Newsletter | 2024 | Mar - Apr | Volume 01

PATHWELtimes

BIMONTHLY NEWSLETTER

PATHWEL CENTER OF HEMATOLOGY & BONE MARROW TRANSPLANT
A project of Pakistan Thalassaemia Welfare Society

Blood donors' hand prints at HITEC Institute of Medical Sciences

INSIDE THIS ISSUE

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From Editor's Desk

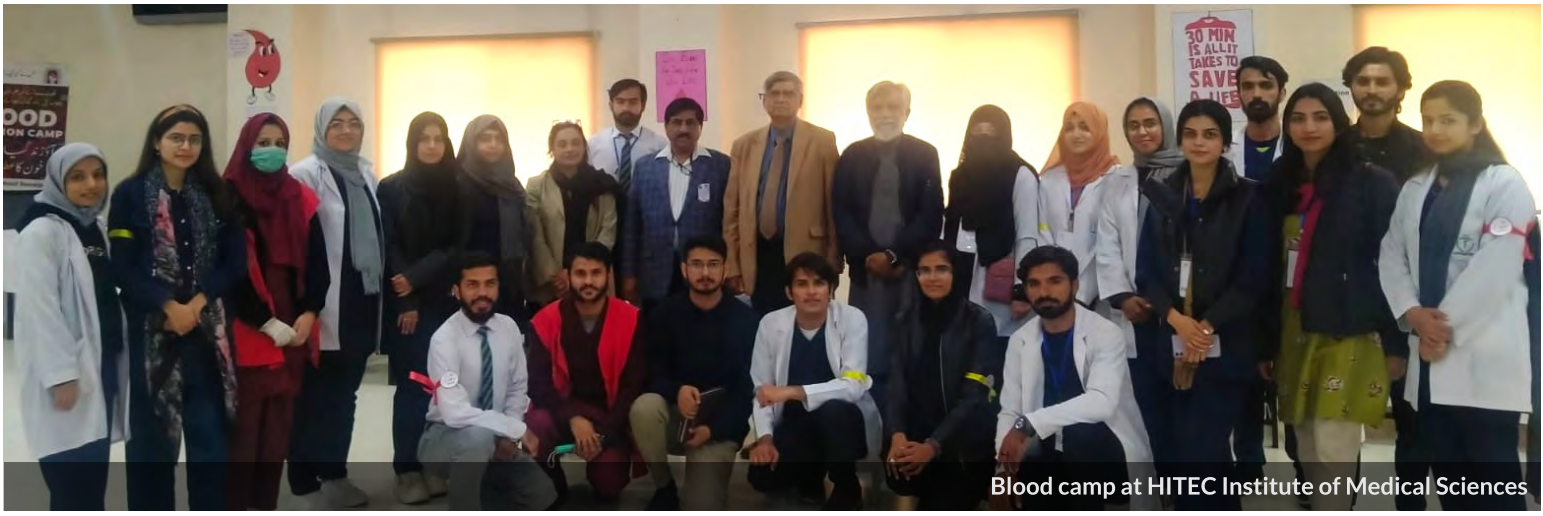
Dear Readers,

Every year the first Friday of March is celebrated as Employee Appreciation Day. Studies have shown that a little appreciation and recognition of employees improves their job satisfaction, retention rate, and productivity. At PATHWEL we owe our success to our employees.

Thanks to our nursing staff, lab technicians, helpers, cleaners, and support staff, in a very short time, we have been able to make good progress. We are running a successful bone marrow transplant program and have established protocols to deliver high dose chemo-immunotherapy to poor risk acute leukemia patients. We have also set up a well-equipped laboratory and blood bank. And all this is being done on a no-profit-no-loss basis.

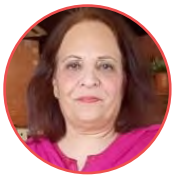
Testament to hard work put up by our workers is the fact that last year we have been able to do 27 bone marrow transplants, treat over 100 patients with acute leukemia, process about 400 bone marrow tests, and collect and transfuse free of cost, around 300 bags of blood per month to children with thalassemia.

PS: This Ramazan, give your zakat to the noble cause of life saving blood transfusions to the children suffering from Thalassemia. Details for giving donations and zakat are given on the back cover.



Blood camp at HITEC Institute of Medical Sciences

Thalassemia Post



By Dr Zohra J Wazir
Chief Medical Officer Thalassemia Wing

Welcome to our bimonthly round up of Pakistan Thalassemia Welfare Society (PTWS). The last couple of months have been very hectic. Lets quickly up date you of what has been happening during this period.

Blood Camps

One of the main targets of any center providing supporting treatment to children with thalassemia is to collect blood by holding camps. These camps are largely dependent on the youth and especially on the students of our colleges and universities.

In December we held multiple camps and collected 333 bags of blood. In January, two mega camps were held. The first big camp was held at Federal Urdu University and second one at Punjab College, Peshawar Road, Rawalpindi. At both places, the students and the administrations were very helpful and forthcoming. Large numbers of male and female students enthusiastically took part in the camps, and we were able to collect over 200 bags of blood from these two institutions.

In February, a blood camp was held at HITEC Institute of Medical Sciences. Large number of students turned out to donate blood. A high-level team from PATHWEL comprising of Medical Director Dr Parvez Ahmed, senior consultant hematologist Dr Qamar un Nisa Chaudhry, and COO Dr Kamran Mushtaq visited the camp. They were received by the principal of the institute Maj. Gen (R) Hamid Shafiq. Dr Parvez Ahmed delivered a talk to the students on blood diseases with special focus on Thalassemia.

Visit of Founder of Hajira Hamza Foundation

Maj Gen (R) Abid Latif Khan, founder of Hajira Hamza Foundation, an NGO aspiring to fight against the menace of thalassemia, visited PATHWEL. He met the children with thalassemia and exchanged views with the doctors. He showed interest in joining hands with PATHWEL to establish program for eradication of thalassemia through preventive strategies.

