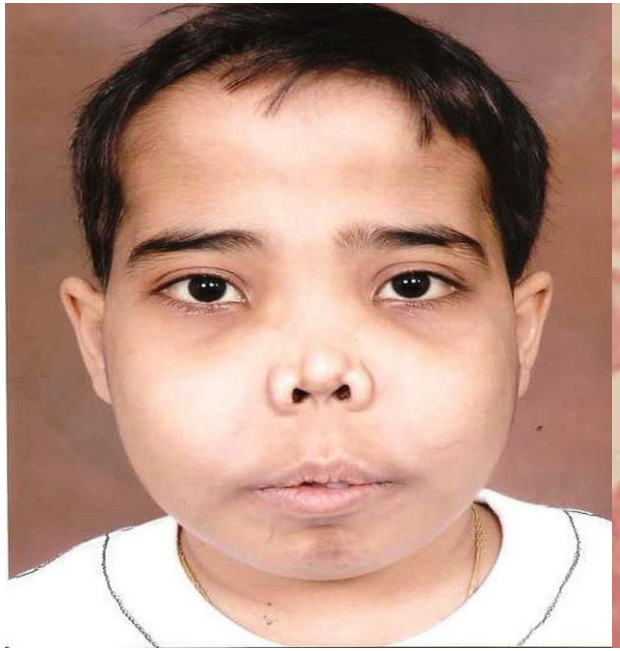
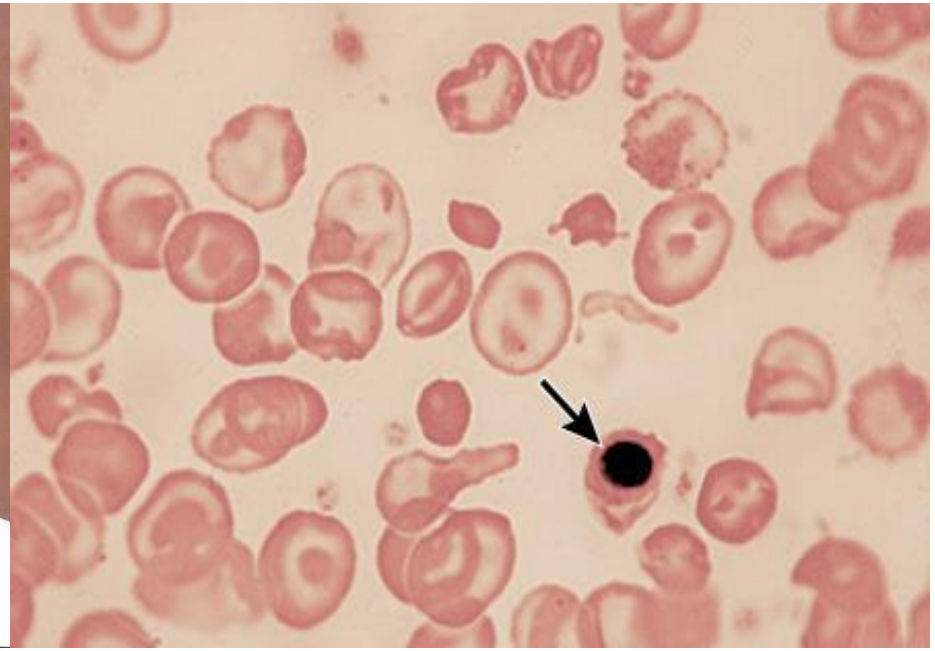

بسم الله الرحمن الرحيم

THALASSEMIA INTERMEDIA





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Definition and Clinical Manifestations

- The term TI is clinically descriptive of beta-thalassemic patients whose clinical manifestations are not as mild as thalassemia minor or as severe as TM .
- The first description of TI was made by Rietti Greppi Micheli in 1955.
- Although TI is a nontransfusion-dependent thalassemia form, some patients occasionally need blood transfusions.
- They also require careful medical attention like TM to improve quality of life.

Definition and Clinical Manifestations

- Genetic heterogeneity of TI is associated with wide clinical spectrum presentations from mild to severe hemolytic anemia and can be divided into two subgroups:
- (1) Some patients are mildly affected leading to mild clinical problems until adult life.
- These patients maintain hemoglobin levels between 7 and 11 gr/dL and are usually transfusion independent or rarely require blood transfusions.

Definition and Clinical Manifestations

- (2)Patients with more severe anemia who generally present at ages 2–6 years old.
- Although they may not require regular transfusions like the first subgroup, without occasional transfusions and appropriate management, they frequently develop clinical symptoms such as skeletal deformities and growth retardation .

