

## The Cardiac Related Thrombocytopenia

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### Abstract

Thrombocytopenia is a common problem in cardiovascular patients. The aetiology and management may be different than those in other populations. The drugs that are used during percutaneous coronary interventions most commonly associated with thrombocytopenia are the glycoprotein (GP) IIb/IIIa receptor inhibitors and heparin. Thienopyridines rarely cause thrombocytopenia. The platelet count falls, primarily due to platelet damage and destruction in the bypass circuit and hemodilution after open-heart surgery. Heparin is the most common drug to be implicated in thrombocytopenia in intensive care unit patients. Determining the etiology for the low platelet count is important for the implementation of appropriate management. Heparin-induced thrombocytopenia is a potentially devastating immune mediated adverse drug reaction caused by the emergence of antibodies that activate platelets in the presence of heparin. Despite thrombocytopenia, bleeding is rare; rather, HIT is strongly associated with thromboembolic complications involving both the arterial and venous systems.

**Keywords:** Thrombocytopenia; Heparin induced thrombocytopenia (HIT); Platelet factor 4; Bleeding; Thromboembolism

### Introduction

Thrombocytopenia is defined as a platelet count below the 2.5th lower percentile of the normal platelet count distribution [1]. The third US National Health and Nutrition Examination Survey (NHANES III) support the traditional value of  $150 \times 10^9/L$  as the lower limit of normal [2]. However, platelet counts between 100 and  $150 \times 10^9/L$  may be normal if it is stable for more than six months [3]. So the cutoff value of  $100 \times 10^9/L$  or 50% reduction compared to baseline (is used for definition of HIT syndrome) may be more appropriate to define pathologic threshold [4]. The severity of thrombocytopenia can be classified into three degree; mild (between  $50-100 \times 10^9/L$ ), moderate (between  $20-50 \times 10^9/L$ ) and severe ( $<20 \times 10^9/L$ ) according to platelet count. A platelet count  $<100 \times 10^9/L$  following percutaneous coronary intervention (PCI) occurs in 3 to 9% of patients [5]. The prevalence may rise to 50% after open heart surgery [6]. It is associated with significant morbidity and mortality due to hemorrhage if unrecognized. There are lots of factors be caused to thrombocytopenia in hospitalised patients, so the diagnosis can be skipped [1]. A structured approach to the diagnosis of thrombocytopenia involves an integration of clinical findings and appropriate support from the laboratory and other medical disciplines [1].

The risk factors for thrombocytopenia in hospitalized patients are advanced age ( $>65$  years), low weight ( $<60$  kg), initial level of platelet count ( $<180 \times 10^9/L$ ), prolonged heparin use (especially unfractionated heparin-UFH), use of glycoprotein IIb/IIIa receptor antagonist (Gp IIb/IIIa), and re-use of Gp IIb/IIIa antagonist. The causes of thrombocytopenia in hospitalised patients can be divided into five main subtitles;

- Pseudothrombocytopenia (Satellite phenomena),
- Sepsis and disseminated intravascular coagulation (DIC),

- Surgical intervention (coronary artery by-pass grafting-CABG, orthopedic surgery): if thrombocytopenia occurs in five days the reason can be hemodilution, platelet consumption or use of intra-aortic balloon pump-IABP. If it occurs after five days heparin induced thrombocytopenia (HIT) can be the reason.),
- Drugs (clopidogrel, heparin, Gp IIb/IIIa antagonist and others),
- Others (after cardio-pulmonary resuscitation-CPR, immune thrombocytopenic purpura-ITP and diseases related to bone marrow or spleen).

