



# ThalassemiaNEWS

A quarterly newsletter keeping the medical and patient community in touch with thalassemia developments

Spring 2024

## IN PROFILE

### An in-depth view of an organization or individual involved in thalassemia

In this issue, we bring you excerpts from an interview with Dr. Ali Amid, co-author of 'Guidelines for the Management of Alpha-Thalassaemia', recently published by the Thalassaemia International Federation (TIF)\*.

#### What are some key take-home messages from the new guidelines for healthcare professionals?

- As the underlying molecular etiology of  $\alpha$ -thalassemia is diverse, genetic diagnosis plays a crucial role in its management.
- The pathophysiology of  $\alpha$ -thalassemia differs from  $\beta$ -thalassemia, necessitating a specific approach.
- Deletional hemoglobin H disease has a distinct pathophysiology from the non-deletional forms. Moreover, the underlying disease process in non-deletional HbH disease can vary based on specific mutations, requiring a tailored approach.
- Data on clinical outcomes and quality of life of individuals with different forms of  $\alpha$ -thalassemia is limited, and the majority of patient management is currently based on  $\beta$ -thalassemia.
- While  $\alpha$ -thalassemia major was once considered a lethal condition, more and more patients are surviving with this condition, which may have major impact on health care systems of countries where the disease burden is most common.

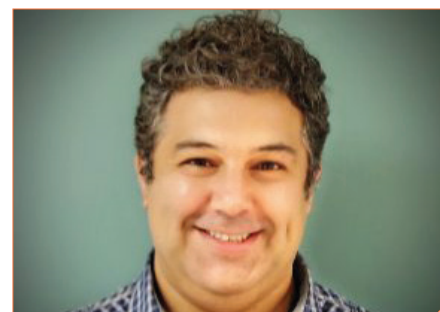
#### What are the priority research gaps in $\alpha$ -thalassemia that need to be addressed?

These can be summarized in 4 categories:

1. The first research priority should focus on addressing the clinical outcomes of deletional HbH disease, which affects

millions of individuals, primarily in Southeast Asia but also worldwide. Questions regarding whether deletional HbH disease is truly a benign condition across all ages remain largely unanswered. Little is known about the outcomes of HbH disease as individuals with this condition age, and there is a scarcity of studies on its impact on quality of life and potential avenues for health improvement.

2. The second priority is to enhance the outcomes of non-deletional HbH disease. Currently, therapeutic options are limited to splenectomy and transfusion (either on-demand or as part of regular transfusion program). However, the optimal approach to each of these treatment options is unknown and again, are largely based on what we practice for  $\beta$ -thalassemia. Although newer disease-modifying treatments may hold promise, dedicated research specifically focused on  $\alpha$ -thalassemia patients, rather than as a small subset within a larger group of  $\beta$ -thalassemia participants, is essential.
3. The third area of interest is the outcomes of patients with  $\alpha$ -thalassemia major. Although rare at present, the number of surviving patients is increasing. It is becoming evident that these patients will experience different complications and require a unique therapeutic approach.
4. Finally, better understanding of the burden of  $\alpha$ -thalassemia, regionally and globally is needed, so that resources can be better allocated and public health policies be better tailored.



Dr. Ali Amid

Division of Pediatric Hematology/Oncology, BC Children's Hospital, Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada,

#### What future steps are needed to ensure prompt clinical management of patients with $\alpha$ -thalassemia?

To enhance the clinical outcomes of patients with  $\alpha$ -thalassemia, several crucial initiatives are necessary:

- Establishing East-West and East-East partnerships among clinicians, healthcare providers, funding agencies, governments, and industry is essential to improve patient outcomes and alleviate the disease burden in resource-limited countries.
- Education, research, and the implementation of evidence-based, cost-effective interventions are imperative.
- High-quality, prospective studies are paramount for better identifying patient outcomes and needs.
- International cooperative registries can address critical questions related to rarer forms of  $\alpha$ -thalassemia.

