SABM®
SOCIETY FOR THE ADVANCEMENT OF PATIENT BLOOD MANAGEMENT
NEWSLETTER
August 2021

Letter from the President – Sherri Ozawa, RN

This will be my final "President's Letter" and it has truly been an honor to serve as President for these two years. I commend each of you for maintaining the needed balance and strength to continue your dedication to this most challenging of callings, caring for others. Although the pandemic persists and is surging in various locations, with most of us are facing extraordinarily busy clinical schedules, we are very grateful that so many SABM members have made the time to contribute to our work, whether that be in Annual Meeting Planning, working on, attending, and promoting our educational initiatives, or even applying important PBM principles in daily clinical practice. I would like to share some exciting updates –

We have recently completed forming alliances with additional Patient Blood Management Organizations worldwide, as we continue to expand our Global Alliance of PBM societies. Most recently, The Asia Society of Patient Blood Management, The Malaysian Society of Patient Blood Management, and The Association for Perioperative Medicine (Austria). These organizations join NATA, and the International Foundation for Patient Blood Management in sharing both the vision and definition of PBM as an urgent clinical and quality priority worldwide.

Many of you were able to join our recently completed webinar series focusing on "Optimizing the Care of Surgical Patients", which featured several SABM leaders who shared current clinical and published data on improved management and mitigation of blood loss and its dangerous consequences. Many thanks to our Education Oversight Committee Chair and President Elect, Carolyn Burns, MD, for her organizing and leadership of this outstanding educational effort. If you were unable to attend, presentations are available on our website.

Additionally, thanks to the hard work of our SABM Pediatric leaders, we have recently submitted a set of Choosing Wisely® recommendations to the American Board of Internal Medicine (ABIM)–we are awaiting their response. This will round out our adult recommendations which were accepted and published a few years ago.

Please take a moment to stop by the Iron Corner section of our website to see exciting updates and visual aids. These updates will help our clinical colleagues understand the burden of anemia and how proactive detection and management contributes to improved patient outcomes. We know you will find this resource invaluable in your practice.

Our management team at Talley has also expanded to include some new faces and roles, including more presence by Wendy Stevens, our meeting manager, who has been working tirelessly to ensure a high quality, accessible and useful platform despite it being another year of virtual meeting. Denise Smith at Talley is taking the lead in assisting with our Global Alliance and working with our Membership and Mentorship committee as they develop relationships with many other organizations and individuals. Under the direction of Haley Brust, we greatly appreciate the stability and consistency that Talley has brought to us.

On that note, Annual Meeting planning is well on its way to being complete – under the guidance of this year's Co – Chairs Rita Schwab, CPMSM, and Micah Prochaska, MD, you will be sure to find an innovative, unique, but highly educational and scientific program. Be sure to register as soon as possible – the virtual nature of the meeting is again allowing us to have expanded participation of both attendees and speakers from around the globe.

We eagerly anticipate filling our upcoming Board vacancies with SABM members who are growing and developing in their fields; please be sure to participate in the Board of Directors poll. Participation in selecting leaders in the organization is vital to its well-being and growth.

Finally, a special word of thanks to our Industry Council members, and a welcome to some additional international representation on the group, with representatives from both Vifor Pharma (Europe) and Zuellig Pharma (Asia). Under the leadership of Trupti Mehta from Octopharma and Patrick Curran from Haemonetics, keep your eye out for a variety of helpful materials and projects.

Your support of SABM has been so important and beneficial, especially through these difficult times, and we look forward to moving strongly into the second half of 2021 with renewed energy. To each of you, a heartfelt thank you for the privilege of serving as your President—see you at the Annual Meeting!

Sincerely,

Sherri Ozawa, RN

SABM NEWSLETTER
AUGUST 2021
ISSUE

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Please consider making a donation to SABM. Your donations will help us to improve the lives of people throughout the world through Patient Blood Management.

SABM 2021 Newsletter Publication

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ANESTHESIA & ANALGESIA

Consider submitting your future manuscripts in PBM for peer review and publication in this new section. The success of this endeavor will depend on the provision of material to make it lively and attractive to our colleagues and other professionals in the field.

Members Invited to Submit Papers CLICK HERE

Looking For Newsletter Content

SABM members want to know:

- Do you have an interesting case study?
- News about your blood management program?
- News about a new program at your institution?
- Have an article about some of the latest technology?
- Submitted an article to a journal for publication?

Deadline for the Spring 2022 issue is February 15, 2022.

Don't wait! Send your articles today to the Newsletter Editorial team at info@sabm.org

Call for Member Accomplishments

If you have been given an award, received recognition, or have been recently published, we would like to publish it in the next issue of the SABM newsletter.

Please send an e-mail with the details to info@sabm.org. Be sure to include your full name and details regarding the award, the recognition you received, or the publication citation.

Call for Interesting Case Studies

Authors: Can be submitted by any discipline (MD's, RN's, technologists, perfusionists, students)

Description/Format/components:

- Patient history and diagnosis
- Problem statement
- Relevant laboratory results or tests
- Medical management
- Follow up
- Brief discussion of the disease/problem/condition with up-to-date literature
- Provide 3-4 multiple choice questions
- Answers to questions to be provided on SABM website 2-3 weeks after publication
- Tables/Figures/images are welcome
- 5-10 annotated references

Call for Book Reviewers!

The newsletter editorial team is looking for members to review books. You can choose to review a book that you already have, or volunteer to review a book of SABM's choice. If you have a book that you would like to submit a review for, or to be considered as a book reviewer, you can send an email to info@sabm.org with your request for consideration.

SABM VIRTUAL ANNUAL MEETING 2021 SEPT 22-25

Society for the Advancement of Patient Blood Management, Inc.
2021 Annual Meeting Announcement

Dear SABM Community,

While we had all intentions of hosting a live in-person meeting this upcoming Fall after much discussion and feedback from the membership we are building on the success of the last Fall meeting and using the virtual format again this year. Many new members and participants were able to view the sessions from the comfort and safety of their own environments and feedback have shown us that an overwhelming majority of members are not ready to travel or meet just yet. While we make this decision with a heavy heart, we are also energized by the prospect of continuing to offer our attendees the exceptional learning and community experience you deserve. Offering a virtual meeting will help make the excellent speakers and content available to a wider audience and we are excited at the prospect of growing our SABM community.

SABM has chosen a state-of-the-art virtual meeting platform that combines an innovative learning environment with reliable functionality and intuitive navigation. The schedule will include a mix of live and on-demand sessions, along with an interactive exhibition hall, networking spaces, and poster hall.

We understand schedules are challenging as many of us are managing new work and home demands during this time. To ensure you have ultimate flexibility, we are excited to offer 24-hour access to the virtual Annual Meeting platform—allowing you to learn and engage at your own pace no matter where you are in the world or your day. Attendees will also be able to access the platform for an additional month following the conclusion of the meeting.

SABM will provide continuous updates about the 2021 Annual Meeting.

Whether this is your first SABM Annual Meeting or you have attended many SABM Annual Meetings, we will make history together in September as we celebrate you, your accomplishments, and this remarkable community.

We look forward to seeing you in September.

Please **CLICK HERE** to access Annual Meeting Program.

Virtual SABM 2021 Annual Meeting Registration Rates

Member - Allied Health/Affiliate	$250.00
Member - Physician/Executive	$300.00
Member - Technologist/Trainee/Student/Resident/Fellow	$75.00
Non-Member - Allied Health/Affiliate	$275.00
Non-Member - Physician/Executive	$362.50
Non-Member - Technologist/Trainee/Student/Resident/Fellow	$175.00

REGISTER NOW!

