THROMBOCYTOPENIA

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Thrombocytes or platelets constitute one of the three cellular elements in blood, and participate in the process of haemostasis using its numerous intracellular organelle and surface receptors having affinity for collagen, von Willebrand factor, fibronectin, and fibrinogen. Phospholipids of platelets provide the requisite surface for generation of Xase and Prothrombinase reactions leading to formation of fibrin clot. Platelets also play a role in fibrinolysis and clot retraction. This requires an adequate number of platelets that are functionally normal, failing which primary haemostatic process is compromised. Other components in the haemostatic process are

1. Vascular
2. Clotting Factors
3. Complement pathway, and
4. Thrombolytic/ fibrinolytic pathway.

This chapter will dwell upon an approach to and management of thrombocytopaenia in medical emergency practice.

DEFINITION:

Thrombocytopaenia is a decrease in platelet count in blood to below 140 x 10^9/l (1,40,000/ cu. mm. or /ul). A normal platelet count ranges 150- 350 x 10^9/l.

CLINICAL MANIFESTATIONS:

These range from asymptomatic thrombocytopaenia to life-threatening bleeding in vital organs. The hallmark of bleeding is skin-bleed as petechiae, purpura and ecchymosis, and/ or superficial mucosal-bleed in form of gum bleeding, epistaxis, haematuria, menorrhagia etc. The most critical bleeding are the intracranial, the intraocular (retinal), and the intraabdominal, and these are associated with high morbidity and mortality. Though such bleeding is infrequent, it is mandatory that all patients with low platelet counts are assessed for such potential risks.

Severity of bleeding correlates with degree of thrombocytopaenia:

MILD	140< >100 x 10^9/l (over 100,000 upto 140,000/cu.mm)
MODERATE	100< >50 x 10^9/l (over 50,000 upto 100,000/cu.mm)
SEVERE	50< >20 x 10^9/l (over 20,000 upto 50,000/cu.mm)
VERY SEVERE	<20 x 10^9/l (upto 20,000/cu.mm)

Whereas severe degrees of thrombocytopaenias risk spontaneous bleeding, mild cases are generally asymptomatic, and moderately severe ones may bleed under stress of trauma, surgery, or drugs.

Besides the rapidity of onset of thrombocytopaenia, manifest bleeding is determined by any co-existing

1. impairment in PLATELET FUNCTIONS

2. impairment in OTHER HAEMOSTATIC parameters
3. exposure to DRUGS/ TOXINS, or
4. presence of SYSTEMIC DISEASE

CAUSES OF THROMBOCYTOPAENIA: (Table I)

Thrombocytopaenia may result from decreased production in the bone marrow or an excessive destruction in the macrophage-monocyte system. A bone-marrow examination helps in making this important distinction. Sequestration in spleen is another important (and frequent) mechanism of thrombocytopaenia. Some diseases may affect the platelet function too.

Table I
CAUSES OF THROMBOCYTOPAENIA

Decreased production	Bone-marrow aplasia/ fibrosis/ or infiltration Myelosuppressive drugs, cancer chemotherapy Megaloblastic anaemia Ethanol, estrogen, thiazides and other drug toxicity Viral infection TAR syndrome
Increased destruction	Idiopathic thrombocytopenic purpura (ITP) DIC, Snake-bite SLE, Vasculitis TTP, HUS Prosthetic valves Drug-mediated, Heparin associated thrombocytopaenia (HAT) Viral illness e.g. Hepatitis B, CMV, HIV
Sequestration	Portal hypertension Storage diseases e.g. Gaucher's disease Myeloproliferative disease Lymphomas

TAR- thrombocytopaenia with absent radii
DIC- disseminated intravascular coagulation
SLE- systemic lupus erythromatosus
TTP- thrombotic thrombocytopenic purpura
HUS- haemolytic uraemic syndrome
CMV- cytomegalovirus
Drug mediated- PAS, quinine, methyldopa, carbamazepine, digoxin, gold, penicillamine, sulphonamides

Autoimmune thrombocytopaenias are common, acquired causes in young subjects in absence of organomegaly and other systemic disease. Exposure to drugs, toxins, venoms, infections (malaria, dengue etc), septicaemia, and DIC must be remembered in a sick patient with thrombocytopaenia. Splenomegaly (of any aetiology)/ hypersplenism leads to thrombocytopaenia quite frequently, from pooling of platelets that also diminishes effectiveness of platelet transfusion in these conditions.

Clinical Approach to thrombocytopaenia is summarized in Table II.

Table II
CLINICAL APPROACH TO THROMBOCYTOPAENIA

History suggestive of
* Platelet disorder - petechial spots, ecchymosis, epistaxis, gum bleed, haematuria, menorrhagia etc.
* Drug intake, chemotherapy
* Antecedent viral illness
* Connective tissue disorder-rash, photosensitivity, joint/ renal involvement
* Similar episode in the past
* Response to haemostatic stress in past
* Requirement for blood transfusions
* Family history of similar illness amongst siblings, parents or relatives
* Immunodeficiency state
* Pregnancy

Clinical examination to look for
* Petechiae, purpura , ecchymosis
* Bleeding from mucosal surfaces, haematuria
* Facial puffiness, BP
* Lymphadenopathy, rash, joint involvement etc
* Splenomegaly
* CNS involvement

