicion of HIT is the immediate discontinuation of all heparins. However, discontinuation of heparin alone is not sufficient to prevent the development or progression of the thrombosis because PF4 is an autoantigen and may form complexes with endogenous polyanions. Thus, antibody-mediated platelet activation will still take place even in the absence of heparin. Consequently, use of non-heparin anticoagulants for patients with high clinical suspicion of HIT is recommended while awaiting laboratory results. Different anticoagulants are available to treat patients with HIT (Table 3).³⁹ However, the lack of clinical experience with some non-heparin anticoagulants that are rarely used outside HIT enhances the risk of complications related to under-dosing (thrombosis) or over-dosing (bleeding). Therefore, it is ex-

tremely important that physicians are able to discriminate between patients who actually have HIT and those who, although they may have PF4/heparin-specific antibodies and some degree of thrombocytopenia, actually do not. Diagnostic algorithms are available for diagnosis of HIT^{40,41} (see Figure 3 for an example).

Alternative anticoagulants for heparin-induced thrombocytopenia

Parenteral anticoagulant: activated factor X (Xa) inhibitors (danaparoid, fondaparinux) - Danaparoid is a low molecular weight heparinoid consisting of a mixture of heparan sulphate, dermatan sulphate and chondroitin sulphate. In a prospective randomized trial that analyzed patients with confirmed HIT, it was shown that danaparoid is efficient in preventing new, progressive, or recurrent thromboembolic complications (including thrombotic death) or limb amputation.⁴² Danaparoid has a low cross reactivity with HIT antibodies and can also mitigate HIT antibody-induced platelet activation through disruption of PF4/heparin complexes and replacing them from the platelet surface.

Fondaparinux is a synthetic heparin pentasaccharide and has a potent indirect anti-Xa inhibitor effect. The off-label use of fondaparinux in HIT has recently increased⁴³ and it has been shown that it is safe for patients with acute thrombosis and heparin-dependent platelet-activating antibodies.⁴⁴ The efficacy and safety of fondaparinux are similar to those of argatroban and danaparoid in patients with suspected HIT.⁴⁵ Despite the lack of randomized clinical trials, there is increasing evidence to indicate that fondaparinux is an efficient and safe option for the treatment of HIT.⁴⁶

Direct thrombin inhibitors - Argatroban is a synthetic direct thrombin inhibitor that binds to the thrombin active site in a reversible manner. It is capable of inhibiting both free and clot-associated thrombin. Clinical trials reported that treatment with argatroban reduces death, amputation and thrombosis compared to historical controls.^{47,48}

Bivalirudin is another synthetic peptide composed of two

Table 3. Non-heparin alternative anticoagulants that may be used to treat heparin-induced thrombocytopenia (HIT) patients.

Anticoagulant	Mechanism of action	Application	Clearance	Half-life	Monitoring
Parenteral					
Argatroban	Direct thrombin inhibition	Intravenously	Hepatic	40-50 minutes	aPTT
Bivalirudin	Direct thrombin inhibition	Intravenously	Renal	25 minutes	aPTT
Danaparoid	Indirect inhibition of FXa	Intravenously, subcutaneously	Renal	24 hours	Danaparoid-anti-Xa
Fondaparinux	Indirect inhibition of FXa	Subcutaneously	Renal	17-24 hours	Fondaparinux-anti-Xa
Oral					
Dabigatran	Direct thrombin inhibition	Peroral	Renal (ca. 85%)	12-14 hours	Not required
Rivaroxaban	Direct inhibition of FXa	Peroral	Renal (ca. 33%)	5-9 hours	Not required
Apixaban	Direct inhibition of FXa	Peroral	Renal (ca. 25%)	8-15 hours	Not required
Endoxaban	Direct inhibition of FXa	Peroral	Renal (ca. 50%)	10-14 hours	Not required

APTT: activated partial thromboplastin time; Xa: activated Factor X; Fxa: Factor Xa.