Definition and Clinical Manifestations

- While TI and TM have some overlap in their clinical presentations, differentiation of the two disorders is essential for optimal management and prevention of their later complications.
- *TI can present with pallor, jaundice, anemia, splenomegaly or skeletal deformities during childhood or later.*

Definition and Clinical Manifestations

- *Diagnosis of TI* is usually made after the age of 2 years with initial Hb levels of 7 gr/dL or more in patients with beta-thalassemia who are free of infection and have adequate folic acid.
- One of their parents is also atypical carrier of beta-thalassemia such as normal or borderline HbA2 or isolated increased HbF (usually up to 10%) .

Definition and Clinical Manifestations

- The patients are usually referred with *microcytic-hypochromic anemia and the peripheral smear shows mild to severe microcytosis and hypochromia, anisopoikilocytosis, polychromasia, target cell, basophilic stippling, and nucleated RBC (NRBC).*
- Hb electrophoresis includes: HbA: 0-80%; HbA2: normal or up to 7%HbF: 10-100%.
- Serum iron, serum ferritin and transferrin saturation may be increased.

Definition and Clinical Manifestations

- Differential diagnosis between TI and TM is essential because :
- the first step for management of patients with TI is usually not transfusion;
- however, the first choice of TM management is blood transfusion.

TABLE 1 Differentiation Between Thalassemia Intermedia and Thalassemia Major

	Thalassemia intermedia	Thalassemia major
Clinical manifestations		
Age of presentation (years)	>2	<2
Splenomegaly	Moderate to severe	Mild in case of optimal management
Transfusion	Nondependent or occasionally	Dependent
Pallor, jaundice	Usually yes	No or mild if optimal management
Skeletal deformities	Usually yes	No or mild if optimal management
Hematologic data		
Hb levels (g/dL)	≥6–7	<6–7
HbF (%)	10–50 (may be up to 100%)	>50 (may be less than 50%)
HbA2 (%)	≥3.5	<3.5
Mean cell volume (MCV)	Decrease	Normal, if optimal management
Nucleated red blood cells (NRBC)	Increase	Normal, if optimal management
White blood cell (WBC)	Increase	Normal, if optimal management
Complications		
Thrombosis	Common	Less common
Pulmonary hypertension	Common	Rare
Right-sided heart failure	Common	Rare
Left-sided heart failure	Rare	Common
Leg ulcer	Common	Rare
Extramedullary hematopoiesis	Common	Rare
Endocrine complications	Uncommon	Common
Viral hepatitis	Rare	Common
Genetic and molecular characteristics		
Parents	One or both are atypical carriers of beta-thalassemia minor	Both are typical carriers of beta-thalassemia minor
Type of mutation	Silent to mild	Severe
Coinheritance of alpha-thalassemia, hereditary persistence of fetal hemoglobin, delta-thalassemia, XmnI polymorphism	Yes	No

Mutation Analysis and Molecular Definition of TI

- TI arises from gene mutations affecting beta-globin production.
- Most patients are homozygotes or compound heterozygotes for beta-thalassemia.
- The different phenotypes of patients with TI arise from different gene defects that cause a mild to severe alpha/beta-globin chains imbalance.

Clinical Complications and Management in TI

- Like TM, three main factors are responsible for the clinical manifestations in untreated TI patients:
- ineffective erythropoiesis,
- chronic hemolytic anemia,
- iron overload.
- Ineffective erythropoiesis is responsible for erythroid marrow hyperplasia and skeletal deformities, hemolytic anemia and extramedullary hematopoiesis (EMH).
- Hemolysis is commonly associated with splenomegaly, hypercoagulable state, and pulmonary hypertension (PHT).

Clinical Complications and Management in TI

- The prevalences of disease complications were as follows:
- ●Osteoporosis – 23 percent
- ●Extramedullary hematopoiesis (radiologic evidence) – 21 percent
- ●Hypogonadism – 17 percent
- ●Cholelithiasis (by ultrasound) – 17 percent
- ●Thrombosis – 14 percent
- ●Pulmonary hypertension – 11 percent
- ●Abnormal liver function – 10 percent
- ●Leg ulcers – 8 percent
- ●Hypothyroidism – 6 percent
- ●Heart failure – 4 percent
- ●Diabetes mellitus – 2 percent

Clinical Complications and Management in TI

- ***EMH:***
- Erythropoietic tissue masses occur as a compensatory mechanism to overcome chronic hemolysis, EMH is most commonly found in the liver, spleen, and lymph nodes.
- Paraspinal masses can cause cord compression and neurological damage .
- Paraspinal EMH mainly presents as pseudotumors, which may possibly cause a variety of neurological symptoms due to spinal compression.

