# Heparin-induced thrombocytopenia

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**Purpose of review**
Thrombocytopenia and heparin exposure are common in critically ill patients, yet immune heparin-induced thrombocytopenia (HIT), a prothrombotic adverse effect of heparin, rarely accounts for thrombocytopenia in this patient population. The review discusses the clinical and laboratory features that distinguish HIT from non-HIT thrombocytopenia.

**Recent findings**
The frequency of HIT in heparin-exposed critically ill patients is approximately 0.3–0.5% versus at least a 30–50% background frequency of non-HIT thrombocytopenia. Most patients who form anti-PF4/heparin antibodies do not develop HIT, contributing to HIT overdiagnosis. Disseminated intravascular coagulation (DIC), particularly in the setting of cardiogenic or septic shock associated with 'shock liver', can cause ischemic limb gangrene with pulses, mimicking a clinical picture of HIT. However, whereas non-HIT-related DIC with microthrombosis can be treated with heparin, HIT usually requires nonheparin anticoagulation. HIT-associated DIC can result in an elevated INR, which could reflect factor VII depletion because of extrinsic (tissue factor) pathway-mediated activation of coagulation.

**Summary**
Greater understanding of the various clinical and laboratory features that distinguish HIT from non-HIT thrombocytopenia could help improve outcomes in patients who develop thrombocytopenia and coagulopathies in the ICU.

**Keywords**
disseminated intravascular coagulation, heparin-induced thrombocytopenia, ischemic limb gangrene with pulses, shock liver

## INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction with counter-intuitive features, such as its strong association with thrombosis, despite being caused by an anticoagulant. At least 50% of patients with serologically-proven HIT develop thrombosis [1–3], a rate 12-fold higher than controls [4]. Thrombi usually involve large veins and/or arteries ('macrothrombosis') [1–3], although some patients with concomitant disseminated intravascular coagulation (DIC) evince microthrombosis [5,6▪▪].

HIT is caused by platelet-activating IgG antibodies [7] that recognize multimolecular complexes comprised of (cationic) platelet factor 4 (PF4) and the (polyanionic) sulfated polysaccharide, heparin [8,9]. Despite its key immunizing role, heparin is not necessarily required for antibody pathogenicity; this is because certain 'strong' HIT antibodies activate platelets even in the absence of heparin [5,10,11▪▪], probably because PF4 forms antigenic complexes with endogenous platelet-associated polyanions (e.g., chondroitin sulfate) [12▪▪]. In-vivo thrombin generation results from formation of procoagulant, platelet-derived microparticles [13] and monocyte activation with tissue factor expression [14].

The review highlights the clinical and serological features of HIT, emphasizing timing of onset of thrombocytopenia in pointing to a potential diagnosis of HIT, and the role of platelet activation assays to judge pathogenicity of heparin-dependent antibodies. The explanations for limb ischemia in the critically ill patient will also be discussed.

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## KEY POINTS

- HIT accounts for only a small minority (at most, 1%) of patients who have thrombocytopenia in the ICU (overall frequency of HIT of 0.3–0.5% among a background frequency of thrombocytopenia of 30–50%).
- Whereas virtually all patients with HIT have anti-PF4/heparin antibodies, only a minority of critically ill patients with detectable anti-PF4/heparin antibodies develop HIT (thus risking HIT 'overdiagnosis' if a positive anti-PF4/heparin immunoassay is automatically considered indicative of HIT).
- The diagnosis of HIT is made most reliably if the patient develops unexpected thrombocytopenia bearing a plausible temporal relationship with a proximate heparin exposure, and if high levels of anti-PF4/heparin antibodies with platelet-activating properties are detected.
- Non-HIT acute disseminated intravascular coagulation with severe depletion of natural anticoagulants (e.g., antithrombin, protein C), particularly in the setting of hypotension and 'shock liver', is associated with symmetrical peripheral gangrene, thus potentially mimicking the clinical picture of HIT (differential diagnosis of thrombocytopenia, coagulopathy, and ischemic limb necrosis).

## CLINICAL PICTURE

Unexpected thrombocytopenia arising from a platelet count fall that begins about 1 week after an exposure to heparin is the hallmark of HIT [15,16▪▪]. With new thrombosis, the likelihood of HIT becomes even greater. Lower-limb deep-vein thrombosis (DVT) with or without pulmonary embolism is the most common complication (~50% of patients) [1–4]; upper-limb DVT occurs less often, and is invariably associated with concurrent or recent intravascular catheter use [17]. Less common venous thromboses include cerebral (dural sinus) and splanchnic (mesenteric, adrenal) veins [15,18]. Adrenal vein thrombosis occurs in approximately 2% of patients, and manifests as adrenal hemorrhagic infarction; when adrenal necrosis is bilateral, acute adrenal failure can result, and adrenal replacement therapy lifesaving [15,19▪]. Arterial thrombosis in HIT typically involves (in descending order) lower limb, cerebral, coronary, mesenteric, and brachial arteries; the appearance of the platelet-rich arterial thrombi popularized 'white clot syndrome' as a synonym for HIT [20].

