

Clinical picture of heparin-induced thrombocytopenia (HIT) and its differentiation from non-HIT thrombocytopenia

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Summary

HIT is an acquired antibody-mediated disorder strongly associated with thrombosis, including microthrombosis secondary to disseminated intravascular dissemination (DIC). The clinical features of HIT are reviewed from the perspective of the 4Ts scoring system for HIT, which emphasises its characteristic timing of onset of thrombocytopenia. HIT antibodies recognize multimolecular complexes of platelet factor 4 (PF4)/heparin. However, a subset of HIT sera recognise PF4 bound to platelet chondroitin sulfate; these antibodies activate platelets *in vitro* and *in vivo* even in the absence of heparin, thus explaining: delayed-onset HIT (where HIT begins or worsens after stopping heparin); persisting HIT (where HIT takes several weeks to recover); spontaneous HIT syndrome (a disorder clinically and serologically resembling HIT but without proximate heparin exposure); and fondaparinux-associated HIT (four distinct syndromes featuring thrombocytopenia that begins or worsens during treatment with fondaparinux), with a new patient case presented with ongoing thrombocytopenia (and

fatal haemorrhage) during treatment of HIT with fondaparinux, with fondaparinux-dependent platelet activation induced by patient serum ("fondaparinux cross-reactivity"). Ironically, despite existence of fondaparinux-associated HIT, this pentasaccharide anticoagulant is a frequent treatment for HIT (including one used by the author). HIT can be confused with other disorders, including those with a) timing similar to HIT (e.g. abciximab-associated thrombocytopenia of delayed-onset); b) combined thrombocytopenia/thrombosis (e.g. symmetrical peripheral gangrene secondary to acute DIC and shock liver); and c) both timing of onset and thrombosis (e.g. warfarin-associated venous limb gangrene complicating cancer-associated DIC). By understanding clinical and pathophysiological similarities and differences between HIT and non-HIT mimicking disorders, the clinician is better able to make the correct diagnosis.

Keywords

Heparin-induced thrombocytopenia, platelet activation, thrombosis

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Introduction

Heparin-induced thrombocytopenia (HIT) is an oftentimes dramatic disorder where the patient can develop life- and limb-threatening thrombotic events resulting from an immune response usually triggered by commonly prescribed anticoagulants: unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or the sulfated pentasaccharide, fondaparinux (1). The pathophysiological aspects of HIT help explain its characteristic clinical picture (2), which this article highlights. I also discuss HIT-mimicking disorders (3).

In some respects, HIT can be considered an autoimmune disorder (4). After all, (pharmacological) heparin is derived from animal sources (e.g. porcine intestinal mucosa), and resembles in its physicochemical properties (endogenous) heparin found in human mast cells (5). Moreover, the mechanism of action of pharmacological heparin – namely to catalyse by approximately 1000 times the covalent binding, and resulting inhibition of, thrombin

(and other serine proteases, e.g. factor Xa, factor IXa) to anti-thrombin (6) – parallels that of an endogenous endothelial-bound glycosaminoglycan, heparan sulfate (a low-sulfated form of heparin) (7).

The autoimmune nature of HIT is underscored by other considerations. First, heparin does not form by itself the antigen(s) of HIT; rather, heparin leads to antigen formation when it binds to a homotetrameric 32-kDa protein, platelet factor 4 (PF4) (8–11). Essentially, both constituents of HIT antigens – cationic PF4 and anionic heparin – are "self" molecules. Second, on rare occasions, a disorder clinically and serologically indistinguishable from HIT – so-called "spontaneous HIT syndrome" – can occur in patients without any history of proximate heparin exposure. Third, HIT antibodies are remarkably transient, usually remaining detectable for only a few weeks or months following an episode of HIT (12), suggesting a timed de-escalation of an autoimmune response that could have a biological basis in an evolutionarily relevant antimicrobial immune response (13).

Clinical features of HIT: 4Ts perspective

The clinical features of HIT can be considered from the perspective of the 4Ts, a clinical scoring system for evaluating clinical probability of HIT (14–16). This system assesses four parameters, **T**hrombocytopenia, **T**iming (of onset of thrombocytopenia or thrombosis), **T**hrombosis, and **o**ther (causes of thrombocytopenia). Each parameter is given a score of 2, 1, or 0 points, depending on whether the parameter strongly fits HIT (2 points) or argues against HIT (0 points), with a single point for features that are less clear or when data are missing. ► Figure 1 lists one version of the 4Ts (17) that recently underwent prospective evaluation (18).

Thrombocytopenia

A large magnitude fall in the platelet count (>50%) that does not reach very low levels (i.e. remains at $20 \times 10^9/l$ or higher) is the

platelet count profile most commonly encountered with HIT (19–21). Note that the "baseline" platelet count is not necessarily the pre-heparin platelet count, but rather the highest platelet count that immediately precedes the putative HIT-related platelet count fall (20). For example, consider the patient who has a preoperative platelet count of $200 \times 10^9/l$, and who receives 40,000 units of UFH intraoperatively during cardiac surgery. This patient might well develop a post-surgical platelet count fall to a near-term nadir value on postoperative day 2 of $\sim 100 \times 10^9/l$, after which the platelet count should rise to $\sim 350 \times 10^9/l$ by day 7, with the further expectation of a continuing rise to $\sim 600 \times 10^9/l$ by postoperative day 14 (as postoperative thrombocytosis typically evinces counts that are 2-3 times preoperative baseline, peaking about day 14) (22). However, if the platelet count were to fall from 350 (day 7) to 275 (day 8), and then continue to fall to 175 by day 10, this would represent a 50% fall in platelet count from the postoperative peak (i.e. 50% fall from 350 to $175 \times 10^9/l$), even though the magnitude

