Challenges during the Pandemic

Regulatory Challenges in Blood Transfusion Services

Experience from Country's Biggest CCP Bank

Transfusion Support in Oncology Patients

"Donate blood, save life"

PGIMER
Transfusion Medicine Alumni Periodical

Volume 1
JANUARY 2021

CONTENT

Editor:

- **Prof (Dr) Ratti Ram Sharma,** Prof. and Head Department of Transfusion Medicine, PGIMER, Chandigarh

Associate Editor:

- **Dr Satyam Arora,** Assistant Professor, Transfusion Medicine, Super Speciality Pediatric Hospital and Post Graduate Teaching Institute, Noida, UP
- **Dr Gopal K Patidar,** Assistant Professor, Transfusion Medicine, All India Institute of Medical Science (AIIMS), New Delhi

Editorial Office:

- Department of Transfusion Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Email: dtmaluminipgimer@gmail.com

Editorial

Dr Ratti Ram Sharma
Professor and Head
Dept. of Transfusion Medicine
PGIMER, Chandigarh, India

Dear All,

At the outset, on behalf of the Dept. of Transfusion Medicine, I would like to express my sincere gratitude to the former Heads, Late Prof. J.G Jolly (Founder Head), Prof. S. K Agnihotri and Prof. Neelam Marwaha, for their invaluable contributions, mentorship and unparalleled commitment for the growth of the Department and speciality as a whole. All of us will always remain indebted to them for giving us opportunities to learn and the freedom to experiment and to grow, enabling each one of us to realize our potential. Their faith and trust in us have shaped us to what we are today, thereby passing on the mantle of learning.

It is really a matter of great pride for all of us to know that the alumni of the DTM PGIMER are performing exceptionally well both in the national and international arena. The current initiative of PGIMER, Transfusion Medicine alumni periodical will act as platform to share your work, latest development in field and to take you down the memory lane of the Department.

In the current issue, Dr Neelam Marwaha has enlightened us with a lucid overview of the Journey of the Dept. of Transfusion Medicine. This article highlights the vision, commitment and hard work our predecessors have put in to develop and transform Blood Bank Services into a specialty of Transfusion Medicine.

Dr. R.N. Makroo, one of our well-known alumni among the transfusion medicine fraternity, has very aptly described the challenges we faced during COVID-19 pandemic to sustain the blood supply chain. Update on Drugs & Cosmetics act by Dr Naveen Agnihotri is also quite relevant in the present time, as it describes the changes in the act, which were long due and are essential to improve the functioning of Blood centers in the country.

Experience on COVID-19 Convalescent plasma therapy by Dr Meenu Bajpai & Dr Ashish Maheshwari is quite enriching and their team deserves full praise & credit for this wonderful work, which has helped in managing the critically sick patients during this pandemic.

I am sure the interesting contributions by Dr Ashish Jain, Dr Manish Thakur, Dr Somnath Mukherjee, Dr Vijay Kumawat, Dr Ravi Dara, Dr Srinivas, Dr Ushashree, & Dr Bala Bhaskar would generate enthusiasm in young professionals in our specialty to explore these areas of research.

I congratulate and thank you all, for sparing your valuable time and contributing to this newsletter, especially Dr Satyam Arora and Dr Gopal K Patidar, Associate editors, who have worked hard for last few months to give this newsletter the current shape. This will help all of us to remain in touch with each other and express our professional & personal viewpoints on various topics.

I also take this occasion to wish each one of you a happy new year 2021 with lots of joy, good health, and success in your professional and personal endeavors.

A tribute to the Doyens of Transfusion Medicine at PGIMER, Chandigarh, India

Late Prof. J G Jolly

Prof. S. K. Agnihotri

Prof. Neelam Marwaha

The Charismatic Late Prof. J G Jolly is credited with the creation of the “Blood Transfusion Department” at the Postgraduate Institute of Medical Education & Research, Chandigarh in 1963 as the founder head. He is popularly known as the “Father of Transfusion Medicine” for his pioneering work in motivating “Voluntary Blood Donation”, component preparation from plastic blood bags and prohibiting the sale and purchase of blood from professional donors in the country. He also conceived the idea of a dedicated postgraduate program in blood transfusion and was founder president of the Indian Society of Blood Transfusion and Immunohematology.

In 1988, the reigns were handed over to Dr. S K Agnihotri and she dedicated more than a decade to strengthen the voluntary blood donation. She is credited with the establishment of laboratories for component preparation and testing of transfusion transmissible infections for basic blood safety. The donated blood was tested for HIV, Hepatitis B virus, Hepatitis C virus, Syphilis and Malaria. She had a passion for teaching and the course of MD in Transfusion Medicine first started in 2000 during her tenure with the introduction of the first student.

In 2002, reigns were handed over to Dr. Neelam Marwaha and the first MD in transfusion was awarded in 2003. Under her dynamic leadership quality practices were strengthened in transfusion transmissible infections testing and immunohematology. She introduced nucleic acid testing and the automation during her tenure. She established bone marrow and peripheral stem cell harvesting and standardized the platelet rich plasma therapy protocols. The department was awarded for the “Voluntary blood donation” by the NACO & NBTC, MoHFW, GoI in 2014 and the “ISBT Award for Developing countries” by the International Society of Blood Transfusion (ISBT), Amsterdam, The Netherlands in 2018”. She chaired the “Technical Resource Group” of the National AIDS control organization for more than a decade and was instrumental in laying the rail track for blood safety in the country. She was the key technical resource person from transfusion medicine in the Hemovigilance program of India.

The dedicated efforts of the three doyens have transformed the laboratory-based blood bank to the modern Department of Transfusion Medicine that is now the model blood centre of the region and the apex teaching and training centre for blood safety under the aegis of the NACO, MoHFW, GoI. All faculty, students and staff of the department remain indebted to all the previous heads for all times to come and express their gratitude for their selfless contributions.

Dr Suchet Sachdev
Associate Professor, Dept. of Transfusion Medicine
PGIMER, Chandigarh, India

Journey of Transfusion Medicine at PGIMER

Dr Neelam Marwaha
Former Professor and Head
Dept. of Transfusion Medicine
PGIMER, Chandigarh, India

The department of Transfusion Medicine was established in 1963 in keeping with the vision of this great institute which is a large tertiary care referral healthcare facility in northern region of India. The key goals are;

- To provide patient care of high quality.
- To train postgraduate students in Transfusion Medicine.
- To conduct research of the highest order.

The department has been one of the pioneers of Voluntary Blood Donation in country and has always promoted voluntary blood donation since its inception. Late Dr J. G. Jolly, the founder head of the department was instrumental in launching this movement and now almost 90% of blood is collected from voluntary blood donors through continued and committed liaison with 250-300 voluntary blood donor organizations and 400-450 voluntary blood donation camps.

The department also took an early start for processing of whole blood into components soon after blood bags were introduced in the country. It was a blessing for patients with thalassemia major and hemophilia. It is creditable that 100% component separation with quality products through leuco-reduction, blast freezing and automated component extractor has been achieved. Apheresis products are supplied where feasible. Safety from transfusion transmitted infections (TTIs) has been enhanced through implementation of nucleic acid amplification technology in addition to the mandatory tests. During computerization of the hospital services, blood bank module was successfully implemented in the first phase.

As and when the clinical services expanded and ramified into further super-specialisation, the department rose to the occasion to match up with clinical needs.

It supports intra-uterine transfusion in allo-immunised antenatal women, various solid organ and haematopoietic stem cell transplants, allo-immunised thalassemic patients, trauma and critical care services amongst many others. Bulk Transfer of stock supplies of blood components to other public sector hospitals for sufficiency outside the institute is also implemented as per recent amendments in regulations.

Journey so far

The department runs an active therapeutic apheresis programme and performs therapeutic cytapheresis procedures and plasma exchange for a variety of clinical disorders. Bone marrow processing lab also deserves special mention; it provides support to the bone marrow transplant programme by harvesting, cryopreservation and quality control of the product. In addition it facilitates preparation of autologous platelet rich plasma as an investigational therapeutic modality for various degenerative disorders such osteoarthritis, planter fasciitis, etc.

The department has been actively engaged both nationally and internationally. It has helped to finalise standards for blood transfusion services, blood safety guidelines, training modules and provide technical expertise for the Haemovigilance Programme of India (HvPI). It has notable collaborations with World Health Organisation and International Society of Blood Transfusion.

The real feather in the cap is the academic and training activities. In the early years a Diploma course in Immunohaematology and Blood Transfusion was conducted. Since 2000 MD Transfusion Medicine and from 2011 onwards MSc Medical Lab Technology in Transfusion Technology was started. The alumni of the department have blossomed into subject experts at the regional, national and international level and each one is remembered with pride and joy. The department is also recognized as an apex training centre for blood bank staff by the National Aids Control Organisation, Ministry of Health & Family Welfare, Govt. of India since 2006-07. For this Department received **“an Award of Excellence**” from National Aids control Organization, Ministry of Health and family welfare, Govt. Of India on National Voluntary Blood donation day in 2014. The faculty has guided research projects and publications of high quality in all the departmental domains including participation in multicentric trials. It is reflecting and fulfilling the vision of the institute as conceptualized by the founding fathers and gaining from strength to strength.

My best wishes for the department to rise to greater heights.

Covid-19 Pandemic – Challenges in Transfusion Medicine

Dr R.N. Makroo
Regional Director
Dept. of Transfusion Medicine
Medeor Group of Hospitals,
Delhi-NCR

Blood Transfusion Services all over the world needs blood donors to meet the supply of blood. As per the various Global & National reports there are apprehensions of contacting the infection among the blood donors & blood donor organizations at blood donation sites.

