Heparin-induced thrombocytopenia: a clinical and economic review

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Abstract
Introduction
Heparin-induced thrombocytopenia is a serious immune-mediated, drug adverse effect. Research over the last 20 years has vastly expanded knowledge, awareness and management of this condition. This review includes findings mostly from primary source clinical and economic literature from this time period to synthesise a concise summary. We have highlighted key points regarding the pathophysiology, epidemiology and presentation, diagnosis and management, as well as the economic impact of heparin-induced thrombocytopenia. It is established that heparin-induced thrombocytopenia is relatively uncommon overall, despite the widespread use of heparin. However, delayed recognition leads to significantly increased morbidity, mortality and disability. Treatment requires prolonged courses of expensive alternative anticoagulants. All of these impose substantial costs to patients, hospitals and society. The aim of this review was to assess the clinical and economic factors influencing heparin-induced thrombocytopenia.

Conclusion
Heparin-induced thrombocytopenia remains a significant clinical problem and is associated with morbidity, mortality and disability. Using heparin products can reduce (but not eliminate) the incidence of heparin-induced thrombocytopenia. Properly administered treatment with factor Xa inhibitors or direct thrombin inhibitors can significantly decrease the direst complications of this condition and mitigate its economic impact.

Introduction
Heparin-induced thrombocytopenia (HIT) is a prothrombotic complication mediated by auto antibodies against heparin-platelet complexes. It causes prolonged morbidity, is fatal in 5%–10% of cases and causes lifelong disability in another 10% of cases1. Over the last two decades in particular, research has advanced our understanding, diagnosis and management of HIT. Nonetheless, the incidence of HIT is unlikely to decline because heparins remain a key therapy for thromboembolic and ischemic disorders. Besides, heparins are recommended and are widely used for prophylaxis of venous thromboembolism (VTE)2,3. Increasing adherence with this recommendation can be expected because it is tracked as a marker of quality improvement with potential reimbursement implications, given the resource constraints in healthcare. Not surprisingly, a growing body of literature, over the last decade, has begun to highlight the economic impact of HIT. This review draws largely on original primary source publications. We distilled this literature for the most salient findings in order to present a consolidated clinical and economic review of HIT.

Discussion
Epidemiology
Up to 8% of patients receive heparins form HIT antibodies4. However, less than 10% of these patients develop HIT and an even smaller proportion experience symptomatic thrombosis5. Similarly, less than 1% of patients in the intensive care unit (ICU) develop HIT although multifactorial thrombocytopenia is common (30%–50%) in this setting6,7. These may be occurring due to platelet and antibody polymorphisms among other, yet undefined, patient factors8. Nonetheless, certain risk factors and specific patient populations at risk have been defined9-12: 1) HIT is far more likely with unfractionated heparins (UFH) than with low molecular weight heparins (LMWHs);2) there is increased risk of HIT with bovine UFH (relative to porcine UFH), therapeutic versus prophylactic doses and prolonged duration of therapy of >5 days and 3) there is a 2:1 female to male gender predilection and an increased incidence in elderly and postsurgical (relative to medical) patients10,11. Cardiovascular or orthopaedic surgery patients are peculiar; in that, 30%–50% develop HIT antibodies although clinical HIT occurs in less than 3% and 5% patients, respectively12. HIT is uncommon in uremic, paediatric and obstetric patients. Interestingly, other risk factors for hypercoagulability such as cancer, diabetes, lupus, antiphospholipid syndrome, infection and trauma, are present in greater than 60% of patients with HIT13.

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Pathophysiology

Two types of HIT have been described: HIT type 1 and HIT type 2. HIT type 1 is now often called heparin-associated thrombocytopenia. It is non-immune mediated, has minimal risk of thrombosis and is seen in 10%–30% of patients receiving heparin. It is caused by a direct aggregating effect of heparin on platelets manifesting in mild thrombocytopenia within a few days of exposure. Platelet count rarely drops to <100 × 10⁹/L and rebounds within a few days after discontinuing all heparin. HIT type 2 (the focus of the rest of this review) is seen in 1%–3% of exposed patients. It is a true immunologic disorder associated with a risk of arterial and venous thromboses 20–40 times to that seen in control populations. This high risk persists for weeks even after the platelet count normalises. It is a true immunologic disorder associated with a risk of arterial and venous thromboses 20–40 times to that seen in control populations. This high risk persists for weeks even after the platelet count normalises. It is a true immunologic disorder associated with a risk of arterial and venous thromboses 20–40 times to that seen in control populations.

