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Review article

Immune-pathophysiology and -therapy of childhood purpura

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Childhood purpura - Overview

Purpura (from the Latin, *purpura*, meaning "purple") is the appearance of red or purple discolorations on the skin that do not blanch on applying pressure. They are caused by bleeding underneath the skin. Purpura measure 0.3-1cm, while petechiae measure less than 3mm and ecchymoses greater than 1cm[1]. The integrity of the vascular system depends on three interacting elements: platelets, plasma coagulation factors and blood vessels. All three elements are required for proper hemostasis, but the pattern of bleeding depends to some extent on the specific defect. In general, platelet disorders manifest petechiae, mucosal bleeding (wet purpura) or, rarely, central nervous system bleeding; coagulation disorders present as ecchymoses or hemarthrosis; and vasculitic disorders present with palpable purpura[2]. Purpura may be secondary to thrombocytopenia, platelet dysfunction, coagulation factor deficiency or vascular defect as shown in table 1.

A thorough history (Table 2) and a careful physical examination (Table 3) are critical first steps in the evaluation of children with purpura[3]. When the history and physical examination suggest the presence of a bleeding disorder, laboratory screening studies may include a complete blood count, peripheral blood smear, prothrombin time (PT) and activated partial thromboplastin time (aPTT). With few exceptions, these studies should identify most hemostatic defects (Figure 1)[4].

Table 1: Etiology of childhood purpura.

Pathogenesis	Etiology
I-Platelet disorders	
a) Immune destruction	
-*Primary (idiopathic)*	
-*Secondary*	Drugs (penicillin, valproic acid, quinidine, sulfonamides, cimetidine and heparin.)
	Infections (immunodeficiency virus, cytomegalovirus and herpesvirus)
	Connective tissue diseases (systemic lupus erythematosus)
	Post-transfusion
	Neonatal allo- and iso-immunization
	Hemolytic-uremic syndrome
b) Non immune destruction	Thrombotic thrombocytopenic purpura
	Disseminated intravascular coagulopathy.
c) Decreased platelet production	
-*Congenital syndromes*	Thrombocytopenia absent radii (TAR) syndrome
	Fanconi anemia
	Wiskott-Aldrich syndrome
	Congenital amegakaryocytic thrombocytopenia
-*Acquired causes*	Drugs (alkylating agents, antimetabolites, anticonvulsants, chlorothiazide diuretics and estrogens)
	Infections (TORCH, septicemia)
	Malignancies (leukemia, histiocytosis, neuroblastoma,)
	Others (storage diseases, osteopetrosis,)
d) Sequestration of platelets.	Splenomegaly
	Giant hemangioma
e)Platelet dysfunction	
-*Congenital etiologies.*	Glanzmann's thrombasthenia
	Bernard-Soulier disease
	Storage pool disease
-*Acquired causes*	Drugs
	Uremia

II- Vascular factors a) Congenital causes b) Acquired causes (vasculogenic purpura):	 Hereditary hemorrhagic telangiectasia Ehlers-Danlos syndrome Henoch-Schönlein purpura, Drugs (atropine and chloral hydrate) Infections (measles, scarlet fever, typhoid, meningococcemia, rickettsial diseases) Mechanical (violent coughing, vomiting, child abuse) Psychogenic conditions.
III- Coagulation factor deficiencies a) Hereditary b) Acquired	 Disseminated intravascular coagulopathy, Circulating anticoagulants, Liver disease, Vitamin K deficiency, uremia.

(Leung and Chan, 2001)[3].

Table 2: Findings of the history and possible etiologies of purpura.

