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Immune thrombocytopenic purpura

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Introduction to immune thrombocytopenia (ITP)

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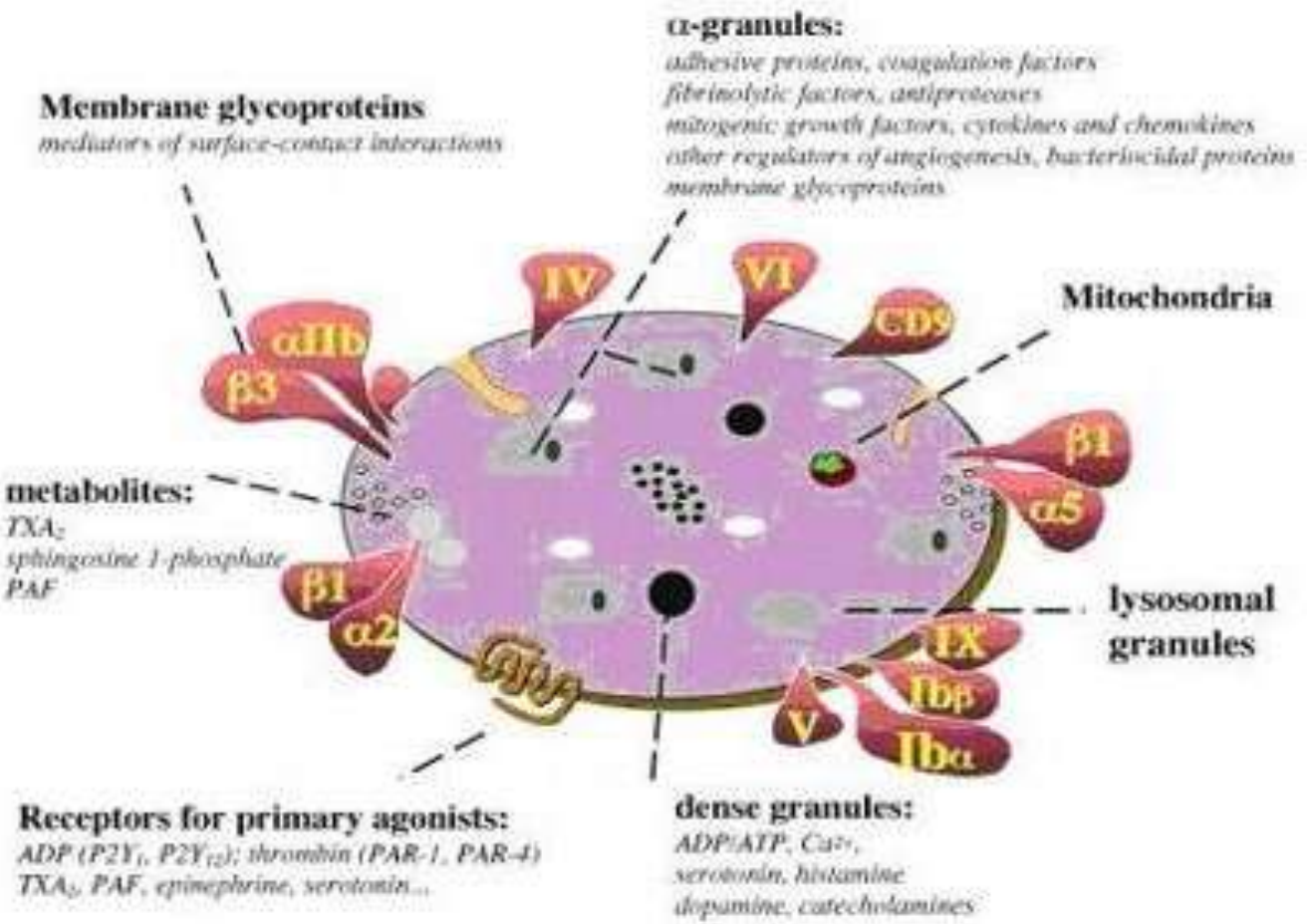
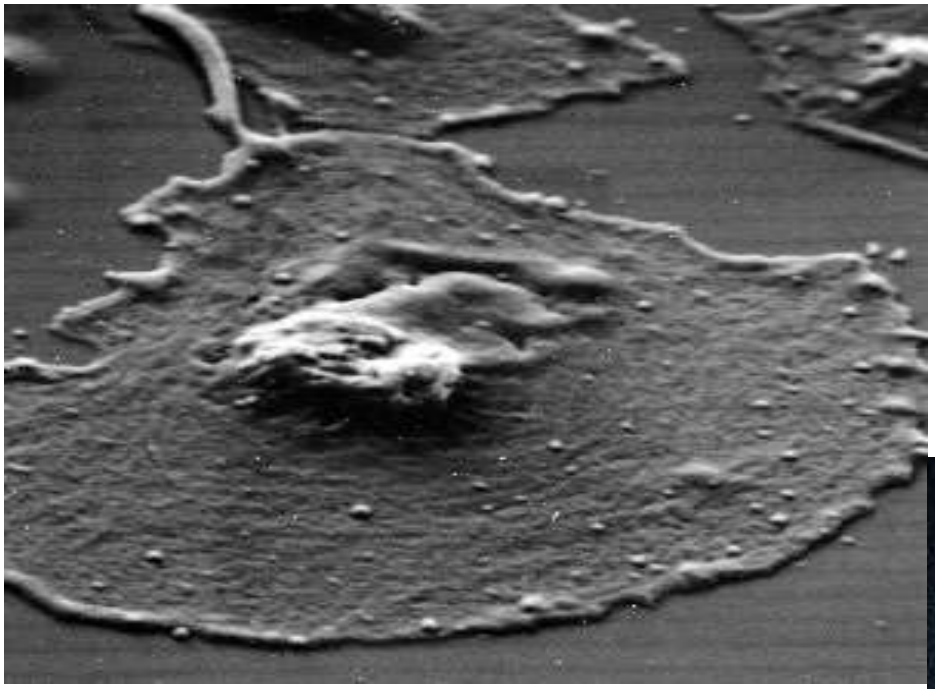
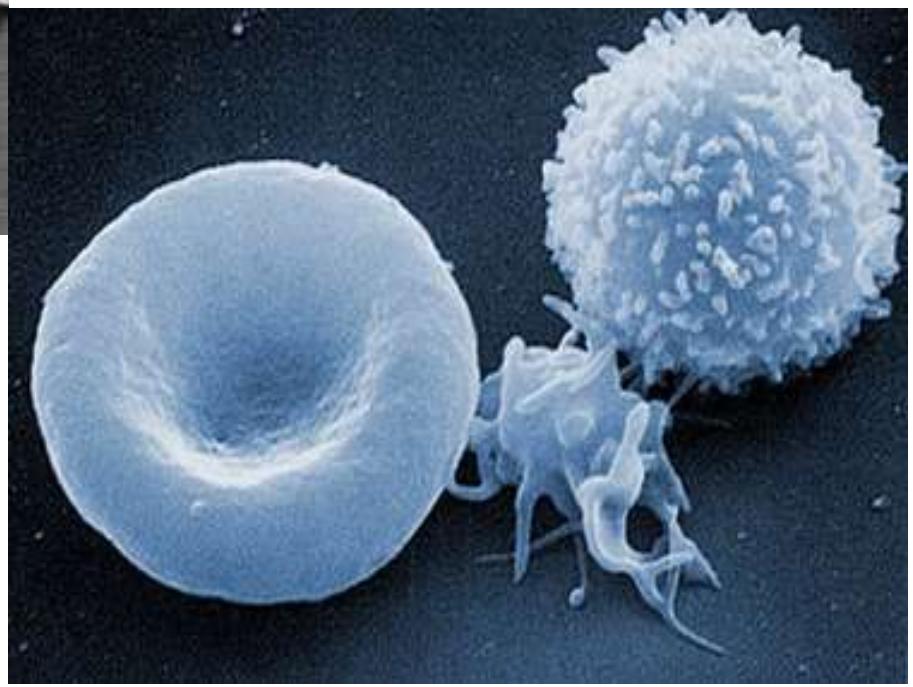
Programme organiser

