

Immune Thrombocytopenia: Single Institute Experience

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Abstract: Immune thrombocytopenia purpura (ITP) is a common hematological disease that is seen frequently either in the clinic or as in emergency. I am reporting my experience for one year since I joined the Saudi Germany hospital (SGH) in Madinah, KSA with patients who have immune thrombocytopenia. My review will focus mainly on ITP, revision of current guidelines with focus on definitions of refractory and severe ITP and role of bone marrow aspiration and biopsy (BMA & Biopsy) in ITP. It is a retrospective analysis of ITP patients seen in Saudi Germany Hospital (SGH) from August 2015 till July 2016. My observations are consistent with other reports of ITP in regards to incidence, sex distribution, significance of bone marrow aspiration and biopsy (BMA) in ITP patients. My concerns mainly are regarding defining severe and refractory ITP patients. In conclusion, I think the current guidelines have to be reviewed with respect of definitions of severe and refractory ITP as well as management of such patients.

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Key words: Immune thrombocytopenia purpura (ITP), refractory ITP, severe ITP, treatment of ITP, guidelines of ITP.

Aberrations: **BM:** Bone Marrow, **MDS:** Myelodysplastic Syndrome, **MF:** Myelofibrosis, **ITP:** Immune thrombocytopenia purpura, **TTP/HUS:** Thrombotic Thrombocytopenic Purpura / Hemolytic Uremic Syndrome, **DIC:** Disseminated intravascular coagulopathy, **HIT:** Heparin induced thrombocytopenia, **CTD:** Connective tissue diseases, **HCV:** Hepatitis c virus, **TPA:** Thrombopoietin receptor agonist, **IVIg:** Intravenous immunoglobulin, Anti-D

1. Introduction:

Immune Thrombocytopenia Purpura is an immune disorder that results in isolated thrombocytopenia with variable clinical presentation ranging from asymptomatic patient to severe bleeding manifestations including intracranial hemorrhage. ITP is primarily a disease of increased peripheral platelet destruction, with most patients having antibodies to specific platelet membrane glycoproteins. Relative marrow failure may contribute to this condition, since studies show that most patients have either normal or diminished platelet production. Chronic ITP persists longer than 6 months without a specific cause whereas acute ITP often follows an acute infection and has a spontaneous resolution within 2 months. (1,2)

Hemorrhage represents the most serious complication; intracranial hemorrhage is the most significant. The mortality rate from hemorrhage is approximately 1% in children and 5% in adults. Spontaneous remission occurs in more than 80% of cases in children. However, it is uncommon in adults. (1,2)

The rationale of the study is to focus on patients who have severe and or refractory ITP though they have not underwent splenectomy despite using

thrombopoietin receptor agonist or and monoclonal antibody.

2. Methods:

The SGH is a private secondary hospital with oncology and hematology services including chemotherapy unit. I have reviewed all the medical records of adult (above 12 years) patients with thrombocytopenia (platelet count less than 140000) who visited my clinical or admitted under my care at SGH in Madinah since August 2015 till July 2016. It is computer based. I have excluded patients who are admitted under other specialty with other medical diagnoses but had or developed thrombocytopenia for other reasons (sepsis, DIC, Chronic liver disease, Drug-induced, HELLP syndrome etc.). Patients who could not offer or referred from other hospital without completing the tests required are excluded. Patients who are diagnosed to have non immune thrombocytopenia (Acute Leukemia, myelodysplasia, myelofibrosis, vitamin B12 deficiency etc.) have been excluded. Patients with platelet count above 100000 are excluded.

3. Results:

All patients have done basic investigations as much as possible. Investigations include H. pylori serology, hepatitis screening, autoimmune screening, B12, folate, TSH and Free T4, and serology for Brucella, Schistosoma disease. Bone marrow aspiration and biopsy was done for those patients with splenomegaly, abnormal peripheral smear, accompanied cytopenia or failed second or third line treatment.

Total number of patients with thrombocytopenia included on the initial review was 84. Forty seven were excluded as they were admitted for non-thrombocytopenia reasons. Twenty-two were excluded later because either of age (less than 12 years) or no lab results were available (patients coming with CBC done in other hospital) or because of being diagnosed as acute leukemia or myelodysplasia or myelofibrosis or severe B12 deficiency. One patient had high ANA test and she was diagnosed as SLE with secondary ITP. One patient has very low B12 and he was excluded. One patient had severe hypothyroidism with TSH more than 400 and she was excluded.

Total number of BMA & Biopsy done was seven. Only two from fifteen patients with ITP have BMA and biopsy. Two patients have acute leukemia and had been excluded. Three patients have myelodysplasia, myelofibrosis and megaloblastic changes and had been excluded. One of the ITP patients who had BMA was above sixty years and failed medical treatment. The other one was young female who failed medical treatment. Both of these ITP patients underwent splenectomy.