Confidence building with social distancing without causing apprehensions among blood donors is needed & accordingly following guidelines to be followed: Exclusion of blood donors for 28 days with history of travel from COVID-19 infested countries, possible close contact with COVID-19 patients/ people under quarantine confirmed case of COVID-19 after complete recovery.

Pandemic is defined as 'worldwide spread of a new disease'. The coronavirus COVID -19 pandemic is the greatest pandemic since World War Two. It all started with the news of an outbreak of pneumonia in the city of Wuhan, China on 31st December, 2019 which on 7 January 2020 was found to be a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1]

On the 30th January 2020, WHO had declared the outbreak of COVID-19 as a Public Health Emergency of International Concern which was soon followed by the announcement of a pandemic on the 11th March, 2020.[2] Panic spread among people with unprecedented global health crisis and massive socio-economic downfall. COVID - 19 reached India and the first confirmed case was detected on 30 January 2020 in Kerala.[3]

Containment measures started coming into action like screening of international passengers on airports for COVID-19 and banning of certain flights.[2] Finally, on the 25th March 2020, the Prime Minister of India announced a national lockdown for 21 days till 14 April 2020. All routine health facilities like Out Patient Department and elective surgeries were shut down except for emergency and essential health services.

Challenges in Transfusion Medicine

The National Blood transfusion council (NBTC) released guidelines on 25 March 2020, discussing the impact on blood transfusion services and deferring criteria of at risk donors.[4]

The lockdown lead to a sudden stop in donations, leading to blood shortage. People with blood disorders like Thalassemia, Sickle Cell Anemia and patients suffering from cancer are heavily dependent on a steady blood supply from the blood center, which is a daunting task to achieve in the pandemic state especially during lockdown periods. Suddenly there was an alarming shortage of blood collection all over the country however the impact on supply of blood to patients was little noticed initially since there was adequate stored blood in the blood centres. Even after the lockdown was lifted, it was a challenge to attract donors to blood centre for making donations. There was fear and panic, people did not want to visit the hospital because of the risk of getting infected.

The ones who came to donate were usually the replacement or family donors and they were screened diligently by questionnaire forms and deferred with the slightest suspicion of COVID-19 since the transmission through blood was not clear.[5]

There was a shortage of supplies of consumables due to lockdown with an increased usage of sanitizers, masks and other personnel protective equipment (PPE) materials because of the pandemic.[6]

There was a shortage of health workers in the blood centre. Many staff members had difficulty reaching the hospital in these times since metros and other forms of public transport vehicles were stopped. Keeping health workers safe was difficult and PPE kits were not readily available. Many staff members once infected used to go into quarantine for two weeks at least, leading to gross shortage of hands.[7]

The Transfusion Medicine department responded to the challenge by introducing few changes and providing a safer environment for both health workers and donors.

- Hygiene and cleanliness of the blood centre was increased several times and surfaces were disinfected at regular intervals.
- In order to increase number of donations, change of practices were introduced at donation sites which included only allowing donors to enter the donation area and all accompanying relatives to be not allowed, to prevent crowding in the centre.
- Also help of certain non-government organizations (NGOs) and setting up of small camps were encouraged with the help of media for increasing voluntary donations.
- All blood donors were screened thermally for checking fever at the entry point of the donation centre. A brief history was taken which included recent travel history, any COVID-19. like symptoms and any history of contact with a confirmed case of COVID-19. Social distancing of at least one meter was enforced in the premises.[8]
- Donor was made to sit in a chair away from the health worker during testing and the two came close only during the process of collection of samples which was less than a minute.
- Wearing a face mask was made mandatory and hand sanitizer was provided to the donors.
- Any donor with even mild symptoms of fever, cough or cold was not allowed in the donation area and was deferred.
- The donation room was spaced out with beds being kept at reasonable distance and masks were worn at all times by the donors.
- Health workers were provided PPE and any staff member with symptoms of cold and cough was sent home and advised to get tested.
- After donation the donors were followed up by call back method after a period of two weeks and were inquired about development of COVID-19 symptoms. In cases of positive donors, their blood was traced and discarded as a precautionary measure, though concrete evidence of transmission of Covid-19 through blood is still not available in literature.[7]

All these measures posed additional challenges in maintaining adequate stock of blood and blood products. Judicious use of blood and blood products is needed and use of alternative blood groups in cases of emergency is advised.

Collection of Convalescent plasma

The department of Transfusion Medicine stepped up in these difficult times by starting the collection of convalescent plasma leading to a form of therapeutic approach in the patients suffering from COVID-19, in the absence of any proper treatment or antiviral drug regimen. The idea behind this approach is based on the fact that humoral immunity helps in resolution of infection and can play a role in preventing re-infection. COVID-19 Convalescent plasma or CCP is collected from recovered Covid patients meeting the donor selection criteria by apheresis.[9]

Apheresis donors for CCP were screened along similar guidelines. A positive RT-PCR test was documented as evidence of COVID-19 infection and the donor was supposed to be symptom free for the last fourteen days prior to donation. Female donors who had conceived even once were deferred. Two samples were collected and one was tested for HIV, HBsAg, Hepatitis C, Syphilis and Malaria. The other sample was checked for antibody titer and only the ones above a set cut off were accepted for donation. The donation process was similar to apheresis donation and around 450 - 500 ml of CCP was collected. Initially the CCP was used only for critically ill patients and the response was positive. Now CCP is given to patients who are unable to develop a humoral response themselves after primary infection. In many cases it has efficiently brought down morbidity.[10,11]

Summary

Blood Transfusion Services all over the world needs blood donors to meet the supply of blood. As per the various global & National reports there are apprehensions of contacting the infection among the blood donors & blood donor organizations at blood donation sites.

Confidence building with social distancing without causing apprehensions among blood donors is needed.

To overcome the challenges & meet the requirement of blood in patients it is important to relook into the strategies as most of the educational institutions (collages & universities) are still closed and corporate offices are working from home. In such situation I feel the voluntary organizations involved with the promotion of voluntary blood donation need to involve resident welfare organization.

- Blood donor education & communication is of paramount importance.
- Donors should be appraised of any changes in donor selection process.
- Blood donor questionnaire can be send to blood donors for self assessment for blood donation.
- Voluntary blood donor organizations should maintain close contact with blood centre to ascertain the need for blood donors.
- Need to gain the confidence of blood donors and donors to be told that all measures are taken to ensure proper safety of blood donors while donating blood.
- We have to change the camp sites from multi-national companies, Colleges, Factories to Housing societies.
- Utilization of blood mobiles to its maximum with daily cleaning & sanitization.
- State Blood Transfusion Council (SBTC) need to get activated & coordinate the activities of blood collection by bringing all NGOs & blood centres under one roof.

References

1. Rabi FA, AL Zoubi MS, Kasasbeh GA, Salameh D M, D Al-Nasser A . SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. *Pathogens* 2020; 9(3): 231.
2. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus.
3. Home | Ministry of Health and Family Welfare | GOI
4. Guidance Document-National Blood Transfusion Council. Ministry of Health and Family Welfare, June 2020.
5. National Guidance to Blood Transfusion Services in India in light of Covid-19 Pandemic 2020.12.
6. Chaib F. Shortage of personal protective equipment endangering health workers worldwide', *WHO Newsletter.* undefined: 2.
7. Dhiman Y, Patidar G K, Arora S. Covid-19 pandemic- response to challenges by blood transfusion services in India: a review report. *ISBT Science Series* 2020; 15(2020): 368.
8. Coroiu A ,Moran C, Campbell T, Geller A C. Barriers and facilitators of adherence to social distancing recommendations during COVID-19 among a large international sample of adults. *Plos One* 2020; 15(10): .
9. Ngo A, Masel D, Cahill C, Blumberg N, Refaai MA. Blood Banking and Transfusion Medicine Challenges During the COVID-19 Pandemic. *Clin Lab Med. 2020* 2020; 40(4): 590.
10. A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease. Version 1.5 Dated 11th May, 2020
11. https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19dated27062020.pdf

Challenges in Blood Transfusion Services Regulations

Dr Naveen Agnihotri

Director Blood Transfusion Medicine Consulting Service LLP, Delhi

Sr Consultant and Head Dept. of Transfusion Medicine

Nayati Medicity, Mathura, UP

YOP: 2004

In March 2020, the Central government notified long awaited amendments (Second Amendments) in the Drugs and Cosmetics Rules governing blood banking in India. These amendments updated the criteria for blood donor selection in addition to some minor substitutions and additions. The impact of changes in blood donor selection criteria have already been reviewed by the author elsewhere.[1] The other major updates in the Second Amendment, were in the areas of manpower experience, accommodation for a blood centre (BC), manpower for blood donation camps, categories of blood components and apheresis using a cell separator. While the updates have been welcomed by the blood banking fraternity unanimously, many of them are also wondering if it is a case of too little, too late?

Blood banking in India is too tightly regulated by the government authorities/ bureaucracy and is reminiscent of the license raj era of pre-1990s. Therefore, everyone in the fraternity had high expectations from these updates in the Drugs and Cosmetics Act and Rules.

If given a chance to revisit the Drugs and Cosmetics Act (1940) and Rules (1945) to meet the aspirations of new and emerging India, my wish list would be as follows.

