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Review Article

Spontaneous HIT syndrome: Knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia

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ABSTRACT

Heparin-induced thrombocytopenia (HIT) is characterized clinically by thrombocytopenia, hypercoagulability, and increased thrombosis risk, and serologically by platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies. Heparin-"*induced*" acknowledges that HIT is usually triggered by a proximate immunizing exposure to heparin. However, certain non-heparin medications (pentosan polysulfate, hypersulfated chondroitin sulfate, fondaparinux) can trigger "HIT". Further, naturally-occurring polyanions (bacterial lipopolysaccharide, DNA/RNA) can interact with PF4 to recapitulate HIT antigens. Indeed, immunologic presensitization to naturally-occurring polyanions could explain why HIT more closely resembles a secondary, rather than a primary, immune response. In 2008 it was first reported that a HIT-mimicking disorder can occur without any preceding exposure to heparin or polyanionic medications. Termed "spontaneous HIT syndrome", two subtypes are recognized: (a) surgical (post-orthopedic, especially post-total knee arthroplasty, and (b) medical (usually post-infectious). Recently, COVID-19 adenoviral vector vaccination has been associated with a thrombotic thrombocytopenic disorder associated with positive PF4-dependent enzyme-immunoassays and serum-induced platelet activation that is maximal when PF4 is added. Vaccine-induced immune thrombotic thrombocytopenia (VITT) features unusual thromboses (cerebral venous thrombosis, splanchnic vein thrombosis) similar to those seen in spontaneous HIT syndrome. The emerging concept is that classic HIT reflects platelet-activating anti-PF4/heparin antibodies whereas spontaneous HIT syndrome and other atypical "autoimmune HIT" presentations (delayed-onset HIT, persisting HIT, heparin "flush" HIT) reflect heparin-*independent* platelet-activating anti-PF4 antibodies—although the precise relationships between PF4 epitope targets and the clinical syndromes remain to be determined. Treatment of spontaneous HIT syndrome includes non-heparin anticoagulation (direct oral Xa inhibitors favored over direct thrombin inhibitors) and high-dose immunoglobulin.

1. Introduction

1.1. The concept of spontaneous HIT syndrome

Spontaneous HIT syndrome denotes a disorder that has striking clinical and serological similarities to immune heparin-induced thrombocytopenia (HIT) but where a proximate (closely preceding) immunizing exposure to heparin is unlikely to have occurred. Clinically, patients have both thrombocytopenia and thrombosis. This is probably because asymptomatic thrombocytopenia is uncommon and usually not identified. Thrombosis occurrence is typically the event prompting the blood work that reveals thrombocytopenia; sometimes, suspicion of thrombosis leads to administration of heparin, resulting in an unexpected abrupt platelet count fall. Serologically, patient blood contains platelet-activating antibodies that recognize PF4.

1.2. Literature review

Spontaneous HIT syndrome was first reported as a distinct entity in 2008 [1,2]. Fig. 1 outlines the strategy used to identify literature. Including a new illustrative case presented in this review, there are 33 cases at the time of writing [2–27]. One of us (TEW) also reviewed

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personal correspondence regarding 7 other patients with spontaneous HIT syndrome ("unpublished cases").

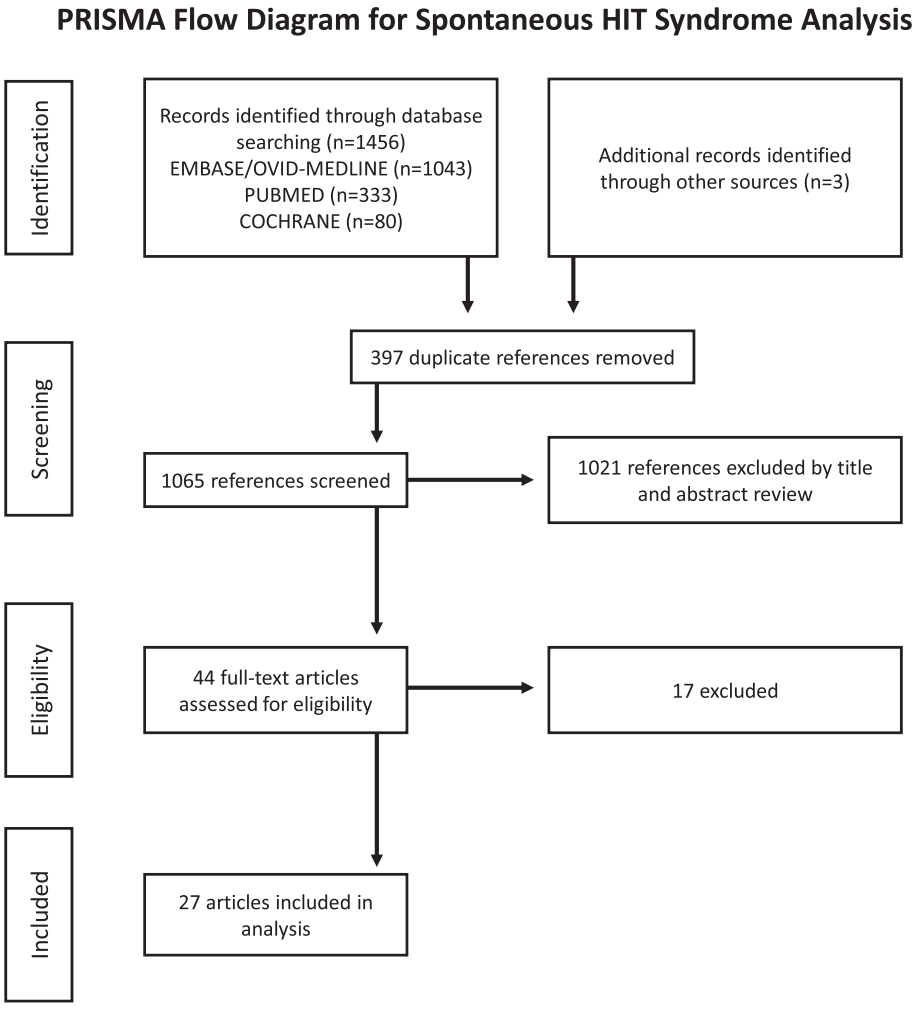
1.3. Certain non-heparin pharmacological polyanions can form HIT antigens and cause HIT

A fundamental observation [28] foreshadowed the biological plausibility of spontaneous HIT syndrome. Almost 30 years ago, one of us (AG) reported that certain polyanions other than unfractionated heparin (UFH)—including low-molecular-weight heparin (LMWH), dextran sulfate, and pentosan polysulfate—can contribute to formation of HIT antigens, as these compounds can substitute for heparin in platelet activation assays used to detect HIT antibodies. This early work occurred prior to the recognition that the antigens of HIT are found on complexes between a (cationic) chemokine—platelet factor 4 (PF4)—and (polyanionic) heparin, a discovery made by Amiral and colleagues in 1992 [29] and corroborated by three other groups [30–32]. One of the investigated polyanions—pentosan polysulfate—also causes a disorder identical to HIT [33–35]. Other non-heparin polyanionic pharmaceutical agents implicated in causing a HIT-mimicking syndrome include polysulfated chondroitin sulfate [36–39], and the antiangiogenic agent, PI-88 [40]. For the purposes of this review, spontaneous HIT syndrome does *not* include HIT-mimicking syndromes caused by polyanionic non-heparin pharmaceutical agents.

