Hypercoagulable State in Thalassemia

By: Divyanka Kavdikar and Preston Reed

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Thalassemia Types

- **Alpha vs. Beta**
  - 4 alpha genes, 2 beta genes
- **Severity**
  - Major - Severe symptoms
  - Intermedia - moderate symptoms, overlap between major & minor
  - Minor - Usually only 1 missing/defective gene, very mild symptoms
  - Silent carriers

Epidemiology

Family History

Middle Eastern, South Asian, African Descent

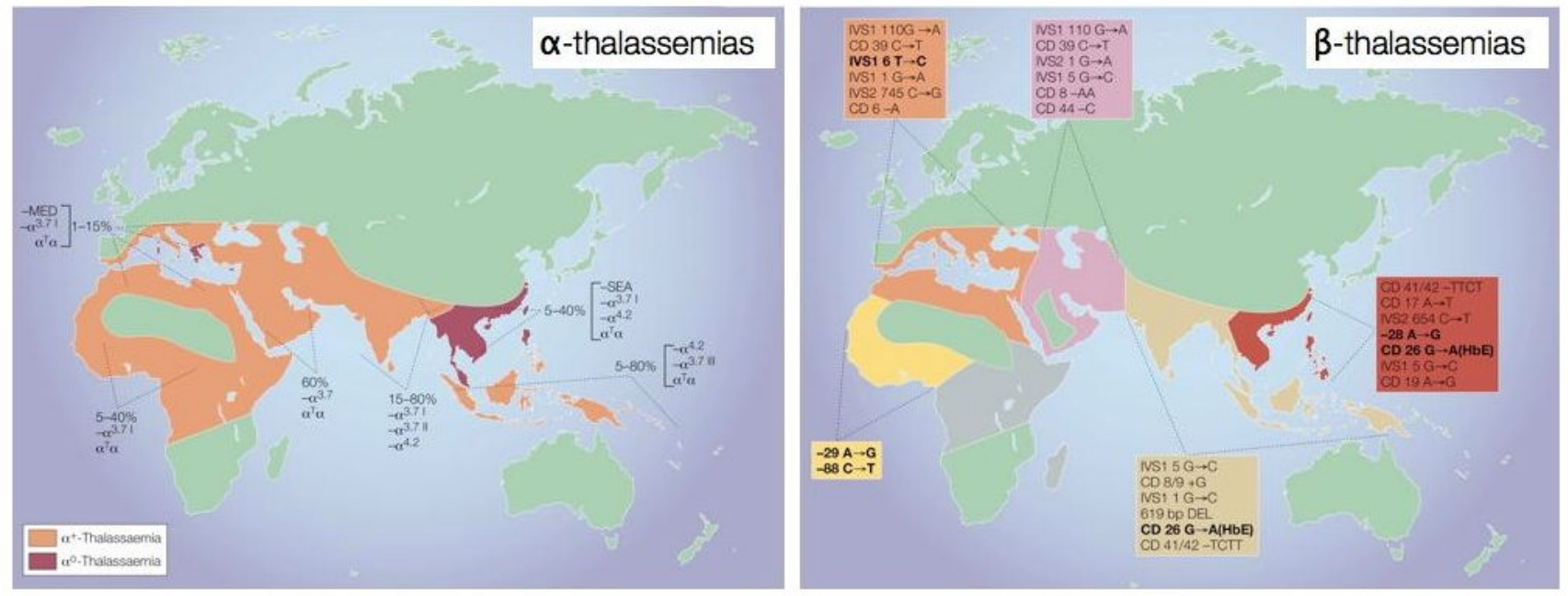


Figure 1: Prevalence of Thalassemia Across the Globe

Incidence Rates

- 4.4 per 10,000 births worldwide
- 10,000 - 12,000 yearly in India
- 28.9% TEE, 10.8% recurring TEE
- 4% TEE, 1.1% recurring TEE

