SILVER JUBILEE 25 Years

शरीरमाद्यं खलु धर्मसाधनम्

8th National Thalassemia Conference

"Cure in Sight"

Saturday - Sunday 17th & 18th December, 2016

Organized by :

National Thalassemia Welfare Society

&

Department of Haematology AIIMS

at Jawahar Lal Auditorium

All India Institute of Medical Science,

Ansari Nagar, New Delhi-110029

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*LIC : Liver Iron Concentration

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SILVER JUBILEE 25 years

Souvenir

8th National Thalassemia Conference

"Cure in Sight"

Saturday - Sunday 17th & 18th December, 2016

at

Jawahar Lal Auditorium

All India Institute of Medical Sciences

Ansari Nagar, New Delhi - 110029

Organizers

National Thalassemia Welfare Society

KG-1/97, Vikas Puri, New Delhi-110018

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e-mail : ntws2015@gmail.com I www.thalassemiaindia.org

&

Department of Haematology, AIIMS

New Delhi

ORGANISING COMMITTEE

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Justice Anil Dev Singh : Former Chief Justice of Rajasthan High Court

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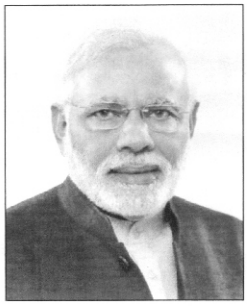

सत्यमेव जयते

प्रधान मंत्री कार्यालय
नई दिल्ली - 110011
PRIME MINISTER'S OFFICE
New Delhi - 110011

MESSAGE

The Prime Minister is happy to learn that National Thalassemia Welfare Society, New Delhi is organising 8th National Thalassemia Conference from 17th- 18th December, 2016 in New Delhi and publishing a souvenir to mark the occasion.

On this occasion, best wishes to the organisers and participants.

(P.K. Sharma)
Under Secretary

New Delhi
November 17, 2016

हंसराज गंगाराम अहिर
HANSRAJ GANGARAM AHIR

सत्यमेव जयते

गृह राज्य मंत्री
भारत सरकार
नार्थ ब्लाक, नई दिल्ली - 110001

MINISTER OF STATE FOR
HOME AFFAIRS
GOVERNMENT OF INDIA
NORTH BLOCK,
NEW DELHI - 110001

MESSAGE

I am extremely happy to learn that National Thalassemia Welfare Society, which is on the forefront in India to provide better care for thalassemics and to initiate control of Thalassemia, is celebrating its Silver Jubilee this year. Thalassemia is a rare disease, causing financial and mental stress on the families of victims. Hence, the steps taken by National Thalassemia Welfare Society in prevention of thalassemia are laudable.

I have been informed that National Thalassemia Welfare Society is organizing its 8th National Thalassemia Conference during 17th & 18th December, 2016 at Jawahar Lal Auditorium AIIMS. I hope, this Conference will help in disseminating information and raise awareness about thalassemia.

I extend my heartiest greetings and best wishes to the organizers and participants of Conference.

(HANSRAJ GANGARAM AHIR)

Place: New Delhi.
Dated: 23.11.2016

सत्येन्द्र जैन
Satyendar Jain
गृह, स्वास्थ्य, ऊर्जा, लोक निर्माण विभाग,
एवं उद्योग मंत्री
Minister of Home, Health, Power, PWD,
& Industries

सत्यमेव जयते

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I.P. Estate, New Delhi-110 002
दूरभाष/Tele No. : 23392116, 23392117
Fax No. : 23392044
E-mail : moh.delhi@gov.in

D.O. No. MinHealth/9318
Date : 30/11/2016

MESSAGE

I am glad to know that National Thalassemia Welfare Society has completed 25 years of its inception and is organizing 8th National Thalassemia Conference in association with Department of Haematology of AIIMS to conclude its Silver Jubilee celebrations.

I have been told that 5.56% population of Delhi is Thalassemia carrier.

We have taken policy decision and devised a thalassemia control programme for NCT of Delhi which will include screening of all pregnant women for thalassemia in 1st trimester of pregnancy. If one partner is confirmed to be carrier then other will be subjected to HPLC test. All students of 10th class of all schools (Government/Private) will be screened. Extended family screening of thalassemia carriers detected will also be done. Concept of thalassemia screening at pre-marital, pre-conceptional and antenatal phase shall be promoted as early as possible.

Delhi Government is also providing free medicines to all patients taking transfusions at Delhi government hospitals. Blood safety is high on our agenda, shortly we plan to introduce NAT testing in donors blood. We are more than willing to provide best care to thalassemics in Delhi.

I extend my best wishes to Dr. J.S. Arora and his team for the success of 8th National Thalassemia Conference and Workshops to be organized pre and post conference.

(SATYENDAR JAIN)

Manoj Jhalani
Joint Secretary & CVO
Telefax : 23063687
E-mail : manoj.jhalani@nic.in

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली - **110011**
Government of India
Ministry of Health & Family Welfare
Nirman Bhavan, New Delhi - 110011

Message

Thalassemia is a serious inherited blood disorder. About 10% of total world thalassemia patients belong to Indian subcontinent, among them 3-4% are carrier. In India, about 32,400 infants are born with hemoglobinopathies. Survival of thalassemia major depends upon lifelong repeated blood transfusion & iron chelating drugs. The disease can be prevented by thalassemia carrier screening before marriage/conception followed by antenatal diagnosis if required.

As of 2013 thalassemia occurs in about 208 million people with about 4.7 million having severe disease. It is most common among people of Italian, Greek, Middle Eastern, South Asian, and African descent. Males and females have similar rates of disease.

Considering the burden of disease MoHFW has developed guidelines on prevention and Management of the disease. The same have been disseminated to states for implementation.

I am happy to learn that the Thalassemia Society is active not only in the areas of diagnosis and management of the Thalassemia but is also playing a key role in spreading awareness about them. I commend the members of Thalassemia Society in coming up with the publication related to Thalassemia. I extend my best wishes to the society in its very important endeavour of helping Thalassemia patients & their families and in creating awareness.

(Manoj Jhalani)

World Health Organization
Regional Office for South-East Asia

Message from Dr Poonam Khetrapal Singh, Regional Director,

WHO South-East Asia Region

National Conference on Thalassaemia, 17 December 2016

Thalassaemias, along with sickle-cell anaemia, are major inherited haemoglobinopathies. Currently, it is estimated that about 5% of the world's population are carriers of a potentially pathological haemoglobin gene that may manifest as thalassaemia or sickle-cell anaemia. Each year, about 300 000 infants worldwide are born with thalassaemia syndromes (30%) or sickle-cell anaemia (70%). Of two categories of thalassaemia, alpha-thalassaemia is common in South-East Asia. In some South-East Asian countries, up to 40% of the population may carry significant haemoglobin mutations, resulting in increased rates of infants born with thalassaemia.

Thalassaemia causes long-term disability for the individual along with associated psychological, social and financial hardships. It also impacts the family, society, health system and development of a nation. With greater awareness and better diagnostic tools, thalassaemia is now being increasingly recognized as a growing health problem even in developing countries. In general, regular blood screening campaigns are the best way to help reduce the presence of hereditary diseases. Screening is the first step in identifying a problem that could extend for generations to come. The health burden of a hemoglobin disorder can be effectively reduced through prevention and management programmes.

Management of thalassaemia is complicated, expensive and carries its own risks. When treatment combining blood transfusion and an iron-chelating agent is started early and maintained, the patient's quality of life can be very good and the prognosis optimistic. Substantial research has started yielding results in improved and safer management of patients with beta-thalassaemia.

Continuous availability of safe blood for transfusion to patients with thalassaemia is an essential prerequisite. Considerable efforts have been made by all Member States in the past 15 years to improve voluntary nonremunerated blood donations and thereby increase availability and access to blood.

Against an annual estimated requirement of 18 million units of blood in the South-East Asia Region, about 16 million units are collected every year, of which approximately 82% of donated blood is obtained from voluntary donors. There is great variation between as well as within countries. There is clearly a need to further enhance this movement to make more blood available so that no patient with thalassaemia suffers because of lack of blood.

Patients with thalassaemia are at greater risk of contracting transfusion transmissible infections (TTIs) because of repeated blood transfusions that they require. Strict screening of donated blood for TTIs is essential to make transfusion safe. According to official reports in the South-East Asia Region, 100 % of blood collected are screened. Member states are now focusing on quality of the reports as well as donated blood units to obviate any harm to the recipients.

WHO shall continuously provide technical support to national efforts in augmenting the availability of safe blood and is working closely with collaborating organizations to promote voluntary blood donations through active involvement of governmental and nongovernmental organizations. Together, we are striving towards the ultimate aim of assuring universal access to safe blood and blood products.

The logical way to address the problem of thalassaemia is therefore to promote and strengthen prevention. It warrants extensive awareness campaigns to stimulate younger people to come forward for information, counselling and testing. Prevention is based on identifying individuals at risk through carrier screening programmes or family history and providing adequate information on risk and possibilities to reduce that risk. Healthy carriers can be identified by simple, inexpensive and accurate blood tests. Carrier couples can thus be detected and informed of genetic risk before starting a family. Screening is affordable and an accessible way to detect carriers, and can be offered in a range of settings in different societies. However, to be effective, thalassaemia preventive services must be sensitive to cultural practices and appropriate for the given social context.

The delivery of thalassaemia services should be integrated at all levels of health care and encompass all genetic disorders with prioritization of those with greater public health importance. To effectively address the problem of thalassaemia, Member States may undertake a holistic approach and design, implement, and reinforce the programme in a systematic and effective manner.

While a nationwide vertical programme may not be feasible in several developing countries in the immediate future, it may be prudent to establish reference centres in different geographical areas. In future, these centres and their reach could be expanded. At the same time, research and surveillance – important for the planning and evaluation of appropriate interventions – must be pursued to develop new tools and generate reliable data on the magnitude of the problem.

WHO is committed to providing technical assistance to all its Member States in framing national policies and strategies for prevention and management of thalassaemia; to promoting intercountry collaboration; to facilitating transfer of affordable technologies and expertise to developing countries; and to assisting them in enhancing their capacity in combating this burgeoning problem both at the preventive and management levels.

Dr Poonam Khetrapal Singh
Regional Director

सत्यमेव जयते

डा. सौम्या स्वामीनाथन
एमडी, एफएससी, एफनएएससी, एफएएमएस
सचिव, भारत सरकार
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
एवं
महानिदेशक, आई सी एम आर

Dr. Soumya Swaminathan
MD, FASc, FNASc, FAMS
Secretary to the Government of India
Department of Health Research
Ministry of Health & Family Welfare
&
Director-General, ICMR

भारतीय आयुर्विज्ञान अनुसंधान परिषद
स्वास्थ्य अनुसंधान विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
वी. रामलिंगस्वामी भवन, अंसारी नगर
नई दिल्ली-110 029 (भारत)

Indian Council of Medical Research
Department of Health Research
Ministry of Health & Family Welfare
V. Ramalingaswami Bhawan, Ansari Nagar
New Delhi-110 029 (INDIA)

Message

Thalassemia is a serious genetic blood disorder requiring multi-specialty approach for its management. Over 200 mutations have been identified to cause thalassemia. According to ICMR 5.51% Delhites are Thalassemia carriers and overall 3.9% population of India are Thalassemia carriers. Public awareness and thalassemia screening followed by antenatal diagnosis is the only way to prevention. Better treatment strategies are also required.

I believe that the deliberations of this conference will give an impetus to better management and control of thalassemia. I extend my heartiest wishes for the success of 8th National Thalassemia Conference.

(Soumya Swaminathan)

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शरीरमाद्यं खलु धर्मसाधनम्

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प्रो0 महेश चन्द्र मिश्र
निदेशक

Prof. M.C. Misra
MS, FRCS, Hon. FRCS (Glasg.) FCLS, FAMS, FACS
DIRECTOR

Dated : 15th November, 2016

MESSAGE

It gives me immense pleasure to note that National Thalassemia Welfare Society is organizing 8th National Thalassemia Conference at AIIMS on 17th & 18th December, 2016 in association with Department of Haematology, AIIMS. I am happy to know that a lot of research has taken place in the management of thalassemia & now **cure is insight**, which is also the theme of this conference.

Though Thalassemia management has improved and cure is visible, **prevention is better than cure** is best suited to thalassemia. Every effort should be made to prevent thalassemia in future generation.

I wish the organizers a grand success.

(Prof. M.C. Misra)

अखिल भारतीय आयुर्विज्ञान संस्थान
अंसारी नगर, नई दिल्ली - 110029, भारत

All India Institute of Medical Sciences
Ansari Nagar, New Delhi - 110029, India

डॉ. बलराम एरन
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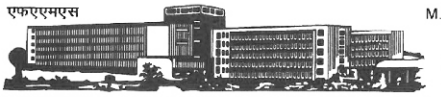
आचार्य एवं विभागाध्यक्ष, सीटीवीएस
प्रमुख, हृदय वक्ष केन्द्र

DR. BALRAM AIRAN
M.Ch(CTVS), FIACS, FAMS
Dean (Academic)
Professor & Head, CTVS
Chief, C.T. Centre



MESSAGE

I am happy to note that National Thalassemia Welfare Society in association with Department of Haematology, AIIMS, New Delhi is organizing the 8th National Thalassemia Conference on 17th & 18th December at Jawahar Lal Auditorium AIIMS, New Delhi.

Thalassemia is an inherited blood disorder which can be prevented by marriage counseling and Thalassemia screening before marriage/ conception. Prevalence of Thalassemia is very high in some Indian Communities.

Every effort should be made to spread awareness on thalassemia amongst society and medical/ Para medical community. A chapter on genetic disorder including thalassemia should be included in the curriculum of 10th standard students.

My best wishes for the success for this Conference.

Balram Aran.

(PROF. BALRAM AIRAN)

Tel. Off. : 26594833, 26588625, 26594835 **Res.:** 26594520
Fax No.: (011) 26588663, 26588641 **E-mail :** dean@aiims.edu, airanbalram@gmail.com

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अन्सारी नगर, नई दिल्ली–110029

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डा० डी० के० शर्मा/Dr. D. K. SHARMA
चिकित्सा अधीक्षक/Medical Superintendent

MESSAGE

It gives me immense pleasure to know that the National Thalassemia Welfare Society is organising '8th National Thalassemia Conference' is association with Department of Haematology AIIMS on 17th & 18th December 2016 at Jawahar Lal Auditorioum AIIMS. In addition, workshop on 'Challenges in Diagnosis of Thalassemia' will be held on Friday 16th December 2016 in the Department of Haematology at AIIMS.

We are all aware that Thalassemia is one of the most common genetic blood disorders in India. Survival of thalassemic patients depends upon repeated blood transfusions. At present around 50 Thalassemic patients are taking transfusion at Haematology Department. These patients are being provided NAT (Nucleic Acid Testing) tested blood so that chances of transmitting Hepatitis B, C & HIV infections can be minimised. It is being contemplated to allot an additional area to the Haematology department which will help in further improving facilities for thalassemia patients.

I extend my best wishes to the organizers for the success of this conference.

(Dr. D.K. Sharma)

National Thalassemia Welfare Society

ORGANISATION FOR AWARENESS OF THALASSEMIA AND TO HELP THALASSEMICS

KG-1/97, VIKAS PURI, NEW DELHI-110018 Tel. : 9311166711, 25511795 / 796

Website : thalassemiaindia.org E-mail : ntws08@gmail.com

(Estd. 1991, R. No.S/26823. Registered under Societies Registration Act XXI of 1860)

MESSAGE

We have just completed 25 years of our inception. To conclude the Silver Jubilee Celebration we are holding our 8th National Thalassemia Conference, in association with Dept. of Hematology, AIIMS on Saturday & Sunday 17th & 18th December 2016, at Jawaharlal Auditorium, AIIMS, New Delhi. We are also organizing two Workshops, one at AIIMS on Friday 16th December, 2016 & another at Army R&R Hospital on 19th December 2016. Upgradation of knowledge of patients/parents and medical professionals has been our prime objective since beginning.

Thalassemia is a crippling disorder even with best possible care and it becomes difficult for a Thalassemia patient to compete with the peers. Above all the high cost of the treatment also adversely affects the financial status of the families, so affected.

We have fought a lot to include thalassemia in the list of disabilities for the purpose of disabilities act. We understand that Thalassemia and Sickle Cell Anemia has been included in 'Rights of Person with Disabilities Bill' which has been tabled before the Parliament on 7th May 2015, we are sure it will be passed soon.

I, appreciate the efforts of my Colleagues, Sponsors, Delegates and distinguished International & National Guest faculty, for their help in organizing the 8th National Thalassemia Conference and also making it a success.

Surendar Saini

(Km. Surrendar Saini)

PROGRAMME

Registration : 8AM to 9AM

Day 1, Saturday 17th December 2016

S. No.	Topic	Speaker	Minutes	Timings	Chairperson
	Session I Transfusion Therapy			**09:30 am to 10:30 am**	
1.	Transfusion Therapy	Dr. A.P. Dubey	20	9:30 to 9:50am	Dr. Mousumi Swami Dr. Kabita Chaterjee Dr. Sanjay Choudhry Dr. V.K. Sharma
2.	Struggling with Hemoglobin Level	Dr. V.P. Choudhry	20	9:50 to 10:10am	
3.	Splenectomy is it Necessary	Dr. Rahul Naithani	20	10:10 to 10:30am	
	Inauguration			**10:30 am to 11:40 am**	
	Session II Chelation			**11:40 am to 01:30 pm**	
1.	Monitoring of Iron Overload	Dr. Praveen Sobti	25	11:40 to 12:05pm	Dr. Ritu Chawla Dr. Sanjeev Digra Dr. Kirti Nanal Dr. Geetanjali Jindal
2.	MRI T2* Iron Studies	Dr. Sameer Sood	15	12:05 to 12:20pm	
3.	Desferal - Do we still need it	Dr. Rajiv Bansal	25	12:20 to 12:45pm	
4.	Combining Chelators	Dr. Amita Trehan	25	12:45 to 01:10pm	
5.	Oral Chelators	Dr. V.K. Khanna	20	01:10 to 01:30pm	
	Lunch			**01:30 pm to 02:30 pm**	
	Session III Transfusion Transmitted Infections			**02:30 pm to 03:30 pm**	
1.	How to ensure Blood Safety	Dr. R.N. Makroo	20	02:30 to 02:50pm	Dr. S.K. Arora Dr. Rakhi Maiwal Dr. R.S. Gupta
2.	Hepatitis C SEAT - Safe Easy and Affordable Treatment	Dr. Yogesh Chawla	30	02:50 to 03:20pm	
3.	HIV in Thalassemia	Dr. Alok Hemal	10	03:20 to 03:30pm	

	Session IV Entering the Adulthood				**03:30 pm to 05:00 pm**	
1.	Cardiac Complications		Dr. Vikas Kohli	20	03:30 to 03:50pm	Dr. D.D. Golani Mrs. Shobha Tuli Dr. Alka Mathur Dr. Jalbala Sardana
2.	Monitoring of Thalassemics		Dr. Sunil Gomber	20	03:50 to 04:10pm	
3.	Adult Care Medical		Dr. Michael Angastionotis	15	04:10 to 04:25pm	
4.	Impact		Dr. J.S. Arora	15	04:25 to 04:40pm	
5.	Success Story		Dr. Ravindra Kumar	10	04:40 to 04:50pm	
6.	U.K. Experience		Mr. Ajay Gandhi	10	04:50 to 05:00pm	
	TEA				**05:00 pm to 05:30 pm**	
	Cultural Programme				**05:30 pm to 08:00 pm**	
	Dinner				**08:00 pm**	
	Day 2, Sunday, 18th December, 2016					
S. No.	**Topic**	**Room**	**Speaker**	**Minutes**	**Timings**	**Chairperson**
	Session V Meet the Expert Session				**08:00 am to 09:00 am**	
	Transfusion & Chelation	Auditorium	Dr. V.P. Choudhry Dr. V.K. Khanna Dr. Sunil Gomber Dr. A.P. Dubey	60	08:00 to 09:00am	
	BMT	Conference Hall	Dr. Dinesh Bhurani Dr. (Brig.) Ajay Sharma (Retd.) Dr. Shishir Seth	60	08:00 to 09:00am	
	NTDT	Seminar Room Dept. of Haematology AIIMS	Dr. Suthat Fuchareon Dr. Prantar Chakrabarti Dr. Sarmila Chandra	60	08:00 to 09:00am	
	Session VI Prevention				**09:00 am to 10:00 am**	
1.	Strategy to Control Thalassemia		Dr. Sujata Sinha	25	09:00 to 09:25am	Dr. Madhulika Kabra

2.	Approach to Prevention among known carriers	Dr. Seema Kapoor	25	09:25 to 09:50am	Dr. Sangeeta Gupta Dr. Suman Mendiratta Ms. Vineeta Shrivastava
3.	Q & A		10	09:50 to 10:00am	
	TEA			**10:00 am to 10:20 am**	
	Session VII Intermedia need extra care			**10:20 am to 11:20 am**	
1.	Hb Enhancers	Dr. Prantar Chakrabarti	20	10:20 to 10:40am	Dr. Rahul Bhargava Dr. Vinky Rughwani Dr. Nikhil Sheth Dr. Rekha Harish
2.	Transfusion & Chelation in NTDT	Dr. Maitreyee Bhattacharyya	20	10:40 to 11:00am	
3.	Complications in NTDT	Dr. Sarmila Chandra	20	11:00 to 11:20am	
	Session VIII A2P (Adolescence to Parenthood)			**11:20 am to 01:00 pm**	
1.	Growth and Puberty in Thalassemia	Dr. Anju Seth	25	11:20 to 11:45am	Dr. Rajni Sharma
2.	Bone Care in Thalassemia	Dr. Rashid Merchant	20	11:45 to 12:05pm	Dr. A. G. Radhika
3.	Thyroid & Diabetes not rare	Dr. Sangeeta Yadav	25	12:05 to 12:30pm	Dr. Poonam Laul
4.	Fertility & Pregnancy in Thalassemia Major & Intermedia	Dr. Vatsla Dadhwal	25	12:30 to 12:55pm	Dr. Inusha Panigarhi
5.	Q&A		5	12:55 to 01:00pm	
	Lunch			**01:00 pm to 02:00 pm**	
	Session IX Cure			**02:00 pm to 04:30 pm**	
1.	Stem Cell Transplantation in Major & NTDT	Dr. Mammen Chandy	25	02:00 to 02:25pm	Dr. N.K. Mehra Dr. Dharma Choudhry Dr. Vikas Dua
2.	Cord Blood MUD Haploidentical	Dr. Rahul Bhargava	25	02:25 to 02:50pm	
3.	Gene Therapy Current status	Dr. Alok Shrivastva	25	02:50 to 03:15pm	
4.	Life after BMT	Dr. Dinesh Bhurani	25	03:15 to 03:40pm	
5.	New Medical Options	Dr. V.P. Choudhry	25	03:40 to 04:05pm	
6.	Panel Discussion	All Speakers and Dr. Vijay Ramanan	25	04:05 to 04:30pm	

	Day 2, Sunday 18th December 2016 Doctor Session				
S. No.	**Topic**	**Speaker**	**Minutes**	**Timings**	**Chairperson**
	Doctor Session I			**09:10 am to 11:00 am**	
1.	Diagonostic Challenges	Dr H. Pati	25	09:10 to 09:35am	Dr. Renu Saxena Dr. Neelam Sood Dr. K.K. Koul
2.	Transfusion Therapy and Allo-Immunisation	Dr. V.P. Choudhry	30	09:35 to 10:05am	
3.	Iron Overload Monitoring	Dr. Tulika Seth	25	10:05 to 10:30am	
4.	Iron Chelation	Dr. Amita Mahajan	30	10:30 to 11:00am	
	TEA			**11:00 am to 11:20 am**	
	Doctor Session II			**11:20 am to 01:00 pm**	
1.	Adult Thalassemia Care	Dr. Anupam Prakash	25	11.20 to 11.45am	Dr. Bhavna Dhingra Dr. Narendra Agarwal Dr. Gaurav Kharya
2.	BMT Pre & Post	Dr. (Brig.) Ajay Sharma (Retd.)	30	11.45 to 12.15pm	
3.	Case Studies	Dr. V.K. Khanna	30	12.15 to 12.45pm	
4.	Technology in Thalassemia Managment	Mr. Gagandeep Singh Khattar	15	12:45 to 01:00pm	
	Lunch			**01:00 pm to 02:00 pm**	
	Doctor Session III			**02:00 pm to 04:00 pm**	
1.	Genotype-Phenotype Aspect of NTDT	Dr. Suthat Fuchareon	20	02:00 to 02:20pm	Dr. Manas Kalra Dr. Anup Mohta Dr. (Brig) Anil Khetrapal (Retd.)
2.	Non - Transfusion Options in Thalassemia	Dr. Vijay Ramanan	20	02:20 to 02:40pm	
3.	Blood Transfusion in NTDT When and Why	Dr. Suthat Fuchareon	20	02:40 to 03:00pm	
4.	Iron Overload and Chelation in NTDT	Dr. Deepak Bansal	30	03:00 to 03:30pm	
5.	Complication of Thalassemia Intermedia, Quality of Life	Dr. Prantar Chakrabarti	30	03:30 to 04:00pm	

