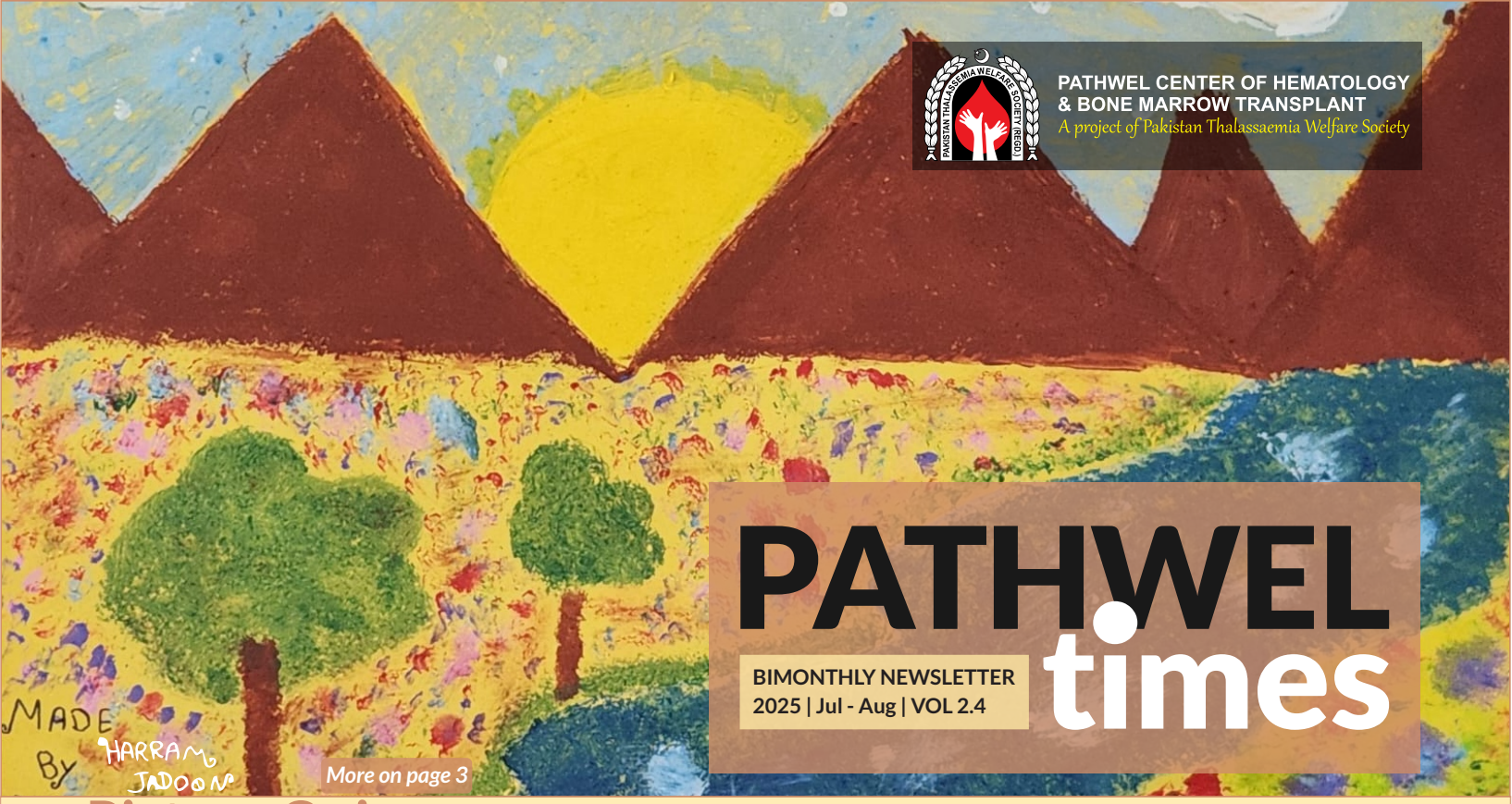
PATHWEL CENTER OF HEMATOLOGY
& BONE MARROW TRANSPLANT
A project of Pakistan Thalassaemia Welfare Society



PATHWEL times

BIMONTHLY NEWSLETTER
2025 | Jul - Aug | VOL 2.4

More on page 3

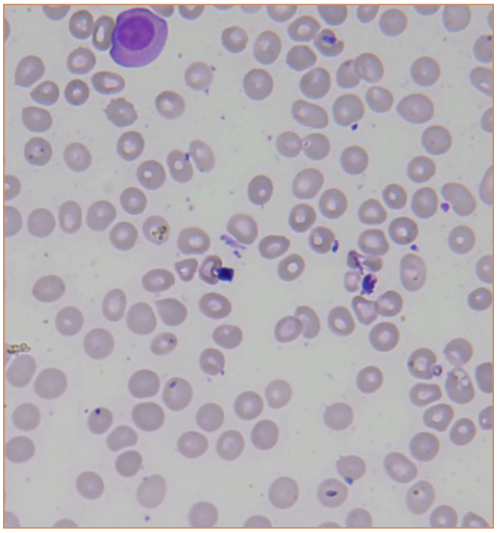
Picture Quiz

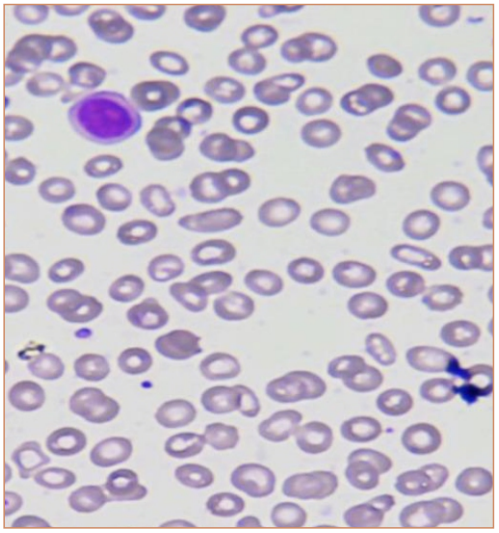
by **Dr Laila Bahadur,** *Consultant Hematologist PATHWEL*

Answer on page :05

A 32-year-old female presented with fever, backache and easy bruising for the last three months. On physical examination, she was pale but not jaundiced; there was no lymphadenopathy, hepatomegaly or splenomegaly. On investigation, CBC revealed Hb 6.1 g/dL, WBC 5.2 × 10^9/L, and platelets 54 × 10^9/L. Renal functions were deranged (urea 135 mg/dL and creatinine 4.04 mg/dL). Serum calcium was 9.5 mg/dL and phosphate 5.3 mg/dL. These are the peripheral blood films of the patient.

What is the most likely diagnosis?





INSIDE THIS ISSUE

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14 Aug 2025

Celebrating 78 years of independence — PATHWEL stands proud to serve Pakistan with dedication, hope, and healing

Haiqa Mahnoor receiving blood transfusion .....
she had her face printed on the T-shirt to celebrate Independence Day!

From Editor's Desk

Technological Independence: The Missing Link

In Pakistan, much has been written about the pharmaceutical industry's struggle to keep pace with neighboring countries. We highlight the lack of infrastructure for advanced therapies and the shortage of essential medicines. Yet one critical issue remains missing: the absence of a biotech and electromedical industry.