Blood collection camp at Fauji Foundation School of Science & Technology

A blood camp was held at FASST, Lalazar Rawalpindi in February. The camp was a big success and a large number of students turned out to donate blood and 83 bags of blood were collected.

Visit of Umeed e Zindagi Welfare Foundation

A team of Umeed e Zindagi Welfare Foundation, a charity NGO, visited our Center on 1 February 2024. The team members met children of thalassemia who were there for the blood transfusions, and distributed gifts and goodie bags among them.

Visit of Students of Center of Advanced Studies in Health and Technology (CASHT), Rawalpindi

Students from CASHT visited our center. They distributed gifts and snacks among children with thalassemia.

Birthday of Saira Yahya

Saira, one of our thalassemia patients, celebrated her 33rd birthday with us on 10th February. Before that she had been to Mecca to perform Umrah. Saira remained in good shape during her pilgrimage and enjoyed the trip. She has done a Masters in Islamiyat and is currently enrolled in a dispensing course. Her aim is to contribute in some way to the field of Medicine and play her role in alleviating the miseries of the patients. We wish her health and best of luck for the future.

PATHWEL News

CPSP Accreditation

It is a matter of great honor and pride for PATHWEL that this center has been recognized by the College of Physicians & Surgeons Pakistan (CPSP) for post-graduate fellowship training in Clinical Hematology. Prof Dr Salman Adil, senior clinical hematologist from Aga Khan University Hospital visited PATHWEL on 8th January 2024 for inspection on behalf of CPSP. He visited all the departments and wards going over the details of facilities and opportunities provided for the training of postgraduate students.

On 30th January 2024 CPSP officially notified the accreditation of Clinical Hematology discipline for FCPS training in Pathwel Center of Hematology & Bone Marrow Transplant.

CPSP Visit

Our First PG Trainee

After accreditation by CPSP, our first post graduate trainee, **Dr Mahroze Fatima** has joined PATHWEL. She is a graduate of Liaqat National Medical College & Hospital, Karachi. We welcome her and wish her success in future endeavors.

Acquisition of Electromedical Equipment

In last couple of months, following electromedical equipment were added to the hospital:

- Multi-head microscopeo
- Autoclave
- Mechanical Ventilator
- Platelet agitator

PATHWEL Stars

A girl with Thalassemia Major

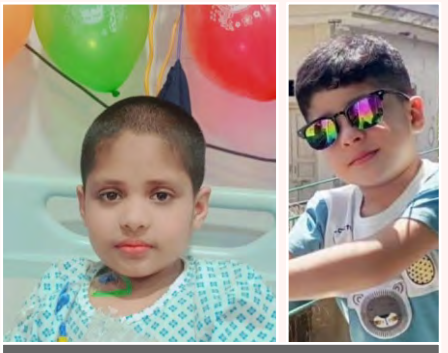
By Dr. Khalil ur Rehman,
Junior Consultant and BMT specialist, PATHWEL

Eight-year-old Sehrish Batool from Kotli Azad Kashmir was diagnosed as Beta Thalassemia Major at the age of 4 months and had been on regular blood transfusion support since then. Initially she did not receive iron chelation, which started at the age of 4 years. Even after that, iron chelation remained irregular and suboptimal.

In the meantime, the parents came to know about the low-cost bone marrow transplant facility at PATHWEL and brought her for consultation. The patient has received over 100 RCC transfusions and her Ferritin levels ranged between 4,000 to 6,500 ng/ml. She was classified as Pesaro Class III Thalassemia (irregular iron chelation, liver 6 cm below RCM, and grade 2 liver fibrosis). She was found to have a fully HLA matched brother. Pre-transplant work up was started and patient was put on intensive iron chelation.

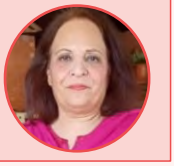
Sehrish underwent allogeneic bone marrow transplant on 2nd February 2023 with modified Long Protocol conditioning (Flu 120, Bu 12.8 iv, Cy 120, and TG 5). Stem cells were harvested from bone marrow. Standard GVHD prophylaxis with Cyclosporine and short Methotrexate was given. Engraftment was prompt. There were no major post-transplant complications. There was mild gut GVHD which responded well to short course of steroid.

Now, one year after transplant, Sehrish is maintaining stable blood counts and is free from GVHD. She is on tapering doses of immunosuppression and undergoing vaccination.



Sehrish on the day of transplant which was also her birthday. On the right, donor Ayaz, brother of Sehrish

A boy with Thalassemia Major



By Dr Zohra J Wazir
Chief Medical Officer Thalassemia Wing

Syed M Taha Kazmi is 11 years of age and studying in 7th grade. Following is an account of coping with Thalassemia in his own words.

"I have Thalassemia major and I manage my life, studies, sports, games and my disease. It's not that difficult. My dreams is only to fulfill my parents dream and I want to be an astronaut and want to discover information from space and raise the name of my country. The message for the other Thalassemia patients from me is that nothing is impossible. Just don't lose your hope and keep trying."

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(Selected Abstracts from HAEMCON2024)

Management of severe hemophilia a: low-dose prophylaxis vs. On- demand treatment

Dr. Rabeea Munawar Ali, Madiha Abid, Sidra Zafar; National Institute of Blood Disease and BMT, Karachi

Objective: Prophylactic clotting factor infusion regimens to prevent bleeding and joint deformity has become the standard of care in severe hemophilia A patients. The aim of this study is to assess low-dose factor prophylaxis in our population as an alternative approach to managing severe hemophilia A.

Methods: A prospective cohort study that included 68 hemophilia A patients divided into two groups, i.e., Prophylaxis and on-demand. The two groups were compared for annualized bleeding rate (ABR), hospitalization, units of factor VIII (FVIII) infused, or plasma products transfused, i.e., fresh frozen plasma (FFP) and cryoprecipitate (CP), and development of FVIII inhibitors.