Capacity Building				02:30 pm to 04:30 pm	
S. No.	**Topic**	**Speaker**	**Minutes**	**Timings**	**Chairperson**
1.	Advocacy	Dr. Michael Angastiniostis	20	02:30 to 02:50pm	Ms. K. Ratnavalli Dr. Suman Jain
2.	Liaisoning	Mr. Prabhat Sinha	20	02:50 to 03:10pm	
3.	CSR Programme	Corporate Representatives	20	03:10 to 03:30pm	
4.	Networking & Alliance	Dr. D Ratna Devi	20	03:30 to 03:50pm	
5.	UKTS Working	Mr. Ajay Gandhi	12	03:50 to 04:02pm	
6.	Fund Raising UP Experience	Mr. Pravir Arya	7	04:02 to 04:09pm	
7.	Blood Donation Jabalpur	Mr. Sarabjit Singh	7	04:09 to 04:16pm	
6.	Low Cost mass Thalassemia Screening	Mr. Thadharam Tolani	7	04:16 to 04:23pm	
7.	Think Foundation Society Experience	Mr. Vinay Shetty	7	04:23 to 04:30pm	

WORKSHOP
on
Challenges in Diagnosis of THALASSEMIA
On Friday 16th December, 2016
at
Dept. of Haematology Building, AIIMS,
Ansari Nagar, New Delhi-110029

PROGRAMME

SESSION I			**10:00 am to 11:30 am**	
S. No.	**Topic**	**Speaker**	**Minutes**	**Timings**
1.	Introduction	Dr. Renu Saxena	15	10:00 to 10:15am
2.	RBC Indices Interpretation	Dr. Jasdeep	20	10:15 to 10:35am
3.	Capillary Electrophoresis	Dr. Seema Tyagi	20	10:35 to 10:55am
4.	Hb HPLC Interpretation	Dr. Dinesh	20	10:55 to 11:15am
5.	Case studies	Dr. Tulika Seth	20	11:15 to 11:35am
	TEA BREAK		**11:35 am to 11:45 am**	
	SESSION II		**11:45 am to 02:00 pm**	
	Topic	**HANDS ON TRAINING**		

		11:45 am to 12:30 pm	**12:30 pm to 01:15 pm**	**01:15 pm to 02:00 pm**
A	**CBC** Dr. Roopam Deka, Dr. Uday, Dr. Richa	**A**	**B**	**C**
B	**Capillary Electrophoresis** Dr. Astha Gupta, Dr. Preeti Dr. Priyanka	**B**	**C**	**A**
C	**Molecular Diagnosis** Dr Ravi Ranjan, Hare Pandey Dr. Karthika	**C**	**A**	**B**
	LUNCH		**02:00 pm**	

WORKSHOP

on

Stem Cells Transplantation
On Monday 19th December, 2016
at
Army R & R Hospital, Dhaula Kuan, Delhi-10

PROGRAMME

S. No.	Topic	Speaker	Minutes	Timings
1.	Introduction	Dr. (Brig.) Ajay Sharma (Retd.)	5	10:30 to 10:35am
2.	Pre-Transplant Identification & Preparation of Patient & Donors; Post-Transplant Domicile Care	Lt. Col Dr. Tarun Verma	35	10:35 to 11:10am
3.	Transplant, Harvesting & Conditioning	Dr. Rahul Nathani	30	11:10 to 11:40am
4.	Cord Blood/MUD and Haplo -Identical Transplant	Dr. Dinesh Bhurani	30	11:40 to 12:10pm
5.	Visit to Transplant unit in groups	Col. Dr. Rajan Kapoor	50	12:10 to 01:00pm
	Lunch		**1:00 pm**	

BIO-DATA SPEAKERS

Dr. (Brig.) Ajay Sharma (Retd.)

- Senior Consultant Deptt. of Clinical Haematology and stem cell transplantation SGRH.
- Formerly Head, Deptt. of Clinical Haematology and stem cell transplantation, R & R Hospital, Delhi Cantt. He has special interest in Haematology & Oncology

Dr. Alok Hemal

- Professor, Department of Pediatrics, RML Hospital, & Post Graduate Institute of Research & Education, Ministry of Health and Family Welfare,Government of India.
- In-charge of Hemato-Oncology & HIV division.

Dr. Alok Srivastva

- Professor of Medicine, Department of Haematology
- Head, Centre for Stem Cell Research. Christian Medical College, Vellore

Dr. Amita Mahajan

- Sr Consultant Pediatric Hematology & Oncology Indraprastha Apollo Hospital, Delhi
- Trained at AIIMS and UK

- Medical Advisor :- Thalassemics India, Foundation Against Thalassemia, Can Kids Leukemia Crusaders

Dr. Amita Trehan

- Incharge Hematology Oncology unit at PGIMER, Chandigarh
- Trained in Oncology through the auspices of the Royal College of Pediatrics and Child Health. UK.
- Participated International Outreach Program organized by St Jude's Children Research Hospital, USA.
- Main areas of interest Leukaemia and lymphoma and Thalassemia Intermedia.

Dr. Anju Seth

- Director Professor Department of Pediatrics & In-charge Div. of Pediatric Endocrinology, Lady Harding Medical College, New Delhi
- Areas of interest: disorders of vitamin D & calcium metabolism, growth & thyroid.
- Have been providing endocrine care to children and adolescents with thalassemia & other chronic disorders for > 10 years

Dr. Anupam Prakash

- Professor of Medicine, LHMC & Associated Hospitals, Delhi
- In-charge Thalassemia unit LHMC Hospital, New Delhi
- Editor-in-Chief, Indian Journal of Medical Specialties
- Associate Editor, API Textbook of Medicine-10th edition, Assistant Editor-9th edition
- DST Award as Young Researcher to Meet Nobel Laureates in Germany- 2003
- Member, Governing Body of API-DSC, DDF & ISAR since 2008-09.
- Member of Faculty Council of ICP (Association of Physicians of India)

Dr. A.P. Dubey

- Director Professor Department of Paediatrics since 2008 & formerly Head, Pediatrics MAMC & LN Hospital
- Started Thalassemia Unit at Lok Nayak Hospital in 1996.
- Chief investigator for Delhi Govt. project on "Antenatal screening of mothers for thalassemia".
- Established a Pediatric Research and Genetics Laboratory at Lok Nayak Hospital.
- MCI inspector for recognition of UG and PG curriculum and also for DNB courses.
- Delhi State Doctor's Award in 2011.

Mr. Ajay Gandhi

- 47 year old Thalassaemia Major patient, born in Nairobi, Kenya diagnosed at 3 months of age, he moved to the UK with his parents when he was 3 years old. Currently he is receiving treatment at University College London Hospital under Professor John Porter.
- Chartered Quantity Surveyor (QS) and is a Director of his own private practice in UK.
- Married to his lovely wife, Natasha and has 2 beautiful children, 11 years old boy Kavish and a 9 years girl, Omisha

Dr. Deepak Bansal

- Professor, Haematology/Oncology Unit
- Dept. of Pediatrics, Advanced Pediatric Center, Postgraduate Institute of Medical Education & Research Chandigarh

Dr. Dinesh Bhurani

- Director, Department of Haemato-oncology & Bone Marrow Transplant unit, Rajiv Gandhi Cancer Institute & Research Centre, Rohini, New Delhi
- He is the first DM of Hematology in India
- DM Clinical Haematology from CMC, Vellore & FRCPA from Australia.
- He has done more than 500 transplants at RGCI & Research Centre, Rohini, New Delhi
- Special interest in Haplo (half matched) transplant.

Mr. Gagandeep Singh Khattar

S/O Sh. Surjit Singh Khattar founder Thalassemic Children Welfare Association, Chandigarh and now Managing Trustee Help Thalassemics was born in Mohali and now settled in London consulting in IT to major financial companies like UBS, RBS, BP etc .

Dr. H. Pati

- Professor of Haematology, AIIMS, New Delhi
- Editor, Indian J Hematology & Blood Transfusion
- Co-editor of 5 Hematology books including deGruchy's Clinical Hematology.
- Fellow of International Medial Sciences Academy Indian College of Pathologists

Dr. J.S. Arora

Thalassemialogist, Msc in Haemoglobinopathy, University College London

Founder President : National Thalassemia Welfare Society (1991-1994)

Founder General Secretary : Federation of Indian Thalassemics since 1994

General Secretary : National Thalassemia Welfare Society since 1994

Member : Ethics Committee IIT Delhi
Ethics Committee LHMC & Associated Hospitals Delhi

Formerly : Coordinator Thalassemia Cell Govt. of Delhi
Member Advisory Committee - DDU Hospital Govt. of Delhi

Patients for Patient Safety (PFPS) Champion India

Member : Patients for Patient Safety Advisory Group

Author : Florilegium of Thalassemia

Co-Author : "Care & Control of Thalassemia

Dr. Maitreyee Bhattacharya

- D.M (Clinical Haematology), AIIMS, New Delhi.
- Professor, Institute of Haematology & Transfusion Medicine, Kolkata.
- Incharge, Nodal Centre for State Thalassemia Control Unit West Bengal.

Dr. Mammen Chandy

- Director, Tata Medical Center. Kolkatta
- Former Professor & Head, Department of Hematology CMC Hospital, Vellore.
- Former Professor of Hematology, Sultan Qaboos University Hospital, Muscat, Oman
- Fellow of the Royal Australasian College of Physicians.

- ❖ Fellow of the Royal College of Pathologists of Australasia.
- ❖ Fellow of the Royal College of Physicians (London)
- ❖ Chair ICMR Expert Group for Stem Cell Research and Therapy. 2013
- ❖ Chair: ICMR-DBT Joint Working Group on Gene Therapy.

Dr. Michael Angastionotis

- ❖ Studied Thalassaemia (Biochemistry-Prenatal diagnosis), Genetics, and Haematology/Oncology from UK through scholarships of the Cyprus government, WHO and the British Council.
- ❖ Member of the Thalassaemia Control Programme, Cyprus and WHO ad-Hoc advisory committee on the control of haemoglobin disorders in the 1980s
- ❖ Served as consultant to the East Mediterranean region of WHO and director WHO Collaborating Centre for thalassaemia.
- ❖ Director, Pediatric Department, Makarios Hospital, Nicosia (1989 – 2001)
- ❖ TIF, Medical Advisor since 2004.

Dr. Prantar Chakrabarti

- ❖ Assistant Professor in Haematology at IHTM, Kolkatta
- ❖ Postdoctoral training in clinical haematology at the AIIMS, New Delhi
- ❖ He was instrumental in setting up the State Thalassemia Control Programme of Government of West Bengal in 2008 and is a nodal officer of the programme till date.
- ❖ He has designed and implemented an innovative software THALAMON for monitoring thalassemia patients and carriers.

Dr. Praveen C. Sobti

- Professor of Paediatrics Incharge Hemato oncology Dayanand Medical College & Hospital Ludhiana
- Visiting fellowship, Royal College of Paediatrics & Child Health, London
- **Awards**
  - National Scholarship Ministry of Education, Govt. of India
  - Honorary Mayor President of Baton Rouge, Louisiana State, USA
- **Membership**
  - Founder of Punjab Thalassemia Welfare Society
  - Member National Advisory Board of Thalassemia
  - Member Global Advisory Board of Thalassemia

Dr. Rahul Bhargava

- DM Haematology from AIIMS.
- Director and Head of Stem Cell transplant – Artemis Hospital.
- Foermerly Consultant, Hematology and Head, Stem cell transplantation, Department of Oncology and Hematology, Medanta –The Medicity, Gurgaon**.**
- Fellow, Department of Hematology and Stem Cell Transplant Vancouver General Hospital

Dr. Rahul Naithani

- DM in Clinical Hematology (AIIMS)
- Senior Consultant - Clinical Hematology & Bone Marrow Transplantation at Max Healthcare since 2011
- Editor-Indian Journal of Hematology & Blood Transfusion
- Performed more than 140 BMTs
- Fellowship in Bone Marrow Transplantation at Hospital for Sick Children, Toronto

- BMT Training at St Jude Children's Research Hospital, Memphis, US
- Fellowship in Pediatric Hematology/Oncology (Toronto)

Dr. Rajiv Bansal

- **Senior Consultant & HoD Pediatrics at Santokba Durlabhji Hospital,**
- In-charge of Thalassemia unit, at SDMH
- Past President of IAP Jaipur branch,
- Recently elected President of Rajasthan state branch of NNF.
- Keen interest in Neonatology, pediatric hematology and pediatric respiratory diseases.

Dr. Rashid Merchant

- Senior Paediatrician in Mumbai, is passionately involved in the care of children by HIV/AIDS, Thalassemia and Primary Immune Deficiency.
- Former Dean and Professor of Paediatrics (Mumbai University).
- Former Honorary Consultant Paediatrician, Nanavati Super Specialty Hospital, Mumbai

Dr. Ravindra Kumar (Thalassemia Major)

- PhD Genetics (SGPGIMS, Lucknow)
- Scientist and Head, Central Research lab, Sri Aurobindo Medical College and Post Graduate Institute Indore
- Fields of Interest : Human Genetics, Molecular Biology
- Research publications: 70 Book Chapter : 1
- Awards : Best Paper Publication award at Hematocon 2015
- Members: Indian Academy of Medical Genetics

Dr. Sameer Sood
Dr. Sameer Sood, Md (Radio-Diagnosis).
Senior Consultant, Star Imaging and Path Labs,Tilak Nagar, New Delhi.

Dr. Sangeeta Yadav

- ❖ Director Professor, Department of Pediatrics, MAMC, University of Delhi.
- ❖ Started the Division of Pediatric & Adolescent Endocrinology at LN Hospital
- ❖ Executive Member IAP Ped. & Adolescent Endocrinology**.**
- ❖ Awarded WHO Fellowship for Pediatric & Adolescent Endocrinology in 1996.

Dr. Sarmila Chandra

- ❖ Haemato-oncologist, trained in AIIMS Delhi and University of Ulm West Germany.
- ❖ She has been working as Consultant Haematologist in Kothari Medical Centre, Bhoruka Blood Bank and recently in Narayana Health RTIICS, Kolkata as head of haematology.
- ❖ Consultant haematologist in IHTM Medical College at its inception.
- ❖ Advisor to Thalassaemia Society and Haematology Foundation

Dr. Seema Kapoor

- ❖ Professor Paediatrics, in-charge Genetic Unit, Maulana Azad Medical College, Delhi.
- ❖ In charge Delhi State Lab For Prenatal Diagnosis In Thalassemia.
- ❖ Member of ICMR task force on inborn metabolic errors.
- ❖ Member of national new born screening committee.
- ❖ Awarded 25 GOLD medals .

Dr. Sujata Sinha (Hematopathologist)

- Consultant, Laboratory Services-RBSK (Rashtriya Bal Swasthya Karyakram, National Health Mission) Adjunct Associate Professor, CCG, Murdoch University, Australia
- Associated with development of national policy, technical guidelines and implementation framework for hemoglobinopathies program and currently nationwide implementation of program under NHM since 2015
- As Project Head and Technical Consultant "Action on Birth Defects Project" NHM, Uttarakhand, developed and piloted a State level program for care and control of Thalassemia (2012-2015)
- President, Varanasi Region Thalassemia Welfare Society and Coordinator, Thalassemia Working Group, (2006-2012)

Dr. Sunil Gomber

- Director, Professor Department of Pediatrics UCMS & Guru Teg Bahadur Hospital, Delhi.
- In-charge Paediatric Hemato-oncology division of the department of Pediatrics.
- Fellow Indian Academy of Pediatrics (FIAP).
- WHO temporary adviser & National faculty for integrated management of child hood & neonatal illness (IMNCI).

Dr. Suthat Fuchareon

Professor Emeritus at the Institute of Molecular Biosciences, and Director of the Thalassemia Research Centre, Mahidol University, Nakornpathom, Thailand.

Dr. Fuchareon is internationally recognized for his work on thalassemia. His scientific interests encompass the spectrum of basic, translational, clinical and epidemiological

research. His Work University has set the standard for defining the molecular genetics, genomics, and genotypic/phenotypic correlations of thalassemic syndromes.

Clinical trials on the use of inducers of fetal hemoglobin and iron chelation, the use of MRI imaging for assessment of iron overload, and public health burden of these diseases.

Outstanding Researcher Award from the National Research Council of Thailand, Outstanding Scientist Award from the Foundation for the Promotion of Science Award Technology under the Patronage of His Majesty the King of Thailand.

Dr. Tulika Seth

- Paediatric Haemato-oncologist
- Additional professor of Haematology, AIIMS, New Delhi

Dr. Vatsla Dadhwal

- Professor Division of Maternal Foetal Medicine Department of Obstetrics & Gynaecology AIIMS New Delhi
- Nodal officer for PPTCT Programme
- Young Researcher Award- International Clinical Epidemiology Network -2002
- Rhogam-FOGSI award – 2008
- ICMR- International Senior bio-medical scientist fellowship award 2015

Dr. Vijay Ramanan

- Consultant Bone Marrow Transplant Specialist associated with Ruby Hall Clinic, Poona Hospital & Research Center, Yashoda Hematology Clinic, Pune.
- Has done over 250 patients of Stem cell and Bone Marrow Transplant.
- Heads support groups for Thalassaemia and Hemophilia.
- Member of European Society for blood and bone marrow transplant.

- First SAARC individual patron
- Chairman of Pune Thalassemia Center, Red Cross, Pune

Dr. Vikas Kohli

- Director, Delhi Child Heart Center
- Founder Trustee, Child Heart Foundation
- Fellow American Academy of Pediatrics
- Fellow American College of Cardiology

Dr. V.K. Khanna

- Chairman, Department of Pediatrics, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi.
- In-charge Preeti Tuli Thalassemia Unit SGRH.
- Vice President Thalassemics India
- Regional scientific coordinator from India to TIF.
- Involved in care of thalassemia patients and research thalassemia for last 32 years.

Dr. V.P. Choudhry

- Former Prof. & Head, Department of Haematology, AIIMS, New Delhi
- Director of Indira Gandhi Institute of Child Health, Afghanistan (1983 – 1986)
- Senior Consultant : Fortis Escorts Hospital Faridabad.
  Batra Hospital & Medical Research Centre, New Delhi
- **Editor :** Recent Advances in Hematology
  - Thalassemia Care & Control

❖ **Advisor :**

- National Thalassemia Welfare Society
- Federation of Indian Thalassemics

Dr. Yogesh Chawla

❖ Professor & Head, Department of Hepatology, PGIMER, Chandigarh

❖ Former Director, PGIMER, Chandigarh 2011 - 2016.

❖ During Directorship of PGI : Awarded by the Hon'ble Prime Minister of India for being the cleanest public sector hospital in the country in September 2016.

Dr. D Ratna Devi

❖ A medical doctor, public health and management professional, has worked with national and international NGOs on donor-funded public health initiatives.

❖ CEO and Co-founder of DakshamA Health and Education, working for access to health, patient education and advocacy.

❖ Leads a cross disease Patient Alliance in India called Indian Alliance of Patient Groups (IAPG) and is a Board member of I - ORD.

Shri Thadharam Tolani

❖ Sh. Tolani ji has set up Tolani Sewa sankapl which conducts Thalassemia Awareness and Detection Camps in various cities all over India.

Mr Pravir Arya

- Founder THALASSEMICS INDIA SOCIETY in 1999 in Lucknow.
- Aiming to unite all thalassemics societies of Uttar Pradesh.
- Organised a major Musical programme with Sachiat & Parampara Thakur for awareness & fund raising.
- Received a grant from Govt. of Rs.5236000/- for treatment of thalassemic children of Uttar Pradesh.
- Appointed Nodal officer by NHM for mobilization of funds in all medical colleges.
- Currently free treatment has started at SGPGI, KGMU, Kanpur Medical College.

Mr Sarabjit Singh

- Founder Disha Welfare Association Samiti Jabalpur MP.
- Organizing regular blood donation camps and Thalassemia awareness camps.
- Arranging blood for emergency patients.

BIO-DATA CHAIRPERSONS

Dr. Alka Mathur

- Graduated from LHMC and received short term training in Hematology at AIIMS
- Established Thalassemia Day Care Centre at Hindu Rao Hospital May 2004, in charge since then.

Dr. Brig. Anil Khetrapal (Retd.)

- Chairperson Transfusion Medicine, Artemis Hospitals, Gurgaon
- Formerly Professor & Head, Department of Pathology.
  - TATA Main Hospital, Jamshedpur,
  - Army Hospital (R&R) Delhi Cantt.
  - Armed Forces Transfusion Centre, Delhi Cantt
  - Base Hospital, Delhi Cant.
  - Transfusion Centre Command Hospital Kolkata

Dr. Anup Mohta

Director & HoD, Pediatric surgery, Chacha Nehru Bal Chikitsalaya, Delhi

- Associate Editor, Indian Paediatrics
- Member, Editorial board Journal of Indian Association of Paediatric Surgeons.
- Fellow and Member of professional bodies IAPS, IAP, NNF, NAMS, ISPU
- Associated with Programmes like Promotion of rational use of drugs,
- Assessor for NABH

Dr. A.G. Radhika

- Consultant, Obs. & Gynae. UCMS & GTB Hospital, Delhi
- Editor, Newsletter NARCHI, Delhi
- WHO Fellow: Advanced Course on Monitoring and Evaluation : Innovations in a Dynamic Health Systems Environment
- Core member 'Matri Suraksha Abhiyan'
- Nodal officer : Thalassemia Control Programme Prevention of Parent to Child Transmission of HIV/AIDS

Dr. Bhavna Dhingra

- Faculty in Pediatrics at AIIMS Bhopal
- Former faculty at KSCH, LHMC Delhi
- US Certified Pediatric Bioethicist
- Hematology Training at AIIMS, Delhi

Dr. D. D. Golani

- MD (Internal medicine)-1985 from Delhi University
- Fellow of Indian Academy of Echocardiography
- Senior consultant at DDU Hospital-Delhi Govt. Hospital
- Keen interest in echo-cardiac study of thalassemic patients

Dr. Dharma Choudhry

- DM clinical haematology from AIIMS.
- Senior Consultant & Director, Department of Haemato-Oncology & Bone Marrow Transplantation, Dr. B. L. Kapur Memorial Hospital, New Delhi.
- Formerly he was Consultant Clinical Haematology Sir Ganga Ram Hospital,
- He got his Clinical Hematology training from CMC Vellore, India

Dr. Gaurav Kharya

- Consultant Paediatric Haematology Oncology, Immunology & Bone Marrow Transplant, BLK Super Specialty Hospital, New Delhi.
- Fellow in paediatric haemato-oncology, immunology & bone marrow transplant Great north Children's hospital, Newcastle, United Kingdom.2012
- He worked in the field of paediatric haemato-oncology, immunology & bone marrow transplant. at St Mary's hospital, Imperial College NHS trust, London, UK

Dr. Geetanjali Jindal

- Professor of Pediatrics, Government Medical College and Hospital, Chandigarh
- Started Thalassemia Day care Centre
- In charge Thalassemia Ward and Hematology

Dr. Jalbala Sardana

- Practicing ophthalmologist in Bareilly since last 30 years
- Proud mother of Late Dr. Anjali Sardana who is an inspiration for her to work for Thalassemia
- Founder secretary of Thalassemia Children Welfare Society, Bareilly
- Joint Secretary of Federation of Indian Thalassemic
- Conferred the Women of the Year 2016 award by Golden Era Society for her services in the field of Thalassemia.
- Honored by IMA on Doctors Day in 2016 for services to Thalassemic children

Dr. Kabita Chaterjee
Incharge Blood Bank, AIIMS

Dr. Kirti Nanal

- MD Paediatrics, In charge, paediatrics Deptt & Thalassemia unit Charak Palika Chikitsaya NDMC, Moti Bagh.(Since 1997).

Dr. K.K. Koul

- Professor & Head of P.G.Deptt. of pathology, Govt. Medical College, Jammu.
- Sr. Consultant Haematology, G.M.C associated Hospitals Jammu.
- Medical Advisor J&K State Thalassemia Welfare Society, Jammu.

Dr. Madhulika Kabra

- Professor, Genetics division, Department of Pediatrics, AIIMS, New Delhi
- Genetics Division has been designated as a WHO Collaborating Center and Center of Excellence for training in Genetics by Government of India
  Chapters in Books : About 25
- Member of the Board of directors of Asian Society for Inherited Metabolic Diseases
- Member Task Force Human genetics, Inborn Metabolic Disorders & LSDs, ICMR,
- Member, Editorial Board of Indian Journal of Pediatrics

Dr. Manas Kalra

- FNB in Pediatric Hematology Oncology
- 3 year Fellowship in Pediatric Oncology and BMT from CHW, Sydney
- Currently, Consultant at Indraprastha Apollo Hospital, Delhi

Dr. Mousumi Swami

- HoD of Blood Transfusion Services, DDU Hospital Govt. of Delhi
- Technical expert, State Transfusion Services Core Coordination Committee
- Certified NABH assessor for Blood Banks
- Chairperson ISBTI Delhi chapter
- Conferred with "**Bhagirathi Samman**" 2013 for her service for mankind.

