Newsletter

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Pakistan Society Of Haematology

President's Column

My Dear Colleagues:

"In my first column I had listed three targets for our new team of office bearers. I also emphasized that these targets can only be achieved with whole hearted efforts from all of you. I am now pondering whether I asked for too much from you? Our first target was to net all present and future haematologists in to PSH membership. Progress in this direction has been slow and confined to Rawalpindi-Islamabad mainly. Senior members have to come into action to achieve this target. PSH membership at one stage was almost 90% of all potential members but to my estimate it has now fallen to 60-. This should not be acceptable for all of us. I will again request you to come in to action to increase it to as near 100% as possible.

Second target of establishing local chapters has also not materialized. This only requires initiative from only one member in each city. The criteria is given in the constitution. I believe that without establishing local chapters, third target of continuing education can not be successfully met. If Society is not contributing to continuing education then it is doing nothing. I once again request you to actively participate for achieving these targets.

An updated version of Society's web site has been launched. In this Newsletter you will find the manual for its use. Please visit the web site and give us your suggestions to further improve it. You will be allotted an e-mail address and password as soon as we receive a request from you. This is an interactive web site and you can make use of it for discussions and other activities.

There is some thing of common concern in the offing. Lately there have been rumors that PMDC is being moved to decrease the Professorial Chairs in the Department of pathology of medical Colleges. Presently there are four chairs for each main discipline of pathology. This was achieved after a great struggle. Now it is being said that there should be only two chairs, one for anatomic pathology and for microbiology. Haematology and Chemical pathology are suggested to be deleted. This will certainly ruin the teaching of these subjects at undergraduate level but will also retard induction of new doctors in these fields as there will be no incentive left for them. This and other moves aimed at reducing the recurrent expenditure of Medical colleges is expected as the number of members from private medical colleges in the Council has become greater than public medical colleges. If Private medical Colleges do not act responsibly and in the best interest of medical education in the country PMDC will certainly lose its regulatory role. This is also food for thought for Ministry of Health which will have to keep a watchful eye on activities of the Council. I am confident that the rumor will not materialize and sense of national responsibility will prevail. I will request you to keep President's office informed of all such developments so that a timely action can be taken.

I hope you will all be preparing for the forthcoming annual conference. Let us all try to make it a big success. Please come up with suggestions about pre and post conference workshops. You are free to invite speakers from abroad but do keep the organizing committee informed about it."

Maj Gen (Retd) Masood Anwar

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Introduction of new PSH Website

Pakistan Society of Haematology has launched an interactive website http://www.psh.org.pk The website is interactive and provides online forum for sharing views with other Haematologist and case discussion with the experts. All members are requested to provide their email address to secretary PSH on parvez101@yahoo.com so that their user ID and password can be emailed to them. PSH members are also requested to give their feedback to improve the website.

Upcoming Events

10th Annual Conference Pakistan Society of Haematology

10th Annual Conference of Pakistan Society of Haematology will be held form 16-18 February 2008 at Pakistan Institue of Medical Sciences Islamab (PIMS). Further details and schedule of the conferece will be announced by organizers in due course of time. For further details please contact Professor Khalid Hassan Department of Hematology & Blood Transfusion Services PIMS at email pshi.isl@gmail.com

HIGHLIGHTS OF CONFERECNES MEETINGS AND SYMPOSIA

First FCPS Haematology Intensive Course

The first Haematology course for the final year residents of haematology was held from 25-30 June 2007 at The Children's Hospital & The Institute of Child Health Lahore in collaboration with Pakistan Society of Haematology and College of Physicians and Surgeons Pakistan. Dr Nisar Ahmed was the chief organizer and course coordinator. Facilitators of the course were Brig Suhaib Ahmed, Brig Parvez Ahmed, Col Tahir Jamil, Col Tariq Mehmood, Professor Fazal-e-Haq, Dr Tahir Shamsi, Dr Saba Jamal, Dr Moona Aziz, Dr Rehan Sajid and Dr Nadia Sajid. Eighteen final year haematology residents from all over the country attended the course. The inaugural session was graced by Professor Abdul Hayee and Professor Tahir Masood Dean of CH & ICH. The first two days covered the transfusion and blood banking followed by one day for coagulation and two days for blood cell morphology. The faculty guidance was vital and unabated for students. Each session consisted of lectures followed by practical and case discussion to give a touch of examination style. Professor Khalid Masud Gondal, Director regional CPSP Lahore, honored concluding session. He appreciated the endeavors of the course organizers and facilitators.




