Heparin-Induced Thrombocytopenia in Critically Ill Patients

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Abstract

Many critically ill patients receive heparin, either before intensive care unit (ICU) admission (e.g., postcardiac surgery), for prophylaxis/treatment of thrombosis, for hemodialysis/filtration, or even incidentally (e.g., flushing of intravascular catheters), and are therefore at risk for developing immune heparin-induced thrombocytopenia (HIT), a prothrombotic drug reaction caused by platelet-activating antiplatelet factor 4 (PF4)/heparin antibodies. However, HIT explains at most 1 in 100 thrombocytopenic ICU patients (HIT frequency 0.3–0.5% vs. 30–50% background frequency of ICU-associated thrombocytopenia), and most patients who form anti-PF4/heparin antibodies do not develop HIT; hence, HIT overdiagnosis often occurs. This review discusses HIT-related issues relevant to ICU patients, including how to (1) distinguish HIT both clinically and serologically from non-HIT-related thrombocytopenia; (2) recognize HIT-mimicking disorders, such as the acute disseminated intravascular coagulation (DIC)/liver necrosis–limb necrosis syndrome; (3) prevent HIT in the ICU through use of low-molecular-weight heparin; and (4) treat HIT, including awareness of “PTT confounding” when anticoagulating patients with DIC.

Keywords

► adrenal hemorrhagic necrosis
► disseminated intravascular coagulation
► heparin-induced thrombocytopenia
► shock liver

Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction caused by platelet-activating immunoglobulin G (IgG) antibodies1 that recognize multimolecular platelet factor 4 (PF4)/heparin complexes2,3 (for review4,5). HIT is highly prothrombotic: approximately 50 to 75% of patients with serologically confirmed HIT develop venous or arterial thrombosis,6–8 which per one analysis corresponded to a relative risk for clinically relevant thrombosis of 12.0 (95% confidence interval [CI], 7.0–20.6; p < 0.0001).9

Unusually severe or atypical thrombosis is a hallmark for HIT. Lower-limb deep-vein thrombosis (DVT) is often bilateral,7,8 and approximately half of patients with DVT exhibit pulmonary embolism (PE).6 HIT-associated ischemic limb necrosis due to arterial or venous/microvascular thrombosis is relatively common,10 and approximately 5% of patients with HIT evince ischemic limb injury.11 Further, diagnostic confusion can result between certain forms of HIT-associated venous limb ischemia versus non–HIT-related disseminated intravascular coagulation (DIC) complicated by symmetrical peripheral gangrene, as both conditions feature thrombocytopenia, consumptive coagulopathy, and acral limb ischemic necrosis despite arterial pulses.

HIT is relatively uncommon in the critically ill patient—explaining at most 1 in 100 patients with intensive care unit (ICU)-associated thrombocytopenia12—and the clinician’s challenge is to distinguish the (relatively) uncommon patient with HIT among the many without.
Heparin-Induced Thrombocytopenia Is a Clinical–Pathological Disorder

A diagnosis of HIT will be made most accurately if HIT is viewed as a “clinical–pathological” syndrome,1,4,13 in which (1) the patient exhibits a clinical profile broadly consistent with HIT, for example, thrombocytopenia and/or thrombosis bearing a temporal relationship with a preceding immunizing exposure to heparin (“clinical”) and (2) the patient's serum (or plasma) is shown to contain heparin-dependent platelet-activating antibodies (“pathological”). One recommended framework14 for defining HIT is a clinical picture judged to be at least intermediate probability (e.g., scoring at least 4 points in the 4Ts pretest probability scoring system15–17) and detectability of heparin-dependent, platelet-activating antibodies (e.g., positive serotonin-release assay (SRA)18,19 or heparin-induced platelet activation test20,21 with a corroborating positive test for anti-PF4/heparin antibodies by a PF4-dependent immunoassay, most often an enzyme immunoassay (EIA).22

Clinical Picture of Heparin-Induced Thrombocytopenia: 4Ts Perspective

To distinguish HIT from non-HIT thrombocytopenic disorders, it is important to appreciate the clinical picture of HIT, here viewed through a widely used scoring system, the 4Ts (►Table 1).15–17

Thrombocytopenia

The first “T,” Thrombocytopenia, is characterized by large-magnitude declines in the platelet count (usually, at least 50%) that, however, do not usually reach very low values. Indeed, in the 4Ts, 0 points are given for a platelet count value < 10 × 10^9/L, and only 1 point for a platelet count result between 10 and 19 × 10^9/L, whereas a > 50% platelet count fall with nadir ≥ 20 × 10^9/L scores as 2 points. (Only ~10% of patients with HIT develop a platelet count nadir < 20 × 10^9/L.23) This (usual) lack of very severe thrombocytopenia probably reflects the fundamental platelet-activating nature of HIT, as other platelet-activating disorders such as DIC are also characterized by moderate thrombocytopenia, whereas destructive thrombocytopenia caused by platelet-reactive autoantibodies or drug-dependent antibodies often reach platelet count nadirs < 20 × 10^9/L.24 Therefore, the magnitude of the platelet count fall is usually not helpful in distinguishing HIT from non-HIT thrombocytopenia in critically ill patients.

