



Review Article

ISSN : 2277-3657  
CODEN(USA) : IJPRPM

## ***An Overview on Thalassemia Diagnosis and Management Approach, Literature Review***

**Tahani Mohammed Manea<sup>1\*</sup>, Faris Suhail Abdalhameed Khan<sup>1</sup>, Renad Mohammed Alsharyufi<sup>1</sup>, Kholoud Mohammed Alghamdi<sup>1</sup>, Manal Khalaf Alzahrani<sup>2</sup>, Fawaz Mohammed Alzubaidi<sup>3</sup>, Ali Abdulaziz Alghanmi<sup>3</sup>, Turki Abdullah Almahdawi<sup>3</sup>, Turki Mohammed Alhasani<sup>3</sup>, Nermeen Nasser Alrajhi<sup>4</sup>**

<sup>1</sup>Faculty of Medicine, Ibn Sina National College of Medicine, Jeddah, KSA.

<sup>2</sup>Faculty of Medicine, Baha University, Baha, KSA.

<sup>3</sup>Faculty of Medicine, Alqunfudah Medical College, Alqunfudah, KSA.

<sup>4</sup>Faculty of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, KSA.

**\*Email:** [Tahani.manea@gmail.com](mailto:Tahani.manea@gmail.com)

---

### **ABSTRACT**

*Thalassemia syndromes are the most common inherited monogenic diseases that kill and affect millions of people worldwide. As Thalassemic diseases became a healthcare system burden for many countries around the world Thalassemia management emerges as a lifetime treatment program that should regularly be monitored with preferable choice for management. In this review we aim to collect and summarize recent articles, studies, and clinical trials in diagnosing and managing thalassemia, and provide a summarized, yet comprehensive study. PubMed database was used for this review and data was collected from relevant journal articles, randomized controlled trials, and observational studies containing the term used in the mesh “Thalassemia” “Management” “Diagnosis” “Laboratory” “Treatment” within the title or abstract. The major pathophysiological change that occurs in thalassemia is the imbalance of the globin chain production. Thalassemia management emerges as a lifetime treatment program that includes intensive medical and surgical care with ongoing monthly clinical visits.*

**Key words:** *Thalassemia, Diagnosis, Clinical laboratory, Management, Treatment*

---

### **INTRODUCTION**

In 2006, WHO declared thalassemia as a major health issue worldwide [1-3]. Thalassemia syndromes are the most common inherited monogenic diseases that kill and affect millions globally. It is globally estimated that 1-5% of the population worldwide are mostly carriers for thalassemia syndromic mutations [4, 5]. Moreover, various forms of thalassemia affect approximately about 56000 conceptions and 300000 babies annually [6]. Thalassemic diseases became a healthcare system burden for many countries around the world especially in Gulf Cooperation council countries where the prevalence of Alpha thalassemia carriers are lower than Beta thalassemia major carriers. Individuals with minor manifestations of the syndrome can be asymptomatic and usually, do not need treatment, while major manifestations that start at a young age are managed with intensive care and regular transfusion therapy [7].

This review will outline recent researches in managing thalassemia and will assist pediatricians and healthcare personnel in better understanding thalassemia and ultimately improving patient care.

## MATERIALS AND METHODS

This comprehensive medical review is collected for the PubMed/MEDLINE only provided with these search terms: ((“Thalassemia” [Mesh] AND “Diagnosis” [Mesh] AND “Treatment” [Mesh] AND “Management” [Mesh])). Only published articles, trials, and documents were recorded in this review. Publications describing thalassemia epidemiology, clinical assessment, and/or management were all included.

### Review

#### *Epidemiology*

Thalassemia has become a major concern in many countries and their health systems around the world since 2006 according to the WHO [1]. About 56000 conceptions end up as thalassaemic patients. Furthermore, about a 1.33million pregnancies for thalassemia carriers are at high risk for the major thalassemia syndrome. About 300,000 babies born worldwide are affected with thalassemia annually. Thalassaemic diseases became a healthcare system burden for many countries around the world especially in Gulf Cooperation council countries where the prevalence of Alpha thalassemia carriers are lower than Beta thalassemia major carriers [7]. Moreover, in many other developing countries thalassemia became the main cause of death because of the expensive management and the noticeable absence of the proper measures in managing hemoglobinopathies [8, 9].

