7th National Thalassemia Conference

"Advances in Thalassemia Care"

Saturday, Sunday 19th & 20th April, 2014

organized by

National Thalassemia Welfare Society

&

Department of Haematology AIIMS

in association with

Indian Academy of Pediatrics

at **Jawahar Lal Auditorium**

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

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7th National Thalassemia Conference

"Advances in Thalassemia Care"

Saturday, Sunday 19th & 20th April, 2014

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All India Institute of Medical Sciences

Ansari Nagar, New Delhi - 110029

Organizers

National Thalassemia Welfare Society

&

Department of Haematology AIIMS

In association with

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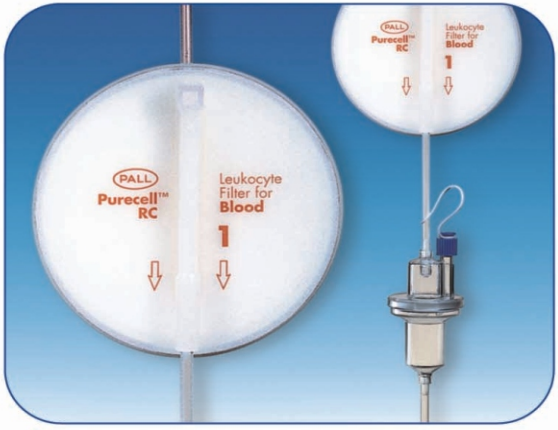

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Leader of Opposition
(Lok Sabha)

सुषमा स्वराज
Sushma Swaraj

28 मार्च, 2014

संदेश

मुझे यह जानकर प्रसन्नता है कि सांतवें नेशनल थैलीसिमिया कांफ्रेस का आयोजन 19 एवं 20 अप्रैल को किया जा रहा है । इस अवसर पर एक स्मारिका का प्रकाशन भी किया जा रहा है ।

थैलीसिमिया एक बेहद गंभीर आनुवांशिक विकार है जिसमें थैलेसीमिक को बार–बार रक्त शरीर में चढ़ाना पड़ता है । इस बेहद गंभीर समस्या का हल खोजने में हमारी सरकार एवं चिकित्सा विज्ञान लगातार प्रयत्नशील हैं । यह आनुवांशिक विकार मॉ–बाप से जन्म लेने वाले शिशु को मिलता है । इसलिए इसका एकमात्र उपचार जागरूकता है ।

कांफ्रेंस एवं स्मारिका की सफलता के लिए मेरी हार्दिक शुभकामनाएं ।

सुषमा स्वराज
सुषमा स्वराज

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ARUN JAITLEY
Member of Parliament
Leader of Opposition
(Rajya Sabha)

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New Delhi-110 001
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March 26, 2014

MESSAGE

I compliment the National Thalassemia Welfare Society and the Department of Haematology, AIIMS who are jointly organizing the 7th National Thalassemia Conference in New Delhi on April 19-20, 2014. Dealing with Thalassemia is going to be a major challenge for health sector in South Asia. Though no data is maintained at national level, but it is estimated that 10,000-12,000 new Thalassemia patients are added every year in India.

Cumulatively it is a huge challenge that government alone cannot address. Therefore, a greater participation of private sector and voluntary organization is called for. Thanks to galloping advances in medical science there is improvement in Thalassemia care & control. I am sure the 7th National Thalassemia Conference will throw up better alternatives/strategies. My best wishes are with the organizers.

(Arun Jaitley)

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Government of India
Department of Health and Family Welfare
Ministry of Health and Family Welfare

MESSAGE

It gives me immense pleasure to know that National Thalassemia Welfare Society is organizing the 7th National Thalassemia Conference in association with Department of Haematology, AIIMS, New Delhi on 19 and 20 April, 2014 at AIIMS, New Delhi.

Thalassemia is one of the most common genetic blood disorders in India. The survival of thalassemics depends upon repeated blood transfusions. The conference is expected to provide the required platform to professionals in the field for delivery of better patient care.

I wish the conference all success.

(Lov Verma)

New Delhi
4th March, 2014

कमरा नं 156, ए-स्कंध, निर्माण भवन, नई दिल्ली-110011
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प्रो० महेश चन्द्र मिश्र
निदेशक

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

संख्या/No.....

दिनांक/Date.....31st March, 2014.....

MESSAGE

I am happy to know that National Thalassemia Welfare Society in association with Department of Hematology, AIIMS is organizing 7th National Thalassemia Conference on 19th and 20th April, 2014. I understand that in this conference many faculty from India and abroad will provide state of art information on "Advances in Thalassemia Care".

Thalassemia is one of the common genetic disorders and it requires a multi-specialty approach for management. That 'Prevention is better than Cure' is best said for Thalassemia. All the doctors including Gynecologists, Pediatricians should make all efforts to prevent this disease and accordingly public awareness about the disease, its prevention, management is to be nurtured and applied with all sincerity.

I wish the event a grand success.

(Prof. M.C. Misra)

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Prof. Narinder K. Mehra
Dean (Research)

MESSAGE

I am delighted to note that the National Thalassemia Welfare Society (NTWS) is organizing their 7th Conference jointly with the All India Institute of Medical Sciences at the Jawaharlal Auditorium of the AIIMS from April 19-20, 2014. NTWS has been associated with us since its inception in 1991 and has been doing a splendid job in creating awareness about the disease both in the society and amongst the experts. It is heartening to note that the society is dedicated for the care and control of Thalassemia by creating facilities for optimum treatment of the disease, educating families and the community, and creating awareness amongst doctors on latest developments in the field.

Survival of a thalassemia major child depends largely upon lifelong blood transfusions, which are beset with several difficulties and complications. Permanent cure lies in hematopoietic stem cell transplantation from an HLA identical sibling donor. Unfortunately, such donors are limited and it is imperative to search for alternate sources by creating voluntary unrelated donor marrow registries. Simultaneously, it is important to create centres of excellence in the country for performing state of the art HLA tissue matching facilities. To that extent, the Department of transplant immunology and Immunogenetics at the AIIMS has been successful in establishing various advanced technologies for providing state of the art tissue typing facilities at the molecular level and make the same available to those who require at the national level. It is critical to develop expertise for performing successful stem cell transplantation using unrelated non-family marrow donors and this will go a long way in providing care to all our Thalassemia patients and in alleviating their suffering. I am confident that with the support and cooperation of everyone including doctors, scientists, families, community and policy makers, this will soon become a reality.

I wish the conference a great success and thank the organizers for their efforts.

New Delhi
April 2, 2014

Prof. N.K. Mehra
Dean (Research)

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THALASSAEMIA INTERNATIONAL FEDERATION
In official relations with the World Health Organization

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Tel.: +357 22 319 129, Fax: +357 22 314 552, E-mail: thalassaemia@cytanet.com.cy

Message from the TIF President, Mr. Panos Englezos
7th International Conference on Thalassaemia
Jawaharlal Nehru Auditorium, AIIMS, New Delhi19-20 April 2014

Dear Friends,

On behalf of the Thalassaemia International Federation (TIF), I would like to say that it is a great honour and a real privilege to address an audience of friends, patients and parents, scientific and medical collaborators and distinguished guests. I take this opportunity to congratulate the organisers, including the President of the National Thalassaemia Welfare Society (NTWS), Dr J. Singh Arora, for their tremendous effort in the organisation of this important educational event. What began as a national event in the past, it has now become a significant bi-annual institution not only nationally, but also regionally. Events of this high calibre serve to spread the current knowledge on the clinical management and prevention of thalassaemia throughout the Indian sub-continent, but also to the neighbouring countries. TIF is indeed honoured to have been invited to participate in this event.

We would like to warmly congratulate the Indian Central and States' health authorities for the many improvements, we are witnessing in the clinical management of haemoglobinopathies provided to our patients in India, through the years, p and for their commitment to include these diseases in the 12th Five Year Plan (FYP).

These observed advances reflect on the improved quality of life of our patients, giving a better chance to live a full and productive life. Indeed, with optimal treatment, there are now no restrictions or limits to the type of activities and exercises these patients can participate in. Patients with thalassaemia prove daily their endurance and their will to strive for the best quality of life. Optimal treatment will enable them to fulfill their goals and dreams. However, there are still many and difficult steps to take in achieving full coverage and access of all patients across India to quality health care. In 2013, TIF embarked on a 3-year project for

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India, in collaboration with the Federation of Indian Thalassaemics and the medical and scientific community of the country, focused on the development of a Charter of Priorities for the Indian Ministry of Health and Welfare, Government of India and eight individualised State Charters, for eight (8) states, namely Maharashtra, Gujarat, Madhya Pradesh, Delhi, Punjab, Haryana, Chandigarh and Uttar Pradesh, included in the project.

The objective of the 'Charters of Priorities' is to identify the needs/gaps in the health care services provided to these patients, and to highlight essential improvements, both at the Central and States' level that, based on international recommendations and guidelines, need to be taken. The compilation/preparation of the 'Charter of Priorities' has been achieved through a collective effort, involving FIT, relevant NGOs, medical/scientific communities and States' officials, to whom TIF is greatly indebted.

The next steps of the project will aim to support and lobby for moving forward the materialisation of the 'Charters of Priorities' to achieve changes, and extend the 'realms of the project' to support other "heavily affected" states.

In light of this information, we would like to encourage the Central Government of India as well as the individual Sates' governments to endorse the above-mentioned Charters. This will serve as the reference starting point towards instigating the implementation of further improvements to the available services, ensuring that all patients with thalassaemia have appropriate and regular access to the best possible treatment, and towards establishing countrywide policies for the prevention of haemoglobin disorders. TIF is ready and very committed to assist in these efforts in every possible way.

We, the thalassaemia worldwide family, must not rely on our governments, alone. It is the duty of the medical community, every association, every club, every parent's group, and every active individual or citizen to do what they can to assist in providing the means to ensure that all patients with these diseases acquire equitable access to quality care. Only then, we can proudly say that 'we have contributed towards a brighter future for our Thalassaemia Family'.

In our long-term work with Thalassaemics India, FIT, the NTWS and other about 14-15

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Thalassaemia Associations members of TIF, but importantly through the representation of India on the Board of TIF, through Mrs Shobha Tuli, and currently through our task force members, including Dr Arora, we have come to evidence the very high level of voluntarism that and academic resources that are present in this country – elements that on their own have achieved most of the advances that we, today, see in this highly populous, but culturally and historically unique country.

TIF has great faith in the sincerity, altruism and competencies of the people of India, its medical community and official health authorities, and will thus continue to invest for a brighter future of our patients and their families. Our guarantee:

"The quality of your soul and the strength of your mind!"

In this context, I would like to encourage each and every one of you to rally behind and fully support the patients associations and FIT, in order to transform them into strong advocates to lead the fight for securing and protecting your rights as patients and human beings.

In ending, on behalf of TIF, I would like to welcome of all you in this highly anticipated, extremely constructive educational event, and we are pleased to count you amongst our members and collaborators. Let us all join our hearts, unite our voices and let us lift our stature to embrace our patients with thalassaemia. Your collaboration is invaluable to our united goal of improving the status of thalassaemia in every country of the world. United we will win!

Unity Is Our Strength!

Panos Englezos
President
Thalassaemia International Federation

National Thalassemia Welfare Society (Regd.)

ORGANISATION FOR AWARENESS OF THALASSEMIA AND TO HELP THALASSEMICS

KG-1/97, Vikas Puri, New Delhi-110018 Ph. : 25507483, 25511795 Fax : 91-11-28543576

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

MESSAGE

It's a matter of pride for us that we are holding our 7th National Thalassemia Conference, in association with Dept of Hematology, AIIMS on Saturday & Sunday 19th & 20th April 2014 at Jawaharlal Nehru Auditorium, AIIMS, New Delhi. We are also organizing a Workshop at UCMS & GTB Hospital on Monday, 21st April 2014.

National Thalassemia Welfare Society has always been in the forefront in disseminating the latest development in the field, among Doctors, Thalassemics & Parents.

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 high cost of the treatment also adversely affects the financial status of the families, so affected.

We have been struggling for long for inclusion of Thalassemia, in the list of Disability for the benefit of People by the Disability Act. The Government has recently introduced bill in Rajya Sabha which includes Thalassemia in the list of Disabilities. We expect this to be passed in the next parliament session as soon as the new Govt. is formed. It will help in improving the status & quality of life of Thalassemics.

I appreciate the efforts of my Colleagues, Sponsors, Delegates and distinguished International & National Guest faculty, for their help in organizing the 7th National Thalassemia Conference and also making it a success.

Surrendar Saini

(Km. Surrendar Saini)

PROGRAMME

Registration : 8AM to 9AM

DAY 1, Saturday 19th April 2014

S. No.	Topic	Speaker	Minutes	Timings	Chairperson
	Session I Diagnosis and Transfusion				
1.	Diagnostic Enigma : Clinical	Dr. VIP Viprakasit	20	9:30 to 9:50am	Dr. Mausumi Swami Dr. Neelam Sood Dr. Kirti Nanal
2.	Diagnostic Enigma : Laboratory	Dr. H. Pati	20	9:50 to 10:10am	
3.	Dus Ka Dum/Power of Ten	Dr. A.P. Dubey	20	10:10 to 10:30am	
4.	Alloimmunisation	Dr. V.P. Choudhry	20	10:30 to 10:50am	
	Innauguration Ceremony & Breakfast			**10:50 am to 12:00 Noon**	
	Session II Chelation	Sposored by NOVARTIS Oncology			
1.	Monitoring of Iron Overload	Dr. Amita Mahajan & Dr. J.S. Arora	30	12:00 to 12:30pm	Dr. J.M. Khunger Dr. C.B. Das Gupta Dr. Alka Mathur
2.	Is Old Still Gold	Dr. Praveen Sobti	20	12:30 to 12:50pm	
3.	Oral Chelation	Dr. Maria D Cappellini	30	12:50 to 1:20 pm	
4.	Combination Options	Dr. Sunil Gomber	30	1:20 to 1:50 pm	
	Lunch			**1:50 pm to 2:40pm**	
	Session III Transfusion transmitted Infections				
1.	Narrowing the window/ How safe blood is secured	Dr. M. Angastiniotis	20	2:40 to 3:00pm	Dr. Neelam Mohan Dr. S. L. Broor Dr. Veena Doda
2.	Natural History and Treatment of Hep B and Hep C	Dr. S. K. Sarin	30	3:00pm to 3:30pm	
	Session IV Splenectomy				
	Splenectomy When+ Why	Dr. Maria D Cappellini	30	3:30 pm to 4:00pm	Dr. R. K. Gupta Dr. Bharat Singh

	Session V Entering the Adulthood	Sponsord by SUN Oncology			
1.	Cardiac Complications in Thalassemia Major and Intermedia	Dr. Vikas Kohli	20	4:00 to 4:20pm	Dr. D. D. Golani
2.	Monitoring of Thalassemics	Dr. Rajeev Bansal	30	4:20 to 4:50pm	Dr. Mrs. J. Sardana
3.	Need for multidisciplinary care	Dr. M. Angastiniotis	20	4:50 to 5:10pm	Mrs. Shobha Tuli
4.	Sweet 16, Crossing the bridge	Sangeeta Wadhwa, Mukesh Agarwal Dr. Rimjhim Bakshi, Dr. J.S. Arora	40	4:50 to 5:30pm	
	TEA			**05:30pm**	

Day 2, Sunday 20th April 2014

S. No.	Topic	Speaker	Minutes	Timings	Chairperson
	Session VI Meet the Expert Session				
	Auditorium- Chelation	Dr. Cappellini & Dr. V. P. Choudhry	60	8.00 to 9.00am	
	Conference Hall- Diagnostic Challenges TM and TI, Transfusion	Dr. Vipraksit & Dr. Jagdish Chandra	60	8.00 to 9.00am	
	LT- BMT, MUD, CBT, HU	Dr. V. K. Khanna & Dr. Dinesh Bhurani	60	8.00 to 9.00am	
	Session VII Roll on to control				
1.	Approach to antenatal diagnosis	Dr. Madhulika Kabra	30	9:00 to 9:30am	Dr. Seema Kapoor
2.	Thalassemia Control Programme	Dr. Sujata Sinha	20	9:30 to 9:50am	
3.	Carriers Diagnosis	Dr. I. C. Verma	20	9:50 to 10:10 am	Dr. Suman Mendiratta
4.	Antenatal Diagnosis	Dr. Sangeeta Gupta	20	10:10 to 10:30am	Dr. N.V. Kamat
5.	Cordocentesis	Dr. Renu Saxena	20	10:30 to 10:50am	
	Session VIII Intermedia Care, Equal Share				
1.	Medical Treatment of Thalassemia Intermedia	Dr. Prantar Chakrabarti	30	10:50 to 11:20am	Dr. Rahul Naithani
2.	Thrombophilic Complications	Dr. V. K. Khanna	30	11:20 to11:50am	Dr. Anupam Prakash

	Session IX Teens to Kings and Queens				
1.	Growth and Puberty	Dr. Anju Seth	30	11:50pm to12:20pm	Dr. Sangeeta Yadav Dr. Radhika A.G. Dr. Rita Ranjan
2.	Bone Disease in Thalassemia	Dr. Rashid Merchant	20	12:20pm to12:40pm	
3.	Diabetes & Thyroid in Thalassemia	Dr. Anju Virmani	30	12:40pm to 1:20pm	
4.	Fertility & Pregnancy in Thalassemia Major & Intermedia	Dr. Vatsala Dadhwal	30	1:20 pm to 1:50pm	
	Lunch			**01: 50 to 02:50pm**	
	Session X Cure				
1.	Stem Cell Transplantation Indications and how it can be supported	Dr. Vikram Mathew	30	2:50 pm to 3:20pm	Dr. Rahul Bhargva Dr. Inusha Panigrahi Dr. N. K. Mehra
2.	Life after BMT/ Impact of Transplant	Dr. Ajay Sharma (Brig.)	30	3:20pm to 3:50pm	
3.	Developments in Gene Therapy	Dr. M.B. Aggarwal	30	3:50pm to 4:20 pm	
	Question Answer Session / Valedictory Function			4:10 pm to 5:20 pm	
	Day 2, Sunday 20th April 2014 Doctor's Session			**01: 50 to 02:50pm**	
S. No.	**Topic**	**Speaker**	**Minutes**	**Timings**	**Chairperson**
	Doctor Session I NTDT	Sposored by NOVARTIS Oncology			
1.	Natural History/ Molecular Aspect of NTDT	Dr. VIP Viprakasit	30	9:30am to 10:00am	Dr. Gaurav Kharya Dr. Rekha Harish Dr. K.K. Kaul
2.	Medical Treatment of NTDT including BT and Chelation	Dr. V.K. Khanna	30	10:00am to 10:30am	
3.	Complication of Thalassemia Intermedia	Dr. M.D. Cappellini	30	10:30am to 11:00am	
	Doctor Session II Thalassemia Major	Sposored by CIPLA			
4.	Overview of Thalassemia Major management	Dr. V.P. Choudhry	30	11:00 am to 11:30am	Dr. M. Angastiniotis Dr. Bhavna Dhingra
5.	Switchover - Paediatrician to Physician	Dr. Jagdish Chandra	30	11:30am to 12:00pm	
6.	NTDT Indian Scenario	Dr. Prantar Chakrabarti	30	12:00 pm to 12:30 pm	
7.	Infections in Transplant	Dr. Dinesh Bhurani	30	12:30pm to 1:00 pm	
8.	Debate Cure vs Care	Dr. Dharma & Dr. V.P. Choudhry	30	1:00pm to 1:30pm	

The 7th National Thalassaemia Conference

Parallel Workshop for Patients Capacity Building 19th Apr 2014

Conference Hall AIIMS, near Jawahar Lal Auditorium

Session A. The Associations

Chairperson: Dr. Madhuben R. Naik

1. The role of national patient support associations in promoting services
   Mrs. Shobha Tuli 3:00-3:20pm

2. The work of TIF and its role in promoting the rights of patients with Haemoglobin disorders
   Dr. M. Angastiniotis 3:20-3.40 pm

Session B. How competent organisations can contribute to service Development

Chairperson: Rtn. Pankaj Tanna

1. Strengthening associations, alliances: the need for a united voice; government advocacy
   Vinay Shetty 3:40-4:00pm

2. Challenges faced by thalassemics in education, employment & marriage
   Lily Cannon 4:00-4:20pm

Session C: Panel discussion

Coordinator: Lily Cannon

Panel: Dr. Praveen Sobti: Ashok Khatuja: Pankaj Tanna 4:20 - 4:50pm

Workshop on Thalassemia

Monday 21st April 2014

Library Block, UCMS & Guru Teg Bahadur Hospital,

Dilshad Garden, Delhi-32

PROGRAMME

Breakfast **9:00am to 9:30 am**

1 Diagnostic Challenges

(a). Patient has been transfused before the diagnosis is made.

Dr. Satender Sharma 9.30am-9.50am

(b). Late diagnosis of Thalassemia Major (>3 years) vis a vis Thalassemia Intermedia

Dr. Seema Kapoor 9.50am-10.10am

2 Transfusion & Chelation

(a). Shifting from lower transfusion to hyper transfusion

Dr. S. Sudha 10.10am-10.30am

(b). When to start transfusion and chelation in Thalassemia Intermedia?

Dr. V. K. Khanna 10.30am-10.50am

(c). Combining chelators How and when?

Dr. Sunil Gomber 10.50am-11.10am

TEA **11:10 to 11:30am**

3 Monitoring

(a). Monitoring of Thalassemia Intermedia

Dr. V. P. Choudhry 11.30am-11.50am

(b). Bone deformity (Disease or chelator complication)

Dr. Jagdish Chandra 11.50am-12.10pm

4 Growth

(a). Optimum Growth with Optimum Chelation 12:10pm-12:30pm

Dr. Rajni Sharma

(b). Arrested Growth and puberty inspite of adequate transfusion & Chelation

Dr. Rajni Sharma 12:30pm-12:50pm

5 Transplantation

(a). When and How to plan Transplantation (Best age for transplantation and preparation, pre transplantation)

Dr. Dinesh Bhurani 12:50pm-1:10pm

(b). Post Transplant care

Dr. Rahul Naithani 1:10pm-1:30pm

Lunch **1:30 pm**

BIO-DATA SPEAKERS

Dr. Ajay Sharma (Brig.)
Head, Deptt. of Clinical Haematology and stem cell transplantation, R & R Hospital, Delhi Cantt. He has special interest in Haematology & Oncology

Dr. Amita Mahajan
Sr. Consultant – Pediatric Hematology-Oncology Indraprastha Apollo Hospital, New Delhi. She is MD (Paediatrics) AIIMS (1992), MRCP (UK) (1996), MRCPCH (Founder Member), CCST (Dual Accreditation in Pediatrics & Pediatric Oncology) (1992), PALS Instructor (1998). She received "Sorel Catherine Freymann Award" for the Best Postgraduate in Paediatrics for the year 1992.

She is member of Royal College of Paediatrics & Child Health, UK Children's Cancer Study Group, International Society of Paediatric Oncology and Indian Academy of Pediatrics

At Apollo hospital she has set up a Pediatric Hematology Oncology service and also a thalassemia unit in association with the Dept of Transfusion Medicine.
She has made numerous presentations at the national and international platforms. She has been invited for presentations and guest lectures at a wide variety of platforms in the country. She has innumerable publications in National and International journals and has written many chapters on haematology and oncology in various books

She has been consultant Pediatric Oncologist (Llandough Hospital, Cardiff).
She is medical advisor to Thalassemics India, Foundation against Thalassemia and Cankids

Dr Anju Seth
Professor of Pediatrics & In-charge Division, of Pediatric Endocrinology, Lady Hardinge Medical College & associated Kalawati Saran Children's Hospital, New Delhi. She has been providing endocrine care to children & adolescents with thalassemia for >10 years

Dr. Anju Virmani

Senior Consultant Diabetologist & Endocrinologist, Apollo, Max, Pentamed & SL Jain Hospitals, Delhi

She did her MD, DNB Endocrinology (AIIMS). She has written 15 chapters in books, several original & review articles and abstracts. Her special interest is in type 1 diabetes and neonatal thyroid screening.

She has been chairperson, Pediatric Endocrine Chapter of IAP, founder President of ISPAE (Indian Society for Pediatric and Adolescent Endocrinology), founder editor of ISPAE Newsletter, Educational ambassador South Asia, International Society for Pediatric & Adolescent Diabetes, member editorial board, Italian J of Pediatrics & International J of Pediatric Endocrinology.

She participates in monthly thalassemia camps at Faridabad since 2003.

Dr. A. P. Dubey has a teaching and research experience of over 35 years after passing MD (Pediatrics) from Gandhi Medical College, Bhopal,

Dr. A. P. Dubey is presently working as Director-Professor and Head, Department of Pediatrics at the prestigious MAMC & associated Lok Nayak Hospital, New Delhi. He is executive editor of Indian Pediatrics, the official journal of IAP and Chairperson of Nutrition chapter of IAP. He had been President of IAP, Delhi state, Convener and Chairperson of IAP Committee on Immunization, Executive member of IAP. He has been awarded Commonwealth Fellowship in Pediatric Hematology at The Children's Hospital Sheffield (UK) in 1993 and Delhi State Doctor's Award in 2011.

Dr Dubey started the Thalassemia Unit at Lok Nayak Hoapital in 1996. He is also the chief investigator for Delhi Govt. project on “Antenatal screening of mothers for thalassemia”. Under his leadership, Department of Pediatrics at LokNayak Hospital has established a Pediatric Research and Genetics Laboratory, the only such laboratory under Delhi Govt.

Dr. Dubey has published over 75 research papers in various International and National indexed journals and edited 2 books and written several chapters in various books.

Dr. **Dharma Ram Choudhary** did his MD Medicine from Dr. SN Medical College, Jodhpur, Rajasthan and DM clinical haematology from AIIMS. He is Senior Consultant and 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, New Delhi. He got his Clinical Hematology training from CMC Vellore, India and under Leukemia/BMT program of British Columbia, Vancouver General Hospital and BC Cancer Agency, Canada.

He started Allogenic Bone Marrow Transplant program at Sir Ganga Ram hospital and Dr. BL Kapur Memorial Hospital, New Delhi and has done more than 200 Allogenic Bone Marrow Transplantation and 50 Autologous Stem Cell Transplantation on both pediatric and adult patients. He has published 21 research papers, 4 chapters in books and presented 18 papers.

Dr. Dinesh Bhurani, Senior Consultant, Haemato-oncologist working as Chief of Haemat-oncology Services from 2007 in Rajiv Gandhi Cancer Institute & Research Centre, Delhi. He is the Chief of Bone Marrow Transplant Unit. He did 67 stem cell transplants in 2012 and completed more than 250 transplants so far.

Dr. Bhurani completed DM Haematology from CMC, Vellore and did FRCPA from Royal College, Australia He has worked as a Consultant in CMC Vellore and Associate Consultant, Chairman at Sir Ganga Ram Hospital, New Delhi. He is a part of Indian Society of Haematology and Blood Transfusion and also The Royal College of Pathologist of Australia. He has been Principal Investigators for different clinical trials based on Lymphoma, Myeloma and CLL and has been Co-Investigator into many of the Medical Oncology Trials since 2007.
He devotes his precious time for the welfare of thalassemia by regularly visiting at thalassemia clinic organised by National Thalassemia Welfare Society.

Dr. H. Pati is Professor of Hematology at AIIMS, New Delhi. He has more than 150 publications to his credit, of which more than 70 are in International journals. His field of work include platelet functional disorders, splanchnic vein thrombosis, enzymopathy and flowcytometry. He has been General Secretary, ISHTM.

Dr. I. C. Verma is currently Director, Center of Medical Genetics at Sir Ganga Ram Hospital, New Delhi. He was earlier Professor of Pediatrics and Genetics in AIIMS, New Delhi. He trained in genetics in UK, USA & Switzerland. He is Fellow of Royal College of Physicians, London, American Academy of Pediatrics and National Academy of Medical Sciences, New Delhi. He has received a number of national awards - Indian Council of Medical Research, National Academy of Medical Sciences, and BC Roy Medical Council of India award. He has been an adviser in genetics to W.H.O. in Geneva, and currently advises the SEARO office regarding birth defects and thalassemia. The Genetic center offers the most comprehensive molecular and prenatal diagnostic program in the country.

Dr. Jagdish Chandra MD, FIAP

Director Professor of Paediatric, In-charge, Paediatric Haematology, & Thalassemia Day Care Centre, Programme Director, Paediatric Centre of Excellence (HIV), Kalawati Saran Children's Hospital and Lady Hardinge Medical College, New Delhi.

He has 44 publications in International Journals and 94 in National Journals.

Dr. J. S. Arora did his MSc in Haemoglobinopathy from University College London and Training course on Haemoglobin Disorders at Belgium. He is Founder President, National Thalassemia Welfare Society (established 1991), General Secretary, National Thalassemia Welfare Society since 1994, Founder General Secretary, Federation of Indian Thalassemics since 1994. He has been instrumental in establishing many new Thalassemia associations in India.

He is PFPS (Patients For Patient Safety) Champion since 2007 under Patients for Patients Safety programme of SEARO, WHO. Member, Ethics Committee IIT Delhi. He has been Co-ordinator, Thalassemia Cell, DHS Govt. of Delhi, Member, Hospital Advisory Committee, DDU Hospital and Member Delhi State VAT Advisory committee, Govt. of Delhi.

He has received "Life Time Service Award" from PHO Chambers of IAP.

He is Co-Author of the Books "Care & Control of Thalassemia: In the New Millennium" 2000

and "Perspectives in Thalassemia" 1994 and executive editor of the "National Thalassemia Bulletin".

Dr. Michael Angastiniotis – TIF Medical Advisor

Dr. Michael Angastiniotis graduated in Medicine from the University of Aberdeen (Scotland) in 1966, and obtained his DCH (Diploma in Child Health) in Paediatrics in 1976 from the Royal College of Physicians of Glasgow. He did various courses, such as Thalassaemia (Biochemistry – Prenatal-diagnosis), Genetics, and Haematology/Oncology in UK.

Dr . Angastiniotis has been a member of the Thalassaemia Control Programme.
Dr. Angastiniotis is also Special Advisor and Consultant for the control of Haemoglobinopathies in the Eastern Mediterranean region. He is member of the Board of Directors of the Cyprus Institute of Neurology and Genetics, and of the WHO Expert Advisory Panel on Human Genetics. He has published a great numberof scientific articles, including on Haemoglobinopathies Until retirement, Dr Angastiniotis was Director of the Paediatric Department of Archbishop Makarios III Hospital and the Thalassaemia Centre. Since 2004, he has been employed by TIF as Medical Advisor.

Dr. Madhulika Kabra, Professor, Genetics division, Department of Paediatrics**,** AIIMS, New Delhi. Her centre has been designated as a WHO Collaborating Centre and recognized by Government of India Centre of Excellence for training in Genetics. She has 200 publications in Indexed Journals and 25 chapters in books**.**

She is president, Genetics chapter of Indian Academy of Paediatrics, Secretary Indian society of Inborn Errors of Metabolism, Joint Secretary, Society of Fetal Medicine, Member of the Board of directors of Asian Society for Inherited Metabolic Diseases, Member Task force for Anatomy, Anthropology & Haematology – ICMR, Member Task Force Human genetics ICMR, Member, Editorial Board of Indian Journal of Paediatrics.

Dr. Maria Domenica Cappellini, MD, FACP, FRCP

Dr. M. Cappellini qualified as an MD in 1974 at the University of Milan, Italy. She is Professor of Internal Medicine at the University of Milan and Chief of the Internal Medicine Department and of the Regional Rare Disease Centre at the Policlinico Foundation, Milan Italy.

Dr. M. Cappellini has been active in the fields of thalassaemia, haemoglobinopathies, and the haem biosynthetic pathway for over 30 years. She has published a large number of peer-reviewed original articles. She contributed to the characterization of the molecular defects of thalassemic globin genes in Italy; she defined the genotypes of Italian patients with thalassaemia intermedia that became nationally important for prenatal diagnosis. Professor Cappellini focused on the phenotypic expression of thalassaemia major and intermedia and evaluated the genotype-phenotype relationship.

She identified the mechanisms underlying the thrombotic risks in thalassaemia intermedia. She is involved in clinical trials for new iron chelators.

Professor Cappellini is President of the European Federation of Internal Medicine (EFIM). She is a member of many International Hematology Associations. She is scientific adviser to the Thalassaemia International Federation (TIF) and contributes to their meetings to establish guidelines for the clinical management of thalassaemia.

Mr. Mukesh Agarwal
He is a parent of a Thalassemia Major child. He has been actively involved inTIF capacity building project in 2013.

Dr. M. B. Agarwal, Head, Department of Haematology, Bombay Hospital Institute of Medical Sciences, Mumbai. Ex-President - Indian Society of Haematology (2009-10) President - Mumbai Hematology Group (2013-14).

Dr. Prantar Chakrabarti did his MD & DNB in General Medicine and DM in Clinical Haematology from AIIMS, New Delhi. He is the recipient of many national and international accolades including Royal College of Physicians International Bursary, Harold Gunson Fellowship, and Marie Curie Action Fellowship.

Dr. Chakrabarti has received specialised training in Ethics of Human Subject Research, Biostatistics from Johns Hopkins University Baltimore, and Stem Cell Transplantation from King's College, London. Dr. Chakrabarti also has many successful research projects (including multicentric ones) to his credit.

Dr. Chakrabarti has a special interest in Haemopoietic Stem Cell Transplantation, Thalassaemia, and Translational Research. He is recipient of many awards including "Best Oral Presentation Award" at the ESO Inside Track Conference on "Leukaemias: Molecular Insights to Treatment Paradigms" at Mumbai [March 2008].