Timing

In contrast, the second “T,” Timing of onset of thrombocytopenia (or thrombosis) in relation to a proximate (preceding) heparin exposure, is much more useful. Most critically ill patients—whether admitted to ICU immediately postsurgery, or directly from the community with acute illness—evince early-onset thrombocytopenia. Indeed, even with elective surgery, early postoperative thrombocytopenia is expected, with nadir platelet counts between postoperative days 1 and 4 (median, day 2).25

In contrast, ►Fig. 1 shows “typical-onset” HIT developing in a critically ill postcardiac surgery patient: here, the unexpected thrombocytopenia that began 5 days postsurgery—with

![Table 1 4Ts scoring system](image-url)

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* of platelet count fall, thrombosis, or other sequelae (1st day of putative immunizing exposure to heparin = day 0) | Days 5–10 onset* (typical/delayed-onset HIT); or ≤ 1 day (with recent heparin exposure within past 30 days (rapid-onset HIT) | Consistent with days 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); hemolysis | 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

Abbreviation: HIT, heparin-induced thrombocytopenia.

Note: The scoring system shown above includes minor modifications compared with previously published versions.

*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 1–3 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).
intraoperative exposure to unfractionated heparin (UFH) and postoperative thrombophlebitis with low-molecular-weight heparin (LMWH)—places HIT firmly in the differential diagnosis. By day 6, the 4Ts score was 5 points (intermediate probability score); however, when multiple limb ischemia developed on postoperative day 8, HIT became the leading diagnosis, and therapeutic-dose anticoagulation with danaparoid was started. The patient tested strongly positive for HIT antibodies by both SRA (95% serotonin-release at 0.1, and 0.3 IU/mL UFH [normal, < 20% serotonin-release] with inhibition to 1% serotonin-release at 100 IU/mL UFH); moreover, 95% serotonin release was also observed at 0 IU/mL UFH (buffer control). The anti-PF4/heparin IgG-specific EIA also tested strongly positive (2.59 units of optical density; normal < 0.45 units). This patient also developed severe HIT-associated DIC, as shown by: (1) hypofibrinogenemia (fibrinogen nadir, 1.0 g/L), (2) elevated international normalized ratio (peak INR, 1.9), and (3) marked increase in fibrin D-dimer (> 20,000 FEU μg/L; normal < 500 FEU μg/L). Although danaparoid helped control the DIC (normalization of the INR and fibrinogen), irreversible limb ischemic necrosis was apparent, and the patient died after life support was withdrawn on postoperative day 11. The inset illustrates application of the 4Ts scoring system, whereby an initial score of 5 points (intermediate probability) on postoperative day 6 increased to 7 points (high probability) on day 8 when limb ischemia developed. DIC, disseminated intravascular coagulation; EIA, enzyme immunoassay; FEU, fibrinogen equivalent units; HIT, heparin-induced thrombocytopenia; IABP, intra-aortic balloon pump; IgG, immunoglobulin G; INR, international normalized ratio; non-STEMI, non-ST elevation myocardial infarction; PCC, prothrombin complex concentrate; PEA, pulseless-electrical activity; PF4, platelet factor4; SRA, serotonin-release assay; WBC, white blood cell count; U, units; UFH, unfractionated heparin.

Fig. 1 Clinical picture of HIT-associated DIC. A 72-year-old man developed HIT beginning on postoperative day 5 following emergency coronary artery bypass surgery. (Despite preoperative administration of vitamin K and 4-factor prothrombin complex concentrate—to reverse warfarin anticoagulation—postoperative coagulopathy/bleeding required treatment with platelet, frozen plasma, and cryoprecipitate transfusions.) Initially, the unexpected thrombocytopenia was attributed to infection (rising white blood count); however, when multiple limb ischemia developed on postoperative day 8, HIT became the leading diagnosis, and therapeutic-dose anticoagulation with danaparoid was started. The patient tested strongly positive for HIT antibodies by both SRA (95% serotonin-release at 0.1, and 0.3 IU/mL UFH [normal, < 20% serotonin-release] with inhibition to 1% serotonin-release at 100 IU/mL UFH); moreover, 95% serotonin release was also observed at 0 IU/mL UFH (buffer control). The anti-PF4/heparin IgG-specific EIA also tested strongly positive (2.59 units of optical density; normal < 0.45 units). This patient also developed severe HIT-associated DIC, as shown by: (1) hypofibrinogenemia (fibrinogen nadir, 1.0 g/L), (2) elevated international normalized ratio (peak INR, 1.9), and (3) marked increase in fibrin D-dimer (> 20,000 FEU μg/L; normal < 500 FEU μg/L). Although danaparoid helped control the DIC (normalization of the INR and fibrinogen), irreversible limb ischemic necrosis was apparent, and the patient died after life support was withdrawn on postoperative day 11. The inset illustrates application of the 4Ts scoring system, whereby an initial score of 5 points (intermediate probability) on postoperative day 6 increased to 7 points (high probability) on day 8 when limb ischemia developed. DIC, disseminated intravascular coagulation; EIA, enzyme immunoassay; FEU, fibrinogen equivalent units; HIT, heparin-induced thrombocytopenia; IABP, intra-aortic balloon pump; IgG, immunoglobulin G; INR, international normalized ratio; non-STEMI, non-ST elevation myocardial infarction; PCC, prothrombin complex concentrate; PEA, pulseless-electrical activity; PF4, platelet factor4; SRA, serotonin-release assay; WBC, white blood cell count; U, units; UFH, unfractionated heparin.

