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Drug-induced immune thrombocytopenia (DITP)

Clinical aspects

Drug-induced immune thrombocytopenia (DITP) is a relatively common complication of treatment with many different medications.

DITP should be suspected in any patient who presents with thrombocytopenia of recent onset and unknown cause. However, the diagnosis is often overlooked.

DITP is idiosyncratic (peculiar to the individual patient). There is as yet no way to predict who will develop this complication.

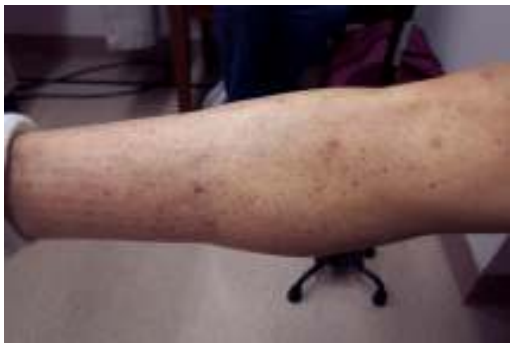
A very large number of medications has been shown to be capable of causing DITP. Heparin is the most common trigger. Heparin-induced thrombocytopenia (HIT) has a quite distinct pathogenesis and the approach to diagnosis and treatment of HIT is very different than that of all other forms of DITP. We will discuss HIT separately after considering DITP induced by drugs other than heparin.

DITP (induced by drugs other than heparin) presenting in an ambulatory patient.

Typically, symptoms occur about one week after starting medication.

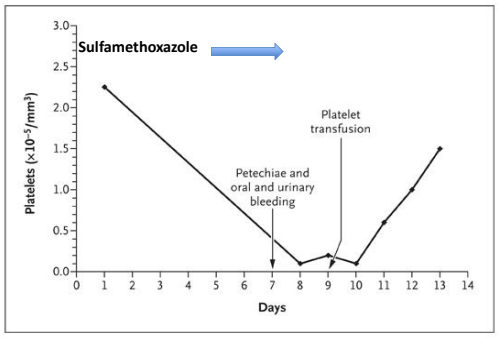
Systemic symptoms may precede bleeding (fever, chills, nausea, light-headedness, even fainting)

Bleeding symptoms vary greatly from one patient to another. At one extreme, patients have florid petechial hemorrhage, ecchymosis, epistaxis, hematuria. At the other extreme, a patient may have only a few petechiae or no symptoms.



Peter Maslak, ASH Image Bank 2011; 2011-3689

Typical course of DITP in a patient treated with sulfamethoxazole



New Engl J Med 357:580-587, 2007

Table 1. Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.*

Drug Category	Drugs Implicated in Five or More Reports	Other Drugs
Heparins	Unfractionated heparin, low-molecular-weight heparin	
Cinchona alkaloids	Quinine, quinidine	
Platelet inhibitors	Abciximab, eptifibatide, tirofiban	
Antirheumatic agents	Gold salts	D-penicillamine
Antimicrobial agents	Linezolid, rifampin, sulfonamides, vancomycin	
Sedatives and anticonvulsant agents	Carbamazepine, phenytoin, valproic acid	Diazepam
Histamine-receptor antagonists	Cimetidine	Ranitidine
Analgesic agents	Acetaminophen, diclofenac, naproxen	Ibuprofen
Diuretic agents	Chlorothiazide	Hydrochlorothiazide
Chemotherapeutic and immunosuppressant agents	Fludarabine, oxaliplatin	Cyclosporine, rituximab

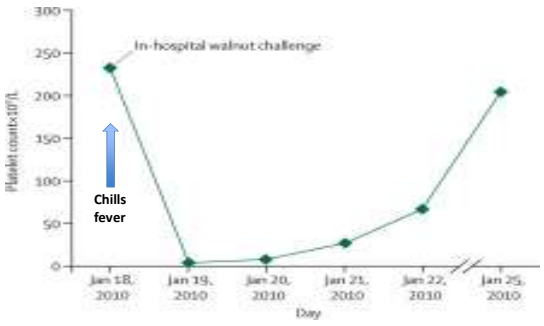
* For a more extensive list, see Aster,[1] Warkentin,[11] and George et al.[12] and the University of Oklahoma Web site (http://www.ouhsc.edu/platelets/DITP.html).

Aster RH, Bougie DW. N Engl J Med 2007;357:580-587.

Substances in foods, folk medicines, herbs, teas and even topical medications can also trigger DITP. Quinine in beverages can cause "cocktail purpura."

A nutty case: 70 yo man experienced recurrent, severe thrombocytopenia and bleeding requiring hospitalization on repeated occasions. Finally associated these episodes with ingestion of walnuts.

A diagnostic challenge with 100 gm of walnuts



Lancet 2012, 379: 776

Any patient who presents with acute thrombocytopenia of unknown etiology should be asked about medications being taken.

It is not uncommon for patients with DITP to deny taking medications. Don't assume the patient has idiopathic (autoimmune) thrombocytopenia (ITP)!