Dr. Praveen C. Sobti
MD, DCH, Fellow of the International Medical Sciences Academy, Visiting fellow, Royal College of Paediatrics & Child Health, London, Diplomate on Paediatric Environmental Health, Athens.

Formerly Professor of Paediatrics, In-charge Hemato-Oncology, Dayanand Medical College & Hospital, Ludhiana Member of various national and international societies and author of 25 chapters.

She developed state-of-the-art medical care centre at DMC Ludhiana. She is recipient of many awards including Honorary Mayor President of Baton Rouge, Louisiana State, USA

She is founder member of Punjab Thalassemia Welfare Society and Arpita Cancer Society and member National Advisory Board on Thalassemia, Global Advisory Board on Thalassemia & Middle East, and ICET International group on Endocrine Complications in Thalassemia. She is member of the editorial board of Italian Journal of Adolescent Medicine.

Dr Rahul Naithani has done his MD paediatrics from LHMC and Kalawati Saran Children Hospital, New Delhi and DM in clinical haematology from AIIMS. Fellowship in Bone Marrow Transplantation and paediatric haematology oncology from The Hospital for Sick Children, Toronto, Canada. Currently he is consultant in charge Haematology and Bone Marrow Transplantation, Max Hospital Saket and Patparganj.

He has presented various papers at International and National conferences and contributed in various articles published in National & International journals Contributed in chapters in three books

He is member of American Society of Pediatric Hematology Oncology (ASPHO) Children's Oncology Group (COG), IAP – Pediatric Hematology Oncology Chapter, Indian Society of Hematology and Transfusion Medicine (ISHTM) and Delhi Society of Hematology.

Dr. Rajiv Kumar Bansal M.D. FIAP is a Consultant in Pediatrics at Santokba Durlabhji Hospital the largest multispeciality private hospital of Rajasthan with DNB accreditation.

He has more than 36 publications to his credit and has presented papers and chaired sessions at various National and International conferences. He is presently the editor of SDMH Journal, an indexed journal. He is also In-charge of Thalassemia unit, at SDMH, was trained at Cyprus and has actively worked in organizing the thalassemics at Jaipur.

He was recently elected President of Rajasthan state branch and also Jaipur branch of NNF.
He was awarded fellowship of Indian Academy of Pediatrics (FIAP) in 2010.

Dr. Rashid Merchant, a well known senior pediatrician in Mumbai, is passionately involved in the care of children, especially those affected by HIV/AIDS and thalassemia.

He was previously the dean and professor of pediatrics (Mumbai University) at the B.J. Wadia Hospital for Children, Mumbai.

He has been Honorary Consultant Pediatrician at the B.L. Nanavati Hospital, Mumbai, where his special area of interest has been the care of thalassemics.

Dr. Renu Saxena has done her MD from AIIMS and is currently Prof. & Head Dept. of Hematology, AIIMS. Her major interest has been in Hemostasis, including coagulation disorders, platelet disorders, Thrombosis, Leukemia, Molecular Genetics and quality assurance.

She has more than 300 publications in National and International Journals. She has more that 30 funded research projects and is member of editorial boards of many national and international journals.

She is recipient of J.B. CHATTERJEE memorial oration by the Calcutta School of Tropical Medicine, 2011, Kshanika oration award by ICMR, 2009, Life time achievement award in Hematology by Mumbai Hematology Group, 2009 , BGRC Silver Jubilee Oration Award by ICMR and many more.

Dr. Rimjhim Bakshi is thalassemia major on regular transfusion with positive approach, strong will power and ability to handle bouncy situations. she did her BDS from Institute of Dental Sciences, Jammu. She is polite & soft spoken but enjoy working under stressful conditions

She has conducted camps in various rural areas on health education programmes and actively participated in camps organized by J & K Thalassemia Welfare Society.

Dr. Sangeeta Gupta, Professor, In-charge, Fetal Medicine Clinic , Obs & Gynae, Maulana Azad Medical College, New Delhi

She was awarded Commonwealth Scholarship in 2007 and trained in Fetal Medicine at St.Georges Hospital, London

She has edited textbooks & contributed chapters in various textbooks of Obs & Gynae & has publications in national & international journals.

Ms. Sangeeta Haridas Wadhwa has done Bachelor's Degree in Management Studies from SNDT University, Mumbai and post graduate diploma in Counseling Psychology from Prafulta Don Bosco Mumbai. She is Public Relation Officer and counsellor at Shri Hashu Advani Memorial foundation Healthcare & Thalassemia center, Chembur, Mumbai.

She is founder member of 'YTA' Youth Thalassaemic Alliance, an alliance of young

Thalassaemic founded with the objective of spread awareness among Thalassaemic patients on various aspects including Healthcare, Medication & Counseling them on Education & Career, Matrimony, etc. She is Member of Thalassemic India, Mumbai Thalassemia Society, National Thalassemia Welfare Society.

Prof. (Dr.) S. K.Sarin, MD, DM, DSc, FNA, FNASc

Prof. S.K. Sarin, is a Senior Professor of Hepatology and Director, Institute of Liver and Biliary Sciences (ILBS), New Delhi. He was instrumental in the establishment of ILBS through the Govt of Delhi, the first Deemed to be University in the field of Liver and Biliary Diseases globally. He is pioneer in clinical protocol innovations. He is Adjunct Prof. Molecular Medicine, JNU. New Delhi, Honorary Professor, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore.

He has made outstanding contribution in the pathogenesis and management of bleeding in liver diseases and helped define new entities; "Acute on Chronic Liver Failure" and "Portal Biliopathy". He has published over 360 original articles in prestigious journals and edited 9 books. He led the development of five major global guidelines for the Asian Pacific Association for the Study of the Liver (APASL). These are widely quoted and practiced.

He was awarded the Padma Bhushan in 2007 and the Most Distinguished Physicians from India by American Association of Physicians of Indian origin USA and many more.

He is the founding Chief Editor of a prestigious international Journal, Hepatology International. He was nominated Chairman of the Medical Council of India (MCI), 2010-2011. He developed the 'Vision 2015' document for Medical Education in India and introduced far reaching reforms in medical education and health sciences.

Dr. Sudha Sreedharan did her MD from MAMC in 1990**.**

She is working in the Dept of Pediatrics at LokNayak Hospital and has been associated with the Thalassemia Unit at LN Hospital since it's inception in 1996

Dr Sujata Sinha, is MD (Pathology) from BHU. Currently she is technical consultant, Action on Birth Defects Project, National Rural Health Mission,

UKHFWS, Directorate, Medical Health & Family Welfare, Dehradun, Uttarakhand and Associate Adjunct Professor, Centre for Comparative Genomics, Murdoch University, Perth, Australia.

She has many publications on thalassemia and haemoglobinopathies in International journals

She has been awarded 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

She is part of the National RBSK (Rashtriya Bal Swasthya Karyakram) team of resource persons, contributing in developing guidelines and resource material for RBSK.

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.

He is Fellow Indian Academy of Pediatrics (FIAP).,WHO temporary adviser & National faculty for integrated management of child hood & neonatal illness (IMNCI). He is Author of various chapters in text books of Pediatrics.

Has around 60 Publications in International & National reputed Journals.

Dr. Vatsla Dadhwal
She is Prof Obs and Gynae AIIMS with special interest in fetal medicines. She has lot of publication to her credit in National and International Literature.

Dr.Vikas Kohli MD (Pediatrics) practised Pediatric Cardiology in Florida, USA. He has been Director of Pediatric Cardiology at RTIICS, Kolkata; and In-charge of Non-Invasive Lab, Sir Ganga Ram Hospital.

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He has been awarded Best Research in Pediatrics Award by IAP, 1991 & Best Research Award in 1996 at the University of Miami; American Heart Association/Genentech Award 1996. Dr. Kohli is Fellow, American College of Cardiology, Diplomate American Board of Pediatrics, American Board of Pediatric Cardiology. He has more than 50 publications. He has written more than 5 chapters. He is currently on the Board of Editors for 3 Journals and reviewer for 5 Journals.

Dr. Vikram Mathews did his M.D. Medicine in 1996 and DM Clinical Haematology in 2001 from Christian Medical College and Hospital, Vellore. He is currently working as Professor in the Department of Haematology at the CMC Hospital, Vellore. He got his fellowship in BMT and Leukemia, Washington University, USA, 2004. He has received best oral presentation award. Asia Pacific BMT meeting, Thailand 2010. He is reviewer of Indian Journal of Haematology and Transfusion, Indian Journal of Medical Research. He is involved in publication of 71 manuscripts and 3 text book chapters. Invited faculty at various national and international conferences**.**

He is member of Indian Society of Haematology and Blood Transfusion, American Society of Hematology and American Society of Blood and Bone Marrow Transplantation.

Dr. Vip Viprakasit

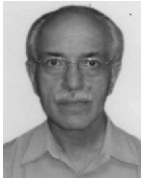
Dr Vip Viprakasit did his paediatric haematology at Mahidol University and D. Phil in molecular medicine at the University of Oxford, UK, where he was awarded a doctorate degree.

He did his fellowship in molecular haematology at the Weatherall Institute of Molecular Medicine, Oxford, UK. He is currently Associate Professor in haematology and has also been Programme Director for thalassaemia research at Siriraj-Thalassaemia CenterBankok.
He is running a research group focusing on molecular genetics in human diseases, in particular, thalassaemia.

Dr. V. K. Khanna is a Senior Consultant Pediatrician and Chairman Department of Pediatrics, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi. Dr Khanna is also in-charge of the PreetiTuli Thalassemia Unit at the hospital. He is Vice President of Thalassemics India.

He has organized many national and international conferences, workshops, seminars and check-up camps for thalassemia.

Dr. Khanna has been invited as speaker and chairperson to international and national conferences on thalassemia, and has presented many scientific papers. He has also authored chapters in books on hematology and hemoglobinopathies and published several papers on thalassemia.



Dr. V. P. Choudhry did his MD (Pediatrics) in 1972 from AIIMS. Dr. Choudhry is presently working Director, Sunflag Pahuja Centre for Blood Disorders, Sunflag Hospital Faridabad and hematology division at Paras Hospital, Gurgaon. Formerly he was Professor and Head Department of Hematology, AIIMS Delhi, Director- Indira Gandhi Institute of Child Health Kabul, Afghanistan and Medical Advisor- Armed Forces Medical Services**.**

He was President – Indian Society of Hematology & Transfusion Medicine, Delhi Society of Hematology and Chairperson- Pediatric Hemato-Oncology IAP.

He is medical advisor to Federation of Indian Thalassemics and National Thalassemia Welfare Society. He regularly provides free consultation at NTWS Thalassemia Centre.

Fellowship

Indian Society of Hematology & Transfusion Medicine, Indian Academy of Clinical Medicine, International Medical Science Academy and Indian Academy of Pediatrics.

He has innumerable awards to his credit including Dr J.G. Parkeh Oration by ISHTM, 2012, Lifetime achievement award by IAP, 2008, Prof. SK Sood Oration by DSH, 2006 and Dr. B.N. Dara Award by National Thalassemia Welfare Society, 2001 and many more.

Bio-Data Chairpersons

Dr. Alka Mathur graduated from LHMC in 1979 and got training in Hematology at AIIMS. She established Thalassaemia Day Care Center at Hindu Rao Hospital in 2004 and is currently in-charge of the Center.

Dr. Anupam Prakash did his M.D (Medicine) in 2000. He is Associate Professor, Department of Medicine, LHMC & Associated Hospitals, New Delhi. He is In-charge, Thalassemia Unit, Dept. of Medicine, LHMC, since 2007. He is member, Thalassemia Welfare Board, Standing Medical Board and Scientific Committee, LHMC & associated hospitals.

He has 102 articles in journals and contributed in 50 chapters in books to his credit. He is editor of API Text book of Medicine 9th Edition.

Dr. Bharat Singh did his MD Pathology from LHMC, Delhi and Certificate Course in Transfusion Medicine Belfast U. K. 1991.

He is Medical Superintendent DDU Hospital and Honorary Director State Blood Transfusion Council, Govt. of NCT of Delhi.

He received State award by Govt. of Delhi for meritorious service in Health Care in Delhi 2000. He has innumerable publications in scientific journals and published a book "Hand book of Transfusion Medicine"

Dr. Bhavna Dhingra

She is Associate Professor, Department of Pediatrics, AIIMS Bhopal.
She has been a Senior Research Associate in the department of Haematology at AIIMS, New Delhi, and Assistant Professor (Pediatrics) at Kalawati Saran Children's Hospital, New Delhi.

Dr. C.B. Dass Gupta, MD is senior consulting Pediatrician & Head Department of Pediatrics Acharya Children Hospital, Kota (Rajasthan). He has been President IAP Hadoti Branch Kota and founder member Care Of Thalassemics in Rajasthan. He has been editorial board member lndian Pediatrics, IJPP, Indian Journal of Pediatrics. He was awarded by Govt. of Rajasthan in 2005 & 2009 for Outstanding Work for Child Health in the State.

Dr. D. D. Golani

He did his M.D. (Medicine) from Safdarjung Hospital, Delhi Univerisity & Fellow of Indian Academy of Echocardiography

He is senior consultant internal medicine at DDU hospital. He is involved in cardiac check-up of Thalassemia patients.

Dr. Gaurav Kharya is Pediatric Hemato-Oncologist & transplant physician. He did his fellowship from Sir Ganga Ram Hospital in Pediatric Haemato-Oncology & BMT. In 2012 he went to UK to pursue further training in pediatric BMT with major emphasis on matched unrelated donor and hapolo identical transplants. Their he worked in prestigious hospital like the The Great North Children's Hospital, Newcastle upon Tyne & St. Mary's Hospital, Imperial college. NHS trust London. In march 2014 he joined BLK Hospital in transplant unit.

Dr. Inusha Panigrahi

She is Associate Professor of Paediatrics at PGI Chandigarh and has special interest in Haemato-Oncology.

Dr. Jitender Mohan Khunger is Consultant Haematologist & Associate Professor of Haematology at Vardhman Mahavir Medical College & Safdar Jang Hospital, New Delhi. He has done DM in Haematology from AIIMS, New Delhi.

He is the Secretary of Delhi Society of Haematology (DSH). He has several publications in National & International Journals and chapters in Haematology books.

Dr. Kirti Nanal

She is Consultant Pediatrician and in-charge Thalassemia Unit at NDMC Hospital, New Delhi

Dr. K. K Kaul

Professor & Head, Deptt of Pathology, and Sr. Consultant Haematology Govt. Medical college, and associated hospitals, JAMMU. He is medical advisor J&K state Thalassaemia Welfare Society. Chief Nodal Officer Haemophilia care centre Govt. Medical College Jammu.

He has received Rashtrya Gaurav Award and Honoured by Glory Of India Award with Gold Medal.

Dr. Mausumi Swami

She is Head of Department of Blood Transfusion Services, DDU Hospital, Delhi. Accepting challenges of Blood Transfusion in Thalassemia cases are very close to her heart.

She is NABH assessor for Blood Banks, Chairperson ISBTI Delhi chapter. She has been Conferred with "Bhagirathi Samman" 2013 and various services award

Dr (Mrs.) J Sardana

She is Mother of Lt. Dr. Anjali Sardana, a thalassemia major. She is an ophthalmologist by profession. She is founder Secretary of Thalassemic Children Welfare Society at Bareilly. She has been instrumental in strengthening the IMA Blood Bank at Bareilly and getting Blood free of cost for thalassemics. She regularly organises thalassemia awareness rallies and checkup camps.

Dr. Neelam Mohan, DNB (Pediatrics), MNAMS, FPGH(UK), FIMSA, FACG (USA). She is Director - Department of Pediatric Gastroenterology, Hepatology and Liver Transplantation Medanta Medicity, Gurgaon. She did her fellowship in Pediatric Gastroenterology, Hepatology & liver transplantation in Birmingham Children's Hospital, U.K.

She has represented as faculty in several International conferences. She has 484 presentations, 182 publications, and has edited 2 books on Pediatric Gastroenterology and Hepatology and has authored 47 chapters in various books in her field. She is presently Secretary of ISPGHAN and executive member of several international associations in Pediatric gastroenterology and liver transplantation such as IASGO, CAPGAN, IPTA, ASPGHAN. She has innumerable awards to her credit.

Dr. Neelam Sood did her MD pathology from MAMC, Delhi. She is consultant and Head of Department of Pathology and Lab medicine, DDU Hospital, New Delhi. She has been involved in the Thalassemia control programme from its inception in Delhi.

She got her training in Lab Management at IIM Ahmedabad -2013 and WHO -FELLOWSHIP in cytology – ICPO, 2007. She has more than 35 publications in the fields related to pathology, cytology, mycology and numerous presentations in national and international forums.

Prof. N. K. Mehra is the Dean (Research) and Head of the Department of Transplant Immunology & Immunogenetics at the AIIMS, New Delhi.
He pioneered this speciality in India and has made fundamental contributions in various aspects of the HLA system.

He is the 'Founder Secretary General' of the Federation of Immunological Societies of Asia-Oceania (FIMSA) and is Visiting Professor to several international universities. He is a Fellow of The World Academy of Sciences (FTWAS), Indian Academy of Sciences (FNASc), Indian National Science Academy (FNA) and Member Honoris Causa of the prestigious Hungarian Academy of Sciences (only one from India).

Professor Mehra has several awards and honors to his credit. Including S.S. Bhatnagar Award of the CSIR, 'Chevalier of the National Order of Merit by the French President, Khwarizmi

International award by the President of Iran (highest award for Science in Iran). He served as a member of the international jury for the prestigious Else Kroner Frsenius Award in Immunology. Professor Mehra and his group have published more than 440 original research papers in leading international journals.

Dr. N. V. Kamat did his M.S. Orthopedics from Patna University (1986). Currently he is Director, Directorate of Health Services since March 2011. Formerly he was Medical Superintendents of Dr. Baba Saheb Ambedkar Hospital, Maharshi Balmiki Hospital and Sanjay Gandhi Hospital, Delhi.

Dr. Radhika A.G. did her DNB Obs & Gynae UCMS & Guru Teg Bahadur Hospital, Delhi. She is specialist Gr I (O&G), UCMS & GTB Hospital. She was observer at Department of Obstetrics & Gynaecology in Wrexham Maelor Hospital, Wales, UK. She has done WHO Fellowship at KIT institute, Amsterdam, Netherlands. on "Advance Course on Monitoring and Evaluation: Innovation in Health Systems Environment". She has 22 research papers to her credit and contributed in 6 chapters.

Dr. Rahul Bhargva did his MD medicine from Gandhi medical college, Bhopal and DM Haematology from AIIMS. Currently he is Director and Head of Stem Cell transplant – Artemis Hospital. He worked as 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, British Coloumbia, Canada, May 2009 to June 2010. He Worked in Vancouver, Canada where he was specifically trained in Voluntary Stem cell transplant and Umbilical cord transplant. He has various research work publications and chapters in National & International journals.

Dr Rekha Harish, A Graduate & Post graduate from KGMC Lucknow,, is presently Professor & Head Department of Paediatrics. She is guide for MD and Examiner to various Universities. Chief-coordinator Thalassemia-Day-Care Centre at GMC Jammu which has 210 registered patients.

A Reviewer for various National and International Journals viz Indian-Pediatrics, Indian-Journal of Paediatrics JIMMS;Journal of Ped Surgery; approximately 40 publications in various Journals.

She been Member National Advisory board for the Journal of JK Sciences. Nominated to FSSAI Expert Group for laying guidelines for National School Canteen Guidelines.

Dr. Rita Ranjan
She is Head of Department of Obs & Gyne at DDU Hospital

Dr. Sangeeta Yadav, obtained her MD from LHMC and associated Kalavati Saran Children's Hospital. Currently She is Director Professor, Department of Pediatrics, Maulana Azad Medical College, University of Delhi. She started the Division of Pediatric & Adolescent Endocrinology at the Institution. She has been Executive Member IAP Ped. & Adolescent Endocrinology**.**

She was awarded WHO Fellowship for Pediatric & Adolescent Endocrinology in 1996. She has presented >100 Papers & Scientific talks at International & National Conferences and published >80 Papers in International & National journals, Books.

Dr. Seema Kapoor, Professor, Pediatrics, Maulana Azad Medical College, In-chage Division of Genetics & Metabolism Genetic Lab, Lok Nayak Hospital & Maulana Azad Medical College, Awarded 25 gold medals during career and the Presidents Medal for the best Lady Medico in 1982, Initiated a center for excellence in biochemical genetics Member of ICMR Task Force on inborn metabolic diseases and newborn screening for Congenial Hypothyroidism.

Shobha Tuli is the Secretary of Thalassemics India since 1993. She supported the establishment of a thalassemia unit at Sir Ganga Ram Hospital, in New Delhi, known as the 'PreetiTuli Thalassaemia Unit', after her daughter's name Preeti.

Mrs.Tuli has been member of the Board of Directors of TIF from India since 1996 and is currently holding the position of Vice President on TIF's Board. Since 2000, she has been President of the Federation of Indian Thalassemics. She was advisor to Indian Red Cross Society from 2003-2006. She is advisor & coordinator to the Bone Marrow Transplant Centre at B. L. Kapur Memorial Hospital, New Delhi. She received the 'George Englezos award' from TIF in 1999.

Dr. S.L. Broor

Dr Broor is Director and Head, Department of Gastro-entrology Apollo Hospital New Delhi. Formerly he was Director, professor and Head Department of Gastro-entrology GB Pant Hospital, Delhi. He has innumerable publications in national and International journals and written many chapters in books.

Dr Suman Mendiratta did her MD (obs & Gynae) from AIIMS, FMAS (WALS). She is Consultant Gynaecologist, Hindu Rao Hospital, Delhi and Project Coordinator, Thalassemia Control Programme, Thalassemia Control Cell, Hindu Rao Hospital, North Delhi Municipal Corporation

She has taken a lead role in initiating Thalassemia Control Programme in MCD and its implementation in municipal hospitals, maternity homes and SHS. Her paper on “Cost Effective Screening for Thalassemia in Pregnancy” was adjudged the best paper in AICOG 2006 (FOGSI). She has compiled a booklet on Thalassemia awareness “An insight into Thalassemia”. She prepared a Documentary on Thalassemia awareness “Jagmag Rahen Taare” in association with P&I Deptt MCD.

Dr. Veena Doda

Dr Veena Doda is head Department of Transfusion Medicine at RML Hospital.

Awards

National Thalassemia Welfare Society has initiated "Dr B.N. Dara" Award since 1997. This award is given to an Indian doctor who has dedicated his services for thalassemics for long time. Dr. B.N. Dara was a leading pediatrician of Jaipur with a special interest and sympathy towards thalassemics. This time NTWS has decided to bestow this award to Dr. I.C. Verma

Dr. I. C. Vermais a former Professor of Pediatrics and Head of Genetics at AIIMS. He established prenatal diagnosis of Thalassemia in India at AIIMS. Currently he is Director of Center of Medical Genetics,Sir Ganga Ram Hospital.

NTWS also initiated "Best Social Worker Award" in 1997. This award is given to a social worker who selflessly devotes his time and energy for the welfare of thalassemia. This time NTWS has decided to confer this award to Dr Madhben R Naik

Dr. MadhubenRamesh bhai Naik,M.D. (Gynecology) is Honorary Chairman, Indian Red Cross Society, Gujarat State Branch.

She is the Honorary Founder President of Red Cross Society, Navsari branch, established in 1974 and held this position till 2000. She established voluntary blood bank under Red Cross Society.

Thalassemia Prevention Program initiated by Dr. MadhubenNaikwas taken up by Gujarat Red Cross in 2004. More than12 lacs college students have been screened under this program.Under Pre-natal Diagnosis Test which was started as a Model Project in 2010, in cooperation with State Health Department and Ahmedabad Municipal Corporation, 93,949 pregnant women were screened. Thereby, 72 Thalassemic children birth were prevented.

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From Secretary's Desk

-Dr. J. S. Arora

National Thalassemia Welfare Society (NTWS) was established in 1991 by patients, parents, doctors and well wishers in this (AIIMS) prestigious institute under the guidance of Dr V.P. Choudhry. NTWS is the largest represented society of India, dedicated for the care & control of Thalassemia. Primary objectives of the Society are to upgrade the facilities for optimum treatment and to educate the thalassemic families & update the medical professionals.

During long 22 years we have achieved many milestones. From 2 Thalassemia units in 1991 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 (Haematologists, Paediatricians, Blood Banks & Heads of the Institutes) and the blessings of Delhi Govt.

To achieve our objective of creating optimum facilities at minimum cost we liaison with the Govt. 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 Govt. 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 Govt. Hospitals, VAT (sales tax) exemption on blood filters and all chelating agents and the latest is FREE pre-natal diagnostic facility for all at LN hospital.**

Following other major activities have been undertaken under this venture:

- Massive Thalassemia campaign. Advertisements were put in various newspapers. Publishing of brochures and posters on Thalassemia awareness. Hoardings have been put at different prominent places in the capital.
- Thalassemia screening of pregnant women in antenatal clinics of all major hospitals Hospitals.
- Separate Thalassemia units have been opened up at five major hospitals of Delhi. Thalassemics are provided free packed RBCs and chelating agents at these centres.
- Directorate of Health Services in association with National Thalassemia Welfare Society produced two 27 minute Docudrama "Chetna" and "Jagriti" on Thalassemia awareness. It was released by Dr. Ashok Walia the then Hon'ble

Minister of Health during our 4th National Thalassemia Conference.

- A five-day mega event "Thalassemia Chetna Yath Yatra"from 22nd Nov to 26th Nov 2001 was flagged off by the then Hon'ble Chief Minister of Delhi, Mrs. Shiela Dixit.
- 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 Sh. Yoganand Shastri in 2005.
- A genetic lab at Lok Nayak Hospital has been established to provide antenatal diagnosis of thalassemia to needy thalassemia couples. Free antenatal diagnostic facility is available for all.

National Thalassemia Welfare Society (NTWS) organises free Thalassemia monitoring and check-up camps at its NTWS centre atTilak Nagar, New Delhi. Experts from various premier institutes give free of cost consultancy at this centre. Subsidized medicines and investigations are provided to poor and needy thalassemics.

We regularly organize Blood Donation Camps in association with Red Cross and Govt. Blood Banks. We organise approx. 50 Blood Donation Camps in a year and collect 3000-4000 units of blood every year.

Besides care and control of Thalassemia, National Thalassemia Welfare Society also has a dispensary at C 2 Block, Palam Vihar, Gurgaon which is dedicated for the primary healthcare of poor and under privileged people in slums and villages in and around Palam Vihar. There we provide free consultation and medicine & other facilities at subsidised rates to poor patients.

The teamwork of general allopathic and homeopathic, Gynae, orthopaedic and well equipped dental and physiotherapy departments. The centre also provides free computer education, personality development and English communication skills to semi illiterate people of the community. Yoga classes and Library for elders are also prime department of this centre. Dispensary is also a good source of Thalassemia Awareness in Gurgaon.

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 supported our cause 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 "dharnas" 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 has been included in the "Disability Bill 2013" which has been approved by the cabinet and introduced in the Rajaya Sabha in last parliament session. There is every possible chance that this bill will be passed before the year end. It will help in improving the status & quality of life of 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, which was inaugurated by DGHS
- 2nd National Thalassemia Conference, Dec.1997 inaugurated by Director AIIMS.
- 3rd National Thalassemia Conference, Apr. 2001, inaugurated by Mrs. Shiela Dixit the then Hon'ble Chief Minister of Delhi
- 4th National Thalassemia Conference, May. 2003 inaugurated by Dr. Ashok Walia, the then Hon'ble Minister of Health, Govt. of NCT, Delhi.
- 6th National Thalassemia Conference, Nov 2010 inaugurated by Dr. V. M. Katoch, Director General ICMR and Secretary Ministry of Health, Govt. of India.
- 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.

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 Dr. Ashok Walia, 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 Dr. Yoganand Shastri was chief guest & Hon'ble Minister of Finance Dr. Ashok Walia was guest of Honour and in association with Department of Paediatrics, UCMS & GTB Hospital organized
- Workshop on Thalassemia in Nov 2006 inaugurated by the secretary health Mr. Wahi

Now NTWS is organizing "7th National Thalassemia Conference" in association with Department of Haematology, A.I.I.M.S on 19th & 20th April, 2014 at Jawahar Lal Auditorium, AIIMS, New Delhi followed by Workshop on Thalassemia on Monday, 21st April 2014 at UCMS and GTB hospital.

In these academic meetings International & National faculty of repute have been invited and over 400-600 patients, parents and doctors benefited every time. 7th National Thalassemia Conference is going to be largest attended thalassemia meeting so far in our country. Participation is expected to be over 1000 persons and the most exciting feature is over 300 thalassemia patients will be gathering to strengthen their knowledge and share their views and feelings. This will be the largest congregation of Thalassemia patients in India so far. . Thalassemia International Federation (TIF) delegation will be part of this great event.

We hope we will be able to provide you a good academic feast, ample opportunity to interact and share your experiences with faculty and peers.

Challenges in Managing Thalassemia

- Dr. VIP Viprakasit

Thalassemia is the most commonly inherited hemolytic anemia worldwide and due to the large population and high prevalence of thalassemia carriers, Asia populations account for the majority of overall thalassemia births. In Thailand alone, the frequency of □thalassemia is 25%, and the World Health Organisation estimates that, without effective prevention and control programs, over 250,000 symptomatic patients will be diagnosed in this country over the next few decades. A similar scenario is predicted to occur in India, Sri Lanka, Indonesia, the Philippines and Malaysia. Hb E is the most common haemoglobin variant found in this region with a very high prevalence in the area adjoining Cambodia, Laos and Thailand known as Hb E Triangle with carrier prevalence up to 50%. Hb S causing Sickle cell anemia or □ thalassemia /Sickel cell disease was commonly found in some region of Indian subcontinent, although only few indigenous individuals with Hb S trait has been identified in the main land of Southeast Asia.

In patients with severe thalassemia syndrome, although stem cell transplantation might be the treatment of choice in patients who have HLA-matched donors, however, such treatment has several drawbacks including limited availability of matched donors, cost of treatment, treatment related mortalities and morbidity and long-term consequences due to exposure of chemotherapy for patients' conditioning. Therefore, the mainstay of management for most patients consists of regular blood transfusions supplemented with iron chelation therapy to prevent the effects of iron accumulation. However such treatment modalities can be a major burden to annual healthcare budget in many developing countries. Therefore, it is important that a prevention and control program for severe thalassemia syndromes must be implemented to reduce the number of new cases and allocate limited health care budget to improve standard of care in existing patients. Understand the epidemiology of this common inherited globin gene disorder in a micro-mapping fashion from an appropriate population survey in all different regions will be important for any given Asian country to tailor their screening strategy to develop a national prevention and control program for thalassemia.

At the beginning, a naked eye single tube osmotic fragility (NESTOF) test using 0.36%NaCl solution has been recommended since 1970s. However such screening tool has several limitations due to quality control, result interpretation and reproducibility making a number of

screening failure from false positive and false negative. This simple tool might remain beneficial only in a remote area or field study. At present, several screening algorithms use microcytosis determined by mean corpuscular volume (MCV) lower than 78 fL as a first screening tool. Alternatively, mean corpuscular hemoglobin (MCH) < 25 pg/dL can be used as another screening cut-off. These two parameters could now be easily detected using automated red blood cell counter that is widely available in many countries in Asia and can now be validated with a high quality control. These two cut-off values are sensitive enough for detection of α^0 and β thalassemia traits. However there are few limitation for these parameter to detect individuals with Hb E carrier; approximately 65% of Hb E trait has MCV and MCH lower than these cut-off. Therefore, in the countries that have a high prevalence of Hb E alleles, it is important to include a test to screen for Hb E using instable property of Hb E such as dichlorophenolindophenol (DCIP) test or by antibody to detect Hb E by ELISA technique. In Thailand, a combination of two screening tools; MCV/OF with Hb E screening has been recommended in our prevention and control program for severe thalassemia since 1990s. This screening algorithm has been proven to be effective in preventing new cases of thalassemia syndromes and might be applicable for other countries in the region where share similar genetic heterogeneity. However, there are several limitations in the clinical setting by this screening algorithm; only common, but not all, significant globin gene defects such as Hb E. homozygous Hb E, α and β-thalassemia trait and all thalassemia disease forms including Hb E/β thalassemia, β thalassemia major and Hb H disease can readily be detected. However several other globin disorders including hereditary persistent of fetal haemoglobin (HPFH) and other abnormal haemoglobin variants such as Hb S, Hb Tak or Hb Constant Spring might have been missed or under-diagnosed and these conditions can also give rise to clinical significant thalassemia syndromes. Therefore it is important to be reminded on the limitation of such recommended tool and warrant a further research study to continuously search for a better and new screening algorithm to help improving the coverage and effectiveness of prevention and control program for severe thalassemia syndrome in any given country.