Introducing SABM International Correspondents

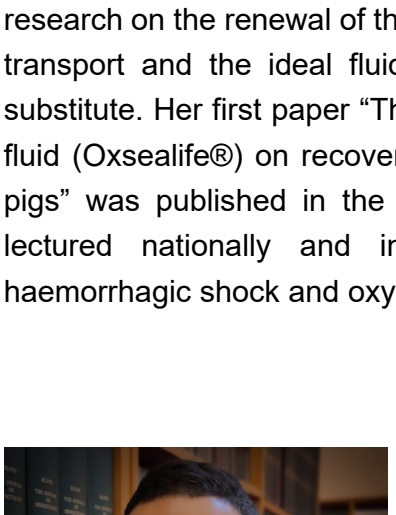
AFRICA

Nathaniel Usoro, MD, is Chief Consultant Surgeon at University of Calabar Teaching Hospital and Senior Lecturer in Surgery in University of Calabar, Nigeria. He is a Fellow of the West African College of Surgeons and the International College of Surgeons and has served a full tenured position as Head of Surgery in his institution. He instituted teaching of Blood Conservation and Bloodless Surgery to medical students and residents in his institution in 2014 and continues teaching those courses to date.

Dr. Usoro is the founding Chairman of the Bloodless Medicine & Surgery Group in University of Calabar Teaching Hospital, a multidisciplinary group of professional volunteers providing bloodless care for patients, with excellent outcomes, since 2007. He is a member of several professional societies, including SABM, where he serves on the Membership Committee, and is currently President of the Bloodless Medicine & Surgery Society, (BMSS). He has presented several papers on the subject of improving clinical outcomes and protecting patients' rights through blood transfusion avoidance in international professional meetings, published in peer-reviewed journals, and has a book chapter to his name. Dr. Usoro is the recipient of several awards, including the 2016 *SABM Kathleen J. Sazama Award* "For Outstanding Leadership in Advancing Patients' Rights in Patient Blood Management."

ASIA

Ananthi Krishnamoorthy, MD, has experience in rehabilitation medicine, primary care & occupational health. Her varied career has included stints at the Blood Management Center, St Luke's Hospital, Kansas City, Missouri, USA, and the Center for Bloodless Medicine and Surgery, University of Pennsylvania, Philadelphia, Pennsylvania, USA. She is a published author in the Medical Journal of Malaysia and has lectured nationally and internationally on a variety of topics related to patient blood management. Dr Krishnamoorthy is a sitting member of the Communications and Membership Committee, for the Society for the Advancement Patient Blood Management (SABM), the Secretary for the Malaysian Society of Patient Blood Management (MyPBM), the Scientific Committee, for the Asian Society of Patient Blood Management (ASPBM) and the Planning Committee for the Bloodless Medicine and Surgery Society (BMSS) congress 2021.



EUROPE

Lara Oller, MD, is an anesthesiologist and critical care physician trained at *Hospital Universitario La Paz*, Madrid, Spain. During her residency, Dr. Oller took special interest in the following: oxygen transport physiology, hemorrhagic shock pathophysiology and hyperbaric medicine. She also spent two months at Englewood Hospital and Medical Center, Englewood, New Jersey, under the supervision of Aryeh Shander, MD.

After finishing her residency, Dr. Oller began as a consultant anesthesiologist in *Clínica La Luz* (Madrid, Spain), and last year (2020) she relocated to Italy and now on staff as a cardiac anaesthesiologist at Maria Pia Hospital, Torino, Italy, where bloodless medicine and surgery is performed. Dr. Oller is currently serving as primary investigator on the project named Oxsealife®. This project encompasses research on the renewal of the physiological basis of oxygen transport and the ideal fluid for resuscitation as a blood substitute. Her first paper "The effect of a novel intravenous fluid (Oxsealife®) on recovery from haemorrhagic shock in pigs" was published in the journal *Anaesthesia*. She has lectured nationally and internationally on Oxsealife®, haemorrhagic shock and oxygen transport physiology.

OCEANIA

Kevin Trentino, MPH, is a medical researcher with the Faculty of Health and Medical Sciences at The University of Western Australia, and senior analyst with The East Metropolitan Health Service, a five-hospital network in Western Australia. Kevin has extensive experience using clinical information systems to drive safety and quality, with expertise in patient blood management, health service research, and benchmarking. He has over 25 peer reviewed publications and is an invited reviewer for several medical journals. He has been invited to present at national and international conferences and workshops on topics including hospital-acquired complications, cost of transfusions and patient blood management.

Nurses Notes: Nurse Triage Improves Blood Utilization

Effective implementation of transfusion guidelines is a key element in a successful patient blood management program. In addition to established transfusion guidelines, nurse-driven, real-time reviews of PRBC orders are reducing unnecessary utilization of blood products.

As the COVID-19 pandemic significantly strained the blood product supply, registered nurses specializing in Patient Blood Management (PBM) at Geisinger Health responded by developing the Blood Bank Triage process. Established in April 2020, this prospective review process requires that all PRBC orders, outside of established transfusion guidelines, be referred to the PBM registered nurses. After reviewing the medical record, the PBM nurse approves or declines orders. If questionable, the nurse contacts the on-call pathologist; if declined at any time, the nurse contacts the ordering provider to communicate denial.

In May 2020, the triage guidelines were reviewed and adjusted. A surgical blood ordering schedule was added and the PBM nurses worked with the Blood Bank to establish other criteria for new captures, such as short-dated units. By August 2020, Covid Convalescent Plasma (CCP) was being used as part of treatment, so we added CCP triage to our process and continued to make adjustments. For example, PBM nurses regularly communicated with the Blood Bank and providers to triage whether a patient would be going to ICU and therefore triage the CCP availability.

As of May 2021, PBM nurses at Geisinger Health reviewed approximately 4,500 RBC transfusions (12% of all orders) with the following results:

83% were approved
17% were denied or modified

Of 4,232 RBC units ordered outside guidelines:

14% were canceled

Of 624 two-unit transfusions ordered:

47% were modified to single-unit transfusions

The Blood Bank Triage role of PBM nurses continues to reduce unnecessary transfusions by empowering nurses to intervene on inappropriate orders, including two-unit orders; communicate with providers on the appropriateness of transfusion; and fill knowledge gaps with current evidence-based criteria. It also has drawn attention to unusual patient situations, inconsistent order practices and inappropriate utilization.

Contributor: Mary Ann O'Brien, RN, MSN, CCRN, CNE

STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management

In a noteworthy collaboration, The Society of Thoracic Surgeons, The Society for the Advancement of Patient Blood Management, The Society of Cardiovascular Anesthesiologists and The American Society of ExtraCorporeal Technology released on June 30, 2021, the STS/SCA/AmSect/SABM Update to the Clinical Practice Guidelines on Patient Blood Management including recommendations for reducing blood loss during heart surgery and improving patient outcomes.

Pierre R. Tibi, MD, immediate past president of SABM and Medical Director of the PBM Program at Dignity Health - Yavapai Regional Medical Center, Prescott, Arizona served as the lead author. Speaking about the project he said, “This guideline provides clinicians with a detailed assessment of patient blood management in the cardiac surgical patient— what has been proven to work and what has not, as well as the ability to incorporate these techniques with the most up-to-date evidence.” Among the most important changes to the practice guidelines is recognition that PBM treats the whole patient and doesn’t simply focus on whether or not to transfuse blood, a “liquid organ.”

These Guidelines “represent the highest ideal of evidence-based medicine written by an interdisciplinary group of investigators whose expertise rests within cardiac surgery and Patient Blood Management,” noted co-author Linda Shore-Lesserson, MD, Professor of Anesthesiology at the Zucker School of Medicine at Hofstra Northwell, Manhasset, NY.