This gap is alarming because biotechnology and electromedical innovation are central to modern healthcare. Advanced diagnostics, monitoring systems, and precision devices form the backbone of critical care. Without them, even the best medicines cannot achieve their purpose. Bone marrow transplantation, chemotherapy, and intensive care all rely not only on drugs but equally on sophisticated and reliable equipment.

Pakistan depends almost entirely on imported devices—infusion pumps, monitors, ventilators, and apheresis machines. These are costly, slow to procure, and vulnerable to supply chain disruptions. In a charity-driven healthcare ecosystem, such dependence means restricted access, unaffordable costs, and avoidable interruptions in patient care.

Imagine instead a healthcare system supported by locally developed and maintained equipment. If infusion pumps, monitoring systems, and apheresis machines were built in Pakistan, they could transform care, much like low-cost generics did for medicines. Local production would reduce costs, create jobs, develop expertise, and ensure sustainability through accessible maintenance and spare parts. It would also enable hospitals to expand lifesaving programs such as free transfusions for thalassemia patients and bone marrow transplants for otherwise fatal diseases.

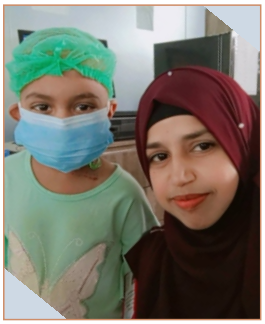
The tragedy is not that Pakistan lacks capacity, but that it has not chosen to prioritize this. Our universities produce skilled engineers, and our healthcare sector is filled with innovators. What is missing is a coordinated national push. We urge policymakers, industry leaders, and academic institutions to demand a roadmap for indigenous biotech and electromedical development—placing healthcare independence at the core of national policy.

A syringe pump prototype being developed by Maj Gen (R) Suhaib Ahmed, President PTWS in his home workshop. This is expected to cost Rs. 10,000 as compared to the Chinese versions available in market for Rs. 100,000.

Healing Through Art

Haram Jadoon, a 6-year-old young artist, underwent a bone marrow transplant in July 2025 for Thalassemia Major. During her stay, she expressed herself through beautiful paintings and drawings, transforming her journey into art that reflected courage, hope, and imagination. Her work stands as an inspiring reminder that even in the midst of illness, the spirit of a child can shine brightly through creativity and passion.

Photos contributed by ***Transplant Nurse Bushra Shaheen***



Sharing a creative moment with the doctor

Welcome "Welcome to the team! We're thrilled to have you with us"

We are deeply honored to welcome Brig (Retd) Kishwar Sultana to PATHWEL as our new Bone Marrow Transplant Coordinator.

Brig (Retd) Kishwar Sultana brings with her a wealth of experience from a distinguished career in the Armed Forces Nursing Service of the Pakistan Army, where she served with dedication and excellence. She is a pioneer in bone marrow transplant (BMT) nursing in Pakistan and a recognized expert in apheresis procedures.

Her contributions as an instructor at AFPGMI have been instrumental in training and mentoring a generation of nurses in hematology, oncology, and transplant care, raising the standards of specialized nursing practice across the country.

At PATHWEL, she will play a pivotal role in coordinating our bone marrow transplant program, ensuring that patients receive the highest quality of care and that our nursing teams continue to benefit from her expertise, guidance, and leadership. We warmly welcome Brig (Retd) Kishwar Sultana to the PATHWEL family and look forward to her continued contributions to advancing BMT care in Pakistan.

Dr Kaleem Raza Shah

The PATHWEL community is delighted to extend a warm welcome to the newest members of our Clinical Hematology Fellowship program, **Dr Kaleem Raza Shah and Dr Abdul Salam Khan .**

We are confident that their skills and dedication will be an invaluable asset to our team and the patients we serve. We look forward to seeing them thrive and contribute to our environment of learning and discovery. Please join us in wishing them a successful and enriching fellowship.

Dr Abdul Salam Khan

Blood Camps' Diary

By Ms Nigar Shah
PRO & Camp Coordinator, PTWS

Organizing blood donation camps poses challenges for PATHWEL, including harsh weather, low turnout due to myths, and public apathy. Administrative hurdles like permissions and venue issues, along with limited staff, medical resources, and transport, further strain efforts. Despite obstacles, PATHWEL perseveres to save lives. Public support, smoother processes, and better infrastructure can ensure more successful drives.

NUTECH (National University of Technology) Sector I-12 Islamabad | 6 May 2025

Blood camp at NUTECH was very successful. A large number of students turn out to donate blood. Dr Syed Kamran Mahmood, a senior consultant at PATHWEL, delivered an insightful lecture on "Introduction to Blood Diseases and Blood Transfusions" to the students and the management of NUTECH. We extend our heartfelt appreciation to the Rector, the Student Affairs Department, and the entire management team of NUTECH for their invaluable cooperation and support in making this blood donation drive possible.

Shifa College of Medicine, Sector H-8 / 4 Islamabad
12 May 2025

A blood donation camp was organized at Shifa College of Medicine, in a collaboration with Al-Khidmat Foundation Punjab North. Prof Dr Muhammad Amir, Dean Faculty of Health Sciences & Mr. Rizwan Ahmed, President Al-Khidmat Foundation Punjab North, inaugurated the event with a ribbon cutting ceremony. A large number of students participated in this healthy activity.

HITEC-IMS, Taxila | 21 May 2025

PATHWEL arranged a blood donation drive led by our MS Dr Nasir Mahmood Khan, in HITEC Institute of Medical Sciences. Principal HITEC Maj Gen (R) Hamid Shafique inaugurated the event. Blood Donation Society Patron in Charge Brig (R) Dr Farhat Abbasi, president student society Dr Falak Shabbir, Dr Nouman and all representatives of blood donation society voluntarily performed active role throughout the activity. The interesting part of HITEC blood donation society is their unique style of decorating the halls and whole building to attract and inspire all visitors and to motivate donors.

Loop Communication, Rawalpindi | 6 June 2025

A unique blood collection drive took place on the night of 6th and 7th June, when dedicated volunteers from Loop Communications arrived after midnight to donate blood before departing for the Eid holidays. We deeply appreciate the contributions of all walk-in donors who selflessly came to PATHWEL to support patients in need.

Allama Iqbal Park Rawalpindi | 20 June 2025

To address the urgent need for blood donations for thalassemia patients, we organized a blood donation drive at Allama Iqbal Park, Rawalpindi. Unfortunately, due to the peak hot weather, we were only able to collect only handful of donations. However, we are incredibly grateful to those who braved the heat to donate, and we extend our heartfelt gratitude to the management of Parks and Horticulture Rawalpindi for their unwavering support in organizing these blood drives. Every donation count, and together, we are making a difference in the lives of those in need.

Lake View Park, Islamabad | 21 June 2025

Organizing blood donation camps in public places presents numerous challenges for PATHWEL's dedicated team. Harsh weather—extreme heat, cold, or rain—often discourages donors and disrupts camps. One such incident happened at Lake View Park. As soon as we established our camp, it started to rain heavily. We had to pack up in a hurry and came back without a single donation.