Approximately 5% of patients develop ischemic limb necrosis [21], most often because of warfarin-induced protein C depletion leading to microthrombosis in a limb affected by DVT ('warfarin-induced venous limb gangrene') or because of acute limb artery thrombosis [6▪▪,15,22,23]. Rarely, severe HIT-associated DIC leads to microthrombosis and critical limb ischemia even in the absence of warfarin therapy [6▪▪].

HIT is uncommon in the ICU; for at most one in 100 thrombocytopenic ICU patients is HIT the explanation [24]. The clinician must distinguish the (relatively) uncommon patient with HIT among the many without. Although scoring systems for HIT are available, such as the 4Ts [25–27] and the HIT Expert Probability [28,29] systems, generally speaking, almost all ICU patients score 'low probability' for HIT. Indeed, for HIT to be realistically entertained in an ICU patient, thrombosis and/or a clear new-onset thrombocytopenia bearing temporal relationship to a preceding heparin exposure would be necessary (vide infra).

## SEROLOGICAL PICTURE

HIT is a 'clinical–pathological' syndrome [30,31], that is, the patient should exhibit both a clinical picture consistent with HIT, for example, thrombocytopenia and/or thrombosis bearing a temporal relationship with a preceding immunizing exposure to heparin ('clinical'), and the serological profile of HIT, namely detectability within patient serum (or plasma) of the pathognomonic, heparin-dependent, platelet-activating antibodies ('pathological'). A recent consensus conference statement recommended the following diagnostic framework [32]: intermediate or high-probability clinical picture (scoring at least 4 points in the 8-point 4Ts scoring system [25–28]) and heparin-dependent, platelet-activating antibodies, as shown either by a positive serotonin-release assay (SRA) [33,34] or heparin-induced platelet activation test [35] along with a corroborating positive PF4-dependent immunoassay, such as an enzyme-immunoassay (EIA) [36]. The approach reduces risk of HIT overdiagnosis [37▪].

## HEPARIN-INDUCED THROMBOCYTOPENIA VIEWED THROUGH THE 4TS

The clinical picture of HIT is reviewed through the 4Ts scoring system (Table 1) [25–28].

### Thrombocytopenia

The first 'T', 'T'hrombocytopenia, evaluates decline in the platelet count. In HIT, there usually is a large-magnitude platelet count decline (usually, >50%) that does not attain very low platelet count values. Indeed, 0 points are assigned if the platelet count falls to $<10 \times 10^9$/l, and only 1 point given for a

**Table 1.** 4Ts scoring system

| | Points (0, 1, or 2 for each of four categories: maximum possible score = 8) | | |
|---|---|---|---|
| | 2 | 1 | 0 |
| Thrombocytopenia | >50% platelet fall to nadir ≥20 | 30–50% platelet count fall (or >50% directly resulting from surgery); or nadir 10–19 | <30% platelet fall; or nadir <10 |
| Timing[a] of platelet count fall, thrombosis, or other sequelae (first day of putative immunizing exposure to heparin = day 0) | Day 5–10 onset[a] (typical/delayed-onset HIT); or ≤1 day [with recent heparin exposure within past 30 days (rapid-onset HIT)] | Consistent with day 5–10 fall, but not clear (e.g., missing platelet counts); or, ≤1 day (heparin exposure within past 31–100 days) (rapid-onset HIT); or, platelet fall after day 10 | Platelet count fall ≤4 days (unless picture of rapid-onset HIT – see two left boxes) |
| Thrombosis or other sequelae (e.g., skin lesions, anaphylactoid reactions) | Proven new thrombosis; or skin necrosis (at injection site); or postintravenous heparin bolus anaphylactoid reaction | Progressive or recurrent thrombosis; or erythematous skin lesions (at injection site); or suspected thrombosis (not proven); hemofilter thrombosis | None |
| oTher cause for thrombocytopenia | No explanation for platelet count fall is evident | Possible other cause is evident | Definite other cause is present |

Pretest probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low. The scoring system shown above includes minor modifications compared with previously published versions.
[a]First day of immunizing heparin exposure considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1 to 3 more days until an arbitrary threshold that defines thrombocytopenia is passed). Usually, heparin administered at or near surgery is the most immunizing situation (i.e., day 0).

platelet count between 10 to $19 \times 10^9$/l, whereas a >50% platelet count fall with nadir $\geq 20 \times 10^9$/l scores the maximum 2 points. (Only ~10% of HIT patients develop a platelet count nadir $< 20 \times 10^9$/l [38].) Many ICU patients develop platelet count falls similar to that seen in HIT, and thus this criterion is usually not very helpful for distinguishing between HIT and non-HIT thrombocytopenia.