#### *Diagnosis and subtypes of thalassemia*

Genetic hemoglobinopathies are caused by mutations that occur in globin genes. The major pathophysiological change that occurs in thalassemia is the imbalance of the globin chain production. Different structural malformations occur on both involved alpha or beta globin chain that alters fetal hemoglobin leading to severe forms hemolytic anemia [10].

Alpha thalassemia is a heterogeneous molecular defect that is associated with numerous alpha-globin gene deficits that alter the alpha globin chain. Alpha thalassemia 1 is one of the most severe forms as it involves mutation and duplication of the alpha-globin gene. However, milder forms of mutations that are rare include two subtypes of alpha thalassemia, deletional and non-deletional alpha thalassemia [11].

Beta thalassemia has different molecular defects as most of the mutations in the beta-globin have based substitutions of one or two nucleotides. In severe forms of homozygous Beta-thalassemia children may appear healthy at birth because of the functioning Hb F. However, after 8 to 12 months of life, it may become asymptomatic but highly pathogenic with no beta globin expressions. Mutations and malformations of the globin genes form impaired chains that reduce the hemoglobin content causing mild to severe microcytic anemia [11].

Diagnosing and detecting thalassemia and other hemoglobinopathies begin with relevant family history, laboratory screening, and invasive prenatal screening via obtaining amniocentesis and chorionic villus sampling when the parents are at high risk for hemoglobinopathies. Moreover, new molecular genetic technologies to map and detect mutation and deletion by sequencing analysis prenatally [10, 12, 13]. Most of these technologies include PCR screening for mutations, electrophoresis, high-performance liquid chromatography (HPLC), and DNA test [10, 14].

Clinically, thalassemia classification depends on the variant type (deletion and non-deletion variants) and the location of the globin within the genes. These variants are examined by several applicable diagnostic molecular techniques in the clinical laboratory that has a direct impact on the accuracy of the diagnosis of thalassemia [15]. **Table 1** describes a brief idea about the common use of molecular techniques for detecting minor genetic mutation, deletion, and insertions [10].

**Table 1.** Molecular techniques used to detect minor genetic mutation, deletion, and insertions [10].

Techniques for known mutations	Techniques for unknown mutations
- Allele-specific PCR	- Denaturing electrophoresis gradient gel
- Gel electrophoresis	- Mismatched analysis
- Real-time PCR with melting curve analysis	- Direct DNA sequencing
- Dot blot analysis	

Multisystem evaluations should be done frequently to ensure any systemic involvement of the disease or progression. Based on any clinical suspicion, imaging is necessary to be done as in gallbladder and biliary tract imaging, cardiac MRI, abdominal ultrasonography to assess and determine the carrier systemic status [16].

#### *Challenges of management in thalassemia*

The care and assessment for thalassemia patients seem pretty challenging as it varies widely depending on the type, subtype, and severity of the underlying syndrome. There are have been effective and adequate treatment programs that are applied parallel with awareness are possible for prevention from thalassemia. Usually, alpha thalassemia carriers do not need treatment. However, carriers of alpha thalassemia can suffer nutritional deficiencies related to homogenesis such as iron deficiency anemia or vitamin B 12 deficiency [17]. On the other hand, the beta-thalassemia carrier's basic clinical manifestation is chronic anemia. However, beta-thalassemia carriers are treated based on their clinical situation: major, intermedia, and minor [18].

The lifetime treatment of thalassemia includes intensive iron chelation medications and blood transfusion, hematopoietic stem-cell transplant, routine laboratory investigations, and recurrent clinical visits for follow-up. However, the challenges and limitations that might interfere with the process of management can obstruct any wanted results. Thalassemia major carriers are usually treated with blood transfusion to treat symptoms of severe anemia and developmental delays [19].

In cases of chronic anemia, iron status should regularly be monitored as it reflects the balance and imbalance of iron and evaluates any signs of iron overload. Iron overload and raised serum ferritin levels are serious problems in thalassemia as well as in other hereditary hemolytic anemias. Iron overload toxicity is associated with increased morbidity rates in both patients with non-transfusion-dependent thalassemia (NTDT) and transfusion-dependent thalassemia (TDT) and several vital organs are affected differently by the underlying condition. Classically, the most prominent and complex clinical complication and has been a major cause of mortality in iron overload is cardiac siderosis. Other endocrine and hepatic dysfunctions are also observed in transfusion-dependent thalassemia [18, 20]. **Table 2** discuss the iron overload complications in both NTDT and TDT [20].