Thrombocyte



Micrographs of platelets



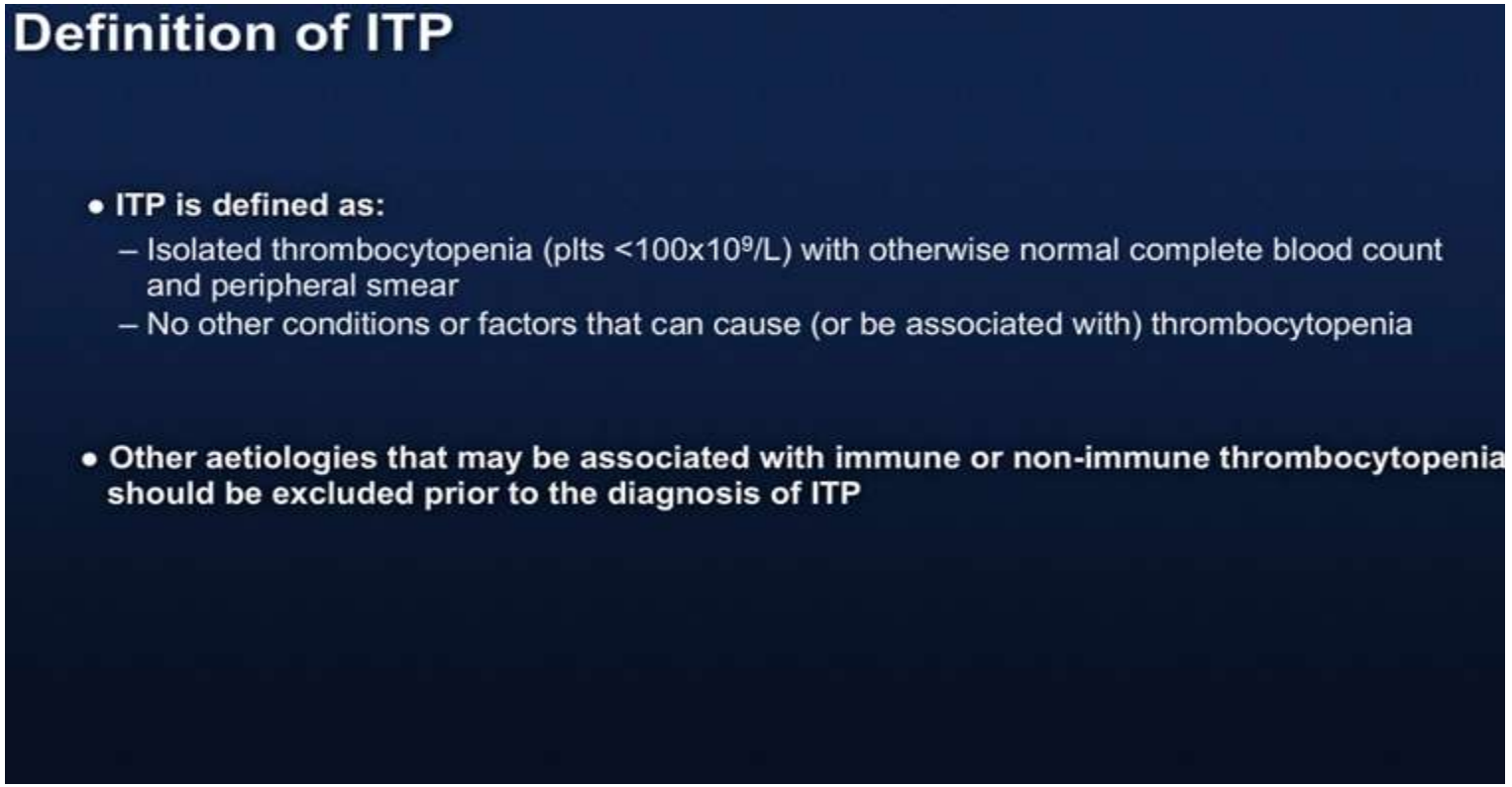


Incidence

- Peak prevalence in adults occurs aged 20-50 years, in children aged 2-4 years.
- ITP is estimated to affect approximately 3.3/100,000 adults/year and between 1.9 and 6.4/100,000 children/year.
- ITP affects people of both sexes and all ages—there is no typical ITP patient.
- Adult-onset ITP was once believed to be a disease largely afflicting young women

Definition

- Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by accelerated platelet destruction and suboptimal platelet production that leads to reduced peripheral blood platelet counts
- "Idiopathic" means the cause is unknown.
- "Thrombocytopenia" means a decreased number of platelets in the blood.
- "Purpura" refers to the purple discoloring of the skin, as with a bruise.
- The normal platelet level in adults is between 150,000 and 450,000/mm^3.

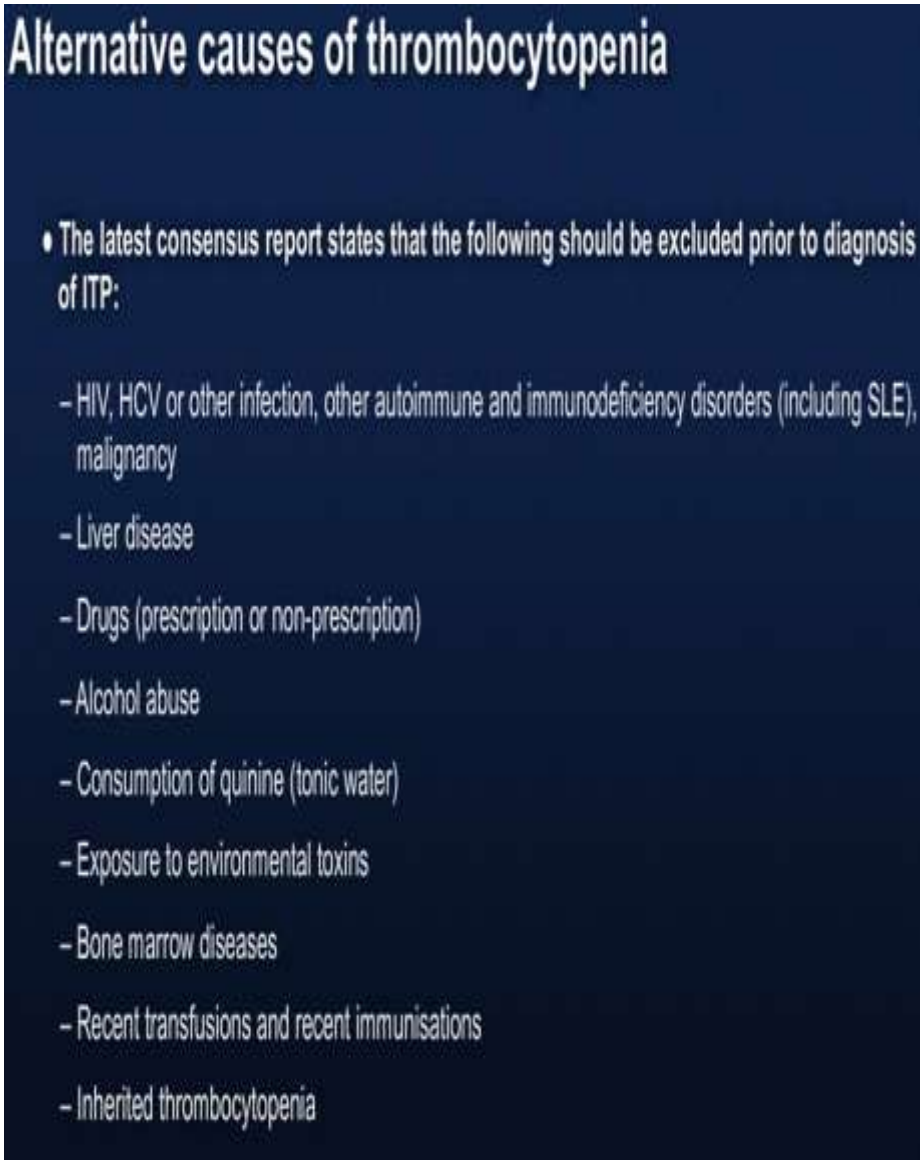


Types of immune thrombocytopenia

1.Primary ITP

2.Secondary ITP:

- HIV
- Hepatitis C
- Helicobacter pylori
- Immunodeficiencies
- Evans' syndrome
- Systemic lupus erythematosus
- Lymphoproliferative disorders
- Vaccine exposure
- Drug-induced



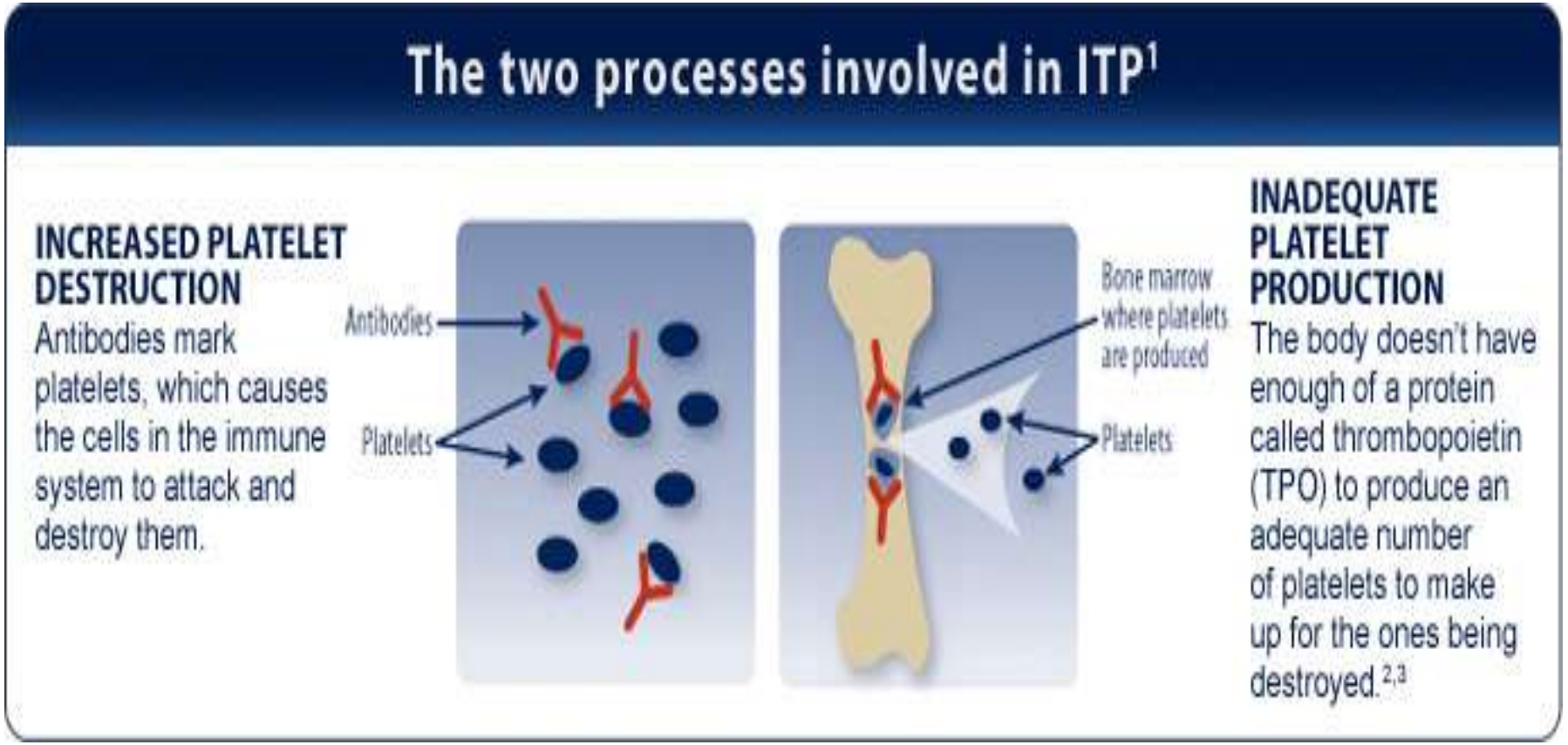
Pathogenesis

- The famous Harrington–Hollingsworth Experiment established the immune pathogenesis of ITP. The coating of platelets with IgG renders them susceptible to opsonization and phagocytosis by splenic macrophages.
- In many cases, the cause is not actually idiopathic but autoimmune, with antibodies against platelets being detected in approximately 60% of patients.
- Most often these antibodies are against platelet membrane glycoproteins IIb-IIIa or Ib-IX, and are of the IgG type.
- The IgG autoantibodies are also thought to damage megakaryocytes, the precursor cells to platelets, but this is thought to contribute only slightly to the decrease in platelet numbers.
- Recent evidence suggests that the stimulus for autoantibody production in ITP is due to abnormal T helper cells reacting with platelet antigens on the surface of antigen presenting cells.
- This important finding suggests that therapies directed towards T cells may be effective in treating ITP.