### Mechanism of Thrombocytopenia

Decreased production and increased destruction of platelets are the main mechanisms for a reduced platelet count. The two mechanisms may be co-exist in some clinical situations. Aplastic anaemia, myelodysplastic syndromes, and chemotherapy-induced thrombocytopenia are typical examples of the reduced platelet count due to bone marrow failure syndromes. On the other side increased destruction is seen in conditions such as DIC and the thrombotic microangiopathies. Platelet sequestration and hemodilution are the other two less common mechanisms. Platelet sequestration is seen in congestive splenomegaly due to portal hypertension. In this situation platelets redistributes from circulating pool to the splenic pool. In patients who have suffered a massive hemorrhage and have received colloids, crystalloids, and platelet-poor blood products, hemodilution is the main mechanism of thrombocytopenia. Multiple mechanisms may contribute to the development of thrombocytopenia in many cases.

### Diagnosis

Medical history can provide invaluable information and may help us to diagnose. We should investigate the presence of a family history of thrombocytopenia (for congenital thrombocytopenia); the initial profile of the thrombocytopenia or of the bleeding manifestations (new onset, chronic, or relapsing); disease history, with particular

reference to autoimmune disorders, infections, or malignancies; pregnancy status; recent medications and vaccinations; travel history (for malaria, rickettsiosis, dengue fever); recent transfusion history; recent organ transplantation history; ingestion of alcohol and quinine-containing beverages; dietary habits; and risk factors for retroviral infections and viral hepatitis. If there is a history of recurrent, symptomatic thrombocytopenia and platelet counts returns to normal within days, we should suspect a drug-induced thrombocytopenia.

When we investigate the cause of thrombocytopenia we must evaluate the patient’s medication carefully. One-third of the thrombocytopenia is based on pseudothrombocytopenia but unfortunately the use of Gp IIb/IIIa antagonist is held responsible for thrombocytopenia by mistake in these patients. There are lots of drugs are related with thrombocytopenia. Certain drugs are associated with thrombocytopenia are listed in Table 1.

Type	Mechanisms	Examples
Hapten-antibody induced	Drug forms covalent linkage to membrane glycoprotein and acts as a hapten to induce a drug dependent antibody response	Penicillin and penicillin derivatives
Drug-dependent antibody	Drugs binds the site on membrane glycoprotein and forms a ‘compound’ epitope or induces a conformational changes elsewhere in the molecule for which the antibody is specific. The immunogene can be a drug metabolite	Quinidine, quinine, NSAIDS, various antibiotics, sedatives, anticonvulsants, many others
Gp IIb/IIIa inhibitors		
Ligand mimetic	Drug reacts with the RGD recognition sequence on (Gp IIb/IIIa) and induces a conformational change elsewhere in the integrin complex that is recognized by antibody?	Tirofiban, eptifibatide, roxifiban and others
Drug-specific antibody	Drug (chimeric Fab fragment) induces antibody-specific for murine sequences that control specificity for GPIIb/IIIa	Abciximab
Drug-induced autoantibody	Drug perturbs the immune response in such a way that drug-independent antibodies specific for a cell membrane GP are produced	Gold salts, procaine amide
Immune complex	Drug reacts with a normal protein (PF4) and reconfigures it to form an immunogenic complex; antibody binds to this complex and forms an immune complex; the immune complex activates platelets via Fc receptors	Heparin

**Table 1:** Drug-induced immunologic thrombocytopenia (DITP): pathogenetic mechanisms.

On physical examination we must pay attention the location and severity of bleeding risk and presence of organomegaly or skeletal abnormalities that can help in the diagnosis of the thrombocytopenia. Mucocutaneous bleeding is an important finding for thrombocytopenia. The presence of joint or extensive soft tissue bleeding occurs in DIC and suggests the presence of coagulation abnormalities. The presence of an ischemic limb of skin necrosis should raise suspicion of heparin-induced thrombocytopenia (HIT) [1].