## Timing

In contrast, the second 'T', 'T'iming of onset of thrombocytopenia (or thrombosis) in relation to a preceding heparin exposure, is more diagnostically helpful. This is because most critically ill patients develop a single phase of thrombocytopenia that occurs early, either when admitted to ICU immediately postsurgery or with acute illness directly from the community. Indeed, even uncomplicated elective surgery is characterized by an early postoperative platelet count fall, with the platelet count nadir usually occurring on postoperative day 2 (range, days 1–4) [39].

However, in patients with HIT there is a second decline in the platelet count that typically begins 5–10 days after an immunizing heparin exposure (usually, heparin given intraoperatively or in the early postoperative period). It is this unexpected second episode of platelet count decline beginning about 1 week after heparin administration that characterizes 'typical-onset' HIT [40].

Indeed, a study [41] of 12 postorthopedic surgical HIT patients with serial blood sample availability showed the following clinical and serological profile of HIT:

(1) Day 0: first day of heparin administration (usually, postoperative day 1);
(2) Day 2: expected postsurgery platelet count nadir;
(3) Day 4: rising platelet count; first day anti-PF4/heparin antibodies detected (EIA);
(4) Day 6: first day of (HIT-related) platelet count fall;
(5) Day 8: first day that the platelet count fall exceeds 50%;
(6) Day 10: first day of thrombosis.

Of course, biological variability was seen around these (median) day values, but the overall pattern is clear. Further, this tight timeline indicates HIT is a point immunization event, antibody formation is triggered soon after surgery, when heparin administration coincides with PF4 released from activated platelets [31].

Sometimes, a patient already has circulating HIT antibodies because of recent heparin exposure (within the previous 100 days); when heparin is restarted, there is an abrupt platelet count drop ('rapid-onset' HIT) [40]. Some patients have associated acute inflammatory or cardiorespiratory symptoms and signs (HIT-associated 'acute

anaphylactoid reaction') [42–44]. Because HIT antibodies are transient, rapid-onset HIT only occurs in patients who have been immunized within the previous weeks or a few months. Importantly, any time HIT antibodies are actively formed – whether for the first time, or on a second occasion in a patient with previous HIT whose antibody levels have waned – there is at least a five-day interval between the immunizing (or reimmunizing) heparin exposure and the beginning of the HIT-associated platelet count fall [45▪▪].

'Delayed-onset' HIT was first used to indicate HIT that begins [10] after stopping heparin. More recently the term has been used to also indicate those patients in whom HIT worsens (progressive or persisting decline in the platelet count) even after stopping heparin [5,6▪▪]. These patients often have unusually severe thrombocytopenia with overt (decompensated) DIC. Patients' sera induce strong platelet activation *in vitro* (and presumably *in vivo*) even in the absence of heparin [10,11▪▪].

### Thrombosis

The third 'T', 'T'hrombosis, reflects HIT's strong association with thrombosis. Indeed, one study showed a HIT-associated venous thromboembolism frequency of ~50% versus a control rate of ~4% [4]. HIT-associated thrombosis begins as early as day 5 (sometimes even before the HIT-related platelet count fall is evident) [46,47], or as late as several weeks post-HIT diagnosis.

Venous predominates over arterial thrombosis (ratio, ~4 : 1). Ischemic limb gangrene despite palpable pulses usually occurs in a limb with DVT, and usually represents a consequence of warfarin therapy [22,23]. The hallmark of so-called warfarin-induced 'venous limb gangrene' is a supratherapeutic international normalized ratio (INR; usually > 4.0), which represents a surrogate marker for severe protein C depletion via parallel severe depletion in factor VII. When limb ischemia arises because of large-artery thrombosis, urgent thromboembolectomy may be limb-saving [48].

Miscellaneous features of HIT include necrotizing skin lesions at heparin injection sites [49] (and rarely at noninjection sites [50▪]) and anaphylactoid reactions [42] beginning within 30 min postintravenous unfractionated heparin (UFH) bolus [43] or within 2 h following low-molecular weight heparin (LMWH) injection [44].