short hirudin peptide fragments. It is widely used for non-HIT patients with coronary disease because some studies showed that it reduced bleeding complications in the setting of invasive cardiology.⁴⁹

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Direct oral anticoagulants - Rivaroxaban, apixaban and endoxaban directly block Xa, while dabigatran is a direct thrombin inhibitor. There is increasing evidence to suggest the safety and efficacy of several direct oral anticoagulants (DOAC) in HIT.⁴⁶ In one small multicenter prospective study good safety and efficacy of rivaroxaban, without new thrombotic events, were observed.⁵⁰ In another case series, the use of rivaroxaban, apixaban or dabigatran showed no recurrent arterial, venous thrombosis or bleeding complications.^{51,52} Although these observations seem encouraging, robust clinical studies investigating the efficacy and safety of these drugs in patients with acute HIT are limited, and this precludes any evidence-based recommendations. Im-

portantly, the observed low trough levels of the drugs may not offer adequate protection for some HIT patients.

Intravenous immunoglobulin treatment

The use of high doses of IVIG was shown to inhibit HIT antibody-mediated platelet activation. Evidence emerging from case reports indicates that patients with prolonged thrombocytopenia who are refractory to standard treatment may benefit from IVIG therapy.⁵³ However, more data are needed to clarify the indications and the appropriate IVIG dosing.

Choice and duration of the anticoagulation

Several factors should be considered when selecting the type and duration of non-heparin anticoagulant: the patient's clinical stability, hepatic and renal functions; the physician's expertise also plays a role. For example, fondaparinux should be avoided in patients with impaired renal function, and a cautious approach should be adopted in patients with hepatic insufficiency when argatroban is used. All the advantages and disadvantages of non-heparin anticoagulants should be weighed up when selecting an agent for the treatment of HIT patients (Table 3). Anticoagulation should be given at therapeutic concentration to HIT patients who have suffered from thromboembolic complication for at least three months. The treatment can be initiated using parenteral agents and a later switch can be made to oral anticoagulants, DOAC, or a vitamin K antagonist. While the timing for the switch has