Quinine, Sulfonamides and other antibiotics, and non-steroidal anti-inflammatory drugs(NSAIDS) should be inquired about specifically.

The George criteria for assessing the likelihood that a drug is the cause of acute thrombocytopenia

Table 2. Criteria and Level of Evidence for Establishing a Causative Relationship in Drug-Induced Thrombocytopenic Purpura.*

Criterion and Level of Evidence	Description
Criterion	
1	Therapy with the candidate drug preceded thrombocytopenia, and recovery from thrombocytopenia was complete and sustained after discontinuation of therapy.
2	The candidate drug was the only drug used before the onset of thrombocytopenia, or other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug, with a sustained normal platelet count.
3	Other causes of thrombocytopenia were ruled out.
4	Re-exposure to the candidate drug resulted in recurrent thrombocytopenia.
Level of evidence	
I	Definite — criteria 1, 2, 3, and 4 are met.
II	Probable — criteria 1, 2, and 3 are met.
III	Possible — criterion 1 is met.
IV	Unlikely — criterion 1 is not met.

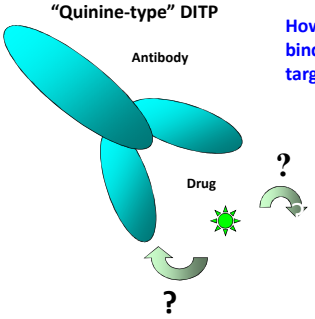
* The information is adapted from George et al.[1]

Aster RH, Bougie DW. N Engl J Med 2007;357:580-587.

DITP is caused by drug-induced antibodies that recognize platelet glycoproteins but many distinctly different mechanisms are involved. Glycoprotein IIb/IIIa (GPIIb/beta 3 integrin) is the most common target.

Often these antibodies can be identified by demonstrating an immunoglobulin that binds to platelets only when a drug is presnt.

"Quinine-type" DITP

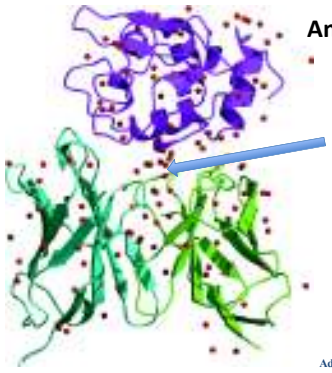


How does drug promote binding of antibody to a targeted protein on platelets?

How do drugs trigger the immune response leading to production of such antibodies?

Glycoprotein IIb/IIIa (α_{IIb}/β_3 integrin)

Drug reconfigures antibody CDR to modify specificity



Adapted from Kondo H et al JBC 1999

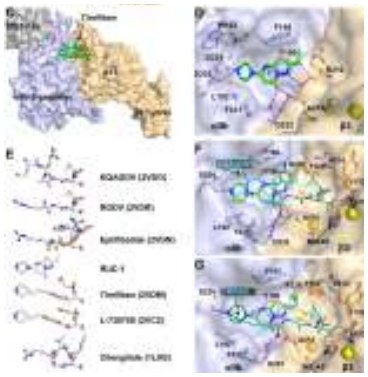
DITP triggered by RGD-mimetic platelet inhibitors

Acute thrombocytopenia, often severe, occurs in 0.5 – 2% of patients treated with RGD-mimetic platelet inhibitors such as eptifibatide and tirofiban.

Thrombocytopenia in patients treated with drugs of this class is caused by a mechanism quite different than that involved in "quinine-type" DITP.

RGD and RGD-mimetics all bind to the same well-defined pocket at the head of the GPIIb/IIIa integrin.

Patient antibodies recognize subtle, drug-specific structural rearrangements clustered about this binding site.



Zhu J et al. Blood 2010;116:5050-5059

Antibodies that cause thrombocytopenia in patient treated with the platelet inhibitors tirofiban, eptifibatide and abciximab are often "naturally occurring."

Therefore acute severe thrombocytopenia can occur within a few hours of the first exposure to drug.

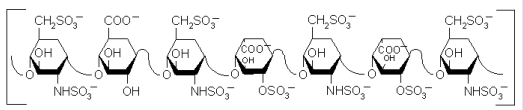
In many patients with DITP, an antibody that reacts with platelets only when the sensitizing drug is present can be detected.

However, it is not unusual for negative results to be obtained in patients with a history strongly suggestive of DITP.

One reason for this is that a drug metabolite may be the sensitizing agent. In such cases, it is necessary to use this metabolite to obtain a positive test result.

Heparin-induced thrombocytopenia and thrombosis (HIT)

Heparin



Highly charged linear glycosaminoglycan (GAG)

Binds to anti-thrombin 3 and enhances its ability to inactivate thrombin and factor Xa.

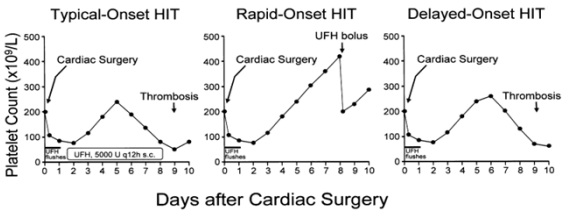
UR Desai 2000

HIT ccurs in 1-5% of patients given unfractionated heparin for 5 days or longer.