Since the Guidelines were last updated in 2011 there has been a “remarkable increase” in minimally invasive procedures contributing to more appropriate blood product utilization and management, according to coauthor Victor A. Ferraris, MD, PhD, from the University of Kentucky College of Medicine in Lexington. Therefore, the practice guideline features 23 new or updated recommendations. Dr. Ferraris noted: “Blood management guidelines are a ‘moving target’ that change with the advent of new or modified evidence.”

Dr. Shore-Lesserson pointed to a notable difference from prior versions of the Guidelines, citing “the inclusion of the tenets of (PBM) in both the title and manuscript. It is our hope that these new Practice Guidelines will help to move the needle toward enhanced care for cardiac surgical patients using the Patient Blood Management evidence base.”

Not surprisingly, the Society for the Advancement of Patient Blood Management is a partner in this collaborative effort. Historically, SABM has been a champion in promoting PBM as the standard of care. Sherri Ozawa, RN, President of SABM, acknowledged, “The Society for the Advancement of Patient Blood Management is extremely honored to be included in this prestigious group of organizations, all with the aligned goal of improving patient care and outcomes through optimal patient blood management in cardiac surgery.”

Dr. Tibi expects that some clinicians will be surprised by several of the recommendations, including the information related to preoperative treatment of anemia and perfusion techniques that may require changes to routine treatments for their patients. For patients, it’s important that hospitals, surgeons, and care teams practice PBM, utilizing the “best, most proven techniques available.” He advises, “Patients should ask their doctor, ‘What do you do so that my chances of receiving blood are minimized?’”

Reflecting on that simple but vital question, we are pleased to announce the release of the Update to the Clinical Practice Guidelines with the goal of reducing the need for blood transfusions during heart surgery and improving patient outcomes.

Contributor: Roland Black

A Case of Severe Coagulopathy Post Traumatic Injury and Hemodynamic Demise

History

27-year-old African American male with no past medical history, presented to the emergency department (ED) as a level I trauma with cardiopulmonary resuscitation in progress after a gunshot wound (GSW) to the groin. In the ED he had return of, and subsequent loss of pulses multiple times. After achieving a sustained cardiac stability, he was taken to the OR with trauma and vascular surgery where he underwent groin exploration and was found to have the following injuries:

- Right profunda artery bleeding/ injury requiring ligation
- Right femoral vein transection requiring ligation
- Right profunda vein transection requiring ligation
- Patent femoral - superficial femoral artery- triphasic PTA at the end of the procedure
- Shattered femur with osseous bleed

Subsequently, in the OR, a right external fixator of femur was placed by orthopedics along with a right sided chest tube placement for moderate right pneumothorax and had multiple Pulseless electrical activity (PEA) arrests while in the OR. The patient was then transferred to the intensive care unit (ICU).

Hospital Course

The initial course in the ICU was complicated by severe coagulopathy. Thromoelastography (TEG) obtained post OR was essentially flat with no evidence of clot formation (Figure 1). He was placed on massive transfusion protocol (MTP) and received aggressive resuscitation with 29 units of red blood cells, 31 units of plasma, 5 doses of cryoprecipitate, and 5 units of platelets. Given the severe coagulopathy and ongoing bleeding, he also received 2500 units of 4-factor prothrombin complex concentrate (4F- PCC, Kcentra, CSL Behring King of Prussia, PA). Slight improvement was detected in the TEG following the Kcentra (Figure 2) but subsequent TEG's were severely abnormal (Table). He continued to receive MTP for correction of his coagulopathy that persisted for the first 3 days of his hospital course. Throughout this period the patient continued to have ongoing post-operative bleeding, though neither trauma nor vascular surgery recommend any additional surgical options at this time.