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall. (Select only 1 option)	<input type="radio"/> >50% platelet fall AND a nadir of ≥ 20 AND no surgery within preceding 3 days	<input type="radio"/> >50% platelet fall BUT surgery within preceding 3 days OR <input type="radio"/> any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (e.g., 30-50% platelet fall or nadir 10-19)	<input type="radio"/> <30% platelet fall <input type="radio"/> any platelet fall with nadir <10
Timing (of platelet count fall or thrombosis*) Day 0 = first day of most recent heparin exposure (Select only 1 option)	<input type="radio"/> platelet fall day 5-10 after start of heparin <input type="radio"/> platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days	<input type="radio"/> consistent with platelet fall day 5-10 but not clear (e.g., missing counts) <input type="radio"/> platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 days <input type="radio"/> platelet fall after day 10	<input type="radio"/> platelet fall \leq day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) (Select only 1 option)	<input type="radio"/> confirmed new thrombosis (venous or arterial) <input type="radio"/> skin necrosis at injection site <input type="radio"/> anaphylactoid reaction to IV heparin bolus <input type="radio"/> adrenal hemorrhage	<input type="radio"/> recurrent venous thrombosis in a patient receiving therapeutic anticoagulants <input type="radio"/> suspected thrombosis (awaiting confirmation with imaging) <input type="radio"/> erythematous skin lesions at heparin injection sites	<input type="radio"/> thrombosis not suspected
oTher cause for thrombocytopenia** (Select only 1 option)	<input type="radio"/> no alternative explanation for platelet fall is evident	Possible other cause is evident: <input type="radio"/> sepsis without proven microbial source <input type="radio"/> thrombocytopenia associated with initiation of ventilator <input type="radio"/> other:	Probable other cause present: <input type="radio"/> within 72 hours of surgery <input type="radio"/> confirmed bacteremia/fungemia <input type="radio"/> chemotherapy or radiation within past 20 days <input type="radio"/> DIC due to non-HIT cause <input type="radio"/> posttransfusion purpura (PTP) <input type="radio"/> thrombotic thrombocytopenic purpura (TTP) <input type="radio"/> platelet count < 20 AND given a drug implicated in causing D-ITP (see list) <input type="radio"/> non-necrotizing skin lesions at LMWH injection sites (presumed DTH) <input type="radio"/> other:
Drugs implicated in drug-induced immune thrombocytopenia (D-ITP) Relatively Common: glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban); quinidine, quinidine, sulfa antibiotics, carbamazepine, vancomycin Less Common: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: this is a partial list.			

Figure 1: 4Ts scoring system. * In some circumstances, it may be appropriate to judge 'Timing' based upon clinical sequelae, such as timing of onset of heparin-induced skin lesions. ** Usually, 'oTher' scores "0 points" if thrombocytopenia is not present. However, it may be appropriate to judge 'oTher' based upon clinical sequelae, such as whether heparin-induced skin

lesions are necrotizing (2 points, i.e. a non-HIT explanation is unlikely) or non-necrotizing (0 points, i.e. a non-HIT explanation is likely). DIC, disseminated intravascular coagulation; DTH, delayed-type hypersensitivity; IV, intravenous; LMWH, low-molecular-weight heparin. Reprinted with permission (17).

of fall based on the preoperative platelet count (from 200 to $175 \times 10^9/l$, i.e. a 12.5% platelet count fall) would seem trivial.

HIT represents a platelet activation syndrome, as HIT antibodies activate platelets through their Fc γ IIa receptors (23), a feature that helps explain why HIT does not usually cause very severe thrombocytopenia. In contrast, classic drug-induced immune thrombocytopenia (e.g. secondary to quinine or vancomycin) usually produces severe thrombocytopenia ($<20 \times 10^9/l$), because each and every platelet is the target of the drug-dependent antibody (24). This differs from platelet activation, or "consumptive", disorders such as disseminated intravascular coagulation (DIC) or HIT. Here, there usually is moderate degree of thrombocytopenia, as the proportion of platelets activated by any given agonist stimulus varies greatly depending on the strength of the stimulus. A platelet count fall that is only moderate (30–49.9%), or that produces severe thrombocytopenia (nadir, $10\text{--}19 \times 10^9/l$) scores only 1 point in the 4Ts, whereas a trivial platelet count fall ($<30\%$) or that attains profoundly reduced nadir ($<10 \times 10^9/l$) scores 0 points.

However, severe HIT with associated DIC can (rarely) produce very severe thrombocytopenia; my personal "record" is a platelet count nadir of $2 \times 10^9/l$ post-cardiac surgery, with thrombocytopenia onset on day 5 (2 points) and progressive bilateral lower-limb microvascular ischaemia (2 points) without another apparent cause (2 points) (25). Despite scoring 0 points for Thrombocytopenia, this patient was judged "high probability" for HIT (6 points). At the other extreme, I diagnosed HIT in a patient with a trivial (13%) fall in platelet count (0 points) that began on day 6 (2 points) with simultaneous development of necrotising skin lesions at heparin injection sites and abdominal pain secondary to adrenal haemorrhagic necrosis (2 points) without another apparent cause (2 points) (26). This latter patient also scored high probability (6 points) in the 4Ts despite having no significant platelet count fall.

Timing

This is the most important 4Ts criterion, as the characteristic timing of onset of HIT (day 5 to 10 for the beginning of the HIT-related platelet count fall [day 0 = heparin exposure]) reflects the immune pathogenesis of HIT. HIT antibodies can be detected as early as day 4 post-heparin exposure (27, 28), with the earliest onset of HIT occurring one day later. (Due to rounding, a platelet count fall precisely timed to day 4.51 would be classified as day 5 (12); although a platelet count fall that begins as early as day 4.6 or day 4.7 (rounding up to day 5) can indicate HIT, in my experience, an onset of thrombocytopenia rounded to day 4 (i.e. beginning between days 3.51 and 4.49) argues against a diagnosis of HIT, as illustrated later when a case of delayed-onset abciximab-induced thrombocytopenia is presented as a HIT-mimicking disorder).