The Drugs and Cosmetics Act (1940) and Rules (1945): a law not originally meant for blood banking or blood transfusion.

The Act which is divided into Chapters and sections, is the part where definitions, prohibitions and punishments are given. On the other hand The Rules cover the procedural part to implement the relevant sections of The Act. The Rules are divided into various Parts, Schedule and Rules.

While there is no mention of the word ‘blood’ in The Act itself, The Rules were modified in 1967 (Part XII-B inserted) to make provisions for blood banking for the first time. Next round of major inclusions came in 1992 as a result of M/s. Ferguson’s Report and the bench mark Public Interest Litigation - Common Cause vs Union Of India And Others [CASE NO.: Writ Petition (civil) 91 of 1992]. These set of inclusions prevailed (barring some minor additions/ substitutions in between) till the recent overhaul in March 2020. In a nut shell, blood banking regulations were ‘accommodated’ in an existing law primarily aimed at regulating the other medicinal drugs in the country. However, to deal with a major healthcare intervention like blood transfusion, in a big country like India, we require more than an “ad hoc” law.

Even after nearly two decades of having a National Blood Policy (NBP), most of its objectives are still on paper – a fact which requires proper root cause analysis. With health being a state subject, approximately 62% of hospital beds being in the private sector[2], nearly 80% of doctors working in private sector and miniscule percentage of health budget available for blood transfusion services (BTS), the objectives probably need to be realigned with the reality on the ground. The objectives of the NBP shall be effected through the provisions in the statute by adequate amendments.

It is high time, the stakeholders press for a proactive legislation for BTS in India, just like the one shown for the medical education in India (The National Medical Commission Act 2019). Until this happens, existing provisions of the Act can also be used to usher in the comprehensive reforms needed for the BTS in India. For example a dedicated subcommittee for The Drugs Technical Advisory Board [Chapter II, 5(5) of The Drugs & Cosmetics Act 1940] can prepare focussed, contemporary, forward looking and comprehensive rules and regulations for BTS in India. The statute should focus more on the outcome, quality and efficiency of the system unlike the current system of focus on the physical infrastructure.

It is also prudent to have such a techno-legal body that can take real time decisions in view of rapid advancements in the medical technology and techniques. During the ongoing COVID-19 pandemic, its need was felt dearly when there was a national confusion on the criteria for COVID-19 Convalescent Plasma (CCP) and its pricing. It will not be an exaggeration to mention it here that many patients paid with their life and/ or life savings due to this confusion. With the pandemic still there and a possibility of similar medical exigencies in the future, need for such a techno-legal body is imminent rather than just desirable.

Some of the other key inputs for a comprehensive legislature for the BTS in India, can be from the narration given below.

Licensing

There is a dual licensing system for blood centres in India. The state is the granting authority while the Drugs Controller General (India) is the central license approving authority. Lack of details in the existing statute makes the rules open to interpretation by the inspectors who are not specifically trained for the BTS. There can be a separate cadre of inspectors specifically trained in BTS or transfusion medicine experts with certain experience and training, doubling up as inspectors. Although not for licensing, this type of system is currently used by the National Accreditation Board for Hospitals and Healthcare Providers (NABH) for both BCs as well as hospitals for granting accreditations. This NABH system is objective, transparent, smooth, time-bound as well as efficient. National Blood Transfusion Council (NBTC) along with State/ Union Territory Blood Transfusion Councils (SBTC) can also take up this function of licensing provided a legal mandate and adequate manpower with funds is allocated for such a functioning. Not-for-profit NGOs like Indian Society of Transfusion Medicine (ISTM) can be formally and/ or conditionally recognized by the government and delegated the responsibility for operating the BTS in the country on the lines of The United States of America where Red Cross Society operates majority of the BTS in the country.

Since there is no written policy/ guideline on the number of desired BCs in India, the licensing authorities are granting/ approving licenses without a vision or a roadmap. Moreover, with no need or any directive to do so, the data obtained during licensing cannot be utilized for any meaningful analysis or use. For example, with 3326 BCs in India (till Jan 2020) it is ironical that no data is available (RTI no. CDSCO/R/E/20/00025) with the license approving authority regarding new BCs approved in the last 5 financial years or annual collection of BCs whose license was renewed recently!

With more than 60% of our population living in rural areas, we need to provide BTS to whatever healthcare exists in these areas. Maternal and neonatal mortality rates can be greatly improved with such a provision. Most of the BCs exist in urban areas and owing to huge capital input to set up a new BC, rural areas hardly have BCs. Freeing blood storage centres (BSC) from the legal clutches is one readily available option. Currently, the law requires either a government, a Red Cross Society or a Regional BC to be the mother blood bank to a BSC. It is a common knowledge that these category of BCs are either already stretched to the capacity or too few in number to support any meaningful number of BSC for rural areas. Allowing any licensed BC to be a mother BC to a BSC can dramatically improve the availability of BSC and thus blood in the rural areas.

Although the new amendments in The Rules have removed some ambiguities in the licensing process, still much needs to be done to do away with the scare that a licensing process evokes.

It is high time licensing system is made easy, transparent and time bound with a vision document made available to all the stakeholders.

Regulatory bodies

Multiplicity of regulatory provisions and supervising bodies plague the entire healthcare industry in India and blood banking is not an exception. The drugs control department (FDA) of the state and Union Territory (UT) enforces the legal requirements and SBTC and/ or State AIDS control Societies, oversee other aspects of the BTS. Local government administration (e.g. district administration) can also intervene independently in BTS functioning. Proper liaising amongst different government departments with different mandates is an uphill task and output is the casualty as a result. Though a registered government society, NBTC/ SBTCs do not have adequate legal mandate and budgetary allocation to smoothly carryout their functions. These bodies have to work through the FDA thus delaying the action on the ground. An adequate budgetary and qualified manpower allocation as well as appropriate legal backing to these bodies can immediately uplift the BTS scenario in India.

Manpower

As compared to the past, there has been a significant increase in the number of qualified and trained manpower in Transfusion Medicine, in India. Though still less than even the total number of BCs in India, this trained manpower is now available throughout the length and breadth of India. There is now imminent need to adequately and judiciously utilize this trained manpower for better functioning of the BTS in India. Adequate changes in statute should be made so that at least one MD/ DNB Transfusion Medicine/ Immunohematology and Blood Transfusion (TM) doctor is made mandatory in all the BCs at the district (and above) level as well as NBTC/ SBTCs. Till the time there are adequate number of such candidates available, they can be allowed a part-time work in more than one BC on the basis of annual collection of the BC. For e.g. a provision can be made for BCs with less than 5000 annual blood collection, to must have, at least a part time MD/ DNB TM doctor. Such requirements can be made mandatory for a new BC or during license renewal of an existing BC. Such a transition should be done in a time bound manner, else with current legal provisions of even MBBS with minimal experience being allowed to run a BC, fewer doctors would opt for MD/ DNB TM in future.

There being no option for a private practice or any scope of further (government approved) academic growth, MD/ DNB TM candidates find themselves at a dead end especially when a substitute is allowed even in their core branch. Similar provisions and relaxations in terms of experience for MD/ DNB TM candidates should be factored in for the teaching posts in the medical colleges, till adequate candidates are available in India.

An Emergency Medicine department (EM) was made mandatory in all the medical colleges in India through a recent notification by the National Medical Commission (NMC). This notification however, ignored the need for a department of TM in all the medical colleges, thus highlighting the apathy towards the BTS in India. It is interesting to note here that the number of current postgraduate seats as well as the colleges offering the course in EM are fewer than that for TM.[3]

Quality assurance

Blood transfusion is a complex multistep process involving various healthcare workers (HCW). Quality assurance (QA) rather than just quality control is better suited to guarantee the quality of the end product and safety of all the stakeholders in BTS. National and international indicators, to ensure quality assurance in BTS, are readily available. These QA indicators need to be incorporated in the statute governing BTS in India, rather than the indicators for quality control only.

Pricing

With the majority of hospital beds in private, mostly out of pocket expenditure by public for healthcare and lack of adequate government funding, cost recovery by BTS is essential. There needs to be a mechanism to address the pricing of current and new products and services in the BTS. In this way profiteering can be eliminated and a sustainable as well as quality BTS can be ensured. The above recommended techno-legal body should regularly (e.g. biannually) update this pricing for BTS in India.

Blood transfusion

While the current statute focusses mostly on the donor and the end product, there is immense scope to cover the ultimate beneficiary of all The Rules – the patient. There is imminent need to include

1. Informed consent
2. Duties and responsibilities of the treating doctor – e.g. taking the informed consent, reporting the adverse reactions, monitoring the patient, checking the end product, etc.
3. Duties and responsibilities of the hospital administration, nurse and other HCW.
4. Roles and responsibilities of the patient

Hospital Transfusion Committee (HTC)

Giving HTC a legal status would benefit the BTS in India, immediately as well as in the long run. As per the Central Bureau of Health Intelligence, GOI, majority of Indians trust and visit private health care and only 23.5% of urban population and 30.6% of the rural people choose government facilities. The private sector health care is highly fragmented with over 90% of it being serviced by the unorganized sector. Eighty percent of the private hospitals are small clinics and nursing homes (less than 30 beds). Six to seven percent are 100 - 200 bed size hospitals and only 2 - 3% of hospitals are 200- plus bed.[4] In nutshell, majority of the patients are treated in the healthcare institutions (HI) which are small and with no BC. Though, it is not known what percentage of blood transfusions is given in these smaller HIs, but it can be presumed to be a big proportion with no monitoring or supervision. A legally mandated HTC can function as a watchdog for blood transfusions in these smaller HI as well as bigger hospitals. For e.g. it can be made mandatory for BCs to have or affiliate with a HTC which in turn should be registered with the government (just like an Ethics committee). For non-hospital based BCs, it must be mandatory to have their own HTC or common HTC amongst few BCs. All the users would have representative members on this HTC so that the data, SOPs, Hemovigilance and other information can be shared and improvement suggested. Legally mandated and centrally registered (for e.g. with SBTC/ NBTC) HTCs would thus form the final link of a complete vein to vein haemovigilance system.