1.4. Other polyanions that create HIT antigens

Following the first description of polyanions substituting for heparin, Visentin et al. systematically looked for other polyanions that could create HIT antigens with PF4, thereby identifying polyvinyl sulfonate (PVS); today PF4/PVS is used in certain commercial enzyme-immunoassays (EIAs) [41]. The resulting IgG-specific and polyspecific (IgG, IgA, IgM) anti-PF4/PVS EIAs have high sensitivity (>99%) for detecting HIT antibodies [42]; however, their diagnostic specificity is limited by frequent detection of (non-pathogenic) non-platelet-activating antibodies [43].

One of us (AG) identified polyanions found in nature that can form immunogenic complexes with PF4, including bacteria [44]—specifically lipid A in bacterial surfaces [45]—and even nucleic acids such as DNA and RNA [46,47]. Further, endogenous polyanions such as polyphosphate interact with PF4 to create HIT antigens [48–50]. Polyanions also enhance binding of PF4 to bacteria, facilitating their opsonization as well as phagocytosis through anti-PF4/heparin antibodies [49]. Palankar and colleagues [51] also showed that anti-PF4/polyanion IgG



The literature search was performed using keywords: "infection" or "knee" or "spontaneous" AND "heparin-induced thrombocytopenia", English only

Fig. 1. Literature search.

opsonizes PF4-coated Gram-positive and Gram-negative bacteria, and specifically kill *E. coli* opsonized with PF4 in the presence of anti-PF4/polyanion antibodies. Platelets become antimicrobial agents, forming platelet microaggregates that engulf pathogens, with degranulation of bactericidal substances [52]. This concept has been extended by Haile et al. [53], arguing that PF4 plays a broad role in innate immunity and inflammatory responses. Besides these PF4-related interactions, PF4-independent platelet-bacterial interactions are an accepted general mechanism of host defense [54,55].

The Greifswald group has proposed that "preimmunization" by exposure to prevalent microbial antigens [56] could help explain such features as the high frequency of HIT (~0.2–3% [57,58]) and the anti-PF4/heparin immune response (e.g., ~25–50% post-cardiac surgery [59,60]), i.e., HIT could represent a misdirected, evolutionarily ancient, antimicrobial response. Indirect support for this concept is found in studies by Zheng and coworkers [61], who found that nearly all humans and mice have circulating B-cells that can produce anti-PF4/heparin antibodies. Moreover, marginal zone B-cells are critical for anti-PF4/heparin antibody formation [62]. The continuing biological importance of the anti-PF4 immune response in the era of an adaptive immune system is questionable. However, if this old defense mechanism becomes misdirected, it can cause severe collateral damage in the vascular system. Administration of pharmacologic heparin is one trigger of a misdirected anti-PF4 immune response. Potentially, too, infection- or trauma-associated increases in circulating nucleic acids [63] could stimulate "spontaneous" formation of anti-PF4/polyanion antibodies [47].

Presensitization by natural exposure to pathogens could also explain why HIT—even when triggered by a first lifetime heparin exposure—does not show features of a "primary" immune response; rather, antibodies of IgG class form quickly, beginning a median of 4 days after the immunizing heparin exposure, irrespective of prior heparin exposure [64,65]. Moreover, antibodies of any of the three major immunoglobulin classes can be formed, in frequency IgG > IgA > 1gM, and in any combination; further, when two or more antibody classes are generated, they are formed at the same time, without IgM precedence.

These unusual features of HIT immunopathogenesis could reflect evidence of presensitization to PF4 bound to polyanions encountered naturally, such as on bacteria. B cells with anti-PF4 reactivity are an inborn part of our antibody repertoire, found in nearly all humans tested, as well as in mice, and stimulated in vitro by exposure to certain proinflammatory molecules. Even PF4 knock-out mice produce anti-PF4 antibodies when challenged with bacteria; cord blood-derived B cells of newborns also produce anti-PF4 antibodies of IgM class, when stimulated in vitro [66]. Murine studies suggest that regulatory T cells control this immune response [67–69].

Recent studies explain how B cells producing anti-PF4 antibodies recognize their antigen during treatment with heparin. Administration of heparin leads to natural IgM binding to PF4/polyanion complexes [70]. Natural IgM activates complement, which results in binding of PF4/heparin/IgM/complement complexes onto B cells (via complement receptors on B cells). [71] Because all B cells express the complement receptor, the PF4 polyanion complexes will bind to most B-cells, including B cells with the cognate anti-PF4 antibody on their surfaces, thus with potential to stimulate a specific anti-PF4 immune response. However, cross-linking of the B cell receptors alone is not sufficient for induction of antibody production; a proinflammatory co-signal is required.

Inflammation or tissue trauma provides this important co-signal. It is well-known from HIT that the anti-PF4 response is much more frequent in patients undergoing major (versus minor) surgery [72]. Proinflammatory markers such as interleukin-6 levels were associated with anti-PF4/heparin formation in one study [73]. Indeed, post-surgery patients with ventricular assist devices have the highest risk for HIT [74].

Consistent with these concepts, Pongas and coworkers [75] showed in non-heparin-exposed septic patients presence of anti-PF4/heparin reactivity that was higher than normal controls. Maharaj and Chang [76] also found that reactivity in anti-PF4/PVS EIAs was greater in patients with sepsis versus non-septic controls; however, in this study, most patients did receive prophylactic-dose anticoagulation with heparin, so an independent role of microorganisms in explaining antibodies was unclear. Prechel et al. [77] found higher anti-PF4/PVS antibody levels in diabetic subjects who had infection versus control subjects. A study by Grigorian and colleagues [78] found a higher frequency of HIT in patients who had bacterial infection, including the subsets of patients with urinary tract infection and pneumonia. One group presented a case of thrombocytopenia in the setting of heparin exposure and bacteremia with methicillin-susceptible *Staphylococcus aureus*, arguing that the bacteremia may have contributed to the clinical picture of HIT [79]. Sartori et al. [80] found somewhat increased levels of anti-PF4/PVS antibodies in septic patients versus controls, although there was no difference in IgG-specific antibodies.

1.5. Spontaneous HIT syndrome is a subtype of "autoimmune HIT" (aHIT)

Autoimmune HIT (aHIT) disorders include: delayed-onset HIT; persisting (refractory) HIT; heparin "flush" HIT; and most cases of fondaparinux-induced HIT [81]. The first recognized aHIT disorder, delayed-onset HIT, was reported 20 years ago [82,83]. The initial report defined delayed-onset HIT as a platelet count fall that began at least 5 days after the last exposure to heparin. However, the term is now used to indicate any HIT-related platelet count fall that begins or worsens after stopping heparin [84]. These patients have a higher frequency of unusual thrombosis and disseminated intravascular coagulation [82] and patient serum contains prominent heparin-independent platelet-activating properties (discussed subsequently) [82].

