ABSTRACT BOOK

2023 TIF INTERNATIONAL CONFERENCE
ON THALASSAEMIA & OTHER
HAEMOGLOBINOPATHIES
3-5 NOVEMBER 2023
KUALA LUMPUR, MALAYSIA

MALAYSIAN SOCIETY OF PEDIATRIC HAEMATOLOGY & ONCOLOGY
### Abstract Review Committee

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### Disclaimer Statement

16th International Conference on Thalassaemia & Other Haemoglobinopathies & the 18th TIF International Conference for Patients & Parents. The Committee members have assessed each abstract in relation to its scientific value, sound methodology, results and conclusions. The spelling, grammar and use of English language have not been reviewed.
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Title: Liver-specific Delivery of GalNac-siRNA Targeting TMPRSS6 in combination with deferiprone therapy reduces ineffective erythropoiesis and hepatic iron-overload in a mouse model of β-thalassaemia

Abstract Category: Iron Overload and Management

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Presentation on 04 November 2023, Grand Salon, at 18.15

Abstract

β-Thalassaemia is an inherited blood disorder characterised by ineffective erythropoiesis and anaemia. Consequently, hepcidin expression is reduced resulting in increased iron absorption and primary iron overload. Hepcidin is under the negative control of TMPRSS6 via cleavage of haemojuvelin (HJV), a co-receptor for the BMP-SMAD signalling pathway. Considering the central role of the TMPRSS6/HJV/Hepcidin axis in iron homeostasis, the inhibition of TMPRSS6 expression represents a promising therapeutic strategy to increase hepcidin production and ameliorate anaemia and iron overload in β-thalassaemia. In this study, we investigated RNAi-mediated reduction of TMPRSS6 in β-thalassaemia (Hbbth3/+) mice using a liver-specific delivery with an optimised GalNac-conjugated siRNA targeting TMPRSS6 (SLN124). Two subcutaneous injections of SLN124 (3mg/kg) were sufficient to normalise hepcidin expression and significantly improve red cell indices, as shown by an increase in haematocrit level, and reduction in reticulocyte counts, red cell distribution width and reactive oxygen species (ROS). We also observed a significant improvement in erythroid maturation, which was associated with a significant reduction in splenomegaly. Treatment with the iron chelator deferiprone (DFP) did not impact any of the erythroid parameters. However, the combination of SLN124 with DFP was more effective in reducing hepatic iron overload than either treatment alone. Collectively, we show that SLN124 can ameliorate multiple clinical symptoms associated with chronic anaemia in a mouse model for β-thalassaemia intermediate. The liver-specific reduction of TMPRSS6 expression using SLN124 represents a promising pharmacologic modality for the treatment of β-thalassaemia, and potentially other disorders associated with ineffective erythropoiesis and iron overload.
Title: Diagnostic accuracy of a fully automatic data analysis tool for measurement of liver iron concentration in patients with thalassaemia using MRI in resource poor settings

Abstract Category: Diagnostic and Monitoring Techniques

Authors: 1Tim St Pierre, 2,3Adlette Inati, 4Janet Poole, 5Johnny Mahlangu, 6Ali Taher, 5Nada Sbeia, 7Evelyne Khoriaty, 7Suzan Koussa, 8Therese Abi Nasr, 8Stephanie Muth.

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Presentation on 04 November 2023, Grand Salon, at 18.25

Abstract

Background
Measurement of liver iron concentration (LIC) with MRI is recommended in several guidelines on the management of iron overload in patients with thalassaemia. However, in resource poor settings, the cost of access to the relevant data analysis and data quality control expertise can be prohibitive. We report the results of two studies in Lebanon and South Africa respectively, comparing the results of LIC measurements using the newly available DLA R2-MRI software tool (FerriSmart®) with FerriScan®. The DLA R2-MRI tool provides both input data quality control and fully automated analysis of MR images to provide LIC.

Methods
MR Image data were collected during clinical studies for the purpose of evaluating LIC with FerriScan®. Images were acquired from thalassaemia major patients following curative stem cell transplantation (Lebanon) and from patients with inherited transfusion dependent anaemias (South Africa), the majority with thalassaemia major. Image data were processed by the DLA R2-MRI analysis tool for both input data quality control and evaluation of LIC. LIC results were compared with the FerriScan® values as a reference.

Results
Sixty-eight (68) and 42 image datasets were available from the two studies from a total of 59 patients. The DLA R2-MRI analysis tool rejected six datasets owing to the lack of DOB provided by the radiologist’s input. LIC results were successfully generated for the remaining 104 datasets in both studies, the bias between the fully automated method and the reference method were very small and not statistically significant, with the geometric mean ratio of the automatically produced results to the reference results being 1.00 [95% CI 0.96-1.05] (Lebanon) and 0.96 [95% CI 0.91-1.03] (South Africa). Sensitivities and specificities at four relevant clinical thresholds were mostly above 90%.

Conclusion
The DLA R2-MRI method can enable reliable, low cost, accessible evaluations of LIC from MRI in resource poor settings.
Title: Survey to assess the quality of services available for thalassemia diagnosis and management in India

Abstract Category: Miscellaneous

Authors: Nita Radhakrishnan, Jagdish Chandra, Mamta Manglani, Armita Trehan, Suman Jain, JS Arora, Preeti Malpani, Sujata Sharma, Vineeta Gupta, Chandrasekhar Sharma, Nishant Verma, Shruti Kakkar

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Presentation on 04 November 2023, Grand Salon, at 18.35

Abstract

Introduction
There is no formal mapping of services although India contributes to the maximum number of thalassemia patients globally. The present survey conducted over 10 months, was done to assess facilities available in India.

Methods
A google-form-based survey was shared among members of INPHOG, PHO chapter and non-governmental-organizations working in thalassemia. Services for diagnosis, treatment, prevention and challenges were evaluated. Ethics approval was received.

Results
68 centers participated (government 26, private 28, charitable 14). >85% catered to low-income families. The survey had pan-India presence reporting a total of 11660 patients with maximum centers from Maharashtra (14/68) and New-Delhi (11/68). 75% reported dedicated daycare centers with manpower. 65 offered HPLC for diagnosis. Molecular testing was available in 43 (63%). Serum ferritin and viral markers were available in all. MRI T2* was offered in 34 centers (50%). 60% kept threshold for first transfusion as <7gm/dl and 69% reported further threshold of 9.5-10.5gm/dl. Leukodepleted packed-red-cells were available in 57 centers (84%) which was at-source in 71%. Filters were purchased by the patients in 41% centers. Difficulty in arranging blood donors was reported by 29%. Access to chelation was available in 59 centers (87%). 85% centers followed TIF guidelines for chelation. The first chelating agent was deferasirox in 82%. Desferrioxamine was used in 5-10% of patients. Challenges faced included financial constraints, GI-intolerance and non-compliance. Access to prenatal diagnosis was reported by 42 centers. 33 centers reported provision for allogeneic BMT. On follow-up hypersplenism (46%), growth retardation (60%), iron overload despite chelation (75%) and psychosocial issues (37%) were reported. 43% adolescent and adult patients report anxiety as per treating physician. Multidisciplinary care was available in 62% centers.

Conclusion
Better transfusion and chelation, early BMT referral and prenatal testing were suggestions by these centers. The data provided here is crucial to planning and policy making in India.
Abstract

Background and aims
MSF started a thalassemia unit in March 2018, as part of a pediatric project in Bekaa area in Lebanon, Aiming at reducing morbidity and mortality among the refugees and underprivileged Lebanese pediatric population with the diagnosis of Transfusion Dependent Thalassemia (TDT) and Non -Transfusion Dependent Thalassemia (NTDT). The unit served a total of 138 patients over a period of 5 years, according to a protocol that was derived from TIF guidelines, and adjusted according to the limited resources of the project. The services provided were free, comprehensive and multidisciplinary, including diagnosis, Rh Kell matching blood transfusion, iron chelation medications and specialty consultations like endocrinology and cardiology, in addition to psychosocial support.

Methods
This is a descriptive analysis of the cohort from March 2018 till May 2023, using routine data collected in an excel database. The data collected include demographic data, clinical characteristics, anthropometric details, quantity of blood transfused, pre transfusion hemoglobin levels, immunization status, iron chelation, iron overload monitoring through serum ferritin levels and MRI T2*, and other laboratory and radiological investigations as indicated. The diagnosis was confirmed by hemoglobin electrophoresis and/or genetic studies. Patients with sickle cell disease and other blood diseases requiring transfusions were excluded from the analysis.

Results
A total of 138 patients in the cohort were analyzed, with the diagnosis of TDT and NTDT. The average age of patients upon enrollment was 5.5 years, ranging between 3 months and 14 years. Average pretransfusion hemoglobin over the years was 9.24 g/dl. The patients were receiving Rh Kell Phenotype matching PRBCs transfusions. The blood supply was through the Lebanese Red Cross blood bank where RBC phenotype and antibody screening was performed for all patients, and antibody free compatible blood units were delivered. The average ferritin level for patients upon enrollment was 3900 ng/dl, excluding the 50 patients who were diagnosed in the unit, ranging between 370 ng/dl and 13200 ng/dl. The average ferritin level for the 89 patients upon closure of the project was 2659 ng/dl, ranging from 424 to 6020 ng/dl. Splenectomy was not performed for any of the patients during this period; however, 25 patients were already splenectomized upon enrollment in the cohort. 2 TDT patients who were candidates for splenectomy, were started on Hydroxyurea 15 mg per kg per day, after which their condition improved, and their hematological triggers for splenectomy were reversed. 13 patients tested positive for Hepatitis C serology upon enrollment in the cohort. PCR showed a high viral load for 6 patients; 4 were successfully treated with Daclatasvir and Sofosbuvir for a period of 12 weeks. One patient developed heart failure due to myocardial iron overload and was treated with IV Desferrioxamine and Deferoxamine over a period of 12 weeks, until the cardiac function improved and then shifted to S/C Desferrioxamine and Deferiprone. 2 male and 1 female patients with TDT were successfully treated for delayed puberty at the age of 15 years. The males received low dose testosterone over a period of 6 months, and the female received low dose estrogen, after which puberty was induced. None of the patients had vitamin D deficiency at the end of the project. 58 patients were found to have zinc deficiency for which they received a course of zinc at a dose of 1-2 mg per kg per day over a period of 12 weeks, after which their zinc levels returned back to normal.
Table 1: Cohort Characteristics

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<tr>
<th>Cohort Characteristics (n=138)</th>
<th>Result</th>
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<tr>
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<td>Gender</td>
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<tr>
<td>Male</td>
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<td>Female</td>
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<td>Nationality</td>
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<td>Lebanese</td>
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<td>Syrian</td>
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<td>Iraqi</td>
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<td>Clinical phenotype</td>
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<td>Transfusion Dependent Thalasemia</td>
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<td>Non-Transfusion Dependent Thalasemia</td>
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<td>Diagnosed in the unit</td>
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<td>Splenectomy before enrollment</td>
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<tr>
<td>Splenectomy after enrollment</td>
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<tr>
<td>Hepatitis C infection before enrollment</td>
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<tr>
<td>Transfusion Transmitted infections after enrollment</td>
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<tr>
<td>Delayed puberty requiring induction at age of 15 years</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Zinc deficiency</td>
<td>58</td>
</tr>
</tbody>
</table>

Conclusion

The presence of Hepatitis C infection, high baseline serum ferritin level and complications upon admission to MSF cohort, are reflective of the difficulties in access to safe and affordable treatment among the population served by the unit. Over a period of 5 years, MSF improved the quality of clinical care of thalassemia patients by maintaining a pre-transfusion hemoglobin at an average of 9.2 g/dl, providing access to 3 iron chelators with resultant decrease in the average ferritin level by more than a 1000 ng/dl, treated hepatitis C infection, and treated their endocrine complications, as shown in the results above. Moreover, MSF advocated with UNHCR for the resettlement of these patients and indeed a total of 30 patients with thalassemia were resettled to different countries. 3 have subsequently had successful bone marrow transplants. Further advocacy is required to be able to sustain free, safe, multidisciplinary care for patients with thalassemia.
Title: Prevalence of depression in adult transfusion dependent thalassemia patients in Indonesia: a cross-sectional study

Abstract Category: Psycho-social issues

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Presentation on 04 November 2023, Grand Salon, at 18.55

Abstract

Background
Thalassemia is an inherited blood disorder affecting the hemoglobin (Hb) gene leading to decrease production of Hb. It is a chronic disease which may require lifelong treatment of routine blood transfusion and iron chelation to prevent anemia and iron overload. This requires a lot of effort and resolve. As a result, the patient’s emotional functioning may be impacted by these rigorous activities, leading to depression. Hence, this study seeks to investigate the prevalence of depressive symptoms in adult transfusion-dependent thalassemia (TDT) patients in Indonesia.

Methodology
Using a non-probability convenient sampling method, we included 92 TDT patients aged 18 and over at various thalassemia centers in Jakarta, Bogor, and Bekasi were surveyed. Data on depressive symptoms were collected using a validated questionnaire derived from the SRQ-20 Sijiwa instrument of the Ministry of Health of the Republic of Indonesia.

Results
Our study demonstrated depression symptoms was found among 40.2% TDT patients. Among those with depressive symptoms, 38% had suicidal thoughts. The prevalence was greater in female patients, at 28.2%, as opposed to 11.9% in male patients. Meanwhile, the highest incidence was found in the 21 to 30 years old age group, at 21.7%.

Conclusion
Improving thalassemia treatment regimes increases life expectancy in thalassemia patients. However, at the same time, it has created significant ongoing health care needs, such as regular visits to hospital, which can cause emotional distress leading to depression. Routine screening is needed to identify individuals at risk so as to obtain good psychological support, with the primary goal of improving emotional and physical health so that they can undergo their treatment properly. Going forward, further research investigating causes and risk factors associated with depression symptoms among TDT patients in Indonesia is imperative.

Keyword: thalassemia, depression, mental health, transfusion dependent thalassemia patients
Title: Healthcare resource use and economic burden in patients with alpha- and beta- thalassemia compared to matched controls in the real-world setting

Abstract Category: Non-transfusion dependent thalassaemia

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Presentation on 04 November 2023, Grand Salon, at 19.05

Abstract

Background

There is limited research on healthcare resource use (HCRU) and economic burden of α-thalassemia and non-transfusion-dependent thalassemia (NTDT; α- and β-thalassemia). This study aimed to evaluate HCRU and costs in adult patients with thalassemia versus matched controls.

Methods

Patients with α- or β-thalassemia ICD-9/10 codes from 1/1/2013-6/30/2021 were selected from MarketScan® Commercial/Medicare and Multi-State-Medicaid claims databases in the US. Patients ≥18 years with 12 months follow-up from index date (first α- or β-thalassemia ICD code) to end-of-enrollment, inpatient (IP) death, or study-end were included. Controls without thalassemia or other hemolytic anemias were matched 5:1 to thalassemia cases on age, sex, payer, follow-up time, and race. Patients were stratified by α- and β-thalassemia, and by transfusion-dependent thalassemia (TDT; ≥8 transfusions ≤12 months post-index, each ≤42 days apart) and NTDT. Chi-square and t-tests used for outcome comparison (two-sided α=0.05).

Results

Commercial/Medicare data analysis included 4,183 patients with thalassemia (40.0% α-thalassemia, 60.0% β-thalassemia) and 20,915 matched controls. 99.9% of α-thalassemia and 96.7% of β-thalassemia group had NTDT. Mean (SD) age was 46.1 (14.8) years and 29.7% were males. Compared to matched controls, a significantly higher proportion of patients with α-thalassemia had ≥1 IP admission (19.8% vs 5.6%; p<0.001), ER visit (27.9% vs 17.1%; p<0.001), or outpatient visit (99.5% vs 85.7%; p<0.001), and significantly higher mean (SD) costs ($21,710 [$55,981] vs $8,641 [$26,570]; p<0.001). A significantly higher proportion of patients with NTDT had ≥1 IP admission (20.0% vs 5.7%; p<0.001), ER visit (28.2% vs 17.6%; p<0.001), or outpatient visits (99.5% vs 84.4%, p <0.001), and significantly higher costs ($21,989 [$53,588] vs $8,686 [$28,949]; p<0.001) than matched controls. β-thalassemia, TDT, and Medicaid data [all groups] showed mostly similar trends.

Conclusion

Patients with thalassemia, including those with α-thalassemia and NTDT, had significantly higher HCRU and costs than matched controls and could benefit from additional therapies.
Title: Safety and Efficacy of RM-001 (Autologous HBG1/2 Promoter-modified CD34+ Hematopoietic Stem and Progenitor Cells) in Patients with Transfusion-Dependent β-Thalassemia

Abstract Category: Gene Regulation & Therapy

Authors: 1Rongrong Liu, 2Li Wang, 3Hui Xu, 4Xiaolin Yin, 5Junbin Liang, 1Wenqiang Xie, 7Gaohui Yang, 7Yaoyun Li, 7Yali Zhou, 7Lei Shi, 8Bin Xiao, 1Lingling Shi, 9Zeyan Zhou, 10Jianpei Fang, 11Xiangmin Xu, 12Yongrong Lai, 13Junjiu Huang and 2Xinhua Zhang

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Presentation on 05 November 2023, Grand Ballroom, at 08.00

Abstract

Background
Reactivating fetal globin (HbF) is a promising treatment for β-hemoglobinopathies. Natural mutations in the promoter region of γ-globin genes (HBG1/2) that disrupt the binding of the transcriptional repressors BCL11A could lead to a lifelong persistence of fetal γ-globin expression. Using gene editing to mimic these mutations should reactivate γ-globin in patients with transfusion-dependent β-thalassemia (TDT) and ameliorate the symptoms of patients. RM-001 is a novel cell therapy that uses non-viral, ex vivo CRISPR-Cas9 gene editing in autologous hematopoietic stem and progenitor cells (HSPCs) at the promoter of the γ-globin genes (HBG1/2) to disrupt the binding site of BCL11A.

Aims
ChiCTR2100053406 and ChiCTR2100052858 are ongoing multi-center, first-in-human studies of RM-001 for TDT. Here, we present available safety and efficacy results from 6patients that have been dosed with RM-001 and followed up more than 3 months.

Methods
Patients (6-35 y of age) with TDT receiving packed red blood cell (pRBC) transfusions of ≥100 mL/kg/y or ≥10 units/y in the previous 2ys were eligible. Peripheral CD34+ HSPCs were collected by apheresis after mobilization with G-CSF and plerixafor. CD34+ cells were edited with CRISPR-Cas9 using a guide RNA specific for the binding site of BCL11A on the HBG1/2 promoter. Prior to RM-001 product infusion (day 0), patients received myeloablative conditioning with Busulfan from day-7 to day-3. Patients were monitored for stem cell engraftment/hematopoietic recovery, adverse events (AEs), Hb production, HbF and F-cell expression, and pRBC transfusion requirements. Bone marrow cells were obtained at 3, 6, 12 and 24 months after RM-001 infusion to measure the on-target allelic editing frequency using next-generation sequencing.

Results
Data presented here for 6 TDT patients have been treated with RM-001 and followed up at least 3 months. As of July 31, 2023, patients were followed up from 7 to 20 months and 5 of them have been followed up more than 15 months. Five patients have β0/β0 genotype (CD17/CD41-42, n=1; CD41-42/CD41-42, n=4) and the other has β0/β+ genotype (CD41-42/IVS-II-654). In addition to β-thalassemia (CD41-42/CD41-42), the sixth patient (25yo) also carries two α-globin genes deletion (-- SEA/αα). Patients had received a mean of 56.2 units/y pRBC transfusions (range: 39-79.6 units/y).
All patients received a single dose of RM-001 cells, and achieved both neutrophil and platelet engraftments 2 to 3 weeks after RM-001 infusion (neutrophil: day 11-19, platelet: day 10-22). All patients ceased pRBC transfusions within 1 month after RM-001 infusion and achieved transfusion-independent (TI, total Hb continued ≥ 9 g/dL) within 2 months (Figure). At 4 month post-RM-001 infusion, HbF reached 9 g/dL in all 6 patients and continuously maintained over this level through the reported period. From 6 month post-RM-001 infusion, hemoglobin of all 6 patients consists of HbF (97.6%–99.8%) and Hba2 only, including the fifth patient who has a Bβ/β- genotype (99.5% HbF). Five participants have remained transfusion independent more than 15 months and the mean HbF in the first 4 patients was 11 g/dL (10.9-11.3 g/dL) at 18 month post-RM-001 infusion.

The safety profile was generally consistent with busulfan myeloablation and autologous hematopoietic stem cell transplantation. No RM-001 related SAE report.

Summary/Conclusion
This updated data reported here from 6 patients with TDT infused with RM-001 demonstrated clinically meaningful increases in total hemoglobin (Hb) and HbF levels. All patients stopped receiving pRBC transfusions within 1 month after RM-001 infusion and remained transfusion-free through the time of this analysis. The safety profile of RM-001 is generally consistent with myeloablative conditioning and autologous hematopoietic stem cell transplantation. These results strongly support continued investigation of RM-001 as a potential cure for patients with TDT.

Data will be updated for the presentation.

Submitted on behalf of the RM-001 Investigators.
Title: Coordinated β-globin expression and α2-globin reduction in a multiplex lentiviral gene therapy vector for β-thalassemia

Abstract Category: Gene Regulation & Therapy

Authors: 1,2,5,10 Tiwaporn Nualkaew, 3,4 Karine Sii-Felice, 5 Marie Giorgi, 2 Bradley McColl, 2 Julie Gouzil, 4 Astrid Glaser, 4 Hsiao P.J. Voon, 1 Hsin Y. Tee, 1 George Grigoriadis, 2,7 Saovaros Svasti, 2 Suthat Fucharoen, 8 Suradej Hongeng, 3,9 Philippe Leboulch, 3,6 Emmanuel Payen and 1,5 Jim Vadolas

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Presentation on 05 November 2023, Grand Ballroom, at 08.10

Abstract

A primary challenge in lentiviral gene therapy of β hemoglobinopathies is to maintain low vector copy numbers to avoid genotoxicity, while becoming reliably therapeutic for all genotypes. In an effort to enhance the therapeutic efficacy of lentiviral β globin gene therapy for the most severe β0/β0-genotypes patients, we developed a novel multiplexed lentiviral β globin gene vector that allows for coordinated expression of the therapeutic βA-T87Q-globin gene with concomitant reduction in α-globin chain synthesis. Our approach was guided by the knowledge that moderate reduction of α-globin chain synthesis ameliorates disease severity in β-thalassemia. Here, we modified the LentiGlobin BB305 by inserting a miR-30 shRNA expression cassette into intron 2 of the βA-T87Q-globin gene vector, thus allowing for stable erythroid-specific expression of functional shRNA from a common primary transcript. We further configured the LVβ-shRNA vector to specifically target the human α2 globin mRNA to generate the LVβ-shα2 gene therapy vector. We demonstrate the LVβ-shα2 vector yields equivalent high viral titre, transduction efficiency and erythroid βA-T87Q-globin gene expression to the parent BB305 vector. Notably, the LVβ-shα2 shows the additional property of decreasing human α2 globin mRNA levels without affecting α1-globin mRNA expression levels in transduced human erythroid cell lines and primary human CD34+ hematopoietic cells derived from normal individuals and β thalassemia patients. Importantly, the LVβ-shα2 vector can achieve a greater degree of correction of α/β-globin mRNA ratios in β thalassemic patient cells at identical VCN when compared to the parent BB305. Collectively, we define a novel therapeutic strategy, which could further improve gene therapy outcomes in β thalassemia patients irrespective of genotype.
Title: Efficacy Of Low Dose Vs Standard Dose of Thalidomide in Patients with Transfusion-Dependent Thalassemia (TDT): a non-inferiority trial.

Abstract Category: New Advances in Treatment

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Presentation on 05 November 2023, Grand Ballroom, at 08.20

Abstract

Background
Recent studies have demonstrated encouraging data regarding the efficacy and safety of Thalidomide (TLD) in TDT. However, the optimal dose of TLD is unclear. The study was designed to compare the efficacy of TLD at low-dose (1 mg/kg/d) vs standard-dose (2 mg/kg/d).

Methods
Patients with TDT > 12 years of age with no recent intake of Hb enhancers were enrolled in a non-inferiority trial across 4 sites in India. Patients with hypersplenism, thromboembolism, HIV, active hepatitis B/C infection, or systemic illness, sexually-active females unwilling to use contraceptives/undergo medical termination of pregnancy were excluded. Patients were randomized to receive low-dose or standard-dose TLD for 6 months. Hb, transfusion volumes and frequency, and adverse effects were recorded. The response was graded based on reduction in transfusion requirement at 24 weeks: Good (> 50 %), moderate (25-50 %), or minimal (<25%).

Results:
A total of 188 patients with mean age of 18.1 ± 5.2 years and M:F ratio of 2:1 were enrolled. 85.6% (80 in low-dose, 81 in standard-dose) participants completed the study period. 14.4% discontinued TLD due to various reasons. The mean Hb and baseline transfusion requirement were 8.6 ± 0.98 g/dl and 35.91 ml/kg in the preceding 12 weeks. The overall response rate was 55.9%. Good, moderate, and minimal responses were seen in 19.3%, 36.6 %, and 44.1% of participants respectively. Response in both arms was similar (63% in low-dose vs 48% in standard-dose) (p=0.135) and was unaffected by any baseline parameter. The commonest adverse events were somnolence (n=40), constipation (n=29), weight gain (n=25), reversible cytopenia (n=22), and peripheral neuropathy (n=14). 3.7% of participants experienced Grade 2/3 events.

Conclusions:
Low-dose TLD was as efficacious as the standard dose in reducing transfusion requirements. TLD is well tolerated and can be considered as an adjunct to optimal transfusion-chelation regimen under close monitoring.
Title: Ventricular assist device implantation in a beta-thalassaemia patient with refractory cardiac failure: a case report

Abstract Category: Heart and Vascular Abnormalities

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Presentation on 05 November 2023, Grand Ballroom, at 08.30

Abstract

Background
Mechanical circulatory support with ventricular assist device (VAD) implantation as a bridge to cardiac recovery or transplant is now becoming a reasonable option for refractory heart failure patients. We present a case report of severe iron overload cardiomyopathy who underwent LVAD and RVAD implantation.

Method
The patient, a 34-year-old splenectomized man with transfusion dependent Haemoglobin-E/Beta-thalassaemia, was admitted for acute decompensated heart failure secondary to iron overload cardiomyopathy (left ventricular ejection fraction 20-25%, with cardiac MRI T2*6.06ms). Iron chelation with continuous IV deferoxamine and oral deferiprone was commenced. Despite optimal medical therapy for heart failure (including levomisendan infusion), he remained hypoperfused, manifested by worsening hyperlactatemia, necessitating intra-aortic balloon pump insertion (IABP). Moreover, dobutamine administration induced narrow and wide QRS-complex tachyarrhythmias. Refractory heart failure and dependence on IABP eventually led to providing mechanical circulatory support with implantation of a HeartMate®3 LVAD. Subsequently, a CentriMag®RVAD was inserted as the patient was unable to be weaned off from cardiopulmonary bypass with LVAD alone. Post-operatively, significant clinical events included bleeding necessitating reopening and haemostasis, acute kidney injury needing continuous renal replacement therapy, and hospital-acquired infections. RVAD was successfully explanted by day eleven. He was eventually discharged stable on continued iron chelation.

Results
Iron overload cardiomyopathy remains to be a significant cause of mortality for transfusion dependent thalassaemic patients. Although it is potentially reversible with chelation, iron clearance takes time to effect clinical improvement. Acute cardiac decompensation often heralds imminent demise despite optimal medical management. Our patient benefitted from ventricular assist device implantation and subsequent treatment challenges were overcome by multi-disciplinary collaboration among subspecialists.

Conclusion
This case highlights the feasibility of providing mechanical circulatory support in thalassaemic patients with advanced heart failure as a bridge to recovery.
Title: The Importance of Self-Care in Improving the Health Level of Thalassemia Patients: Our Achievement in Iran

Abstract Category: Quality of Life

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Presentation on 05 November 2023, Grand Ballroom, at 08.40

Abstract

Self-care is a series of conscious and targeted actions to maintain physical, mental and social health. It is vital in prevention, management, and rehabilitation of chronic diseases, which is considered a key component in maintaining health. Continuous training is necessary for self-care and commitment to optimal treatment. Considering that thalassemia is one of the most common genetic diseases in Iran, the need to educate these patients regarding their health care seems worthy. Our experience is based on the capacity of available technologies. Care of different physical and mental aspects was carried out to the followers with text and video training tools on the virtual page. In different stages of needs assessment, introduction of scientific references, question and answer and emphasis on vital and important points were done periodically and information. These cases were answered by the guests in a live interview and by posing questions related to the country’s experts in the field of thalassemia. At the same time as assessing the level of information of the patients, the field of education was provided in the form of questions and answers. Then, a summary of the important points of the topic is shared and republished in the relevant social networks. Various topics include blood transfusion and iron removal treatment, disease complications and prevention methods, quality of life and commitment to treatment, dental care, skin, exercise and nutrition in patients and psychological topics in acceptance of the disease, control of anxiety and dealing with bereavement were covered, which was qualitatively declared very satisfactory by the patients for the patients of deprived areas without access to a specialist doctor.
Title: What does it mean to live with thalassemia: a qualitative study.

Abstract Category: Quality of Life

Authors: Veeresh Pavate, Richard Hovey, Simon Tran

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Presentation on 05 November 2023, Grand Ballroom, at 08.50

Abstract

Background (Purpose)
This in-depth study is part of the doctoral research to gain an understanding of the lived experiences within the Montreal thalassemia community.

Design
Sixteen adult thalassemia patients volunteered and consented for interview who receive their treatment at McGill University Health Centre, Montreal. Open-ended semistructured interviews were audio-recorded then transcribed verbatim into written text and was analyzed by the research team using individual reflection of what was relevant to help answer the research questions.

Method
Qualitative Description (QD) is the methodology of choice when a researcher asks questions and seeks a straightforward and accurate description of human experiences. Findings are analyzed from their narratives using QD for generating insights on a topic with a lack of existing research from a patient’s perspective. These qualitative studies can describe what already exists, determine the frequency with which something occurs, and help to categorize these narratives to inform a specific topic of interest.

Findings
Research participants viewed this qualitative research as a significant step in thalassemia community to address the key concerns of living with thalassemia. Considering the limited awareness of thalassemia in Canada due to its prevalence only in certain ethnic immigrant populations there is lack of research about lived experiences. Notably, the participants reveal that there was a lack of psychosocial support provided in the clinical setup nor offered externally which they felt would have helped them cope with their health issues in a meaningful holistic way.

