Published in final edited form as:
Semin Hematol. 2009 January ; 46(1 Suppl 2): S2–14. doi:10.1053/j.seminhematol.2008.12.005.

Pathobiology of secondary immune thrombocytopenia

Douglas B. Cines, MD[1], **Howard Liebman, MD**[2], and **Roberto Stasi, MD**[3]

1*From the University of Pennsylvania School of Medicine, Philadelphia, PA*

2*University of Southern California, Los Angeles, CA*

3*Ospedale "Regina Apostolorum," Albano Laziale, Italy*

Abstract

Primary immune thrombocytopenic purpura (ITP) remains a diagnosis of exclusion both from nonimmune causes of thrombocytopenia and immune thrombocytopenia that develops in the context of other disorders (secondary immune thrombocytopenia). The pathobiology, natural history, and response to therapy of the diverse causes of secondary ITP differ from each other and from primary ITP, so accurate diagnosis is essential. Immune thrombocytopenia can be secondary to medications or to a concurrent disease, such as an autoimmune condition (eg, systemic lupus erythematosus [SLE], antiphospholipid antibody syndrome [APS], immune thyroid disease, or Evans syndrome), a lymphoproliferative disease (eg, chronic lymphocytic leukemia or large granular T-lymphocyte lymphocytic leukemia), or chronic infection, eg, with *Helicobacter pylori*, human immunodeficiency virus (HIV), or hepatitis C virus (HCV). Response to infection may generate antibodies that cross-react with platelet antigens (HIV, *H pylori*) or immune complexes that bind to platelet Fcγ receptors (HCV) and platelet production may be impaired by infection of megakaryocyte bone marrow-dependent progenitor cells (HCV and HIV), decreased production of thrombopoietin (TPO), and splenic sequestration of platelets secondary to portal hypertension (HCV). Sudden and severe onset of thrombocytopenia has been observed in children after vaccination for measles, mumps, and rubella or natural viral infections, including Epstein-Barr virus, cytomegalovirus, and varicella zoster virus. This thrombocytopenia may be caused by cross-reacting antibodies and closely mimics acute ITP of childhood. Proper diagnosis and treatment of the underlying disorder, where necessary, play an important role in patient management.

Keywords

thrombocytopenia; antibodies; drug-dependent antibodies; HCV; HIV; heparin

Introduction

Primary immune thrombocytopenic purpura (ITP) is a disorder of unknown etiology caused by antibody-, and possibly T-cell mediated, platelet destruction by tissue macrophages and suppression of platelet production.[1] ITP remains a diagnosis of exclusion.[2,3] This means not only excluding nonimmune causes of thrombocytopenia, but also other conditions in which an

Correspondence to: Douglas B. Cines, M.D., Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, 513A Stellar-Chance Labs. 422 Curie Boulevard, Philadelphia, Pennsylvania 19104, Phone: (215) 622-3966, Fax: (215) 573-2012, Email: E-mail: dcines@mail.med.upenn.edu.

ITP-like syndrome is present, including those associated with autoimmune and lymphoproliferative disorders, acute and chronic infection, and certain drugs. Although these secondary forms of immune thrombocytopenia share with ITP the generation of self-reactive antiplatelet antibodies, they differ in specific aspects of pathobiology, natural history, and responsiveness to ITP-directed therapy. Moreover, optimal treatment strategies include management of the underlying disorder.

Normal platelet production

Platelet production starts with the complex bone marrow hematopoietic differentiation pathway known as megakaryopoieis.[4] Pluripotent hematopoietic stem cells commit to differentiation as either a common lymphoid progenitor or common myeloid progenitor (CMP). The CMP then commits to another level of differentiation into either the granulocyte-macrophage progenitor or the megakaryocyte-erythroid progenitor (MEP). The signals that cue the stages of commitment are as yet only beginning to be understood. GATA-1, a 50 kDa zinc finger DNA-binding protein encoded by an X-linked gene, acts in concert with another protein, friend of GATA (FOG), which affects transcription without binding to DNA.[5,6] Cells committed to the megakaryocytic lineage and thrombopoiesis, rather than erythropoiesis, begin to express CD41 and CD61 (integrin αIIbβ3 or αIIbIIIa), CD42 (glycoprotein Ib), and glycoprotein V.[7,8] Once committed, each primitive megakaryocyte (MK) progenitor or burst forming unit (BFU-MK), a large complex with satellite collections of megakaryocytes, is capable, under the influence of thrombopoietin (TPO) and interleukin (IL)-3 and Steel factor, of producing up to several hundred mature megakaryocytes. Another form of mature progenitor, the colony-forming unit (CFU-MK) produce colonies that consist of 3 to 50 MKs responsive to TPO, though ~25% require both TPO and IL-3 to generate platelets.[9,10] Each MK produces up to about 4,000 platelets before undergoing apoptosis. A normal adult human produces about 10^{11} platelets daily, and this rate can increase 20-fold, if needed, with exogenous TPO.[4]

TPO and its receptor, c-Mpl, are the major identified regulators of megakaryocyte and platelet production and also have key roles in the differentiation of hematopoietic stem cells. TPO signals via c-Mpl through the Jak-STAT,[11-14] Ras-Raf-MAPK,[15] and PI3K pathways,[16] which promotes survival, proliferation, and polyploidy in megakaryocytes. In vitro studies have shown that TPO induces expression of *c-MYC* in, a proto-oncogene active in various physiologic processes and in the dysregulation of megakaryocyte production.[17] The implications of this finding are yet to be addressed in vivo. The stages of thrombopoiesis include regulation of transcription, megakaryocyte development, endomitotic spindling of the megakaryocyte nucleus, cytoplasmic maturation, formation of active projections (propellants) from the megakaryocyte cytoplasm, extrusion of these propellants from the bone marrow stroma into the circulation, and lastly, separation and maturation into individual platelets.[18]

Primary ITP

Increased platelet destruction

There is extensive evidence that patients with ITP develop autoantibodies, generally IgG, that bind to platelets, which leads to their phagocytosis via Fcγ receptors expressed on tissue macrophages located predominantly in the spleen and liver.[1,19-22] What provokes autoantibody production is unknown, but most ITP patients have antibodies against integrin αIIbβ3 (glycoprotein IIa/IIIb), glycoprotein Ib/IX, or multiple platelet proteins by the time clinical disease, characterized by thrombocytopenia and mucocutaneous bleeding, is evident.[23] Platelet destruction within macrophages or dendritic cells degrades platelet antigens to peptides. Peptides are expressed on the cell surface in the context of MHCII and costimulatory help for presentation to T cells, amplifying the initial immune response and possibly generating

cryptic epitopes from other platelet glycoproteins, which spreads the immune response to involve multiple platelet antigens.[24] ITP is characterized by reducing T-regulatory cells (reviewed in Stasi et al[25]) and Thy-2 cytokines,[26] leading to a Thy1/Thy0 profile (reviewed in Ho-Yen et al[27]) and up regulation of costimulatory molecules[28,29] that facilitates proliferation of antigen-derived CD4-positive T cells and T-cell B-cell cooperation to generate isotype-switched, high affinity antibodies.[30] There is emerging evidence that cytotoxic T cells are increased in the bone marrow[31] and may contribute to platelet destruction[32,33] or impaired production (see below). The importance of platelet destruction in the periphery is affirmed by the fact that two-thirds of patients develop and maintain remission after splenectomy, which curtails phagocytosis, but may also reduce antibody production over time. Likewise, most first- and second-line medical therapies for ITP are believed to work by impeding platelet destruction.[2,3]

Decreased platelet production

For many years, it was assumed that platelet production increased dramatically in patients with ITP as a compensatory response to thrombocytopenia mediated by peripheral destruction. However, it has become apparent, based on studies of in vivo kinetics, that platelet production varies from mildly increased to mildly impaired in most patients with ITP.[34-36] Synthesis of TPO in the liver is not regulated at the level of transcription.[37] Plasma TPO levels in patients with ITP are normal to minimally increased[38] as a result of increased clearance of the hormone and binding to an expanded megakaryocyte mass.[39] ITP antibodies, and possibly T cells,[24] inhibit megakaryocyte development in vitro [35,36,40] and may cause apoptosis and intramedullary destruction of platelets in vivo,[41] contributing to failure of splenectomy and other treatments that act by inhibiting clearance. These findings also provide additional rationale for the effectiveness of TPO-receptor agonists.