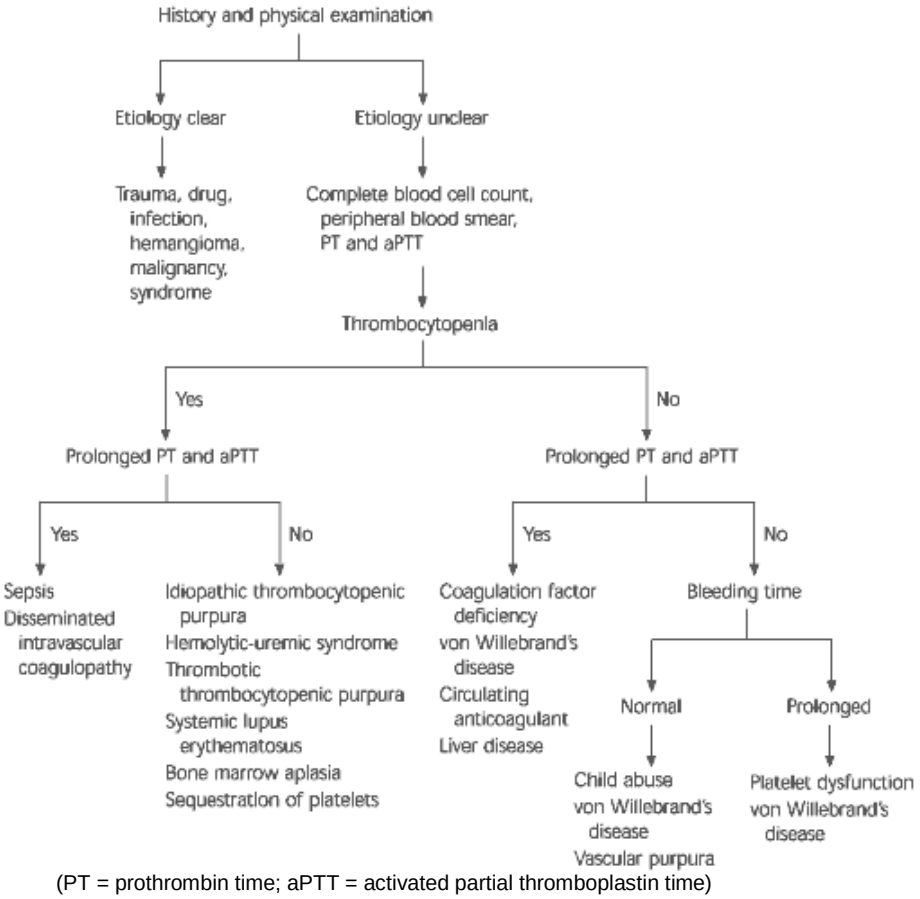
Historical data	Possible etiology
Age of Onset	
Birth	Intrauterine infection, maternal idiopathic thrombocytopenic purpura, maternal systemic lupus erythematosus, maternal medication, TAR syndrome, congenital amegakaryocytic thrombocytopenia
2 to 4 years	Idiopathic thrombocytopenic purpura
4 to 7 years	Henoch-Schönlein purpura
Onset/chronicity	
Acute onset	Idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura, medication, mechanical cause
Long duration	Abnormality of platelets, coagulopathy
Pattern of bleeding	
Mucosal bleeding	Thrombocytopenia, von Willebrand's disease
Intramuscular and intra-articular bleeding	Hemophilia
Associated symptoms	
Abdominal pain, blood in stools, joint pain	Henoch-Schönlein purpura
Lethargy, fever, bone pain	Leukemia
Intermittent fever, musculoskeletal symptoms	Systemic lupus erythematosus
Lethargy, polyuria, polydipsia, failure to thrive	Uremia
Purpura, but otherwise healthy	Idiopathic thrombocytopenic purpura
Drug use	
Alkylating agents	Thrombocytopenia
Antimetabolites	Thrombocytopenia
Past health	
Antecedent viral infection, especially an upper respiratory tract infection	Idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura
Systemic lupus erythematosus	Systemic lupus erythematosus
Liver disease	Cirrhosis or chronic hepatitis
Renal disease	Chronic renal failure
Family history	
von Willebrand's disease	von Willebrand's disease
TAR syndrome	TAR syndrome
Wiskott-Aldrich syndrome	Wiskott-Aldrich syndrome
Maternal history	
Maternal idiopathic thrombocytopenic purpura	Immune thrombocytopenia
Maternal systemic lupus erythematosus	Immune thrombocytopenia

(Leung and Chan, 2001)[3].

Table 3: Physical findings and possible etiologies of purpura.

