INTRODUCTION
The upper limit of the normal platelet count is generally between 350,000/µl (350x10^9/l) and 450,000/µl (450x10^9/l). The value varies among different laboratories. In a sample of 10,000 healthy adults aged 18 to 65 years, 99 (1%) had platelet counts greater than 400,000/µl. Among these individuals, thrombocytosis is confirmed in only 8 at repeated examination 6 months to 1 year. [1]

CLINICO-PATHOLOGICAL CATEGORIES
There are three major categories:
1. Clonal type which includes essential (or primary) thrombocythaemia and other myeloproliferative disorders involving thrombocytes also.
2. Familial type, which includes rare cases of non-clonal myeloproliferation resulting from thrombopoietin mutations.
3. Reactive type, in which thrombocytosis occurs secondary to a variety of non-related acute and chronic clinical conditions.

ESSENTIAL THROMBOCYthaEMIA
This condition often remains asymptomatic and is discovered incidentally from blood counts. Its diagnosis comes in the process of exclusion. It is one of a group of myeloproliferative disorders which include polycythaemia, chronic myelogenous leukaemia and myeloid metaplasia with or without myelofibrosis.[2]. Major causes of morbidity are bleeding and thromboses, the latter most commonly involving arterial circulation. Reactive thrombocytosis does not cause these complications and does not require treatment.

REACTIVE THROMBOCYTOSIS
There are several causes of this type of thrombocytosis, the causes belong to different diseases:
A. Transient- arising out of acute blood loss, recovery from thrombocytopenia, acute infection or inflammation, response to exercise.
B. Sustained- arising out of iron deficiency, post-splenectomy/asplenic state, malignancy, chronic infection or inflammation, inflammatory bowel disease, temporal arteritis, tuberculo-

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C. Thrombocytosis may occur as a part of paraneoplastic syndrome, as a complication of surgery, in Wegner’s granulomatosis, in Castleman disease in rheumatoid disease and in vitamin E deficiency.
D. Primary acquired thrombocytosis may occur in temporal arteritis, Kostman disease, as an autosomal dominant hereditary disorder, benign familial thrombocytosis, and as a part of Blackman-Diamond anaemia.
E. Thrombocytosis may occur as a symptom of poisoning like chronic pesticide poisoning, toxic reaction to the medications e.g. Ceftrizoxime, Cefzox, Cefazidine, Fortaz, Tazicef. Transretinoic acid used for treatment of promyelocytic leukaemia produces transcriptional up regulation of thrombopoietin production and thrombocytosis. [3]

Some conditions can lead to high platelet count only for a short time. These are recovery from serious blood loss, recovery from high platelet count caused by excessive alcohol use and lack of vitamin B12, or folate, acute infection or inflammation and response to physical activity.

III FAMILIAL THROMBOCYTOSIS
This is a genetically determined heterogenous disorder. There are two main types. Specific mutation in thrombopoietin gene, including single nucleotide deletion in 5’ untranslated region in the gene leading to markedly elevated thrombopoietin level. In another variety a unique dominant activating point mutation developed in c-mpl gene causing autonomous thrombopoietin activation. [4,5]

HISTORICAL BACKGROUND
The first description of essential thrombocythaemia was given by De Gugliemo in 1920 and by Epstein and Goedel in 1934 in association with other myeloproliferative disorders [6,7]. The separate existence of thrombocytosis as a disease category was first established in 1960. [8]
PATHOGENESIS

The clonal nature of the disease was established by discovery of a single gene (Gl6-PD) isoenzyme expressed in all blood cell lines of women with essential thrombocythemia who were coincidentally heterogenous for two types of Gl-6-PD isoenzymes “A” and “B”. This is further confirmed by several approaches using X-linked markers in female patients [9]. Possible explanation for findings of polyclonality include to detect a small population of clonal cells against a polyclonal background, progression of non-clonal essential thrombocythemia to clonal disease or restriction of clonality in some patients to the megakaryocytic lineage. This explains heterogenous nature of the disease. Despite the origin in multipotential stem cell, dominant phenotypic change involves megakaryocytic lineage. Usually erythropoiesis and granulopoiesis are normal at diagnosis. [10]

Thrombopoietin, the ligand for megakaryocytic growth factor receptor c-mpl, is the major humoral regulator of megakaryocytopoiesis and platelet production. Although thrombopoietin supports the entire population of megakaryocyte development at different stages, along with other cytokines (IL-6, IL-11), in synergy.