Symptoms

Basic

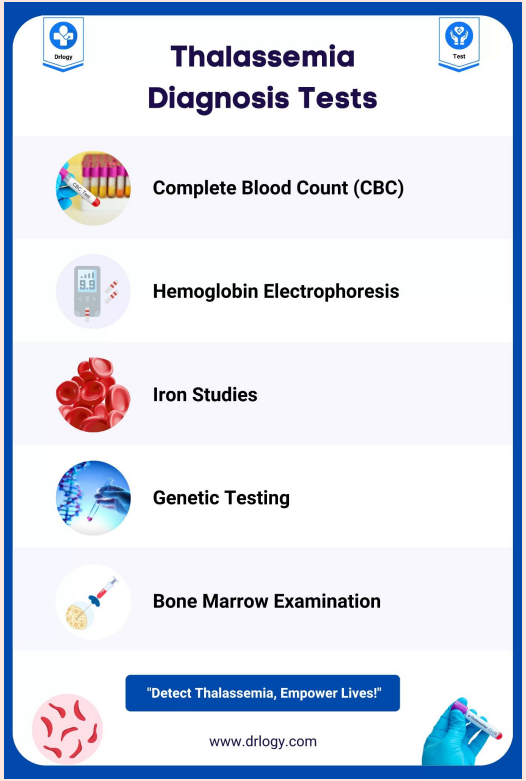
- Fatigue
- Yellowing skin
- Poor appetite
- Abdominal/ leg swelling
- Dark urine

Severe

- Splenomegaly
- Heart failure
- Bone changes
- Irregular heartbeat
- Splenectomy & pacemaker