HIT antibodies are transient, with time to antibody non-detectability after recovery from HIT ranging from a median of 40 to 100 days, depending on the assay performed (12). We have even reported four HIT patients (27, 29) whose platelet counts recovered despite continued heparin administration, and in the two patients

where serial blood samples were available we proved that HIT antibody levels were declining despite heparin continuation (27). The importance of HIT antibody transience is that it explains the characteristic association between "rapid-onset HIT" and recent exposure to heparin (12, 30): in the 4Ts, an abrupt and unexpected decline in platelet count (within 24 hours [h]) upon starting heparin strongly supports a diagnosis of HIT if the patient was exposed to heparin within the last 30 days (2 points), although less so if the previous exposure occurred within the previous 31 to 100 days (1 point). If preceding exposure to heparin occurred >100 days ago, then the likelihood of an abrupt heparin-associated fall in platelet count being due to HIT is low (0 points), because of antibody transience.

There is no apparent immune memory for HIT (12, 28, 30, 31). In other words, the dichotomous profile described above, in which either a new heparin-induced immunisation leads to a platelet count fall that begins within the characteristic day 5 to 10 "window" (only occasionally later), or that occurs abruptly (within 1 day) upon heparin re-exposure in a patient who had a recent exposure, represents the only two temporal patterns reported in HIT. Even if a patient has had numerous previous heparin exposures, or even has a previous history of proven HIT (31), onset of HIT does not occur before day 5, irrespective of whether *de novo* generation or regeneration of HIT antibodies occurs.

There is a disorder called "delayed-onset HIT" (32). Despite its name, the timing of delayed-onset HIT resembles that of "typical-onset HIT", i.e. the platelet count fall begins 5–10 days after the immunising exposure to heparin. Thus, there really is not any "delay" in onset of HIT (the term "delayed-onset" was intended to help the clinician remember that HIT can begin several days after all heparin has been stopped). In recent years, the concept of delayed-onset HIT has expanded to include patients whose HIT worsens even after stopping heparin (25, 33). As discussed later, delayed-onset HIT can occur when HIT antibodies strongly activate platelets even in the absence of pharmacological heparin, both *in vitro* and *in vivo*.

HIT-associated thrombosis, including venous limb gangrene

Thrombosis is the clinical hallmark of HIT: in my experience, most patients with serologically-confirmed HIT develop thrombosis (34). This is not a referral bias, as prospective studies have also found HIT-associated thrombosis rates of $>50\%$ (19, 20, 29). One analysis (35) reported a 55.6% frequency of HIT-associated thrombosis vs a 4.6% frequency in (non-HIT) controls, i.e. a relative risk (RR)=12.0 (95% confidence interval [CI], 7.0–20.6; $p<0.0001$). Likelihood of HIT is higher with certain types of thrombosis, e.g. bilateral lower limb DVT (RR=18.0; $p=0.0097$); pulmonary embolism (RR=35.9; $p=0.0040$) (35).

Venous, arterial, and microvascular thrombosis can occur (2). The first reports on HIT emphasised arterial thrombosis, and HIT was once called the "white clot syndrome" based on the appearance of the platelet-rich arterial thrombi removed at surgical embolectomy (36). However, it is now accepted that venous

thrombosis – lower-limb deep-vein thrombosis (DVT) with or without pulmonary embolism (19, 20), upper-limb DVT at a central venous catheter insertion site (37), splanchnic vein thrombosis (adrenal, mesenteric) (2, 38), and cerebral vein/dural sinus thrombosis (39) – are strongly associated with HIT, and indeed predominate over arterial thrombosis (venous:arterial ratio, ~4:1) (34). Adrenal vein thrombosis presents important clinical pearls: occurring in 2–3% of HIT patients, unilateral adrenal vein thrombosis presents as abdominal, flank, or chest pain due to associated adrenal haemorrhage; however, when adrenal haemorrhagic necrosis is bilateral, the patient can develop acute and chronic adrenal failure, and corticosteroid therapy can be life-saving (2, 38).

HIT-associated DVT can progress to venous limb gangrene, especially during vitamin K antagonist (VKA) therapy (33, 40). Although ~80–90% of cases of HIT-associated venous limb gangrene are VKA-associated, severe HIT-associated DIC can also cause this complication (41). HIT patients with VKA-associated venous limb gangrene usually exhibit a supratherapeutic INR (>4.0); the high INR is a surrogate marker for critically reduced protein C activity explained by parallel severe reduction in factor VII. As discussed later, there is a parallel syndrome of VKA-induced venous limb ischaemia/gangrene complicating cancer-associated DIC (33), as well as a novel syndrome of symmetrical peripheral gangrene in the setting of cardiogenic or septic shock complicated by acute or chronic liver injury (33).

Other complications of HIT include anaphylactoid reactions (e.g. fever/chills, dyspnea, transient global amnesia, cardiopulmonary arrest) that occur 5–30 minutes post-intravenous heparin bolus (2, 42, 43) or up to 2 h post-subcutaneous injection of LMWH (44), necrotising skin lesions at heparin injection sites (26) and, rarely, skin necrosis at non-injection sites (45).

Other

The fourth criterion, *o*Ther, assesses whether another potential explanation for thrombocytopenia is definitely present (e.g. proven bacteraemia), or possible (e.g. possible picture of septicaemia), or unlikely (no apparent explanation despite a careful clinical and laboratory evaluation). The fourth "T" is the most subjective, and requires assessor clinical acumen. For example, as discussed later, there exist several HIT-mimicking syndromes that warrant a score of zero points, assuming sufficient clinician awareness. Efforts have been made to standardize the 4th criterion, "*o*Ther" (► Figure 1) (17, 46).