Number of patient that are labelled as primary ITP is fifteen. Seven out of fifteen were admitted. Male patients were 8 out of 15 (table 2 patient

characteristics & lab investigations). Majority of outpatient were asymptomatic. Main symptoms were petechial rash, bruises and ecchymosis.

H. Pylori was negative in all our patients who had done the test (seven out of fifteen).

One patient has spontaneous recovery without any intervention. Number of primary ITP patients who required treatment is five.

First line Treatment include steroid or dexamethasone and intravenous immunoglobulin. Number of patients who required first line treatment only is two.

Second line treatment includes splenectomy, monoclonal antibody (Rituximab) and thrombopoietin receptor agonists (TPA). Number of patients who required medical second line treatment is three. Splenectomy is considered in two patients. One had a relapse after previous splenectomy and she was treated with Imuran.

Third line treatment includes other immunosuppressive medications (like Imuran, vincristine and cyclophosphamide etc.). One patient who had previous splenectomy required Imuran after failing first line therapy.

Two patients are considered as refractory and severe ITP before undergo splenectomy as their platelet count did not improve despite using TPA and or monoclonal antibody. Though this is not as defined by the current guidelines which I will discuss further in the discussion part.

Supportive treatment include factor VII, platelet and packed red blood cell transfusion, vitamin D. Factor VII is used in one patient who had melena and drop in his hemoglobin to seven with platelet count less than 10000 despite being on IVIG, intravenous dexamethasone, Rituximab and TPA (Romiplostim).

Table 1. Causes of thrombocytopenia

Decreased production	Increased destruction
Hematological malignancy	ITP
Aplastic Anemia	Heparin induced thrombocytopenia (HIT)
Myelodysplastic syndrome (MDS)	HIV
Drugs	Post transfusion Purpura (PTP)
Radiation	Connective tissue disease (CTD)
Human immunodeficiency virus (HIV)	Disseminated intravascular coagulopathy (DIC)
Metastasis to bone marrow	Sepsis
Hereditary	Mechanical
	Thrombotic thrombocytopenic purpura- hemolytic uremic syndrome (TTP-HUS)
	Splenic sequestration

Table 2. Patients' characteristics and laboratory investigations

Patient number	Age	Sex	Platelet Count X 10 ⁹ /L	WBC* X 10 ⁹ /L	Hgb** g/dL
1	51	M	20	6.6	14.6
2	24	F	6	6.6	7.4
3	60	F	12	5	12.9
4	76	F	35	8.5	9.2
5	24	M	20	16	14.2
6	38	F	40	30	12.2
7	62	M	12	11	13.4
8	42	M	86	3	12.6
9	62	F	100	4.6	13.5
10	66	M	89	4.5	12.1
11	65	M	26	8.8	15.4
12	53	M	35	4	11.8
13	31	F	45	7	11.2
14	41	M	64	6.2	17.9
15	45	F	83	11.9	12.1

WBC * white blood cell Hgb** hemoglobin

Table 3. Points need to be readdressed in the future guidelines:-

Point of interest	comments
Definition	Refractory does not mean severe and vice versa. Refractory should not be limited to splenectomized patients only. Severe should not be limited to bleeding symptoms only. Risk of spontaneous bleeding according to platelet count should be considered in defining severe.
Time to response	More important in severe compared to refractory. When to go for second line therapy? How long should I wait to add another second line therapy? How long should I wait to use TPO antagonist?
Failure of treatment	When?
Clinical relevant bleeding	Wet petechia vs hemoglobin level vs vital signs vs others?
Splenectomy	When? What is the save platelet level? If below the recommendation then s the patient still considered non responder or refractory? Vaccination usage before splenectomy after using other second line modalities?
Platelet transfusion	When? Why? What type (single vs random donor)?
Factor VII utilization	When? Low vs high dose?