Mechanisms of immune thrombocytopenia in secondary ITP

Autoimmune disorders

Systemic lupus erythematosus (SLE)—Antinuclear antibodies are common in patients with ITP, but few develop SLE. However, ~20%-25% of patients with SLE develop moderate-severe thrombocytopenia, which can be readily managed if immune mediated or can be a marker of severe systemic disease.[42] The pathogenesis of thrombocytopenia is multifactorial and includes: (1) antiplatelet glycoprotein antibodies as found in ITP; (2) immune complexes of diverse composition; (3) antiphospholipid antibodies (APLA) (see below); (4) vasculitis; 5) thrombotic microangiopathy; (6) hemophagocytosis; (7) autoantibodies to the c-Mpl receptor[43] and megakaryocyte, and (8) bone marrow stromal alterations[44] not characteristic of ITP.[45] Therefore, a thorough clinical and laboratory assessment is often required before a diagnosis of secondary immune thrombocytopenia should be entertained. It is also important to limit the use of corticosteroids and cytotoxic agents in these often heavily treated patients. Splenectomy may provide only transient benefit and is reserved for patients in whom severe thrombocytopenia is the predominant reason for treatment.[46]

Antiphospholpid syndrome (APS)—Antiphospholipid (APLA) antibodies (lupus inhibitors and those that bind anionic phospholipids, beta-2-glycoprotein I [β2GPI] and prothrombin, among other specificities) are found in 20%-70% of patients with ITP, depending on the thoroughness of the search, but their significance is debated and few patients develop APS.[47-50] The presence of APLA per se does not influence the effectiveness of ITP therapy in terms of inducing a platelet response. However, some, but not all, studies suggest such patients may be at risk for thrombosis once they do respond.[47-51] The diagnosis is complicated by the fact that approximately 25% of patients with APS[45] develop mild-moderate thrombocytopenia. Severe thrombocytopenia in APS correlates more closely with the presence

of antiplatelet glycoprotein antibodies than either APLA or clinical manifestations.[52-55,56] However, platelets do express receptors for β2GPI,[57-59] which in theory could lead to APLA-mediated platelet activation alone or in association with other agonists,[60] and there are anecdotal reports of response to aspirin, perhaps by inhibiting coagulation-mediated platelet consumption.[61-63]

Thyroid disease—Mild-moderate thrombocytopenia is found commonly in patients with hyperthyroidism. Platelet survival is reduced, but returns to normal with restoration of the euthyroid state. Similarly, mild thrombocytopenia responsive to hormone replacement also occurs in some patients with hypothyroidism, possibly due to impaired production.[64,65] However, patients with immune thyroid disease develop immune thrombocytopenia requiring ITP-directed therapy more commonly than can be attributed to chance.[66] Moreover, antithyroid antibodies occur commonly in adults and children with ITP,[67,68] leading some to recommend testing thyroid function in nonresponsive patients and prior to splenectomy.

Evans syndrome (ES)—Patients with ES develop immune hemolytic anemia, immune thrombocytopenia, and occasionally immune neutropenia.[69,70] The remarkable coincidence of two or three seemingly unrelated hematopoietic cell antibodies has now been associated with an underlying complex immunodeficiency in some patients (see below). Hemolysis may precede or follow the onset of thrombocytopenia and is typically more refractory to intervention, and the two cytopenias are often dyssynchronous in their manifestations. The response rates to ITP-directed therapy, including splenectomy, are less than in primary disease. Over 50% of children and some adults with ES have a clinical and pathological presentation that overlaps with the autoimmune lymphoproliferative syndrome (ALPS). ALPS is characterized by the chronic accumulation of nonmalignant lymphocytes leading to lymphadenopathy and (hepato)splenomegaly, >1% CD3+, CD4-, CD8- (double negative) T cells, impaired Fas-receptor/ligand mediated apoptosis in vitro due to mutations in Fas (CD95/Apo-1), or less commonly *Fas* ligand (Fas-L), caspase-8 or -10. Immune thrombocytopenia develops in ~20% of patients [71,72-74,75,76] and may respond relatively poorly to ITP therapies, although recent experience with rituximab and mycophenylate have been encouraging. Immune thrombocytopenia and ES also occur in approximately 10%-15% of patients with common variable hypogammaglobulinemia. The onset of immune thrombocytopenia is typically in the third decade, though onsets from childhood to old age have been reported and typically precede the diagnosis of common variable immune deficiency (CVID) by several years. The diagnosis should be sought in any patient with recurrent infection, as immunosuppressive therapy poses some risk and replacement with immune globulin is indicated.

Lymphoproliferative disorders

There is an increased incidence of immune thrombocytopenia in patients with chronic lymphocytic leukemia (CLL),[77] CD8 T-lymphocyte large granular lymphocytic leukemia (LGL),[78] and possibly Hodgkin's disease.[79,80,81] In CLL, it may be difficult to distinguish immune thrombocytopenia from marrow infiltration and splenomegaly[82] or in the setting of treatment with fludarabine.[83] Severe thrombocytopenia, which occurs in about 1% of patients with LGL, has been associated with clonal suppression of megakaryopoiesis.[84,85]

Infectious agents

Human immunodeficiency virus—The association between immune thrombocytopenia and the acquired immunodeficiency syndrome and subsequently as a presenting feature of HIV infection has been recognized since the early to mid 1980s.[86,87,88] Thrombocytopenia is characterized both by an immune component similar in presentation and response to ITP most evident in the early stages of disease,[89] and progressive ineffective hematopoiesis with a

decrease in platelet production as a result of megakaryocyte infection[90-93] or marrow infiltration[94,95] as the disease progresses. HIV binds the CD4 receptor and coreceptors expressed on megakaryocytes,[96,97] is internalized,[98,99] and replicates within the infected cells[100] leading to dysplasia, blebbing of the surface membrane, and vacuolization of peripheral cytoplasm.[100,101] The immune component is mediated through molecular mimicry involving anti-HIV antibodies that cross-react with platelet-membrane glycoproteins,[102, 103,103-106] immune complexes,[87,107,108,109] and anti-GPIIIa49-66 antibodies that induce platelet lysis, at least in vitro, through a peroxidase-mediated pathway.[106] Secondary causes of thrombocytopenia during HIV infection are generally the result of underlying opportunistic infections, malignancy, medications (eg, chemotherapeutic agents, interferon, and antiviral agents), or, less frequently, thrombotic microangiopathy.

HIV should be excluded in at-risk patients who present with ITP. Patients who present with immune thrombocytopenia early in the course of HIV infection respond to medical therapy (corticosteroids, IV anti-D, and IVIG) and splenectomy as well as patients with ITP without proliferation of HIV infection or untoward incidence of opportunistic infection. Thrombocytopenia in patients with more advanced disease generally responds to highly active antiretroviral therapy.

Hepatitis C virus—In some parts of the world, HCV infection has been detected in up to 30% of patients presenting with immune thrombocytopenia, even in the absence of overt hepatitis.[110,111, 112] The diagnosis of immune thrombocytopenia is confounded in patients with advanced liver disease because of hypersplenism[113,114] and decreased production of TPO.[115-119] Antiplatelet antibodies are so common as to lack diagnostic utility.[120] Possible mechanisms leading to immune destruction include binding of HCV followed by anti-HCV antibody to the platelet membrane, circulating anti-viral immune complexes,[121, 122,123] and direct infection of megakaryocytes[124] with expression of HCV RNA in platelets.[125] Bone marrow production may be suppressed by HCV[126] or interferon antiviral treatment.[127] Patients typically present with significant bleeding in the presence of moderate thrombocytopenia.[110] Optimal management involves suppression of viral replication. Use of TPO-receptor agonist may raise platelet counts sufficiently to permit sustained treatment with interferon-based therapy in a high proportion of patients.[128]

Helicobacter pylori (H pylori)—The success of eradication infection with *H pylori* among patients presenting with otherwise typical ITP varies from less than 1%-5% in the US to over 60% in Italy and Japan, with intermediate values reported from other countries.[56,129,130] Several hypotheses relating *H pylori* to immune thrombocytopenia and to explain this variation have been proposed including: (1) regional differences in the expression of CagA-related genes,[131-133] to which antibodies that cross-react with ITP platelets are generated through the process of molecular mimicry[134]; (2) cross-reactivity between platelet antibodies and *H pylori* cytotoxin-A protein[135]; (3) adsorption to platelets of Lewis antigens, which are induced by *H pylori* in a strain-specific manner, where they are targets for anti-Lewis antibodies in patients with appropriate genetic backgrounds;[136] (4) platelet activation and clearance through an interaction with *H pylori*-bound von Willebrand factor via platelet glycoprotein Ib[137]; (5) somatic mutation of antibacterial antibodies from which antigen-independent autoantibodies emerge[138]; (6) monocytes from *H pylori*-positive patients demonstrate low levels of the inhibitory Fc-γ receptor IIB and enhanced platelet phagocytosis, both of which are reversed after successful eradication,[139] and (7) genetic variation, eg, the frequency of HLA-DRB*11,*14, and HLA-DQB1*03 is higher in patients with immune thrombocytopenia positive for *H pylori* than in those who are *H pylori*-negative, and those expressing HLA-DQB1*03 have a higher probability of a platelet response to eradication therapy.[140] Of interest, titers of autoantibodies fall 12-24 weeks after successful eradication, whereas responses often occur in 1-2 weeks, suggesting additional mechanisms are operative.