Haematology Day

A Haematology Day for FCPS residents was organized at Bismillah Taqee Institute of Health Sciences & Blood Diseases Centre in collaboration with Pakistan Society of Haematology on 26th July 2007. Brig Dr Suhaib Ahmad and Dr Tahir Shamsi covered haemoglobin disorders and haemostasis respectively. FCPS - II residents in different institutions attended the programme enthusiastically and made a plea that PSH should organize similar activities regularly

Two - day workshop on Transfusion Medicine

A two day training workshop on "Transfusion Medicines Techniques" was conducted on 8th and 9th August 2007. The workshop was organized by Armed Forces Institute of Transfusion (AFIT) Rawalpindi in collaboration with Pakistan Society of Haematology. The inaugural session of the workshop was presided by Lt Gen Mushtaq Ahmed Beg, HI(M) Surgeon General DGMS (IS) Pakistan Army.
The session was attended by many senior serving and retired doctors form army as well as civil. During the session ex commandants of AFIT were presented

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shields for their services for AFIT. The Commandant of AFIT also delivered a lecture on evolution of transfusion services which was highly appreciated by the audience. The objective of the training workshops was to enhance the knowledge base and laboratory bench work skills of the technical personnel, both technicians and doctors, working in the various blood banks all over the country. The academic program of the workshop included technical presentations by the facilitators in interactive sessions, followed by comprehensive demonstrations and hands on training in the laboratory. The technical topics selected included training in routine and advanced blood transfusion investigations, which should be available in all medium and large size blood banks. The benefit to the general public would be in the form of improved blood transfusion safety.

Transfusion and transplantation sciences: A tale of two worlds

Nuzhat Mushahid
MBBS; FCPS; CTM (UK), Consultant Haematologist CMH Multan

In developed world, the largest impact of HIV epidemic has been on the blood banks and transfusion medicine. The amount of money that has been invested in this field and the regulatory frameworks that have been implemented in this branch of medicine has been unprecedented. This has obviously ensured the safety of blood and its products to a very satisfactory level. Individual unit NAT testing is the target for their screening standards, which they are striving to achieve. Developments in pathogen activation have also complemented the safety of blood products. In addition so much awareness has been created among the clinicians that they know the dangers associated with the blood and have lowered the transfusion triggers, developed different forms of autologous transfusion and started using alternatives to transfusion and literature is replete with ongoing trials on these aspects. The emerging technologies in blood banks have helped to introduce innovative and safe procedures like pre storage filtration, cryopreservation, extended shelf lives of different products etc. Different types of audits in transfusion have also been institutionalized. The education and professional developments of medical students, doctors, nurses and clinicians in transfusion medicine have touched new and very high standards. Since 70's Royal College of Pathologist UK has been offering separate MRC Path in Transfusion medicine while there is separate fellowship qualification in USA in this discipline. Different programmes for Diplomas, MSc and PhD are also available in developed countries in the field of transfusion and transplantation sciences. The tissue preservation for solid organs and support for transplantation of these organs was not possible without development in this field. The backbone for the development of any science and discipline is the human resource. No efforts in Pakistan to improve transfusion practices and safety will bear fruit unless enough qualified manpower is available. The essential steps in this direction should come from the institutions responsible for postgraduate degree awards and research institutes. The human resource development in this field should be at all tiers i.e. physicians (transfusion medicine specialist), nurses (transfusion nurses), technicians (blood bank technicians), transfusion utilization specialists from all major disciplines and specialists in donor recruitment and collection. The incentives to join such specialty will only come if government realizes this need and gives handsome incentives to people joining this field. This realization however has to come to academic community first and they can be instrumental in demanding Government action. District blood transfusion officers are the only cadre available in Punjab and their diploma is recognized by Punjab University alone and not PMDC. Blood transfusion services in Pakistan are in shambles and we cannot excuse the learned community of doctors and pathologist particularly, for this sad state of affairs. Implementation of Safe Blood Ordinance is also victim of bureaucratic delays and not having right people for the job. The bold step of drastic structural reforms is nowhere being contemplated. We cannot achieve results by trying to regulate the fragmented, scattered and liable to corruption, existing system through inspectors. This step alone will be repitition of what happens with drug regulation. We do not have any single public institute, which is involved in checking and certifying quality of viral screening kits available in the market that are purchased by the relatives of patient for screening even in public sector. Many devices are available at as low as 25 rupees and nobody knows their efficacy. Principally the

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information on the quality of different devices should be public domain, but this question arises only after an exercise for checking quality is undertaken. Our professional bodies like PAP and PSH have not really contributed any thing worthwhile for the development of this field and neither have these played the role of lobbying at right quarters for the right reasons.