Dr. Narendra Agarwal

- Consultant Hemato-Oncology and BMT, Rajiv Gandhi Cancer Institute, Rohini, New Delhi, India

Dr. Neelam Sood

- Head of Department, Pathology and Lab Medicine, DDU Hospital, Govt. of NCT, New Delhi.
- Nodal Officer for Thalassemia Screening Programme, DDUH, NCT
- WHO Fellowship in Cytopathology in 2006

Dr. Nikhil Sheth

- Senior Paediatrician
- He Has Worked Under Dr A. Piga (Italy) and Dr Paul Telfer (U K)
- Exclusively working for Thalassemics All over Gujarat since 2000.

Dr. N.K. Mehra

- National Professor, Former Dean (Research) and Head of the Department of Transplant Immunology & Immunogenetics AIIMS, New Delhi.
- Fellow of the Indian National Science Academy (FNA), Indian Academy of Sciences (FNASc), Member Honoris Causa of the Hungarian Academy of Sciences and Fellow of The World Academy of Sciences (FTWAS).

Dr. Poonam Laul

- Specialist Grade 1 (Gynae. & Obst.) Deen Dayal Upadhyay Hospital, Hari Nagar, New Delhi.

Dr. Rajni Sharma

- Assistant Professor, Division of Pediatric Endocrinology AIIMS, New Delhi
- Formerly Assistant Professor (Pediatrics) at LHMC and associated Kalawati Saran Children's Hospital, New Delhi

Dr. Rakhi Maiwal

- DM in Gastroenterology from Christian Medical College, Vellore in 2011.
- Associate Professor of Hepatology at the Institute of Liver and Biliary Sciences.
- Special interest in critical care medicine and renal failure in patients with liver disease, liver regeneration and artificial liver support therapies.
- Member of the editorial board of Hepatology International

Dr. Rekha Harish

- Professor & Head Department of Paediatrics .
- Examiner to various Medical Universities in North India.
- Reviewer for Indian-Paediatrics, IJP, JIMMS Journal of Paediatric Surgery;
- Chief-coordinator Thalassemia-Day-Care Centre at GMC Jammu

- ❖ National Convener IAP Task Force for Prevention of Childhood Obesity and Life Style Disorders 2012 -2015.
- ❖ Chairperson FSSAI Expert Group for laying guidelines for National School Canteen.

Dr. Renu Saxena

- ❖ Professor & Head, Dept. of Hematology, AIIMS, New Delhi
- ❖ Major interest : Hemostasis, Leukemia, Molecular Genetics, quality assurance.
- ❖ Publications : More than 350 in National and International Journals.
- ❖ Funded Research Projects: more than 30
- ❖ Coordinator : ISHTM-AIIMS EQAP for Hemogram

Dr. Ritu Chawla

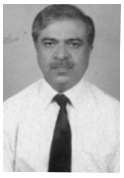
- ❖ MD. Paediatrics, Kalawati Saran Children Hospital
- ❖ Incharge of Thalassemia centre of DDU Hospital for last 15 years

Dr. R.N. Makroo

- ❖ Director Professor Dept. of Transfusion Medicine, Molecular Biology & Transplant Immunology Indraprastha Apollo Hospital
- ❖ W.H.O. National Consultant Transfusion Medicine 1990 –1992
- ❖ Consultant, Transfusion Medicine, Riyad Military Hospital 1992-1993
  - Member National Blood Transfusion Council, Govt. Of India
  - Member National Accreditation committee on Blood Banks, Govt. Of India.
  - Qualified Assessor for NABH certification for Blood Banks
  - Member Task Force on Blood & Blood Safety Government of India
  - Member Haemovigilance Advisory Committee Govt. of India

Dr. R.S. Gupta

- Deputy Director General(BTS/CST) & Director (NBTC)
- Ministry of Health & Family Welfare
- National AIDS Control Organization, New Delhi



Dr. Sanjay Choudhry

- Fellow In Neonatalogy (AIIMS)
- Advanced Training In Pediatric Intensive Care (P.G.I.M.E.R)
- HoD Paediatrics & In-charge Thalassemia Unit, B.S. Ambedkar Hospital Rohini.

Dr. Sanjeev Digra

- Associate professor of Paediatrics, Government Medical College Jammu
- In-charge Thalassemia Day Care Centre & Paediatric Cancer Ward SMGSH, Jammu.

Dr. S.K. Arora

- Addl. Director Health, Directorate of Health Services, Govt. of Delhi. Presently he is looking after Thalassemia Control Programme, Tobacco control programme, Programme for Health care for Elderly at State level in Delhi Govt. He is heading State IEC committee & coordinating IEC activities of all Health Programmes in Delhi State.

- He is recipient of WHO Award, Prestigious Delhi State Award & Delhi University Researcher Association Award.

Dr. Sangeeta Gupta

- Professor, Obstetrics & Gynecology, Maulana Azad Medical College, New Delhi
- Incharge, Fetal medicine Clinic at MAMC & LNH , New Delhi
- Awarded Commonwealth Scholarship in 2007 & trained in Fetal Medicine at St.George's Hospital, London
- Has many publications & contributions in various text-books

Dr. Suman Mendiratta

- Sr. Consultant & Unit Head Obst & Gynae Deptt. North DMC Medical College & Hindu Rao Hospital, Delhi
- Project Coordinator Thalassemia Control Cell, North Delhi Municipal Corporation
- In-charge Premarital Counselling Clinic Hindu Rao Hospital, Delhi
- Awarded CL Jhaveri First prize for best paper presentation AICOG 2006, Kochi, Kerala

Dr. Shishir Seth

- Consultant- Hemato-Oncology & Bone Marrow Transplant, Apollo Cancer Institute, Indraprastha Apollo Hospitals, Delhi
- Worked as Consultant, - Hemato-oncology & Stem Cell Transplant (BMT), at Rajiv Gandhi Cancer Institute, New Delhi
- Fellow- Bone Marrow Transplantation, General Hospital, Vancouver, BC, Canada
- Performed more than 200 Hematopoietic stem cell Transplants (BMT).

Ms. Shobha Tuli

- Secretary Thalassemics India since 1992
- Vice President Thalassaemia International Federation (TIF) since 2006
- President Federation of Indian Thalassemics (FIT) since 2000.

Dr. Vikas Dua

- Senior consultant of paediatric haematology oncology and bone marrow transplant at Artemis Hospital, Gurgaon, India,
- Associated with National University Hospital, Singapore.
- He has done close to 100 paediatric bone marrow transplants.

Dr. Vinky Rughwani

- Child Specialist, Rughwani Child Care Centre and Hospital, Nagpur
- **Director :-** Thalassemia and Sickle Cell Center, Nagpur (Maharashtra)
- **President :-** Thalassemia Society of Central India.
- **Member:-** Maharashtra State Blood Transfusion Council

Dr. V.K. Sharma

- HoD Blood Bank Mata Chanan Devi Hospital
- Blood Bank is equipped with components & apheresis ID NAT

DR B.N DARA AWARD

Dr. Sujata Sinha

She is Consultant, Laboratory Services-RBSK (Rashtriya Bal Swasthya Karyakram, National Health Mission) & Adjunct Associate Professor, CCG, Murdoch University, Australia

Associated with development of national policy, technical guidelines and implementation framework for hemoglobinopathies program and currently nationwide implementation of the program under National Health Mission Since 2015

As Project Head and Technical Consultant, Action on Birth Defects Project, National Health Mission, Uttarakhand developed and piloted a State level program for care and control of Thalassemia (2012-2015)

As Hematopathologist and President, Varanasi Region Thalassemia Welfare Society and Coordinator, Thalassemia Working Group, initiated work on Thalassemia in community and on public health perspectives 2006-2012

Areas of Interest :

Thalassemias & Hemoglobinopathies, Birth Defects
Community genetics , Public Health Genomics, Bioinformatics , Public Health Policy and Planning.

Awards and Honors :

Endeavour Executive Award (2010), Commonwealth Government of Australia
Member, Australia Awards Alumni Network (AAAN),.
Honorary Visiting Fellow, PHG Foundation, Cambridge, UK January 2012 - December 2013

BEST SOCIAL WORKER AWARD

Vinay Shetty

He is B.E.(Civil) and M.M.S.(Marketing) from, Mumbai, Established an NGO "Citizen" in 1997, changed it to Think Foundation in 2006. He is Vice President of Think Foundation

- Has organized more than 5000 blood donation camps in the last 15 years.
- Daily blood donation drives for a continuous period of 6 months at Dadar and Andheri stations in 2007, 2008, 2009.
- Organizes pan-India blood donation drives at corporates offices across the country.
- Member of the Governing Board of the State Blood Transfusion Council.
- Opened 6 new thalassaemia day care centres in Mumbai.
- Opened Thalassaemia Day Care Centres in Jalna, Aurangabad with free facilities
- Assisted in the formation of the Goa Thalassaemia Society and Day Care Centre at Goa Medical College.
- Liaised with Health Minister to make iron chelators available free to thalassaemia patients in Maharashtra under the Rajiv Gandhi Jeevandayi Arogya Yojana.
- Liaised with Health Minister for establishing Day Care Centres in Thane, Nasik, Satara and Amravati districts.
- Organized more than 1700 Thalassaemia Screening camps in the past 10 years

Awards to Vinay Shetty :

A.N. Kashyap Award by the ISBTI for vital contribution in voluntary blood donation.

Mother Teresa Memorial Award by the Harmony Foundation for contribution in blood donation and thalassaemia.

CONTENTS

From Secretary's Desk

-Dr. J. S. Arora

"25 YEARS" Sound Great.

Though as per Indian Constitution one attains adulthood at the age of 18 years, but actual end of childhood is at **25** years. Now we are **25** years old. We started our 25th year celebrations by observing foundation day on 22nd Nov 2015 at residence of our great well-wisher Shri Hansraj Ahir then MoS chemicals and now MoS Home Affairs. It was followed by Raahagiri at Connaught Place on 14th February the Valentine Day to spread awareness amongst youngster. Then we had International Thalassemia Day celebrations at Adventure Island, Rohini, Delhi, where more than 600 patients and parents enjoyed rides and water games.

National Thalassemia Welfare Society was formed on **23rd November, 1991** by patients, Parents, Doctors & well-wishers at AIIMS. At that time the word Thalassemia was hardly known, even amongst medical fraternity. If I look back at my Thalassemia journey in 1991 there were only 3 transfusion centers in Delhi with little amenities even at AIIMS. The transfusions were given in casualty along with seriously ill patients. Blood was in acute shortage and most of the thalassemics were dependent upon single Blood Bank Indian Red Cross Blood Bank. Pack cells were not easily available and Leuco depletion was unheard. Though Desferal was available but cost and unavailability of infusion pump was a great barrier besides painful administration. Transmission of transfusion transmitted infections was very high. Though pre-natal diagnostic facility was available in AIIMS but thalassemia carrier screening was hardly advised to pregnant women resulting into many Thalassemia Major Births. Outside Delhi things were worst except Mumbai & Vellore.

From 3 Transfusion Centres in1991 now we have 20 (12 Govt.) Thalassemia units in Delhi & NCR. The most remarkable achievement of NTWS has been in getting cooperation from all the concerned doctors (Hematologists, Pediatricians, Blood Banks & Head of the Institutes) and the blessings of Delhi Government

To achieve our objective of creating optimum facilities at minimum cost we liaison with the Government of Delhi. Under Bhagidari scheme **Directorate of Health Services** in

consultation **with National Thalassemia Welfare Society formed a "Thalassemia Cell"** to monitor the various initiatives taken by the Government. I have been privileged coordinator of the Thalassemia Cell since its inception. **I am proud to say that our major achievements have been FREE all three chelating agents for every patient registered in Delhi Government Hospitals, VAT (Sales tax) exemption on blood filters and all chelating agent & the latest is FREE pre-natal diagnostic facility for all at Lok Nayak Hospital**.

Following other major steps have been undertaken under this venture:

- Massive Thalassemia campaign. Advertisements were put in various newspapers. Publishing of brochures & poster on Thalassemia awareness. Hoardings have been put at prominent places in the Capital.
- Thalassemia screening of pregnant women in antenatal clinics of all major Hospitals.
- DHS Govt. of Delhi in association with NTWS produced two 27 minutes film "Chetna" and "Jagriti" on Thalassemia awareness.
- A five-day mega event "Thalassemia Chetna Yath Yatra" from 22nd Nov to 26th 2001, flagged off by the then Hon'ble Chief Minister of Delhi.
- A health parade with a Tableau on Thalassemia marked the World Health Day observed by Directorate of Health Services, Govt. of Delhi in 2003
- A protocol on thalassemia was published in both English and Hindi languages. It was launched by the then Hon'ble Health Minister in 2005.
- Directorate of Health Services assigned NTWS to prepare registry of thalassemia patients taking transfusions in Delhi, which NTWS completed proficiently in 2013.

In February 1994, we organized our 1st National Thalassemia Conference which was also 1st of its in India. At that time there were only 11 Thalassemia Societies in India. We Invited and offered free registration & accommodation to all of them so that everybody should attend. Over 300 persons attended the 2 day conference. A meeting of all the associations was called during the conference, 6 of them joined to form the Federation of India Thalassemics.

To fulfill our objective to enrich power of knowledge amongst thalassemia families and doctors, we in association with Department of Haematology A.I.I.M.S. organized

- 1st National Thalassemia Conference, Feb. 1994, inaugurated by DGHS.
- 2nd National Thalassemia Conference, Dec.1997 inaugurated by Director AIIMS.
- 3rd National Thalassemia Conference, Apr. 2001, inaugurated by the then Hon'ble Chief Minister of Delhi.
- 4th National Thalassemia Conference, May. 2003 inaugurated by the then

Hon'ble Minister of Health, Govt. of NCT, Delhi.

- 6th National Thalassemia Conference, Nov 2010 inaugurated by Director General ICMR and Secretary Ministry of Health, Govt. of India.
- 7th National Thalassemia Conference, April 2014 inaugurated by Dean AIIMS
- Symposium on Thalassemia & Deferiprone in March 1995 to launch the world's first Oral iron chelator, inaugurated by the Dean AIIMS
- Workshop on Prenatal Diagnosis of Thalassemia in Pregnancy Nov' 2010.
- Workshop on Challenges in Diagnosis of Thalassemia Nov 2010.
- Workshop for patients Capacity Building, April 2014

NTWS in association with Department of Paediatrics, LHMC and Kalawati Saran Children's Hospital organized

- Training Program on Thalassemia Care, Apr. 2004 inaugurated by MS & Principal of LHMC & KSC Hospital
- 5th National Thalassemia Conference, Nov. 2006 inaugurated by the then Hon'ble Minister of Finance, Govt. of NCT, Delhi.
- "Thalassemia Symposium III", Aug'08

NTWS in association with Directorate of Health Services Govt. of Delhi and MAMC & LN Hospital organized

- Symposium on Thalassemia. May 2005, the then Hon'ble Minister of Health was chief guest & Hon'ble Minister of Finance was guest of Honour

NTWS in association with Department of Paediatrics, UCMS & GTB Hospital organized

- Workshop on Thalassemia in Nov 2006 inaugurated by the secretary health Govt. of NCT Delhi.
- Workshop on Thalassemia, April 2014.

TIF patient Capacity Building workshop was a finest initiative taken to motivate the patients for a better treatment, to live a near normal healthy life.

Now NTWS is organizing "8th National Thalassemia Conference" in association with Department of Haematology, A.I.I.M.S on 17th & 18th December, 2016 at Jawahar Lal

Auditorium, AIIMS, New Delhi, preceded by **Workshop on Challenges in Diagnosis of Thalassemia** on Friday 16th December, 2016 and followed by **Workshop on Stem Cells Transplantation** On Monday 19th December, 2016 at Army R & R Hospital, Dhaula Kuan, New Delhi.

In these academic meetings International & National faculty of repute have been invited and over 400-600 patients, parents and doctors benefited every time. In our last conference (7th NTC), we had a jumbo representation of over 1200 patients/parents/Doctors out of which over 300 were adult patients. This was the highest represented conference till then. This time we expect to surpass this figure.

Since inception our aim has been to strengthen existing societies and encourage the formation of new Thalassemia societies in other districts. Wherever there were more than 25 patients, we encouraged them to join & form new Thalassemia association. Where Thalassemia associations already existed but were in active we infused enthusiasm and made them vibrant.

In this regard within two months of formation of NTWS we started visiting other parts of India and started organizing CMEs and checkup camps. First such camp was organized at Kota in February 1992. During last 25 years we have visited and organized lectures and check-up camps several times in most of cities like Faridabad, Gurgaon, Rohtak, Hisar, Sirsa, Agra, Meerut, Bareilly, Varanasi, Aligarh, Lucknow, Dehradun, Kota, Jodhpur, Shri Ganganagar, Udaipur, Gwalior, Jabalpur, Bhopal, Shahdol, Indore, Raipur, Amritsar, Jalandhar, Patiala, Jammu, Srinagar, Patna, Dhanbad, Bhillai, Dibrugarh and many more.

Voluntary blood donation drive has been another area where we focused since beginning and gave an impetus in last 10 years. In last 10 years we have organized about 500 blood donation camps and collected around 25,000 units of blood.

I associated with disability moment since Jan 1996 when first "People with Disability" act was passed, which did not have any mention of Thalassemia. Our President Km Surrendar Saini Ji played a key role in bringing thalassemia in the first amendment list. We had written countless letters, had innumerable meetings with the authorities & activists of other disabilities and participated in various meetings, workshops and protests to strongly put our demand for inclusion of Thalassemia in the list of disabilities for the purpose of disability act. We are delighted to say that at last we have reached a stage where Thalassemia and sickle cell anemia have been included in the "Disability Bill 2014". The bill has been placed in Lok Sabha &

Rajya Sabha on 7.5.15. There is every possible chance that this bill will be introduced in the winter sessions of parliament 2016. If it is passed it will help in improving the status & quality of life of Thalassemics.

Realistic wish list which we would like to accomplish ASAP

NAT tested blood without replacement

Free all three chelating agents for every thalassemic

Thalassemia screening of all pregnant women

Anti Natal diagnostic facilities in all state capitals

Disability status for Thalassemia and Sickle Cell Anemia

I am confident if we all (Thalassemia associations, medical fraternity, central & state governments) work together these goals are feasible within a decade.

Unity is strength

Blood Transfusion Therapy in Thalassemic Children

- Dr A.P. Dubey

Thalassemia is one of the most common genetic disorders resulting from an inherited abnormality of globin chain production. According to an estimate about 10000 thalassemic children are born in India every year. Now it is well established that thalassemia is not a single disease entity but a group of disorders known as hemoglobinopathies. The basic defect lies in the rate of synthesis of one or more globin chains. This leads to imbalanced globin chain production, ineffective erythropoiesis, increased hemolysis and variable degree of anemia. If these children are not treated properly, all of them invariably die in the first decade of life following severe anemia, congestive heart failure and other complications. Therefore, the only and most important management to prevent death and other complications is to give red blood cell transfusions at regular intervals to maintain a near normal hemoglobin which will permit normal growth and development and improve the survival of these children.

Regular Blood Transfusion (BT) Therapy :

Regular Blood Transfusion (packed red blood cells) therapy has remained the main stay of the management of thalassemia. Blood transfusion should be started without delay once the diagnosis of thalassemia major is confirmed. The results of transfusion therapy regularly and methodically repeated are absolutely superior to those achievable with transfusions given irregularly and only when the child appears anemic. Thus a regimen of chronic BT to eliminate hypoxia and its side effects should be followed in all the cases. In majority of the cases such children require 15-20 mL /Kg packed red blood cells at an interval of every 3-4 weeks. This transfusion regimen should not allow the hemoglobin to fall below 9.5-10g/dL to prevent cardiomegaly and cardiac failure and to arrest abnormal extra medullary hematopoiesis, prevent hepato-splenomegaly and facial changes which are the hallmark of a poorly managed or noncompliant child. This also prevents iron absorption from the intestines and thus reduces overall iron load in the body.

Type of Blood :

In the present era, it is necessary to give only blood components (not the whole blood) in all cases. For thalassemic patients, only packed RBC's are required. Preferably fresh packed red blood cells (not more than 4-5 days old) should be transfused. Filtration of blood to remove WBCs and plasma will prevent unnecessary infusion of plasma proteins and white cells thus preventing transfusion reactions and other allergic reactions.

Frequency of Blood Transfusion :

For all practical purposes, majority of the thalessmic children (without hypersplenism) require B.T. at an interval of 3 - 4 weeks. Our aim should be to maintain a pre-transfusion Hb of around 10g/dL in such a thalassemic child. In an individual patient, the pre-transfusion Hb level required to maintain the recommended mean Hb of 12g/dL will vary with the transfusion interval. However, the post transfusion Hb should not exceed 16g/dL, since higher Hb levels

increase blood viscosity, reduce tissue oxygenation and increase the risk of thrombosis.

Amount of Blood :

In principle, it is easy to calculate the amount of blood to be given to a thalassemic patient to raise the desired Hb. As a general guideline for packed cells to raise the Hb by 1g/dL, the blood volume required is 3 ml/kg body weight. Thus patients on monthly transfusions, would require approximately 12 ml/kg of packed cells which is equivalent to 20 ml/kg of whole blood. Older children may require 1-2 units of packed res blood cells depending upon their body weight.

If there is no cardiac problem, a child can be given 5 – 7 ml of blood or packed cells/kg body weight per hour. When cardiac failure is present or Hb is < 5g/dL, small BT at frequent intervals (1 – 2 weekly) can be given along with a diuretic (mostly frusemide). On a single occasion not more than 5ml/kg of blood should be transfused at an infusion rate of not exceeding 2 ml/kg/hour.

Evaluation of Transfusion Treatment :

The following data should be regularly recorded at each transfusion:

- Date of transfusion
- Bag number of the blood transfused
- Amount of blood transfused
- Height and Weight
- Hepato-splenomagaly
- Transfusion reactions (details)

Thalassemia Unit/Day Care Centre

Ideally blood transfusion should be done in a separate thalassemia unit during the day time, where all the facilities of a trained doctor & nurse are also available. This unit should also have facilities for Hb estimation, growth recording, ferritin estimation, dispensing of drugs like iron chelators and some recreation facilities. It should keep all the patient records, a copy of which can be given to the patient as well. In Delhi almost all the major Govt./Private Hospitals have this kind of facility available for such children.

Leukodepletion :

Now, it is well recognized that WBC's present in the blood could sensitize the recipient following a blood transfusion. Therefore any subsequent B.T. could cause a non hemolytic febrile transfusion reaction (NHFTR) in these patients.

Main Consequences of Transfusion of Allogenic Leucocytes

Adverse Effects :

- Non – hemolytic febrile transfusion reactions
- Platelet refractoriness
- Immunosuppression
- Graft versus host disease (caused by transfusion of live lymphocytes to immuno deficient patients)
- Transmission of viruses (CMV, HTLV – I)

Beneficial Effects:

- Immuno tolerance (prolonged survival of renal transplants)
- Immuno modulation (beneficial effect in women with spontaneous abortions)
- Graft vs. leukemia effect (in patients with leukemia following bone marrow transplantation)

To prevent the deleterious effects of the leucocytes, one can use micro filtration techniques which are designed for removal of micro aggregates or one can use leucocyte depleting filters (LDF) meant for removing leucocytes from red cell preparations or platelet concentrates. High cost of these filters is the only deterrent in their regular use by majority of these patients in our country.

Current Thalassemia Care Survival & Quality Of Life

- Dr V.P. Choudhry

WHO has estimated that 4.5% of the World's populations are affected by Thalassemia & allied disorders. Thalassemia belt that spans across counteries such as Italy, Greece, Cyprus, Sardinia, Turkey, Saudi Arabia, Iran, Afganisthan, Pakistan, India & South East Asian countries Indonesia, Burma & Thailand. (Fig. - 1). National wide survey by ICMR under Jai Vigyan Mission project has revealed that nearly 4% of people in India have Thalassemia Minor (5 crore), while nearly twelve thousands children with Thalassemia major are born in India every year. There are nearly 1.25 lakh Thalassemic children in India. Thalassemia is very common in certain communities like Punjabies, Sindhis, Gujaratis, Bengalies, Parsis etc. It is more common among Punjabies who have migrated from West Pakistan with prevalence of over 15%. Prevalence of Thalassemia in Northern Western & North East Part of India is higher while it is less common in South. Hemoglobin E. Disease either alone or in combination with Thalassemia is much more common in North Eastern states.

Clinical Presentation

Based upon the age of onset, clinical presentation & course of the disease thalassemia has been classified in three subtypes (a) Thalassemia minor which is heterozygous state in which individuals are either asymptomatic or have mild anemia which worsens during stress or in presence of nutritional deficiency (b) Thalassemia major is a homozygous state where severe anemia develops during infancy along with hepatosplenomegaly. These children require regular blood transfusion and (c) clinical course which is in between thalassemia minor & major is termed as thalassemia intermedia or non transfusion dependant thalassemia (NTDT). Management of NTDT is all together different & will not be reviewed here.