Point Immunization
Postoperative HIT exhibits a characteristic timeline (all values in parentheses represent median values): early postoperative thrombocytopenia (onset, day 0) followed by expected postoperative (non–HIT) thrombocytopenic nadir (day 2) followed by initial detection of anti-PF4/heparin antibodies (day 4) followed by the beginning of the HIT-associated platelet count fall (day 6) followed by progressive platelet count decline to > 50% (day 8), often complicated by symptomatic thrombosis (day 10). This characteristic timeline infers a preceding “point immunization,” where intra-/early postoperative heparin exposure, coinciding with perioperative PF4 release from activated platelets, together with inflammation, trigger the anti-PF4/heparin immune response.

Typical, Rapid, Delayed, and Spontaneous Onset of HIT
The platelet count fall usually begins between days 5 and 10 (inclusive) following the immunizing heparin exposure (day 0). For a patient recently exposed to heparin (within the previous several weeks or months), and who therefore already has circulating HIT antibodies, resumption of heparin can trigger an abrupt platelet count fall, termed “rapid-onset” HIT. Here, the characteristic association with recent (but not remote) preceding heparin exposure reflects the unusual transience of HIT antibodies, which become undetectable a median of 50 to 80 days (depending on the assay performed) following an episode of HIT. The transience of HIT antibodies is striking: we have observed patients whose antibody
levels waned—along with platelet count recovery—even as heparin was continued. Of note, any time that HIT antibodies are actively being generated (whether de novo or recurrent) requires at least 5 days postimmunizing heparin exposure (or reexposure) before HIT-related thrombocytopenia can begin.

“Delayed-onset” HIT refers to HIT that begins or worsens after stopping heparin. These patients can have unusually severe or persisting thrombocytopenia, often accompanied by overt (decompensated) DIC. In such patients, the SRA shows very strong serum-induced platelet activation even in the absence of heparin. The ability of such highly pathogenic antibodies to activate platelets directly helps explain why the patient’s thrombocytopenia can begin or worsen without further heparin being given.

“Spontaneous” HIT syndrome indicates a disorder clinically and serologically indistinguishable from HIT except for the absence of a proximate heparin exposure. Approximately half of these patients developed this disorder postorthopedic surgery (during prophylaxis with warfarin or a new oral anticoagulant) and the remaining usually postinfection (perhaps, joint cartilage provide a template for PF4-dependent immunization). Postorthopedic surgery spontaneous HIT syndrome appears to be a high-risk situation for adrenal hemorrhagic necrosis, which if bilateral leads to life-threatening adrenal failure. Sera from spontaneous HIT patients also exhibit strong platelet-activating properties in the absence of heparin.

Thrombosis

The third “T,” Thrombosis (or other clinical sequela of HIT), is an important diagnostic clue for HIT. This is because HIT is strongly associated with thrombosis, both in absolute and relative terms; in one study, the relative risk for thrombosis (≈12) reflected a frequency of venous thromboembolism in HIT of approximately 50% versus a non-HIT background rate of approximately 4%. Although HIT-associated thrombosis occurs at a median of day 10, the range is wide, and many patients develop symptomatic thrombosis at the beginning of the HIT-associated platelet count fall even before criteria for thrombocytopenia are met.