Conclusion
Findings from this study offered concrete suggestions towards the improvements in thalassemia care. Especially with psychosocial support-oriented programs and health care delivery services. These outcomes will help transcend patient care and offer transferability of findings for the improvement of overall patient care globally. These new findings may extend clinician’s understanding on the impact of thalassemia not only on their patients’ biomedical well-being, but also on their psychosocial health.
Abstract

Introduction
Antibody formation against red blood cells (RBC) is one of the major complication in chronically transfused patients. Red cell antibodies could be against RBC antigens absent in the recipient (alloantibodies) or against recipient’s own RBC antigens (autoantibodies). Antibody formation can result difficulty in provision of compatible blood for the patient. This study aimed to evaluate the frequency of antibody formation against RBCs in chronically transfused patients referred to Adolescent and Adult Thalassaemia Care Unit - Ragama Sri Lanka.

Methods
In this study antibody screening tests were done as a part of pre transfusion compatibility testing for patients transfused in 6 months duration. Antibody identification was performed by 11 cell panel.

Results
In our study female and male patients comprised 138(49.1%) and 135(48.04%), respectively. The mean age is 28.29 years. Our patient population comprises of β Thalassemia major 144 (69.23%), β thalassemia intermedia 14(06.73%), E β Thalassemia 39 (18.75%) and other conditions 9(04.33%). Red cell alloantibodies were formed in 24(8.54%), autoantibodies were formed in 03(1.07%) and auto+ allo antibodies were found in 05 (1.78%). Antibodies against RBCs were not detected in 249(88.61%). 19 (6.76%) patients had formed clinically significant alloantibodies. The commonest antibody type found is Anti E, in 14 patients, followed by Anti K in 07 patients. Total of 19 patients had Rh and Kell antibodies. 8 patients had multiple alloantibodies.

Conclusion
The prevalence of red cell antibody formation among patients treated in Adolescent and Adult Thalassaemia Care Unit - Ragama is comparable with other studies. Since commonest alloantibodies were Rh and Kell, further reduction of red cell antibody formation can be achieved by introduction of Rh and Kell matched red cell provision.
Title: Red blood cell alloimmunization and autoimmunization in transfusion dependent thalassemia: a single centre retrospective review

Abstract Category: Blood Transfusion

Authors: 1Kee Tat Lee, 2Norhaza Abdul Rahim, 1Sui Keat Tan, 1Ai Sim Goh

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Abstract

Background:
Development of alloantibodies and autoantibodies against red blood cell (RBC) antigens remains a major problem in thalassemia patients. These antibodies complicate transfusion therapy and lead to increase need for blood transfusion and its complications. The aim of this study is to evaluate the frequency of red cell alloimmunization and autoimmunization in our adult transfusion dependent thalassemia (TDT) and analyze the factors that possibly affect antibody formation.

Materials and Methods:
A retrospective review of all adult TDT who received treatment in Hospital Pulau Pinang was conducted. Clinical and transfusion records were analyzed.

Results:
A total of 83 adult TDT patients (34 males and 49 females) were included in this study with median age of 30 years old (range 19-60). Majority of TDT in our centre were Malay (63.9%) and followed by Chinese (31.3%) and others (4.8%). Among the TDT, beta thalassemia major (48.2%) are most common, followed by HbE-Beta thalassemia (43.4%) and non-deletional HbH (8.4%). The frequency of RBC alloantibodies was 26.5% (22/83) and autoantibodies was 9.6% (8/83). Of the 22 patients that were positive for alloantibodies, 68.2% had single alloantibody and 31.8% had at least two or more of alloantibodies. A total of 31 alloantibodies were identified and majority were directed against Rh and MNS antigen. Anti-E (41.9%) was the most frequent, followed by anti-S (16.2%) and anti-c (12.9%). Three patients were positive for both autoantibodies and alloantibodies. Twenty-one patients (25.3%) had been splenectomized and sixteen patients had prior pregnancies. However, the alloimmunization incidence was not influenced by age, gender, diagnosis, blood group, history of pregnancy and splenectomy.

Discussion & Conclusion:
Our study demonstrated that antibodies against the Rh and MNS were more frequent among the adult TDT in our centre. The high incidence of alloimmunization in the study population re-emphasizes the importance of RBC antigen typing before first transfusion.
Abstract

Introduction
Hyperhemolysis syndrome is an uncommon but potentially fatal type of delayed hemolytic transfusion reaction characterised by a drop in haemoglobin to below the pre-transfusion levels and reticulocytopenia.

Summary
We report 6 cases of hyperhemolysis syndrome in transfusion dependent beta thalassemia patients at our centre they presented with hemoglobin of 2.3-4.5g/dL 1-2 weeks post transfusion with elevated lactate dehydrogenase levels (LDH), indirect hyperbilirubinemia, low haptoglobin levels and reticulocytopenia cold agglutination was seen on full blood picture in 3 out of these 6 patients Direct antiglobulin test was positive in all these patients with a strong positive IgG in all 6 patients and concomitant C3d positivity in 3 patients antibody identification revealed clinically significant allo-antibodies. Anti-E in 2 patients, Anti-C in 1 patient, Anti-c in 1 patient, Anti-Cw in 2 patients, Anti-K in 1 patient and 1 patient did not have alloantibody identified. These patients were transfused with crossmatch compatible(antigen negative) blood prior to the incidence of hyperhemolysis transfusion was withheld temporarily and they were given IVIG (intravenous immunoglobulin) and methylprednisolone. Most patients responded to these 2 agents. However, 1 patient received Rituximab and mycophenolate mofetil due to ongoing hemolysis, 2 patients had been splenectomised before, 1 patient developed a cerebral venous sinus thrombosis and succumbed.

Discussion
Transfusion of antigen-negative crossmatch compatible RBCs does not prevent hyperhemolysis. Bystander hemolysis, RBC alloimmunization, complement regulation dysfunction, incomplete IgA antibodies and hemolysis due to HLA antigen and antibody reaction by hyperactive macrophages in addition to suppression of erythropoiesis can lead to this syndrome.

Conclusion
Reducing transfusion burden using erythrocyte maturation agent such as Luspatercept, enrollment into a clinical trial or splenectomy in these patients would help to prevent another episode of hyperhemolysis which is life threatening.
Title: Blood transfusions profile among thalassemia patients in thalassemia clinic at Universitas Indonesia Hospital: A descriptive study

Abstract Category: Blood Transfusion

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Abstract

Introduction
Indonesia, located in South-East Asia, falls within the thalassemia belt and experiences a considerable incidence of thalassemia. The treatment for thalassemia in Indonesia primarily involves supportive measures, including blood transfusions and iron chelation therapy. To gain insight into the profile and characteristics of blood transfusions among thalassemia patients in the region, this study aimed to describe the transfusion data obtained from thalassemia patients in our center.

Methods
The present study is a descriptive investigation conducted between November 2021 and June 2023. It involved 51 thalassemia patients who received routine blood transfusions at Thalassemia Clinic UI Hospital, and their medical records were used to collect data. The data encompassed various parameters, including age, sex, occupation, pre-transfusion hemoglobin (Hb) value, post-transfusion Hb increment, and the frequency of transfusions per month for each patient.

Result
The study population comprised 56.86% pediatric patients and 43.14% adult patients, with a higher proportion of male patients (70.59%) compared to female patients (29.41%). Pre-transfusion Hb values were categorized into three groups: 6-8 g/dL (9.8%), 8-9 g/dL (41.18%), and 9-10 g/dL (49.02%). The frequency of transfusions per month was distributed as follows: 5.88% once a week, 39.22% every two weeks, 39.22% every three weeks, and the remaining 15.68%. According to the Indonesian Thalassemia National Guidelines, the target Hb value for pre-transfusion was set between 9-10 g/dL. In this study, 49.01% of patients achieved the target Hb value, while 50.98% did not.

Conclusion
This study reveals that approximately half of the thalassemia patients at our center did not achieve the national hemoglobin pre-transfusion target yet. Further analysis is required to identify strategies to improve the achievement of the pre-transfusion Hb recommendation.

Keywords: thalassemia, blood transfusion, pre-transfusion hemoglobin
Title: Red blood cells alloimmunisation and autoimmunisation among transfusion dependent thalassaemia patients in Hospital Wanita Dan Kanak-Kanak Sabah.

Abstract Category: Blood Transfusion

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Abstract

Background
Thalassaemia is a common autosomal recessive blood disorder in Malaysia and of all the states, Sabah has the greatest number of thalassaemia patients. Transfusion dependent thalassaemia patients are subjected to life-long red blood cells transfusion unless cured by a stem cell transplant. Development of red blood cells alloantibodies and autoantibodies complicate patient management as patients would require more frequent transfusion and additional treatment for the haemolysis. Compatible blood will also be difficult to get.

Methods
Clinical and transfusion records of all transfusion dependent thalassaemia patients registered to our centre from January 2017 to May 2023 were reviewed. We collected data on race, age of first transfusion, total number of transfusions to alloimmunization, type of alloantibodies, interventions and outcome.

Results
Of 343 patients, 29 (8.5%) developed alloantibodies and 50 (14.6%) had red blood cell autoantibody. Of the alloantibodies detected, 20 (69%) belonged to Kidd and 18 (62%) belonged to Rh and 3 from the MNS blood group system. 25 out of 29 (86%) with alloantibodies had autoantibodies as well. Of these patients, 12 (40%) are of Dusun ethnicity, 7 (23.35) are of Kadazan ethnicity. Majority developed alloantibodies after less than 5 transfusions and most of them had their first blood transfusion when they were below 2 years old. Of all the 50 patients with autoantibodies, 23 (46%) had cold antibodies, 20 had mixed antibodies (40%) and 7 (14%) had warm antibodies. All the above patients received phenotyped blood after the development of antibodies. Prednisolone was the main drug used to treat the haemolysis.

Conclusions
In view of the high prevalence of development of alloantibodies in Sabah, there is a need to issue phenotypically matched blood at least for Rh and Kidd antigen from the first transfusion in order to reduce the risk of alloimmunization.
Title: Alloantibodies among chronically transfused thalassemia patients in Sarawak

Abstract Category: Blood Transfusion

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Abstract

Introduction
Thalassaemia is the commonest inherited blood disorder in Malaysia where blood transfusion remains the mainstay of treatment. Sarawak is the largest state in Malaysia with a diverse population formed by 26 ethnic groups living on the island of Borneo, comprising of 40% Dayaks, 24% Malays and 24% Chinese. Thalassaemia patients in Sarawak are provided with phenotyped and filtered packed cells. Despite that, the development of alloantibodies still poses a significant challenge to the management of these patients. This is a multi-centre study aimed to determine the prevalence of RBC alloimmunization and to understand the clinical heterogeneity among Thalassaemia patients in Sarawak.

Methods
Retrospective clinical and transfusion records of regularly (receiving >6 pints of packed cell annually) transfused thalassaemia patients from Jan 2020 to June 2023 were reviewed. Patients that developed alloantibodies were identified and analysed using SPSS version 25.

Results
A total of 115 chronically transfused patients were identified with the mean age of 21.67±11.66 years, 61 (53.0%) were females with a majority from Malay ethnicity (57.4%). Antibodies were identified in 23 patients (20.0%), majority among male patients (84.6%) and Beta thalassaemias. Alloantibodies were identified in 11.3% while autoantibodies were found in 7.0%. The commonest alloantibodies were anti-E followed by suspected anti-Mia. Multivariate analysis showed that male gender remains significantly associated with alloantibodies (OR=5.615 95%CI [1.14-27.72] p-value=0.034). Other factors such as age, ethnicity and number of units transfused were insignificant towards positive alloantibodies development.

Conclusion
The prevalence of alloantibodies among our diverse ethnicity regularly transfused thalassemia patients was 11.3%, which is consistent with various study from different ethnicity background. Although majority of patients on transfusions were female, male patients developed more alloantibodies in our study. The most common antibodies were anti-E and illustrate the need for matched Rh subgroup to avoid alloimmunization during transfusion.
**Title:** The usefulness of reverse dot blot hybridization method for molecular characterisation of haemoglobin E β-thalassaemia - Data from a single thalassaemia reference center in Malaysia

**Abstract Category:** Diagnostic and Monitoring Techniques

**Authors:** Faridah Ahmad Maulana, Norzihan Mohd Tawil, Noraesah Mahmud, Munirah Abdul Razak

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**Abstract**

**Background**

Haemoglobin E β-thalassaemia (HbE β-thalassaemia) is the most common thalassaemia intermedia, particularly in Southeast Asia region including Malaysia. The clinical spectrum of HbE β-thalassaemia is heterogeneous ranging from moderate to severe disease. Genotypically it is divided into HbE β0 thalassemia and HbE β+-thalassaemia, depending on the type of beta mutations or deletions. The reverse dot-blot hybridization method using Hybribio’s Thalassemia Gene Diagnostic Kit -b25MY (Hybribio) is designed to detect simultaneously 25 types of common β-thalassaemia mutations and deletions, including HbE mutation. We evaluate the usefulness of this method in molecular characterization of HbE β-thalassaemia for cases from the Central Zone of Peninsula Malaysia referred to our laboratory for confirmation of the diagnosis.

**Methods**

Cases were retrieved from thalassaemia DNA analysis database, Hospital Kuala Lumpur (HKL) for the years 2021 and 2022. DNA analysis of the beta gene was performed using the Hybribio kit. A few cases were referred to Institute for Medical Research for further DNA analysis of beta gene by Sanger sequencing when the Hybribio assay detected only HbE mutation.

**Results**

A total number of 195 cases were identified, among them 44.6% were males and 55.4% were females. Majority of the cases were found in Malay ethnicity (94.9%). Twelve β-gene mutations were found (excluding Hb E mutation) using the Hybribio kit in 179 cases (91.8%). The most common β-gene mutations identified were IVS1-5 (29.7%), IVS1-1 (G>T) (15.9%), and Codons 41/42 (11.8%). The remaining sixteen cases which only detect HbE mutation by Hybribio, were positive for rare beta mutation.

**Conclusion**

The majority of the β-gene mutations in HbE β-thalassaemia cases in our cases were detected using a Hybribio kit, thus this Method allows rapid diagnosis and cost-effective. The remaining unidentified mutations would require DNA sequencing. However, it only involved a small number of cases for rarer beta gene mutations.
Abstract

Background
Reference intervals (RIs) are important medical decision-making tools that help physicians in differentiating healthy from sick individuals. These intervals vary between age groups. Hemoglobinopathies are prevalent in Pakistan. Quantification of hemoglobin variants is pivotal in screening out hemoglobin disorders. Establishment of RIs using a direct approach is difficult, specifically in children. We chose an indirect data mining method for determination of Hemoglobin A2 RIs in infants.

Method
Hemoglobin A2 measurements performed for all patients aged birth to 1 year between January 2013 and December 2020, were retrieved from laboratory management system of clinical laboratories at the Aga Khan University Hospital. The study population was approximately representative of the entire geographical distribution of the country. Hemoglobin A2 was measured on Bio-Rad Variant™ II analyzer. Reference intervals were computed using an indirect KOSMIC algorithm. The KOSMIC package function on the assumption that the non-pathologic samples follow a Gaussian distribution (after Box-Cox transformation of the data), following an elaborate statistical process to isolate distribution of physiological samples from mixed dataset.

Results
A total of 88,690 specimens were analyzed for HbA2 during the study period. After the exclusion of patients with multiple specimens obtained during the study period, RIs were calculated for 22,713 infants with stratification into 5 age sub-groups. A comparison of our 2.5th and 97.5th percentile results with those of RIs from Mayo Clinic Laboratories Website showed good agreement in between age groups.

Conclusions
This study corroborates data mining as a substitute approach for establishing HbA2 RIs, particularly in resource-constrained settings. The results obtained are specific to studied population, instrument and reagent and allow understanding of the fluctuations in HbA2 synthesis with increasing age. These intervals, hence, will aid in superior clinical decision-making based on HbA2 results.

Keywords: data mining, hemoglobin A2, reference intervals, Pakistan, infants
Title: Beta thalassemia carrier detection in individuals with borderline normal hemoglobin A2 levels

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
Beta-thalassemia is a significant health problem in many countries. Proper management of a patient with transfusion dependent beta thalassemia requires around USD:6000 per annum. Carrier detection is the key to successful prevention of the condition as at-risk couples can be counselled about choice of their partners and probable antenatal screening. Therefore, knowing about grey zone cases is important because it can have great financial and psychosocial impact. Beta-thalassemia carrier state is usually diagnosed by high levels of hemoglobin A2 above the reference range (≥3.5%). A proportion of individuals exist where hemoglobin A2 level might be in grey zone i.e 3.0-3.5%. The correct identification of these carriers is of utmost importance, especially when facing a couple who intends to have children.

Method
The Aga Khan University Clinical Laboratories are the largest network in the country. Samples are received from various cities of the country for analysis. All samples with hemoglobin A2 level in between 3.0-3.5% were included for analysis. Patients were contacted and informed consent was taken for subsequent serum ferritin level and beta gene sequencing. Serum ferritin was performed to exclude cases with suppressed A2 due to iron deficiency. Hemoglobin A2 levels were quantified by High Performance Liquid Chromatography on Biorad Variant II analyzer. Pathogenic mutations confirmed by DNA sequencing in a sample were associated to a phenotype using “Hemoglobin Variant Database” (a database of human hemoglobin variants and thalassemia mutations) at the globin gene server website (http://globin.cse.psu.edu/). Appropriate statistics for categorical and quantitative variables were applied using Statistical Package for Social Sciences.

Results
From July 2022 to May 2023, a total of 72 samples were identified as borderline A2. Twenty-nine were males; 43 were females with Mean ± SD age of 17.5 ± 12.8 years. Mean ± SD HbA2 was 3.23 ± 0.14%. Of these, beta gene sequencing was performed on 45 (62%) samples. Twenty-seven samples were not included either because consent was not given by patient or serum ferritin was low. Of 45 samples included for beta gene sequencing, 12 are still pending or cancelled due to DNA reaction failure. Four of 33 (12%) in which beta gene sequencing was completed were positive for beta gene mutations. Cap +1 mutation was detected in 3 patients whereas 1 sample was positive for IVS-1-5 (G>C).

Conclusion
Borderline A2 levels are not uncommon specifically in populations with high prevalence of beta thalassemia. In this ongoing study, beta chain mutations were detected in 12% of subjects with borderline A2 levels. This finding necessitates investigation of such cases at molecular level to avoid missing at risk individuals.
Title: Molecular genotyping of suspected cases of Alpha thalassaemia: Five-Year experience from the Malaysian Institute for Medical Research (IMR)

Abstract Category: Diagnostic and Monitoring Techniques


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Abstract

Background
Identification of α⁰-thalassaemia carriers is important to prevent the birth of Hb Bart’s hydrop foetalis. In Malaysia, an algorithm for molecular diagnosis of α-thalassaemia is based on the MCH value of 25pg to distinguish between α⁻ and α⁺-thalassaemia. MCH <25pg are coded as D13 and MCH 25-27pg are coded as D16. This study aims to illustrate the distribution of molecular genotypes in both groups.

Method
The clinical and haematological data for D13 and D16 cases referred to IMR from 2017 to 2021 were collected using a computerized record. These data were produced by the hospitals and some of which were tested negative for common α-variant. Record on further molecular analysis done by IMR using multiplex gap-PCR, direct DNA sequencing and MLPA techniques are also retrieved.

Result
A total of 730 D13 and 156 D16 were retrieved. No variant was found in 50.6% (369) of D13 and 55.4% (87) of D16. 12.6% (93) α⁰-thalassaemia was identified in D13 and none in D16. α⁺-thalassaemia was identified in 4.4% (97) and 30.6% (47) cases in D13 and D16. Other findings for D13 include α-globin variant (12.1%, 88), variant of unknown significant (VUS, 4.4%, 32) and β⁺-thalassaemia (3.2%, 23). In D16 group, α-globin variant consisted of 6.4% (10) followed by VUS for 5.1% (8). Hb H, β- and δ-variants were also discovered in 0-1% of the total number of cases in each group.

Conclusion
Our study demonstrated that the cut-off point for MCH value in D13 is needed to be revised. A few studies have shown that a high percentage of α⁰-thalassaemia carriers have MCH <25pg. A local study has proposed 23.5pg as the cut-off point for further testing of α⁰-thalassaemia. Implementation of the lower MCH cut-off value is expected to reduce the workload for DNA analysis while ensuring no individuals for α⁰-thalassaemia be missed in the screening.

Keywords: α⁰-thalassaemia, α⁺-thalassaemia, MCH <25pg, MCH 25-27pg
Title: The prevalence of β-globin gene mutations among thalassemia family members: Early screening for thalassemia genetic traits in urban village populations, Waled, Cirebon, West Java

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
Thalassemia trait family members’ role significantly increases new thalassemia cases, while early detection is still scarce. Identifying the thalassemia genotypes in carriers is one of the practical ways for the succession of genetic counselling for them. This study investigated the prevalence of thalassemia mutations and genotypes in patients’ family members.

Method
A cross-sectional study integrated with society service for community empowerment and early detection of thalassemia trait was performed on 87 subjects who were family members of thalassemia patients registered in Waled Cirebon District General Hospital, Cirebon, West Java. A simple polymerase chain reaction (PCR) applying all exons and introns of the β-globin gene followed by Sanger sequencing was designed and employed to investigate β-thalassaemia patients’ family members.

Results
IVSNT5 +/-, HBE +/-, IVS1NT1(G>A) +/-, and CD35(-C) +/- were the most common mutations in the beta genes, respectively. The frequency of these genotypes was 54%, 18%, 5%, and 2%, respectively.

Conclusion
Thalassemia genetic screening among family members urgently lowers new thalassemia major babies.
Title: The hidden beta thalassemia mutation in hemoglobin fraction analysis: HBB. IVS-II-666 (C>T)

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
Hemoglobinopathy is listed as the 5th disease in Indonesian National Health Insurance. Beta Thalassemia, Indonesian most common Thalassemia type, can be detected from Hb analysis alteration. To identify HBB mutation in Beta Thalassemia, we conducted screening in patients’ family.

Method
Hemoglobinopathy screening study was performed in Yogyakarta in 2022. Subjects were examined for iron status. Normal iron samples were proceed to Hb analysis to determine the hemoglobinopathy types and molecular analysis to identify the genotyping.

Results
The 85 subjects’ results were as follows: 7.06% iron deficiency then excluded from Hb analysis alteration, 12.94% HbE, 31.76% subjects had non-HbE HBB mutation, 7.06% had HBA mutations, 15.29% microcytic/hypochromic with no defect in HBA/HBB then subjected to NGS in next study, while 25.88% subjects showed normal haematology laboratory which were not examined to iron, Hb and molecular analysis. Beta Thalassemia usually showed alteration in Hb analysis. However, heterozygous HBB mutation of IVS-II-666 (C>T) found in this study showed no alteration of Hb analysis, uncommon for Beta Thalassemia mutation. This non-Hb analysis alteration phenomenon might mislead the choice of target gene in molecular analysis into Alpha Thalassemia’s HBA. New diagnosis algorithm of hemoglobinopathy is needed in Indonesia.

Conclusion
IVS-II-666 (C>T) heterozygous of HBB did not show any alteration of Hb analysis. This might mislead the diagnosis into Alpha Thalassemia suspicion.

Keywords: Beta Thalassemia, hemoglobinopathy, mutation, HBB, IVS-II-666 (C>T)
Title: Genetic modifiers contributing to phenotypic heterogeneous of Hb E/β thalassemia.

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
Hb E/ Beta thalassemia disease is the highest transfusion dependent thalassemia patients in Kedah State. HbE/Beta Thalassemia disease is clinically variable. Several genetic modifiers have been reported to play important role in disease severity.

Aim
To determine genetic factors that can predict phenotypic severity of patients with Hb E/β thalassemia diseases and to assess the relationship between the genotype and phenotype of the disease based on the scoring system.

Method
Total of 68 samples were recruited from thalassemia clinic. Data used in this study is retrospectively evaluated. Clinical features were recorded based on scoring system for the classification of β-thalassemia/Hb E disease severity. Hematological analysis were performed. Molecular studies were performed for both alpha and beta globin chain using dot blot and reverse dot blot hybridization, multiplex ARMS PCR. Detection of Gγ-globin gene (158 (C>T) XmnI polymorphism) were performed using Restriction Fragment Length Polymorphism (RFLP).

Results
Based on the scoring system 10% of cases were characterized as mild, 44.5% as moderate and 45.5% severe cases. β+/βE genotype associated with mild disease severity include βIVS1-1/βE, β-28/βE and βIVS1-5/βE. Mixed of β+/β0/βE genotype such as βIVS1-1/βE, β IVS1-5/βE, β CD41/42/βE, β IVS 1-25 bp del /βE, β XmnI-158 (C>T) XmnI polymorphism (C-T), βIVS1-5/βE and βIVS1-1. For XMN1 polymorphism, 97% of the samples shows heterozygous state XmnI -158 Gγ polymorphism (C-T).

Conclusion
This study have showed variety of primary modifiers as compared to the previous study. Co-inheritance of alpha thalassemia or red cell ovalostomatocytosis (SEAO) shows milder and moderate phenotype.
**Title:** Hemoglobin E with co-inheritance alpha thalassemia: HbE level and hematological parameter

**Abstract Category:** Diagnostic and Monitoring Techniques

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**Abstract**

**Background**

Thalassemia is the commonest genetic disorder in Malaysia. Kedah is the third highest state reported to have Transfusion Dependant Thalassemia (TdT) patients. Hemoglobin E (Hb E), β-hemoglobin variant frequently diagnosed in Peninsular Malaysia. We conducted a study to determine optimal cut off Hb E level with and without co-inheritance of alpha thalassemia.

**Methods**

A total of 114 blood samples were collected from January to December 2021. Presumptive diagnosis by Capillary Electrophoresis (CE) of Hb E level of less than 25% were included to exclude co-inheritance alpha thalassemia. Hematological parameter as described in results were retrospectively analysed. Molecular studies of alpha globin chain analysis using multiplex Gap and multiplex ARMS PCR to detect common mutations and deletions.

**Results**

From 117 samples 70 of the samples are characterized as Hb E trait with no common mutation detected. While 27 samples are positive for single gene deletion. Another 13 samples are positive for double gene deletion. Seven samples characterized as Hb E trait with alpha mutations. Hb E with double alpha gene deletions shows low MCV (60.76 to 68.24), MCH (20.10 to 21.90) with Hb E level range from 15.20% to 16.20%. While co-inheritance of Hb E with single gene deletion shows MCV (75.87 to 4.44), MCH(24.30 to 26.70) with with Hb E level range from 21.70 % to 23.30%.

**Conclusion**

This study shows lower cutoff level of Hb E less than 24% by CE can be use for screening samples. However, more samples with variable mutations need to be analysed.
Title: Role of serum ferritin in predicting cardiac and liver iron overload in patients with transfusion dependent thalassemia.

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
MRI T2*, though reliable, is not universally available to patients with TDT in developing countries. Serum ferritin (SF) remains the investigation of choice for diagnosing and monitoring iron overload. The current study was undertaken to assess the correlation of SF with cardiac and liver iron overload.

Material and Methods
A retrospective study was conducted in the thalassemia daycare center. Patient records were reviewed for baseline MRI T2* reports. Demographic details and corresponding SF values were retrieved from the hospital records. SF values were correlated with the cardiac MRI T2* and liver iron concentration (LIC).

Results
A total of 154 patients were included in the study with a mean age of 20.47 ± 6.34 years and M: F ratio of 2.1:1. The mean cardiac MRI T2* for the cohort was 26.07 ± 10.2 ms with mild (10-20ms), moderate (6-10 ms), and severe (<6 ms) cardiac iron overload in 9.6%, 7.0%, and 6.1% patients respectively. The mean LIC was 16.56 ± 10.76 mg/g/dry wt. LIC was classified as mild (3-7), moderate (7-15), and severe(>15) in 11.4%, 29.5%, and 50.5% respectively. SF (ng/ml) was < 1000 in 9.1%, 1000-2500 in 47.4%, and > 2500 in 43.5% of participants. The proportion of patients with cardiac iron overload was 0%, 10.7%, and 40% for serum ferritin <1000,1000-2500 and >2500 ng/ml respectively. The proportion of patients with hepatic iron overload for similar ferritin cut-offs were 71.4%, 87.8%, and 98% respectively.

Conclusion
More than 90% of patients with TDT have hepatic iron overload. Serum ferritin < 1000 ng/ml rules out cardiac iron overload.
Deceptive Phenotypic Manifestation in HbE/Beta Thalassemia with Coinheritance Deletional HbH.

Diagnostic and Monitoring Techniques

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Introduction
Coinheritance of alpha thalassaemia is one of the modifying factors in the clinical phenotype of HbE/beta-thalassemia. The degree of alpha and beta globin chain imbalance can cause variations in disease severity.

Case report
We reported a case of a 20-year-old Malay lady at gravida 2 para 1 at 34 weeks of gestation. She presented to the antenatal clinic with symptoms of anaemia. Physical examination showed unremarkable findings. There was no history of transfusion given. Otherwise, she has no other premorbid medical illness. The values of haemoglobin, RBC count, MCV, MCH, and RDW were 8.7 g/dL, 5.89x10^12/L, 47.8 fL, 14.8 pg, and 23.6%, respectively. Hemoglobin analysis of the patient using capillary electrophoresis showed HbA 8.1%, HbA2 12.3%, and HbF 2.4% with an abnormal peak presence at zone 4 and zone 6 of 76.9% and 0.3% respectively. Haemoglobin quantification using high-performance liquid chromatography showed an HbA2 concentration of 85.7% and HbF of 3.0%. A presumptive diagnosis of Hb E/beta variant was given based on full blood count and Hb analysis findings. Molecular analysis of beta multiplex amplification-refractory mutation system (MARMS) and HBB gene sequencing showed compound heterozygous Hb E with beta plus, IVS 1-5 mutation. Interestingly, alpha multiplex Gap-PCR and alpha multiplex ligation-dependent probe amplification (MLPA) identified the deletional Hb H of compound heterozygous state of (-α3.7) and (--THAI) deletions.

Discussion
Classically, compound heterozygous Hb E/IVS 1-5 presented with moderate to severe thalassaemia phenotype as IVS 1-5 is classified as beta plus severe thalassaemia. The balancing effect of the deletion alpha globin gene has led to distinct hemoglobin analysis parameters and ameliorated the clinical phenotype in this case. This case highlights the important role of comprehensive molecular analysis along with genotype-phenotype correlation in the diagnostic confirmation, hence precise genetic counseling can be given to the patient.

Keywords: HbE/beta, deletional HbH, genotyping, molecular analysis
Title: Identification of the α3.7 deletion by Next-Generation Sequencing Assay

Abstract Category: Diagnostic and Monitoring Techniques


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Abstract

Background
Several types of α-thalassaemia are caused by copy number variants (CNVs), with -α17 deletion being the most common. Next-Generation Sequencing (NGS) technologies have been widely used for the comprehensive diagnosis of CNVs and point mutations of thalassaemia. Yet, detecting CNVs from targeted NGS remains a challenge due to the short-read sequencing platform. This study aims to assess the ability of the NGS-based approach for genotyping of -α17 deletion.