### OTher

The fourth 'T', o'T'her cause(s) of thrombocytopenia, is also relatively unhelpful, since most critically ill patients have plausible non-HIT explanations for thrombocytopenia. Accordingly, one might score 0 or 1 points (virtually never 2 points) when applying this criterion to an ICU patient.

## HEPARIN-INDUCED THROMBOCYTOPENIA -ASSOCIATED DISSEMINATED INTRAVASCULAR COAGULATION

HIT has been classically viewed as a pure platelet activation syndrome. However, in recent years, the marked hypercoagulability of HIT has been appreciated, including its association with DIC [4,5,6▪▪,15]. Although 10–20% of patients with HIT have overt DIC, probably DIC exists in most patients, as even normal fibrinogen levels are relatively low for the patient's usual postoperative state. Also, HIT-associated elevations in INR and activated partial thromboplastin time (APTT) are less common than in other DIC conditions. Nonetheless, HIT-associated DIC is associated with poor patient outcomes, such as microvascular cerebral ischemia [51] and acral limb ischemic necrosis [6▪▪,15], and often occurs in delayed-onset HIT [5].

Figure 1 illustrates a patient who developed an elevated INR (from 1.2 to 1.5) and a falling fibrinogen (from 6.2 to 4.2 g/l) at the time that HIT developed. Coagulation factor levels were measured, and mildly reduced factors, particularly factor VII [nadir, 0.37 U/l (normal, 0.50 to 1.50)], explained the elevated INR, perhaps indicating extrinsic (tissue factor) pathway activation in HIT (as could be explained by tissue factor expression by activated monocytes [14]). Interestingly, this patient's extrinsic factor level profile (VII < X < II) has also been observed in warfarin-associated hypercoagulability complicating both HIT [22] and cancer-associated DIC [52▪]. Another interesting aspect illustrated by this patient's clinical course was the abrupt increase in fibrin D-dimer level after intravenous therapeutic-dose UFH was discontinued (because of HIT diagnosis) and despite subsequent (subtherapeutic) fondaparinux dosing, supporting the (counterintuitive) notion that stopping heparin could paradoxically 'worsen' HIT-associated hypercoagulability, if there is inadequate dosing of nonheparin anticoagulation.

## NONHEPARIN-INDUCED THROMBOCYTOPENIA ACRAL LIMB ISCHEMIC SYNDROMES

There are explanations besides HIT for ischemic limb gangrene syndromes encountered in ICU patients, such as symmetrical peripheral gangrene (SPG) and purpura fulminans (PF) [6▪▪]. 'Shock liver' (acute ischemic hepatitis) coinciding with (non-