Diagnosis

- 6 months - 2 years old
- Symptoms of anemia
- Blood tests
- Prenatal testing



Treatment

Chelation Therapy

Chronic Blood Transfusions

Bone Marrow Transplants

Impact

Coagulation Cascade

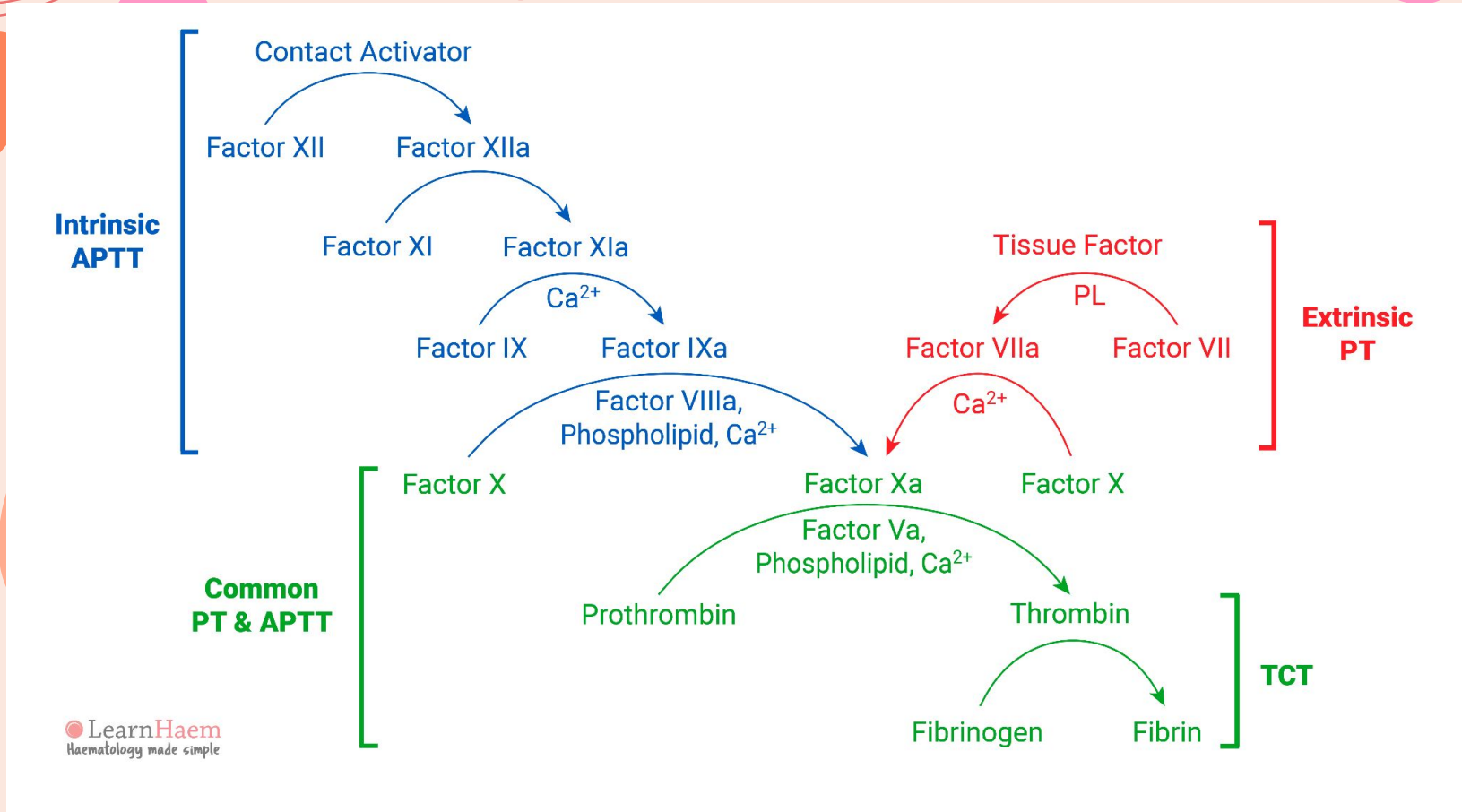


Figure 2: Coagulation Cascade

Pathophysiology

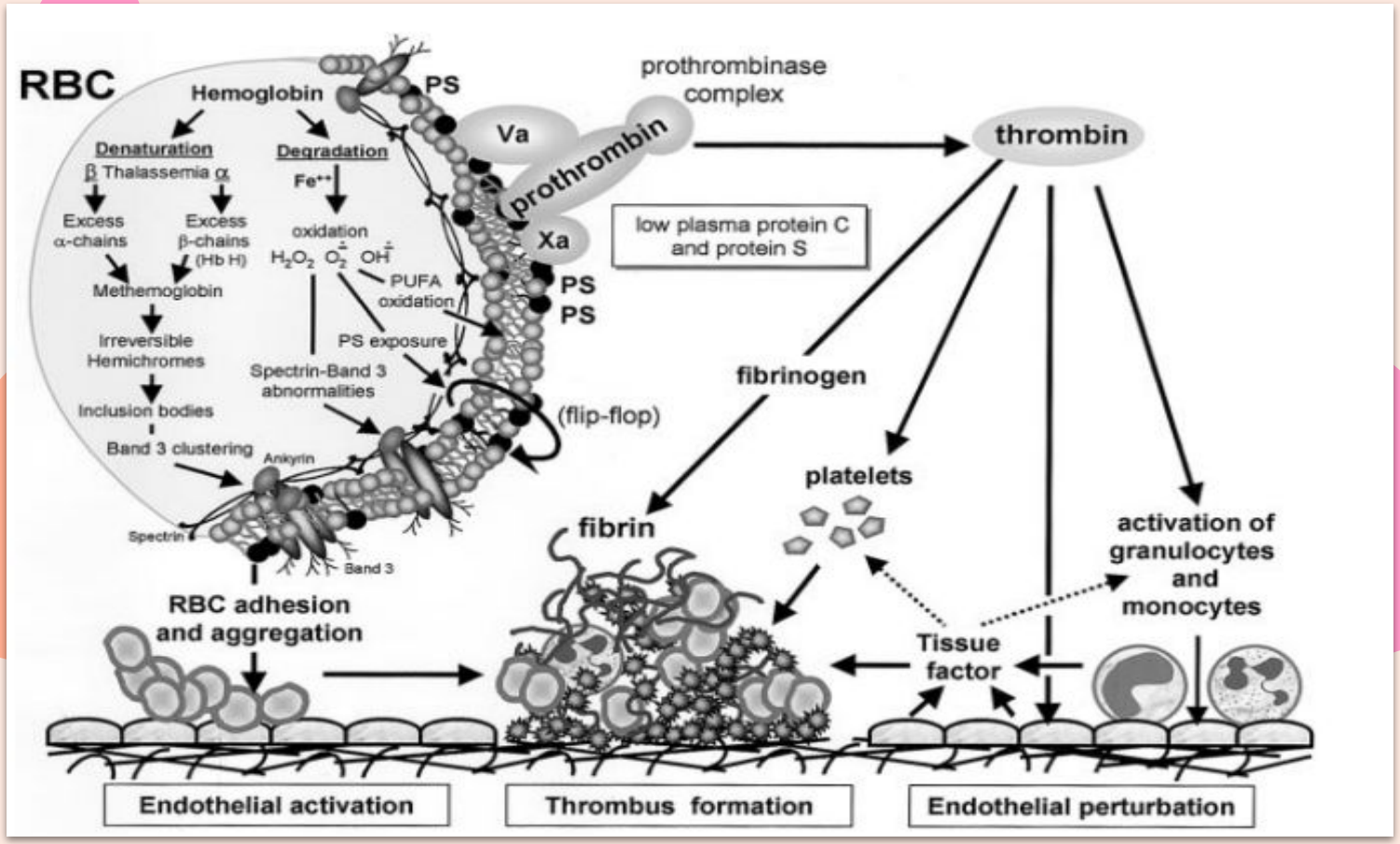


Figure 3: Pathophysiology of Thrombogenesis in Beta-Thalassemia Major

Evidence of Hypercoagulability

Mean Platelet Life Span

	B-TM Patient	Healthy Control	P
Splenectomized	107 +/- 36 hours	248 +/- 51 hours	< 0.001
Non-splenectomized	102+/- 64 hours	224 +/- 23 hours	< 0.01