Clinical Complications and Management in TI

- EMH has also been reported in
- pleura,
- pericardium,
- chest ,
- intracranial cavity,
- adrenal glands,
- and some other organs .

Risk factors for extramedullary hematopoietic tumors :

male sex,

older age,

and lower HbF levels

Clinical Complications and Management in TI

- Hydroxyurea (HU) therapy, blood transfusion, and radiation therapy are therapeutic options for EMH in these patients.
- The dosage of HU should be higher (20–30 mg/kg/d) compared to the dosage that it is usually used for TI for enhancement of gamma globin chain synthesis (8–15 mg/kg/d).
- The other treatment modalities should be considered if the patient does not respond to HU therapy.
- Surgery is not recommended as it has been related to bleeding in these patients.

Clinical Complications and Management in TI

- ***Thrombosis***:

- In a cohort study that was done it was demonstrated that thromboembolic event (TEE) occurred 4.38 times more frequently in TI than TM patients .
- The most important factor involved in hypercoagulability is exposure of negatively charged phospholipids on the RBCs membrane remnants as a result of oxidative stress and subsequent activation of the prothrombinase complex and enhanced thrombin generation.

Clinical Complications and Management in TI

- However, some other factors like decreased levels of the antithrombotic proteins C and S,
- endothelial exposure to inflammation,
- oxidative effects of hemolysis
- increased number of activated platelets in splenectomized patients

Independent risk factors for thromboembolic disease .

splenectomy,
serum ferritin level > 800-1000 ng/mL,
hemoglobin level < 9 g/dL,
age >35 years
In splenectomized NTDT patients,
nucleated RBC count > 300*10 6
platelet >500000,
and RBC transfusion naivety
patients with a history of pulmonary hypertension

Clinical Complications and Management in TI

- *Splenectomized TI patients have a higher incidence of TEE compared to non splenectomized TI patients .*

- Furthermore, *high NRBC and platelet counts as well as transfusion naivety are associated with earlier development of TEE after splenectomy .*

Clinical Complications and Management in TI

- Deep and portal vein thrombosis, pulmonary embolism, and brain ischemia and infarction resulting in stroke are the main thromboembolic complications in TI patients .
- *Overt stroke is much more common in TM than TI due to higher stroke related risk factors such as diabetic mellitus, heart failure and arrhythmia in these patients but silent ischemic brain lesions are more common in TI.*
- studies in Iran and Lebanon showed the frequency of silent ischemic brain lesions in 26% and 60%, respectively.

Clinical Complications and Management in TI

- (CVA) and silent ischemic lesions are reported especially frequently in the subgroup of TI patients who are :
- *adults, transfusion-independent, splenectomized, and have a platelet count >500 ×10 9/L.*
- It is highly recommended that patients with silent infarcts be treated with antiplatelet drugs Blood transfusion on a regular basis should be strongly considered in such patients
- and definitely initiated for patients with symptomatic CNS disease.

Clinical Complications and Management in TI

- Prophylactic anticoagulation therapy is also recommended in TI patients who are undergoing some types of surgery
- Low molecular weight heparin can be used for a period of 7–14 days postoperatively to prevent postsurgery thrombosis.
- However, in patients with TEE life-long anticoagulation seems to be rational and effective in prevention of recurrent TEE.

Clinical Complications and Management in TI

- ***PHT*:**

- PHT, defined as systolic pulmonary artery pressure >35 mmHg, may be a common complication in TI patients with a frequency that has been reported to be as high as 60%.
- However, other studies found a frequency of 10–12%.
- *PHT is the primary cause of right sided congestive heart failure* in these patients,.
- Hemolysis has a key role in the development of PH in TI patients.
- It was shown that chronic hemolysis leads to nitric oxide depletion due to nitric oxide scavenging, arginine catabolism, and endogenous nitric oxide synthesis inhibition.

Clinical Complications and Management in TI

- It also contributes to enhanced platelet activation and increased endothelin-1 release ,and thus, endothelial dysfunction, increased vascular tone, inflammation, hypercoagulability, vascular remodeling, and destruction of pulmonary vasculature, which ultimately results in hemolytic anemia–associated PH .
- Blood transfusion and sildenafil (in some cases) are recommended as an optimal therapy in *β*-TI patients with PAH.
- Some studies have shown that *HU therapy alone or in combination with l-carnitine or magnesium* can be effective in improving hematologic parameters and cardiac status in patients with TI .