Venous predominates over arterial thrombosis. Most often, lower-limb DVT is observed (sometimes bilateral), whereas upper-limb DVT is strongly associated with intravascular catheter use. Severe HIT-associated DIC can be complicated by microvascular thrombosis (e.g., acral ischemic necrosis despite palpable pulses) (Fig. 1). Warfarin therapy—resulting in acquired severe protein C (PC) depletion—is a major risk factor for venous limb gangrene, and thus warfarin is contraindicated during the acute (thrombocytopenic) phase of HIT (and vitamin K is indicated if warfarin has already been given). Large-artery thrombosis secondary to platelet-rich “white clots” is the classic picture of HIT recognized > 40 years ago usually requires urgent thromboembolectomy for limb salvage. Miscellaneous features of HIT include unusual sites of venous thrombosis (adrenal vein thrombosis leading to hemorrhagic necrosis, mesenteric vein thrombosis, cerebral venous/dural sinus thrombosis), necrotizing skin lesions at heparin injection sites (and rarely at noninjection sites), and anaphylactoid reactions that begin within 30 minutes of an intravenous UFH bolus or within 2 hours of subcutaneous injection of LMWH.

HIT-Associated Disseminated Intravascular Coagulation

Approximately 10 to 20% of patients who develop HIT evince overt (decompensated) DIC, as shown by an otherwise unexplained increased international normalized ratio (INR) or absolute/relative hypofibrinogenemia. The pathogenesis includes procoagulant, platelet-derived microparticles and monocyte activation. Patients often exhibit unusually severe thrombocytopenia and microthrombosis (e.g., acral limb ischemia), and patient serum demonstrates strong platelet activation even in the absence of heparin.

**Other (Differential Diagnosis)**

The fourth “T,” Other cause(s) of thrombocytopenia, is also relatively unhelpful in the ICU, since virtually all critically ill patients have plausible non-HIT explanations for their thrombocytopenia. Prospective studies in critically ill patients have found a frequency of thrombocytopenia of approximately 30 to 50%, which if bilateral leads to life-threatening adrenal failure. Sera from spontaneous HIT patients also exhibit strong platelet-activating properties in the absence of heparin.

**HIT-Mimicking Disorder: Acute DIC/Hepatic Necrosis-Limb Necrosis Syndrome**

Certain HIT-mimicking disorders have been recognized. For example, a postcardiac surgery patient who develops acute-onset and persisting thrombocytopenia, DIC, and multiple organ failure, and who then develops symmetrical peripheral gangrene (i.e., two- or four-limb acral ischemic necrosis) can be misdiagnosed as HIT, particularly since postcardiac surgery patients often test EIA positive. The author has reported several critically ill patients who have developed multiple limb ischemic necrosis postcardiac surgery and has noted the combination of DIC with preceding “shock liver” (also termed “acute hepatic necrosis” or “ischemic hepatitis”). The pathogenesis of microvascular thrombosis reflects profoundly disturbed procoagulant–anticoagulant balance, for example, marked increased in thrombin generation with concomitant severely reduced antithrombin (AT) and PC levels, and is analogous to warfarin-induced venous limb gangrene complicating HIT (Table 2).

**Table 3** summarizes aggregate data for 15 non-HIT patients who developed microvascular ischemic limb necrosis (“gangrene with pulses”) complicating acute DIC; none was given warfarin before onset of limb ischemia. All patients evinced the clinical picture of symmetrical peripheral gangrene, with lower limbs characteristically involved, but fingers/hands also affected in approximately one-third of cases. A preceding clinical picture of “shock liver” was seen in 14/15 (93%) patients, consistent with a pathogenic role of natural anticoagulant depletion associated with severe hepatic dysfunction.
Table 2  Ischemic limb necrosis with palpable/Doppler-identifiable pulses: comparison of two thrombocytopenic syndromes

<table>
<thead>
<tr>
<th>Feature</th>
<th>HIT-associated DIC (incl. warfarin-induced venous limb gangrene)</th>
<th>Acute DIC/hepatic necrosis-limb necrosis syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of thrombocytopenia</td>
<td>5–10 days after immunizing heparin exposure</td>
<td>Usually &lt; 4 days after preceding heparin exposure (early-onset and persisting thrombocytopenia)</td>
</tr>
<tr>
<td>Onset of limb ischemia</td>
<td>2–5 days after onset of HIT (or warfarin treatment of HIT)</td>
<td>2–5 days after onset of acute liver dysfunction</td>
</tr>
<tr>
<td>Concomitant large-vessel thrombosis (e.g., DVT)</td>
<td>Usually yes</td>
<td>Usually no</td>
</tr>
<tr>
<td>HIT antibodies</td>
<td>Strong positive EIA and SRA</td>
<td>Severely impaired, with preceding “shock liver” (transaminis) although severe hepatobiliary dysfunction can also be seen</td>
</tr>
<tr>
<td>Liver function</td>
<td>Normal or minor impairment</td>
<td>Severe liver dysfunction; multiple triggers, e.g., cardiogenic or hemorrhagic shock, septicemia, fungemia, and so forth</td>
</tr>
<tr>
<td>Explanation for increased thrombin generation</td>
<td>HIT antibody-induced platelet and monocyte activation</td>
<td>Multiple triggers, e.g., cardiogenic or hemorrhagic shock, septicemia, fungemia, and so forth</td>
</tr>
<tr>
<td>Explanation for natural anticoagulant depletion</td>
<td>Decreased production of PC (warfarin); increased consumption of PC and AT (DIC)</td>
<td>Decreased production of PC and AT (liver dysfunction); increased consumption of PC and AT (DIC)</td>
</tr>
</tbody>
</table>

Abbreviations: AT, antithrombin; DIC, disseminated intravascular coagulation; DVT, deep-vein thrombosis; EIA, enzyme immunoassay; HIT, heparin-induced thrombocytopenia; PC, protein C; SRA, serotonin-release assay.