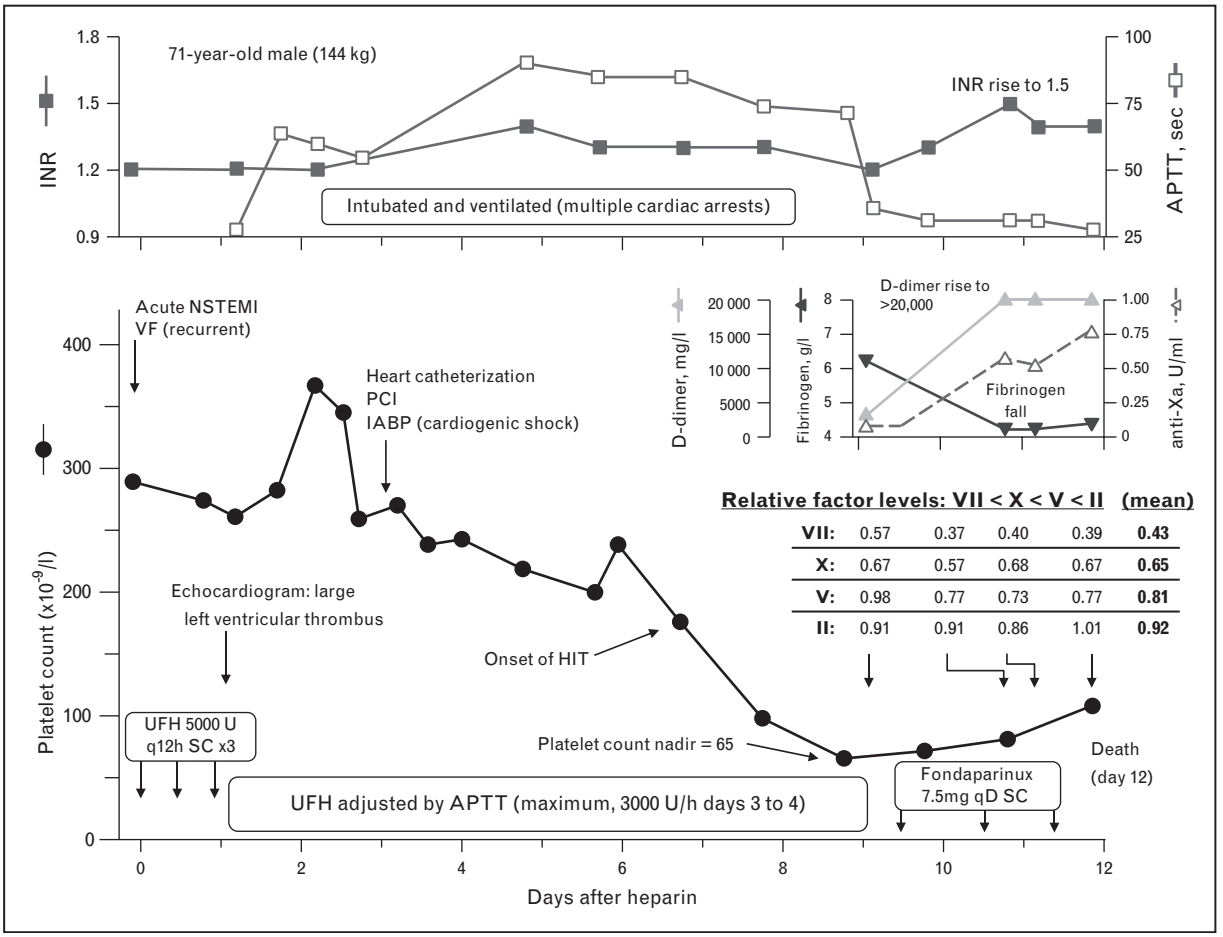


**FIGURE 1.** HIT-associated DIC. Following onset of HIT, the patient developed an elevated INR (from 1.2 to 1.5), a falling fibrinogen (from 6.2 to 4.2 g/l), and a rising fibrin D-dimer level (from 3140 to >20 000 mg/l fibrinogen equivalent units). Interestingly, the D-dimer increase occurred after stopping heparin, indicating that cessation of heparin can worsen HIT-associated hypercoagulability. Dosing of fondaparinux was probably inadequate for this 144-kg patient. Factor studies revealed that the elevated INR was likely explained mostly by decreased levels of factor VII. APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; IABP, intra-aortic balloon pump; INR, international normalized ratio; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; q12 h, every 12 h; qD, every day (once-daily); SC, subcutaneous; U, units; UFH, unfractionated heparin; VF, ventricular fibrillation.

HIT) DIC, called 'acute DIC/hepatic necrosis-limb necrosis syndrome', has been linked to acral limb ischemic necrosis in patients with septic shock or cardiogenic shock [6▪▪,53,54,55▪▪,56▪▪]; in essence, shock liver is a 'warfarin equivalent' predisposing to severe depletion in protein C (as well as antithrombin). Patients have profoundly disturbed procoagulant–anticoagulant balance, that is, marked thrombin generation coincides with protein C depletion [6▪▪,54]. Just as DVT localizes microthrombosis to areas distal to the DVT in HIT, in SPG and PF, hypotension and vasopressors lead to sluggish acral blood flow, predisposing to acral microthrombosis. Despite the clinical picture mimicking HIT (thrombocytopenia, coagulopathy, acute limb ischemia with pulses), the anticoagulant of choice is heparin [6▪▪].

## EARLY-ONSET AND PERSISTING THROMBOCYTOPENIA

Many ICU patients develop thrombocytopenia soon after admission. When heparin is given and early-onset thrombocytopenia persists beyond 5 days, the issue of HIT may be raised. However, Selleng *et al.* [57] showed that 'early-onset and persisting thrombocytopenia' was unlikely to indicate HIT, even if the patient formed anti-PF4/heparin antibodies;

rather, the thrombocytopenia reflects the natural history of critical illness-associated thrombocytopenia plus the high frequency of forming clinically-irrelevant antibodies. However, if a superimposed platelet count fall and/or thrombosis occurs within the day 5–10 'window' of HIT, and platelet-activating antibodies are demonstrated, then the patient plausibly has concomitant HIT [57–59].

## AVOIDING HEPARIN-INDUCED THROMBOCYTOPENIA OVERDIAGNOSIS

By insisting on both a positive EIA and washed platelet activation assay (SRA or heparin-induced platelet activation), the risk of a wrong diagnosis of HIT is reduced. For example, certain platelet aggregation tests commonly give false-positive results when testing blood from patients, compared with the (washed platelet) SRA [60,61,62▪]. Thus, if the EIA is negative (or weakly positive), a false-positive platelet activation test should be considered [37▪]. A more common issue is a false-positive EIA; indeed, for approximately three-quarters of ICU patients, a positive EIA is not accompanied by a positive SRA, and the patient is unlikely to have HIT [63,64]. The risk of HIT 'overdiagnosis' [65] is minimized by considering the 'strength' of the EIA result, for example, a strong-positive EIA (>2.00 units of optical density) points to a 90% probability of a positive SRA [66].