NTDT patients (4.8%) are 5 times more likely to have PHT thanTDT (1.1%) patients.

Risk factors :

splenectomy,

naivety to iron chelation therapy,

naivety to hydroxyurea treatment,

naivety to RBC transfusion therapy,

a nucleated RBCcount greater than 300 *10 6,

a history of previous thromboembolic events,

and older age

Clinical Complications and Management in TI

- ***Iron overload and Endocrine complications:***
- *Increased* iron absorption due to chronic hemolytic anemia can cause iron overload and serious iron-related organ complications like cardiac dysfunction and endocrine dysfunction including diabetic mellitus, hypogonadism, infertility, and hypoparathyroidism .
- Endocrine complications are less common in TI patients in comparison with TM patients because of fewer blood transfusions and therefore less severe overload.

Clinical Complications and Management in TI

- ***Leg ulcer:***
- Leg ulcer is a serious complication in TI patients occurring in almost one third of patients with poorly controlled disease .
- They usually appear in the second decade of life and are generally located on the medial or lateral malleoli.
- The ulcers can develop after minor trauma and tend to expand rapidly.
- Chronic anemia, reduced oxygen delivery to the distal regions and venous stasis in TI patients may cause leg ulcers in older patients.
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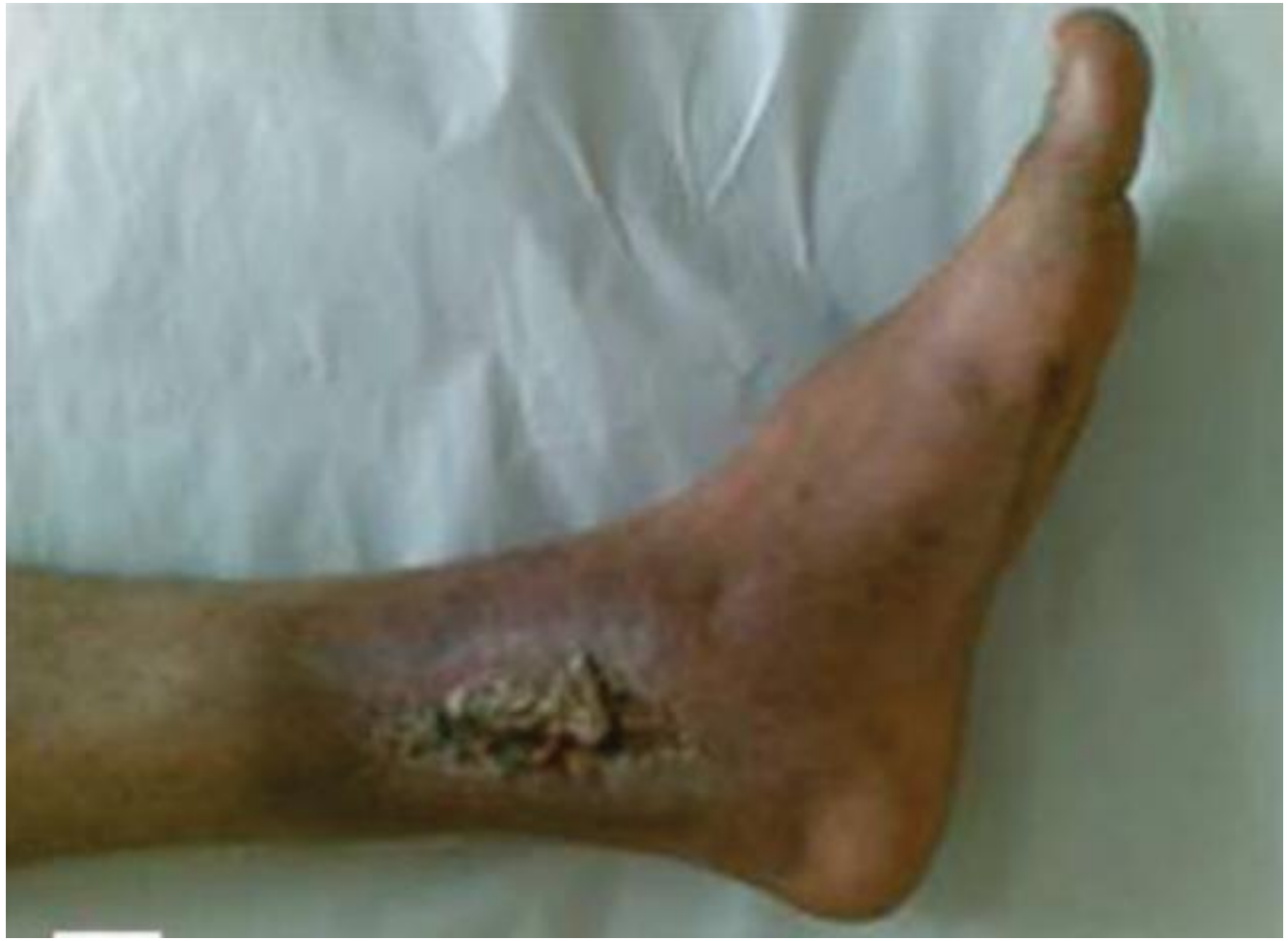
Leg ulcer