Methods
Thirty-nine cases suspected to have thalassaemia variants by screening tests were recruited. The DNA was extracted and proceeded to gap-PCR and NGS assay. The NGS assay was done using a Devyser kit according to the manufacturer’s protocol and the results were analysed using Amplicon Suit Software. The detection of CNVs was either via direct detection, CNV-aided or CNV-pattern analysis. The results were then compared to gap-PCR findings.

Result
All 39 cases were genotyped as -α17 deletion by gap-PCR analysis. The NGS results were concordant with gap-PCR findings in 37 (94.5%) cases. Of 39 cases, 17 (43.6%) were annotated as -α17 deletion by the CNV-aided method. The CNV events were detected in 19 (48.7%) cases, but no annotation to -α17 deletion was observed. Among these 19 cases, 17 had a CNV pattern of -α17 deletion and two had an otherwise pattern. The remaining three (7.7%) cases were interpreted as unreliable (noise) despite having a discrete pattern of -α17 deletion.

Conclusion
The -α17 deletions were identified via CNV-aided and visual pattern analysis but not through the direct detection method. These results are not trustworthy as the normalisation factors for the two methods are inconsistent and affected when more than 50% of the samples in the same run have -α17 deletion. Due to these limitations, the NGS approach should be used in conjunction with gap-PCR analysis for molecular diagnosis of -α17 deletion.
Title: A rare case of haemoglobin muravera [B47 GAT->GTT, (CD6) ASP->VAL] in a Malay boy

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
Haemoglobin (Hb) Muravera is a rare beta globin chain variant that was first described in the Southern Sardinian family in 2002. We herein report a case which was incidentally detected in a 17 years old Malay boy during a thalassaemia screening programme at school in Putrajaya, Malaysia. He is clinically asymptomatic and healthy.

Method and Result
The full blood count showed normal haemoglobin of 14.2 g/l, with slightly low mean corpuscular volume (MCV) 77.6 fl and mean corpuscular haemoglobin (MCH) 25.4 pg. The red cell count is slightly raised, 5.58 x 106/uL with normal white cell count and platelets. Peripheral smear showed slightly hypochromic and microcytic erythrocytes. The haemoglobin analysis of the proband performed by capillary electrophoresis (CE) revealed presence of HbD at zone 6 with the following results; HbA 61.8%, HbD 35.4% and HbA2 2.8%. Meanwhile, the high performance liquid chromatography (HPLC) showed raised HbA, (36.3%), normal HbF level (0.5%) and HbA level of 54.7%. On cellulose acetate electrophoresis at alkaline pH, prominent band at S/D/G region appeared leading to a preliminary diagnosis to exclude Hb D Iran. However, further confirmatory test using beta sequencing revealed heterozygous codon 47 mutation [GAT->GTT, (CD6) Asp->Val], Hb Muravera.

Conclusion
In recent years, the discovery of haemoglobin variants is increasing in numbers due to advances in diagnostic methods especially through DNA sequencing. Most of these variants are clinically insignificance but a few can cause symptoms such as anaemia and haemolysis. Hb Muravera is slightly unstable haemoglobin resulting from a GAT-GTT mutation at codon 47 of the B globin gene, which predicts an Aspartic acid to Valine amino acid substitution. However, M Corda et al. (2002) reported normal functional studies with normal hemoglobin level despite the mild instability, likely as a consequence of the increased oxygen affinity.

Keywords: Haemoglobin Muravera; Rare variant; DNA sequencing
Title: A population-oriented genetic scoring system to predict phenotype in Iraqi β-thalassemia patients.

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
The heterogeneity of β-thalassemia phenotype has been attributed to several genetic modifiers, which may vary in different populations. Our aim was to investigate the roles of potential modifier genes in Iraqi β-thalassemia patients and to assess whether a population-oriented genetic scoring system could be created to predict phenotype.

Methods
A total of 224 Iraqi patients with homozygous or compound heterozygous β-thalassemia were assessed for α-thalassemia deletions and five polymorphisms at hemoglobin F QTLs (rs7482144 C>T at HBG2; rs1427407 G>T and rs10189857 A>G at BCL11A; rs28384513 A>C and rs9399137 T>C at HMIP) using gap-PCR and StripAssay. The predictive ability of β-globin genotype, concomitant α-thalassemia and each of the five HbF QTLs in relation to phenotype was assessed using SPSS software.

Results
The enrolled patients had a median age of 14 years, with 96 males and 128 females. They included 144 thalassemia major (TM) and 80 thalassemia intermedia (TI) patients. Multivariate logistic regression revealed that a model including four out of the seven presumed genetic modifiers, namely β+ alleles, HBG2 rs7482144, α-thalassemia deletions and BCL11A rs1427407, could significantly predict phenotype (TM versus TI) with an overall prediction accuracy of 83.9%. A cumulative favorable allele score based on these significant predictors had an area under curve of 0.875 (95% CI 0.830-0.919), which was highly significant (P=1.594E-20).

Conclusion
The current study identified four significant genetic predictors of phenotype in Iraqi β-thalassemia patients. Furthermore, the population-oriented cumulative favorable allele scoring system created had a good ability to discriminate between TM and TI. The application of our new scoring system may pave the way to more personalized medicine in these patients.
Title: Vertebral compression fracture and the associated factors in children with thalassemia major

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
Osteoporosis is a common complication and has a multifactorial pathogenesis. Based on the ISCD, the presence of a vertebral compression fracture is a diagnostic criterion for osteoporosis in children.

Methods
A cross-sectional study design using secondary data on a population of children with thalassemia major aged 7-18 years was conducted at Cipto Mangunkusumo Hospital.

Result
This study obtained 115 subjects (54% male, 66% homozygous -β thalassemia) with a mean age was 11 years. The prevalence of vertebral compression fractures was 54.8% with 71.4% of fracture locations in the lumbar region. There were no subjects with fractures who had complaints of pain or a history of previous trauma. Hypovitaminosis D occurred in 82.6% (33.9% deficiency, 48.7% insufficiency) subjects with the median vitamin D level [25(OH)D] was 15.1 (8-36.2) ng/mL. The mean pre-transfusion hemoglobin level was 8.79 ± 0.81 g/dL. The median serum ferritin level was 5018.8 (798.5-38750.3) ng/mL. Severe malnourishment occurred in 12.2% of subjects and moderate malnourishment in 48.7% of subjects. There was no significant relationship between the mean pre-transfusion Hb level, mean serum ferritin, vitamin D, blood calcium, and calcium ion levels on the incidence of vertebral compression fractures. There is a significant relationship between nutritional status and the incidence of vertebral compression fractures.

Conclusion
Plain radiographs of the vertebrae can be used to detect osteoporosis in children with thalassemia major. Risk factors associated with vertebral compression fractures are gender and nutritional status. Further research is needed to look for other risk factors.

Keywords: vertebral compression, osteoporosis, children, thalassemia
Title: Mutation analysis of HBB and BCL11A in β-thalassemia patients at a tertiary hospital in Indonesia

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Introduction
β-Thalassemia is the most common inherited blood disorder caused by mutation in HBB gene resulting in decreased or absent β-globin chains production. This leads to ineffective erythropoiesis, increased hemolysis and disturbed iron homeostasis. The severity level β-Thalassemia is not only related to HBB mutation but also the level of fetal hemoglobin (HhF) which is regulated by genetic modifiers such as polymorphism in BCL11A. This study aims to perform mutation analysis of HBB and BCL11A in β-Thalassemia and observe the effect of BCL11A genetic variant to HbF level.

Methods
Thirty-nine β-Thalassemia patients were enrolled in this study and blood samples were collected consecutively. Hemoglobin electrophoresis was performed for diagnosis purposes. DNA isolation was performed using Quick-DNA Plus Kit (Zymo). Mutation analysis of HBB (all exons and introns) and BCL11A (exons only) were performed using PCR followed by Sanger Sequencing.

Results
The most common genotype of HBB mutation in this population was HBE/IVS1-nt5 (38.5%) followed by homozygous IVS1-nt5 (33.3%). Ten BCL11A mutations were identified in 12 patients (30.7%) and all of the mutations located in exon 4. Seven were missense mutations and 3 were silent mutations. The average HbF level of those with missense mutations were 2.7% while those with silent mutations were 0%.

Conclusion:
HBE/IVS1-nt5 is the most common HBB mutation identified in this population. BCL11A mutations most likely lead to increased HbF level in β-Thalassemia patients.

Keywords: β-Thalassemia, BCL11A, HBB, HbF level
Title: Molecular diagnostics in beta-thalassemia and sickle cell anemia: experience from past to present

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Many gene functions have been identified since the completion of the Human Genome Project, but many more gene functions remain to be unveiled. We are able to study these fascinating complicated connections thanks to the cutting-edge technological tools that have been introduced to the molecular and cell biology settings. Though known as single gene disorders, hemoglobinopathies such as beta-thalassemia and sickle cell anemia are far from being fully resolved in terms of cure, considering the less complex nature of the beta globin gene compared to more complex multi-factorial genetic disorders such as cancer. Currently, beta-thalassemia and sickle cell anemia patients have no effective therapy choices, and it is vitally necessary to gain new knowledge about the etiology of these life-threatening conditions. Population wide education is crucial in parts of the world where hemoglobin disorders are most prevalent. Hemoglobin disorders must be treated and prevented with services that are both affordable and effective. Molecular diagnostic approaches are presented from past to present experiences that illustrate strategies for tackling beta-thalassemia and sickle cell anemia in Cyprus and Turkey. Studies suggest that the best hope for therapeutic development may lie in the discovery of agents that target the physiologic effects of the altered pathways and processes in addition to their individual gene components. Study of gene expression profiling coupled with proteomics may shed further light into the functional aspects and differences between patients.

Key Words: Beta globin gene, beta-thalassemia, hemoglobinopathies, diagnostics, Cyprus.
Title: Correlation of serum ferritin with cardiac and liver iron overload measured by T2*MRI in TDT and NTDT

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Background
MRI for assessing iron overload (IOL) is accepted as the gold standard globally. Despite this, acceptance is limited due to poor access to testing, cost and difficulty in testing young children due to the need for breath holding. We correlated cardiac and liver IOL as determined by MRIT2* with serum ferritin in either transfusion-dependent (TDT) or non-transfusion dependent thalassemia (NTDT).

Methods
Children and young adults followed up at our center for TDT or NTDT who underwent MRIT2* between Jan-June 2023 were evaluated. Patients were receiving chelation as per standard of care using serum ferritin 3 monthly for guiding clinical decisions previously. The MRIT2* was performed at AIIMS, Delhi, where a modified technique of T2* free breathing motion corrected sequence was used. Transfusion and chelation data from patient files were used.

Results
45 patients were evaluated. Median age was 13 years (6-25 years). M:F 1.2:1. 8/14 were NTDT and rest TDT. 2 were E-beta thalassemia and rest were beta thalassemia. 44/45 (97%) patients had evidence of liver IOL (mild-7, moderate-15, severe-22). 10/45 (22%) had myocardial IOL (mild-1, moderate-4, severe-5); all of them had normal cardiac function as per 2D-ECHO. Overall, ferritin values and myocardial T2* values negatively correlated with correlation quotient of -0.51. Out of these, 26 patients showed near zero correlation. The correlation between serum ferritin and liver T2* values was -0.4. Patients with moderate correlation had lower median age and were on higher dose of chelators. Correlation values of serum ferritin with myocardial and liver T2* values in TDT were -0.52 and -0.44 respectively whereas in NTDT they are -0.50 and -0.003 respectively.

Discussion
The prevalence of liver IOL is extremely high when serum ferritin was used alone to guide decisions. The correlation between ferritin and MRIT2* is poor. The correlation is worse for liver IOL and for NTDT.
Title: From uncertain to likely: The impact of an update on variant classification

Abstract Category: Diagnostic and Monitoring Techniques

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Abstract

Introduction
Following the guideline from the American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP) for variant classification, an attempt has been made to reclassify the variants in our institution based on the criteria to support both benignity and pathogenicity. ACMG/AMP guidelines incorporated few criteria’s for variant classification from very strong evidence of pathogenicity to supporting criteria for benign impact.

Objective
We re-analyze the set of variants following the ClinGen Haemoglobinopathy Expert Panel Specification to the ACMG/AMP Variant Interpretation Guideline recommendation to assess the impact in the final classification.

Methods
Variants were detected by HBB, HBA1 and HBA2 gene sequencing data by sanger sequencing. Some of variants have been classified into Variant of Uncertain Significance (VUS) and Likely Pathogenic (LP/Pathogenic (P) variant previously. The variants were classified based on few criteria’s as proposed by the guidelines including population data, computational and predictive analysis, functional criteria, and allelic and co-segregation data using the ClinGen Variant Curation Interface (VCI).

In silico criteria strength was redetermined for all variants according to the following RAVEL score threshold and reclassified accordingly to all the variants.

Results
In this study, re classification of four different mutations in HBB, HBA1 and HBA2 genes may have impact in clinical practice. Two alpha variants have been classified into LB/B variant namely Hb J Singapore CD 79 GCG>GGG [HBA2:c.239C>G] and Hb Singapore CD 141 CGT>CCT [HBA2:c.425G>C]. One HBB gene variant (CD 122 HBA2:c.46_47delinsC ) has been classified into LP/P variant and one Hba1 gene variant classified into LP/P variant. Both CD 122 (TTC>TGC) [HBB:c.368T>G] and CD 15 (-GG, +C) [HBA2.c.46_47delinsC] were novel variant reported in our laboratory. Uniquely, Hb Singapore and Hb J-Singapore were found exclusively among Malay ethnicity with high incident of the variant was found in Kelantan, that located in the north-eastern corner of the peninsula Malaysia.

Discussion/Conclusion
Reclassification of the variant according to specific classes based on updated criteria in ACMG/AMP guidelines is important especially for genetic counselling of individuals and partners where both are carriers so that they are aware of the mode of inheritance, the genetic risk of having affected children, and the natural history of the disease, including treatment, allowing them to make an informed decision about their reproductive choices. Although more evidence is necessary, applying the ClinGen proposal seems promising and may have the impact on overall management of patients with thalassaemia/haemoglobinopathy.

Keywords: ACMG/AMP guidelines for variant classification, benign/likely benign variant, pathogenic/likely pathogenic variant
Title: The hidden beta thalassemia mutation in hemoglobin fraction analysis: HBB. IVS-II-666 (C>T)

Abstract Category: Epidemiology

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Abstract

Background
Hemoglobinopathy is listed as the 5th disease in Indonesian National Health Insurance. Beta Thalassemia, Indonesian most common Thalassemia type, can be detected from Hb analysis alteration. To identify HBB mutation in Beta Thalassemia, we conducted screening in patients’ family.

Method
Hemoglobinopathy screening study was performed in Yogyakarta in 2022. Subjects were examined for iron status. Normal iron samples were proceed to Hb analysis to determine the hemoglobinopathy types and molecular analysis to identify the genotyping.

Results
The 85 subjects’ results were as follows: 7.06% iron deficiency then excluded from Hb analysis, 12.94% HbE, 31.76% subjects had non-HbE HBB mutation, 7.06% had HBA mutations, 15.29% microcytic/hypochromic with no defect in HBA/HBB then subjected to NGS in next study, while 25.88% subjects showed normal haematology laboratory which were not examined to iron, Hb and molecular analysis. Beta Thalassemia usually showed alteration in Hb analysis. However, heterozygous HBB mutation of IVS-II-666 (C>T) found in this study showed no alteration of Hb analysis, uncommon for Beta Thalassemia mutation. This non-Hb analysis alteration phenomenon might mislead the choice of target gene in molecular analysis into Alpha Thalassemia’s HBA. New diagnosis algorithm of hemoglobinopathy is needed in Indonesia.

Conclusion
IVS-II-666 (C>T) heterozygous of HBB did not show any alteration of Hb analysis. This might mislead the diagnosis into Alpha Thalassemia suspicion.

Keywords: Beta Thalassemia, hemoglobinopathy, mutation, HBB, IVS-II-666 (C>T)
Title: Impact of Covid-19 pandemic on transfusion dependant thalassaemia patients of Keningau Hospital, Sabah

Abstract Category: Epidemiology

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Abstract

Objectives:
With the COVID-19 pandemic, the already inadequately transfused thalassaemia patients due to the geographical challenges in Sabah, Malaysia received a severe blow putting their lives at stake during the pandemic. This study aimed to assess the impact of COVID-19 on routine blood transfusion and hospitalization.

Material and Methods:
A single centre retrospective analysis of the transfusion registry of Keningau Hospital Thalassaemia Daycare Unit from March 2019- February 2020 (before COVID-19) and March 2020 to March 2021 (during COVID-19) was done. The sample includes transfusion dependant thalassaemia aged >14 years that was regularly treated in the centre. The dependent variables of this study were records of pre-transfusion haemoglobin level and the number of hospitalization which was analyzed using SPSS version 25.0.

Results:
There was a significant reduction in the mean pre-transfusion haemoglobin level during the COVID-19 pandemic (p-value < 0.001). The mean haemoglobin level before the pandemic was 7.2g/dL and during the pandemic was 6.4g/dL. Out of the 48 patients that we analyzed, there was 2 mortality as a consequence of severe anemia and its related complication. However, there was no death due to COVID-19 infection.

Conclusion:
The COVID-19 pandemic adversely affected the already sub-optimally transfused thalassaemia patients in Keningau. The restricted mobility due to the lockdown and fear of contracting the virus has limited the patient’s access to get a transfusion. The main factor for this was the limited blood supply due to the lack of donation and stringent criteria for donation during the pandemic. The high number of COVID-19 cases also put a strain on the healthcare system and made it difficult to provide optimal care for thalassaemia patients.
Title: Epidemiology and survival outcome of thalassaemia patients in Sarawak, Malaysia

Abstract Category: Epidemiology

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Abstract

Background
Malaysia is among the country with a high prevalence of thalassaemia, an inherited blood disorder. Sarawak accounts for 2.79% of total thalassaemia patients in Malaysia as reported by an earlier study. This retrospective study was conducted to describe the demographics and survival outcome of thalassaemia patients in Sarawak.

Method
Demographic and outcome data collected through the Malaysian Thalassaemia Registry from 2007 to January 2023 were extracted and analyzed using SPSS v29. Descriptive data, multivariate and survival analysis were reported.

Results
A total of 299 thalassaemia patients were recorded in Sarawak as of January 2023. 166 patients were transfusion-dependent thalassaemia (TDT) (55.5%), and 133 were non-transfusion-dependent thalassaemia (NTDT) (44.5%) with beta-thalassaemia (37.5%), HbH (35.5%) and HbE/beta (19.1%) being the commonest type. The current mean age was 24.5 years (±15.7), and the gender distribution was almost equal (ratio 0.99). The majority ethnic groups were Malay (46.2%) and Chinese (35.1%), followed by Iban (8.4%) and Kedayan (4.7%). Kuching district reported the highest population of thalassaemia patients (50.5%), followed by northern districts of Miri, Lawas and Limbang (13%, 7% and 6% respectively). Hypogonadism was the commonest complication observed (7.4%). There were 29 deaths among our thalassaemia population and mainly (55.2%) were due to cardiac complications. Multivariate analysis revealed independent risk factors for death were TDT (HR11.76, 95%CI:4-33, p=<0.001), splenectomy (HR6.69, 95%CI:1.8-24.9, p=0.005) and patients without chelation (HR50, 95%CI:12.2-200). In the TDT cohort, OS at 20 years was 93.9% in the birth cohort after year 2000 compared with 86.7% in the birth cohort before year 2000 (p=0.409).

Conclusion
Demographic and outcome data is important to guide distribution of thalassaemia funding and healthcare improvement in Sarawak. Continuous public education and awareness is imperative to further reduce the incidence of TDTs and NTDTs and their complications.
Title: Mutation spectrum of β-globin gene in patients with β-thalassemia at Dr. R. Goeteng Taroenadibrata Hospital, Purbalingga, Central Java, Indonesia

Abstract Category: Epidemiology

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Abstract

Background
β-thalassemia is a type of hereditary hemolytic disease that occurs due to interference with the synthesis of the β-globin chain that makes up hemoglobin. There are more than 300 mutations of the β-globin gene that have been found and more than 30 variant mutations reported in the thalassemia population in Indonesia. IVSI-5 (G>C) and CD-26 (G>A) are mutations that are frequently found in β-thalassemia patients in Indonesia. This study was conducted with the aim to identify the variant mutations in β-thalassemia patients at RSUD dr. R. Goeteng Taroenadibrata Purbalingga, Central Java, Indonesia.

Methods
Detection of mutations was performed using the Amplification Mutation Refraction System (ARMS) method and inconclusive samples will continue with sequencing analysis.

Results
Results showed that the mutation variants were Cd 26/IVSI-5 32%, Cd 26/IVSI-1 16%, IVSI-5 /IVSI-1 10%, Cd 26/Cd 35 4 %, IVSI-5/CD35 2% and 36 % still require DNA sequencing. The most prevalent alleles would be recommended to be used as part of screening for β-thalassemia in the Javanese ethnicity in Central Java, especially for families affected by thalassemia.

Keywords: Mutation, beta thalassemia, ARMS, Purbalingga.
Title: Beta-thalassaemia major in Sabah: a 15-year mortality study

Abstract Category: Epidemiology

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Abstract

Background
Beta-thalassaemia is one of the commonest inherited disorders in Malaysia. It is characterised by a reduced or absent production of functional beta-globin, which is essential for the formation of adult haemoglobin A (HbA). Located in northern Borneo, the East Malaysian state of Sabah bears the highest burden of thalassaemia cases in the country, with almost two-thirds of thalassaemia patients having transfusion-dependent beta-thalassaemia major.

Method
A retrospective cross-sectional study was conducted on mortality cases of beta-thalassaemia major at Queen Elizabeth Hospital, Sabah, between January 2008 and December 2022. Data was retrieved from local hospital database, clinical case notes, and laboratory reports. Statistical analysis was done using IBM SPSS Statistics version 29.0.

Results
Over a 15-year period, 100 deaths were recorded, with 56% being male and 44% female. The mean age of death was 23.17 years, and 84% of deaths occurred before the age of 30. Among them, the majority were from the Kadazan-Dusun ethnic group (62%), followed by Bajau (13%), Murut (7%), Rungus (7%), Chinese (6%), Malay (3%), and others (2%). Cardiac complications (52%) and infections (31%) were the primary causes of death, followed by thrombosis (4%), malignancy (3%), liver disease (2%), and other causes (8%). The mean (±SD) serum ferritin level was 7698.52 ng/mL (± 5923.23), significantly higher among those who died before the age of 30 compared to those after 30 (8219.86 ± 6141.45 vs 4610.57 ± 3043.05, p < 0.05). Notably, 75% of deaths were observed in individuals with serum ferritin levels exceeding 2500 ng/mL, whereas only 7% had ferritin levels below 1000 ng/mL.

Conclusion
While substantial progress has been made in enhancing life expectancy for thalassemia patients in recent decades, the long-term risk of severe complications, mainly from cardiac events and infections, remains a significant concern. Iron overload is a crucial factor contributing to early death.
Title: The diversity and peculiarity in molecular thalassaemia characteristics among the Sabahan population

Abstract Category: Epidemiology

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Abstract

Introduction
The Malaysian thalassaemia registry (MTR) recorded the highest burden of β-thalassaemia major in Sabah. With the total population of 3.2 million, the number of registered patients from Sabah was 1814 patients (22.72%). The objective of this study is to report the spectrum of β-thalassaemia mutations among Sabah population, focusing on the diversity and peculiarity of the mutations characteristic of an ethnic group.

Materials and Methods
Retrospective analysis of three-year data on the molecular spectrum of thalassaemia among 707 samples of the Sabah population were done. The data was retrieved from Institute for Medical Research (IMR) database from 2019 to 2021. Various molecular techniques were used for α and β-thalassaemia genotyping for Sabah population, including multiplex gap-PCR, multiplex amplification-refractory mutation system (ARMS), direct gene sequencing and multiplex ligation dependent probe amplification (MLPA).

Results
Majority of samples were from Kadazan-Dusun, followed by other indigenous groups and Malay ethnicity that account for 33.7%, 19.2% and 14.9% respectively. Indian population was the minority of the samples analysed (<1%). Uniquely, the spectrum of mutations among Kadazan-Dusun were peculiar to more than 96% consist of large deletion of (β)°-thal, Filipino (NG_000007.3:g.66258_184734del) followed by Poly A [AATAAA>AATAGA] (β+) (NG_000007.3:g.72130A>G) (2.4%) and Codon 26 [GAG>AAG] (βΕ) (NG_000007.3:g.70673G>A) (1.6%). The spectrum of Malays and Chinese ethnicity from East Malaysia were similar to those reported in Peninsular Malaysia. However, few of them carried (β)°-thal, Filipino deletion that was possibly as the result of mixed marriage between indigenous group of Sabah. Hb A2-Deventer δcd 67 [GTG>ATG] was found unique among indigenous group from this area.

Discussion
The knowledge from this study is important for planning of genetic counselling and prenatal diagnosis programs in Sabah population. Apart from that, the effective approach to thalassaemia genotyping in this population should be selected considering the effect of large deletions involved, with peculiar point mutations.

Keywords: (Large deletion of (β)°-thal, Filipino, peculiar mutation, indigenous group)
**Title:** Disease form characteristics of thalassemia patients at the national institute of hematology and blood transfusion for the period 2020 - 2022

**Abstract Category:** Epidemiology

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**Abstract**

**Objectives**

To describe the distribution of Thalassemia patients at the National Institute of Hematology and Blood Transfusion for the period 2020 - 2022.

**Subjects and Methods:**

A cross-sectional study was conducted on 3097 Thalassemia patients treated at the Thalassemia Center, National Institute of Hematology and Blood Transfusion, from January 2020 to March 2022.

**Results**

The β-Thalassaemia/HbE accounted for the highest percentage (55.9%), followed by β-Thalassaemia major and α-Thalassaemia (about 19%), β-Thalassaemia intermedia only accounted for 6.6%. The mean age of β-thalassemia major was the lowest (10 years old). In the group of β-thalassemia major, 100% of the patients were under the age of 30 (57.2% were under 10 years old). The majority of Kinh, Thai and Muong patients were β-Thalassaemia/HbE. Meanwhile, Tay, Nung, Dao, San Diu ethnic patients were mostly β-Thalassaemia major. Among patients with β-Thalassaemia major, the Red River Delta region had the highest mean age (13.3 years old), the North West region had the lowest mean age (8.6 years). SEA and HbCs were the most common mutations in α-thalassaemia patients while Cd17 and Cd41.42 were the most common mutations in β-thalassaemia patients.

**Conclusion**

There were differences in Thalassemia type distributions among ethnic groups and age groups. Patients with β-Thalassaemia major had the lowest age and higher proportion in the Tay, Nung Dao, and San Chay ethnic groups. β-Thalassaemia/HbE had a higher rate in Kinh, Thai, and Muong ethnic groups. SEA, HCs were common mutations in α-Thalassaemia, Cd17 and Cd41.42 were common mutations in β-Thalassaemia patients.
Title: Mutation detection of β and δ globin gene in thalassemia traits using polymerase chain reaction and DNA sequencing

Abstract Category: Epidemiology

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Abstract

Introduction
Thalassemia is an autosomal recessive disease caused by a mutation in human globin genes. All human hemoglobins consist of two different pair of globin chains, the α-like chains (α, ζ) and the β-like chains (β, ε, γ, δ). The thalassemias result from mutations or gene deletions that involve transcription and translation globin chain synthesis. This study aimed to identify molecular basis of three thalassemia traits with decreased HbA2 ratio.

Methods
This study aimed to identify the molecular basis of four thalassemia traits in the β-globin gene that may be coinheritance with a mutation in the δ-globin gene, so have decreased HbA2. Previously, we found no mutation in the α-globin, including the Vanuatuan mutation that results in α-thalassemia. Mutation detection of β and δ-globin genes were done for all genomic DNA samples by amplification and DNA sequencing.

Results
Sequencing analysis of all genomic DNA samples showed polymorphism at codon 2, IVS II nt.16, IVS II nt. 74 and IVS II nt. 81 in β-globin gene. In addition to those common polymorphisms, a silent mutation at codon 131 CAG>CAA (HBB:c.396G>A) heterozygote was found. This mutation did not change the amino acid (Glycine) in the β-globin chain. We detected a missense mutation in the δ-globin gene in one sample at codon 138 GCT>GAT (HBB:c.416C>A). Moreover, we noticed polymorphism at -199 T>C in the 5’-UTR and polymorphism at +1689 C>A in the 3’-UTR found in δ-globin gene of all samples.

Conclusions
Nucleotide substitutions found in β and δ-globin genes were new and had never been reported. Besides, all samples had a polymorphism whose effect on globin gene synthesis is still unknown. We still have to find the molecular basis of the samples that have yet to obtain mutation types by other methods.

Keywords: Thalassemia, Globin Gene, Mutation.

Abstract Category: Fertility and Pregnancy

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Abstract

Background
Tranfusion dependent thalassemia (TDT) patients can have spontaneous reproduction as a result of improvement in their treatment including transfusion and chelation. The objective of this study is to assess the complications and outcome of pregnancies in TDT in our center.

Method
A retrospective study was conducted in Hospital Pulau Pinang with review of all pregnancies in TDT patients and their spouse between 2000 and July 2023.

Results
77% out of 26 married TDT patients (14 females, 6 males) had spontaneous reproduction. Twelve had 1 offspring, five patients had 2 offsprings and three had 3 offsprings with a total of 31 pregnancies. The mean pubertal ferritin was 3776ng/ml (range 1088-7455). The mean age of pregnancy was 26.4 years old (range 17-39). Mean ferritin level was 2258ng/ml (range 442-3937) pre-pregnancy compared to 3065ng/ml (range 1188-4712) after pregnancy. Mean T2* iron burden in the liver was 3.9 ms pre-pregnancy compared to 1.5ms post-delivery. 66.7% of female patients were on deferiprone before pregnancy. The mean maternal haemoglobin was 9.1 g/dl. All patients had live births except for two miscarriages. Mean birth weight was 2.61kg and the mean gestation week was 37.2weeks. There were 5 term intrauterine growth retardation (IUGR) cases (16%) and birth weight ranged from 1.76kg to 2.3kg whilst 3 preterm deliveries (9.7%) including one twin pregnancy had birth weight ranging 1.5kg to 2.3kg. There were no fetal abnormalities or maternal venous thromboembolism.