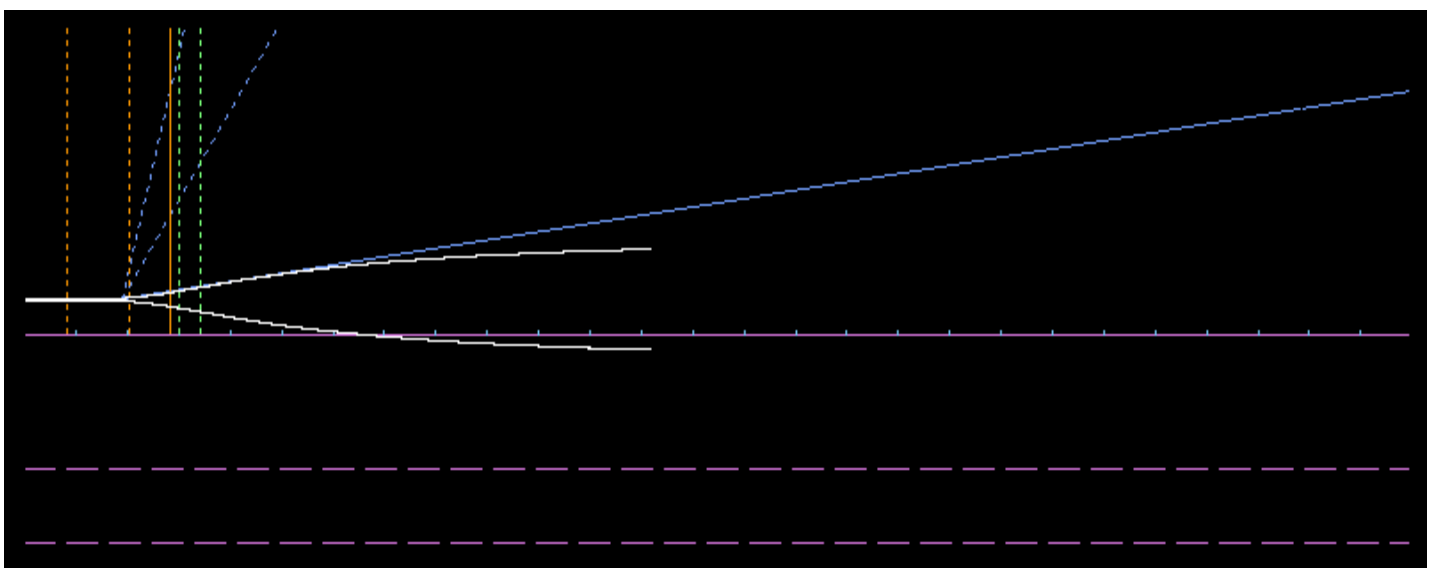


Figure 1

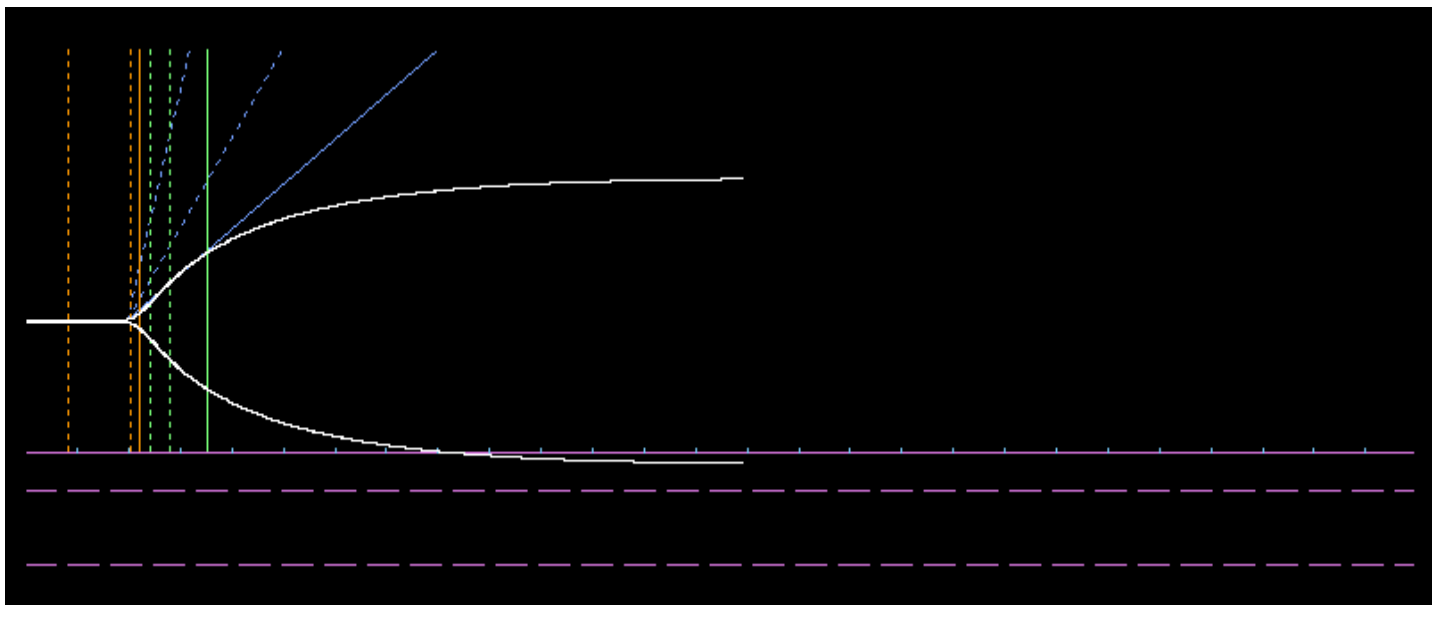


Figure 2

On POD 2, a Urology consult was ordered to assess the right scrotal and inguinal lacerations. Based on their findings the patient returned to the OR and received a small superficial femoral branch ligation. He underwent multiple washouts and wound vacuum changes with vascular, orthopedics, and plastic surgery throughout his hospitalization.

A Case of Severe Coagulopathy Post Traumatic Injury and Hemodynamic Demise

The hospital course was also complicated by acute kidney injury, hemorrhagic shock requiring vasopressors, and shock liver secondary to hypotension. On POD 4, a hemodialysis line was placed and continuous renal replacement therapy was initiated. A head CT scan revealed a loss of gray-white differentiation. Electroencephalogram (EEG) was performed on POD 5 and revealed an absence of background frequencies with overall background suppression and brief periods of slightly faster frequencies consistent with minimal reactivity to external stimuli. A somatosensory evoked potential test (SSEP) was performed. Absence of negative 20 somatosensory evoked potentials (N20) is suggestive of poor neurological outcome.[1] In this case, N20 was negative on the left but preserved on the right. MRI was unable to be obtained due to retained bullet fragments. At this time, the Neuro ICU was consulted for neuroprognostication.

Per Neurology, there was injury of the brain as a result of anoxia as evidenced by the head CT imaging. This injury was present prominently in the visual cortices as well as diffusely with some cortical cerebral edema and loss of grey-white differentiation throughout. The EEG has shown low amplitude slowing off sedation, therefore may represent further evidence of injury, and likely indicates some level of disability.

On POD 12 the patient underwent right total knee amputation due to tissue necrosis with vascular surgery.

Two days later, the patient lost pulses, requiring one round of CPR with return of spontaneous circulation obtained after 2 minutes. After thorough discussion with his family, a decision was made to provide comfort measures only and to terminally extubate. The patient subsequently died shortly thereafter with the preliminary cause of death listed as septic shock secondary to bacteremia from the necrotic right leg secondary to a GSW.

Table

TEG results compared to blood component and hemostatic drug administration during the first 48 hours post admission

TIME	R (min)	K (min)	α Angle (°)	MA (mm)	LY30 (%)	EBL (mL)	#RBC (units)	#FFP (units)	#PLT (dose)	#Cryo (dose)	Other Products
	4-10	1-3	53-73	50-72	0-8						
21:34-3:50						5000	29	31	5	5	Kcentra 2500u @ 3:10
3:50	7.1	16.6	17.7	25.8	0		4	4	2	1	
5:50	7	n/a	7	10.4	0		4	4	0	1	
9:13	11.8	21.6	14.4	21.4	0		8	8	1	1	TXA100mg @ 9:54
10:54	10.1	12.9	19.8	28.2	0	500	4	4	2	2	
17:32	6.8	3.1	56.4	50	0		0	0	0	0	
22:28	10.9	6.7	33.5	39	0		0	0	0	0	
5:03	11.6	5.8	34.6	43.7	0		0	2	1	1	

EBL-Estimated Blood Loss
TXA-Tranexamic Acid

Discussion

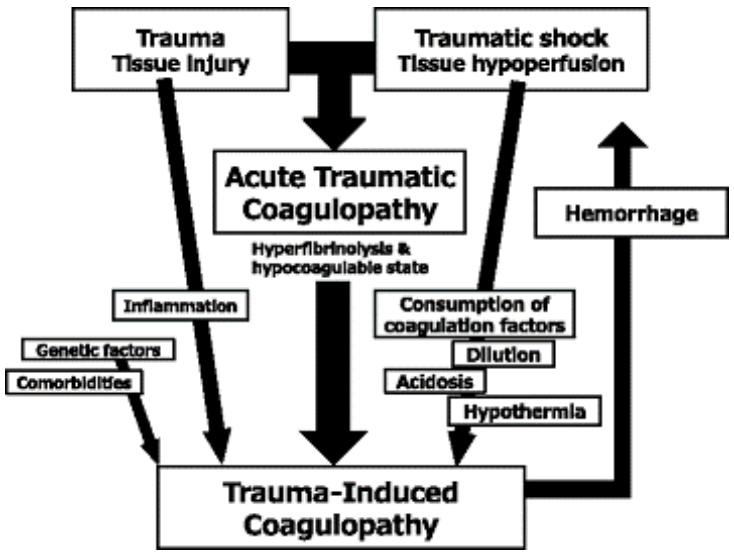
Damage control resuscitation refers to the prevention of coagulopathy by limiting blood loss early on and replacing blood components and other pharmacologic agents in a balanced ratio to restore hemostasis. Blood components are widely used and preferred to crystalloid in severe hemorrhage. Prothrombin complex concentrate (PCC) has recently been utilized as an important adjunct to damage control resuscitation. In a study comparing PCC and plasma transfusions, 4-F PCC has shown far better return to hemostasis and outcomes than historical transfusion products.[2]

Additionally, a number of observational and retrospective studies of viscoelastic guided transfusion in bleeding trauma patients has been shown to possibly reduce mortality by up to 50%. Other findings indicate the use of TEG in traumatic bleeding correlates with a reduction in total blood products transfused, reduce ICU length of stay, and reduce costs. Because trauma patients can be both hypocoagulable and hypercoagulable (Figure 3), viscoelastic assays give a more global picture of hemostasis than standard coagulation tests and also provide guidance in appropriate therapies.[3]

Figure 3

Acute traumatic coagulopathy (ATC) and Trauma-induced coagulopathy (TIC) are clinical manifestations of both of the hypocoagulability to hypercoagulability seen in traumatic injury, which may lead to complications including uncontrolled bleeding and thrombotic disease

A Case of Severe Coagulopathy Post Traumatic Injury and Hemodynamic Demise



From: Acute traumatic coagulopathy and trauma-induced coagulopathy: an overview [4]

In this case

- This patient had very severe bleeding and coagulopathy, lab-based TEG was less helpful since hemostasis changes so quickly during severe bleeding.

- Based on TEG parameters, the high K and low α angle represent low fibrinogen and factor XIII concentrations, which are usually replaced by cryoprecipitate. An earlier administration was suggested; however, the patient's coagulopathy was profound. Factor XIII is an important factor clot stabilization by enhancing $\gamma\gamma$ crosslinking of fibrin molecules.