Many, but not all studies indicate that *H pylori* is found more commonly in patients with disease that is milder in severity and of more recent onset.[141] Thus, *H pylori* should be sought in all patients who come from regions where there is a strong association, but no consensus has emerged in the US as to whether all ITP patients should be tested and/or treated.

Vaccination and other infections—Transient but severe thrombocytopenia occurs with an incidence of 1 in 25,000-40,000 vaccinations for measles, mumps, and rubella,[142-144] and less commonly after vaccination against pneumococcus, *H influenzae* B, varicella zoster virus (VZV), and hepatitis B.[145,146] Over 80% of patients recover within 2 months, typically within 2-3 weeks,[147-149][27,30] with less than 10% evolving into chronic ITP[150] responsive to ITP-directed therapy. Thrombocytopenia occurs occasionally after naturally occurring infection with cytomegalovirus, rubella, Epstein-Barr virus, VZV, the severe acute respiratory syndrome coronavirus, and many others.[151-153, 154] Thrombocytopenia may be immune, due to infection of megakaryocytes or progenitors, or result from peripheral consumption, eg, purpura fulminans due to VZV.

Post-transfusion purpura (PTP)

PTP is a rare but dramatic cause of immune thrombocytopenia. The typical patient is a multiparous or multitransfused female who presents with hemorrhage and the sudden onset of profound thrombocytopenia a mean of 7 days after transfusion of a blood product containing platelet antigens. The disease occurs primarily among the ~1% of Caucasians who are homozygous for HPA1b allele on GPIIIa, although other specificities have been reported. Patients not only develop anti-HPA1a antibodies, but also self-reactive antibodies of undetermined specificity, presumably as a result of epitope spread. Remarkably, PTP is not seen in women with neonatal alloimmune thrombocytopenia due to anti-HPA1a antibodies. Patients are at a high risk of bleeding and the clinical course is often protracted without therapy. IV immune globulin is the standard of care. The utility of preventing subsequent exposure to the inciting antigen using washed HPA1b blood products is logical but unproven.

Drug-induced thrombocytopenia

The first case of drug-induced thrombocytopenia (DITP) was identified with quinine 140 years ago.[155] DITP can result from bone marrow toxicity or immune-mediated destruction of platelets. Several hundred therapeutic agents have been implicated,[156] but few reports are compelling.[157] The diagnosis of DITP is generally based on this clinical scenario: (1) therapy with a candidate drug precedes thrombocytopenia by sufficient time to develop antibody; (2) there is no such temporal relationship with another drug; (3) all other reasonable causes have been excluded; (4) recovery occurs upon the discontinuation of the drug, and (5) re-exposure to the drug, if attempted, leads to recurrent thrombocytopenia. However, these criteria are rarely met, as underlying clinical circumstances are often complex and introduction and withdrawal of multiple drugs within a short time frame is common. Moreover, testing for drug-dependent antibodies is fraught with difficulty (solubility, concentration, effect on platelet activation, in vivo metabolism, lack of control patients on drug but without thrombocytopenia, etc), and few patients require rechallenge.

DITP typically affects only a small percentage of exposed patients, with the exception of heparin-induced thrombocytopenia (see below), and no known genetic predispositions or environmental criteria have been identified. Diverse mechanisms have been postulated to cause DITP, including immune complexes (heparin); induction of autoantibody (gold salts); anti-drug-specific antibodies (abciximab); drugs that induce conformational changes in platelet antigens that are recognized by antibody (fiban drugs); drug-induced antibodies that bind to platelet membranes in the presence of soluble drug (quinine); and hapten-dependent antibodies (some beta-lactam antibiotics)[158, 157] (Table 1). Immune or nonimmune marrow suppression

or nonimmune destruction (typified when ristocetin was introduced as an antibiotic), or thrombotic microangiopathy (eg, ticlopidine and possibly clopidogrel) occur less commonly.

Not surprisingly, most drug-dependent antibodies appear to recognize antigens involving prevalent platelet glycoprotein complexes such as αIIbβ3 or Ib/V/IX.[159,160] It has been hypothesized that drugs become immunogenic when they bind to a larger molecule, such as a protein generating antibodies to the drug itself or a drug-protein complex or a drug-induced alteration of a binding protein to induce neoepitopes.[161] These hypotheses have been based primarily on the kinetics of drug-dependent inhibition of antibody binding to platelets or other cells rather than isolation of drug-protein, drug-antibody, or drug-protein-antibody complexes. Bougie and colleagues have proposed a model to reconcile existing hypotheses using quinine-dependent antibodies as a model.[162] They posit that the drugs enhance the affinity of preexisting antiplatelet glycoprotein antibodies by providing a bridge between the complement determining region on the former with a drug-binding epitope on the latter. Whether the drug binds first to the antibody or to the platelet membrane protein depends on its relative affinity.

Thrombocytopenia induced by platelet inhibitors—Tirofiban and eptifibatide used to prevent restenosis after coronary angioplasty can cause severe thrombocytopenia within hours of the first or subsequent doses. These ligand-mimetic drugs (fibans) competitively inhibit fibrinogen from binding to the platelet αIIbβ3 integrin receptor.[163] These drugs may act as mixed agonists/antagonists. It is presumed that binding induces novel epitopes on αIIbβ3 that are recognized by preexisting (possibly preactivated) or drug-induced antibodies.

Abciximab is a chimeric antibody human Fab fragment linked to specificity-determining sequences from a murine antibody to β3 integrin that blocks fibrinogen binding. Sudden and often profound thrombocytopenia[163-165] develops within hours in ~0.5%-1% of patients treated with abciximab for the first time, and in ~10% of those treated a second time. Delayed onsets after first exposure occur less commonly. Most healthy individuals have naturally-occurring antibodies to the C-terminus on human Fab (the papain cleavage site), which is present in the chimeric antibody. In contrast, patients who develop severe thrombocytopenia within a few hours of starting an infusion[166] have preexisting antibodies that recognize the region that imparts GPIIIa specificity, although an effect of the drug on the conformation of GPIIbIIIa cannot be excluded.[165] Abciximab-coated platelets may be detected for 10 to 14 days after treatment in some individuals, presumably due to coating of megakaryocytes or shuttling between destroyed and circulating platelets.[167] IVIG and platelet transfusions have been used successfully to treat patients with profound abciximab- and fiban-induced thrombocytopenia.

Thrombocytopenia from drug-induced autoantibodies—Rarely, drugs stimulate the formation of autoantibodies that target platelets in the absence of the inciting drug.[168] Autoantibodies with an affinity for platelet glycoprotein V have developed in a few patients with rheumatoid arthritis treated with gold salts.[169] Drug-independent autoantibodies have also been reported in occasional patients treated with quinine, procainamide, sulfonamide antibiotics, and interferons alfa and beta.[157,170] Thrombocytopenia is often protracted and may require ITP-directed therapy.

Heparin-induced thrombocytopenia—Heparin-induced thrombocytopenia (HIT) develops in 1%-3% of patients who receive unfractionated heparin (UFH) intravenously in therapeutic doses for a minimum of 5 days. The prevalence is lower in patients treated exclusively with low-molecular-weight heparin or when UFH is given as thromboprophylaxis. The incidence is highest in patients undergoing cardiopulmonary bypass surgery, which is associated with intense platelet activation, inflammation, and underlying vascular disease, and lowest in children, during pregnancy, and patients receiving heparin during dialysis.

Approximately 25% of patients develop arterial and/or venous thrombi,[171] a number that may exceed 50% if the disease is not recognized and managed promptly.[172] In naïve subjects, an unexplained fall in the platelet count of greater than 40% begins 5-10 days after exposure; thrombosis typically follows soon after but can occur concomitantly or on occasion precede the fall in platelet count.[173] Thrombocytopenia may occur within hours after exposure to heparin in patients who had been treated within the preceding 100 days in whom circulating antibodies may persist.[174]. Rarely, thrombocytopenia may be discovered or develop 1-2 weeks after the last known exposure (delayed HIT).[175]

HIT antibodies recognize oligomeric complexes formed between platelet factor 4 (PF4) released from activated platelets and heparin or glycosaminoglycans expressed on endothelium, monocytes, and platelets.[176-178] Heparin/PF4-IgG complexes bind to FcγRIIa (CD32) on platelets, targeting them for clearance, but also stimulating cell activation with release of additional PF4. Binding of these complexes to endothelial cells[179] and monocytes[180,181] stimulates the expression of tissue factor, accelerating coagulation and reinforcing platelet activation. Heparin-independent anti-PF4 antibodies have been postulated to account for delayed HIT.[175]

Diagnosis rests on clinical recognition of the temporal relationship between heparin exposure and the signature clinical manifestation. ELISA-based assays that detect IgG, IgA, and IgM antibodies have a high sensitivity and negative predictive value but a false positive rate that can exceed 50% in patients post-bypass surgery,[182] with unacceptably high false positive rates in other settings as well. The performance characteristics may be improved using newer assays that measure only IgG antibodies and using higher diagnostic cut-off optical density measurements, with little loss of negative predictive value.[183] Assays based on platelet activation are more specific but less sensitive and the results are not routinely available in real-time. Once the diagnosis is strongly suspected (moderate-high pretest probability), exposure to all forms of heparin (including flushes, heparin-bonded catheters, etc) must be discontinued and anticoagulation begun with either a direct thrombin inhibitor, such as hirudin or argatroban or an anti-Xa agent such as danaparoid, where available.[184] Therapy reduces new thromboembolic events by approximately two-thirds, but mortality rates and amputations due to preexisting clots are not affected. Therapy is continued until thrombocytopenia resolves and is overlapped with coumadin at a therapeutic international normalized ratio (INR) for 3-5 days. Anticoagulation is generally continued for 3 months, but may be extended depending on the underlying reason for the initial use of heparin and the sequelae of HIT-induced thrombosis.