Fig. 2 shows the interrelationship between HIT, aHIT, and spontaneous HIT syndrome. Broadly speaking, both (classic) HIT and aHIT represent antibody-mediated immune responses directed at PF4; in the case of HIT, the antigen is PF4 complexed with heparin; in the case of aHIT, the antigen is PF4 in the (relative) absence of polyanion. Of course, strong reactivity in platelet activation assays without addition of heparin could still involve polyanions, e.g., PF4 bound to endogenous platelet-associated polyanions. Future research will need to determine the role of endogenous polyanions.

As indicated by Fig. 2, most cases of aHIT are triggered by heparin; however, "spontaneous HIT syndrome" can be viewed as an aHIT disorder triggered by some environmental trigger (post-viral, post-bacterial) or by a stimulus that remains to be defined (post-TKA; post-vaccine). Although most aHIT disorders are triggered by heparin, patients are believed to have both heparin-dependent and heparin-independent platelet-activating properties, although heparin-dependent reactivities are not readily evident unless sera are diluted [85].

1.6. Heparin-independent platelet-activating properties

A consistent finding of spontaneous HIT syndrome is the detectability of antibodies that activate platelets in the absence of heparin but are inhibited by high concentrations of heparin (10–100 U/mL). This is also a serological feature of aHIT, i.e., heparin-*independent* platelet-activating properties. This is an important phenomenon, because even if an individual encounters a polyanion in nature that is capable of triggering an anti-PF4/polyanion immune response, this still would not explain subsequent occurrence of thrombocytopenia in most cases, as it is doubtful there would be sufficient concentrations of the polyanion in circulating blood (especially a week later) to lead to sufficient quantities of PF4/polyanion/IgG immune complexes to produce platelet activation. Thus, the key phenomenon to explain heparin-independent platelet-activating properties is highly pathogenic anti-PF4 antibodies

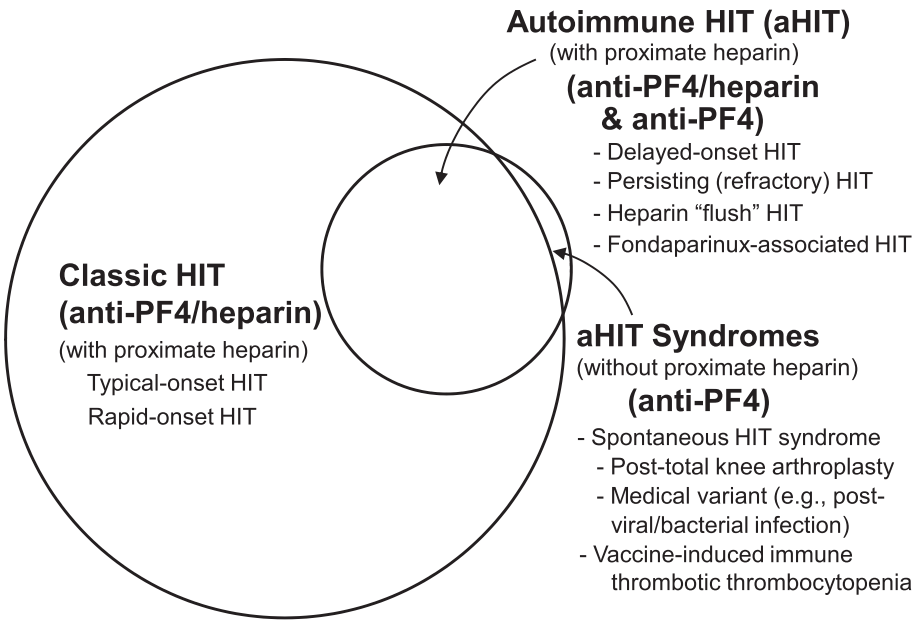


Fig. 2. Interrelationship of classic HIT, autoimmune HIT, and spontaneous HIT syndrome.

(discussed subsequently).

As noted earlier, heparin-independent platelet-activating properties are associated with delayed-onset HIT [82]. Studies using serial blood samples have also shown that slow platelet count recovery ("persisting" or "refractory" HIT) correlates with waning of heparin-induced platelet-activating properties of serum [85,86]. Further, in a study of heparin "flush" HIT (triggered by exposure to small quantities of heparin), there was a strong association with heparin-independent serum-induced serotonin-release: 4/4 sera obtained from patients with heparin flush HIT evinced heparin-induced platelet activating properties versus 34/100 HIT control sera ($P = 0.0161$) [85]. Finally, sera obtained from patients with putative fondaparinux-associated HIT also often contain heparin-independent platelet-activating properties [87–89].

Prechel and coinvestigators [90] also studied the phenomenon of heparin-independent platelet-activating properties of HIT sera. They showed that residual heparin did not account for this property of HIT sera, but rather was intrinsic to the antibodies. Heparin-independent platelet activation by HIT antibodies remains incompletely understood. However, affinity purified anti-PF4 antibodies from patients with autoimmune HIT activate washed platelets in the same way as the patient serum [91]. This makes requirement for a plasma cofactor unlikely. However, platelet-associated polyanions may facilitate binding of PF4 to the platelet surface, supporting the close approximation of two PF4 molecules [91]. Three such polyanions include: chondroitin sulfate [92], polyphosphates [48–50], and nucleotides such as DNA and RNA [46].

1.7. Repulsive PF4 tetramers and HIT "superantibodies"

PF4 is a highly cationic, tetrameric protein, and thus PF4 tetramers usually repel one another; however, certain polyanionic molecules, such as longer chain heparin, can neutralize these repulsive forces [93] (Fig. 3). Once the two PF4 tetramers become closely approximated to one another, their two clouds of positive charges fuse into one cloud, a process that releases the energy required for conformational change in PF4 that results in exposure of HIT antigen(s) [94–97]. A small proportion of HIT "superantibodies" (shown in red) are able to strongly bind PF4 tetramers together; the resulting fused PF4 tetramers now provide additional antigen targets for less reactive (i.e., otherwise heparin-"dependent") antibodies (shown in blue) to bind, resulting in formation of large PF4-IgG immune complexes (with or without platelet-associated polyanions), resulting in massive pancellular activation (platelets, monocytes, neutrophils) [89].

1.8. Challenges in ascertaining the trigger of autoimmune HIT

Several polyanions can trigger aHIT. Often the trigger is clear, such as a single dose of heparin administered perioperatively [98]. But what if there is a single exposure to heparin together with a known non-heparin trigger of aHIT, such as total knee arthroplasty (TKA)? This is illustrated by a case reported by Tardy-Poncet et al. [99] of a patient who underwent TKA and who did not receive postoperative heparin thromboprophylaxis (rather, rivaroxaban was given). However, the patient did receive intraoperative exposure to UFH via a blood salvage device.

Another example is a case of post-TKA seroconversion to heparin-dependent platelet-activating antibodies in which a patient's only heparin exposure was through intraoperative arterial line heparin flushes; the patient developed rapid-onset HIT when heparin was given to treat deep-vein thrombosis 2 weeks post-surgery [100]. Did the TKA or the heparin flushes trigger the antibodies?

This issue is especially notable in cases of so-called fondaparinux-associated HIT. Several [87,88] although not all [89] cases of putative fondaparinux-induced HIT occurred in the context of preceding knee replacement surgery. In these post-TKA patients, did fondaparinux trigger the HIT immune response, or was this caused by the knee replacement surgery itself?