## PREVENTION OF HEPARIN-INDUCED THROMBOCYTOPENIA

LMWH (vs. UFH) use is associated with an approximate ten-fold reduced risk of HIT [2,67,68], attributable to a three-fold lower immunization risk and (among those forming clinically-relevant antibodies) three-fold lower 'breakthrough' of thrombocytopenia [2,3]. The greater capacity of UFH (vs. LMWH) to form highly immunogenic ultra large complexes with PF4, and for the larger PF4/heparin/IgG complexes to activate platelets, likely explains differences in HIT risk [9]. The reduced risk of HIT with LMWH is best established for enoxaparin [2,3], but seems likely also with certoparin [69] and dalteparin [56▪▪,67,70]. Indeed, the Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT) trial [71] suggested that dalteparin (vs. UFH) prophylaxis reduces risk of HIT in critically ill patients by ~75% [70], a risk reduction also supported by observational studies from France [72,73]. Dalteparin can be given in prophylactic doses in ICU patients, since bioaccumulation is negligible even in renally-compromised or dialysis patients [74,75].

## TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA

The treatment principles of strongly-suspected (or confirmed) HIT include [56▪▪]:

(1) Three do's
   (a) do stop/avoid heparin (including 'flushing' intravascular catheters);
   (b) do commence alternative nonheparin anticoagulant (usually in therapeutic doses);
   (c) do indicate potential diagnosis of HIT in the medical record;
(2) Three don'ts
   (a) don't give warfarin (treat with vitamin K if warfarin already given [21,76,77]);
   (b) don't order prophylactic platelet transfusions [21,77];
   (c) don't insert an inferior vena cava filter;
(3) Three diagnostics:
   (a) test for HIT antibodies (immunoassay and platelet activation assay);
   (b) test for DIC;
   (c) image for lower-limb DVT (presence of DVT influences duration of anticoagulant therapy).

Some of these recommendations may not be helpful. For example, stopping heparin could paradoxically increase HIT-associated hypercoagulability. Indeed, as shown in Figure 1, the patient's fibrin D-dimer levels rose dramatically after stopping IV therapeutic-dose UFH. Further, progression to venous limb gangrene in severe HIT typically occurs after stopping heparin [22].

The suggestion (i.e., 'weak' recommendation) [21,77] to avoid prophylactic platelet transfusions reflects observational studies indicating that platelet transfusions did not seem deleterious [78,79] and the reality that in the ICU a non-HIT diagnosis is overwhelmingly more likely than HIT, and so the risk-benefit analysis in a severely thrombocytopenic patient would likely favor platelet transfusions even if HIT is a possibility.

A recent administrative database study suggested that platelet transfusions were associated with arterial thrombosis and mortality in patients with HIT [80▪]. However, implications regarding platelet transfusions for HIT cannot be drawn. The authors did not have access to laboratory results, and so HIT diagnosis could not be ascertained. More importantly, the authors had no access to platelet count values, or even whether the platelet transfusions were given before or after thrombotic events. The lack of platelet count data is a fatal methodological flaw, as severity of thrombocytopenia is both a transfusion trigger as well as a known risk factor for