Early-Onset and Persisting Thrombocytopenia: Coinciding HIT Is Rare

Critically ill patients often develop early-onset thrombocytopenia that persists until death or that resolves with survival. Selleng et al.\textsuperscript{56} identified 25 patients with so-called “early-onset and persisting thrombocytopenia” out of 581 prospectively studied postcardiac surgery ICU patients, and found that the frequency of seroconversion to a positive anti-PF4/heparin EIA did not differ from patients without persisting thrombocytopenia, indicating that the vast majority of seroconversion events are incidental and nonpathogenic. However, if a patient develops a superimposed platelet count fall within the characteristic days 5 to 10 “window” of HIT\textsuperscript{56,57} and/or associated thrombosis\textsuperscript{58} and platelet-activating antibodies are detectable\textsuperscript{56–58} this would indicate “true” HIT coinciding with thrombocytopenia of critical illness. Given that only approximately 1 to 2% of postcardiac surgery patients develop HIT (i.e., a small subset of the \textasciitilde 50–75\% who form anti-PF4/heparin antibodies postcardiac surgery\textsuperscript{59,60}), comparatively few patients would also develop HIT in the setting of early-onset and persisting thrombocytopenia.

Other HIT-Mimicking Disorders in Critically Ill Patients

Other HIT-mimicking disorders\textsuperscript{53} include septicemia (e.g., septic endocarditis with embolic strokes), non-HIT PE-associated consumptive coagulopathy, or even catastrophic antiphospholipid syndrome complicating transition from warfarin to LMWH in a patient with antiphospholipid antibodies who becomes pregnant or requires an invasive procedure.

Serological Picture of Heparin-Induced Thrombocytopenia

Platelet Serotonin-Release Assay (Washed Platelet Assay)

The SRA was invented 30 years ago in the laboratory of Prof. John Kelton,\textsuperscript{18} and even today remains the “gold standard” for diagnosing HIT, given its high sensitivity and (relatively) high diagnostic specificity for detecting pathological HIT antibodies; in contrast, PF4-dependent immunoassays frequently detect nonpathological antibodies.\textsuperscript{22} Our laboratory (McMaster Platelet Immunology Laboratory) performs the SRA at two pharmacological concentrations of heparin (0.1 and 0.3 IU/mL UFH, i.e., conditions where HIT antibody-induced platelet activation is optimal) and supra-pharmacologic UFH (100 IU/mL), where HIT antibody-induced platelet activation is characteristically inhibited.\textsuperscript{18} We also measure serotonin release at 0 IU/mL UFH (i.e., buffer control); by performing this last reaction condition, we are able to identify those unusually strong HIT sera obtained from patients with delayed-onset HIT, HIT-associated DIC, persisting HIT, and so forth. Even without ongoing heparin exposure, an episode of severe HIT often reaches its peak intensity (platelet count nadir) approximately 10 to 17 days after the proximate immunizing heparin exposure.\textsuperscript{4,10,30,31} These patients can fail alternative (nonheparin) anticoagulant therapy that is monitored using the (activated) partial thromboplastin time (PTT), due to the phenomenon of “PTT confounding” (see section, “PTT and INR confounding”).
False-Positive Platelet Activation Assays in ICU Patients

Perhaps because of elevated levels of proinflammatory proteins (e.g., fibrinogen), false-positive platelet activation assays employing a platelet aggregation endpoint—such as citrate-antiocoagulated platelet-rich plasma\(^{61,62}\) or even washed platelets\(^{63}\)—occur commonly in ICU patients, in comparison with the (washed platelet) SRA. A negative or weak-positive PF4-dependent EIA in such a patient points to a false-positive platelet activation assay.\(^{61,62}\)

False-Positive PF4-Dependent Immunoassays

A far more common problem is that of false-positive EIAs. As a general rule, 50% of referred sera with detectable anti-PF4/heparin antibodies by EIA do not contain platelet-activating antibodies, and thus represent false-positive assays.\(^{64,65}\) The frequency may be even higher (70–80%) in the critically ill,\(^{66,67}\) perhaps because of more frequent testing in low pretest probability situations, and possibly also because bacterial infection could trigger formation of nonpathogenic...
Heparin-Induced Thrombocytopenia in Critically Ill Patients