Results: Of the 68 patients recruited in this study, 25 (36.7%) were in the prophylaxis group, and 43(63.3%) were in the on- demand group. The on-demand group presented a higher median-IQR ABR [8(20-3) vs. 5(10-1.5), p-value 0.024], several hospitalizations (39.7% vs. 0, p-value 0.001), and inhibitor development (9.3% vs. 0, p-value 0.289) compared to the prophylaxis group. The prophylaxis approach demonstrated a significant negative correlation of ABR with FVIII prophylaxis (r=-0484, p=value=0.014). Moreover, no hospitalizations or inhibitor development was observed in the prophylaxis group. The estimated annual consumption of FVIII was 328 IU/kg/year in the on- demand group and 1662.6 IU/kg/year in the prophylaxis group. However, a highly significant difference in plasma product utilization was observed between the two groups, i.e., p-value <0.001 and 0.038 for FFP and CP, respectively.

Conclusion: Low-dose factor prophylaxis resulted in improved outcomes compared to on-demand treatment in terms of ABR, joint bleeding, hospitalization, and the development of inhibitors. This treatment approach should be adopted as an economically feasible alternative to high-dose Prophylaxis in resource constrained countries.

Outcome of Allogenic Bone Marrow Transplantation in Aplastic anaemia: A Comprehensive Analysis of 100 Days Post-Transplant at a Single-Centre in a Remote Area

Dr Hafiz Muhammad Nadeem, Dr Shehzad Sarwar, Dr Muhammad Farhan, Dr Asghar , Dr Maryam Asghar , Dr Rozina, Dr Uzair, Dr Maria, Dr Muhammad Afzal, Dr Ayesha Arooj, Dr Parvez Ahmed Department of Clinical Hematology and BMT Gambat, Sindh

Objective: To evaluate the outcomes of allogenic bone marrow transplantation in patients with aplastic anemia Study

Design: Retrospective observational study Study Duration and Place: Department of Clinical Hematology and BMT Gambat, Sindh, from June 2021 to December 2023

Methodology: Total 37 patients were included in final analysis. The patients were admitted to isolation rooms fitted with laminar airflow and HEPA filters. All recipients received stem cells from 10/10 antigen matched siblings. Patients received antifungal prophylaxis with Amphotericin B from start of conditioning protocol. Conditioning regiment used consisted of Fludarabine120, Cy120, ATG20.High risk patients received Cy160. Cyclosporin was used for GVHD prophylaxis to achieve target trough levels of 200 - 300 ng/ml. Patients demographics, donor characteristics, source and dose of infused stem cells, complications during and after the transplant, disease-free survival (DFS), and overall survival (OS) were recorded. SPSS version 26 was used for statistical analysis. utilizing Pearson Chi-square test, a P value < 0.05 considered statistically signi cant.

Results: Among 37 participants, 23 were male, 14 were female with median age of 19 years (range: 5 - 41). Patients had received mean 40 RCC and 26 platelets prior to transplantation. Ferritin level was 1650. Source of stem cells was bone marrow (BM) in 24 patients (64.9%),

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BM and PBSC in 13 (45.1%) patients. Mean total nucleated cell (TNC) and CD34 doses were 6.78x106/kg and 6.1x108/kg respectively. Average time for neutrophil and platelet engraftment was 12 and 17 days respectively. Immediate post-transplant complications were fungal infections (45.9%), followed by cyclosporine (CSA)-induced hypertension (21.6%). Acute graft-versus-host disease (aGVHD) was observed in 7 patients (18.9%), primarily affecting the skin (75.1%) followed by gut. CMV reactivation occurred in 12 patients (32.4%), all of whom were administered valganciclovir. Overall and disease free survival was 73%. Leading causes of death were neutropenic sepsis, followed by graft failure. Three patients (8.1%) experienced primary graft failure, all of whom received stem cell boosts without any response. One patient exhibited poor graft function, which improved following stem cell boost.

Conclusion: Despite facing challenges like fungal infections and graft failure, the 73% overall survival and disease-free survival rates underscore the feasibility of this treatment approach in our resource-limited context. The findings underscore the significance of rigorous infection control measures and refinements in posttransplant care protocols.

Evaluation of Circulating Syndecan-1 As A Diagnostic Marker of Disseminated Intravascular Coagulation

Dr Aisha Waqas, Dr Ikram Din Ujjan, Dr kiran Amir; LUMHS Jamshoro/Hyderabad

Objective: To evaluate circulating syndecan-1 as a diagnostic marker of disseminated intravascular coagulation

Methods: A descriptive cross-sectional study conducted at LUMHS hospital Hyderabad from 01-01-23 to 31-06-2023 on 90 DIC patients admitted in ICU with data collection done on structured proforma. (SPSS-20) version was used to analyze the data.

Results: In this study, total 90 patients of DIC were studied for serum Syndecan-1 level. Mean age of patients were 39.64± 17.32 years. Among patients most common cause of DIC were sepsis (36.67%) and obstetric complications (35.56%). Mean Platelets was 99.05 ± 24.04, PT was 20.13 ± 7.11, Fibrinogen was 141.8± 28.40, D. Dimer was 0.56± 0.23. Among patients at time of DIC diagnosis, serum Syndecan-1 level of 40 (44.44%) were in normal range group(0-45ng/ml), 19 (21.1%) were in mild range group(45-60ng/ml), 28 (31.1%) were in moderate range group(60- 85ng/ml), & 3 (3.3%) were in severe range group(>85ng/ml).

Conclusion: Endothelium is a main contributing factor in pathogenesis of DIC so its biomarker (serum Syndecan-1) can be used as a diagnostic tool for Disseminated Intravascular coagulation that can help to assess endothelial injury in early phase of DIC and in early management to prevent mortality.