Diagnostic Challenges in Hemoglobinopathies

- Dr. H. Pati

Haemoglobinopathies are inherited disorders of globin chain synthesis. The term is usually used to include both disorders with reduced rate of globin chain synthesis (thalassaemia) and those disorders in which a structurally abnormal globin chain and thus a structurally abnormal haemoglobin molecule are synthesised (variant haemoglobin). Diagnosis of haemoglobinopathies, including thalassaemias, can result from either a clinical suspicion of a disorder of globin chain synthesis or from follow-up of an abnormality detected during screening. Screening in the setting of haemoglobinopathies may be directed at optimizing management of a disorder by early diagnosis, or preventing a serious disorder by offering termination of pregnancy. Diagnostic methods and algorithms will differ according to the setting. As the primary test, high performance liquid chromatography is increasingly used and haemoglobin electrophoresis less so with isoelectric focussing is being largely confined to screening programmes and referral centres, particularly in newborns. All these methods permit only a presumptive diagnosis with definitive diagnosis requiring either DNA analysis or protein analysis, for example by tandem mass spectrometry**.**

Indications for testing or screening for a haemoglobinopathy

- ✓ Clinical suspicion of sickle cell disease, β thalassaemia major or intermedia, haemoglobin H disease or haemoglobin Bart's hydrops fetalis
- ✓ Unexplained microcytosis, or haemolytic anaemia
- ✓ Unexplained cyanosis or polycythemia
- ✓ Suspicion of a variant haemoglobin when HPLC is used to quantitate haemoglobin A1C for the management of diabetes
- ✓ In a neonate or in relation to pregnancy or a potential future conception

Although DNA diagnostics have made a major impact on our understanding and detection of the haemoglobinopathies, DNA mutation testing should never be considered a short cut or the test of first choice in the workup of a haemoglobinopathy. The detection and characterisation of a haemoglobinopathy involves a 3 tier work up. (1) Full blood count (2) Special haematological tests such as HPLC and (3) DNA Mutation Testing. Just as important as the laboratory investigations is **the family work up.** DNA analysis for globin gene disorders is generally performed in referral laboratories. It is important that such laboratories are given accurate information on ethnic origin and all relevant haematological details so that appropriate tests are performed. Technical and interpretive problems can lead to misdiagnosis, that are unique to this field.

Techniques must be appropriate; for example, haemoglobin A2 can be satisfactorily quantified using HPLC, microcolumn chromatography or cellulose acetate electrophoresis followed by elution but IEF and scanning densitometry on electrophoretic strips are not satisfactory. The graphical output of HPLC instruments (the chromatogram) must always be inspected by an experienced person since the software algorithms of the instrument may lead to peaks being mis-labelled. In addition, with some HPLC programmes, haemoglobin Bart's and haemoglobin H are not identified or quantitated and inspection of the chromatograms is needed for their recognition. The laboratory interpreting HPLC chromatograms must be aware that glycated haemoglobin S is likely to appear in the haemoglobin A0 window and those interpreting IEF must be aware of the positions of a considerable array of bands representing glycated and acetylated adducts of normal and variant haemoglobins.

The HPLC results must always be assessed in relation to the haemoglobin concentration and red cell indices if a distinction is to be made between homozygosity for a variant haemoglobin and compound heterozygosity with β0 thalassaemia, and between δβ thalassaemia and hereditary persistence of fetal haemoglobin. For example,when there is a double heterozygosity for hereditary persistence of fetal hemoglobin (HPFH) and b thalassemia, the clinical picture is that of beta thalassemia intermedia in spite of finding very high (more than 80%) HbF levels. Such cases can be identified by family studies and molecular studies of mutations in beta genes If screening for thalassaemia is selective, on the basis of red cell indices, then occasional patients with β thalassaemia trait will be missed because liver disease, vitamin B12 and folic acid deficiency or zidovudine therapy has raised the MCH and MCV into the normal range. Laboratories using the MCV for selecting individuals who require screening must be aware that with some instruments the MCV rises with storage of the blood, e.g. for more than 24 hours. β thalassaemia trait may be mis diagnosed if a laboratory does not interpret the results of haemoglobin A2 estimation in relation to red cell indices and does not appreciate that there are other causes of an elevated haemoglobin A2 such as HIV infectionor the presence of an unstable haemoglobin.

Another dilemma for the DNA laboratory is the equivocally-raised HbA2 result because it means that normal HbA2 β thalassaemia cannot be excluded. In this circumstance, the HbA2 test should be repeated.Further ,the possibility of haemoglobin Bart's hydrops fetalis may also be missed if one partner has β thalassaemia heterozygosity and the other a possible α0 thalassaemia heterozygosity; in this circumstance both partners must be tested for α0thalassaemia since a diagnosis of β thalassaemia heterozygosity does not exclude co-

existing α0 thalassaemia heterozygosity.Failure to find HbH inclusions when they are present is an important error that produces a lot of unnecessary DNA testing. In these circumstances, the DNA testing laboratory may be unsure of whether to test for α or β thalassaemia. Prior to ordering expensive and time consuming DNA tests, it is often beneficial to check again for HbH inclusions.

An interesting challenge when working with the haemoglobinopathies is the heterogeneity of mutations and gene-gene interactions possible in these disorders. Thus, the finding of an α or β globin gene mutation in one member of a family does not exclude the possibility that the other side of the family may have a completely different mutation affecting the same or another globin gene. Therefore, it is important to always keep this in mind when interpreting results.

Detection of increasing numbers of different Hb variants, and their effects per se, or in combination with the thalassemias can further add to the confusion.

The majority of Hb variants fortuitously discovered are of minimal clinical interest. Conversely, those found during the course of a haematological disorder bring frequently the aetiological answer for the disease. Often unusual clinical presentations may be explained by the interaction of several Hb abnormalities and their identification may require further investigations. The double heterozygosity for α and β chain variants leads to formation of abnormal hetero-dimer hybrids, which can lead to diagnostic dilemmas.The hybrids of abnormal α and β chains have unpredictable elution times on HPLC and uncharacterized bands on Hb electrophoresis. It is important to identify and characterize these abnormal peaks on Hb HPLC .

Very rarely mutations in either the HS-40 or the β LCR have been reported, and their effect is to inhibit the related downstream globin gene complex. In the case of the β LCR this produces a normal HbA2 thalassaemia since down-regulation of the δ globin gene would occur. Because these types of mutation are very rare, they are not normally sought by conventional mutation analysis strategies or even DNA sequencing. Hence, irrespective of how much DNA mutation testing is undertaken, failure to find a mutation does not exclude an underlying thalassaemia.

Diagnosis and Transfusion

- 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 has been 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 around 10gm% (Das Ka Dam) 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
- 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 consequences:

- 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 consequences:

- 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.

Alloimmunization in Thalassemia

- Dr. V. P. Choudhry

Alloimmunization is defined as immune disorder caused by incompatibility between recipient and donor antigens. Alloimmunization to red cell antigens is the major complication following blood transfusion. The factors for alloimmunization are complex and are dependent on three major factors viz.

a. Red cell antigenic difference between the donor & the recipient
b. Recipient immune status
c. Immunomodulatory effect of red cell antigens on recipient immune system.

The donor antigens induce an immune response in the recipient resulting in production of specific antibiotics against the donor antigens. These anti RBC antibodies (allo-antibiodies or autoantibodies) complicate the transfusion therapy. Some allo-antibodies are hemolytic in nature and results in hemolytic reactions of varying severity,while others are clinically insignificant and do not cause any minor reactions.

Based upon the red cell antigens, red cells have been divided into major blood group antigens such as A,B,AB and O. Incompatibility of these blood antigens during transfusion results in severe hemolysis which may be fatal if not detected early and treated actively . Most blood banks in our country match blood against A, B, AB and O along with Rh-D matching. Besides these major antigens these are host of red cell antigens of Rh system (most common C&E) and while other common antigens comprise kell (V,hr^b,C^w, Js ^{b}) kidd (Jk^b> Jk^8) dufty (Fy^a>Fy^b) lewis (Le^a>$L2^b$) and MNS (M,S) systems. Anti lewis antibodies are usually clinically insignificant. Most blood banks in India do not cross match blood against these minor blood groups. Thalassemic children requiring multiple blood transfusions develop allo-antibodies on repeated exposure to these minor red cell antigens. Based upon the level and type of allo-antibodies the following reaction may develop following blood transfusions:

a. Severe hemolytic reactions.
b. Delayed hemolytic reaction.
c. Increased frequency of blood transfusion requirements action.

Prevalance

Rate of alloimmunization are highly variable. Its prevanlance in general population varies between 1-4% while among thalassemic children is varies from 4 to 37%. Data from our country is limited . In a study from Chandigarh 3.4% of multi transfused patients were found to have allo antibodies. While in study from Maharashtra 50% of thalassemic children were found to have allo antibodies but majority of them did not develop any hemolysis.

RISK FACTORS FOR ALLOIMMUNIZATION

- Dr. V. P. Choudhry

Donor Factors :

Differences in alloimmunization have been obsereved to ethmic or racial disparity of donor & recipient population. In one study from USA Asian patients with thalassemia had alloimmunization rate of 20% while only 5% of local blood donors were Asians. Extended RBC antigen matching to include C, E and Kell has been recommended to reduce the alloimmunization.

Host Factors: Duration of transfusion support (more number of transfusions) and older age is associated with increased risk of alloimmunization. Children with thalassemia intermedia have been found to have higher risk of developing antibodies. Spleenectomy also increases the risk of alloimmunization. Spleenectomy continuous to play an important role in immune function. It has been postulated that post spleenectomy changes in RBC membrane enchances immunomoduation resulting in alloimmunization. Allogenic white blood cells within RBC also cause allergic febrile reactions and results in alloimmunization through reduced activity of CD 4+ cells.

Strategies for prevention of alloimmunization

The major cause of alloimmunization is exposure to foreign RBC antigens. Thus it is logical that alloimmunization can be early prevented by not exposing the recipient to foreign RBC antigens.

This is possible by doing the extended RBC phenotype before starting blood for thalassemic children to determine blood groups A,B,AB,O Rh system D.C.E.e K, Fy^a, Fy^b, JK^b, M,N,S s, Le^a, Le^b, and P1 status . The extended phenotype is useful in guiding the serological work up of new RBC antibody and for prospective matching.

Extended RBC matching :

It has been observed that limited (c,E,Kell) phenotyped matched blood reduces the risk of alloimmunization significantly. Thus in the consensus recommendations of US & UK it is stated that limited cross matching(C,E,Kell) in addition to A,B, AB ,O,Rh D is justified. However in some countries it is practice to provide antigen matching to Fufty,Kidd and /or MNS in additionto matching as suggested above. Further extended phenotype matching can be undertaken on individual case who have developed positive coomb's test or have development alloantibodies.

Leucocyte Reduction

Some studies have shown that leucoreduction reduces the risk of alloimmunization significantly . In addition leucoreduction also reduces risk of febrile reactions and cytomegalovirus virus transmission.

Treatment

Once the patient has developed all- antibodies should be managed by immunomodulation. Immuno-modulation treatment has been undertaken with conventional or high dose steroids. IV IgG alone or in combination with steroids have been used in small case studies. In refractory cases ritxumab has been used with beneficial results.

Such children in future should receive only blood which has no foreign RBC antigens. In addition it is desirable that leucoreduced RBC should be given always.

Monitoring of Chelation/Iron Overload in Thalassemia

- Dr. Amita Mahajan

Monitoring of iron overload is one of the most important and crucial aspects of management in thalassemia. The overall outcome of individual patients is dependent on optimal monitoring and management of iron overload. The tools available for monitoring iron overload are:

S. Ferritin

Serum Ferritin continues to be the commonest test used for monitoring of iron overload in patients. It is readily available, relatively inexpensive and non-invasive. There is extensive data that demonstrates significantly increased risk of cardiac and hepatic toxicity if S.ferritin is consistently above 2500. Current guidelines recommend for chelation to commence once S.Ferritin is > 1000. The aim has been to maintain S.Ferritin< 1500 but increasingly, with the availability of efficacious chelators, more and more physicians are aiming for values of 500-1000. Rather than a single value, it is the trend that is important. The S.ferritin should be measured every 3 to 6 months.

However, the problem with S.Ferritin is that it is an acute phase reactant and is frequently elevated in acute infection, inflammation and hepatitis.

Liver biopsy

Till the establishment of standardized MRI evaluation to measure tissue iron concentration, liver biopsy and the estimation of liver iron concentration (LIC) was considered to be the gold standard for the measurement of iron overload in the body. It also gave information about the presence and severity of fibrosis and cirrhosis in the hepatic tissue. It is an invasive test with a small risk of complications from bleeding. With the advent of radiological methods to measure iron overload, it is no longer used as a routine measure of evaluation.

Squid (Superconducting quantum interference device)

This method can accurately measure tissue iron overload. However, only four such machines are available worldwide hence this method is currently only used for research purposes.

MRI

Tissue iron measurement using magnetic resonance imaging has now become the gold standard and has by and large replaced liver biopsy analysis. It is a non-invasive technique and MRI machines are currently widely available.

This technique is based on the principle that the tissues containing iron darken much more rapidly than normal tissues due to the local magnetic field disturbances produced by iron. The time interval required by tissues to become twice as dark is termed as T2* and the rate of darkening is termed as R2* with the relationship being: R2* = 1000/ T2*. There are specific

software programmes available which can be used in the 1.5 Tessla MRI machines to accurately determine iron concentration in the heart and liver. In some ways, it is perhaps even better than liver biopsy as this technique measures the liver iron concentration in the whole liver while the liver biopsy assesses a specific area. Currently, a number of studies are evaluating its role in estimating iron in other tissues such as pancreas and pituitary gland.

In India, the problem has been that though MRI equipment is widely available, very few centers have the specialized software and expertise required to measure T2* and R2* values. There is now an initiative to overcome this limitation. DrJuliano has introduced a mathematical calculation using the physical properties of this technique so that any MRI machine can be used to measure the iron concentration in liver and heart. This strategy is currently being evaluated in a number of centers in India and appears to be promising.

MRI evaluation is recommended on an annual basis. The values for interpretation are as below:

Liver MRI

Hepatic T2*(ms)	Hepatic Iron Overload
> 6.3	None
2.7-6.3	Mild
1.4-2.7	Moderate
< 1.4	Severe

Cardiac MRI

Myocardial T2*(ms)	Cardiac Iron Overload
> 20	None
12-20	Mild
8-12	Moderate
< 8	Severe

Echocardiography

This is another non-invasive method to evaluate cardiac dysfunction secondary to iron overload. It detects diastolic and systolic dysfunction and the diastolic function precedes systolic dysfunction. It detects the consequences of iron overload but not the iron overload itself. It is recommended that children older than 10 years have echocardiography as part of their annual evaluation.

Monitoring for Chelation therapy

Deferasirox

For patients on deferasirox for chelation, it is recommended that Serum Creatinine, liver enzymes (SGOT, SGPT) and urine for microalbuminuriaare evaluated monthly at least for the first few months. If stable, the frequency may be subsequently decreased to every 3 months. S.Ferritinshould be measured every 3 to 6 months for all patients on chelation.

Desferroxamine

It is recommended that patients on desferroxamine undergo ophthalmic and auditory evaluation on an annual basis. In addition growth should be monitored.

Deferiperone

Deferiperone can vary rarely cause agranulocytosis which may be fatal. It is therefore recommended that patients on deferiperone should have regular monitoring of CBC fortnightly. They should also have liver function tests every 3 months.

Role of MRI T2* in Monitoring of Iron Overload

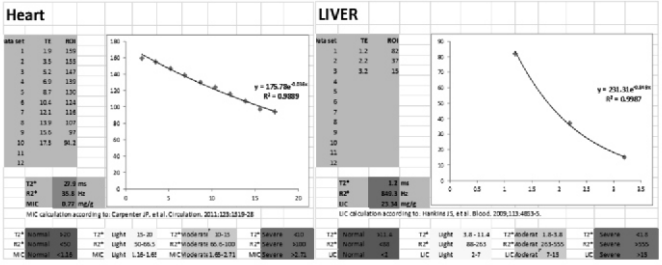
in NTDT and Thalassemia Major-Case Studies

-Dr. J. S. Arora

Case 1

A 1968 born NTDT female, who was diagnosed at the age of 2-½ years had splenectomy in1989 & cholecystectomy in 1995. She was maintaining Haemoglobin level 7.4 – 8.8gm/dl without transfusions. She had just 2-3 units of blood transfusion at the time of surgery. She had intermittent pedal oedema, ankle pain, pain abdomen, raised uric acid & rheumatoid factor, osteoporosis and hypothyroidism since 2010. Till 2009 she was maintaining her ferritin between 1000-2000ng/ml on intermittent Kelfer therapy. At this time she developed arthritis for which she was shifted to Asunra 10-15mg/Kg/day.

In Oct 2013 she developed ascites. Her biochemical parameters were serum ferritin 1010ng/ml, SGOT 61 IU, SGPT 36 IU, GGTP 14 IU, total protein 5.9g/dl, Albumin 2.7g/dl. She was negative for HBV, HCV & HIV. Her MRI T2* heart 27.9 ms (MIC 0.77mg/gm), liver T2* 1.2 ms (LIC 23.34mg/gdwl). Her Fibroscanscore E(kpa) median 13.8 (<7N, >9.5 fibrosis, >12.5 Severe fibrosis, >17 Cirrhosis).



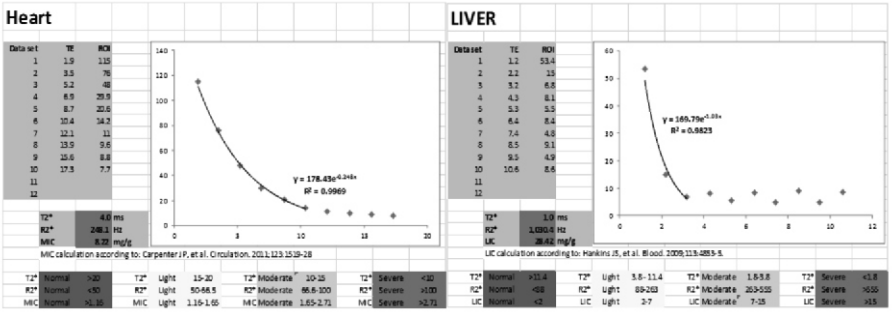
Lesson learnt:-If we had reliable MRI T2* facility available in 2008-09, we would have given full dose of Asunra i.e. 30-40mg/Kg and saved her from developing liver failure

Case 2

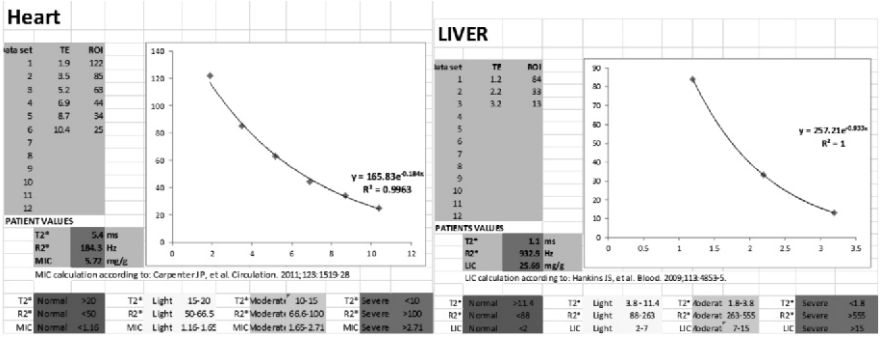
A male thalassemia major born in 1994 diagnosed at the age of 3 months, was maintaining his haemoglobin level above 10gm/dl on regular transfusion. He started chelation at the age of 7 years that too irregular. His serum ferritin during 2010-2013 was between 5500-7000ng/ml. He was taking inadequate doses of Kelfer. During his treatment for HCV from March 2013 to Sep 2013 he was advised to stop Kelfer and start Desferal. He did not administered any chelation during this period. His HCV infection also relapsed within 4 weeks of end of treatment. In October 2013 his ferritin was 6200 ng/ml, MRI T2* heart 4.0 ms (MIC

8.22mg/g) and MRI T2* liver 1.0 (LIC 28.42mg/gdwl). At this point he started 50mg/kg Desferal s.c 12-16 hours a day and 24 hour i.v. 4-5 days every time post transfusion along withAsunra 40mg/kg/day all 7 days a week. There was significant reduction in ferritin, improvement in cardiac T2* and reduction in myocardial iron concentration but there was not much reduction in liver iron concentration. Improvement in values is tabulated below (after graphs)

MRI T2* dated 25.10.13



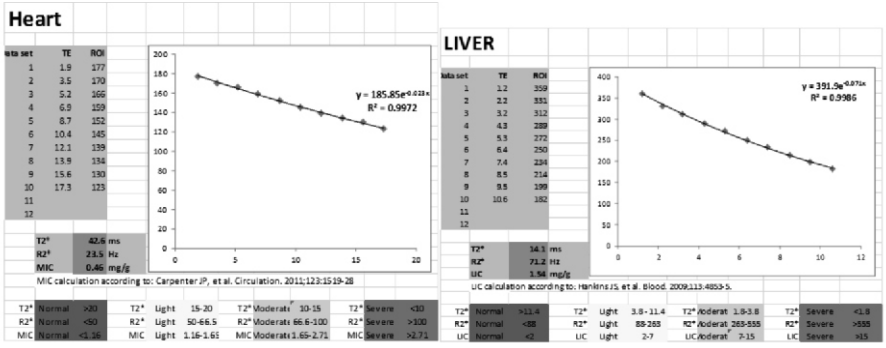
MRI T2* dated 26.3.14



Lesson learnt : Though serum ferritin has come down drastically but still there is sever iron overload in heart & liver. His serum ferritin is not correlating with severity of iron load in heart & liver so he need to be monitored on MRI T2* six monthly. Iron chelation from heart is faster than from liver as already revealed by various studies. This patient also carries higher risk ofdeveloping liver fibrosis and cirrhosis due to concomitant HCV infection. Long term intensive combination therapy is required to prevent further complications

Case 3

A male thalassemia major born in 1995 was having serum ferritin around 4000ng/ml in 2001. He was put on Desferal 35mg/kg s.c and Kelfer 80mg/kg/day. For last 3 years he is on Desferal 40mg/Kg 2-3 times a week and Kelfer 75mg/kg and maintaining his serum ferritin between 600-800ng/ml. His MRI T2* heart is 32.4 ms (MIC 0.65 mg/gm) and liver T2* is 7.4ms (3.34mg/gdwl).



Lesson learnt: His serum ferritin level is well below 1000 ng/ml and cardiac MRI T2* is very good, but still he has mild iron overload in the liver. Kelfer is not a good chelator of iron from liver. Kelfer and Desferal are not recommended for serum ferritin below 1000ng/ml. Ideally he should be put on Asunra 30mg/Kg/day because it can be safely given upto serum ferritin as low as 500ng/ml and it is a good chelator of iron from liver. MRI T2* revealed that even though ferritin at values < 1000ng/ml there can be iron overload in the liver.

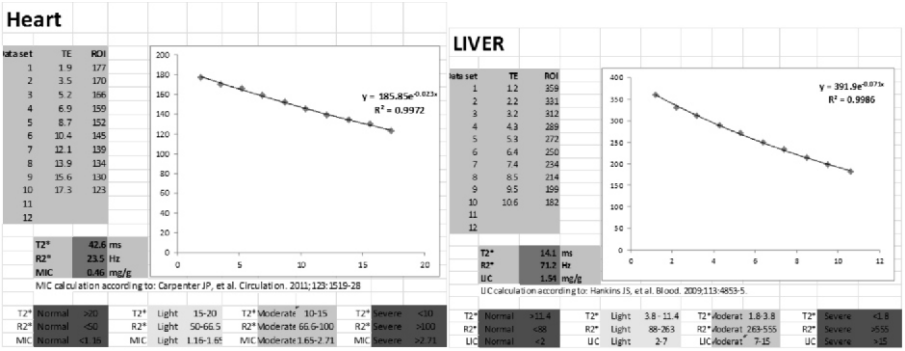
Case 4

A male thalassemia major born in 93 developed cardiac failure at the age of 10 years. His ferritin was14,000ng/ml. His LVEF was 23%, which improved to 52% in two years on combination therapy with Kelfer & Desferal. In 2008 his serum ferritin was still > 4000 ng/ml. In 2010 he was put on intermittent Desferal i.v and daily Defrasirox 40mg/Kg/day. Since 2013 his ferritin is 700-800ng/ml and he is taking only Defrasirox 40mg/Kg/day. His MRI T2* heart is 37.5 ms (MIC 0.54 mg/gm) and liver T2* is 7.3ms (3.38m/gdwl).

Lesson learnt: Same as above. At serum ferritin level of ~700-800ng/ml patient can still have iron overload in the liver. At under control serum ferritin (<1000ng/ml) the need of MRI T2* is still more to monitor iron overload.

Case 5

A female thalassemia major born in 1996 was having serum ferritin 1000-1500ng/ml in 2011.With improved compliance in 2012-13 she brought her ferritin to ~400-600ng/ml. Her MRI T2* heart is 42.6 ms (MIC 0.46 mg/gm) and liver T2* is 14.1ms (1.54mg).



Lesson learnt : She does not have any iron overload. Her dose has to be tapered down. She needs only that much of Asunra (~20mg/kg/day) which is required to chelate iron released from on-going transfusions.

Conclusion: MRI T2* is dependable and reproducible non-invasive tool to measure iron over load in the body, especially vital organs like heart and liver. If MRI T2* is not feasible thengoal of the chelation should be to achieve the target of serum ferritin ~500ng/ml

Deferrioxamine: The Old Is Gold

-Dr. Praveen Sobti

Introduction

Patients with β-thalassemia major require regular transfusion therapy to sustain life. While such therapy effectively treats their anemia, the iron present in the hemoglobin of the transfused blood is retained in the body in absence of any physiological means of excreting it. Iron accumulates primarily in the liver and spleen, and to a lesser extent in the heart, pancreas, and other organs. This excess iron catalyzes the formation of reactive oxygen species, which damage a variety of macromolecules and cell structures leading to hepatic cirrhosis, endocrine abnormalities cardiac disease and eventually premature death(1, 2). Since the availability of chelating therapy, the survival curves for patients with thalassemia has become better and with increasing experience and combination therapy is improving further (1,3).

Objectives of Chelation

The primary objective of Iron chelation Therapy is to maintain body iron at safe levels at all times.

The chelation should be started when the patients have received 10 to 20 blood transfusions or serum ferritin reaches to 1000 mcg/L or liver iron exceeds 3.2 mg/ gdw iron. The safe iron burden is agreed to be of serum ferritin levels 500 µg/L - 1000 µg/L , Liver iron concentration 3.2 mg/g - 7.0 mg/gdw and cardiac iron (T2* CMR) >20 ms.

Chelating Agents

The use of chelating agents has proven to be highly effective, being associated with reductions in both morbidity and mortality. However, the available chelating agents have significant limitations. The first iron chelator that became available in 60s was Deferrioxamine (DFO). The subsequent usage clearly showed a major impact on survival and iron related complications. However the search for better chelator continued with Deferiprone (DFP) becoming available in1999 and Deferesirox (DFX) in 2005. But none of them is anywhere near being called an ideal chelator

Table1. : PROPERTIES OF AN IDEAL CHELATOR

Efficacy

- Maintenance of iron balance or achievement of negative iron balance
- High and specific affinity for ferric iron (Fe^{3+})
- Effective tissue and cell penetration
- High-chelating efficiency
- No iron redistribution
- Slow metabolism and elimination rate
- 24-hour chelation coverage

Convenience

- Oral bioavailability
- Half-life compatible with once-daily dosing
- Good compliance

Tolerability

- Good adverse event (AE) profile

Different Agents in Comparison

DFO must be given parenterally, the most effective regimens involving daily subcutaneous infusion over 8 to 12 h, at doses of 40 to 60 mg/kg/day. To overcome this hurdle, attempts to develop safe and effective oral agents have been ongoing since the mid 1970s. The first candidate to receive regulatory approval was deferiprone (DFP). It is generally recommended that this drug be taken at doses of 75 to 100 mg/kg/day in three divided doses, 5 to 7 days a week. While DFP is not as effective as DFO in most patients, adherence to its use is somewhat better. With prolonged use, it is quite clear that body iron load is reduced and cardiac function is improved. It does, however, have side effects that limit its usefulness. Chief among these are musculoskeletal (arthralgia, arthropathy), gastric (nausea, vomiting) and hematologic (neutropenia, agranulocytosis) effects. Thus, up to 30% of patients discontinue its use for one reason or another (1). DFX, is used as once-daily oral iron chelator and is generally used as first line therapy for patients over 2 years of age with chronic iron overload due to blood transfusions. Although DFX has some mild adverse events, some studies indicated that it has a positive effect on lowering liver iron and producing high patient compliance (3). The comparative analysis of these agents is given in table 2.

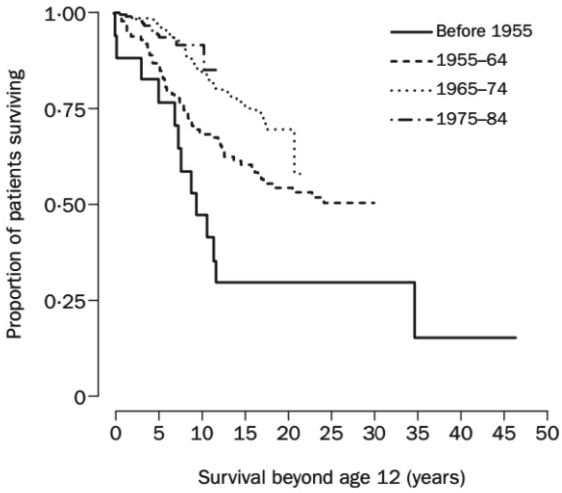
	DFO (DFO)	DFP (DFP)	DFX (DFX)
Molecular weight	560	139	373
Chelator: iron	1:1 (hexandentate)	3:1 (bidentate)	2:1 (tridentate)
Route of administration	Subcutaneous or intravenous	Oral tablets or liquid	Oral suspension
Iron excretion	Urine, fecal	Urine	Fecal
Plasma half-life	20 min	1-3 h	8-16 h
Usual dose	40 mg/kg/d	75-100 mg/kg/d	20-40 mg/kg/d
Licensed	Licensed for treatment of chronic iron overload resulting from transfusion-dependent anemia	In Europe, North America, and Asia: for treatment of iron overload in TM where DFO is contraindicated or inadequate	In the United States, licensed for treatment of transfusional iron overload in patients 2 years or older. In Europe, approved for treatment of transfusional iron overload in TM, 6 years and older and when DFO is contraindicated and inadequate, in patients with other anemias, patients 2-5 years old and in nontransfusion-dependent thalassemia
Cardiac iron removal	Compliance problem; not effective in all compliant patients; continuous infusion more effective	Most effective of the 3 chelators; used with continuous DFO in cardiac failure	Reduces LIC and improves liver pathology; reduces cardiac iron in 3-year study
Annual cost (54 kg body weight) (United Kingdom NHS) Not applicable at the same rate in all countries	40 mg/kg/5 d = £4788*	75 mg/kg/d = £4505 100 mg/kg/d = £6007	20 mg/kg/d = £13 245 30 mg/kg/d = £19 865 40 mg/kg/d = £26 490
Main side effects	Local reactions, auditory, retina, allergy, bone abnormalities, Yersinia infection	Gastrointestinal, neutropenia/ agranulocytosis, arthralgia, liver enzyme rise, zinc deficiency†	Gastrointestinal, rash, renal, liver†
Advantages	36 years of experience	Best for cardiac iron removal	Once-daily administration
Disadvantages	Mode of administration, lack of compliance	Weekly blood count monitoring in first year	Cost

Blood.2012;120(18):3657-3669

DEEFERRIOXAMINE

Deferoxamine (DFO), introduced in the 1960s, was the mainstay for more than 30 years. Regular use, with improved clinical management has significantly increased the average lifespan of patients with thalassemia (1,2,3).

Fig. 1 Survival in thalassaemia major in the UK: data from the UK Thalassaemia Register.



Clinical Pharmacology

DFO has a strong affinity towards iron. It chelates iron by forming a stable complex that prevents the iron from entering into further chemical reactions. It readily chelates iron from ferritin and hemosiderin but not from transferrin. It does not combine with the iron from cytochromes and hemoglobin. DFO does not

cause any demonstrable increase in the excretion of electrolytes or trace metals. Once bound, the complex is stable and is not redistributed. Theoretically, 100 parts by weight of Desferal is capable of binding approximately 8.5 parts by weight of ferric iron. Desferal is metabolized principally by plasma enzymes. The chelate is readily soluble in water and passes easily through the kidney, giving the urine a characteristic reddish color. Some is also excreted in the feces via the bile. DFO is poorly absorbed from GIT hence requires S/C administration. The daily dose is 20 to 60 mg/ kg / day. Higher doses are frequently associated with adverse effects which commonly become a cause for non compliance. Recently more intensive chelation by

24 hour continuous IV infusion of DFO in doses of 100 mg/kg/day is being used for patients with cardiac siderosis presenting as arrhythmias and severe left ventricular failure.

Ascorbic acid (vitamin C) increases the excretion of iron in the presence of deferoxamine. It is started after the initial month of deferoxamine therapy. It is given orally in the dose of 2 to 4 mg/kg per day (100 to 250 mg) and taken soon after the deferoxamine infusion has been initiated. Ascorbate should not be taken in absence of DFO infusion as it can cause cardiac damage by releasing iron.

The role of deferoxamine against transfusional iron overload continues to evolve. The experience with this drug goes back to the 1960s, and the advent of convenient subcutaneous pumps and compelling data for subcutaneous efficacy led the way for widespread deferoxamine therapy. Among all three chelators, DFO seems to be better at producing a negative iron balance (2,3,4). A multicenter study conducted in Italy showed better survival in children receiving regular DFO chelation therapy (2). The drug has transformed life expectancy for many patients with thalassemia major and other refractory anemias. It has also reduced endocrine and hepatic complications. Many patients with thalassemia major are not satisfactorily chelated by it, however, and then may develop a fatal cardiomyopathy. The reasons being 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 (4) and Yersinia infection.