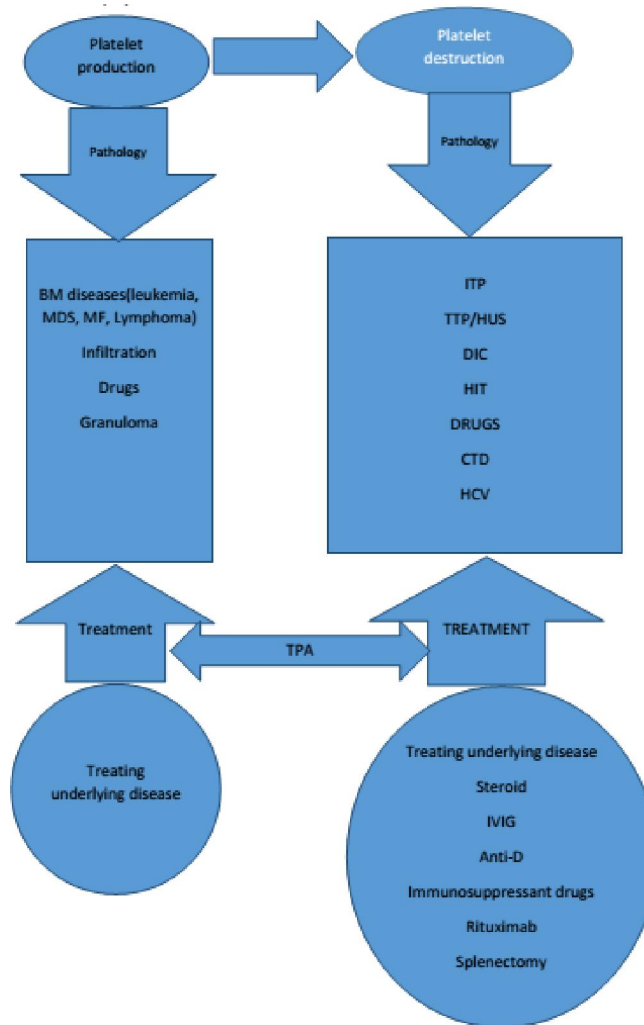


Figure 1. Causes of thrombocytopenia and treatment

4. Discussion:

Platelet is one of the cell components of the blood. Its main function is to prevent bleeding. It is produced in the bone marrow and circulate in the blood with half-life of five days only. It is destroyed mainly in the spleen. Platelet disorders can be either quantitative or qualitative. Normal platelet count is from 150 to 400 X 10⁹/L. Low platelet is referred as thrombocytopenia with count less than normal. (Table 1 causes of thrombocytopenia). Thrombocytopenia is a common daily practice that is seen in either hematological or non-hematological clinics. Immune Thrombocytopenia is defined as platelet count less than 100 X 10⁹/L. [1, 2]

Primary ITP is a diagnosis of exclusion. Our male to female ratio incidence is consistent with international figures. Thrombocytopenia is usually occur because either low bone marrow production or increased peripheral destruction. Figure 1.

ITP is defined as an autoimmune disorder characterized by immune mediated destruction of otherwise normal platelets most commonly occurring in response to an unknown stimulus (Primary). A primary ITP is a diagnosis of exclusion. ITP may occur in association with other immune disorders (secondary). [1, 2]

The actual frequency of ITP is uncertain as patients may have unnoticeable low platelet count that do not have any clinical consequences and require no therapy. Adult-onset ITP was once thought to be a disease of young women though there is no much real differences. [1, 2]

The pathology of ITP is contributed to autoantibody-mediated platelet destruction of otherwise normal platelet. The role of cytotoxic T-lymphocyte has been thought as an important factor in platelet lysis. Other mechanisms including impaired megakaryocyte maturation, and insufficient platelet

production are the rule behind the new modalities of treatment.[3, 4]

Recommendations for the initial evaluation of primary ITP are to exclude secondary causes. Initial evaluation includes but not limited to the following tests; peripheral smear, hemolysis markers, Coomb's test, H. pylori serology, hepatitis screening, autoimmune screening, B12, folate, Thyroid function test. Occasionally CMV and EBV antibodies are done but these are not based on consensus recommendations. [5, 6, 7, 8]

In general, a bone marrow aspiration and biopsy is not indicated when ITP is suspected. However, in elderly patients, patients with accompanied abnormalities in red and/or white cells, patients with abnormal peripheral smear or have organomegally, or failed therapy and in patients requiring splenectomy, a bone marrow examination is indicated to rule out the presence of a primary marrow disorders, such as myelodysplasia, leukemia or lymphoma.[5, 6]

The current ASH guidelines are against doing BMA for patients with ITP unless there are signs to suggest other diagnoses like abnormal peripheral smear, organomegally or accompanied cytopenia or failure of treatment.

The prevalence of H. Pylori in our ITP patients is against doing the test for each and every patients and I suggest it should be limited to refractory patients only.

Treatment options for thrombocytopenia in general and ITP is summarized in figure 1.