http://www.ejournalofdentistry.com/articles/e-JOD7B695FBBA5-7D6C-46E7-98FF-F607C900EEBC.pdf

Pathogenesis

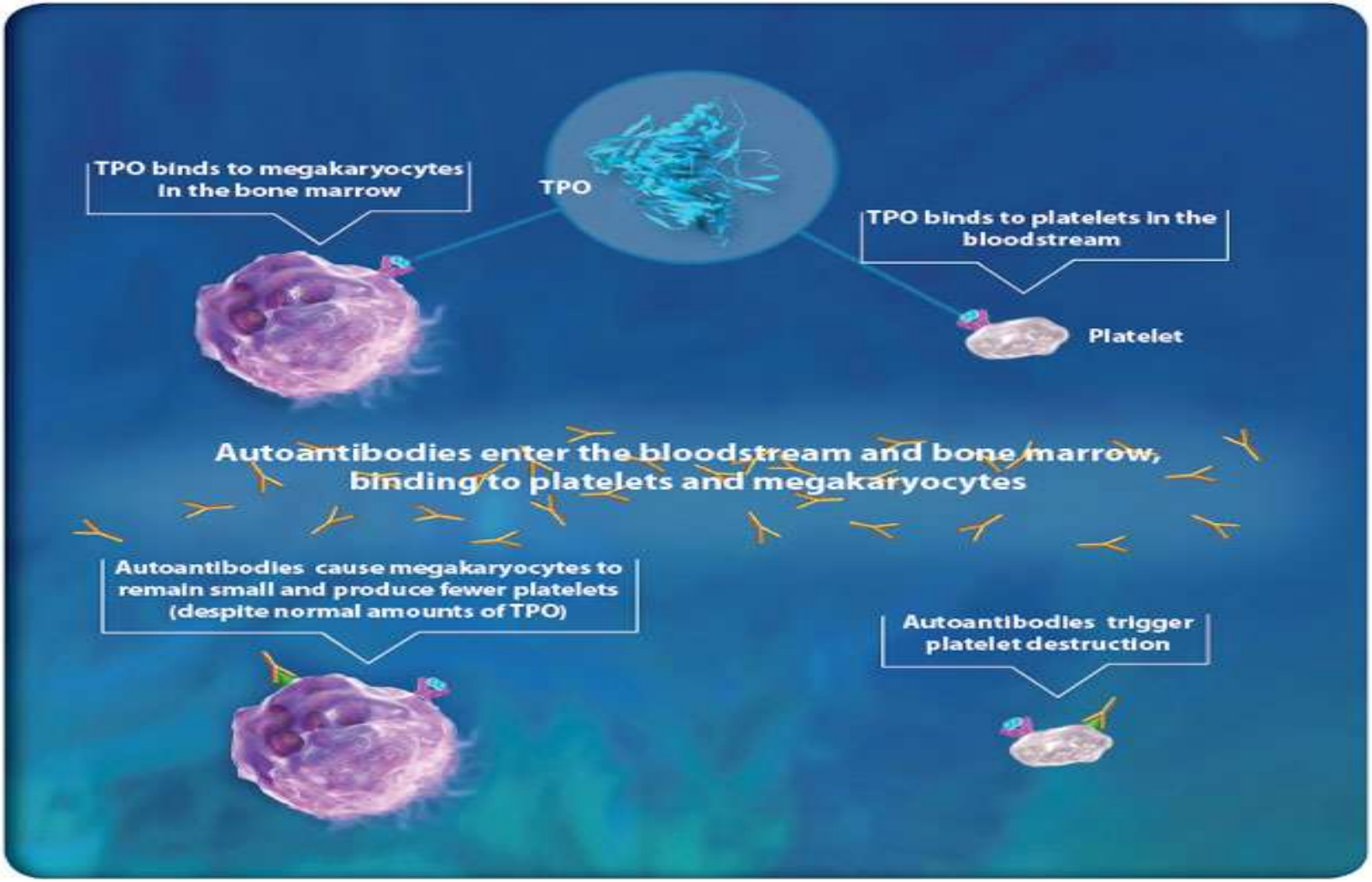
ITP is known to be associated with both: increased platelet destruction and impaired platelet production



http://www.nplate.com/patient/understanding-itp/causes-itp.html

Pathogenesis

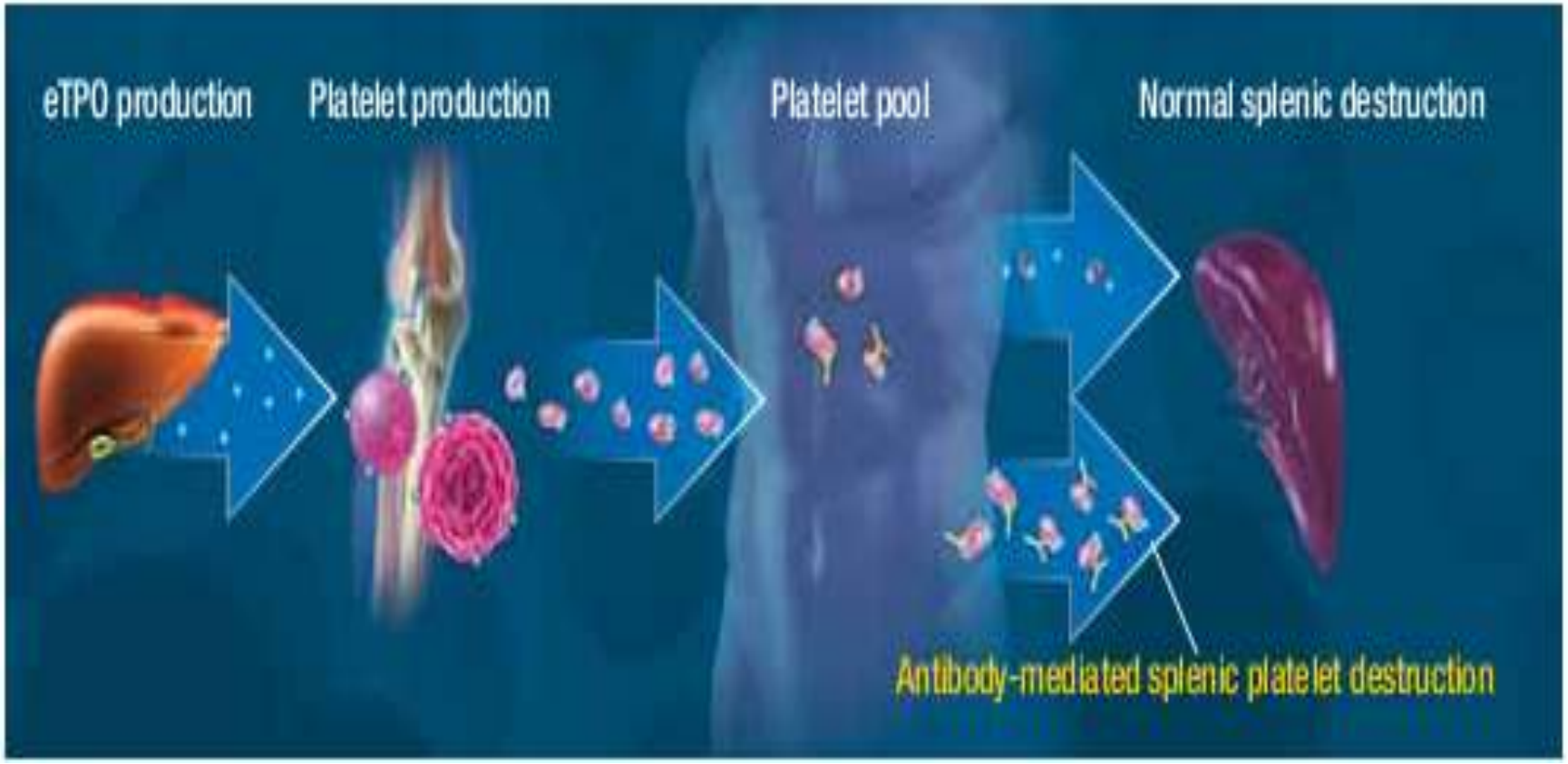
Effects of ITP on platelet production and destruction