Morphology Updates

Thrombopoietin mimetic-induced bone marrow fibrosis

KirsteenHarper[1] | CatherineBagot[2] | MikeLeach[1] | BarbaraJ.Bain[3]
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DOI:10.1002/ajh.27154

A 67-year-old man with an 8-year history of autoimmune thrombocytopenic purpura ("ITP"), previously intolerant or unresponsive to multiple treatments (azathioprine, mycophenolate mofetil, rituximab, eltrombopag, and romiplostim), was commenced on avatrombopag. A baseline blood count showed hemoglobin concentration 132 g/L, WBC 8.5 x 10^9/L, and platelet count 16 x 10^9/L, with the blood film confirming the platelet count but otherwise being normal. After 4 months of avatrombopag therapy, there was no significant improvement in the platelet count but his blood film now showed prominent tear-drop poikilocytes. Bone marrow trephine biopsy sections were hypercellular (80% overall) (top left) with a dense meshwork of fine and coarse reticulin fibers (MF-2) (top center) with occasional collagen fibers. Megakaryocytes were markedly increased in number, size, and ploidy with the formation of large clusters (CD42b, top right). Molecular analysis for JAK2 V617F, CALR exon 9 mutation, and MPL W515L showed no abnormality. Avatrombopag was discontinued. He remained thrombocytopenic (platelet count 11 x 10^9/L) but without hemorrhage for the next 4 months at which point the marrow biopsy was repeated. The biopsy sections now showed cellularity of 50% overall with a reduction in megakaryocyte size (bottom left) and only a mild increase in reticulin (MF 0–1) (bottom center). There was a mild excess of megakaryocytes but no clustering or abnormal localization (CD42b, bottom right).

Thrombopoietin receptor agonists (TPO-RA) stimulate megakaryopoiesis and can increase platelet production in ITP. An increase in bone marrow reticulin is a well-recognized phenomenon1 though clinically significant, severe grades with collagen deposition are rare. Discontinuation of TPO-RA may not be necessary in all cases but has been shown to lead to regression of bone marrow fibrosis in cases reported.

COI STATEMENT
The authors declare no conflicts of interest.

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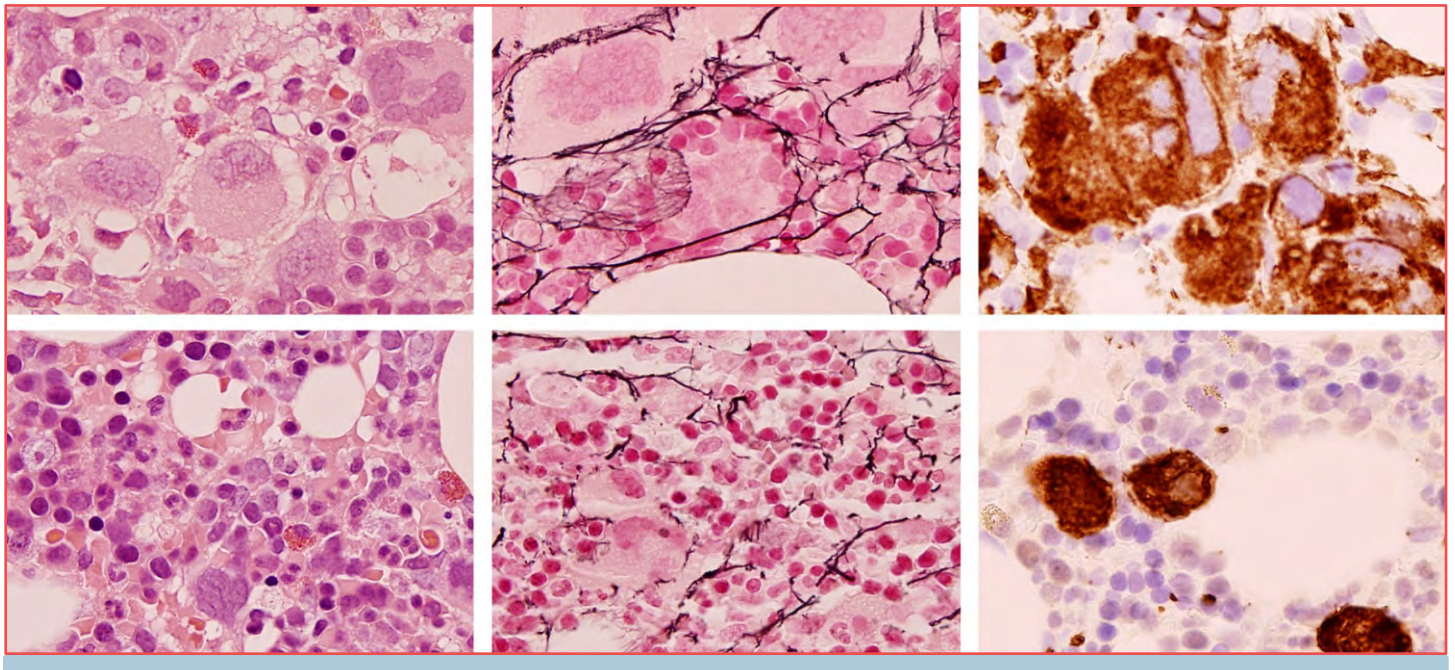
REFERENCE
1. Kuter DJ, Mufti GJ, Bain B, et al. Evaluation of bone marrow reticulin formation in chronic immune thrombocytopenia (ITP) patients treated with romiplostim. Blood. 2009;114(18):3748-3756.



Tidbits Tidbits Tidbits Tidbits Tidbits Tidbits Tidbits

Past meets present: Reviving 80-year-old Canadian dried serum from World War II and its significance in advancing modern freeze-dried plasma for prehospital management of haemorrhage

Singh K, Peng HT, Moes K, Kretz CA, Beckett A. Br J Haematol. 2024;00:1–8. https://doi.org /10.1111/ bjh.19298

During World War II, Charles H. Best utilized Charles R. Drew's plasma isolation and drying technique to lead Canada's initiative to provide dried serum as a means of primary resuscitation for British casualties on the frontlines. Serum was likely utilized over plasma for its volume expansion properties without the risk of clotting during prolonged storage.

The authors reconstituted dried serum from 1943 and discovered intact albumin, as well as anti-thrombin, plasminogen, protein C and protein S activity. Proteomic analysis identified 71 proteins, most prominent being albumin, and positive for hepatitis B by serological testing. Transmission of blood-borne diseases ended the program, until modern advances in testing and pathogen reduction revived this technology.