Adverse Effects

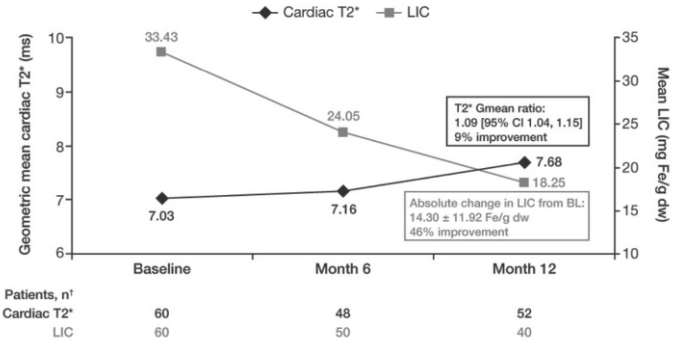
The main side effects due to DFO occur with high doses. These are visual due to retinal injury (night blindness, visual field loss, retinal pigmentation, and changes on electrical tests) and high tone sensory neural hearing loss. Growth and bone defects may also occur in children, with rickets-like bone lesions, metaphyseal changes, and spinal damage with loss of sitting height. A therapeutic index for DFO can easily be calculated as follows: mean daily dose (mg/kg) divided by current serum ferritin (mic g/L). If this is < 0.025 at all times, these side effects of DFO are less likely to occur (6). Regular checks are needed for visual or auditory defects, in children every 6 months and in adults annually. In children, checks of growth, particularly sitting height compared with total height, detect early spinal growth defects.

Moving Towards Combination Therapy

The main challenge now with deferoxamine is to understand how best to use it in combination regimens. Only very preliminary trials of deferasirox and deferoxamine in combination have been published (8, 9). The HYPERION study (11) demonstrated a significant improvement in cardiac T2 * during 12 months of treatment with DFX–DFO in patients with severe transfusional body iron burden. Overall, as LIC decreased cardiac T2* increased, most notably after 6 months. Cardiac T2* improvements were observed irrespective of BL LIC value, but were most marked in those with BL LIC <30 mg Fe/g dw, consistent with previously

published data. Safety of DFX–DFO was consistent with established monotherapy profiles,
Fig. 2 : Kattamis A et al. Blood 2013;122:2257

Figure. Geometric mean cardiac T2* and mean LIC over time in patients treated with DFX–DFO in combination then DFX monotherapy over 1 year (full analysis set)



†n for T2* refers to the last observation carried forward at each time point, and for LIC is the last available value within each visit window.

Conclusion

Despite all its flaws, DFO is still considered as a gold standard of chelating therapy. Weather used alone or in combination with other chelator, it is an essential of any chelating regimen. It has not only improved the survival of thalassemic patients, it has also improved their quality of life. The search for an ideal chelator is going on, till then deferrioxamine continues to be the choice of iron chelator by most physicians.

Combination Options

-Dr. Sunil Gomber

Complications of Iron overload in Thalassemia

- Liver fibrosis/cirrhosis/cancer
- Cardiac failure
- Diabetes mellitus
- Infertility
- Growth failure

(1)

Recent Advances in the chelation of Thalassemia

Dr. Sunil Gomber
I/C Hematology-oncology
Dir Prof . Pediatrics
UCMS & GTB Hospital
Delhi.

29.03.2014

(2)

Iron overload occurs due to:

- IRON FROM TRANSFUSION.
- IRON FROM INEFFECTIVE ERYTHROPOIESIS
- IRON FROM FOOD

(3)

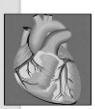
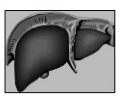
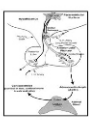
WHY CHELATION

- IRON GETS DEPOSITED INTO VARIOUS BODY TISSUES
  - HEART
  - LIVER
  - PANCREAS
  - ENDOCRINE GLANDS
  - EVERY WHERE

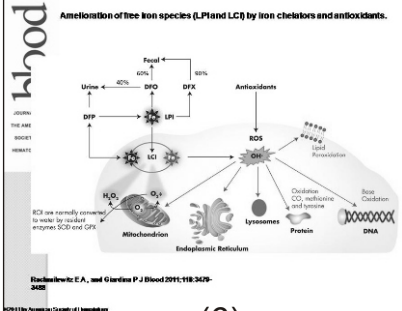
(4)

Iron Overload in Thalassemia Syndromes

- Iron overload has a significant impact on morbidity and mortality in thalassemia
- The organs affected are:

(5)



Rachmilewitz E.A., and Giardina P.J Blood 2011;118:3479-3488

(6)

Monitoring Iron Overload during Treatment

Serum ferritin: *Relatively easy test

*Values<1500µg/l recommended

* Level<2500µg/l reduces the risk of cardiac complications.

*Prediction of iron overloading from serum ferritin alone is poor.

Liver iron concentration: Reference standard .

Usually measured by liver biopsy.

Non invasive methods: SQUID , MRI

Urinary iron estimation: Can help in assesing optimal dose of iron chelator & presence or absence of negative iron balance.

(7)

MRI

- Non- invasive novel imaging tool for assessment of tissue iron levels
- Useful tool for monitoring iron burden in heart and liver

MRI images darken at a rate proportional to iron concentration

- Iron mediated darkening characterized by Half life time constant (T2*)

Myocardial T2* <20ms— indicative of iron overload
<10ms— severe iron overload

- In Hepatic iron overload T2* < 6.3ms

(8)

IDEAL CHELATING AGENT

- EFFECTIVE
- CHELATE IRON ONLY
- EASY TO TAKE
- NO SIDE EFFECTS
- ECONOMICAL
- NO INTERFERENCE

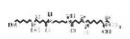
(9)

OPTIONS

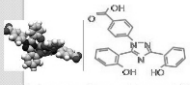
- DESFERRIOXAMINE
- DEFERIPRONE
- DEFERASIROX

(10)

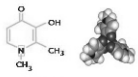
Iron Chelators Presently Available



Desferrioxamine (Desferal, DFO)
Hexadentate (1:1)
High molecular weight (MW)



Deferasirox (Asunra, Desirox, DFX)
Tridentate (2:1); low MW



Deferiprone
(Kelfer, DFP, L1)
Bidentate (3:1); low MW

(11)

DESFEROXAMINE

- FIRST IRON CHELATOR
- PROLONGED MANY THALASSAEMIC LIVES
- EFFECTIVE
- SOMEWHAT SPECIFIC
- SIDE EFFECTS
- PARENTERAL ADMINSTRATION

(12)

CHELATION THERAPY:

Desferrioxamine (DFO) Therapy:

Most widely tested and effective form of therapy.

- A siderophore (naturally occuring iron-carrier)
- 1 gm of DFO binds almost 93 mg of iron.
- Dose: 20-40 mg/kg
- Routes of Admn: Subcutaneous infusion
  Intravenous

I/M route : inconvenient & poorly effective.

Chelated iron is excreted via urine and stools.

(13)

Desferrioxamine (DFO) Therapy:

Each 500mg vial of DFO should be dissolved in at least 5ml of water.

Continuous I/V infusion– By implanted Port-a-cath.

Indications:

- ***Severe Iron Overload*** - ferritin value >300µg/l
  - liver iron >15mg/g dry wt
- ***Significant cardiac disease*** - cardiac dysarrythmias
  - failing ventricular function

(14)

CHELATION THERAPY:

Desferrioxamine (DFO) Therapy:

Most widely tested and effective form of therapy.

- A siderophore (naturally occuring iron-carrier)
- 1 gm of DFO binds almost 93 mg of iron.
- Dose: 20-40 mg/kg
- Routes of Admn: Subcutaneous infusion
  Intravenous

I/M route : inconvenient & poorly effective.

Chelated iron is excreted via urine and stools.

(15)

DEFERIPRONE

- 2ND IN LINE
- SPECIFIC
- SIDE EFFECTS
- CARDIAC EFFECTIVITY
- ORAL

(16)

CHELATION THERAPY:

Deferiprone (L1, Kelfer) Therapy:

- Orally active iron chelator from the bidentate hydroxypyridinones
- Licensed for use in India since 1995. Recently licensed in Europe

(2000) as second line monotherapy for patients unable to take DFO . FDA Approved

Dose 50-100 mg/kg.

Deferiprone in the usual prescribed dose of 75 mg/kg/ day is 65% as effective as DFO in removing excess iron with large variation between patients

(Victor A Hoffbrand & Beatrix Wonke)

(17)

Deferiprone (L1)

- **Adverse effects:**
- Arthropathy(20%-30%)
- Neutropenia
- Agranulocytosis (2-3%)
- GIT Problems as nausea, vomiting, diarrhea & Pain abdomen
- Zn Deficiency : due to binding of drug causing effect on growth and development
- Hepatotoxicity :

(18)

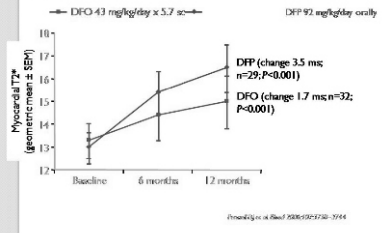
Deferiprone (Kelfer;L1)

- Iron Excretion is almost exclusively in urine.
- Recently found to be a good chelator of Myocardial iron (Lancet, 2000)
- One study described hepatic fibrosis during treatment with L1 (Oliveri et al NEJM 1998, 339, 417-423)

Other workers from multicentric study in Italy failed to report progression of liver fibrosis (Blood 2002, 100, 1566-1569)

(19)

Significant Improvement in Myocardial T2* with both DFO and DFP



(20)

Deferasirox (DFX)

- New synthetic oral iron chelator
- Approved by FDA in November 2005 and available in India since April 2008
- Highly selective for iron
- Can be used in children > 2 yrs.
- Half-life: 8-16 hours
- Long half-life appropriate for 24hr protection from NTBI
- Once a day dose required
- Mainly excreted in feces

(21)

Deferasirox

- Efficacy similar to DFO
- Some patients may have suboptimal response to maximum approved doses (30mg/kg/day) because of lower systemic drug exposure

Chirnomas et al Blood published online Sep.1, 2009

- Safety and efficacy in ped. patients similar to that in adult patients
- Removes iron from heart (further studies required)
- Dose : 20-40mg/kg/day
- Response dependent on transfusional iron load
- Not recommended to be combined with other chelators yet
- Availability Asunra :400mg (Rs. 85)
  100mg (Rs. 28)
  Desirox :500mg (Rs. 30)
  250mg (Rs. 18)

(22)

Dose Dependent Efficacy of Deferasirox

Dose of DFX mg/kg/day	Iron excretion mg/kg/day
10	0.13
20	0.34
40	0.56

A linear correlation between dose and iron excretion by deferasirox

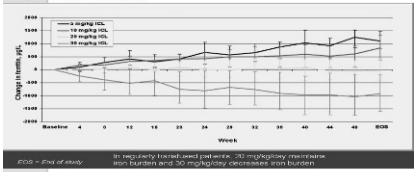
Nisbet et al Lancet 2003, 361: 597-602

(23)

A Phase III Study of Deferasirox in Patients with ß Thalassemia

586 pts. with thalasemia from 65 centres

Effect of DFX on Serum Ferritin

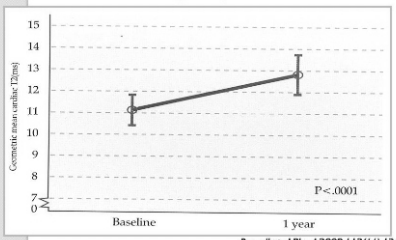


EOS = End of study

In regularly transfused patients, 20 mg/kg/day maintains iron burden and 30 mg/kg/day decreases iron burden

(24)

Improved Cardiac T2* at 1 Year (n=105) with Deferasirox



Pennell et al Blood 2008;112(11):318

(25)

Efficacy & Safety of Deferasirox Doses of >30mg/kg/per day in patients with Transfusion -dependent Anaemia & Iron Overload

Ali Taher, Maria D. Cappellini, Eliezer Vichinsky, Renzo Galanello, Antonio Piga, Tamsen Lewisohn, Yean Clark, Dany Habr and John B. Porter
August, 2009

- Retrospective analysis of 264 pts. with median exposure to deferasirox >30mg/kg/day for 36 wks.
- Dose : 30 – 42.5mg/kg/day
- High doses should be reserved for pts. with very high levels of iron loading who are not responding to doses <30mg/kg/day

(26)

Combination Chelation Therapy

It is the prescription of more than one chelator ,to be taken in the same day for a significant part of the treatment period.

2 variants of combination therapy:

a) Sequential : 2 chelators are taken in sequence with no substantial overlapping of the two drugs.

b) Simultaneous or concomitant : When in a single day 2 chelators are taken at the same time.

(27)

Combination chelation Therapy

- combination treatment potentially considered for a need of searching for synergistic or additive effect.
- The new treatment option greatly enhances the efficacy of iron chelation for preventing & treating iron overload.

(28)

Combination Chelation Therapy

Newer approach to chelation therapy.

Various studies available in literature:

Wonke B et al (NEJM 1998) studied 5 patients.

Urinary Iron Excretion was additive

Aydinok Y et al (Acta IIematologica, 1999) studied the effect in 7 turkish thal. Children.

Decrease in hepatic concentration observed.

(29)

Combination chelation therapy

Advantages:

- Different drugs may access different iron pools.
- L_1 of small molecular size can enter inside the cells hence can bind (Chelate) iron from inside the cells.
- L_1 Makes iron available for more stable DFO, the "sink" to pass it out of the body in urine or stools, a process referred to as "shuttle effect".

(30)

Combination Chelation Therapy

UCMS & GTB Hospital Study,2001

Gomber Sunil, Saxena R, Madan Nishi
Indian Pediatr 2004; 41; 21-27

- Total of 30 Thalassemia children((2yr-19yr) enrolled & divided in 3 groups, receiving DFO, L1 or combination of two.
- Serum ferritin &24 hr urinary iron excretion carried out for each child.
- Children followed up for 6 months.

(31)

Results of UCMS Study

❖Desferrioxamine is the most effective chelating drug in multi transfused transfused patients.

❖Combination of DFO (2 days/wk) & deferiprone daily is an effective alternative mode of chelation.

❖Combination chelation therapy is a cheap & effective method of chelation to be utilized in developing countries like India.

(32)

Journal of Cardiovascular Magnetic Resonance

The efficacy of iron chelator regimes in reducing cardiac and hepatic iron in patients with thalassaemia major: a clinical observational study

Vasilios Berdoukas*, Giorgos Chouliaras, Panagiotis Moraitis, Kiriykos Zannikos, Eleni Berdoussi and Vassilios Ladis

- Conclusion : **Combination therapy is best in reducing both cardiac and hepatic iron while DFP and DFX monotherapies are effective in heart and liver respectively. If reduction of iron load is regarded as being relatively urgent, combining DFP and DFO is the most appropriate option**

Journal of Cardiovascular Magnetic Resonance 2009, 11:20

(33)

Combined Chelation with Deferasirox & Deferioxamine

Pilot Clinical Trial done on 22 Thalassemia major patients with :
Deferasirox (DFX) : 20-30 mg/kg/day
Deferioxamine(DFO) :35-50mg/kg 3-7 days/week
In 18 subjects completing 12 months of therapy :
- Median Liver conc. Decreased by 31% from 17.4mg/g to 12.0mg/g
- Median Ferritin decreased 24% from 2465 ng/ml to 1875ng /ml.
- Improvement in MRI T2 * in all patients with increased myocardial iron

- Simultaneous administration of DFO & DFX rapidly reduced systemic & Myocardial iron overload.

Lal A, Porter j et al . Blood Cells Mol Dis 2013,50(2) : 99-104

(34)

UCMS , Delhi

Comparative Efficacy and Safety
Of
Oral Iron Chelators
and
Their Novel Combination
In
Thalassemics

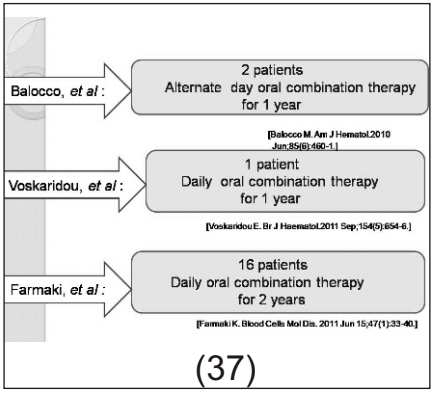
(35)

No such study so far
Reported in Indian Literature

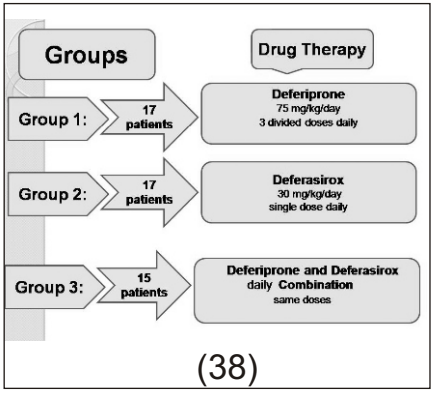
Safety of Combination of oral iron chelators

NOT yet established in **children**

(36)



(37)



(38)

Serum Ferritin

Measured at various intervals :

1. at **start** of study
2. at **6 months** of respective chelation therapy
3. at **12 months** of respective chelation therapy

CRP : to exclude factitious rise in Serum Ferritin

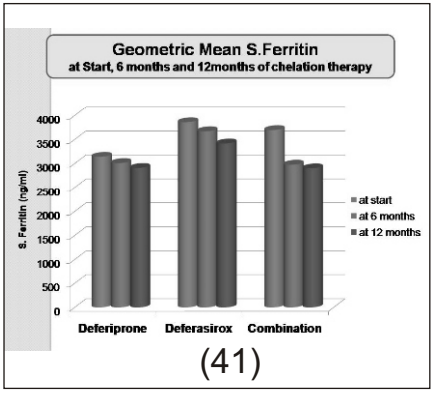
(39)

MRI T2* of Liver and Heart

Randomly chosen 5 patients of each group
(due to financial constraints)

1. at **start** of the study
2. at **6 months** of respective chelation therapy

(40)



(41)

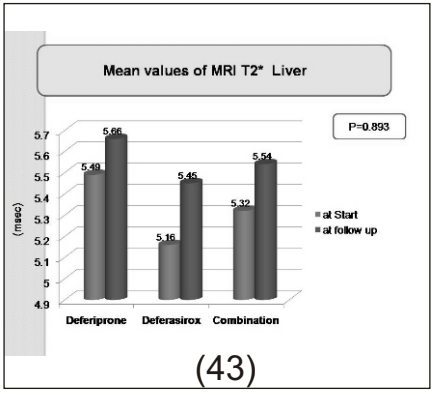
Grades of MRI T2* of Liver and Heart Iron Loading

Iron Load	MRI T2* Liver (msec)	MRI T2* Heart (msec)
None	More than 6.3	More than 20
Mild	6.3-2.7	12-20
Moderate	2.7-1.4	8-12
Severe	Less than 1.4	Less than 8

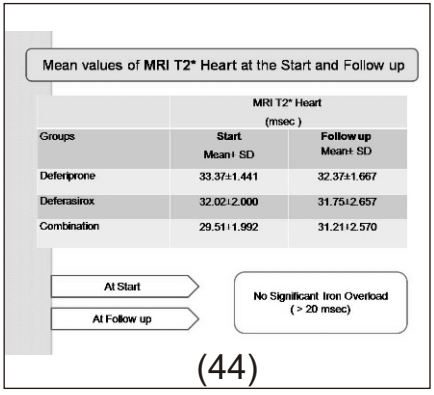
Values measured in milliseconds (msec)

[Pennell DJ. Ann N Y Acad Sci.2005;1054:373-8.]

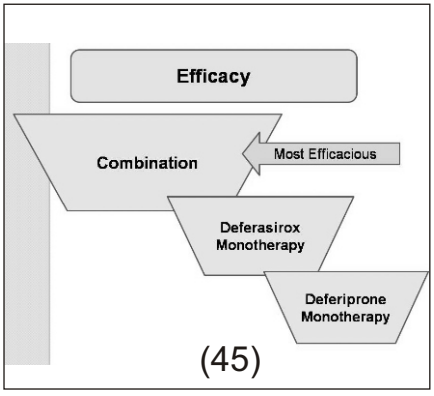
(42)


Mean values of MRI T2* Liver
P=0.893
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5
4.9
(msec)
5.49
5.66
5.16
5.46
5.32
5.54
at Start
at follow up
Deferiprone
Deferasirox
Combination

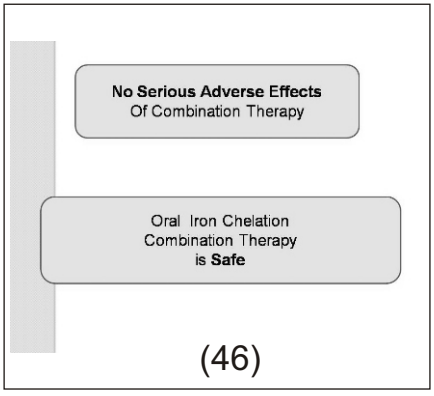
(43)


Mean values of MRI T2* Heart at the Start and Follow up
MRI T2* Heart
(msec)
Groups
Start
Mean± SD
Follow up
Mean± SD
Deferiprone
33.37±1.441
32.37±1.667
Deferasirox
32.02±2.000
31.75±2.657
Combination
29.51±1.992
31.21±2.570
At Start
At Follow up
No Significant Iron Overload
(> 20 msec)

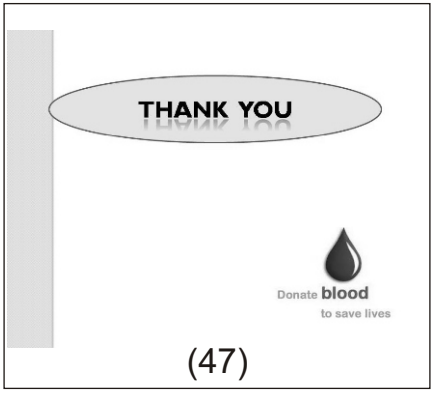
(44)


Efficacy
Combination
Most Efficacious
Deferasirox
Monotherapy
Deferiprone
Monotherapy

(45)


No Serious Adverse Effects
Of Combination Therapy
Oral Iron Chelation
Combination Therapy
is Safe

(46)


THANK YOU
Donate blood
to save lives

(47)

Monitoring of Thalassemics

-Dr. Rajeev Bansal

A patient of Beta Thalassemia Major needs regular monitoring of various parameters as it is a multi-system disease. To lead a normal life regular monitoring is a must, as any loopholes in monitoring leads to significant long term complications.

Monitoring of blood transfusion.

- Extensive blood group typing that includes at least C,c,E,e,and Kell other than ABO and Rh
- Full cross match and screen for newer antibodies
- Pre transfusion Hb monitoring before each transfusion- keeping Hb 9- 10.5 gm/dl
- Post transfusion Hb monitoring, to keep Hb 14-15 gm/dl. This allows assessment of rate of fall of Hb levels
- Careful record of transfused blood – volume or weight of administered unit,
- haematocrit of the unit and weight of the patient. Calculate the annual blood requirements
- Hb fall should not exceed 1 gm/dl/week in patients with intact spleen and 1.5 gm/dl /week in patients with Splenectomy
- Easy way to gauge adequacy and desirability is – non palpable spleen and less than 2 cm liver. Spleen and liver size should be assessed at each visit
- Less than 5% normoblasts and especially less than 1% normoblasts on PBF is a good indicator of transfusion adequacy
- Liver function tests (SGPT especially)., Serology of HBV, HCV, HIV and CMV status
- Se Creatinine levels and urine examination exam, if patient is on deferasirox
  Anti HBV antibodies levels monitoring

Monitoring of Growth

- Regular monitoring of weight, height and sitting height
- Plotting of growth charts and growth velocity
- Pubertal staging
- Bone age assessment

Monitoring of Iron overload (discussed elsewhere in detail) – Se Iron, TIBC, Se Ferritin levels, T2* MRI of liver, Heart, Liver biopsy

Monitoring of Cardiac functions

- ECG – combined with exercise
- 24- hour ECG – to detect abnormalities of heart rhythm
- Echocardiogram – measuring the size of the chambers and how well each part of heart is functioning
- MUGA scan
- Cardiac MRI - T 2* MRI of Liver , Heart and Pancreas

Cardiac MRI is an excellent tool for measurement of ventricular size and performance. LV impairment becomes increasingly likely when T2* falls below 20 milliseconds (ms) (Anderson et al 2001). Nearly all patients with clinical evidence of heart failure have a very low T2* (<10 ms).

A lack of correlation between myocardial T2* and serum ferritin or liver iron is there.

Cardiac T2* MRI is indicated every 2 years if T2* >20 ms, every year if T2* 10-20 ms, 6 monthly if T2*<10 ms, 3 monthly if T2*< 10 ms and any evidence of cardiac impairment

Monitoring of Endocrine and bone disorders

- Free T4 & TSH
- PTH level , Se Calcium & Phosphorous levels
- FSH , LH
- Testosterone or estradiol
- Oral glucose tolerance test
- X ray hand and wrist, elbow for bone age
- DEXA Scan

Ophthalmological Exam

Audiology Examination

Clinical and laboratory evaluation checklist

Monthly

- CBC

Every 3 months

- Serum Ferritin
- Clinical chemistry – viz: glucose, Creatinine, SGPT, SGOT etc.

Every 6 months

Complete physical examination and anthropometry and growth charting

Cardiac evaluation (especially in children > 10 yrs. of age)

- Cardiac ECHO., ECG

Yearly

Virology: Hepatitis B panel (HBsAg, anti HBs, anti HBcIgG
Hepatitis C panel (anti HCV, anti –HCV RNA)
Anti HIV 1+2

T2* MRI for Heart and Liver iron overload estimation, if available. (May be done 2 yearly, if initial evaluation shows insignifant overload)

Endocrine function evaluation: (over 10 yrs. of age)

Bone age (by X rays after 6-7 yrs.) and Bone density measurement (> 10 yrs.)

Ophthalmic and audiologic exam

Need for Multi-disciplinary Care

-Dr. Michael Angastiniotis

Thalassaemia is a lethal hereditary disease which, with medical intervention has been converted to a chronic disorder. Despite this the chronic anaemia and the iron overload which is the result mainly of the regular blood transfusions has resulted in the appearance of complications which eventually may kill the patient and will certainly significantly affect the quality of life. The complications include those due to chronic anaemia, such as gallstones, bone marrow expansion, extramedullary haemopoiesis and hypersplenism. Blood transfusions can also cause immune reactions and transmit viruses and other infectious agents. Iron overload can seriously affect the heart, the liver and the endocrine glands. The end result is that over time thalassaemia becomes a multi-organ disease. Despite this all the complications can be controlled if diagnosed early with an effective intervention provided at the early stages. To achieve this monitoring is required by specialists such as cardiologists, endocrinologists and hepatologists. In addition psychosocial support is needed in many cases. All these specialists must work in a coordinated way and this is the responsibility of the lead consultant who can be a haematologist or an internist. It is necessary to share the patients' medical records and this is best achieved by electronic files.

Enjoying Thalassemia

- Mrs. Sangeeta Wadhwa

Why should I behave like normal??? I am normal, God "s chosen one. This deep meaning, I came to understand when I got to know that I am a thalssaemia Major.

I am Sangeetah Wadhwa, 37yrs old, complete my graduation BMS and my post graduation Diploma in psychology and counselling. Presently I am working in Shri Hashu Advani Memorial Foundation Health care and thalassaemia center as PUBLIC RELATION OFFICER & COUNSELLOR.

My journey started when I was ten years old and started to understand many things surrounding me, many times I observed my dad arranging blood for my sister and for me, my mother, father and brother every one in my family sacrificing many things to give us a single smile and better treatment. I truly believe in my parents, I trust my doctors and I keep hope for every new morning.

When I was detected as thalassemia there is no one who knew about this disease. Everyone gave advice about things like babji ka powder, puja, ayurvedic, etc but because my parents are educated they did not believe in as such, I remember in 1983 when my dad arrange first desferral vial for me that time no one knew about it, painful days ,low HB, shortage of blood, ,maximum time I was in hospital because I am weak ,or may be I am not getting proper treatment because no one knows what is Thalassemia exactly. I also remember my worst day when doctor said my feraat in is 4000, seriously while listening this I felt as I have failed in exams because till I had understood the importance of chelator, hanging deferral pump and traviling in train, feeling like going to fight a war.

Kelfer gave me a comfortable life but joint pains seriously was too difficult to handle, I felt bad, I can't run, because I am different from others, teacher don't allow me to take a part in hiking, picnic because no one wanted to take care? I had to skip my exams and attendance but my mother was never ready to compromise my studies, but she motivated me in every path of my life.

The psycho social aspect can NOT and should NOT be ignored. Coping with a chronic health problem is stressful for both the parents and the child and the child may feel like an alien and even be treated as such compared to his or her peers if there is no empathy and a lack of support. Psycho social issues on top of medical issues can be a double whammy in terms of the child's sense of self image, self confidence, and general outlook on life.

Slowly and gradually me and my sister started to help out to my father for arranging blood donation drives, our picnic day used to be the transfusion day, our family picnic is attending thalassemia National and International conferences. Sometime its very painful to know that

we are different from others.

Question is why ?? why Me?, Parents are trying to explain us that we are special a child-chosen one, that's why we suffer a lot, because god is talking our test, we have to prove that we are strong. one thing I understood if I have to serve with my dignity, with respect like other person I have to be become Normal, in short behave like a normal, learn many courses, help many societies & trusts for raising their funds, because I have to prove myself that I am normal and only difference between me and others is that I never hide that I am a thalassemic from anyone.

13 Aug 2010 when I lost my sister and then I realize that I lost my world, because I am not strong, but I believe, that day I realize, because of lack of knowledge we lost her, and I again started to work for thalassemia, but this time not for my dignity but for my all thalassemic friends.

One thing also I realise after her is that it is not necessary to behave like a normal, the only thing you is that you accept what you are, what exactly is thalassemia and what are myths and truth about it because if one thing is with us our whole life and even we didn't know about it any thing is amazing ? Fact, but its truth.

In 2011 we Thalassemia patients started youth Thalassemia Allience (YTA) in Mumbai The objective of this alliance is to work towards Thalassemia awareness and Educated thalassemic patients and parents arranging donation drives etc.

In Sept 2013 Thalassemia International Federation, FIT& NTWS gave me a great Platform to work as Mumbai Zone coordinator.

We don't want thalassemia major in this world its not a only duty of Doctors, Parents, Society, firstly its mine (patients) duty to finish thalassemia from world.

Give me best so that we can face-fight and finish thalassemia.

"Life with Thalassemia"

- Dr. Rimjhim Bakshi

"Do not follow where the path may lead, go instead where there is no path and leave a trail" & "Donot worry if you have built your castle in the air, they are where they should be, now just put the foundations under them." With this quote I warmly welcome all of you in the 7 th National Thalassemia conference and stand before you to share my enriching Thalassemia journey and what has led me to achieve my goal.

When I was born, I was as normal as any other kid as soon as I was diagnosed with Beta Thalassemia. After that the brightest days of my life became the darkest days. My childhood was the most difficult time of my life . Besides my multiple visits to the hospital and my school bunks, I was having a lot of other medical problems related to Thalassemia. At that time Thalassemia was my biggest enemy whom I hated the most. But as I grew up I started exploring life.I immersed myself in education was determined to do something and ensure the world that anybody with a disease as devastating as Thalassemia would be able to fulfill their dreams and live a happy, productive and a successful life. & it was during that phase of my life when I realized that Thalassemia is a hidden jewel inside me, the treasure of dedication and passion. Thalassemia is no longer a monster to me, rather it has became my companion for life. What was once a weakness a flaw to me, is now my priceless gem. It is because of Thalassemia that the motivation to succeed runs through my veins.

I can't deny the fact that sometimes me and many of my Thalassemia friends gave up multiple of times due to the confronting obstacles that we face during our life journey and feel helpless. But that is the time friends when we again have to ignite the fire of passion and inspiration inside us and stand up again.

Never give up and always embrace obstacles as obstacles are actually the valuable lessons that are clever planned by God . Without confronting obstacles you will never grow. Enduring pain always makes us strong. Obstacles will never crush you as long as you have the courage to overcome them.

At last I want to tell all my Thalassemic friends that you are special. Please don't let Thalassemia rule your life. Donot worry for tomorrow, live happily today. Never give up and always fight like a fighter. I want you all to know that you are the best. Please don't give up,

Because you won't give up..!!!!!

Approach to antenatal diagnosis

-Dr. Madhulika Kabra

Hemoglobinopathies are considered to be a serious health problem by WHO as approximately 25 crore people carry an abnormal hemoglobin gene and about 300,000 infants are born each year affected with a major hemoglobin disorder. In India the carrier frequency of beta thalassemia varies from 1-17% (mean 3.3%) in different ethnic groups. It is estimated that about 7600 babies affected with beta thalassemia are born every year and about 3 crore people are carriers of the gene in this country.

Strategies for prevention and control of these hemoglobinopathies are well defined. Identification of carrier status followed by genetic counseling and prenatal diagnosis is the mainstay of control of hemoglobinopathies. However, the option of carries not marrying carriers is too personal and difficult to implement in our country. The ideal way is to have national program for carrier screening, counseling and offering prenatal diagnosis. Prevention by prenatal diagnosis as a major component of these programs has an important role to play in a country like India where there are limited resources for medical care of affected cases. However, such facilities are available in a handful of centers in the country.