http://www.itpvillage.com/html/hcp/library-mechanisms-of-disease.aspx

Pathogenesis

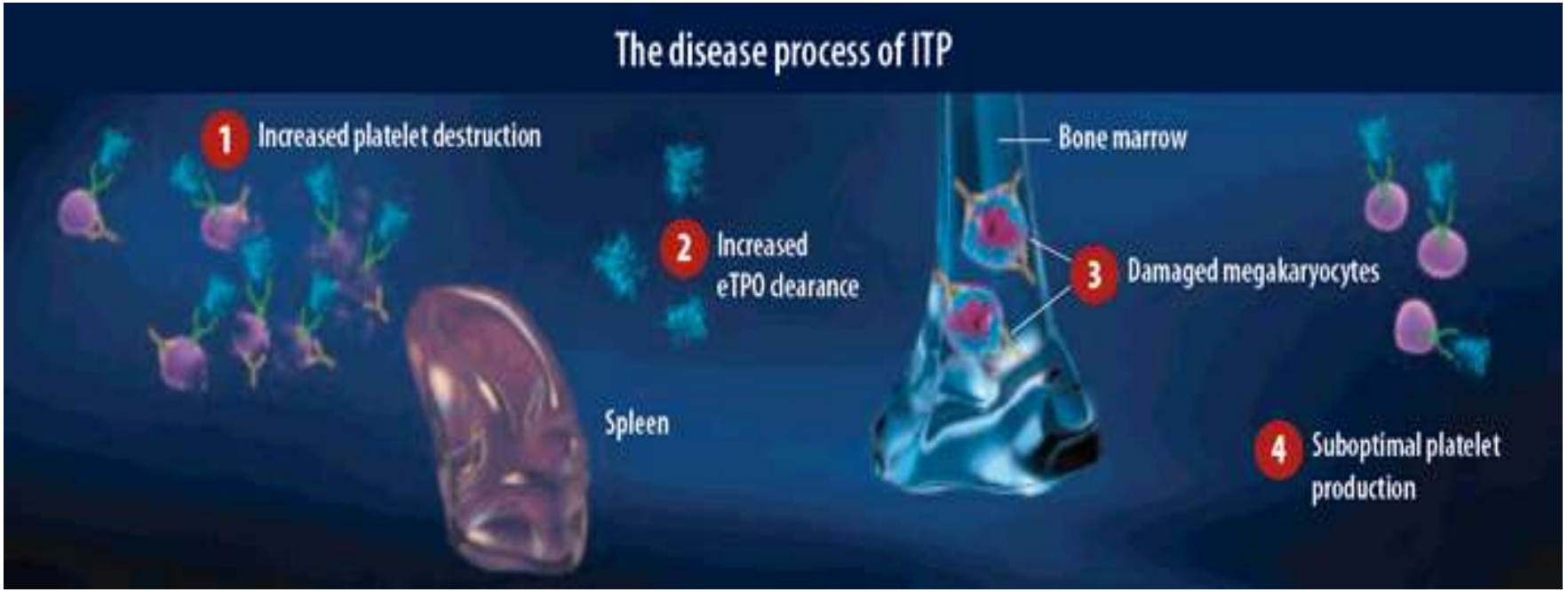
Antibody-coated platelets are recognized by macrophages primarily in the spleen leading to their destruction



http://www.ebmt.org/Contents/Resources/Library/Resourcesfornurses/Documents/ITP%20Handbook.PDF

Pathogenesis

1. Increased platelet destruction is caused by autoantibody binding to platelets.
2. Increased endogenous thrombopoietin (eTPO) clearance results in reduced eTPO levels. Increased platelet destruction leads to increased TPO clearance, resulting in less TPO available to stimulate platelet production.
3. Megakaryocytes may be damaged by antibodies, making them less productive than normal.
4. Suboptimal platelet production results from damaged megakaryocytes and reduced eTPO levels.



Recommended ITP classification from

"International Consensus report on ITP investigation"

TERMINOLOGY	DISEASE DURATION
Newly diagnosed (previously acute)	**< 3 months**
Persistent	**3 to 12 months**
Chronic	**>12 months**

http://www.ihtc.org/wp-content/uploads/2010/05/Final%20BT%20Spring%202010%20PRINT.pdf

The platelet count is a marker for the risk of serious bleeding

Platelet count (x 10^9/L)	Symptoms
>50	None
30–50	Excessive bruising with minor trauma
10–30	Spontaneous petechiae or bruising
<10	At risk of internal bleeding

Data taken from Cines & Blanchette. *N Engl J Med* 2002.[35]

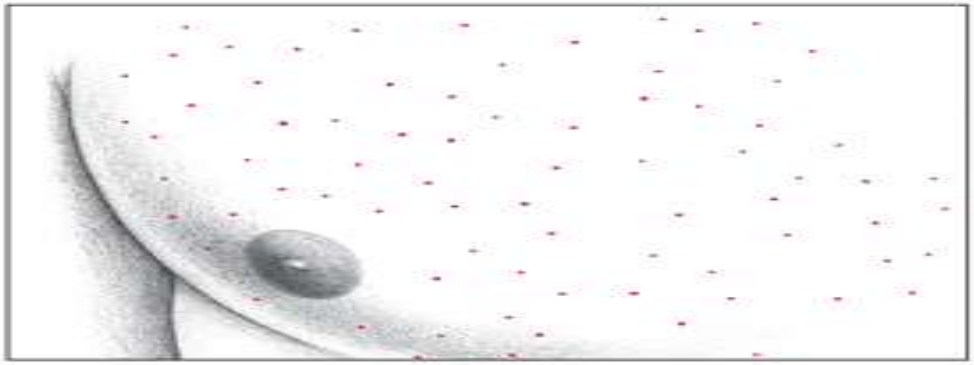
- Counts below 20,000/mm^3 increase the risk of spontaneous bleeding
- Major bleeding, including spontaneous intracerebral hemorrhage, occurs predominantly in patients with platelet counts less than 20 000 × 10^9/L, generally less than 10 000 × 10^9/L.
- Patients typically present with petechiae or purpura that develop over several days accompanied by platelet counts less than 20 000 × 10^9/L
- Severe cutaneous bleeding, prolonged epistaxis, gingival bleeding, overt hematuria, or menorrhagia may develop at platelet counts less than 10 000 × 109/L.
- Those with platelet counts between 30 000 and 50 000 × 109/L may note easy bruising, whereas platelet counts above 50 000 × 109/L are usually discovered incidentally.
- Rarely, do patients present with bleeding disproportionate to the platelet count because of antibody-induced platelet dysfunction.

Symptoms

SITE	SYMPTOMS
Skin	Petechiae, purpura, ecchymoses, subcutaneous hematomas
Mucosal	Gingival bleeding, epistaxis, conjunctival bleeding, menorrhagia, hematuria, gastrointestinal hemorrhage
Internal	Intracranial hemorrhage, bleeding within other organs such as the liver, spleen
Hemostatic challenges	Prolonged bleeding after minor surgical interventions or injury. Bleeding after T&A, menorrhagia, bleeding after dental extractions, post-partum bleeding

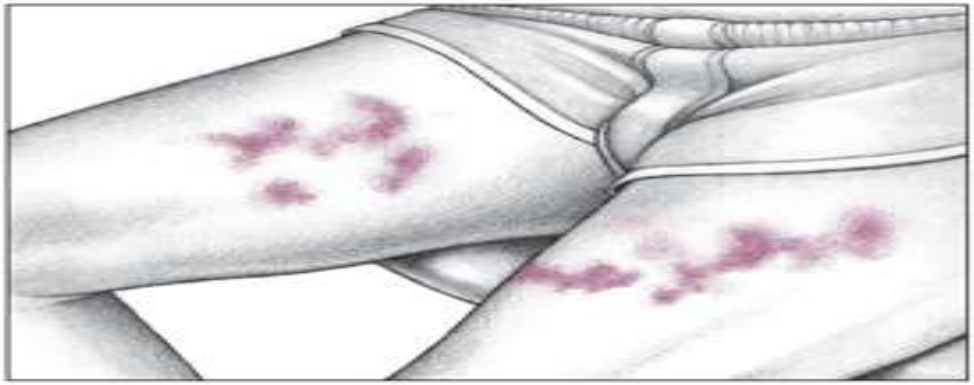
Identifying purpuric lesions

Purpuric lesions fall into three categories: petechiae, ecchymoses, and hematomas.



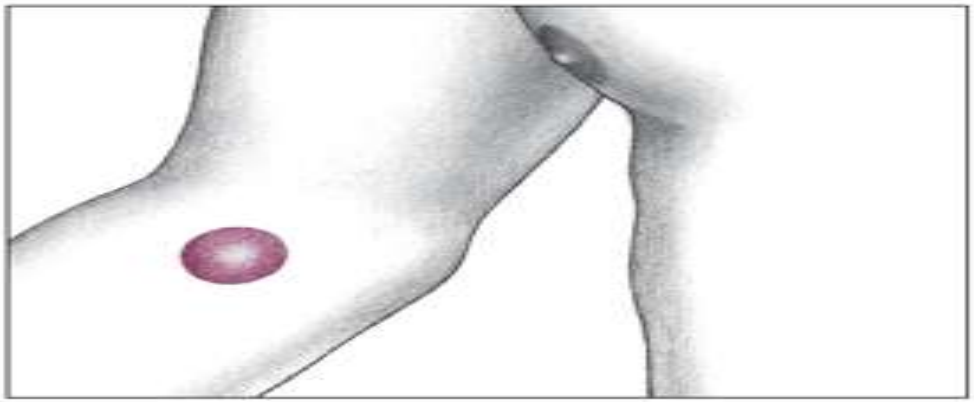
Petechiae

Petechiae are painless, round, pinpoint lesions, 1 to 3 mm in diameter. Caused by extravasation of red blood cells into cutaneous tissue, these red or brown lesions usually arise on dependent portions of the body. They appear and fade in crops and can group to form ecchymoses.