Physical findings	Possible etiology
General findings	
Poor growth	Chronis disorder
Fever	Infection
hypertension	Chronic renal failure, renal vasculitis
Characteristics of purpura	
Location on lower extremities	Henoch-Schönlein purpura
Location on palms and soles	Rickettsial infection
Palpable purpura	Vasculitis
Associated signs	
Arthritis, abdominal tenderness, subcutaneous edema, scrotal swelling	Henoch-Schönlein purpura
Hemarthrosis	Hemophilia
Butterfly rash, pallor, arthritis, lymphadenopathy	Systemic lupus erythematosus
Lymphadenopathy	Infection, drugs, malignancy
Jaundice, spider angioma, palmar erythema, hepatosplenomegaly	Liver disease
Pallor, lethargy, generalized bone tenderness, hepatosplenomegaly, lymphadenopathy	Leukemia
Skeletal anomalies	TAR syndrome, Fanconi's syndrome
Pallor, café au lait spots, short stature	Fanconi's syndrome
Telangiectasia	Hereditary hemorrhagic telangiectasia
Hyperelasticity of skin, hypermobility of joints	Ehlers-Danlos syndrome

(Leung and Chan, 2001)[3].



(PT = prothrombin time; aPTT = activated partial thromboplastin time)

Figure 1. Algorithm for the diagnosis of purpura in children.
(From Cohen,1993)[4].

Patho-physiology of immune purpura

Immune thrombocytopenic purpura (ITP):

The appearance of antibodies against blood cells, including platelets, is often associated with viral infections. Viral disease may change the complex immune response of the host at different levels. Antigen-presenting cells may be disturbed; T cells may be influenced by altered cytokine production and release, thus disturbing further activation of the network of the immune system; B cells may produce increased amounts of antibodies and, as one of the consequences, the feedback mechanism of the immune system may be dysregulated[5].

For example, Epstein-Barr viruses (EBV) stimulate B lymphocytes to enhanced production of antibodies which cross-react with normal tissue proteins exhibiting configurations similar to those of the infectious agent[6]. This corresponds to molecular mimicry. Agranulocytosis due to EBV infection has been observed also in conjunction with bone marrow hypoplasia[7]. Cytomegalovirus (CMV) protein is similar to the human leucocyte antigen (HLA)-DR β-chain protein, and shares a common epitope with it[8]. Thrombocytopenia has been observed in both congenital and acquired CMV infection. CMV infection is known to induce multiple autoantibodies[9], and human CMV can suppress haematopoiesis[10]. Human parvovirus (B19) inhibits hematopoietic colony formation in vitro. Thrombocytopenia, neutropenia and erythrocytopenia, as well as pancytopenia due to parvovirus infection, have been reported[11].

Evidence for platelet destruction in ITP includes the following: (1) infusion of ITP blood or plasma into normal recipients may result in thrombocytopenia; (2) there is decreased intravascular survival of radiolabeled platelets in most ITP patients; (3) morphologic and in vitro evidence of platelet phagocytosis can be demonstrated; and (4) cytotoxic T cells can induce lysis of autologous platelets. Evidence for suppressed platelet production in ITP includes the following: (1) morphologic studies show megakaryocyte damage in most ITP patients; (2) there is normal or decreased platelet turnover in the majority of patients; (3) in vitro studies show antibody-induced inhibition of megakaryocyte production and maturation; and (4) an increase in the platelet count occurs in many ITP patients receiving treatment with thrombopoietin mimetics[12].

There is laboratory evidence that platelet alloantibodies decrease platelet reactivity to selected agonists. Deficient platelet function underlying immune thrombocytopenia may contribute to bleeding tendency seen at similar platelet levels[13]. The principle of downregulation of platelet function by antibodies has been used in producing monoclonal antibodies for clinical use[14].

ITP can be classified as primary (known also as idiopathic thrombocytopenic purpura) or as secondary to an underlying condition such as a malignant or nonmalignant disorder.

Primary ITP is caused by an inappropriate response of the immune system usually following a viral infection or immunization. Although ITP is primarily mediated by IgG autoantibodies, the production of these autoantibodies is regulated by the influence of T lymphocytes and antigen-presenting cells (APC). There is evidence that enhanced T-helper cell/APC interactions in patients with ITP may play an integral role in IgG antiplatelet autoantibody production[15]. Some patients have evidence of oligoclonality whereas others have polyclonal autoantibodies[16].