Thalassemia Minor

Individuals with thalassemia minor are usually asymptomatic or have mild anemia. Anemia may worsen in presence of iron deficiency anemia. (IDA) or blood loss. It is important to differentiate between IDA & thalassemia minor (Table 1).
Thalassemia minor have the same risk of developing IDA as general population & can be given iron therapy whenever indicated.

Table – I Differences Between IDA & Thalassemia Minor

	Thalassemia Minor	IDA
Hemoglobin	Normal / low	Low
Erythrocyte count	Normal / Slightly increased	Decreased
Peripheral smear	Microcytic & Hypochromic	Microcytic & Hypochromic
S. Iron,	Normal	Reduced
UIBC,	Normal	Reduced
TIBC	Normal	Increased
Transfusion saturation	Normal	Decreased
S. Ferintin	Normal	Reduced
Protoporphrin & Haem Ratio	Normal	Increased
Hb A_2 level	Increased	Normal

Thalassemia Major

It is serious inherited blood disorder in which red cell survival in greatly reduced due to imbalance between α & β chains. The clinical picture is dependent on four major factors viz (i) reduced hemoglobinisation of red cells (ii) incresed hemolysis (iii) ineffective erythropoiesis & (iv) extramedullary hematopoiesis.

Infarits are normal at birth & develop anemia between 3-18 months of age. Anemia is progressive, persistant and does not respond to any hematanic therapy. Infants become irritable and have poor development if left untreated. They develop prominence of frontal, facial bones and hepatosplenomegaly as a result of ineffective erythropoiesis. Facial changes are termed as thalassemic facies. (Fig II) They are at higher risk of developing recurrent infectious due to decreased heart immunity. Iron absorbtion increases as a result of (a) hypoxia and (b) ineffective erythropoiesis which gets deposited in skin, liver, heart & endocrine glands. However, the main source of iron overload in these children is from blood transfusion. Poor growth, abnormal facies and hepatosplenomegaly does not occur if these children are managed early with current protocols.

Diagnosis

It is based upon the presence of (a) moderate to severe anemia (b) reduced red cell indicies such as MCH, MCV, MCHC (c) microcytic & hypochromic picture with anisocytosis and poikilocytosis on peripheral smear (d) increased foetal hemoglobin level for age (20-90%) and normal or reduced Hb A2 levels. Bilirubin levels may be raised which will be predominently unconjugated. S. Iron levels, transferrin saturation & ferritin level may be normal or raised depending upon the age of the child. Radiological changes are often present in older children, which are secondary to marrow expansion which include sun-ray appearance of skull, cortical thinning of long bones with osteoporosis of vertebrae and (b) small bones of hands & feet.

Management

With current protocols of management it has been observed that children born after 1995 have normal life.

Principles of Management.

I) Regular blood transfusion to maintain pre transfusion Hb above 10 gm/dl
ii) To maintain S. Ferritin level below 1000 ng/ml by use of irons chelators either singly or in combination.
iii) Early detection & management of complications of blood transfusion & chelation therapy
iv) Regular monitoring of growth & development, hematological & biochemical parameters.
v) Spleenectomy if required
vi) Early detection & management of endocrine problems
vii) Pyschosocial support.

Blood Transfusion Therapy

Current recomendations state blood transfusion therapy should be initiated as soon as diagnosis is established & if hemoglobin levels are below 7 gm /dl at least on two occasions.

Investigations such as :- a) Complete blood grouping (ABD, Rh, + along with Kell, Kidd, M,N, lewis etc systems b) Family studies for genetic counselling c) HLA typing of sibling & parents for future possibility of bone marrow transplantation. Should be carried before starting transfusion therapy & d) Hepatitis B vaccination should be given if it has not been given earlier.

Among various transfusion regimens now it is recomended to treat these children with high transfusion therapy in which pre transfusion hemoglobin should be maintained at 10 gm because of its multiple advantages.

Advantages of high transfusion

i) Ensures normal growth & devleopment
ii) Decreases ineffective erythropoiesis & prevents osteoporosis & facial deformities.
iii) Prevents splenomegaly
iv) Decreases iron absorption from intestines
v) Normal development of immune system
vi) Normal physical & psychological well being
vii) Better quality of life

It is preferable to transfuse fresh blood which is leucodepleted as transfusion of lymphocytes results in (a) suppression of the immune system and (b) reduces the risk of non hemolytic febrile reaction, (c) prevents the development of alloimmunisation of human leucocyte antigen (HLA) class I antigens and (d) prevents CMV infection. Packed cell transfusion should be given at 3-4 weekly interval and each time 10-15 ml/kg of blood can be transfused over 3-4 hours.

Approximately 180 ml/kg of packed cell are required per year in non splenectomised children. Children with cardiac disease or in presence of congestive cardiac failure should receive only 5 ml / kg of blood under close monitoring.

Chelation Therapy

Each unit of packed cell contains 200-250 mg of elemental iron which is released in the body with breaking of red cells. It is the major source of iron which gets deposited in liver, heart & various endocrine glands. Increasing iron deposition in various organs results in their dysfunction. Body iron levels can be measured by (a) serum ferritin (b) liver & cardiac biopsies, (c) SQID & MRI T2. Ferri scan etc. Among these serum ferritin in most practical & can be monitored every three monthly. Among various other tests MRI T*2 is now practical and provides liver & cardiac iron overload more precisely. Now, it is of great help in chelation therapy. Other tests are carried to assess the function of various organs, such as ECHO, TSH,

T3 T4, growth hormone levels, serum Testesterone, FSH, LH, bone mineral density etc .

Presently three iron chelators have been approved & are being widely used either ringly or in combination to ensure effective chelation therapy. Chelation therapy should be initiated when S. ferritin is > 1000 ng/ml or child has received 15-20 units of transfusion.

Desferrioxamine (DFO) is an hexadentate where one molecule of DFO binds with one molecule of iron. It has very short life & needs to be administered continuously with the help of infusion pump subcutaneously (SC) over 12-14 hours daily. It should be started by 2 years of age & ferritin level should be maintained between 1000-1500 ng/ml. Its dose is 30-50 mg / kg/day. Addition of vitamin C (100 mg / day) increases the iron excretion. It is fairly safe & has minimal toxicity. Its parentral administration may results in bradycardia, hypotension, rigors, headache, photophobia. Subcutaneou administration causes local pain, induration, irritability & redness. Prolonged administration may results peripheral field defects, sensori-neural hearing loss.

Deferiprone was the first oral drug developed in Hider's laboratory. It has been shown to the effective in dose of (70-100 mg / kg /day). It is more effective than DFO in mobilizing intracellular iron from the heart. It needs to be given in 2-3 daily doses. Its side effect include nausea, abdominal pain, diarrhea. Nearly 20% of children wiht high serum ferritin level develop arthropathy and less 1% develop severe neutropenia.

ICL 670 is new class of tridentate two molecules of chalator binds with one iron molecule to form ferric molecule complex. It is twice as effective as DFO. It chelates iron from reticulo-endothelial cells and parenchymal cells of various organs. It also prevents myocardial cell iron uptake & removes iron directly from myocardial cells. This drug has half life of 11-16 hours & needs to be given in single dose of 30-40 mg / kg daily. Its side effects include abdominal pain, diarrhoea, vomiting skin rash etc. These symptoms are usually mild. There is no arthralgia, cardiac, occular or vestibular side effects. Now, it is considered as gold standard chelating agent.

Combination Therapy

Children who have high levels of serum ferritin or have cardiac liver & endocrine dysfunctions should be treated with combination therapy such as. a) DFO & deferiprone b) DFO & ICL – 670. or c) Deferiprone & ICL – 670. The advantage of combination therapy includes a) Access to different iron pools, b) prevents non transferrin bound iron accumulation, c) better compliance and above all improves quality of life. DFO may be given twice or thrice a week while other agents are given daily. It is preferable that combination therapy should be administered under supervision of an expert care.

Splenectomy

It has been proved that if we maintain hemoglobin above 10 gm /dl, hypersplenism doesn't occur. With standard treatment, splenomegaly and hypersplenism have become a rarity in the developed countries. However, in our country many children develop splenomegaly and hypersplenism because of poverty and poor facilities. If the child has already developed splenomegaly and signs of hypersplenism, then splenectomy is indicated. It should be undertaken only after 6 years of age because of higher chances of sepsis. Splenectomy is also indicated if the yearly requirement of packed cells is 200 cc/kg or more. Decrease in WBC and platelet count is a late manifestation of hypersplenism. All children needing splenectomy should receive pneumococcal, H influenza and meningococcal vaccine at least 3 to 4 weeks prior to surgery. The family should be counseled regarding the risks & benefits of splenectomy. Prophylactic penicillin therapy must be continued life-long after splenectomy. Episode of infection should be treated promptly with broad spectrum antibiotics and children should be hospitalized. All efforts should be made to isolate the micro organism for appropriate antibiotic therapy.

Bone Marrow Transplantation

It offers permanent cure and better future for children. The credit for the first bone marrow transplantation in thalassemia major goes to E. Donald Thomas who performed this procedure in an 18 month old thalassemia child in 1982 using a HLA matched elder sister as donor. This child was cured of thalassemia. Since then many centers in the world and twenty five in India have initiated BMT facilities. The principles of bone marrow transplatation include (a) to destroy and prevent regeneration of defective stem cells, (b) sufficient immune suppression for good engraftment, (c) to infuse stem cells with the normal gene, (d) to prevent GVHD with proper combination of immuno suppression and infection management.

Three most important adverse prognostic factors for survival and event-free survival have been observed in large studies which include. a) Presence of hepatomegaly (2 cm below costal margin), b) Portal fibrosis & c) Iron overload (S. Ferritin > 1000 ng/ml).

Based upon these factors children have been divided into three classes. Class I when all these factors are absent. Class II when one or two factors are present and children with presence of all factors are termed as class III. Event free survival in more than 97 percent of cases in class I & 66 percent in class III cases. All children should be treated with current protocols to maintain them in class I & perform BMT at the earliest possible.

Key Messages

1. Thalassemia is very common in country.
2. Diagnosis should be established during infancy.
3. Current protocols of therapy have improved the survival & quality of life. Now, child can live near normal life.
4. Bone marrow transplant offers, complete cure & should be undertaken as soon as possible.

MRI T2* Iron Studies

- Dr. Sameer Sood

Iron Assessment in Liver and Heart by MRI

Introduction

The use of magnetic resonance imaging (MRI) to estimate tissue iron was conceived in the 1980s, but has only become a practical reality in the last decade. The technique is most often used to estimate hepatic and cardiac iron in patients with transfusional siderosis and has largely replaced liver biopsy for liver iron quantification. However, the ability of MRI to quantify extrahepatic iron has had a greater impact on patient care and on our understanding of iron overload pathophysiology. Motivation for MRI measurements
Iron overload is a surprisingly common clinical problem, arising from disorders of increased absorption such as hereditary hemochromatosis or thalassemia intermedia syndromes or through frequent blood transfusion therapy. Before the routine availability of chelation therapy, chronically transfused patients died from cardiac iron overload in their teens and twenties. Since the introduction of deferoxamine in the early 1970s, life expectancy has improved dramatically. However, despite improvements, mortality in middle age continued to be problematic. There are several reasons that mortality continued to be high. Recently, cardiac and liver iron estimates by MRI have become the primary outcome measures for clinical studies of iron chelation therapy.

Theoretical Basis of MRI Tissue Measurements

The use of MRI to estimate tissue iron was conceived in the early 1980s, but did not become practical until MRI technology matured 20 years later. The general concept is simple. MRI machines can generate images at various observation or "echo" times to vary the contrast among different organs. All organs darken with increasing echo time, but those containing iron darken more rapidly (Figure 1). T2* represents the echo time necessary for a tissue to become twice as dark. It may be thought of as a half-life, with small values representing rapid signal loss. Alternatively, image darkening can be expressed by R2*, its rate of darkening. Some investigators prefer to report R2* values rather than T2* values, because R2* is directly proportional to iron concentration. However, R2* values are simply 1000/T2* and vice versa, making it easily to convert one representation to another.

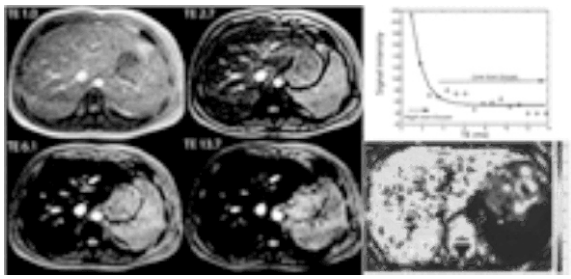


Figure 1.

(Left) Open circles represent liver signal intensity and solid line reflects the R2* fit at different echo times (TE). (Right) A map generated by calculating R2* values for every voxel in the image, with the reported liver iron concentration (LIC) represent the average liver R2* value scaled by a linear equation.

MRI scanners can also collect images suitable for T2 (and R2) analysis instead of T2* analysis, using radio waves rather than magnetic gradients to generate images at different echo times. Image analysis and iron quantification is similar whether using R2 or R2* images. R2 images take longer to collect and are used more frequently to evaluate liver iron concentration (LIC). Whereas cardiac T2 imaging is also possible, it is more challenging because of respiratory motion, limiting its widespread acceptance.

What Goes MRI Actually Measure?

Iron itself is invisible on an MRI. Instead, MRI detects iron's influence on the magnetic milieu of water protons diffusing in tissues. Typically, the magnetic fields in a clinical scanner are extremely homogenous, but iron within the tissues creates local magnetic field disturbances that cause the images to darken faster. Not all forms of iron are equally magnetically potent. Labile iron species, although toxic to the body, are magnetically silent at physiologic concentrations. Ferritin, the body's initial line of defense against circulating free iron, is weakly detectable by MRI when it is dispersed freely in the cytosol. However, ferritin aggregates and their breakdown product, hemosiderin, overwhelming determine tissue R2 and R2* (or T2 and T2*). The size and distribution of these iron stores powerfully modulate the relationship between iron concentration and the MRI signal intensity.

Impact of MRI Iron Imaging on Patient Management

The introduction of MRI to quantitate liver and cardiac iron had a profound impact on our understanding and management of cardiac iron overload. Anderson et al in 2001 demostrated all patients with cardiac T2* in the normal range (> 20 milliseconds) showed normal ventricular performance. As cardiac T2* decreased below 20 milliseconds (reflecting increasing cardiac iron), the likelihood of left ventricular dysfunction increased; this decline coincided with an increase in the estimated heart iron concentration. However, most patients with MRI-detectable cardiac iron still exhibited normal cardiac function and therefore MRI was able to detect cardiac problems before toxicity was manifested.

MRI Assessment of Liver Iron

Either liver R2 or liver R2* can be used to estimate LIC, depending on local expertise. Liver R2* images are the easiest and quickest to collect, but require specialized software to generate R2* and iron estimates. The upper limit of liver iron that can be reliably estimated by R2* depends on scanner specifications, but is generally 30-40 mg/g dry weight at 1.5 Tesla.

MRI Assessment of Cardiac Iron

Cardiac R2* (or T2*) is generally measured using the same scanner and software tools as those used for the measurement of liver R2* with associated ECG gating.

Future Impact of MRI

With routine cardiac screening, patients are now living long enough to encounter increasing iron-mediated endocrine morbidities. Diabetes, hypothyroidism, and hypogonadism remain common among thalassemia patients and are probably underdiagnosed. The pituitary gland is perhaps the most important initial target for further study because it is easily injured and damage can be difficult to detect until puberty. Hypogonadism occurs in approximately half of thalassemia patients and has long-term consequences for fertility, bone density, and quality of life. Preclinical iron deposition can be detected using R2 techniques whereas severe iron deposition is associated with decreased response to gonatropin releasing hormone challenge. Shrinkage of the pituitary gland is associated with more significant, irreversible loss of gonadotrophic production. Further clinical validation and technical standardization is necessary before pituitary MRI can be incorporated into routine clinical monitoring, but this is an active area of research.

Desferal - Do we still need it

- Dr. Rajiv Bansal

Desferoxamine - DFO-(Desferal) is the first iron chelator to be used in humans for treatment of iron toxicity. Since desferoxamine has been around for over 50 years, there has been significant clinical experience. Due to its established efficacy it continues to be the standard iron chelator used.

Iron chelators work by neutralising unbound iron and removing excess iron in tissues. Iron has six active sites and to achieve complete inactivation of a single atom of iron, all six sites must be bound by the chelator. Hexidentate chelators, such as desferoxamine, can bind to all six sites, while tridentate chelators such as deferasirox can bind to three sites and bidentate chelators, such as deferiprone, can bind to only two sites. Therefore, a hexidentate chelator binds at a 1:1 ratio.

The use of iron chelating agents has significantly increased the survival rates and decreased morbidity related to organ system toxicity. In a 10-year New England Journal of Medicine study published in 1994 (N Olivieri), all paediatric patients who were able to achieve controlled serum ferritin levels with 12-hour subcutaneous desferoxamine infusion survived without cardiac disease.

Desferoxamine is capable of reversing hepatic iron overload. In the liver, desferoxamine is internalized by hepatic parenchymal cells where it binds with intracellular iron and is excreted in bile. Studies in paediatric groups showed that intermittent desferoxamine infusion decreased iron storage in the liver and prevented hepatic fibrosis. Desferoxamine is also able to remove iron from cardiac cells. Iron released by macrophages is immediately chelated and excreted in urine. Deferoxamine binds free iron by preventing the uptake of NTBI (Non-Transferrin Bound Iron) into organs but it also acts within the cell where it enters by endocytosis, stimulates the degradation of ferritin via the lysosomes and subsequently binds the released iron. The iron bound to desferoxamine is then excreted in urine and faces. The drug is rapidly absorbed after intramuscular and subcutaneous administration, but it cannot be absorbed orally. The serum protein binding is less than 10% and the drug undergoes the following metabolic reactions: transamination and oxidation; beta-oxidation; decarboxylation and N-hydroxylation. The drug has transformed life expectancy for many patients with TM and other refractory anaemias. It has also reduced endocrine and hepatic complications. Having a short plasma half-life of 20–30 minutes, DFO should be administered over a span of 8–12 hours a day, on 5–7 days a week. Given the pharmacokinetics of DFO, it does not provide

24-hour-long chelation of NTBI. The side effects of DFO include irritation at the infusion site, growth retardation, skeletal changes, and ocular and auditory disturbances. Several dosing regimens and routes of administration have been proposed and used in the past for deferoxamine in patients affected by transfusion-dependent haemoglobinopathies.

Subcutaneous administration is preferred except in patients with severe cardiac iron deposition for whom continuous intravenous deferoxamine therapy is recommended . Oral ascorbic acid at the equivalent of 2– 3 mg/kg/d is usually prescribed at the beginning of an infusion.The average recommended daily dose lies between 20 and 60 mg/kg.

Despite the availability of new oral iron chelators and several limitations regarding the use of desferoxamine, such as compliance issues due to the parenteral administration, inadequate cardiac iron removal and auditory, ocular and neurological toxicities , desferoxamine is still the most common used therapy for the treatment of iron overload.

Many patients with TM are not satisfactorily chelated by it, however, and then may develop a fatal cardiomyopathy. The reasons for these "failures" of DFO therapy include cost of the drug, pump and tubing, poor compliance, allergy, toxicity, local problems at the site of the infusions, lack of 24-hour binding of NTBI, and Yersinia infection (not a complication of the oral chelators). Even among patients apparently complying with DFO infusions at least 5 times a week and with serum ferritin levels 1000 g/L, some may develop cardiac iron overload and failure. Approximately 20% of patients receiving DFO alone in the United Kingdom, Italy, and Cyprus have cardiac T2* levels 10 ms.

Dose-related desferoxamine toxicities including visual changes, auditory toxicity, attenuation of linear growth, and skeletal dysplasia may be minimised by maintaining doses of no more than 25 –30 mg/kg in young children . In both children and adults, as the hepatic iron concentration approaches optimal levels , dose reduction is recommended; a useful recommendation is that the daily dose (mg/kg) divided by the serum ferritin (mg/L) should not exceed 0.025 . Allergy to desferoxamine is rare and most patients may be desensitized successfully , with patients thereafter able to take desferoxamine.

In certain cases, monotherapy may be insufficient to achieve treatment goals. At this point the clinicians should either increase the current dose of the drug or switch to a different chelator. However, if treatment goals are still not achieved, then the clinician may opt to initiate combination therapy. Combination chelators tend to be more effective than monotherapy

because chelators utilise different mechanisms for removing iron. Combination therapy has been shown to be useful for patients with mild-to-moderate hepatic and cardiac iron overload, as well as severe degrees of cardiac siderosis and impaired left ventricular function.

Combination of deferoxamine and deferiprone has been extensively studied in the recent past with excellent results. A combination of deferoxamine and deferasirox has also shown promising results. In a few anecdotal difficult cases all the three chelators were given together to achieve goals of lowering the iron overload.

In nutshell even in an era of oral iron chelators , deferoxamine has a place in all those patients who cannot tolerate the oral chelators for some reason or other or who are difficult to chelate with oral agents alone and improve significantly on a combination of oral and parenteral agents.

Dual chelation in Thalassemia major

- Dr. Amita Trehan

Conventional iron chelation utilizes either of the three drugs, Desferrioxamine (DFO), Deferiprone (DFP) or deferasirox (DFX). DFO use is fraught with problems such as parenteral route of administration, cost and adverse events. Monotherapy with DFP or DFX may not result in adequate chelation in all patients. The use of combination of DFP and DFO has already been established as safe and efficacious. The principle of this combination is the shuttle-sink mechanism. DFP, a small molecule is able to enter cells and chelate stored iron and bring it to the circulation, where the large DFO molecules acts as the sink.

Based on the same principle, DFX can be combined with DFP. DFX being long acting can replace DFO as the sink. Compliance would be better with oral drugs, and combination would allow lesser doses of individual drugs and hence, lesser adverse events due to individual drugs. Additionally, DFP has shown to be a good chelator for cardiac iron while DFX brings about all round chelation in the body. A Greek study on 16 patients and Egyptian Randomized control trial comparing DFP/DFX with DFP/DFX have shown that the oral combination is safe as well as efficacious in reducing iron overload. The study conducted in our centre was a prospective observational study of 36 patients who were administered DFP/DFX combination therapy. Reasons for discontinuation in 4 of the 36 included gastrointestinal intolerance, joint pain and swelling and skin rash. Of the remaining 32, 29 showed significant decline in serum ferritin from baseline. Combination requires stringent monitoring of blood counts, serum OT,PT, creatinine and urine protein which was performed monthly during the study. A similar study from UCMS, delhi has also established comparable efficacy of combination as compared to monotherapy with no additional adverse events. While there was significant decrease in serum ferritin from baseline, T2*MRI results at baseline and after combination were equivocal.

The combination is an attractive alternative for patients who are intolerant or refractory to monotherapy with available drugs for chelation. Large RCTs incorporating liver iron concentration and T2*MRI are required to further establish this as a standard of care in patients with thalassemia major.

Summary of studies on dual chelation

S.no	Country, year, Reference	Number of patient(s)	Age (years)	Design of study, dosing of drugs	Outcome measures	Key findings
1	**USA, 2010 [1]**	3	17-27	Case report; DFP 75-100 mg/kg/day and DFX 20-40 mg/kg/day	Serum ferritin, LIC, T2*MRI	Improved T2* MRI. No major adverse effects
2	**Italy, 2010 [2]**	2	20-33	Case report; Daily alternating DFP 75-85 mg/kg/day and DFX 30 mg/kg/day	Serum ferritin, LIC, T2*MRI	Decrease in ferritin and LIC with stable T2*MRI. No major adverse effects
3	**Greece, 2011 [4]**	16	20-45	Open-label, observational, single center study, DFP 75-100 mg/kg/day and DFX 20-25 mg/kg/day	Serum ferritin, LIC, T2*MRI, T2*L Ferriscan	Significant decrease of total body iron load as estimated by serum ferritin, LIC and MRI T2* indices. No major adverse effects
4	**Greece, 2011 [5]**	1	34	Case report; DFP 75mg/kg/day and DFX 30 mg/kg/day	Serum ferritin, Liver and cardiac T2*MRI	Serum ferritin normalized, liver and cardiac T2* values improved
5	**Egypt, 2015 [6]**	96	10-18	Prospective RCT comparing DFP-DFO and DFP-DFX	Serum ferritin, LIC, T2*MRI and QOL	Better improvement in T2*MRI with oral combo; similar LIC, ferritin in both arms and better compliance

HIV in Thalassemia

- Dr. Alok Hemal

Transfusion transmitted infections remains a great concern in many parts of the world and HIV is one of the most important and deadly infection among them.among the most common modes of transmission of HIV, transfusion of infected blood and blood products constitute 3-6% of all pediatric AIDS cases. Since the risk of transmission through blood transfusion is about 98%, transfusion dependent children are at alarmingly high risk. Thalassemia major constitute one such group who suffer the disadvantage.