Platelets have an important role in regulating plasma thrombopoietin level as their receptors (c-mpl) remove it from plasma. Thus, as the platelet count drops, increased free plasma thrombopoietin levels stimulate megakaryocytopoiesis. This modulation maintains steady state level of platelet production. [11] Unlike erythropoietin, thrombopoietin levels are normal or elevated in thrombocythemia. The increased thrombopoietin level may result from abnormal binding and consumption by defective platelets. In support of this platelet expression of c-mpl is markedly reduced.

The increased number of colony-forming units- megakaryocytes (CFU-Meg) have been cultured from the blood or marrow of patients with essential thrombocythemia who are less sensitive to transforming growth factor B, an endogenous inhibitor of megakaryocytopoiesis.[12]

Thus, despite the decreased production of thrombopoietin receptors (c-mpl) on megakaryocytes of patients with essential thrombocythemia, increased megakaryocytic proliferation and production reset for hypersensitivity to stimulator and/or decreased sensitivity to negative regulators of megakaryocytopoiesis. [13]

MOLECULAR PATHOGENESIS

JAK Kinase 2 (JAK2) is a tyrosine kinase inhibitor which functions as an intermediate between cell membrane receptors for haemopoietic growth factors and downstream signaling molecules. Mutation involves a valine to phenylalanine substitution at position 617 in the autoinhibitory domain, thereby interrupting normal regulation. One study found that patients with JAK2, V 617F mutation had a significantly higher rate of complications (fibrosis, bleeding, thrombosis) [14]

CLINICAL FEATURES OF THROMBOCYTOSIS

Two out of every three patients have no symptoms at the time of diagnosis. Younger patients may remain symptom-free for years. Enlargement of spleen is detected in 60% of patients with thrombocytosis. The liver may also be enlarged. As many as half of patients experience bleeding from the skin, gums or nose and 20-50% have blockage of arteries.

Other symptoms include bloody stool, bruising, dizziness, headache, haemorrhage, prolonged bleeding having surgery or having a tooth pulled, redness or tingling of hands or feet. In rare instances lymph nodes are enlarged.

Highest platelet count shows most severe symptoms. Younger patients especially women may not have symptoms. Complications include stroke, heart attack and formation of blood clots in arms or legs. A doctor should be always informed when bleeding is prolonged or unexplained or if the patient develops chest or leg pain, confusion, numbness, weakness. [15]

In contrast to other myeloproliferative disorder, hypermetabolic symptoms such as fever, sweat, weight loss are highly uncommon in essential thrombocythaemia.

Physical findings usually are limited to mild splenomegaly which is present in 40% of patients.

Echocardiography may reveal aortic and mitral valvular lesions, including leaflet thickening and vegetations similar to the lesions described in non-bacterial thrombotic endarteritis. The relationship of cardiac valve lesions to thromboembolic complications in essential thrombocythaemia is unclear [16]

LABORATORY FEATURES

Untreated patients have elevated platelet count ranging from slight elevation to several millions per microlitre. Platelet morphology on blood film shows large, pale, blue staining, hypogranular, occasional nucleated megakaryocytic fragments may have lymphoblastoid appearance.

Increased platelet turnover is indicated by increased reticulated platelets (young) in the circulation, which can be detected by flow cytometric analysis of platelets RNA. Although both the percentage and absolute number are elevated, compared to healthy individuals, whether this finding can distinguish it from other forms of thrombocytosis is unclear.

Serum Erythropoietin (Epo) is normal or mildly elevated in clonal form, do not correlate with platelet count. Serum Epo level is elevated, so this test can not distinguish essential thrombocythaemia. Plasma level of IL-6 and CRP are low in essential thrombocythaemia, elevated in secondary thrombocytosis, which often accompanies acute and chronic inflammatory states.

Pseudohyperkalaemia may be found with extreme thrombocytosis. It is diagnosed when serum potassium
concentration exceeds plasma potassium concentration. It is caused by release of intracellular potassium during blood clotting.

Marrow pathology reveals increased cellularity with megakaryocytic hyperplasia. There are frequently giant megakaryocytes with increased ploidy that occur in clusters. Large number of platelet debris are seen in marrow samples (platelet drifts).