Digitalization

BCs are lagging as far as a dream of digital India is there. There is ample scope for digitalization in BTS in India. Documents, records, consents, software, licensing, reporting etc. all can be brought under the ambit of digitalization as India has already shown its potential in many other fields. Provisioning for digital records, signatures, etc. in the statute governing BTS, only can enable such a transition.

Conclusion

Thus it can be safely concluded that the latest updates in the Drugs and Cosmetics Rules have definitely done some good for Indian BTS but more still remains to be done. To achieve the target of safe blood for all through a quality BTS in India, nothing short of a comprehensive reform would work.

References

1. Impact Analysis of the National Guidelines for Blood Donor Selection in India: A Single Center Study. Agnihotri, N., Chaturvedi, Y.M. & Agnihotri, A. Indian J Hematol Blood Transfus (2019)
2. https://www.statista.com/statistics/1128673/india-number-of-public-and-private-hospital-beds-estimated. Last accessed on 31.12.2020
3. https://www.nmc.org.in/information-desk/college-and-course-search. Last accessed on 31.12.2020
4. Ethical issues in healthcare sector in India. Chirantan Chatterjee and Vasanthi Srinivasan. IIMB Management Review 2013;25:49-62.

Role of Social Media in Donor Motivation

Dr CH Srinivasa Rao
Assistant Professor
Dept. of Transfusion Medicine
ESIC Medical College,
Sanathnagar, Hydrabad
YOP: 2013

Dr Ushasree Ravula
Senior Resident
Dept. of Transfusion Medicine,
ESIC Medical College,
Sanathnagar, Hydrabad
YOP: 2018

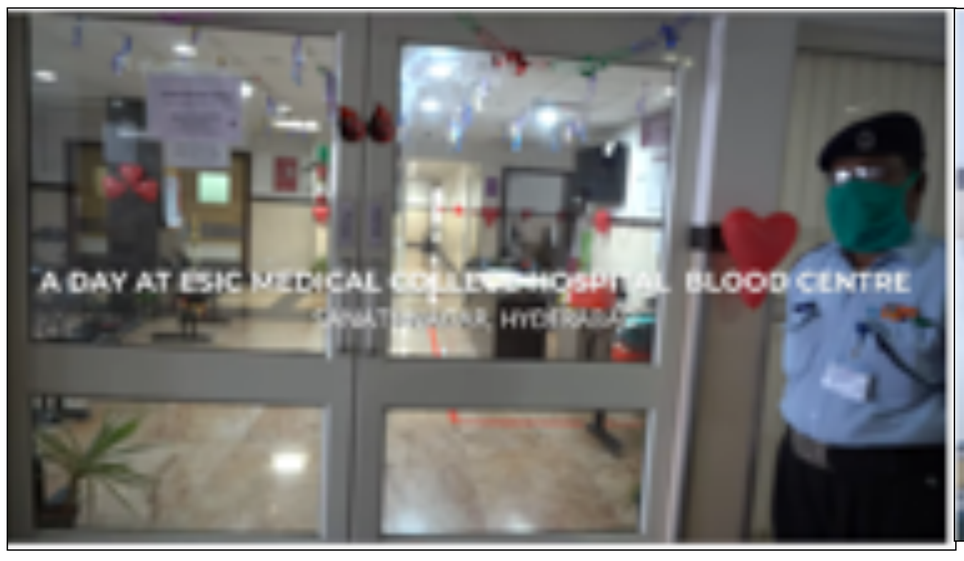
Man is by nature a social animal' as quoted by Aristotle which implies, we were social before we were Human. For decades' human-human physical interaction has been the mode of communication. However, through the centuries the modes of communication evolved. The way people communicate with each other today is entirely different from the prehistoric era.[1] Earlier days, communication was limited to interpersonal interaction – person to person. Later on it evolved to signs, alphabets, words, and then communication using letters, telegrams, radio, television, telephone, and internet and so on.

Currently, the Internet has paved way to hundreds of social media means of communication. Technology has indeed redefined communication. People no longer have to wait for years, months, weeks, and days to receive an information or message.[2] Today, texts, e-mails, tweets, and personal messages can reach the recipient in just a matter of seconds. We have witnessed a blast of information and content in last few years and cannot deny the power of social media in our lives.

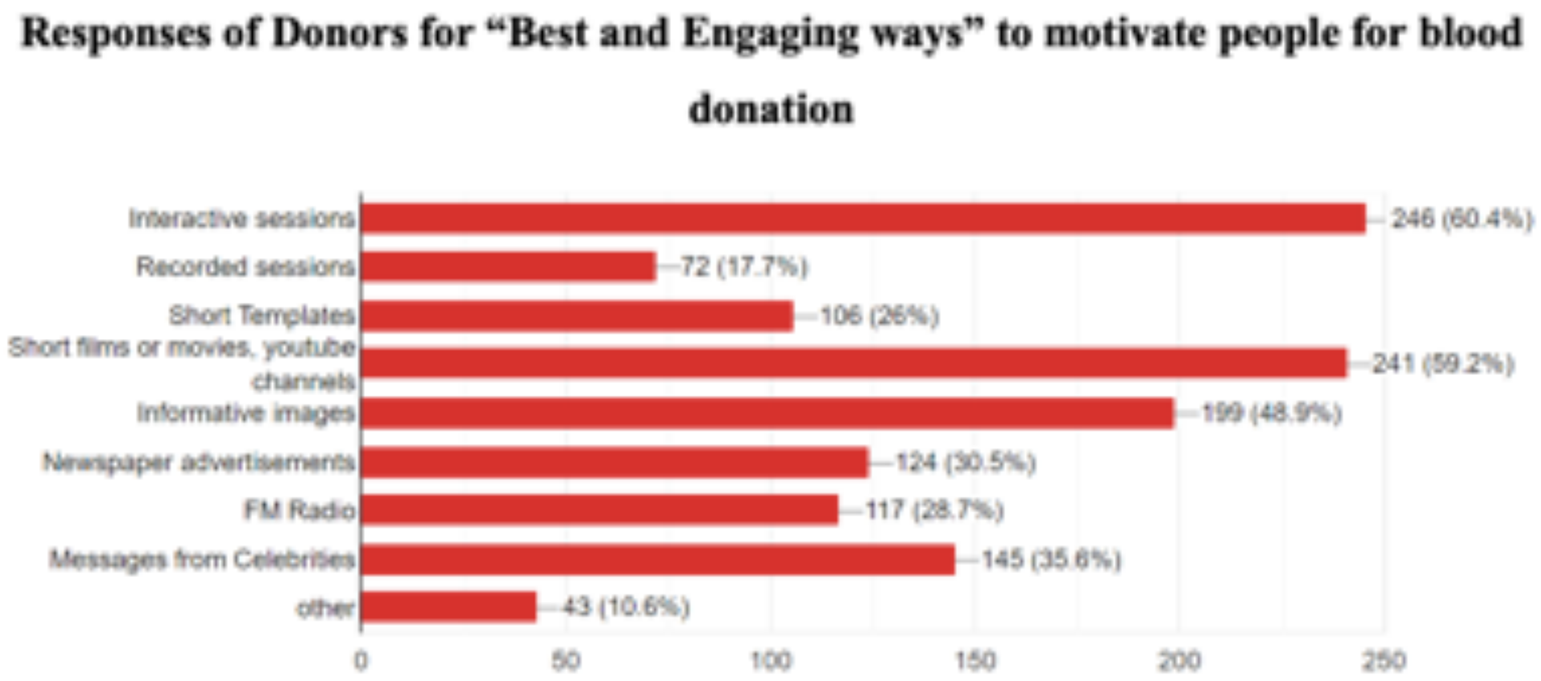
In current Covid-19 pandemic situation, the social media usage has seen a steep upsurge due to social distancing norms and lockdowns imposed across the world.[3] Yet, the communication remained intact, thanks to the social media. Covid-19 has also affected the blood donation services leading to crisis. Using various social media platforms, patients, hospitals and healthcare centres which were facing a shortage have been able to connect with potential blood donors, book appointments and carry out blood donation while maintaining social distancing and other COVID-19 regulations.[4,5]

Materials and Methods:

With the passing of 1st wave of Covid-19, we wanted to look back and take the opinion of noble blood donors who came forward during the crisis, regarding the social media and its influence on donor motivation with a short survey conducted at our Department of Transfusion Medicine, using google forms.



What's New: Blood Donation



Results: Survey respondents were actively using social media applications which majorly included WhatsApp (92%), followed by Facebook (68%), YouTube (56%), Instagram (55%), Telegram (24%), Twitter (22%), Skype (9%), and others. Most of the participants opined that the 'Best and Engaging' ways to motivate people for blood donation as Interactive sessions (60%) followed by short films or movies regarding donation, Informative posters etc.