- A large, randomized trial in >20,000 trauma found evidence of the usefulness of Tranexamic acid (TXA) in promoting hemostasis and is the only drug with prospective clinical evidence to support use in the population.[5] Although we are not aware of all medication given in the OR, TXA should have been administered as early as possible to reduce fibrinolysis. This was not appreciated on the TEG via LY30 because the MA was too low to show any effect.

Conclusion

In our center, we have encouraged providers to utilize the expertise of the transfusion medicine/blood management team as a consult service in complex situations such as this. The most important objective is utilizing the most up to date evidence in development of MTP's and to analyze appropriate of use of blood bank resources. Robust communication channels are imperative among clinical and laboratory team members in order to ensure timely and appropriate use of blood products and hemostatic pharmaceuticals. Additionally point-of-care testing should be used to provide goal-directed therapy as early as possible. In this case, the blood management team was called upon to evaluate the effectiveness of our MTP ratios and to assist in interpretation of TEG results and therapeutic response. Though the outcome was not ideal, this case provided educational value and strengthened lines of communication between the blood and trauma service.

Contributors: Christine M. Cahill MS, BSN, RN; Majed A. Refaai MD

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Questions

1. When analyzing TEG, K time represents:

   A. Coagulation factors activity
   B. FVII concentration
   C. Crosslinking of fibrin molecules
   D. Platelet Function
   E. Degree of fibrinolysis

2. Administration of tranexamic acid will improve _____, which is well documented by _____of TEG parameters.

   A. Platelet activity, alpha angle
   B. Fibrinogen concentration, MA
   C. Coagulation factors activity, K time
   D. Fibrinolysis activity, LY30
   E. Fibrinolysis activity, R time

3. Cryoprecipitate has a significant amount of _____ in which activity is measured by _____ TEG parameter.

   A. Factor VIII, R time
   B. Factor XIII, K time
   C. Fibrinogen, LY30
   D. AdamsTS-13, α angle
   E. Vitamin K, MA

Hemorrhagic Shock Pathophysiology

Hemorrhagic shock is the result of inadequate blood flow to meet the metabolic demands of organs resulting in a flow dependent impairment of oxygen consumption by cells (VO2).[1] The standard treatment for bleeding patients is assumed to restore oxygen delivery (DO2) to adequate levels and therefore restore VO2 and improve outcome. This notion comes from a simplistic understanding of basic physiology whereby DO2 appears to be solely dependent on cardiac output and arterial oxygen carrying capacity. However, oxygen transport physiology is not governed by any equation and is dependent on O2 movement in the microcirculation. Interventions to increase arterial DO2, such as blood transfusion, do not necessarily correlate with increased VO2 or changes in morbidity and mortality outcomes. Increasing data points to the need for supporting both microcirculatory and mitochondrial function after hemorrhagic shock and therefore provide adequate tissue oxygen delivery and consumption (Figure 1).

Mitochondria are the ultimate consumers of oxygen; over 90% of available cellular oxygen is consumed by mitochondria in the processes of oxidative phosphorylation in the electron transport chain (ETC).[2] Electrons are transferred through a series of complexes to generate the proton gradient required to synthesize ATP. Electrons transferred ultimately react with O2 (electron acceptor) to form H2O, this being catalyzed by cytochrome c oxidase (COX). However, this process is not completely efficient and electron transfer to O2 may occur either at Complex I or Complex III, resulting in the generation of Reactive Oxygen Species (ROS). Generation of ROS is a consequence of aerobic metabolism, but normal levels of ROS are managed by endogenous antioxidant systems.[3] At the mitochondrial level, hemorrhagic shock can result in mitochondrial dysfunction manifested by decoupling at the ETC that leads to anomalous electron transfer and subsequent generation of ROS with secondary free radical damage.[1] Mitochondrial dysfunction is therefore associated with impaired VO2 despite restoration of adequate DO2, resulting in decreased mitochondrial ATP synthesis and increased risk of multiorgan failure (MOF), given that the survival of cells depends on the utilization of O2 as a substrate for COX.[1]

Acute bleeding episodes are characterized by a decrease in the circulating blood volume with a redistribution of the remaining blood volume from the splanchnic, renal, and musculocutaneous circulations to vital organs, such as the brain and the heart. In the microcirculation, hypovolemia induces capillary collapse due to decreased in mean arterial pressure and perfusion pressure. Non-survivable shock is directly related to significant impairment of the microcirculation as measured by decreased functional capillary density (FCD) and accumulation of toxic metabolites involving local and systemic blood acidosis. Therefore, improving metabolic management and long-term survival after severe hemorrhagic shock may depend on therapeutic interventions aimed at maintenance of adequate FCD and perfusion.[4] Nitrate (NO_3-) and nitrite (NO_2-), previously thought to be inert ions resulting from NO generation by the classic L-Arginine-NOS-Nitric Oxide pathway, are now considered a source of NO via the nitrate-nitrite-NO pathway, which is greatly enhanced during hypoxia and acidosis.[5] Cabrales P. reported low dose exogenous nitrite enhancement of microvascular perfusion after fluid resuscitation for hemorrhagic shock, and concluded that nitrite acts as a source of nitric oxide (NO) when the surrounding tissue is acidotic.[6] Given that nitrate (NO_3-) and nitrite (NO_2) are considered a source of NO, it is enticing to hypothesize that addition of nitrates and nitrites to a crystalloid solution could enhance NO generation at the microcirculatory level in hemorrhagic patients with tissue hypoxia and acidosis. NO generation would help to restore collapsed capillary perfusion, thus improving FCD and removal of lactate and other toxic metabolites, thereby enhancing repayment of oxygen debt.

Accumulation of oxygen debt, measured by lactate and base excess, is associated the severity of reperfusion and inflammatory injury, and ultimately mortality.[7,8] The extent of damage to the endothelium is largely influenced by duration of hypoperfusion and accumulation of oxygen debt.[8] Oxygen debt accumulation leads to redox potential imbalances in cells. Redox potential involves the quantification of electron exchange between oxidants and reductants in a system. These redox reactions reflect the overall oxidative stress. Redox state stands for electron pressure in a given system just like pH stands for proton pressure in a given system. Both redox potential and pH of a biological system are kept within a narrow range under normal physiological conditions, however in clinical scenarios like hemorrhagic shock and consequent inflammation, imbalances in both pH and redox potential ensue. Non-physiological imbalances in both pH (acid-base balance) and between oxidants and reductants are incompatible with life and are likely to contribute to MOF. Therefore, restoration of redox balance appears to be critical for improving the metabolic derangements in shock.[9]

Restoration of blood flow to an ischemic organ is essential to prevent irreversible cellular injury, but reperfusion per se may augment additional tissue injury in excess of that produced by ischemia alone. During reperfusion, rapid reactivation of complex I in the ETC results in massive generation of ROS and ETC disturbances. ROS are involved in redox reactions (oxidant species) being key elements in oxidative stress and inflammation. The endothelial glycocalyx (GCX) is one of the most oxidation-sensitive components of the endothelium. A healthy GCX forms a functional barrier between blood and the endothelium that maintains microvascular homeostasis by regulating vascular permeability, vascular tone, and leukocyte adherence. ROS-mediated degradation of the GCX may exacerbate ischemia-reperfusion injury (IRI) by inducing vasoconstriction (VC), facilitating leukocyte adherence-induced mechanical obstruction of blood flow, and interstitial fluid accumulation. The result is increased inflammation and microvascular dysfunction.[10]

Integrity of the GCX plays a fundamental role in balancing fluid movement from the vascular compartment and subsequent effects on oxygen diffusion. Oxygen diffusion is limited by diffusion distance and pO2 gradient that drives

oxygen movement from red blood cells to plasma, then across cell membranes into cytosol and finally to the mitochondria.[11] It is thought that cells cannot survive if greater than 40-50 microns from blood vessels.[12] Interstitial edema may increase the distance from cell to blood vessel beyond the functional oxygen diffusion distance. Furthermore, edema may contribute to mechanical obstruction of capillaries due to pressure from swollen tissues. Therefore, a degraded endothelial GCX may prevent adequate tissue oxygenation long after restoration of blood flow and oxygen delivery to the microcirculation.