In the past decade, a new form of therapy based on biological rather than pharmacological intervention has been developed. The term 'cell therapy' as applied to this new therapeutic tool, means the administration of living, non-germ line somatic cells to humans for diagnostic or therapeutic purposes. Cell therapy products (CTP's) are generated by ex vivo processes, which comprise cell harvesting from patients or healthy donors, in vitro manipulation and administration of the manipulated cells to patients. The aim of these processes is to obtain cell subsets with defined functional properties that are capable of replacing or repairing damaged tissues or organs. Some examples of cell therapy are transplantation of expanded haematopoietic stem cells (HSC), adoptive immunotherapy and dendritic cell vaccination to augment or restore immune response for the treatment of malignant and infectious diseases. Although CTPs should be produced according to good manufacturing practices, they differ from traditional pharmaceutical products with regard to quality control and safety aspects. These developments have lead to number of documents issued by regulatory bodies, which specifically address CTPs. I have narrated these developments to highlight the direction of emerging roles of transfusion services in developed world and the place where we stand today. If we do not develop some center(s) for this type of therapy and research in this field according to international standards, then I foresee that we might be importing such products once these become standards of care. We have missed industrial, information technology and biotechnology revolution and I hope that we do not miss the CTPs and stem cell therapies revolution! but better late than never. The aim of my narrative is to apprise the learned readers, the varied challenges we are facing in the field of transfusion medicine and blood banking and to highlight the contrasts and request for concerted efforts to improve the present situation.

Haemoglobin F Augmentation in β -Thalassaemia: can β -thalassaemia syndrome be managed without blood transfusion?

Dr Saqib H Ansari, Dr Tahir S Shamsi

Bismillah Taqee Institute of Health Sciences & Blood Diseases Centre, Karachi, Pakistan.

There is a marked heterogeneity of clinical presentation of thalassaemia disorders due to gene-gene interaction. Despite a monogenic disease there is a marked difference in phenotypes of β-thalassaemia; sometime making it difficult to differentiate thalassaemia intermedia from thalassaemia major. Most cases of thalassaemia syndromes with more than 90% Hb-F and moderate anaemia are reported as "consistent with β-thalassaemia major". Mislabelling of such cases of thalassaemia intermedia as thalassaemia major has a high cost to pay by the family, blood bank and thalassaemia centre. Whereas if correctly diagnosed these patients could have been managed with Hb-F augmenting agents and with no or minimal transfusion.

Preliminary data from small case series of Hb-F augmenting agents published so far suggest their usefulness in compound heterozygotes and double heterozygotes i.e. clinical phenotypes of thalassaemia intermedia[1,2,3]. A randomised placebo controlled multicenter study using hydroxyurea (HU) in sickle cell disease (SCD) showed a marked reduction in clinical severity of SCD resulting from a modest rise in Hb-F levels in these patients. This Hb-F augmenting effect of HU was exploited in small studies in other β-globin disorders like Hb-E / β-thalassaemia, and β-thalassaemia intermedia. A median rise of 0.5 2.0 gm/dl total haemoglobin concentration was shown[4,5,6].

FDA now approves HU for the treatment of adult patients with moderate or severe SCD. HU appears to have a modest activity in patients with Hb-E/β-thalassaemia and thalassaemia intermedia[5]. Overall, the response to hydroxyurea is variable and around 30% of patients with β-haemoglobin disorders do not respond. More recently, Bradai et al[6] reported transfusion independence in children with β-thalassaemia major.

Although Hb-F augmentation proved useful in Sickle cell disease and has become standard of care but in thalassaemia syndrome, despite being an attractive option, it did not prove useful with currently available agents. However Indian and North African thalassaemics did fairly well with overall response of 60-70% while half the responders did not require transfusion any more maintaining Hb between 7 - 11 g/dl. In the remaining 30-40% non-responders, although transfusion dependency continued but their performance status, exercise tolerance, quality of life improved[6]. These North African/French studies also reported a fall in serum ferritin level as well. As far as safety issues are concerned; short term toxicity is minimal and reversible, at least up to 40 months follow up in our patients while 18 years follow up in Sicklers did not show any long-term side effects or teratogenicity[4].