Conclusion: Social media is an effective medium of donor motivation, with innovative ideas and information shared that keeps them engaging. Care should be taken not to discourage donors with repeated requests or make donors think of reliability of repeated donation requests circulating through social media. The essence of human impact should be maintained even when communicated via social media. Therefore, in order to give deep impact of human touch Interactive sessions, Online videos, short films, short informative templates etc. can be implemented to bring about motivation among blood donors.

References

1. Louis Leung. Generational differences in content generation in social media: The roles of the gratifications sought and of narcissism. Computers in Human Behavior. 2013; 29(3):997-1006
2. Wikipedia contributors. "Impact of the COVID-19 pandemic on social media." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 22 Nov. 2020. Web. 26 Nov. 2020.
3. Rodney Duffett. The YouTube Marketing Communication Effect on Cognitive, Affective and Behavioral Attitudes among Generations. Sustainability. 2020;12:5075 doi:10.3390/su12125075
4. Rabeeh Ayaz Abbasi et al. Saving lives using social media: Analysis of the role of twitter for personal blood donation requests and dissemination.
5. Turki Alanzi, Batool Alsaeed. Use of Social Media in the Blood Donation Process in Saudi Arabia. J Blood Med. 2019; 10: 417–423. doi: 10.2147/JBM.S217950

Experience of COVID-19 Convalescent Plasma (CCP) collection

Dr Meenu Bajpai
Professor
Dept. of Transfusion Medicine
ILBS, New Delhi
YOP: 2003

Dr Ashish Maheshwari
Assistant Professor
Dept. of Transfusion Medicine,
ILBS, New Delhi
YOP: 2014

COVID-19 convalescent plasma (CCP) is plasma that contains antibodies against the SARS CoV-2 virus, which are produced by the immune system in response to the virus. It is obtained from recovered COVID-19 patients. CCP is transfused to moderately sick COVID-19 patients, and this passive transfer of antibodies is proposed to enhance the ability to fight the infection and reduce the severity of symptoms. Although CCP is still under evaluation as a therapeutic agent for COVID-19, it is widely used across the world in the absence of definitive therapy for the disease.

Convalescent Plasma (CP) has been used both as post-exposure prophylaxis as well as treatment for diverse infectious diseases. Previous case series on MERS and SARS Coronavirus-1 suggested that CP therapy confers clinical benefits in such patients by inducing faster viral clearance on early administration with a very good safety profile. The current studies on CCP for COVID-19 provide some encouraging but inconclusive evidence regarding its efficacy. All suggest that CCP, preferably with high antibody titer, should be given early, before intubation and development of life-threatening inflammatory end-organ failure, in order to expedite viral clearance and prevent further tissue damage.

India's biggest Plasma Bank was started at the Institute of Liver and biliary sciences, New Delhi for catering to the need for CCP in COVID-19 patients on 2nd July 2020. We have collected and issued around 4000 CCP units and catered more than 100 hospitals around the National Capital Region of the country.

Issues and Challenges in CCP collection:

Finding eligible donor population: It was not easy to find the plasma donors for CCP as a very narrow range of the COVID-19 recovered persons fit the eligibility criteria. The donors needed a positive as well as a negative virological report of COVID-19 disease, and there had to be a gap of at least 14 days from recovery in addition to the donor selection criteria outlined in the Drugs and Cosmetics Act, 1940 and Rules 1945, amended 11.03.2020. Additionally recovered COVID-19 patients were not willing to come to the hospital settings again in the view of the perceived risk of re-infection and post- COVID hospital phobia. As our institute was not a COVID-19 treatment centre, CCP donors felt more comfortable to come here for donation. We provided a website and telephone helpline support regarding information and registration of Plasma Donors.

What's New: Apheresis

Recently recovered patients: The motivation level of CCP donors was low as they had recently recovered and had undergone a long isolation phase. The majority of the donors donating CCP were replacement donors who presented within a month of recovery from the disease. These donors needed prior counselling by a trained counsellor and medical officer to address their stigmas, fears and anxieties related to CCP donation during the post-COVID-19 phase.,

Procedural challenges: CCP donors had to undergo counselling and medical screening procedure. If CCP donors were found fit on screening and physical examination, blood sampling is done for blood grouping, TTI testing, antibody testing, assessment of protein levels, and SARS CoV-2 antibody titer. It required at least 2 hours, multiple resources and coordination between different labs for timely reporting of the results. Donors were informed and counselled regarding the waiting time. They usually waited in the plasma bank lounge.

Donor reactions: Plasma donation was safe in most of the donors, but a few donors developed hematoma, citrate toxicity or developed a vasovagal reaction.

Donor deferral: The deferral rate of the prospective donors who came to donate was quite high, with more than 50% of the donors being deferred. The common causes of deferral were medical issues, inadequate venous access, and out of eligibility range laboratory parameters. The deferred were thanked courteously and explained regarding the reason for deferral, and further, they were encouraged for donation in future if possible.

Post donation advice and issues: After donation donors were given post-donation advice, and they were felicitated with a certificate of appreciation and issued replacement/voluntary donation cards. Donors were informed that they could donate again after 14 days.

Emerging Transfusion Transmitted Infection Disease Risk

Dr Vijay Kumawat
Associate Professor
Dept. of Transfusion Medicine
NIMHANS, Bengaluru
YOP: 2010

Dr Bala Bhaskar
Consultant
Dept. of Transfusion Medicine,
Sparsh Hospital, Bengaluru
YOP: 2018

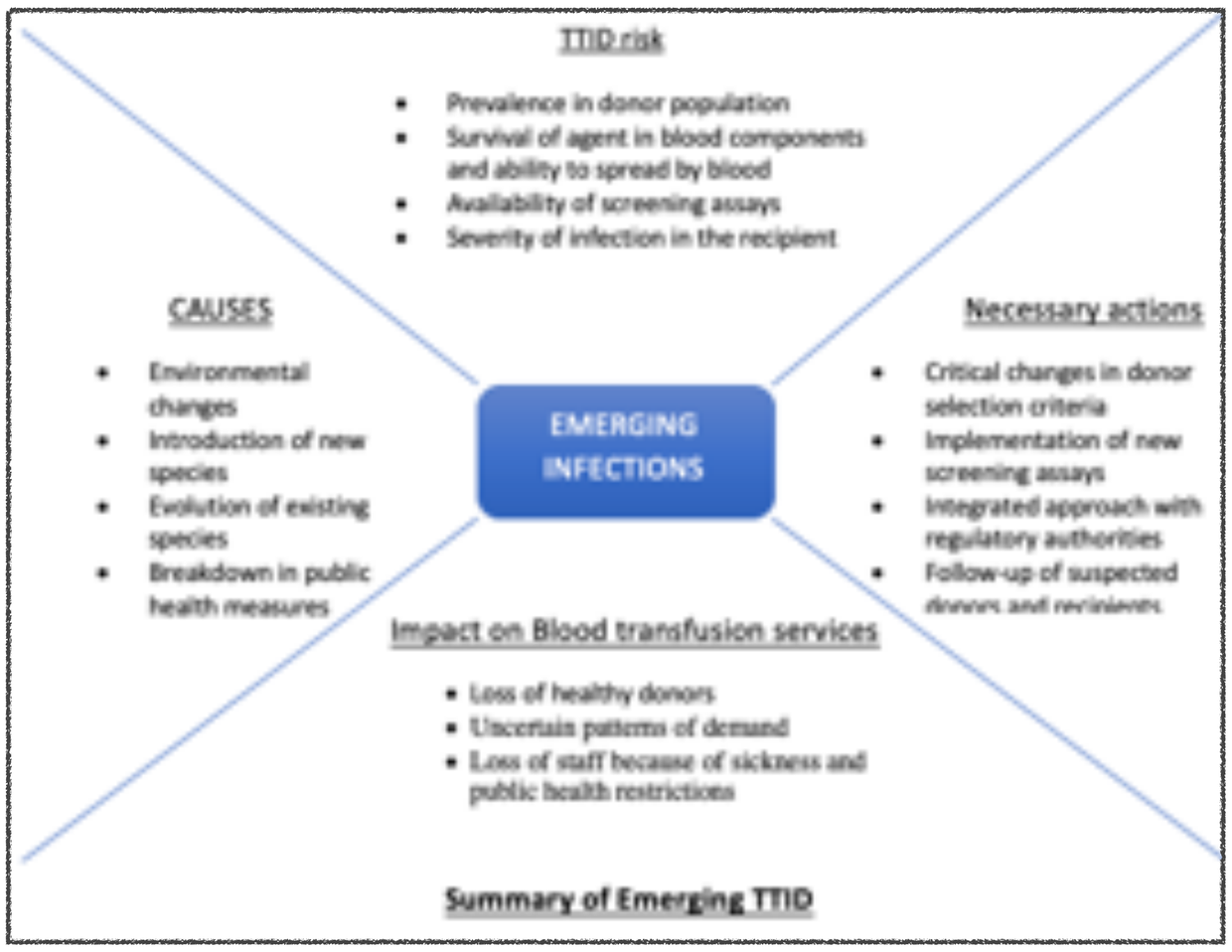
Emerging infections have been identified as a continuing threat to human health and many such infections are known to be transmissible by blood transfusion, while others have properties indicating this potential.