**Table 2.** Iron overload complications in Transfusion dependent thalassemia and Non-dependent transfusion thalassemia [20]

Systems	Transfusion dependent thalassemia	Non- transfusion dependent thalassemia
Cardiovascular	Siderosis left ventricular failure	Pulmonary hypertension, venous thrombosis, right ventricular heart failure
Liver	Liver fibrosis, Viral hepatitis, and cirrhosis	Liver fibrosis, hepatocellular carcinoma, liver cirrhosis
Endocrine	Hypothyroidism Developmental retardation Hypoparathyroidism Osteoporosis Hypogonadism Diabetes mellitus	Osteoporosis
Other		Gallstones Leg ulcers Hematopoietic extramedullary tumors, silent cerebral ischemia

Iron chelation therapy is required in iron overload management after confirming several noninvasive confirmation assessments that involve serum ferritin levels monitoring [20]. The aim of adding iron chelators includes maintaining a safe iron load and removes deposited excess iron loads in the tissues that promote reversal organ failure effects. Three iron chelators are actively used. The first effective oral film-coated Deferasirox tablet is an advanced oral chelator that is well tolerated and is given at 20-30mg/kg once/day [21]. Deferipone tablets also have proven efficacy in removing iron overload from several vital organs mainly the heart [22]. However, Deferoxamine is subcutaneously infused slowly and continuously through a portable pump [23].

Stem cell transplant remains be a preferable choice in some selected cases as it can diminish the probability of the need for blood transfusions [24]. Although stem cell transplant is considered a potential option this

procedure has its challenging risks that include graft failures, immunosuppressive therapy, graft vs host disease, and transplantation-related mortality [25].

Patients with thalassemia can undergo splenectomy and cholecystectomy in many phases as part of the therapeutic process. Splenectomy limits the number of blood transfusions and regresses the spread of extramedullary hematopoiesis [26]. Cholelithiasis can occur in thalassemia after Hemoglobin breakdown and the influence of bilirubin deposition in the gallbladder if it becomes symptomatic patients should undergo cholecystectomy with splenectomy [27].

Follow-up thalassemic patients are asked to monitor the progress of the disease as its recommended to have a clinical visit every month for routine physical and clinical laboratory assessments. Also, a Multisystemic assessment is recommended to be performed every two months up to every 6 months. In Gilbert syndrome patients, it's recommended to perform gallbladder echography to detect cholelithiasis [28, 29].

## CONCLUSION

Thalassemia has been declared a major health issue worldwide. The major pathophysiological change that occurs in thalassemia is the imbalance of the globin chain production. Thalassemia management emerges as a lifetime treatment program that includes intensive medical and surgical care with ongoing monthly clinical visits. However, health professions should carefully review clinical laboratory results especially in cases of chronic anemia where the iron status should regularly be monitored and undergo focused physical examinations for other multisystemic complications and associated thalassemia complications that are suspected.

**ACKNOWLEDGMENTS :** The authors are greatful to all support and guidance they got from their supervisor.

**CONFLICT OF INTEREST :** None

**FINANCIAL SUPPORT :** None

**ETHICS STATEMENT :** None

## REFERENCES

1. Premawardhana AP, Mudiyanse R, De Silva ST, Jiffry N, Nelumdeniya U, de Silva U, et al. A nationwide survey of hospital-based thalassemia patients and standards of care and a preliminary assessment of the national prevention program in Sri Lanka. *PloS one*. 2019;14(8):e0220852.
2. Faller EM, Hernandez MT, Hernandez AM, Gabriel JR. Emerging Roles of Pharmacists in Global Health: An Exploratory Study on their Knowledge, Perception, and Competency. *Arch Pharm Pract*. 2020;11(1):40-6.
3. Ghanatpisheh MA, Amini M, Tabari P, Moosavi M. The effect of game-based learning technique on the knowledge of health-volunteers in 2017. *J Adv Pharm Educ*. 2019;9(2):95-8.
4. Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. *Lancet*. 2018;391(10116):155-67.
5. Motta I, Bou-Fakhredin R, Taher AT, Cappellini MD. Beta Thalassemia: New Therapeutic Options Beyond Transfusion and Iron Chelation. *Drugs*. 2020;80(11):1053-63.
6. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. *Blood*. 2010;115(22):4331-6.
7. Kim S, Tridane A. Thalassemia in the United Arab Emirates: Why it can be prevented but not eradicated. *PLoS One*. 2017;12(1):e0170485.
8. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. *Bull World Health Organ*. 2001;79(8):704-12.
9. Kolnagou A, Kontoghiorghes CN, Kontoghiorghes GJ. Transition of Thalassaemia and Friedreich ataxia from fatal to chronic diseases. *World J Methodol*. 2014;4(4):197-218.
10. Munkongdee T, Chen P, Winichagoon P, Fucharoen S, Paiboonsukwong K. Update in Laboratory Diagnosis of Thalassemia. *Front Mol Biosci*. 2020;7:74.
11. Fucharoen S, Winichagoon P. Haemoglobinopathies in Southeast Asia. *Indian J Med Res*. 2011;134(4):498-506.