ITP patients develop autoantibodies that bind to platelet antigens (such a glycoprotein IIb/IIIa (GPIIb/IIa) or GPIb/IX)[17]. Many patients produce multiple antibodies; this has been attributed to the phenomenon of epitope spreading (figure 2). Once produced, autoantibody may either bind to platelets, causing their destruction by either phagocytosis or possibly complement activation and lysis, or bind to megakaryocytes, resulting in decreased thrombopoiesis[12]. Immune-mediated clearance of particles via the reticuloendothelial system (RES) is a function of immunoglobulin class, complement activation, and specific effector cells within the RES[18,19].

Three discrete pathways may result in the destruction of antibody-coated platelets. In one path-way, the direct activation of the complement cascade results in the formation of a membrane attack complex that produces pores in the platelet membrane and subsequent platelet lysis. Platelet destruction may also occur via engagement of complement receptors (CR1), Fcγ receptors (FcγR), or both[20-21]. Fcγ chain deficient mice cannot develop ITP[22], and ITP is palliated by therapy with anti-FcγR antibodies[23] and Fcγ fragments of intravenous immunoglobulin[24]. Several studies have shown that ITP patients demonstrate elevated levels of platelet-associated C3, C4, and C9, suggesting in vivo complement activation[25], and some of the effects of IVIG may occur by reducing C3 and C4 deposition on platelets[26]. Additionally, it has been suggested that FcγR-mediated platelet elimination most likely occurs in the spleen and that complement-mediated platelet elimination most likely occurs in the liver; as such, complement-

mediated platelet elimination may be of particular importance in splenectomized ITP patients. The competitive blockade of Fcγ R reduces Fcγ R-mediated elimination of platelets, thereby increasing platelet counts in ITP[27]. This is the basis of present anti-D and possible future treatments like antibody-coated liposomes[28].

Secondary ITP: Commonly occurring conditions associated with secondary ITP include lymphoproliferative disorders (Hodgkin's disease and non-Hodgkin's lymphomas), autoimmune collagen vascular diseases (systemic lupus erythematosus [SLE], thyroid disease, antiphospholipid syndrome [APS]), and chronic infections (human immunodeficiency virus [HIV], helicobacter pylori and hepatitis C virus [HCV])[5].

The mechanism of platelet destruction in thrombocytopenias associated with lymphoproliferative disorders and collagen vascular diseases is identical to the autoimmune mechanism seen in primary ITP. Platelet destruction in infection-associated ITP occurs via various mechanisms including accelerated platelet clearance due to immune complex disease as seen in HIV infection or cross-reactivity of anti-platelet glycoprotein antibodies and viral antigens in HIV, HCV, and H pylori infections (antigenic mimicry). In patients with HCV-related cirrhotic liver disease, splenic sequestration secondary to portal hypertension and decreased production of thrombopoietin may further contribute to development of thrombocytopenia[29].

Neonatal allo immune thrombocytopenia (NAT) is a life-threatening bleeding disorder caused by maternal platelet antibodies produced in response to fetal platelet antigens (platelet-specific alloantigens) inherited from the father[30]. Antiplatelet antibodies cross the placenta and cause destruction of fetal platelets, leading to severe thrombocytopenia, and potentially bleeding, including fatal intracerebral hemorrhage. Among platelet-specific alloantigens, Human Platelet Antigen (HPA) 1a is by far the most commonly involved in NAT in Caucasians[31], followed, at a much lower frequency, by HPA 5b[32]. In Asians, NAT is essentially linked with HPA-4 system. Other cases have been reported due to rare or private alloantigens[33-36]. Diagnostic testing for NAT involves genotyping of maternal, paternal, and sometimes fetal DNA; platelet antigen phenotyping; and maternal platelet antibody investigations using specialized platelet glycoprotein specific assays[37].