Ordinarily, heparin and PF4 are devoid of immunogenicity but when bound, the resultant macromolecule is antigenic and attaches to the surface of activated platelets. The mechanism for antigenicity appears to involve a conformational change in platelet surface-bound PF4 which then stimulates immunoglobulin G (IgG) production. The avidity of IgG binding to the neoantigen is optimal when there is about a 1:1 ratio of PF4 to heparin molecules. This may, in part, explain the relatively low (<3%) incidence of clinical HIT despite the presence of heparin-PF4 antibodies in 20%–50% of cardiac surgery patients. It has been postulated that surface-bound PF4 levels are depleted by excess concentrations of UFH used during cardiopulmonary bypass, leading to suboptimal conditions for neoantigen formation and subsequent antibody binding. IgG binding to the platelet-surface bound heparin-PF4 neoantigen creates a self-amplifying process by inducing intense platelet activation and the release of procoagulant factors. Further, the immune complexes interact with monocytes and endothelial cells causing endothelial damage and tissue factor expression. Platelet activation is a pivotal feature of clinical HIT and the resulting cascades lead to intravascular thrombogenesis (Figure 1). The immune complexes are cleared by the reticuloendothelial system causing moderate thrombocytopenia, but spontaneous bleeding is not a feature of HIT. As long as heparin is withdrawn, the antibody response is extinguished over time with antibodies undetectable after 3–4 months.

Presentation

Three patterns have been described in the presentation of HIT: rapid, delayed or typical. In 25% of patients, a rapid onset characterised by an abrupt decrease in platelets within a few hours of heparin exposure, is seen. This form is mostly attributable to a prior immunising heparin exposure in the preceding 100 days with residual circulating levels of HIT antibodies. Although uncommon, delayed-onset HIT can occur after 40 days but is not always associated with thrombocytopenia. Thrombocytopenia occurring 5–10 days after exposure to heparin is the typical pattern for about 65% of patients without prior heparin exposure or whose last exposure was >100 days prior. After surgery with cardiopulmonary bypass, patients experience a transient consumptive and dilutional thrombocytopenia which typically starts to recover by postoperative day four. Therefore in these patients, thrombocytopenia that persists or a recurrent decline observed after four days should raise suspicion for HIT.

Approximately 50%–75% of patients will eventually develop a thrombosis if untreated, and indeed, a thrombotic event is recognized before thrombocytopenia in 20% of patients.

Figure 1: Simplified pathophysiological cascade of HIT:

1 IgG, Immunoglobulin G.
Thrombocytopenia >50% fall in platelet count or a trough of 20–100 × 10^9/L
Timing Onset within 5–10 days of exposure or <1 day if prior exposure within 100 days
Thrombosis New thrombosis; skin necrosis at heparin injection sites
Other causes of thrombocytopenia No other cause identified

### Table 1. 4T score prediction model for pretest probability of HIT.

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<th>4Ts</th>
<th>Score</th>
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<tr>
<td>Thrombocytopenia</td>
<td>&gt;50% fall in platelet count or a trough of 20–100 × 10^9/L</td>
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is a 5% daily risk of thrombosis if untreated.32 Given this urgency, plus the slow turnaround of laboratory testing, the diagnosis of HIT is initially primarily clinical. HIT should be suspected whenever thrombocytopenia and/or thrombosis occur in the context of a temporal relationship to heparin exposure. Suggestive clinical criteria have been defined: unexplained thrombocytopenia up to <50% of the baseline that occurs 4–10 days after starting heparin, skin necrosis at heparin injection sites and anaphylactoid reactions following an intravenous heparin bolus.33,34 However, the picture is often confounded by the concurrence of multiple other reasons for thrombocytopenia. Additionally, a positive diagnosis has major implications that include initiation of a prolonged expensive course of alternative anticoagulation, attendant risks of bleeding and treatment of any thrombotic complications. Therefore, confirmatory tests are necessary.