PRIMACO, EOBI Tower, G-10/4, Islamabad | 26 June 2025

A blood donation drive was held in Pakistan Real Estate Investment and Management Company (Pvt) Ltd (PRIMACO) located in EOBI Tower, Islamabad. Although we distributed pamphlets to every tenant in the building and tried to motivate them to donate blood to save the lives of little patients but due to extreme hot weather the response was not good and we could only collect a few blood bags.

"The heat tested us today, but our resolve will bring the donors tomorrow."

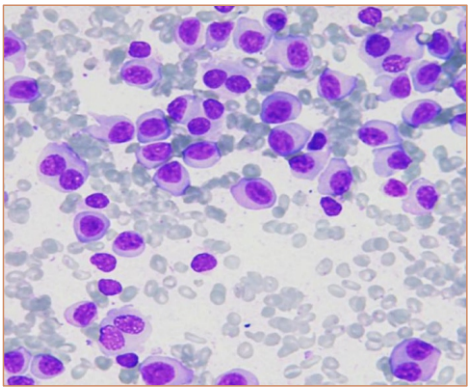
Picture Quiz Answer

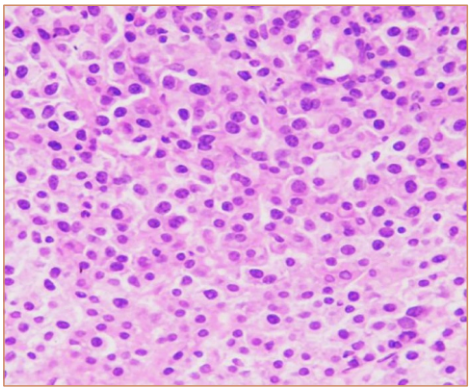
by **Dr Laila Bahadur**, *Consultant Hematologist PATHWEL*

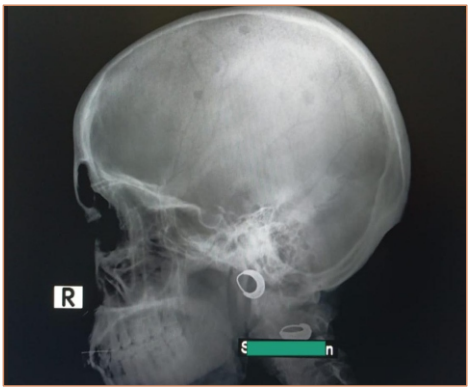
Answer: Plasma Cell Leukemia

IMWG diagnostic criteria for plasma cell leukaemia

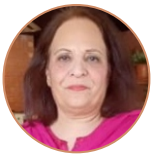
Essential: Presence of more than or equal to 5% circulating plasma cells in peripheral blood smears in patients otherwise diagnosed with multiple myeloma.







Understanding the Hidden Struggles of Children with Thalassemia



By Dr Zohra J Wazir, Chief Medical Officer Thalassemia Wing, PATHWEL

Writer is a graduate of Fatima Jinnah Medical College. At Pakistan Thalassemia Welfare Society, she has been closely associated with caring for children with thalassemia major since 2013. This article is based on her first-hand experiences with these children and their families.

Children with thalassemia major often face a variety of psychological, social, and emotional challenges due to the chronic nature of the disease, frequent hospital visits, physical symptoms, and social limitations.

Anxiety and Fear: Frequent medical procedures such as blood transfusions, chelation therapy, and injections can cause fear and trauma. Worry about the future, disease complications, and thoughts about death are common, especially as the child gets older.

Depression: Feelings of sadness, hopelessness, or low energy may arise due to chronic fatigue from low hemoglobin levels, physical appearance changes (e.g., facial bone deformities, growth delays), limited participation in peer activities, and awareness of a lifelong illness.

Social Withdrawal and Isolation: Children may miss school frequently, making it hard to maintain friendships. They may feel different or excluded due to their condition. Social stigma in some communities can also contribute to isolation.

Low Self-Esteem and Body Image Issues: Short stature, delayed puberty, or facial changes due to bone marrow expansion can lead to poor self-image, embarrassment in social situations, and bullying or teasing by peers.

Cognitive and Academic Challenges: Chronic anemia and iron overload may affect concentration, memory, or learning. Missed school days due to hospital visits can impact academic performance.

Behavioral Problems: Irritability, aggression, or defiance may arise due to frustration, emotional pain, or side effects of treatment. Overprotection by parents can lead to dependence or reduced confidence.

Family and Parental Stress: Mothers often say that the burden of caring for a child with thalassemia is so great that they cannot deal with it alone. They complain of disability in physical, psychological, and economic dimensions. They need support to maintain their health, especially if they are single parents. They may experience psychological distress, extra financial burden, fear of worsening of the disease, and concern for the future of their child. The transfer of the thalassemia gene to the child and the responsibility towards the child's illness can cause feelings of guilt and emotional distress.

How to Support These Children:

- Psychological Interventions: Cognitive behavioral therapy (CBT), play therapy, or art therapy can be beneficial.
- Support Groups: Connecting with other children with thalassemia can provide emotional support.
- School and Social Support: Special academic accommodations, encouraging peer inclusion and awareness, and anti-bullying initiatives can help.
- Open Communication: Providing age-appropriate education about their condition and allowing children to express their fears and emotions is crucial.

For Caregivers:

- Learning Relaxation Techniques: Breathing exercises, meditation, and mindfulness can help reduce stress.
- Counseling: Cognitive behavioral therapy or counseling can provide emotional support and coping strategies.

PATHWEL Stars

A Gift of Life Twice Over: Successful Bone Marrow Transplant from a Pregnant Donor

*by **Dr. Khalil ur Rehman**, Clinical Hematologist and BMT specialist, PATHWEL*

Seventeen-year-old Irfan Azizi, a bright young boy from the village Tajak, Kabul, Afghanistan, had always been full of energy. He had a with passion for cricket and was part of Afghanistan's under 19 cricket team. His life took a sudden and heartbreaking turn when he began experiencing frequent nosebleeds, extreme fatigue, and shortness of breath. A series of tests revealed the devastating diagnosis of very severe aplastic anemia, a life-threatening condition where bone marrow stops making blood. For a young boy with dreams of playing cricket, the reality of depending on blood transfusions just to survive was crushing—not only for him but also for his loving parents, Ahmad Jan and Zulaikha.

With limited treatment options in his home country, the family's hope lay in Pakistan, where he was referred for a bone marrow transplant (BMT). Fortunately, his sister, Zahra Nazneen, was found to be a full HLA match. The only caveat was that she was in the early stages of pregnancy. Out of love and courage, Zahra waited until second trimester when it was safe to donate bone marrow without risking

From transplant to triumph — uncle and nephew, both thriving

herself and the baby. It was truly an act of selfless sacrifice—one sibling giving life to another.

On 7th November 2023, Irfan underwent allogeneic bone marrow transplant at PATHWEL. His journey was not without hurdles. He battled through neutropenic fever, nausea, vomiting, and cyclosporine toxicity. Yet, with resilience, medical support, and the prayers of his family, he overcame all the challenges successfully.

Now, more than 21 months post-transplant, Irfan's story is nothing less than inspirational. He is GVHD-free, infection-free, and maintaining stable blood counts off immunosuppressants. The once pale and fatigued boy is now a healthy young man, full of life and hope, no longer chained to hospital beds and transfusions. His parents, who once feared for his life, now see him smiling again, while his sister takes pride in having given him a second chance at life.