Meningococcal sepsis in children develops when the initial host response to the infection becomes inappropriately amplified and dysregulated. After the development of the first petechiae, the patient rapidly deteriorates and may subsequently develop shock, disseminated intravascular coagulation (DIC), and ultimately organ failure[38,39]. Interferon-alpha (INF- α) levels are raised in all patients with meningococcal disease and there is a positive correlation between their levels and severity scores, coagulopathies (including DIC), and outcome[40].

Drug-induced thrombocytopenia; Many drugs are capable of causing antibody-mediated thrombocytopenia. Some drugs become bound covalently to platelet membrane glycoproteins in vivo and stimulate the production of hapten-dependent antibodies that recognize drug-membrane protein targets. Others, such as quinidine, quinine, and sulfonamide antibiotics, induce the formation of an unusual class of antibodies that bind to membrane glycoproteins only when the drug (or one of its metabolites) is present in solution. Certain drugs trigger the production of true autoantibodies capable of binding to cell membrane glycoproteins in the absence of drug[41]. Heparin-induced immune thrombocytopenia (HIT) is associated with antibodies specific for complexes formed between heparin and platelet factor 4 (PF4), a basic protein of the chemokine family found normally in platelet alpha granules. Immune complexes consisting of heparin, PF4, and antibodies are important in the pathogenesis of HIT[42]. For many drug-induced thrombocytopenias, the targeted membrane glycoproteins are readily accessible for laboratory investigation and methods for detecting the responsible antibodies are well developed. Studies of drug-induced ITP may provide clues to the general mechanisms whereby drugs and other xenobiotics induce immune diseases. Clinicians should consider the possibility of an exogenous trigger in patients who present with apparent autoimmune thrombocytopenia[43].

Vascular purpura

Multiple mechanisms contribute to the pathogenesis of systemic vasculitides: 1. vasculitides resulting from the deposition of circulating immune complexes, comprising polyarteritis nodosa associated with hepatitis B virus infection, cryoglobulinemia associated systemic vasculitides, mainly the consequence of hepatitis C virus infection, and Schonlein Henoch purpura, which results from the deposition in the mesangium and vessels of IgA forming complexes; 2. vasculitides associated with anti-neutrophil cytoplasm

antibodies (ANCA), comprising Wegener's granulomatosis associated with anti-proteinase 3 ANCA, and microscopic polyangiitis and Churg-Strauss syndrome, associated with anti-myeloperoxidase ANCA. The pathogenic role of ANCA has been demonstrated in vitro and in vivo in the case of anti-myeloperoxidase antibodies, whereas it has only been demonstrated in vitro in the case of anti-proteinase 3 antibodies; 3. polyarteritis nodosa unrelated to viral infection results from rheologic phenomenon that explains the localisation of vasculitis lesions at the bifurcation of arteries and the presence of microaneurysm[44].

Schönlein-Henoch purpura (HSP) is a common vasculitis in children, characterized by the presence of immunoglobulin A (IgA) dominant immune deposits in the small vessels in skin, the gastrointestinal (GI) tract, the joints and sometimes the kidney[45]. Serum eosinophil cationic protein (ECP) levels have been shown to be significantly higher in children with HSP than those with IgA nephropathy or healthy controls. Serum levels of ECP were found to be even higher in HSP patients with nephritis compared to those without nephritis. Another recent study from Japan also found higher serum concentrations of ECP and interleukin (IL)-5 in patients with HSP nephritis[46]. Another possible player are the IgA anti-neutrophilic cytoplasmic antibodies (ANCA), which have been detected in anywhere from 10% to 82% of patients with HSP[47,48]. Whether they have a role in the pathogenesis in HSP and HSP nephritis needs further investigation. Lastly, complement C4B deficiency has also been reported to be associated with severe HSP nephritis and could possibly have a pathogenic role[49].