Emerging infectious diseases (EIDs) are defined as those whose incidence in humans have increased within the past 2 decades or threaten to increase in the near future. Emergence may be due to evolution of an existing organism, to the spread of a new agent, to the recognition of an infection that has been present in the population but has gone undetected.[1]

The first emerging infection to have a major effect on blood safety was human immunodeficiency virus (HIV). The HIV epidemic had sensitized us to be alert to emerging infections which can impact blood safety.[2]

The ongoing COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a recent example of emerging infections with major implications for blood transfusion, leading to uncertain patterns of demand, reductions in donations and loss of crucial staff because of sickness and public health restrictions.[3]

Any EID with an asymptomatic blood-borne phase has the potential to cause transfusion-transmitted infection (TTI). The pathogen characteristics that are necessary for transmission by transfusion are the persistence of the infectious agent in collected blood and its ability to cause infection by the intravenous route.[4] The summary of emerging TTIDs is given in the chart below.



Summary of Emerging TTID

What's New: Transfusion Transmitted Infection Disease

The frequency with which an infection is transmitted to blood recipients and severity of the disease depends directly upon the length of the asymptomatic blood-borne period and the immune status of the recipient population.[4]

There is no simple process for recognizing that an EID leading to TTI particularly in the case of an unusual disease agent.[5] The knowledge of the potential for transmission of an EID, sharing experience and developing expert consensus will help transfusion services and hospitals to tackle it efficiently.

The post-transfusion events that are not usual with a suspected infectious origin should be brought to the attention of infectious disease experts and public health agencies for assistance in identification and follow-up. A thorough investigation of an illness occurring within few days or observed more recently after transfusion using serologic or molecular evidence of infectious agents in post transfusion samples is required to establish EIDs affecting blood transfusion.[6]

Donor recall and subsequent testing of associated donors is required to find the likely source of the infection. Ideally, the responsible agent needs to be isolated from both donor and recipient to prove TTI.[7]

References

1. Emerging Infections. Microbial threats to health in the United States. Washington, DC: Institute of Medicine; 1992.
2. Morens DM, Folkers GK, Fauci AS. Emerging infections: a perpetual challenge. Lancet Infect Dis 2008; 8:710-19.
3. WHO COVID-19 global literature on coronavirus disease https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/ (2020).
4. Wolfe ND, Dunavan CP, Diamond J. Origins of major human infectious diseases. Nature 2007;447:279-83.
5. Dodd RY. Emerging infections, transfusion safety, and epidemiology. N Engl J Med 2003;349:1205-6.
   Alter HJ, Stramer SL, Dodd RY. Emerging infectious dis- eases that threaten the blood supply. Semin Hematol 2007;44:32-41.
6. Matsubayashi K, Kang JH, Sakata H. A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food- borne route. Transfusion 2008;48:1368-75.

Drug interactions in Immunohematology Testing

Dr Ashish Jain
Additional Professor
Dept. of Transfusion Medicine
PGIMER, Chandigarh
YOP: 2007

Dr Ravi C Dara
Consultant and Head
Dept. of Transfusion Medicine,
Manipal Hospital Jaipur
YOP: 2013

Many drugs have been known to interfere with immunohematology testing including antibiotics (e.g. Penicillin, cephalosporins), antihypertensives and analgesics, leading to difficult or erroneous interpretation and thus impacting the transfusion management of the patient.[1] Monoclonal antibodies like Daratumumab (DARA, anti-CD 38) used for treatment in multiple myeloma directly binds with high affinity to CD 38 molecule on RBC, causing false positive antibody screen, direct antiglobulin test (DAT) and incompatible crossmatch as well.[2] High-dose intravenous immune globulin may also interfere with routine immunohematologic tests.[2]

Drug-induced immune hemolytic anemia (DIIHA), though rare (1 in a million), is caused by IgM or IgG antibodies directed to drug, drug and membrane proteins and/or membrane proteins, formed as a result of their binding to RBCs and or platelets.[3] Almost 125 drugs have been known to cause DIIHA. The proposed mechanisms are – immune complex formation, drug adsorption in the red blood cell (RBC) membrane, autoantibody formation and modification in RBC membrane.[1] The antibodies could be drug-dependent - reactive to RBCs in vitro in presence of drug, or drug-independent - reactive to RBCs in vitro without the presence of drug; and thus appear as autoantibodies rather than the antibody to the drug, and may lead to a positive DAT.[3] So, the serological findings become indistinguishable from warm autoimmune hemolytic anemia. Therefore, a temporal relationship to a specific drug is a vital clue for the diagnosis of DIIHA. If the patient's serum/plasma, or an eluate from their RBCs, yields a negative antibody screen, and if the history suggests DIIHA, then a possibility of drug-dependent antibodies exists and further work up is done accordingly.

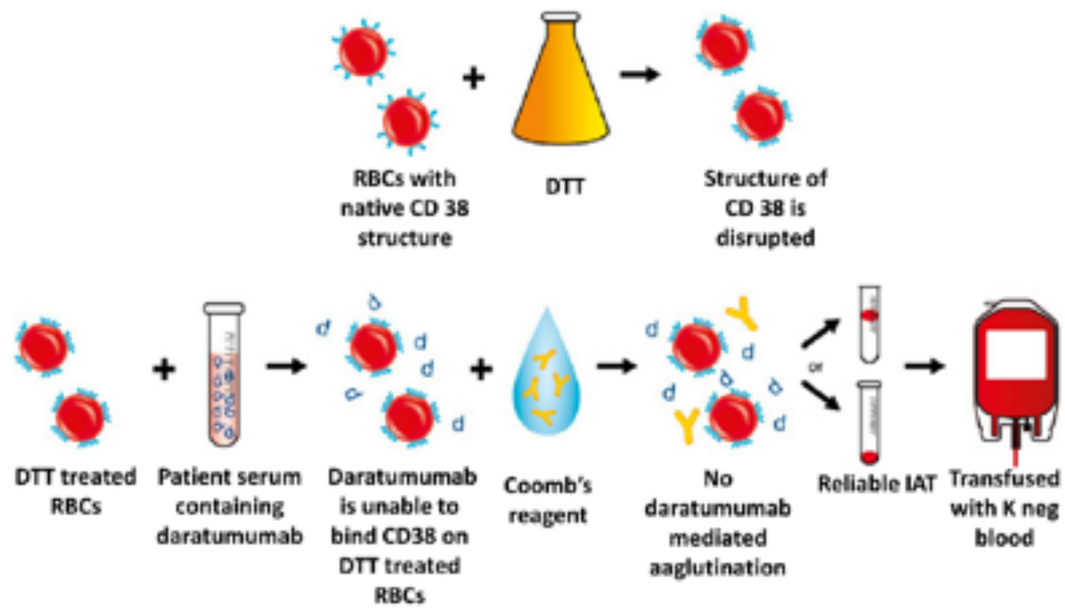
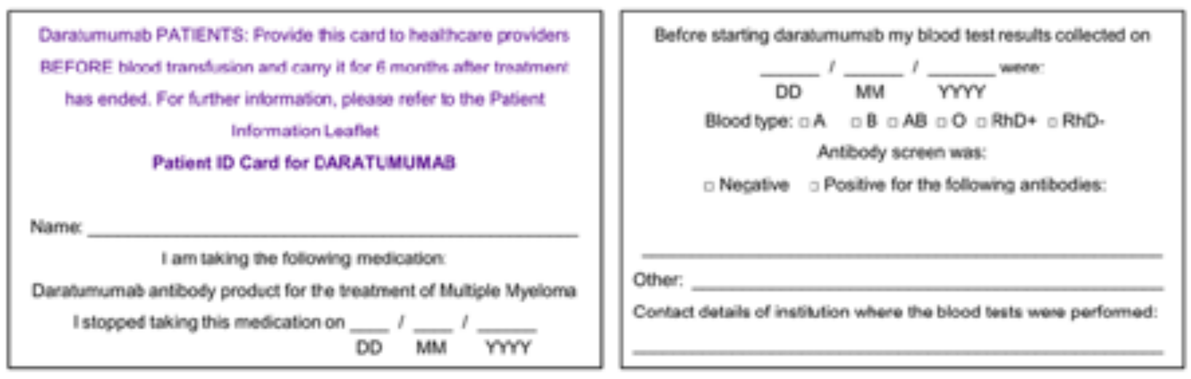


Figure 1: Di-thiothreitol (DTT, 0.2 mol/L) treatment of RBCs

Drug-treated RBCs are tested in parallel with the control untreated RBCs by tube technique. Two drops each of sample and control are tested with one drop of the drug-treated or the control untreated RBCs (3–5% suspension in phosphate buffer saline - PBS), the tubes are then incubated at 37°C for 1 hour and then centrifuged and examined for hemolysis (if serum was tested) and agglutination. The RBCs are washed four times with PBS, two drops of antihuman globulin are added, and the tubes are centrifuged and examined for agglutination. The drug treated RBCs will give agglutination, while the control untreated RBCs will not.

Treatment of RBCs with reducing agents like di-thiothreitol (DTT, 0.2 mol/L) eliminates the DARA interference,[5] as it disrupts the disulphide bonds in the extracellular domain of CD 38 molecule (figure 1). Agglutination due to DARA may occur in saline, low ionic strength solution, polyethylene glycol and by all methods of testing including tube, column agglutination and solid phase techniques.[4] Since Kell blood group antigens are also sensitive to DTT treatment, units should be supplied which are matched for K-or k-patients, based on their phenotype or genotype, after ruling out or identifying alloantibodies using DTT-treated RBCs (figure 2).

Thus, an active coordination between the clinician and transfusion services is needed to identify and overcome the issues related to drug interference in immunohematology testing and to effectively manage the transfusion needs of the patient.