Conclusion

There is compelling reason why the diagnosis of ITP requires the exclusion of other causes of thrombocytopenia, including conditions classified as secondary immune thrombocytopenia[185]. The pathobiology of the various causes of secondary immune thrombocytopenia is often more complex than ITP (eg, marrow suppression or intravascular consumption due to clotting or vascular damage), they differ in natural history and responsiveness to ITP-directed therapy (eg, Evans syndrome), and optimal therapy requires treatment of the underlying condition, eg, chronic infection, lymphoproliferative disease (CLL, LGL), and autoimmune conditions (eg, SLE, APS). Treatment of *H pylori*, HIV, or HCV may suffice to increase the platelet count and avoid protracted and sometimes ineffective and toxic treatments required to manage ITP. Drug-induced thrombocytopenias require recognition and withdrawal of the inciting agent. Posttransfusion purpura requires immediate recognition and treatment with IVIG. Patients with APS may be at risk for thrombosis. Treatment strategies for these forms of immune thrombocytopenia are discussed in greater detail elsewhere in this issue.

References

1. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med 2002;346:995–1008. [PubMed: 11919310]
2. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3–40. [PubMed: 8704187]
3. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 2003;120:574–596. [PubMed: 12588344]
4. Kaushansky K. Historical review: megakaryopoiesis and thrombopoiesis. Blood 2008;111:981–986. [PubMed: 18223171]
5. Martin DI, Zon LI, Mutter G, Orkin SH. Expression of an erythroid transcription factor in megakaryocytic and mast cell lineages. Nature 1990;344:444–447. [PubMed: 2320112]
6. Tsang AP, Visvader JE, Turner CA, et al. FOG, a multitype zinc finger protein, acts as a cofactor for transcription factor GATA-1 in erythroid and megakaryocytic differentiation. Cell 1997;90:109–119. [PubMed: 9230307]
7. Roth GJ, Yagi M, Bastian LS. The platelet glycoprotein Ib-V-IX system: regulation of gene expression. Stem Cells 1996;14:188–193. [PubMed: 11012220]
8. Hodohara K, Fujii N, Yamamoto N, Kaushansky K. Stromal cell-derived factor-1 (SDF-1) acts together with thrombopoietin to enhance the development of megakaryocytic progenitor cells (CFU-MK). Blood 2000;95:769–775. [PubMed: 10648384]
9. Broudy VC, Lin NL, Kaushansky K. Thrombopoietin (c-mpl ligand) acts synergistically with erythropoietin, stem cell factor, and interleukin-11 to enhance murine megakaryocyte colony growth and increases megakaryocyte ploidy in vitro. Blood 1995;85:1719–1726. [PubMed: 7535585]
10. Kaushansky K, Broudy VC, Lin N, et al. Thrombopoietin, the Mp1 ligand, is essential for full megakaryocyte development. Proc Natl Acad Sci U S A 1995;92:3234–3238. [PubMed: 7536928]
11. Gurney AL, Wong SC, Henzel WJ, de Sauvage FJ. Distinct regions of c-Mpl cytoplasmic domain are coupled to the JAK-STAT signal transduction pathway and Shc phosphorylation. Proc Natl Acad Sci U S A 1995;92:5292–5296. [PubMed: 7777500]
12. Bacon CM, Tortolani PJ, Shimosaka A, Rees RC, Longo DL, O'Shea JJ. Thrombopoietin (TPO) induces tyrosine phosphorylation and activation of STAT5 and STAT3. FEBS Lett 1995;370:63–68. [PubMed: 7544303]
13. Tortolani PJ, Johnston JA, Bacon CM, et al. Thrombopoietin induces tyrosine phosphorylation and activation of the Janus kinase, JAK2. Blood 1995;85:3444–3451. [PubMed: 7780132]
14. Drachman JG, Sabath DF, Fox NE, Kaushansky K. Thrombopoietin signal transduction in purified murine megakaryocytes. Blood 1997;89:483–492. [PubMed: 9002950]
15. Nagata Y, Todokoro K. Thrombopoietin induces activation of at least two distinct signaling pathways. FEBS Lett 1995;377:497–501. [PubMed: 8549784]
16. Nakao T, Geddis AE, Fox NE, Kaushansky K. PI3K/Akt/FOXO3a pathway contributes to thrombopoietin-induced proliferation of primary megakaryocytes in vitro and in vivo via modulation of p27(Kip1). Cell Cycle 2008;7:257–266. [PubMed: 18256550]
17. Chanprasert S, Geddis AE, Barroga C, Fox NE, Kaushansky K. Thrombopoietin (TPO) induces c-myc expression through a. Cell Signal 2006;18:1212–1218. [PubMed: 16380230]
18. Battinelli EM, Hartwig JH, Italiano JE Jr. Delivering new insight into the biology of megakaryopoiesis and thrombopoiesis. Curr Opin Hematol 2007;14:419–426. [PubMed: 17934346]
19. Cines DB, McMillan R. Pathogenesis of chronic immune thrombocytopenic purpura. Curr Opin Hematol 2007;14:511–514. [PubMed: 17934360]
20. Tavassoli M, McMillan R. Structure of the spleen in idiopathic thrombocytopenic purpura. Am J Clin Pathol 1975;64:180–191. [PubMed: 1171614]
21. Handin RI, Stossel TP. Phagocytosis of antibody-coated platelets by human granulocytes. N Engl J Med 1974;290:989–993. [PubMed: 4594526]

22. McMillan R, Longmire RL, Tavassoli M, Armstrong S, Yelenosky R. In vitro platelet phagocytosis by splenic leukocytes in idiopathic thrombocytopenic purpura. N Engl J Med 1974;290:249–251. [PubMed: 4855568]
23. McMillan R. Autoantibodies and autoantigens in chronic immune thrombocytopenic purpura. Semin Hematol 2000;37:239–248. [PubMed: 10942218]
24. He R, Reid DM, Jones CE, Shulman NR. Spectrum of Ig classes, specificities, and titers of serum antiglycoproteins in chronic idiopathic thrombocytopenic purpura. Blood 1994;83:1024–1032. [PubMed: 8111044]
25. Stasi R, Cooper N, Del PG, Stipa E, Laura EM, Abruzzese E, Amadori S. Analysis of regulatory T-cell changes in patients with idiopathic thrombocytopenic purpura receiving B cell-depleting therapy with rituximab. Blood 2008;112:1147–1150. [PubMed: 18375792]
26. Stasi R, Del Poeta G, Stipa E, Evangelista ML, Trawinska MM, Cooper N, Amadori S. Response to B-cell depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. Blood 2007;110:2924–2930. [PubMed: 17548576]
27. Ho-Yen DO, Hardie R, Sommerville RG. Varicella-induced thrombocytopenia. J Infect 1984;8:274–276. [PubMed: 6736670]
28. Solanilla A, Pasquet JM, Viallard JF, et al. Platelet-associated CD154 in immune thrombocytopenic purpura. Blood 2005;105:215–218. [PubMed: 15191945]
29. Nagahama M, Nomura S, Kanazawa S, Ozaki Y, Kagawa H, Fukuhara S. Significance of chemokines and soluble CD40 ligand in patients with autoimmune thrombocytopenic purpura. Eur J Haematol 2002;69:303–308. [PubMed: 12460235]
30. Roark JH, Bussel JB, Cines DB, Siegel DL. Genetic analysis of autoantibodies in idiopathic thrombocytopenic purpura reveals evidence of clonal expansion and somatic mutation. Blood 2002;100:1388–1398. [PubMed: 12149222]
31. Olsson B, Ridell B, Carlsson L, Jacobsson S, Wadenvik H. Recruitment of T cells into bone marrow of ITP patients possibly due to elevated expression of VLA-4 and CX3CR1. Blood 2008;112:1078–1084. [PubMed: 18519809]
32. Olsson B, Andersson PO, Jernas M, Jacobsson S, Carlsson B, Carlsson LM, Wadenvik H. T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. Nat Med 2003;9:1123–1124. [PubMed: 12937414]
33. Zhang F, Chu X, Wang L, et al. Cell-mediated lysis of autologous platelets in chronic idiopathic thrombocytopenic purpura. Eur J Haematol 2006;76:427–431. [PubMed: 16480433]
34. Stoll D, Cines DB, Aster RH, Murphy S. Platelet kinetics in patients with idiopathic thrombocytopenic purpura and moderate thrombocytopenia. Blood 1985;65:584–588. [PubMed: 4038614]
35. McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood 2004;103:1364–1369. [PubMed: 14576051]
36. Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. J Clin Invest 1987;80:33–40. [PubMed: 3597777]
37. Nagata Y, Shozaki Y, Nagahisa H, Nagasawa T, Abe T, Todokoro K. Serum thrombopoietin level is not regulated by transcription but by the total counts of both megakaryocytes and platelets during thrombocytopenia and thrombocytosis. Thromb Haemost 1997;77:808–814. [PubMed: 9184382]
38. Kosugi S, Kurata Y, Tomiyama Y, et al. Circulating thrombopoietin level in chronic immune thrombocytopenic purpura. Br J Haematol 1996;93:704–706. [PubMed: 8652398]
39. Emmons RV, Reid DM, Cohen RL, Meng G, Young NS, Dunbar CE, Shulman NR. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction. Blood 1996;87:4068–4071. [PubMed: 8639762]
40. Chang M, Nakagawa PA, Williams SA, Schwartz MR, Imfeld KL, Buzby JS, Nugent DJ. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. Blood 2003;102:887–895. [PubMed: 12676790]