Conclusion
TDT patients are generally able to conceive and have successful pregnancies. However, the main complications observed were IUGR (16%) and worsening of iron overload. The maternal haemoglobin should be kept above 10g/dl in IUGR cases. It is important to resume chelation therapy after delivery in view of iron accumulation during pregnancy.
Title: In vitro modelling of β0-thalassaemia: a cellular platform enabling experimental and therapeutic investigations

Abstract Category: Gene Regulation and Therapy

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Abstract

The complex pathophysiology of β-haemoglobinopathies, along with the desire to understand the developmental regulation of globin gene expression has driven the generation of several in vitro model systems that closely recapitulate both human erythropoiesis and red blood cell disorders. The immortalised human erythroid progenitor cell line HUDEP-2, which predominantly expresses human adult β-globin, represents a rational target for modelling β haemoglobinopathies. Here, we report the generation and characterisation of an in vitro model of β0 thalassaemia, termed β0-HUDEP-2 cells. Notably, β0 HUDEP-2 cells failed to progress past the polychromatophilic erythroblast stage of erythroid differentiation recapitulating the erythroid differentiation blocked of β thalassaemia. In addition, loss of β globin expression, was associated with increased fetal haemoglobin (HbF) production typifying enriched F-cells production in β thalassaemia. RNA sequencing (RNA-seq) of differentiating β0-HUDEP-2 cells revealed an altered transcriptional program favouring γ globin gene expression. We demonstrate β0 HUDEP-2 cells to be responsive to HbF induction, producing equivalent HbF levels to primary human β thalassaemia cells, whereas the same drugs were less effective in wild-type HUDEP-2 and primary human erythroid cells. Decitabine, pomalidomide and UNC0638 treatments achieved 75-85% HbF production, as measured by high-performance liquid chromatography, and significantly counteracted α-globin accumulation in the membrane fraction. In addition, we show the clinically approved BA-T87Q-globin gene therapy vector (BB305) was sufficient to restore β0 HUDEP-2 erythroid differentiation, adult haemoglobin (HbA) synthesis and survival to wild-type HUDEP-2 levels. Overall, this study demonstrates the β0-HUDEP-2 cell line represents a robust in vitro model system of β0 thalassaemia and is anticipated to facilitate the exploration of alternative therapeutic strategies.
Title: A phase 2a study evaluating the safety and pharmacokinetics (PK) of luspatercept in pediatric patients with transfusion-dependent β-thalassemia (TDT)

Abstract Category: Gene Regulation & Therapy

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Abstract

Background

β-thalassemia causes ineffective erythropoiesis and anemia. TDT patients require lifelong RBC transfusions from early childhood. Luspatercept is approved for treatment of adult TDT patients.

Methods

In this phase 2a study (NCT04143724), eligible patients (N=54) will be 6 to <18 years of age with β-thalassemia, hemoglobin (Hb)E/β-thalassemia, or α-thalassemia/β-thalassemia; require ≥4 red blood cell units/24 weeks before enrollment (no transfusion-free period ≥42 days; regular transfusion history for ≥2 years); have baseline Karnofsky or Lansky performance status score ≥50. Exclusion criteria include HbS/β-thalassemia or HbH disease, prior treatments with erythropoiesis-stimulating agents or hydroxyurea, and transplant/gene therapy.

In Part A of the staggered study, patients 12 to <18 years will receive luspatercept at 0.75 mg/kg (n=6; Cohort 1) or 1.0 mg/kg (n=6; Cohort 2) subcutaneously once Q3W for ≤4 cycles. Expansion cohort (n=30; Cohort 3; patients 12 to <18 years) will receive recommended dose (RD) of luspatercept for ≥1 year. In part B, patients 6 to <12 years will receive luspatercept at 1.0 mg/kg (n=6; Cohort 4) or 1.25 mg/kg (n=6; Cohort 5) subcutaneously Q3W for ≤4 cycles. Patients with clinical benefit may continue treatment for ≤5 years from first dose. Best supportive care is permitted. Primary objectives are determining luspatercept’s safe and tolerable RD and PK in pediatric TDT patients. Key secondary measures include mean changes in transfusion burden, Hb levels, iron chelation therapy dose, and serum ferritin levels. Type, severity, seriousness, and frequency of treatment-related adverse events will be assessed. Exploratory endpoints include exposure-response, health-related quality of life, iron overload markers, and ineffective erythropoiesis assessments.

Results:

The study is currently enrolling. 8/9 sites have been activated and 17 patients enrolled (June 2023).

Conclusion

This phase 2a study will evaluate luspatercept’s safety, PK, and RD in pediatric TDT patients. Recruitment is ongoing. Previously published (Viprakasit V, et al. Blood 2021;138(S1)4161).
Title: The integrated circulating lncRNA-miRNA-mRNA Network in Beta Thalassemia patients; a preliminary report

Abstract Category: Gene Regulation & Therapy

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Abstract

Background
A lncRNA-miRNA-mRNA networks have revealed a mode of RNA interaction and are essential for many biological processes. They could be used as therapeutic targets, prognostic, and diagnostic indicators. This study aimed to identify the lncRNA-miRNA-mRNA network in Beta Thalassemia patients.

Methods
RNA was extracted from the serum samples of Beta-thalassemia patients (major and traits, n=6 each) and healthy controls (n=6). LncRNA expression analysis was performed using Human SurePrint Microarray v3 (Agilent Technologies), and data analysis was performed using the Genespring software v14 (Agilent Technologies). Differentially expressed genes (DEGs) and lncRNAs with p-value < 0.05 from three comparisons were selected: 1) Beta thalassemia major vs. controls, 2) Beta thalassemia trait vs. controls, and 3) Beta thalassemia major vs. trait. Then, lncRNA-miRNA and mRNA-miRNA interactions were predicted using the lncRNA-miRNA-mRNA database (LncBook, RNAcentral, LncBase, LNCipedia, miRNet), and the network was constructed using Cytoscape software.

Results
A total of 1053, 452, and 349 circulating DEGs and lncRNAs were identified in the three comparisons consecutively. Nineteen lncRNAs were significantly different in Traits compared to controls, 34 lncRNAs were different in Major compared to controls, and 94 lncRNAs were different in Major compared to Traits. LncRNA-miRNA-mRNA network was constructed by combining these DEGs and lncRNAs that were shared between the three comparisons consisting of 31 lncRNAs, eight miRNAs, and five mRNAs. A specific analysis identified 21 lncRNAs significantly different in beta-thalassemia individuals with 41/42 beta zero mutation, and one lncRNA, Inc-DNAC8-1, was significantly reduced in all major patients regardless of mutation profiles.

Conclusions
To conclude, we constructed a network of lncRNA-miRNA-mRNA in both beta-thalassemia major and traits and found that the Inc-DNAC8-1 was present in all major patients. This lncRNA could be a biomarker for beta-thalassemia major, and further research on the molecular mechanism is needed to confirm this.

Keywords: thalassemia, lncRNA, network, CD 41/42 mutation, microarray
Title: Retrospective analysis of the paediatric haematopoietic stem cell transplantation outcome in thalassemia patients in Sabah

Abstract Category: Haematopoietic Stem Cell Transplantation (HSCT)

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Abstract

Background and Aims
Haematopoietic stem cell transplant (HSCT) remains the only cure for Thalassaemia. In Sabah, the Malaysian state with over 2000 patients, only 53 patients have been transplanted in various centres. The Paediatric Bone Marrow transplant unit in Sabah Women and Children Hospital (SWACH) started the bone marrow transplant unit since 2014. Our focus is to review the outcome of transplant in thalassaemia patients in SWACH.

Methods
Data was collected for all Thalassemia patients that underwent HSCT from 2014 to September 2023 in Hospital Wanita dan Kanak-Kanak Sabah. Data collection was through review of patient files.

Results
27 patients have had an allogenic HSCT with a matched sibling donor since 2014. Mean age was 6.9 (range 3-10) years old. 16 out of 27 patients were male. Dusun ethnicity represent most of our transplant candidates. All patients are B thalassemia major requiring regular monthly transfusion. Their mean pre transplant Haemoglobin was 8.3g/dL. 85% of the patients were PESARO Class II while the remaining patients were PESARO Class III. Mean time to neutrophil engraftment was 14 days (range 10-21). Platelet recovery was 17 days (range 14-21). The most common complication post-transplant was infection followed by Veno-occlusive disorder. Chronic GVHD occurred in 16%. One patient (Pesaro III) passed away post-transplant due to severe infection with hypoxic ischemic.

Conclusion
The overall good outcome for patients in PESARO II who underwent hematopoietic transplant shows the importance of this service in the region.
Title: Evaluation of a national thalassemia major allogeneic hematopoietic cell transplant program in India

Abstract Category: Haematopoietic Stem Cell Transplantation (HSCT)

Authors: 1Biju George, 2Rohan Haldar, 3Sunil Bhat, 4Santanu Sen, 4Joseph John, 5Manoranjan Mohapatra, 6Soniya Nityanandan, 7Alka Khadwal, 8Rajesh Patil, 9Aby Abraham, 9Niharika Bhatia, 10Pooja Mallya, 11Kavitha M. Lakshmi, 12Sandeep Jain, 12Narendra Agarwal, 13Shobha Tuli, 13Vishal Chauhan, 13Vikram Mathews

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Abstract

Allogeneic hematopoietic cell transplant (allo-HCT) remains the only widely available curative option for Thalassemia major (TM). However, it is still inaccessible for most patients in India, mainly due to the high cost of this procedure. Ministry of Health and Family Welfare (MoHFW), India, developed a program funded by Coal India Ltd (CIL) as part of its Corporate Social Responsibility (CSR) program coordinated by Thalassemics India (TI). TM patients who had either a fully matched HLA sibling/related (MSD/MRD) or a matched unrelated donor (MUD). The individual centers (n=10) were given INR 1,000,000 / case (US$12,000) to cover the cost. From April 2017 to June 2023, 334 approved cases underwent an allo-HCT. The median age of the patients was 7 years (range: 1 - 12), and there were 224 (66.2%) males. 167 (50%) received a Busulfan-based conditioning, while 167 (50%) received a Treosulfan-based conditioning regimen. The stem cell donor was an MSD 284 (85.0%), MRD 38 (11.4%), or a MUD in 12 (3.6%). The stem cell source was bone marrow in 140 (41.9%) and a PBSC graft in 192 (57.5%). Primary engraftment happened in 327 (97.9%) with a median time to neutrophil engraftment of 15 days (range: 7-37). Day 28 chimerism study was available in 321, and among these, 88% were complete chimerism. Acute GVHD Grade III/IV occurred in 30 (9%) and chronic extensive GVHD in 12 (4.4%) of evaluable cases. At a median follow-up of 24 months, the 2-year KM thalassemia-free survival was 86.1±2.0%, and the 2-year KM overall survival was 90±1.8%. This program is an illustration of the potential of public and private partnerships involving the government of India (MoHFW), a company (CIL), and an NGO (TI) to run an efficient and effective one-time curative therapy for Thalassemia major and potentially other rare diseases in a LMIC.
Title: Cholelithiasis in teenage girl with hemoglobin E - β thalassemia: a case report

Abstract Category: Hepatological Complications

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Abstract

Background

Complications of cholelithiasis are more common in thalassemia intermedia than in thalassemia major due to the ineffectiveness of erythropoiesis and the occurrence of peripheral hemolysis. The interaction of HbE and β-thalassemia results in thalassemia phenotypes ranging from a condition thalassemia major to mild form thalassemia intermedia.

Case

A thirteen-years old girl presented to the emergency unit with nausea and fatigue. She had intermittent abdominal pain in the right upper quadrant region. She had been hospitalized with similar complaints 1 month before admission. Her family history was not significant for any blood related disorder or any genetic disease. On physical examination, the patient looked pale and jaundiced. Both of her extremities looked pale and yellow-tinged fingertips. There was spleen enlargement but there was no hepatomegaly. She was undernourished and short stature. Laboratory findings showed moderate anaemia with Hb 8.3 g/dl, Ht 26.3%, MCH 21.4 pg, MCV 68 fl, reticulocyte 2.10%, ferritin 615.1 ug/L, ALT 33 u/L, AST 9 u/L, and total bilirubin, direct bilirubin, indirect bilirubin level was 3.57 mg/dL, 0.55 mg/dL, 3.02 mg/dL respectively. Electrophoresis examination revealed Hemoglobin E - βThalassemia, HbA, HbA2, HbF, and HbE levels 56.7%, 4.2%, 12.8%, and 26.3%. Abdominal ultrasound revealed hepatosplenomegaly with homogenous parenchyma, multiple cholecystolithiasis (± 0.8 cm). She then consulted to pediatric surgery department to undergo cholecystectomy procedure.

Conclusion

In patients with thalassemia intermedia prevalence of cholelithiasis is elevated, then the gallbladder should be routinely inspected and considered to remove if there are gallstones in symptomatic patients.

Keywords: Cholelithiasis, Hemoglobin E, Thalassemia Beta
Title: Adult beta thalassemia patients with hepatocellular carcinoma in a tertiary centre in Malaysia: risk factors and outcome

Abstract Category: Hepatological Complications

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Abstract

Background
Advancement in the clinical management of thalassemia patients has led to longer survival. There is now an increase in incidence of adult thalassemia patients with hepatocellular carcinoma (HCC) globally. Etiologies of development of HCC in thalassemia patients include liver iron overload, viral hepatitis B and C and liver cirrhosis.

Method
We report a case series of four adult beta thalassemia patients diagnosed with HCC from 2012- March 2023 reviewing their demographics, clinical characteristics, and risk factors for development of HCC, laboratory investigations and radiological findings, mode of therapies given and clinical outcome. The data was retrieved retrospectively from their medical records.

Results
The median age of HCC diagnosis was 39.5 years (Range: 26-47 years). Two had beta thalassemia major and the other two were beta thalassemia intermedia. Three patients had history of viral hepatitis which were treated, and one had previous exposure but cleared spontaneously. One patient had liver cirrhosis. All patients were well chelated with median serum ferritin 570ug/L (Range 334-1015ug/L). MRI T2* showed absent liver/ cardiac iron overload for three patients and one had light liver iron overload. Serum alpha fetoprotein at HCC diagnosis was normal for three patients and one had elevated levels. Three patients diagnosed at early stage of HCC successfully underwent hepatoma resection and are alive to date, whereas the only patient diagnosed at advanced stage with liver failure has succumbed.

Conclusion
Risk factors for adult beta thalassemia patients to develop HCC are often overlapping, predominantly due to viral hepatitis and iron overload. Because of this, the age of onset for HCC is shifted to a much younger age group when compared to the general population. Active surveillance should be done for adult thalassemia patients with any risk factors for HCC and those with liver cirrhosis should be done at closer intervals.

Keywords: thalassemia, hepatocellular carcinoma, iron overload, viral hepatitis
Title: Multiple cholelithiasis and pancreatitis in adolescent girls with thalassemia: case reports

Abstract Category: Hepatological Complications

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Abstract

Background
Cholelithiasis is one of the most common complications of Thalassemia. The pathophysiology is multifactorial, with the precipitation of bilirubin due to hemolysis as the main contributing factor and involvement of iron deposition within the gallbladder. Diagnosis can be made through abdominal ultrasound, and cholecystectomy is the treatment of choice. Pancreatitis related to gallstones also is common.

Case 1
A 14-year-old girl diagnosed with β-thalassemia major who regularly received blood transfusions. She presented with worsened abdominal pain and recurrent vomiting over three months. The patient exhibited a distended abdomen with a positive Murphy sign. Laboratory tests revealed elevated total bilirubin levels (5.59 mg/dl) and ferritin levels (4500 ng/ml). Abdominal ultrasound and MRCP revealed multiple cholelithiasis with a dilated common biliary duct and distal stricture due to passing stones. An endoscopic sphincterotomy (EST) procedure was performed through Endoscopic Retrograde Cholangiopancreatography (ERCP). Although clinical symptoms improved after EST, she experienced post-ERCP pancreatitis, which resolved with conservative treatment. Subsequently, the patient underwent cholecystectomy through a laparoscopy procedure one month later.

Case 2
A 12-year-old girl diagnosed with β HbE thalassemia was admitted to the hospital with severe abdominal pain. Laboratory tests showed increased amylase and lipase enzymes, indicating pancreatitis, with total bilirubin levels at 2 mg/dl and ferritin levels at 13,367 ng/ml. Abdominal ultrasound revealed multiple cholelithiasis, and MRCP confirmed necrotizing pancreatitis in association with gallstones. An ERCP procedure was performed.

Conclusion
Cholelithiasis and pancreatitis are significant complications in thalassemia patients, adversely affecting their quality of life and posing potential fatal risks. Awareness of the symptoms and timely diagnosis is important. Medical treatment and surgical intervention are effective to improve a patient’s condition.

Keywords: Cholelithiasis, Pancreatitis, Thalassemia
Title: Treatment of Hepatitis C among children with Beta thalassemia major: The MSF Experience in Lebanon

Abstract Category: Hepatological Complications

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Abstract

MSF France ran a one- day thalassemia unit in Bekaa Valley in Lebanon targeting vulnerable children with thalassemia aged up to fifteen years. The cohort served a total of 138 patients, out of which thirteen had positive hepatitis C antibodies upon enrollment in the cohort. Four patients had virus RNA detected by polymerase chain reaction. The patients were treated with a combination of Daclatasvir and Sofosbuvir for twelve weeks. PCR repeated after three months of treatment showed negative viral load.

Background

In March 2018, MSF started a thalassemia one day unit in Bekaa Valley in Lebanon targeting vulnerable children with thalassemia aged up to fifteen years. The cohort served a total of 138 patients with the diagnosis of Transfusion Dependent Thalassemia and non -Transfusion Dependent Thalassemia. A protocol for the management of patients was developed, derived from the Thalassemia International Federation protocol, and it included screening of the patients for hepatitis B, C and HIV serology upon enrollment in the cohort then annually. The protocol also included transfusing the patients with Rh kell compatible blood units that test negative for HIV, HBsAg, HCV, VDRL and anti HBC.

Discussion

Thirteen patients were found to have positive serology for HCV upon enrollment, and all had negative HBV and HIV serology. Detection and quantification of Hepatitis C virus RNA by reverse transcription quantitative PCR (m2000 Abbott) was undertaken for the thirteen patients. Six patients had positive viral load for HCV. Viral load was repeated after 6 months and it was still high, so the decision was made to treat these patients. Four patients were started on a combination of Daclatasvir 60 mg+ Sofosbuvir 400 mg PO once daily for twelve weeks. The two tablets were taken at the same time every day and they were well tolerated. The 4 patients weighed more than 30 kg upon initiation of treatment. Liver function tests repeated at the end of treatment were within normal range for the four patients. PCR repeated 4 months after end of treatment showed no viral load. PCR repeated 12 months after end of treatment showed continued remission. Clinical improvement was noted for two patients who both reported less fatigue and better appetite, in addition to a decrease in the size of the liver upon physical examination, from sixteen cm and six cm below costal margin before initiating treatment to seven and three cm below costal margin after end of treatment. The other two patients reported no significant clinical changes. During treatment with antiviral therapy there was no increase in the transfusion requirements. No side effects were reported, specifically no neutropenia, no thrombocytopenia, no increase in serum bilirubin.
The below table shows both demographic and clinical data related to the patients who received Direct Acting Antivirals (DAA), prior and post treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Chelation</th>
<th>Genotype</th>
<th>PCR at baseline</th>
<th>Platelet</th>
<th>ALT (UI)</th>
<th>AST (UI)</th>
<th>Hb (g/dL)</th>
<th>Platelet</th>
<th>ALT (UI)</th>
<th>AST (UI)</th>
<th>Hb (g/dL)</th>
<th>PCR 12 weeks post completion of DAA</th>
<th>Platelet</th>
<th>ALT (UI)</th>
<th>AST (UI)</th>
<th>Hb (g/dL)</th>
<th>PCR 12 weeks post completion of DAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>31</td>
<td></td>
<td>DFP (37 mg/kg/day) + DFP (100 mg/kg/day)</td>
<td>6.73x10^5</td>
<td>3</td>
<td>10.8</td>
<td>868000</td>
<td>105</td>
<td>132</td>
<td>10.6</td>
<td>804000</td>
<td>49</td>
<td>43</td>
<td>not detected</td>
<td>10.2</td>
<td>760000</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>46</td>
<td></td>
<td>DFP (35 mg/kg/day) + DFP (70 mg/kg/day)</td>
<td>6.87x10^5</td>
<td>4</td>
<td>10.4</td>
<td>957000</td>
<td>40</td>
<td>34</td>
<td>5.8</td>
<td>102700</td>
<td>63</td>
<td>43</td>
<td>not detected</td>
<td>9.4</td>
<td>814000</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>36</td>
<td></td>
<td>DFP (40 mg/kg/day)</td>
<td>3.15x10^5</td>
<td>4</td>
<td>10</td>
<td>264000</td>
<td>118</td>
<td>12</td>
<td>9.4</td>
<td>245000</td>
<td>9</td>
<td>21</td>
<td>not detected</td>
<td>8.8</td>
<td>234000</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>33</td>
<td></td>
<td>DFP (40 mg/kg/day) + DFP (100 mg/kg/day)</td>
<td>1.03x10^5</td>
<td>4</td>
<td>9.3</td>
<td>312000</td>
<td>60</td>
<td>42</td>
<td>10.5</td>
<td>272000</td>
<td>30</td>
<td>34</td>
<td>not detected</td>
<td>9.2</td>
<td>304000</td>
<td>25</td>
<td>43</td>
</tr>
</tbody>
</table>

**Conclusion:**
The report confirms the therapeutic efficacy and good tolerance of the combination of Daclatasvir + Sofosbuvir in this pediatric population suffering from thalassemia, regardless of the genotype of the HCV and the fibrosis status. Systematic HCV screening should be proposed in all Thalassemic children and DAA should be made available for them.

**Keywords:** chronic hepatitis C, thalassemia major, Daclatasvir, Sofosbuvir.
Title: The association between non-alcoholic fatty liver disease and liver fibrosis in patients with transfusion-dependent beta thalassaemia

Abstract Category: Hepatological Complications

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Abstract

Background
Non-alcoholic fatty liver disease (NAFLD) is an emerging global health problem. Iron overload and transfusion-transmitted hepatitis infection are the leading causes of liver damage in transfusion-dependent thalassemia (TDT) patients. The data on the contribution of NAFLD to liver damage in TDT patients is limited. Therefore, the aim of this paper is to assess hepatic steatosis, associated factors, and its impact on liver fibrosis in patients with TDT.

Methods
Forty-five heavily transfused HCV naïve TDT patients who didn’t have biochemical or ultrasonic evidence of liver cirrhosis were recruited to the study. At the time of recruitment, age, gender, height, and weight were recorded. They were evaluated for effects of iron overload, including the presence of diabetes mellitus, hypogonadism, serum ferritin, liver iron concentration (LIC) assessed by MRI R2, and liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Liver fibrosis and steatosis were estimated using transient elastography (TE). Data were analysed using R programming language.

Results
Of the 45, 9(20%) patients had significant steatosis(S1), and their Body Mass Index (BMI) and liver fibrosis scores were higher than in patients without significant steatosis(S0) (P = 0.03 and P = 0.004, respectively). On regression analysis, the controlled attenuation parameter (CAP) score (i.e., degree of liver steatosis) was associated only with increasing BMI. The TE score (i.e., degree of liver fibrosis) was associated with increasing age, CAP score, male gender, and presence of diabetes. Neither liver steatosis nor fibrosis showed significant association with the liver iron concentration or iron-related organ damage, hypogonadism.

Conclusion
Liver steatosis, which is associated with increasing BMI, has been shown to increase the risk of liver fibrosis in this cohort of TDT patients. Therefore, we believe that liver steatosis should be considered a risk factor to be eliminated in preventing liver injury in these patients with TDT.
Title: Does intensive chelation therapy reverse liver fibrosis in patients with transfusion-dependent beta thalassaemia - a follow-up study

Abstract Category: Hepatological Complications

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Abstract

Background
Transfusion-related iron overload and transfusion-transmitted hepatitis infection are the leading causes of liver fibrosis (LF) in transfusion-dependent thalassaemia (TDT). Chelation of excess iron is considered a potential mean of LF regression. This study aimed to evaluate LF reversibility with intensive chelation therapy in Sri Lankan TDT patients.

Method
Forty-five patients with TDT from the Adult and Adolescent Thalassaemia Unit, Kiribathgoda, Sri Lanka, were recruited. Age, gender, BMI, serum ferritin, AST, ALT, LF, liver steatosis (CAP score), liver iron concentration (LIC in mg Fe/g dw), and endocrine complications were recorded at recruitment and after 2½ years of intensive chelation therapy with both deferoxamine and deferasirox for their maximum chelation regimen. Drug compliance was monitored and recorded as good(gc), moderate(mc), and poor(pc) compliance based on the number of days the iron chelators were ingested. Regression analysis was performed for the LF difference.

Results
22/45 (49%) were males [mean age (SD)-19 (4.78) years], and 23 (51%), 12 (27%), and 10 (22%) were with gc, mc, and pc, respectively. Of the total population, the LIC decreased in 36(80%), while LF declined in 23(51%) patients. Median LIC reduction after 2½ years was as follows: gc group-13.5 to 5.1 (P=0.0002); mc group-25.5 to 17.75 (P=0.001). In the pc group, the LIC increased by 10.4 (P =0.058). The LF at recruitment and after 2½ years was 7.6 and 7.1 kPa (P=0.08) in gc group. In both mc and pc groups, LF increased on follow-up [significantly worsened in pc group (P=0.04)]. Multiple regression analysis for LF difference revealed CAP score, age, and drug compliance are independent predictors of LF reduction.

Conclusion
Reversibility of liver fibrosis was achieved in those with good compliance. Liver fibrosis was significantly elevated (p=0.037) in TDT patients with pc. The CAP score was identified as an independent predictor of liver fibrosis regression.
Title: Evaluation of plasma biomarkers for liver fibrosis in β-thalassaemia patients

Abstract Category: Hepatological Complications

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Abstract

Introduction
Iron overload in the liver of β-thalassaemia patients may cause organ failure. If left untreated, initial liver fibrosis can progress to cirrhosis and hepatocellular carcinoma. Having a method to easily, reliably and quickly detect and stage liver fibrosis would allow personalized management of iron chelation in β-thalassaemia patients. Liver biopsy is the gold standard for the accurate evaluation of liver, however, it is not a routine examination technique due to its invasive nature. Alternatives such as the Fibroscan® test and existing plasma biomarkers lack accuracy and specificity, especially for diagnosing initial stages of fibrosis. The aim of this project is to test the diagnostic value of five plasma-derived miRNAs, identified from the literature, as potential biomarkers for distinguishing between healthy controls and fibrotic patients, as well as between different stages of liver fibrosis in β-thalassaemia patients.

Methods
Demographics and blood samples were collected from healthy controls and β-thalassaemia patients and plasma was extracted. RNA levels were evaluated with quantitative real-time PCR in order to determine the expression of the five candidate biomarkers (let-7a, miR-21, miR-29a, miR-34a and miR-122), and two control microRNAs (miR-16 and miR-221). Additionally, ROC curves and AUC values were generated to evaluate the diagnostic power of the candidate miRNAs.

Results
There was a significant (p<0.05) downregulation of let-7a in F0-F1, F2 and F3 stage fibrotic patients compared to healthy controls. Similarly, there was a significant downregulation of miR-21 in F0-F1, F2 and F3 stage fibrotic patients compared to healthy controls, and in F4 compared to F3 patients. Expression of miR-34a was significantly upregulated in all stages of fibrotic patients compared to the healthy controls. Additionally, expression of miR-122 was significantly upregulated in F2 stage fibrotic patients compared to the healthy controls. ROC curves showed that let-7a, miR-21, miR-34a and miR-122 could significantly discriminate between fibrotic stages and healthy controls (AUC>0.7, p<0.05). Candidate miRNAs showed differences only between healthy controls and fibrotic patients, and not between the stages of fibrosis. Further investigation should be done in order to evaluate if the changes are due to liver fibrosis or β-thalassaemia.

Conclusion
This study has the potential to identify plasma biomarkers with diagnostic value for liver fibrosis in β-thalassaemia patients.
Title: Predictors of infection among transfusion-dependent thalassemia patients in a tertiary government hospital in the Philippines

Abstract Category: Infections

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Abstract

Background
For the average Filipino child living with thalassemia, the definitive cure for the disease remains to be out of reach. Thus, healthcare workers are challenged to make the most of what is available to arrest the inevitable deterioration that transfusion-dependent thalassemia (TDT) patients face without definitive cure. Since it is known that bacterial infection is common among TDT patients, identifying which factors can predict bacterial infection can provide the healthcare team with a powerful tool to intervene early and take necessary action.

Methods
Records of all TDT patients admitted within 15 years were reviewed. Predictors of bacterial infection were identified using univariate and multivariate statistics. Chi-square test and logistic regression were used in the univariate analysis, and multiple logistic regression for multivariate analysis.

Results
141 patients were included. The prevalence of any bacterial infection was 51%. The most common types of infection were pneumonia (35%), skin infection (11%), and sepsis (9%). Patients with bacterial infection had a longer history of thalassemia and more frequent use of Deferiprone. History of splenectomy, vaccination status, and serum ferritin levels were not revealed to be significantly associated with bacterial infection status. The odds of a concurrent bacterial infection were 3.04 times as much in patients with >1 year of disease as in those with shorter duration, and 2.23 times as much in children with history of Deferipone use as in those without.