Daratumumab PATIENTS: Provide this card to healthcare providers BEFORE blood transfusion and carry it for 6 months after treatment has ended. For further information, please refer to the Patient Information Leaflet

Patient ID Card for DARATUMUMAB

Name: _____

I am taking the following medication:

Daratumumab antibody product for the treatment of Multiple Myeloma

I stopped taking this medication on ___ / ___ / _____
DD MM YYYY

Before starting daratumumab my blood test results collected on

_____ / _____ / _____ were:
DD MM YYYY

Blood type: □ A □ B □ AB □ O □ RhD+ □ RhD-

Antibody screen was:

□ Negative □ Positive for the following antibodies:

_____

Other: _____

Contact details of institution where the blood tests were performed:

_____

Figure 2: Patient card specimen

References

1. Bub CB, Reis IND, Aravechia MG, Santos LD, Bastos EP, Kutner JM, Castilho L. Transfusion management for patients taking an anti-CD38 monoclonal antibody. Rev Bras Hematol Hemoter 2018;40:25-9.
2. Murphy MF, Dumont LJ, Greinacher A; BEST Collaborative. Interference of New Drugs with Compatibility Testing for Blood Transfusion. N Engl J Med 2016;375:295-6.
3. Garratty G. Immune hemolytic anemia associated with drug therapy. Blood Rev 2010;24:143-50.
4. Bub CB, Reis IND, Aravechia MG, Santos LD, Bastos EP, Kutner JM, Castilho L. Transfusion management for patients taking an anti-CD38 monoclonal antibody. Rev Bras Hematol Hemoter 2018;40:25-9.
5. Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson PG, Doshi P, Kaufman RM. Resolving the daratumumab interference with blood compatibility testing. Transfusion 2015;55:1545-54.

Transfusion Support in Oncology Patients

Dr Manish K Thakur
Hematologist/ Medical Oncologist
Boston Methodist Hospital,
Kalamazoo, Michigan, USA
YOP: 2007

Dr Arshad Raja
Senior Resident
Dept. of Hematology,
AIIMS, Bhubaneswar, Odisha, India
YOP: 2018

The decision for transfusion support in patients depends upon multiple factors that include clinical status and need to oxygen delivery, prophylaxis for bleeding risk and correction of coagulopathy. Oncology patients are a high risk group where complications from existing cancer or cancer treatment especially with myelosuppressive chemotherapy poses unique challenges in every patient. In general transfusion support can be broadly undertaken as that for patients who are in active treatment and then those who are considered for palliative care. Another consideration is curative intent vs palliative intent treatment that can influence transfusion decision. Some hematological malignancies like myelodysplastic syndromes can have longer duration of transfusion requirement with multiple donor exposure. In similar situations, use of growth factor support to prevent febrile neutropenia is generally favoured for curative intent treatment. In situation requiring concurrent chemotherapy and radiation there is consideration for issues with thrombocytopenia[1] and reduced locoregional control[2] when concurrent growth factor support used and hence in general avoided. There have been pilot studies to determine threshold for transfusion for patient with acute leukemia and stem cell transplantation.

A multicenter randomized pilot study explored the effectiveness of standard transfusion strategy of transfusion at less than 8 g/dl of hemoglobin vs augmented transfusion strategy of transfusion at 12 g/dl.[3] There was no difference in clinically significant bleed or time to first bleed. Although the control group received less red blood cells (RBC) transfusion, there was no difference in mean number of donor exposure to RBC and platelet transfusions. Another pilot study compared hemoglobin trigger of 7 g/dl to 8 g/dl in a 2:1 randomization.[4] In the ninety patients randomized, there was no significant difference in bleeding events. Events of neutropenic fever was also studied but again no difference was found in outcome. Both these studies were however able to establish feasibility of larger randomized control trials (RCTs) for hemoglobin threshold in this patient population. Patients with cancer who are on active treatment that is curative intent, should be transfused on similar thresholds as for other patients without cancer. Although there are no randomized trials for patient in hospice care, a Cochrane review[5] identified 12 studies that showed a subjective response of 31-70% especially to symptoms of fatigue and breathlessness. There was however significant (25-35%) 14 day end of life mortality. However, whether this high mortality was related to advanced cancer or inappropriate transfusion is a question for high quality studies in this area.

References:

1. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. Bunn PA Jr. J Clin Oncol. 1995;13(7):1632
2. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. Staar S. Int J Radiat Oncol Biol Phys. 2001;50(5):1161
3. A multicenter pilot-randomized controlled trial of the feasibility of an augmented red blood cell transfusion strategy for patients treated with induction chemotherapy for acute leukemia or stem cell transplantation. Webert KE. Transfusion. 2008;48(1):81. Epub 2007 Sep 24
4. Red blood cell transfusion triggers in acute leukemia: a randomized pilot study. DeZern AE et al. Transfusion. 2016;56(7):1750. Epub 2016 May 20
5. Blood transfusions for anemia in patients with advanced cancer. Preston Nj. Cochrane Database Syst Rev. 2012 Feb; 2012(2): CD009007

CAR T cells: Myth or Reality

Dr Somnath Mukherjee
Associate Professor
Dept. of Transfusion Medicine
AIIMS, Bhubaneswar, Odisha, India
YOP: 2008

Dr Karan Kumar
Senior Resident
Dept. of Transfusion Medicine,
NCI-AIIMS, Jhajjar, Haryana
YOP: 2017

In the last five years, there have been dramatic advances in the field of cellular therapy, which includes the application and development of natural killer cells, dendritic cells and T cells, virus-specific T-cells, T-cell receptor (TCR)-engineered T-cells, and chimeric antigen receptor (CAR) T-cells. The recent FDA approval of CAR T-cell therapy has heralded a paradigm shift in the treatment of lymphoma and leukemia. CAR T-cells, one of the fastest-growing cancer immunotherapies, have proven to be highly efficacious against B-cell malignancies. Patients with hematologic malignancies who have failed standard therapies are often treated with CAR T-cells, which can be curative or serve as a bridge to transplant. Normally, CAR T-cells are manufactured over 7 to 11 days, with many distinct steps along the process; cell collection through apheresis, enrichment, separation, cell programming through lenti/retro viral transduction, and expansion. (Figure:1)

However, despite the immense potentials of CAR T, the successful development of these therapies for routine clinical use poses significant challenges. Growing experiences with CAR T cells have revealed that remissions are brief in a substantial number of patients. These complexities may be attributable to the incomplete understanding of the mechanism of action, heterogeneity of disease process, significant variation in the starting material for the production of CAR T cells, variability of the product manufacturing process, end-product characterization including potency CARTs, variability standardization of these "living drugs" and last but not the least development of cancer resistance and/or antigen escape/modulation to CAR T cells.