Clinical Complications and Management in TI

- Also, **increased rigidity of erythrocytes cellular membrane,**
- **local edema due to venous stasis,**
- **right sided heart failure,**
- **repetitive local trauma,**
- **skin infections,**
- **hypercoagulablility, and prothrombotic tendency** are other contributing factors to ulcer formation.
- *Blood transfusion (in some cases), local wound care, and HU therapy are the major strategies in these cases.*

Leg ulcer

- Topical sodium nitrite cream may be considered
- Dialzep (vasodilators)
- oxygen chamber
- platelet derived wound healing factors

Clinical Complications and Management in TI

- *Other complications*:
- Cachexia and hyperuricemia due to the hypercatabolism of erythroid hyperplastic tissue (more prevalent in TI in comparison to TM)
- and cholelithiasis induced by hyperbillirubinemia are some other metabolic complications in TI .
- Allopurinol therapy is recommended in cases with hyperuricemia.

TREATMENT OF TI

- Treatment of TI is essential for prevention of clinical complications.
- The limited options available for management of TI include :
- transfusion therapy,
- iron chelation,
- splenectomy,
- modulation of gamma-globulin chain production,
- stem cell transplantation.

Transfusion Therapy

TABLE 4 Indications of Blood Transfusion in Thalassemia Intermedia

Regular transfusion	Occasional transfusion
Pulmonary hypertension (PHT)	Decrease exercise tolerance
Congestive heart failure (CHF)	Cord compression
Persistent symptomatic severe anemia (Hb < 6-7 gr/dL) leading to persistent growth retardation	Thrombosis
	Pregnancy
Progressive skeletal deformities	Growth failure
Progressive pathologic fracture	Leg ulcer
	Priapism
	Severe anemia (Hb < 6-7 gr/dL)

Iron Chelation Therapy

- Iron overload in TI is frequently derived from transfusion therapy.
- In addition, chronic hemolysis, ineffective erythropoiesis, and hypoxia may lead to increased intestinal iron absorption through suppression of the regulatory protein hepcidin .
- Until recently, the cutoff for starting chelation was an LIC of 7 and above.

Iron Chelation Therapy

- The (TIF) **recommends** to initiate iron chelation therapy corresponding to a ferritin level of above 800 ng/mL and an LIC of 5 mg Fe/g dry weight or above.

Iron Chelation Therapy

- Suspension of therapy should be initiated when serum ferritin level is 300ng/ml corresponding to an LIC level of 3 mg Fe/g dry weight or less.
- The TIF also recommends that all patients above the age of 10 be frequently evaluated for iron overload by LIC at 1–2 year intervals along with serial measurements of serum ferritin every 3 months.

Iron Chelation Therapy

- It can be said that *serum ferritin alone is not a reliable measure of iron overload* in these patients because it underestimates the iron load,
- and annual assessment of LIC by biopsy or preferably by noninvasive imaging methods like R2 and T2* MRI sequences have more reliable and reproducible results .

Modulation of Gamma-Globin Chain Production

- Enhanced gamma-globin chain production might address some of the major clinical manifestations in TI patients by increasing the production of HbF and reducing the alpha/beta-globin chain imbalance.
- One of the best known drugs to enhance gamma-globin chain production is *HU.*

Modulation of Gamma-Globin Chain Production

- The results show that a significant number of transfusion-dependent TI patients became transfusion free or needed only occasional transfusions.
- Significant increases of Hb levels in not transfused patients were also reported .
- A recent study showed that combination therapy of HU (8–15 mg/kg/d) with L-carnitine or magnesium chloride could be more effective in improving hematologic parameters and cardiac status in patients with TI than HU alone .

