

**Proactive Prophylaxis: Multidisciplinary Prevention of Pulmonary Embolism and
Deep Vein Thrombosis
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**Heparin Induced Thrombocytopenia: Management and Challenges
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Objectives:

1. Define HIT
2. Outline an appropriate diagnostic approach
3. Identify effective and safe therapeutic management options

Abstract:

Heparin-induced thrombocytopenia (HIT) is a rare but serious complication of heparin therapy. In some patients, heparin causes platelets to release large quantities of platelet factor 4 (PF4), with which it forms complexes. Patients may form antibodies to these complexes, which activate platelets, causing them to aggregate. This can cause the platelet count to decline, and the platelet-rich aggregates can form thrombi in both the venous and arterial systems. These clots can be life-threatening if they form pulmonary emboli or arterial thrombi in the renal, cerebral, or coronary circulation. This syndrome is known as HITT: heparin induced thrombocytopenia and thrombosis.

Four days of heparin exposure are usually required before HIT develops, although rapid onset of HIT can occur in patients given heparin after a recent prior exposure. Although HIT can develop after heparin has been stopped, this is extremely rare. Occasionally, HIT may present with skin necrosis at the site of heparin injection, rather than thrombocytopenia and thrombosis. The risk of HIT is lower with low molecular weight heparin, but it has been described in such patients as well.

Hospitalized patients may have numerous potential causes of thrombocytopenia, and these must be explored at the same time that HIT is considered. Clinical suspicion for HIT is triggered either by a rapid decrease of >50% in the platelet count or by true thrombocytopenia (below 100,000), usually beginning after 4-10 days of heparin exposure. However, it is key to recognize that many patients treated with heparin have a mild and transient decrease in platelet counts 1-4 days after starting therapy. The thrombocytopenia is generally mild (median 50,000-60,000), so careful attention should be paid to *relative decreases* in the count. If a patient has a very low platelet count (<10,000), HIT is extremely unlikely. More than 95% of cases of HIT are a benign HIT-type I, a self-limited process that is not immune-mediated. These patients can safely remain on heparin therapy. In contrast, the more serious antibody-driven syndrome is classified as HIT-type II.

Despite the thrombocytopenia, HIT is a hypercoagulable state, so patients in whom bleeding is the main presentation should be presumed to have other causes of thrombocytopenia. If unexpected thrombotic events occur while a patient is being treated with heparin and in the patient has relative thrombocytopenia, a presumptive diagnosis of HIT should be made, and treatment should begin immediately.

The evaluation of thrombocytopenia without thrombosis can be complicated by limitations in the available diagnostic tests. There is no single laboratory test available to diagnose HIT. Tests are available to determine the presence of antibodies and the degree of platelet aggregation, which should be used in combination with the clinical picture. The most common test for the more serious form of HIT detects antibodies to the heparin-PF4 complex. It has good sensitivity (false negative tests are uncommon) but poor specificity (i.e., the presence of antibody is not diagnostic for HIT). This is particularly important in cardiac surgery, where about 50% of patients may develop antibodies without clinically significant HIT. The evidence does *not* support routine antibody testing of patients who have normal and stable platelet counts and no clinical manifestations of thrombosis.

For patients with HIT, two direct thrombin inhibitors (DTI) are approved for medical treatment: intravenously administered argatroban and lepirudin. In addition, subcutaneously administered fondaparinux, a selective inhibitor of factor Xa, has shown promise for treatment of HIT in preliminary studies, as has bivalirudin, another intravenously administered DTI. Bivalirudin is approved for use in the cardiac catheterization laboratory for both diagnostic and interventional procedures. In the clinically stable patient with HIT but no thrombosis, fondaparinux is an appealing option, since it can be given as a once daily subcutaneous dose, while the other agents require continuous intravenous infusion. All DTIs carry significant risk of hemorrhage; unlike heparin, none of them have antidotes, so careful evaluation is necessary to prevent bleeding.

In summary, HIT is a potentially serious adverse drug reaction requiring appropriate diagnosis and timely management. A multidisciplinary approach is instrumental in providing comprehensive care for the patient.

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