Prevention of Heparin-Induced Thrombocytopenia in the ICU

Reduced Risk of HIT with LMWH and Fondaparinux

Almost 20 years ago, a substantial reduction in the risk of HIT with LMWH versus UFH was reported,1 a finding confirmed in meta-analyses.68,69 This difference in risk of HIT reflects the combination of an approximate threefold lower immunization risk and—among patients with HIT antibodies—a threefold lower risk of “breakthrough” of thrombocytopenia, among patients treated with LMWH versus UFH.7,8 Thus, the overall risk reduction of HIT with LMWH versus UFH is approximately 10-fold (i.e., 2 vs. 0.2% frequency among postoperative patients exposed to prophylactic-dose UFH vs. LMWH for at least 7–10 days),68 and is probably at least an order of magnitude lower still with fondaparinux versus LMWH.70 The greater capacity of UFH (vs. LMWH and fondaparinux) to form ultra-large, more immunogenic, complexes with PF4, and for these larger complexes to activate platelets, likely explains differences in HIT risk.3 Moreover, fondaparinux is much less likely than both UFH and LMWH to potentiate activation of platelets by HIT antibodies.71 The reduced risk of HIT with LMWH appears to be a drug class effect, since reduced immunization frequency has been observed with enoxaparin,72 certoparin,73 and dalteparin.74 The PROPhylaxis for ThromboEmboli in Critical Care Trial (PROTECT) trial75 suggested that dalteparin (vs. UFH) prophylaxis reduces risk of HIT in critically ill patients.

PROTECT Randomized Trial: UFH versus Dalteparin in Critically Ill Patients

The PROTECT trial randomized 3,764 ICU patients in multiple medical centers to receive either dalteparin (5,000 IU once-daily) or UFH (5,000 IU twice-daily), with the primary outcome being proximal-leg DVT (detected by compression ultrasonography).75 Secondary end points included PE and HIT (confirmed by the McMaster SRA). By intention-to-treat analysis, 12 of 1,873 (0.6%) patients randomized to receive UFH developed HIT, compared with 5 of 1,873 (0.3%) patients randomized to receive dalteparin (hazard ratio, 0.47 [95% CI, 0.16–1.35]; p = 0.16). These reported frequencies of HIT are consistent with the expected 0.3 to 0.5% range reported for HIT in critically ill patients.

The HIT Substudy within the PROTECT Trial

A prespecified per-protocol analysis (which excluded patients who already had HIT upon study enrolment) found that significantly fewer patients in PROTECT who received dalteparin versus UFH developed HIT (hazard ratio, 0.27; 95% CI, 0.08–0.98; p = 0.046).75 We performed a PROTECT substudy74 evaluating the potential confounding role of incidental (non-study) heparin exposure (including heparin administered before study enrolment), as a potential factor explaining anti-PF4/heparin immunization and/or breakthrough of thrombocytopenia. When taking such nonstudy heparin exposures into account, fewer study drug-attributable HIT-related seroconversion and breakthrough events occurred with dalteparin versus UFH (p = 0.020).74 Moreover, among patients investigated serologically for HIT, those randomized to dalteparin (vs. UFH) were half as likely to test positive for anti-PF4/heparin IgG (13 vs. 27%; p < 0.001).74

Dalteparin for Postcardiac Surgery Thromboprophylaxis

Based on the findings of PROTECT trial, our hospital now uses dalteparin for routine postcardiac surgery thromboprophylaxis (first dose [2,500 U], with subsequent doses 5,000 U continued until mobilization/discharge) (→Fig. 1). Observational studies of dalteparin versus UFH by Pouplard et al76,77 (→Fig. 2) suggest that the frequency of HIT could be approximately 80% lower (0.5 vs. 2.5%) with dalteparin versus UFH, a finding that corresponds to the aforementioned 73% reduction (i.e., hazard ratio of 0.27) we observed in the per-protocol analysis reported for PROTECT trial.75

Dalteparin Thromboprophylaxis in Critically Ill Patients

Dalteparin was selected for study in the PROTECT trial because it was shown not to bioaccumulate when given in prophylactic doses to renally compromised patients (including patients with dialysis-dependent renal failure).78,79 This is an important consideration when choosing an agent for thromboprophylaxis in the critically ill patient population.