41. Houwerzijl EJ, Blom NR, van der Want JJ, et al. Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. Blood 2004;103:500–506. [PubMed: 12969975]
42. Nossent JC, Swaak AJ. Prevalence and significance of haematological abnormalities in patients with systemic lupus erythematosus. Q J Med 1991;80:605–612. [PubMed: 1946940]
43. Kuwana M, Okazaki Y, Kajihara M, Kaburaki J, Miyazaki H, Kawakami Y, Ikeda Y. Autoantibody to c-Mpl (thrombopoietin receptor) in systemic lupus erythematosus: relationship to thrombocytopenia with megakaryocytic hypoplasia. Arthritis Rheum 2002;46:2148–2159. [PubMed: 12209520]
44. Ziakas PD, Routsias JG, Giannouli S, Tasidou A, Tzioufas AG, Voulgarelis M. Suspects in the tale of lupus-associated thrombocytopenia. Clin Exp Immunol 2006;145:71–80. [PubMed: 16792676]
45. Gernsheimer T. Epidemiology and pathophysiology of immune thrombocytopenic purpura. Eur J Haematol. 2008
46. Arnal C, Piette JC, Leone J, et al. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. J Rheumatol 2002;29:75–83. [PubMed: 11824975]
47. Stasi R, Stipa E, Masi M, et al. Prevalence and clinical significance of elevated antiphospholipid antibodies in patients with idiopathic thrombocytopenic purpura. Blood 1994;84:4203–4208. [PubMed: 7994034]
48. Diz-Kucukkaya R, Hacihanefioglu A, Yenerel M, Turgut M, Keskin H, Nalcaci M, Inanc M. Antiphospholipid antibodies and antiphospholipid syndrome in patients presenting with immune thrombocytopenic purpura: a prospective cohort study. Blood 2001;98:1760–1764. [PubMed: 11535509]
49. Dash S, Marwaha RK, Mohanty S. Lupus anticoagulant in immune thrombocytopenic purpura. Indian J Pediatr 2004;71:505–507. [PubMed: 15226559]
50. Bidot CJ, Jy W, Horstman LL, Ahn ER, Yaniz M, Ahn YS. Antiphospholipid antibodies (APLA) in immune thrombocytopenic purpura (ITP) and antiphospholipid syndrome (APS). Am J Hematol 2006;81:391–396. [PubMed: 16680753]
51. Bidot CJ, Jy W, Horstman LL, et al. Antiphospholipid antibodies in immune thrombocytopenic purpura tend to emerge in exacerbation and decline in remission. Br J Haematol 2005;128:366–372. [PubMed: 15667539]
52. Galli M, Daldossi M, Barbui T. Anti-glycoprotein Ib/IX and IIb/IIIa antibodies in patients with antiphospholipid antibodies. Thromb Haemost 1994;71:571–575. [PubMed: 8091382]
53. Macchi L, Rispal P, Clofent-Sanchez G, Pellegrin JL, Nurden P, Leng B, Nurden AT. Anti-platelet antibodies in patients with systemic lupus erythematosus and the primary antiphospholipid antibody syndrome: their relationship with the observed thrombocytopenia. Br J Haematol 1997;98:336–341. [PubMed: 9266930]
54. Godeau B, Piette JC, Fromont P, Intrator L, Schaeffer A, Bierling P. Specific antiplatelet glycoprotein autoantibodies are associated with the thrombocytopenia of primary antiphospholipid syndrome. Br J Haematol 1997;98:873–879. [PubMed: 9326182]
55. Fabris F, Steffan A, Cordiano I, Borzini P, Luzzatto G, Randi ML, Girolami A. Specific antiplatelet autoantibodies in patients with antiphospholipid antibodies and thrombocytopenia. Eur J Haematol 1994;53:232–236. [PubMed: 7957808]
56. Liebman HA, Stasi R. Secondary immune thrombocytopenic purpura. Curr Opin Hematol 2007;14:557–573. [PubMed: 17934365]
57. Pennings MT, Derksen RH, Urbanus RT, Tekelenburg WL, Hemrika W, De Groot PG. Platelets express three different splice variants of ApoER2 that are all involved in signaling. J Thromb Haemost 2007;5:1538–1544. [PubMed: 17470198]
58. Pennings MT, Derksen RH, van L M, et al. Platelet adhesion to dimeric beta-glycoprotein I under conditions of flow is mediated by at least two receptors: glycoprotein Ibalpha and apolipoprotein E receptor 2′. J Thromb Haemost 2007;5:369–377. [PubMed: 17096706]
59. Shi T, Giannakopoulos B, Yan X, et al. Anti-beta2-glycoprotein I antibodies in complex with beta2-glycoprotein I can activate platelets in a dysregulated manner via glycoprotein Ib-IX-V. Arthritis Rheum 2006;54:2558–2567. [PubMed: 16868978]