Heparin re-exposure despite previous HIT

The striking temporal features of heparin-induced immunisation, antibody transience, and lack of immune memory have implications for heparin re-exposure in patients with a previous history of HIT. For example, once platelet-activating HIT antibodies are no longer present, heparin can be given without risk for triggering rapid-onset HIT (31, 47). Remarkably, the risk of regenerating

HIT antibodies does not seem greater than that expected for a given heparin exposure (although the probability of forming anti-PF4/heparin antibodies with platelet-activating properties appears relatively high) (47), so deliberate heparin exposure is usually restricted to the perioperative period. Heparin re-exposure also appears safe in patients with previous HIT who remain immunoassay-positive but without detectable platelet-activating antibodies (31, 47).

Despite the apparent safety of short-term heparin re-exposure (usually, to permit cardiac or vascular surgery), there is a possibility that recurrent HIT could be triggered, beginning at least five days after re-exposure, even if further postoperative heparin is not given. Thus, platelet count monitoring should be performed for up to 10 days post-reexposure. Recurrence of HIT in this setting would reflect formation of highly pathogenic delayed-onset (or autoimmune) HIT antibodies (31, 47).

Syndromes of autoimmune HIT: delayed-onset, persisting, spontaneous, and fondaparinux-associated HIT

There are at least four clinical presentations of HIT associated with anti-PF4/heparin antibodies that activate platelet strongly even in the absence of pharmacological heparin, as assessed in washed platelet activation assays such as the platelet serotonin-release assay (SRA) or heparin-induced platelet activation assay. These include: delayed-onset HIT, persisting HIT, spontaneous HIT syndrome, and fondaparinux-associated HIT. HIT antibody-induced platelet activation occurs without heparin in these disorders because the HIT antibodies recognise PF4 bound to platelet-associated chondroitin sulfate (48).

Delayed-onset HIT

As noted earlier, delayed-onset HIT indicates HIT that begins or worsens despite stopping heparin (2, 25, 32, 33). Patients' HIT antibodies activate platelets in the absence of heparin, with activation inhibited by high heparin (100 IU/ml) and by Fcγ receptor-blocking antibodies (25, 32). These patients have a higher frequency of HIT-associated DIC, lower platelet count nadirs, and greater likelihood of severe sequelae, including venous limb gangrene (25, 41). Sometimes, heparin "flushes" are the only proximate heparin exposure identified (49).

Persisting HIT

After stopping heparin, platelet count recovery in HIT occurs within ~4 days in about 50% of patients, and within a week in 90% (2); however, ~1% of patients have thrombocytopenia that persists for at least one month (50). ► Figure 2 illustrates one such patient with "persisting HIT" (50). Remarkably, the slowly recovering platelet counts corresponded inversely to the declining strength of serum-induced platelet activation (percent serotonin-release at 0 U/ml UFH ["buffer control"]) (50).