Irfan's journey is a beacon of hope for many families battling similar blood disorders. It is a story of courage, sacrifice, and the miracles that happen when science, family love, and faith come together. Today, as he trains to regain physical fitness, Irfan carries with him not only good health but also the promise of a bright future—a young boy who conquered one of life's toughest battles and emerged victorious.

Back to training for Afghanistan cricket team

PATHWEL Galaxy

Contributed by Dr Zohra J Wazir, Chief Medical Officer Thalassemia Wing

Little warriors facing a big battle, one transfusion at a time!

Celebrating Pakistan Day

Birthday of Huzaima Mumtaz - our thalassemia patient

Grand Round Case Report

A Bleeding Patient

By Dr. Mehroze Fatima, Resident Clinical Hematology
PATHWEL Center of Hematology & Bone Marrow Transplant

Case Presentation

A 36-year-old housewife, from Afghanistan, presented with recurrent episodes of bleeding. Her past medical history included three C-sections, all uneventful with no abnormal bleeding. There was no history of menorrhagia, GI bleeding, or drug use. There was no family history of bleeding disorders.

In July 2024, she presented to a local hospital with epistaxis, hematuria, and spontaneous bruises. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were markedly prolonged. Transfusion of fresh frozen plasma (FFP) resulted in symptomatic improvement, and she was discharged with oral vitamin K.

In August 2024, she came to Pakistan for further evaluation. She looked well with no active bleeding except that there were bruises on her tongue & forearms. She was not pale or jaundiced. Lymph nodes, liver & spleen were not palpable.

The investigations were as shown in the table. Besides low Hb, the main abnormalities were in the coagulation profile; PT and APTT were prolonged. Thrombin time & D-dimers were normal. Mixing studies were suggestive of deficiency of vitamin K–dependent factors (II, VII, IX, X). Further investigations confirmed deficiency of Factors II and X.

Table

CBC:
- Hb 9.9 g/dl,
- TLC 9.4 × 10^9/L
- Platelets 394 × 10^9/L

Coagulation Profile:
- PT 120 sec (control 14)
- APTT 140 sec (control 32)
- Bleeding time 3 min 55 sec
- Thrombin time 18 sec (normal)

Other Labs:
- LDH 435 U/L
- D-dimers <150 ng/ml
- ANA negative
- RA factor <20 U/ml
- LFTs within normal

Mixing Studies (in seconds):
- Patient plasma+normal plasma: PT 16
- Patient plasma+normal plasma: APTT 34
- Patient plasma+adsorbed plasma: PT 97
- Patient plasma+aged plasma: PT 36

Factor Assays:
- Factor II: 7.2% (low)
- Factor X: 1% (severely low)

At that point the cause of vitamin K–dependent factors deficiency was a mystery. On direct questioning the patient recalled that few weeks before her first presentation she bought rat poison and has been regularly using it without any specific precautions. This vital piece of history solved the mystery.

Final diagnosis:
Rodenticide Poisoning

Case Discussion

Rodenticides, commonly known as "rat poisons," are widely used to control rodent populations. These compounds are primarily anticoagulants, with superwarfarins being the most group. Superwarfarins, such as brodifacoum and difenacoum are chemically related to warfarin but are 100 times more potent & have a longer duration of action.

Mechanism of Action. Superwarfarins inhibit the Vitamin K epoxide reductase enzyme, which is essential for recycling vitamin K into its active form. Without active vitamin K, the body cannot synthesize clotting factors II, VII, IX, and X. This results in defective blood coagulation, prolonged PT and APTT, and a tendency to bleed.

Clinical Features of Poisoning. Bleeding symptoms can emerge days to weeks after ingestion, as existing clotting factors are depleted. Common clinical features include:
- Nosebleeds and gum bleeding.
- Easy bruising & petechiae.
- Hematuria.
- Blood in stool.
- Intracranial or internal bleeding.

Patients may have a history of accidental or intentional ingestion of rodenticide, although they may not always recall the event clearly, especially if there is a delayed presentation.

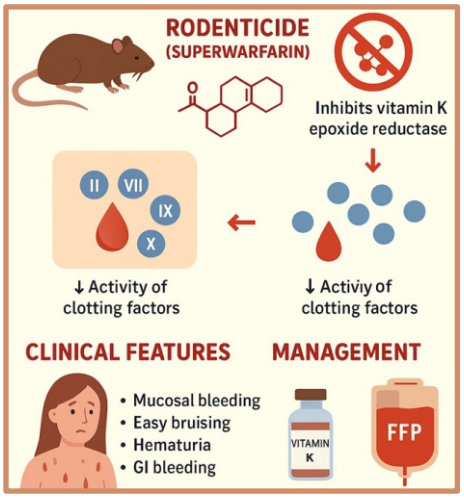
Laboratory Findings.
- Prolonged PT & APTT (sometimes very high, e.g., PT > 100 seconds).
- Normal thrombin time, which rules out fibrinogen abnormalities.
- Mixing studies that corrects with normal & aged plasma but not with adsorbed plasma, suggesting a factor deficiency rather than an inhibitor
- Low levels of vitamin K–dependent factors (II, VII, IX, X).

Diagnosis. The diagnosis is based on a combination of history (exposure to rodenticide), bleeding symptoms, and coagulation profile. It is confirmed by factor assays showing low levels of vitamin K–dependent factors.

Management
- Vitamin K therapy: High doses, (e.g., 10 mg/day or more), sometimes prolonged for weeks due to the long half-life of superwarfarins.
- FFP or Prothrombin Complex Concentrate (PCC): Used for active bleeding.
- Close monitoring of PT and APTT until they stabilize.

Conclusion

Rodenticide poisoning is a serious condition that requires prompt diagnosis & management.