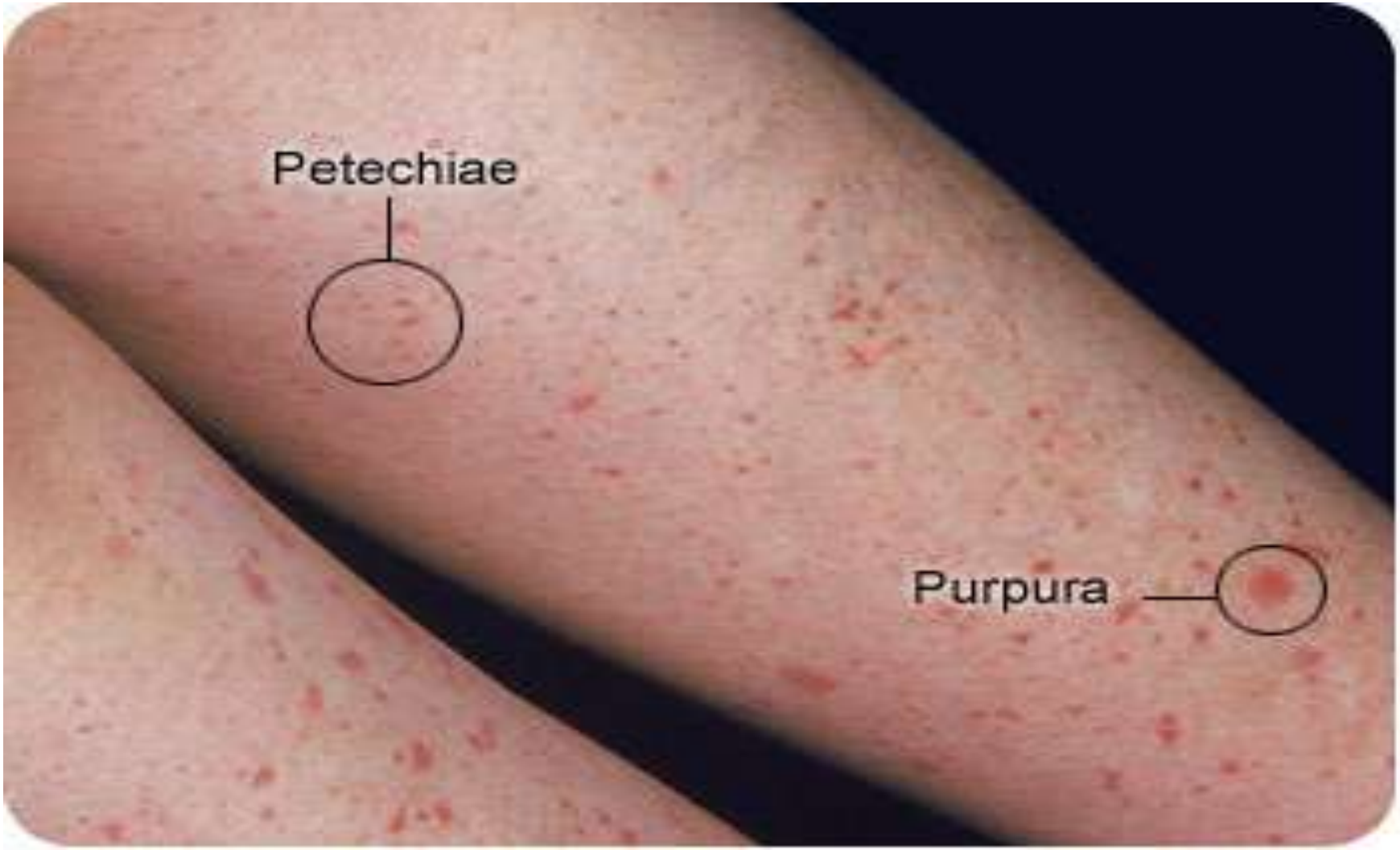
Ecchymoses

Ecchymoses, another form of blood extravasation, are larger than petechiae. These purple, blue, or yellow-green bruises vary in size and shape and can arise anywhere on the body as a result of trauma. Ecchymoses usually appear on the arms and legs of patients with bleeding disorders.

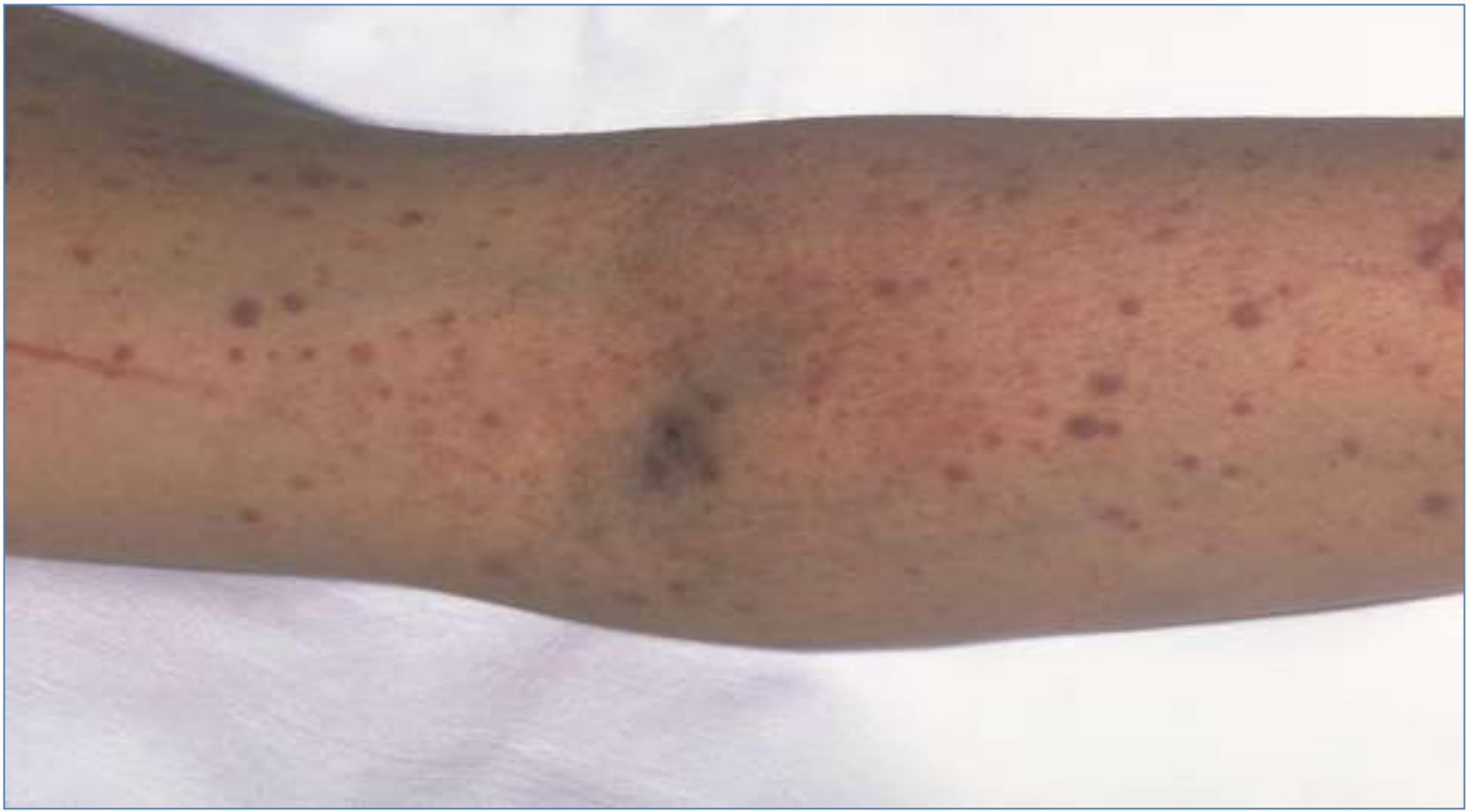


Hematomas

Hematomas are palpable ecchymoses that are painful and swollen. Usually the result of trauma, superficial hematomas are red, whereas deep hematomas are blue. Hematomas commonly exceed 1 cm in diameter, but their size varies widely.

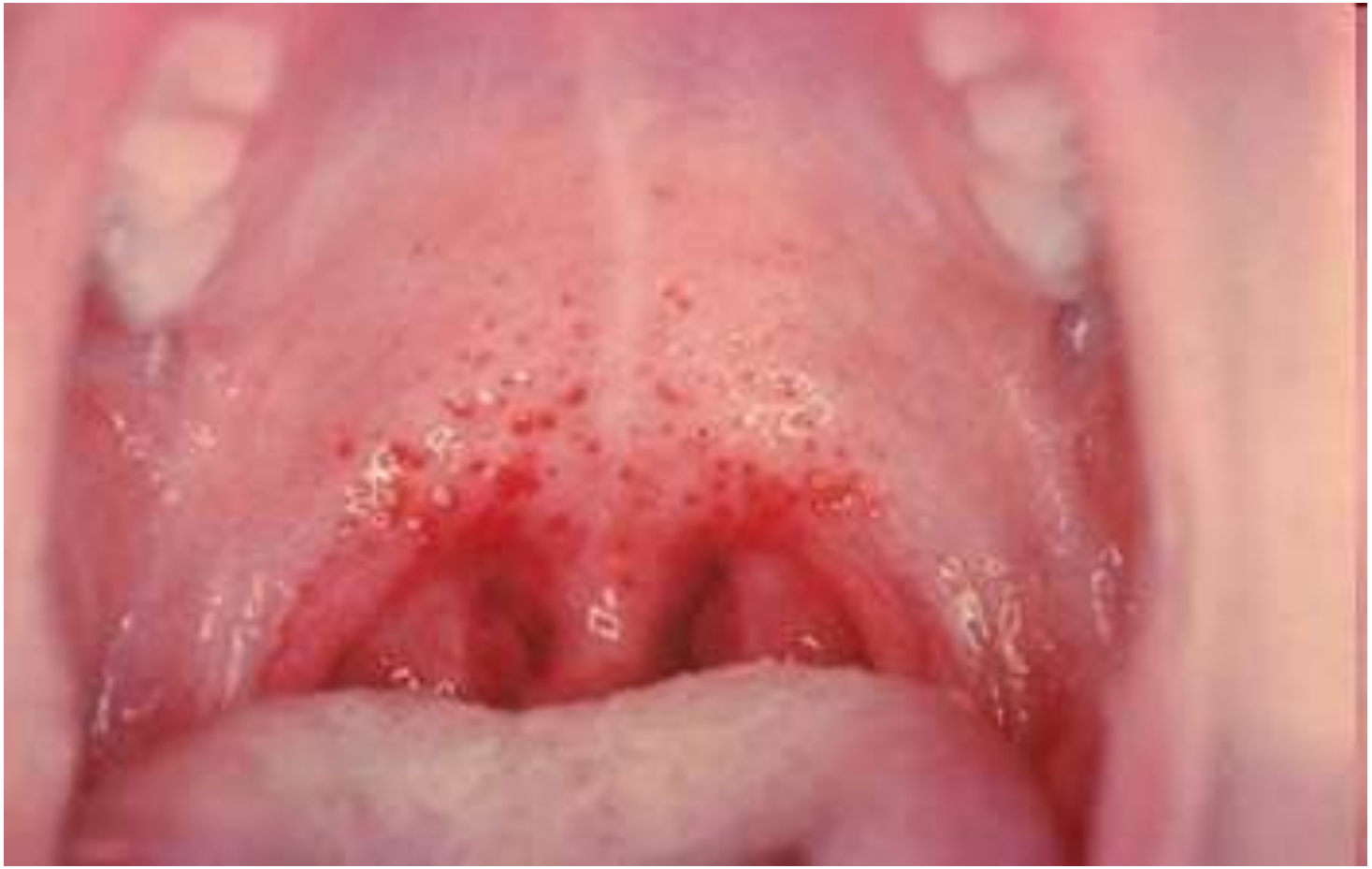

Petechiae
Purpura

Petechiae and Purpura



http://www.getwellnatural.com/idiopathic-thrombocytopenic-purpura-itp.aspx

Petechial hemorrhages on the palate



http://www.ispub.com/journal/the-internet-journal-of-hematology/volume-6-number-2/corticosteroid-resistant-idiopathic-thrombocytopenic-purpura-case-report-and-literature-review.html