Examination of the peripheral blood film is the most important diagnostic approach to thrombocytopenia. Peripheral blood examination helps us to make differential diagnosis between real thrombocytopenia and pseudothrombocytopenia. We can see erythrocyte fragmentation (due to thrombotic microangiopathy), blasts (due to leukemia) on peripheral blood film and these are facilitating findings for definite diagnosis. Liver and renal functional tests, a clotting screen with D-dimers, and measurement of lactate dehydrogenase (LDH) are the additional investigations to put definite diagnosis. Second-tier investigations are clinical findings and peripheral blood smear. Bone marrow aspiration and biopsy should be performed when the aetiology is unclear. Reticulated platelets or the equivalent immature platelet fraction can help in discriminating between thrombocytopenia due to bone marrow failure (low percentages) and hyperdestructive thrombocytopenia (high percentages) [7,8], although the specificity of these tests has not been validated prospectively. Limited evidence suggests that plasma glyocalicin and thrombopoietin levels can increase the specificity of reticulated platelets in thrombocytopenia due to increased platelet destruction [9].

When we investigate the cause of thrombocytopenia we must evaluate the patients medication carefully. One third of the thrombocytopenia that are related to the use of Gp IIb/IIIa antagonist is pseudothrombocytopenia. There are lots of drugs are related with thrombocytopenia. Table 1 is showing drug-induced immunologic thrombocytopenia (DITP): pathogenetic mechanisms.

### Heparin Induced Thrombocytopenia (HIT)

Heparin-induced thrombocytopenia (HIT) is the most important and the most frequent drug-induced, immune-mediated type of thrombocytopenia. It is associated with significant mortality and morbidity if unrecognized. It has been found that 8% of heparinized patients develop the antibody associated with HIT and that approximately 1-5% of patients on heparin progress to develop HIT with thrombocytopenia [10].

It increases the risk mortality and morbidity because frequently the diagnosis is missed. Heparin is used for a variety of clinical situations such as atrial fibrillation, prophylaxis of deep vein thrombosis, cardiopulmonary surgery, and percutaneous coronary intervention. Thrombocytopenia is one of the important complications of heparin after bleeding. HIT is defined as a decrease in platelet count during or shortly after exposure to heparin. Sinan et al. (2014) described a patient with a giant thrombus on the apical wall of the left ventricle due to HIT syndrome after anterior MI [11].

Two different types of HIT are recognized. HIT type 1 was formerly known as heparin-associated thrombocytopenia. It is a benign form of HIT syndrome since it does not increase the risk of vascular thrombosis. The principal mechanism is not known but it seems to be

nonimmune mediated. It is probably related to the proaggregation effect of heparin. It occurs in 10% of heparinized patients on the first few days of heparin use. Thrombocytopenia is not serious (platelet count rarely decreases under  $100,000/\text{mm}^3$ ) and is temporary. HIT type 2 is immune mediated and associated with a risk of thrombosis. This type constitutes the majority of cases of HIT syndrome. It is the malignant form and the HIT syndrome discussed herein refers to HIT type 2.

One third of HIT patients have arterial or venous thrombosis. Girolami et al. [12] reported that 5 of 598 patients taking subcutaneous unfractionated heparin (UFH) had HIT syndrome. This study showed that HIT-related antibodies occur much more in patients who underwent cardiovascular surgery than in patients who underwent orthopedic surgery. Also, these antibodies occurred more frequently due to the use of UFH than the use of LMWH. However, the antibodies developing in patients receiving UFH frequently cross-react with LMWH. In a study on 665 patients undergoing elective hip arthroplasty who had been randomized to receive either UFH or LMWH for thrombophylaxis, Warckenitn and colleagues reported that HIT occurred in 9 of 332 patients who received UFH and in none of 333 patients who received LMWH (2.7% vs. 0%,  $p=0.0018$ ) [13].

HIT syndrome occurs owing to antibodies against heparin and platelet factor 4 complex. The immune complex induces platelet aggregation causing thrombocytopenia. The immune complex is also located in the endothelium and induces tissue factor. This provokes the occurrence of thrombosis both in arteries and in veins. The initiation of HIT syndrome can be early or late. Generally, the syndrome occurs 5 or more days after initiation of heparin. However, if the patient has been previously sensitized it may occur within a few days or hours [14-16].