For more information about the  $\alpha$ -thalassemia guidelines, visit

<https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%CE%B1-thalassaemia/>



\*Agiost provided an independent educational grant as partial support towards the development of these guidelines\*

## IN-DEPTH

### New guidelines for the management of alpha-thalassemia from the Thalassaemia International Federation

Thalassemia has become a global health concern; due to population migration its prevalence is no longer restricted to regions where malaria is endemic<sup>1</sup>. It is a complex disease characterized by a wide range of clinical presentations, and its management is made even more challenging by the rarity of the disorder.

Historically,  $\alpha$ -thalassemia has often been perceived as clinically milder than  $\beta$ -thalassemia. However, a recent systematic literature review reported considerable disease burden among adults with a clinically

significant form of  $\alpha$ -thalassemia, known as hemoglobin H (HbH) disease<sup>2</sup>. Almost a third of patients had moderate-to-severe iron overload (31%), and two-thirds had iron overload of unspecified severity (66%). In addition, one in every 5 patients (20%) had advanced liver fibrosis<sup>2</sup>. There was also a high burden of other clinical complications, including cholelithiasis (28–52%) and osteoporosis (up to 20%)<sup>2</sup>.

Due to the non-specific nature of symptoms, such as fatigue, patients may remain undiagnosed and not be routinely monitored for signs of developing serious comorbidities.

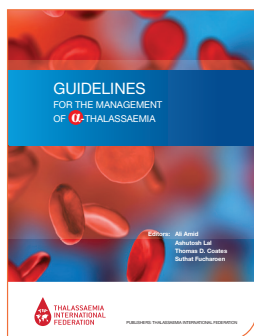
This is a valuable missed opportunity to improve outcomes in  $\alpha$ -thalassemia; a recent retrospective analysis reported a high level of comorbidity among patients with  $\alpha$ -thalassemia as compared to matched controls<sup>3</sup>.

As awareness and understanding of  $\alpha$ -thalassemia have increased in recent years, experts have recognized the value in considering it as a distinct clinical condition that requires specially tailored management considerations.

## Guidelines for the Management of $\alpha$ -thalassaemia

The Thalassaemia International Federation has recently published their first-ever guidelines dedicated to the diagnosis and treatment of  $\alpha$ -thalassaemia<sup>4</sup>.

This comprehensive evidence-based guideline represents a critical step towards improving the management of this disorder and, consequently, the lives of patients worldwide.



### Diagnosis

The guidelines reiterate that accurate diagnosis of  $\alpha$ -thalassaemia requires a range of diagnostic techniques, including complete blood count (CBC) with reticulocyte (immature red blood cell) count, hemolytic panel, hemoglobin analysis, and molecular analysis appropriate to the patient's clinical phenotype, and the prevalence of specific mutations in the region.

Hematologic parameters in conjunction with the presence of hematologic anomalies help determine the subclass of  $\alpha$ -thalassaemia<sup>4</sup>. HbH disease (three non-functional  $\alpha$ -globin genes) is the most common clinically significant form of  $\alpha$ -thalassaemia. Non-deletional mutations of the  $\alpha$ -globin genes tend to be associated with more severe  $\alpha$ -thalassaemia clinical phenotypes than large deletions of  $\alpha$ -globin genes.

### Alpha-thalassaemia treatment and monitoring recommendations

The guidelines emphasize the importance of pre-empting the development of serious disease complications and comorbidities by correcting abnormalities as they arise, often before they have become symptomatic. Monitoring of disease status every 3–6 months according to disease severity is recommended for all patients with  $\alpha$ -thalassaemia. Complete blood count with reticulocyte count, hemolytic markers, serum ferritin and transferrin saturation, and liver enzymes should be measured at every visit. In addition, for pediatric patients, assessments of growth, bone changes, spleen size and pubertal development are also essential at each visit.

### Blood transfusion

Individuals with HbH disease are largely non-transfusion-dependent (NTD), but blood transfusion may be required to restore a patient's hemoglobin to baseline levels after an acute episode. The guidelines stress that a transfusion is not a replacement for appropriate evaluation and treatment of the underlying cause of an acute event, e.g., infection, inflammation, aplasia.