Available tests fall into two categories immunological and functional assays.35 The immunoassays detect the presence of the heparin-PF4 complex antibody.36,37 Examples include the PF4-enzyme-linked immunosorbent assay (ELISA) and particle gel immunoassays.38 The PF4ELISA assay utilises photometric analysis at 405 nm as a quantitative indicator of HIT antibodies. An optical density (OD) >0.4 is considered positive—the higher the OD, the more strongly positive the result. These immunoassays are widely available, relatively quick and highly sensitive (90%–97%).39 However, specificity (<80%) and positive predictive values (50%) are poor due to cross-reactivity with other antibodies.40 Consequently, a strongly positive OD (≥2) does not necessarily indicate the presence of platelet-activating IgG antibodies. This creates potential for inappropriate therapy, particularly if the clinical picture is uncertain and OD weakly positive (0.4–1.0).

Therefore, general and disease-specific clinical prediction models have been developed to define the pretest probability of HIT and aid the decision to proceed with testing and interpreting of results.41–43 The 4T test has been validated and is widely used; it assigns points for clinical characteristics that include thrombocytopenia, timing, thrombosis and other causes for thrombocytopenia (Table 1). A score of ≤3 indicates a low pretest probability of HIT [0%–3% chance of HIT] and lab testing is not indicated or recommended. A score of 4–5 indicates an intermediate risk, while a score ≥6 indicates a high risk of HIT.

Functional assays measure the ability of circulating heparin-PF4
antibodies to aggregate or to activate normal platelets; they are highly specific, technically demanding, time-consuming and require selected donor platelets. As such, they are mostly limited to reference laboratories for use in confirming positive immunoassays. Examples include heparin platelet aggregation test, flow cytometry, heparin-induced platelet activation and serotonin release assay (SRA). SRA, the gold standard test, is highly specific and sensitive for HIT. It is complex and expensive because it utilises radioactive isotopes. First, platelets from donors, previously shown to be reactive to a panel of heparin-PF4 antibodies, are incubated for uptake of $^{14}$C serotonin. Next, they are washed to remove free serotonin. Then, they are mixed with patient serum before being exposed to therapeutic and supra-therapeutic concentrations of heparin. Platelet activation is measured by the percentage of serotonin radio-isotope released. The test is positive if at least 20% is released in the presence of therapeutic heparin levels (0.1 U/ml) with substantially reduced release in the presence of supra-therapeutic (100 U/ml) heparin concentrations. The test is indeterminate if there is >20% release with high heparin concentrations.

The complexity involved in making a certain diagnosis of HIT, as discussed, underscores why HIT has been described as a clinico-pathological syndrome. Clinical suspicion and symptoms must be interpreted in context of subsequent laboratory findings and vice versa. It is often helpful, if not imperative, to involve a haematologist in the management of these patients.

Prevention and management
Prevention of HIT is hampered by the lack of inexpensive and easily reversible alternatives to heparins. Consequently, if clinically appropriate for prophylaxis of VTE, limiting the duration of the use of UFH or substituting LMWHs for UFH, particularly in female postsurgical patients, are considered.
the only two practical options available for reducing the incidence of HIT at present. Although there is such a paucity of data, the direct factor Xa inhibitor–fondaparinux may be considered as an option, since just like LMWHs, it is administered by a subcutaneous injection, once or twice daily. Close monitoring of platelet count in the highest risk patients facilitates prompt diagnosis and early treatment which helps in limiting morbidity. Fortunately, more options are now available and a more widely accepted approach to management has now been established (Figure 2). Once HIT is suspected or diagnosed, all sources of heparin must be immediately discontinued and the patient must be evaluated for new thromboses or necrosis. Platelet transfusion for thrombocytopenia is not recommended due to concerns about precipitating a thrombotic complication. Platelets can be, and have been, safely used for active bleeding or invasive procedures. Merely discontinuing heparin is insufficient, given the ongoing risk of new thromboses. Therefore, unless contraindicated (such as by active bleeding), systemic anticoagulation with an alternative agent is imperative.