We tested the latest iteration of Canadian freeze-dried plasma (FDP), which was stored for 4 years, and demonstrated that its clotting capacity remained equivalent to fresh frozen plasma. We recommend that FDP is a strong alternative to contemporary prehospital resuscitation fluids (e.g. normal saline/lactated Ringer's) in managing prehospital hemorrhage where whole blood is unavailable.

Interpretable Artificial Intelligence (AI) Differentiates Prefibrotic Primary Myelofibrosis from Essential Thrombocythemia: A Multi-Center Study of a New Clinical Decision Support Tool

Andrew Srisuwananukorn et al, ASH 2023, Oral Abstracts

Artificial Intelligence Model Successfully Differentiates Myeloproliferative Neoplasms

An interpretable artificial intelligence (AI) algorithm is a rapid and accurate way to differentiate between two myeloproliferative neoplasms (MPNs) according to a study presented at the annual meeting of the ASH 2023.

This was an image-based AI study within MPNs with external validation. Patients included in the study had a clinical or histopathological diagnosis of prefibrotic primary myelofibrosis (prePMF) or essential thrombocythemia (ET) according to the International Consensus Classification of Myeloid Neoplasms. The training cohort included 200 patients (100 prePMF, 100 ET) from the University of Florence in Italy, with an external test cohort of 26 patients (six prePMF, 20 ET) from the Moffitt Cancer Center in Tampa, Florida.

The AI model was trained on a total of 32,226 patient-derived diagnostic bone marrow biopsy digital whole-slide images (WSI). A fivefold cross-validation within the training cohort yielded a mean area under the receiver operating characteristic curve (AUC) of 0.90 (standard deviation, 0.04).

When reviewing the slides associated with the highest prediction values per class, the researchers found the model relied heavily on areas of cellular marrow. Furthermore, the model took approximately 6.1 seconds to evaluate WSI it had not seen before (4.9 for preprocessing and 1.2 for evaluation).

Overall, the test cohort saw a final diagnostic classification accuracy of 92.3 percent, with a sensitivity for prePMF diagnosis of 66.6 percent and a specificity of 100 percent.

The authors concluded, “We developed a novel AI model with high accuracy for distinguishing between prePMF and ET in distinct clinical cohorts. To our knowledge, this study represents the largest image-based AI study within MPNs with external validation. Our proposed model may assist clinicians in appropriately identifying patient cohorts who would benefit from disease-specific therapies or enrollment onto clinical trials. We imagine that a potential high-speed, low-cost algorithm may reliably distinguish prePMF from ET patients with high specificity”.

Transplant TidingsTransplant TidingsTransplant Tidings

A randomized phase 2 trial of oral vitamin A for graft-versus-host disease in children and young adults

P Khandelwal, L Langenberg, N Luebbering, et al; Blood 2024 Jan 16; [EPub Ahead of Print]; doi.org/10.1182/blood.2023022865

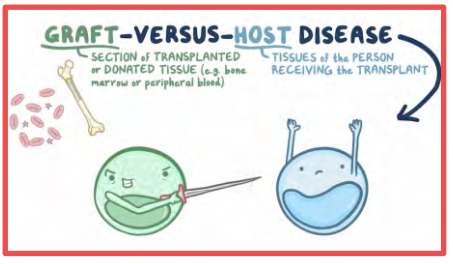
Vitamin A plays a key role in the maintenance of gastrointestinal homeostasis and promotes a tolerogenic phenotype in tissue resident macrophages. This phase II trial evaluated the use of high-dose pretransplant vitamin A to reduce GVHD in children and young adults undergoing hematopoietic stem cell transplant (HSCT). Eighty HSCT recipients were randomized 1:1 to receive pre-transplant high-dose vitamin A or placebo. A single oral dose of vitamin A of 4000 I.U/kg, maximum 250,000 I.U was given prior to conditioning.

Overall, no statistical differences were observed between the vitamin A and placebo groups in the incidence of acute GVHD at day +100 (mostly driven by skin GVHD; incidence rate, 12.5% with vitamin A vs 20.0% with placebo). However, vitamin A was associated with a lower cumulative incidence of acute GVHD at day +180 (2.5% vs 12.5%). The incidence of chronic GVHD was 5% in the vitamin A arm and 15% in placebo (p=0.02) at 1 year. The cumulative incidence of both acute & chronic gastrointestinal GVHD was lower with the use of vitamin A. The only possibly attributable toxicity was asymptomatic grade 3 hyperbilirubinemia in one vitamin A recipient at day+30, which self-resolved. Various immune markers associated with GVHD were also downregulated in the vitamin A group.

The use of pre-HSCT vitamin A is an inexpensive, low-toxicity intervention that may reduce the incidence of (gastrointestinal) GVHD in young patients undergoing HSCT.

Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation

Prof Olaf Penack, Monia Marchetti, Prof Mahmoud Aljurf, et al; doi.org/10.1016/S2352-3026(23)00342-3; published January 3, 2024.



Graft-versus-host disease (GVHD) is a major factor contributing to mortality and morbidity after allogeneic HSCT. In the last 3 years, there has been regulatory approval of new drugs and considerable change in clinical approaches to prophylaxis and management of GVHD.

To standardize treatment approaches, the EBMT has updated its clinical practice recommendations. We formed a panel of one methodologist and 22 experts in the field of GVHD management. We applied the GRADE process to ten PICO (patient, intervention, comparator, and outcome) questions: evidence was searched for by the panel and graded for each crucial outcome. In two consensus meetings, we discussed the evidence and voted on the wording and strengths of recommendations.