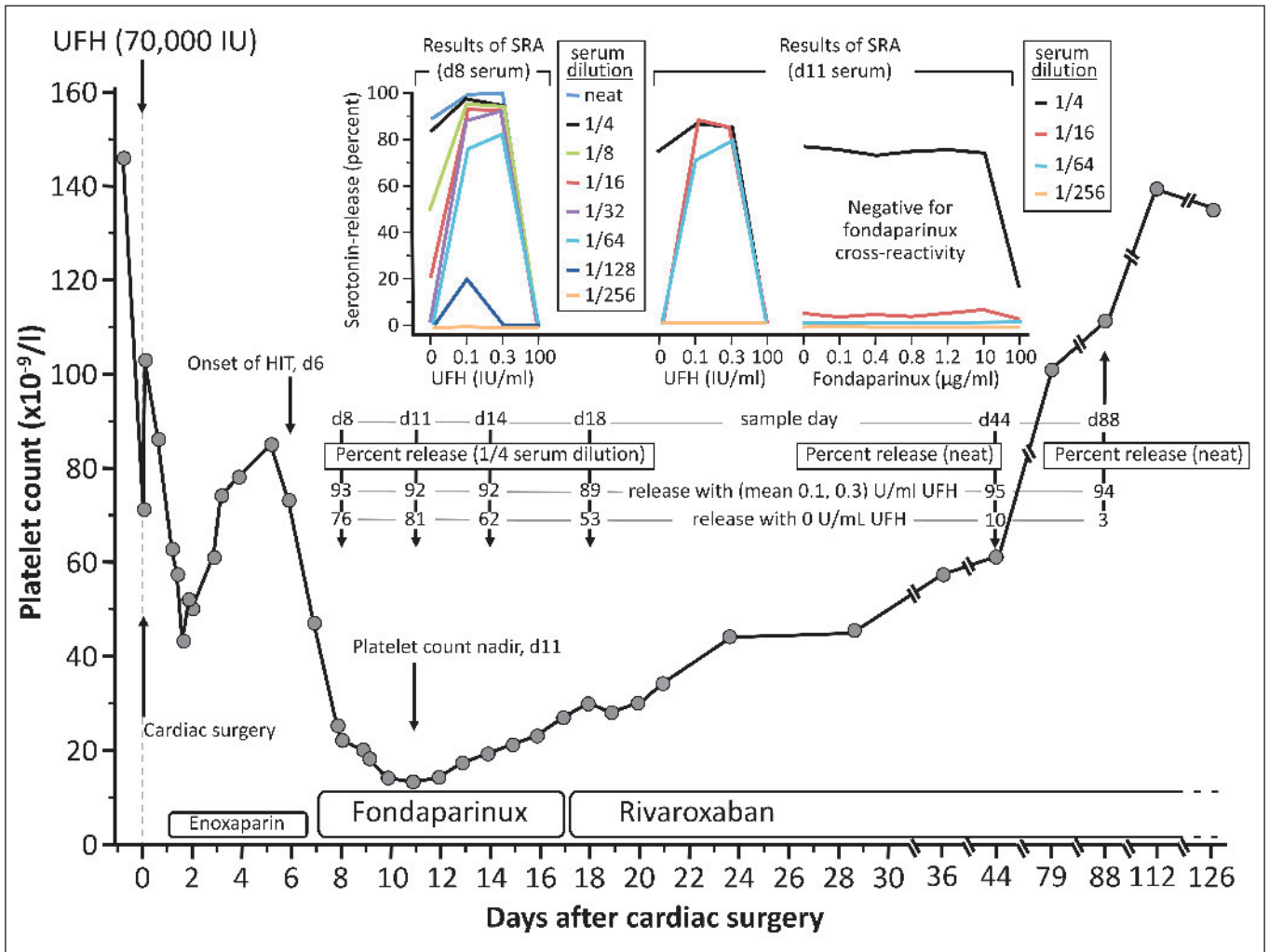


Figure 2: Delayed-onset and persisting HIT post-cardiac surgery. Onset of HIT occurred on postoperative day 6. Patient serum obtained on day 8 (d8) and diluted as much as 1/64 tested strongly positive (>80% serotonin-release) for HIT antibodies in the SRA. Patient serum obtained on d11—when thrombocytopenia was maximal (platelet count nadir, $13 \times 10^9/l$)—did not show evidence of fondaparinux cross-reactivity: despite strong heparin-dependent serotonin-release using patient serum diluted 1/16 and 1/64, no fondaparinux-dependent platelet activation was seen at

these serum concentrations. Also shown is percent serotonin-release induced by patient serum (samples obtained on days 8, 11, 14, 18, 44, and 88) in the presence of heparin (mean percent release at 0.1 and 0.3 IU/ml UFH), as well as in buffer control (0 IU/ml UFH). There is an inverse correlation between percent serotonin-release at 0 IU/ml heparin and the severity of thrombocytopenia. d, day; HIT, heparin-induced thrombocytopenia; IU, international units; UFH, unfractionated heparin. Reprinted with permission (50).

Spontaneous HIT syndrome

At least 12 patients have been reported with "spontaneous HIT syndrome" (38, 51–57). Their clinical picture (thrombocytopenia, thrombosis – including adrenal haemorrhages) and serological profile (positive PF4-dependent enzyme-immunoassay [EIA], positive SRA) indicates a diagnosis of HIT but without any (or recent) proximate heparin exposure. Patients typically come to medical attention because of thrombosis; unexplained thrombocytopenia triggers testing for HIT antibodies.

A large proportion of patients with spontaneous HIT syndrome had preceding orthopaedic surgery (usually, knee replacement) without heparin administration, perhaps implicating a heparin-like trigger (e.g. non-heparin glycosaminoglycans released

from cartilage). If such a post-surgical patient develops adrenal haemorrhagic necrosis while receiving a non-heparin anticoagulant (e.g. warfarin, rivaroxaban, apixaban), the "bleeding" event could be misattributed to the postoperative anticoagulant given (38). One group recently reported a high frequency of anti-PF4/heparin antibodies (but without HIT) in postorthopedic surgery patients who were not given heparin, with antibody frequency higher when mechanical thromboprophylaxis was applied (58).

Patients have also been reported who developed a clinical and serological picture of rapid-onset HIT upon heparin exposure, but without any plausible previous exposure to heparin (51, 59–61). These patients' HIT antibodies lack the serological feature of heparin-independent platelet activation.

Fondaparinux-associated HIT

Fondaparinux has a low frequency of *in-vitro* cross-reactivity with HIT antibodies (62) and a proven low *in vivo* cross-reactivity risk vis-a-vis UFH and LMWH (63). Indeed, fondaparinux is emerging as a common (64) and recommended (65) therapy of HIT. Case-series reporting its use have generally observed successful outcomes without apparent exacerbation of HIT (65–68).

Whether fondaparinux can cause HIT *de novo* or worsen the clinical course of HIT when used for its treatment is complex and controversial (69). As summarised in ►Table 1, there are at least four different syndromes of fondaparinux-associated HIT (50, 70–76), only one of which features fondaparinux as an "innocent bystander" (50,75). Interestingly, two patients reported with *de novo* fondaparinux-induced HIT had a previous remote history of HIT secondary to UFH (72) or LMWH (77), suggesting that platelet count monitoring for HIT should be performed if fondaparinux is given to a patient with previous HIT (72). However, because most of the patients with apparent *de novo* fondaparinux-induced HIT were post-knee replacement surgery (70, 72, 77) – a (relatively) common precipitant of spontaneous HIT syndrome (52, 53, 56, 57) – it remains uncertain whether fondaparinux itself, versus the surgery, was the true HIT trigger. An argument implicating fondaparinux is serological evidence for fondaparinux-dependent platelet activation, i.e. representative patient serum usually causes greater serotonin-release in the presence of fondaparinux than in buffer alone (71, 72).

Table 1: Four syndromes of fondaparinux-associated HIT.