Investigations to include
* **Complete blood counts** (including reticulocyte count, peripheral blood smear for morphology and abnormalities of platelets/ RBC/ WBC
* **Blood Biochemistry**-especially renal/ liver function tests, LDH, vitamin B12/ Folate, and ferritin levels
* **Bone-marrow study**
* **Coagulation profile**
* **Serology**- viral and for connective tissue disorders
* **Special tests**- platelet function tests, platelet antibodies
* **Imaging studies**- Ultrasonography, CT scans as required
* **Investigations** for primary disease

Questions important in assessing thrombocytopaenia are:

- Is it ASYMPTOMATIC OR SYMPTOMATIC?
- If symptomatic, HOW SEVERE AND WIDESPREAD is the bleeding?
- Whether bleeding is present in any VITAL REGION/ ORGAN such as intracranial/ retinal haemorrhage or intraabdominal/ haematuria etc?
- How SEVERE is the thrombocytopaenia?
- How RAPID is the onset of thrombocytopaenia?
- What is the DURATION of thrombocytopaenia?
- Is there CONCOMITANT anaemia/ leukopaenia (and their severity)?

- Any CO-EXISTING platelet function defect (including use of NSAID), or derangement in other haemostatic functions (DIC etc), or illness exacerbating bleeding?
- FAMILY HISTORY of similar illness or of anaemia?

MANAGEMENT:

It is crucial to institute treatment while assessing patient on above guidelines, in order to save from life-threatening or organ-damaging complications.

General

- Avoid trauma. Early attention in case of trauma.
- Stop use of hard tooth brushes, dental floss, or metal razors
- Avoid use of non-steroidal anti-inflammatory agents (NSAIDs)
- Avoid intramuscular injections
- Stop drugs known to interfere with platelet function or induce thrombocytopaenia by virtue of marrow suppression or immune mediated destruction.
- Minimize rectal examination, suppositories and enemas
- Minimize phlebotomy. Apply pressure to venipuncture sites for at least 10 minutes.

Haemostatic measures

- Compression bandages
- Nasal or other local packing
- Application of thrombin or other haemostatic agents
- Start intravenous line in presence of any bleeding
- Treat other haemostatic abnormalities
- Transfuse platelets

Urgent investigations to be ordered

Complete Blood Counts including platelet count, blood smear, and reticulocyte count
Blood Group and Cross-match
Blood biochemistry
Urine examination for presence of blood and microscopy
Ocular fundus examination
Others as warranted (e.g. DIC screen, auto-antibody screen, bone-marrow etc)

Platelet transfusions

In case of life threatening or severe/critical haemorrhage, platelet transfusion should be given to maintain a count above 100×10^9 /l. Else a target platelet count of 50×10^9 /l is adequate.

Prophylactic platelet transfusion are justified in very severe thrombocytopaenia, even though the threshold of 20×10^9 /l may be too high.

Platelet transfusions are not of much value in states of accelerated destruction e.g. ITP and are not used in thrombotic states like HUS/ TTP.

If you must, it is best to use single-donor platelet apharesis in autoimmune states.

ABOUT PLATELET TRANSFUSIONS

* Platelets for transfusion are derived either from Random Donor Blood or apharesis from Single Donor.

* These days, every donated blood-pack is subjected to component separation, one of which may be platelets obtained by centrifugation. Such sub-pack from single units contains platelets suspended in about 50- 60 ml of plasma which imparts a pale-yellow colour to the contents. A single pack contains approximately 5.5 x 10^{10} /l platelets which, on transfusion, raises platelet count by 6-8 x 10^{10}/l in the recipient's blood. Thus to achieve a rise of 50x 10^{10}/l, one may need transfuse 6 such packs of **Platelet Concentrate** coming from 6 different donors.

- On the other hand, **Apharesed Platelets** from single donor are prepared by repeatedly circulating donor's blood through a mechanical device using centrifugation or membrane filtration to separate platelets out from the donor-blood. This process achieves a high concentration of platelets viz. 30 x 10^{10} *per* pack of 300 to 400 ml. The rise in recipient's platelet count after transfusion of such one **apharesed single-donor platelet** pack is of the order of 50 x 10^{10}/ l. Furthermore, such an apharesis pack derived from a single donor also minimizes transfusion-related risks. Further,

Points to remember regarding platelet transfusion:

- Platelets have a shelf life of 5 days only.
- Platelets should be transfused rapidly within 10 minutes.
- Transfuse platelets using a filter to reduce leukocytes.
  (Do not use microaggregate filter)
- Platelet count may be done after 45-60 minutes to assess efficacy of transfusion.
- Platelets for transfusion are stored at room temperature (20^0- 24^0 C), in a gently agitated state.
- Platelet transfusion does not require cross-matching. Group-compatibility of donor platelets/ plasma may be ideal. But do not withhold emergency platelet transfusion on that account.
- Unwarranted platelet transfusion generates alloimmunisation, reducing efficacy of future transfusions.

Treatment of underlying cause/ primary disease

- **Withdrawal** of offending drug/ toxins, and use of antitoxin (anti-snake venom) as warranted

- **ITP**- steroids, intravenous Immunoglobulin (IVIG), immunosuppressive drugs, danazol, splenectomy
- **HUS/ TTP**- plasmapharesis, FFP, IVIG, steroids, vincristine
- **INFECTIONS**- antibiotics, antimalarials
- **MALIGNANCY**- appropriate chemo-/ radiotherapy

Interleukins and recombinant Thrombopoeitin may emerge as means to prevent or reduce thrombocytopaenia in patients receiving cytotoxic chemotherapy.

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