Morphology Updates

Dutcher bodies and Russell bodies in a case of t(11;14) multiple myeloma

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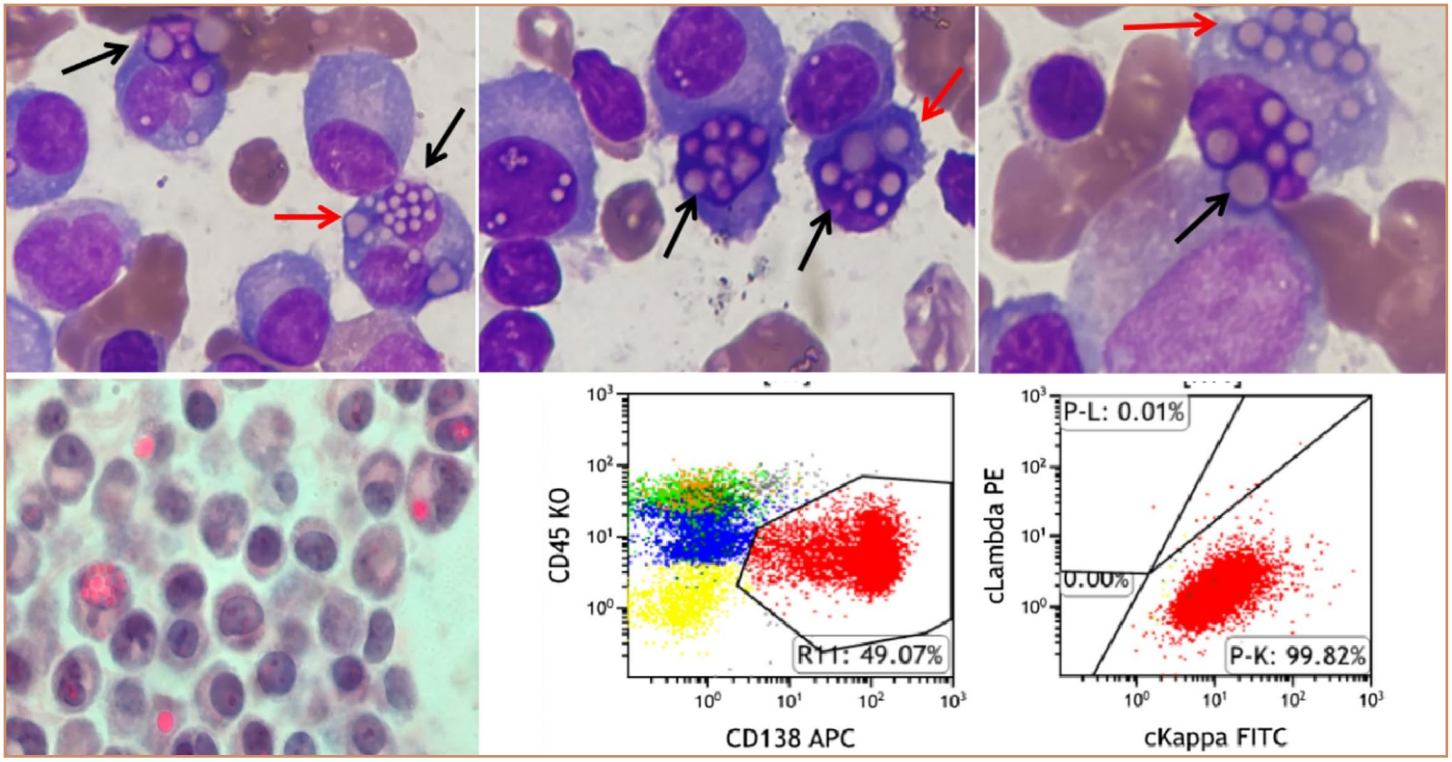


A 65-year-old woman presented with back pain. Serum immunofixation electrophoresis demonstrated immunoglobulin G (IgG) kappa type monoclonal protein. Bone marrow aspirate showed 41% abnormal plasma cells with different sizes, regular or irregular nuclei, most of which contained pink or colourless Dutcher bodies overlying nuclei entirely or partly (upper images, Dutcher bodies indicated by black arrows, Wright stain, ×100 objective) or/and Russell bodies within cytoplasm (upper images, Russell bodies indicated by red arrows). Bone marrow biopsy revealed pink Dutcher & Russell bodies in haematoxylin and eosin stain (bottom left image). Flow cytometry analysis showed the plasma cells to be clonal (bottom middle and right images, red: plasma cells). Cytogenetic analysis displayed an abnormal karyotype: 45,X,-X,t(11;14)(q13;q32) [4]/46,XX[16]. Overall findings were consistent with t(11;14) multiple myeloma (MM).

Dutcher bodies are now known as immunoglobulin inclusions overlying or invaginating into nuclei with no essential differences with Russell bodies. This case shows Dutcher and Russell bodies—uncommon morphological features most commonly seen in abnormal plasma cells. Literature search shows that Dutcher bodies in MM are highly associated with t(4;14) & IgA isotype, with the tendency of poor prognosis, whereas this case involved IgG-kappa isotype and t(11;14) translocation. The correlation of Dutcher & Russell bodies with both immunoglobulin heavy chain gene (IGH) rearrangement caused by chromosome 14 translocation calls for further study.

FUNDING INFORMATION
This work was supported by the Scientific and Technological Research Program of Chongqing Municipal Education Commission (KJQN202000443).

ETHICS STATEMENT
Not applicable (no ethical approval was necessary for this case).

PATIENT CONSENT STATEMENT
Not applicable (no privacy of the patient is involved and no photographs of the patient or any parts will be published).

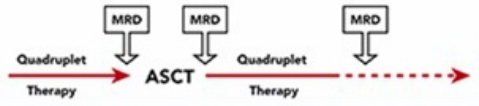
REFERENCES
1. Eyre TA, Littlewood TJ, Bain BJ. Dutcher bodies: cytoplasmic inclusions within the nucleus. Br J Haematol. 2014;166(6):946–7.
2. Jiang N, Qi C, Chang H. Dutcher bodies in multiple myeloma are highly associated with translocation t(4;14) and IgA isotype. Br J Haematol. 2015;171(5):890–2.

Tidbits Tidbits Tidbits Tidbits Tidbits Tidbits Tidbits

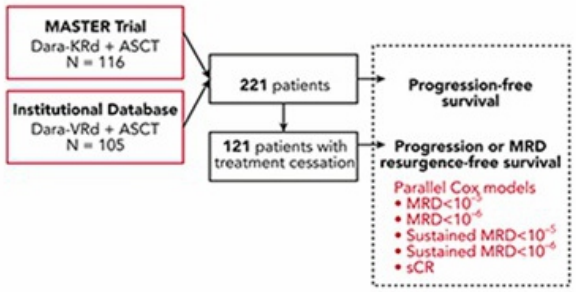
The Search for an Optimal MRD-Based End Point for Treatment Cessation in Newly Diagnosed Multiple Myeloma *Giri et al. DOI: 10.1182/blood.2024027674*

Context of Research

Quadruplet therapy + autologous stem cell transplantation (ASCT) yields outstanding results in NDMM. The optimal MRD end point to inform treatment cessation is unknown.

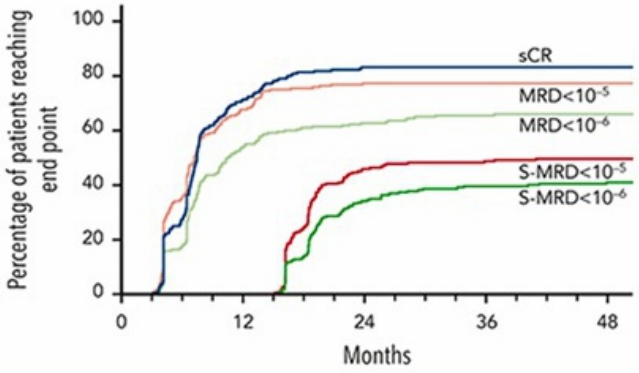


Methods



Findings

- International Staging System (ISS), high LDH, and number of high-risk chromosome abnormalities contribute to all models.
- Sustained MRD end points, particularly at 10^{-5} threshold, outperform single point MRD assessment and sCR in prediction of progression-free survival, and progression or MRD resurgence-free survival.
- Patients without high-risk chromosome abnormalities achieving sustained MRD<10^{-5} have <10% risk of progression or MRD resurgence at 5 years, despite treatment cessation.