Figure 4: Mean Platelet Life Span of Splenectomized Beta Thalassemia Patients

- Shorter in B-TM patients due to enhanced platelet consumption
- Correlates to greater prevalence of thrombotic episodes

Platelet survival in patients with beta-thalassemia

A Eldor [1], Y Krausz, H Atlan, D Snyder, A Goldfarb, E Hy-Am, E A Rachmilewitz, H F Kotze, A D Heyns

Affiliations + expand

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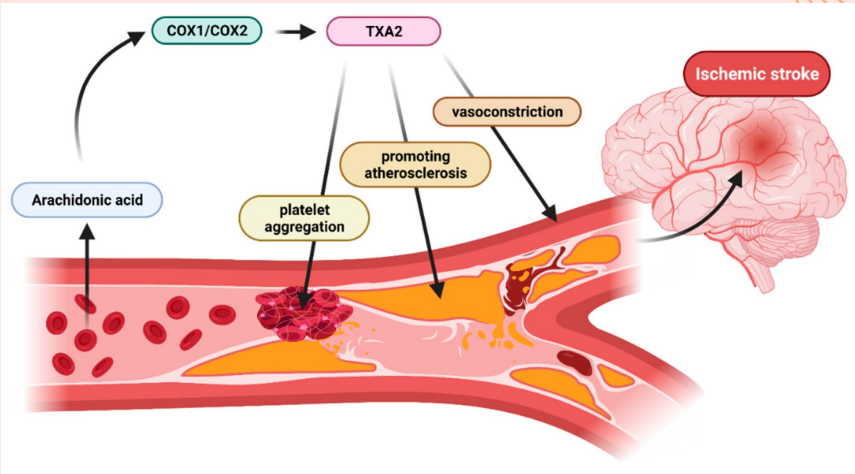
Thromboxane Metabolites

- Thromboxane
  - Platelet aggregation.
  - Chronic platelet activation
- Urinary excretion was 4-10 times higher
- Metabolites measured:
  - 2,3-dinor-TXB
  - 11-dehydro-TXB
  - 2,3-dinor-6-keto-prostaglandin.



In vivo platelet activation in beta-thalassemia major reflected by increased platelet-thromboxane urinary metabolites

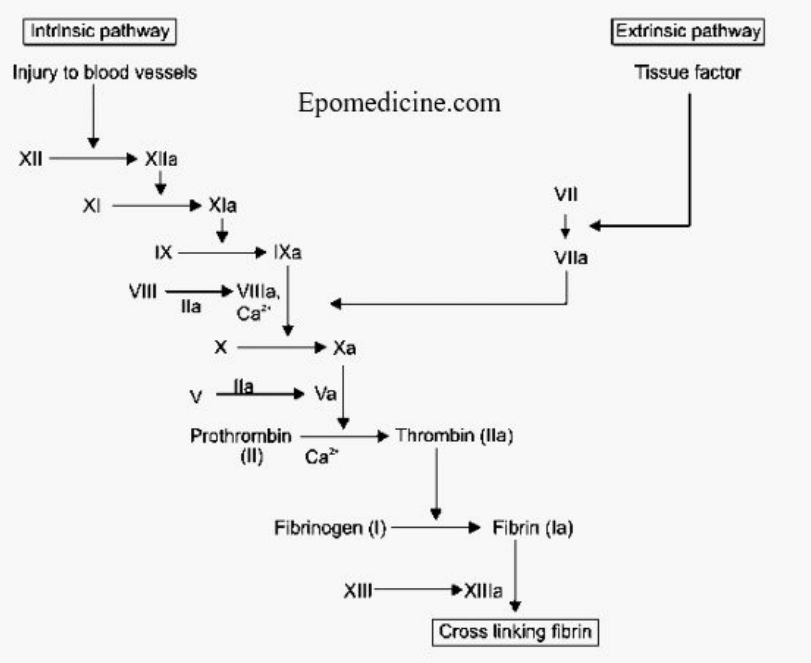
A Eldor [1], F Lellouche, A Goldfarb, E A Rachmilewitz, J Maclouf

Coagulation Factors

- Lower plasma prothrombin was observed
- Factors V, VII, X, and plasminogen were consistent between B-TM adult patients (19-30) and the healthy control group.