1.9. Anti-PF4/heparin antibodies after knee replacement surgery

Japanese investigators performed prospective observational studies of the frequency of anti-PF4/polyanion IgG in patients undergoing TKA and total hip arthroplasty (THA) with different anticoagulant regimens [101–103]. Seroconversion frequencies were approximately twofold greater with TKA than with THA. Not unexpectedly, UFH thromboprophylaxis post-TKA was associated with the highest frequency of seroconversion (~39%) with lower frequencies seen in those patients who received LMWH (~16%) or fondaparinux (~25%) [101]. However, the frequency of seroconversion was 26% in TKA patients who did not receive any type of heparin [101]. Subsequently, investigators have

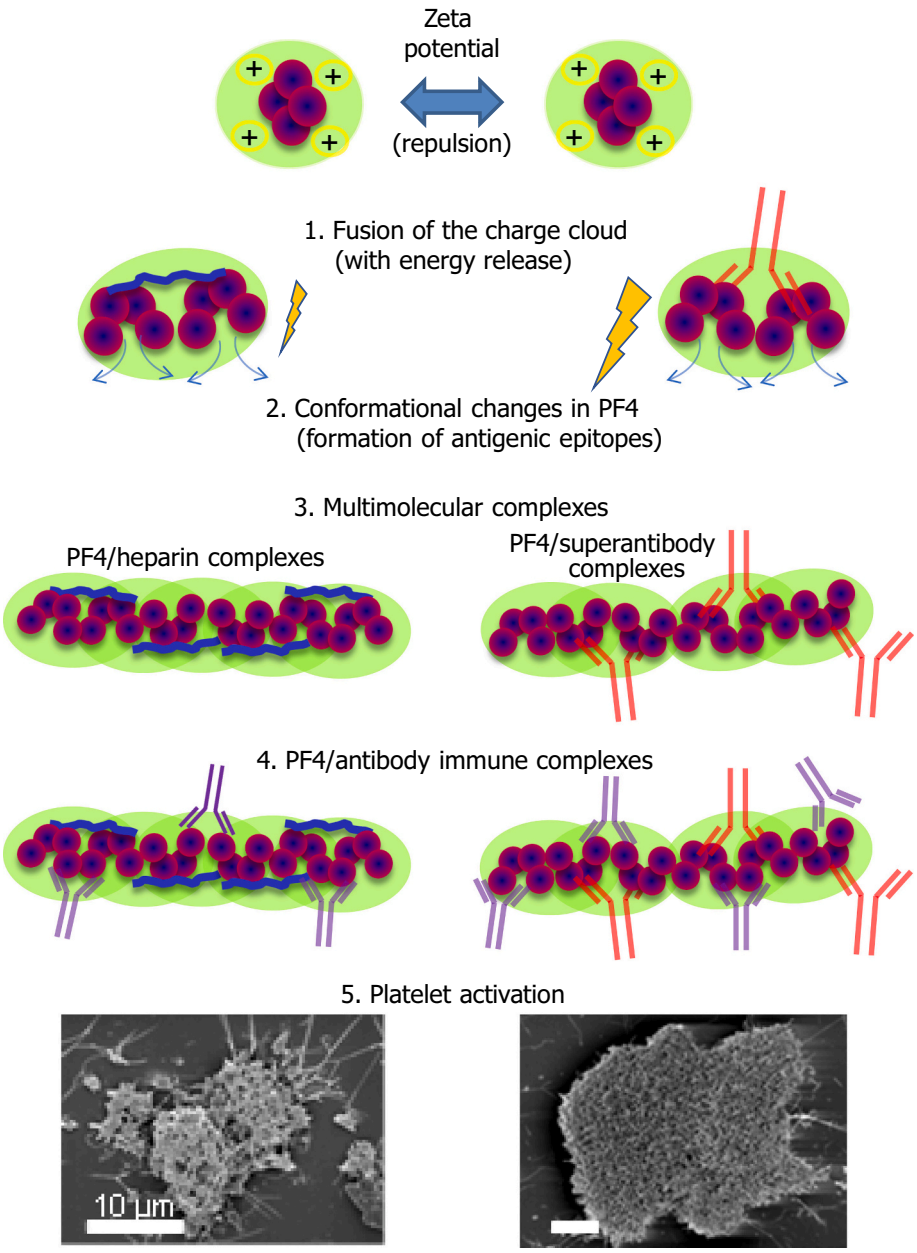


Fig. 3. Cationic PF4 tetramers usually repel one another. However, in the presence of heparin (left column), PF4 tetramers can come together, resulting in fusion of their respective charge clouds (shown in green), with energy release, resulting in formation of antigenic epitopes which can be recognized by classic heparin-dependent HIT antibodies (shown in purple). However, unusual HIT "super-antibodies" (shown in red) can recognize PF4 antigenic epitopes in the absence of heparin; the resulting immune complexes comprised of PF4 and super-antibodies from antigens to which heparin-dependent antibodies can bind, creating large highly platelet-activating immune complexes. Modified, from [81]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

found high frequencies of anti-PF4/PVS IgG seroconversion (~20%–25%) in patients undergoing TKA with prophylaxis with edoxaban (oral factor Xa inhibitor) [104].

Dynamic mechanical thromboprophylaxis (DMT) was also shown to be an independent risk factor for seroconversion even in the absence of receipt of any type of heparin [102,103]. Indeed, the frequency of seroconversion in patients treated with DMT but no anticoagulation (~15%) was similar to that of patients who did not receive DMT but who received UFH (~15%) or LMWH (~14%). These studies also found female sex to be a risk factor for seroconversion (OR ~3.2; $P < 0.001$). In view of other polyanions including nucleotides being able to induce a conformational change in PF4 allowing binding of HIT antibodies, it might be that polyanions (RNA, DNA) released due to the hypoxia in the leg during TKA (performed using a tourniquet) are the trigger for spontaneous HIT syndrome post-TKA (potentially, endogenous heparin from activated mast cells could also be involved). In the next section, we discuss the clinical and laboratory features of post-orthopedic surgery spontaneous HIT syndrome.

2. Post-surgical (post-orthopedic) spontaneous HIT syndrome

TKA is the most common trigger of spontaneous HIT syndrome. Table 1 lists a summary of 23 patients with spontaneous HIT syndrome after orthopedic surgery; this includes 3 patients designated in Table 1 as "presumptive" based on TEW assessment, as the reporting authors did not regard adrenal hemorrhage as being HIT-related [12,19,21]. The most striking finding is that all but two cases involved preceding TKA. The two exceptions: one patient had preceding shoulder surgery [8], the other had curettage of femoral bone [25]. The timing of thrombocytopenia and thrombosis (at least 5 days post-surgery) indicates the knee surgery as representing the "trigger" of HIT; indeed, the day of surgery can be considered as "day 0" when applying the 4Ts scoring system for evaluating clinical likelihood of HIT [105].

2.1. *Clinical and laboratory features*

Noteworthy clinical features of post-orthopedic surgery spontaneous

Table 1
Post-orthopedic surgery spontaneous HIT syndrome.