The diagnosis of HIT remains a clinical one, supported by confirmatory laboratory testing. The criteria include: (a) thrombocytopenia (a drop of the platelet count to below  $1,000 \times 10^9/\text{L}$  or a drop of >50% from the patient's baseline platelet count); (b) the exclusion of other causes of thrombocytopenia; and (c) the resolution of thrombocytopenia after cessation of heparin. HIT-antibodies can be demonstrated in vitro by functional tests and immunoassays. Functional tests, which measure platelet activity in the presence of the patient's serum and heparin, include heparin-induced platelet aggregation (HIPA) and the serotonin release assay (SRA) [17]. Although functional platelet tests and immunoassays are important for the diagnosis of HIT, the "4 Ts" scoring system allows evaluation of the pretest probability of HIT. The 4 Ts scoring system is based on thrombocytopenia, timing of onset, thrombosis, and absence of other causes. Patients with low pretest scores (5 points) scores are more likely to test positive (21.4–100% confirmed +) [18].

When HIT syndrome is suspected, cessation of all heparin types must be the first precaution. However, it is not possible to prevent thrombosis at all times, even if heparin is ceased at the earliest moment that the decrease of platelets is recognized [19]. Messmore et al. [20] developed a simple scoring system to aid in the early clinical management of patients suspected of HIT regarding the decision of whether or not to continue with the heparin therapy. The system was designed to arrive at low (0) or possible (1) probability scores without knowledge of laboratory test results (except platelet counts) so as to avoid delays [19]. According to their study, if heparin therapy during the first 5 days of therapy did not result in a platelet count drop or the platelet count did not fall by 30% or there was a significant competing cause for thrombocytopenia [e.g. recent CABG (2–3 days), sepsis,

shock, balloon pump, drugs other than heparin], the score was 0 and the clinical management was to continue heparin therapy if clinically indicated, while waiting for HIT laboratory test results. If thrombocytopenia occurred on heparin therapy and there was no significant competing cause for thrombocytopenia and the platelet count fell by >30% or there were new thromboses, the score was 1 and heparin was discontinued, while waiting for HIT laboratory test results, and an alternative anticoagulant was administered if clinically indicated [20].

The management is as follows: First we should stop all types of heparin therapy. Then, to prevent thrombosis, alternative anticoagulant therapies must be started. Three alternative anticoagulant drugs that do not cross-react with heparin are danaparoid, lepirudin, and argatroban. Since LMWH cross-reacts with UFH, it is contraindicated. Treatment duration is uncertain but at least 2 or 3 months of anticoagulant therapy with danaparoid, lepirudin, or argatroban is necessary. Guidelines from the American College of Chest Physicians recommend the direct thrombin inhibitors as first-line therapy for HIT. Bivalirudin is approved for use in patients with HIT who undergo percutaneous coronary intervention (PCI) [21]. A novel synthetic heparin pentasaccharide, fondaparinux, which does not cross-react with HIT antibodies, can be successfully used for the treatment of patients with HIT [22,23]. Infact fondaparinux does cause antibody generation to the fondaparinux: PF4 complex, but this most often does not result in clinical symptoms of HIT. Warfarin may be the first treatment choice until the platelet count normalizes. However, use of warfarin alone may increase the risk of thrombosis (skin necrosis and gangrene of the lower extremities); warfarin must be used together with one of the three drugs (danaparoid, argatroban, or lepirudin) for at least 5 days.

## Conclusion

Thrombocytopenia in cardiovascular patients, particularly those who are in critical care units and following open-heart surgery, is common, and the differential diagnosis can be extensive. In almost all of these patients, heparin therapy and HIT are included in this differential diagnosis due to the extensive use of heparin in cardiac patients. The diagnosis of HIT is particularly important because of the high incidence of early thromboembolic events after this diagnosis has been entertained. A diagnosis of HIT, as opposed to other causes of thrombocytopenia, may often be made based on clinical or laboratory testing results, allowing appropriate management over both the short and long term. The early initiation of therapy with a direct thrombin inhibitor is recommended when HIT is suspected after PCI or open-heart surgery, or in patients with acute coronary syndromes. If a diagnosis other than HIT is made, heparin therapy can be safely reinitiated.

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