Some patients with more severe forms of the disease will require regular transfusions. The guidelines indicate that a pre-transfusion hemoglobin target of 8–9 g/dL is acceptable for most patients. The criteria for starting regular blood transfusion in individuals with

HbH disease remain to be well defined, and are based on expert opinion. The guidelines present the following as examples where regular transfusions may be indicated for HbH:

- Ongoing decline in effective hemoglobin concentration
- Symptomatic anemia that is detrimental to quality of life
- Risk of long-term sequelae of chronic hemolytic anemia
- Excessive ineffective erythropoiesis
- Frequent acute hemolytic events requiring on-demand transfusions.

Once regular transfusions have been initiated, it is important that the need for regular transfusion is frequently re-assessed, so a patient does not continue receiving regular transfusions unnecessarily.

### Iron overload and chelation

Iron overload control is important as a prophylactic measure against organ damage.

The guidelines recommend that ferritin levels should be measured at each transfusion in patients who are transfusion-dependent or every 6–12 months for patients who are non-transfusion dependent. Liver iron concentration (LIC) should be calculated from magnetic resonance imaging if ferritin levels exceed 300 ng/mL.

When iron accumulation is detected, the guidelines support the introduction of iron chelation agents to combat iron overload and protect against organ toxicity from exposure to reactive ferrous iron. Treatment with an iron chelation agent should be initiated if ferritin levels exceed 500 ng/mL or LIC is >5 mg/g dry weight. Vigilance regarding the potential emergence of side effects from these agents, however, must be maintained.

### Splenectomy

The guidelines highlight the importance of careful consideration before choosing splenectomy. Although removal of the spleen may raise the hemoglobin level, it may not reduce transfusion requirements. Furthermore, splenectomy may give rise to complications such as thrombosis or infection.

Splenectomy should only be considered for patients with HbH disease who have moderately severe anemia, frequent acute hemolytic events, or long-term complications of chronic hemolytic anemia. It is not recommended for children younger than five years of age.

### Organ damage

Liver disease, one of the leading causes of morbidity and mortality among patients with thalassaemia, is often a result of iron overload. If iron overload has occurred (LIC  $\geq$ 5mg/g dry weight or serum ferritin  $\geq$ 500 ng/mL) the liver should be screened annually using transient elastography and ultrasonography for signs of liver fibrosis and cirrhosis.

Patients with  $\alpha$ -thalassaemia are at increased risk of developing endocrine complications, especially if they have iron overload. Regular monitoring of hormone levels is recommended to enable early detection of hypogonadism, hypothyroidism, and diabetes mellitus.

### Infection

Irrespective of transfusion status, patients with  $\alpha$ -thalassaemia are susceptible to various kinds of infection. The risk is further increased after splenectomy.

To facilitate initiation of treatment at the first signs of infection, it is recommended that patients are encouraged to regularly check their body temperature and be made aware of other potential signs of infection in order to enable early recognition.

### Cardiovascular complications

Thalassaemia is associated with a state of hypercoagulability, which can increase the risk of thromboembolic events. This risk is further increased by splenectomy. Patients should be made aware of the signs of potential thrombosis so treatment can be initiated rapidly.

### Bone mineral density

Ineffective erythropoiesis in  $\alpha$ -thalassaemia and the subsequent widening of the marrow space can impact bone health. This can be further impacted by iron overload. A DEXA scan to assess bone density should therefore be performed every 3 years from the age of 12 years to confirm that there is a normal growth rate. Bone mineral density should continue to be monitored regularly to confirm adequate bone strength is maintained.

### Recommendations for the management of Hb Bart's hydrops fetalis

Hb Bart's hydrops fetalis syndrome (also known as  $\alpha$ -thalassaemia major) is the most severe form of  $\alpha$ -thalassaemia<sup>6</sup>. It arises with the deletion of all four  $\alpha$ -globin genes that results in the formation of Hb Bart's from which oxygen release is minimal. The resultant hypoxia, heart failure, and hydrops fetalis is generally fatal. Those that do survive experience severe long-term outcomes and require lifelong blood transfusions and iron chelation treatment.