A chronic hypercoagulable state in patients with beta-thalassaemia major is already present in childhood

A Eldor [1], R Durst, E Hy-Am, A Goldfarb, S Gillis, E A Rachmilewitz, A Abramov, J MacLouf, Y C Godefray, E De Raucourt, M C Guillin



Coagulation Inhibitors

	Healthy Control	B-TM Adult	B-TM Child	P
Mean Protein C Antigen Levels	94.1% +/- 21%	51.2% +/- 11.2%	46%+/- 9.1%	<0.001
Protein C Activity	99.2% +/- 16.1%	52.3% +/- 12.1%	48.8% +/- 14.7%	<0.001
Free Protein S	85.1% +/- 18.2%	49.3% +/- 9.6%	43.4% +/- 8.7%	<0.001

Figure 5: Coagulation Inhibitor Levels in Beta Thalassemic Patients

- Protein C and Protein S are coagulation inhibitors that prevent excessive clotting.
- Hypercoagulability already present in childhood

A chronic hypercoagulable state in patients with beta-thalassaemia major is already present in childhood

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Biomarkers in Thalassemia

- Elevated Levels-
  - Endothelial Adhesion Proteins
    - ELAM-1 (E-selectin)
    - ICAM-1 (Intercellular adhesion molecule)
    - VCAM-1 (Vascular cell adhesion molecule)
  - Microparticles
  - CD62P & CD63
- Lowered levels of antithrombin
- Promote thrombosis at vascular Inflammation Sites - vessel obstruction, tissue hypoxia and death

Coagulopathy in Beta-Thalassemia: Current Understanding and Future Perspectives

M Domenica Cappellini [1,✉], Khaled M Musallam [2], Alessia Marcon [1], Ali T Taher [2]

Risk Assessment

- Contribute to coagulation
- Repeat frequently
- Use to evaluate for potential prophylaxis

Development of a thalassemia-related thrombosis risk scoring system

Ali T. Taher ✉, Maria Domenica Cappellini, Khaled M. Musallam

Risk factor at time of assessment	Score
Age >35	2.5
Hemoglobin level [a, b] <9 g/dL	2.5
Serum ferritin level [b] ≥1000 µg/L	2.0
Not regularly transfused [c]	3.5
Splenectomized	6.5
TRT-RSS Total Score minimum	0.0
TRT-RSS Total Score maximum	17.0
TRT-RSS risk categories	
Low risk	<9.5
Intermediate risk	9.5-13.5
High risk	>13.5

Figure 6: Thalassemia-related thrombosis risk scoring system (TRT-RSS)

Management

Prolonged Antithrombin Therapy

- For patients with previous thrombotic episodes

Stem Cell Transplants

- Require a donor

Continuing Blood Transfusions

- Deter development of excessive clotting in adults especially

Modern Treatment Regimes

β-Thalassemia: evolving treatment options beyond transfusion and iron chelation

Arielle L. Langer[1] and Erica B. Esrick[2]

Table 1. Current limitations of thalassemia care

Limitation	Potential solutions
Regular transfusion appointments	Reduce transfusion requirement Stem cell transplantation
Iron overload	Reduce transfusion requirement Block intestinal iron absorption Escalate chelation
Iron chelator toxicity	Reduce transfusion requirement Block intestinal iron absorption Additional chelation options
Lack of allogeneic stem cell donor	Genetically modified autologous transplantation Nontransplant therapies that preclude desirability of transplant