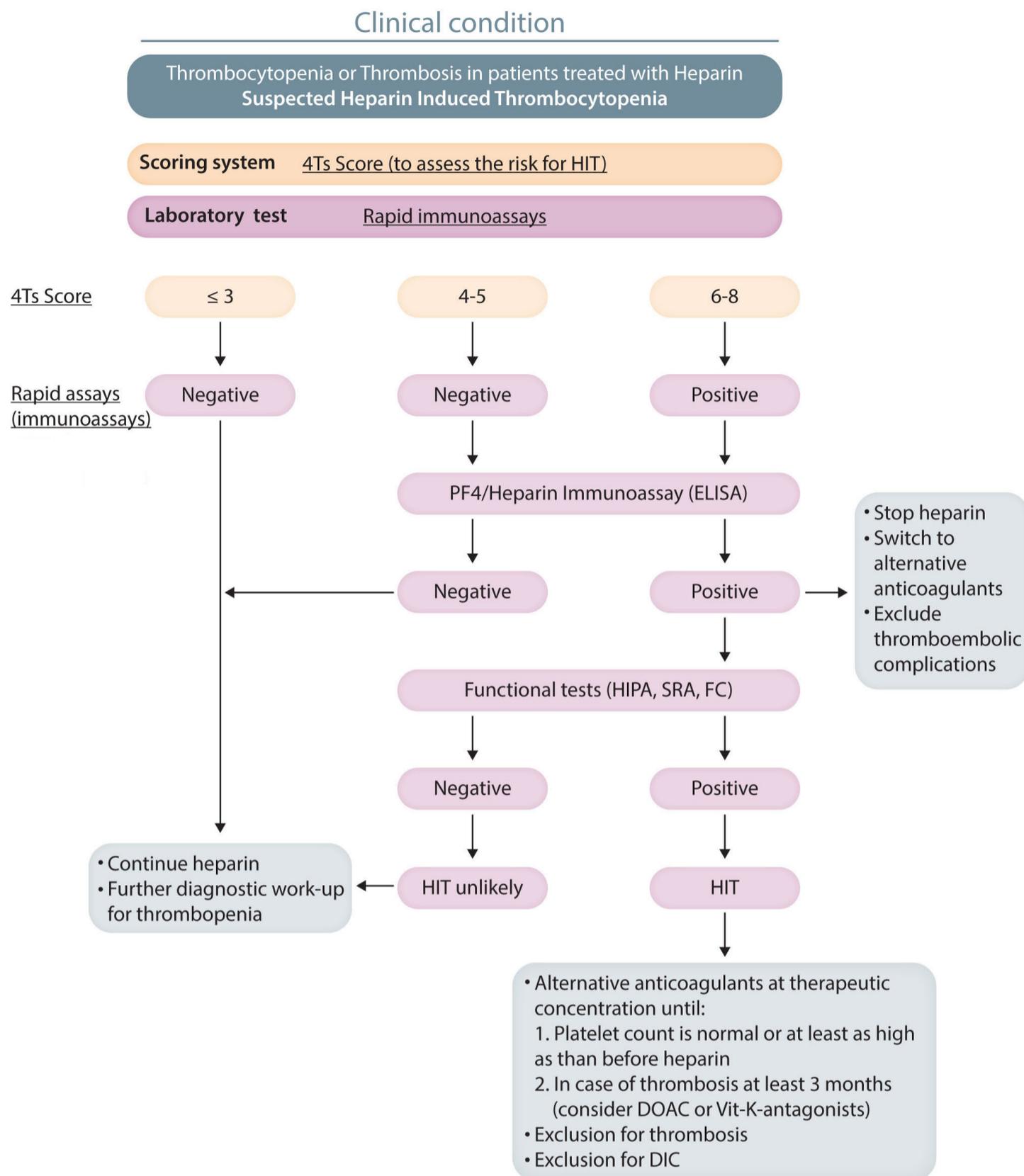


Figure 3. Management of patients with suspected heparin-induced thrombocytopenia (HIT) based on clinical assessment supported by complementary laboratory investigations. Screening platelet factor 4 (PF4)-dependent immunoassays are indicated for patients with at least intermediate probability of HIT. If the ELISA assay is positive, heparin should be stopped, an alternative anticoagulant should be started, and thromboembolic complications should be excluded. Next, functional assays should also be performed to confirm or refute a diagnosis of HIT. HIPA: heparin-induced platelet activation assay; SRA: serotonin release assay; FC: flow cytometric assay; DOAC: direct oral anticoagulants; Vit-K: vitamin K; DIC: disseminated intravascular coagulation. (Figure modified, with permission, from Bakchoul and Marini¹).

not standardized, vitamin K antagonists should always be given together with parenteral anticoagulants for at least five days and until an international normalized ratio (INR) of over 2.0 is achieved. Since vitamin K antagonist and argatroban prolong prothrombin time/INR beyond that of vitamin K antagonist alone, combined therapy should be given until INR is >4.

There is, however, no evidence of the use of therapeutic anticoagulation in patients with isolated thrombocytopenia

who have no other indication for anticoagulation. In such cases, we prefer to treat the patient (serologically confirmed HIT type II with no suggestion of thrombosis) with non-heparin anticoagulants at a therapeutic concentration until the platelet count has reached pre-heparin values, or at least $150 \times 10^9/L$. Before ending the treatment, it is also recommended to re-evaluate the thrombotic risk and exclude the presence of asymptomatic thrombosis.

COVID-19 vaccines and thrombocytopenia

Vaccine-induced thrombotic thrombocytopenia

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by coronavirus type 2 (SARS-CoV-2). In a very short time, different types of vaccines (mRNA vaccine, adenoviral vector-based vaccine, and protein-based vaccine) were developed. Reports of the development of thrombocytopenia and thrombosis at unusual sites with fatal outcome started to emerge shortly after the rollout of adenoviral vector-based vaccines; this phenomenon is now termed a vaccine-induced immune thrombotic thrombocytopenia (VITT).