Modulation of Gamma-Globin Chain Production

- predictors of a good response to HU:
- Co-inheritance of alpha- thalassemia, Hb E/β thalassemia,
- younger age,
- higher Hb levels,
- higher age at the first transfusion before HU therapy
- history of splenectomy

Modulation of Gamma-Globin Chain Production

- During 10 years of observation, HU had no significant adverse effects in these patients such as
- malignancy,
- infertility,
- bone marrow suppression when used at a dose of 8–15 mg/kg/d .

Modulation of Gamma-Globin Chain Production

- Recombinant human erythropoietin (rHuEPO) is another erythropoiesis and HbF inducer that was shown to ameliorate the thalassemia clinical symptoms by increasing HbF cells and HbF induction.
- A recent study also showed that rHuEPO combined with HU has a superior therapeutic effect in the clinical and hematological responses and improved quality of life in TI patients in comparison with HU therapy alone .
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Splenectomy

- Removal of the spleen may be a useful treatment strategy in severe forms of TI increasing the Hb levels by 1–2 g/dL and improving growth and development.
- Indications for splenectomy in TI are numerous, however, splenectomized patients are at greater risk of thrombosis, infection, and PHT, therefore, the decision to remove the spleen should be made with considerable caution.
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Splenectomy

- TIF guidelines on splenectomy indicate that splenectomy should be avoided in nontransfusion dependent thalassemia patients younger than 5 years of age.
- **Splenectomy should be reserved for cases of:**
- Worsening anaemia leading to poor growth and development
- When transfusion therapy is not possible or iron chelation therapy is unavailable
- Hypersplenism leading to worsening anaemia, leucopenia, or thrombocytopenia and causing clinical problems such as recurrent bacterial infections or bleeding
- Splenomegaly Accompanied by symptoms such as left upper quadrant pain or early satiety

massive splenomegaly (largest dimension >20 cm) with concern about possible splenic rupture

Splenectomy

- Moreover, it is very important to keep in mind that abdominal sonography is mandatory before surgery because the gallbladder and accessory spleen should be inspected during splenectomy and removed in case of cholethiasis or accessory spleen.

Stemcelltransplantation:

- *It is not usually recommended in not transfused or irregularly transfused patients with TI,*
- *although if these patients are transfusion dependent, it may be considered.*

Other treatment considerations:

- These include:
- daily folic acid supplementation,
- antioxidant,
- anticaogulation in the perioperative period,
- and adequate dietary or supplemental vitamin D and calcium for prevention of osteoporosis .

Improving Ineffective Erythropoiesis

- Recent studies have elucidated the roles of (JAK2) and the transforming growth factor (TGF)-b superfamily in the control of erythropoiesis.
- Binding of erythropoietin to its cell membrane receptor activates the cytoplasmic JAK2, which in turn activates multiple signal transduction pathways to increase proliferation, differentiation, and survival of erythroid progenitors.

Improving Ineffective Erythropoiesis

- JAK2 inhibitors, such as ruxolitinib, have shown promise for amelioration of average hemoglobin concentration and potential spleen size reduction in patients with TDT; the results of such trials in TDT may lay the basis for studies in NTDT especially in patients with enlarged spleens.

Improving Ineffective Erythropoiesis

- Two activin receptor fusion proteins, sotatercept (ACE-011) and luspatercept (ACE-536), have been developed for the treatment of conditions caused by ineffective erythropoiesis, including β-thalassemia.
- These recombinant proteins bind to select TGF-b superfamily ligands that regulate late-stage erythropoiesis
- Thus, the mechanisms of action of sotatercept and luspatercept are distinct from erythropoiesis-stimulating agents and erythropoietin, which act on earlier stages of erythropoiesis.

Survival and Health-Related Quality of Life in TI

- In conclusion, although the clinical manifestations of TI are usually milder that TM, the prognosis and the rate of complications are often worse.
- Right sided heart failure due to long-standing PHT, thrombosis and brain ischemia, EMH in some vital regions like spinal cord, and iron overload are major and life-threatening complications of TI.

CHALLENGES IN NTDT

- Transfusion therapy,
- Iron chelation,
- Splenectomy,
- Modulation of gamma-globulin chain production,(HU)
- Stem cell transplantation.
- Improving Ineffective Erythropoiesis