60. Nojima J, Suehisa E, Kuratsune H, et al. Platelet activation induced by combined effects of anticardiolipin and lupus anticoagulant IgG antibodies in patients with systemic lupus erythematosus--possible association with thrombotic and thrombocytopenic complications. Thromb Haemost 1999;81:436–441. [PubMed: 10102474]
61. Alliot C, Messouak D, Albert F, Barrios M. Correction of thrombocytopenia with aspirin in the primary antiphospholipid syndrome. Am J Hematol 2001;68:215. [PubMed: 11754406]
62. Alarcon-Segovia D, Sanchez-Guerrero J. Correction of thrombocytopenia with small dose aspirin in the primary antiphospholipid syndrome. J Rheumatol 1989;16:1359–1361. [PubMed: 2810261]
63. Cohen MG, Lui SF. Multiple complications of the antiphospholipid syndrome with apparent response to aspirin therapy. J Rheumatol 1992;19:803–806. [PubMed: 1613714]
64. Panzer S, Haubenstock A, Minar E. Platelets in hyperthyroidism: studies on platelet counts, mean platelet volume, 111-indium-labeled platelet kinetics, and platelet-associated immunoglobulins G and M. J Clin Endocrinol Metab 1990;70:491–496. [PubMed: 2298861]
65. Stiegler G, Stohlawetz P, Brugger S, Jilma B, Vierhapper H, Hocker P, Panzer S. Elevated numbers of reticulated platelets in hyperthyroidism: direct evidence for an increase of thrombopoiesis. Br J Haematol 1998;101:656–658. [PubMed: 9674737]
66. Cordiano I, Betterle C, Spadaccino CA, Soini B, Girolami A, Fabris F. Autoimmune thrombocytopenia (AITP) and thyroid autoimmune disease (TAD): overlapping syndromes? Clin Exp Immunol 1998;113:373–378. [PubMed: 9737665]
67. Ioachimescu AG, Makdissi A, Lichtin A, Zimmerman RS. Thyroid disease in patients with idiopathic thrombocytopenia: a cohort study. Thyroid 2007;17:1137–1142. [PubMed: 17887931]
68. Pratt EL, Tarantino MD, Wagner D, Hirsch Pescovitz O, Bowyer S, Shapiro AD. Prevalence of elevated antithyroid antibodies and antinuclear antibodies in children with immune thrombocytopenic purpura. Am J Hematol 2005;79:175–179. [PubMed: 15981229]
69. Pegels JG, Helmerhorst FM, van Leeuwen EF, van de Plas-van Dalen C, Engelfriet CP, von dem Borne AE. The Evans syndrome: characterization of the responsible autoantibodies. Br J Haematol 1982;51:445–450. [PubMed: 7104228]
70. Miller BA, Shultz Beardsley D. Autoimmune pancytopenia of childhood associated with multisystem disease manifestations. J Pediatr 1983;103:877–881. [PubMed: 6644422]
71. Wang W, Herrod H, Pui CH, Presbury G, Wilimas J. Immunoregulatory abnormalities in Evans syndrome. Am J Hematol 1983;15:381–390. [PubMed: 6606357]
72. Fisher GH, Rosenberg FJ, Straus SE, et al. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 1995;81:935–946. [PubMed: 7540117]
73. Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IA, Debatin KM, Fischer A, de Villartay JP. Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. Science 1995;268:1347–1349. [PubMed: 7539157]
74. Le Deist F, Emile JF, Rieux-Laucat F, Benkerrou M, Roberts I, Brousse N, Fischer A. Clinical, immunological, and pathological consequences of Fas-deficient conditions. Lancet 1996;348:719–723. [PubMed: 8806292]
75. Rieux-Laucat F, Le Deist F, Fischer A. Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways. Cell Death Differ 2003;10:124–133. [PubMed: 12655301]
76. Teachey DT, Manno CS, Axsom KM, et al. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). Blood 2005;105:2443–2448. [PubMed: 15542578]
77. Hamblin TJ, Oscier DG, Young BJ. Autoimmunity in chronic lymphocytic leukaemia. J Clin Pathol 1986;39:713–716. [PubMed: 3488334]
78. Dhodapkar MV, Li CY, Lust JA, Tefferi A, Phyliky RL. Clinical spectrum of clonal proliferations of T-large granular lymphocytes: a T-cell clonopathy of undetermined significance? Blood 1994;84:1620–1627. [PubMed: 8068951]
79. Xiros N, Binder T, Anger B, Bohlke J, Heimpel H. Idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia in Hodgkin's disease. Eur J Haematol 1988;40:437–441. [PubMed: 3378597]

80. Landgren O, Engels EA, Pfeiffer RM, et al. Autoimmunity and susceptibility to Hodgkin lymphoma: a population-based case-control study in Scandinavia. J Natl Cancer Inst 2006;98:1321–1330. [PubMed: 16985251]
81. Martinelli G, Zinzani PL, Magagnoli M, Vianelli N, Tura S. Incidence and prognostic significance of idiopathic thrombocytopenic purpura in patients with Hodgkin's disease in complete hematological remission. Haematologica 1998;83:669–670. [PubMed: 9718878]
82. Hamblin TJ. Autoimmune complications of chronic lymphocytic leukemia. Semin Oncol 2006;33:230–239. [PubMed: 16616070]
83. Montillo M, Tedeschi A, Leoni P. Recurrence of autoimmune thrombocytopenia after treatment with fludarabine in a patient with chronic lymphocytic leukemia. Leuk Lymphoma 1994;15:187–188. [PubMed: 7858499]
84. Ergas D, Tsimanis A, Shtalrid M, Duskin C, Berrebi A. T-gamma large granular lymphocyte leukemia associated with amegakaryocytic thrombocytopenic purpura, Sjogren's syndrome, and polyglandular autoimmune syndrome type II, with subsequent development of pure red cell aplasia. Am J Hematol 2002;69:132–134. [PubMed: 11835350]
85. Lai DW, Loughran TP Jr, Maciejewski JP, Sasu S, Song SX, Epling-Burnette PK, Paquette RL. Acquired amegakaryocytic thrombocytopenia and pure red cell aplasia associated with an occult large granular lymphocyte leukemia. Leuk Res 2008;32:823–827. [PubMed: 17915315]
86. Morris L, Distenfeld A, Amorosi E, Karpatkin S. Autoimmune thrombocytopenic purpura in homosexual men. Ann Intern Med 1982;96:714–717. [PubMed: 6178333]
87. Walsh CM, Nardi MA, Karpatkin S. On the mechanism of thrombocytopenic purpura in sexually active homosexual men. N Engl J Med 1984;311:635–639. [PubMed: 6540841]
88. Abrams DI, Kiprov DD, Goedert JJ, Sarngadharan MG, Gallo RC, Volberding PA. Antibodies to human T-lymphotropic virus type III and development of the acquired immunodeficiency syndrome in homosexual men presenting with immune thrombocytopenia. Ann Intern Med 1986;104:47–50. [PubMed: 3000249]
89. Murphy MF, Metcalfe P, Waters AH, Carne CA, Weller IV, Linch DC, Smith A. Incidence and mechanism of neutropenia and thrombocytopenia in patients with human immunodeficiency virus infection. Br J Haematol 1987;66:337–340. [PubMed: 3620353]
90. Zon LI, Arkin C, Groopman JE. Haematologic manifestations of the human immune deficiency virus (HIV). Br J Haematol 1987;66:251–256. [PubMed: 3606961]
91. Ballem PJ, Belzberg A, Devine DV, et al. Kinetic studies of the mechanism of thrombocytopenia in patients with human immunodeficiency virus infection. N Engl J Med 1992;327:1779–1784. [PubMed: 1435932]
92. Landonio G, Nosari A, Spinelli F, Vigorelli R, Caggese L, Schlacht I. HIV-related thrombocytopenia: four different clinical subsets. Haematologica 1992;77:398–401. [PubMed: 1483588]
93. Najean Y, Rain JD. The mechanism of thrombocytopenia in patients with HIV infection. J Lab Clin Med 1994;123:415–420. [PubMed: 8133154]
94. Bahner I, Kearns K, Coutinho S, Leonard EH, Kohn DB. Infection of human marrow stroma by human immunodeficiency virus-1 (HIV-1) is both required and sufficient for HIV-1-induced hematopoietic suppression in vitro: demonstration by gene modification of primary human stroma. Blood 1997;90:1787–1798. [PubMed: 9292511]
95. Moses A, Nelson J, Bagby GC Jr. The influence of human immunodeficiency virus-1 on hematopoiesis. Blood 1998;91:1479–1495. [PubMed: 9473211]
96. Kowalska MA, Ratajczak J, Hoxie J, Brass LF, Gewirtz A, Poncz M, Ratajczak MZ. Megakaryocyte precursors, megakaryocytes and platelets express the HIV co-receptor CXCR4 on their surface: determination of response to stromal-derived factor-1 by megakaryocytes and platelets. Br J Haematol 1999;104:220–229. [PubMed: 10050701]
97. Sato T, Sekine H, Kakuda H, Miura N, Sunohara M, Fuse A. HIV infection of megakaryocytic cell lines. Leuk Lymphoma 2000;36:397–404. [PubMed: 10674912]
98. Zucker-Franklin D, Seremetis S, Zheng ZY. Internalization of human immunodeficiency virus type I and other retroviruses by megakaryocytes and platelets. Blood 1990;75:1920–1923. [PubMed: 2337668]