Heparin Use and HIT Post-Cardiac Surgery

Fig. 2 Results of an observational study of the frequency of HIT in patients receiving UFH or LMWH (dalteparin) postcardiac surgery: the Tours (France) experience. The data to construct this figure are obtained from two publications by Pouplard et al.76,77 The area of each box corresponds to the number of patients treated with UFH and LMWH for each respective time period, and thus the data show increasing use of dalteparin over time. The asterisks (*) indicate the patients diagnosed with HIT (by SRA). Although the data do not represent results of a randomized trial, they do nonetheless suggest a reduced risk of HIT (~80% reduction) with dalteparin (8/1,703 = 0.5%) versus UFH (11/437 = 2.5%); p = 0.0004 by Fisher exact test. HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; SRA, serotonin-release assay; UFH, unfractionated heparin.
The treatment principles of strongly suspected (or serologically confirmed) HIT can be summarized as the “do’s, don’ts, and diagnostics”80:

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 (and do give vitamin K if warfarin already given11,42)
   b. Don’t order prophylactic platelet transfusions
   c. Don’t insert an inferior vena cava filter

3. Three diagnostics
   a. Test for HIT antibodies
   b. Test for DIC
   c. Image for lower-limb DVT (as DVT is the most common complication of HIT, and its presence influences duration and intensity of anticoagulant therapy).

Although the author does not believe that heparin flushes adversely influence the clinical course of severe HIT (vis-à-vis the severe consequences of HIT antibodies that strongly activate platelets even without heparin being present), they should be avoided because of their medical-legal risk. Note also that the proscription against platelet transfusions is only a “suggestion” (i.e., a “weak” recommendation),11,81 given that (1) platelet transfusions have not been proven to be deleterious in HIT (rather, two small retrospective studies found no increased thrombotic risk,82,83) and (2) in the ICU a non-HIT diagnosis is much more likely than HIT, and a risk-benefit assessment that includes diagnostic uncertainty would likely favor platelet transfusions for severely thrombocytopenic patients. Inferior vena cava filter use in HIT patients is often associated with DVT progression—including to critical limb ischemia and limb loss84—and their use is not recommended.

These treatment principles should not be applied indiscriminately to the critically ill patient, for several reasons. First, thrombocytopenia in an ICU patient is attributable to HIT only in a small minority of patients; thus, the expected risk-benefit profile of therapeutic-dose, nonheparin anticoagulation in a patient with “true” HIT (high thrombosis with low bleeding risk) does not apply in a non-HIT, critically ill patient (high bleeding risk). Second, renal and hepatic dysfunctions are common in critically ill patients, which can lead to anticoagulant accumulation and increased bleeding risk. Third, coagulopathies are common in ICU, which can confound PTT-adjusted DTI therapy (see section, “PTT and INR confounding”).

PTT and INR Confounding
Confounding of PTT- and INR-monitored anticoagulant therapy results when prolongation of these tests occurs for reasons independent of the anticoagulant being monitored.55 For example, if a patient has a baseline (preargatroban) PTT that is elevated (e.g., secondary to HIT-associated DIC), there is a real risk that the (postargatroban) PTT will be supratherapeutic, typically triggering (inappropriate) interruption/reduction of argatroban dosing,86,87 which given argatroban’s short half-life (40–50 minutes), will lead to rapid loss of anticoagulation. PTT confounding can occur with DIC, liver dysfunction, nonspecific inhibitor (“lupus anticoagulant”), or any other factor that prolongs the PTT.55

INR confounding occurs commonly during argatroban-warfarin overlap, as argatroban itself prolongs the INR. There are reports of limb loss caused by venous limb gangrene when argatroban treatment was prematurely interrupted (because of an elevated INR) during overlap with warfarin.55,88

Choice of Nonheparin Anticoagulation
Only one anticoagulant, argatroban, is approved and currently marketed to treat HIT in the United States (lepirudin has been discontinued). Ironically, argatroban was never proven safe and effective for treating HIT, as the prospective cohort studies89,90 used for regulatory approval did not require positive testing for HIT antibodies, and most enrolled patients likely did not have HIT, whereas most of the (historical) controls likely did have HIT, as they were identified from laboratory logs of test-positive patients. Another concern: the limb amputation rate in the argatroban-treated study patients was relatively high (13.7%),11 perhaps reflecting the aforementioned issue of INR confounding during warfarin overlap. Further, argatroban has undergone minimal formal study in non-HIT patients, a relevant point given that comparatively few ICU patients develop HIT.

Indirect (Antithrombin-dependent) Factor Xa Inhibitors
In the author’s opinion, the indirect (AT-dependent) factor Xa inhibitors, danaparoid and fondaparinux, have numerous advantages over argatroban (for review5,22, and thus the author has mainly treated HIT with danaparoid91 and (more recently) fondaparinux,22 with good overall outcomes.
A major advantage of danaparoid and fondaparinux is that they are not monitored by a global coagulation test such as the PT (thus avoiding the problem of PTI confounding); rather, if desired, drug concentrations can be measured directly (as antifactor Xa levels). However, the indirect Xa inhibitors can accumulate in renal insufficiency, and reduced dosing is appropriate in renally compromised patients. Moreover, prophylactic dose (vs. therapeutic dose) should be given in ICU patients, unless thrombosis is proven, or the clinician is reasonably sure that HIT is present (this is especially important given that danaparoid is largely ineffective when given in prophylactic doses for confirmed HIT\textsuperscript{21}). \textbf{Appendix A} summarizes my current approach for treating a patient with HIT using fondaparinux.\textsuperscript{94} Recent data\textsuperscript{85} suggest that clinicians—such as the author—are increasingly treating patients with suspected HIT with fondaparinux, despite its off-label status for this indication.