Definition of vaccine-induced immune thrombotic thrombocytopenia - Vaccine-induced immune thrombotic thrombocytopenia is characterized by thrombosis, thrombocytopenia, and the presence of PF4 reactive antibodies developed 4-30 days from the administration of an adenoviral vector-based vaccine.⁵ An incidence of from 2.5 to 38 per million doses has been reported after the administration of the first dose of ChadOx1 nCov19⁵⁴ (<https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions>). See and co-workers recently reported an incidence of 3.5 per million doses after vaccination with Ad26.Cov2.S in the USA.⁵⁵ Although even more rarely, VITT can also develop after a second dose of ChadOx1 nCov19 with an incidence of 1.9 per million doses.⁵⁴ Early case reports indicated young women (<40 years of age) represented the high risk group, but recent case series reported an even distribution of VITT across gender groups.⁵

Pathophysiology vaccine-induced immune thrombotic thrombocytopenia - IgG antibodies reactive to PF4 are the drivers of the pathophysiology of VITT⁵⁶ (Figure 1). However, the link between vaccination and the development of anti-PF4 antibodies is not clear. One of the proposed mechanisms is the generation of a neoantigen with the binding of PF4 to vaccine components such as human and non-structural viral proteins or free DNA.⁵⁷ Another theory suggests cross-reactivity between spike protein of the virus and PF4.⁵⁸ However, anti-PF4 antibodies do not cross-react with spike protein,⁵⁸ and no correlation between anti-SARS-CoV-2 antibodies and anti-PF4 antibodies has been found.⁵⁹

Anti-PF4 antibodies bind to PF4 on the platelet surface and these complexes activate platelets by engaging their FcγRIIA, thus causing the generation of procoagulant platelets and promoting thrombus formation.^{56,60}

Clinical manifestations of vaccine-induced immune thrombotic thrombocytopenia - In most cases, the first physical signs occur within two weeks of vaccination, but a delay in presentation is also possible. Petechiae, bruising or even

hematoma can be seen in patients with severe thrombocytopenia. Cerebral venous sinuses (CVST) are the most common sites of thrombosis and the first symptom is a severe headache.⁵ Intracranial hemorrhage is present in almost one-third of patients with CVST, which is associated with a high mortality rate.⁶¹ Patients with cerebral ischemia and hemorrhage present with altered mental status and/or focal neurological deficits. Abdominal pain is a sign of splanchnic vein thrombosis, while dyspnea and chest pain suggest pulmonary artery embolism. Patients with lower extremity DVT have leg pain or swelling. A mortality rate as high as 60% has been reported in an initial case series⁶² and recent case series report this to still be over 20%.⁶¹

Diagnosis of vaccine-induced immune thrombotic thrombocytopenia - The suggested clinical and laboratory criteria include: 1) symptom onset within 5-30 days of vaccination with an adenoviral vector-based COVID-19 vaccine (ChadOx1 nCov19 and Ad26.COV2.S); 2) documented venous or arterial thrombosis; 3) thrombocytopenia (<150x10⁹/L); 4) D-dimer >4,000 ng/mL fibrinogen equivalent units; and 5) positivity of anti-PF4 IgG ELISA test and modified functional platelet activation assay.^{5,63} If all five criteria are met, the diagnosis of VITT is considered definite; if one criterion is missing, the diagnosis is considered probable; in these cases, anticoagulation and IVIG may be considered according to the clinical and laboratory findings.⁵ A suggested approach for the diagnosis and initial management of patients with suspected VITT is reported in Figure 4.