Several direct factor Xa inhibitors and direct thrombin inhibitors (DTIs) have been introduced and approved for anticoagulation in HIT. Danaparoid is approved for HIT but is unavailable in the USA. Lepirudin is no longer being manufactured. Bivalirudin and argatroban are currently approved for use in HIT, and there is growing evidence supporting the use of Fondaparinux. These are all parenteral medications and the role, if any, for the newer oral anticoagulants–rivaroxaban, apixaban and dabigatran, remains undefined. Bivalirudin (short half-life and predominant proteolytic metabolism) is US Food and Drug Administration-approved for use in cardiopulmonary bypass in patients with active or suspected HIT. After adequate systemic anticoagulation is achieved, transition to long-term anticoagulation with warfarin is started. Some crucial points need emphasis here. Warfarin is started in low doses and only after the platelet count has recovered to normal. This is to reduce the risk of early hypercoagulability caused by depletion of protein C and avoid precipitating venous limb gangrene or skin necrosis. Also, DTIs can prolong the International normalised ratio (INR), so there should be at least a five day overlap with warfarin to ensure that a therapeutic INR is achieved before the DTIs are discontinued. Duration of anticoagulation is at least three months (if no thrombotic complications occur) or six months (if thromboses do occur).

Economic considerations

The economic impact of HIT is ultimately borne by society and it encompasses the additional acute costs imposed on hospitals and third party payers for its diagnosis and management. Total hospital costs are increased when patients develop HIT and even more so if heparin-induced thrombotic thrombocytopenia (HITT) ensues. Patients, at the very least, require longer hospital stay for parenteral administration of alternative anticoagulation as well as management of any thrombotic complications. Among medical patients in the US who developed HIT, hospital costs were reported higher by an average of about US $41,000 compared to those without HIT. Patients, at the very least, require longer hospital stay for parenteral administration of alternative anticoagulation as well as management of any thrombotic complications. Among medical patients in the US who developed HIT, hospital costs were reported higher by an average of about US $41,000 compared to those without HIT. Likewise, European researchers found a mean incremental cost of €3500–€9000 with higher costs in surgical patients than in medical patients, and the cost drivers were extended hospital stays and cost of alternate anticoagulants. Similarly, a small US case-control study found that HIT patients had a two week increase in length of stay, incurring an average loss of $14,000–$20,000 per patient, depending on the payer.

These additional costs carry greater impact when hospital reimbursement is based on diagnosis related groups (DRG) as with US Medicare patients. In such systems, a global payment is made per DRG, and specific items such as laboratory, medications and diagnostic procedures are not separately reimbursable. Medicare does make additional payments for certain complications, but the sums are small and rarely cover their true cost. Leykum et al. estimated additional DRG reimbursements for HIT at $820.05 and for HITT at $1749.98.

Given these extra costs, researchers have performed economic analyses of the prevention and management of VTE, considering the different costs and incidence of HIT with different drugs. The most commonly compared have been UFH and LMWH because the unit cost of UFH is far cheaper, but it has a much higher incidence of HIT as compared with LMWH. Does the reduced incidence of HIT and differences in other complication rates justify using the more expensive LMWH? One study addressed this concern in a retrospective analysis of over 10,000 patients who received either UFH or LMWH. The incidence of HIT was higher for UFH at 0.51% as compared with 0.084% for LMWH, and costs with LMWH were $13.88 less per patient as compared with UFH. In another clinical study, researchers analysed data from a prospectively collected registry of 349 patients with serologically confirmed HIT. They found no difference in length of stay, but overall hospital costs for patients exposed to UFH were about double the costs for those exposed to LMWH ($113,100 versus $56,325).

However, these cost comparisons of actual clinical practice were limited by the variables that were analysed. For example, neither UFH nor LMWH could be compared to no prophylaxis, because use of prophylaxis is considered standard of care nor were the costs considered in a
mortality or quality of life context. These and other limitations can be overcome with the use of a decision analytical model. One such study analysed the cost effectiveness of enoxaparin versus UFH in a cost per quality adjusted life year context (QALY)\(^5\). QALY's are used to consider both the quantity and quality of the years of life gained by an intervention. A year in full health is given a value of 1, death a value of 0 and alternate health states are assigned values in between. Enoxaparin was found to be the cost-effective option with savings of $4550.17/QALY.