Study [reference]	Age Sex	Surgery (joint arthroplasty)	Postoperative anticoagulant	POD onset	Platelet nadir	Complications	HIT tests	Comment (including treatment and outcome)
Jay & Warkentin 2008 [2]	69 F	Knee	Warfarin	7	11	BAH, DIC/digital necrosis, DVT	aHIT-Abs+[a]	Fatal outcome; platelet fall from 33 to 11 during UFH; anoxic brain damage secondary to adrenal failure/shock
Pruthi et al. 2009 [3]	61 F	Knee	Warfarin	6	15	SVT, DVT, BAH	aHIT-Abs+[a]	Plt <100 × ~4wk; DVT progression after IVC filter, and also during arg Rx;
Mallik et al. 2011 [4]	60 M	Knee (bilateral)	Warfarin	8	15	Bilateral DVT	EIA+, SRA+	Plt <100 × ~4wk; new DVT during arg; platelet increase with IVIG
Ketha et al. 2013 [7]	60 F	Knee	Warfarin	NR	81	BAH, +thrombosis	EIA+, SRA+	Unspecified additional thrombosis (besides BAH); clinical picture of "sepsis"
Ketha et al. 2013 [7]	65 M	Knee	Warfarin	NR	115	BAH, +thrombosis	EIA+	Unspecified additional thrombosis (besides BAH); clinical picture of "sepsis"
Ketha et al. 2013 [7]	71 F	Knee	Warfarin	NR	20	BAH, +thrombosis	EIA+	Unspecified additional thrombosis (besides BAH); clinical picture of "shock"
Warkentin et al. 2014 [8]	54 F	Shoulder	Nil	15	37	CVA, DVT	aHIT-Abs+[a]	Platelet fall from 61 to 37 during UFH; arg Rx successful;
Warkentin et al. 2015 [11]	71 F	Knee	Apixaban	9	37	BAH, DVT, PE	aHIT-Abs+[a]	Per authors, potential for misattribution of BAH to DOAC; Rx successful (arg transitioned to fondaparinux);
Machhadieh et al. 2015 [12]	75 M	Knee	Rivaroxaban	NR	NR	BAH	EIA+	*PRESUMPTIVE*: Misattribution of BAH with shock to riv; patient had HIT
Elshoury et al. 2015 [13]	48 F	Knee	Aspirin	8	15	BAH, PE (bilateral)	EIA+, SRA+	Plt fall from 187 to 15 during LMWH; recurrent PE during arg
Baker & Lim 2017 [14]	72 F	Knee	Aspirin	12	14	DVT (bilateral), UL-SVT, PE (bilateral)	EIA+, SRA+	Platelet fall from 85 to 25 during UFH; symptomatic intracranial hemorrhage during treatment with arg and tissue-plasminogen activator.
Poudel et al. 2017 [16]	53 F	Knee	Aspirin	14	12	SVT; PE	aHIT-Abs+[a]	Plt <100 × ~4wk; persisting DIC (fx cross-reactivity); new DVT on arg Rx
McCarthy et al. 2018 [17]	76 F	Knee (bilateral)	Aspirin	14	53	DVT (bilateral); PE (bilateral)	EIA+, SRA+	No platelet count fall during LMWH; successful apixaban Rx;
Ly & Quintero 2019 [19]	61 M	Knee (bilateral)	Rivaroxaban	5	NR	AH (left)	Not tested	*PRESUMPTIVE*: Adrenal insufficiency despite unilateral adrenal hemorrhage; the authors did not indicate any suspicion of HIT
Mohanty et al. 2019 [20]	52 F	Knee	Aspirin	12	21	Mesenteric vein thromb.	aHIT-Abs+[a] CLIA+	Rapid platelet count increase with high-dose IVIG; successful fx Rx;
Alidoost et al. [21]	68 F	Knee	Rivaroxaban	8	35	BAH; DVT (bilat)	EIA+, SRA+	*PRESUMPTIVE*: Misattribution of BAH to riv; DVTs occurred after IVC filter placed; successful Rx arg followed by warfarin;
VanderVeer et al. [22]	68 M	Knee	Rivaroxaban	8	71	Bilat adrenal necrosis	aHIT-Abs+[a]	Platelet fall from 166 to 71 during LMWH; successful riv Rx;
Hornick & Ayafor 2020 [24]	51 M	Knee (bilat)	Aspirin	16	63	DVT; PE	EIA+, PAT+	Platelet fall from 111 to 63 with UFH; successful Rx riv;
Swarup et al. 2020 [25]	33 M	Curettage/graft femur lesion	None	10	21	DVT (bilateral); PE (bilateral)	EIA+, SRA+	Successful Rx arg/warfarin
Hwang et al. 2020 [26]	56 F	Knee	Aspirin	11	43	CVT (venous)	aHIT-Abs+[a] LIA+	Successful treatment with bivalirudin/warfarin; plt increase with IVIG
Olevsky & Rosove 2021 [27]	57 F	Knee	Aspirin	6	70	DVT; PE	EIA+, SRA+	Successful treatment with arg ➔ riv
Olevsky & Rosove 2021 [27]	70 F	Knee	Aspirin	NR	27	Limb artery thrombosis; PE	EIA+, SRA+	Unsuccessful Rx with embolectomy, UFH, LMWH (above-knee amputation); ultimately, recovery with arg transitioned to riv
New illustrative case (see text)	70 F	Knee	Aspirin	28	19	Iliac artery; DVT	aHIT-Abs+[a] PIFA-negative	Platelet fall to 19 with UFH; delayed diagnosis (false-negative PIFA); above-knee amputation; Rx failure with argatroban (symptomatic PE); partial response to IVIG (subtherapeutic dosing); see Figure

Abbr.: AH, adrenal hemorrhage (unilateral); aHIT Abs+, presence of autoimmune heparin-induced thrombocytopenia antibodies by serotonin-release assay (SRA); positive EIA also documented; arg, argatroban; BAH, bilateral adrenal hemorrhage; CLIA+, positive test by chemiluminescence immunoassay; CVA, cerebral vascular accident (arterial stroke); DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; DVT, deep-vein thrombosis; EIA+, positive enzyme-immunoassay; F, female; fx, fondaparinux; IVC, inferior vena cava; IVIG, (high-dose) intravenous immunoglobulin; LIA+, positive latex-enhanced immunoassay; LMWH, low-molecular-weight heparin; M, male; NR, not reported; PAT+, positive platelet aggregation test; PIFA, particle immunofiltration assay; Plt, platelet count; *PRESUMPTIVE*, authors did not consider spontaneous HIT syndrome, but rather attributed adrenal hemorrhage to preceding DOAC therapy; riv, rivaroxaban; Rx, treatment; SRA+, serotonin-release assay-positive; SVT, superficial vein thrombosis; +thrombosis, additional thrombosis (not specified); UFH, unfractionated heparin; UL-SVT, upper-limb superficial vein thrombosis.

[a] Patients had documented positive serotonin-release both in the presence and the absence of heparin.