Oxygen solubility may be more critical for tissue oxygen delivery than previously thought. Hematocrit (Hct) in the microcirculation is substantially lower than Hct in the macrocirculation, as low as 15% ±5%.[11] Some capillaries are devoid of erythrocytes, having only dissolved oxygen delivered in transiting plasma. Erythrocytes release oxygen into surrounding plasma depending on conditions driving the dissociation curve of oxyhemoglobin.[12] Then, it is dissolved oxygen that cells use for their metabolism. The extent to which Hb releases oxygen into surrounding plasma is, at best, a surrogate for oxygen carrying capacity and not an estimator for DO2/VO2.[11] In addition to this, it has been shown that the coefficient of oxygen solubility in plasma is not static, but is, in fact, dynamic and can be increased according to the choice of resuscitation fluid.[13]

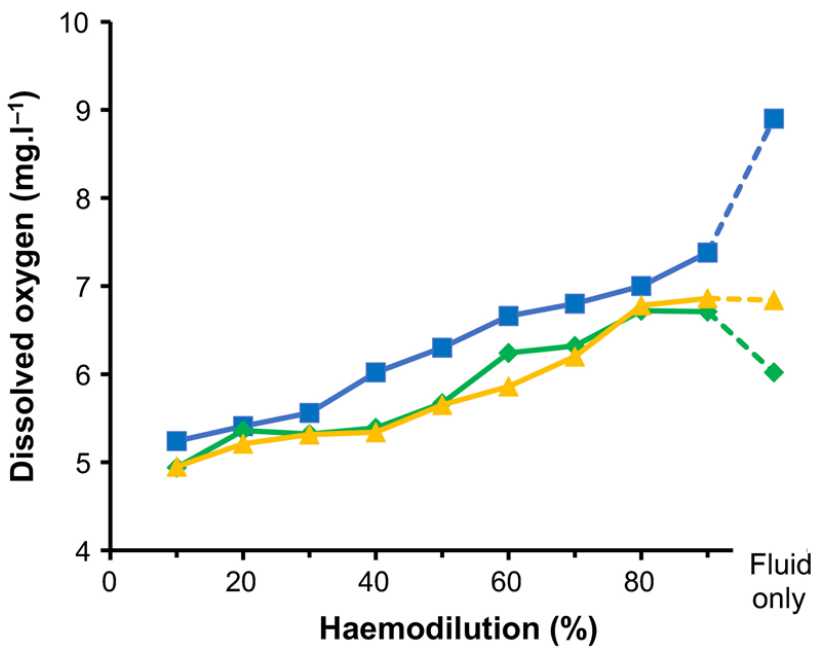

Figure 1
The oxygen solubility coefficient of blood is dynamic and increased during progressive haemodilution with Oxsealife (squares), PlasmaLyte (diamonds) and Voluven (triangles).

Blood transfusion has been the standard treatment for bleeding patients; however, this approach is based on tradition rather than scientific evidence. As explained before, oxygen delivery is not the sole function to be addressed after hemorrhagic shock. Other disorders that relate to survival, such as endothelial integrity and FCD, might have a higher impact on survival rather than oxygen carrying capacity per se. Increasing data is pointing to the fact that the ideal fluid for resuscitation should protect and reconstitute endothelial glycocalyx, mitigate endothelial injury and inflammation, favor higher oncotic potential and viscosity, and restore the microcirculation.[14,15] New strategies that are being developed might address these requirements.

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Platelet Transfusion for Patients on Anti-Platelet Therapy Who Require an Urgent Invasive Procedure or Who Are Actively Bleeding

Anti-platelet therapy is increasing as the population ages and the prophylaxis of arterial or stent thrombosis becomes a more common concern. The traditional anti-platelet agent is aspirin (ASA) which exerts its anti-platelet effect by inhibiting a platelet enzyme, cyclo-oxygenase 1 (COX-1) which oxidizes arachidonic acid. This decreases the generation of a pro-aggregating substance in the platelet called thromboxane A2 (TxA2) which is a potent platelet aggregating and releasing agent. The action of ASA is illustrated in Figure 1 below, together with a normal tracing for comparison:

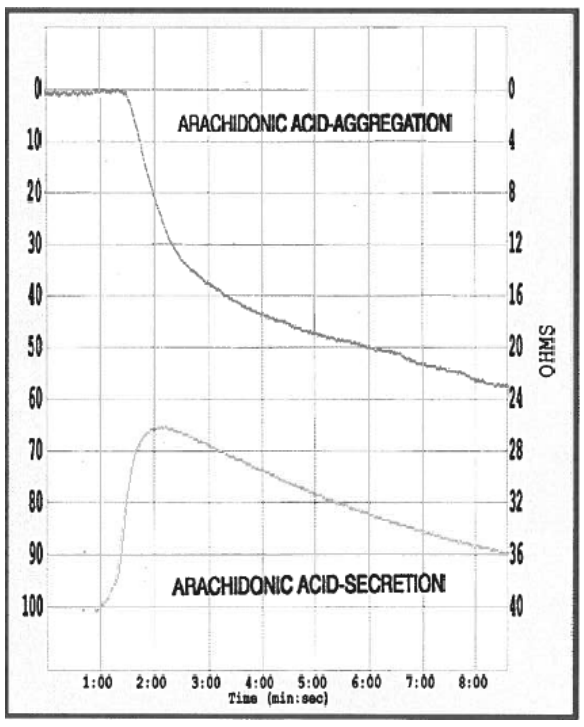

Figure 1a: Normal Arachidonic acid aggregation and secretion.

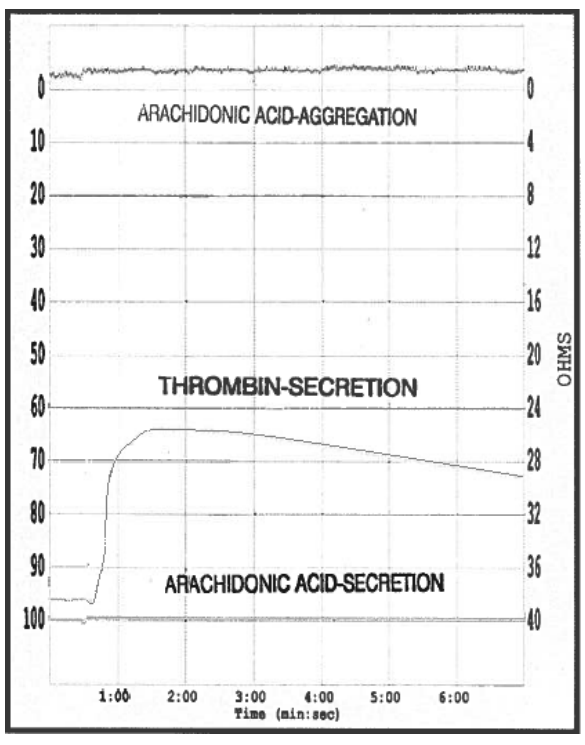

Figure 1b: ASA Inhibition with no arachidonic induced acid aggregation or secretion. Platelets are still reactive to thrombin.