Of note, rapid immunoassays are not suitable for the detection of anti-PF4 antibodies in VITT⁶⁴ and a sensitive anti-PF4 ELISA is recommended.^{63,64} The Scientific and Standardization Committee on Platelet Immunology of the International Society on Thrombosis and Haemostasis also recommends additional laboratory confirmation of the diagnosis by functional platelet activation assays (heparin-induced platelet activation assay, serotonin release assay or P-selectin expression assays).⁶³

It is important to know that some patients do not have thrombosis at presentation but may later develop it.⁶⁵ Moreover, a subgroup of patients may have a normal platelet count at presentation but they develop thrombocytopenia after a couple of days.^{5,66}

Treatment of vaccine-induced immune thrombotic thrombocytopenia - Several societies have published recommendations regarding the management of patients with VITT⁶⁷ that are mainly based on experience with the treatment of HIT patients. Because of the rapid deterioration in their clinical condition and the high mortality rate, patients with suspected or confirmed CVST should be transferred to a center with capability for neurosurgical intervention (see below).

To avoid further thrombotic complications, anticoagulation in therapeutic doses is required.⁶⁸ It is recommended to avoid heparin and LMWH in patients with VITT,⁶⁹ although

successful use of heparin has been reported in some cases.⁷⁰ It has not yet been demonstrated that heparin-based treatments worsen the clinical condition of patients with VITT, but one of the following non-heparin anticoagulants may be preferred: DOACs such as apixaban or rivaroxaban; direct thrombin inhibitors like argatroban,

dabigatran, bivalirudin, and fondaparinux. Bleeding risk, renal or hepatic impairment, and the need for oral or parenteral application should be considered when choosing the anticoagulant. In patients with CSVT, parenteral agents should be preferred over DOAC due to the increased bleeding risk in these patients.⁶⁸ The anticoagulant can be