Prevalence of HIV infection in thalassemia varies greatly worldwide from 1-20% . HIV seropositivity reported by various authors of India ranges from 0.7-3%. However, there is no increased risk of TTI in thalassemia patients compared to other multi transfused patients. Unscreened blood and blood products transfusion is the mode of transmission of HIV in thalessemic patients.

Recipients of multiple transfusions are known to have abnormalities in their immune status reflected by alterations in the number and proportions of T- cell subsets with decrease in CD4/CD8 and hypergammaglobulinemia and depressed delayed type hypersensitivity. This makes them prone to HIV infection and rapid progression to AIDS. In a large multicentric study, It was found that there was no relation between disease progression and age, sex, acute infection or splenectomy(Costagliola 1992).

In a study conducted by Sen et al ,it was found that lymphadenopathy and increased transfusion requirements were more common in HIV infected thalassemics. Other clinical features were prolonged diarrhoea, weight loss, prolonged pyrexia(more than 1 month), epistaxis, thrombocytopenia, oropharyngeal candidiasis, aloplecia, salivary gland enlargement, LIP and PCP infections.

Since thalassemics are already at increased risk of infections , HIV-AIDS , being an immunodeficient state flare up the risk of opportunistic infections. Increased risk of complications due to anemia is also seen due to HAART therapy in AIDS patients.

Diagnosis is similar to guidelines followed in non thalassemic patients. All thalassemics should be screened for seropostivity for hepatitis A, hepatitis B, HIV annually.There are no specific guidelines for management of HIV infected thalassemics. HAART remains the mainstay of treatment in HIV in thalassemia patients. However , there has been case reports of zidovudine induced worsening of anemia in thalassemia patients.

Though splenectomy has not been implicated as poor prognostic factor in HIV patients , it has been recommende that a splenectomy treatment strategy should be decided with caution in an HIV-1 positive patient. Optimal control of body iron with iron chelation regimen is recommended in HIV positive TDT patients.

In India, drug and cosmetics act 1992 mandates testing of each unit of donated blood for presence of markers of HIV, HBV, malaria and syphilis. Since 1997, professional blood donors has been banned in India. Introduction of NAT testing of minipools performed on antibody non reactive blood donations (to identify donations made during window period) reduced the further residual risk of transfusion transmitted infections.

Deferral of high risk prospective donors should characterise donor selection. Repeat Voluntary non remunerated blood donor will be one who follows safe lifestyle, will be tested for infections regularly and chances of falling in window period will be low and thus will be the safest choice of being blood donor.

Since HIV is not a vaccine preventable disease, transfusion dependent individuals cannot be protected by vaccine and donor selection, proper screening of the blood products and hemovigilance form the mainstay of control of HIV incidence in transfusion dependent thalassemics.

Monitoring of Thalassemics

- Dr. Sunil Gomber

Why to monitor?

- Chronic lifelong blood transfusions has significantly improved life expectancy in thalassemia major.
- However, complications of chronic blood exposure and chelating agents are the predominant challenges in disease management which requires continuous monitoring.

1

What to monitor?

- Iron overload
- Adverse effects of chelation therapy
- Growth and development
- Endocrine functions
- Liver function
- Cardiac function
- Bone complications
- Infections

2

Guidelines

- Various guidelines are available for monitoring of thalassemia patients-
  - Thalassemia International Federation(TIF) Guidelines for the management of transfusion dependent thalassemia.
  - Standards for the clinical care of children and adults with Thalassaemia in the UK.
  - Guidelines for the Clinical Care of Patients with Thalassemia in Canada.
- There is not much difference between the Canadian guidelines and the guidelines by TIF.
- The salient points for monitoring by all these guidelines will be described further.

3

Baseline

- Full red cell extended phenotype
- S. ferritin
- Liver function test
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody

4

Monitoring during iron chelation

- Ferritin – 3 monthly
- Neutrophil count- if on DFP, weekly.
- Creatinine – if on DFX, weekly for 4 weeks after initiation or change of dose. Thereafter, monthly.
  - Also, twice before start*.
- ALT- if on DFX, monthly.
  - Twice before start, then 2 weekly for first month after initiation or change of dose. Thereafter, monthly*.
- Liver biopsy- annually**

*Yardumian A, Telfer P, Shah F et al. Standards for the clinical care of children and adults with Thalassaemia in the UK.3 rd edition, 2016.
**Sayani F, Warner M, Wu J et al. Guidelines for the Clinical Care of Patients with Thalassemia in Canada. 2008.

5

Contd.

- Audiology and ophthalmology evaluation- if on DFO or DFX, annually.
- T2* MRI- annually starting at 8 yrs.
  - For cardiac iron levels, it is repeated at intervals based on previous results**
    - >20 ms- 2 yearly
    - 10-20 ms- yearly
    - <10 ms- 6 monthly

*Yardumian A, Telfer P, Shah F et al. Standards for the clinical care of children and adults with Thalassaemia in the UK.3 rd edition, 2016.

6

Growth, development and endocrine

	TIF	UK*
Height, sitting height, weight	3 monthly	6 monthly
Tanner's staging	6 monthly from 10 years	Yearly from 10 years
Thyroid function	Annually from 5 years	Annually from 12 years
Oral glucose tolerance test	Annually from 10 years	Annually from puberty, or 10 years if family history
Ca/ PO4/ ALP	3 monthly from 5 years	6 monthly from 12 years
PTH	Annually from 5 years	If calcium low
FSH/ LH/ Estradiol	Noted delay in puberty	If menstrual disturbance develops
Vitamin D	6 monthly	Annually from 2 years
Growth hormone stimulation test	At noted growth delay	If declining growth velocity from age 8

*Yardumian A, Telfer P, Shah F et al. Standards for the clinical care of children and adults with Thalassaemia in the UK.3 rd edition, 2016.

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- Besides these tests, the UK guidelines also advise the following tests:
  - Morning cortisol level: annually from 14 years
  - Morning testosterone level: annually from 14 years
  - FSH/ LH and sex hormone binding globulin level: if morning testosterone level is low.

8

Liver function and disease

- LFTs- 3 monthly (monthly if on DFX)
  - Monthly*
- Hepatitis serology- annually
- Ultrasonography- annually
- Fibroscan- 2 yearly
- If estabilished cirrhosis, surveliance for hepatocellular carcinoma: alpha fetoprotein, liver USG or cross sectional imaging (MR or CT) every 6 monthly.*
- Liver biopsy- Annually**

*Yardumian A, Telfer P, Shah F et al. Standards for the clinical care of children and adults with Thalassaemia in the UK.3 rd edition, 2016.
**Sayani F, Warner M, Wu J et al. Guidelines for the Clinical Care of Patients with Thalassemia in Canada. 2009.

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Cardiovascular assessment

ECG/ ECHO- annually from 7-10 years

- T2* MRI- discussed earlier
- MUGA- annually from 10 years**

**Sayani F, Warner M, Wu J et al. Guidelines for the Clinical Care of Patients with Thalassemia in Canada. 2009.

10

bone complications

- DEXA scan- 2 yearly from puberty

Infections

- Hepatitis serology- Annually
- HIV- Annually

11

Some less frequently talked about tests

- Dobutamine/ Exercise stress echocardigraphy-
  - The test was carried out by a multivariate study according to which mortality prediction was better by resting echo than with stress echo.*

*Hahalis G, Kourakli A, Gerasimidou L et al. Cardiac mortality in b-thalassemia major: resting but not dobutamine stress echocardiography predicts mortality among initially cardiac disease free patients in a prospective 12-year study. European Journal of Heart Failure (2009) 11, 1178–1181.

- MUGA (Multigated Acquisition) scan-
  - It is time consuming, should not be performed frequently as it involves radionucleide injection and has almost the same limitations as echo.**

**Aessopos A, Berdoukas V, Tsironi M. The heart in transfusion dependent homozygous thalassaemia today – prediction, prevention and management. European Journal of Haematology. 2008;80(2):93-106.

12

Contd..

- Fibroscan-
  - A study on 51 HCV antibody positive thalassemia major patients showed liver fibroscan as reliable methods as surrogate for liver biopsy to assess fibrosis progression.*
  - Another study on 20 transfusion dependent hereditary anemia did not demonstrate any correlation between fibroscan result and MRI-estimated hepatic iron concentration.**
  - Another study on 41 thalassemia major patients demonstrated transient elastography as a reliable non-invasive tool to evaluate liver iron content and fibrosis in patients with b-thalassemia major who are candidates for hematopoietic stem cell transplantation and can be an alternative to liver biopsy.***

*Elalfy M, Esmat G, Matter R et al. Liver fibrosis in young Egyptian beta-thalassemia major patients: relation to hepatitis C virus and compliance with chelation. Annals of hepatology. 2013; 12 (1): 54-61.

**Hatoon Ezzat, Utility of Transient Elastography (Fibroscan) in Estimating Hepatic Iron Concentration in Comparison to MRI in Patients with Transfusion Dependent Hemoglobinopathies. Blood. 2014;124:4888.

***Hamidieh A, Poustchi H, Shazad B et al. Assessment of Liver Fibrosis by Diagnostic Value of Transient Elastography (Fibroscan) in the in Patients with β-Thalassemia Major Considered as Candidates for Hematopoietic Stem Cell Transplantation. Biology of blood and marow transplantation. 2012; Vol 18(2): 330–331.

13

Contd..

- Pulmonary function test-
  - Not in routine practice.
  - However, multiple studies show patients have restrictive lung disease, which directly correlates with ferritin levels and age.*
  - Hence, we recommend annual spirometry from adolescence to monitor lung function.

*Boddu A, Kumble A, Mahalingam S. Pulmonary dysfunction in children with beta thalassemia major in relation with iron overload - a cross sectional hospital based study. Asian Journal of Medical Sciences. 2015; 6(5):47-50.

*Ozyoruk D, Misirlioglu E. Pulmonary Functions in Children With Thalassemia Major. J Pediatr Hematol Oncol. 2015 Nov;37(8):605-10.

14

Entering Adulthood in Thalassaemia

- Dr. Michael Angastionotis

Introduction:

Thalassaemia major patients during childhood require regular blood transfusion and iron chelation as well as clinical monitoring of their growth and general health. However apart from infections there are few complications which they face if treatment is adhered to. Treatment is generally guided by the parents and if they are compliant the child adheres, provided of course access to such care is economically supported. As they enter adolescence the effects of iron overload and its effective or poor control during childhood, become manifest and a closer monitoring is required.

Monitoring needs to be intensified in two areas : physical health and psychological health. Consideration of the issues raised by the transition from paediatric to adult care services.

Monitoring of physical health:

Iron accumulation may have reached toxic levels by the time the hormonal changes of adolescence are expected and organ damage, including the endocrine glands, heart and liver, is already progressing. This is seen clinically in a poor growth spurt and delay in the appearance of sexual characteristics. For this reason, careful monitoring of growth and the use of Tanner scales for the assessment of pubertal development of both sexes is necessary. In addition, the introduction of imaging techniques such as MRI T2* must be initiated by the age of 8-10 years. Annual visits to cardiologists and endocrinologists is added to the laboratory and other monitoring methods.

Monitoring of emotional and social health:

- The factors which cause stress and psychological risks to the patient and the family must be recognised by all. These include poor self-image, and low self-esteem due to altered appearance, poor growth and delayed puberty. In addition there is the sense of being different, the fear of rejection, the uncertain future, and guilt for being a burden on the family. These may lead to significant, in some patients, emotional and conduct disorders such as dependency, dysphoric moods, fears, and anxiety. The lifelong and demanding treatment is always a factor and the appearance of complications will add to feelings of fear and anxiety.

- In the family there may be depression, guilt feelings, overprotection, engulfement, denial

and helplessness when faced with the burdens of care. Low income, poor education, social isolation, and poor service delivery are all stressors, which must be taken into account. Low income will endanger the provision of adequate and affordable treatment for the child, making it a very serious consideration in the psychosocial balance as wel as the physical condition of the patient and the family.

- Society prejudice, ignorance, insensitivity, making the patient and family feel different with the result that often there is reluctance to disclose the diagnosis in school, to employers, to future in-laws etc. In adolescence in particular peer relationships are very important and the fear of stigmatisation will lead to anxiety related to marriage, education and career prospects.

Adaptive and coping mechanisms counterbalance these negative influences and are usually identified in those with positive models of self and optimistic attitudes. Seeking social support from family and friends and feeling deserving of support, will protect from the tendency of social withdrawal and isolation. Parents and patients need a sense of control over the condition, which comes from being well informed so as to avoid worrying too much and taking each day as it comes. For coping, children and adolescents adopt several strategies, most of which are positive in their result, although some can be negative, passive and maladaptive. Examples of the latter are avoidance/denial, resignation and aggressive behaviour, blaming

The health care team must promote the positive coping strategies by giving emphasis to patient education, talking and listening to patients and the family, spending time, respecting privacy and confidentiality and being willing to discuss issues other than the medical condition e.g. sexuality, puberty, diet, risky behaviour, school problems and any others that the patient may bring up.

An important issue in chronic care is adherence to treatment. Doctors should understand that non-adherence is not an irrational act resulting from psychological stress or ignorance but many patients comply if this makes sense according to beliefs about the illness and its treatment, if it seems effective and safe, and if it fits with their life activities.

In adolescence, staff must be willing to spend time and to listen in privacy and confidentiality and to recognise the adolescents' wish to take hold of their life and their disease, will strengthen the maturation process. This requires organisation and time. Doctors are not always masters of their time so that health administration must be sensitised to the needs of patients and recognise psychosocial support as a necessary aspect of chronic care especially of adolescents.

At this age preparation for transition to adult clinical care must be initiated.

Transition from paediatric to adult care services

The paediatricians who were the protagonists of the management in childhood, are often the trusted physicians for both the child and the family. Transfer of responsibility to the adult physicians should be gradual, and with preparation of the young patient who has to move to unfamiliar surroundings and with staff who may have different attitudes towards the patient. Transition to adult care should be a painless process for patients. Adolescent patients in need of inpatient care are admitted to adult wards which may also be a novel experience for them. A sense of self care and responsibility in their management should be instilled as the growing and maturing thalassaemia patients develop into being partners in their treatment.

Strategies for Prevention of Thalassemia

- Dr. Sujata Sinha

Over the past two decades there has been considerable deliberation over developing suitable strategies for prevention of thalassemia in our country. These efforts have led finally to formulation of a national policy for prevention and control of Hemoglobinopathies under the aegis of National Health Mission. It has provided the muchrequired platform for Hemoglobinopathies to find place among health priorities of the State. The policy outlines the scope and approaches for implementation of prevention and control strategies and at the same time alerts and sensitizes the authorities towards technical, social and ethical considerations that are likely to be encountered during implementation of program for a recessively inherited disorder. The guidelines for prevention and management have been drawn on the basis of current understanding and will require updation on a regular basis.

That effective implementation of prevention programs can lead to significant reduction in affected births over time has been demonstrated in several countries but at the same time the need for a careful selection and implementation of prevention strategies cannot be overemphasized. The premise for adoption of detection of carriers as a strategy is built on the fact that if the carrier status of an autosomal recessive disorder becomes known it can empower an individual to take steps to avoid birth of an affected child. The individual choices in India are largely limited to avoidance of marriage between two carriers and termination of an affected pregnancy subsequent to prenatal diagnosis. Availability of pre implantation genetic diagnosis may further alter the public discourse on preventive strategies. Further, today with improvement in management regimens and availability of facilities in the form of slow but steady increase in number of blood banks with component separation units providing packed red cells, availability of effective oral iron chelators and availability of monitoring facilities in more districts, an affected child born to carrier parents has a greater opportunity to live a quality and fulfilled life in this country than those born a decade ago. This leads to recognition of the third choice that may be made by some of the parents to go ahead with the birth of an affected child after prenatal diagnosis while many others may choose not to abort due to religious, social or emotional considerations. The preventive strategies adopted for implementation need to be viewed in the light of the aforementioned facts.

'Hemoglobinopathies' has been adopted as an inclusive term for Thalassemia and variant hemoglobins and prevention strategies have been targeted towards control of beta - thalassemia, HbS and HbE recognizing that these together constitute the burden of disease in our country through Thalassemia (Thal major & intermedia) and Sickle Cell Disease (SCD) syndromes.

Screening strategies for detection of carriers

Screening for thalassemia carrier status can be done in adolescents and young adults, at premarital or pre-conceptional stage or during antenatal period. Accessibility to screening and diagnostic services backed by counseling to all of these groups is the initial step for setting up a

prevention program. This should be backed by a community wide effective information, education and awareness campaign.

Selection of target groups for universal screening

Selection of target groups for universal screening is the core of preventive strategy in public health and should be done by assessment of accessibility to target population for screening and follow up to ensure maximum coverage, effectiveness, acceptability and achievement of stated outcome. Adolescents in schools and pregnant women fulfill the above mentioned criteria and hence have been selected as target groups for implementation of universal screening.

1. Adolescent screening in schools

Adolescents can be easily accessed and followed up for counseling through schools. Adolescents largely aged 15 years or up have the required curiosity and the maturity to seek, imbibe and retain the information provided regarding genetics of inheritance, carrier status, selection and purposes of tests used during screening and confirmation and have optimal maturity to understand implications of the reproductive issues and decisions. A prescreening awareness and educational talk also precisely informs the student on all steps of the screening protocol. The follow up with a counseling session in presence of parents or guardians of those suspected to be carriers provides an opportunity to educate the family and provide required support to the adolescent for the confirmatory test required for affirming the hemoglobinopathy carrier status. With legal age of marriage being eighteen years in our country that coincides with the age at which most students pass out from schools, **this strategy ensures that an individual is empowered with the information on his or her carrier status before reaching marriageable age and hence has an opportunity of exercising both the options of avoidance of marriage with a carrier or prenatal diagnosis during pregnancy.** With increasing emphasis on ensuring school education to all by increasing enrolment in schools maximum coverage can be ensured .

The selection of screening protocol also should be such that it is cost- effective, easily applicable in an outreach program and minimizes errors in identification of carriers. At present the most commonly acceptable criteria for identification of a beta thalassemia carrier is based on the raised HbA2 levels with an acceptable cut- off value. However, it is widely accepted that there are 'silent' carriers that is those which do not show up with an increase in HbA2 levels and then there are those where the HbA2 level may be increased in the individual and yet fall below the agreed 'cut-off' value thus by definition falling in an equivocal zone. There may be still a few who may have HbA2 at or slightly above the cut-off value yet not be a carrier of the Beta thalassemia trait. So the identification of causative mutation remains the confirmatory test for diagnosis of a carrier and should be part of the screening protocol. **The limitations of the adopted screening protocol should be clearly spelt out in the information provide to the target population**. A multi step screening protocol that includes simple low cost tests with high negative predictable value such as NESTROFT, Solubility Test

and DCIP test respectively for BTT, HbS trait and HbE trait, helps in reducing the screening cost per person and also increases feasibility of screening through an outreach program ensuring maximum population coverage. The costlier diagnostic test of Hemoglobin HPLC or capillary electrophoresis can then be conducted in the 2nd step and confirmatory test of mutation identification in 3rd step. This approach is possible in schools as one can follow up students in the organized campuses and systems of school unlike in colleges, universities and community where follow up and tracking becomes an onerous task.

The integration of adolescent screening with the Rashtriya Bal Swasthya Karyakram targeting birth to 18 years age group has made the process more feasible with availability of lab facilities and manpower and to establish required coordination from field to secondary and tertiary levels.

Thus one- time screening of students while in school between class VIII and XII has the potential to turn into a long term sustainable screening strategy.

2. Antenatal screening of pregnant women

All pregnant women are likely to interact with the health system at some point of pregnancy and with increasing emphasis of maternal health programs on early registration of pregnant women through health workers such as ASHAs and ANMs, the inclusion of screening for carrier status in routine antenatal work –up provides another opportunity for achieving universal coverage. However, screening during pregnancy provides the couple only one option of preventing the birth of affected child and that is termination of affected pregnancy. This preventive intervention is invasive and immediate requiring sensitive counseling and clinical services. Care also needs to be taken to avoid unscrupulous use of the provision both by caregivers, pregnant woman and her family.

Screening protocols applied here are also multi step protocols with feasibility of conduction of simple low cost initial screening tests at primary level at primary and community health centres and diagnostic tests of CBC, HPLC and electrophoresis at District level. Required support for transporting the woman / couple to the district level testing facility is provided though existing maternal health programs. The only limitation at present is availability of limited tertiary centres with facilities for prenatal diagnosis. However, setting up of such facilities is part of program implementation and will be taken up in due course.

3. Newborn Screening

By definition, newborn screening is a tool for early detection and intervention to minimize the severity and handicap due to disease and thus it can be regarded as strategy for 'tertiary' prevention. In case of Sickle Cell Disease, an intervention as early as within the neonatal period is often required to prevent the damaging effects of the disease. Fortunately, the hematological methods available today for newborn screening can pick up variant

hemoglobins at birth in a Dried Blood Spot sample enabling detection of sickle cell disease at birth. These methods also pick up beta thalassemia syndromes where there is complete absence of Hb A such as those caused by homozygous beta 0 or Hb E- beta 0 genotypes. The advantage of acquiring DBS samples is that they can be obtained by paramedical or field level healthcare staff and can be mailed to District, Regional or State level laboratory for testing. Further, all thalassemia syndromes requiring management can be timely detected by screening of children aged 6 months to 6 years having severe anemia. Thus integration with Rashtriya Bal Swasthya Karyakram is again beneficial as screening and referral for severe anemia is part of this program.

Thus the overall strategy for prevention that includes universal screening in adolescence, during pregnancy and at birth and early childhood should be effective but only tracking of program outcomes through a decade will demonstrate its effectiveness in reducing the burden of disease.

Growth & Puberty in subjects with Thalassemia

- Dr. Anju Seth

As children with thalassemia grow older, they become vulnerable to develop many endocrine complications. The underlying patho-physiological mechanism underlying these complications is excessive iron load, a consequence of repeated blood transfusions that these children receive from early childhood.

Endocrine glands have high levels of transferrin receptors that promote iron accumulation and hence increase vulnerability of these glands to iron toxicity. Iron stored in endocrine glands binds to intracellular transferrin. As the storage capacity of transferrin gets exceeded, pathological quantities of metabolically active iron catalyzes formation of free radicals, which in turn damage intra-membrane lipids and other macro-molecules, ultimately causing cell death and organ failure. In addition to magnitude of iron overload, the severity of clinical manifestations is also dependent upon presence of specific gene mutations.

Short stature and pubertal abnormalities are the commonest endocrinopathies observed in multi-transfused thalassemic subjects. At our Center, among the 89 thalassemic subjects above 10 years of age, 64% had short stature , while 54% had a pubertal abnormality.

Short stature:

Growth faltering can occur at all ages in these children. Many causes contribute toward growth galtering/short stature in these children (table 1). The relative contribution of various factors may vary at different ages. In children <5 years of age, hypoxia, nutritional factors and anemia are the major factors leading to short stature. These are all preventable in well managed children. In the age group of 5-10 yrs, the contributing factors include anemia and effect of iron over-load on GH-IGF1 axis. Beyond the age of 10 years, absent /reduced pubertal spurt due to involvement of hypothalamo-pituitary-gonadal axis makes a significant contribution. At all stages, co-morbidities can add further adverse influence. Children who are well transfused and adequately chelated have the best prognosis for reaching optimum height. At our Center we observed a negative correlation between height SDS and mean ferritin level and age at starting chelation.

Pubertal abnormalities :

A variety of pubertal disturbances can be seen in children with thalassemia (table 2). The underlying cause is usually damage to gonadotrophs situated in anterior pituitary leading to failure of adequate production of gonadotrophins LH & FSH. Direct gonadal damage by iron overload is much less likely. In fact many subjects have normal ovarian function and can produce expected number of ova after stimulation and thus achieve fertility.
Presence of pubertal abnormalities has many implications apart from potential infertility. It contributes towards short stature due to absent/poor pubertal growth spurt. Associated poor sexual development contributes towards poor body image in the adolescent subject with thalassemia. Since sex steroids have an important role to play in pubertal bone mass accrual,

these subjects fail to achieve optimum bone mass, a factor that contributes towards osteopathy observed thalassemia.

Clinical evaluation :

All children with thalassemia should have their growth monitored regularly since childhood. A record of height and weight should be maintained on a growth chart at 6 monthly interval to facilitate early detection of growth faltering. This would facilitate early evaluation and prompt management of underlying abnormality. In addition, evaluation for signs of onset of puberty and its progression should be assessed annually for all children above 10 years of age. All children with short stature and/or pubertal abnormalities should also be evaluated for presence of other endocrinopathies and co-morbidities (table 3).

Management :

Prevention is the best approach since efficacy of intensive chelation in reversing established endocrinopathies is unknown. Thus, preventing anemia through a regular transfusion schedule, optimum chelation, maintaining an adequate nutritional status and prompt recognition and treatment of co-morbidities form the cornerstones of endocrinopathy prevention.

Treatment of short stature involves addressing the underlying cause. These include :

- Treatment of anemia
- Correction of nutritional deficiencies if any
- Treatment of overt hypothyroidism
- GH treatment is indicated in established GH deficiency. These subjects often need higher doses due to co-existing partial GH insensitivity. In children with pubertal delay best results are observed with concomitant sex steroid replacement.