Key recommendations include:

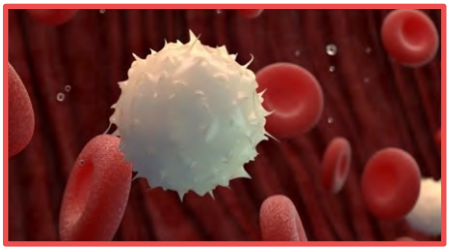
1. Primary use of ruxolitinib in steroid-refractory acute GVHD and steroid-refractory chronic GVHD as new standard of care.
2. Use of rabbit anti-T-cell (thymocyte) globulin or post-transplantation cyclophosphamide as standard GVHD prophylaxis in PBSC transplantations from unrelated donors.
3. The addition of belumosudil to the available treatment options for steroid-refractory chronic GVHD.

The EBMT proposes to use these recommendations as the basis for routine management of GVHD during allogenic HSCT. The current recommendations favor European practice and do not necessarily represent global preferences.

Transplant TidingsTransplant TidingsTransplant Tidings

Rituximab added to conditioning regimen significantly improves erythroid engraftment in major incompatible ABO-group hematopoietic stem cell transplantation.

Maria Chiara Finazzi, Alessandra Weber, Chiara Pavoni, et al; Bone Marrow Transplantation; doi.org/10.1038/s41409-024-02247-w



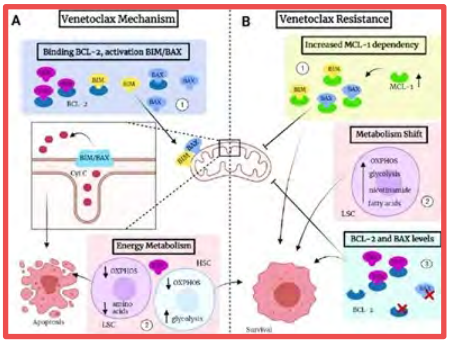
ABO-group major incompatibility HSCT increases the risk of delayed red cell engraftment and other immunological complications. In this study, the authors evaluated the efficacy of pre-transplant infusion of rituximab in patients with ABO-incompatibility in improving RBC engraftment after HSCT, measured by time to reach transfusion independence. In this study the authors performed a retrospective, single-center study including 131 consecutive patients transplanted with major or bidirectional ABO-incompatible grafts between 1st January 2013 and 31st December 2019. Fifty-one patients received an infusion of rituximab during the conditioning regimen, while 80 patients did not receive any additional preventive treatment.

Time to transfusion independence was significantly reduced for patients treated with rituximab (1 month, 95% CI, 0.5–2) compared with the control group (3.2 months, 95% CI 1.5–3.2, p = 0.02). By multivariable analysis, rituximab use was associated with a faster RBC engraftment (RR 1.88, 95% CI 1.17–3.03, p = 0.009), while a pre-transplant anti-donor isohemagglutinins titer >1:128 was associated with delayed transfusion independence (RR 0.61, 95% CI 0.37-0.99, p = 0.05).

Although limited by the retrospective nature of the study, the results of this analysis suggest that rituximab added to conditioning regimens is feasible, safe, and able to improve post-transplant RBC engraftment.

Addition of venetoclax to myeloablative conditioning regimens for allogeneic hematopoietic stem cell transplantation in high-risk AML

Xing-yu Cao, Jia-qi Chen, Hui Wang, et al; Annals of Medicine, 55:1, 388-400, DOI: 10.1080/07853890.2022.2164610



Venetoclax monotherapy is an effective option for patients with AML. Venetoclax has also been used in non-myeloablative conditioning allogeneic hematopoietic stem cell transplantation (allo-HSCT) for high-risk AML with a tolerable toxicity profile. However, the efficacy and safety of a venetoclax-containing myeloablative conditioning (MAC) allo-HSCT regimen for high-risk AML have not been evaluated.
In this study from China, the authors evaluated the safety and efficacy of addition of venetoclax to a MAC regimen for high-risk AML who underwent allo-HSCT. A total of 31 patients were analyzed.

At the time of transplantation, 21 patients were in first complete remission (Cr1), 4 were in a second complete remission (CR2), and 6 in non-remission (NR). Twenty-four patients (77.4%) were MRD positive before transplant. The FLT3-ITD gene mutation was present in 51.6% of patients. NUP98 rearrangement, MLL rearrangement or MLLPTD and DEK::CAN fusion genes were found in 5 (16.1%), 7(22.6%) and 2 (6.5%) patients, respectively. Twenty-nine (93.6%) patients underwent haploidentical allo-HSCT.

The median follow-up time was 278 days (range: 52–632 days). The 100-day cumulative incidence of grade 3 to 4 acute GVHD) was 16.1% (95%CI, 7.2–36.0%). The 180-day cumulative incidence of moderate to severe chronic GVHD was 7.1% (95%CI, 1.9–26.9%). Cumulative incidence of 100-day CMV viraemia was 61.6%. The 600-day overall survival (OS) and leukemia-free survival (LFS) were 80.9% and 81.3%, respectively. The 600-day relapse incidence (RI) and non-relapse mortality (NRM) was 6.9% and 11.7%.

This study shows that the addition of venetoclax to a MAC allo-HSCT is feasible, safe, and effective for high-risk AML patients.

A Success story – life saving surgery in a young female with Von Willebrand Disease (VWD)

By Dr Tahira Zafar
Consultant Hematologist | Director, Hemophilia Treatment Centre

In Patients with inherited bleeding disorders, like VWD, replacement of deficient factor is of paramount significance. This becomes more crucial when these patients undergo emergency surgical procedures.

Case Report

This 15-year-old girl from Faisalabad was a known case of VWD. She presented to a local hospital with sudden onset of severe abdominal pain and vomiting. The patient was hemodynamically stable. There was generalized abdominal tenderness in the abdomen. USG scan showed left adnexal cystic lesion with mild amount of fluid in pelvis and cul-de-sac. She was referred to PIMS for further evaluation.

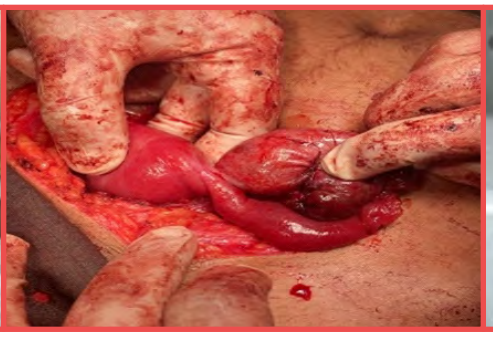
An emergency laparotomy was planned. The gynecology team of PIMS in liaison with the Hemophilia Treatment Center (HTC) Rawalpindi chalked out a detailed pre-operative, intra-operative, and post-operative strategy.