Another analysis was a three way comparison of enoxaparin, UFH and no prophylaxis with an averted death being the outcome measure\(^5\). Enoxaparin was also found to be the cost-effective option, completely dominating UFH which was both more costly and less effective. The incremental cost per death averted between enoxaparin and no prophylaxis was only $9100, a very compelling result supporting prophylaxis. These data support the use of enoxaparin for VTE prophylaxis. It is noteworthy that similar cohort simulation models of enoxaparin versus fondaparinux for VTE prophylaxis, in major orthopaedic surgery of the lower extremities, have found fondaparinux to be both more effective and less costly\(^5\).

The discussion so far only covers cases of confirmed HIT. However, suspected HIT is far more common and involves real costs to an institution regardless of subsequent HIT confirmation. Whereas, thrombocytopenia can occur for many reasons, and clinicians now maintain such a high index of suspicion for HIT that testing with the widely available immunoassays is common practice. One study estimated that HIT is over-diagnosed by as much as 100% using such tests\(^5\). This risks overtreatment because a positive ELISA would prompt initiation of anticoagulation with a DTI or direct factor Xa inhibitors before confirmatory functional assays are completed. In 2006, the daily cost of therapy with different DTIs, based on average wholesale price, ranged from $533–$1749\(^6\). This daily cost would then be incurred until confirmatory test results are available which could take as long as one to two weeks if the tests are not performed locally. Thus, the cost of testing is compounded by the high acquisition costs of DTIs plus the risk of bleeding complications\(^6\). It is therefore crucial to ensure appropriate use of DTIs—limiting them to those with an intermediate or high clinical probability of HIT. Protocols to support this have been tested and shown to be cost-effective by avoiding unnecessary drug costs, averting the cost of DTI-associated bleeding and ensuring prompt cessation of treatment after negative confirmatory testing\(^6\).

There are also acute costs to the patients of mortality and prolonged morbidity, including costs of long-term anticoagulation as well as chronic costs of disability from strokes and limb amputation. These substantial costs also ultimately accrue to society. For instance, it has been estimated that for the first two years after trauma-related amputation, mean healthcare costs in 2002 were about $91,000 with an estimated lifetime cost of about $509,000\(^6\). There is about a 10% rate of amputation among HIT patients who develop thrombotic complications\(^6\). Even considering this in the context of the US alone gives an indication of the enormity of the costs involved. For instance, there are over 5 million ICU admissions annually in the US with an estimated 0.3%–0.5% incidence of HIT\(^6\). Roughly extrapolating the HIT-related amputation rate to just this group would result in well over 1000 attributable amputations with consequent costs of several tens of millions of dollars annually.

**Conclusion**

Given the rising healthcare costs, aging population and resource constraints, costly and potentially avoidable conditions are a high priority target. This review provides evidence to support that HIT remains a significant clinical problem, and it is associated with prolonged and expensive morbidity, mortality and disability. Judicious use of heparin products can reduce (but not eliminate) the incidence of HIT. Vigilance and selective use of testing will ensure prompt diagnosis. Appropriately directed treatment with factor Xa inhibitors or direct thrombin inhibitors can significantly decrease the direct complications and mitigate the economic impact. Prophylaxis of venous thromboembolism using LMWHs or fondaparinux is cost-effective; however, acquisition costs and the costs of treating any associated complications must be considered while choosing the prophylactic agent.

### Abbreviations list

DRG, diagnosis related groups; DTI, direct thrombin inhibitors; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; HIT-T, heparin-induced thrombotic thrombocytopenia; ICU, intensive care unit; IgG, immunoglobulin G; INR, international normalised ratio; LMWHs, low molecular weight heparins; OD, optical density; PF4, platelet factor 4; QALY, quality adjusted life year; SRA, serotonin release assay; UFH, unfractionated heparins; VTE, venous thromboembolism.

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