Our phase II study has been published in the Journal of Pediatric Hematology Oncology this year[7]. Twenty-three patients with β-thalassaemia major received HU mean dose, 16mg/kg/day. The results were analyzed at the end of 24 months. Transfusion requirement 6 months before starting HU was considered as control. 20 patients were evaluable after 24 months. Mean volume of PRC transfused was reduced in all. Mean PRC requirements for six months before starting HU was 2126.45 ml where as after 24 months on HU was 1489.59 ml (mean difference: 637.3 ml; 95% CI: 402.8 817.8; p <0.001). Interval between transfusions was increased by 68.7%. Mean increase was 12.1 days (CI: -18.0, -6.3; p : <0.001) Statistically insignificant increase was noted in ferritin levels with mean difference of 657.1 ng/L (95% CI: -1475.3, 161.1; p-value: 0.1). Grade I myelosuppression was seen in four & diarrhoea in two patients. HU was

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found to be a safe medicine in β-thalassaemia. It showed a reduction in transfusion requirement and increased interval between PRC transfusions[7]. HU has minimal effect on multi-transfused β-thalassaemia major with moderate to massive splenomegaly who started transfusions within first year of life and those with homozygous genetic mutations or 619 del. HU reduced the transfusion requirement by 63% in another group of thalassaemia major/intermedia who did not have splenomegaly, who started transfusion after 1st year of life had double heterozygous thalassaemia mutations. Third group was transfusion naïve who received HU; they were late presenters whose parents refused blood transfusion completely or were moderately anaemic on presentation. They had minimal moderate splenomegaly, double heterozygous thalassaemia mutations and minimal iron overload. This group never required transfusion and showed a moderate to high response i.e. Hb increase of 2-5 g/dl. This group actually needed iron replacement with hydroxyurea because they became iron depleted on this treatment (unpublished data from our group).

Single Hb-F augmenting agents tested so far produced a rather modest effect in β-thalassaemia intermedia and minimal or no effect in β-thalassaemia major[8]. A combination of agents with a synergistic interaction would be more likely to increase Hb F production sufficiently to correct the anaemia of β-thalassaemia. The use of agents like 5-azacytidine or decitabine in combination therapy may be advantageous because 100% of patients with SCD seem to respond to this treatment. Since same agents induce Hb F production by modifying the epigenetic composition of the γ-globin gene cluster, it might be possible to personalize the targeted therapy by custom designing a combination of drugs based on the patient's own epigenotype.

The clinical endpoint for a therapeutic effect of Hb-F induction in the β-thalassaemia is abolishing or substantially decreasing requirements for blood transfusion. A haemoglobin level of 7.0 g/dl may be satisfactory. Haemoglobin levels > 8 g/dl provide better exercise tolerance while Hb > 9 g/dl typically render the patient asymptomatic. Achieving these functional endpoints obviously requires different magnitudes of therapeutic effect for different thalassaemia patients. In thalassaemia intermedia patients with basal haemoglobin levels of 6-8 g/dl, a 1-2 g rise would be quite adequate to prevent the need for a regular transfusion while subjects with thalassaemia major with a baseline haemoglobin less than 5 g/dl would require higher levels of Hb-F induction in the range of 4-5 g/dl above baseline. Investigators in this area are increasingly coming to the realisation that this latter type of patient will likely require combination therapy with more than one agent acting at different molecular levels to achieve an adequately potent and therapeutic response.

Take Home **Message:**

- Blood transfusion and iron chelation therapy remains the mainstay for the management of thalassaemia syndrome.
- Bone marrow transplantation is the only known curative treatment to date.
- Hb-F augmentation in thalassaemia is an exciting concept. With current knowledge of genetic interaction and available Hb-F inducers there is modest response in β-thalassaemia intermedia.

Suggested **Reading:**

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YOUR VIEWS AND NEWS

Dear Colleagues

"Your contributions to PSH newsletter are vital for its success .Please send short communications, case reports, scientific activities and developments in your departments and issues of common interest. Easiest way to send these contributions is by email. Photographs of scientific events/meetings are also welcome."

UPDATING ADDRESS

We strive hard to communicate to all our members Please update your addresses in case there is any change in your address. All members are requested to email us their mobile/phone contact and email address

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