About 35 years ago, a new drug called ticlopidine (Ticlid) was introduced as a platelet inhibitor. This drug inhibited one of the two ADP receptors on the platelet surface (P2Y12 receptor). Soon after, it became apparent that ticlopidine caused a rare severe blood disorder called thrombotic thrombocytopenia purpura and was replaced by a new drug called clopidogrel (Plavix). Clopidogrel was shown to be effective in preventing ischemic strokes and arterial stent thrombosis and has come into common use. Since up to one third of patients show clopidogrel resistance (sometimes termed high on treatment reactivity) two other drugs, prasugrel (Effient) and ticagrelor (Brilinta), have become popular with neurologists and cardiologists. It is important to know which drug the patient is taking because "reversal" using platelet transfusion is not necessary for clopidogrel resistant patients, is possible with clopidogrel responsive patient but may require 1-2 doses, is more difficult with prasugrel and is an exercise in futility with ticagrelor. The effect of these anti-P2Y12 drugs on aggregation and secretion is shown in Figure 2.

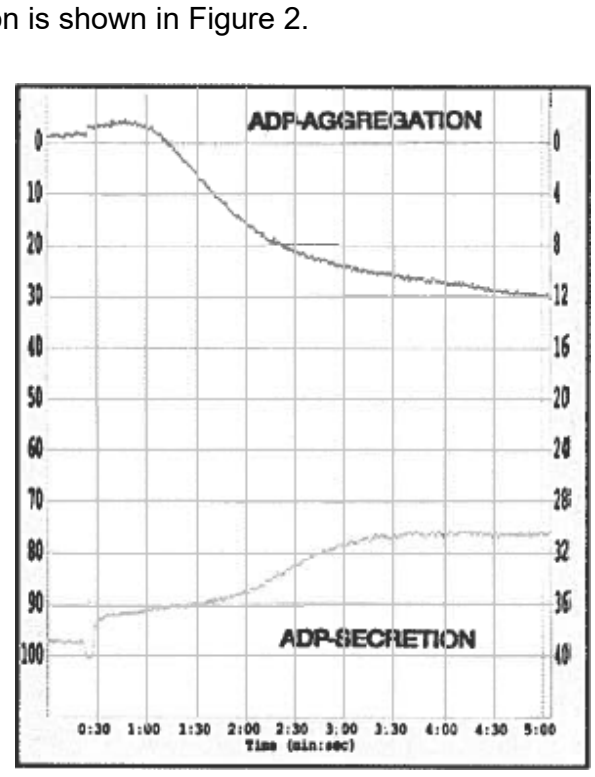

Figure 2a: Normal aggregation and secretion with ADP agonist.

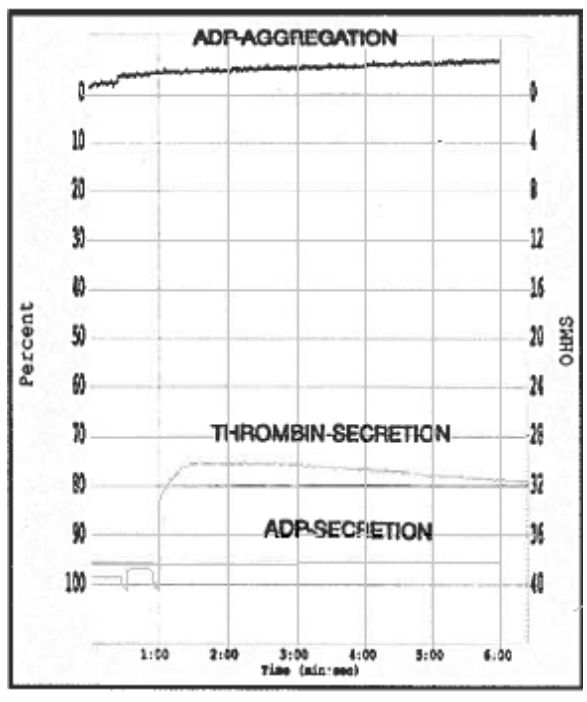

Figure 2b: Clopidogrel effect with P2Y12 inhibition showing the absence of aggregation and secretion. Secretion to thrombin is still retained.

These drugs can also be tested using a point of care device called the VerifyNow which measures aggregation in PRU or platelet reactive units. Normal is > 195 PRU and patients on an anti-P2Y12 drug will have a PRU result typically 50-150. This is illustrated below.

Platelet Transfusion for Patients on Anti-Platelet Therapy Who Require an Urgent Invasive Procedure or Who Are Actively Bleeding

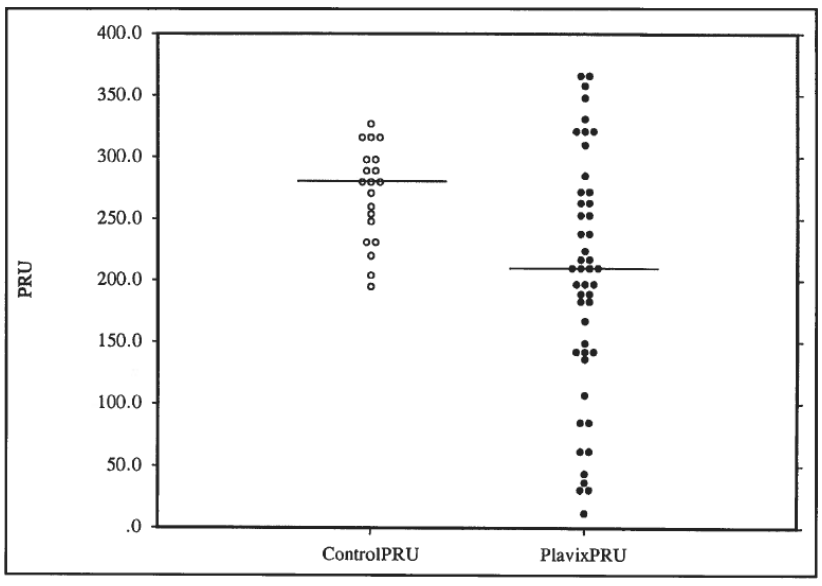

Figure 3: Plavix effect on aggregation in platelet reactive units (PRU). The horizontal bars indicate the median PRU.

Note that about 1/3 of the patients on clopidogrel show results within normal (> 195 PRUs)

There are other anti-platelet drugs such as cilostazol (Pletal- an inhibitor of phosphodiesterase which increases cAMP levels in platelets), vorapaxar (Zontivity- a PAR receptor inhibitor) and dipyridamole (Persantine- PGE inhibitor and adenosine re-uptake inhibition) but nothing is known about their reversal.

The use of platelet transfusions to reverse anti platelet therapy for patients on APA typically ASA and an anti-P2Y12 agent is one of the more difficult areas of platelet transfusion therapy as there is great heterogeneity in the clinical situation and minimal high quality clinical data.

There is Heterogeneity on the patient side:

1. The type of antiplatelet agent: Aspirin alone (monotherapy) or aspirin plus a specific agent (clopidogrel, prasugrel or ticagrelor).
2. Time interval since the last oral dose.
3. Organ involved with bleeding or invasive procedure (GI tract, oral/upper respiratory, central nervous system) and the extent (Grade) of bleeding.
4. If bleeding, whether spontaneous or provoked (traumatic).
5. Specific site within organ (for example for intracranial bleeding, whether subdural, intracerebral, or subarachnoid).

Heterogeneity on the product or platelet side:

1. What dose should be used and what about ABO compatible?
2. What is the timing of any transfusion related to any invasive procedure?

The role of hemostatic adjuncts:

1. DDAVP
2. Tranexamic acid

The Role of point of care testing to drive the decision or timing of platelet transfusion

1. VerifyNow device
2. PFA-100

<u>In the absence of high-quality data, recommendations are as follows:</u>

<u>Non-bleeding patient requiring an urgent procedure:</u>

Patients on ASA only: DDAVP infusion 4 uG/Kg in 50 mls saline over 20 minutes pre-surgery.