99. Sakaguchi M, Sato T, Groopman JE. Human immunodeficiency virus infection of megakaryocytic cells. Blood 1991;77:481–485. [PubMed: 1991165]
100. Zucker-Franklin D, Cao YZ. Megakaryocytes of human immunodeficiency virus-infected individuals express viral RNA. Proc Natl Acad Sci U S A 1989;86:5595–5599. [PubMed: 2748605]
101. Zucker-Franklin D, Termin CS, Cooper MC. Structural changes in the megakaryocytes of patients infected with the human immune deficiency virus (HIV-1). Am J Pathol 1989;134:1295–1303. [PubMed: 2757119]
102. Karpatkin S, Nardi MA, Hymes KB. Sequestration of anti-platelet GPIIIa antibody in rheumatoid factor immune complexes of human immunodeficiency virus 1 thrombocytopenic patients. Proc Natl Acad Sci U S A 1995;92:2263–2267. [PubMed: 7892259]
103. Li Z, Nardi MA, Karpatkin S. Role of molecular mimicry to HIV-1 peptides in HIV-1-related immunologic thrombocytopenia. Blood 2005;106:572–576. [PubMed: 15774614]
104. Bettaieb A, Fromont P, Louache F, Oksenhendler E, Vainchenker W, Duedari N, Bierling P. Presence of cross-reactive antibody between human immunodeficiency virus (HIV) and platelet glycoproteins in HIV-related immune thrombocytopenic purpura. Blood 1992;80:162–169. [PubMed: 1611083]
105. Hohmann AW, Booth K, Peters V, Gordon DL, Comacchio RM. Common epitope on HIV p24 and human platelets. Lancet 1993;342:1274–1275. [PubMed: 7694021]
106. Nardi M, Tomlinson S, Greco MA, Karpatkin S. Complement-independent, peroxide-induced antibody lysis of platelets in HIV-1-related immune thrombocytopenia. Cell 2001;106:551–561. [PubMed: 11551503]
107. Karpatkin S, Nardi M, Lennette ET, Byrne B, Poiesz B. Anti-human immunodeficiency virus type 1 antibody complexes on platelets of seropositive thrombocytopenic homosexuals and narcotic addicts. Proc Natl Acad Sci U S A 1988;85:9763–9767. [PubMed: 3200854]
108. Karpatkin S, Nardi M. Autoimmune anti-HIV-1gp120 antibody with antiidiotype-like activity in sera and immune complexes of HIV-1-related immunologic thrombocytopenia. J Clin Invest 1992;89:356–364. [PubMed: 1737832]
109. Koefoed K, Ditzel HJ. Identification of talin head domain as an immunodominant epitope of the antiplatelet antibody response in patients with HIV-1-associated thrombocytopenia. Blood 2004;104:4054–4062. [PubMed: 15315970]
110. Rajan SK, Espina BM, Liebman HA. Hepatitis C virus-related thrombocytopenia: clinical and laboratory characteristics compared with chronic immune thrombocytopenic purpura. Br J Haematol 2005;129:818–824. [PubMed: 15953010]
111. Pyrsopoulos NT, Reddy KR. Extrahepatic manifestations of chronic viral hepatitis. Curr Gastroenterol Rep 2001;3:71–78. [PubMed: 11177698]
112. Pockros PJ, Duchini A, McMillan R, Nyberg LM, McHutchison J, Viernes E. Immune thrombocytopenic purpura in patients with chronic hepatitis C virus infection. Am J Gastroenterol 2002;97:2040–2045. [PubMed: 12190174]
113. Yabu K, Kiyosawa K, Ako S, et al. Type C chronic hepatitis associated with thrombocytopenia in two patients. J Gastroenterol Hepatol 1994;9:99–104. [PubMed: 8155875]
114. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of “hypersplenic” thrombocytopenia. J Clin Invest 1966;45:645–657. [PubMed: 5327481]
115. Espanol I, Gallego A, Enriquez J, Rabella N, Lerma E, Hernandez A, Pujol-Moix N. Thrombocytopenia associated with liver cirrhosis and hepatitis C viral infection: role of thrombopoietin. Hepatogastroenterology 2000;47:1404–1406. [PubMed: 11100362]
116. Adinolfi LE, Giordano MG, Andreana A, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. Br J Haematol 2001;113:590–595. [PubMed: 11380442]
117. Jiang XH, Xie YT, Tan DM. Study on the influencing factors of thrombocytopenia in viral hepatitis. Zhonghua Gan Zang Bing Za Zhi 2004;12:734–736. [PubMed: 15619340]
118. Peck-Radosavljevic M, Zacherl J, Meng YG, et al. Is inadequate thrombopoietin production a major cause of thrombocytopenia in cirrhosis of the liver? J Hepatol 1997;27:127–131. [PubMed: 9252085]

119. Goulis J, Chau TN, Jordan S, Mehta AB, Watkinson A, Rolles K, Burroughs AK. Thrombopoietin concentrations are low in patients with cirrhosis and thrombocytopenia and are restored after orthotopic liver transplantation. Gut 1999;44:754–758. [PubMed: 10205219]
120. Panzer S, Seel E, Brunner M, Kormoczi GF, Schmid M, Ferenci P, Peck-Radosavljevic M. Platelet autoantibodies are common in hepatitis C infection, irrespective of the presence of thrombocytopenia. Eur J Haematol 2006;77:513–517. [PubMed: 17042765]
121. Hamaia S, Li C, Allain JP. The dynamics of hepatitis C virus binding to platelets and 2 mononuclear cell lines. Blood 2001;98:2293–2300. [PubMed: 11588022]
122. Kajihara M, Kato S, Okazaki Y, Kawakami Y, Ishii H, Ikeda Y, Kuwana M. A role of autoantibody-mediated platelet destruction in thrombocytopenia in patients with cirrhosis. Hepatology 2003;37:1267–1276. [PubMed: 12774004]
123. Doi T, Homma H, Mezawa S, Kato J, Kogawa K, Sakamaki S, Niitsu Y. Mechanisms for increment of platelet associated IgG and platelet surface IgG and their implications in immune thrombocytopenia associated with chronic viral liver disease. Hepatol Res 2002;24:23. [PubMed: 12243789]
124. Bordin G, Ballare M, Zigrossi P, et al. A laboratory and thrombokinetic study of HCV-associated thrombocytopenia: a direct role of HCV in bone marrow exhaustion? Clin Exp Rheumatol 1995;13:S39–S43. [PubMed: 8730475]
125. de Almeida AJ, Campos-de-Magalhaes M, de Melo Marcal OP, et al. Hepatitis C virus-associated thrombocytopenia: a controlled prospective, virological study. Ann Hematol 2004;83:434–440. [PubMed: 14963696]
126. Iga D, Tomimatsu M, Endo H, Ohkawa S, Yamada O. Improvement of thrombocytopenia with disappearance of HCV RNA in patients treated by interferon-alpha therapy: possible etiology of HCV-associated immune thrombocytopenia. Eur J Haematol 2005;75:417–423. [PubMed: 16191092]
127. Peck-Radosavljevic M. Thrombocytopenia in liver disease. Can J Gastroenterol 2000;14:60D–66D.
128. McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med 2007;357:2227–2236. [PubMed: 18046027]
129. Michel M, Cooper N, Jean C, Frissora C, Bussel JB. Does Helicobater pylori initiate or perpetuate immune thrombocytopenic purpura? Blood 2004;103:890–896. [PubMed: 12920031]
130. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of Helicobacter pylori. Lancet 1998;352:878. [PubMed: 9742983]
131. Maeda S, Ogura K, Yoshida H, et al. Major virulence factors, VacA and CagA, are commonly positive in Helicobacter pylori isolates in Japan. Gut 1998;42:338–343. [PubMed: 9577338]
132. Maeda S, Yoshida H, Ikenoue T, et al. Structure of cag pathogenicity island in Japanese Helicobacter pylori isolates. Gut 1999;44:336–341. [PubMed: 10026317]
133. Emilia G, Luppi M, Zucchini P, et al. Helicobacter pylori infection and chronic immune thrombocytopenic purpura: long-term results of bacterium eradication and association with bacterium virulence profiles. Blood 2007;110:3833–3841. [PubMed: 17652264]
134. Franceschi F, Christodoulides N, Kroll MH, Genta RM. Helicobacter pylori and idiopathic thrombocytopenic purpura. Ann Intern Med 2004;140:766–767. [PubMed: 15126268]
135. Takahashi T, Yujiri T, Shinohara K, et al. Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. Br J Haematol 2004;124:91–96. [PubMed: 14675413]
136. Gerhard M, Rad R, Prinz C, Naumann M. Pathogenesis of Helicobacter pylori infection. Helicobacter 2002;7:17–23. [PubMed: 12197905]
137. Byrne MF, Kerrigan SW, Corcoran PA, Atherton JC, Murray FE, Fitzgerald DJ, Cox DM. Helicobacter pylori binds von Willebrand factor and interacts with GPIb to induce platelet aggregation. Gastroenterology 2003;124:1846–1854. [PubMed: 12806618]
138. Cines DB. Inside Blood; ITP: time to “bug off”? Blood 2007;110:3818–3819.