Ecchymoses in Immune-Mediated Thrombocytopenic Purpura

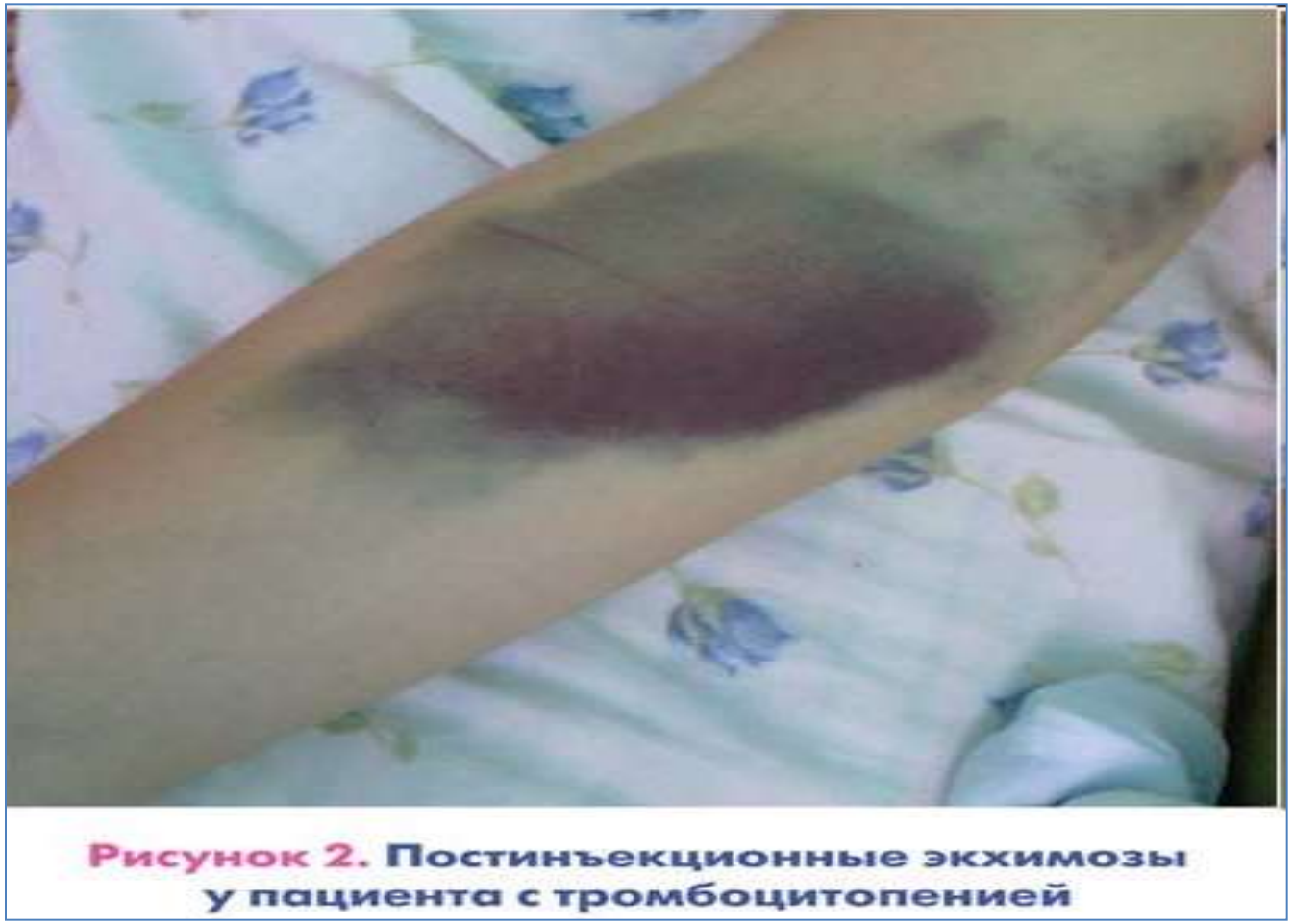
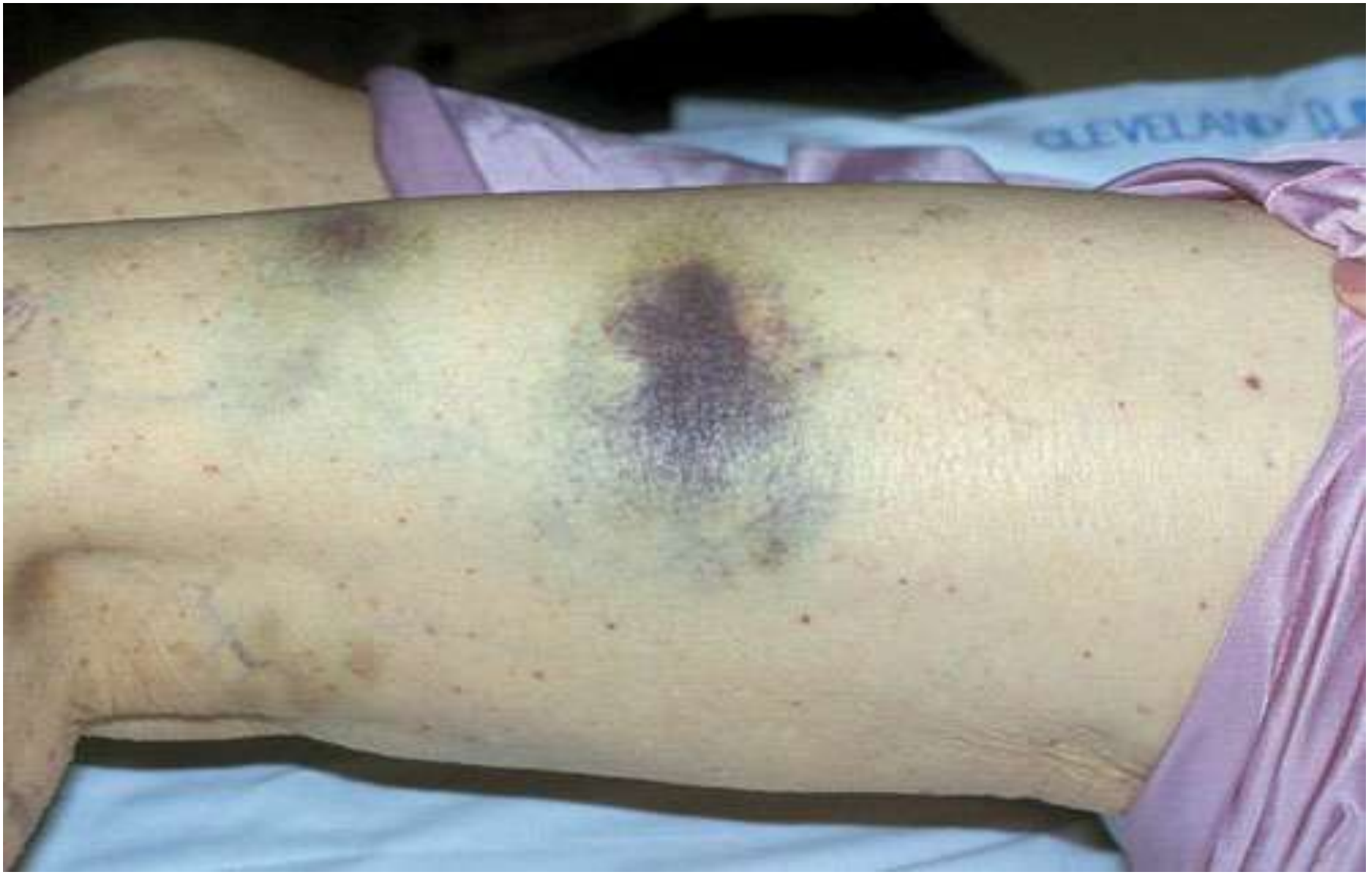


Рисунок 2. Постинъекционные экхимозы у пациента с тромбоцитопенией

http://d-l.com.ua/pics/tabl/Tretjakova_2(9)_2_2011.jpg

Ecchymoses in Immune-Mediated Thrombocytopenic Purpura



If you see someone with this ugly-looking bleeding in gums, and ecchymosis, you really need to get moving on a treatment because this could be a warning of potential intercranial hemorrhage, which we always worry about.

http://www.hopkinsarthritis.org/physician-corner/rheumatology-rounds/round-8-autoimmune-thrombocytopenia/

Dignostics

Basic assessment parameters

- **There is no 'gold standard' in the diagnosis of ITP**
- **Basic assessment parameters to confirm diagnosis of ITP include:**
  - Patient/family history
  - Liver disease
  - CBC and reticulocyte count
  - Peripheral blood film
  - Quantitative immunoglobulin level measurement
  - Bone marrow examination (in selected patients)
  - Blood group (Rh)
  - Direct antiglobulin test
  - *H. pylori*, HIV, HCV

Recommendations for diagnosis

- There is no 'gold standard' test to establish the diagnosis of ITP
- Diagnosis is based on the exclusion of other causes of isolated thrombocytopenia
- Bone marrow examination is appropriate in patients >60 years old and in patients not responding to first-line therapy options
- HIV, HCV and *H. pylori* should be routinely tested for in adult patients
- Quantitative Ig level testing is indicated to exclude an immune deficiency syndrome or when treatment with intravenous immunoglobulin is considered

Recommended diagnostic approaches for ITP

Basic evaluation	Tests of potential utility
Patient history	Glycoprotein-specific antibody
Family history	Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant)
Physical examination	Anti-thyroid antibodies and thyroid function
Complete blood count and reticulocyte count	Pregnancy test in women of childbearing potential
Peripheral blood smear	Antinuclear antibodies
Quantitative immunoglobulin level measurement*	Viral polymerase chain reaction (PCR) for parvovirus and cytomegalovirus (CMV)
Bone marrow examination (in selected patients)	
Blood group (rhesus)	
Direct antiglobulin test	
Helicobacter pylori†	
Human immunodeficiency virus (HIV)†	
Hepatitis C virus (HCV)†	

The Peripheral Blood Smear in ITP

- **Consistent with the diagnosis of ITP**

1. Thrombocytopenia. Platelets are normal in size or may appear larger than normal, but consistently giant platelets (approaching the size of red blood cells) should be absent.