Immune therapy of purpura

Immune thrombocytopenic purpura: Acute and chronic ITP are benign conditions with a high probability of spontaneous recovery with or without therapy. Rates of 80-90% complete remission can be achieved irrespective of the treatment given. In only 10-20% of children, thrombocytopenia persists for more than six months, showing a chronic course, which also has a high probability of remitting over time (up to 80% or more). The variability of the clinical course, and the lack of consistent clinical features, make the decision on whether and how to treat difficult. Most physicians are driven to treat all children with symptoms by concern over life-threatening hemorrhage, although the risk of intracranial hemorrhage (ICH) is only 0.1-0.9%[50]. It has been generally agreed that bleeding - not platelet count - should be the rationale for treatment. Despite the absence of prospective, controlled studies, there is consensus that bleeding risks are significantly greater in patients with platelet counts $<20 \times 10^9$-30×10^9/L, and therefore treatment is indicated for these patients. For those with platelet counts that are higher, but still $<50 \times 10^9$/L, treatment is also indicated if accompanied by substantial mucous membrane bleeding [51].

Based on understanding antibody production and immune dysregulation (Figure 3) in ITP, the commonly used treatment regimens for acute ITP are corticosteroids, intravenous immunoglobulins (IVIG) (table 4), or intravenous anti-D immunoglobulin (anti-D). So far, there is no evidence that initial therapy can prevent ICH or a chronic course of the disease[5,50].

Table 4. Treatment of ITP with IVIG.

Initial treatment Day 1: 0.8 g IVIG/kg body weight Day 3: • If platelet count is > 30×10^9 /1, no further treatment • If platelet count is < 30×10^9/1, repeat IVIG as on day 1 • If platelet count is < 10×10^9/1, bone marrow analysis for exclusion of production disorders of platelets, leukemia, etc. **Emergency treatment (**severe bleeding, pre-surgery) 1-2 x 1.0 g IVIG/kg body weight until platelet counts are at least > 30×10^9/l or there is no more bleeding. Eventually, combination with high-dose methyl prednisolone (8-12 mg/kg body weight, intravenously or orally) and/or with platelet transfusion **Preventive treatment and treatment in chronic ITP** (platelet count < 10-30 x 10^9/l) 0.4-0.8 g IVIG/kg body weight, once

(Imbach et al., 1995)[5].

The standard initial treatment for ITP is oral corticosteroids to increase platelet counts. Excellent early responses to oral prednisone (4 mg per kilogram per day for four consecutive days) have also been reported in an uncontrolled prospective study[52]. Behavioral changes, weight gain, osteopenia, and glycosuria can occur during even brief courses of high-dose corticosteroids[19]. Intravenous immunoglobulin or anti-D immunoglobulin can also increase platelet counts and are particularly useful for stimulating rapid

platelet increases before planned procedures[52]. A single dose of intravenous immune globulin (0.8 g per kilogram) is generally effective[53]. Adverse reactions are generally transient and related to the rate of infusion; these include headache, fever, nausea, and rarely, aseptic meningitis that may arouse concern about the possibility of intracranial hemorrhage[54]. Renal failure and pulmonary insufficiency may occur, and anaphylaxis may occur in recipients who have a congenital deficiency of IgA[19]. A larger dose of anti-D immune globulin (75 µg per kilogram) evokes a response similar to intravenous immune globulin[55]. The average decrease in the hemoglobin level is 1.3 g per deciliter[56] and intravascular hemolysis is rare[57]. In presence of neurologic symptoms, internal bleeding, or emergency surgery, immediate intervention is demanded; Methylprednisolone (30 mg per kilogram per day; maximum, 1.0 g per day for two to three days) should be administered intravenously over a period of 20 to 30 minutes[58,59] together with intravenous immune globulin (1 g per kilogram per day for two to three days) and an infusion of platelets that is two to three times the usual amount infused[60]. In relapse, if Rh-positive, anti-D immune globulin, if clinically effective, is preferred to intravenous immune globulin because of its ease of administration, similar efficacy, and lower cost[19].

In chronic ITP the same drugs are generally used and it seems that pulses with steroids may be just as effective as IVIG. Anti-D may also be considered a reliable and cheap alternative for chronic disease. A major problem in the management of chronic ITP is the question of whether repeated infusions of Ig (IVIG or anti-D) and/or corticosteroids, high-dose dexamethasone, intermittent anti-D immuno-globulin infusions, and rituximab can postpone or ultimately preclude splenectomy, which must be considered only for a small proportion of patients resistant to therapy. In these cases, a laparoscopic approach should be preferred. Children who fail to respond to splenectomy (<20% of cases) warrant second line treatment with an immunosuppressant that inhibits T- and B-cell function and cooperation, including azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, or anti-CD20, and deserve a revisit of diagnosis for exclusion of secondary ITP. Patients may be more responsive to these same modalities after splenectomy[50-51]. Therapy of chronic or refractory ITP with thrombopoietin, antiCD40 ligand antibody, and Helicobacter pylori eradication have been reported[61].