139. Asahi A, Nishimoto T, Okazaki Y, et al. Helicobacter pylori eradication shifts monocyte Fcgamma receptor balance toward inhibitory FcgammaRIIB in immune thrombocytopenic purpura patients. J Clin Invest 2008;118:2939–2949. [PubMed: 18654664]
140. Veneri D, De Matteis G, Solero P, et al. Analysis of B- and T-cell clonality and HLA class II alleles in patients with idiopathic thrombocytopenic purpura: correlation with Helicobacter pylori infection and response to eradication treatment. Platelets 2005;16:307–311. [PubMed: 16011982]
141. Stasi R, Rossi Z, Stipa E, Amadori S, Newland AC, Provan D. Helicobacter pylori eradication in the management of patients with idiopathic thrombocytopenic purpura. Am J Med 2005;118:414–419. [PubMed: 15808140]
142. Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. Arch Dis Child 2001;84:227–229. [PubMed: 11207170]
143. Abramson JS, Pickering LK. US Immunization Policy. JAMA 2002;287:505–509. [PubMed: 11798374]
144. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. Br J Clin Pharmacol 2003;55:107–111. [PubMed: 12534647]
145. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. Vaccine 2005;23:3876–3886. [PubMed: 15917108]
146. Neau D, Bonnet F, Michaud M, Perel Y, Longy-Boursier M, Ragnaud JM, Guillard JM. Immune thrombocytopenic purpura after recombinant hepatitis B vaccine: retrospective study of seven cases. Scand J Infect Dis 1998;30:115–118. [PubMed: 9730294]
147. Naidu S, Messmore H, Caserta V, Fine M. CNS lesions in neonatal isoimmune thrombocytopenia. Arch Neurol 1983;40:552–554. [PubMed: 6615286]
148. Beeler J, Varricchio F, Wise R. Thrombocytopenia after immunization with measles vaccines: review of the vaccine adverse events reporting system (1990 to 1994). Pediatr Infect Dis J 1996;15:88–90. [PubMed: 8684885]
149. Nieminen U, Peltola H, Syrjala MT, Makipernaa A, Kekomaki R. Acute thrombocytopenic purpura following measles, mumps and rubella vaccination. A report on 23 patients. Acta Paediatr 1993;82:267–270. [PubMed: 8495082]
150. Jadavji T, Scheifele D, Halperin S. Thrombocytopenia after immunization of Canadian children, 1992 to 2001. Pediatr Infect Dis J 2003;22:119–122. [PubMed: 12586974]
151. Chou AL, Huang WW, Tsao SM, Li CT, Su CC. Human herpesvirus type 8 in patients with cirrhosis: correlation with sex, alcoholism, hepatitis B virus, disease severity, and thrombocytopenia. Am J Clin Pathol 2008;130:231–237. [PubMed: 18628092]
152. Hui DS. Review of clinical symptoms and spectrum in humans with influenza A/H5N1 infection. Respirology 2008;13:S10–S13. [PubMed: 18366521]
153. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J 2008;5:47. [PubMed: 18371229]
154. Yang M, Ng MH, Li CK. Thrombocytopenia in patients with severe acute respiratory syndrome (review). Hematology 2005;10:101–105. [PubMed: 16019455]
155. Vipan W. Quinine as a cause of purpura. Lancet 1865;2:37.
156. Drug-induced thrombocytopenia. 2008. No authors listedhttp://moon.ouhsc.edu/jgeorge/DITP.html9-11-2008
157. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med 2007;357:580–587. [PubMed: 17687133]
158. van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf 2004;27:1243–1252. [PubMed: 15588119]
159. Visentin GP, Newman PJ, Aster RH. Characteristics of quinine- and quinidine-induced antibodies specific for platelet glycoproteins IIb and IIIa. Blood 1991;77:2668–2676. [PubMed: 1710517]
160. Asvadi P, Ahmadi Z, Chong BH. Drug-induced thrombocytopenia: localization of the binding site of GPIX-specific quinine-dependent antibodies. Blood 2003;102:1670–1677. [PubMed: 12738668]

161. Parker CW. Hapten immunology and allergic reactions in humans. Arthritis Rheum 1981;24:1024–1036. [PubMed: 7284049]
162. Bougie DW, Wilker PR, Aster RH. Patients with quinine-induced immune thrombocytopenia have both “drug-dependent” and “drug-specific” antibodies. Blood 2006;108:922–927. [PubMed: 16861345]
163. Aster RH. Immune thrombocytopenia caused by glycoprotein IIb/IIIa inhibitors. Chest 2005;127:53S–59S. [PubMed: 15706031]
164. McCorry RB, Johnston P. Fatal delayed thrombocytopenia following abciximab therapy. J Invasive Cardiol 2006;18:E173–E174. [PubMed: 16775895]
165. Curtis BR, Swyers J, Divgi A, McFarland JG, Aster RH. Thrombocytopenia after second exposure to abciximab is caused by antibodies that recognize abciximab-coated platelets. Blood 2002;99:2054–2059. [PubMed: 11877279]
166. Tcheng JE, Kereiakes DJ, Lincoff AM, et al. Abciximab readministration: results of the ReoPro Readministration Registry. Circulation 2001;104:870–875. [PubMed: 11514371]
167. Curtis BR, Divgi A, Garritty M, Aster RH. Delayed thrombocytopenia after treatment with abciximab: a distinct clinical entity associated with the immune response to the drug. J Thromb Haemost 2004;2:985–992. [PubMed: 15140135]
168. von dem Borne AE, Pegels JG, van der Stadt RJ, van der Plas-van Dalen CM, Helmerhorst FM. Thrombocytopenia associated with gold therapy: a drug-induced autoimmune disease? Br J Haematol 1986;63:509–516. [PubMed: 3089270]
169. Garner SF, Campbell K, Metcalfe P, et al. Glycoprotein V: the predominant target antigen in gold-induced autoimmune thrombocytopenia. Blood 2002;100:344–346. [PubMed: 12070047]
170. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, Vondracek T. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998;129:886–890. [PubMed: 9867731]
171. Hirsh J, Heddle N, Kelton JG. Treatment of heparin-induced thrombocytopenia: a critical review. Arch Intern Med 2004;164:361–369. [PubMed: 14980986]
172. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med 1996;101:502–507. [PubMed: 8948273]
173. Lubenow N, Kempf R, Eichner A, Eichler P, Carlsson LE, Greinacher A. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. Chest 2002;122:37–42. [PubMed: 12114336]
174. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 2001;344:1286–1292. [PubMed: 11320387]
175. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. Ann Intern Med 2001;135:502–506. [PubMed: 11578153]
176. Reilly MP, Taylor SM, Hartman NK, et al. Heparin-induced thrombocytopenia/thrombosis in a transgenic mouse model requires human platelet factor 4 and platelet activation through FcgammaRIIA. Blood 2001;98:2442–2447. [PubMed: 11588041]
177. Rauova L, Poncz M, McKenzie SE, et al. Ultralarge complexes of PF4 and heparin are central to the pathogenesis of heparin-induced thrombocytopenia. Blood 2005;105:131–138. [PubMed: 15304392]
178. Rauova L, Zhai L, Kowalska MA, Arepally GM, Cines DB, Poncz M. Role of platelet surface PF4 antigenic complexes in heparin-induced thrombocytopenia pathogenesis: diagnostic and therapeutic implications. Blood 2006;107:2346–2353. [PubMed: 16304054]
179. Cines DB, Tomaski A, Tannenbaum S. Immune endothelial-cell injury in heparin-associated thrombocytopenia. N Engl J Med 1987;316:581–589. [PubMed: 3807952]
180. Arepally GM, Mayer IM. Antibodies from patients with heparin-induced thrombocytopenia stimulate monocytic cells to express tissue factor and secrete interleukin-8. Blood 2001;98:1252–1254. [PubMed: 11493478]
181. Thachil J. Heparin induced thrombocytopenia with thrombosis: a two step process? Hematology 2008;13:181–182. [PubMed: 18702877]

182. Bauer TL, Arepally G, Konkle BA, et al. Prevalence of heparin-associated antibodies without thrombosis in patients undergoing cardiopulmonary bypass surgery. Circulation 1997;95:1242–1246. [PubMed: 9054855]

183. Warkentin TE, Sheppard JI, Moore JC, Sigouin CS, Kelton JG. Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. J Thromb Haemost 2008;6:1304–1312. [PubMed: 18489711]

184. Greinacher A, Eichler P, Lubenow N, Kiefel V. Drug-induced and drug-dependent immune thrombocytopenias. Rev Clin Exp Hematol 2001;5:166–200. [PubMed: 11703814]

185. Liebman H. Other immune thrombocytopenias. Semin Hematol 2007;44:S24–S34. [PubMed: 18096469]

Table 1

Mechanisms underlying drug-induced thrombocytopenia

Classification (Drugs)	Mechanism	Incidence
Hapten-dependent antibody (Penicillin, some cephalosporin antibiotics)	Hapten links covalently to membrane protein and induces drug-specific immune response	Very rare
Quinine-type drug (Quinine, sulfonamide antibiotics, nonsteroidal antiinflammatory drugs)	Drug induces 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
Fiban-type drug (Tirofiban, eptifibatide)	Drug reacts with glycoprotein αIIbβ3 to induce a conformational change by antibody (not yet confirmed)	0.2–0.5%
Drug-specific antibody (Abciximab)	Antibody recognizes murine component of chimeric Fab fragment specific for platelet β3	0.5–1.0% after first exposure,10–14% after second exposure
Autoantibody (Gold salts, procainamide)	Drug induces antibody that reacts with autologous platelets in absence of drug	1.0% with gold, very rare with procainamide and other drugs
Immune complex (Heparins)	Drug binds to platelet factor 4, producing immune complex for which antibody is specific; immune complex activates platelets through Fc receptors	3–6% among patients treated with unfractionated heparin for 7 days, rare with low-molecular-weight heparin

Table adapted from Aster and Bougie[157][INSERT CORRECT LANGUAGE HERE IF TABLE IS USED]