HIT syndrome include: (a) postoperative anticoagulation followed historical trends, i.e., initially warfarin (2008 through 2013) followed (2015 and later) by direct oral anticoagulants (DOACs: apixaban, rivaroxaban) and aspirin; (b) female predominance (16/23 [69.6%]) is approximately the same as that seen in knee replacement surgery (~65%) [106]); (c) high frequency of thrombotic events (100% of reported cases); (d) high frequency of lower limb venous thromboembolism and/or pulmonary embolism (78.3% of reported cases); (d) high frequency of adrenal hemorrhage/necrosis (47.8% of reported cases) often complicated by symptomatic adrenal failure; (e) occurrence of arterial thrombosis (13.0%), including arterial stroke (1 case) and limb artery thrombosis resulting in limb amputation (2 case). Other complications included mesenteric vein thrombosis (1 case) and cerebral venous thrombosis (1 case).

The high frequency of adrenal hemorrhage/necrosis warrants further discussion. This is a known complication of HIT that (for unknown reasons) occurs most often orthopedic surgery patients (2/3 of patients) [107]. The pathogenesis reflects adrenal vein *thrombosis* with secondary hemorrhage, rather than as a result of anticoagulant bleeding. One of us (TEW) has suggested [11] that this paradox could result in misattribution of adrenal hemorrhage to anticoagulant-induced bleeding when the real trigger was TKA-associated HIT.

2.2. Illustrative case

Fig. 4 summarizes the clinical and laboratory features of a previously unreported case of spontaneous HIT syndrome. The case also illustrates a common feature of reported cases, namely the failure of direct thrombin inhibitor (argatroban) therapy, as well as a likely beneficial effect of high-dose IVIG in raising the platelet count and, presumably, decreasing in vivo platelet activation.

2.3. Unpublished cases

Through e-mail correspondence and consultation, one of us (TEW) became aware of 7 other cases of post-TKA spontaneous HIT syndrome (unpublished cases). Features include: female predominance (5/7), overall high thrombosis frequency (100%) including DVT and/or PE (6/7), adrenal hemorrhage (3/7; including one death from adrenal failure), limb artery thrombosis (1 patient; with limb amputation), and portal vein thrombosis (1 patient). Two patients had lower-limb DVT progression after IVC filter placement, including one patient who developed limb amputation secondary to warfarin-induced microthrombosis.

2.4. What is the frequency of post-knee replacement spontaneous HIT syndrome?

There were approximately 750,000 knee replacement surgeries performed in the United States in 2015 [108], with numbers growing each year, and projected to increase substantially by the year 2040. This review identified 30 cases of post-TKA spontaneous HIT syndrome (including unpublished cases) over an approximate 12-year period.

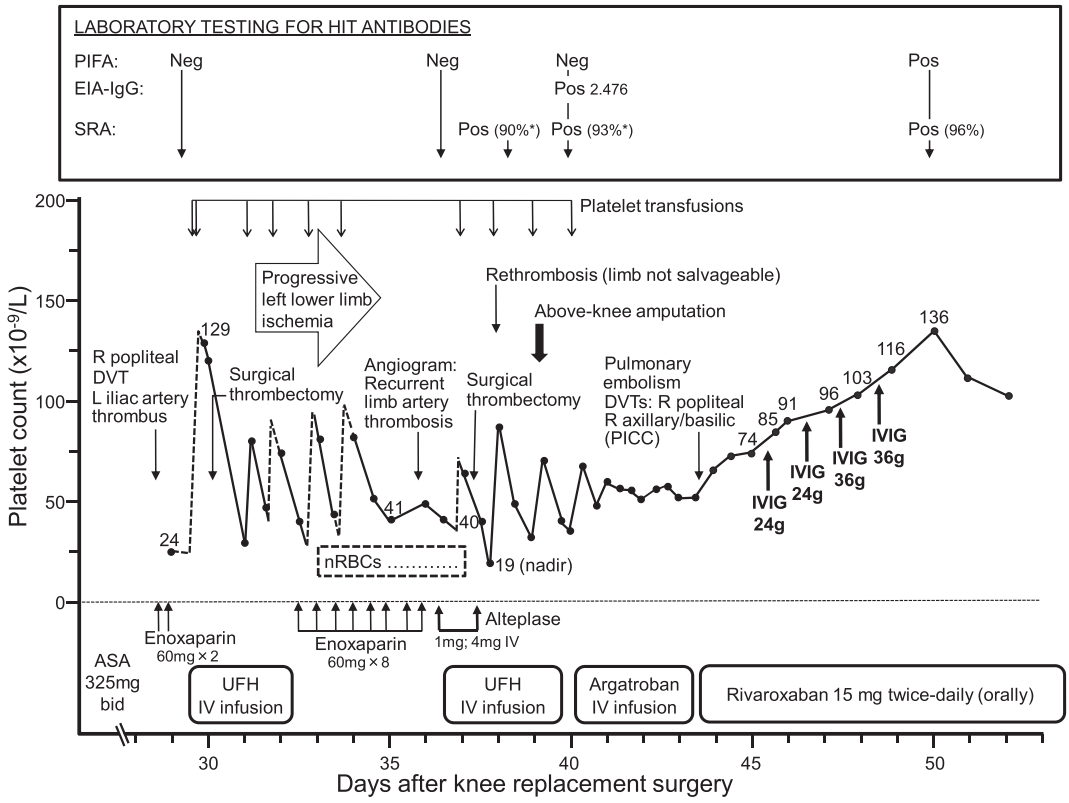


Fig. 4. Post-TKA spontaneous HIT syndrome.
70-year-old woman with post-total knee arthroplasty spontaneous HIT syndrome. False-negative testing in the particle immunofiltration assay (PIFA) resulted in delayed diagnosis. Both PF4/PVS IgG enzyme-immunoassay (EIA) and serotonin-release assay (SRA) results were strongly positive (EIA: 2.476 optical density units [reference range, <0.400]; and SRA: 90%, 93%, and 96% serotonin-release at 0.1 U/mL heparin [reference range, <20%], tested with 3 different sera). Both assays (EIA, SRA) were inhibited (>90%) by high heparin. Asterisks (*) indicate that serotonin-release at 0 U/mL heparin was also strongly positive (90% or greater). The patient developed symptomatic deep-vein thrombosis (DVT) and pulmonary embolism after treatment with argatroban was initiated. Ultimately, the patient recovered without further sequelae after switching to rivaroxaban and high-dose intravenous immunoglobulin (IVIG).
Abbr.: ASA, acetylsalicylic acid (aspirin); DVT, deep-vein thrombosis; EIA, enzyme-immunoassay; HIT, heparin-induced thrombocytopenia; IV, intravenous; L, left; Neg, negative; nRBCs, nucleated red blood cells; PICC, peripherally inserted central catheter; PIFA, particle immunofiltration assay; Pos, positive; R, right; SRA, serotonin-release assay; UFH, unfractionated heparin.

Thus, the minimum frequency of this complication (assuming ~9 million operations over the time period) would be ~1 in 300,000; of course, the frequency could be substantially greater if there is under-recognition/under-reporting.

3. Medical spontaneous HIT syndrome

"Medical" spontaneous HIT syndrome denotes those cases that occur in post-infection scenarios or where no proximate illness or surgery is identified. Patients can present either with thrombocytopenia (usually accompanied by thrombosis) or can present with a normal platelet count, but where heparin administration leads to an abrupt decline in the platelet count, despite the absence of a preceding exposure to heparin that would explain the presence of HIT antibodies. Table 2 shows the cases identified in this review.