Intra-uterine fetal blood transfusion given before 28 weeks gestation has been shown to resolve fetal hydrops and reduce the risk for maternal complications. Post-partum, it is recommended that the infant receive packed red blood cell transfusions of 5–10 mL/kg within the first few hours of life to achieve an effective hemoglobin level of 11–12 g/dL. Exchange transfusion may be considered for the treatment of critical illness.

Hb Bart's hydrops fetalis poses a high risk of developmental delay in infants and children, and so continued close developmental screening, especially of neurodevelopmental status, is required. Furthermore, Hb Bart's hydrops fetalis is associated with a higher risk of disease or treatment-related complications than other forms of thalassaemia, and so patients should continue to be monitored closely.

### Curative therapy

Allogeneic hematopoietic stem cell transplantation provides a potential curative option for patients with  $\alpha$ -thalassaemia and is a particularly relevant option for long-term survivors of Hb Bart's hydrops fetalis.



As outcomes of stem cell transplant have improved significantly over the last decade it has become a more viable option for less severe forms of  $\alpha$ -thalassemia. Nonetheless, stem cell transplantation increases a patient's long-term risk of developing infections, cancer and autoimmune conditions and so lifelong monitoring is needed, even though transfusion may no longer be required.

Transplant for thalassaemia should be offered as early as possible as the best outcomes are achieved before iron overload has started to affect organ function.

### Future potential treatments

Developmental treatments from several drug classes, including erythroid maturation agents and pyruvate kinase activators, are currently being evaluated in clinical trials. Preliminary evidence supports their potential use in  $\alpha$ -thalassemia for increasing hemoglobin levels and reducing the need for blood transfusion<sup>7,8</sup>. Phase 3 data are expected for some of these agents within the next few years.

Clinical trials are also evaluating intra-uterine haploidentical hematopoietic stem cell transplant using maternal bone marrow for fetuses with Hb Bart's hydrops fetalis.

### References

1. Weatherall DJ. Thalassaemia as a global health problem: recent progress toward its control in the developing countries. *Ann N Y Acad Sci.* 2010;1202:17–23. doi: 10.1111/j.1749-6632.2010.05546.x;
2. Musallam KM, Lombard L, Gilroy K, Vinals L, Tam C, Rizzo M. Characterizing the Clinical, Health-Related Quality of Life and Economic Burden of Alpha-Thalassaemia: A Systematic Literature Review and Evidence Gaps Assessment. *Blood* (2022) 140 (Supplement 1): 2491–2493. <https://doi.org/10.1182/blood-2022-167125>;
3. Langer AL, Lombard L, Gilroy KS, et al. Poster 2351 Presented at the 64th ASH Annual Meeting and Exposition, December 10–13, 2022, New Orleans, LA, US;
4. Thalassaemia International Federation. Guidelines for the Management of  $\alpha$ -thalassaemia. 2023. Eds. Arnid A, Lal A, Coates TD, Fucharoen S. ISBN 978-9963-717-28-6;
5. Capellini MD, Viprakasit V, Taher AT, Georgiev P, Kuo KHM, Coates T, et al. A phase 3 trial of luspatercept in patients with transfusion-dependent  $\beta$ -thalassaemia. *N Engl J Med.* 2020;382:1219–31.
6. Chui DH. Alpha-thalassaemia: Hb H disease and Hb Barts hydrops fetalis. *Ann N Y Acad Sci.* 2005;1054:25–32. doi: 10.1196/annals.1345.004. PMID: 16339648;
7. Jackson N, Khairullah S, Bee PC. Luspatercept-induced reduction in transfusion requirement in  $\alpha$ -thalassaemia. *EJHaem.* 2020 Jul 9;1(1):297–299. doi: 10.1002/jha2.54. PMID: 35847726; PMCID: PMC9175791;
8. Kuo KHM, Layton DM, Lal A, Al-Samkari H, Bhatia J, Kosinski PA, et al. Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion dependent alpha-thalassaemia or beta-thalassaemia: an open-label, multicentre, phase 2 study. *Lancet.* 2022;400:493–501. doi: 10.1016/s0140-6736(22)01337-x.