Refractory ITP is more frequent in adults. 25% of primary ITP patients will fail corticosteroid as first line treatment. (1,2, 9). Splenectomy is recommended as a second line of treatment but with the new modalities of treatment there has been less splenectomy in ITP 9. Although it is a save procedure but it is not without complications. It will require a save platelet count (more than 30000) to start with. (1,2, 9)

Refractory ITP patients may not be able to undergo such a major surgery especially when their platelet count is very low as in our patient. Taking these in consideration there should be another way to define refractory ITP and most importantly to find a way to manage severe and refractory patients. Specific treatment for rapid increment of platelet count in refractory severe ITP is lacking. The aim of treatment of refractory and severe ITP is to prevent bleeding and to achieve a save platelet count. Patients who are not responding to IVIG or anti-D who have very low platelet count and have significant bleeding as in our patient are very challenging. Using factor VII to control bleeding till other second line modalities work may be helpful. Platelet transfusion usually does not help as it will be destroyed rapidly. American society of hematology has recently published an updated

guidelines on immune thrombocytopenia. It includes definition of severe and refractory ITP taking in consideration the recommendations of the International Working Group (IWG) terminology.(1,2) According to these guidelines a refractory ITP is defined as presence of severe thrombocytopenia after splenectomy. They have considered non-splenectomized patients as non-responders but not as refractory. Severe thrombocytopenia is defined as having clinically relevant bleeding either at presentation or later that require initial treatment or additional treatment respectively.

Francesco et al defined refractory ITP as those patients who have both failed splenectomy and have severe thrombocytopenia with bleeding symptoms requiring treatment.(2) He defined severe thrombocytopenia as presence of bleeding symptoms either at presentation or later that require initial treatment or additional treatment respectively.(2)

Both have limited the refractory ITP to splenectomized patients and not given any consideration to platelet count in their definition of severe thrombocytopenia.

These definitions do not include refractory form of ITP which failed other new modalities of treatment or patient who are not able to undergo splenectomy because of either very low platelet count not save for splenectomy or have other contraindications for splenectomy. This would exclude some patients who should be labelled as refractory ITP even if they have not undergone splenectomy.

By the definition of both ASH and Francesco et al refractory ITP include severe thrombocytopenia while responders are defined as having platelet count more than 30000 and 2-fold increase in the baseline platelet count and absence of bleeding. This will not include a good number of patients who have a platelet count more than 30000 but still considered refractory by the above mentioned definitions. Severe thrombocytopenia does not necessarily mean refractory ITP and vice versa.

Time to response is an important issue in severe ITP compared to refractory ITP. So separation of severe ITP from refractory ITP might be necessary. Another point to be considered is refractory ITP should include patients who failed other modalities of treatment weather splenectomized or not especially with the availability of new second line treatment and probable relative and absolute contraindications of splenectomy.

Time to expected response and type of treatment should be part or defining refractory ITP. Severe ITP should be considered whenever platelet count is less than 20000. Very severe ITP should be considered whenever platelet count is less than 10000 in addition to presence of clinically significant bleeding

symptoms. Clinically significant bleeding should also be redefined to drop off baseline hemoglobin that require transfusion instead of leaving it without specific definition.

Treatment options for refractory ITP might not be similar to severe ITP. Severe ITP patients will require immediate action while refractory ITP patients may not require any treatment if their platelet count is more than 30000. Severe ITP patients would probably require platelet transfusion, antifibrinolytics and recombinant factor VII to manage their acute bleeding episodes while waiting for their response to specific treatments. Treatment options for refractory ITP may include immunosuppressant like Vincristine, Cyclophosphamide, Azathioprine, Cyclosporine, Danazol, high dose of Vitamin D, Thrombopoietin receptors agonist and Rituximab. **(10-15)** These treatment options might not be an option for severe ITP as they will need at least 7-14 days to show any response.

Individuals with immune thrombocytopenia produce anti-platelet antibodies that destroy circulating platelets and megakaryocytes in the bone marrow. Circulating platelets in patients with ITP tend to be highly functional, and platelet counts tend to be well above 30,000/microL. Bleeding is rare even in patients with severe thrombocytopenia (ie, platelet count <30,000/microL). Our general approach to platelet transfusion in patients with ITP is to transfuse for bleeding rather than at a specific platelet count (16).

Conclusions:

This is a single institute experience which showed the importance of ITP and its variety in clinical presentation and its severity. ITP HAS MAJOR consequences on quality of life with limited management options available for severe and refractory patients. Although the ASH guidelines and others have added a lot to our practice of managing patients with ITP and established a universal approach to manage such common disease there are still area to be developed further. Redefining refractory ITP and severe ITP is necessary. Refractory ITP should include patients who failed second line treatment whether splenectomized or not-splenectomized. Severe ITP has to be addressed more clearly with utilization of available platelet count to assess the severity of the disease instead of developing a complicated bleeding scoring system or using non-specific wards like clinically relevant bleeding. These will guide the clinicians to take more aggressive action when dealing with such patient. Definition of clinically relevant bleeding needs more precise tools to identify it. Table 3 summarizes the points that need to be readdressed in the future guidelines.

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