**Table 2.** Diagnostic and therapeutic approach to HIT: highlighting use of fondaparinux

| |
|---|
| A. Baseline (pretreatment) diagnostic evaluation: |
| Complete blood count/differential with blood film, including assessment of nucleated red blood cells (normoblasts), reticulocyte count, and red cell fragments[a] |
| Coagulation tests:[b] PT (INR),[c] PTT,[d] fibrinogen,[e] fibrin D-dimer (quantitative[f]), and/or other fibrin-specific marker(s) (e.g., fibrin monomer), AT[g] |
| Chemistry tests: creatinine, LDH[h] (compared with simultaneously-measured AST, ALT, and CK), bilirubin |
| Lower-limb ultrasound for DVT (routine)[i] |
| Upper-limb ultrasound for DVT (if upper-limb swelling[j]) |
| B. Serial laboratory assessment (at least once-daily): |
| Complete blood count (follow normoblast count, if elevated) |
| Coagulation tests:[b] PT (INR),[c] PTT,[d] fibrinogen,[e] fibrin D-dimer (quantitative[f]), and/or other fibrin-specific marker(s), ± AT[g] |
| Antifactor Xa level calibrated for fondaparinux (drawn at ~0600 h each morning), especially if there is renal dysfunction (e.g., estimated creatinine clearance <60 ml/min/1.73 $m^2$); |
| ± creatinine (if there is renal dysfunction); |
| ± LDH (if initially elevated and hemolysis is suspected); |
| ± AST, ALT, and bilirubin (if hepatic dysfunction is suspected); |
| ± CK (if ischemic limb injury is suspected) |
| C. Therapeutic-dose fondaparinux regimen for treatment of (strongly-suspected or confirmed) acute HIT, including HIT-associated thrombosis: |
| First dose (afternoon/evening[k]): 7.5 mg (or 10 mg[l]) by subcutaneous injection[m] for patient weighing 50–100 kg[n] |
| Second and subsequent doses (morning at ~0800 h[o]): 7.5 mg by subcutaneous injection |
| Dosing adjustments for renal failure: |
| Do not reduce the first dose or two; subsequently, reduce daily dose to 5 or 2.5 mg, depending on the extent of renal dysfunction, and results of antifactor Xa levels (if available) |
| Target (trough) anti-Xa level (fondaparinux) is 0.60–1.00 anti-Xa U/ml[p] |
| AT concentrates: give ~1000 U every 12 h (if AT depletion is documented and fondaparinux is being used for anticoagulation)[g] |
| D. Prophylactic-dose regimen for fondaparinux[q] |
| 2.5 mg by subcutaneous injection[r] |
| E. Freeze residual plasma samples |
| Facilitate retrospective analysis of cases |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, antithrombin; CK, creatine kinase; DIC, disseminated intravascular coagulation; DVT, deep-vein thrombosis; FEU, fibrinogen equivalent units; LDH, lactate dehydrogenase; PT (INR), prothrombin time (international normalized ratio); PTT, (activated) partial thromboplastin time. Reprinted with permission from [56▪▪].

[a]Normoblastemia, reticulocytosis, and, less often, red cell fragments can be seen in severe HIT-associated DIC.

[b]The author follows serial coagulation markers, especially in patients with severe HIT-associated DIC, where effective anticoagulation should result in decrease in INR, increase in fibrinogen, and decrease in fibrin D-dimer levels.

[c]An otherwise unexplained elevated INR in a patient with HIT suggests possibility of HIT-associated DIC.

[d]An elevated (A) PTT increases risk of '(A) PTT confounding' with use of (A) PTT-adjusted anticoagulant, for example, argatroban or bivalirudin.

[e]As HIT usually occurs in postoperative patients, an elevated fibrinogen level is expected; thus, a fibrinogen level that is low [<1.5 g/l (<100 mg/dl)] or low-normal [1.5–2.5 g/l (150–250 mg/dl)] can be seen in severe HIT-associated DIC.

[f]In our laboratory, fibrin D-dimer is routinely reported up to 4000 FEU μg/ml (higher values are reported as >4000 FEU μg/ml), but on request can be further quantitated up to 20 000 FEU μg/ml; serial D-dimers are useful in assessing response to therapy.

[g]AT is measured at baseline, and followed serially if there is HIT-associated DIC (fondaparinux is an AT-dependent factor Xa inhibitor).

[h]Lactate dehydrogenase (LD or LDH) is a marker of hemolysis, and elevated levels are sometimes seen in severe HIT-associated DIC. Initial assessment of LDH should be compared with liver enzymes (ALT, AST) and muscle enzymes (AST, CK), as an isolated increase in LDH is most specific for hemolysis.

[i]Approximately 50% of patients with HIT are found to have lower-limb DVT.

[j]Upper-limb DVT occurs in ~10% of patients with HIT and is invariably associated with concurrent/recent use of an intravascular catheter.

[k]As HIT is often recognized by reduced platelet counts, and as routine CBCs are generally drawn in the morning in hospitalized patients, treatment for HIT is thus frequently started in the afternoon or evening.

[l]10 mg, rather than 7.5 mg, may be appropriate even for a 50–100 kg patient if HIT is judged very severe (e.g., with overt DIC), or if initial dose is given in the morning and therefore a 20–24 h interval before next (morning) dose is anticipated.

[m]Intravenous (i.v.) injection can be considered if immediate anticoagulation is desired. If given i.v., flush the line afterwards, or administer the fondaparinux in 25 to 50 ml normal saline over 3–5 min.

[n]Dosing decreased to 5 mg if body weight <50 kg and increased to 10 mg if body weight >100 kg.

[o]The rationale for administering second and subsequent doses in the morning – even if the first dose was given in the preceding afternoon or evening – is that it will help to achieve early therapeutic levels of anticoagulation (since there will usually be <20 h interval between the first two doses); in addition, it will facilitate determining trough plasma anticoagulant levels (if desired) by drawing antifactor Xa levels at the morning blood draw.