Summary/ Conclusion
There is a high prevalence of bacterial infection among TDT patients. Duration of disease and the use of Deferiprone were significantly associated with the occurrence of bacterial infection, and thus are the identified predictors thereof. Data from this research is recommended to be used as a starting point in the development of a scoring system to predict the occurrence of bacterial infection among TDT patients.
Title: Gut microbiota alteration in β-thalassemia patients is associated with iron

Abstract Category: Infections

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Abstract

In recent years, studies on gut microbiota have yielded important information on its crucial role in health and disease. The availability of nutrients within the gut influences the environment, determining the species, richness and its effect on health. Thalassemia, a hereditary blood disorder that arises from defective globin synthesis, requires frequent blood transfusions in order to complement the anemia resulting from lack of globin and ineffective erythropoiesis. The long-term effect is the deposition of iron in tissues and organs, and systemic iron overload. Iron is a limiting nutrient of bacteria in the gut and thus, the question arises as to whether iron overloading in thalassemia could alter the intestinal microbiota, which in turn could influence the susceptibility of thalassemic patients to infection. Here, we analyzed fecal microbiota of 70 non-transfusion dependent (NTDT) β-Thalassemia/HbE Thalassemia patients and 30 healthy controls, and showed that the bacterial diversity and community structure of the microbiota of patients was less diverse and distinct than that of healthy subjects. Using reference frames, we were also able to show that bacterial taxa, that are known to produce short chain fatty acids (SCFAs), from the genera Alistipes, Coprococcus and Oscillospira, and those from the family Ruminococcaceae, were less prevalent the patients. In contrast, bacterial taxa known to be associated with non-healthy gut, including genus Clostridium, and those from the families of Fusobacteriaceae, Enterobacteriaceae, and Peptostreptococcaceae, were more prevalent in patients, and were also found to be correlated with higher levels of ferritin. Collectively, these changes in microbiota could be regarded as markers of raised ferritin levels and therefore, awareness should be exercised as they could interfere, indirectly, in the treatment of the co-morbidities of thalassemia.
Title: Polarization of rat (Rattus Norvegicus) spleen macrophages after treatment of sappan wood extract (Caesalpinia Sappan L.) as an adjuvant iron chelator

Abstract Category: Iron Overload and Management

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Abstract

Thalassemia patients suffer chronic excess iron due to their regular blood transfusions and iron chelation therapy. Iron will accumulate throughout various organs and affect macrophage polarization, which will have consequences for the immune system’s function necessities. Sappan wood (Caesalpinia sappan L.) has anti-inflammatory and iron-chelating compounds, which can be used as an alternative step in the treatment of thalassemia. This study aims to determine the effect and optimum dose of sappan wood extract as an adjuvant on spleen iron levels and spleen macrophage polarization. This research was conducted experimentally for 28 days in a completely randomized design (CRD) consisting of 7 adjuvant test groups on 35 male Wistar rats (Rattus norvegicus). Iron dextran (60 mg/kg BW) is given to create excess iron conditions. Deferiprone (1.35 mg/kg BW) was given as a comparison iron chelator. Sappan wood extract (SWE) was given to each test group at doses of 50, 100, 150, and 200 mg/kg BW. The parameters observed included spleen iron levels and the amount of M1 (CD86) and M2 (CD163) expression measured using immunohistochemical techniques. A one-way ANOVA analysis with a 95% confidence level on Duncan’s test showed that SWE could reduce spleen iron levels, raise M2 (CD163), and decrease M1 (CD86) amounts. The findings showed that the dosage of 50 mg/kg BW SWE and 1.35 mg/kg BW of Deferiprone is an effective dose for iron chelation, lowering inflammatory macrophages and increasing anti-inflammatory macrophages to facilitate reducing inflammation.

Keywords: Adjuvant, Macrophage, Iron Overload, Sappan wood (Caesalpinia sappan L.)
Title: Effect of iron accumulation on lipolysis 3T3-L1 murine pre-adipocytes

Abstract Category: Iron Overload and Management

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Abstract

Background
Excessive iron, as seen in chronic blood transfusion, is accumulated in various organs including the heart and liver. Iron accumulation further promotes the production of reactive oxygen species (ROS) and results in organ damage. Our previous study showed that Fatty Acid Binding-4 (FABP-4), a lipid chaperone that is mainly expressed in adipose tissue and macrophage, has a negative correlation with cardiac function in transfusion-dependent thalassemia patients. However, the effect of iron accumulation in adipocytes is still under investigation. This study aimed to investigate the effect of iron accumulation in 3T3-L1 adipocytes.

Method
The 3T3-L1 pre-adipocyte cell line was induced with MDI medium (Methyl isobutyl xanthine, Dexamethasone, Insulin) and insulin medium to differentiate into adipocyte-like cells. After differentiation, 3T3-L1 adipocytes were treated with ammonium ferric citrate (AFC) at 20 mM, 70 mM, and 120 mM for 24 hours. Cell lysate was harvested for lipolysis assay and medium was collected for non-esterified fatty acid (NEFA), triglyceride, and FABP4 measurement. Staining with Oil Red-O was performed to monitor lipid accumulation.

Results
Measurement of glycerol levels in the presence of isoproterenol showed a significant decrease in AFC 120 mM compared to the control (p<0.05). The level of NEFA and triglyceride were higher in the AFC treated 3T3-L1 adipocytes compared to the control (p<0.05). The levels of FABP4 showed a significant decrease in AFC 70 mM and 120 mM compared to the control (p<0.05). Differentiate of 3T3-L1 adipocytes cells was stained with Oil Red-O, characterized by intracellular lipid droplets.

Conclusion
Iron accumulation promotes the destruction of adipose tissue which decreases FABP4 levels and enhances lipolysis in 3T3-L1 adipocytes.

Keywords: 3T3-L1 murine pre-adipocytes, FABP4, Iron overload, Lipolysis
Title: Effect of iron overload on pancreatic beta cell structure and blood glucose levels of male Wistar rats (Rattus norvegicus Berkenhout, 1769)

Abstract Category: Iron Overload and Management

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Abstract

Excess body iron will be deposited in various organs, including the pancreas, causing structural and functional disruptions. This study investigated the effect of iron overload on the pancreatic beta cell structure and blood glucose levels in male Wistar rats (Rattus norvegicus). This complete randomized design experimental study was conducted in a laboratory with seven treatments and four replications. Iron dextran (ID), an inductor of increased iron levels, was injected intravenously at a dose of 10 and 20 mg/kg body weight every three days until the treatment doses are completed. The treatment included a control group (normal saline), P1 (ID 10 mg/kg BW), P2 (ID 20 mg/kg BW), P3 (ID 30 mg/kg BW), P4 (ID 40 mg/kg BW), P5 (ID 50 mg/kg BW), and P6 (ID 60 mg/kg BW). Parameters assessed included transferrin saturation (TS) level, pancreatic beta cell necrosis score, and blood glucose levels. The data were analysed parametrically with the one-way ANOVA and Duncan’s post-hoc test, or non-parametrically with the Kruskal-Wallis test and Mann-Whitney U with a 95% confidence level. Pearson’s correlation was used to determine the relationship between parameters. Based on the TS level, the minimum dose of iron dextran required to induce an iron overload condition in subjects was 20 mg/kg BW. Based on the pancreatic beta cell necrosis score, ID 50 mg/kg BW began to show moderate damage. The blood glucose level at ID 20 mg/kg BW is categorized as prediabetes. Pearson’s test showed a strong correlation between ST level with beta cell necrosis score and blood glucose levels. It was concluded that iron overload damaged the structure of pancreatic beta cells led to an increase in blood glucose levels in rats.

Keywords: Blood Glucose, Iron Overload, Pancreatic Beta Cells, Rat (Rattus norvegicus).
Title: Management of iron overload in post-allogeneic hematopoietic stem cell transplantation in a thalassemia major patient

Abstract Category: Iron Overload and Management

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Abstract

Introduction
Hematopoietic stem cell transplantation (HSCT) is the definitive therapy in Transfusion Dependant Thalassemia Major (TDTM) patients. Pre-transplant red cell transfusions causes iron overload (IO). IO causes poor transplant engraftment and eventually promotes relapse by mediating oxidative stress in hematopoietic stem cells. Appropriate management of Iron levels is essential for successful engraftment.

Case report
08 years old boy successfully undergone allogenic HSCT for TDTM, from his own elder brother with a 10/10 high resolution HLA match was referred to Consultant transfusion physician, at blood bank, Teaching Hospital Ragama for venesection due to IO with a Ferritin level of 1900ng/dl, 01-year post transplant child was completely normal and had no other complications despite high Ferritin value. Heamatology recovery was seen from post-transplant D13. There was no evidence of GvHD and chimenisim reports showed 100% donor DNA since 05 months post-transplant 6-8ml/kg venesections were planned every 2-3 weekly until serum Ferritin level is <500ng/dl, maintaining Pre venesection Hb>9g/d Venesections were performed under aseptic conditions at paediatric unit with close monitoring. Initial 03 venesections were done one month apart due to poor adherence. With removal of 130ml, 140ml, 150ml of blood in respective visits Ferritin dropped to 1700ng/dl within 03 months. Then he was on deferasirox 300mg daily for 08 months and it was withheld due to rising liver enzymes (AST- 218, ALT-418.4). One month later liver enzymes started declining. Ferritin level was still 1494ng/dl (02 years 03 months posttransplant).

Then he was referred back for venesection and 200ml (10ml/kg) of blood was removed and advised to visit for review in 3 weeks with FBC and Ferritin levels to decide on further venesection parents were advised thoroughly to be compliant as IO can cause systemic Iron toxicity leading to graft failure, infections, GVHD and organ damage which would be devastating in this successful HSCT.

Conclusion
Venesection is the simplest approach of removing excess iron with no adverse effects, nevertheless use is limited to patients with good venous access, platelet engraftment and good graft function as in this patient. Chelation agents with close monitoring and venesection both would gain better removal of excess iron levels.

Keywords: HSCT, Iron overload, Iron chelation, venesection
Title: The effect of sappan wood (Caesalpinia Sappan L.) extract as an adjuvant of iron chelator on the structure and function of kidney in rats (Rattus norvegicus L.) iron overload model

Abstract Category: Iron Overload and Management

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Abstract

Excessive amounts of iron in the body can cause plasma membrane damage resulting in cell death and various organ damage including the kidneys. The use of iron chelators has been shown to reduce iron accumulation. This study aims to determine the effect of giving secang wood (Caesalpinia sappan L.) extract as an iron chelator adjuvant on kidney structure and function. This research was conducted experimentally for 28 days in a completely randomized design (CRD) consisting of 7 adjuvant test groups on 35 male Wistar rats (Rattus norvegicus L.). Iron dextran 60 mg/kg BW is given to create excess iron conditions. Deferiprone 1.35 mg/kg BW was given as a comparison iron chelator. Secang wood extract was given to each test group at doses of 50, 100, 150, and 200 mg/kg BW. Parameters observed were kidney iron levels, histological structures (necrosis, fatty degeneration, and hydrophilic degeneration) and physiology (Urea, Creatinine, and Total Protein) of the kidneys. The data obtained were analyzed using analysis of variance (ANOVA) at a 95% confidence level and if there were differences, a Duncan test was performed. The research showed that giving secang wood extract at a dose of 50 mg/kg BW as an adjuvant with 1.35 mg/kg BW deferiprone effectively lowers iron levels in the kidneys and prevents kidney damage.

Keywords: Kidney, Iron Overload, Rat (Rattus norvegicus L.), Sappan Wood (Caesalpinia sappan L.).
Title: Monitoring and management of iron overload in transfusion dependent thalassemia patients in low resource settings: the MSF experience in Lebanon

Abstract Category: Iron Overload and Management

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Abstract

Background and Aims
MSF started a thalassemia unit in March 2018, as part of a pediatric project in Bekaa area in Lebanon, aiming at reducing morbidity and mortality among the refugees and underprivileged Lebanese pediatric population with the diagnosis of Transfusion Dependent Thalassemia (TDT) and Non-Transfusion Dependent Thalassemia (NTDT). The unit served a total of 138 patients over a period of 5 years. The services provided were free, and included supply of the 3 iron chelators, Deferasirox, Desferrioxamine and Deferoxamine. The iron chelation regime was individualized for each patient, and prescribed according to a protocol derived from the TIF guidelines and adjusted according to the low resource settings of the project.

Methods
This is a descriptive analysis of the cohort from March 2018 till May 2023, using routine data collected in an excel database. The data collected includes patients’ age, weight, serum ferritin levels every 3 months, liver and kidney function tests, echocardiography and MRI T2*. Few patients were selected for evaluation by MRI T2*, according to their ferritin levels (>2500 ng/dl), taking into consideration the budget limitations, in addition to the iron chelation regime prescribed for the patients.

Results
The average ferritin level for patients upon enrollment was 3900 ng/dl, excluding the 50 patients who were diagnosed in the unit, ranging between 370 ng/dl and 13200 ng/dl. The average ferritin level for the 89 patients upon closure of the project was 2659 ng/dl, ranging from 424 to 6020 ng/dl. The first iron chelator to be used in the project was Deferasirox (EXJADE from NOVARTIS), but the cost was very high and the number of patients was increasing, so MSF shifted to local supply of a Jordanian generic named DEFIRAX from HIKMA, until MSF started importing the drugs through international orders, when we shifted the patients to a Canadian generic named APO-DEFERASIROX from APOTEX INC.

Desferrioxamine (Desferal) was available in limited quantities and there was no access to Deferoxamine. Desferrioxamine was the iron chelator of choice for patients aged less than 2 years. MRI T2* was done for 19 patients with TDT in December 2018 and the results are shown in graph 1 below. The patients with the highest ferritin levels were selected to do the MRI T2* tests in order to assess their iron burden. After analyzing the results of the MRI, Deferiprone was added to the iron chelation regime of 5 patients at a dose of 70-100 mg per kg per day, 2 were already on DFX and 2 were already on DFO.
MRI T2* was repeated in 2021 for 11 out of the 19 patients, and the results of the MRI as well as the ferritin levels are shown in graphs 1 and 2 below. The patients with the highest ferritin levels were selected to do the MRI.

17 patients were receiving the Deferasirox at a dose ranging between 30 and 39 mg per kg per day.

2 patients were receiving Desferrioxamine at a dose of 40 mg per kg per day due to liver toxicity caused by Deferasirox and their baseline active hepatitis C infection.

After analyzing the results of the MRI, Deferiprone was added to the iron chelation regime of 5 patients at a dose of 70-100 mg per kg per day, 3 were already on DFX and 2 were already on DFO.

Graph 2: Variation in the results of MRI T2* between December 2018 and September 2021.
In 2020, MRI T2* was done for another 13 patients, and repeated again in 2021 for the same patients; analysis of the results of the MRI as well as their ferritin levels is shown in graphs 3 and 4 below. To note that 8 patients showed mild to moderate pancreatic iron overload.

**Conclusion**

Over time all the patients had significant improvement in their iron burden as reflected by a significant improvement in the serum ferritin. MRI assessments in a low resource setting can be useful in targeting improvements in the most severely iron overloaded patients as shown by improvements in Cardiac T2* and LIC.
Title: A case of beta thalassemia major increased approach to the treatment by multidisciplinary approach

Abstract Category: Iron Overload and Management

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Abstract

Background
In thalassemia major patients, problems associated with iron accumulation have increased significantly, with early diagnosis and treatment, and prolongation of life expectancy. In these patients, the bone marrow remains hyperactive even with optimal transfusions. Therefore, transfusions, iron chelation and associated iron overload cause failure in many organs. We present a Case who developed comorbidities due to non-compliance with iron chelation therapy while being followed up with the diagnosis of thalassemia major, and was treated under regular oral iron-iron chelation therapy, which was evaluated and followed-up with a multidisciplinary approach.

Case
A 23-year-old male patient was admitted to our center with the complaints of growth retardation, difficulty in walking for the last 1 year, joint limitation, pain, regression in activities of daily living, unhappiness and depression. He was diagnosed with thalassemia major at the age of 1 and had been receiving intermittent blood transfusion and chelation therapy for 20 years. The patient, whose ferritin levels were high due to non-compliance with the treatment, developed short stature, panhypopituitarism, growth hormone deficiency, delayed puberty, Type I diabetes mellitus, osteoporosis, diabetic nephropathy, peripheral neuropathy, mental retardation and depression. The patient’s compliance with the treatment was increased and serum ferritin levels were decreased with oral iron-iron chelation therapy and a multidisciplinary approach, which were applied regularly in our center for 6 month period.

Conclusion
It is seen that the most important point in reducing iron accumulation in thalassemia patients with regular transfusion and chelation therapy is to increase treatment compliance.
Title: Potential of secang wood (Caesalpinea sappan L.) extract as hepatoprotector in iron dextran induced rat as a model of hemocromatosis

Abstract Category: Iron Overload and Management

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Abstract

Excess iron in the body can occur due to metabolic disorders, excess iron absorption and repeated transfusions such as in patients with thalassemia. Iron can accumulate in one of the organs especially in liver. Secang (Caesalpinea sappan L.) is a plant that has an active compound in the form of brazilin which has a bidentate ligand so it can bind free iron. This study aims to see the effect of giving secang wood extract as a protective agent against iron induced in test animals. The research method used a post-test control group consisting of the normal, positive group and the administration of sappan wood extract at doses of 100 mg/kg, 150 mg/kg, and 200 mg/kg. The research group used Wistar rats aged 2 months and weighing 150-200 grams. Secang wood extract was administered orally for 28 days and on the 29th day an iron dextran dose of 20 mg/kgBW was given intravenously. The measurement parameters were in the form of histological features and iron density in liver measured using imageJ. The results of the study on the histology of the liver showed that the greatest damage occurred in the positive control group, while there was almost no damage in the secang wood extract group. The results of the density analysis showed a unique thing where the higher the dose of secang wood extract, the higher the density of iron accumulated in the liver due to an increase in the number of Kupffer cells that bind iron in the liver. Statistical analysis using ANOVA showed a p value <0.001 and DUNCAN post hoc test showed that all groups had significant differences where the effective dose that was able to prevent iron damage and reduce iron levels in the liver was a dose of 100 mg/kg BW of secang wood extract.

Keywords: protective agent, iron dextran, intravenous, imageJ
Title: The role of secang wood (*Caesalpinia sappan* L.) extract as an immunomodulator in rat model of iron overload

Abstract Category: Iron Overload and Management

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Abstract

The effects of excess iron suffered by patients with hemochromatosis on the body are organ damage and a decrease in the immune system. Sappan wood (*Caesalpinia sappan* L.) is a plant that contains brazillin so it has potential as an immunomodulator. This study aims to observe the potential of secang wood extract as an immunomodulator by measuring changes in levels of IL-6, IL-10 and TNF-α in rats iron overload model. The research method uses a posttest only control group. The study group was divided into 6 groups consisting of the normal group, the negative control group, the comparison group (deferiprone) and the sappan wood extract treatment group which consisted of a dose of 50 mg/kgBW, 75 mg/kgBW, and 100 mg/kgBW. The rats before being treated were induced with iron dextran at a dose of 20 mg/kg BW 3 times with an interval of 3 days. On the 13th day until 31th day, the rats were given oral treatment with distilled water (normal & negative group), doses 1.35 mg/kgBW of deferiprone (comparison) and various doses of secang wood extract. All treatment given 3 times a day (divided doses). Data were collected using the spleen organs which were made homogenate and parameter measurements were carried out using ELISA. ANOVA analysis showed significant differences in all parameters with p<0.001. The iL-10 level showed that the group given secang wood extract at a dose of 100 mg/kgBW was the most effective dose in increasing iL-10 levels compared to the normal group. The measurement of iL-6 and TNF-α levels showed that the administration of secang wood extract at a dose of 50 mg/kg BW was the best dose in reducing all of them. The results of the correlation between the three parameters did not show a correlation between levels of iL-10, iL-6 and TNF-α.

Keywords: iron overload, immunomodulator, IL-6, IL-10 and TNF-α.
Title: Impact of pharmacist-led Medication Therapy Adherence Clinic (MTAC) towards the management of thalassemia patients in a tertiary hospital in Malaysia: a preliminary result

Abstract Category: Iron Overload and Management

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Abstract

Background
Empowering adherence to the long-term use of iron chelation therapies is imperative in preventing complications following systemic iron overload among thalassemia patients. A pharmacist-led medication therapy adherence clinic (MTAC) was implemented to deliver pharmaceutical care to thalassemia patients. Patients with serum ferritin concentrations > 2500 μg/L and/or abnormal MRI T2* measurements were recruited in the MTAC program.

Aim
To evaluate the impact of pharmacist-led MTAC towards the management of thalassemia patients in terms of (i) knowledge of thalassemia and iron chelation therapies, (ii) serum ferritin concentrations, and (iii) magnetic resonance imaging T2-star (MRI T2*) measurements of cardiac and hepatic iron.

Methods
Data from thalassemia patients with ≥ two serum ferritin concentrations were collected (n=22; adult, n=30; paediatrics). Knowledge assessment on thalassemia and iron chelation therapies was performed at baseline and fourth MTAC visit (3 - 9 months from MTAC recruitment). Instead, the caregiver’s knowledge was assessed for patients ≤ 10 years old. The questionnaire for assessment was adopted from thalassemia MTAC protocol published by Pharmaceutical Services Programme Ministry of Health Malaysia. One MRI T2* measurement (cardiac and hepatic iron) and the mean of two serum ferritin concentrations were compared before and after MTAC recruitment. Data was analysed using IBM SPSS Statistics v28.0.

Results
Most thalassemia patients (94%) were blood transfusion dependent. The median (range) age was 16 (3 - 55) years. Patient’s (or caregiver’s) knowledge of thalassemia and iron chelation therapies improved by 30% (p < 0.001, n=26) at the fourth MTAC visit. The mean serum ferritin concentrations reduced by 10% (p = 0.03, n = 52). No changes in MRI T2* measurements were observed (p > 0.05, n = 15) following MTAC program.

Conclusion
Effective involvement of pharmacists as integral members of the healthcare team in thalassemia management can positively impact patient outcomes.
Title: Splenectomy in splenomegaly patient with β-thalassemia major: a case report

Abstract Category: Iron Overload and Management

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Abstract

Background
β-Thalassaemia represents a heterogeneous group of inherited diseases characterised by the lack, or reduced production, of β-globin chains as the main component of haemoglobin (Hb). Its common pathophysiological features is increased destruction of red blood cells by the reticuloendothelial system, particularly the spleen, which combined with extramedullary haemopoiesis, results in splenomegaly. The main therapeutic rationale for splenectomy in transfusion-dependent thalassemia (TDT) in patients with β-thalassaemia major (TM) is to decrease blood consumption and transfusion requirements which ultimately reduce iron overload.

Case
A sixteen-year-old boy came to the hospital for a splenectomy. He was diagnosed with TM at 1 year old. He received hypertransfusion to maintain the haemoglobin but the target was not reached due to poor compliance. On physical examination, we found Facies Cooley, the liver was 4 cm below the ribs, and the spleen was schufner VI. Laboratory results showed Hb of 6.8 - 8.7 gr/dL, thrombocytopenia 19,000 - 30,000/μL, and ferritin 10,445 ng/mL. Chest x-ray within normal limit, bone age revealed retarded boy with osteopenia. MRI T2* result revealed no heart hemosiderosis, severe liver, and mild pancreatic iron overload. His bone mineral density (BMD) is within normal limits. He received a complete vaccination. He was indicated for splenectomy due to huge spleen, bicytopenia, and ineffective iron chelators for 6 months. After splenectomy, his laboratory results showed improvement. His Hb stabilized at 9 g/dL without transfusion, with no thrombocytopenia (thrombocyte 776,000/μl). His condition was good, He got prophylaxis antibiotic with amoxycillin clavulanate for 2 years.

Conclusion
Splenectomy is the recommended intervention to reduce excessive blood consumption and consequent iron overload. Optimal Transfusion regimens and iron chelation have considerably reduced the incidence of splenomegaly and iron overload in TDT patients. Optimal vaccination before splenectomy and prophylactic antibiotics post-splenectomy should be done.

Keywords: Splenomegaly, splenectomy, Transfusion Dependent, Thalassemia
Title: The effective dose of sappan wood (Caesalpinia Sappan L.) ethanol extract administration as an adjuvant therapy in iron overloaded rat cardiac tissue

Abstract Category: Iron Overload and Management

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Abstract

Background
Iron overload leads to excess iron accumulation which provoke organ damage including the heart. Synthetic iron chelator administration developed the adverse side effects when used for a long term. To overcome with this condition, alternative natural resource with iron chelating properties is required. Sappan wood (Caesalpinia sappan L.) contains flavonoids and braziliin, which exhibit potent antioxidant and iron chelating properties, suggesting their potential as iron chelators. The study aimed to determine the effective dosage of sappan wood ethanol extract (SWEE) as iron overload adjuvant therapy in heart.

Method
The experimental study involved seven treatment groups; a normal control (aquades), a negative control (iron dextran (ID)), a positive control (ID, deferiprone (DFP)), and adjuvant test groups (ID, DFP, and SWEE at doses of 50, 100, 150, and 200 mg/kg BW/day). The ID was administered intravenously at a dose of 15 mg/kg/day, four times over the initial 12 days, with a three-day interval between each administration. Subsequently, DFP and SWEE were orally administered daily for 28 days after the ID administration. The study conducted by measuring the area of Fe3+ iron by Perls Prussian Blue staining.

Result
As the result, there was an increase of the Fe3+ area in cardiac tissue in the negative control. The combination of SWEE at a dose of 50 mg/kg BW and DFP at a dose of 1.8 mg/kg BW effectively reduced the area of Fe3+ in cardiac tissue.

Conclusion
Thus, it can be concluded that SWEE at a dose of 50 mg/kg BW, and potentially act as an effective adjuvant.

Keywords: Cardiac Tissue, Iron Overload, Perls Prussian Blue, Rat, Sappan Wood Ethanol Extract.
Title: Investigating iron-chelating and lipophilic properties of fungal siderophore “coprogen”: a potential hexadentate iron chelator

Abstract Category: Iron Overload and Management

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Abstract

Background
Iron chelators are used for the treatment of iron overload in thalassemia patients, decontamination of heavy metals and radio-nuclei, and PET imaging tumor cells, but they come along with their side effects. Thus, novel iron chelators need to be procured, as a better alternative to current modalities. Here, we determined the iron-chelating and lipophilic properties of a hexadentate siderophore Coprogen B (CPGB) produced from a saprophytic fungus Talaromyces marneffei in vitro.

Method:
Coprogen B, desferrioxamine (DFO), deferiprone (DFP) and deferasirox (DFX) (12.5-200 μM) were prepared in MOPS buffer pH 7.0 and optical density (OD) values measured between 200-700 nm. The chelators were incubated without/with ferrous ammonium sulphate (FAS) or ferric ammonium citrate (FAC) for different times and measured OD values at their specific wavelengths. Then, 1-octanol was mixed stirring with the chelators for 60 min, centrifuged the mixture, and transferred the upper 1-octanol layer for measuring OD values at 230 nm for the chelator and 450 nm for the iron-chelator complex.

Results:
Free CPGB as well as DFO exhibited maximal absorption at 230 nm and bound Fe^{2+} and Fe^{3+} rapidly to form the iron-CPGB complexes in a concentration-dependent manner giving the maximal absorption at 450 nm. In addition, importantly, the measured K_{o,ax} values for free CPGB and iron-CPGB complex were 0.3 and 0.04, respectively; in contrast, those for DFO and ferrioxamine (FO) were 0.17 and 0.05, respectively.

Conclusion:
The CPGB exerted molar absorptivity and iron-chelating activity in a swift and concentration-dependent manner similar to DFO. In addition, the chelator demonstrated greater solubility in a hydrophobic environment than DFO and the iron-CPGB complex, whereas both of the complexes were equally hydrophobic. Thus, our CPGB could be an effective alternative to a sink chelator “DFO” and adjunctive to a shuttling chelator “DFP” for the treatment of iron overload conditions.
Results
Figure 1 Spectral profiles of DFO, DFP, DFX and CPGD (0-200 mM) (A-D), and the chelators complexed with 500 μM FAS (E-H) or 500 μM FAC (I-L).

Figure 2 Dose responses of DFO, DFP, DFX and CPGD (0-200 mM) (A-D), and the chelators complexed with 500 μM FAS (E-H) or 500 μM FAC (I-L). Data obtained from four independent experiments are expressed as mean±SD.
Figure 3 Time-course bindings of DFO (A), DFP (B), DFX (C) and CPGD (D) (32.5-600 mM each) with 600 μM FAC. Data obtained from four independent experiments are expressed as mean ± SD.
Title: Prediction of drug-related toxicity of deferasirox and deferiprone in thalassemia patients of Iran by studying UGT1A1 polymorphisms

Abstract Category: Iron Overload and Management

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Abstract

Background
Transfusion-associated iron overload induces systemic toxicity. Deferasirox and Deferiprone are convenient oral iron chelation agents, which have recently been introduced and have shown a promising efficacy. But there are some patients who experience drug-related toxicities (DRT) and cannot tolerate it. These DRTs are defined as Hepatotoxicity occurrence or Creatinine elevation in this study.

Purpose
To investigate effect of genetic variations on the toxicities and find optimal target population, we analyzed two genetic polymorphisms of UDP-glucuronosyltransferase 1A (UGT1A) subfamily which are functional genetic variants of enzymes to metabolize and transport Deferasirox and Deferiprone.

Methods
UGT1A1*6 and UGT1A1*28 polymorphisms were analyzed by Sanger sequencing method in 110 Iranian Major Beta-Thalassemia patients who received Deferasirox or Deferiprone to reduce transfusion-induced iron overload. We retrospectively reviewed the medical records to find out the drug-related toxicities. DRTs are described as escalation in AST, ALT or Bilirubin levels to more than 3 times, or increase in Creatinine levels to above 30% of their initial figures.

Results
There have been 49 (44.54%) UGT1A1*28 Wild Homozygote, 47 (42.73%) UGT1A1*28 Heterozygote, 14 (12.73%) UGT1A1*28 Mutant Homozygote, 99 (90%) UGT1A1*6 Wild Homozygote, 11 (10%) UGT1A1*6 Heterozygote and no (0%) UGT1A1*6 Mutant Homozygote patients. Eleven (10%) patients developed hepatotoxicity. Creatinine elevation was observed in 23 patients (20.91%).

Conclusion
According to our results, no significant correlation was found among these SNPs and drug-related toxicities. However further studies are strongly recommended to detect pharmacogenetic biomarkers of Deferasirox and Deferiprone.
Title: Get Connected! Mission #IronCtrl The #ironchelation Challenge Campaign

Abstract Category: Iron Overload and Management

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Abstract

With over 855 registered patients under thalassaemia and other haemoglobinopathies in Maldives, Sickle cell and thalassaemia have long been considered a disease where children are left with severe anaemia, poor growth, huge abdominal organs, and childhood death. Regular transfusions have alleviated these symptoms and had improved their survival through childhood. However, blood contains large amounts of iron, which the body is incapable of naturally eliminating, and hence many face with severe morbidity and mortality due to complications of iron overload in their early adolescent ages.

Introduction to iron chelators such as Desferoxamine (Desferal), Deferiprone (L1 or Ferriprox), Deferasirox (Asunra or Exjade) have dramatically improved the quality of lives of those who adhere to the iron chelation therapy. However, there is a heavy focus from clinicians and patients on maintaining optimum Haemoglobin levels through blood transfusion and not so much focus on iron chelation therapy as well as monitoring of the patients on the aspects of growth and development.

Get Connected! Mission #IronCtrl - inspired by TIF theme for International Thalassaemia Day 2017, #Getconnected, an #ironchelation challenge campaign was initiated by our Maldivian thal/sickle patients to motivate and take active measures to decrease iron overload complications by reducing Serum Ferritin levels to a safe range below 1000ng/mL. The focus of this campaign is to improved patient knowledge and their positive attitude regarding iron chelation and complications. Thematic sessions were organized to help shape up their compliance and healthy progression to adulthood by breaking the stigma towards underestimation of our capabilities and possibilities towards a normal healthier life.

Ferritin levels of 61 participating from our session have been recorded. Only a few had the knowledge and acceptance of the impact of iron overload on their health. Many are living with a ferritin level that is life threatening and are not aware of its impact on health as the damages and complications are not readily visible as soon as iron overload begins.

Our vision is to initiate Get Connected! Mission #IronCtrl as a global #Ironchelation Challenge Campaign to inform communities, medical professionals and educators, and other transfusing patients and their families to learn that iron overload is a chronic condition that if not addressed properly can lead to death. Let’s all stand with Mission #IronCtrl to tell the community that our condition does not define us. We are not sufferers to be pitied, but survivors.