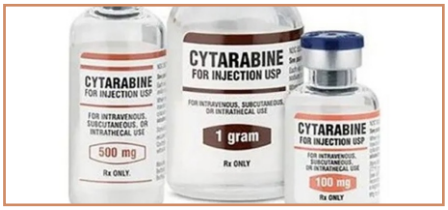


Conclusions: In patients with newly diagnosed multiple myeloma treated with quadruplet therapy and ASCT, sustained (12 months) MRD <10-5 is the optimal short-term efficacy end point to identify patients at low risk of progression upon treatment cessation.

blood Visual Abstract

Intermediate-Dose Cytarabine as Postinduction AML Therapy

M Hunault, C Pautas, S Bertoli et al; DOI: 10.1056/EVIDoa2400326, NEJM Evid 2025;4(7)



We conducted a randomized controlled trial to compare intermediate doses (IDAC) with high doses of cytarabine (HDAC) as postinduction therapy in patients 18 to 60 years of age with newly diagnosed AML.

Patients with core-binding factor, acute promyelocytic, Philadelphia chromosome–positive, or post–myeloproliferative neoplasm AML, were excluded. After the induction, we randomly assigned patients to either IDAC (1500 mg/m2/12 hours) or HDAC (3000 mg/m2/12 hours). Patients with intermediate- and adverse-risk AML were eligible for allogeneic HSCT in CR1. The primary analyses were performed in 1132 randomly assigned patients, with a noninferiority outcome adjusted on the ELN 2022 risk group, the use of induction anthracycline, the response to induction, and HSCT as a function of time following treatment.

At 5 years, OS was estimated at 59.3% in the IDAC group versus 57.5% in the HDAC group (noninferiority test, P=0.0042). A preplanned analysis was unable to detect any interaction between IDAC or HDAC treatment effect and patient subgroups. In addition, the severity of chemotherapy-induced myelosuppression and the incidence of related adverse events were lower after IDAC.

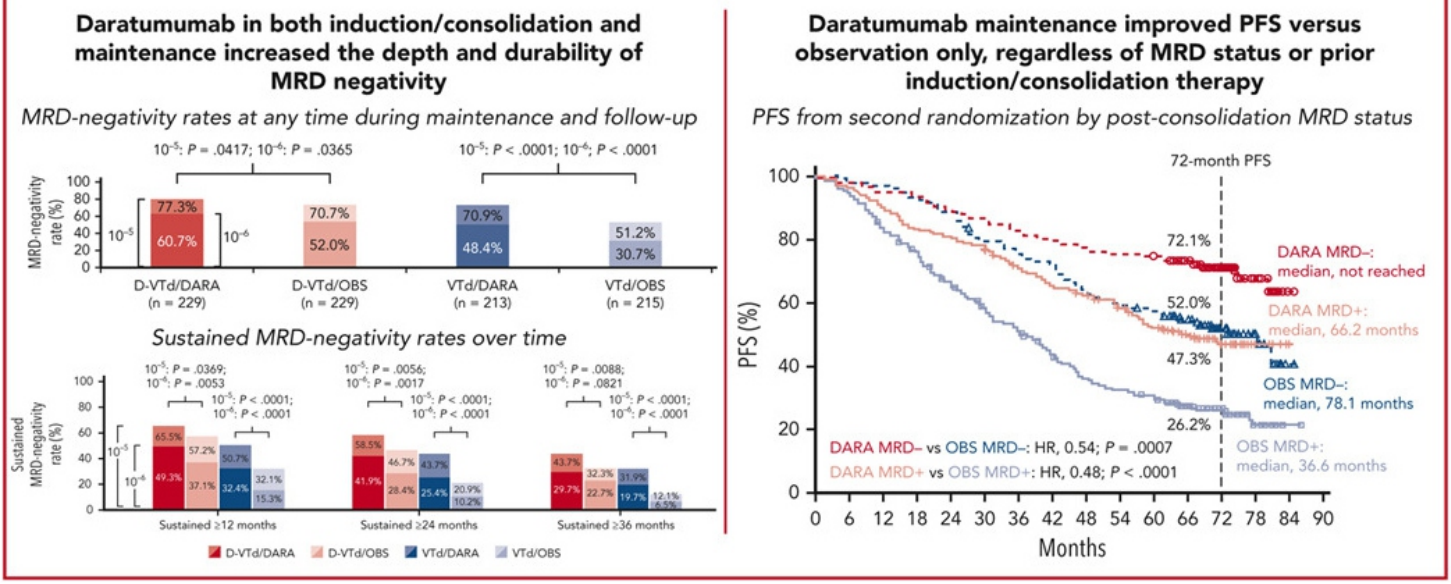
Our trial shows noninferior outcomes in patients 18 to 60 years of age with newly diagnosed AML treated with low- versus high-dose cytarabine; this occurred with similar or lower toxicities.

Tidbits Tidbits Tidbits Tidbits Tidbits Tidbits Tidbits

Daratumumab/Bortezomib/Thalidomide/Dexamethasone in Newly Diagnosed Myeloma: CASSIOPEIA Minimal Residual Disease Results

Corre et al. DOI: 10.1182/blood.2024027620

This analysis provides the final, long-term MRD and PFS results from the phase 3 CASSIOPEIA study, representing a highly comprehensive MRD analysis in transplant-eligible patients with NDMM



Conclusions: Daratumumab-based induction/consolidation (D-VTd) followed by 2 years of daratumumab maintenance therapy resulted in the highest rates of deep and durable MRD negativity, leading to superior PFS outcomes. These results strongly support D-VTd induction/consolidation as a standard of care and demonstrate the added benefit of daratumumab monotherapy during maintenance.

blood Visual Abstract

Severe toxicity and poor efficacy of reinduction chemotherapy are associated with overall poor outcomes in relapsed B-cell acute lymphoblastic leukemia (ALL):

A report from the Children's Oncology Group AALL1331 trial

Laura E. Hogan et al: Haematologica. 2025 June 26. doi: 10.3324/haematol.2025.287386

Children's Oncology Group AALL1331 utilized an intensive chemotherapy induction (Block 1) based on UK ALLR3 induction for children, adolescents, and young adults with ALL in first relapse, followed by risk-stratified therapy. High/intermediate risk patients were subsequently randomized to receive 2 blocks of chemotherapy or 2 blocks of blinatumomab followed by HSCT. Low risk patients were randomized to chemotherapy or chemotherapy cycles intercalated with three blinatumomab blocks. Patients who had an early treatment failure were eligible to receive blinatumomab for up to 2 salvage cycles.

We reviewed Block 1 responses, risk stratification, randomization rates, adverse events (AE), and event-free survival and overall survival for all enrolled patients. AALL1331 enrolled 661 patients: 24 died during Block 1 and 42 experienced early treatment failure. Overall, 531/661 (80.3%) attained CR with 586 risk-assigned and only 471 were randomized. Of 532 patients with marrow involvement, 290 (54.5%) were minimal residual disease positive (≥ 0.01%) after Block 1. Grade 3/4/5 AE occurred in Block 1 in 44.9, 24.1, and 3.6% patients respectively, with febrile neutropenia, infections, and sepsis most frequent. Notably, 190 enrolled patients (28.7%) did not proceed with post-induction therapy, including 115 (17.4%) risk stratified but not randomized.

These patients had dismal survival. More effective and less toxic reinduction strategies are needed for B-ALL in first relapse.

(Trial Registration No.: NCT02101853.)