[p]A target trough drug level of 0.6–1.0 anti-Xa U/ml is currently being used by the author; although the anti-Xa level (drawn at approximately 0600 h) will not be available at the time that the fondaparinux injection is given (approximately 0800 h), the goal of serial anti-Xa levels is to assess whether drug accumulation that warrants subsequent dose reduction is occurring.

[q]Low-dose (prophylactic-dose) fondaparinux regimen may be appropriate if: patient has low (or intermediate) probability for acute HIT and no thrombosis is evident; or for various other settings of prophylactic-dose anticoagulation, for example, patient with history of previous HIT who requires postoperative thromboprophylaxis.

[r]Assumes normal renal function.

HIT-associated thrombosis [15,38,81], thus confounding any putative association.

Inferior vena cava filters are not recommended for use in patients with HIT given risk of DVT progression to critical limb ischemia [82].

### Choice of anticoagulant

UFH is the preferred anticoagulant for critically ill patients; it is the only agent approved by the US Food and Drug Administration for the 'treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation)' [83]. Its advantages include nonrenal/nonhepatic clearance, short half-life, availability of antidote (protamine sulfate), accurate lab monitoring (antifactor Xa level), and low cost. Given that the efficacy and safety of nonheparin anticoagulants are unknown in coagulopathic ICU patients, and given that non-HIT thrombocytopenia exceeds HIT 100-fold, there are relatively few thrombocytopenic ICU patients where HIT is strongly considered. Finally, the approved drug for HIT (argatroban) is ineffective in many coagulopathic patients because of 'APTT confounding'.

### Activated partial thromboplastin time confounding

Incorrect anticoagulant dosing because of misleading APTT values during lab monitoring is 'APTT confounding' [6▪▪,55▪▪]. For example, if the baseline (preargatroban) APTT is elevated, perhaps because of liver dysfunction or HIT-associated DIC, then nomogram-adjusted argatroban dosing can lead to systematic underdosing [51,55▪▪,84▪].

### Argatroban

Only argatroban, a direct thrombin inhibitor, is currently approved to treat HIT in the USA (lepirudin has been discontinued). However, no controlled studies are available to show that argatroban is effective to treat HIT. The approval trials [85,86] did not require positive laboratory testing for HIT, and so most enrolled patients likely did not have HIT, in contrast to the (historical) controls who were antibody-positive. Further, the high limb amputation rate in the argatroban-treated study patients (13.7%) [21] raises concerns about argatroban-warfarin overlap, a situation with risk for venous limb gangrene [87,88] (both agents prolong the INR [89]). Argatroban is also a costly medication.

### Indirect factor Xa inhibitors

Indirect (antithrombin-dependent) factor Xa inhibitors, such as danaparoid (not available in the USA) and fondaparinux, have advantages over argatroban, and I prefer using one of these to treat HIT [5,36]. Neither pose risk of APTT confounding, as drug levels are measured directly (as antifactor Xa levels). However, reduced dosing (after a full loading dose) is appropriate in renally-compromised patients [56▪▪]. Prophylactic dosing is probably appropriate for ICU patients, unless there is thrombosis or strong suspicion (or confirmation) of HIT. Fondaparinux is increasingly being used to treat HIT despite its off-label status for this indication [90▪▪]. Table 2 summarizes my diagnostic and therapeutic approach to managing HIT from the viewpoint of treatment with fondaparinux.

## CONCLUSION

There are numerous diagnostic and treatment challenges in the critically ill patient with thrombocytopenia, including the difficulty in distinguishing HIT from non-HIT thrombocytopenia, and the quintessential dilemma of choosing the right anticoagulant when heparin is contraindicated for HIT but the ideal anticoagulant for non-HIT thrombocytopenia with DIC.

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### Conflicts of interest

*T.E.W. reports receiving fees for serving on an advisory board from Instrumentation Laboratory, consulting fees from W.L. Gore, lecture fees from Instrumentation Laboratory and Pfizer Canada, fees for providing expert testimony in cases regarding thrombocytopenia, coagulopathy, or ischemic limb losses, and royalties from Taylor & Francis Group (Informa) for editing a book on heparin-induced thrombocytopenia. He also reports that his institution has received fees from W.L. Gore to provide laboratory testing for a randomized controlled trial of heparin-coated versus nonheparin-coated hemodialysis grafts. No other potential conflicts of interest relevant to this article were reported.*

*Off-label treatments: The article discusses fondaparinux and danaparoid as off-label options for the treatment of HIT.*

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