Subjects with spontaneous pubertal onset are monitored carefully for progress of puberty. Those with failure to achieve spontaneous onset of puberty or with poor progression need replacement with sex steroids.

Key messages :

- Multiple endocrinopathies can develop in multi-transfused thalassemic children/adolescents
- Short stature & pubertal disturbances most common
- It is possible to have growth & sexual maturation without assistance, though many have stunted growth, sexual infantilism & poor fertility
- Regular clinical & lab screening after 10 years of age facilitates early detection & management.

Table 1 : Causes of short stature in children with thalassemia

Anemia causing chronic hypoxia
Calorie depletion
Delayed puberty
Thyroid dysfunction
Abnormalities of GH-IGF1 axis
Co-morbidities: HIV, hepatitis B
Bone dysplasia due to deferoxamine
Micro-nutrient deficiency specially Zn secondary to chelation
Hypersplenism

Table 2: Spectrum of pubertal abnormalities in children with thalassemia

Delayed onset
Arrest at different stages
Common manifestations -Women
• Primary/secondary amenorrhoea
• Oligomenorrhoea
• Poor breast development
Common manifestations - Men
• Sparse facial & body hair
• Impotence
• Sperm abnormality-quality, morphology, motility

Table 3 : Evaluation of a child with short stature/ pubertal abnormality

- Bone age assessment
- Co-morbidity screening: specially, hepatitis B,C, HIV
- T4,TSH
- LH, FSH, sex hormones (after 12-13 years if no clinical pubertal development, any time thereafter in case of pubertal arrest)
- IGF1 & IGFBP3: height SDS <-3: low levels indicate GH deficiency or defect in IGF1 generation
- GH provocation testing: ht SDS <-3 with delayed bone age

Endocrine Complications of Thalassemia Major : Diabetes Mellitus and Hypothyroidism

Dr. Sangeeta Yadav

Thalassemia represent a group of common recessively inherited hemoglobinopathies characterised by reduced globin chain production, beta-thalassemia being the most common. Homozygous state, known as thalassemia major, results in chronic haemolytic anemia, requiring frequent blood transfusions.

Although transfusion therapy has decreased the severity of the disease and increased the longevity of the thalassemics, it results in positive iron balance and secondary hemosiderosis, often leading to vital organ damage and dysfunction in second decade of life. Iron overload is also due to increased gut absorption of iron.

When iron levels increase in the body, there is saturation of transferrin and increase in plasma non-transferrin bound iron species. Unbound iron is labile and generates reactive oxygen species, leading to lipid peroxidation, which is implicated in cellular dysfunction, cytotoxicity and cell death.

For these reasons, current management of thalassemia major includes frequent blood transfusion (every 2-4 weeks) and intensive chelation therapy. Current guidelines recommend pretransfusion threshold not exceeding 9.5g/dl, which seems to be associated with adequate marrow inhibition and relatively low iron burden.[1]

Endocrine dysfunction in thalassemia is amongst the most common complications and is principally attributed to excessive iron overload and suboptimal chelation. The prevalence is quite high particularly in multiethnic populations but determining the prevalence is often difficult due to the widespread heterogeneity of the population and timing of exposure to chelation therapy.[2] Endocrine complications include disturbance in growth and puberty, hypogonadotrophic hypogonadism, diabetes mellitus(DM), hypothyroidism, hypoparathyroidism, osteopenia and osteoporosis.

DM and hypothyroidism are commonly encountered complications in thalassemia major, usually seen in second decade of life, requiring further intensification of chelation therapy and specific management. Intensive combination chelation therapy can prevent and even reverse multiple endocrine complications.[3]

Glucose Intolerence And Diabetes Mellitus

Prevalence : A multicentre study in Cyprus[4] showed that 9.4% of thalassaemic patients had diabetes. Najafipour *et al*[5] have shown the prevalence rates of diabetes mellitus, impaired fasting glucose and impaired glucose tolerance in their group of thalassaemic patients to be 8.9%, 28.6% and 7.1% respectively.
Zhe meng et al[6] showed that 10.3% had diabetes. Kortoglu et al[7] showed 10% had diabetes and 7.3% had impaired glucose tolerance.

Etiology : Multifactorial- genetic predisposition, insulin deficiency, insulin resistance, liver dysfunction secondary to viral hepatitis, beta cell defect secondary to iron overload, poor compliance to chelation therapy.

Unique features of diabetes mellitus in thalassemia major[1] :

1. Ketoacidosis is rare presenting symptom
2. High renal glycosuria threshold
3. No islet cell antibodies
4. No association with HLA-haplotypes B8-DR3, BW15, DR4.

Diagnostic criteria for glucose tolerance :

1. Fasting blood sugar(FBS) >126 mg/dl is diagnostic of diabetes mellitus
2. OGTT serum glucose at 2 h > 200 mg/dl is diagnostic of diabetes mellitus
3. Oral glucose tolerance test(OGTT) serum glucose at 2 h >140 and <200 mg/dl indicates glucose intolerance
4. Fasting blood glucose >110 and <126mg/dl is impaired fasting glucose

Guidelines for screening :

1. Once every 2 yrs starting from 10 yrs upto 16 yrs
2. Once yearly thereafter

Tools for screening:

1. FBS, 2 hr PP blood sugar, OGTT
2. Complementary screening tools are fasting glucose/insulin and MRI R2*. MRI R2* estimates pancreatic iron load which is the strongest predictor of beta cell toxicity[8]

Management :

1. Intensive iron chelation therapy- In a study by Farmaki et al[3], out of 39 patients with abnormal glucose metabolism, 44% normalized after combined chelation with desferrioxamine and deferiprone.
2. Dietary modification and weight reduction
3. Insulin therapy, as required (0.15-1.72U/kg/d)[1]
4. Oral hypoglycemics-role undetermined[1]

Follow-up :

1. Periodic monitoring for metabolic control: Fructosamine testing rather than HbA1c because hemoglobiopathies can affect reliability of the test by altering the normal process of glycation of HbA to HbA1c.
2. Monitoring for complications: KFT, fundus.
3. Growth monitoring

Hypothyroidism :

Prevalence : There is preponderance in females. Majority have primary overt hypothyroidism, ranging from 5.9% to 16% in various studies.[5-8] Much greater percentage have subclinical hypothyroidism.[2] Secondary hypothyroidism is very rare.[1]

Etiology : Chronic tissue hypoxia or poorly chelated iron overload. No role of autoimmunity.

Screening : Annual thyroid function test(TFT) beyond 9 yrs of age.

Management :

1. Intensive chelation therapy- hypothyroidism is reversible at early stage. In a study by Farmaki et al[3], out of 18 children requiring thyroxine, 10 were able to discontinue and 4 could decrease the dose of thyroxine after intensive combination chelation therapy.

2. Overt hypothyroidism (TSH>7mIU/ml) require L-thyroxine replacement therapy. Subclinical hypothyroidism (TSH 5-7mIU/ml) require regular follow-up and optimisation of chelation therapy.[1]

Follow-up :

1. Regular TFT monitoring (3-6 monthly)
2. Growth monitoring

Conclusion

Endocrine complications are a common occurrence in patients with thalassemia major, primarily due to iron overload. Periodic endocrine evaluation and regular growth monitoring are imperative for comprehensive thalassemia care. Regular transfusion therapy and intensive chelation therapy with good compliance are essential for prevention of such complications and also in reversal of established endocrinopathies. Focus of the standard of care must shift from management of established endocrinal complications to early screening and primary prevention, so that morbidity and mortality due to these complications is decreased and quality of life is further improved.

Fertility & Pregnancy in Thalassemia Major & Intermedia

- Dr. Vatsla Dadhwal

Beta Thalassemia is a hemoglobinopathy characterized by decreased production of beta globin chains causing alpha globin chains to accumulate and aggregate. This results in inadequate hemoglobin production. There is microcytic hypochromic anemia, ineffective erythropoiesis and hemolytic anemia. Diagnosis is made by detecting low HbA and increased HbA2 and HbF.

Types

β thal minor/ trait: mild or no anemia
β thal major (BTM): severe form, only HbA2 and F detected. Severe anemia, transfusion dependent and develop complications of iron overload
β thal intermedia (BTI): present late in life, mild anemia, not transfusion dependent, may develop iron overload.

Fertility

BTM: infertility or subfertility is due to iron deposition in endocrine organs. Direct iron deposition occurs in hypothalamus and pituitary and ovaries. Iron deposition leads to organ damage through oxidative stress.

Majority of patients are infertile due to hypothalmic hypogonadism , associated with amenorrhoea, anovulation and infertility. Ovarian functions are usually preserved. These women require ovulation induction with gonadotropins to conceive.

Spontaneous pregnancy can occur in well chelated and transfused patient

Pregnancy Management

BTI

Spontaneous conception and successful pregnancies occur but pregnancies are associated with complications.

Chronic anemia leads to abortions, preterm labour and intrauterine growth restriction. Endocrine complications due to hemosiderosis can occur, though less common compared to BTM.

In a large study which included 83 pregnancies in 44 women, 20.5% ended in abortion, 77.1% had live biths and 2 had intrauterine death. Mean gestational age at delivery was 36.5 weeks and birth weight 2551gms. Cesarean section rate was 72.7%. 79.5% women required blood transfusions and 27.3% required transfusion for first time. There was increase in average ferritin levels before and after pregnancy.

Patients with BTI have increased incidence of thrombotic events.

BTM

Aggressive transfusion and iron chelation therapy has improved life expectancy and fertility with decrease in medical disability. Many cases of successful pregnancy have been reported. These pregnancies need to be monitored carefully for adverse outcome.

Preconception evaluation

- Transfusion needs
- Compliance with chelation
- Iron load status
- Indirect coomb's test
- Screen for infections-HIV, Hepatitis B and C
- Assess end organ damage from iron overload
- Genetic evaluation of partner and need for prenatal testing

Adverse effect on pregnancy depends on

- Presence of alloimmune antibodies
- Cardiac dysfunction
- Severe diabetes mellitus
- Liver dysfunction
- Active hepatitis/HIV
- Significant enlargement of spleen

Prenatal care

- Folic acid
- Interdisciplinary team
- Ferritin levels and blood counts
- Blood transfusions to maintain Hb 10g/dl
- Cardiac, endocrine, hepatic function at initial visit and repeat in each trimester
- Screen for diabetes and hypothyroidism
- Fetal growth and well being
- Iron chelating agents to be stopped in pregnancy .

In a recent large series of 58 pregnant women with BTM, intrauterine growth restriction and preterm delivery occurred in 40%, 15% developed IGT/abnormal GTT, there was increased need for transfusion , there was 60% increase in baseline ferritin. There were many twin pregnancies as most women conceived on ovulation induction using gonadotropins.
Cardiac involvement and arrhythmias are important cause of morbidity and death.

Delivery: route of delivery as per obstetric indications. Cesarean section rates are high because of cephalopelvic disproportion due to short stature or other pregnancy related complications.

Stem Cell Transplant in Thalassemia : Options & Dilemmas

- Dr. Mammen Chandy

Haematopoietic Stem Cell Transplantation (HSCT) today offers an alternative to life long transfusion and chelation for patients with thalassemia major. In December 1981 the first allogeneic bone marrow transplant for thalassemia major was performed in Seattle. That patient is now alive and well 35 years post transplant. The team at Pesaro in Italy under the leadership of Professor Guido Lucarelli has since shown with 1003 patients that bone marrow transplantation is in fact a good alternative to transfusion chelation for thalassemia. However the procedure is associated with risk of infection, regimen related toxicity, graft versus host disease and relapse particularly in those patient who because of inadequate treatment and poor chelation have developed hepatomegaly and hepatic fibrosis. The team in Pesaro have developed a risk stratification based on these three criteria :

Class I : well chelated, no hepatomegaly, no hepatic fibrosis
Class II : one to two adverse risk factor
Class III: all three adverse risk factors

Data from Pesaro in Italy show that there is a 90% chance of disease free survival post transplant in patients who are in Class I, 85% in Class II and only 65% in Class III.

The decision that a family with a child with thalassemia has to make if there is a histocompatible sibling who can serve as the donor is whether they should continue transfusion chelation with its low present risk but significant late morbidity or have a transplant with its immediate risk but high probability of good quality life without the burden of life long transfusion and chelation. Transfusion and chelation can provide a near normal life expectancy in those children who remain compliant with the therapy.\

Therefore there is little doubt that this is a time-tested form of treatment with little immediate risk. The difficulty is that it has to be continued life long and is expensive and sometimes the child becomes non-compliant with the chelation later in life.

In a country like India the economic advantage of a bone marrow transplant for thalassemia is compelling because many families can manage a one-time investment of RS 8-12 lakhs but a life long expenditure of RS 1-2 lakhs a year is a difficult proposition.
The question of whether to wait for gene therapy or accept the current risk of transplantation is a difficult one since there is some progress in this area.

Once the decision to have a bone marrow transplant has been made then the next step is to perform HLA typing on the patient and sibling. If there are no matched siblings who can serve as a donor then the following alternative donors can be considered:

- Cord Blood
- Matched Unrelated Donors from registries
- Half matched donors: sibling or parent

If the parents are planning another baby then cord blood can be collected and stored: if the patient and the next baby are HLA matched, when the baby is two years old bone marrow and the stored cord blood can be used for transplantation. Matched unrelated cord blood transplants have a higher risk of rejection.

With the availability of large numbers of HLA typed donors in international registries, it is possible to find matched unrelated donors for patients with thalassaemia. Currently these transplants should be done only if there is a 10/10 match: there is a higher risk compared to sibling matched related transplantation.

Some centers are offering half matched transplants for thalassaemia: this must be considered experimental for the present till such time as more data is available.

Diagnostic Challenges in Hemoglobinopathy Detection

- Dr. H. Pati

Summary

Hemoglobinopathies leading to hemolytic anemia as a result of abnormal globin chain production are the most common inherited genetic disorders worldwide which affect around 1.5% of the human race globally. The carrier rate is even higher at around 7%. In the present day due to rapid and accurate globin chain screening methods like cation exchange high-performance liquid chromatography(HPLC) or capillary zone electrophoresis (CZE), identification of these disorders has improved vastly. But still there are patients in whom coming to a definitive diagnosis is a challenge due to the inherent variability in the phenotypic presentation of hemoglobinopathies. This phenotypic variation is caused by the large number of point mutations affecting the production or quality of globin chains, the presence of disease modifiers, complex inheritance, and therapy altering the course of the disease. Therefore diagnosis of hemoglobinopathies requires a comprehensive approach which integrates the clinical features, ethnicity, red blood cell indices, family studies and knowing the factors leading to their variations. In some cases where diagnostic dilemma still exists, the help of molecular methods is needed.

Key words: Hemoglobinopathy, Diagnosis, Thalassemia, HPLC

Introduction

The hemoglobinopathies are the most common inherited monogenic disorders globally(1). Around 7% of the population worldwide are carriers of these monogenic disorders accounting for greater than 3,00,000 severely affected babies born every year(2). Hemoglobinopathies affect one or more of the alpha, beta, gamma or the delta globin chains or a combination of them. Most of the hemoglobinopathies are due to missense mutations in the coding sequence of a globin gene which cause a single nucleotide substitution that alter the amino acid sequence of the resulting protein. Deletions, insertions, gene fusions and alterations in the noncoding regulatory regions of the gene, which may affect splicing or transcription/expression levels are also known. There are greater than thousand such mutations which have been described which can be accessed on the globin gene library (3).

High prevalence of hemoglobinopathies is present in populations in the Mediterranean, Middle-East, Central Asia, Indian subcontinent, and South East Asia . It is also relatively common in populations of African descent. The highest incidences are reported in Cyprus (14%), Sardinia (12%), and South East Asia (4).

Hemoglobinopathies can be broadly classified into qualitative defects in which the genetic defect gives rise to a structural change in the hemoglobin (Hb) molecule leading to the production of variant hemoglobin and thalassemias which are quantitative defects, where the

genetic defect leads to a quantitative change in the amount of the affected globin chain produced.

Hb variants and alpha thalassemia are characterized by hemolysis in the peripheral blood, whereas beta(β) thalassemias are characterised by ineffective erythropoiesis and red blood cell (RBC) destruction in the bone marrow. The degree of anemia is generally less severe with Hb variants and alpha(α) thalassemia trait, whereas α and β thalassemia major are associated with life-threatening anemia and transfusion dependence. Sickle cell disease is associated with vasoocclusive episodes. There are also differences in the approach to diagnostic testing for suspected hemoglobinopathies and thalassemias. The variability in phenotypic presentation and overlap in heterozygous states throws up major challenges for both, the clinician as well as hematopathologist.

Clinical and Hematological Features in Thalassemia Major

Individuals with thalassemia major usually present within the first year of life with severe anemia when the fetal Hb gene is switched off, requiring regular RBC transfusions. Findings in untreated individuals with thalassemia major are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extra medullary hematopoiesis, and skeletal changes that result from the expansion of the bone marrow. Peripheral blood smear shows, in addition to microcytosis and hypochromasia, anisocytosis, poikilocytosis, and nucleated RBCs (erythroblasts). Due to the severe phenotype these patients are detected early and start undergoing transfusion therapy, so all the classical clinical features described above may not manifest.

Thalassemia Intermedia

Patients have a moderate anemia and show a markedly heterogeneous hematological picture, ranging in severity from that of the beta-thalassemia carrier state to that of thalassemia major. The patients require infrequent transfusions and usually manifest by the age of two to three years, especially during febrile illnesses. The patients who are inadequately treated have a greater propensity for clinical features ascribed to extramedullary hematopoiesis and skeletal changes due to bone marrow expansion. This is the most heterogenous group of thalassemia syndrome due to the variable interaction between different globin chains and Hb variants (Table1).

Thalassemia Minor

Carriers of β thalassemia and other hemoglobinopathies are clinically asymptomatic. The characteristic laboratory features are microcytosis (reduced RBC volume), hypochromasia (reduced red blood cell Hb content) with increased RBC count and normal red cell distribution width (RDW).

Diagnosis of Hemoglobinopathies

The diagnosis of hemoglobinopathies requires sequential modalities of hematological testing which include measuring of RBC indices, peripheral blood smear examination, qualitative and quantitative hemoglobin analysis by methods like electrophoresis [Cellulose acetate, immune electro focusing (IEF), capillary zone electrophoresis(CZE)] or high-performance liquid chromatography (HPLC). Cases which do not fit the phenotypic presentation with protein detection require further workup by parental testing and molecular genetic testing. Tests like: sickling test, Heinz body preparation also contribute to the diagnosis. In cases where confirmation is required or where quantitative analysis is confounded by therapeutic transfusions or variable phenotypic presentation require further molecular genetic testing for mutation detection. β thalassemias can be caused by more than 200 different hemoglobin beta(HBB) gene mutations(5) ; however, the prevalent molecular defects are limited in each at-risk population. The most commonly used methods are reverse dot blot analysis or primer-specific amplification ARMS PCR, real-time PCR or microarray technology. Deletion/duplication analysis is done to detect deletions of a variable extent of the HBB gene or of the β globin gene cluster that result in β thalassemia or in the complex β thalassemias called γδβ thalassemia and δβ thalassemia. If these modalities do not produce results then sequence analysis may resort to using Sanger's sequencing which can detect mutations in the HBB coding region and associated flanking regions. Its sensitivity of mutation detection approaches 99%(6).

Conditions Leading to Difficulties in Diagnosis in Various Hemoglobinopathies

Due to the variability in phenotypic presentation, co-existence of nutritional deficiencies altering protein detection, variability in genotype, presence of epigenetic modifiers leading to increased HbF, double heterozygous states, variant hemoglobins and therapy related changes, the diagnosis of hemoglobinopathies becomes a challenge. Awareness about these factors helps in making an informed decision about the use of further investigative modalities and giving a confirmed diagnosis.

Alterations in HbA2 values in β Thalassemia Trait

On Hb electrophoresis or HPLC in patients with β thalassemia trait have HbA greater than 90 % along with an elevation in the HbA2 value, sometimes as high as 7 or 8% with a positive cutoff greater than 3.5% for diagnosis (7). Around 40 to 50% cases may also show an increase in HbF, which is usually less than 5%(8). There are certain mutations where the HbA2 levels are not elevated greater than 3.5%, like cap site mutations(9). In these cases, the indices may indicate a low MCV with high total RBC count. If these mutations are inherited along with a missense mutation leading to a homozygous thalassemia genotype but the phenotype

manifestation would be of thalassemia intermedia. These mutations can be detected using molecular methods.

The mean HbA2 level may be slightly reduced in those with both β thalassemia trait with concomitant moderate iron deficiency anemia, which is more pertinent in the Indian scenario due to the increased burden of nutritional iron deficiency. However, some recent studies have postulated that iron deficiency does not lower HbA2 levels below 3.5%, but this opinion is not supported by all(10). In these cases hematological indices, serum ferritin levels may help as iron deficiency is associated with reduced total RBC count, increased red cell distribution(RDW) width and reduced serum ferritin. It is therefore economically and temporally more viable to test for iron deficiency simultaneously along with hemoglobinopathy screening.

Some forms of β thalassemia trait are not associated with an elevated HbA2 level, such as those with δβ0 or γδβ thalassemia trait or when β thalassemia trait is co-inherited with a δ globin gene mutation(11). Therefore, a normal concentration of HbA2 does not rule out the presence of β thalassemia trait. Detection of these mutations requires further molecular workup to confirm the double heterozygous states.

Falsely elevated HbA2 levels are reported in megaloblastic anemia, thyrotoxicosis, both human immunodeficiency virus (HIV) infection and its treatment (specifically with Zidovudine). HbA2 level returns back to normal after replacement therapy with Vitamin B12 and folic acid. Therefore globin protein detection and analysis studies must not be interpreted in isolation but along with RBC indices and peripheral smear morphology(12).

HbA2 estimation by HPLC has confounding factors as HbE, HbLepore (δβ+), HbD Iran, all of which elute in the same retention time window 3.5-3.72. Their respective concentrations and mild variation in the retention times provide a clue to diagnosis, HbA2<10% in heterozygous thalassemia, HbLepore <20%(14%), HbE<35%, HbD Iran >40%. HbLepore is associated with raised HbF and the downward slope of the peak has a hump with a retention time of 3.5minutes, Hb E has a retention time of 3.7 minutes and HbD Iran peak is broad-based which does not touch the baseline. In CZE HbE (Zone 4) peak comes in a separate zone from HbA2 (Zone 3) and Hb Lepore comes in Zone 6, thus providing an accurate assessment of HbA2 in these heterozygous states.

Type of β Globin Chain Mutation and the α Globin Chain Burden

It is pertinent to understand that the burden of α globin chain inclusions is the predominant driver of clinical severity in patients with β thalassemia. It explains some of the factors that are responsible for the clinical variability in this disease. β thalassemia mutations which entirely

ablate β globin synthesis, the β 0 variants, while others are compatible with the production of up to 35 or 40% of the normal of β globin chain production (β + variants). In cases of compound heterozygosity with the combination of severe and a mild mutation, the degree to which β+ globin chain production is impaired, results in a milder phenotype than homozygosity for a mutation that leads to no β0 globin chain synthesis whatsoever(13).

Similarly in a gain of α gene, when are greater than four results in α globin chain excess with a greater mismatch between α and β chains leading to a more severe phenotype of the disease. The presence of extra copies of α globin genes in thalassemia heterozygotes leads to aggravation of the globin chain imbalance in such individuals and predicts a thalassemia intermedia phenotype. Triplication of the α globin gene (ααα/αα) results due to mispairing of homologous sequences in the α globin gene followed by unequal cross-over. Quadruplication of alpha genes is also known due to nondisjunction (αααα/αα), but this is rarer. Triplication exists in two forms, anti3.7 configuration, and anti4.2 configuration. The highest incidence is known in Samoans (11%), although it is generally thought to be less common in Southeast Asians and Indians(14). The Hb level in these patients are lower than expected for thalassemia minor and associated with the frequent occurrence of jaundice and splenomegaly. The red cell abnormalities in terms of hypochromasia and anisopoikilocytosis are more marked than that seen in thalassemia minor. Nucleated RBCs are more common even in the absence of splenectomy. The the HbF level of these patients is also significantly higher.

Effect of Concomitant α Thalassemia

α thalassemia is also common in the populations where β thalassemia is prevalent. Coinheritance of α thalassemia trait leading to reduced α globin chain production, thus reducing the α:β chain mismatch which ameliorates the severity of β thalassemia. This is explained by a reduction in the burden of α globin inclusions without significantly affecting the amount of actual Hb being produced.