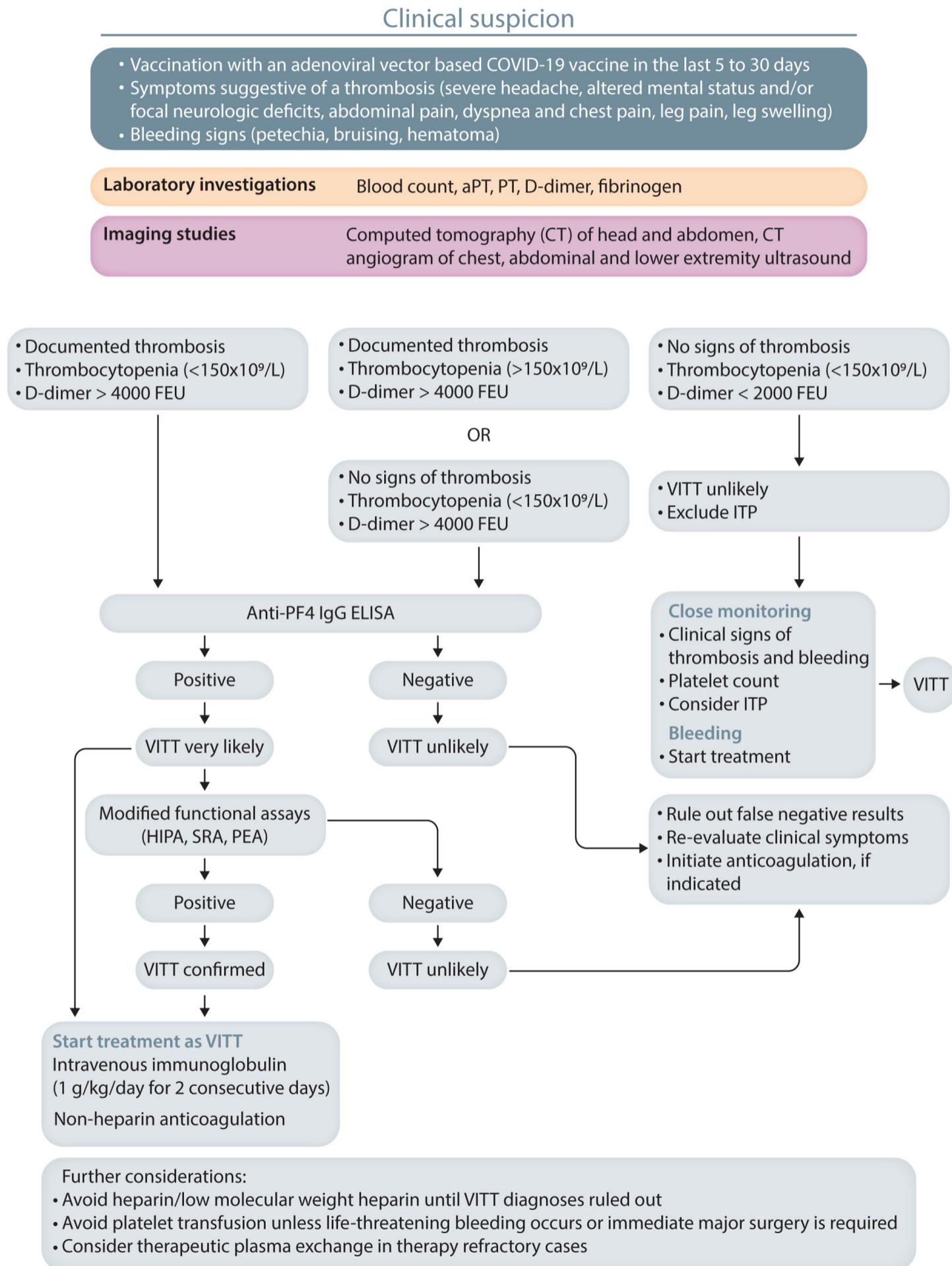


Figure 4. Suggested approach to diagnosis and initial management of patients with suspected vaccine-induced immune thrombotic thrombocytopenia (VITT). FEU: fibrin equivalent units; PT: prothrombin time; aPTT: activated partial thromboplastin time; HIPA: heparin-induced platelet activation assay; SRA: serotonin release assay; PEA: P-selectin expression assay.

switched to an oral alternative after the acute phase, or at discharge in patients receiving a parenteral anticoagulant in hospital,⁶⁸ and anticoagulation should continue for at least three months after the platelet count has normalized. Patients without a documented thrombosis but with severe headache suggestive of CSVT should also receive anticoagulation.⁷¹

Intravenous immunoglobulin is the only available therapy that can interfere with the pathological anti-PF4 antibodies and limit the progression of VITT.^{72,73} High-dose IVIG treatment (1 g/kg/day) should be started promptly in suspected cases without waiting for the results of confirmatory tests. Additional IVIG administrations should be performed on the second day in case of CSVT and splanchnic thrombosis, or later in patients not responding to the first dose.⁷¹ It has been shown that IVIG inhibits VITT sera-induced procoagulant platelet formation and activation in functional assays.^{56,72,73} In accordance with these *in vitro* data, several case reports showed a rapid increase in platelet count after IVIG administration.^{72,73} In a recent case series investigating VITT patients with CSVT, a significantly lower mortality rate in the subgroup receiving IVIG than in those who did not (40% vs. 73%; $P=0.022$) has been reported.⁷⁰

Furthermore, steroids (e.g., prednisone 1-2 mg/kg/day or dexamethasone 40 mg/day for 4 days) could also be considered to mitigate the immune response when IVIG is not available,⁷¹ although the benefit of steroids in VITT is uncertain.⁷⁰ Based on the successful use of plasma exchange in a few refractory patients,⁷⁴ this treatment might be applied to patients not responding to IVIG. The rationale for this approach is that plasma exchange not only removes the IgG antibodies causing VITT from the circulation, but also replaces factors consumed during the process of thrombosis.⁷⁵ In addition, endovascular treatment and neurosurgical interventions might be required in selected cases with CSVT. While platelet transfusion should generally be avoided, it must be considered in cases where life-threatening bleeding occurs or when immediate major surgery is required.⁷¹ Finally, it is important to consider that patients may develop a new thrombosis during the course of the disease. Therefore, patients should be constantly monitored for clinical signs of thrombosis and platelet counts should be checked.