Our experience of screening pregnant mothers in early antenatal period as an activity of multicentric project funded by ICMR made us believe that this alternative is probably most feasible. Screening of couples before and after marriage and inductive screening are also feasible . Due to socio-cultural issues of mass screening (stigmatization of carriers particularly girls) ,these modalities have been tried as pilot research projects in India.

Prenatal Diagnosis :

Prenatal diagnosis of -thalassemia was initially done using fetal blood for globin chain synthesis studies and still is the method of choice in situations where mutations are not identified or the couple reports at advanced gestation. Subsequently DNA based methods became more popular. Amplification Refractory Mutation System (ARMS) technique is based on the fact that under appropriate conditions the Oligonucleotide primers with a mismatch at 3' terminal nucleotide do not function as primers. ARMS using PCR is a reliable and relatively simple method and is being widely used in our country and abroad. Now many centers including ours use direct sequencing .Linkage studies using restriction frequent length polymorphisms (RFLP) are useful in families where mutations are not identified but markers are informative.

For beta thalassemia five common mutations are reported in Indian population namely, IVS-1, nt5 (G.C), IVS-1, nt1 (G.T), codon 8/9 (+G), codon 41/42 (-CTTT) and 619bp deletion. For

prenatal diagnosis by molecular studies fetal tissue like Chorionic villus sample (CVS), amniotic fluid or cord blood sample can be used. CVS is the preferred tissue as it gives a good yield of DNA. Chorionic villus sampling (CVS) is usually performed at 11-12 weeks of gestation under ultrasound guidance and a sample weighing 10-20 mg is taken. Pretest counseling includes explaining about the 25% risk of recurrence and risk of fetal loss due to the procedure, which is about 1-2% . Chorionic villi are cleaned from maternal tissue under inverted microscope. DNA extraction from the whole blood and CVS is done by proteinase K digestion and phenol/chloroform method. CVS is tested for parental mutation(s). Wherever parents' mutations are identical, normal as well as mutant primers are used in separate reaction tubes to differentiate between heterozygous and homozygous cases. Positive and negative controls are run with each sample.

In our laboratory we are using ARMS technique and direct sequencing for molecular diagnosis and prenatal diagnosis of -thalassemia and are able to detect mutations in almost all families. Maternal contamination is ruled out by polymorphism of Apolipoprotein B (Apo B) and other markers using PCR..

Non-Invasive Prenatal Diagnosis (NIPD) :

Recent research in the area of NIPD is promising in which test is done on maternal blood peripheral after isolating fetal DNA from maternal plasma. This avoids the risk associated with invasive testing. The techniques utilized are real time PCR and next generation sequencing. The technique is still experimental and has not come to routine practice.

Conclusions :

Implementing heterozygotes screening and prenatal diagnosis on a nationwide basis would require community education, creating awareness amongst pediatricians, obstetricians and peripheral health workers. They have a key role in counseling and implementing carrier-screening progammes. At the same time there is an urgent need to increase awareness among the masses about the feasibility of genetic services.

An essential prerequisite before starting the awareness campaign on a war footing is to create adequate facilities to meet the gigantic demand for heterozygotes screening and prenatal diagnosis of haemoglobinopathies. Peripheral centers should be able to screen couples at risk and refer them to tertiary centers. The handful of tertiary centers themselves need strengthening and more centers should come forward to share the workload.

The success of the prevention programme will depend entirely on the combined efforts of health professionals, governmental and non-governmental organizations and, above all, the people who need these services.

Thalassemia Control Program

-Dr. Sujata Sinha

That there is a need for a national strategy in India for control of thalassemia and hemoglobinopathies has been a rallying point for majority of the doctors and scientists involved in thalassemia care and research and for patients and parent organizations for thalasssemics for over a decade now. The purpose received support and validation from international agencies such as Thalassemia International Federation and World Health Organization urging member countries to take steps to control thalassemia. The Consensus Meeting convened for developing a roadmap leading to a national strategy or programme during the Indo-US Symposium on Genetic Disorders with Focus on Hemoglobinopathies held at Varanasi in 2006 provided the necessary kick start to the process. National Thalassemia Welfare Society along with the network of Federation of Indian Thalassemics has been instrumental in bringing together all the stakeholders working towards a common goal. The concerted efforts have culminated in initiation of a screening and intervention program for thalassemia and hemoglobinopathies within the framework of Action on Birth Defects Project, a component of the Rashtriya Bal Swasthya Karyakram (RBSK) in Uttarakhand, a program for child health screening and early intervention services for 4D's-Defects at Birth, Deficiencies, Diseases and Developmental Delays including Disabilities launched under the aegis of National Health Mission formerly National Rural Health Mission. The following paragraphs present a brief summary of the concept and guiding principles and challenges in initiation and implementation of the program through the public health system and its continuation and development within the framework of a comprehensive national initiative for child health- Rashtriya Bal Swasthya Karyakram (RBSK) launched in 2013.

Birth Defects and Thalassemia: Birth Defects are synonymous with congenital disorders and are defined by WHO as 'structural or functional disorders, including metabolic disorders, present since birth'. Major data on global prevalence of Birth Defects has been provided by March of Dimes (MOD, 2006). Accordingly one third of under five childhood mortality globally can be attributed to Birth Defects with the highest incidence in low and middle income countries. In India, 6-7% of births were estimated to be affected by serious Birth Defects. Congenital Heart Defects, Neural Tube Defects, Hemoglobin Disorders (Thalassemia and Sickle Cell Anemia), Down Syndrome and G6PD Deficiency are estimated to account for 25% of all Birth Defects. The WHO Secretariat Report on Birth Defects (2010) provides guidelines for taking steps to reduce mortality and burden of disease by establishing a screening and referral system for early detection of Birth Defects through primary health givers. Thalassemias and Hemoglobinopathies and other Birth Defects thus also find mention among the health priorities in the 12th Five year Plan of Government of India.

Action on Birth Defects Project (2011-12): It was on the basis of the appraisal on Birth Defects as provided above and with inputs from Public Health Genomics Foundation, Cambridge, during the International Workshop on Community Genetics held in Dehradun in 2011, that it was considered appropriate to develop a comprehensive framework for action on Birth Defects that included thalassemias and hemoglobiopathies as well . Thus the Action on Birth Defects Project (ABD Project) was conceptualised and initiated as a pilot project under NRHM in Uttarakhand in 2011-12 in Dehradun district with its nodal centre at the district hospital, Govt. Doon Hospital. Developing and establishing a comprehensive State level screening and intervention program for Thalassemias and Hemoglobinopathies and newborn screening for other common congenital disorders -Congenital Heart Defects, Down Syndrome, Neural Tube Defects, Orofacial Clefts, G6PD Deficiency and Congenital Hypothyroidism- at the District Women's Hospital were the major components of this NRHM -funded project.

Thalassemia Control Program and Anemia

Thalassemia as a Birth Defect provides an opportunity for application of all the three strategies of prevention and control –primary prevention by premarital screening for detection of carriers followed by genetic counselling; secondary prevention by post marital or post conceptual detection of carrier followed by prenatal diagnosis and selective termination of pregnancy; and tertiary prevention by early detection of thalassemia disease to initiate timely management of disease and where possible take steps for curative treatment. A successful thaassemia control program would be one that incorporates all the three strategies.

Anemia- Thalassemia Carrier Screening and Counseling

However, concurrent high prevalence of iron deficiency anemia and other nutritional in target populations for screening for thalassemia carriers- premarital screening in adolescents and young adults that comprise non pregnant females, post conceptual screening in pregnant women. made it imperative to devise screening protocols that would overcome the masking effect of anemia on thalassemia carrier state as well as address the overriding public health concern of reducing anemia prevalence in the target populations. Thus it was considered prudent to devise a cost effective ' anemia – thalassemia carrier screening' protocol based on a judicious combination of standard available tests for the two conditions. Thus a three visit protocol was developed for the detection of common types of anemia, and for Thalassemia cases and carriers, by using five tests in a stepwise protocol: Hemoglobin by digital hemoglobinometer; NESTROFT (Naked Eye Single Tube RBC Osmotic Fragility Test; Complete Blood Counts by automated blood cell counter; Serum Ferritin immunoassay; and Hemoglobin fraction analysis by HPLC. The carrier detection program is being supported by a three step system of pre test educative and post test informed genetic counselling for detected thalassemia carriers. A supportive laboratory referral service for DNA analysis for

mutation detection is being undertaken with the nearest tertiary public institution, PGIMER Chandigarh, both for confirmation of the diagnosis and for empowering the individual to avail the secondary prevention step later in life if required.

Screening of Pregnant women:

Universal screening of pregnant women was undertaken in the first year of the Project at District women Hospital of Dehradun but due to non availability of prenatal diagnostic services in the State the intervention could not be assured in all and hence now has been modified to provide referral support for prenatal diagnosis to PGIMER Chandigarh under the Janani Shishu Surakhsha Karyakram.

Screening for thalassemia disease and management

Children between 6 months and 6 years of age referred for severe anemia to the District hospital are investigated for common causes of anemia including thalassemia disease. Children detected with thalassemia disease are registered under the thalassemia care for free of cost transfusion, chelation and laboratory services required for management of thalassemia disease as per management protocols with consultative assistance support provided to the treating /paediatricians from experts from LHMC and AIIMS, New Delhi. If required patients are referred to these higher centers for evaluation.

Patient detected to have severe anemia due to any other cause were treated accordingly.

ABD Project and RBSK (2013-14)

In 2013-14, the Project has been up scaled for implementation in three more districts as component of the RBSK that has been launched mainly to address Birth Defects and Developmental Delays and Disabilities. Common childhood deficiencies and diseases have been included to provide comprehensive coverage to health concerns in the 0-18 year age group with provision of free of cost services required for detection diagnosis and management of 30 enlisted conditions. While screening by physical examination for 29 conditions that include 9 Birth Defects, 5 common childhood diseases, 5 common deficiencies and 9 types of developmental delays has to be undertaken by all States, inclusion of screening for conditions requiring blood tests - thalassemia, sickle cell anemia, congenital hypothyroidism and other inborn errors of metabolism including G6PD deficiency-listed under the 30th head are kept optional for the States to undertake them as per capacity and requirements. The ABD Project has been incorporated within the RBSK in the State as a component to build capacity for screening and intervention services for these disorders. The Project has been up scaled to three more districts of the State with the objective of developing the DEICs of these districts as regional referral centers to provide laboratory and clinical support for all distrcts of the State. The DEICs of these districts is being equipped with additional equipments and Human Resource for the purpose.

The target population of 0- 18 years has been divided into three groups of 0 to 6 weeks, 6 weeks to 6 years and 6 to 18 years to facilitate age appropriate screening and also to guide access of target populations. The first group is accessed at public health delivery points and at those born at home are screened for Birth Defects , second group is screened at Aanganwadis and third group at government and government aided schools. Thus, screening for thalassemia disease is done in 2nd age group and anemia- thalassemia screening is undertaken in 15 to 19 yr sub group of students of class IX to XII included under the 3rd age group.

Capacity building

The infrastructural capacity is being created to provide screening and referral services at Block level through recruitment of Mobile Health Teams comprising of Medical Officers and paramedics trained in screening and provision of early intervention services for management and treatment at District level through establishment of District Early Intervention Centres (DEICs). The establishment of DEICs includes providing infrastructure in the form of building, furnishing, equipments, laboratory facilities, dedicated staff comprising of medical professionals and paramedics including various therapists required to deal with cases of developmental delays and mental and physical disabilities.

IEC (Information, Education and Counseling):

Material for training and community education and awareness on common Birth Defects including thalassemia has been developed and incorporated within the RBSK resource material. It includes basic information on genetics and its impact on health,and steps for the prevention and intervention of inherited disorders. At the same time, a capacity-building process has been initiated through training programs for various levels of healthcare professionals within the State health system.

The presentation will discuss in some detail the above mentioned aspects including screening protocols, implementation mechanisms and their outcomes till date and possibility of replication of the model in other States with modifications as per requirements and will also discuss the progress made towards creation of information systems to support a nation wide network .

Carrier Screening in β-thalassemia – Who and How?

-Dr. I.C. Verma

The necessity of prevention of thalassemia is obvious. The cost of prevention to treatment is about 1:4. The strongest argument for prevention is providing optimal care for those affected, by limiting their number. By applying prevention to those couples who already have an affected child, there is only a limited reduction of the burden, as many affected infants are born to couples whom do not have an affected child.

The risk of having a child with thalassemia major arises only in those couples both of whom are carriers. Therefore recognizing carriers, and informing them of the various options available to them, is the key to prevention. Carrier screening can be done at various times and ages:

Premarital screening is useful, as if carriers do not marry carriers there will be no birth of children with thalassemia major. This is easier to advise but difficult to implement. It is the only option in countries that do not allow abortion. However, in countries abortion of a fetus affected with a genetic disease is legally permitted it has met with limited success. Carriers tend to be get stigmatized. Finding a partner, which is always difficult, is made even more so by the introduction of matching for a genetic trait. The technology of prenatal diagnosis in couples where both partners are carriers has been highly successful around the world in preventing the birth of children with thalassemia major.

In Cascade screening In this, one begins with an affected child, and screens siblings and relatives. This is a highly cost effective and practical screening approach. The number of β-thalassemia carriers they identified is 5-6 times more using cascade screening than conventional population screening.

Preconception Screening refers to screening for carrier status after marriage but before conception. This allows for appropriate counseling, time for the partners to understand the associated risks and the need for prenatal diagnosis. It also allows the laboratory to identify the mutations and be prepared for the prenatal testing. It is however difficult to implement in practice. As the carrier frequency is high in India, all couples going to obstetricians for counseling or infertility clinics must be screened to identify the carries and provided appropriate counseling.

Antenatal Screening is currently the most prevalent mode of screening in India. Women should be screened at the first antenatal visit. Husbands of carrier women are subsequently screened for carrier status and given appropriate counseling. The major limitation of this

method is that pregnant women often do not attend the antenatal clinic early in pregnancy. A concerted effort is required to ensure that women attend the antenatal clinic in the first trimester. There are also delays in getting the husbands for carrier screening, leading to late recognition of couples at risk that require prenatal diagnosis. If the husband is accompanying the wife we advise both to be screened together. It is recommended that carrier screening should be done even if the woman presents in advanced gestation. It will identify the couple at risk, and prenatal diagnosis assures the ¾ of the couples where the fetus is not affected.

Mandatory vs Voluntary Screening. In many countries like Cyprus, Saudi Arabia and Iran, carrier screening is mandated by law. However, WHO recommends that screening should be voluntary and most countries follow this after appropriate counseling. It is recommend that in India, screening should continue to be voluntary and not made mandatory. We just do not have the infrastructure to cope with mandatory carrier screening in all pregnant women, and this approach is not suited for a democratic society.

It is **recommended that in India,** as part of pre-marriage counseling carriers may be advised not to marry carriers, as it avoids prenatal diagnosis, which can be unpleasant. Carriers should ideally be identified in the preconception period, or in early pregnancy so that prenatal diagnosis can be offered to the at risk couples. It is strongly recommended that initially in every region all pregnant women be screened for carrier status, and once this is established, then go to screen the community.

Multiples laboratory tests are available for carrier testing. The gold standard remains hemoglobin A2 estimation by high performance liquid chromatography (HPLC), along with estimation of red cell indices. The application of this as a universal screening technique in developing countries, such as in India is limited by its cost. It is recommended that in India the **primary strategy** to screen for carriers of β-thalassemia should be to study red cell indices, along with HPLC analysis. If facilities for HPLC are not available then red cell indices may be tested alone; but in subject with even mild abnormalities of red cell indices (MCV less than 80, and MCH less than 27) confirmation must be sought by HPLC analysis. In areas whether neither of these tests can be done, then study by NESTROFT technique may be carried out, with confirmation by HPLC and red cell indices in all positive and doubtful positive cases.

Cordocentesis for thalassemia

-Dr. Renu Saxena

Most of the centers offering prenatal diagnosis search for five common mutations prevalent in India, which cover more than 90% of patients. However in those families where the mutation is not identified in the parents or mothers come late in pregnancy, prenatal diagnosis becomes difficult by mutation detection. In such situations,the technique followed in some centers is globin chain synthesis ratio in second trimester on cord blood. In this procedure fetal blood sample is collected after 18 weeks of gestation and globin chains are separated on CM cellulose column. Ratio of β/α chains is studied. However this technique is cumbersome and not available in most of the centers. Cord blood High performance liquid chromatography (HPLC) is an effective technique for identification of normal and abnormal hemoglobins. During intrauterine life HbF is the dominant hemoglobin in the body. Higher value of HbA for normal or heterozygous infants (2.1-10.6%) than for thalassemia major fetuses (0.0-0.4% or 0.0-0.8%) has been reported by many studies. The advantages of using this method are the ease, rapidity and cost-effectiveness. Since the implication of giving a prenatal diagnosis of affected baby is termination of pregnancy, there is further need for standardization of this procedure so as to offer this potentially beneficial technique to the affected families.

Risks of Cordiocentesis :

- Procedure related fetal loss 1.2%-4.9%
- Cord bleeding
- Transient bradycardia - 8%
- PROM, PTL
- Chorioamnionitis
- Failed procedure

Medical Treatment of Thalassemia Intermedia

Dr. Prantar Chakrabarti

What is NTDT?

Non-transfusion-dependent thalassemias (NTDT) is a term used to label patients who donot require such lifelong regular transfusions for survival, although they may require occasionalor even frequent transfusions in certain clinical settings and for defined periods of time (eg. for growth failure, pregnancy, infections).

There are 3 types of NTDTs

- β-Thalassaemiaintermedia
- Haemoglobin E β-thalassaemia
- Haemoglobin H disease

Although, patients with hemoglobin S/β-thalassemia and hemoglobinC/β-thalassemia may have transfusion requirements similar to NTDT patients, these formshave other specific characteristics and management peculiarities.

Pathophysiology and clinical complications

Three main factors are responsible for the clinical sequelae of TI: ineffective erythropoiesis, chronichaemolyticanaemia, and iron overload. The degree of ineffective erythropoiesis is the primarydeterminant of the severity of anaemia, while peripheralhaemolysis of mature red blood cells (RBCs) remains secondary.

Ineffective erythropoiesisis also associated with skeletal deformities andosteopenia attributed to erythroid marrow expansion as well as compensatory extramedullaryhaematopoiesis (EMH) leadingto tumour formation anywhere throughout the body. Ineffectiveerythopoiesis and chronic anaemia also lead to an increasein gastrointestinal iron absorption, resulting in non-transfusional iron overload, in the liver andless so in the heart.

Haemolysis has mainly been associatedwith splenomegaly. It has also been recognized as the hallmark of ahypercoagulable state in TI. Hypercoagulability accounts for the high rate ofthromboembolic phenomena in patients with TI and may explain other complications such aspulmonary hypertension (PHT) with secondary right heartfailure (HF)

Optimal Management

It is very important before embarking on any form oftreatment to establish the particular variety of thalassaemiaand to obtain full blood group genotype of the patient. It isalso essential to assess the patient carefully over the first fewmonths after the diagnosis is established and not to embark onany treatment modality, especially transfusion therapy, toohastily.

Blood Transfusion

Patients with thalassemia intermedia mayrequire occasional blood transfusions during infection, pregnancy, surgery, or any setting with anticipated acute blood loss. During childhood, they may require more frequent, yet temporary, transfusions in case of poor growth or development .Patients who receive transfusions experience fewer leg ulcers, thrombotic events, pulmonary hypertension, and silent brain infarcts compared with transfusion- naïve patients. Hematopoietic compensatory extramedullarypseudotumors may be managed well using transfusion therapy with and without radiation or surgery, even in the most debilitating cases with paraspinal involvement.

However, it is absolutely essential to assess the patient carefully over the first few months after the diagnosis is established and not to start on any treatment modality, especially transfusion therapy, too hastily. Even if a few transfusions have been administered in the acute situation,it is worthwhile trying to evaluate the patient in the non-emergency situation from the untransfused baseline. In fact, some children with NTDT, specifically with hemoglobin E/β-thalassemia, have a remarkable ability to adapt to low hemoglobin levels. Instead, the patient's wellbeing, particularly with respect to activity, growth, development and the early appearance of skeletal changes or other disease- complications are the factors to be taken into consideration.

Table 1: Indications for transfusion therapy in Thalassemia Intermedia

Haemglobin level < 50 g/l

Declining haemoglobin level in parallel with profound enlargement of the spleen (at a rate exceeding 3 cm/year)

Growth failure (height is more indicative of growth pattern than weight) or poor performance at school

Diminished exercise tolerance

Failure of secondary sexual development in parallel with bone age

Severe bony changes

Pregnancy

Infection

Other specific complications (e.g. Heart failure, pulmonary hypertension, thromboembolic disease, leg ulcers, priapism)

The main concern with transfusion therapy is the risk of iron overload, who havealready accumulated considerable amounts of iron due to increased intestinal absorption. The risk of alloimmunization should also be considered in minimally transfused and newly transfused patients, those at an old age at first transfusion,and in splenectomized patients. The risk of alloimunization is 1-1.6% after transfusion of one blood unit.

Iron chelation therapy

Measurement of liver iron concentration by non-invasive means (R2 or R2* magnetic resonance imaging) is recommended whenever available.

Assessment of liver iron concentration is not required before patients reach ten years of age, because of the slow kinetics of iron loading in thalassemia inter-media patient. In resource-poor countries where measurement of liver iron concentration may not be available, serial measurements of serum ferritin level every 3 months is recommended. However, serum ferritin levels should beinterpreted with caution. Although there is a positive correlation between serum ferritin level and liver iron concentration in these patients, the ratio of serum ferritin to liver iron concentration is lower than in patients with β-thalassemiamajor.

Patients with thalassemia intermedia are less likely to develop cardiac siderosis,however, cardiac magnetic resonance T2* assessment may still be warranted in older patients with high iron burden.

Iron chelation therapy with Deferasirox is indicated in patients aged ten years or over, (or fifteen years and over in deletional hemoglobin H disease) and having liver iron concentration levels >5 mg Fe/g or over dry weight (or serum ferritin level ≥800 ng/mL when liver iron concentration measurement is unavailable) as these thresholds indicate increased iron related morbidity risk.

Splenectomy

Splenectomy in thalassemia intermedia patients can increase the total hemoglobin level by 1-2 g/dL and avoid blood transfusion therapy. However, in view of adverse events associated with splenectomy, it is suggested that splenectomy should be reserved for cases of:

1) Worsening anemia leading to poor growth and development when transfusion therapy is not possible or iron chelation therapy is unavailable;
2) Hypersplensim leading to worsening anemia, leukopenia, or thrombocytopenia and resulting in recurrent bacterial infection or bleeding; and
3) Splenomegaly accompanied by symptoms such as left upper quadrant pain or early satiety or massive splenomegaly (largest dimension >20 cm) with concernabout possible splenic rupture.

Abnormalities of platelets and pathological red blood cells are believed to be the key factors in causing a hypercoagulable state in TI patients. These abnormalities become more prominent following splenectomy as the beneficial role of the spleen in scavenging these procoagulant platelets and red blood cells is lost.

As a result this subgroup of patients are at a higher risk of thrombotic and vascular events i.e; venous thromboembolism (approx. 5-fold), pulmonaryhypertension (approx. 4-fold), leg ulcers (approx. 4-fold), and silent cerebral infarction than non-splenectomized patients. The median time to thrombosis following splenectomy is approximately eight years. This delay indicates the need for long term treatment and modalities for prevention.

Spleen is also a reservoirof excess iron and may have a possible scavenging effect on iron free species such as non-transferrin bound iron. This explains the higher serum level of this freeiron species in splenectomized TI patients and also a higher rate of iron-related organ morbidity than their non-splenectomized peers.

Splenectomy also places these patients of all ages at risk of morbidity and mortality due to infection which may have an overwhelming fatal course such as in meningitis and sepsis. Appropriate vaccinations and antibiotic prophylaxis are critical steps in preventing overwhelming infection after splenectomy.

Fetal hemoglobin induction

Increased production of γ-globin, which is similar to β-globin, combines with α-globin chain (fetal hemoglobin) and results in improvement in α/β-globin chain imbalance and more effective erythropoiesis. This partly explains the more favorable phenotype in some patients with β-thalassemia intermedia and hemoglobin E/β-thalassemia compared with transfusion-dependent β thalassemia major. DNA methylation inhibition with 5-azacytidine increases HbF production and has an ameliorating effect but there are concerns about the safety of this agent. A safer demethylating agent, decitabine also has a similar effect.

Hydroxyurea has became one of the key therapeutic agents for the management of patients with sickle cell disease as a potent inducer of fetal hemoglobin. It also increases total hemoglobin level by approximately 1.5 g/dL. This increase remains important since a difference between a severe and mild hemoglobin E/β-thalassemia patient is only 1-2 g/dL.

Improvement in anemia is usually associated with better exercise tolerance, appetite, and sense of general well being. Favorable effects on certain morbidities such as pulmonary hypertension, leg ulcer, and extramedullary hematopoietic pseudotumors have also been observed.

Hydroxyurea may improve the hypercoagulable state of the disease through effects on phosphatidylserine externalization in the red cell. Short-chain fatty acid (butyrate derivatives) are also inducers of fetal hemoglobin although effects are less notable in long-term therapy.

The use of recombinant human erythropoietin or the newer erythropoietic stimulating agent darbepoetinalfa in patients with TI is associated with increases in total hemoglobin level. However, its use still remains investigational.

Novel therapeutic approaches

Potential new treatment modalities for ineffective erythropoiesis and iron overload in patients of TI are under development.

JAK2 inhibitors have shown rapid reversal of hepatosplenomegaly; improvement of anemia .Hepcidin modulators also cause reversal of hepatosplenomegaly, prevent iron overload and improve anemia.

Management for specific clinical complications

Pulmonary hypertension: sildenafil citrate, a potent inhibitor of cyclic guanosinemonophosphate-specific phosphodiesterase-5 and a selective smooth musclerelaxant, showed promising results for the management of pulmonary hypertension in small studies in β-thalassemia intermedia patients and also has shown to improve cardiopulmonary hemodynamics in patients at risk for pulmonary hypertension. Bosentan (endothelin receptor antagonist) and epoprostenol (prostacyclin) were also reported to be effective in some patients.

Extramedullary hematopoietic pseudotumors

Management options includeblood transfusion therapy which helps decrease the demand for extramedullaryhematopoiesis, radiotherapy of the tumors, or fetal hemoglobin induction byhydroxyurea. Combinations of these modalities have also been used.

Surgery is not always possible due to the diffuse nature of the mass and thelikelihood of recurrence. Furthermore, immediate total resection of extramedullary hematopoietic masses can lead to clinical decompensation and deterioration because these masses play a crucial role in maintaining an adequate hemoglobin level.

Leg ulcers

Simple measures such as keeping the patient's legs and feet raised above the level of the heart for 1-2 hours during the day or sleeping with the end of the bed raised along with blood transfusion. Pentoxifylline which alters the rheological properties of the red blood cell can accelerate the healing of ulcers.Hydroxyurea also has some benefit, either alone or in combination witherythropoietin. The use of an oxygen chamber can also provide moderate relief where tissue hypoxia may be an underlying cause of the ulceration.

Endocrine disease and pregnancy

Fractures and bone pain can be devastatingconsequences of osteoporosis in TI patients. Different regimens of vitamin D andcalcium are frequently prescribed to patients with TI, but with careful monitoringof renal function. Although the efficacy and safety of bisphosphonates has beenproven in patients with β-thalassemia major, data on patients with TI arelimited. Other endocrine complications can be treated as with patients with β-thalassemia major. In pregnant women with TI, there is an increasedrisk of abortion, pre-term delivery, intrauterine

growth restriction, Caesarean section delivery, and thromboembolic events. Although the use of blood transfusions may be required to address these complications, the risk of alloimmunization in never transfused women should always be taken into consideration. Splenomegaly can interfere with the enlargement of the uterus and can be complicated by hypersplenism. Splenectomy can therefore become necessary during gestation or after delivery. Anticoagulation should be considered especially in women with additional prothrombotic risk factors.

Thrombotic disease

Aspirin has been shown to lower recurrence rate of thrombotic events in β-thalassemia intermediapatients .

Hemolytic crisis

These commonly occur in hemoglobin H disease, more so innon-deletional forms. Sudden, severe anemia following even mild febrile illnessfrequently occurs. Immediate intervention is necessary and management includes blood transfusion, adequate hydration, correction of blood electrolytes, control body temperature, and identifying and treating the cause of infection.

Thrombophilic Complications in Thalassemia

Dr. V.K. Khanna

Life expectancy of thalassemics has increased with modern available treatment. However, some of the complications of the disease process which were under-recognised and under-reported earlier have recently sprung into prominence . One of these complications which needs due attention in clinical management is the hypercoagulable state. A hypercoagulable or thrombophilic state has been identified in children and adults with thalassemia. Thromboembolic events (TEE) occur more frequently in thalassemia intermedia (TI) than in thalassemia major (TM). In TI patients, thrombotic events are mostly venous and are seen primarily in splenectomized patients.

The hypercoagulable state in thalassemia has been attributed primarily to abnormalities in platelets and pathological red blood cells, although several other factors are believed to be involved. It is often a combination of these factors that leads to the hypercoagulable state. These factors (fig.1) are discussed briefly below.

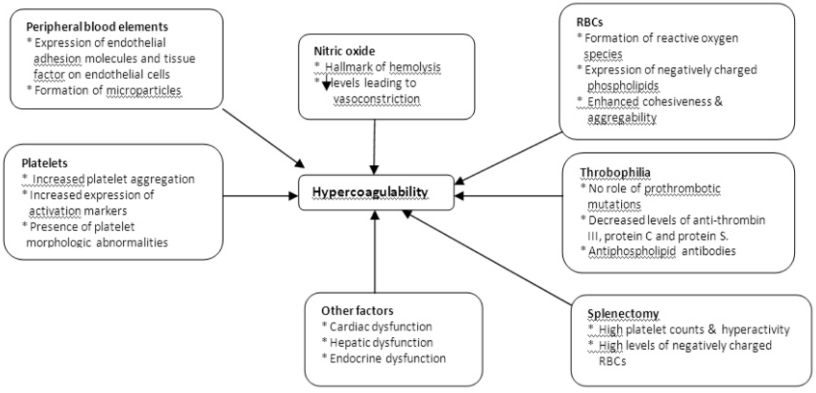


Fig. 1 Factors contributing to hypercoagulable state and thrombosis

Patients with thalassemia have activated platelets and increased platelet aggregation. Splenectomized β-thalassemia patients have high platelet counts and a shortened platelet survival due to enhanced platelet consumption. This shortened platelet life-span along with increased platelet aggregates may be associated with a chronic hypercoagulable state. The procoagulant effect of thalassemic RBCs might be the result of the presence of negatively charged phospholipids which increase thrombin generation. Splenectomized patients have a significantly higher number of these pathological negatively charged RBCs. It has also been shown that RBCs from thalassemia patients show increased cohesiveness and aggregability.

Presence of non-transferrin bound iron in patients with iron overload can cause oxidative

vessel injury. Iron overload with subsequent hepatic and endocrine dysfunction may also contribute to hypercoagulability. Thalassemia patients also have low levels of proteins C, protein S and antithrombin III and show monocyte, granulocyte and endothelial cell activation.

Splenectomy significantly increases susceptibility to thrombosis. Venous thrombosis is more prevalent in splenectomized β-TI who are not regularly transfused. Hypercoagulable state following splenectomy has been attributed to the presence of high platelet counts and to increased number of abnormal RBCs.

Clinical Experience

In a series of 83 patients followed for 10 years by Cappellini et al (2000), 29% developed either deep vein thrombosis, pulmonary embolism or portal vein thrombosis. All patients except one had undergone splenectomy. In a study of 8860 patients by Taher et al (2006) TEE were found to be 4.38 times more common in TI than in TM. More venous events were seen in TI while patients with TM had more arterial events. Most of the patients with TI who developed a TEE were splenectomized, non-transfused or had a Hb level below 9g/dl.

In one of the earlier studies, Logothetis and colleagues (1972) described a 'stroke syndrome' and neurological deficits consistent with transient ischemic attacks (TIAs) in 20% of 138 cases of TM. Borgna-Pignatti and colleagues (1998) described TIA along with other features like headache, seizures and hemiparesis in 2.2% of TM cases.

The incidence of overt stroke is higher in TM than in TI. Different studies have reported silent ischemic brain lesions in NTDT (fig.2). Older age, transfusion naivety and splenectomy were associated with a higher incidence.

Study	Patients (no.)	Mean age (yrs)	Result (silent ischemic brain lesions)
Manfree 1999	B-TI (16)	29	37.5%
Taher 2010	B-TI(30) Splenectomized	32	60%
Karimi 2010	B-TI(30) Splenectomized	24	26.7%
Metarugcheep 2008	HbE/β-Thal	31	24%

Guidelines for the management of NTDT. TIF Publication No. 19, 2013

Incidence of silent strokes in healthy individual of similar age group : 0-11%)

Manfree L et al. Am J Roentgenol 1999;173(6):1477-1480
Taher AT el al. .J Thromb Haemost 2010;8(1):54-59
Karimi M et al. Thromb Haemost 2010 ;103(5):989-993
Metarugcheep P et al.J med Assoc Thai 2008;91(6):889-894

Fig. 2 Presence of cerebrovascular disease in NTDT

Pulmonary hypertension in NTDT patients (primarily β-TI and HbE/β-thalassemia) is found to occur at a relatively high frequency compared to β-thalassemia major cases. A prevalence (based on echocardiographic findings) of 10% to 78.8% has been reported in β-thalassemia with high prevalence in NTDT patients. The diagnosis was based on tricuspid valve regurgitant jet velocity (TRV) exceeding 2.5-2.8m/s which corresponds to a pulmonary artery systolic pressure exceeding 30-35mmHg. The use of echocardiography alone results in considerable number of false positive diagnosis. It is recommended that the diagnosis should be confirmed by right heart catheterization. However, it has been observed that when a threshold TRV of 3.2m/s is used, the positive predictive value of echocardiography was as high as 93.3%. PHT is the leading cause of right heart failure in NTDT.