Elevated Hemoglobin F levels

Fetal hemoglobin (HbF) synthesis persists to some degree in most patients with symptomatic β thalassemia due to stress erythropoiesis , this is even true in adults. Elevated levels of HbF also appear to vary in the population due to polymorphisms for a heterocellular hereditary persistence of fetal hemoglobin (HPFH), as well as mutations in the erythroid-enriched transcription factor 'Kruppel like factor 1 (KLF1)' gene. The association of KLF1 with HbF levels was identified through genetic studies in a Maltese family with beta thalassemia and HPFH. Linkage studies have also identified loci on chromosome 19p13 that encompasses KLF1 and has been confirmed by expression profiling of erythroid progenitor cells as the

gamma globin gene modifier leading to increased HbF(15).
Persistent synthesis of HbF has beneficial effects in thalassemia as it provides additional oxygen carrying capacity and the ϒ globin chains bind the free α globin chains, thus reducing α globin inclusions. In some of the ethnic groups and locations, thalassemia also tends to be milder because of increased HbF levels .The increased production of HbF has also been proved by many studies due to enhancers of the quantitative trait loci (QTL) for HbF which are Xmn1HBG2 on chromosome 11p, HBS1LMYB which is an intergenic region on chromosome 6q23, and BCL11A on chromosome 2p16(16). These loci contribute towards the inheritance of heterocellular HPFH.

Increased levels of HbF with different βS–globin gene haplotypes have shown C>T single nucleotide polymorphism (SNP) at position 1585' of the G ϒ globin gene promoter, which was named as Xmn1HBG2 polymorphism. Linkage association studies done on an extended Indian family with β thalassemia and HPFH showed that locus on chromosome 6q23 is also a HbF QTL. These two QTLs were also confirmed by genome-wide association studies (GWAS). GWAS has also identified a new HbF QTL in intron 2 of the BCL11A((B-cell lymphoma/leukemia 11A) gene on chromosome 2p16(17). Earlier this gene was considered as an oncogene involved in leukemogenesis. The variation in these QTLs usually accounts for 10 to 50 percent of the variation in HbF levels in healthy adults as well as in patients with hemoglobinopathies. The other unexplained variation in HbF levels may be due to many loci with relatively small effects which may be difficult to identify by population-based studies.

δ β Thalassemia Leading to HbA2 Variability

Large deletions in the HBB gene cluster that remove the β and δ globin genes but sparing both ϒ globin genes or HBG2 alone cause δβ thalassemia. These deletions vary from less than 1kb to greater than100 kb (median 30kb). δβ thalassemias are associated with elevated HbF which may be due to the removal of regulatory regions between HBG1 and HBD. This leads to silencing of the ϒ globin gene expression; the area of the Corfu deletion may also be responsible for this. These deletions cause G ϒ/Aϒ ($\delta\beta^0$) thalassemia or G ϒ ($\delta\beta^0$) thalassemia(18) .

Heterozygotes for G ϒ/Aϒ ($\delta\beta^0$) thalassemia resemble a mild β thalassemia trait but with normal HbA2. They have between 4 and 24 percent HbF, with most cases averaging approximately 10 to 12%. Microcytosis is usually mild, and the MCV may even be normal. HbF distribution among erythrocytes is heterocellular.

G ϒ/ A ϒ ($\delta\beta^0$) HPFH heterozygotes are characterised by normal HbA2 levels and HbF levels of 15 to 30 percent. There are only minor reductions in the RBC indices, which are frequently within the normal range. Homozygotes have been described and their hemoglobin consists

entirely of HbF. These individuals are clinically unaffected and have normal or high Hb levels (15 to 18 g/dL), presumably as a result of the higher oxygen affinity of HbF. They have mildly microcytic, hypochromic red cells due to globin chain synthesis imbalance similar to that of β thalassemia trait , indicating that the output of ϒglobin chains does not fully compensate for the lack of β globin chains(19).They may develop more severe anemia during infections. Red cell morphology is more abnormal than β thalassemia trait, and Hb consists of100% HbF, containing both G ϒ and A ϒglobin chains(20).

Hb E Variant and its Variable Phenotype

HbE (β-26 glutamine→lysine) is commonest hemoglobin variant in Southeast Asia with a prevalence rate of 30%(21). In India, it has a high prevalence in the northeastern region (5-50%). HbE may not be of clinical significance as in heterozygous or homozygous states, but its interaction with beta thalassemia produces a variable phenotype. The thalassemia phenotype of HbE is due to activation of cryptic donor splice site by the mutation (22). Manifestations of E-β thalassemia range from thal intermedia to thalassemia major, clinically manifesting in childhood as refractory anemia requiring regular or irregular transfusions depending on the partner β thalassemia mutation, splenomegaly and sometimes, unexplained jaundice. Co-inheritance of α thalassemia reduces the chain mismatch and homozygosity for Xmn I site polymorphism leading to raised HbF modifies the phenotype, making it less severe (23). The diagnosis of HbE-β thalassemia shows HbE, elevated HbF and elevated HbA2 on CZE but in HPLC HbE migrates along with HbA2 thus making quantitation of HbA2 inaccurate. The parental study is required to confirm the diagnosis. But the diagnosis may be confounded in patients who have received transfusions by suppressing the HbF levels, in these cases parental study and molecular methods are useful in confirming the diagnosis.

Phenotypic Variation in Sickle Cell Disease

Replacement of glutamic acid by valine at the sixth position in the β globin chain leads to HbS formation. On deoxygenation, Hb S molecules form long helical polymers of HbS due to the hydrophobic interactions between the β6 valine of one tetramer and the β85 phenylalanine and β88 leucine of an adjacent tetramer leading to irreversible sickling of RBCs, vaso-occlusive episodes and end-organ damage(24). The mutation is common to all HbS but the clinical variability in the pattern and severity of disease manifestations is vastly inconsistent.

Some disease modifying factors have been used to explain this variability in clinical presentation. HbF is protective in HbS disease as it does not participate in polymer formation. Not only the mean level of fetal hemoglobin in the circulation is important but also the distribution of fetal hemoglobin between the cells is also significant. Heterogeneity of HbF distribution does not prevent occlusions in microvasculature caused by RBCs lacking HbF (25).

Co-inheritance of α thalassemia with sickle cell disease produces less severe hemolytic anemia due to reduced HbS concentration, retarded HbS polymer formation, and low frequency of dense cells. The effect of α thalassemia on other manifestations of sickle cell disease such as painful crises and vaso-occlusion are more variable(26).

Haplotypes of sickle cell disease are described by polymorphic restriction endonuclease sites in the mutant ß globin gene and are designated by the geographic areas in which they were first identified. They have been enumerated as; Senegal, Benin, Central African Republic (or Bantu), Cameroon and Arabo-Indian type (27). Sickle cell disease in India and the Persian Gulf region due to the Arabo-Indian haplotype follows a benign course as compared to other haplotypes. For instance, leg ulcers, priapism, stroke are uncommon and splenomegaly is a common occurrence here, while the spleens of most patients in the Americas are small and poorly functional due to recurrent splenic infarctions (28). In the Arabo-Indian haplotype spleen usually does not regress thus as the duration of the disease progresses the spleen may increase in size which may be due to splenic infarction or development of portal hypertension due to portal vein thrombosis by vaso-occlusion.

Not only is there clinical variability in sickle cell disease but also a greater pattern variability in HPLC due to the presence of variants, HbA2 adduct formation by HbS. HbF is mildly elevated in homozygotes for HbS associated with the Bantu, Benin or Cameroon haplotypes (5–7%) but may be more markedly elevated in association with the Senegal haplotype (7–10%) and even more in association with the Arab-Indian haplotype (10–25%). Furthermore, the HbF percentage is increased if there is co-inheritance of non-deletional HPFH. Compound heterozygosity for βs and β0 thalassemia can be distinguished from βs homozygosity by an increased HbA2 , values usually range from 4-5.6% for HbSβ0 thalassemia in comparison with 1.6 – 3.6% for HbSS. However, there may be some overlap in HbA2 with co-inheritance of α thalassemia as it raises the HbA2 in HbSS. There is also an overlap in HbF levels, which are usually 5 – 15% in compound heterozygotes. If the red cell indices are normal, HbSβ0 thalassemia can be excluded, but in patients with microcytosis, the differential diagnosis is between HbSS with co-existing α thalassemia and HbSβ0 thalassemia. To confirm, molecular methods have to be resorted to. Parental study and confirmation by supplementary techniques are required, like the sickle cell solubility test to detect sickling variants that are caused by a second mutation in addition to HbS like HbS Antilles and HbS Oman(29).

Other Causes of Disease Variability

Although features of the globin genotype in families with thalassemia account for some of the clinical variability encountered in this disorder, much still remains to be explained. For example, siblings in some families appear to have identical globin genotypes, yet exhibit

rather notable differences in clinical severity or in the prominence of individual manifestations of the disease. There is thus a substantial effort underway to use gene expression profiling, the study of single nucleotide polymorphisms(SNP), and other technologies in an effort to associate polymorphic variations in other genes with altered clinical phenotype(30).To date, despite a considerable accumulation of preliminary data still, no definitive clues are available.

Conclusion

Diagnosis of hemoglobinopathies requires an integrated comprehensive approach using relevant clinical details, RBC indices, peripheral smear morphology, globin chain detection with quantification and sometimes molecular methods. Quantitations of normal and variant hemoglobins by methods like HPLC or CZE are most common. Clinically relevant hemoglobin variants, such as HbE, HbS, HbD Punjab, HbO Arab and also rarer β variants like HbC as well as α variant like HbJ Meerut, HbQ India can be detected. HPLC and CZE can also accurately quantities HbA2 and HbF which can be used for detection of heterozygous β thalassemias. The cases where there is variation in the phenotype and genotype these conditions must be looked into (Table 2) for arriving at a diagnosis. There are many mutations associated with hemoglobinopathies and it is economically not viable to test for them in the clinical setting. In spite of this marked heterogeneity, a limited number of molecular defects are prevalent in the population of interest, as is highlighted here in the Indian context (Table 3), which account for greater than 90% of the genotype abnormalities. This may be very useful in practice because the most appropriate probes or primers can be selected according to the ethnicity of the patient. For unknown mutations, Sanger's sequencing may be used.

The future challenges in our country include not only diagnosing hemoglobinopathies but also instituting a national policy for screening , prenatal detection of these inherited disorders to reduce the disease burden.

Table 1: Globin Chain Interactions Leading to Thalassemia Intermedia

Double heterozygote for mild beta thalassemia mutation or single severe deletion	β(+) thal/β(+) thal, β(0) thal/β(normal)
Beta globin chain variants with beta thalassemia mutation	HbE/β thal, HbD/β thal, HbS/β thal
Compound heterozygote for alpha chain deletion with or without beta thalassemia mutation	HbH, HbH/β thal
Additional alpha gene with beta thalassemia	ααα,αα/β thal or αααα, αα/β thal
HbLepore or δβ with or without beta thalassemia	δβ(+)/β thal, δβ(+)/δβ(+), δβ(0)/β(normal)
Hereditary persistence of HbF	HBFH [δβ(0)/δβ(0)]

Table 2: Phenotypic-Genotypic variations in thalassemia

PHENOTYPE	GENOTYPE
Normal red cell indices	α and β thalassemia interaction
Normal HbA2 with normal MCV	Mild β thalassemia mutations like del 101 C/ T, del 92 C/ T, IVS II –844 C/ G
	Triplicate α genes
Elevated HbF	Hb Lepore, Arabo-Indian haplotype of HbS, Xmn polymorphism or presence of QTLs
Severe heterozygous β thalassemia	Hyper-unstable haemoglobin
	Double heterozygote for β and additional α genes

Hb- Hemoglobin, MCV- Mean corpuscular volume, QTL- Quantitative trait locus

Table 3: Common β Thalassemia Mutation in the Indian Population (31)

Mutation	Prevalence %	Type
IVS 1-5(G-C)	22.4	β+
del 619 bp	21.5	β0
FR 8/9	19.5	β0
IVS1-1 (G-T)	13.6	β0
FR 41/42	11.7	β0
Codon 15 (G-A)	4.5	β0

Iron Chelation Monitoring

- Dr. Tulika seth

Reasons for iron overload and need for chelation.

If transfusion is given according to the recommended transfusion scheme for thalassaemia major then an equivalent of 100–200 ml of packed red blood cell (PRBC) per kg body weight per year are transfused. This is equivalent to 116-232 mg of iron/kg body weight / year, or 0.32-0.64 mg/kg/day. Regular blood transfusion therapy therefore increases iron stores to many times the norm unless chelation treatment is provided. Chelation therapy aims to balance the rate of iron accumulation from blood transfusion by increasing iron excretion in urine and or faces with chelators. If chelation has been delayed or has been inadequate, it will be necessary to excrete iron at a rate which exceeds this.

Consequences of Extra Iron

Iron increase in the organs of patients with thalassemia major results in serious life limiting sequelae. Iron metabolism is deranged in these patients due to excess iron which results in forms of iron not usually found in the body, and toxic to the body like Non transferrin bound iron (NTBI).

Methods to assess body iron burden:

A) Standard measures of body iron
- Assessment of Liver Iron
- Accurate reflection of total body iron burden
- Measurement of serum ferritin levels

B) Special measures of iron levels
- Evaluation of Heart iron
- Assessment of NTBI

Advantages and disadvantages of present techniques for iron chelation monitoring

Serum ferritin (SF) -correlates with body iron stores, and is relatively easy inexpensive. Can be measured repeatedly and consistently. Serum ferritin is most useful in identifying trends. Observations maintenance of serum ferritin of 1,000 µg/L associated with additional clinical advantages. Long term control of serum ferritin has prognostic significance. Clinical judgment is needed to interpret these trends. Most SF assays developed for detecting IDA, the linear range of assay at high SF values needs to be known SF does not always predict body iron or trends in body iron accurately. In TM, variation in body iron stores 57% of variability in plasma ferritin distribution of liver iron between macrophages (Kupffer cells). The advantages and disadvantages are discussed in tables 1,2, 3.

Table :1 Assessment of Serum Ferritin

Advantages of serum ferritin monitoring	Disadvantages of serum ferritin monitoring
Easy to assess repeatedly	Indirect estimate of iron burden
Inexpensive	Increased by inflammation
Trend identification with repeat samples	Cannot determine iron balance directly
Long term control linked to outcome	Non-linear response to iron load at high levels
Useful for dose adjustment	Absence of decrease does not exclude response
	• Relationship to iron load varies with chelator • Relationship to LIC differs with disease

Liver Iron Concentration (LIC)

This is a clinically important measurement, to identify whether body iron is adequately controlled. Adequate control of LIC is linked to reduced risk of hepatic damage. Normal LIC values are up to 1.8 mg/g dry weight (wt) . Sustained high LIC (above 15-20 mg/g dry weight) have been lined to worsening prognosis, liver fibrosis progression (Angelucci 1997) or liver function abnormalities. LIC is the most reliable indicator of body iron load.

Total body iron stores in mg iron /kg body wt = 10.6 x the LIC (in mg/g dry wt) Sequential measurement best way to determine iron balance. Best to use LIC determination in patients whose serum ferritin levels deviate from expected trends, assessment of new chelating regimes are being used. At high levels of SF (>4000 µg/L), the relationship to LIC is not linear.

T2*MRI

Principle MRI techniques - radio-frequency (rf) magnetic field pulse applied to tissue (liver or myocardium). Protons take up energy, altering their spin orientation & later relax returning to

their original state. With spin echo, after pulse, nuclei take time to relax "relaxation time"; T1 in longitudinal plane, and T2 in transverse plane. Values may be expressed as relaxation rates, R1 rate (is same as 1/T1) and R2 rate (same as 1/T2). Shorter acquisition improves sensitivity, measured as T2* (in ms), 1/T2* = 1/T2 + 1/T2', and T2 is tissue relaxation time and T2' is magnetic in-homogeneity of tissue.

Table : 2 Assessment of Liver Iron Concentration

Advantages of LIC	Disadvantages of LIC monitoring
Reliable estimate of body iron	Expensive (either by biopsy or MRI
Allows calculation of iron balance (LIC change)	Cannot be repeated as frequently as SF (cost with MRI or inconvenience with biopsy
Long term LIC control - linked to prognosis	LIC unreliable as predictor of heart iron in chelated patients
LIC not affected by inflammation (unlike SF)	Biopsy risks complications (low in expert centre)
Biopsy shows degree of liver damage	Biopsy method affected by sampling artifact
MRI non-invasive with good patient acceptance	MRI method is not universally available
MRI method can readily be set up and stardardised across different centres	MRI method requires external Validation. MRI determination unreliable above LIC of 30 mg/g dry

Myocardial iron estimation : T2*MRI

Physical principles iron measurement heart same as liver -challenge of measuring a moving object.T2* (or R2*) techniques best -require shorter acquisition times, single breath hold .Relationship of myocardial iron concentration (MIC) to T2* is: MIC (mg/g dry wt) = 45 * (T2* ms)^-1.22 (Kirk 2009). This relationship is non-linear so small changes in mT2* at values <10 ms may indicate relatively large changes in MIC. Utility of mT2*MRI identified shortened T2* values <20 ms patients with decreased left ventricular ejection fraction (LVEF). Even 5.98 mg/g dry weight iron (3.2 to 9.5 mg/g) causes severe heart failure; not harmful to liver. The risk of developing heart failure increases with T2* values <10 ms, associated with a 160 fold increased risk heart failure in the next 12 months (Kirk 2009b). Centres where T2* validated, may have predictive value in identifying patients at high risk of developing

deterioration in LVEF, thus allowing targeted intensification of treatment before heart failure develops. Recommended as part of yearly monitoring of multi-transfused patients at risk of developing myocardial iron loading. Very important that measurements are independently validated and calibrated. Else inappropriate assessment of heart failure prognosis may result.

Table : 3 Assessment of Myocardial Iron

ADVANTAGES	DISADVANTAGES
Rapidly assessed iron content in myocardial septum	Indirect non-linear relationship with myocardial iron
Reproducible method	Requires a validated centre with dedicated methods
Linked to heart iron	Technically demanding
Potential to measure heart function at same visit	Methodology requires standardisation
Potential to measure LIC at same visit	Does not predict liver body iron overload
Linked to LVEF at time of measurement	Requires continuous quality assurance e,g, phantom scanning
Linked to risk of heart failure in next year	

Optimal chelation in the current era

- Dr. Amita Mahajan

Optimal iron chelation is the cornerstone of management of patients with thalassemia. In cases of ongoing transfusion therapy, with each RBC unit containing ~ 200 mg of iron,cumulative iron burden is an inevitable consequence. Increased GI tract iron absorption resulting from anemia and IE, which down-regulate the synthesis of hepcidin, a protein that controls iron absorption from the GI tract and increases release of recycled iron from macrophages can further add to this burden though more significantly in non-transfusion dependent patients.

Chelation therapy aims to balance the rate of iron accumulation from blood transfusion by increasing iron excretion in urine and or faces with chelators. The availability of three chelators now allows informed choices to be made for patients.

The major challenge in chelation therapy is to achieve regular adherence to treatment regimens throughout a lifetime, as even short periods of interruption in treatment can have damaging effects. While the convenience and tolerability of individual chelators is important in achieving this goal, other factors such as psychological wellbeing, family and institutional support also impact on adherence and outcomes.

Chelation generally begins at around 2 years of age, after 20-25 RBC units are transfused, with a serum ferritin level > 1000 μg/dL. To date, there are 3 major classes of iron chelators: hexadentate deferoxamine [DFO], bidentate deferiprone [DFP]), and tridentate deferasirox [DFX].

DFO, a naturally occurring sideraphore derived from *Streptomyces pilosus* with a high molecular weight and a very short half-life of 8-10 minutes, requires intravenous or subcutaneous parenteral administration. DFO enters hepatic parenchymal cells, chelates iron, and appears in the serum and bile as the iron chelator feroxamine. It also chelates iron released after catabolism of senescent RBCs and is excreted in the urine. Maintaining normal ascorbic acid levels optimizes DFO iron excretion. Continuous slow subcutaneous infusions of DFO with a lightweight portable battery-operated pump enables longer exposure to circulating labile plasma iron. The initial recommended dose is 30-40 mg/kg per day for daily use 5-7 days each week in regularly transfused thalassemia patients.

DFP (L1) is a synthetic compound originally identified in the 1980s in London, hence the designation L1. It is absorbed by the GI tract and has a plasma half-life of 1.5-4 hours. The recommended daily dose is 75 mg/kg per day, which can be increased to 100 mg/kg per day,

given orally in 3 divided doses with meals. DFP penetrates cell membranes more rapidly than DFO, expediting the chelation of toxic intracellular iron species. Initial clinical efficacy studies were encouraging, indicating that DFP is capable of rapidly removing intracellular iron, and subsequent studies confirmed its efficacy in removing iron from the heart, improving cardiac function, and preventing iron-induced cardiac disease.

The sequential combination of DFP and DFO has an additive, if not synergistic, chelating effect. The "shuttle hypothesis" suggests that intracellular iron chelated by DFP may be transferred to DFO, a stronger chelator, in the plasma. Subsequently, DFP may reenter cells to bind with more iron, inducing greater iron excretion. Regular monitoring of blood counts is mandatory because of the potential risk of agranulocytosis in 1% of the patients treated with DFP. In addition, approximately 20-30% patients end up discontinuing DFP due to arthralgias and arthropathy.

DFX (Exjade), approved in 2005 for use in transfusional overload patients, is an orally ingested, highly bioavailable chelator that is absorbed in the GI tract. Because of its dose-dependent half-life of 12-18 hours, it can be taken once a day. Daily use of a single oral dose of 20-40 mg/kg per day results in dose-dependent decreases in LIC with similar trends in serum ferritin comparable with those achieved by subcutaneous 8-hour administration of 40-60 mg/kg per day DFO. The efficacy of DFX dosing is related to transfusional iron intake. Close monthly monitoring of serum ferritin and creatinine levels and liver function is indicated. Interruption or discontinuation of DFX is required in cases of unexplained progressive increase in transaminase, progressive increase in serum creatinine, or progressive GI symptomatology.

Currently, in view of the equivalent efficacy, safety, and ease of adminstration, DFX has become the chelator of choice. However, a proportion of patients are unable to achieve the requisite iron balance and a combination of DFX with DFO and DFP may be indicated. There is now ample evidence that these combinations can be used safely and efficaciously to achieve an optimal iron balance. Use of combination therapy should, however, be done under close clinical supervision and does mandate more intense monitoring.

In some cases, patients who were not treated or insufficiently treated with iron chelators present, for the first time, with heart failure induced by IO. These patients should be started with DFO in a dose of 60 mg/kg by daily 24-hour continuous intravenous infusion together with DFP. This treatment has been shown to result in improvement in cardiac function. Concomitantly, cardiac function tests have to be monitored in an intensive care setting in collaboration with a cardiologist until significant improvement is achieved.

Another unique group of patients is composed of pregnant women who require iron chelation. For these patients, it is recommended to delay chelation until the second trimester and to use subcutaneous DFO according to the guidelines of IO parameters. DFX is not approved for use during pregnancy.

Despite the fact that iron chelation therapy has been available for more than forty years, iron cardiomyopathy is the most common cause of death in patients with transfusion dependent anemia. In the last decade, however, such deaths have been significantly reduced. This improvement has been attributed in part to greater iron chelation options and the ability to recognize pre-clinical cardiac iron deposition by Magnetic Resonance Imaging studies (MRI). Patients with low cardiac T2*, as measured by MRI, have a significant risk of developing overt heart failure over a 12-month period if changes to their chelation regime are not made.

Although the ability of a chelator to control cardiac iron is important, control of total body iron overload remains critical. By using all current information available today with respect to cardiac protection and achieving this, we will be able to pay greater attention to reducing deaths from infection and hepatic cancer and cirrhosis. As patients are becoming older, the incidence of hepatic cancer and cirrhosis is increasing.

The biggest challenge that we currently face is keeping patients committed to their chelation regimes that may be complicated and even cumbersome. Efforts are ongoing to develop new efficient iron chelators that may have acceptable side effects adding to our armamentarium options

The ability to optimizing iron chelation, should mean that deaths from cardiac failure will become of historical interest. Maintaining low iron burden in the liver and other organs should also reduce the common morbidities and mortality even further.

Adult Thalassemia Care

- Dr. Anupam Prakash

Thalassemia patients, over the years, with rapid advances in the field of medical sciences and improved management facilities have witnessed a significant improvement in the quality of life as well as the longevity of life has also increased. This, thalassemia care has moved out of the realms of a paediatrician and now requires adequate attention of physicians with a holistic care. This transition has resulted in a totally new perspective and a new challenge to the adult physicians who have not been dealing with thalassemia in their adult patients till very recently.

This write-up tries to cover the salient features of adult thalassemia care. By and large the principles of management are derived from the pediatric expertise and the experience gained at our set-up.

The main issues that concern adult Thalassemia are enumerated in Table 1.

Table 1: Adult thalassemia: Issues

- Transfusion
- Chelation
- Transfusion-transmitted infections
- Splenectomy
- Cholecystectomy
- Vaccination
- Hormonal problems
- Fertility issues
- BMT/Umbilical Cord Blood stem cell transplantation

The most important management issue in thalassemia is the requirement of blood transfusion because of ongoing hemolysis (thalassemia being a haemoglobinopathy) and the whole life the patient is transfusion dependent. The aim is to maintain target haemoglobin of 11g/dL. Patients usually require blood transfusion fortnightly and this alone can be sufficient to achieve the target. However, frequent blood transfusions bring with them the problem of iron overload and transfusion transmitted infections (1,2). Iron overload requires active management. Desferrioxamine is a time-tested iron chelator and is quite effective. However, the disadvantage is that it needs to be given as subcutaneous infusion daily; apart from its cost. Deferiprone and Deferasirox are two alternative iron chelators, can be administered orally and are widely available and used in practice. Patients who do not respond to a single iron chelator or develop toxicity,may need to be given a combination of both the oral drugs.