Clinical and serological picture	Selected references
"Autoimmune" HIT antibodies are demonstrated	
<ul style="list-style-type: none"> HIT occurs with proximate exposure to fondaparinux alone, with demonstration of autoimmune HIT antibodies (serum with heparin-independent platelet activation, usually also exhibiting with "cross-reactivity" with fondaparinux) 	70*-72
<ul style="list-style-type: none"> HIT (triggered by proximate heparin) that begins or worsens during subsequent treatment with fondaparinux; <i>in vitro</i> cross-reactivity demonstrated with fondaparinux 	See Figure 3; 73**,74
<ul style="list-style-type: none"> HIT begins during use of fondaparinux with timing of onset of HIT consistent with proximate exposure to heparin; no <i>in vitro</i> cross-reactivity with fondaparinux ("innocent bystander") 	50,75
"Autoimmune" HIT antibodies are not demonstrated	
<ul style="list-style-type: none"> HIT antibodies (triggered by proximate heparin) that result in HIT when fondaparinux is subsequently administered; <i>in vitro</i> cross-reactivity demonstrated with fondaparinux 	76
*Fondaparinux-dependent serum-induced platelet activation for the patient reported in reference 70 was reported subsequently (71).	
**Fondaparinux-dependent serum-induced platelet activation was shown for patient 11 reported in reference 73 (the <i>in vitro</i> studies indicating fondaparinux cross-reactivity were shown in Fig. 1E in reference 71); this patient developed HIT due to dalteparin, but thrombocytopenia persisted and new thrombosis developed during subsequent treatment with fondaparinux.	

In my opinion, the possibility of *in vitro* (and corresponding *in vivo*) cross-reactivity of fondaparinux for HIT antibodies does not argue against the use of fondaparinux for treating HIT, for two reasons: a) the risk of *in vitro* cross-reactivity appears to be low (probably, 1% or less), and b) fondaparinux has numerous advantages for treating HIT over direct thrombin inhibitors, such as argatroban, which can fail because of issues such as systematic underdosing in patients with HIT-associated DIC (so-called "PTT confounding") (33, 65, 73, 78). Nonetheless, ►Figure 3 shows that fondaparinux treatment of HIT can occasionally fail as a result of *in vivo* cross-reactivity of HIT antibodies for fondaparinux.

HIT-mimicking syndromes

HIT-mimicking syndromes can be classified based upon: a) timing of onset of thrombocytopenia (e.g. post-transfusion purpura [PTP], delayed-onset abciximab-induced thrombocytopenia); b) combined thrombocytopenia and thrombosis (e.g. acute DIC/hepatic necrosis-limb necrosis syndrome); and c) both timing of thrombocytopenia and occurrence of thrombosis (e.g. VKA-induced venous limb ischaemia/gangrene complicating cancer-associated DIC (►Table 2).

Post-transfusion purpura

Several reports highlight confusion between PTP and HIT (79–81). PTP is characterised by severe thrombocytopenia associated with anti-platelet alloantigen immunisation triggered by exposure to blood product, usually at surgery. Thrombocytopenia begins 5–10 days post-surgery, and so resembles HIT temporally if postoperative heparin thromboprophylaxis is given. However, the platelet count nadir is lower than usually seen in HIT, thrombosis does not occur, and petechiae and other bleeding complications are characteristic.

Rapid-onset and delayed-onset abciximab-induced thrombocytopenia

Abciximab-induced immune thrombocytopenia usually occurs abruptly, within 4 h of administration (even in patients without previous exposure to this glycoprotein IIb/IIIa antagonist) (82). Since heparin and abciximab are usually coadministered during percutaneous coronary intervention (PCI), diagnostic confusion can occur. However, abrupt onset of severe thrombocytopenia (platelet count <20 × 10⁹/l) in this context usually points to abciximab.

►Figure 4 illustrates a case of moderate thrombocytopenia that began 3.5 days after exposure to UFH and abciximab during primary PCI (day 7 platelet count nadir = 57). The fibrin D-dimer was normal (264 µg/l; reference range, <500 µg/l), arguing against a hypercoagulability state such as HIT, and pointing rather to abciximab-induced immune thrombocytopenia of delayed-onset (83), a diagnosis supported by a negative SRA.