We believe change must happen, it is up to us as survivors, to change our lives and lives of others and make it happen. Therefore, apart from transforming our lives against the stigma towards thalassaemia and other haemoglobinopathies, our mission is also to transform the attitude and perception from the communities and achieve acceptance so that it can help patients to face the challenges and motivate them to keep adherence to #ironchelation therapy.

Keywords: iron control, ironctrl, chelation therapy, thalassaemia, blood transfusion, break the stigma
Title: Explorative research into physical activity of adult transfusion dependent thalassemia (TDT) patients: A Case study in Indonesia

Abstract Category: Lifestyle Issues

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Abstract

Background
Thalassemia, affecting around 1.5% of the global population, often leads to lower quality of life, especially in transfusion-dependent beta-thalassemia (TDT) patients. Despite the potential benefits of physical exercise on quality of life, many TDT patients refrain from engaging in physical activities. This study aimed to explore factors influencing their attitude towards exercise and assess their overall physical fitness.

Methodology
Using non-probability voluntary sampling, 50 TDT patients aged 18 to 40 from Indonesian thalassemia centers participated. Quantitative data were collected using the WHO’s Global Physical Activity Questionnaire, while qualitative data were gathered from three interviews.

Results
Results showed that 80% of respondents did vigorous-intensity activity for at least 10 minutes continuously during work, and 60% engaged in moderate-intensity activity similarly. However, 68% stated they did not participate in recreational sports or physical activities due to concerns about their health, fear of injury, family warnings, and fatigue. The interviews corroborated the questionnaire findings, revealing that the respondents were more active during their youth, particularly at school. However, as adults, their lifestyles became more sedentary due to work commitments and fatigue.

Conclusion
In conclusion, many adult TDT patients in Indonesia engage in physical activity as part of their daily routines or jobs but avoid recreational exercise. Primary reasons cited were concerns about health, fear of injury, family warnings, and work-related tiredness. Further research could build upon this data to understand better how to encourage physical exercise among TDT patients for improved quality of life.

Keywords: thalassemia, quality of life, exercise, physical activity, school, adult TDT patients.
Title: Low Oxygen Affinity Haemoglobinopathy- Hb Bruxelles with Co-inheritance of Double Heterozygous Alpha Variations: A Case Report.

Abstract Category: Miscellaneous

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Abstract

Introduction
Haemoglobin(Hb) Bruxelles is a rare congenital Heinz body anaemia. It is caused by a frameshift mutation resulting from the deletion of three nucleotides(-TTT) at codon 42 of the HBB gene. This deletion leads to the absence of a phenylalanine residue in the beta-globin chain, causing the formation of unstable Hb with low oxygen affinity. We describe our first case of Hb Bruxelles along with double heterozygotes of alpha variations in Malaysia.

Case report
A 13-year-old Malay girl was admitted for acute tonsillitis and anaemia. She had a history of similar presentation at 5 months old and required a blood transfusion. There was no family history of hemoglobinopathy. On examination, she was comfortable and not in respiratory distress. She had persistently low peripheral oxygen saturation (SpO2<80%) with normal arterial oxygen saturation. She had mild pallor, jaundice, and peripheral cyanosis. Cardiovascular, respiratory, and abdominal examinations were normal. She had normocytic normochromic anaemia(Hb 6.8g/dl, MCV 92.7fl, and MCH 27.5pg) with the presence of polychromasia, spherocytes, and basophilic stippling in peripheral blood smear. The H-inclusions were positive. G6PD enzyme and methaemoglobin levels were normal, and Coomb's test was negative. Capillary electrophoresis showed raised HbA2(4.5%) and HbF(5.5%), which concordance with high-performance liquid chromatography(HPLC) findings(HbA2/E at 7.4% and HbF at 3.5%). Abnormal peak was observed in both methods, zone 1 in CE (3.0%) and C window in HPLC (1.0%, retention time of 5.18 minutes). DNA analysis showed heterozygous Hb Bruxelles mutation co-inheritance with heterozygous -4(C>G) variation in HBA1 and HBA2 genes of unknown clinical significance.

Conclusion
The case’s manifestation is likely attributed to Hb Bruxelles’s functional characteristics, resulting in falsely reduced SpO2 levels in the absence of cardiac or respiratory pathologies. The consideration of low oxygen affinity hemoglobinopathy is warranted for asymptomatic individuals displaying unexplained low SpO2. Timely diagnosis is vital to avoid unnecessary cardiorespiratory tests.
Title: The effect of thalassemia intervention program among thalassemia patient with severe iron overload

Abstract Category: Miscellaneous

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Abstract

Background
Iron chelation therapy is the primary treatment for iron overload in thalassemia patients. Despite extensive research documenting the problems and barriers leading to poor adherence to iron chelation therapy, research has lagged in the development and interventions to improve adherence for this highly prevalent patient group in Sabah.

Aim
To assess the effect of Thalassemia Intervention Programme (TIP) among beta-thalassemia patient with severe iron overload.

Method
A quasi experimental pre & post study design was conducted from July 2017 until october 2018. Thalassemia patients with severe iron overload (serum ferritin >4000ng/ml) were recruited in this study. Baseline ferritin level and initial pill count was recorded upon recruitment to assess patient’s adherence to iron chelation therapy. Participants were then given the intervention which consisted of two modules: 1) patient counselling, 2) 180 days challenge on the following appointment. Post intervention outcomes on serum ferritin levels were measured 3-monthly while compliance were measured by monthly pill count for total 6 months. Outcomes evaluated were serum ferritin level [ng/ml] (Baseline, 3 & 6 months) and iron chelation therapy compliance as measured by pill count monthly. Data were analyzed using Repeated Measure ANOVA.

Results
A total of 13 male (65%) and 7 female (35%) patients with mean age of 22 ± 5.3 years old were recruited in this study. Serum ferritin reduction was recorded at month 3 (4843.8ng/ml [95% CI 4314.7,5372]) and 6 (4076ng/ml [95% CI 3547.1,4605.3]) compared to baseline (6474ng/ml [95%CI 5945.8,7004.1], p<0.001) post intervention. Mean difference were -1631.1ng/ml (95% CI -2545.1,-717.1) (month-3) and -2398.7ng/ml (95% CI -3312.7,-1484.7) (month-6) compared to baseline respectively. Compliance significantly increased from 42.3% (95%CI,33.1,51.5) to 87.2% (95%CI,77.9,96.3) upon intervention at month-1 compared to baseline and maintained throughout the study period (month-6, 74.8% (95%CI 65.6,83.9)).

Conclusion
TIP was found to significantly reduced serum ferritin level in and improved compliance to iron chelation therapy in severe iron overloaded patients.
Title: Detection of common beta thalassaemia mutations and deletions using reverse dot blot method: Hospital Kuala Lumpur’s experience

Abstract Category: Miscellaneous

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Abstract

Background
Beta thalassaemia is an inherited autosomal recessive haemoglobin disorder mainly caused by point mutation. Hospital Kuala Lumpur (HKL) utilises the reverse dot blot hybridization method (Hybribio beta thalassaemia diagnostic kit-b25MY) which is designed for the simultaneous detection of 23 types of beta gene mutations and 2 types of beta gene deletions for Malaysian population. The main objective of this study was to verify the reliability of this Hybribio beta thalassaemia diagnostic kit and its capability for detecting beta thalassaemia.

Method
A correlation study was carried out using confirmed negative and positive cases obtained from the Institute of Medical Research (IMR) versus the Hybribio Diagnostic Kit method. The analysis includes DNA amplification and hybridization. The extracted DNAs were amplified using biotinylated primers designed for specific amplification of β-globin mutation/deletion regions. The amplified DNA amplicons were then hybridized to the target probes, which are immobilised on the membrane. The hybridization process utilises the “flow-through hybridization” technique and was performed on a Hybribio AutoMax instrument. The enzyme immunoassay method was then applied for colour development to obtain test results and differentiate whether the patient is heterozygous, homozygous or compound heterozygous thalassemia. The positive results were obtained from manual inspection of the dot blot pattern using the Hybribio kit reference manual.

Results
All known cases of negative and positive beta thalassaemia mutations and deletions were accurately identified by the Hybribio Diagnostic Kit Method.

Conclusion
In Conclusion, our results showed that Hybribio Beta Thalassaemia Diagnostic Kit has good sensitivity and specificity, reproducible with a short reaction time for detecting common Beta Thalassaemia mutations and deletions. However, precautions need to be taken during result interpretation as the limitation of low dot probe signal (faint) of certain mutations on the membrane.
Title: Post splenectomy outcomes of transfusion dependent thalassemia (TDT): experience from adult thalassemia clinic of a tertiary care teaching hospital of north India.

Abstract Category: Miscellaneous

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Abstract

Background
Progressive splenomegaly is seen in inadequately transfused thalassemia patients in resource-constraint settings and may become symptomatic with hypersplenism necessitating splenectomy. While splenectomy helps in reducing the transfusion requirements, it is also associated with major complications like sepsis, thrombosis, and pulmonary hypertension.

Aim
To study the incidence of different complications and long-term outcomes in post splenectomy TDT patients.

Methods
In this retrospective study, medical records of patients (>18 years) registered from July 2013 to June 2023 in the adult thalassemia clinic at PGIMER, Chandigarh were reviewed. All patients who underwent splenectomy or splenic embolization, before or after registration in the adult thalassemia clinic were included. Demographic and clinical characteristics, surgery details, vaccination, antimicrobial prophylaxis, infectious and non-infectious complications, and survival were noted.

Results
A total of 105 out of 289 (36.3%) thalassemia patients, had splenectomy/splenic embolization done at the median age of 12 (range 5-34) years. Splenectomy was open in 101 (94.3%), laparoscopic in 2 (1.9%) and via splenic embolization in 2(1.9%). All received pre-splenectomy vaccination and 103 (98.1%) received penicillin prophylaxis. Surgical complications-viz., diaphragmatic pleural rent and surgical site infection was seen in one each. 50 episodes of infections were recorded in 43 patients, including 4 cases of overwhelming post-splenectomy infection and 8 cases of extrapulmonary tuberculosis. Thrombosis and pulmonary hypertension were seen in 4.7%, and 9.5% respectively. Endocrinopathies (53.4%), chronic liver disease (14.3%), heart failure (11.4%), arrhythmia (4.7%) occurred because of iron overload. Post-splenectomy overall survival at 20 years was 85.5% & median age at last follow-up was 30 (range 18-48) years. 16 patients died, and cardiac complications contributed to death in 50%.

Conclusions
In TDT patients with suboptimal transfusion therapy, splenectomy may decrease the transfusion requirement and ameliorate other cytopenia but at the cost of increased infections and thrombotic complications. Under-chelation results in long-term iron overload-related complications and deaths.
Title: Systemic Lupus Erythematosus (SLE) in children with transfusion-dependent thalassemia: diagnostic and comprehensive care

Abstract Category: Miscellaneous

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Abstract

Background
The association between systemic lupus erythematosus (SLE) and beta-thalassemia is rare, and patients with SLE generally have a lower overall incidence of beta-thalassemia. However, when these two conditions coexist, they can lead to more severe systemic symptoms. Here we report a girl with HbE/beta-thalassemia and SLE.

Case
A ten-year-old girl was diagnosed with HbE/beta-thalassemia at the age of three. Due to hypersplenism and unresponsiveness to hypertransfusion, she underwent a splenectomy. However, her hemoglobin level remained low even after the splenectomy, leading to her referral to our center. On physical examination, we observed Cooley’s facies with a moon face, short stature, and hepatomegaly. Laboratory results showed a hemoglobin level of 8 - 8.7 g/dL, normal platelet count, and high ferritin levels at 14,512 ng/mL. MRI T2* revealed mild heart hemosiderosis, a normal liver, and severe pancreatic iron overload. Additionally, she tested positive for Coomb’s test, lupus anticoagulant, anti-nuclear antibody, and Anti-ds DNA, indicating systemic lupus erythematosus (SLE). Currently, she is undergoing treatment with methylprednisolone and hydroxychloroquine for SLE, deferasirox for thalassemia, and continues to receive regular transfusions. During her ongoing treatment for SLE and thalassemia, she experienced seizures and contracted varicella due to incomplete immunization. Despite these challenges, she is currently continuing her treatment for both SLE and thalassemia.

Conclusion
Having awareness of the association between SLE and thalassemia may help in early diagnosis and treatment, thus preventing severe disease manifestations. Early awareness of such associations plays a crucial role in facilitating prompt diagnosis and treatment, thereby potentially preventing the development of severe disease manifestations.

Keywords: Systemic Lupus Erythematosus (SLE), Transfusion Dependent Thalassemia, severe anemia, early diagnosis
Abstract

Blood transfusion remains indispensable in modern clinical management. For patients with thalassaemia major, lifelong regular transfusion is a must unless they could receive haematopoietic stem cell transplantation. Though adoption of routine antenatal thalassaemia screening has reduced the number of newly diagnosed cases in some countries year by year, with regular blood transfusion support and iron chelation therapy, their survival is much prolonged which also put pressure to the healthcare system.

Unfortunately, availability of stable blood supply and iron chelation therapy (and also its compliance) remain difficult in many countries. The former was further impacted by COVID-19 pandemic in the last three years. Besides, it is also understandable that with prolonged survival, quite some patients suffered from complications of iron overload that needs monitoring and treatment. Needless to say, problems and adverse events from regular blood transfusion are not uncommon, with development of alloimmunization that might make the provision of compatible blood units difficult. Therefore, for better patient management, there is a growing need to have systematic monitoring and follow up of essential patient demographics, laboratory and radiological findings, transfusion and pharmacological data so as to allocate appropriate healthcare resources for their management.

In a recent 11-year survey by regional blood center in a city of 7.4M inhabitants, we identified 394 patients with diagnosis of thalassaemia requiring transfusion in 2020. An average of 14,103 units of red cells were needed annually to support them and these amounted to about 5.9% of the territory wide blood demand. In the same study, 85 drop out and 53 new cases were identified when compared to that in 2010. Of them, these included 44 deaths, 14 haematopoietic stem cell transplantations but 27 had insufficient information. Whereas 53 new cases consisted of 28 beta-thalassemia major, 10 beta-thalassemia intermedia, 11 HbH disease, 2 Hb Barts disease and 2 HbE/ beta-thalassaemia. With regards to their demographics a mean age of 26.7 35.2 (range: 1 - 85) were noted by 2020. More interestingly, the number of thalassaemia major reduced from 339 in 2010 to 307 in 2020 with corresponding decrease in annual transfusion requirement from 13,180 to 11,569 units.

On the other hand, 22.3% of them had at least one red cells alloantibodies with 12 having 2 or more (up to 5) alloantibodies. A total of 146 alloantibodies with known specificities in 127 were identified. The commonest were anti-E (47, 37.0%), anti-Mia (37, 29.1%) and anti-c (15, 11.8%). Obviously, timely updates of clinical data of this group of patients were unavailable, which emphasize a need to set up a proper territory wide thalassaemia registry. Now, with the support of public health organization, such a thalassaemia registry will set up soon. Doctors involved in thalassaemia care could then make use of the registry for a better and systematic monitoring of their patients and planning of the appropriate management in order to have as normal life as possible.
Title: The study about coagulation condition on thalassemia patients after splenectomy at the National Institute of Hematology and Blood Transfusion stage 2022 -2023

Abstract Category: Miscellaneous

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Abstract

Background
Splenectomy is a supportive treatment for Thalassemia patients. However, splenectomy also increases the risk of complications for the patient.

Objectives
To describe the clinical characteristics and coagulation tests in Thalassemia patients after splenectomy.

Method
Descriptive, longitudinal, prospective study.

Results
The patients were monitored for 30 days after splenectomy. We identified portal vein thrombosis in 8/51 patients (accounting for 15.7%) by Doppler ultrasound of the abdominal vessels, including 2 patients with clinical symptoms (abdominal pain). No patient was found to have deep vein thrombosis of the lower extremities. All patients had thrombocytosis, markedly elevated at days 10 to 15 after splenectomy. There is no statistically significant between mean of platelet count between patients with and without thrombosis. Changes in coagulation index after splenectomy suggested hypercoagulation state. Patients with thrombosis had statistically significant lower protein C level and anti-thrombin level than patients without thrombosis.

Conclusion
Factors such as protein C level and anti-thrombin level pre-splenectomy can suggest the risk of thrombosis in patients with β-Thalassemia post-splenectomy.
Title: Refractory autoimmune hemolytic anemia in a thalassemia patient with positive Paroxysmal Nocturnal Hemoglobinuria (PNH) clone in erythrocyte: a Case report

Abstract Category: Miscellaneous

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Abstract

Introduction
Concomitant autoimmune hemolytic anemia (AIHA) and paroxysmal nocturnal hemoglobinuria (PNH) in thalassemia is a rare condition. We report a case of refractory AIHA in thalassemia patient with positive PNH clone in red blood cells.

Case presentation
An eight-year-old female patient has been diagnosed with β-thalassemia major since the age of two. In the past two years, her transfusion interval has been shortened to weekly, but pre-transfusion hemoglobin level always remains below 5 g/dL. The patient also experiences jaundice and dark urine. Coombs’ test confirmed the presence of IgG and C3d antibodies. Despite multiple treatments, including steroids, immunosuppressive agents, and rituximab, she did not respond well. Due to indications of hypersplenism and refractory AIHA, the patient underwent a splenectomy. However, she still experienced persistent intravascular hemolysis characterized by dark urine, that was most prominent in the morning, sudden drops in hemoglobin levels leading to severe anemia, hemoglobinuria, and an increase in LDH levels. Tests for various viral infections were negative. Flow cytometric analysis revealed the presence of PNH clones comprising 88.3% CD59-negative and 5.3% CD55-negative red blood cells. There was no evidence of bone marrow failure or thrombosis. We plan to administer eculizumab, but unfortunately, the drug is not available in our country. Therefore, the current treatment consists of red blood cell transfusion using a washed/leucodepleted filter, azathioprine, and monitoring for complications related to thalassemia, AIHA, and PNH.

Conclusion
Paroxysmal nocturnal hemoglobinuria testing should be considered in AIHA patients with persistent hemolysis and poor response to treatment. The management of concurrent PNH clones and AIHA in thalassemia patient remains a significant challenge in our country. Further studies are needed to improve the diagnosis and treatment of these complex cases.
Title: Evaluation of membranopathies using EOSIN-5-MALEIMIDE ASSAY (EMA) in Sri Lanka

Abstract Category: Miscellaneous

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Abstract

Background
Flow cytometric eosin-5-maleimide assay (EMA) is an advanced screening method to diagnose membranopathies. The mean fluorescence intensity (MFI) of EMA dye which binds mainly to band3 red cell membrane protein, is measured by flow cytometry. In membranopathies, defects in membrane proteins cause a reduction in MFI compared to healthy controls, which aids in diagnosis. In Sri Lanka, the diagnosis of membranopathies is restricted to conventional screening methods, including peripheral blood smear (PBS), osmotic fragility test, and cryohemolysis test. The present study aimed to assess the use of EMA assay as a screening method and to establish a reference range for our laboratory. To our knowledge, this is the first study done in Sri Lanka to diagnose membranopathies using EMA assay.

Method
We evaluated the EMA assay in 24 healthy controls and 60 cases of suspected membranopathies based on medical history, clinical presentation, and PBS (30 Hereditary Spherocytosis (HS), 5 Hereditary Pyropoikilocytosis (HPP), 4 Hereditary Ovalocytosis (HO) and 1 Hereditary Eliptocytosis (HE)). The mean fluorescence intensity was measured using flow cytometry. Data were analyzed using an independent sample test in SPSS software.

Results
The MFI of healthy controls was 5814 ±368. Out of the study group, 90% of HS patients, 80% of HPP and 50% of HO patients showed a positive EMA result. The HE patient showed a negative EMA result. The mean MFI values were significantly decreased in HS suspected patients 4059±528 (p<0.005) and HPP suspected patients 4503±229 (p<0.005) compared to healthy controls.

Conclusion
In addition to conventional methods, the EMA assay can also be used as a first-line screening method for the diagnosis of membranopathies, especially HS. Every laboratory should establish its reference range.

Keywords: Eosin-5-maleimide assay, flow cytometry, membranopathies, hereditary spherocytosis
Title: Towards a perfect public private model for high end thalassaemia care - the Tamilnadu model

Abstract Category: Miscellaneous

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Abstract

Introduction
The long-term financial burden of caring for a person with Thalassaemia Major is high and this results in suboptimal care and early morbidity and mortality in low-and-middle income countries. In Tamil Nadu in India, the Chief Minister’s Comprehensive Health Insurance Scheme (CMCHIS) provides free medical treatment to people living below the poverty line. The CMCHIS is a government-sponsored health insurance scheme launched in 2012 that provides free healthcare services to families living below the poverty line (BPL) and the beneficiaries of the scheme are entitled to cashless treatment at empaneled hospitals, which include both public and private hospitals across the state. We share our experience over a ten-year period in enrolling patients for curative options like haematopoietic stem cell transplantation (HSCT) for patients with transfusion dependent Thalassaemia Major.

Patients and Methods
In 2012 December we signed an MoU between the community thalassaemia centre - VHS Thalassaemia Centre and the adjacent corporate hospital - Apollo Cancer Hospitals, Chennai to work with the government insurance scheme to provide access to high end care like HSCT for patient with Thalassaemia Major. The patients needed to submit proof of diagnosis, treatment, unique government identification in the form of Aadhar Card and Ration card to prove that they did come from poor socioeconomic background. With the HLA typing of the child and family members we counselled the family regarding the feasibility of a matched family donor (MFD), matched unrelated donor (MUD) and haploidentical donor HSCT. Social worker and administrative staff ensured that the entire process of enrolling the patients, applying for the CMCHIS authorisation and clearance and admission was seamless for the families. The HSCT packages provided by the government was substantially lower than actuals at 11,300 USD for a MFD and 22,000 USD for an alternate donor HSCT for the HSCT and one year follow up. All donor related expenses were also covered in the package. The private hospital provided the service as part of their Corporate Social Responsibility (CSR) activity. We documented the immediate and long-term outcomes of HSCT.

Results
We performed a total of 163 HSCT procedures for patients with Thalassaemia Major over a ten-year period. The patients aged from 11 months to 19 years with an equal male to female ratio. The number of children undergoing complex procedures like unrelated donor HSCT and haploidentical HSCT with post-transplant cyclophosphamide increased after 2017. All children received treosulfan, thiotepa and fludarabine based conditioning and the transplant related mortality was low at 5 %. The Thalassaemia Free Survival was 94% in the MFD group and 84% in the alternate donor group. The patient satisfaction feedback forms were collected during every visit and scored over 90%.

Conclusion
The Public- Private partnership model is the way forward for resource limited settings as the infrastructure required to set up multiple high-end facilities for a population of over 1 billion is a challenge in the real world. The cost of care over a twenty-year period worked out lower as most patients over the age of ten years accrued an annual expense of 1500 USD. The major impact of the HSCT procedure was that it resulted in increased awareness about Thalassaemia Major and helped in taking the prevention programme forward.
Title: Spinal extramedullary hematopoiesis in thalassaemia: a case series

Abstract Category: Miscellaneous

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Abstract

Background
Extramedullary hematopoiesis (EMH) is a non-malignant growth of hematopoietic tissue outside the bone marrow. As a compensatory mechanism for ineffective erythropoiesis in severe thalassemia, EMH most commonly occurs in the liver and spleen. Rarely it develops in the spine, leading to spinal cord compression and significant morbidity. In this case series, we present two cases of spinal EMH with cord compression and the treatment strategies employed.

Method
We describe a case series of patients with thalassemia diagnosed with spinal EMH between June 2022 and June 2023.

Results
Case #1 describes a 21-year-old woman with transfusion-dependent beta-thalassemia who experienced gradual lower limb weakness over three weeks. Physical examination showed spastic paraplegia with bilateral lower limb power of 0/5 and loss of sensation from T8 downwards. MRI revealed an intradural EMH lesion extending from T4 to T8. With a treatment approach involving dexamethasone, hydroxyurea and hypertransfusion, followed by radiotherapy, the patient achieved full neurologic recovery. In case #2, an 18-year-old man with transfusion-dependent beta-thalassemia presented with sudden onset bilateral lower limb weakness for a week. MRI confirmed spinal extradural EMH from T3 to T7, causing severe spinal canal stenosis. An urgent intervention consisting of radiotherapy, hypertransfusion, dexamethasone and hydroxyurea resulted in a complete neurologic recovery.

Conclusion
This case series not only adds to the limited literature on EMH but also highlights that invasive surgical intervention can be avoided with early diagnosis and prompt medical management, including hydroxyurea, dexamethasone, hypertransfusion and radiotherapy. Full neurological recovery remains possible despite more than a week of symptom onset. Indeed, a multidisciplinary approach involving haematologists, radio-oncologists and blood bank services plays a crucial role in achieving positive outcomes.
Title: Scalp vein set for venous cannulation in transfusion dependent thalassaemia major - a safe and effective long-term measure

Abstract Category: Miscellaneous

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Abstract

Background
Venous cannulation is among the most stressful and painful experiences for patients with thalassemia who need regular blood transfusion. The quality of life improves dramatically when we use methods to reduce pain and thrombophlebitis. We share our experience with the use of scalp vein sets over a 15-year period to reduce the pain of venous cannulation and thrombophlebitis in patients with thalassemia.

Methods
We performed a retrospective study at our VHS Thalassaemia Centre, Chennai, India between October 2006 and June 2023 and enrolled all patients undergoing regular transfusion at the centre. We cannulated all patients using a blue 23-gauge butterfly needle 0.6 mm x 19 mm to obtain a sample for checking the haemoglobin level and cross matching and we used the same venous access to complete the transfusion. We ensured that we accessed either the dorsal vein of the hand or the brachial vein in the antecubital fossa. Three experienced nurses performed the all cannulation over the 15 year period. We measured the intensity of pain by a Visual Analogue Scale (VAS). We also documented the incidence of thrombophlebitis and the incidence of more than two attempts at cannulation at every patient visit.

Results
A total of 394 patients received regular transfusion at our centre for at least five years. Some patients had a successful haematopoietic stem cell transplantation (HSCT) and stopped the transfusion programme. There are currently 129 patients on regular transfusion and most of the adult patients come two times a month for transfusion. A total of 46440 cannulations have been performed over this time period. The percentage of patients needing over two attempts at cannulation was 0.001% (52/46440). The pain score as per Visual Analogue Score (VAS) was less than 3/10 for all cannulation attempts. The incidence of permanent thrombophlebitis resulting in failure to cannulate the vein occurred in 1.7% of the patients.

Conclusions
The use of scalp vein set to cannulate patients for blood transfusion is an effective method in the reduction of venous cannulation pain. Needle phobia--fear of medical devices--is a significant problem in children and adults on long term transfusion. Studies have shown that sixty-eight percent children and 52% of adults are needle phobic. Single cannulation by experienced and familiar staff helped reduced aversion, anxiety, fear, and overall stress. Our study highlights the use of simple measures to prevent long term thrombophlebitis in multiply transfused individuals.
Title: Scurvy in thalassemia: a case series

Abstract Category: Miscellaneous

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Abstract

Background
Thalassemia patients are “advised” to limit dietary consumption of vitamin C as it enhances gastrointestinal iron absorption of non-heme iron, reduces both ferric and ferrous ions in tissues which lead to cellular death. Thalassemia patients are at higher risk of vitamin C deficiency which causes scurvy.

Case Illustrations
A 11 year-old girl with β/HbE-thalassemia was admitted due to recurrent gum bleeding for 3 months. Within the last two weeks, a hemorrhaging mass was growing on her mouth. Secondary infection soon followed, accompanied by a painful sensation during eating. Biopsy result showed chronic inflammatory granulomatosis without signs of malignancy. Laboratory test revealed low level of serum vitamin C. She received vitamin C 200 mg (5 mg/kg/day) per oral for 14 days, resulting in symptom improvement within 4 days of consumption. A 15 year-old girl with α-thalassemia complained of bilateral knee swelling and fatigue for 1 month. She experienced walking difficulties due to pain during active movement. Simultaneously, progressive gum swelling occurred. During admission, paracetamol could not relieve the pain (visual analogue scale 4), hence morphine was administered as needed. She seldom eats fruits and vegetables; therefore, scurvy was suspected. X-ray examination of the knee joints only revealed bilateral Hoffa pad edema without sign of subperiosteal hemorrhage, scurbitic zone, Wimberger’s ring, or Pelken’s spur. Her complaints were resolved after she received vitamin C 300 mg/day (10 mg/kg/day) per oral for three days, which then continued for 14 days.

Conclusion
Scurvy can be diagnosed based on clinical manifestation, serum vitamin C level, and clinical improvements after vitamin C administration. Pathognomonic radiologic signs may not appear in early onset of the disease. Vitamin C administration may relieve bone pain significantly. Low dose vitamin C (5-10 mg/kg/day) for 14 days was effective in these patients, with significant clinical improvement after 5 days of treatment.
Title: Effects of Educational Intervention on Transition Readiness Scores Among Adolescent and Young Adult Thalassaemia Patients

Abstract Category: Miscellaneous

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Abstract

Background
In Malaysia, transition of care for thalassaemia patients from paediatric to adult healthcare system is done without proper assessment of patients’ readiness. The objectives of this study were to examine the effect of educational intervention on thalassaemia patients’ transition readiness scores and to determine the possible factors which may affect the scores.

Methodology
This quasi-experimental study was conducted over a 3-month period in thalassaemia daycare of a tertiary paediatric hospital. Subjects were required to complete a modified UNC TRxANSITION Scale, a transition readiness assessment tool, pre- and post-educational intervention. The tool consisted of 10 domains; one point was awarded for correct answers in each domain, with a maximum score of 10 points for the whole questionnaire. Educational interventions were administered via pamphlets and videos. Pre- and post-intervention scores were obtained and analysed.

Results
Twenty-one transfusion-dependent thalassaemia patients aged 13 to 18 years old participated in the study. Overall pre-intervention score for the patients was low with a median of 3.84 (IQR 25th 2.00; 75th 4.67). Patients demonstrated improvement in the total score after the educational interventions, median score of 5.17 (IQR 25th 5.17; 75th 5.29) (p<0.05). A significant improvement post-intervention was observed for domains involving type of illness, treatment, adherence, self-management skills and nutrition (p<0.05 for all domains). There were no association between age, gender, duration of illness, level of education and financial status on transition readiness scores.