3.1. Presenting with thrombocytopenia

Five of the 10 patients listed in Table 2 were thrombocytopenic at initial presentation with a thrombotic event, whereas a sixth patient had a normal but rapidly falling platelet count (prior to heparin administration); 5 of these 6 patients presented with stroke (4, CVT; 2, arterial). Limb artery thrombosis was also observed in 3 of the 6 patients. One unusual case had an IgGκ paraprotein, which the authors believed to have platelet-activating properties.

3.2. Rapid-onset spontaneous HIT syndrome

For 4 other patients listed in Table 2, the platelet count was initially normal but fell abruptly after UFH or LMWH was given. Three of these 4 patients presented to medical attention because of thrombosis, which prompted the heparin treatment that was associated with the subsequent abrupt platelet count fall. The only patient who did not have thrombosis at presentation received subcutaneous injection of enoxaparin for clinically-suspected pulmonary embolism (subsequently ruled out); she had an abrupt platelet count fall associated with chills and fevers, which in retrospect was diagnosed as an acute anapylactoid reaction associated with post-heparin rapid-onset spontaneous HIT.

3.3. Association with cerebral venous thrombosis and arterial stroke

A striking observation of Table 2 is that 4/10 (40%) of patients with medical spontaneous HIT syndrome presented with CVT; a further 2/10 (20%) developed arterial stroke. Although CVT is a known complication of HIT (and also of pentosan polysulfate-associated HIT [34,35]), it occurs in only approximately 1% of patients with HIT [109]. Hemorrhagic transformation is a common occurrence of HIT-associated CVT [110]. Several patients with HIT-associated CVT clearly had aHIT based on clinical or serological features [98,110] or demonstration of heparin-independent platelet-activating properties [111].

Table 2
Medical spontaneous HIT syndrome.

Study [reference]	Age Sex	Setting (precipitant)	Initial platelet count (pre-heparin)	Platelet nadir ($\times 10^9$/L) (post-heparin[a])	Thrombosis	HIT tests	Comment (including treatment and outcome)
Warkentin et al. 2008 [1]	69 M	Periodontitis	17	17	Multiple arterial, hepatic vein	EIA+ SRA+[a]	Failure of ancrod (defibrinogenating agent); post-mortem examination showed multiple arterial thrombi (lower limb arteries, coronary arteries), pulmonary embolism, and hepatic vein thromboses
Warkentin et al. 2008 [1]	40 F	Incision & drainage (groin cysts)	175 (falling)	59[a]	Arterial CVA; limb artery thrombosis	EIA+ SRA+[a]	Platelet count fell on admission for acute stroke from 297 to 175 (pre-heparin); the platelet count continued to fall after heparin was given; disabling stroke and limb amputation
Warkentin et al. 2008 [1]	24 F	Upper respiratory tract infection/ pneumonia	301	62[a]	None	EIA+ SRA+	Rapid-onset thrombocytopenia and anaphylactoid reaction after receiving LMWH (enoxaparin); heparin-dependent antibodies were detected (no heparin-independent reactivity)
Olah et al. 2012 [5]	64 F	Staphylococcal infection	259	86[a]	Skin necrosis, venous limb gangrene	EIA+ PaGIA+ FCAT+	Rapid-onset thrombocytopenia and venous limb gangrene affecting left-upper and left-lower limbs, as well as skin necrosis at enoxaparin injection site
Perrin et al. 2012 [6]	80 M	No precipitant	231	54[a]	DVT, PE	EIA+ PAT+ SRA+	Presented with DVT/PE and normal platelet count; rapid-onset thrombocytopenia when UFH and LMWH were given
Greinacher. 2014 [9]	31 F	Viral illness	31	15[a]	CVT, DVT	EIA+ HIPA+[a]	Post-viral CVT and thrombocytopenia; death secondary to cerebral infarction;
Okata et al. 2015 [10]	70 M	No precipitant	212	91[a]	CVT, DVT	EIA+ FCAT+	Patient presented with CST; developed abrupt platelet count fall with UFH treatment; DVT identified shortly following admission
Faille et al. 2017 [15]	62 M	IgG1κ MGUS	80	NR[a]	CVT	EIA+ HIPA+[a]	"cerebral thrombophlebitis" and thrombocytopenia on presentation; HIT antibodies with heparin-independent reactivity found in blood sample obtained prior to heparin treatment
Irani et al. 2018 [18]	30 M	No precipitant	84	41[a]	CVA, limb artery	EIA+ PEA+ SRA+[a]	Patient presented with acute stroke and developed limb artery thrombosis after LMWH heparin treatment; rapid increase in platelet count with high-dose IVIG
Moores et al. 2020 [23]	26 M	Viral illness	38	24 (no fall on heparin	CVT	EIA+ SRA+[a]	Post-viral CVT and thrombocytopenia; platelet count fell from 38 (admission value) to 24 (nadir value, pre-heparin); full recovery on fondaparinux anticoagulation

Abbr.: CVA, cerebral vascular accident; CVT, cerebral venous (sinus) thrombosis; DVT, deep-vein thrombosis; EIA, enzyme-immunoassay; FCAT, flow cytometry (platelet) activation test; HIPA, heparin-induced platelet activation test; IVIG, (high-dose) intravenous immunoglobulin; LMWH, low-molecular-weight heparin; MGUS, monoclonal gammopathy of unknown significance; NR, not reported; PaGIA, particle gel immunoassay; PAT, platelet aggregation test; PE, pulmonary embolism; PEA, P-selectin expression assay; SRA, serotonin-release assay; UFH, unfractionated heparin.

[a] Serum-induced platelet activation was observed in the absence of heparin.

4. Comparing classic HIT with aHIT (including spontaneous HIT syndrome)

Table 3 compares "classic" with aHIT; spontaneous HIT syndrome is defined as a subtype of aHIT in which proximate heparin is not implicated. In general, aHIT disorders—including spontaneous HIT syndrome—are associated with atypical features such as severe and persisting thrombocytopenia, unusual thromboses (including higher risk of microthrombosis), and high frequency of overt DIC. Special treatment considerations for spontaneous HIT syndrome are included in the next section.

5. Treatment considerations

The principles of treatment include achieving effective anticoagulation and interrupting Fc receptor-mediated platelet activation using high-dose intravenous immunoglobulin (IVIG). Pitfalls include unusually severe thrombotic events refractory to treatment, including the phenomenon of (activated) partial thromboplastin time (aPTT) confounding, as well as avoiding prothrombotic factors, e.g., inferior vena cava (IVC) insertion.

5.1. Anticoagulation

It is unknown whether heparin (or LMWH) is safe and effective for treating spontaneous HIT syndrome. Given the similarities to HIT, anticoagulation with non-heparin anticoagulation is usually given once a diagnosis of spontaneous HIT syndrome is strongly suspected or confirmed. One patient with post-orthopedic surgery spontaneous HIT had clinical and serological evidence of cross-reactivity with fondaparinux (i.e., antibody-induced platelet activation was enhanced in the presence of fondaparinux) [16]. Many patients who received argatroban developed new, progressive, or recurrent thrombosis, perhaps due to "aPTT confounding."