The patient underwent left ovarian cystectomy along with repair of left ovary under VWF concentrate cover (Details of Factor Replacement Plan are given in Table-A). The procedure was a complete success and patient made a smooth recovery with no major post-operative complications.

Women with bleeding disorders are more prone to develop obstetric & gynecological cysts (Hoc's) show a high prevalence in patients with rare bleeding disorders (RBD's). It is important to diagnose these cases early & ensure optimal management to prevent complications.

Table-A: Factor Regalement Plan

Tranexamic Acid		
	Start night before operation and continue post-op	Dose: 600 mg x 8 hourly (15 mg/kg 8 hourly for 10 days)
VWF concentrates		
1. Pre-Op	1 hour before surgery	Dose: 2400 IU stat (60 IU/kg IV stat)
2. Post-Op	Day 1 – 3	Dose: 1600 IU OD(40 IU/kg OD)
	Day 4 – 6	Dose: 800 IU OD(20 IU/kg OD)
	Day 7 – 10	Dose: 400 IU OD(10 IU/kg OD)


Clinical Practice Guidance

Antithrombotic Treatment in Patients with Hemophilia: an EHA-ISTH-EAHAD-ESO Clinical Practice Guidance. Summary of Recommendations (Part-I)

Roger E.G. Schutgens, Victor Jimenez-Yuste, Miguel Escobar, et al; HemaSphere (2023) 7:6(e900); doi.org/10.1097/HS9.0000000000000900

Section 1: General Considerations

What is the FVIII/FIX threshold to safely start aspirin or oral anticoagulation in patients with hemophilia (PWH)?

Recommended: Use of any form of antithrombotic therapy (including single-antiplatelet therapy [SAPT]) in severe hemophilia without clotting factor prophylaxis.

Not recommended: Use of any form of antithrombotic therapy (including SAPT) in PWH with inhibitors not using emicizumab.

Recommended: A minimum trough FVIII/IX level of 1–5 IU/dL for SAPT.

Recommended: A minimum trough FVIII/IX level of 20 IU/dL for dual antiplatelet therapy (DAPT).

Recommended: A minimum trough FVIII/IX level of 20 IU/dL for oral anticoagulation (vitamin K antagonist [VKA] with INR levels 2–3 or full dose direct oral anticoagulant [DOAC]).

Recommended: A minimum trough FVIII/IX level of 80 IU/dL for triple therapy (oral anticoagulation & DAPT).

Recommended: Apply the lowest factor level measured in case of discrepancy between 1-stage or chromogenic assays.

What is the bleeding risk in PWH using antiplatelet or oral anticoagulant therapy?

Recommended: Use of empiric proton pump inhibition in all PWH on antiplatelet therapy.

Recommended: Actively managing anemia in association with antithrombotic treatment.

Should clotting factor prophylaxis be adapted in PWH in need for anticoagulation therapy?

For PWH with baseline clotting factor levels >20 IU/dL in need for any form of antithrombotic therapy:
Recommended: Start antithrombotic therapy and not to start additional clotting factor prophylaxis.

For PWH with baseline clotting factor levels <20 IU/dL with an indication for long-term prevention of thrombotic complications with oral anticoagulation (VKA or DOAC): **Recommended:** Not to start with oral anticoagulation therapy. PWH should be considered as being naturally anticoagulated when clotting factors are <20 IU/dL.

For patients with severe hemophilia using clotting factor prophylaxis in whom long-term oral anticoagulation therapy is considered: **Recommended:** Adapt clotting factor prophylaxis to maximum peak levels of 25 IU/dL and not to start additional anticoagulation therapy (more frequent lower dose rather than once weekly higher dose prophylaxis).

For patients with severe hemophilia with an indication for long-term prevention of thrombotic complications with SAPT :
Recommended: Start SAPT and maintain FVIII/FIX trough levels >1 IU/dL using regular clotting factor prophylaxis. In severe hemophilia with on demand clotting factor supplementation, switch to regular prophylaxis and SAPT.

For patients with severe hemophilia in need of short-term DAPT or oral anticoagulation: **Recommended:** Adapt clotting factor prophylaxis to maintain a factor trough level of ≥20 IU/dL.

For patients with non-severe hemophilia with baseline clotting factor levels <20 IU/dL with a very high thrombotic risk in need of (short-term) DAPT or oral anticoagulation: **Recommended:** Adapt clotting factor prophylaxis to maintain a factor trough level of ≥20 IU/dL for as long as DAPT or oral anticoagulation is given.

If the decision for oral anticoagulation in PWH has been made, is there a preference for a specific type of drug?

Recommended: Use DOACs over VKA in nonvalvular AF or VTE due to their favorable safety profile and the ability to individualize treatment regimens. DOACs are preferred over VKAs in PWHB.

Recommended: If PWH are using VKAs, promote INR self-monitoring.

If the decision for oral anticoagulation in PWH has been made, is there a need for monitoring anticoagulation treatment and dose adjustment?

Recommended: Similar INR ranges in PWH on VKA as that of the general population.

Recommended: In PWH with AF, administer DOACs at fixed standard dose without routine lab monitoring for dose adjustments.

Recommended: Give DOACs in reduced dose to those PWH who meet the criteria of anticoagulant dose reduction as in the general population.

Does the use of emicizumab suggest a safe threshold for antithrombotic therapy?

In PWHA using emicizumab (with or without inhibitors), we consider it acceptable to use SAPT.

