INVITED COMMENTARY

Management of Thalassemia: Blood and Beyond

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It has been almost a century since cases of thalassemia were reported by Cooley and Lee for the first time globally [1], and over eighty years since they were reported by Mukerjee and Coelho for the first time in India [2,3]. India has come a long way since then in reducing thalassemia-related morbidity and mortality, through collaborative efforts between government bodies, medical institutions and NGOs. Societies run by affected individuals and their parents have played an incredible role in spreading awareness and helping the thalassemia community navigate the medical and psychosocial complexity of adapting to the condition [4]. Numerous novel therapies, diagnostics, and approaches to management – stemming from decades of biomedical research – are on the horizon and hold great promise for improving the status-quo.

Though better management has substantially reduced morbidity and mortality, the consequent increase in life expectancy necessitates multidisciplinary care to mitigate the clinical sequelae of iron overload such as endocrine dysfunction and nutritional deficiencies. A study in this issue conducted by Bhat, et al. [5] suggests that low levels of vitamin C might be very common amongst individuals affected by transfusion-dependent thalassemia. In the study group a large majority of children were found to have vitamin C deficiency, which was in turn found to be associated with iron overload and higher oxidant levels. Supplementation with vitamin C in deficient patients led to a safe reduction of oxidant levels, which suggests that supplementation of vitamin C along with dietary counseling might reduce oxidative stress and thereby protect against myocardial damage. Another study in this issue by Singh and colleagues [6] reported that over a quarter of patients in their study cohort required hormone replacement therapy due to pubertal arrest/failure despite regular transfusions, intensive chelation, and regular follow-up. High systemic iron load was found to be the only statistically correlated determinant of pubertal arrest/failure, signaling the need for further personalization of iron chelation regimes based on genetic susceptibility to higher iron-overload.

Novel treatments such as Hb-F induction therapy and gene therapy are eagerly awaited as they have the potential to reduce the need for frequent blood transfusions and consequent iron overload. The use of hydroxyurea (hydroxycarbamide) has been studied in India [7], where the authors found a mixed response to hydroxyurea in cohorts of thalassemia intermedia and thalassemia major patients. The correlation of certain haplotypes with response to hydroxyurea supported the hypothesis that response was governed by variable genetic mutations, biochemical interactions, and γ/γ globin chain production. In a unique study included in this issue, Chandra and colleagues [8] report that over 75% of transfusion-dependent thalassemia patients in their cohort experienced a significant reduction in transfusion requirement and serum ferritin levels after administration of thalidomide over a 6-month period. Though encouraging, larger studies will be required to establish a safe and effective dosage regime, adverse event profile, drug interactions, and long-term effects of this intervention.

Repurposing drugs such as hydroxyurea and thalidomide might provide an effective way to reduce dependence on blood transfusions and iron chelation therapy; however, purpose-built novel therapies can take this a step further. Luspatercept, the activin II receptor trap, targets ineffective erythropoiesis and thereby decreases transfusion frequency in transfusion-dependent thalassemia patients – other similar therapies undergoing trials include Sotatercept and JAK2 inhibitors [9]. Minihepcidin, Ferroportin and TMPRSS6 inhibitors are promising novel therapies that improve iron dysregulation, especially in non-transfusion-dependent thalassemia patients [9]. In this issue, Soni [10] reviews gene therapy treatment strategies including gene insertion-based lentiviral vectors such as the recently EU-approved Zynteglo, and CRISPR-Cas9 based gene-editing of *BCL11A*, amongst others; these novel therapies will provide a long-awaited alternative to patients who do not have an HLA-matched donor for allogeneic hematopoietic stem cell transplant.

There is a high cost associated with thalassemia management, novel therapies, and allogeneic hematopoietic stem cell transplants, hence reducing the burden of thalassemia will simultaneously necessitate robust and multi-pronged preventive interventions including preconception, prenatal, and newborn screening. India's regional heterogeneity of *HBB* mutations has been studied by Colah, et al. [11] amongst others and has led to the establishment of such programs at various centers in India. It is important that such programs also include appropriate counselling to address fear and stigma associated with being diagnosed as a carrier and enable informed reproductive decision-making amongst high-risk couples [12].

In India, β-thalassemia poses a significant socio-economic burden [13]. The discoveries and innovations covered in this issue have the potential to greatly reduce this burden and improve the quality of life of affected individuals. Simultaneous public health interventions that improve access and adherence will be necessary to tap into this potential. Given India's underdeveloped reimbursement landscape, relatively low healthcare expenditure, and myriad public health priorities, successful implementation of new therapies, management strategies, and prevention programs will require structured and sustained collaboration between stakeholders across healthcare, government, social, and private sectors. All in all, innovative public health interventions coupled with cross-sector collaboration will enable translation of the exciting new research published in this issue and elsewhere into better outcomes for India's large thalassemia community.

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REFERENCES

1. Cooley T, Lee P. A series of cases of splenomegaly in children with anemia and peculiar bone changes. Trans Am Pediatr Soc.1925;37:29-30.
2. Mukherji M. Cooley's anaemia (erythroblastic or Mediterranean anaemia). Indian J Pediatr. 1938;5:1-7.
3. Coelho C. Erythroblastic anemia- Cooley's anemia. Med Bull Bombay. 1939;7:291-3.
4. Moirangthem A, Phadke S. Socio-demographic profile and economic burden of treatment of transfusion dependent thalassemia. Indian J Pediatr. 2018;85:102-7.
5. Bhat KV, Sharma R, Sharma S, et al. Vitamin C deficiency and oxidant levels in children with transfusion-dependent β-thalassemia. Indian Pediatr. 2021;58:631-4.
6. Singh P, Samaddar S, Parakh N, Chandra J, Seth A. Pubertal development and its determinants in adolescents with transfusion-dependent thalassemia.Indian Pediatr. 2021;58:611-6.
7. Italia K, Jijina F, Merchant R, et al. Response to hydroxyurea in β thalassemia major and intermedia: Experience in western India. Clinica Chimica Acta. 2009;407:10-15.
8. Chandra J, Parakh N, Sidharth, et al. Efficacy and safety of thalidomide in patients with transfusion-dependent thalassemia. Indian Pediatr. 2021;58:635-8.
9. Motta I, Bou-Fakhredin R, Taher A, Cappellini M. Beta thalassemia: New therapeutic options beyond transfusion and iron chelation. Drugs. 2020;15:1-11.
10. Soni S. Gene therapies for transfusion-dependent β-thalassemia. Indian Pediatr. 2021;58:667-74.
11. Colah R, Gorakshakar A, Nadkarni A, et al. Regional heterogeneity of beta-thalassemia mutations in the multiethnic Indian population. Blood Cells Mol Dis.2009;42:241-6.
12. Gupta V, Sharma P, Jora R, Amandeep M, Kumar A. Screening for thalassemia carrier status in pregnancy and pre-natal diagnosis. Indian Pediatr. 2015;52:808-9.
13. Verma I, Saxena R, Kohli S. Past, present and future scenario of thalassaemic care and control in India. Indian J Med Res. 2011; 134:507-21.