Conclusion
Educational intervention via educational videos and pamphlets successfully improved patients’ transition readiness scores. Lower baseline, the pre-interventional score shows the need for a structured healthcare transition preparation programme.
Title: Assessment of serum folate level among β-thalassaemia traits-a Case-control study

Abstract Category: Miscellaneous

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Abstract

Background
There is no consensus amongst clinicians about the need for regular folic acid replacement for individuals with the heterozygous state of β-thalassemia state (BTT). The increased ineffective erythropoiesis, albeit to a mild degree, could make them vulnerable to folate deficiency, especially if there is an associated dietary deficiency. Community-based studies in Sri Lanka have previously shown a high prevalence of folate deficiency in the community reaching even 43%, very likely suggestive of dietary deficiency. This study was designed to assess dietary folate consumption and serum folate levels in those with BTT viz a viz healthy matched controls.

Method
This case-control study includes 100 sets of samples, including a β-thalassaemia trait and an age, sex and BMI matched normal individual from the same household in each set, aged between 5-25 years. Serum folate levels were determined using a fully automated Cobas immunoassay analyzer. The dietary intake of each participant was determined by recording 24-hour dietary recall on three consecutive days and calculating the average daily intake of macro and micronutrients.

Results
33/98 (34%) cases (mean; 4.88 ng/mL) and 24/99 (24%) controls (mean; 4.76 ng/mL) had serum folate deficiency (<3 ng/mL) while 37% (36/98) of cases and 49% (48/99) of controls were at risk (3-5.9 ng/mL) for deficiency. Statistically significant differences were not observed (p>0.05) in serum folate levels between cases and controls. Dietary folate intake was low but not significantly different between those with BTT (mean; 181 μg) and controls (mean; 182 μg). There was no significant correlation between serum folate or dietary folate levels among cases (r= 0.097) or controls (r=0.098).

Conclusion
There were high levels of folate deficiency in both controls, and those with BTT (>24% and 34%), but those with BTT were no more likely to be folate deficient than the controls. This research was funded by the AHEAD (grant number; AHEAD/PhD/R1/AH/040).
Title: Foetal haemoglobin inducers for reducing blood transfusion in non-transfusion-dependent-beta-thalassaemias

Abstract Category: New Advances in Treatment

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Abstract

Background
Non-transfusion-dependent-beta-thalassaemia (NTDßT) is a subset of inherited haemoglobin disorders which led to anaemia of varying severity. People with NTDßT tend to have higher foetal haemoglobin (HbF) levels, making them less dependable on blood transfusion for survival. However, intermittent transfusions may be required to prevent complications of chronic anaemia, hypercoagulopathy and excessive gut iron absorption. This has led to the emergence of treatments that could increase HbF levels. HbF inducers stimulate HbF production without altering any gene structures have been used in the treatment for people with NTDßT.

Objective
To summarise available data that compare the effectiveness and safety of HbF inducers for reducing blood transfusion in people with NTDßT.

Method
Searches from study registries and databases, including three in Chinese (CENTRAL, PubMed, Embase, clinicaltrials.gov, WHO ICTRP, CNKI, VIP, Wan Fang) were conducted from inception till August 2022, using key search terms. Randomized controlled trials (RCT) and quasi-RCTs using HbF inducers on people with NTDßT were selected. The selection, data extraction and management of included studies were done using standard Cochrane methods.

Results
Seven RCTs involving 291 people with NTDßT, aged two to 49 years, from five countries were included. There were 10 comparisons using eight different HbF inducers (four pharmacological and four natural): three RCTs compared a single HbF inducer to placebo and seven to another HbF inducer. None of the studies reported changes to the frequency of blood transfusion. With low certainty evidence, all inducers may have caused small differences in haemoglobin and HbF between intervention groups. Data on adverse effects and optimal doses are limited.

Conclusion
There is uncertainty whether any of the eight HbF inducers have a beneficial effect on people with NTDßT. More studies comparing a HbF inducer with a placebo are needed to evaluate its safety, efficacy and therapeutic duration.
Title: Educational, employment and marital status of young adults with transfusion-dependent thalassemia in India

Abstract Category: New Advances in Treatment

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Abstract

Background
Recent evidence suggests that 63% of patients with transfusion-dependent thalassemia (TDT) are expected to survive through the age of 50 if treated optimally. Whilst the average life span varies widely in low-middle income countries owing largely to disparities in access to healthcare, significantly increased proportion of patients are surviving well into adulthood. It is, therefore, vital to evaluate if they are achieving academic and professional goals comparable to their peers. This study aimed to: a) evaluate the proportion of adults at 4 thalassemia centres in North India b) collate their educational, employment status and compare this data for healthy young adults in India.

Methodology
Data was collected on the proportion of adults with TDT at thalassemia day care services at 4 centres representing public, private and trust sectors of healthcare in North India with regards to age, educational and employment status, marital status and parenthood.

Results
A total of 514 patients were attending for treatment regularly at these centres with 222 (43%) being above the age of 18 years. 93 (18%) were above 25 years of age. 59% of the adults in this cohort had a graduate, post-graduate or professional degree. Ninety-eight (44%) of adult patients were employed or self-employed. Thirty three(35.4%) of the patients above 25 years were married and 17.2% were already parents.

Conclusions
The above data reaffirms that whilst a lot more needs to be done, a significantly higher proportion of TDT patients are surviving well into adulthood. The majority of these adult patients had received higher education and this proportion was much higher than the average status reported for healthy young adults in India. Employment status was comparable to national statistics for healthy peers. The educational, marital and parental status documented in this study may well reflect improved medical management and societal perceptions regarding transfusion-dependent thalassemic patients in India.
Title: The efficacy of fetal hemoglobin inducers in adult transfusion dependent beta thalassemia patients: a comprehensive look and feasibility analysis in Indonesia

Abstract Category: New Advances in Treatment

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Abstract

Background
HbF induction is well known to alleviate thalassemia beta. This review was aimed to explore the possibility of using HbF inducers, namely hydroxyurea (HU), butyrate and derivatives (BU), decitabine (DC), and thalidomide (TD), in Indonesian adult patients.

Methods
Records were retrieved from Pubmed (Medline), Embase, and Cochrane. Keywords used were combinations of “hydroxyurea”, “butyrate”, “decitabine”, “thalidomide”, and “thalassemia beta major”. Exclusion and inclusion criteria were made to select suitable articles, which obeyed the PRISMA algorithm. Selected records undergone data extraction and critical appraisal using therapeutic study checklist from CEBM Oxford.

Result
As many as 2 RCTs and 5 NRCTs from 1995 to 2022 were found to fit the criteria. HU was used predominantly across studies. All studies were found to be valid and important according to CEEBM checklist, however a few deemed to offer weak evidences. HbF induction were found to be moderate-to-highly improving the transfusion dynamic, such as blood volume per unit weight (d = -0.34—(-1.33)) and transfusion independency measured in month (d = 2.60 to totally independent), but remains inconsistent in term of improving hematologic profiles, such as pre-transfusion Hb (d = -1.33—6.10), as well as erythropoietic stress, ferritin, and hemolysis. Genotype Xmn1 polymorphism (especially T/T), IVSII-1 (G>A), increased HbF > 1.5%, and HbE (Cd26) were found to respond well to the therapy, while genotype IVSI-5 (G>C) predicted poor response. These findings do not support HbF induction in Indonesia thalassemia patients as IVSI-5 is the major genotype and low frequency of Xmn1 polymorphism. Main adverse effects include myelosuppression and gastrointestinal symptoms, of which were found to be mild and improved after drug cessation.

Conclusion
HbF induction moderate-to-highly improves transfusion dynamic, therefore is a viable option as an adjuvant in patients with major βthalassemia. However, researcher highly recommends commencing a clinical trial in Indonesia.
Title: Retrospective analysis of the response of Luspatercept among a small cohort of transfusion dependent beta thalassemia patients in Hospital Ampang

Abstract Category: New Advances in Treatment

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Abstract

Introduction
Luspatercept has been shown to act as a ligand trap, selectively suppressing the deleterious effects of GDF11 that blocks terminal erythroid maturation, restoring normal erythroid differentiation and improving anemia in Beta Thalassemia and MDS-RS.

Abstract
We analysed the use of luspatercept in 4 patients with transfusion dependent beta thalassemia at our centre. We targeted a certain group of patients with Beta Thalassemia who had difficulty achieving pre transfusion hemoglobin levels due to alloimmune antibodies or hypersplenism of these patients, 1 patient had hypersplenism, 2 had alloimmune antibodies and the other had neither of these problems. Genotypically 2 of them have beta zero thalassemia and 2 have HbE Beta Thalassemia.

All these patients were given the standard 1mg/kg and subsequent dose increment to 1.25mg/kg according to recommendation. We analysed the average increment in hemoglobin concentration after initiation of Luspatercept. The median hemoglobin concentration over 24 weeks before initiation of Luspatercept was compared to the median hemoglobin concentration on optimal dose of luspatercept for 24 weeks.

The average hemoglobin increment for the patients with beta zero thalassemia was 1-1.5g/dL and for the patients with HbE beta thalassemia the average increment was 2.0-2.4g/dL. With this we were able to either reduce the number of packed cells transfused or increase interval of transfusion.

Conclusion
We can therefore conclude that the use of Luspatercept has Resulted in an increment in hemoglobin levels in all the patients analysed. In this series of 4 patients analysed, patients with HbE Beta thalassemia seem to fare better with a greater hemoglobin increment and subsequent reduction in transfusion burden.
Title: Phenotypic diversity - interaction of hemoglobin E with δβ thalassemia and Hereditary Persistant Fetal Hemoglobin (HPFH)

Abstract Category: Non-transfusion Dependent Thalassaemia

Authors: Hafizah Hashim, Siti Zaharah I, Nor Syamsuridah A, M.Hafiz S

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Abstract

Background
Hemoglobin E (Hb E) is the most common Hb variant in Peninsular Malaysia around 3 to 40 percent. δβ-thalassemia or Hereditary Persistant of Fetal Hemoglobin (HPFH) is uncommon in Kedah. Presumptive diagnosis of δβ-thalassemia and HPFH estimated around 2.0% from 8000 samples. We described three cases of compound heterozygous of Hb E with δβ-thalassemia and one case of compound heterozygous of Hb E with HPFH 6.

Case presentation
Case 1 and 2 were from thalassemia screening programme. Both samples were from 16 years old Malay boys, asymptomatic noted to have microcytic hypochromic RBC. Third case was 9 years old boy presented at 2 years of age due to pneumonia. He had multiple admission due to infection, however his hemoglobin levels able to maintain more than 7.0g/dL and he only required twice blood transfusion. Fourth case was a 70 years old Malay man noted to have mild microcytic hypochromic anemia during routine checkup in the clinics. Never had any history of blood transfusion. Hb analysis from all samples shows reduced Hb A less than 5%, normal Hb A2, increase Hb F range from 40.8% to 60.6%, increase Hb E range from 35.8% to 53.7%. Molecular characterization of all cases confirmed compound heterozygous of Hb E with δβ(Thai), Gy(AAy68)^ Asian Indian Deletion inversion , HPFH 6 for case 1, case 2 and 3, case 4 respectively.

Conclusion
All of these cases highlight phenotypic diversity in compound heterozygous Hb E with δβ thalassemia or HPFH.
Title: Long-term erythroid response data from Non-Transfusion-Dependent (NTD) patients with beta-thalassemia receiving luspatercept in the beyond trial

Abstract Category: Non-transfusion Dependent Thalassaemia

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Abstract

Background
There are no approved treatments for NTD β-thalassemia associated anemia. Luspatercept durably increases hemoglobin levels in NTD β-thalassemia patients.

Aim
To report long-term efficacy of luspatercept in NTD β-thalassemia patients from the BEYOND trial (NCT03342404).

Methods
Patients (N=145) had either NTD β-thalassemia or HbE/β-thalassemia and hemoglobin ≤10 g/dL. Patients received luspatercept (1.0-1.25 mg/kg) or placebo subcutaneously for ≥68 weeks. Assessments included mean change in hemoglobin from baseline (continuous 12-week intervals), erythroid response (mean hemoglobin change from baseline of ≥1 g/dL, rolling 12-week intervals), and RBC transfusion incidence.
Results
As of 22Sep2021, 83 (86.5%) and 16 (32.7%) luspatercept and placebo patients completed ≥ 96 weeks of treatment, respectively. Median (range) treatment duration was 150.1 (15.0-185.4) versus 61.1 (3.0-138.0) weeks for luspatercept versus placebo, respectively. Mean hemoglobin change from baseline with luspatercept was 1.28 g/dL (weeks 1-12) and 1.48 g/dL (weeks 13-24). Hemoglobin change from baseline with luspatercept was nominally significant up to week 96. Proportion of patients with an erythroid response increased from 91.7% (88/96) to 93.8% (90/96) between the primary (14Sep2020) and current data cutoffs, respectively. The proportion of luspatercept responders with ≥ 12-week rolling response increased from 35.2% (31/88) to 61.1% (55/90) and mean total erythroid response duration from 611.1 to 873.1 days, between the primary and current data cutoffs, respectively. 10.4% (10/96) vs 32.7% (16/49) of luspatercept versus placebo patients received ≥ 2 transfusions (weeks 1-96). Mean RBC units (0.7 vs 2.2) and transfusion events (0.4 vs 1.3) per patient was lower in luspatercept arm and remained stable with luspatercept (0.2 units and 0.2 events; weeks 97-144).

Conclusion
Hemoglobin levels were sustained and significantly improved; erythroid response duration improved in NTD β-thalassemia patients with long-term treatment. Few patients required transfusions, with cumulative incidence remaining low and relatively stable through week 144. (First published: Taher et al. Blood 2022;140[Suppl 1];8210-8212).
Title: Detection of Thalassaemia/Hemoglobinopathy among 16-year-old students under Thalassaemia school screening program in the state of Kelantan

Abstract Category: Prevention

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Abstract

Background
Thalassaemia and Hemoglobinopathies are the most common inherited red blood cell disorders. It is classified into transfusion dependent Thalasaemias (TDT) and Non transfusion dependent Thalasaemias (nTDT). The TDTs has significant morbidity, mortality, financial and emotional burden to the families and health care system. The disease is preventable if an individual or couple are able to make informed choice of their genetic risk of having offspring with thalassaemia. Thus, the screening program is an effective method in detection of carrier and consequently couple at risk in Malaysia, a national screening program under Ministry of Health targeting 16 year old secondary school students was introduced in 2016.

Aim
To determine number of thalasaemia or hemoglobinopathy cases detected from school screening program to identify the common type of thalasaemias/hemoglobinopathy in state of Kelantan.

Methodology
Retrospective study of 16-year-old students in thalassaemia screening throughout all district in Kelantan in 2017,2018, 2019 and 2022. Full blood counts were performed as a screening tool, followed by Hb analysis by Sebia Capillary 2 and HPLC beta thalassaemia short program.

Results
A total of 93,237 students were screened for Thalassaemia. The most common Thalassaemia/hemoglobinopathy detected are Hb E heterozygous (5.3%), possible Hb Constant Spring (1.8%) and Beta Thalassaemia trait (0.9%). Cases suspected for alpha thalasaemia trait accounts for 5.4 % and suggested for confirmation by molecular study.

Conclusion
Hb E heterozygous, Hb Constant Spring and Beta Thalassaemia trait are common in Kelantan state. The thalassaemia screening program has increased the detection of carriers and hopefully it will help to reduce the birth of new TDTs if carriers are aware of their status.
Title: A pilot study- Thalassemia Screening program in Bangladesh

Abstract Category: Prevention

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Abstract

Background
In Southeast Asia Hb-E & Hb-Beta-Thalassemia are most prevalent. According to WHO, Bangladesh has 7% thalassemia carriers (Hb-E 4% & Hb-Beta thalassemia 3%) in decades back, but on recent statistics this figure increases to 10-12% and approximately total 1.7 million people are thalassemia carriers. This high prevalence of thalassemia diseases is due to consanguineous marriage, lack of awareness, social stigma. Prevention of thalassemia is the main strategy to control the disease by mass screening.

Objectives
The primary objective is to identify thalassemia carriers in university students age group between 18 to 24 years. Secondary objective is to raise awareness about thalassemia and for no marriage between carriers.

Methods
One thousand university students from three colleges in three districts voluntarily participated in this pilot study. Questionnaire were provided to participants before final selection, based on inclusion criteria who were apparently healthy, had no previous history of blood transfusion and were not known cases of thalassemia. CBC was performed by automated cell analyzer for all participants. Hb-electrophoresis and ferritin were tested in those with MCV<80fl and/or MCH<27pg.

Results
Among 1000 students, 184 had MCV< 80fl &/or MCH<27pg, so Hb-electrophoresis and ferritin tests were done for them. Among them 124(12.4%) students had abnormal Hb- electrophoresis: Hb E-trait 58(5.8%), beta-thalassemia trait 17(1.7%), Hb-E disease 16(1.6%, including one Hb-EE/D variant), Sickle cell disease 3(0.3%), HPFH 1(0.1%) and low Hb-A2 29(2.9%). Prevalence of thalassemia carriers in Dinajpur, Dhaka and Chattogram districts were 9.9%, 6.5%, 5.9% respectively. Low Hb-A2(value <2.5%) associated with normal ferritin (≥24 ng/ml) in 14 samples were suspected for alpha thalassemia (1.4%, not included in carrier as not confirmed).

Conclusions
Prevalence of Hb-E trait(5.8%), Hb-beta trait(1.7%) & alpha-Thalassemia carrier(1.4%) are high in Bangladesh and varies regionally. Prevention of thalassemia requires accurate national carrier detection and subsequent adoption of national thalassemia prevention plan.

Keywords: pilot study, thalassemia, screening, carrier.
Title: Assessing the level of thalassemia awareness and prevention practices amongst Indonesian citizens

Abstract Category: Prevention

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Abstract

Background
Indonesia lies in the world’s thalassemia belt, signifying its high thalassemia gene frequency. Approximately over 2,500 thalassemia major cases were reported annually in Indonesia. Moreover, Thalassemia is the number 5 most expensive disease paid by BPJS Kesehatan (Indonesian National Insurance). However, there is a lack of awareness about Thalassemia, particularly among Indonesian youth. Therefore, this research is conducted to assess thalassemia awareness and prevention in Indonesia to reduce the burden on individuals and the healthcare system by promoting awareness and prevention practices in creating a Thalassemia-aware and healthier nation.

Research Method
Using a cross-sectional design and convenient sampling method, we included 200 participants aged 15 to 35 from 5 regions around Java. Structured questionnaires about thalassemia knowledge, preventive measures, and information sources were spread and analyzed.

Results
We found that 92.1% (186/200 participants) were aware of Thalassemia, but only 82.2% (166/186 participants) demonstrated clear understanding. DKI Jakarta had the highest population 59.6% (99/166 participants) with a clear understanding. Targeted awareness campaigns and educational programs are needed to enhance Thalassemia knowledge in Indonesia. TV and Social Media were major influencers with 42.4% (70/166 participants), emphasizing the importance of utilizing these channels for effective campaigns. A majority of participants with clear understanding (94.6%) recognized the significance of thalassemia screening before marriage, suggesting potential for preventive measures.

Conclusions
This research highlighted the need for targeted awareness campaigns and educational programs to enhance Thalassemia knowledge and prevention in Indonesia. In Conclusion, though most people were aware about Thalassemia, a smaller proportion showed clear understanding with DKI Jakarta leading and mass media played a major role in spreading the awareness. Continuation of the research is needed in order to promote deeper understanding amongst Indonesian youth.

Keywords: Thalassemia, Prevention, Awareness, Screening, Indonesia, Youth.
Title: Barriers to cascade screening and prenatal testing in families with thalassemia

Abstract Category: Prevention

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Abstract

Introduction
Identification of carrier state and prenatal testing is one of the strongest interventions for preventing hemoglobinopathies. In reality many parents proceed with next pregnancy untested. We evaluate the reasons for not opting for prenatal testing in families with >1 child with hemoglobinopathy.

Methods
Parents who had >1 child with hemoglobinopathies were interviewed. The survey analyzed demographic variables, awareness regarding preventing the disease, barriers for prenatal testing, financial implications and current opinion regarding prenatal testing.

Results
The center caters to 310 children with beta thalassemia, sickle cell anemia and sickle-beta thalassemias. Of these 22 families had >1 child with same disease. Of these, 17 families were surveyed. 3 families had disease in first-degree relatives. Consanguinity was reported by 1 and endogamy in 5. The median age of the index child was 14 years (2-22 years) and that of second child was 9 years. 23.5% fathers were illiterate. 47% were daily-wage earners. Majority belonged to lower or lower-middle class.

None of the parents were aware of hemoglobinopathies before the birth of their index child. 6/17 were informed that this disease is hereditary in nature. 4 knew that it could be prevented. None of them opted for prenatal testing for next pregnancy due to ignorance and misconceptions regarding the test. 11/17 had the second child even before the first baby was diagnosed. 41.2% has a second baby within 2 years of the first. 12/17 reported moderate and 5 reported severe financial stress, due to increased out-of-pocket expenditure and job absenteeism. All unanimously agreed that they will endorse prenatal testing for themselves and their family members. 7/17 have advised their relatives to undergo carrier testing for thalassemia.

Conclusion
Cascade screening is a strong tool to prevent genetic hematological diseases. Counseling to allay the myths is needed to motivate families to proceed with prenatal testing.
Title: Revolutionizing Thalassaemia Genetic Testing through the Incorporation of NGS-Based Thalassemia Assay

Abstract Category: Prevention

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Abstract

Background
Haemoglobinopathies, are widespread monogenic conditions posing a global health concern. Thalassaemia is significant in Cyprus, impacting about 12% beta-thalassaemia carriers and around 19% alpha-thalassaemia carriers. Traditional thalassaemia diagnosis focuses on common mutations or key genes, HBA and HBB. However, employing multiple methods leads to extended processing times, considerable expenses, and potentially inconclusive results.

Methods
We assessed Devyser’s commercial CE-IVD NGS Thalassemia kit, covering alpha and beta globin clusters (HBA1, HBA2, HBB). This kit detects SNVs, Indels, employing dual methods for CNV detection simultaneously. Initial assessment used 25 DNA samples, genotypically known and previously analyzed. Validation involved 100 DNA samples, analyzed with NGS Thalassemia kit and conventional methods. Amplicon Suite software (SmartSeq) facilitated data analysis, interfacing with databases like IthaNet, ClinVar, dbSNP, and GnomAD, enhancing real-time variant interpretation.

Results
The initial assessment of the NGS thalassemia assay highlighted its robust ability to accurately detect variations in the studied genetic loci. Additionally, the assay revealed variations previously unidentified through our traditional approach. This confirms its capacity for in-depth thalassaemia analysis. Validation successfully exhibited full agreement between NGS and our standard protocol. As a result, the NGS Thalassemia assay was smoothly integrated into our daily clinical practice from 2021, effectively managing around 3500 cases.

Conclusion
The NGS Thalassemia kit offers holistic genetic profiling in a single run with streamlined multiplexing. Its “one patient, one tube” approach enhances precision and accelerates assessment, saving time and resources. The integrated bioinformatics pipeline links seamlessly with vital resources like IthaNet, enhancing accuracy. The kit improves lab processes, aids physicians with precise data, and benefits patients’ diagnostic journeys.
Title: THALA_SCREEN/LINTAS - Developing a mobile application to identify screening targets in the extended family of thalassemia

Abstract Category: Prevention

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Abstract

Background
Thalassemia poses a double burden on medical care and healthcare financing due to increased prevalence and survival rates. In Indonesia, the thalassemia prevention program is in its early stages. Families with thalassemia cases have a higher risk of being carriers. To address this, the Thala_screen/LINTAS mobile application was developed as a screening tool for thalassemia carriers within the extended families of index cases with thalassemia.

Methods
The development of the application followed four phases. Firstly, content creation involved literature research, discussions with five experts, and pedigree design. Secondly, trial phase was conducted with a forum group discussion involving 30 subjects to evaluate the application’s acceptability and user experience through quantitative and qualitative research. Thirdly, content validation was performed using an assessment sheet, which was reviewed by the experts twice. Lastly, a usability study was conducted with 25 parents of thalassemia patients at Hasan Sadikin General Hospital, using ABCs questionnaires after using the application.

Results
The application’s content data was aligned with its objectives, including family demographic data presented in a pedigree chart. The initial dataset included thalassemia registry data. Quantitative research showed an 80.25% acceptability rate, while qualitative research indicated that the application provided relevant, useful, and accurate information presented in an appealing format. However, accessibility received an unsatisfactory response initially, which improved after reevaluation, raising the total validity index from 0.63 to 0.86. The usability study revealed favorable mean scores for the action (2.92) and behavior (0.85) sections, indicating the subjects’ interest and ease of using the application.

Conclusion
The THALA_SCREEN mobile application proved to be an acceptable and feasible tool for identifying thalassemia carrier screening targets in extended families. Its potential benefits could aid in the early detection and prevention of thalassemia, contributing to better healthcare management and cost-effectiveness in managing this hereditary condition.

Keywords: extended family, index, case, mobile application, screening, thalassemia
Title: What the parent felt - a survey of what parents of children with thalassemia perceive regarding disease and its management

Abstract Category: Psycho-social issues

Authors: Jedidiah Daniel, Manju Singh, Nita Radhakrishnan, Archit Pandharipande, Shruti Saxena, Eby P Baby

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Abstract

Introduction
During management of chronic diseases in children, the awareness and motivation of parent is vital to optimal care. Often anticipatory guidance provided by older parents are helpful for new families diagnosed with thalassemia. We analyzed parental awareness regarding various aspects of management of thalassemia patients at our center.

Methods
A paper-based questionnaire was administered to one parent accompanying children with either transfusion dependent (TDT) or non-transfusion dependent thalassemia (NTDT) at our center. Institutional ethics committee clearance was obtained. The center provides regular counseling for adherence to medicines, good dietary practices and for genetic counseling to all patients.

Results
The center caters to 310 children with beta thalassemia, sickle cell anemia and sickle-beta thalassemias. 59 parents of 69 children with thalassemia participated in the survey. 66 were TDT. Majority were from lower socioeconomic status. The median age was 8.38 years. Mean pre-transfusion Hb was 8.8gm/dl. 17 required fortnightly transfusions. The average cost spent by family for each transfusion ranged from 1.2 - 96 USD. The cost of admission, investigations, NAT tested leukodepleted blood and chelation is borne through governmental funds. Around 40% expressed difficulty despite free treatment received. Most families were counseled to give normal diet to children. 23 reported loss of appetite. 96% denied usage of any indigenous medicines/food items to improve hemoglobin. 59.6% adhere to dietary counseling given from hospital. Majority were aware of the genetic counseling received regarding preventing thalassemia. However, only 22 (37%) were aware that bone marrow transplant is a treatment option for their child.

Conclusion
Although efforts are put into place for education and counseling of parents, misconceptions still remain probably because of poor educational status. Repeated reinforcement is needed so that families perceive the disease correctly and contribute to better outcome of their children.
Title: Depression, anxiety, and stress among thalassemia patients in Aceh Indonesia

Abstract Category: Psycho-social issues

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Abstract

Background
According to the Indonesia’s basic health research of the Ministry of Health. Aceh is the province with the highest prevalence of thalassemia carriers in Indonesia with a rate of 13.4%. This is reinforced by the increasing number of new thalassemia transfused at various regional hospitals throughout Aceh. Currently there are more than 750 people with thalassemia major and 60% of them are children, which means their life expectancy is low so that the number of adults with thalassemia is less. For adult’s thalassemia, several life challenges need a special endurance which may cause a mental breakdown.

Aim
This study aims to measure the Depression, Stress and Anxiety (DASS) of the people with thalassemia in the city of Banda Aceh.

Method
As many as 91 people are surveyed through an online questionnaire form using a 42 DASS questionnaires and the data is scored and analysed using SPSS. The results show that 33% respondents are in the state of moderate to extreme Depression, 53% respondents are in the state moderate to severe anxiety and 34% respondents are in moderate to severe stress.

Conclusion
Mental health is also a serious issue for people with thalassemia. Hence a good mental health program must also be prepared by health services so that the physical and mental well-being of patients can be considered and increase life expectancy.

Keywords: Thalassemia, Depression, Anxiety, Stress, Aceh, Mental Health
Title: Dramatic improvement in patient compliance with chelation with cardiac T2* imaging - experience from a non-profit Thalassaemia society in India

Abstract Category: Psycho-social issues

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Abstract

Background
Advances in monitoring iron burden and access to optimal chelation is improving the prognosis and survival of Thalassaemia patients worldwide. However, compliance remains an important issue in these patients and iron overload results in cardiac disease, particularly in low-resource settings. We present here, our data on the impact of cardiac T2* MRI in improving the compliance with chelation in our cohort.

Patients and Methods
We conducted a study at the VHS Thalassaemia Centre in Chennai in India between January 2019 and June 2023 and included all patients above 12 years of age with transfusion dependent thalassemia major. We collected data retrospectively from their chart reviews. We documented demographic data and serial serum ferritin and the iron chelation details. We referred the patients every two years for evaluation of cardiac and LIC (liver iron concentration) to estimate total body iron with a 1.5-Tesla MRI scanner. We defined iron overload as cardiac T2* value of less than 20 milliseconds and liver iron over 7.5 mg/gm weight of the liver. We discussed the results with the patient and their family and recommended injection deferoxamine subcutaneous 5 days a week at 40mg/kg/day. We replaced new vials every two weeks once the used vials were returned to ensure compliance.

Results
A total of 57 patients with 30 male and 27 female patients underwent at least two cardiac MRI evaluation during the study period. There were interruptions in our study during the Covid 19 pandemic due to issues in logistics especially with the delivery of iron chelation to patients in remote areas. MRI scan revealed iron overload in the heart in 7 patients and liver in 50 patients. The compliance with deferoxamine improved from 38% to 74% in our cohort. The remaining 26% could not continue at least 5 days a week injectable chelation due to financial constraints, painful swelling at the injection sites, planning pregnancy, pregnancy, and lactation. The follow up MRI showed a reduction in tissue iron overload in over 50% of our patients which further improved compliance.

Conclusion
The management of iron overload in thalassaemia involves a multidisciplinary team. We need to encourage long-term patient adherence through patient education, serial monitoring that a patient or their family can understand and feel rewarded for the effort. We recommend that all patients in low-middle-income countries undergo cardiac T2* MRI to help understand their body tissue iron balance and improve chelation compliance.
Title: **TIF Research Project: Mental Health Impact of COVID-19 in Thalassaemia Patients**

**Abstract Category:** Psycho-social issues

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**Abstract**

**Background**
The purpose of this qualitative descriptive study was to better understand the mental health of persons living with Thalassemia from their real-world perspectives. A total of 6 research participants participated in this study. Semi structured interviews were conducted post pandemic to help to gain insight into the totality of this experience from different geographical locations, three participants are from Cyprus and three from northern Greece. Transcribed into written text and was analyzed by the research team using individual reflection of what was relevant to help answer the research questions, which were then complied and aggregated with qualitative consensus was reached followed by content analysis where Findings from the study were identified.

**Methods**
The research method qualitative description (QD) was utilized for this study, with the intention of describing the experiences, concerns, and realities of people living with Thalassemia (PLT) during the COVID 19 pandemic. A qualitative descriptive design is the methodology of choice when a researcher asks questions and seeks a straightforward and accurate description of human experience.