### Take home messages

- The presentations and severity of  $\alpha$ -thalassemia vary widely, even among patients with an identical genotype, making its management especially challenging.
  - Hemoglobin Bart's Hydrops Fetalis is the most severe and requires intra-uterine transfusion to enable survival
- Patients with  $\alpha$ -thalassemia are at risk of serious comorbidities and require monitoring to detect worsening anemia and iron overload.
- Current treatment approaches to manage the effects of  $\alpha$ -thalassemia include transfusions, iron chelation, and splenectomy, but each carry the risk of potential adverse effects.
  - The benefits and risks of each management approach must be considered and careful monitoring is required for all
- Thalassaemia can be cured by hematopoietic stem cell transplantation, and success rates with transplantation have improved significantly in recent years. However, lifelong monitoring and follow-up is required for long-term consequences of the procedure and residual symptoms of the disease.
- Novel agents are in development and may potentially provide effective treatment of anemia in patients with  $\alpha$ -thalassemia.

## COMMUNITY RESOURCES

Discover new resources for thalassaemia healthcare providers, patients, and their caregivers

### International Thalassaemia Day – May 8 2024

The theme of 2024's International Thalassaemia Day is:

*Empowering Lives, Embracing Progress: Equitable and Accessible Thalassaemia Treatment for All.*



### Thal Pals Podcasts

The thalassaemia podcasts *Thal Pals: The Alpha Beta Revolution™* aims to facilitate ongoing collaboration between patients, caregivers, and medical experts. The monthly broadcasts feature members of the thalassaemia community from around the world discussing current topics relevant to both  $\alpha$ - and  $\beta$ -thalassaemia.



### Fast Facts

A series of educational booklets and information sheets written by experts for patients, families, and healthcare providers on the key topics of thalassaemia screening,  $\alpha$ -thalassaemia and  $\beta$ -thalassaemia.




### Cases in $\alpha$ -thalassaemia: What is the role of Primary Care?

This Medscape CME program is intended for physicians and nurse practitioners, and uses cases to highlight the important role primary care can play in diagnosing and supporting patients with  $\alpha$ -thalassaemia.



Supported by funding from an independent medical education grant from AGIOS

More information and resources can be found on here. 

Fourteen episodes are available and can be accessed here: 

You can access and download the Fast Facts resources here: 

Visit the website here: 

## KEY DATES

April 3–6, 2024  
American Society of Pediatric Hematology/Oncology (ASPHO)  
Seattle – USA

May 8, 2024  
International Thalassaemia Day  
Thalassaemia International Federation (TIF)

May 16–19, 2024  
TIF Patients & Healthcare Professionals Capacity Building Workshop, Bucharest – Romania

June 13–16, 2024  
European Hematology Association (EHA)  
Madrid – Spain

# CLINICAL RESEARCH UPDATE

Sharing the latest news on clinical research in thalassemia: The Adelphi Thalassemia Disease Specific Programme (DSP)\*

The overall objective of this survey is to capture real-world data to understand current standard of care, patient management, symptomatology, impact of thalassemia on healthcare systems and health-related quality of life, and overall unmet needs for patients with  $\alpha$ - and  $\beta$ -thalassemia.