12. Ferrão J, Silva M, Gonçalves L, Gomes S, Loureiro P, Coelho A, et al. Widening the spectrum of deletions and molecular mechanisms underlying alpha-thalassemia. *Ann Hematol.* 2017;96(11):1921-9.
13. Russo R, Andolfo I, Manna F, Gambale A, Marra R, Rosato BE, et al. Multi-gene panel testing improves diagnosis and management of patients with hereditary anemias. *Am J Hematol.* 2018;93(5):672-82.
14. Barnhart-Magen G, Gotlib V, Marilus R, Einav Y. Differential diagnostics of Thalassemia Minor by artificial neural networks model. *J Clin Lab Anal.* 2013;27(6):481-6.
15. Lee JS, Cho SI, Park SS, Seong MW. Molecular basis and diagnosis of thalassemia. *Blood Res.* 2021;56(S1):S39-s43.
16. Gosein M, Maharaj P, Balkaransingh P, Banfield R, Greene C, Latchman S, et al. Imaging features of thalassaemia. *Br J Radiol.* 2019;92(1096):20180658.
17. Farashi S, Hartevelde CL. Molecular basis of  $\alpha$ -thalassemia. *Blood Cells Mol Dis.* 2018;70:43-53.
18. Fibach E, Rachmilewitz EA. Pathophysiology and treatment of patients with beta-thalassemia - an update. *F1000Res.* 2017;6:2156.
19. Olivieri NF, Brittenham GM. Management of the thalassemias. *Cold Spring Harb Perspect Med.* 2013;3(6):a011767.
20. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. *Hematol Am Soc Hematol Educ Program.* 2017;2017(1):265-71.
21. Thakor DR, Desai CK, Kapadia JD, Dikshit RK, Mehariya KM. Efficacy and Safety of Deferasirox in Pediatric Patients of Thalassemia at a Tertiary Care Teaching Hospital. *Indian J Med Paediatr Oncol.* 2017;38(2):103-10.
22. Botzenhardt S, Felisi M, Bonifazi D, Del Vecchio GC, Putti MC, Kattamis A, et al. Long-term safety of deferiprone treatment in children from the Mediterranean region with beta-thalassemia major: the DEEP-3 multi-center observational safety study. *Haematologica.* 2018;103(1):e1-e4.
23. Haghpanah S, Zarei T, Zahedi Z, Karimi M. Compliance and satisfaction with deferasirox (Exjade®) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. *Hematology.* 2014;19(4):187-91.
24. Jariwala K, Mishra K, Ghosh K. Comparative study of alloimmunization against red cell antigens in sickle cell disease & thalassaemia major patients on regular red cell transfusion. *Indian J Med Res.* 2019;149(1):34-40.
25. Sarkar SK, Shah MS, Begum M, Yunus AM, Aziz MA, Kabir AL, et al. Red Cell Alloantibodies in Thalassaemia Patients Who Received Ten or More Units of Transfusion. *Mymensingh Med J.* 2019;28(2):364-9.
26. Sharma A, Mathew ME, Puri L. Splenectomy for people with thalassaemia major or intermedia. *Cochrane Database Syst Rev.* 2019;9(9):Cd010517.
27. Pelizzo G, Bussani R, De Silvestri A, Di Mitri M, Rosone G, Amoroso S. Laparoscopic Cholecystectomy for Symptomatic Cholelithiasis in Children: Defining Surgical Timing. *Front Pediatr.* 2020;8:203.
28. Cao A, Galanello R. Beta-thalassemia. *Genet Med.* 2010;12(2):61-76.
29. Needs T, Gonzalez-Mosquera LF, Lynch DT. Beta Thalassemia. *StatPearls.* Treasure Island (FL): StatPearls Publishing, 2020.