Treatment of female VITT patients who are pregnant or breastfeeding requires special considerations. IVIG can be used safely in these patients. If IVIG is not available, short-term corticosteroid treatment may be considered in consultation with obstetricians.⁷¹ The preferred anticoagulation is heparin/LMWH, but danaparoid or fondaparinux may also be used in these patient populations.⁷¹ In contrast, direct oral factor Xa inhibitors should be avoided.

Vaccine-associated immune thrombocytopenia

Recently, the development of *de novo* ITP has been re-

ported after COVID-19 vaccines. It is not yet clear whether ITP after receiving COVID-19 vaccines is coincidental or consequential. *De novo* ITP development has been reported after both mRNA and adenoviral vector vaccines. The mechanism(s) of vaccine-associated ITP are yet to be clarified. Molecular mimicry and underlying predisposition to autoimmunity have been proposed as potential etiological factors.⁷⁶ Furthermore, exacerbation of a previously undetected ITP after vaccination could be another explanation. Most of the patients present skin purpura or oral mucosal bleeding, but severe bleeding seems to be rare. In the largest case series reported so far, Lee and co-workers found a response rate of over 90% to first-line treatments (IVIG, corticosteroid, platelet transfusion).⁷⁶ In another case series, 5 out of 9 patients responded to first-line treatment with IVIG and corticosteroid, but most of the patients remained on corticosteroids for at least 30 days.⁷⁷ Further studies are needed to evaluate the long-term outcome of patients developing ITP after receiving COVID-19 vaccines.

Vaccination in patients with immune thrombocytopenia

Case series reported ITP exacerbation after COVID-19 vaccination. Visser and co-workers reported exacerbation of ITP in 13.8% of ITP patients. Factors associated with exacerbation after vaccination were platelet count $<50 \times 10^9/L$, young age, and ITP treatment at the time of vaccination. Five patients (2.2%) suffered from a bleeding event.⁷⁸ Similarly, in another study, exacerbation was observed in 19 out of 109 (17%) ITP patients after the first vaccination and in 14 out of 70 (20%) after the second dose.⁷⁶ Splenectomy and refractory cases (>5 lines of therapy) were risk factors for ITP exacerbation.

If ITP patients tolerate the first vaccine well, there is less likely to be an exacerbation of the ITP after the second dose.⁷⁶ Furthermore, based on the currently available data, patients with ITP exacerbation after vaccination responded favorably to treatment.⁷⁶⁻⁷⁹ In conclusion, ITP patients should receive vaccination for COVID-19. A platelet count 3-7 days before and another after the vaccination will help to identify any immediate drop in platelet values.⁷⁹ A second dose should be avoided in ITP patients who experienced a major exacerbation of ITP after the first dose of the vaccine.⁷⁹

Conclusion and future aspects

Thrombocytopenia after drug administration can be associated with bleeding or thrombosis, depending on the pathophysiology of platelet destruction. Significant progress has been made over the last two decades in understanding the pathogenetic mechanism of DITP. However, there are still numerous diagnostic and treatment challenges, especially

in critically ill patients, including the difficulty in distinguishing drug-associated thrombocytopenia from secondary thrombocytopenia caused by underlying disorders.

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the current work. Other authors declare no competing financial interests.

Contributions

IM conducted the literature search, created the figures, and wrote the sections on the pathophysiology and diagnosis of DITP and HIT. GU conducted the literature search and wrote the sections on clinical manifestations and treatment of VITT. KJ conducted the literature search and wrote the section about ICI-induced ITP. TB designed the original layout and edited the manuscript. All authors approved the final version of the manuscript.

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