5.2. aPTT confounding

Patients with aHIT disorders typically have DIC, which can result in prolongation of the aPTT. This results in systemic underdosing of aPTT-monitored therapy, such as the direct thrombin inhibitors (DTIs), argatroban and bivalirudin. DTIs cause a non-proportional prolongation of the aPTT when Vitamin K dependent clotting factors are decreased [112,113]. Table 2 shows that at least 5 patients with post-TKA spontaneous HIT syndrome developed thrombotic events during DTI therapy (Fig. 4) [3,4,13,16].

5.3. High-dose intravenous immunoglobulin

High-dose IVIG is reported to be safe and effective for the treatment of severe autoimmune HIT: for review [80]. This conclusion is based upon in vitro data (namely, marked inhibition of platelet activation by HIT antibodies in the presence of IVIG), as well as favourable clinical experience, including in patients with spontaneous HIT syndrome [18,20]. Given that thrombocytopenia can persist for several weeks, we recommend use of IVIG (1 g/kg body weight for two consecutive days, with option for third dose of 0.5–1.0 g/kg depending on response).

5.4. Avoiding prothrombotic risk factors

Inferior vena cava (IVC) filters should not be placed in patients with severe HIT or aHIT, because of the high risk of contributing to progressive lower-limb venous thrombosis, including venous limb gangrene [3,21]. Further, in the absence of bleeding, transfusions of platelets should probably be minimized.

5.5. Is future heparin exposure safe? Can a second knee replacement be performed?

To our knowledge, there are no reported cases of patients who have recovered from spontaneous HIT syndrome and who have subsequently been challenged with heparin. Further, there are no reported cases of post-orthopedic surgery spontaneous HIT syndrome in which repeat orthopedic surgery has been reported. However, one of us (TEW) was contacted by a physician who asked about this possibility. A patient was described who was believed to have developed post-TKA spontaneous HIT syndrome and who—post-recovery—is under consideration for contralateral TKA. This represents an imponderable scenario where the risk of recurrent HIT is possible, but not definite (given analogies with known repeat heparin exposure for cardiac and vascular surgery in patients with a prior history of HIT [114]); if repeat surgery is performed, postoperative anticoagulation should be given with a DOAC, with daily platelet count monitoring until day 10. Then, if an otherwise unexplained platelet count fall occurs in the HIT "window" (between postoperative days 5 and 10), therapeutic-dose anticoagulation and high-

Table 3
Comparison of classic HIT and autoimmune HIT (aHIT), including spontaneous HIT syndrome.

Features	Classic HIT	Autoimmune HIT (aHIT) (triggered by heparin)	Spontaneous HIT syndrome (aHIT that is not triggered by heparin)
Relation to proximate heparin	Onset 5–10 days after starting heparin, with platelet count fall usually occurring while on heparin	Onset 5–10 days after immunizing exposure to heparin; can present after heparin has been stopped	No proximate heparin; onset 5–10 days after total knee replacement or preceding infection (if present)
Severity of thrombocytopenia	Often, mild to moderate	Often severe	Often severe
Duration of thrombocytopenia	Rapid platelet count recovery after stopping heparin (median, 4 days)	Thrombocytopenia often persists >1 week despite stopping heparin	Thrombocytopenia can persist for several weeks
Disseminated intravascular coagulation (DIC)	Sometimes	Often[a]	Often[a]
Thrombosis	Wide spectrum, usually macrovascular (venous > arterial)	Wide spectrum, usually macrovascular (venous > arterial); higher frequency of microvascular thrombosis	Wide spectrum, usually macrovascular (venous > arterial); higher frequency of stroke (CVT, arterial) in "medical" variant; adrenal hemorrhage/necrosis in post-TKA variant
PF4-dependent EIAs	Usually, moderate to strong positive	Usually strong-positive	Usually strong-positive
Washed platelet activation assay	Positive in the presence of heparin	Positive in both the presence and absence of heparin	Positive in both the presence and absence of heparin
Treatment	Non-heparin anticoagulation	Non-heparin anticoagulation[a]; consider high-dose IVIG	Non-heparin anticoagulation[a]; consider high-dose IVIG

Abbr.: CVT, cerebral venous (sinus) thrombosis; HIT, heparin-induced thrombocytopenia; IVIG, intravenous immune globulin; TKA, total knee arthroplasty.
[a] DIC in aHIT disorders is associated with increased risk of treatment failure with aPTT-adjusted non-heparin anticoagulants, such as argatroban and bivalirudin, perhaps as a result of "aPTT confounding".

dose IVIG could be immediately begun.

6. Vaccine-induced immune thrombotic thrombocytopenia

Very recently, two adenoviral vector vaccines, ChAdOx1 nCov-19 (AstraZeneca) and Ad26.COV2·S (Johnson & Johnson/Janssen), have been implicated in a rare complication, "vaccine-induced immune thrombotic thrombocytopenia" [115–119]. The clinical picture is distinct and strongly HIT-mimicking, i.e., patients developed unusual and severe thrombotic events (most often, CVT; also, splanchnic vein thrombosis) beginning between 5 and 30 days post-vaccination. When thrombosis occurrence prompts blood testing, moderate to severe thrombocytopenia is observed. Most patients have laboratory markers of overt DIC. Most affected patients are females of relatively young age (between 20s through 50s), but whether this reflects a particular predisposition to this adverse effect or rather the vaccinated population (hospital workers) is unclear. Serologically, these patients test strongly positive in PF4-dependent EIAs (particularly, the commercial PF4/PVS EIA); interestingly, rapid assays for HIT are negative. Further, patient serum contains strongly positive platelet-activating antibodies that are maximally reactive in the presence of PF4, rather than heparin. The standard serotonin-release assay (SRA) sometimes yields negative results. It therefore appears the adenoviral vector vaccines are able somehow to trigger a highly prothrombotic HIT-mimicking disorder that targets PF4.

Based on the concepts described in this review, this novel vaccine-induced disorder appears to be a hybrid of post-TKA spontaneous HIT syndrome (with a clear temporal relationship after the inciting TKA, and a high frequency of splanchnic or adrenal vein thrombosis), and "medical" spontaneous HIT syndrome (with a proximate infectious/inflammatory trigger in most cases and a high frequency of cerebral infarction, especially CVT). As seen in aHIT disorders, treatment of VITT with high-dose IVIG appears to increase platelet counts and decrease hypercoagulability, at least in some patients [120]. Elucidating the pathophysiological basis of newly recognized VITT may provide important insights into the concept of "spontaneous HIT syndrome" more generally. However, we recognize that VITT is an emerging vaccine-induced disorder, and further clinical and laboratory data will be needed to ascertain more clearly its relationship to other aHIT disorders.

CRediT authorship contribution statement

Theodore E. Warkentin wrote the first draft of the paper. Andreas Greinacher contributed several concepts and revised the paper. We acknowledge the assistance of Ms. Jo-Ann I. Sheppard in contributing to the literature review and assisting in the preparation of the figures.

Declaration of competing interest

TEW has received royalties from Informa (Taylor & Francis) and lecture honoraria from Alexion Canada and Instrumentation Laboratory; has provided consulting services to Aspen Canada, Aspen Global, Bayer, CSL Behring, Ergomed, Instrumentation Laboratory and Octapharma; has received research funding from Instrumentation Laboratory; and has provided expert witness testimony relating to HIT and non-HIT thrombocytopenic and coagulopathic disorders.

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