2. Normal red blood cell morphology.

3. Normal white blood morphology.

- **Not consistent with the diagnosis of ITP**

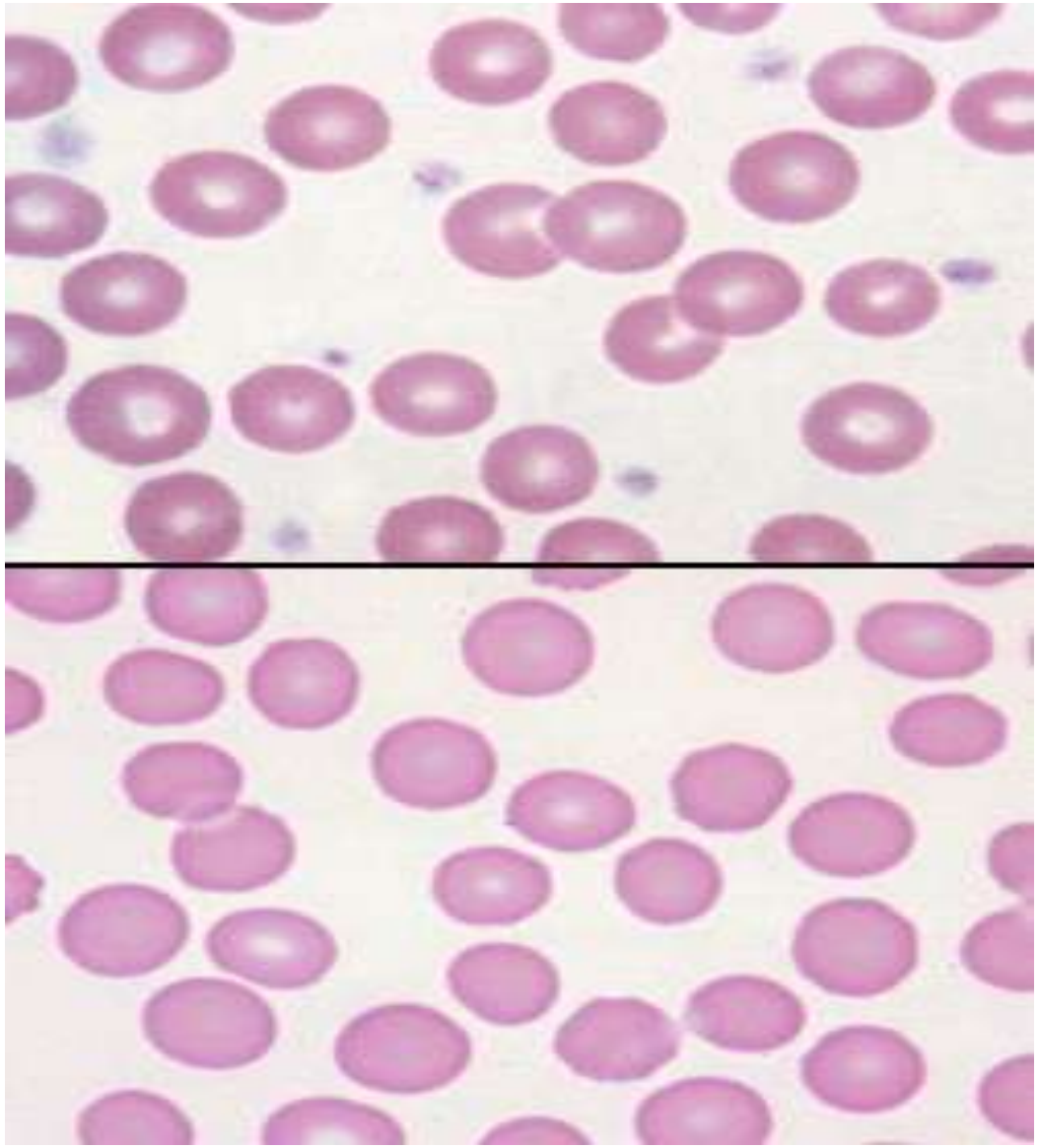
1. Predominant giant platelets.

2. Red blood cell poikilocytosis, schistocfles, polychromatophilia (unless response to bleeding), macrocytes, nucleated red blood cells.

3. Leukocytosis or leukopenia, with immature or abnormal cells

(although atypical lymphocytes and eosinophilia may occur in children with ITPI).

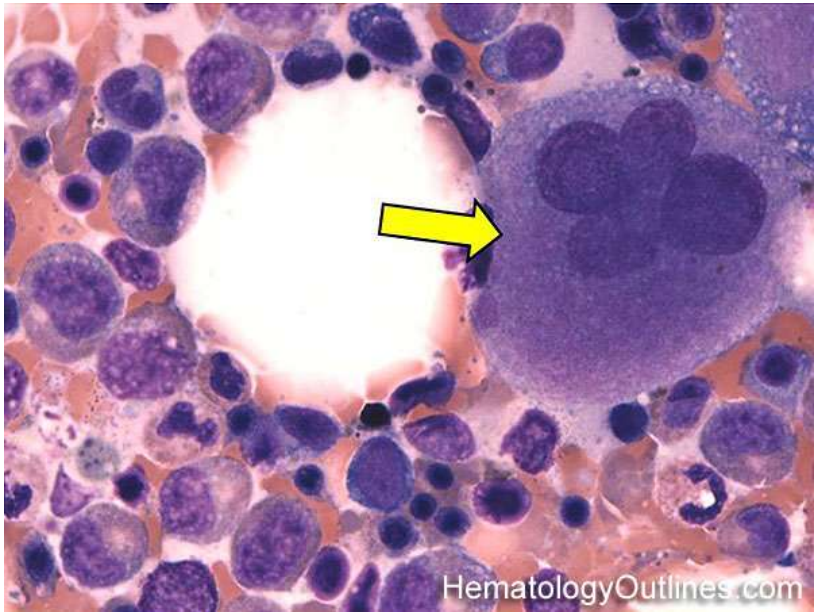
Upper panel: normal platelet count.
Lower panel: severe thrombocytopenia.

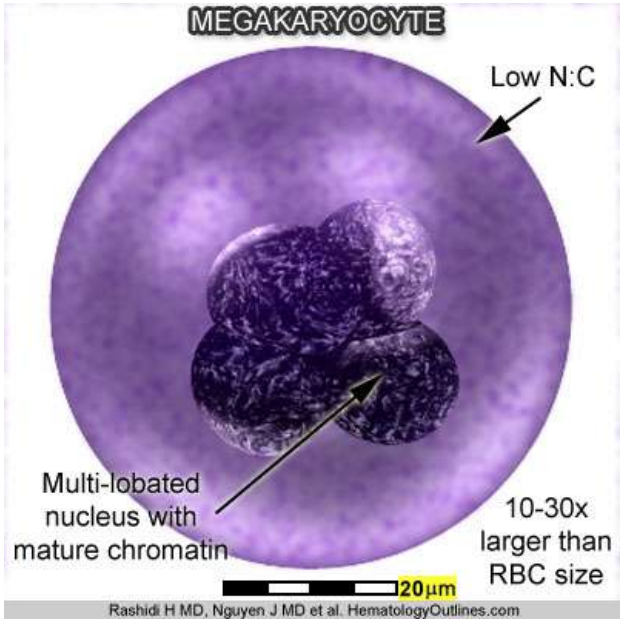


Bone marrow aspirate- megacaryocyte

Microscopic Features:

- 10-30x larger than a mature RBC (Largest hematopoeitic cell)
- Lower nuclear to cytoplasmic ratio because of increased cytoplasm
- Multilobated Nucleus (2-8 lobes on top of each other) with mature chromatin (clumped)
- Nucleoli are absent
- Cytoplasm is abundant and light blue and usually lacks granules





http://hematologyoutlines.com/atlas_topics/56.html

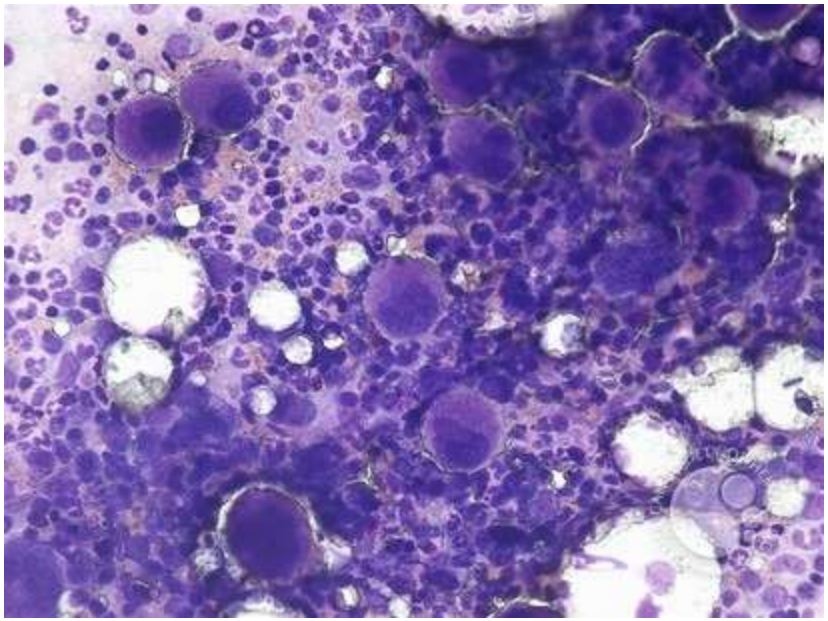
Indications for bone marrow aspirate in ITP

Bone marrow aspiration is used to exclude other diagnoses and is indicated in:

- older patients (particularly those over 60 years of age to exclude myelodysplastic syndrome)
- in those with an atypical presentation (e.g. abnormalities observed on peripheral blood smear suggestive of other haematological disorders)
- in those with a poor response to first-line therapy and
- in those being considered for splenectomy.

ITP - bone marrow aspirate

- The typical finding in a bone marrow biopsy of a patient with ITP is an **increase in megakaryocytes** without other concomitant abnormalities.



A high-power view shows that some of the megakaryocytes appear relatively immature with hypolobulated nuclei and hypogranular cytoplasm.