The exact mechanism for the pathogenesis of PHT is not clear. Chronic anemia and hypoxia, iron overload, splenectomy, hypercoagulability and microthrombotic disease of the pulmonary circulation have been implicated in the pathophysiology of pulmonary hypertension in NTDT.

Preventive Strategies

The lower rate of thrombotic events in regularly-transfused β-TM patients than TI patients may be explained on the basis of transfusion therapy. Blood transfusion may reduce hypercoagulability by decreasing the number of abnormal RBCs with thrombotic potential. Since most thalassemia patients suffering from thrombotic events are splectomized and have large number of abnormal RBCs, one approach that has been suggested but needs confirmation is, to initiate regular blood transfusion in splenectomized patients.

Hydroxyurea has been shown to reduce phospholipids expression on the surface of RBCs thereby decreasing the production thrombin and coagulation activation in NTDT patients. The role of hydroxyurea in preventing thromboembolism in NTDT patients has not been established. However, lower rates of silent strokes in β-TI patients using hydroxyurea has been suggested in one study.

Although there is no data from clinical trials for effectiveness of anticoagulant and antiplatelet therapy for the prevention of thrombotic and cerebrovascular disease in thalassemia patients but few observations tend to support this form of therapy. One of these is the association between high platelet count and thrombosis and, the other, is the observed lower recurrence rate of thrombotic events in splenectomized β-TI patients who took aspirin after their first thrombotic event. It has also been suggested that aspirin and anticoagulants could be considered in patients with conditions that are known independent predictors of thrombosis like pregnancy, sepsis and surgery.

The strong association between splenectomy and thrombotic events suggest that the procedure should be performed only when it is absolutely necessary, such as in cases of symptomatic massive splenomegaly or hypersplenism.

Recommendations of Thalassemia International Federation on NTDT and Thrombotic Disease

- NTDT patients with following factors should be considered at higher risk:
  - β-thalassemia intermedia.
  - splenectomy
  - never or minimally transfused
  - platelet count $\geq 500X10^9/L$
  - nucleated RBCs counts $\geq 300\ X10^6/L$
  - Hb< 9g/dl
  - history of pulmonary hypertension
  - iron overload (LIC ≥5mgFe/g dry weight or serum ferritin ≥800ng/ml)
  - pregnancy
  - personal or family history of thrombosis
  - conventional risk factors for thrombosis or cerebrovascular disease.
- Prophylactic intervention with anticoagulants or anti aggregants in high risk patients should follow standard guidelines.
- Aspirin therapy should be considered in splenectomized NTDT patients with platelet counts $\geq 500\ X10^{9/}L$.
- Transfusion therapy should be considered for primary or secondary prevention of thrombotic or cerebrovascular disease in high risk patients.
- There is not sufficient data to recommend iron chelation or hydroxyurea therapy for the primary or secondary prevention of thrombotic or cerebrovascular disease, although when used for different indications, a beneficial effect may be observed.

The hypercoagulable state in thalassemia is due to multiple factors and a combination of these factors is responsible for a clinical thromoembolic events. The higher incidence of thrombotic events in TI as compared to TM is mainly related to transfusion naivety and splenectomy. For prevention of this complication an individualized approach after taking into consideration all associated risk factors is recommended.

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

Table2: 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

No Bone Deserves A Break

- Dr. Rashid Merchant

Osteopathy in thalassemia major has emerged as a topic of interest since optimized transfusion regimens have increased life expectancy and improved quality of life in these children. It is clear that a large number of factors interact at the level of the osteoblast, osteoclasts and other cells to regulate the balance between net bone resorption and formation. Due to chronic anemia and expansion of bone marrow cavity there is loss of trabecular bone tissue resulting in osteopathy. The other factors are iron overload, iron chelators (especially deferioxamine) and genetic factors (polymorphism of VDR gene and COL1 gene). Endocrine factors like hypogonadism, aberrant vitamin D and PTH axis and low IGF-1 also contribute significantly for low bone mass. The important variables for evaluation of bone formation and resorption are 25 hydroxy vitamin D, parathyroid hormone (PTH), insulin like growth factor-1 (IGF-1), serum osteocalcin, urine or serum crosslaps and gold standard test for osteoporosis evaluation and risk for fracture is bone mineral densitometry (BMD).

in our experience in children with thalassemia major between 10-25 years of age 6had fractures, 9 avascular necrosis of hip, 2 tetany, 2 hypocalcemic seizures and 1 bowing of legs.Dual energy X-ray absorptiometry (DEXA) revealed osteopenia/ osteoporosis in 81% of children. All of them had high serum ferritin levels (Mean 5344 ng/ml). Serum calcium levels were low in 16% and high alkaline phosphatase was seen in 37% cases only. 25-OH vitamin D was low in 62%, hyperparathyroidism in 38%, high urinary crosslaps in 55%, low IGF-1 in 52% and elevated serum osteocalcin in 36% of these children. Endocrine evaluation in these series showed low levels of FSH, LH, estradiol and free testosterone in 14%, 3%, 44% and 90% respectively. As age advances the incidence of osteoporosis increased and was statistically significant. There was no statistical significant difference in any of the biochemical parameters studied between those with normal or abnormal DEXA. Pre-transfusion hemoglobin (Hb), transfusion requirement and chelation therapy used also did not show any significance in children with or without normal DEXA.

We recommend that for prevention and management of children for osteoporosis in thalassemia is to maintain adequate transfusion regimen to achieve Hb level above 9 g/dL and appropriate chelation therapy to target serum ferritin below 1000 ng/ml.BMD is the gold standard test for diagnosis of osteoporosis as it is non-invasive and easy to interpret. BMD by DEXA should be evaluated annually from 10 years onwards and earlier if symptomatic. Age matched Z scores in young children and T score in adults should be measured for diagnosis of osteopenia/osteoporosis.X-rays are indicated in symptomatic children for diagnosis of

fractures, avascular necrosis or compression of spinal vertebrae. MRI may be useful to diagnose degenerative changes, extramedullary hematopoiesis and disc prolapse.Biochemical evaluation (serum calcium, phosphorus, alkaline phosphatase) should be monitored after receiving 2 years of transfusion every 3-6 months.Hormonal investigations (25 OH vitamin D, PTH, endocrine hormones) and if needed serum osteocalcin, crosslaps should be monitored once a year if initial biochemical evaluation shows abnormality or if symptomatic or after 12 years of age.

All children should receive daily calcium intake from dietary source and supplements (0.5-1.0 g/day) upto 2.5 g/day. All children also should receive maintenance vitamin D (cholecalciferol) of 1000 IU/day. In case of deficiency (25 OH vitamin D levels <30 ng/dL) should be treated with 60,000 IU/week for 2-6 months with monitoring for hypercalciuria and renal stone disease till vitamin D levels are within normal range. In children with hypogonadism and osteoporosis, hormone replacement therapy (HRT) is the first choice of treatment for 2 years with monitoring of correction of hypogonadism with trough sex steroid levels.Bisphosphonates should be used as second choice and in children without hypogonadism for duration of 3-5 years. Combination therapy with bisphosphonate and HRT can also be used in children with severe osteoporosis.Calcitonin nasal spray (200 IU/day) can be used to inhibit osteoclastic activity (elevated crosslaps or PTH levels) and especially in children with vertebral fractures. Teriparatide (iPTH) can be used in severe osteoporosis as anabolic agent for 2 years in children more than 18 years not responding to above therapies.

Diabetes And Thyroid Disorders In Thalassemia Major

-Dr. Anju Virmani

Adequate transfusions have increased the life span of thalassemics, but cause iron overload, requiring ongoing chelation. The combination of anemia, iron toxicity and other factors lead to several endocrine problems, including hypogonadism, short stature, poor bone health, and less often, diabetes mellitus (DM) and hypothyroidism. All these impair the quality of life, and require ongoing monitoring to prevent, or detect and treat early. Encouragingly, several studies, including the large one from the Ferrara Center (Gamberini MR, PediatrEndocr Rev, 2008) have shown that with better chelation the incidence of all these problems has been reduced. Diabetes and hypothyroidism correlate with serum ferritin levels of about 3000 ng/ml, emphasizing the need for paying attention to adequate ongoing chelation.

Diabetes is rare before adolescence, and is likely due to a combination of insulin deficiency and insulin resistance. Risk factors include older age, higher number of blood units transfused, higher ferritin levels and poorer chelation, hepatic impairment e.g. hepatitis C, splenomegaly, family history of T2DM, and genetic modifiers of iron overload. Diagnosis is based on glucose levels, but some authors are now suggesting continuous glucose monitoring systems (CGMS) may be more useful. HbAic obviously cannot be used for diagnosis, and also fares poorly for monitoring. The incidence of abnormal glucose tolerance may vary greatly from none (Suvarna J, Indian Pediatrics, 2006) to 5.4% (Borgna-Pignatti, Ann NY AcadSci,2005) to 24% (Hafez M, Hemoglobin 2009), to as high as 86% (Zuppinger K, HelvPediatrActa, 1979). These variations may reflect different populations, as well as better chelation in recent years. Before frank diabetes, there may be hyperinsulinemia, higher HOMA-IR and lower HOMA-B (Hafez M, Hemoglobin2009).

Typically, management is based on insulin therapy, with little role for oral drugs. The insulin is given on a basal-bolus regimen. The basal component is provided by glargine, levemir or NPH insulin (one or two doses daily), while the bolus component is provided by regular, lispro or aspart insulin given before each meal. The doses of insulin should be based on regular home monitoring of blood glucose SHBG). Acute complications like hypoglycemia, hyperglycemia and ketosis can be minimized by SHBG and timely dose adjustment. Chronic complications (microvascular like neuropathy, nephropathy, and retinopathy; or macrovascular like heart disease, peripheral vascular disease) can be minimized by good glycemic control.

Hypothyroidism similarly tends to be seen after the first decade of life. The prevalence may vary from 4% (Zervas A, Thyroid 2002) and 5.9% in Skordis' group (Toumba M, PediatrEndocr Rev, 2007) to 35% in Qatar (Soliman AT, Indian J EndocrMetab, 2013). In the Survival and Complications study Borgna-Pignatti el reported hypothyroidism in 11.6% in the

period up to 1987 (Ann NY AcadSci 1998) and again 11% in recent years (Ann NY AcadSci2005). The incidence of hypothyroidism may be higher in splenectomised patients (Skordis N, Eur J Hemat, 2006). It may be primary or secondary (iron deposits in the pituitary), so screening with TSH alone may not suffice: T4 should also be tested. Testing for antibodies may not be useful. A small study found no significant association of hydroxyurea therapy with thyroid function in patients of thalassemia intermedia (Zekavat OR, Iran J Med Sci, 2014). Treatment is with thyroxin. It is important to remember that TSH cannot be used for monitoring therapy in central hypothyroidism.

We studied survival and disease complications in 1,146 patients with thalassemia major, born from January 1, 1960 to December 31, 1987. At last follow-up, in March 1997, probability of survival to age 20 years was 89% and to age 25 years was 82% for patients born in the years 1970-1974. Patients who died had a serum ferritin level, measured the year before death, significantly higher than those who survived. Diabetes was present in 5.4% of the patients; heart failure in 6.4%; arrhythmias in 5.0%, thrombosis in 1.1%, hypothyroidism in 11.6%, HIV infection in 1.8%. Hypogonadism was diagnosed in 55% of 578 patients who had reached pubertal age: 83.5% of hypogonadic females and 78.6% of males were receiving substitutive hormonal therapy. In conclusion, the survival of patients with thalassemia major is good and improving, but the prevalence of severe complications is still high.

BACKGROUND : The clinical severity in thalassaemia major (TM) depends on the underlying mutations of the beta-globin gene and the degree of iron overload.OBJECTIVE:The aim of the study was to investigate the impact of genotype on the development of endocrine complications in TM in our center. Subjects and methods: 126 (62 males, 64 females) thalassaemic patients of Greek Cypriot origin with a mean age of 31.2 (17-68) yr were included in the study. All patients, who were on the standard treatment protocol, were subsequently divided into two groups according to their genotype, group A (92): TM with no mitigating factor and group B (34): TM carrying one or more mitigating factors in the beta- and/or alpha-globin genes. Iron overload calculation was based on the amount of red cell consumption and the mean ferritin level over a 12-year period. Statistical analysis was performed with the SPSS program.RESULTS:Patients in group A, who were consuming larger amounts of blood on transfusions, were more likely to develop hypogonadism (P = 0.001) compared with patients in group B, despite their similar mean ferritin levels. The incidence of other endocrinopathies (short stature, hypothyroidism, and diabetes mellitus) was similar in the two groups. The prevalence of hypothyroidism in splenectomized patients was significantly higher (P = 0.005), whereas the presence of hypogonadism, impaired glucose homeostasis and insulin resistance, although more frequent, was not statistically

significant. The clinical severity of TM had no impact on bone mineral density (BMD) in both men and women. BMD was only influenced by gonadal function.CONCLUSIONS:This study demonstrates that the underlying genetic defect in TM is a contributing factor for gonadal dysfunction, because the patients with the more severe defects have a greater rate of iron loading through higher red cell consumption.

Patients with multi-transfused thalassaemia major may develop severe endocrine complications due to iron overload. The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion resulting in hypogonadism, short stature, acquired hypothyroidism and hypoparathyroidism. Glucose intolerance and diabetes mellitus are also common in thalassaemic patients. The severity of the clinical manifestation and laboratory findings in thalassaemia largely depends on the genotype; thus homozygotes or compound heterozygotes for the mutations beta0 or beta+ depend for life on frequent transfusions. A multicenter study in Cyprus including 435 patients showed hypogonadotrophic hypogonadism in 32.5%, short stature in 35%, acquired hypothyroidism in 5.9%, hypoparathyroidism in 1.2% and diabetes mellitus in 9.4%. A slowing down of growth velocity and a reduced or absent pubertal growth spurt is observed in early adolescence leading to short adult height. Delayed or absent puberty and hypogonadism may result in fertility problems which affect enormously the life of thalassemics. Glucose intolerance in adolescence and diabetes mellitus later in life are also frequent complications mainly due to iron overload, chronic liver disease and genetic predisposition. Primary hypothyroidism and hypoparathyroidsm usually appear in the second decade of life; are related to iron overload and may be reversible at an early stage by intensive chelation. Osteopenia and osteoporosis due to a complicated pathogenesis represent prominent causes of morbidity in young adults of both genders with thalassaemia. Early recognition and prevention of the endocrine complications, by early and regular chelation therapy, is mandatory for the improvement of the quality of life and psychological outcome of these patients.

Ferrara Centre

273 patients with thalassaemia major followed from diagnosis in the Ferrara Centre were divided into 3 cohorts (C) according to the year of birth (C1=1954-1964, 85 patients; C2=1965-1974, 129 patients; C3=1975-2001, 59 patients) in order to study the trends of endocrine complications. Menarche occurred in 52 out of 112 patients (46%), without significant differences among the 3 groups, at the mean age of 13.9+/-1.4 years. Sixty-five percent of these patients had secondary amenorrhoea at the mean age of 18.8+/-3.7 years. In males complete pubertal development occurred in 48% of patients (C1:31%, C2: 44%, C3: 63%, $p<0.05$) followed by secondary hypogonadism in 24% of patients above 21 years of age.

Primary (80%) and central 20%) hypothyroidism were diagnosed in 31% of patients (C1: 55%, C2: 31.5%, C3: 13.4%, p<0.05), diabetes mellitus (DM) in 17% of patients (C1: 28.6%, C2: 17.2%, C3: 3.4%, p<0.05), and hypoparathyroidism in 10.6% of cases (C1: 18.7%, C2: 10.1%, C3: 3.4%, p<0.05). No difference was found in patient mean age of diagnosis of hypothyroidism, DM or hypoparathyroidism (20.4+/-8.2 years, 19+/-5 yrs and 18.5+/-5.8 yrs respectively) but in all three groups age at diagnosis significantly increased over time (hypothyroidism and DM: p<0.001; hypoparathyroidism: p<0.01). Over time the prevalence of hypothyroidism, diabetes mellitus and hypoparathyroidism increased to 24.4%, 14.7%, and 6.7%, respectively, at the time of the study. Incidences peaked in the early 1980's, and declined in the following years (primary hypothyroidism from 6.5% in 1981 to 0.9% in 2007, p<0.01; DM from 3.9% in 1986 to 0.8% in 2007, p<0.05; hypoparathyroidism 2.4% in 1984 to 0% in 2007, p<0.01) and correlated with the decrease in annual mean serum ferritin levels in all patients (p<0.001). The main risk factors associated with endocrine complications were high serum ferritin levels, poor compliance with desferioxamine (DFO) therapy, early onset of transfusion therapy (only for hypogonadism) and splenectomy (only for hypothyroidism). Serum ferritin levels of approximately 2000 ng/ml were found to correlate with hypogonadism, and 3000 ng/ml for hypothyroidism, hypoparathyroidism and DM. The incidences of hypothyroidism, DM and hypoparathyroidism were not significantly different in 18 patients on long term treatment with deferiprone (DPO) compared with 64 patients continuously treated with DFO, from 1995 to 2007. In conclusion, our longitudinal study shows that in the last 30 years in the Ferrara Centre the incidences of hypothyroidism, diabetes mellitus, and hypoparathyroidism declined, and pubertal development in males with thalassemia major improved in patients, on DFO treatment, born after 1976. The efficacy of alternative chelation regimes with deferiprone or deferasirox to monotherapy with desferioxamine remains to be established.

INTRODUCTION:Primary hypothyroidism is one of the most frequent complications observed in-patients suffering from thalassemia. We investigated and reviewed the thyroid function in all thalassemic patients attending the Pediatric Endocrine Clinic of Hamad Medical Center, Doha, Qatar during the last 10 years of follow-up.PATIENTS AND METHODS:A total of 48 patients with í-thalassemia major between 5 years and 18 years of age. Thyroid dysfunction was defined as follows: Overt hypothyroidism (low Free thyroxine [FT4] and increased thyroid-stimulating hormone [TSH] levels >5 µIU/ml); subclinical hypothyroidism (normal FT4, TSH between 5 µIU/ml and 10 µIU/ml) and central (secondary) hypothyroidism (low FT4 and normal or decreased TSH).RESULTS:A total of 48 patients (22 males and 26 females) completed a 12 year-period of follow-up. During this period, hypothyroidism was diagnosed in 17/48 (35%) of patients. There was no significant

difference in the prevalence in males 7/22 (32%) versus females 10/26 (38%). Sixteen of the patients had hypothyroidism after the age of 10 years (94%). The prevalence of overt hypothyroidism had risen from 0% at the age of 7 years to 35% at the age of 18 years. None of the patients had high anti-thyroperoxidase antibody titers. Out of 17 patients, 13 patients with hypothyroidism had normal or low TSH level (not appropriately elevated) indicative of defective hypothalamic pituitary response to low FT4 (central hypothyroidism). Three patients (6.3%) had subclinical hypothyroidism (TSH between 5 uIU/ml and 10 uIU/ml and normal FT4). The general trend of FT4 level showed progressive decrease over the 12 years, whereas, TSH levels did not show a corresponding increase. These data suggested defective hypothalamic pituitary thyroid axis involving both TSH and FT4 secretion in patients with thalassemia major over time. There was a significant negative correlation between serum ferritin and FT4 (r = -0.39, P = 0.007), but no correlation was found between ferritin and TSH.CONCLUSIONS:Worsening of thyroid function was observed in 35% of the studied thalassemic patients by the age of 18 years. The lack of proper increase of TSH in response to the low circulating levels of FT4 in 13/17 (76%) of these patients indicates a relatively high incidence of defective pituitary thyrotrophic function in these patients.

Despite improved hematologic care, multiendocrine dysfunction is a common complication of homozygous transfusion-dependent beta-thalassemia. In this study our goal was to estimate the prevalence of thyroid dysfunction in a large homogenous group of thalassemic patients. Two hundred patients with beta-thalassemia major (100 males and 100 females; mean age, 23.2 +/- 6.7 years; age range 11-43 years), regularly transfused and desferioxamine chelated, were randomly selected from a pool of approximately 800 patients with beta-thalassemia followed in our department. Thyroid function and iron-load status were evaluated by measurements of free thyroxine (FT4), free triiodothyronine (FT3), thyrotropin (TSH), and serum ferritin levels. Of the subgroup of patients who proved to have normal thyroid hormone values, 26 (12 males, 14 females; mean age, 23.6 +/- 6.8 years; age range, 15-36 years) were randomly selected and underwent a standard TRH stimulation test. Thyroid dysfunction was defined as follows: overt hypothyroidism: low FT4 and/or FT3, increased TSH levels; subclinical hypothyroidism: normal FT4, FT3, increased TSH levels; exaggerated TSH response: normal FT4, FT3, normal basal TSH, deltaTSH> or = 21 microIU/mL (TSH levels measured prior and 30 minutes after intravenous TRH administration). Normal thyroid hormone values were found in 167 (83.5%) of the 200 patients studied. Eight (4%) of the remaining patients had overt hypothyroidisim, and 25 (12.5%) had subclinical hypothyroidism. Exaggerated TSH response to TRH was revealed in 7 of the 26 patients with normal hormone values tested (26.9%). Antithyroglobulin and anti-thyroid peroxidase (TPO) antibody titers were negative in 191 patients (95.5%). Mean ferritin levels in hypothyroid and

euthyroid patients were 2707.66 +/- 1990.5 mg/L and 2902.9 +/- 1997.3 mg/L, respectively, (p = 0.61), indicating no correlation between ferritin levels and thyroid functional status. Mean ferritin levels in the patients who responded normally to TRH stimulation and in those who overresponded, were 2,586 +/- 1791 mg/L and 3,228 +/- 2473 mg/L, respectively (p = 0.46; NS). Thyroid failure is a rather rare endocrine complication in patients with beta-thalassemic from Greece. In our series, no case of central hypothyroidism was observed. No correlation was found between thyroid functional status and ferritin plasma levels. Approximately 1 of 5 beta-thalassemic patients with normal thyroid hormone values showed an exaggerated TSH response to TRH test. It is to be investigated how many of these patients will establish overt or subclinical hypothyroidism in the future.

Hydroxyurea (HU) has been successfully used in patients with β-thalassemia intermedia (β-TI). We aimed to evaluate the effect of the long-term use of HU on thyroid function in patients with β-TI. Seventy-five patients with β-TI aged≥ 11 years and taking HU were randomly selected during 2010 in southern Iran. Thirty-one patients with β-TI without HU were considered as a control group. Serum levels of thyroid stimulating hormone (TSH) and T4 were measured. The mean age of the participants was 22.7±5.1 years (age range=12-41 years). Serum ferritin level had no significant correlation with HU consumption (P>0.05). Overall, we detected 10 (9.4%) patients with hypothyroidism. We found that the use of HU at a dose of 8-15 mg/kg/day has no significant association with thyroid function in β-TI patients. However, due to the small sample size in our study, documentation of this finding needs further studies with higher numbers of patients.

BACKGROUND: Thyroid dysfunction is a known complication of transfusion-dependent β-thalassemia. However, information on its frequency and risk factors among Egyptian Children is still unclear. OBJECTIVE: We aimed to determine the frequency of functional thyroid abnormalities among young patients with β-thalassemia and compare the thyroid function status among patients with β-thalassemia major (TM) and β-thalassemia intermedia (TI). MATERIALS AND METHODS: This was a cross-sectional study that included 52 β-thalassemia children [27 boys and 25 girls; 34 (65.4%) with TM and 18 (34.6%) with TI]. Their mean age was 16.0±1.91 (range: 12-18) years. Thyroid function and iron load status were assessed by measurement of free tetraiodothyronine, free triiodothyronine, thyroid stimulating hormone (TSH), and serum ferritin concentrations. RESULTS: Serum TSH of the studied cases ranged from 0.28 to 25 μIU/ml with a mean of 4.5±4.8 μIU/ml. None of the studied cases had overt primary hypothyroidism and the frequency of subclinical hypothyroidism was 19.2%. No risk factors for thyroid dysfunction could be identified among our cases. The thyroid profile was comparable in TM and TI patients (P>0.05) and the

frequency of subclinical hypothyroidism among TM cases was 20.6% and it was comparable to the 16.7% found among TI patients (P>0.05). No correlations were found between TSH, serum ferritin, chelation therapy, and frequency of blood transfusion. CONCLUSION AND RECOMMENDATIONS: Both TM and TI patients are at risk for subclinical thyroid failure regardless of their iron overload status. Early evaluation of thyroid function in β-thalassemia children and thyroid replacement therapy for subclinical hypothyroidism should be introduced in the treatment protocols.

Fertility & Pregnancy in Thalassemia Major & Intermedia

-Dr. Vatsala 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

Thal minor/ trait: mild or no anemia

Thal major (BTM): severe form, only HbA2 and F detected. Severe anemia, transfusion Dependent and develop complications of iron overload

Thalintermedia (BTI): present late in life, mild anemia, not transfusion dependent, may Develop iron overload.

Fertility

BTM: infertility is due to iron deposition in endocrine organs. Direct iron deposition occurs in hypothalamic pituitary axis and female reproductive system. Indirect effect is due to iron induced oxidative stress.

Majority of patients are infertile due to hypothalmichypogonadism , associated with amenorrhoea, anovulation and infertility. Ovarian functions are 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 births 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 alloimmuneantibodies
- 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.

Allogeneic stem cell transplantation for thalassemia major

- Dr. Vikram Mathews

An allogenic stem cell transplant remains the only curative option for patients with β thalassemia major. Significant advances have been made over the last two decades to improve the clinical outcome for patients with this disorder undergoing such a procedure. Currently in patients with good risk features it is reasonable to anticipate a greater than 90% chance of a successful transplant outcome. Parameters for risk stratification for this disorder prior to transplant are unique to this condition. The conventional risk stratification system has limitations and alternative systems are being explored to better identify subsets that require innovative approaches to improve their outcome. Better understanding of graft characteristics and immune re-constitution post transplant has the potential to identify interventions to further improve clinical outcomes. The role of splenectomy prior to transplant has not been clearly addressed and we will present our experience. A number of innovative conditioning regimens have been evaluated to improve the clinical outcome of patients with high risk thalassemia major. Of significance is the use of treosulfan based conditioning regimens which have significantly reduced the regimen related toxicity and early treatment related mortality. Alternative donor sources are being evaluated in an effort to improve results in high risk patients and also to increase the proportion of patients who could benefit from an allogeneic stem cell transplant. These are some of the issues that will be briefly addressed in this review.

Introduction:

Allogenic stem cell transplantation (SCT) remains the only curative option for patients with β thalassemia major. The correction of this disorder by an allogeneic stem cell transplant was first described by Thomas et al1. Subsequently, a conditioning regimen of busulfan and cyclophosphamide was established for stem cell transplantation in this condition2. This myelo-ablative therapy forms the basis for the currently used conditioning regimens in this condition. Reduced intensity conditioning regimens have been attempted, with some success, though the increased risk of rejection with this approach has limited its widespread acceptance. The current risk stratification of patients with β thalassemia major undergoing a myelo-ablative allogeneic stem cell transplantation (SCT) classifies them into three risk groups (Lucarelli Class I, II and III), based on liver size (>2cm), presence of liver fibrosis and inadequate iron chelation3,4. Recent advances have attempted to improve on the risk stratification to better identify subset that are likely to do poorly and need alternative / improved strategies to reduce rejection and treatment related mortality (TRM) among patients in Class III. The role of splenectomy prior to allogeneic SCT is unclear, though there are

theoretical benefits. There has been some progress in developing new protocols; preliminary studies have demonstrated the ability of such regimens to reduce TRM and rejection. Of special interest is the role of intravenous busulfan and treosulfan in conditioning regimens. Of relatively recent interest is the role of matched unrelated donor (MUD) stem cell transplants and cord blood stem cell transplants, there potential lies in expanding the number of recipients for this curative strategy. We have also recently reported on the immune re-constitution patterns among patients with thalassemia major and the potential impact on engraftment, prognostication and survival. In this review we will attempt to address some of these issues and the advances in each of these areas.

Risk Stratification:

The conventional risk stratification of patients with β thalassemia major undergoing a myelo-ablative allogeneic stem cell transplantation (SCT) classifies them into three risk groups (Lucarelli Class I, II and III), based on liver size (>2cm), presence of liver fibrosis and inadequate iron chelation3,4. In the initial report by the authors proposing this risk stratification, hepatomegaly > 2cms, poor quality chelation and portal fibrosis were reported to be associated with an adverse impact on thalassemia free survival (TFS) on a univariate analysis. Only hepatomegaly > 2cms retained its adverse impact on a multivariate analysis3. Based on their observations the authors had initially classified patients based on the presence or absence of hepatomegaly > 2cms and portal fibrosis into Class III if both these adverse factors were present, Class II if only one of these factors were present and as Class I if neither were present. The authors further demonstrated the ability of this classification to discriminate the TFS and overall survival (OS) between these groups. Importantly, in that study age up to 15 years was not found to impact TFS.

In the subsequent reports from the same group inadequate chelation (adequate chelation was defined as initiation of chelation by 18 months from date of first transfusion and chelation with desferoxamine administered subcutaneously over 8 – 10 hours/day for at least 5 days a week) was included as an adverse factor. The risk stratification was then re-defined such that Class 1 patients were those who had none of the three risk factors, Class II had one or two of these risk factors while Class III had all three risk factors4. This risk stratification has since been the established standard for patients with β thalassemia major undergoing an allogeneic SCT.

This risk stratification has not been validated in different populations, especially in a group of patients with inadequate medical care prior to an allogeneic SCT (as commonly seen in our

country). In a series of 271 transplants done at our center only 17 (6.3%) would belong to Class I while 121 (44.6%) and 133 (49.1%) belonged to Class II and III respectively. It is clear that there are limitations to applying this classification to our population and probably to other developing countries where allogeneic stem cell transplant is increasingly being used. We further demonstrated that patients in Class III were a heterogeneous group with a subset that had clinical outcomes similar to Class II patients while another subset had a dismal outcome (Figure 1)5. Differentiating these subsets was possible by combining the risk factors age>7 years and liver size >5 years which were both significant on a multivariate analysis. We have since further analyzed our data set and have proposed a new classification which is potentially universally relevant and better risk stratifies patients undergoing an allogeneic stem cell transplant (Presented at ASH 2009). In this retrospective analysis of 271 first transplants, on a univariate analysis, factors associated with an adverse impact on EFS were patients' age, donor age, liver size, serum AST level, serum ferritin level, number of packed cell transfusions received, spleen size and splenectomy. On a multivariate analysis only liver size (both 2-5 cm and >5 cm) retained its significant adverse impact. The remaining parameters that were significant on a univariate analysis as a continuous variable were further evaluated after dividing them into quartiles. On a cox-regression analysis of the quartiles only age retained significance in all quartiles while the rest were significant only in the highest quartile. For the latter, the cut offs of the highest quartile was used to dichotomize the cohort into two groups for each parameter and a score given proportional to relative risk (Table 1). The total score could therefore range form 0 to 13 for each patient. Kaplan-Meir estimates of EFS were generated for each of these scores and clustered into groups. Three groups could be recognized; Group A with a score <3.5 (n=125 [46%], Group B 3.5-7.5 (n=87 [32%]) and Group C >7.5 (n=59 [22%]). Figure 1 illustrates the Kaplan-Meir estimates of event free survival (EFS) and cumulative risk of rejection between these groups which were significantly different (Figure 2). There were 133 (49%) patients in this cohort who belonged to the conventional Lucarelli Class III subset. Of these, using the current risk stratification 18(13%) would be in Group A, 58(44%) in Group B and 57(43%) in Group C. The proposed risk stratification does not require a liver biopsy, has a good distribution of cases in the defined groups and better identifies a high risk subset of patients, than the conventional risk stratification system. This high risk subset may need innovative strategies for improving outcomes following an allogeneic SCT. The proposed risk stratification system will need to be validated prospectively.

Stem cell dose and immune re-constitution post transplant and its impact on clinical outcomes:

The clinical efficacy of a SCT is limited by regimen related toxicity secondary to the conditioning regimen, immune response by donor cells to recipient antigens resulting in graft versus host disease (GVHD) and delayed or inadequate immune reconstitution leading to infections, recurrence of a malignancy and occasionally rejection of the graft6,7. While immune reconstitution post SCT has been extensively studied in adult's, there is limited data in the pediatric population6. An early low plasmacytoid dendritic cell count has been reported by us and others to be associated with acute and chronic GVHD8,9. Rapid lymphocyte and lymphocyte subset recovery have been reported to be associated with a favorable outcome10-12. It is known that the ability to generate CD4+CD45RA+ (naïve T helper cells) decreases with age, since this is thymic dependent13,14. It is also recognized that their is earlier generation of helper T cells and B cells in children than in adults6. There is, however, limited data on the impact of these variations in the pattern of immune reconstitution on clinical outcomes post SCT in children with thalassemia major under going an allogeneic stem cell transplant.