Figure 7: Challenges in Thalassemia Treatments

Modern Medications

Table 4. Novel medications for β-thalassemia

Medication	Mechanism of action	Route and frequency of administration	Phase of development	Current target patient population	In development for sickle cell disease?	Comments
Luspatercept[1,5]	TGF-β inhibitor	Subcutaneous, every 3 weeks	EMA and FDA approved	NTDT, TDT	No	Full data for NTDT pending; in use for MDS
Sotatercept[36,37]	TGF-β inhibitor	Subcutaneous, every 3 weeks	Development halted	NTDT, TDT	No	In development for pulmonary hypertension
Sirolimus[25–28]	mTOR inhibitor; HbF induction	Oral, daily	Phase 2 trials	TDT	No	In use for other disorders
Benserazide[31,32]	HbF induction	Oral, daily	Phase 1 trial	NTDT	Yes	In use for Parkinson disease
IMR-687[29,30]	PDE-9 inhibitor; HbF induction	Oral, daily	Phase 2 trial	NTDT, TDT	Yes	
Apotransferrin[19–21]	Hepcidin upregulation	Intravenous, every 2 weeks	Phase 2 trial	NTDT	No	
VIT-2763[22]	Ferroportin inhibitor	Oral, one or twice daily	Phase 2 trial	NTDT	Yes	
PTG-300[23]	Hepcidin mimetic	Subcutaneous, once weekly	Phase 2 trials	NTDT, TDT	No	In development for hemochromatosis and polycythemia vera
Mitapivat[33–35]	Pyruvate kinase activator	Oral, twice daily	Phase 3 trials	NTDT, TDT	Yes	In development for pyruvate kinase deficiency
Ruxolitinib[38]	JAK 1/2 inhibitor	Oral, twice daily	Development halted	TDT	No	Spleen size reduction; no change in transfusion

EMA, European Medicines Agency; FDA, Food and Drug Administration; JAK, Janus-associated kinase; MDS, myelodysplastic syndrome; mTOR, mechanistic target of rapamycin.

Figure 8: Modern Medications for Thalassemic Patients

Luspatercept

- Targets erythropoiesis
- Goal:
  - Decrease transfusion requirements
  - Decrease iron overload
- High risk for thalassemia patients more prone to TEE & splenectomized

Fetal Hemoglobin Inducing Agents

1. Hydroxycarbamide/Hydroxyurea

Reduces...

- Phospholipid expression
- RBC adhesion to thrombospondin
- Plasma markers of thrombin generation

1. Sirolimus

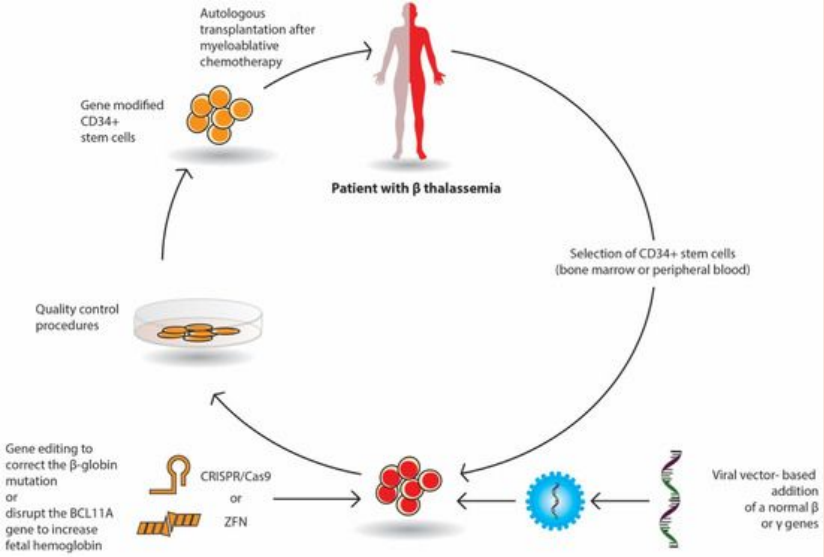
- Increases HbF expression
- Decreases ineffective erythropoiesis
- Removes alpha precipitates

Iron Metabolism Agents

- Improved iron metabolism improved erythropoiesis
- Increased hemoglobin
- Decreased transfusion dependence
- PTG-300
  - Hepcidin - Blocks iron absorption and ineffective RBC production
  - Improved anemia
  - Consistent iron levels

Autologous Gene Therapies

- No donor required
- Beticel
  - Focused on increased TI and reducing TD
  - Modifies hematopoietic cells
  - Uses lentiviral vector and myeloablative conditioning
- CASGEVY (FDA approved)
  - Removes stem cells
  - Intensive chemotherapy
  - Replace with modified cells



Cangrelor

- Intravenous, antiplatelet treatment
- Targets P2Y12 receptor on platelets
- Rapid reversal of effects
- In thalassemia patients:
    - Hemolysis can increase platelet aggregation through release of ADP (adenosine diphosphate)
    - Conditions including thalassemia worsen this action
    - Cangrelor can block the ADP receptor on platelets

Conclusions

- Thalassemia condition
- Intrinsic pathway
  - Phospholipids
  - Damaged RBC adhesion
  - Lowered Protein C & S levels
- Evidence of hypercoagulability
- Management
- Treatment Regimes

Acknowledgments

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Thanks