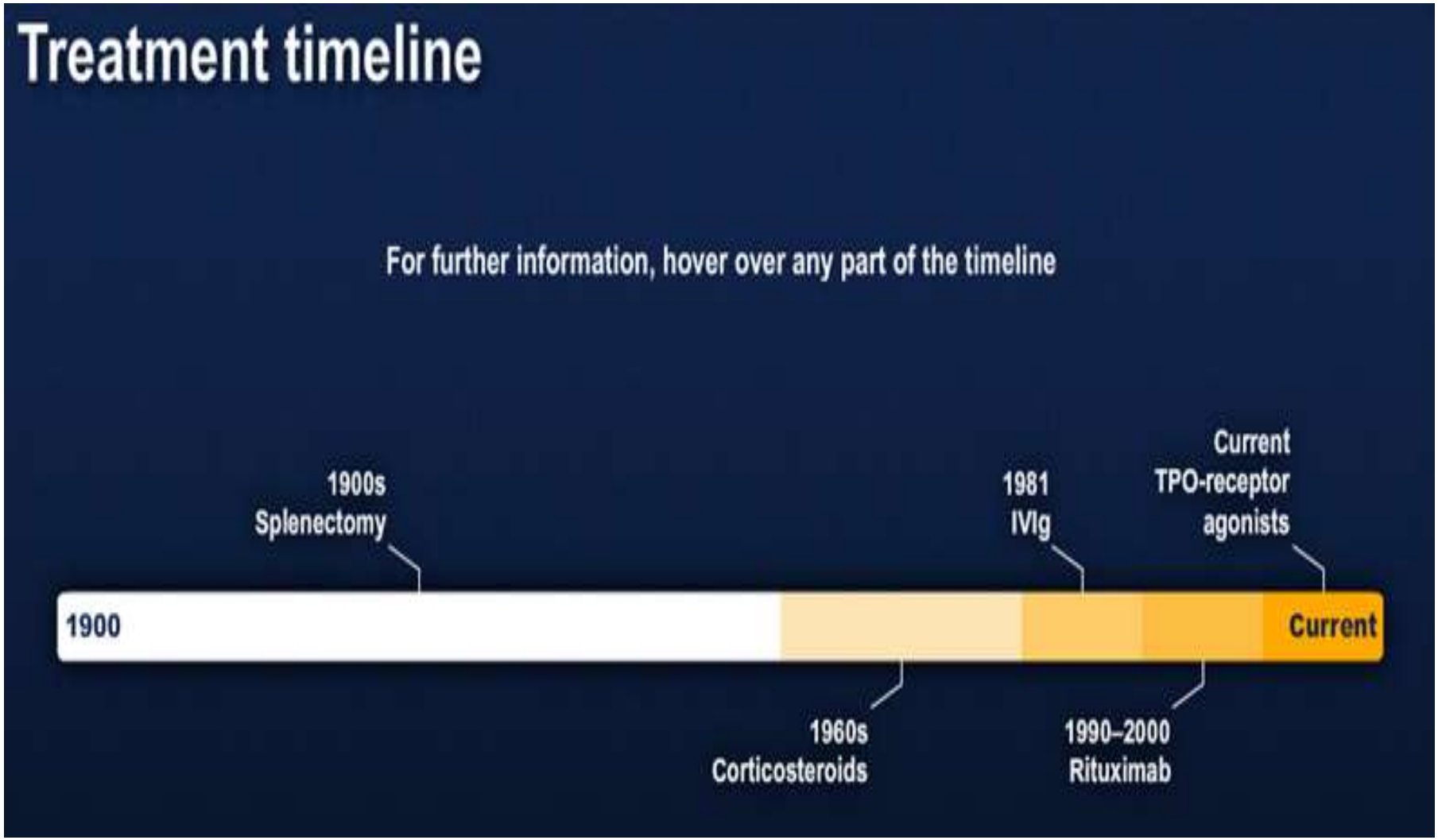
http://imagebank.hematology.org/AssetDetail.aspx?AssetID=3613&AssetType=Asset

Treatment

Who should be treated? (2)

- **Treatment is rarely indicated in patients with platelet counts above 50×10^9/L in the absence of:**
  - Bleeding due to platelet dysfunction or another haemostatic defect
  - Trauma
  - Surgery
  - Clearly identified comorbidities for bleeding
  - Mandated anticoagulation therapy
  - Individuals whose profession or lifestyle predisposes them to trauma

History of ITP treatment



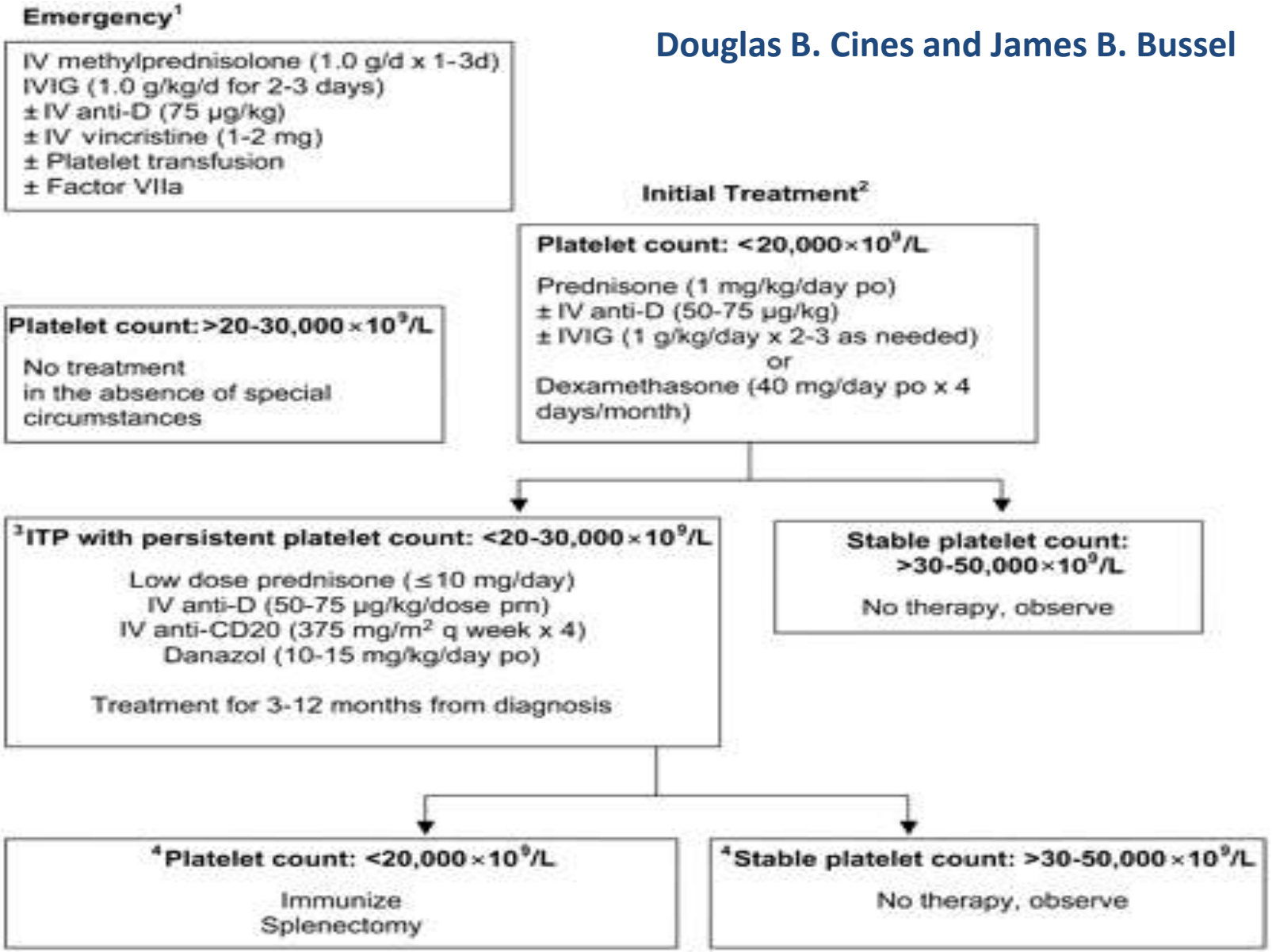
Overview of management options

- According to the latest consensus report, the following treatment classifications are apparent:

Clinical situation	Therapy option	
First-line (initial treatment for newly diagnosed ITP)	Anti-D Corticosteroids: dexamethasone, methylprednisolone, prednis(ol)one IVIg	
Second-line	Azathioprine Cyclosporin A Cyclophosphamide Danazol Dapsone	Mycophenolate mofetil Rituximab Splenectomy Thrombopoietin (TPO)-receptor agonists Vinca alkaloids
Treatment for patients failing first- and second-line therapies	**Category A: treatment options with sufficient data** TPO-receptor agonists **Category B: treatment options with minimal data and considered to have potential for considerable toxicity** Campath-1H Combination of first- and second-line therapies Combination chemotherapy Hemopoietic stem cell transplantation (HSCT)	

Algorithm of therapy of adult ITP

Douglas B. Cines and James B. Bussel



http://bloodjournal.hematologylibrary.org/content/106/7/2244.full#F1

Emergency treatment

- 1. i.v. methylprednisolone 500mg to 1g/day for 3 days
- 2. IVIG 1g/kg/day for 2 consecutive days
- 3. Platelet transfusion
- Emergency splenectomy is considered if above measures fail to increase platelet count to safe level i.e. above 50x109/L.

http://www.acadmed.org.my/view_file.cfm?fileid=256

Prognosis

- Adults are more likely to develop chronic ITP and spontaneous recovery is uncommon.
- Many adult ITP patients, however, experience mild and stable disease requiring no treatment.
- In contrast, ITP is usually acute in children, particularly in those under 10 years of age, with recovery observed in the majority of cases even after several weeks to months of severe thrombocytopenia.
- Around 80% of children will spontaneously recover within 6 months with or without receiving treatment.
- Some 15–20% of children will, however, develop chronic ITP.
- Among ITP patients who respond to therapy, mortality is similar to that of the general population.
- Among those who do not respond within the first few years of receiving therapy there is a higher risk of morbidity and mortality.
- Deaths are rare, but may be as high as 3% per year in refractory ITP patients and are usually related to **intracranial haemorrhage or infection**

The end