Natural killer (NK) cells are innate immune cells critical to host defense against invading pathogens and malignant transformation. NK cells have been extensively studied in the post transplant period as they are potentially associated with both rejection and a graft versus leukemia effect15,16. Experimental data suggests that they have a number of potentially beneficial effects, including NK cell versus leukemia effect reducing relapse; NK cell versus residual host T cells reducing graft rejection rate; and NK cell versus host dendritic cells potentially reducing the risk of GVHD15,17,18. In the pediatric population with high risk thalassemia major, graft rejection is a major problem and can occur in 20 – 50% of cases19. The impact of the pattern of NK cell reconstitution in this population has not been studied. We prospective analyzed the effect of immune reconstitution in a pediatric population of patients with ß thalassemia major undergoing a myeloablative HLA matched related allogeneic SCT. We were able to demonstrate that a CD34 cell dose above the median value of 7.3 x 106/Kg had a lower incidence of bacterial (P=0.003) and fungal (P=0.003) infections in the post-transplant period and was not associated with an increased risk of GVHD. Among cases that did develop grade II-IV GVHD the absolute CD8 (116 vs.52 cells/µl, P=0.012), CD8 naïve (74 vs. 9 cells/µl, P=0.005) and CD8 memory counts (44 vs.21 cells/µl, P=0.010) were significantly higher on day 15. Fifteen patients (24%) rejected their graft (7 primary and 8

secondary). The day 28 NK cell count was significantly associated with secondary graft rejection, EFS and OS (P=0.044, 0.013 and 0.034 respectively). On a multivariate analysis, patients with a day 28 NK cell count below the median value of 142/µl had a significantly higher rejection rate (HR=11.1, P=0.038) and a lower EFS (HR=16.3, P=0.034) (Figure 3)20. Data from this analysis suggests that in this cohort of patients, increasing the stem cell dose reduces the risk of post-transplant bacterial and fungal infections. We hypothesize that faster immunologic recovery occurs with higher CD34 cell doses and, consequently, diminishes the risk of bacterial and fungal infections as observed in a previous report 21. We were however not able to demonstrate a correlation in speed of recovery of any specific cellular subset in relationship to the stem cell dose. We also noted that patients in the highest quartile of the stem cell dose did not have an increased risk of acute or chronic GVHD (data not shown). While the number of events is few and the cohort studied small, it would still be reasonable in future to target a CD34 cell dose of 10 x 106/Kg or an MNC dose of 6 x 108/Kg in the graft (lower limit of the fourth quartile values of graft cell dose) in these patients. At these doses, our data would suggest that there should be a significant reduction in post transplant bacterial and fungal infections without an increased risk of GVHD.

Studies in MHC mismatched transplants done in mice and human have shown that donor NK cells target hematopoietic tissues of the host, eliminating host antigen presenting cells and exert GVL effect against leukemia22. A similar effect has been noted with the NK cell dose in the allograft, a higher dose of NK cell infusion being associated with a lower risk of GVHD even in matched sibling transplants23. Savani et al have demonstrated that rapid NK cell recovery (NK>150/µl around day 30) as an independent determinant predicting less relapse and better survival after T-cell depleted matched SCT in patients with myeloid malignancies18. Previously, the same group had shown that the day 30 NK cell count was a surrogate marker for rapid molecular remission in CML patients24. Matthes-Martin et al highlighted the role of NK cells during the early post-transplant period. This group has showed a strong correlation of secondary graft rejection and detection of recipient NK cells on day 2825. Our observations in this cohort of patients are consistent with some of the above reports.

The day 28 NK cell count was noted to be independent of the Lucarelli risk stratification and would serve to complement it as a post transplant parameter to stratify patient's risk of secondary rejection. Whether interventions based on the day 28 NK cell count would alter the

rejection rates remains to be validated in prospective clinical trials. The potential intervention that could be considered, in the setting of a clinical trial, is the infusion of in-vitro expanded NK cells as part of the conditioning regimen or on day 28 based on the re-constitution counts.
Beneficial effect of pre-transplant splenectomy on transplant outcomes?

Massive splenomegaly in patients with β thalassemia major is often a reflection of inadequate medical care and / or advanced disease and is often seen in Class III patients26. It is associated with increased blood transfusion requirement27. Splenectomy is conventionally indicated when the transfusion requirement exceeds 220 ml RBC/kg/year 28. Splenectomy is also indicated if there is significant abdominal discomfort, splenic infarction or symptomatic hypersplenism27.

Presence of splenomegaly prior to a SCT raises the theoretical concern of sequestration of infused stem cells which could potentially have an adverse impact on engraftment. Splenectomy prior to a SCT could alter engraftment kinetics which in turn could have an impact on graft tolerance and development of graft versus host disease (GVHD)29. Splenectomy prior to an allogeneic SCT has the theoretical potential of reducing peri-transplant transfusion requirement and hastening engraftment30.

Splenectomy in patients with β thalassemia major is also considered a surrogate marker of high risk disease, since it is often performed in older patients or in those who have had inadequate medical care. Splenectomy is reported to be associated with increased risk of pulmonary hypertension31, progressive restrictive pulmonary disease31 and alteration in hemostatic parameters that favour thrombosis32-34. It has also been reported to be associated with an increased risk of infections35. All the above factors could contribute to an adverse outcome following an allogeneic SCT.

The impact of pre-transplant splenectomy on patients with β thalassemia major undergoing an allogeneic SCT has never been reported. We undertook a retrospective analysis of patients with β thalassemia major who underwent an allogeneic stem cell transplant at our centre to study the impact of pre-transplant splenectomy on clinical outcome. Twenty seven Class III patients (29 transplants) had a pre-transplant splenectomy. The outcome of these 29 transplants was compared with 76 transplants in Class III who did not have a splenectomy. Patients in the splenectomy group were older (11.7±5.0 years vs. 8.5±3.5, P=0.003) and had a larger liver size (5.7±1.8 cms vs.

4.4±1.6, P=0.000). Splenectomized patients had a significantly faster time to ANC > 500/mm3 (15.4±5.9 vs. 17.5±4 days, P=0.002) and platelet >20000/mm3 (22.5±6.7 vs. 32.5±13.6 days, P=0.000). The splenectomized group had a significantly reduced requirement of blood transfusion in the first 100 days post transplant (5.5±5.1 vs. 7.2±5.4 units, P=0.017). There were significantly more deaths related to peri-transplant infections in the post splenectomy group (24% vs. 5.3%, P=0.0001). The graft rejections were comparable between the two groups (20.7% vs. 14.5%, P=0.55). The incidence of acute and chronic GVHD, late infections and deaths from regimen related toxicity (RRT) was not significantly different between the two groups. The 5 year EFS (31.0±8.6 vs. 60.8±5.98; P=0.003) and OS (39.7±9.3 vs. 71.8±5.5; P=0.002) was significantly worse in the splenectomized group. Our analysis would suggest that though pre-transplant splenectomy among patients with β thalassemia major was associated with faster engraftment and reduced transfusion support, a higher incidence of peri-transplant infection related deaths that lead to a reduced EFS and OS. However, this adverse effect may not necessarily be directly related to splenectomy but due to splenectomy being a surrogate marker for other adverse pre-transplant features such as older age and inadequate medical therapy prior to transplant. In fact by subset analysis we were able to demonstrate that the adverse outcome in this group was not related independently to the splenectomy. We could not however demonstrate any significant beneficial effect that would warrant considering this routinely prior to transplant36,37.

New conditioning regimens to improve outcome in Class III patients:

The Pesaro group had initially reported the adverse outcome in Class III patients conditioned

with a similar regimen as used for Class I and II, with a TFS of 53% among

Class III patients vs. 85% for the rest19. They also noted a non rejection mortality of 39% in this group. To improve on the outcome and reduce non transplant related mortality they reduced the dose of cyclophosphamide to 160mg/kg from 200mg/kg. This relatively small change reduced TRM but resulted in an increase in rejection rate from 7% to 30%38. Subsequently the same group, in March 1997, developed a conditioning regimen which started on day -45 with azathioprine and hydroxyurea, fludarabine from day-17 to -13 and Bu 14mg/kg with Cy 160 mg/kg. With this new regimen, this group reported a 85% event free survival and a rejection rate of 8%39. These findings have not been duplicated by any other group to date.

The introduction of intravenous busulfan into conditioning regimens had the promise of more uniform pharmacokinetics and reduced toxicity (reviewed in Andersson et al40). A recent study of 57 patients with thalassemia major conditioned with intravenous busulfan along with oral defibrotide for veno-occlusive disease (VOD) prophylaxis was found to have a very low incidence of VOD, with only one out of 63 patients fulfilling the criteria for VOD41. There is however limited data on clinical outcomes comparing oral versus intravenous busulfan to conclusively state that the latter is superior with regards to TFS and OS of more recent interest is the use of Treosulfan in conditioning regimens. Treosulfan is a pro-drug of a bifunctional alkylating agent, which differs from busulfan by the introduction of two hydroxyl groups in the molecule and a different mode of alkylation. The pharmacokinetics of this agent is linear, with low inter-patient variability42 and displays profound killing of both committed and immature progenitors of the haematopoietic system. Additionally it is easily administered to children and has

limited extra-medullary toxicity43. A recent study using a treosulfan based conditioning regimen has reported very good results even among Class III patients44. We have recently used this agent in what we have defined as Class III high risk patients5 and found it to be well tolerated. At our center we currently use this treosulfan based regimen for patients who are class III or class IIIHR and we have demonstrated a significant improvement in clinical outcomes in this subset in comparison to our historical controls (Figure 4)45.

Matched unrelated stem cell transplants:

Unfortunately, majority of patients with thalassemia major do not have a HLA matched sibling which limits the utility of a related HLA matched allogeneic SCT. Use of a matched unrelated donor (MUD) SCT has the potential to over come this. The initial results with this approach were dismal with a 55% graft rejection46. Since then there has been significant interval improvement in MUD SCT with high resolution molecular typing becoming standard in donor selection, and outcome in malignant disorders with MUD being comparable to that of HLA matched sibling transplants. More recent data suggests that OS of 79% can be achieved with this approach with TFS of 66% and a 25% chance of TRM47. The study also suggested that an extended haplotype match was associated with a superior outcome. The overall data would suggest that MUD SCT should only be considered in centers that have reasonable experience with this approach and preferably in low risk patients.

Cord blood transplants:

A lot of attention has been placed on cord blood transplants in the last decade. It is the most rapidly growing source of stem cells for unrelated transplants. However, for patients with thalassemia major there is limited data. Using cord blood stem cells for transplant can be considered under two headings (i)related cord blood transplant: when a HLA matched or partly mismatched sibling is the source or (ii) as matched or partly matched unrelated donor when cord blood is procured from a cord blood bank as part of donor search for an allogeneic SCT.

Using related cord blood the Eurocord Transplant Group reported a 2 year probability of EFS of 79% in 33 patients with thalassemia. There was a 21% (7 rejections) risk of rejection of the graft,in spite of none of the patients being Class III, in fact 20(61%) of the patients were Class I48. We would consider this an unacceptably high rejection rate for patients in the low risk group. Besides, one could wait for two years and do a regular bone marrow harvest and stem cell transplant from the same donor without this risk. More recent data has shown lower rejection rates but the numbers are small49,50. There is a theoretically reduced risk of GVHD and more importantly less donor discomfort if one were to do a related donor cord blood transplant. We would not consider a related cord blood transplant as standard of care at present for our country and would recommend it only in a center that regularly deals with cord blood transplant and more importantly a cord blood bank which has a very good track record and quality control systems in place. At times a regular bone marrow harvest is done from the HLA matched sibling and the previously stored cord blood also infused at the time of stem cell transplant without any particular rationale and claims of cord blood transplant made (more likely the bone marrow harvest contributed to engraftment), for all practical purposes this only provides additional benefit (and profit) to the cord blood bank.

Unrelated cord blood transplant genuinely increases the potential pool of donors for patients with thalassemia major. Unfortunately the published data is limited. In a recent review over 6 studies a total of 19 patients were reported51. The results are encouraging but numbers too small to recommend this as a standard of care.

Concluding remarks

Significant progress has been made in the understanding of allogeneic stem cell transplant with regards to risk stratification, optimal conditioning regimens, alternative stem cell sources and this has translated to improved outcomes for patients. There are limitations as to which of these advances can be readily translated to our country, due to the various constrains we face. Most important among these is the cost of therapy; as a result an allogeneic SCT is an option

available to only small fraction of patients. Conditioning regimens and other interventions with potential benefits but an increased cost is likely to further reduce the number of patients who can avail of this intervention. Risk stratification, conditioning regimens and other interventions need to be continually re-evaluated and optimized in our setting. They should be functionally applicable and viable options not only to physicians but also to patients and their care givers alike.

Carry home message:

1. Allogeneic stem cell transplant remains the only curative option for patients with thalassemia major.
2. Current risk stratification strategies have limitations in our population.
3. Their does not appear to be a benefit of a pre-transplant splenectomy in this group.
4. Increasing the stem cell dose in the graft above those conventionally recommended has the potential to improve clinical outcomes without an increased risk of graft versus host disease.
5. Quantitation of early NK cell re-constitution can predict graft rejection.
6. Use of treosulfan based conditioning regimens can significantly reduce regimen related toxicity and improve clinical outcomes in high risk patients.
7. Results from matched unrelated donor stem cell transplant have improved with the use of high resolution HLA typing and can be considered especially in low risk patients.
8. There is a limited role for related cord blood transplants and if done should be in a center which has facilities with considerable experience in this procedure. Unrelated cord blood transplants should preferably be done only in the setting of a clinical trial. Allogeneic stem cell transplant remains the only curative option for patients with thalassemia major.

Natural History/Molecular Aspect of NTDT

-Dr. VIP Viprakasit

Non transfusion dependent thalassaemia (NTDT) encompasses a group of thalassaemia patients who need no or minimal blood transfusions in order to survive1. Although NTDT is present world-wide, its prevalence is highest in Asia, the Middle East, and the Mediterranean region. NTDT can be categorized into five different forms where Several thalassaemia syndromes including haemoglobinE (HbE)/β-Thalassaemia (β TM) which is the predominant form in Asia, Hb H and Hb H-CS disease, Hereditary Persistent of Foetal Hemoglobin (HPFH) with beta thalassaemia or beta globin variants are among common forms of NTDT found in Asia. HbE/β-Thalassaemia is the genotype responsible for approximately 50% of all severe β-Thalassaemia cases worldwide and affects at least 1 million people worldwide2,3. Early clinical recognition of NTDT and close clinical monitoring is essential to prevent affected children to appropriately tailor management plan for individual patients and prevent some patients from being mistakenly placed on lifelong transfusion therapy.

Despite the fact that NTDT patients do not require regular transfusions, they are burdened with number of clinically significant symptoms. These symptoms include anaemia, splenomegaly, and cardiopulmonary complications. In paediatric patients, NTDT is also associated with retardation of growth and of sexual maturation, which can be avoided by early initiation of regular blood transfusions in the first decade of life their pubertal period. In addition, red blood cell transfusions aim to can suppress bone marrow activity and decreasing iron absorption6.

Over time, NTDT patients become severely iron overloaded even if they do not receive regular blood transfusions at all. This build-up of iron occurs mostly due to increased absorption of iron through the gut resulting from anaemia and ineffective ery thropoiesis low haemoglobin levels. The increased absorption in turn is sufficient to cause additional morbidities and increased mortality in NTDT patients, which is consistent with findings in transfusion-dependent patients, where iron overload is long been recognised to be associated with higher incidence of organ dysfunction, infections, and decreased overall survival. In order to measure iron burden direct LIC assessment is advised as recent studies demonstrated that more than half of patients with β-Thalassaemia Intermedia (the most common form of NTDT in European popultions) and with serum ferritin <1000 ng/ml had LIC >5 fe/g dw4,5. By this time, patients with a LIC above 6 and 7 mg Fe/g dw have most likely established vascular, endocrine and bone morbidity. Therefore, current guidelines recommend iron chelation in β-Thalassaemia Intermedia NTDT patients when LIC > 7.

There is an urgent need to revisit on clinical management and treatment recommendation in patients with NTDT since several recent studies have shown that they might surprisingly be more suffer from several complcations related to the disease's pathology and unaware iron overload than patients with thalassaemia major (TM). Therefore, a clinical practice guideline based on recent evidences for patients with NTDT will certainly help improve standard of care and reduce unwarranted mortality and morbidity in Asian NTDT patients.

Despite the fact that NTDT patients do not require regular transfusions, they are burdened with number of clinically significant symptoms. These symptoms include anaemia, splenomegaly, and cardiopulmonary complications. In paediatric patients, NTDT is also associated with retardation of growth and of sexual maturation, which can be avoided by early initiation of regular blood transfusions in the first decade of life. In addition, red blood cell transfusions aim to suppress bone marrow activity and decreasing iron absorption6.

Medical Treatment of NTDT including BT and Chelation

-Dr. V. K. Khanna

Non-transfusion dependent thalassememia (NTDT), a recently introduced term, comprises of β-thalassemia intermedia, α-thalassemia intermedia (HbH disease), HbE/β-thalassemia, HbS/β-thalassemia and HbC/β-thalassemia. NTDT is a group of thalassemias, for which patients do not require regular red cell transfusions for survival. Patients with NTDT often present in late childhood or even adulthood since they generally maintain level of hemoglobin ranging between 7-10g/dl which is adequate to sustain life without blood transfusions. The milder presentation in NTDT is due to the lesser imbalance between α - and β- globin chains. Some NTDT patients are asymptomatic until adult life, whereas others may become symptomatic from as early as 2 years of age.

Presently, the genotype and phenotype correlation is poor. Patients with NTDT may have phenotype with normal growth and may require occasional blood transfusion during severe infection, surgery, pregnancy etc. whereas some may have severe anemia, growth retardation, gross splenomegaly and a number of morbidities that may ultimately require regular transfusion therapy.

Early diagnosis and monitoring of NTDT patients is crucial to ensure appropriate and timely treatment of symptoms and to prevent serious complications later in life. Without proper monitoring and early intervention the incidence of these complications increases with advancing age.

Management options for NTDT patients include:

- Transfusion therapy
- Iron chelation therapy
- Fetal hemoglobin induction
- Splenectomy
- Management of specific complications
- Vitamins and supplements
- Curative therapy

We shall discuss here the medical treatment options e.g. transfusion therapy, iron chelation therapy and fetal hemoglobin induction.

Transfusion Therapy

In patients with NTDT, ineffective erythropoiesis and peripheral hemolysis lead to a number of pathophysiological mechanisms and clinical complications during the course of the disease. Transfusion therapy, by supplying normal erythrocytes, suppresses ineffective erythropoiesis. At present, transfusion therapy is not a routine treatment approach for NTDT. Though it offers significant benefits, the decision to provide transfusions should be based on severity of signs and symptoms and also on the complications of NTDT. In an emergency situation, where the NTDT patient may present with severe anemia, transfusion may be required for clinical stabilization. Even if a few transfusions have been administered in the acute situation, it is worthwhile to evaluate the patient in the non-emergency situation before embarking upon a regular transfusion programme. Some patients with HbE/β-thalassemia have remarkable capacity to adapt to low Hb levels. Therefore, hemoglobin level alone should not be an indication for initiation of transfusion therapy (except in cases of persistent severe anemia, Hb<5g/dl). Instead, the patients' well-being as reflected by activity, growth and development and disease complications such as skeletal changes and other disease related morbidities should be taken into consideration.

Following are the recommendations for transfusion therapy in NTDT.

- Occasional blood transfusion should be considered in situations with anticipated acute stress, hemoglobin drop or blood loss:
  - pregnancy
  - surgery
  - infection
- More frequent transfusions should be considered in the following situations with reassessment for tapering or withdrawal when a sustained clinical effect is achieved:
  - persistent severe anemia (Hb < 5g/dl)
  - declining Hb level in parallel with gross enlargement of spleen (at a rate >3 cm/year), in periods of maximal growth and development.
  - growth failure

- diminished exercise tolerance
- failure of secondary sexual development
- severe bony changes
- poor quality of life

- Transfusions may be considered for primary prevention (in high risk population), management or secondary prevention of the following complications :
  - extramedullary hemopoietic pseudotumors
  - thrombotic or cardiovascular disease
  - pulmonary hypertension
  - leg ulcers
  - priapism.

Blood transfusion, if initiated in NTDT patients, will require closer monitoring and should be individually tailored to meet patients' needs. Cases requiring frequent transfusions should be managed as thalassemia major.

THE OPTIMAL CARE study showed that transfusion therapy was protective for thrombosis, extramedullary hematopoiesis, pulmonary hypertension, heart failure, leg ulcers and cholelithiasis.

The main concern with transfusion therapy is the risk of iron overload in NTDT patients, who can additionally collect significant amount of iron due to increased absorption from gut. Alloimmunization is more common in NTDT patients. The risk is highest in never or previously minimally transfused patients, in splenectomized patients or during pregnancy. This can be minimized by transfusing fully-phenotype matched blood.

Iron Chelation Therapy

Ineffective erythropoiesis in NTDT patients leads to inappropriately low hepcidin levels which eventually cause increased intestinal iron absorption. In addition transfusions received during infections, growth spurts or pregnancy further increases this iron overload. The accumulation of iron in NTDT is slower as compared to transfusion dependent thalassemia. The positive iron balance in NTDT may be 1.0-3.5g/year as compared to 2-12g/year in

regularly transfused patients. Liver is the main organ bearing the brunt of iron overload while cardiac siderosis is less in patients with NTDT. Liver iron concentration of ≥5mgFe/g dry weight and serum ferritin level of ≥800ng/ml are associated with a significantly increased risk of developing morbidities.

In view of the slow accumulation of iron in NTDT, the liver iron concentration (LIC) assessment is generally initiated after the age of ten years. The choice of the method of estimation of iron overload depends on the facilities available. Serum ferritin is the most accessible, practical and inexpensive test. However, serum ferritin should be interpreted with caution in NTDT. As compared to thalassemia major serum ferritin underestimates the LIC in NTDT. A positive correlation between serum ferritin level and LIC has been noted but the ratio of serum ferritin to LIC is lower than in patients with thalassemia major. Liver biopsy, being an invasive procedure and one which cannot be performed repeatedly, is not a preferred method of assessment of LIC. Moreover, liver iron accumulation has been shown to be uneven leading to inaccurate results.

MRI using R2(1/T2) or R2*(1/T2*) is a noninvasive, reliable and an accurate way of assessing LIC. It has been validated against liver biopsy measurements. At present, it is the preferred method of assessment of LIC in NTDT. Devices like Superconducting Quantum Imaging Device (SQUID) and Magnetic Iron Detector (MID) estimate the magnetic susceptibility and can also be used for quantitatively assessing LIC. However, SQUID cannot measure accurately LIC ranging between 3-10mgFe/g dry weight. Room temperature MID may be available in the future as a low cost and non-invasive method of quantification of iron.

Iron overload should be assessed periodically in all NTDT patients ≥10 years (or ≥15 years in patients with deletional HbH disease). It is recommended to check LIC by MRI at every 1-2 year interval and serum ferritin should be checked every 3 months.

Iron chelation therapy is indicated in NTDT patients having LIC levels ≥5mgFe/g dry weight or serum ferritin level ≥800ng/ml as these thresholds indicate increased iron related morbidity risk. LIC has a grater predictive value than serum ferritin level. Deferasirox is the only iron chelator which has been evaluated in a randomized clinical trial in NTDT patients. It is

approved for use in NTDT by US Food and Drug Administration and the European Medicines Agency. Deferasirox should be started in a dose of 10mg/kg/day and the dose may be increased to 20mg/kg/day in patients with LIC >7mgFe/g dry weight or serum ferritin level 1500-2000ng/ml or if after 6 months there is less than 15% decline from baseline values. Deferasirox should be discontinued when LIC falls to ≤3mgFe/g dry weight or serum ferritin ≤300ng/ml.

Evidence on efficacy and safety of deferoxamine and deferiprone in decreasing iron overload in NTDT is limited to case reports and small case series only, although benefits have be observed.

Fetal Hemoglobin Induction

Increased production of the -globin chain, which like the β-globin chain pairs with α-globin chain, causes an improvement in α-/β-globin chain imbalance. This results in more effective erythropoiesis. Several drugs for instance 5- azacytidine, decitabine, butyrate, erythropoietin and hydroxyurea have been tried with variable success to induce fetal Hb.

Hydroxyurea is a fetal hemoglobin inducer for which maximum data is available pertaining to NTDT. The exact mechanism by which hydroxyurea induces fetal hemoglobin production is not clear. The most commonly accepted mechanism is that the cytotoxic effect of hydroxyurea results in stress erythropoiesis leading to increased HbF levels. By decreasing the expression of phosphatidylserine on red cells, hydroxyurea has the potential of correcting the hypercoagulable state. A beneficial role of hydroxyurea has been noted in patients with pulmonary hypertension, leg ulcers and extramedullary hematopoietic pseudotumors. Co-inheritance of α-thalassemia or homozygosity for Xmn1 polymorphism were described as predictors of good response to hydroxyurea in some studies while others failed to corroborate this . Patients with Lapore/β- thalassemia usually show a favorable response.

In studies including NTDT patients, a mean increase in total hemoglobin averaging 1.5g/dl (0.5 to 2.5g/dl) has been reported, although results in these studies are variable.

Hydroxyurea may be considered in following groups of patients:

- β-thalassmia intermedia homozygous for Xmn1 polymorphism

- lepore/β-thalassemia
- alloimmunized patients requiring blood transfusions.
- NTDT patients with following morbidities.
    - pulmonary hypertension
    - hypercoagulability
    - leg ulcers
    - extramedullary pseudotumors

Hydroxyurea should be started in a dose of 10mg/kg/day. Depending upon the response, the dose should be titrated. It can be increased by 3-5mg/kg/day every 8 weeks to a maximum tolerated dose but not exceeding 20mg/kg/day. Folic acid supplementation should also be given. The response should be evaluated after 3-6 months of therapy and is defined as a total rise of Hb > 1g/dl at 6 months. If there is no response the drug should be discontinued. Patients receiving hydroxyurea should be monitored for:

- CBC every 2 weekly for first three months and thereafter, monthly
- decrease in number of nucleated RBC/100WBC
- liver function and renal function tests every 2 weekly for first three months and thereafter, monthly
- gonadal functions should be carefully followed

Hydroxyurea is generally a well tolerated drug. Some of the noted side- effects are:

- dose dependent myelotoxicity (2-30%)
- gastrointestinal adverse effects (1-30%)
- dermatological side effects like hyper pigmentation, rash etc
- variable reports on adverse effect on gonadal function on long-term use

The purpose of medical treatment of NTDT cases is to provide optimal health, growth and development and quality of life. Medical treatment is also instituted with the vision of primary and secondary prevention and the management of complications. It is very important to carefully observe and evaluate the patients over the first few months after the diagnosis of NTDT is established and not to institute upon any treatment modality, without through assessment.

Management of Thalassemia

-Dr.V. P. Choudhry

Introduction

The Thalassemia is most common single gene disorder in the world and represents a major health burden worldwide. Its prevalence in India varies between 0-18% with a mean of nearly 3.5 percent. Over forty million people are expected to carry this gene in India. It is a recessively inherited disorder resulting from various mutations of the genes which code for globin chains of Hb, leading to reduced or absent synthesis of globin chains. Production of alpha or beta globin chain may be affected leading to alpha and beta thalassemia respectively. First case was described by Cooley and Lee in 1925 and the first case of beta-thalassemia in India was reported from Calcutta in 1938.One lakh children are born world over with the homozygous state for thalassemia while twelve thousand children are born in India every year. The frequency of thalassemia trait is 3 to 18 percent in northern India and 0 to 3 percent or less in south. A higher frequency of gene has been observed in certain communities like Sindhis, Punjabis, migrants from Pakistan to north India such as Khatris and Multanis; Bhanushalis, Lohanas, Baniyas from Gujrat, Mahars, Kolis, Goud Saraswats from Maharashtra, Gouds and Lingayat from Karnataka, etc. higher frequency of gene in these communities is possibly secondary to marriages in the same community.

Clinical Manifeatations of Beta-thalassemia

The spectrum of clinical manifestations of Beta-thalassemia varies widely. One end of the spectrum is the serious homozygous form (thalassemia major) that presents early in infancy (6 to 18 months) with progressive pallor, hepatomegaly, splenomegaly and bony changes. Infants usually present with persistent anemia, excessive crying, poor weight gain, irritability, anemia not responding to various therapies. Anemia progressively increases leading to congestive heart failure during the first few years of life. Other end of the spectrum is a heterozygous form (thalassemia minor) in which the patients have normal life. In between these two extremes are forms with varying degree of clinical manifestations of anemia, splenohepatomegely and bony changes, who maintain their life fairly comfortably and are not dependent on blood transfusion and are called thalassemia-intermedia. Children with thalassemia Intermedia can be homozygous or heterozygous.

Diagnosis

These infants have low hemoglobin with low MCV, & MCH. Peripheral blood smear is diagnostic with presence of microcytosis, hypochromia, poikilocytosis, polychromasia,

basophilic stippling and fragmented erythrocytes, target cells, bizarre picture and large number of normoblasts. Reticulocyte count ranges from 2 to 4 percent. Diagnosis can be confirmed by hemoglobin electrophoresis, family studies and DNA mutation studies. High fetal hemoglobin in the patient and high HbA2 levels (over 3.5 percent) in both parents is diagnostic of thalassemia. DNA mutation studies can be done to detect the causative mutation. In situations where the child has received even a few transfusions, the fetal Hb is not raised and the diagnosis becomes difficult. In these situations, the family studies and mutation analysis help to confirm the diagnosis.

Iron studies reveal increased serum iron level, reduced total iron binding capacity and increased transferring saturation and increased ferritin level. S ferritin levels depend upon the number of transfusions, age and many other factors.

Management of Thalassemic Child

Management of thalassemia major should be preferably done at a comprehensive thalassemia care centre with outdoor transfusion facilities.

Basic principles of Management include:

1. Confirmation of diagnosis
2. Correction of the anemia
3. Removal of iron with iron chelating agents
4. Treatment of complications
5. Cure of the disease by bone marrow transplantation
6. Pharmacological methods to increase gamma chain synthesis

Transfusion therapy in thalassemia has two goals:

1. To prevent anemia
2. To suppress endogenous erythropoiesis to avoid ineffective erythropoiesis.

Blood transfusion is mandatory for all children with thalassemia major and for those children with thalassemia Intermedia who cannot maintain their Hb at 7 gm/ dl or those who have progressive evidence of growth retardation, severe bone changes, significant hepatoslenomegaly. Regular blood transfusions are presently the mainstay of treatment of thalassemia major.

Packed cell Transfusion

Transfuse these children with coombs' cross matched packed RBCs. It is preferred to give leucodepleted blood which can be done by bed side filters or by prestorage leucoreduction systems. Pre storage filtration is better than bed side filters. Children who develop recurrent transfusion reaction should receive saline washed red blood cells to minimize reactions due to depletion of leukocytes and plasma proteins. Blood from near relatives should be avoided to prevent alloimmunization and for possible bone marrow transplantation in the future.

How much to Transfuse

The ideal transfusion regimen is hyper transfusion regime in which the aim is to maintain mean hemoglobin levels at 12.5gm/dl and pre-transfusion hemoglobin level not less than 10gm%. This regimen permits normal growth and physical development, suppresses the erythropoiesis, thus preventing skeletal changes and gastrointestinal iron absorption. It also inhibits extramedullary hematopoiesis, thereby preventing the hepatomegaly, splenomegaly and hypersplenism.

Frequency of Transfusion

It is desirable that children should receive not more than 10-15 ml of packed cells/kg/day, which raises Hb level by about 3.5 gm/dl. Packed cell transfusion every 2-4 weeks is adequate to maintain pre-transfusion baseline Hb level between desired levels (10 to 11 gm / dl). Blood should be transfused over 4-6 hours. Frequency varies from case to case and it needs to determine for each child. Usually children require blood transfusion between 2-4 weeks depending upon their age and weight and amount of blood they are receiving during each visit

In patients with cardiac insufficiency packed cell transfusion in small amount every second week is able to maintain the hemoglobin above 11 gm/dl.

The Patients should be assessed annually for mean hemoglobin levels, overall blood requirement, physical growth and development, evidence of hypersplenism, iron overload and development of antibodies.

COMPLICATIONS OF TRANSFUSIONS

Complications of repeated blood transfusions include increased non-hemolytic febrile reactions; Transfusion transmitted infections like HBV, HCV, HIV, malaria, etc. Other major problem encountered in the management of thalassemia is iron overload. Screening of the blood for HIV, HBV, HCV viruses and malaria by sensitive tests such as ELISA is mandatory to prevent these infections. Screening of blood, by nucleic acid testing for various viral infections have reduced the window period significantly and studies have clearly shown that the risk of post transfusion hepatitis B, Hepatitis C, HIV infections etc have reduced significantly. P24 antigen and RNA PCR are helpful in detecting HIV infection during the window period.

All thalassemic who are negative for the hepatitis B surface antigen should receive hepatitis B vaccine 4 doses at day 0,1month, 2^{nd} month and 12^{th} month. It can be given intradermally in the dose of 0.1 ml. It is recommended that hepatitis B booster vaccination should be given to these children at every five years.

NEOCYTE TRANSFUSION

Normally transfused red cells have a survival of 60 days. The mean age of a neocytes being 120 days, they survive in the recipient for 90 days and thereby reducing the amount of blood

required and prolonging the interval between two transfusions. IBM- 2991 unit is capable of collecting the neocytes. There is reduction in the total units of blood transfused and iron overload. However, this is not cost effective and is not used at any center.