Thrombocytopenia itself is not usually of clinical significance. However, a subset of affected patients develop arterial or venous thrombosis, which can be life-threatening.

HIT is still a major cause of morbidity and mortality in patients treated with heparin.

HIT can develop acutely in a patient with pre-existing antibodies and (rarely) up to one or two weeks after stopping heparin (delayed onset HIT).



TE Warkentin, Br J Haematol 121:535. 2003

Digital or limb gangrene due to arterial insufficiency is one of the most dramatic complication of HIT.

However, venous thrombosis +/- pulmonary embolism is more common.

TE Warkentin 2003

Antibodies that cause HIT are specific for complexes formed between heparin and platelet factor 4 (PF4), a basic protein stored in platelet alpha granules.

J Amiral et al 1993
GP Visentin et al
J Kelton et al
A Greinacher et al

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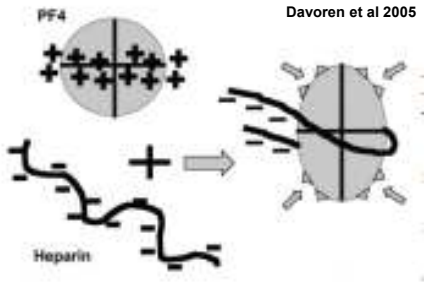
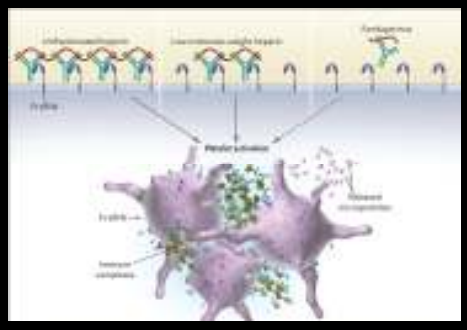


Davoren et al 2005

Current thinking holds that the negatively-charged heparin polymer binds to positive charges on the platelet factor 4 chemokine and modifies its shape. HIT antibodies recognize certain of the resulting structural changes (arrows).

Platelet Activation by Antibodies against the PF4–Heparin Complex.



Kelton JG et al. N Engl J Med 2013;368:737-744.

HIT is a very serious complication of heparin therapy.

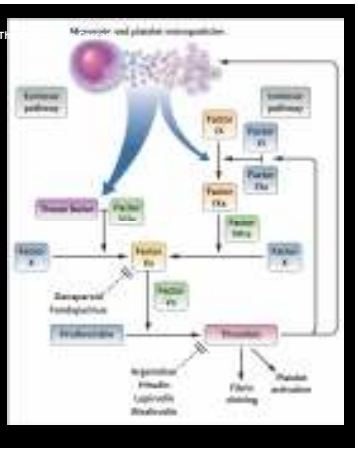
Platelet counts should be monitored daily in all patients receiving heparin in a hospital setting.

If a significant, unexplained drop in platelet levels occurs, a PF4 ELISA test for HIT antibodies should be done and consideration should be given to stopping heparin.

Management of HIT

- Stop heparin!
- Start an alternative anticoagulant
  - Direct thrombin inhibitor (argatroban, lepirudin. others
  - Fondiparinux (Arixtra)
  - Don't start warfarin until recovery from HIT is well underway!

Procoagulant microparticles released from platelets (and possibly monocytes and other tissues) promote generation of thrombin and increase thrombotic risk.



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Mechanisms underlying drug-induced immune thrombocytopenia

Classification	Mechanism	Incidence	Examples of Drugs
Hapten-dependent antibody	Hapten binds covalently to membrane protein and induces drug-specific immune response	Very rare	Penicillin, possibly some cephalosporin antibiotics
Quinine-type drug	Drug-induced antibody that binds to membrane protein in presence of soluble drug	26 cases per 1 million users of quinine per week; probably fewer cases with other drugs	Quinine, sulfonamide antibiotics, nonsteroidal anti-inflammatory drugs
Fiban-type drug	Drug reacts with glycoprotein IIb/IIIa to induce a conformational change (neoepitope) recognized by antibody (one per membrane)	0.2–0.5%	Tirofiban, eptifibatide
Drug-specific antibody	Antibody recognizes cryptic component of thiazide (rib fragment specific for platelet membrane glycoprotein IIIa	0.1–1.8% after first exposure; 1.8–1.9% after second exposure	Abciximab
Autoantibody	Drug induces antibody that reacts with autologous platelets in absence of drug	1.8% with gold; very rare with procainamide and other drugs	Gold salts, procainamide
Immune complex	Drug binds to platelet factor 4, producing an immune complex for which antibody is specific; immune complex activates platelets through Fc receptors	3–4% among patients treated with unfractionated heparin for 7 days; rare with low-molecular-weight heparin	Heparins

* The information is adapted from Aster.[1]

Aster RH, Bougie DW. N Engl J Med 2007;357:580-587.