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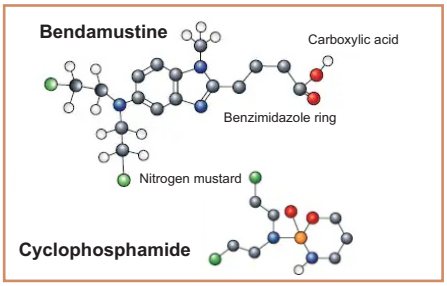
Feasibility and efficacy of partial replacement of post transplantation cyclophosphamide (PT-CY) with Bendamustine (BEN) on day +4 for graft versus host disease prophylaxis in patients undergoing allogeneic hematopoietic cell transplantation

Nair, V., Kathrotiya, M., Shirure, V. et al. Bone Marrow Transplant 60, 994–1001 (2025). https://doi.org/10.1038/s41409-025-02581-7



PT-CY use in T cell-replete haploidentical HCT has significantly improved outcomes. However, hyperhydration with MESNA in CY administration poses a challenge, in patients with cardiac/ renal problems. PT-CY also increases VOD risk with prior exposure to hepatotoxic drugs.

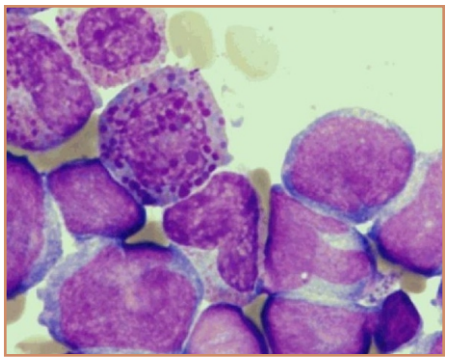
Katsanis et al. in a phase Ia trial in patients undergoing HCT for hematological malignancies showed that partially replacing PT-CY with PT-BEN had comparable outcomes to conventional PT-CY.

We conducted an ambispective study in 54 patients [haplo (39), MSD(14), and MUD(1)] with non-malignant hematological disorders and hematological malignancies in pediatric and adult patients undergoing HCT (MAC/RIC) from February 2019 to May 2024. GvHD prophylaxis comprised of PT-CY/BEN (PT-CY 50mg/kg Day +3; PT-BEN 90mg/m2 Day +4) in a prospective arm (n=21) and PT-CY/CY (50mg/kg on Days +3, +4; comparator arm) in ambispective (prospective 12; retrospective 21) arm. In both groups, immunosuppression with CNI and MMF was also given.

PT-CY/BEN was comparable to PT-CY/CY in terms of safety, efficacy, and GVHD prevention. In the PT-CY/BEN group, there was earlier neutrophil (0.008) and platelet (0.0057) engraftment with significantly lower BK viremia. Incidence of bacterial infection, TRM, EFS, and OS were comparable in both groups.

Allogeneic stem cell transplantation in de novo core-binding factor acute myeloid leukemia in active disease: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Tarantino, S., Labopin, M., Zeiser, R. et al. Bone Marrow Transplant 60, 1027–1035 (2025); doi.org/10.1038/s41409-025-02596-0



Core-binding factor acute myeloid leukemia (CBF-AML) generally has a favorable prognosis, with allogeneic hematopoietic stem cell transplantation (allo-SCT) recommended for relapsed/ refractory (R/R) cases achieving second complete remission (CR).

However, clinical outcomes remain suboptimal for patients who relapse or fail to achieve CR following induction chemotherapy. Allo-SCT in non-CR is a potential strategy for such patients, though supporting evidence in CBF-AML is limited.

To assess outcomes and prognostic factors of allo-SCT in R/R CBF-AML with active disease, we conducted a retrospective analysis of 610 patients with CBF-AML in non-CR undergoing allo-SCT from 2010 to 2021 across 174 centers within the European Society for Blood and Marrow Transplantation. Graft sources included matched sibling (MSD, n=151), unrelated (UD, n=368), and haploidentical donors (Haplo, n=91). Among patients, 124 had inv(16), and 486 had t(8;21).

Two-year overall survival (OS) and leukemia-free survival (LFS) were 53.6% and 42.7%, respectively. Haplo-SCT showed inferior OS compared to MSD (HR 1.79, p=0.003) and UD (HR 1.64, p=0.004) and reduced chronic graft-versus-host disease. Patients with t(8;21) exhibited higher relapse incidence (HR 2.04, p=0.002) and poorer survival outcomes than those with inv(16). These findings confirm the therapeutic role of allo-SCT in R/R CBF-AML in non-CR, supporting its favorable risk profile.

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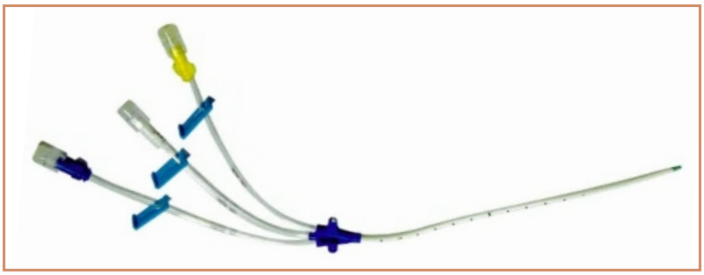
Defining Bloodstream and Central Venous Catheter-Related Infections in Patients Following Haematopoietic Cell Transplantation: Position Paper of the EBMT Infectious Diseases Working Party and Practice Harmonization and Guidelines Committee

Dina Averbuch, Malgorzata Mikulska, Jan Styczynski, et al; https://doi.org/10.1016/j.cmi.2025.06.037



Definite bloodstream infection (BSI):

1. One positive blood culture or non-culture based microbiologic testing (NCT) with non-commensal.
2. Two separate positive blood cultures with commensal pathogens (same genus and species; such as coagulase-negative staphylococci, Bacillus spp., Micrococcus spp., or
3. Two separate positive blood cultures with commensal pathogens (same genus and species; such as coagulase-negative staphylococci, Bacillus spp., Micrococcus spp. or Propionibacterium spp.) with the same susceptibility profile if tested in the presence of any sign of deterioration in patient clinical condition that can be compatible with infection or increase in inflammation markers (per local protocol).

Probable BSI: One positive blood culture with viridans group streptococci (VGS) in the presence of any sign of clinical or laboratory deterioration compatible with infection.

Definite BSI of presumed mucosal barrier injury source:

1. One positive culture or NCT with intestinal pathogen (the following pathogens are excluded as primary bloodstream infection pathogens as they are eligible for use in secondary BSI determinations: Campylobacter, Salmonella, Shigella, Listeria, Vibrio and Yersinia as well as C. difficile, Enterohemorrhagic E. coli, and Enteropathogenic E. coli) in a patient with appropriate clinical context:
   a. Allogeneic stem cell transplantation with gut GVHD grade III-IV OR ≥1 litre diarrhea in a 24-hour period with onset on or within the 7 days before the date the positive blood specimen was collected *OR*
   b. Neutropenia: 2 separate days with <500 cells/mm^3 within 3 days before and the 3 days after sample collection.
2. Two or more positive blood cultures with VGS and/or Rothia spp. in the presence of any clinical or laboratory sign compatible with infection in patients with an appropriate clinical context.

Probable BSI of presumed MBI source:

One positive blood culture with VGS in the presence of any sign of clinical or laboratory deterioration compatible with infection in patients with an appropriate clinical context.