IRON OVERLOAD AND CHELATION THERAPY

Two factors contribute to iron overload in a thalassemic child.

A. Transfusional iron overload
B. Enhanced gastrointestinal iron absorption

Each ml of packed cells contains 1 to 1.6 mg of iron. The average annual transfusion requirement is nearly 180 cc/ kg of packed cells. The body accumulates 200 mg/kg of iron every year. One mg of iron is absorbed daily from the gut in a normal person while in a thalassemic child it may be as high as 10mg/day. However, iron overload from gut is minimal. Transfusional iron overload leads to deposition of iron in the heart leading to cardiomyopathy and irregularity of heartbeats. Its deposition in the pancreas causes diabetes, while in the liver and spleen may results in hepatosplenomegaly, hepatic fibrosis and cirrhosis of liver. The iron overload in the pituitary glands causes growth retardation, delayed puberty while in the thyroid and parathyroid gland it may cause sub clinical or clinical organ dysfunction, and in the skin it results in black discoloration of skin. Iron overload in thalassemic children causes increased susceptibility to bacterial infection. High serum iron levels may favor bacterial growth like Yersinia, or may cause blockage of the mononuclear phagocyte system.

Monitoring for Iron overload:

Iron levels of thalassemic can be monitored by serum Ferritin levels which are readily available and easy to monitor. Its value of above 1000 ng/ml reflects the iron overload.

Level of Serum ferritin above10, 000 ng/ml is found to be associated with significant organ dysfunction. The limitation of serum ferritin is that its interpretation may be complicated by a number of factors, including inflammation, ascorbate deficiency, hepatic damage, hemolysis and ineffective erythropoiesis, all of which are common in severe chronic anemia. Since other methods, which are available for estimation of iron, are not convenient and are costly, ferritin still remains most common test to access the iron store. The trends in serum ferritin levels over a period (rise or fall) serve as a good indicator of body iron burden.

Other methods to detect iron overload are Liver biopsy, MRI and SQUID.

Liver biopsy has been the gold standard for iron overload. It allows direct evaluation of non-heme liver storage iron and the his tochemical examination of differential accumulation of iron in hepatocytes and Kupffer cells. The test also provides insight into liver tissue histology and pathology through assessments of inflammation, fibrosis, and cirrhosis. But it is invasive, expensive, associated with the risk of internal bleeding and subject to variability within liver at different sites. Presently this is used primarily as a research tool.

SQUID (*Superconducting Quantum Interference Device*) is an imaging modality that uses a very low-power magnetic field with sensitive detectors that measure the interference of iron within the field. Although SQUID is still considered investigational, linear correlations have been demonstrated between SQUID measurements and iron levels from liver biopsy. Although SQUID directly measures the magnetic susceptibility of ferritin and hemosiderin, at present it does not serve as a good tool to evaluate myocardial iron. However SQUID facility is available only at 4-5 centers in the world.

MRI provides a non-invasive, quantitative method of estimating parenchymal iron levels by measuring tissue iron concentration indirectly via the detection of the paramagnetic influences of storage iron (ferritin and hemosiderin) on the proton resonance behavior of tissue water. Liver iron levels determined using MRI shows excellent correlation with that obtained from liver biopsy. Furthermore, unlike liver biopsy, MRI has the ability to evaluate the entire organ. It may therefore be a more accurate measurement of LIC, particularly in patients with heterogeneous iron content. In addition, the pathologic status of the liver can also be assessed using MRI. It also remains the only non-invasive modality in clinical use with the ability to detect cardiac iron deposition. Though this technique is neither widely available nor standardized, it holds promise in the monitoring of patients at high risk for cardiac damage due to iron overload. T2* MRI is rapidly becoming the new standard for measuring cardiac iron levels. One study found that below a myocardial T2* of 20 ms there was a progressive and significant decline in left ventricular ejection fraction (LVEF). In general, the lower the T2* value, the higher the risk of cardiac dysfunction, with a T2* <8 ms suggestive of severe iron overload.

DESFERRIOXAMINE (DFO)

Desferrioxamine is a hydroxylamine compound produced by streptomyces pyloses. It is hexadentate; one molecule of DFO binds with one molecule of iron. It has short half life and cannot be administered orally. Therefore, it needs to be given continuously with the help of an infusion pump.

Desferal (Desferrioxamine) should be started before the age of 2 years. It is given on daily basis for a minimum of 5 to 6 times per week, over 6 to 8 hours with the help of subcutaneous infusion pump. The daily dose of desferal is about 30 to 50 mg/kg and should be tailored according to the need of the patient. It is advisable to keep the serum ferritin level between 1000-1500 ng/ml. Nearly two third of iron is cheated through stool and remaining through urine. It offers significant benefit to variety of organs such as liver, heart, endocrine glands. As it needs to be administered by slow subcutaneous or intravenous infusion, the compliance with this therapy is often poor resulting in poor efficacy.

TOXICITY OF DESFERAL

It is fairly safe and has minimal toxicity. Its parenteral administration leads to liberation of

histamine leading to bradycardia, hypo/ hypertension, rigors, headache, photophobia, feeling cold and hot, etc. Its subcutaneous administration causes local pain, in duration, irritability and redness. Visual abnormality may occur and includes decreased acuity of vision, peripheral field vision defects, and defective dark adaptation, thinning of retinal vessels, and abnormal visual evoked responses and cataract, in 4 to 10 percent of patients. High incidence of high frequency sensori-neural hearing loss has been observed. Auditory and visual toxicity are reversible if detected early. Therefore slit lamp and audiometry examination are advised annually for early diagnosis and management. Children who are started on desferal therapy from first year of life with aim to maintain serum ferritin levels below 1000 ng/ml may develop delayed linear growth and it may be accompanied by abnormalities such as short trunk sternal protrusion and genu valgum.

Vitamin C

Ascorbic acid deficiency increases insoluble iron hemosiderin. Vitamin C helps in conversion of hemosiderin into ferritin from which iron can be chelated. Addition of vitamin C 100 mg daily prior to DFO therapy increases iron excretion.

Deferiprone

This was the first oral drug developed in Hider's laboratory – also called as Deferiprone and available in India as Kelfer.It mobilizes iron from transferring, ferritin and hemosiderin.It has undergone extensive trials in USA, UK, Canada, India and various other centers and has been found to be an effective iron chelating agent. It is administered in the dose of 50 to 100 mg/ kg body weight. It has been shown that it is 70 to 100 percent as effective as desferrioxamine. It has been found to be more effective than desferroxime in mobilizing intracellular iron especially from heart. There has been no evidence of ear or eye toxicity. Urinary excretion of Ca, Cu, Mn, and Mg was not affected. Kidney and liver parameters did not show any alteration. Nearly 20 percent of children develop gastrointestinal symptoms like nausea, vomiting, pain in abdomen and diarrhea. Advent of deferiprone has improved the compliance for therapy.

Twenty to thirty percent children develop arthropathy, which was reversible after reducing the dose or on stopping deferiprone. Unless the drug is discontinued in time or its dosage reduced, this may lead to destruction of joint cartilage and irreversible damage to the joint. Physical findings included synovial thickening, synovial effusion, and mild flexion deformity of the knee, painful external rotation of the hip and vague generalized backache. Absolute neutropenia and thrombocytopenia also have been reported in occasional cases. Therefore, physical examination of the joints and complete blood count including platelet count must be done regularly.

Combination Therapy

Desferal and Deferiprone act differently therefore, both have been used to improve the compliance, efficacy of the chelation therapy and to reduce the side effects as well as its cost. Oral deferiprone 75 mg/kg/day for 5 to 7 days in a week and desferal in dose of 30-40 / kg / day is given subcutaneously with the help of subcutaneous infusion pump over 6-8 hours at weekend (2 days). This combination has been found to be good and proved to be an acceptable regimen. Deferiprone mobilizes the tissue iron and is then exchanged in the bloodstream by parenteral desferal and then excreted through stools and urine. On the basis of shuttle hypothesis, sequential administration of two chelators is being tried with success to have synergic effect. It is recommended for patients with high ferritin levels and patients having cardiac problems.

ICL-670(Exjade)

ICL 670 is a member of a new class of tridentates iron selective synthetic chelator - the bis-hydroxyphenyl-triazoles. Two molecules of the chelator are required to form a complete complex with ferric iron. In iron loaded rats and marmosets, oral ICL 670 is twice as effective as subcutaneous DFO. The iron excretion is predominantly fecal. Iron is chelated, both from the reticulo-endothelial cells (RE cells) as well as various

parenchymal organs and the chelated iron is cleared by the liver and excreted through the bile. It also has the ability to prevent myocardial cell iron uptake, remove iron directly from myocardial cells and exchange iron with DFO. In fact, ICL 670 readily yields iron to DFO. In animal models, on molar basis, it has been shown to be 5 times more potent than DFO (hexadentate) and 10 times more potent than deferiprone (bidentate). It is highly selective for iron and does not induce the excretion of zinc or copper. Phase-I iron balance studies have shown that the elimination half-life (t½) of ICL 670 ranged from 11-16 hours. Thus, it is feasible to give it once daily. Its oral bioavailability is 70%. It has undergone extensive phase I, II and multicentric phase III trials. In comparative studies 20 mg/kg of Deferasirox is found to be as effective as 40 mg/kg of DFO. Maximum dose recommended is 30 mg/kg. The most common side effects noted are transient GI disturbances like abdominal pain, nausea and vomiting, diarrhea etc and skin rashes. Symptoms are usually mild and rarely lead to discontinuance of drugs. There is no arthralgia, cardiac, ocular or vestibular side effects. Drug is safe in children over 2 years. Data for safety in pregnancy, lactating mother and children below 2 years is not available. It has been approved by FDA and made available in over fifty countries of the world. It is likely to be made available in other countries including India soon

SPLENECTOMY

It has been proved that if we maintain hemoglobin consistently at normal or near normal a value, hypersplenism doesn't occur. But this can be achieved only at few centers. 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 for management of thalassemia.If the child has already developed splenomegaly and sign of hypersplenism, then splenectomy is indicated. It should be undertaken only after 6 years of age because of higher chances of sepsis by encapsulated organisms.

Splenectomy is indicated if yearly requirement of packed cells is 200 cc / kg or more. Decrease in WBC and platelet count is 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. Family should be counseled regarding the risks & benefits of splenectomy prior to surgery. Prophylactic penicillin therapy must be continued life-long after splenectomy.

Episodes 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 of first bone marrow transplantation in thalassemia major goes to E Donald Thomas who performed this procedure in 18 months old thalassemic child in 1982 using HLA matched elder sister as donor. This child was cured of thalassemia. Since then many centers in the world and few in India have initiated BMT facilities.

The principles of bone marrow transplantation include (a) to destroy and prevent regeneration of defective stem cells, (b) sufficient immune suppression for good engraftment of normal marrow,(c) to infuse stem cells with normal gene. (d) To prevent GVHD with high dose therapy of Busulphan, Cyclophosphamide, total body irradiation and other modalities.

The three most important adverse prognostic factors for survival and event – free survival have been observed in large studies which include

a) Presence of hepatomegaly Hepatomegaly of 2 cm.below costal margin.
b) Portal fibrosis and
c) Irons 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. Results of bone marrow transplantation is best in class I children with event free survival of more than 95 percent of cases.

The cost BMT in India is around 5 to 8 lacs and is regularly being done at Christian Medical College Vellore , Tata Memorial Hospital Mumbai and AIIMS in Delhi.

Pharmacological Methods to increase Gamma Chain Production and Gene Manipulation

Main pathology of β-thalassemia is reduced production of β-chain leading to excess of unpaired alpha-globin chain which precipitates in the red cells leading to hemolysis of RBCs resulting in anemia and ineffective erythropoiesis.

Drugs have been used to increase the production of HbF and to prevent the precipitation of unpaired Hb chains. Augmenting the production of Y-chain reduces the imbalance between α versus non α chains as the gamma chain binds to the unpaired alpha chains. the increase in synthesis of HbF reduces the severity of the disease. Many chemotherapeutic agents have been tried. Among them hydroxyurea has been the most promising. Hydroxyurea has been found to increase HbF level. It is not found to be very useful in thalassemia major. However, it has been found to be quite helpful in patients of thalassemia Intermedia. It was found to effective in nearly 70% of cases of thalassemia Intermedia. Hydroxyurea is more effective in cases with Alpha deletions, Xmn Ploymorphism and HbE/beta thalassemia. Other novel agents which are being tried are Butyrate derivatives.

Adult Thalassemics: Switchover from Pediatrician to Physician

-Dr. Jagdish Chandra

Over the last two to three decades, care of transfusion dependent thalassemia (TDT) has immensely improved in India. On one hand, the curative treatment- stem cell transplantation (SCT) has become more widely available across the country. On the other hand survival and quality of life (QOL) of those patients with TDT who do not undergo SCT has also seen a sea change on account of improved transfusion –chelation facilities. Such scenario, though pleasant to know, puts up several challenges as the care of these patients has to switch from pediatricians to physicians caring for adults.

Need for care of TDT patients by physicians:

An Italian multicenter study going on for the past 26 years including almost 1,000 patients born since 1960, has demonstrated that, in 2009, 60% of the patients were older than 30 years. Of the 363 TDT patients in Hongkong, 78% are adult with a mean age of 23 (range, 1-52) years. Similar data are available from the USA, UK and several other developed countries.

Exact data on adult thalassemics from India is not available but it is estimated that nearly20-30 % patients with TDT in India are now over 18 years. At our centre approximately 25% patients on regular follow up are over 18 years. However, such data is only from metropolitan and other large cities in India.

Transition from pediatric care to adult services has therefore become an important issue for the TDT community.

Situation in developed countries

In several developed countries, care of TDT patients are being managed by department of Hematology. Initially, the patients are managed by Pediatric Hematology unit or department. When the patients attain adult age, they are transferred to hematology units and departments looking after other hematological diseases of adults.

In Italy and several other countries, most patients are cared for in thalassemia centers, often developed from pediatric day care units, which have developed a large experience in treating the disease, both in children and adults. In these centres, in addition to the physicians, specialized nurses are of great clinical and psychological support.

Indian scenario:

In India, there are very few specialized departments of Hematology particularly in the public sector hospitals. Even in private sector, the departments of Hematology are rarely interested in managing the patients with TDT though gradually the situation is changing for the better. Outside the metropolitan and large cities, even in medical colleges, thalassemia care is not fully developed. There are issues related to free availability of packed red cells for transfusion and drugs for iron chelation. As a result, the doctors have not taken consistent desired interest in thalassemia care.

In cities where the proportion of TDT patients entering adulthood is on the rise, attempts need to be made to involve physicians into thalassemia care. This is more important for public sector hospitals where faculty and beds for pediatric patients are limited.

Dilemma the patients face:

For the adult TDT patients, it may not always be very easy to accept the transition to adult care. It is difficult for some of these young adults to leave the comforts of the pediatric care where they have been treated for many years and where they know everybody, and everybody knows them. On the other hand, some of them feel the need to be free from the protected environment of the pediatric patient care settings and finally become part of the world where they are recognized as adults with adult needs and where the physicians are more prepared to face the physical and psychological complications affecting them.

Transition to adult settings;

The transition from pediatric to the adult care setting is a stressful time for young adults and their families. A standardized process can help to ensure the proper steps are taken to equip and prepare the individual for transition. As the needs of each patient can be very different, this process should also be individualized. Following are the guidelines being followed in some countries:

- The transition from pediatric to adult care setting should be planned well in advance of the actual event (at least 2 years) and should be discussed with the patient and family.
- Preparation for transition should consider the child's developmental stage and the readiness of the patient and family to take on new responsibilities.
- The patient and the family should be educated and equipped with tools to deal with the transition. The multidisciplinary pediatric team should focus on promoting independence in the young adult to take charge of his/her own care, and to problem solve on health-related issues including risks and complication that might arise.
- The pediatric and adult thalassemia teams should schedule a joint clinic where patients and their families can meet both teams together and become familiar with members of the adult team assuming their care. Optimally, the transition clinic should occur in the familiar setting of the pediatric site where patients and families feel most comfortable.
- A familiar member of the multidisciplinary pediatric team should take the young adult and family to the new adult clinic and where they can become familiar with the new site. At least one member of the adult team should assist in this process and the visit should occur prior to the patient's first appointment.
- The pediatric team should ensure that there is a good transfer letter summarizing all the pertinent patient information, including medical, psychosocial care, and other

relevant aspects.

- To ease the transition and reduce anxiety, the patient should not be transferred during an acute illness or during a period of other stress. Attempts should be made to organize the transfer when the patient is well.
- Psychosocial support in both the pediatric and adult settings should include a social worker, a psychologist, an education nurse, a specialist nurse, and a physician.

Physicians taking charge of TDT:

Physicians taking charge of TDT patients need to educate themselves about diagnosis and management of TDT. Monitoring the patients of TDT assumes more significant place as the patients grow up as several of the iron overload related complications appear during second decade of life or later. National and international guidelines for regular monitoring of TDT are available and they should be adhered to.

In addition to medical management, the physicians caring for adult thalassemics need to address issues related to timing of day care centre functioning to suit the requirement of young adult patients undergoing higher studies or having to attend to their jobs. Issues related to sexual development and fertility are important areas of concern. Several of adult thalassemics are getting married and may need close supervision and assistance during pregnancy. Psychological support which gets started during childhood and adolescence needs to switch gears to handle issues arising out of autonomy and factors related to college and workplace. Physicians thus need to take leadership role of the multidisciplinary team taking care of young adults with TDT.

Infectious complications post allogeneic stem cell transplantation

-Dr. Dinesh Bhurani

Introduction

Allogeneic stem cell transplantation involves identification of a suitable stem cell donor who is matched at Human Leukocyte Antigens (HLA), and then preparation of the patient with a combination chemotherapy/ chemo-radiotherapy (conditioning regimen), stem cell infusion, graft versus host disease (GvHD) prophylaxis and infection prophylaxis/ monitoring. The patients remain immuno-suppressed during and after the transplantation for a prolonged period of time and at risk of variety of infections.

Reasons for heightened risk of infections in various phases of transplantation are:

1. Damage to mucosal barrier (usually recovers after 2-4 weeks, as soon as engraftment occurs)
2. Neutropenia (usually recovers after 2-4 weeks)
3. Humoral (B cell) immune-deficiency (usually recovers after 2-6 month or may be many years)
4. Cell mediated (T cell) immune-deficiency (usually recovers after 6 months to 1 year)
5. Thymic dysfunction due to effects of chemo-radiotherapy and GvHD also common in adults

Factors which may further prolong the immune recovery are

1. GvHD and its treatment specially steroids
2. HLA disparity/ mismatch
3. T cell depleted graft
4. CMV infection
5. Source of stem cells (more prolonged immune-suppression with cord blood and bone marrow stem cell transplantation as compared to peripheral blood stem cell transplants)

Infectious complications

Bacterial, fungal, protozoal and viral infections are a major cause of morbidity and mortality after allogeneic transplantation. The temporal pattern of infectious complications after allogeneic SCT is shown in Figure-1

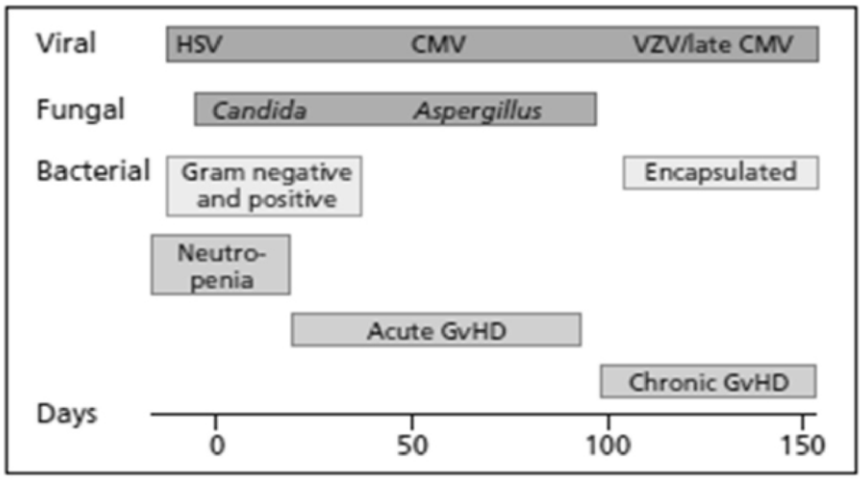


Fig-1. Temporal pattern of infectious complications after allogeneic stem cell transplantation

Bacterial Infections:

Bacteria are ubiquitous and even human body is colonized by many commensals. During transplantation, as soon as the mucosal barrier damages and neutrophil counts fall, these bacteria may invade the blood stream or may produce local site infections. Common bacterial infections in early post transplant phase are gram negative (E. Coli, Klebseilla, Pseudomonas species) and gram positive (staphylococcus species). Bacterial infections can produce septicaemia, hypotension and can rapidly be fatal.

Monitoring for bacterial infections include a close watch on body/ oral temperature as well as other vital signs like pulse rate, blood pressure respiratory rate and urine output. A temperature reading of 100.4F for 1 hour or a single reading of 101 F indicates a serious infection and warrant urgent treatment. The treatment consists of sending blood culture and other appropriate culture (urine/sputum/ mucosal swabs) and starting broad spectrum antibiotics (specially covering gram negative bacilli) within 60 minutes of documentation of fever. Antibiotic policy depends upon institutional culture sensitivity pattern. Usually a third generation cephalosporin is preferred with or without an aminoglycoside. With currently prevalent B-lactamase producing bacteria, the sulbactam/ tazobactam can be combined with an antibiotic. A carbapenem antibiotic can be used in first line or be reserved for 2nd line therapy. Antibiotics should be optimized as soon as the culture reports become available.

During later phases after transplantation (months to year), patient may remain immuno-deficient, especially for humoral immunity. This makes him vulnerable for infections with encapsulated bacteria (Pneumococcus and Haemophillus species). Long term prophylaxis with penicillin and immunization can help prevent these infections. These infections can be life threatening and should be treated aggressively with appropriate antibiotics.

Fungal infections

Fungal infections still remain a major complication and cause of death after SCT. A high index of clinical suspicion is therefore required in transplant patients, and most units administer systemic antifungal therapy early in the management of neutropenic fever. Risk factors for the development of fungal infection include prolonged neutropenia after SCT (early post transplant phase, 2-4 weeks), the use of high dose corticosteroids for treatment of GVHD (usually after 1 month of transplantation) and a history of prior fungal infection.

Candida infections typical manifest as oral thrush and less commonly as oesophageal candidiasis. Hepato-splenic candidiasis is seen occasionally, presenting with high spiking fevers at the time of engraftment in association with abnormal liver function tests. Ultrasound or computed tomography (CT) of the liver and spleen will confirm the diagnosis. Prophylactic use of fluconazole (400 mg daily) has proved effective in reducing the incidence of both superficial and invasive candidiasis. Patients who develop either hepato-splenic candidiasis or candidemia should be treated with systemic antifungals, usually liposomal amphotericin. All indwelling catheters must be removed. Culture and sensitivity must be sought as fluconazole - resistant Candida species such as Candida kruseii or Candida glabrata is of concern.

Aspergillus infections usually present prior to or shortly after engraftment. The most common manifestation is as invasive pulmonary aspergillosis (IPA), which typically presents with an antibiotic resistant fever, a significantly raised C reactive protein, and abnormal chest radiography or high resolution CT. Rarely invasive Aspergillus infections can present with cerebral or hepatic disease. Accurate diagnosis of Aspergillus infections remains problematic since spores are only rarely cultured from broncho-alveolar lavage fluid or infected tissues and the sensitivity and specificity of other currently available diagnostic techniques is low. Galactomannan in blood or broncho-alveolar lavage (BAL) and PCR technology are not enough sensitive and specific, though may be of help in establishing a probability of aspergillus infeciton. Operationally, the most helpful test in deciding whether IPA is a clinical possibility is high resolution CT of the chest, which should be obtained in all patients with a neutropenic fever that has persisted for more than 72 hours. While the characteristic radiographic features of peripheral nodular shadows,

with or without evidence of cavitation or a 'halo' sign, may take weeks to develop, the presence of any significant pulmonary infiltrate substantially increases the likelihood of Aspergillus infection and is an indication for the consideration of treatment doses of liposomal amphotericin or voriconazole.

Viral Infections (Herpesvirus infection: CMV, HSV and Varicella zoster).

Though many viruses can cause illness during or after transplantation, the common and preventable viral infections are herpes viruses that are cytomegalovirus (CMV), herpes simplex virus HSV, varicella zoster (VZ).

CMV: Human CMV is ubiquitous and present in 90-100% of the general population in India. CMV remains dormant for lifelong and can be reactivated in immunosuppressed states. CMV reactivation after allogeneic SCT can give rise to either asymptomatic infection or, less commonly, end organ damage (CMV disease) and death.

Patients at the highest risk of CMV reactivation are seropositive recipient, especially those who receive T Cell depleted or unrelated donor grafts, and patients who develop GVHD requiring steroid therapy. CMV reactivation occurs in 40 80% of at risk patients and until recently a substantial number of such patients developed CMV disease (commonly pneumonia and rarely gastrointestinal ulceration, hepatitis and retinitis).

Primary infection of CMV seronegative patients may occur as a result of the infusion of stem cell or blood products from a CMV positive donor. For this reason seronegative transplant recipients should receive CMV negative or leucodepleted blood products to limit the possibility of primary infection.

Until recently CMV was the commonest cause of infectious death after allogeneic transplantation. It is now possible to detect low levels of CMV viremia after transplantation, using either polymerase chain reaction (PCR) based detection of CMV or detection of pp65 antigen in peripheral blood leucocytes (CMV antigenemia). The introduction of these sensitive diagnostic techniques coupled with the development of effective antiviral drugs has markedly reduced the incidence of CMV disease.

All patients at risk of CMV infection/ reactivation should undergo weekly/ biweekly PCR or CMV antigenemia testing from engraftment until 100 days after transplantation.

There are two strategies for prevention of CMV disease. One is primary prophylaxis and the other one is pre-emptive therapy. Giving anti CMV therapy to all patients or to specially high risk patients for prevention of viral reactivation is called primary prophylaxis. The drug of choice was injectable gancyclovir. The disadvantage of this strategy was that there was a high rate of neutropenia and secondary infections (neutropenic sepsis) in patients receiving gancyclovir. To avoid the risk of neutropenia to all patients, the primary prophylaxis strategy was dropped. Currently adapted strategy is

pre-emptive therapy, where the patient is regularly monitored for CMV viremia or antigenemia and as soon as the CMV reactivation is detected, the patient is subjected to gancyclovir therapy. The pre-emptive strategy is effective in preventing CMV disease while avoiding unwanted neutropenia/ toxicity to all patients.

Doses of ganciclovir 5 10 mg/kg daily adjusted according to renal function. The major side effect of ganciclovir is myelosuppression, which is especially problematic in patients transplanted using an unrelated or cord blood donor. Randomized studies have confirmed that this pre - emptive treatment strategy reduces the risk of CMV disease and death after sibling allogeneic transplantation. The use of prophylactic ganciclovir, which is administered regardless of whether there is evidence of CMV infection, does not improve outcome and is associated with significant bacterial and fungal infections consequent on high rates of my elotoxicity.

Foscarnet, a DNA polymerase inhibitor, has less myelotoxicity than ganciclovir and is effective as part of a pre - emptive approach, although it is associated with significant nephrotoxicity.

The incidence of CMV pneumonitis after allogeneic transplantation has substantially reduced since the advent of effective screening and pre - emptive treatment strategies. It occurs in patients with evidence of CMV reactivation within the first 100 days after transplantation and typically presents with dyspnoea, hypoxaemia and pulmonary infiltrates. Ganciclovir and foscarnet are often ineffective in patients with established CMV pneumonitis. However, recent studies have demonstrated significant activity of cidofovir, which is considered in some units as first line treatment in all patients with CMV pneumonitis. Cidofovir is nephrotoxic but can usually be safely administered if attention is paid to adequate hydration and other nephrotoxic drugs, particularly foscarnet, are discontinued. The role of high titre CMV immunoglobulin in the treatment of CMV pneumonitis remains unclear, although it is still widely used, if available. The effective treatment of CMV infection delays the development of an immune response to CMV and as a result late (beyond 100 days post - transplant) CMV reactivation and disease is increasingly observed. Risk factors for late CMV infection include previous CMV reactivation, lymphopenia and the presence of active GVHD.

HSV and VZ: Other members of the herpesvirus family have the potential to cause significant morbidity after allogeneic SCT. The incidence of HSV, which used to be very common in the first 30 days after SCT, has been sharply reduced by the use of prophylactic aciclovir. Reactivation of varicella zoster virus (VZV) occurs in up to 50% of at - risk patients after allogeneic SCT and typically presents as shingles with severe pain and a dermatomal vesicular eruption. Less commonly, VZV reactivation presents

with atypical pain (headache or undiagnosed abdominal pain) in the absence of a rash. Prompt treatment of VZV infections with high - dose intravenous aciclovir is indicated after allogeneic SCT to prevent dissemination but also to reduce the severity of post - herpetic neuralgia.

Prevention/ Prophylaxis of infections:

Considerable progress has been made in the development of strategies to reduce the risk of infection after allogeneic SCT.

1. All patients should be nursed in single rooms, preferably with laminar airflow or high - efficiency particulate air (HEPA) filtration.
2. Antifungals for prophylaxis: fluconazole 400 mg daily, as an effective means of reducing Candida infection.
3. Anti viral prophylaxis: Aciclovir (200 400 mg four times daily) is usually administered to prevent herpes simplex virus (HSV) reactivation.
4. Antibiotics for prophylaxis:

a. Quinolone antibiotics (e.g. ciprofl oxacin 500 mg twice daily) are used by some units to reduce the risk of severe Gram -negative infections, although the evidence supporting this measure is inconclusive and practice should be guided by advice from local microbiologists concerning the prevalence and sensitivity of drug - resistant organisms.

b. Co -trimoxazole (480 mg twice daily three times per week) at the time of neutrophil engraftment (neutrophils >500 per uL) to prevent Pneumocystis jirovecii infection.

c. If allergic to co -trimoxazole, nebulized pentamidine (300 mg monthly) can be substituted, although it should be remembered that this provides incomplete protection from Pneumocystis pneumonia and for this reason some units prefer to use dapsone.

d. Allogeneic transplants, particularly recipients of TBI containing regimens, continue to be at long - term risk from infections caused by encapsulated bacteria such as Streptococcus pneumoniae and Haemophilus influenzae and require lifelong prophylaxis with penicillin (250 mg twice daily) or erythromycin (250 mg twice daily) if allergic to penicillin.

5. Vaccination: Antibody titres to diseases for which childhood vaccination is performed decline after SCT. Revaccination is therefore recommended, particularly in allograft recipients, and most centres commence such a programme 12 months after transplantation or after stopping all immunosuppressive medicines.

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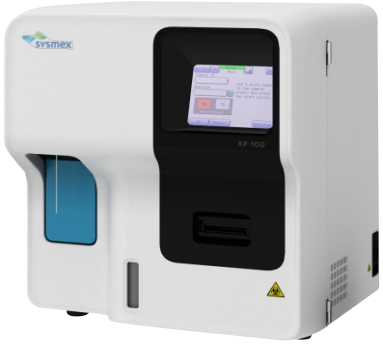

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1. Data on file
2. Taher A, El-Beshlawy A, Elalfy M, et al. efficacy and Safety of Deferasirox, an Oral Iron Chelator, in Heavily Iron-Overloaded Patients with β-thalassaemia from the ESCALATOR Study: Eur J Haematol. 2009;82:458-65.

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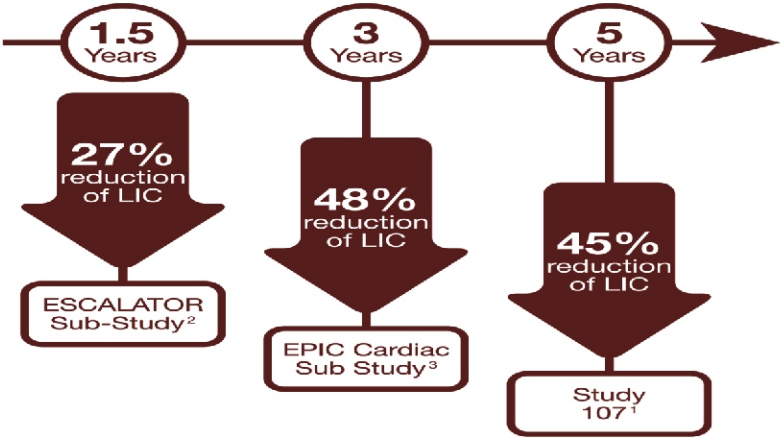

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Pediatric Patients are classified as 2 years and above

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 IPL dated 15th July, 2013

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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 <1,000 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. •Discontinue 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, rifampicin). Careful monitoring of glucose levels should be performed when repaglinide is used concomitantly with ASUNRA. Interaction with other CYP1A2 substrates (as paracetamol) 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: anxiety, sleep disorder, dizziness, early cataracts, neuropathy, hearing loss, pharyngolaryngeal pain, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, gastritis, herpetic, cholelithiasis, pigmentation disorder, renal tubulopathy (Fanconi's syndrome), pyrexia, edema, fatigue. •Rare: optic neuritis, erythema multiforme, exophthalmia. •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: 1 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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India IBSS dated 10 Oct 2013 based on international IBSS dtd 15 Jul 2013

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