There is currently insufficient data to draw conclusions on the safety of DAPT or oral anticoagulation in PWHA using emicizumab; therefore, we suggest not to switch PWHA from FVIII prophylaxis to emicizumab for this purpose. *(...to be continued)*

Thalassemia Major

(Part-1)

By Dr Tahira Zafar, Consultant Hematologist

تھیلیسیمیا میجر

(حصہ اوّل)

ڈاکٹر طاہرہ ظفر، کنسلٹنٹ ہیماٹولوجسٹ

We are starting page for information of blood diseases for our patients in Urdu. The first in this series of articles is on thalassemia major. This article is from a booklet written by Dr Tahira Zafar, Senior Consultant Hematologist. We are publishing this booklet in three parts.

۱۔ تھیلیسیمیا خون کی ایک موروثی بیماری ہے جو نسل در نسل بچوں میں منتقل ہوتی ہے۔

۲۔ یہ پاکستان کی سب سے عام بیماری ہے ایک تخمینے کے مطابق اس وقت پاکستان میں تقریباً ۹۰ لاکھ (۵ء۵ فیصد) افراد میں تھیلیسیمیا کے اثرات (Gene) موجود ہیں۔

۳۔ تھیلیسیمیا کے بارے میں ایک انتہائی اہم اور بنیادی حقیقت یہ ہے کہ اسکی دو اقسام ہیں۔ تھیلیسیمیا مائیز اور تھیلیسیمیا میجر۔ ذرائع ابلاغ اور روزمرہ کی زندگی میں جس تھیلیسیمیا کا ذکر ہوتا ہے وہ تھیلیسیمیا میجر ہے۔

۴۔ دونوں اقسام موروثی ہیں اور صرف والدین ہی بچوں میں منتقل ہوتی ہیں۔ اس بیماری کا کسی بیرونی عوامل یعنی کھانا، پینا، رہائشی علاقہ، تعلیم، آبائی پیشہ، کمپیوٹر، جراثیم، آب وہوا، ساتھ رہنا، کپڑوں وغیرہ سے کوئی تعلق نہیں ہے۔ نہ ہی یہ بیماری کسی شخص سے دوسرے کو لگی ہے۔ تھیلیسیمیا کی دونوں اقسام صرف اور صرف والدین سے ہی ان کے بچوں میں منتقل ہوتی ہیں۔

۵۔ اگر والدین میں صرف ایک (والد یا والدہ) کو تھیلیسیمیا مائیز ہو تو بچوں میں صرف تھیلیسیمیا مائیز کی منتقلی ہے اور یہ چانس ہر حمل میں ۵۰ فیصد ہے ایسی شادی کے نتیجے میں بچوں کو تھیلیسیمیا میجر نہیں ہو سکتا۔

۶۔ اگر دونوں والدین کو تھیلیسیمیا مائنیر ہے تو ایسی شادی کے نتیجے میں کچھ بچوں کو تھیلیسیمیا مائیز ہو سکتا ہے جبکہ کچھ بچے بالکل نارمل بھی ہو سکتے ہیں۔ ان نارمل بچوں میں تھیلیسیمیا میجر یا مائیز منتقل نہیں ہوگا۔ شومئی قسمت سے چند بچے تھیلیسیمیا میجر کا شکار ہوں گے۔ یہ صرف چانس کی بات ہے۔ ایسے ازدواجی رشتے کے ہر حمل میں تھیلیسیمیا کی منتقلی کا چانس درج ہے:۔

نارمل بچے ۲۵ فیصد، تھیلیسیمیا مائیز ۵۰ فیصد۔ تھیلیسیمیا میجر ۲۵ فیصد یاد رہے کہ یہ چانس ہر حمل کے لئے ہے۔ یہ نقطہ ٹیبل نمبر 1 میں واضح طور پر بتایا گیا ہے۔

۷۔ تھیلیسیمیا چاہے میجر ہو یا مائیز یہ پیدائش کے وقت بچے میں موجود ہوتا ہے۔ یہ پیدائش کے بعد کسی حالت میں بھی نہیں لگ سکتا۔ سب سے اہم بات یہ ہے کہ تھیلیسیمیا مائیز تا زندگی تھیلیسیمیا مائیز رہے گا اور تھیلیسیمیا میجر ہمیشہ تھیلیسیمیا میجر ہی رہے گا۔ یہ ایک دوسرے میں کبھی تبدیل نہیں ہو سکتے۔

۸۔ تھیلیسیمیا ایک موروثی بیماری ہے جو کہ بوقت حمل بچے کو منتقل ہوتی ہے اور تاحیات اس میں موجود رہتی ہے یہ کسی علاج سے نہ تو اپنی شدت میں تبدیلی کرتی ہے اور نہ ہی یہ متاثرہ فرد کے جسم سے ختم ہو سکتی ہے۔

۹۔ تھیلیسیمیا مائیز عام طور پر کسی بیماری کے زمرے میں نہیں آتا۔ یہ خون کی ایک کیفیت ہے۔ یہ ایک لیبل ہے۔ جن لوگوں میں تھیلیسیمیا مائیز ہے ان کو تھیلیسیمیا کا مریض کہنا مناسب نہیں کیوں کہ اکثر و بیشتر افراد میں اس کی علامات بالکل نہیں ہوتی۔ ان میں تھیلیسیمیا کی تشخیص خون کے ایک خاص معائنے سے ہوتی ہے۔

۱۰۔ تھیلیسیمیا مائیز کی اہمیت یہ ہے کہ اگرچہ یہ لوگ بذات خود تندرست ہوتے ہیں لیکن یہ بیماری انکی آئندہ نسل میں منتقل ہو سکتی ہے۔ ایسے لوگ (Carriers) کہلاتے ہیں۔

ٹیبل نمبر 1

والدین میں تھیلیسیمیا کی کیفیت		بچوں میں تھیلیسیمیا کی کیفت اور اس کا فیصد تناسب		
والد / والدہ	والد / والدہ	نارمل	تھیلیسیمیا مائیز	تھیلیسیمیا میجر
نارمل	نارمل	100	--	--
تھیلیسیمیا مائیز	نارمل	50	50	--
تھیلیسیمیا مائیز	تھیلیسیمیا مائینر	25	50	25

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