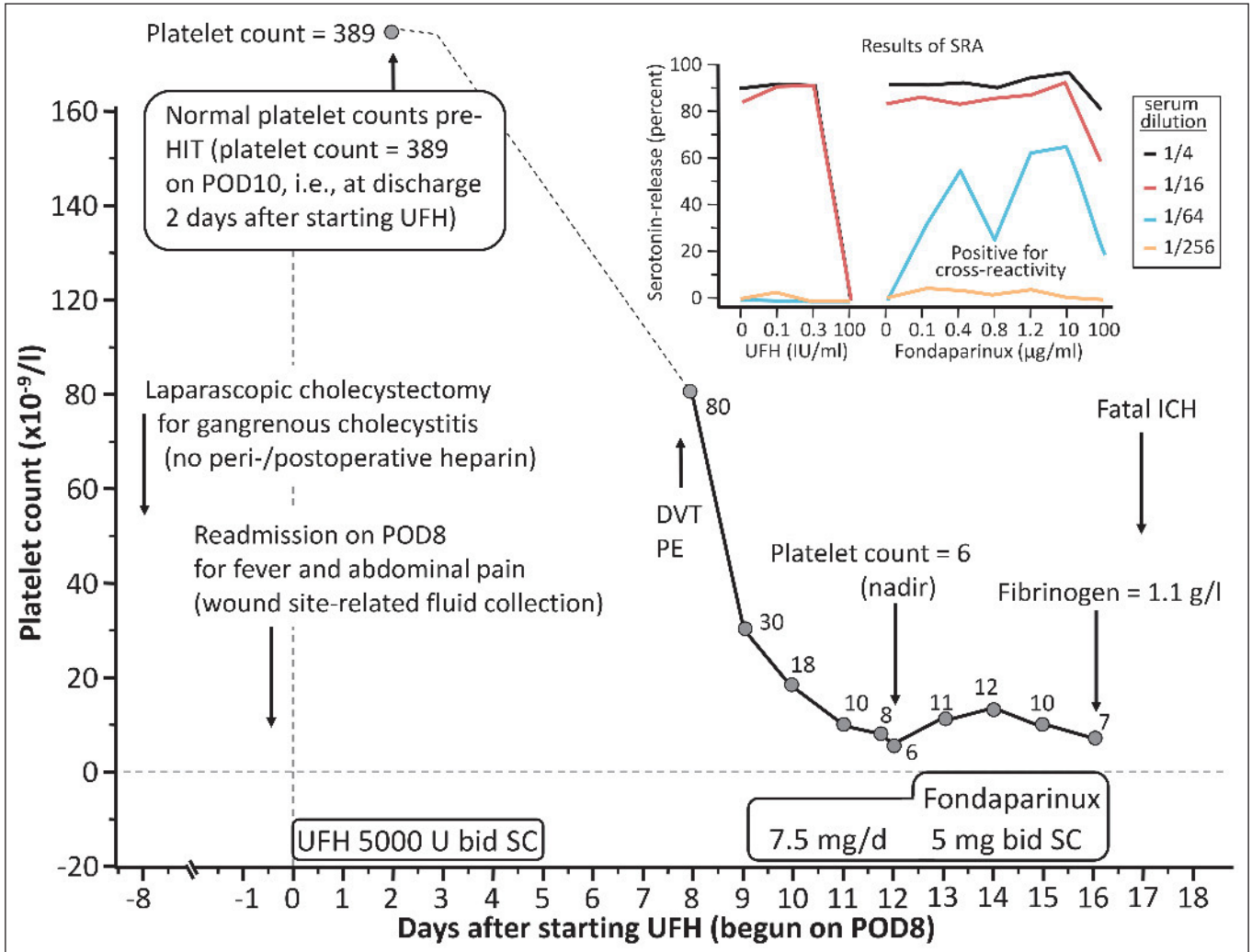


Figure 3: Patient with delayed-onset HIT and HIT-associated DVT/PE with subsequent failure of fondaparinux treatment of HIT: in vitro evidence for cross-reactivity of the HIT antibodies for fondaparinux. The inset ("Results of SRA") shows strong patient serum-induced platelet activation in the absence of heparin (>80% serotonin-release at 0 IU/ml UFH at 1/4 and 1/16 serum dilutions [final, 1/20 and 1/80 dilutions, respectively, as the McMaster SRA is performed with 20 µl serum in final 100 µl reaction mixture]). Cross-reactivity of patient serum for fondaparinux is shown at the

1/64 serum dilution (final, 1/320 dilution), in which serum-induced serotonin-release is enhanced (vs buffer control [0 IU/ml UFH]) in the presence of fondaparinux, 0.4 to 10 µg/ml [final]). The patient also had evidence of hypofibrinogenaemia secondary to HIT-associated DIC that persisted despite therapeutic-dose fondaparinux therapy. bid, twice-daily; DVT, deep-vein thrombosis; ICH, intracranial haemorrhage; IU, international units; PE, pulmonary embolism; POD, postoperative day; SC, subcutaneous; SRA, serotonin-release assay; U, units; UFH, unfractionated heparin.

Acute DIC/hepatic necrosis-limb necrosis syndrome

Ischaemic limb necrosis occurs in a small proportion of patients with DIC secondary to cardiogenic or septic shock (33). Recently, acute (33, 41, 84) or chronic (85) liver disease in the setting of acute DIC has been linked to microthrombosis and ischaemic limb gangrene despite presence of arterial pulses. This entity represents profoundly disturbed procoagulant-anticoagulant balance, i.e. uncontrolled thrombin generation (DIC secondary to shock) with natural anticoagulant depletion (protein C, antithrombin) exacerbated by hepatic dysfunction, with hypotension/vasopressor use predisposing to acral limb microthrombosis (33).

Cancer-associated venous limb gangrene

Cancer-associated venous limb gangrene is a HIT-mimicking disorder (86). The clinical picture includes: a) initial presentation with "idiopathic" DVT; b) onset of thrombocytopenia that begins after stopping an approximate one-week course of UFH or LMWH given for DVT; c) increase in the INR to supratherapeutic levels (median, 6.0) after completing heparin-VKA overlap; with d) metastatic cancer (usually adenocarcinoma) ultimately revealed to e) explain underlying DIC. These patients usually f) test negative (or weakly-positive) for HIT antibodies, and g) if heparin is restarted, the platelet count increases (thus pointing against a diagnosis of HIT). This syndrome of cancer-associated venous