Definite catheter-related BSI (CRBSI):

1. Pathogen grows from a culture of the catheter tip AND same pathogen (genus and species) from at least 1 percutaneous blood culture + in vitro susceptibility testing results in the same resistance pattern.
2. If semi-quantitative or quantitative cultures were performed – they shall meet criteria: semi-quantitative (>15 CFU per catheter segment) or quantitative (>102 CFU per catheter segment).
3. Two blood cultures (from a catheter hub and percutaneous) with the same pathogen. If quantitative criteria with a ratio of >3:1 CFU/mL of blood (catheter vs. percutaneous) OR if meet differential time to positivity (DTTP) criteria (growth in a culture of blood obtained through a catheter hub is detected by an automated blood culture system at least 2 hours earlier than a culture of simultaneously drawn peripheral blood of equal volume).

Probable CRBSI:

1. Two blood cultures (from a catheter hub and percutaneous) with the same pathogen: CoNS, S. aureus, Candida parapsilosis, Bacillus spp., Micrococcus spp., or Propionibacterium spp. AND do not meet quantitative/ DTTP criteria (or not performed) AND other sources excluded.
2. Pathogen detected in blood cultures (catheter only or percutaneous only if drawing blood cultures from central catheter is impossible) that typically causes CRBSI:
   a. At least two positive blood cultures for the same genus and species CoNS, Bacillus spp., Micrococcus spp., or Propionibacterium spp. cultures (same genus and species) with the same susceptibility profile if identified in both.
   b. Single positive blood culture with S. aureus and Candida parapsilosis with the absence of another plausible source.

Global Summit Advances Care for Bleeding Disorders: Key Highlights and Pakistan's Notable Contributions

Pakistan's Contributions at the 2025 WFH Comprehensive Care Summit in DubaiThe 2025 WFH Comprehensive Care Summit (CCS) in Dubai provided an international forum for hematology experts to exchange insights on evolving strategies in bleeding disorder management. A notable highlight was the strong representation from Pakistan, where investigators presented several impactful studies addressing clinical, psychosocial, and genetic challenges in resource-limited settings. These contributions not only reflected regional realities but also proposed scalable approaches relevant to global practice.

1. Efficacy of Treatment Modalities in Hemophilia Patients with Joint PainResearchers from PIMS Hospital, Islamabad, presented a retrospective analysis evaluating treatment strategies for hemophilic arthropathy, a common complication of recurrent hemarthrosis. Outcomes of three interventions—fresh frozen plasma (FFP) alone, FFP combined with physiotherapy, and factor replacement therapy—were compared. FFP alone provided limited benefit, with 52.5% of patients reporting no improvement. Combining FFP with physiotherapy significantly improved outcomes, with 54.5% experiencing pain reduction (p=0.001). Factor infusion proved most effective, achieving complete pain resolution in 57.1% of patients, reaffirming its role as the gold standard. The study underscored the value of multimodal management, particularly where factor concentrates remain scarce.

2. Inhibitor Screening in Hemophilia A Patients at PIMSAnother PIMS-led study emphasized the importance of systematic inhibitor screening in Hemophilia A. Early detection of inhibitors enables timely intervention, reducing morbidity even in resource-constrained environments. This work contributed crucial real-world evidence to global discussions on optimizing hemophilia care across diverse healthcare systems.

3. Clinical Spectrum of Rare Bleeding Disorders in Females: A Two-Center ExperienceA collaborative effort by the Hemophilia Patients Welfare Society (HPWS) in Rawalpindi explored rare bleeding disorders (RBDs) in women, an underrepresented group in hematology. Among 50 female patients, 72% were born to consanguineous parents, highlighting genetic risk. Menorrhagia (74%) and epistaxis (58%) were predominant, with over half experiencing major bleeding as defined by ISTH criteria. The study revealed frequent diagnostic delays and unique challenges related to gynecologic and obstetric care. Authors advocated for increased clinician awareness, early diagnosis, and tailored interventions for women in high-consanguinity regions.

HEMOPHILIA
PATIENTS WELFARE SOCIETY
RAWALPINDI CHAPTER

4. PACT Project: Psychosocial Empowerment of Women with Bleeding DisordersThe PACT (Path to Access Care and Treatment) project, jointly run by HPWS and WFH, showcased an innovative psychosocial support framework for women and girls with bleeding disorders (WGBD). Through locally delivered seminars, the program integrated medical education, genetic counseling, and mindfulness practices such as yoga. Post-intervention surveys reported a 70% improvement

in participants' understanding of genetic inheritance, a 75% uptake of yoga for symptom relief, and a 95% confidence boost among healthcare providers in gender-sensitive care delivery. These results highlighted the transformative role of holistic, community-based interventions.

5. ATHN Transcends: Pakistan's Experience with Glanzmann ThrombastheniaMarking a milestone in genetic research, HPWS presented findings from Pakistan's participation in the ATHN Transcends study, the first large-scale natural history and genetic analysis of Glanzmann Thrombasthenia (GT) in the region. Pathogenic variants in ITGA2B (87% of cases) and ITGB3 were identified,

including two previously unreported mutations. Most patients were diagnosed at a median age of one year with severe mucocutaneous bleeding. The study emphasized the need for expanded genetic testing in high-consanguinity populations to improve diagnostics and enable precision therapies.

Conclusion

Collectively, these studies demonstrate Pakistan's growing contribution to global hematology. Key lessons include the effectiveness of physiotherapy as an adjunct to transfusion therapy, the urgent requirement for gender-inclusive care models, and the necessity of genetic research in consanguineous populations. The WFH CCS 2025 highlighted how resource-driven, patient-centered innovation can inform equitable strategies for managing bleeding disorders worldwide.

Case Report

By Ms. Hina Fatima

Management of Intracranial Hemorrhage in a Teenager with Severe Hemophilia A

A 16-year-old male with severe Hemophilia A (Factor VIII <1%) presented with spontaneous intracranial hemorrhage following minor head trauma. He developed acute neurological symptoms, including severe headache, persistent vomiting, and altered mental status over 48 hours. Laboratory evaluation demonstrated severe anemia and markedly prolonged coagulation parameters. Neuroimaging revealed multifocal hemorrhages: subdural hematomas in the left frontoparietal and temporal regions, and subarachnoid hemorrhage in the perimesencephalic cisterns, without vascular malformations or mass effect.

Hematologic management included immediate high-dose Factor VIII replacement (2000 IU bolus, followed by 40 IU/kg every 12 hours) to achieve hemostasis. Adjunctive therapy with tranexamic acid was administered to enhance clot stability. Daily Factor VIII infusions were maintained, supplemented by evening transfusion of three units of fresh frozen plasma (FFP). On day two, five units of cryoprecipitate were administered to augment fibrinogen levels. Packed red blood cell transfusions were required for correction of profound anemia and optimization of cerebral perfusion.

The patient was monitored with serial neurological examinations, daily hemoglobin levels, and coagulation profiles, including Factor VIII activity, which guided therapeutic adjustments. Clinical stabilization was achieved with resolution of neurological symptoms and normalization of hematologic indices.

This case underscores the necessity of prompt factor replacement, multidisciplinary management, and vigilant monitoring in hemophilia-related intracranial hemorrhage. It highlights therapeutic challenges in

resource-limited settings with restricted access to factor concentrates. Prophylactic regimens, including extended half-life factor products and non-factor therapies, represent important strategies to reduce recurrence and long-term morbidity in severe hemophilia patients.

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