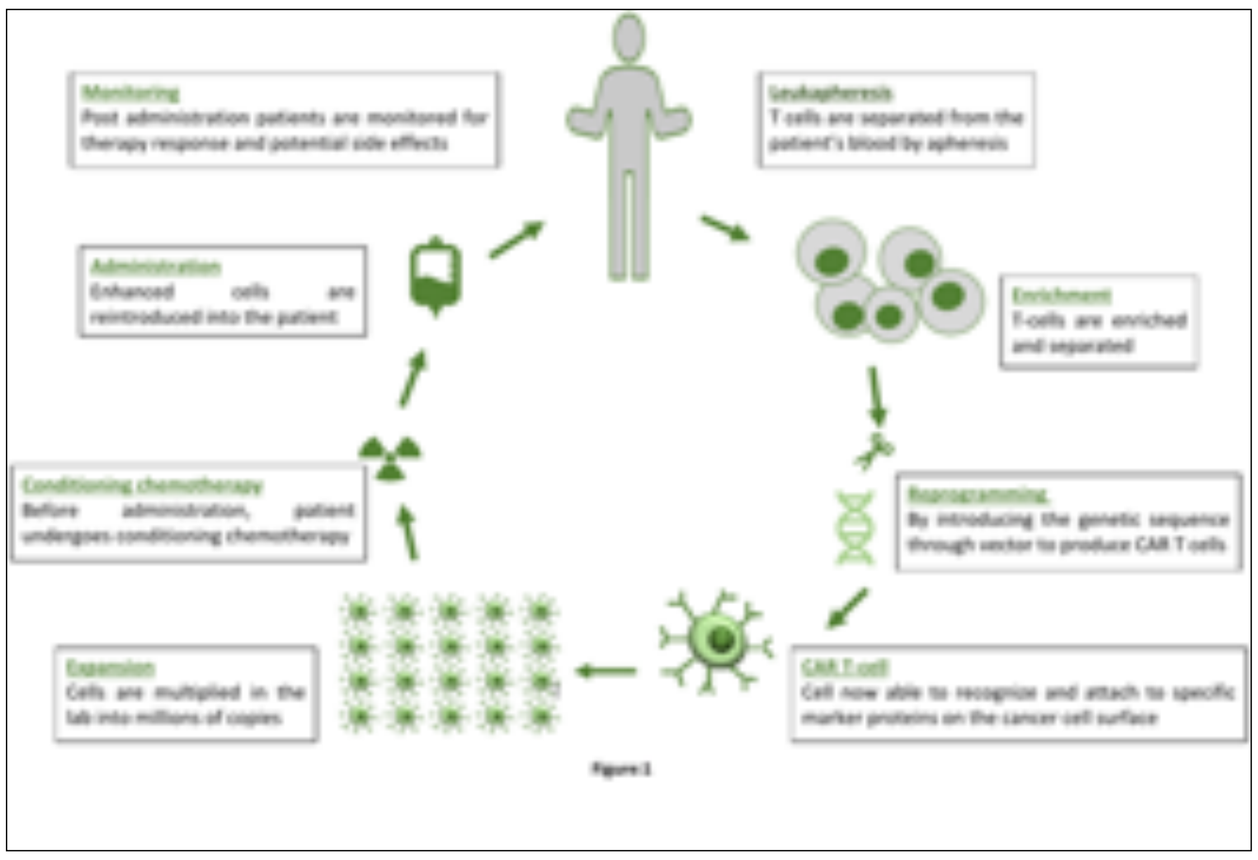


Figure:1

All these factors can preclude durable remissions following CAR T cell therapy and fail CAR T cell treatment. Given the aggressive nature of most of the diseases, the first barrier is the collection of adequate T cells to be used for the generation of CAR T cells. Patients with a disease like ALL when heavily pretreated with cytotoxic chemotherapy, often excluded from consideration of CAR T cell therapy, typically because of pre-existing lymphopenia as a result of chemotherapy. Moreover, manufacturing CAR T cells from patients with solid tumor are even more challenging than ALL of CLL. Reasons are under investigation, but possibly the presence of more number of circulating myeloid-derived suppressor cells found in solid tumors as these cells are considered to have inhibitory property on the growth of CAR T cells. T cell enrichment is possibly another important factor that also affects the characteristics of CAR T cells product. Construction and designing of CAR T cells are also important in maintaining the potential and efficacies. The construction of newer TCR co-stimulatory domains such as CD 28 and /or 41-1 BB markedly affect the persistence of CAR T cells in the circulation. Additionally, further analysis of observations in patients with a notable expansion and/or persistence of the CAR T cells suggests a role for targeted genomic integration of the CAR construct to enhance persistence. Recent utilization of the CRISPR-Cas9 gene-editing technique for specific integration of the CAR gene into the TCR alpha constant region has resulted in better antitumor response than those with conventional lenti/retrovirally transduced CAR T cells in preclinical models.

Thus, the advances in gene-editing technology, combined with an improved understanding of the various factors determining the potency of CAR T cells will be the most crucial steps to designing next-generation CAR T cells. Future direction to improve CAR T cell efficacy, as well as persistence, will rely heavily on an optimum understanding of the disease process as well as T cell biology. These understandings not only will help in better optimization of CAR T cells but also expand the horizon of the therapeutic potential of CAR T cells in non-B cell malignancies and solid tumors as well.

Reference

1. Golchin A, Farahany TZ. Biological Products: Cellular Therapy and FDA Approved Products. Stem Cell Rev Rep. 2019;15(2):166-75. Epub 2019/01/10. doi: 10.1007/s12015-018-9866-1. PubMed PMID: 30623359.
2. Kenderian SS, Porter DL, Gill S. Chimeric Antigen Receptor T Cells and Hematopoietic Cell Transplantation: How Not to Put the CART Before the Horse. Biol Blood Marrow Transplant. 2017;23(2):235-46. Epub 2016/09/18. doi: 10.1016/j.bbmt. 2016.09.002. PubMed PMID: 27638367.
3. Stroncek DF, Reddy O, Highfill S, Panch SR. Advances in T-cell Immunotherapies. Hematol Oncol Clin North Am. 2019;33(5):825-37. Epub 2019/08/31. doi: 10.1016/j.hoc. 2019.05.006. PubMed PMID: 31466607.
4. Highfill SL, Stroncek DF. Overcoming Challenges in Process Development of Cellular Therapies. Curr Hematol Malig Rep. 2019;14(4):269-77. Epub 2019/07/07. doi: 10.1007/s11899-019-00529-5. PubMed PMID: 31278568.
5. Fraietta JA, Lacey SF, Orlando EJ, Pruteanu-Malinici I, Gohil M, Lundh S, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med. 2018;24(5):563-71. Epub 2018/05/02. doi: 10.1038/s41591-018-0010-1. PubMed PMID: 29713085.
6. Mac L eod DT, Antony J, Martin AJ, Moser RJ, Hekele A, W etzel KJ, et al. Integration of a CD19 CAR into the TCR Alpha Chain Locus Streamlines Production of Allogeneic Gene-Edited CAR T Cells. Mol Ther. 2017;25(4):949-61. Epub 2017/02/27. doi: 10.1016/j.ymthe. 2017.02.005. PubMed PMID: 28237835.
7. Hu W, Zi Z, Jin Y, Li G, Shao K, C ai Q, et al. CRISPR/Cas9- mediated PD-1 disruption enhances human mesothelin-targeted CAR T cell effector functions. Cancer Immunol Immunother. 2019;68(3):365-77. Epub 2018/12/14. doi: 10.1007/s00262-018-2281-2. PubMed PMID: 30523370.
8. Elavia N, Panch SR, McManus A, Bikkani T, Szymanski J, Highfill SL, et al. Effects of starting cellular material composition on chimeric antigen receptor T-cell expansion and characteristics. Transfusion. 2019;59(5):1755-64. Epub 2019/04/12. doi: 10.1111/trf. 15287. PubMed PMID: 30973976.

Ek- Anubhavi soch: *exam se pehle sona jaruri hai*

Dr Prasun Bhattacharya
Professor and Head
Dept. of Immunohaematology and Blood Transfusion
Medical College Hospital, Kolkata
YOP: 2004

Dr Anubhav Gupta
Assistant Professor
Dept. of Transfusion Medicine,
AIIMS, Jodhpur, Rajisthan
YOP: 2017

Those were the days, aahh PGIMER Chandigarh, Naam hi kafi ha! yes I am PGlite. Every medical student dream of it but I have lived my dream.

My first day in Department of Transfusion Medicine and the first person I met was Dr (Prof.) Neelam Marwaha, 16th July 2014. The day when I introduced myself with Transfusion Medicine. The day when I learned the different beautiful colours of Transfusion Medicine, a rainbow. And the day when I learned Beta teen saal mushkil hone wale ha😊)! I was sent to Dr (Prof) Ratti Ram Sharma, sir who said kakke dhyan se pdna😉 Next was Dr (Prof) Ashish Jain, naam hi kafi ha!, Dr Hari Krishan Dhawan (HKD), milkar pata laga koi itna acha kaise ho sakta hai yaar, Dr Suchet Sachdev, common saying Betaaa and yes hamari apne Dr Rekha Hans.

How can I forget to name Romesh Jain, yes GOLU, my batchmate. He is the one who was with me, three years 24*7. I can't remember a single day when he was not with me, a true friend indeed, thoda kamina jaroor ha! Then I met everyone's favourite Shaggy sir (Late Dr Saugata Chaudhary). A passionate, enthusiastic and a beautiful soul. There were the nights when we three at 3 am (early morning) sit together and used to discuss the philosophy of life😉 It was the phase when I went through a period of major reconstruction in my personality.

Here I would like to share my one incident here. It was my last written exam of MD transfusion medicine on recent advances. I was anxious, so anxious, unable to hold on the stress that I was going through. I went around 40 hours without sleep. My eyes were red like amber, it was too painful to take upon the paper, recent advances, which was considered to be the most volatile one in entire syllabus or say "out of syllabus". I had nightmares remembering the "ullta pultta" questions coming in exam. My unabridged fate has to be decided on this day itself. After an hour of starting the exam in examination hall I had fell into sleep without my intention and alertness. The invigilator came, "Hey, get up, it's an exam!!" I looked at the clock I had slept for an hour completely out of three allotted for exams. I completely lost hope, somehow gathered courage and scribbled whatever I knew. After exam Romesh said abe pagal ha kya, are u a fool to sleep in such an intense exam and yes then he asked one million dollar question, Bhai Kitne Panne Bhare Tune? ;) 😉))) Latter comes the day of practical exam. To confirm that I and Romesh are passed, Romesh asked Dr Neelam maam in front of external examiners Maam Mithai Le aai? Maam said yes with a smile and we just ran away😉)))))))

Though my TM faculty guided me out but YES I still laugh at the incident , Lol!!

So, the lesson is, have a proper sleep before exams and yes panne jaroor bharo😊)) and always ask Maam Mithai le aai😊))))))))))))

Prof. J.G. Jolly: Carving the field of Transfusion Medicine in India

It was 1st October 1963 when he joined the PGIMER Chandigarh. Transfusion Medicine at that time was in infancy all around the world. He pioneered the voluntary blood donation in the region on those early days. His passion and dedication lead to the development of this new branch of science in our country. He was instrumental in introducing commercial antisera, plastic blood bags, development of thalassemia transfusion programme, haemophilia care programme, Rh Clinic are few to name. He was the founder president of Indian Society of Blood Transfusion & Immunohaematology (ISBTI), first scientific society of Transfusion Medicine in our country. He was first to start Diploma in Blood Transfusion and Immunohematology (1977) in PGIMER, Chandigarh. After superannuation from PGIMER Chandigarh, he was Founder Head of the Department of Transfusion Medicine at SGPGI Lucknow where he started his dream project of starting academic programme: MD Transfusion Medicine course at SGPGI Lucknow and PGIMER Chandigarh became the second institute to start MD Transfusion Medicine course in 2000. Transfusion Medicine fraternity in India will always be indebted from his contributions, and he must be happy and blessing us from heavens seeing the growth of the tree he planted.

Dr Hari Krishan Dhawan
Associate Professor
Dept. of Transfusion Medicine
PGIMER, Chandigarh
YOP: 2007 (June)

Volume 1
JANUARY 2021