Most patients have no cytogenetic abnormality. However, some patients may have Philadelphia chromosome. They do not have any feature of CML. Some patients with essential thrombocythaemia may have BCR-ABL gene rearrangement in absence of Philadelphia chromosome. Deletion of long arm of Chromosome 5(q-) has been reported. [17]

CLINICAL TESTS OF HAEMOSTASIS:

Bleeding time is prolonged in fewer than 20 p.c. of cases. Test does not correlate with platelet count or clinical findings, and/or predict reliably bleeding or thrombosis. Platelet aggregation abnormalities are variable. There is reduced platelet response to collagen. Platelet storage pool defect (aspirin-like) is not affected. Epinephrine stimulated defect is abnormal on aggregation. This unusual abnormality is also noted in other myeloproliferative disorder. Some patients have platelet hyperagreagability or spontaneous aggregation in vitro.

DIAGNOSTIC CRITERIA FOR ESSENTIAL THROMBOCYTHAEMIA

1. Platelet count >60,000/µl
2. Haemoglobin 13g/dl or normal red cell mass (in male >36ml/kg, in female>32ml/kg)
3. Stainable iron in marrow or failure of iron trial (<1g/dl rise in Hb after one month of therapy
4. No Philadelphia chromosome
5. Collagen fibrosis of marrow: a) Absent b)1/3rd biopsy area without both splenomegaly or leucoerythroblastic reaction
6. No known cause of reactive thrombocytopoiesis
7. Megakaryocytes in clumps

Clinical features of Clonal and Reactive Thrombocyto-

<table>
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<tr>
<th>Features</th>
<th>Clonal Type</th>
<th>Reactive Type</th>
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<tbody>
<tr>
<td>Splenomegaly</td>
<td>Yes in – 40% of cases</td>
<td>No</td>
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<tr>
<td>Platelet Morphology</td>
<td>Giant Platelets</td>
<td>Normal Platelets</td>
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<tr>
<td>Platelet Function</td>
<td>Often abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>Increased cellularity</td>
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<td></td>
<td>with giant, dysplastic</td>
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<td></td>
<td>platelets having</td>
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<td></td>
<td>increased ploidy and</td>
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<td></td>
<td>masses of platelet debris</td>
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FEATURES

Thrombotic Complications

<table>
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<th>Features</th>
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<th>Reactive Type</th>
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<tr>
<td>Thrombotic</td>
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<tr>
<td>Bleeding Complications</td>
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<tr>
<td>Underlying Disease</td>
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<td>Often clinically apparent</td>
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COURSE AND PROGNOSIS

Thrombotic complications in secondary thrombocytosis are often linked to underlying disease like cancer, postoperative state. One exception is splenectomy for haemolytic anaemia, notably thalassaemia, incompletely relieved by surgical procedure. Therapy to reduce platelet count or antiplatelet therapy is not beneficial in secondary thrombocytosis.

Major causes of mortality and morbidity in essential thrombocythaemia are thrombosis and haemorrhage. Although the condition has no potency to revert to acute leukaemia like other myeloproliferative disorder, association is less clear. Treatment with radiophosphorus or alkylating agent increases the potency. A high proportion will develop AML and MDS with hydroxyurea when they have chromosome 17q deletion and other 17p syndrome. Survival study shows no decrease in life expectancy, though significantly worse than that of age and sex-matched controls. [18]

CLINICAL RISKS OF COMPLICATIONS IN ESSENTIAL THROMBOCYTHAEMIA

Complications are more common if there is previous history of thrombosis, associated risk factors for cerebrovascular accident (e.g. smoking), inadequate control of thrombocytosis in high risk patients. Use of aspirin and non steroidal anti-inflammatory drugs are highly risky in these patients and risk is very high if platelet count is>1,50,000/µl.

If there is no associated risk, occurrence of complications depend upon degree of thrombocytosis and prolongation of bleeding time.

COMPLICATIONS

1. Thrombotic Complications

Although 25% of all thrombotic events are deep vein thrombosis of the lower extremity, the most common site of arterial thrombosis involve cerebrovascular, peripheral vascular and coronary arterial circulation.

Erythromeralgia or digital microvascular ischaemia is characterized by intense burning, throbbing in a patchy distribution in the extremities most proximally involving the feet. The pain is accompanied by warmth, duskeness and mottled edema, sometimes livedo reticularis. The pain tends to be exacerbated by excertions and dependency. Erythromeralgia may be confused with Raynaud's syndrome, shoulder hand syndrome or causalgia. Histopathological study shows endothelial swelling, fibromuscular intimal proliferation and
Thrombocytosis

This complication may occur in 50% of pregnancy with III. complications in pregnancy. Gastrointestinal, genitourinary or cutaneous bleeding may occur. Superficial, mucosal, spontaneous or in response to minimal trauma. Reduction of elevated platelet count. [19]

Arterial thrombotic complications occur more frequently than venous. Cerebrovascular Complications may present as headache, dizziness, decreased mental activity, focal neurodeficit or seizure and ischaemic stroke, retinal artery occlusion. Coronary circulation is also affected. 50% of patients had at least one thrombotic episode in 9 years. Ischaemic stroke often responds to aspirin and platelet reduction. [20]

25% of all thrombotic events are deep vein thrombosis of lower extremities. Hepatic and portal vein thrombosis are more common in polycythaemia vera.