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Appendix A Diagnostic and therapeutic approach to HIT: highlighting use of fondaparinux

A. Baseline (pretreatment) diagnostic evaluation

- CBC/differential with blood film, including assessment of nucleated red blood cells (normoblasts), reticulocyte count, and red cell fragments*
- Coagulation tests*: PT (INR), aPTT, fibrinogen, fibrin ð-dimer (quantitative), and/or other fibrin-specific marker(s) (e.g., fibrin monomer), AT³
- Chemistry tests: creatinine, LDH⁴ (compare with simultaneously measured AST, ALT, and CK), bilirubin
- Lower-limb ultrasound for DVT (routine)⁶
- Upper-limb ultrasound for DVT (if upper-limb swelling)⁴

B. Serial laboratory assessment (at least once-daily)

- CBC (follow normoblast count, if elevated)
- Coagulation tests*: PT (INR), aPTT, fibrinogen, fibrin ð-dimer (quantitative) and/or other fibrin-specific marker(s). ± AT³
- 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 m²)
- ± 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): 7.5 mg (or 10 mg) by subcutaneous injection for patient weighing 50–100 kg
- Second and subsequent doses (morning at ~0800 h): 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/mL³
  - AT concentrates: give ~1,000 U every 12 hours (if AT depletion is documented and fondaparinux is being used for anticoagulation)⁶

D. Prophylactic-dose regimen for fondaparinux⁶

- 2.5 mg by subcutaneous injection

E. Freeze residual plasma samples

Facilitate retrospective analysis of cases

Abbreviations: ALT, alanine transaminase; AT, antithrombin; CBC, complete blood count; DIC, disseminated intravascular coagulation; DVT, deep-vein thrombosis; FEU fibrinogen equivalent units; HIT, heparin-induced thrombocytopenia; LDH, lactate dehydrogenase; PT (INR), prothrombin time (international normalized ratio); PTT, (activated) partial thromboplastin time.

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

²The 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 ð-dimer levels.

³An otherwise unexplained elevated INR in a patient with HIT suggests possibility of HIT-associated DIC.

⁴An elevated PTT increases risk of “PTT confounding” with use of PTT-adjusted anticoagulant, for example, argatroban or bivalirudin.

⁵As HIT usually occurs in postoperative patients, an elevated fibrinogen level is expected; thus, a fibrinogen level that is low (< 1.5 g/L [< 150 mg/dL]) or low normal (1.5–2.5 g/L [150–250 mg/dL]) can be seen in severe HIT-associated DIC.

⁶In our laboratory, fibrin ð-dimer is routinely reported up to 4,000 FEU/µL (higher values are reported as > 4,000 FEU/µL), but on request can be further quantitated up to 20,000 FEU/µL; serial ð-dimers are useful in assessing response to therapy.

⁷AT is measured at baseline, and followed serially if there is HIT-associated DIC (fondaparinux is an AT-dependent factor Xa inhibitor).

⁸LD 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.

⁹Approximately 50% of patients with HIT are found to have lower-limb DVT.

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

¹¹As 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.

¹²10 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 to 24-hour interval between next (morning) dose is anticipated.

¹³Intravenous (i.v.) injection can be considered if immediate anticoagulation is desired. If given i.v., flush the line afterward, or administer the fondaparinux in 25 to 50 mL normal saline over 3 to 5 minutes.

¹⁴Dosing decreased to 5 mg if body weight < 50 kg and increased to 10 mg if body weight > 100 kg.

¹⁵The 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 achieve early therapeutic levels of anticoagulation (since there will usually be < 20-hour 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.

¹⁶A target trough drug level of 0.6 to 1.0 anti-Xa U/mL is currently being used by the author; although the anti-Xa level (drawn at ~0600 h) will not be available at the time that the fondaparinux injection is given (~0800 h), the goal of serial anti-Xa levels is to assess whether drug accumulation that warrants subsequent dose reduction is occurring.

¹⁷Low-dose (prophylactic-dose) fondaparinux regimen may be appropriate if: (1) patient has low (or intermediate) probability for acute HIT and (2) no thrombosis is evident; or (3) for various other settings of prophylactic-dose anticoagulation, for example, patient with history of previous HIT who requires postoperative thromboprophylaxis.

¹⁸Assumes normal renal function.