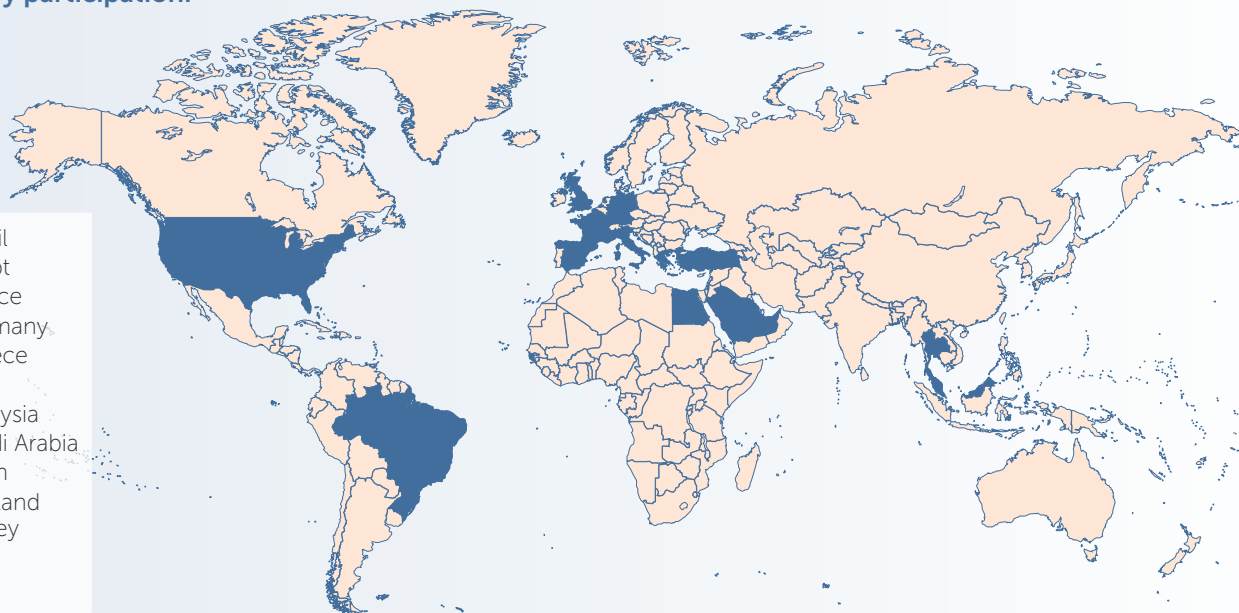
The Adelphi Thalassemia Disease Specific Programme™ (DSP) is an international point-in-time survey of thalassemia-treating physicians and the patients they see. Physicians complete a structured online survey for consecutive patients with  $\alpha$ - or  $\beta$ -thalassemia seen during the survey period. The survey includes data on demographics, clinical characteristics, comorbidities, symptoms/complications, treatment, and healthcare resource utilization. Patients are also invited to complete a patient-reported survey while they are in the doctor's office. Patient-reported outcome assessments such as the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) and the Work Productivity and Activity Impairment (WPAI), and other questions about health-related quality of life, are included<sup>23</sup>.

Inclusion criteria are as follows:

Physician inclusion criteria	Patient inclusion criteria
<ul style="list-style-type: none"><li>• Hematologist or hematologist-oncologist</li><li>• Currently involved in the treatment of patients with thalassemia</li><li>• Currently manages at least one patient with <math>\alpha</math>- or <math>\beta</math>-thalassemia</li><li>• Consented to participate in the study</li></ul>	<ul style="list-style-type: none"><li>• Not currently participating in a mitapivat clinical trial</li><li>• Diagnosed with <math>\alpha</math>- or <math>\beta</math>-thalassemia</li><li>• Adult (ages 18+)</li></ul>

## Country participation:

- Brazil
- Egypt
- France
- Germany
- Greece
- Italy
- Malaysia
- Saudi Arabia
- Spain
- Thailand
- Turkey
- UAE
- UK
- US



The study started recruiting in the US and UK in February 2024, and recruitment is being rolled out across the other countries. Recruitment and data collection is expected to take approximately six months.

Health Care Providers interested in participation can contact Emily King

[emily.king@adelphigroup.com](mailto:emily.king@adelphigroup.com)

\*The Adelphi Thalassemia Disease Specific Programme is owned by Adelphi\*

## EDITORIAL POLICIES & TEAM

The objective of this newsletter is to provide updates on new scientific information, resources, and activities of interest to the thalassemia medical and patient community. The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. All of these experts serve as paid consultants for Agios Pharmaceuticals.

The following experts are involved in this initiative

- Khaled Musallam, MD, PhD
- Thomas Coates, MD
- Ali Taher, MD, PhD
- Kevin Kuo, MD
- Sujit Sheth, MD
- Vip Viprasit, MD, DPhil
- Hanny Al-Samkari, MD
- Maria Dominica Cappellini, MD

Contact:  
[ThalassemiaNews@agios.com](mailto:ThalassemiaNews@agios.com)

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