Transfusion and chelation form the corner stone or treatment of thalassemia patients and the key to resolve other related issues also lies in providing effective transfusion-chelation to each thalassemia subject. In fact, effective transfusion-chelation can prevent and/or delay most of the complications of thalassemia ensuring a longer life span for thalassemia subjects during

which they can live a near-normal life.

Splenectomy

After transfusion-chelation, the commonest issue of concern to thalassmeia subjects is that of "splenectomy". Liver and spleen are the predominant sites of extravascular hemolysis (characteristically seen with thalassemia) and many subjects have had splenectomy by the time they reach their adulthood. However, increasingly with better care during paediatric age group, splenectomy may not be a necessity. The indications of splenectomy are outlined in Table 2.

Table 2- Indications of Splenectomy

- PRBC (packed red blood cell) requirement > 220 mL/kg/year or 1.5 times rise from previous years
- Hypersplenism
- Persistent abdominal discomfort due to massive spleen

It is recommended that all thalassemia subjects should undergo simultaneous **cholecystectomy** if gall stones are present. However, gall stones, tough commonly seen with other hemolytic anemias, are not so commonly seen in association with thalassemia. Blood transfusions also entail the risk of transfusion-transmitted infections, for which periodic screening is a must and prompt treatment is also essential. Hepatitis B, Hepatitis C and HIV infections are commonly seen.

Vaccination

It is recommended that subjects undergoing splenectomy should be vaccinated 2-4 weeks prior to surgery against capsulated organisms viz. H. influenzae, Pneumococci and Meningococci. All thalassemia subjects should undergo their primary vaccination in childhood. Although universal hepatitis B (HBV) immunization is being practiced these days, however, if any adult thalassemia person has not been vaccinated, vaccination against hepatitis B virus should be carried out without any further delay.

Endocrine problems

With thalassemia subjects growing through adolescence and into adulthood, endocrine and fertility issues are increasingly being witnessed (3-5). Various endocrine problems that have been reported are outlined in Table 3.

Table 3- Endocrine problems in thalassmeia subjects

- Poor growth- 40-50% prevalence
  - Chronic anemia
  - Malnutrition
  - Iron overload
  - Hypersplenism
  - Desferrioxamine (DFO) toxicity
  - Chronic liver disease
  - Hypogonadism-is a prominent feature & contributes as well
  - Hypothyroidism
  - Reduced GH
  - Hypocortisolism

- Short stature
- Delayed puberty, prolonged growth period
- Secondary amenorrhoea- due to anemia and hypogonadism
- Hypothyroidism
- Hypoparathyroidism
- Impaired Glucose Tolerance and Diabetes mellitus
- Hypogonadism
- Fertility issues

It is to re-emphasise that most of these endocrine issues can be prevented by effective transfusion-chelation therapy. Growth disturbances are known and poor growth, short stature and delayed puberty are so very characteristic of thalassemia, even in childhood. Contributory factors are listed in Table 3.

Hypothyroidism is noted in 6-16%, up to 30% has been reported inclusive of sub-clinical hypothyroidism. Hypothyroidism seen is primary hypothyroidism and hemosiderosis of the thyroid has been demonstrable.

Hypoparathyroidism has been observed in 3.6-22.5% and is believed to be caused by deposition of iron in the parathyroids, additionally contributed by free radical induced mitochondrial & lysosomal membrane damage. It manifests as asymptomatic hypocalcemia, bony pains, spasms and tetany. Chelation therapy improves hypoparathyroidism and vitamin D3 and calcium supplementation are recommended.

Impaired Glucose Tolerance and Diabetes Mellitus have been reportedly observed in 2.3 to 24% of thalassemia subjects above the age of 10 years (6). The prevalence has been found to correlate with serum ferritin levels. Notable other risk factors include age, number of transfusions received, stage of puberty, status of iron chelation, family history of diabetes and presence/absence of chronic hepatitis. Insulin resistance is a major feature coupled with iron

deposition in pancreas. Diabetic ketoacidosis is uncommon but the other features are similar to usual diabetes mellitus.

Hypogonadism is common in both sexes. Delayed puberty and menarche, or secondary amenorrhoea are commonly seen in female subjects. Delayed or secondary hypogonadism is observed in males. Delayed or arrested growth with low testicular volume & decreased sperm motility has been reported. Replacement doses of testosterone or estrogen may be required to address these issues.

Fertility Issues

Despite all the above endocrine issues, the good thing is that fertility has been reported in well-treated thalassemia patients. Counseling before planning a pregnancy is important. Even pre-marital counseling plays a role. If a thalassemia major patient marries a carrier, 50% risk of thalassemia major is there in the offspring and it will require prenatal diagnosis. If a thalassemia major female marries a normal male (neither carrier/affected), children will be asymptomatic (normal/carrier). Assisted reproduction for few thalassemia subjects may be required.

Thalassemia Heart Disease

In cases of chronic iron overload, majority of deaths are due to cardiac failure & sudden death. The cardiac effects begin with accumulation of 20g of iron, usually after age of 10 years, in a regularly transfused child maintained with an Hb of 9-10 g/dL; without adequate chelation. The cardiac involvement is clinically apparent but symptomatically silent. Usually, cardiomyopathy develops by 16 years and the mean survival falls to 3 months, once congestive heart failure develops. In fact, thalssemia heart disease is a distinct and novel entity (7).

Chelation therapy improves cardiac function, improves outcomes and prevents development of complications. It is important to know about this entity since successful reversal of this type of cardiomyopathy has been reported even if chelation therapy is started late (7,8).

There are a number of other problems which are faced by thalassemia subjects but are not specific to adults. These are enumerated in Table 4.

Table 4- Problems in thalassemia, not specific to adults

- Liver dysfunction and secondary bleeding manifestations
- Hepatic siderosis
- Increased risk of Hepatocellular carcinoma
- TTI (Transfusion transmitted infections)
- HBV
- HCV
- HIV

- Psychosocial problems
- Thalassemic osteopathy

For the sake of completion, it is important to mention that bone marrow transplantation is a modality which can provide cure to thalassemia, however, it should be offered soon after diagnosis and presently the cost is too high. Bone marrow stem cell transplantation requires HLA-matched sibling donor. Only around 30% patients are able to get a fully matched sibling donor. The results are better, earlier the bone marrow transplantation (BMT) is done.
Patient characteristics associated with survival & event-free survival after BMT are-

1. Degree of hepatomegaly (>2 cm/< 2 cm)
2. Portal fibrosis on liver biopsy (present/absent)
3. Effectiveness of iron chelation (irregular/regular)

Umbilical cord blood (UCB) & peripheral blood stem cell transplanatation (PBSCT) are also being offered and have advantages of easier processing and lower risk of graft-vs-host disease and infection. However, the large scale experience is less. If there is a rejection following UCB transplantation, success rate of subsequent bone marrow SCT further decreases. One can preserve the UCB and later use along with bone marrow SCT if it is HLA matched.

Care of thalassemia patients is continuously evolving and there is a need for increased awareness among the adult physicians (9,10), so that optimum care can be provided to reduce the suffering of thalassemia patients, and also provide them improved quality of life.

Genotype-Phenotype Interaction in HbE/β-Thalassemia Disease : The Molecular aspect.

- Dr. Suthat Fuchareon

Thalassemia Research Center, Institute of Molecular Biosciences, Mahidol University, Nakhon Pathom, Thailand

Defective synthesis of the β-globin chain in HbE-β-thalassemia leads to the imbalance of α- to non-α-globin chains production and consequently precipitation of the excessive unmatched α-globin chains. The α-hemoglobin precipitation occur in the bone marrow, leads to erythroid membrane rigidity and accelerated apoptosis and premature destruction of the erythroid precursors in the bone marrow (ineffective erythropoiesis), and premature red blood cell destruction. Therefore, the mechanism underlying the pathophysiology of the HbE-β-thalassemia results from the inadequate β-globin chain production, and can be related to the deleterious effects of imbalanced globin chain synthesis on erythroid maturation and survival. Although the β-thalassemia disorder occurs from mutation on the β-globin gene, the disease phenotype is the result of a multigene interaction as shown that the clinical feature of the patients ranging from severely affected as Cooley's anemia to mildly affected as non-transfusion dependent thalassemia (NTDT). Hb level in HbE-β-thalassemia range from 3 to 12 g/dl with an average level of 7 g/dl. The severity of anemia in β-thalassemia reflects the degree of α- and non-α-globin chain imbalance and the excess of unmatched α-globin chains, therefore, any factors that can reduce the degree of globin chain imbalance and the size of the free α-globin chains pool could moderate the clinical features of the β-thalassemias. The primary modifying factor is the nature of the underlying β-thalassemia mutation itself. To date, it is known that there are nearly 300 β-globin gene mutations underlying β-thalassemia. Generally, the interaction of a β^{+}-thalassemia allele, in which there is some β-globin production, results in a milder disease. Hb level in HbE-β^{+}-thalassemia maintains between 9 and 11 g/dl and usually does not require any treatment. Furthermore, it is proposed that the amount of alternative spliced β^{E}-globin mRNA may play role in the variability of HbE-β-thalassemia disease severity. β-Thalassemia patients who co-inherit α-thalassemia have less redundant α-globin chains and tend to have less severe symptoms. The degree of amelioration depends on the number of functional α-globins, however a single α-globin gene defect is sufficient to improve the clinical phenotype of HbE-β-thalassemia patients. On the other hand, the co-inheritance of triplicated α-globin genes (ααα) may result in increased globin chain imbalance and severe anemia. In addition, the role of increased fetal hemoglobin (HbF; α_{22}) as an ameliorating factor of β-thalassemias becomes more evident, its effect mediated by reducing the degree of imbalance globin chain synthesis. HbF level in HbE-β-thalassemia is vary heterogeneity, range from 2% to 76%, and associated with the disease severity. Genetic linkage analysis and genome-wide association approaches have identified susceptibility loci

for the persistence of HbF in adulthood or *trans*-acting quantitative trait loci (QTLs) controlling HbF levels, including (i) the β-like globin cluster (11p locus), (ii) HBS1L, MYB and HBS1L-MYB intergenic region (6q locus), and (iii) BCL11A (2p locus). Each of these genetic determinants may themselves show considerable heterogeneity, and the frequency of different alleles may vary widely in particular populations. Hence the various interactions of these modifiers may result in the considerable various HbF level and clinical diversity of HbE-β-thalassemia. A better understanding of how genetic factors contribute to the HbE-β-thalassemia disease heterogeneity may lead to the new efforts or therapy for the patients.

Thalassaemia- The true story so far !

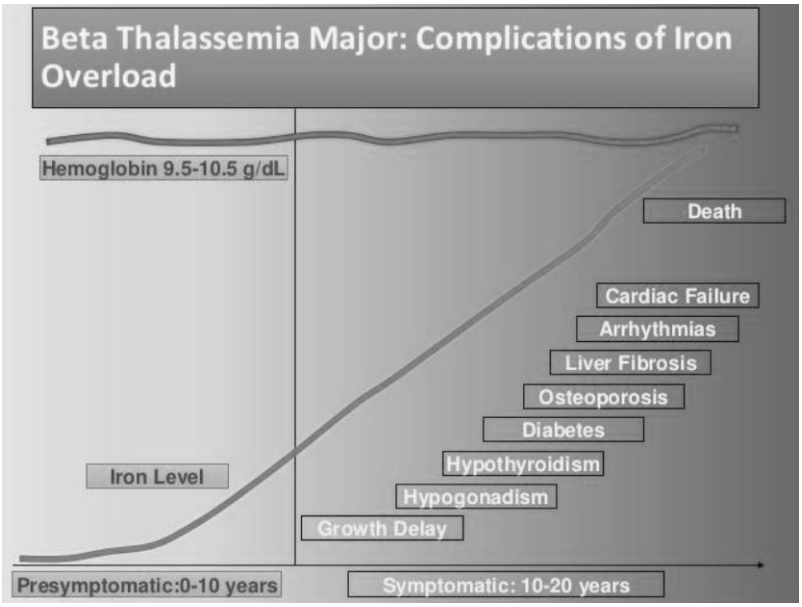
- Dr. Vijay Ramanan

What is the story so far?

Persons with thalassemia trait have a normal life expectancy. Persons with beta thalassemia major live an aver- age of 17 years and usually die by 30 years of age. Most deaths are caused by the cardiac complications of iron overload.

The options available today for Thalassaemia Major are

1) Blood Transfusion---Iron Overload---Chelation---complications



2) Bone Marrow transplant with about 25 to 45 % risk to life and later complications of infertility, secondary malignancies, chronic GVHD, infections

- In India, the largest experience with transplantation for b-thalassaemia is from the Christian Medical College, Vellore; in 106 patients the EFS was 66% in class I patients (n=6), 90% in class II (n=30) and 55% in class III (n=70) at a median follow up of 26 months (range 2–87 months)
- For patients <16 years of age, the probability of survival in classes I, II and III is 95%, 87% and 89%, respectively. Similarly, the event-free survival (EFS) in these classes is 90%, 84% and 64%, respectively.

3) Genetherapy- still a dream

4) Novel Therapy- Life without transfusions with medicines—it CAN NOT REDUCE THE RISK OF PRECEDING IRON OVERLOAD. NO side effects of Bone Marrow Transplant

The only way to prevent Iron related complications is by STOPPING Transfusions.

Many studies were done in field of Hb-F induction.

Wheatgrass was used by Prof R K Marwaha but in a very small study. But people started believing they will be cured by growing wheatgrass in backyard and drinking juice daily. It did not help many.

Then came data of Hydroxyurea with large data from Iran. The promise was realized in few Thalassaemia Intermedia.

I was looking at helping my Graft Failures from allogenic transplants. I had 13 of them. I stumbled about articles be Aguilar Lopez of 2008 on use of Thalidomide for HbF induction. She used a dose of 75 to 100 mg per kg which I thought was too high so I decided to use 5 to 10 mg per kg. So the known side effects would be lower.

The data was interesting so I decided to use it in my patients. One of patient's was a seropositive Thalassaemia Major who had unrelated cord followed by Haploidentical Transplant rescue which failed in 9 months. She had promising response in 4 months and is transfusion independent for over 3 years. Then we got 10 out of our 13 patients.

That's when I thought of using this on non-transplanted Thalasaemia Major patients. The results were better than Hydroxyurea.

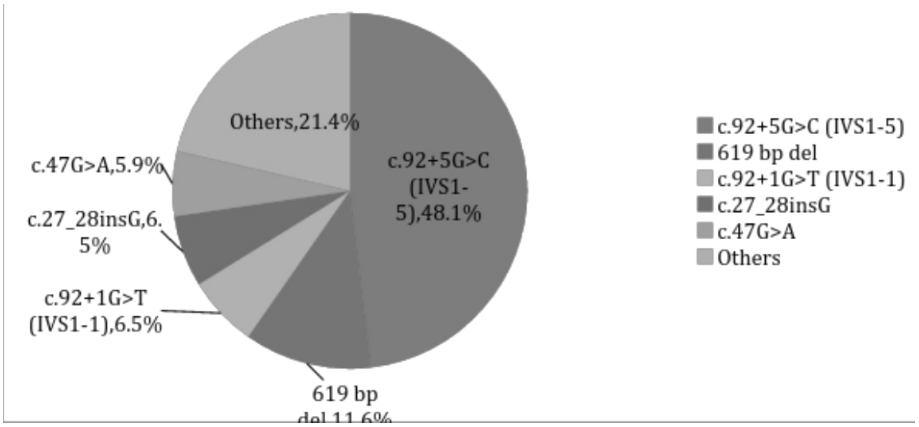
We used our tool called the Thalassaemia Score and found the response to better than Hydroxyurea.

Thalassaemia Cure Score takes into account-

a) First Transfusion – if less than 1= 0; if >1= 1
b) Spleen size- if large=0; if normal/removed=1
c) Use of Deferiprone- if yes=0; if no=1

Score	Hydroxyurea	Thalidomide
3	50%	90%
2-1	30%	60%
0	10%	30%

Today we have over 25 post transplant graft failures cases with 70% response.
Today our data of over 200 patients is analysed with mutation analysis.
We have normal pregnancy by using Hydroxyurea as bridge in Sickle Homozygous.



The response of IVS1-5 has been very encouraging as it's a Beta+ mutaion. XMN polymorphism did not have any influence in our series.

We have also treated Sickle homozygous ; Hb-E diease and Hb-E Beta Thalassaemia with response of over 80% increased hemoglobing.

We have found over 95% incidence of osteoporosis in our Thalassaemia Major cohort due to iron overload.

This therapy need wider usage to get normal quality of life for Thalassaemia Major vis-à-vis save blood for the nation. It could save over 400000 bags per month for the nation. It will prevent Iron induced mortality at young age. It will pave way for easier Thalassaemia patient rehabilitaion.

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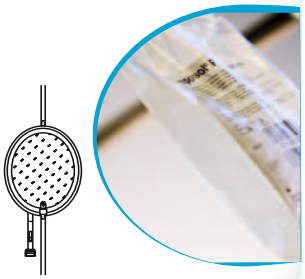

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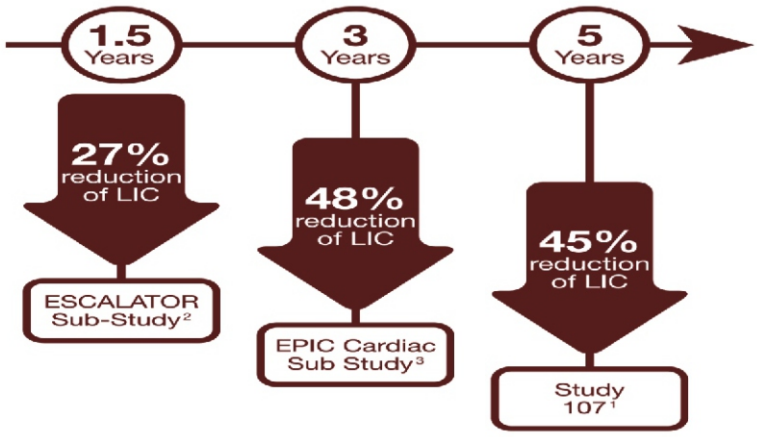
reduction of liver and total body iron overload with long-term Deferasirox treatment in patients of β Thalassemia[1]



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A novel once a day oral iron chelator

They are in your heart, take care of their liver.

The most frequent reactions reported during chronic treatment with Asunra in adult and pediatric patients include gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhea, or abdominal pain), and skin rash in about 7% of patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued. Mild, non-progressive increases in serum creatinine, mostly within the normal range, occur in about 36% of patients. These are dose-dependent, often resolve spontaneously and can sometimes be alleviated by reducing the dose [4]

Pediatric Patients are classified as 2 years and above

1. Cappellini MD, et al. Blood. 2011;118:884-93; 2. Pathare A, et al. Ann Haematol. 2010;89:405-9;3. Cappellini MD. et al.Haematological 2010: 95(4) 557 – 566
4. India package Insert dated 16th Aug, 2013 based on the IPI dated 15th July, 2013

Brief Summary Statement
ASUNRA®
Presentation: dispersible tablets containing 100 mg and 400 mg of deferasirox.
Indications: •for adults and pediatric patients aged 2 years and over with chronic iron overload due to blood transfusions (transfusional hemosiderosis).
Dosage: transfusional iron overload •Starting daily dose recommended initial daily dose is 20 mg/kg body weight. Another 30 mg/kg for patients receiving ≥14 mL/kg/month of packed red blood cells (≥4 units/month), and for whom the objective is the reduction of iron overload; consider 10 mg/kg for patients receiving <7 mL/kg/month of packed red blood cells (<2 units/month), and for whom the objective is the maintenance of the body iron level; for patients already well-managed on treatment with deferoxamine, consider a starting dose of ASUNRA® that is numerically half that of the deferoxamine dose. •50% starting dose reduction in moderate hepatic impairment (Child Pugh B). Should not be used in severe hepatic impairment (Child Pugh C). •Monthly monitoring of serum ferritin for assessing patient's response to therapy. •Dose adjustment if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 to 10 mg/kg, in patients not adequately controlled with doses of 30 mg/kg, doses of up to 40 mg/kg may be considered. In patients whose serum ferritin level has reached the target (usually between 500 and 1000 microgram/L), dose reductions in steps of 5 to 10 mg/kg should be considered to maintain serum ferritin levels within the target range. ASUNRA should be interrupted if serum ferritin falls consistently below 500 microgram/L. •Maximum daily dose is 40 mg/kg body weight.
Administration: ASUNRA must be taken once daily on an empty stomach at least 30 minutes before food. •ASUNRA tablets to be dispersed in water or apple or orange juice.
Contraindications: •Hypersensitivity to deferasirox or to any of the excipients. •Creatinine clearance <60 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal. •High risk MDS patients and patients with other hematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.
Women of child bearing potential, pregnancy, breast feeding and fertility: •Pregnancy: No clinical data on exposed pregnancies are available for deferasirox. Studies in animals have shown some reproductive toxicity at maternally toxic doses. The potential risk for humans is unknown. As a precaution, it is recommended that ASUNRA not be used during pregnancy unless clearly necessary. •Breast-feeding: It is not known if deferasirox is secreted into human milk. Breast-feeding while taking ASUNRA is not recommended. •Fertility: ASUNRA did not affect fertility or reproduction in rat studies even at toxic doses.
Warnings/Precautions: •Caution in elderly patients due to a higher frequency of adverse reactions. •Caution in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function. Monthly monitoring of creatinine clearance, serum creatinine and proteinuria; dose reduction may be needed in some cases of non-progressive increase in serum creatinine; ASUNRA should be interrupted if serum creatinine shows a progressive rise beyond the age-appropriate upper limit of normal. More frequent creatinine monitoring recommended in patients with an increased risk of renal complications. Rare reports of acute renal failure, some of which required dialysis. Reports of renal tubulopathy mainly in children with beta-thalassemia and serum ferritin levels >1,500 microgram/L. •Not recommended in patients with severe hepatic impairment (Child-Pugh C). Monitoring of serum transaminases, bilirubin and alkaline phosphatase: before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. ASUNRA should be interrupted if persistent and progressive unattributable increase in serum transaminases levels. Post-marketing cases of hepatic failure have been reported. •Gastrointestinal irritation may occur. Upper gastrointestinal ulceration and hemorrhage have been reported in patients, including children and adolescents. Multiple ulcers have been observed in some patients. There have been rare reports of fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Caution in patients with platelet counts <50 x 10⁹/L. • Cases of Stevens-Johnson syndrome (SJS) have been reported during the post-marketing period. If SJS is suspected ASUNRA should be discontinued. •Skin rashes: ASUNRA should be interrupted if severe rash develops. •Cirrhotic risk if severe hypersensitivity reaction occurs. •Annual ophthalmological/audiological testing. •Should not be used during pregnancy unless clearly necessary. •Not recommended when breast-feeding. •Must not be combined with other iron chelator therapies. •Product contains lactose.
Interactions: •Should not be taken with aluminium-containing antacids. •Caution when combined with drugs metabolized through CYP3A4 (e.g. ciclosporin, simvastatin), hormonal contraceptive agents, midazolam). •Increases in the dose of Asunra should be considered when concomitantly used with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, mitotane). •Careful monitoring of glucose levels should be performed when repaglinide is used concomitantly with ASUNRA. Interaction with other CYP2C8 substrates like paclitaxel cannot be excluded. •Consider monitoring of theophylline concentration and possible theophylline dose reduction. Interaction with other CYP1A2 substrates may be possible. •Caution when combined with drugs with ulcerogenic potential (e.g. NSAIDS), corticosteroids, oral bisphosphonates) or with anticoagulants.
Adverse reactions: •Very common: blood creatinine increased. •Common: nausea, vomiting, diarrhea, abdominal pain, abdominal distension, constipation, dyspepsia, rash, pruritus, transaminases increased, proteinuria, headache. •Uncommon: anuria, sleep disorder, dizziness, early cataracts, neuropathy, hearing loss, pharyngolaryngeal pain, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, renal tubulopathy (Fanconi's syndrome), pyrexia, edema, fatigue. •Rare: optic neuritis, erythema multiforme, encephalitis. •Adverse drug reactions from post-marketing (frequency unknown): Stevens-Johnson syndrome, acute renal failure, tubulointerstitial nephritis, hepatic failure, leukocytoclastic vasculitis, urticaria, alopecia, hypersensitivity reactions (including anaphylaxis and angioedema), aggravated anemia and cytopenia (relationship with ASUNRA uncertain).
Packs: 5 strips of 6 dispersible tablets.
Before prescribing, please consult full prescribing information available from Novartis Healthcare Private Limited, Sandoz House, Dr. Annie Besant Road, Worli, Mumbai- 400 018, Tel: 022 2495 8888
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