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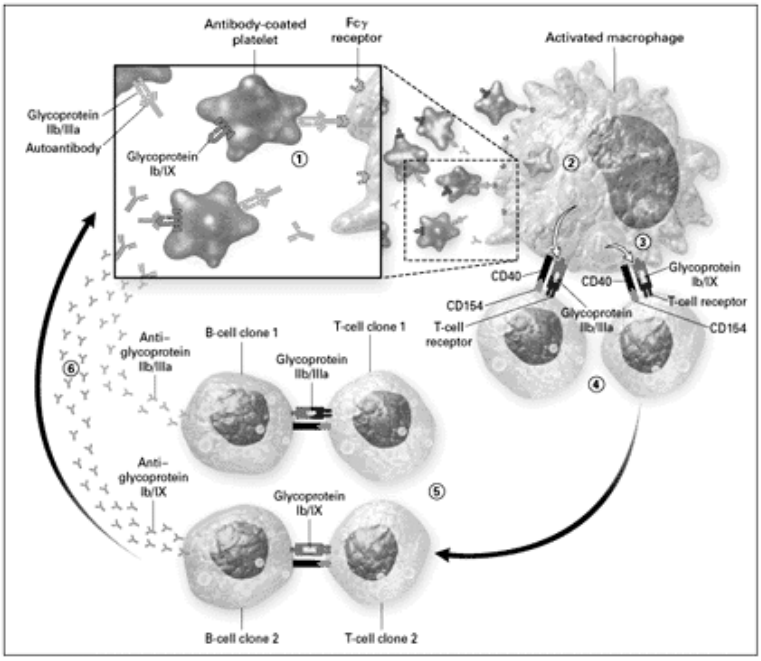

Figure 2. Pathogenesis of epitope spread in immune thrombocytopenic purpura *(From Cines and Blanchette, 2002)*[19].

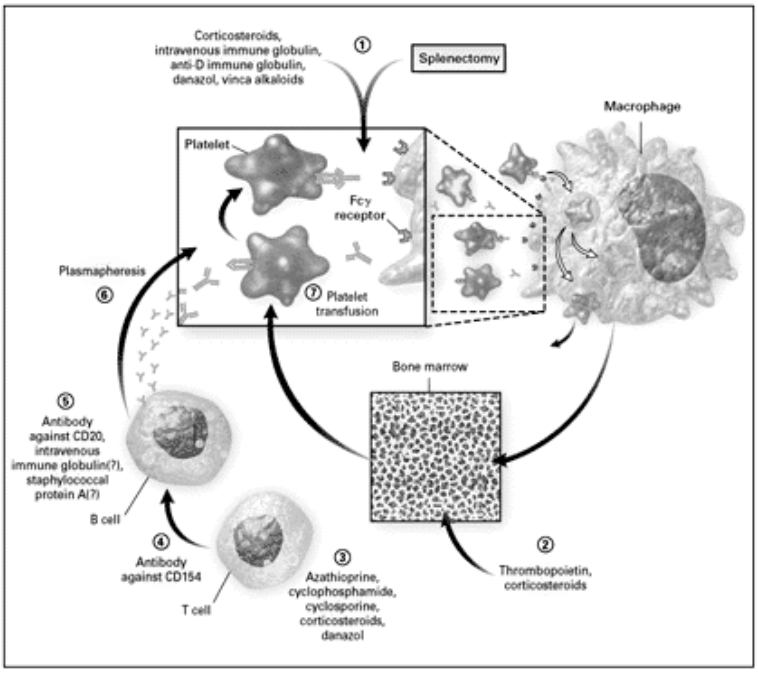

Figure 3. Mechanisms of action of therapies for immune thrombocytopenic purpura *(From Cines and Blanchette, 2002)19.*

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