II. Bleeding complications

Superficial, mucosal, spontaneous or in response to minimal trauma is most common.

Gastrointestinal, genitourinary or cutaneous bleeding may also occur. Some studies indicate that older patients are at markedly increased rate of haemostatic complications, while younger patients are relatively protected from these problems. However, other reports have documented no age related difference.

III. Complications in pregnancy

Multiple placental infarcts may produce placental insufficiency. This may lead to recurrent spontaneous abortion, foetal growth retardation, premature delivery or abruptio placentae.

This complication may occur in 50% of pregnancy with thrombocytosis. However, successful pregnancy outcome is possible without any form of therapy. To risk of haemorrhage, maternal or neonatal, aspirin should be avoided for at least one week prior to delivery. [21]

THERAPEUTIC MODALITIES

1. Platepheresis is reserved in selected cases of acute and threatening thrombotic and haemostatic problems. Reduction of platelet count is transient and may be followed by rebound increase in thrombocytosis.

2. Use of Radiophosphorus and Alkylating agents (e.g. methyl- busulphan) has largely been abandoned because of this leukomogenic potential, except in selected elderly patients who can not tolerate other drugs.

3. Hydroxyurea, a non-alkylating myelosuppressive agent is highly effective as initial therapy for essential thrombocythaemia. Doses required for thrombocytosis control are generally 10-30mg/kg/day. Blood count should be checked in 7 days of therapy for rapid myelosuppression. Maintenance dose is to be adjusted according to blood count. Daily treatment reduces count to 500,000μl within 8 weeks in 80% of cases. Painful but reversible leg ulceration may occur. Leukomogenic potential is highly controversial, but may occur in essential thrombocythaemia with deletion of 17p chromosome. [22]

4. Anagrelide is effective as alternative first line of therapy. This quinazone derivative can be given orally and reduces platelet count by inhibiting marrow megakaryocyte maturation. Dose is 0.15mg q.i.d or 1mg b.i.d with dose adjustments at weekly interval up to a maximum to 10mg/day. Dose required to reduce platelet count in average sized adult is 2-3mg/day. The time of reduction by 50% is average 11 days. It reduces platelet count without altering white blood cell count. About 30% of patients can not tolerate due to positive inotropic action e.g. fluid retention, palpitation, heart failure, arrhythmia. Side effects diminish over time. Discontinuation gives rise to rapid rise. Important side effects are anorexia, nausea, vomiting, palpitation, edema. Anagrelide is associated with increased risk of arterial thromboses, major bleeding, myelofibrotic transformation but decreased venous thromboses. Hydroxyurea should be the first line of therapy in high risk patients.

5. Interferon alpha is also an effective therapy. The drug suppresses the proliferation of abnormal megakaryocytic clone, with decrease in its size and ploidy. Platelet counts are reduced at normal or near normal level within 1 month of starting. An effective therapy is to administer Interferon S.C. at a dose of 3,000,000 units per day initially, doses subsequently adjusted according to individual tolerance and response. Suppression can be maintained for several years, relapse occurs after discontinuation.

Side effects make intolerable in 20% of cases, often accompanied by lowering of white blood cell count but no effect on haematocrit is noted. Although it is non-leukomogenic, toxicity and cost cant make the drug the first line of thera-
As Hydroxyurea is teratogenic and Anagrelide crosses the placental barrier (with unknown safety), Interferon alpha is the treatment of choice in high risk women patients with essential thrombocytopenia, who are contemplating pregnancy.

6. Haemopoietic Stem Cell Transplantation can be considered for highly selected with younger patients who have complicated advanced disease. Finding of JAK2 V617 F mutation stimulate the targeted therapy against mutant form of kinase [24].

7. Anti-platelet agents Aspirin (and not warfarin) is highly effective adjunctive therapy in essential thrombocytopenia, digital or cerebrovascular disease can cause prolongation of bleeding time and serious bleeding, improves platelet turn over and clinical symptoms of erythromegalgy. Low dose aspirin (100 mg/day effectively reduces thrombotic complications. However, its use is still controversial. [25]

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