**Results (findings)**
Pre pandemic care for their Thalassemia for the research participants was described as effective and reliable. The pandemic - common experiences, The three most common themes mentioned were the following:
1. **Fear/Anxiety** brought on by the pandemic, this was expressed by all interviewees with varying degrees.
2. **Vaccination** attracted the attention of all interviewees.
3. **Social isolation** was mentioned.

**Conclusion**
This qualitative study revealed that Covid-19 was an additional layer that affected the mental aspect and played a critical impact on thalassemia patients who already were handling a lot on day-to-day basis of taking care of themselves in clinical as well as in social setup. If a holistic and psychosocial care is provided diligently, then long survival is to be expected while inadequate treatment will lead to increasing complications and a reduction in lifespan.
Title: Investigating health literacy in thalassemia: The importance of obtaining multi-stakeholder perspectives in improving health outcomes among patients

Abstract Category: Quality of Life

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Abstract

Background
Thalassemia is a rare hereditary hemolytic anemia with global prevalence. Patient populations consist of different genotypes with varying clinical expression. Healthcare professionals (HCPs) understanding and patient unmet needs vary between sub-populations and regions. The Thalassemia Advocacy Advisory Council (AAC) (supported by Agios Pharmaceuticals) was founded to define ways to address community needs. It is an international, multi-stakeholder group including patients, caregivers, advocates, and HCPs with a clear vision: People affected by thalassemia can collaborate to address educational needs and have their voice heard, irrespective of disease sub-type, background, or geography.

Method
To understand how their vision translates into action, AAC Members each shared their personal perspective on community unmet needs through a qualitative survey. The survey consisted of open-ended questions which aimed to collect each Council Member’s perspective on the top three unmet needs for patients and HCPs in their region and globally. This was consolidated thematically by Agios and presented for prioritization by all the Council Members.

Results
Council Members agreed that a priority unmet need is a lack of disease understanding, including its complications, among patients. They suggested that this could drive poor treatment adherence to the standard of care. They also acknowledged a need for improved education and advocacy among HCPs to better support patients. An audit of published literature was also conducted to understand what was known on this priority topic, and to guide the group’s ideation of their project.

Conclusion
By considering the community’s needs from a multi-stakeholder perspective, a rigorous and thorough assessment was conducted. As a next step, the group will conduct a global survey to better understand the community’s perspective and identify initiatives to address patients’ health literacy based on the survey insights.
Title: The expertise center of hemoglobinopathies and their complications of Hippokration General Hospital Athens: Enhancing patient outcomes and care through integrated teamwork

Abstract Category: Quality of Life

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Abstract

Introduction
The abstract discusses the impact of the Expertise Center of Hemoglobinopathies and Their Complications in Greece, which employs an integrated and multidisciplinary approach to address the challenges posed by hemoglobinopathies. By providing comprehensive care, this center aims to improve access, patient outcomes, resource utilization, and daily care for individuals affected by these complex blood disorders.

Material-Method
The collaborative model of the center is built upon several fundamental principles, including humanity and understanding, innovation, and teamwork. This teamwork involves diverse specialists, such as hematologists, cardiologists, hepatologists, endocrinologists, nephrologists, psychiatrists, pain specialists, radiologists, nurses, and technicians, to ensure a holistic approach to treatment. The center also prioritizes nationwide accessibility to cater to patients from all over Greece and focuses on equity in improving quality of life, regardless of their geographical location. Moreover, efficient financial resource utilization is emphasized through preventive measures to reduce long-term complications.

Results
Over the 2-year period from 2020 to 2022, the center served more than 1800 patients annually, achieving remarkable outcomes in various areas. Notably, 120 multi-transfused patients from the Thalassemia and Sickle Cell Unit received consistently scheduled transfusions. No adverse reactions were observed during blood transfusions due to the use of concentrated and leucoreduced red cells with proper antigen matching. The introduction of luspatercept therapy resulted in a 30% reduction
in transfusion requirements for 22 thalassemia patients. The center also achieved impressive results in clinical trials, with over 90% of patients with sickle cell disease meeting clinical trial endpoints. Almost all patients were successfully vaccinated against COVID-19, leading to zero mortality after illness. Furthermore, the center successfully treated 90% of patients with Hepatitis C Virus infection and enabled early detection and treatment of hepatocellular cancer cases through biannual liver ultrasounds.

For patients with cardiac dysfunction, the center provided comprehensive monitoring, advanced diagnostic evaluation, and newer therapeutic and intervention services, resulting in early detection of arrhythmic events. Quality of life significantly improved for patients with severe aortic stenosis who underwent TAVI, with a 50%+ increase observed.

**Conclusion**

The Hemoglobin Diseases Expertise Center’s patient-centered and innovative approach has revolutionized blood disorder management in Greece. With its comprehensive framework, the center can serve as a guide for managing hemoglobinopathies on a global scale.
Title: Ageing with Thalassaemia and Sickle Cell disease in Greece: Assessing quality of life and supportive interventions

Abstract Category: Quality of Life

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Abstract

Introduction
Hemoglobinopathies like thalassemia and sickle cell disease are among the most prevalent inherited blood disorders worldwide and have high prevalence in Greece. Regular blood transfusions and iron chelation therapy may prevent complications and enhance quality of life (QoL) in these lifelong illnesses, but substantial disease burden and morbidity persist. This cross-sectional study evaluated clinical practices and patient-reported experiences among Greek adults with hemoglobinopathies.

Materials and Methods
Anonymous online questionnaires were completed by 114 Greek adults with hemoglobinopathies (mean age 49.4 ± 9.6 years, 69% female) after informed consent and ethics committee approval. Questionnaires assessed demographics, disease characteristics, treatments, health monitoring, concerns, and QoL. Participants self-reported their diagnosis and treatments.

Results
Most participants had transfusion-dependent ß-thalassemia (66%) or ß-thalassemia/sickle cell disease 29/114 (25%). Regular transfusions began before age 5 for 60% and 82% currently receive biweekly transfusions. While 77% used iron chelation, only 46% were fully compliant. Patients commonly saw cardiologists (88%), endocrinologists (61%) and other specialists annually. Reported complications included osteoporosis (54%), arrhythmias (32%) and thyroid disorders (28%). While patients expressed concerns about blood shortages (54%) and reactions (48%), most felt secure about blood safety (79%) and trusted physicians (90%) regarding transfusions.

Conclusions
This study provides valuable insights into current clinical practices and patient perspectives for Greek adults with hemoglobinopathies. Specialized medical care has enhanced patient QoL compared to earlier treatment eras. Further optimizing treatment adherence, guaranteeing appropriate monitoring, fully addressing patient worries, and supporting patient-provider relationships present important opportunities for improvement. As modern therapies increase survival, managing lifelong complications and impacts of these chronic disorders will be an ongoing challenge. A patient-centered approach that fully integrates patient concerns and experiences into care is required. Maintaining QoL gains and making further progress will require persistently supporting patients across their lifelong illness journey.
Title: Quality of life and challenges experienced by the surviving adults with transfusion dependent thalassaemia in Malaysia: a cross sectional study

Abstract Category: Quality of Life

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Abstract

Background
Improvement in medical management has enabled transfusion dependent thalassaemia (TDT) patients to survive beyond childhood, building families, and contributing to the labour force and society. Knowledge about their adult life would provide guidance on how to support their needs. This study aimed to explore the general well-being of adults with TDT, their employment status and challenges.

Methods
This study recruited 450 people with TDT, aged 18 and above, through all regional Thalassaemia societies in Malaysia and from two participating hospitals, over five months in Year 2016. A self-administered questionnaire including ‘Healthy Days Core Module’, WHOQOL-BREF and employment measurements was used. Multiple linear regression models were fitted with associations adjusted for several potential confounders.

Results
A total of 196 adults with TDT responded. Almost half (45%) had comorbidities and 9% suffered multiple complications, resulting in 23% seeking treatment more than twice monthly. Within a month, they suffered for at least three days with poor physical and or mental health and their normal daily activities were disrupted for up to three days. 36% were jobless and 38% of those with a job were receiving salaries below RM1000. The mean WHOQOL-BREF score (mean(SD)) was: physical health 62.6(15.5), psychological health 64.7(15.7), social relationship 64(15.9), environmental health 60.8(16.7). Having days with mental issues, financial status, education level, ethnic and marital status were main factors affecting QOL scores. Open questions showed dissatisfaction with health service provision, conflicting judgement in prioritising between health and job, and poor public empathy.

Conclusion
The adults with TDT in this study perceived their health as good with infrequent unhealthy days. Some have experienced substantial life disruptions in a rather non-supportive community and perceived that health services do not meet their needs. Future qualitative studies are needed to focus on their perceived needs and to look for more tailored supportive approaches.
Title: “Authentic Historicalness”: Making our history our Own

Abstract Category: Quality of Life

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Abstract

It is through the process of ownership of the past, of “authentic historicalness”, as Heidegger refers to it, that we can choose our fate. Acceptance and integration of our past lived experiences can help us open up to the world of possibilities. The past does not change but our experience of it in the now can change. This new understanding and experience of our world can create new perspectives for the future.

“The DNA of the Soul” (2002) is a synthesis of developmental theories that is progressively expanding with evidences from neuroscience and my growing psychotherapeutic experience. It is continuously enriched by my new understanding of what it means to be a human being-in-time. Always aware of finitude the element of time is crucial for understanding myself and life. We constantly change and evolve. Sometimes consciously and often unaware of the changes. The imprint of our lived experiences, however, never disappears. This realization prompted the allegory of a ‘psychic DNA’. Coming to terms with our thrownness facilitates “authentic historicalness” and the “choosing of our fate”. Physical, cognitive and emotional changes are re-integrated in our self-concept and understanding of others and the world. Crises, relationships and psychotherapy transform the way we are and relate, re-negotiating our existential dilemmas, i.e. our need and desire for connection vs our desire for autonomy and independence; needs for safety and stability vis a vis constant changes and impermanence, self-esteem and self-efficacy in a constant dialectic with self-doubt and diffidence. These ”dialectical tensions” are integral to our existence and everyday life. Making our history our own and liberating our hidden potentialities can be an important psychotherapeutic outcome.
Title: Education and employment status of patients with transfusion-dependent thalassemia: “Padhega India, Tabhi Toh Badhega India”

Abstract Category: Quality of Life

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Abstract

Background
The literacy rate in India is nearly 77% with a school dropout rate of 16.7% at the secondary level. Patients with transfusion-dependent thalassemia (TDT) face great difficulties in continuing education due to repeated hospital visits, the presence of comorbidities, and psychosocial issues. This survey was undertaken to assess the educational and employment status of adults with TDT.

Material and Methods
A survey was conducted amongst all patients with TDT > 18 years of age registered at Thalassemia Day Care Center (TDCC) in our hospital after obtaining informed consent. It consisted of demographic details, educational qualifications, and employment status of the patient. The socioeconomic status of the family was assessed as per the modified Kuppuswamy scale for the year 2022. The education and employment status were correlated with the age, sex, residence, education level of the parents, and socioeconomic status of the family.

Results:
A total of 117 patients were enrolled in the study with mean age of 24.7 ± 6.3 years and M: F ratio of 2.07:1. 19.6% of the participants belonged to rural backgrounds. 38.6% of patients had completed graduation and 19.7% had completed post-graduation or a professional degree. Nearly half (52.4%) of patients were employed and independent. The education and employment status correlated with the education status of both parents and the socioeconomic status of the family. A higher number of individuals residing in urban areas were employed.

Conclusion:
Patients with TDT can achieve desired goals if given appropriate opportunities. Achieving educational and employment goals will enhance the quality of life of patients.
Title: Prevalence of peripheral neuropathy in thalassaemia patients in Penang and their quality of life: preliminary study

Abstract Category: Quality of Life

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Abstract

Introduction
Peripheral neuropathy (PN) in thalassemia patients may be subclinical and attributable to a variety of factors.

Objective
This study is to determine PN prevalence in thalassemia patients and assess their health-related quality of life (HRQOL).

Method
Thalassemia patients over the age of 18 were enrolled using convenient sampling technique. EQ-5D-3L was completed by patients, while neuropathy symptom score (NSS) and neuropathy disability score (NDS) were completed by a medical officer. Multiple linear regression was performed to identify the determinants of HRQOL and PN.

Results
Of 119 patients, 74 (62.2%) were women with mean age of 33 ± 10.3 years (range 19-60). There were 38 (31.9%) non-transfusion-dependent thalassemia (NTDT) and 81 (68.1%) transfusion-dependent thalassemia (TDT) with mean transfusion year of 23.4±9.8 years (range 2-53). Malays were 79% (n=94), 17.65% (n=21) Chinese, four were other ethnics. The NSS in NTDT (mean=3.52; SD=3.12) was significantly higher (p<0.05) if compared to TDT (mean= 3.48; SD=3.30). There were 5.88% (n=7) patients with sum of NDS + NSS >10 while 13.5% (n=16) had sum score more than 8 which was suggestive of PN clinical diagnosis. In this study, 56.3% (n=67) of patients exhibited mild to severe neuropathy symptoms, whereas 2.5% (n=3) exhibited neuropathy signs. The mean (SD) of EQ5D-3L utilities of TDT was 0.974(0.568) significantly higher than NTDT with 0.9468(0.0872) (p=0.038). Mean (SD) EQVAS in NTDT were 85.45 (13.26) and 85.65 (16.65) in TDT (p=0.947). Subtype of thalassemia and NSS score were significant predictors of EQ-5D-3L utilities, while age and NDS were significant indicators of patients’ NSS.

Conclusion
Prevalence of PN is substantial in our thalassemia patients and warrants further study. NSS and NDS can be used as a bedside tool for PN prior to nerve conduction studies to facilitate early detection of PN and HRQOL.
Title: The relationship between burden and quality of life among caregivers TDT patients during COVID-19 pandemic: a cross-sectional study

Abstract Category: Quality of Life

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Abstract

Background
Thalassemia, being a chronic condition, has the potential to impact the caregiver’s quality of life due to the stress they experience. The present study examines the relationship between burden and quality of life among (QoL) caregiver TDT patients during COVID-19 pandemic in West Java.

Method
This analytical cross-sectional study uses convenience sampling to select 129 caregiver TDT patients. A TranQoL questionnaire and zoom interviews to assess risk factors were used to collect data in 2022. The data were analyzed with SPSS software (version 26) using frequency, percentage, chi-square and independent samples t-test. subject

Result
The majority of caregivers with compromised quality of life are those who have children with an extended illness duration of 10 years and have not completed high school education. Caregivers experiencing a disturbance in their quality of life had low incomes (88.1%), were responsible for supporting more than four families, and faced job losses during the pandemic (35.8%). There was significant relationship between the concerns regarding the effects of COVID-19 and the QoL (P < 0.005) and between the ability to reach of health facilities during pandemic and the QoL (P < 0.001).

Conclusion
Thalassemia major caregivers faced burdens during the pandemic, which primarily included worrying about the potential transmission of COVID-19 to their children during activities and encountering challenges in accessing healthcare services for their own medical condition. The quality of life of the caregiver plays a crucial role in the success of patient treatment. Interventions are essential to promote, prevent, and detect psychosocial issues that contribute to the caregiver’s burden, thus ensuring it does not further affect the quality of life of the children.

Keywords: caregiver; COVID-19; TDT; quality of life
Title: A comparative analysis of the quality-of-life in child-parent dyad with thalassemia major using PedsQLTM

Abstract Category: Quality of Life

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Abstract

Background
With good treatment, thalassemia major patients lead better lives than their counterparts few decades ago. The main concern in chronic care is financial, which is offset now by governmental support. Despite this, children need to report to a health facility 1-2 times in a month and undergo painful investigations. We analyzed the quality of life of children-parent dyads who follow up with us for regular treatment.

Methods
Children aged 2-18 years were interviewed along with the accompanying parent to know the impact of thalassemia on quality of life (QoL). QoL was measured using age specific PedsQLTM version 4 specific for each age group. For 2-4 years only parental response was included. QoL was divided into 4 sections (physical, emotional, social, school aspects) with points scored from 0-4 as 0-100 points. The maximum score achievable was 1500 in total. The score was compared between child-parent dyad from same family. The institute provides standard of care treatment, free of cost to the patient and helps patients avail governmental concessions.

Results
55 children and 49 parents were interviewed. The age breakup is as follows (2-4 years:19, 5-7 years:14,8-12 years:12, 13-18 years:10). For 2-4-year-old children only parents’ response was documented. The QoL total score was lesser for children compared to parent for every age range (850 vs 1025 age 5-7years, 825 vs 1000 age 8-12 years and 835 vs 1025 age 13-18 years). Between different age groups, the QoL deteriorated with increasing age group with worst reported in 8-12 years (p=0.095). Among parents in 4 age cohorts the worst was reported in 2-4 years (p=0.047).

Conclusion
Despite the provision of governmental aids, QoL still suffers. Children feel and suffer more than their parents. The study is a cry for implementing screening tools in community and reducing the burden of these chronic diseases.
Title: Unveiling the rarity: A case report of a child with Sickle Cell Beta Thalassemia in Indonesia

Abstract Category: Sickle Cell Disease

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Abstract

Background
Mostly Hb S was found in the Mediterranean region, African Saharan desert, the Middle East, but not in Southeast Asia including Indonesia. Awareness of this disease is still small in Indonesia, so it’s often misdiagnosed and treated.

Aim
Reporting Hb S/ Beta Thalassemia cases from Sumatra, Indonesia.

Case
A thirteen-year-old girl from Bengkulu Province, Sumatra Island, belonging to the Minang native tribe, was diagnosed with sickle cell beta thalassemia. At the age of nine, the patient experienced frequent joint pain and appeared pale. Initially, the patient was diagnosed with juvenile rheumatoid arthritis and autoimmune hemolytic anemia. She was treated with steroids for a month, which reduced pain but necessitated transfusions every two to three months. The patient became paler, jaundiced, and weak, with dark tea-colored urine. Physical examination revealed anemic conjunctiva, jaundiced sclera, with hepatosplenomegaly. Laboratory tests showed normocytic normochromic anemia and hemolysis in peripheral blood. Hb electrophoresis result HbA2 2%, Hb F 28%, and Hb S 70%. Subsequently, the patient was diagnosed with sickle cell/beta thalassemia. Hydroxyurea therapy 5 mg/kg/day was administered, leading to the absence of joint pain and anemia. Her current hemoglobin level ranged from 10.5 g/dL to 11 g/dL, ferritin level was 768 ng/mL, hepatomegaly was decrease in size. The patient is now able to actively engage in school activities.

Conclusion
The rarity of this case in Indonesia can lead to misdiagnosis. Healthcare professionals should be aware of sickle cell disease symptoms to prevent complications like sickle cell crisis.

Keywords: sickle cell beta thalassemia, joint pain, sickle cell crisis, hydroxyurea
Title: Drepacomunidade: joining lusophone Drepa-speakers to improve knowledge and care

Abstract Category: Sickle Cell Disease

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Abstract

The community of Portuguese-speaking countries consists of Angola, Brazil, Cape Verde, Guiné-Bissau, East Timor, Equatorial Guinea, Mozambique, Portugal and São Tomé and Príncipe. Together, they are home to 230 million people, with Portuguese being the most widely spoken language in the southern hemisphere. However, sickle cell disease information in these countries and in Portuguese is still scarce, especially among the - possibly most affected - African ones. In 2022 the Portuguese Association of Patients with Hemoglobinopathies (APPDH) gathered similar associations in other Portuguese-speaking countries to create Drepacomunidade. This pretends to be a platform for a common share of knowledge and information between patients, relatives, carers and healthcare workers around the disease. Besides, we Aim to promote clinical and research cooperation between countries and to create content to help patients to cope with the disease and to raise their visibility, in our native language. Since its beginning, Drepacomunidade already organized five meetings with people from seven countries. Together, we already managed to introduce newborn screening for sickle cell disease in Portugal and conducted the first nationwide study on the prevalence of sickle cell trait in São Tomé e Príncipe. Right now, we are in a moment of gathering and enforcement of the community, with some events to be announced soon. We hope that this year we can start to transform the Portuguese-speaking panorama on sickle cell issues and continue to give them a voice in the international community.
Title: Sickle cell trait in São Tomé e Príncipe: a population-based prevalence study in women of reproductive age

Abstract Category: Sickle Cell Disease

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Abstract

Background
Sickle Cell Disorder is Africa’s most prevalent genetic disease. Yet, it remains a neglected condition, with high mortality under five, and a lack of population-based studies in the region. This is the first of its kind in São Tomé e Príncipe, aiming to estimate the prevalence of sickle cell trait and other haemoglobin variants in women of reproductive age and its associated factors.

Methods
We conducted a cluster survey in 35 neighbourhoods. Haemoglobin was assessed through point of-care capillary electrophoresis or high-performance liquid chromatography, and sociodemographic data through questionnaires. The weighted prevalence of sickle cell trait and HbC was estimated with a 95% confidence interval (95% CI). For its association with age and individual and collective genetic heritage, we calculated weighted prevalence ratios (95% CI) through robust Poisson regression.

Findings
The prevalence of sickle cell trait in women of reproductive age in São Tomé e Príncipe (n = 376) was 13.45% (95% CI: 9.05-19.00). The prevalence of HbC carriers was 8.00% (95% CI: 4.71-12.00). Older age and speaking Forro or Angolar were positively associated with having sickle cell trait.

Interpretation
The prevalence of sickle cell trait in São Tomé e Príncipe ranks high in the West African region. The country should follow international guidelines, implementing neonatal screening and comprehensive healthcare management. Funding: CIAS-UC (FCT: UIDB/00283/2020), APPDH and Forum Haematologico.
Title: An incidental finding of the rare S/E hemoglobinopathy

Abstract Category: Sickle Cell Disease

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Abstract

Introduction
Hemoglobinopathies are disorders characterized by abnormal hemoglobin structure. Among the hemoglobin variants, the most common in South East Asian/Malay population is hemoglobin E (HbE). Double heterozygous S/E are uncommon however with population migrations and increasing racial intermarriages, Hb SE disease is expected to be encountered more often.

Abstract
We report a Case of a 40 year gentleman of Malay ethnicity who presented to a primary health care centre for routine health screening. The health care centre sent off a HbA1c as a screening for diabetes and his results were inconclusive for 2 consecutive tests. He had a hemoglobin level of 13g/dL, normal mean corpuscular volume and mean corpuscular hemoglobin concentration. He has no family history of blood disorders and has been perfectly well till date. On examination he was anicteric and did not have any hepatosplenomegaly. Capillary electrophoresis was performed which was suggestive of S/E hemoglobinopathy with HbS of 66.4% and HbE of 30%. A HPLC confirmed a similar finding. A full blood picture showed microcytes with many target cells occasional sickle cells and Howell Jolly bodies. A Sanger sequencing of the beta globin gene showed compound heterozygous of codon 26 (GAG>AAG) HbE and codon 6 (GAG>GTG) HbS mutation confirming a compound heterozygous HbE and HbS beta variant. Hb electrophoresis of both his parents confirmed that his father had HbS trait and his mother was heterozygous for HbE.

Discussion
Heterozygous HbS/E may have variable presentation. The symptoms are usually due to low allelic expression of HbE leading to HbS predominance. Similar to HbCS, sickle crisis phenomenon are less reported.

Conclusion
Patients with Hb SE disease should be followed and managed in a similar fashion as those with Hb S/β+thalassemia and treated appropriately when they develop sickling-related symptoms and complications.
Title: Milestones along my personal journey with Hydroxyurea

Abstract Category: Sickle Cell Disease

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Abstract

For long sickle cell and thalassaemia were thought to be childhood diseases. It was believed that there was no future for these kids but to suffer the consequences of inheriting the genes and so their future was unplanned.

I am Shifneez, 40 years old sickle beta-thalassaemic from Maldives. My parents were told I will not live up to be 14. I grew up as a very active student in school, graduated in teaching and worked at the very school I studied at.

I had my first sickle crisis at the age of 14. After about 5 years of not knowing what sickle cell can do, I was introduced to this drug called Hydroxyurea (HU) in 2003. After I got married and was ready to have a family, I was advised by my physicians to avoid becoming pregnant while taking HU. Understandably, they told me about the potential harm to the fetus. I was left with a real dilemma. Take a drug with unknown effects on fetal development or give up a helpful, necessary medication that has kept me healthy since I started it.

Many SCD patients are not willing to take a chance and go through pregnancy, let alone take the risk of continuing pregnancy with HU. Hence, there is not a lot of clinical evidence with pregnancy while taking HU. My determination to start a family, despite being aware of the risks associated, past 19 years, I have had 3 pregnancies each experience different with regard to HU therapy. Today, I am a mother of 2. I had my last pregnancy and lactation while taking HU.

HU, the only disease-modifying therapy approved for SCD, has continuously shown to improve the quality of life of adults and children with sickle cell. I hope the story of my experiences can break the barrier to open the possibility for others like me to reach their milestones and dreams.
Title: An observational study on the characteristics of Haemoglobin H disease in a northern hospital of Malaysia

Abstract Category: α-thalassaemia syndromes

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Abstract

Background
Haemoglobin H (HbH) disease is an alpha thalassaemia which typically occurs when three of four α-globin genes are defective. HbH disease may be deletional or non-deletional with the latter usually having a more severe phenotype. We describe here the clinical characteristics of patients with HbH disease in our hospital.

Method
We conducted a retrospective observational study of adult HbH patients aged ≥18 years old from our centre registered in the Malaysian Thalassaemia Registry from 01 December 2017 to 30 November 2022. Diagnosis of HbH was established based on Hb analysis or DNA analysis. Clinical data from the last 12 months was collected from hospital electronic medical records and analysed using SPSS software.

Results
A total of 84 HbH patients were identified. Median age was 36 years old (range 18-81), with a female preponderance; 62 (73.8%) females, 22 (26.2%) males. Majority were Malay (95.2%, n=80), with Chinese (2.4%, n=2) and Siamese (2.4%, n=2) being the minority. 59.5% (n=50) were deletional HbH and 40.5% (n=34) were non-deletional HbH. There was no significant difference in transfusion dependency between the types of HbH diseases (p 0.261). A greater proportion of patients with non-deletional HbH had moderate to severe liver iron concentration as measured by MRI T2* compared to deletional HbH (90.5% vs 63.6%, p 0.037). 67.6% of non-deletional HbH required iron chelation therapy compared to 42.0% of deletional HbH (p 0.021).

Conclusion
In our cohort, deletional HbH was more prevalent than non-deletional HbH, but molecular data were not available for all patients. We did not find a statistical difference in transfusion dependence between deletional and non-deletional HbH, potentially limited by our small sample size. Phenotypically, non-deletional HbH appeared to be more severe with greater liver iron overload and a higher proportion requiring iron chelation therapy.
Title: Etiology of anemia among women living in Indonesia two years after delivery: iron deficiency anemia or thalassemia carrier?

Abstract Category: α-thalassaemia syndromes

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Abstract

Introduction
Anemia in pregnancy is common in developing countries, mostly due to iron deficiency. Therefore, 90 iron tablets have been given during antenatal care as a national program in Indonesia. However, anemia may persist after delivery in some cases. The aim of this study was to explore the etiology of anemia among women 2 years after delivery.

Methods
Data of mothers who visited the Primary Health Care for their toddler’s regular examination were checked, and those with a history of anemia during pregnancy were consented for a complete blood count examination. Erythrocyte indices such as Mentzer (MCV/RBC) were calculated to determine whether anemia was due to iron deficiency or thalassemia carrier. In addition, those with low MCV and/or low MCH were further examined for HbA2 analysis (Mini Sebia) and DNA examination (Vienna Linear Assay) was performed to confirm the α- or β-globin gene deletion or mutation.

Results
Of 171 women visited the Primary Health Care, 40.9% (n=70) had history of low Hb (3.5%, indicating HbE variation (cd26 heterozygote) and beta-thalassemia carrier (IVS1nt5 mutation), respectively, as confirmed by DNA examination. Others had normal HbA2 (2-3.5%) with Mentzer Index >13, and DNA examination showed no α-globin gene deletion or mutation, suggesting iron deficiency anemia.

Conclusion
Although iron deficiency anemia is common in Indonesia, thalassemia carrier screening is necessary since the country is located in the thalassemia belt area. Hb analysis as well as DNA examination is becoming a significant tool in detecting thalassemia carrier in Indonesia, therefore, anemia that persists after delivery requires further exploration.
Title: Trial in progress: a phase 2, double-blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of luspatercept to treat anemia in adults with alpha-thalassemia

Abstract Category: α-thalassaemia syndromes

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Abstract

Background
α-thalassemia hemoglobin H (HbH) disease may lead to chronic anemia, and in some cases transfusion dependence. Luspatercept, which is approved for treatment of anemia in transfusion-dependent (TD) and non-TD β-thalassemia, will be evaluated in TD and non-TD α-thalassemia in a phase 2, double-blind, randomized, placebo-controlled, multicenter study (NCT05664737, EudraCT 2021 004928-15).

Methods
Eligible patients will be ≥18 years old, have documented α-thalassemia HbH disease diagnosis (combination β-thalassemia diagnosis is allowed if ≥1 non-mutated β-chain gene is present), ECOG score of 0-1, TD (≥6 RBC units/24 weeks before randomization with no transfusion-free >56-day period) or non-TD (<6 RBC units/24 weeks before randomization, without transfusions for ≥8 weeks before randomization and mean hemoglobin ≤10 g/dL). Exclusion criteria are: α-thalassemia traits, ATR-X α-thalassemia, Bart’s hydrops, HbS/β-thalassemia or HbE/β-thalassemia; use of erythropoiesis-stimulating agents; history of thromboembolic events (24 weeks prior); non-α-thalassemia-related hemolysis/anemia. TD (n=93) and non-TD (n=84) patients will be randomized 2:1 to luspatercept (1.0 mg/kg) or placebo subcutaneously every 3 weeks and stratified by region and either transfusion burden (TB; TD cohort) or baseline hemoglobin (non-TD cohort). Primary endpoints are ≥50% TB reduction from baseline over any continuous 12 weeks (weeks 13-48; TD cohort) and ≥1 g/dL increase in mean hemoglobin from baseline in the absence of transfusions (weeks 13-24; non-TD cohort). Secondary endpoints include ≥33% TB reduction over 24-week intervals, longest duration of ≥50% TB reduction (TD cohort), hemoglobin change from baseline (week 24), longest duration of mean hemoglobin increase ≥1 g/dL from baseline (non-TD cohort), safety and health-related quality of life.

Results
In this currently enrolling study, 19/27 sites have been activated and 42 patients screened, as of 28June2023.

Conclusion
This study will assess efficacy and safety of luspatercept in α-thalassemia HbH disease patients, who have limited treatment options. Recruitment is ongoing. Previously published (Viprakasit et al. HemaSphere 2023; [Suppl 3], 4812-4813)