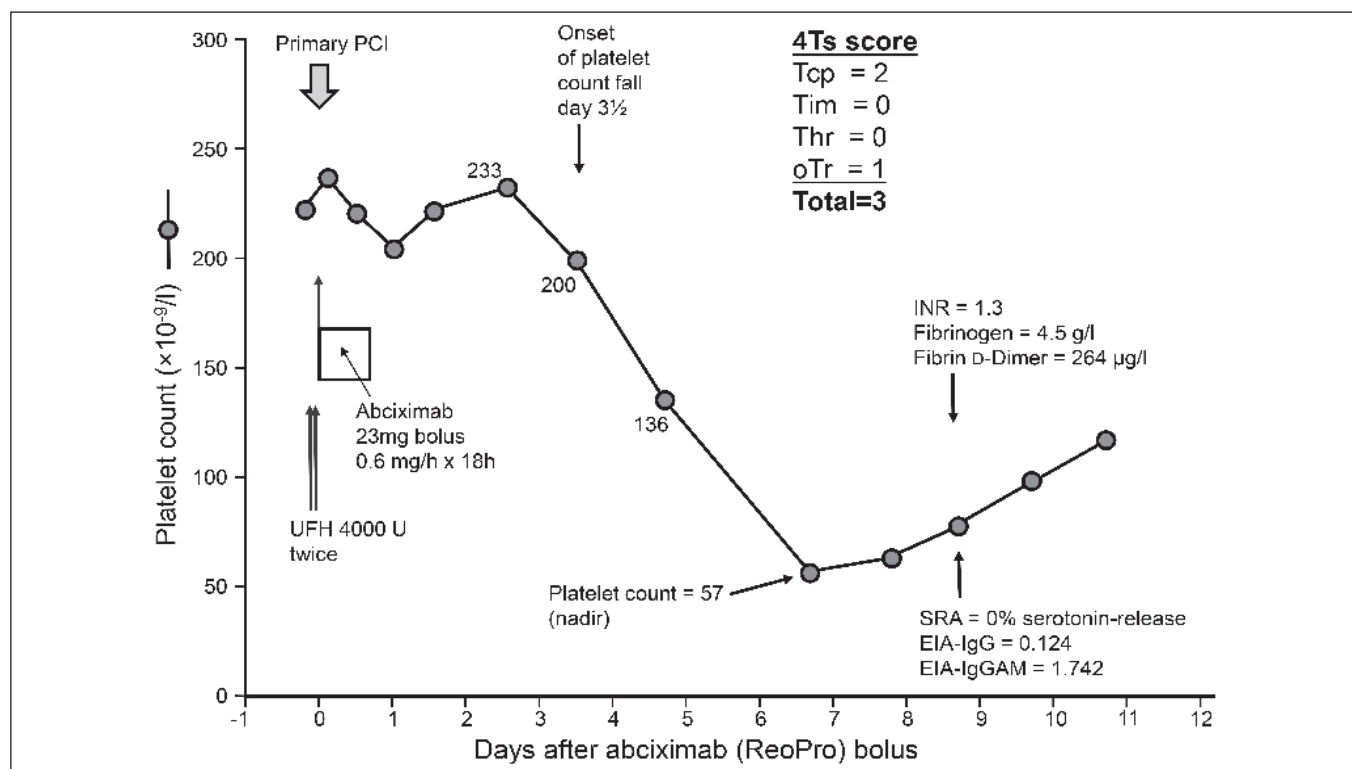


Figure 4: Patient with abciximab-induced thrombocytopenia of delayed-onset. A 71-year-old woman received UFH and abciximab for primary percutaneous coronary intervention (PCI). The platelet count began to fall 3.5 days after beginning abciximab (and 3.55 days after beginning UFH). The consulting haematologist suspected abciximab-induced thrombocytopenia based upon the normal fibrin d-dimer, a diagnosis supported by the negative serotonin-release assay (SRA), a test for platelet-activating HIT antibodies. Although the IgG-specific anti-PF4/heparin enzyme-immunoassay (EIA) was negative, a commercial polyspecific EIA

(EIA-IgGAM) that detects anti-PF4/heparin antibodies of IgG, IgA, and/or IgM classes was positive (however, a positive EIA-IgGAM with a negative SRA argues against a diagnosis of HIT). Further, the overall clinical picture, as shown by the 4Ts score, was unlikely for HIT, based in part on the onset of thrombocytopenia (day 3.5), which is too soon to be HIT. 4Ts score (Tcp=thrombocytopenia, Tim=timing, Thr=thrombosis, oTr=other); EIA, enzyme-immunoassay; INR, international normalised ratio; PCI, percutaneous coronary intervention; SRA, serotonin-release assay; U, units; UFH, unfractionated heparin.

Table 2: HIT-mimicking syndromes.

Timing of thrombocytopenia suggests HIT
Post transfusion purpura
Abciximab-induced thrombocytopenia (acute or delayed-onset)
Classic drug-induced immune thrombocytopenia
Concurrence of thrombocytopenia and thrombosis suggests HIT
Acute DIC/hepatic necrosis-limb necrosis syndrome
Septicaemia with symmetrical peripheral gangrene/purpura fulminans
Infective endocarditis (septic emboli)
(Catastrophic) antiphospholipid syndrome
Pulmonary embolism-associated DIC
Diabetic ketoacidosis complicated by thrombocytopenia and arterial thrombosis
Thrombolytic therapy
Postoperative thrombotic thrombocytopenic purpura (TTP)
Paroxysmal nocturnal haemoglobinuria complicated by thrombosis
Timing of thrombocytopenia and thrombosis suggests HIT
Venous limb ischaemia/gangrene complicating cancer-associated DIC

gangrene is explained by microthrombosis secondary to profoundly disturbed procoagulant-anticoagulant balance, with the characteristic supratherapeutic INR indicating greatly reduced protein C activity levels via parallel severe reduction in factor VII (86, 87). These observations are especially interesting given that both protein C and factor VII share key biological features, including short half-life and low (nanomolar) concentrations (33).

Other syndromes

► Table 2 lists other disorders that have been confused with HIT. Supporting references can be found elsewhere (3, 88).

Conclusions

HIT is an unusual prothrombotic disorder of striking pathophysiology. Diagnostic testing for HIT antibodies has clarified the clinical picture of HIT vis-a-vis certain mimicking non-HIT disorders. Greater understanding of thrombosis pathogenesis in HIT has led to insights into pathophysiology of thrombosis in some non-HIT

disorders, such as the acute DIC/hepatic necrosis-limb necrosis syndrome. Here, parallels with VKA-induced venous limb ischaemia complicating HIT (and cancer-associated DIC) led to the insight that a profound disturbance in procoagulant-anticoagulant balance attributed to DIC and acute hepatic dysfunction ("shock liver") can result in ischaemic limb injury ("symmetrical peripheral gangrene").

Conflicts of interest

TEW has received lecture honoraria from Instrumentation Laboratory and Pfizer Canada and royalties from Informa (Taylor & Francis); has provided consulting services to Aspen Global, Medtronic Diabetes, and W.L. Gore; has received research funding from Instrumentation Laboratory, Medtronic Diabetes and W.L. Gore; and has provided expert witness testimony relating to HIT and non-HIT thrombocytopenic and coagulopathic disorders.

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