Patients on clopidogrel or prasugrel: < 6 hours since drug administration: DDAVP as above; > 6 hours since last administration: for clopidogrel, perform VerifyNow test: if PRU < 195 units, 1- 2 doses (AEU) of platelets, as platelet inventory allows, 1-2 hours pre-operatively. Prasugrel: 1-2 doses (AEU) of platelets, as platelet inventory allows, 1-2 hours pre-operatively; Ticagrelor: DDAVP only unless > 24 hours post last dose, in which case platelet given as above. Tranexamic acid: 1-2 G bolus followed by 1 G in 250mls saline as an 8-hour infusion for 24 hours can be considered on a case-by-case basis.

<u>Patient with clinically relevant bleeding (WHO Grade II- IV):</u>

<u>Spontaneous bleeding:</u> Patients taking ASA only or DAPT: No platelet transfusion. Upper aerodigestive- local measures and tranexamic acid only; Gastro-intestinal bleeding- proton pump inhibitors and therapeutic endoscopy.

<u>Intracranial spontaneous bleeding:</u> DDAVP or TxA on a case-by-case basis. Platelet transfusion (1-2 AEU) for spontaneous ICH *only if a neurosurgical intervention* is about to be performed and adequate time has elapsed for partial drug/metabolite clearance- > 6 hours for clopidogrel and prasugrel; > 24 hours for ticagrelor. The futility of platelet transfusions is shown in a patient who has an intracerebral bleed who was on ticagrelor and received 4 doses (AEU) of platelets with no response. See figures 4 and 5 below.

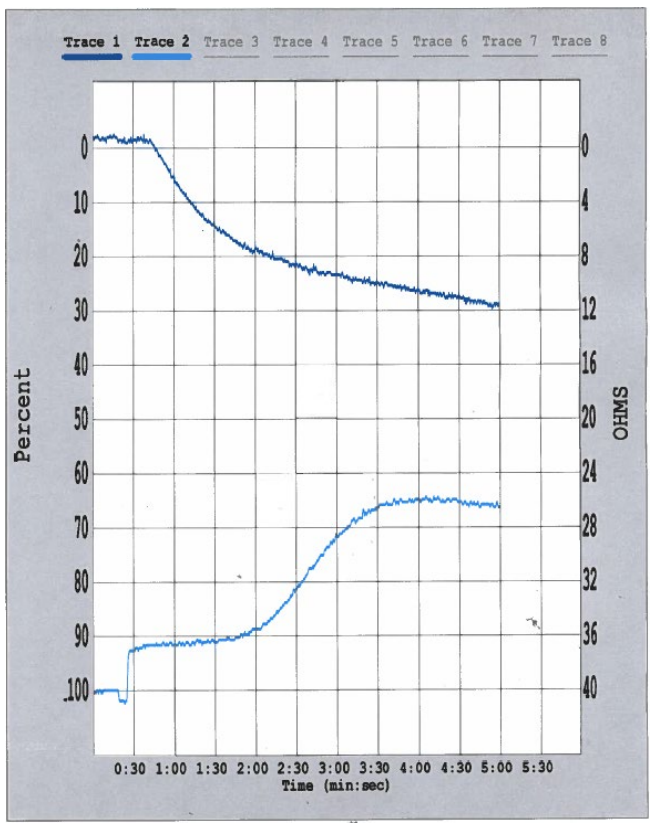

Figure 4: Normal platelet aggregation with ADP Agonist

Platelet Transfusion for Patients on Anti-Platelet Therapy Who Require an Urgent Invasive Procedure or Who Are Actively Bleeding

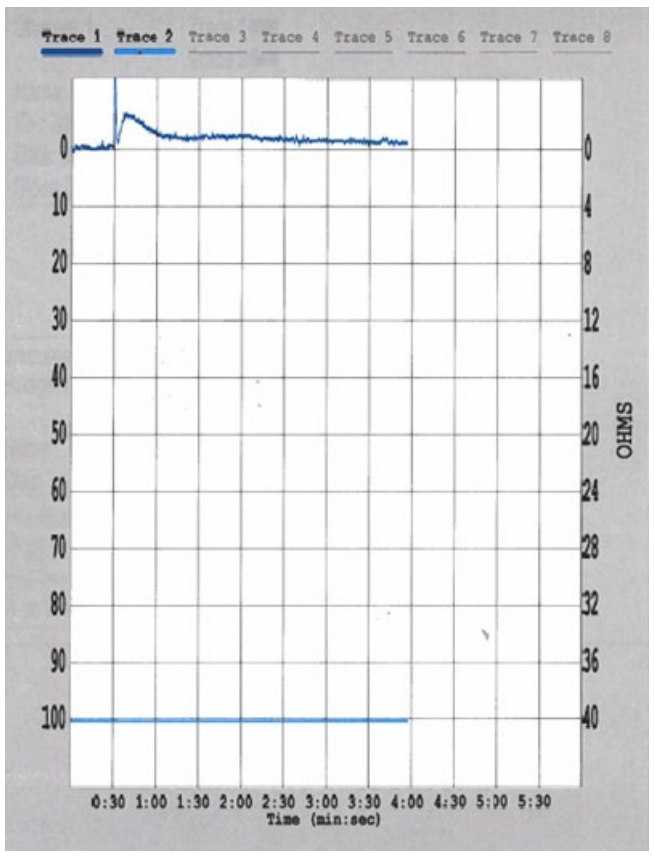

Figure 5a: Patient with intracerebral bleed on Ticagrelor. Platelet aggregation with ADP agonist after 2 doses of apheresis platelets.

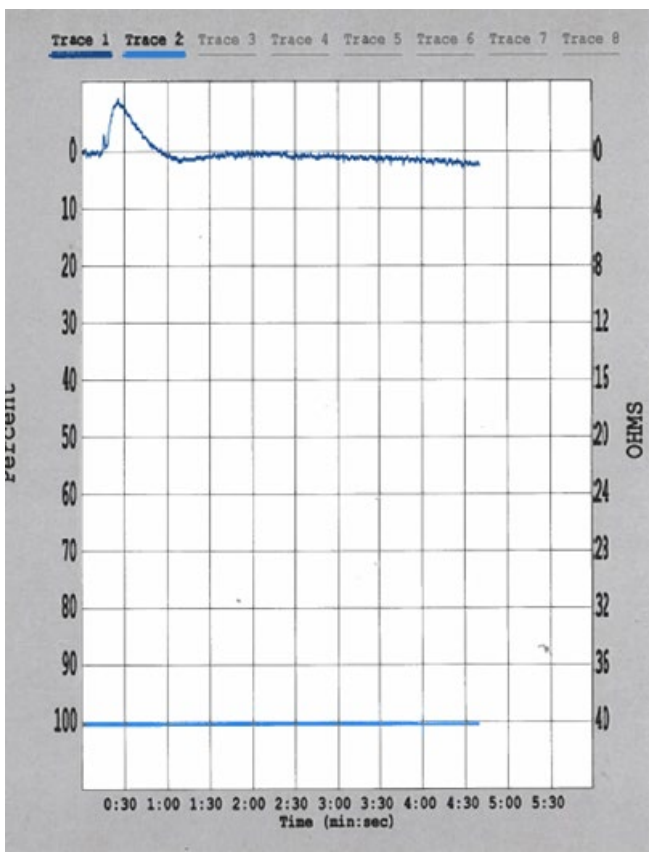

Figure 5b: Platelet aggregation for same patient 2 hours later, after receiving a total of 4 doses (AEU) of platelets. The lack of aggregation and secretion response to ADP is evident, emphasizing the futility of platelet transfusion in this context.

Provoked bleeding such as trauma: ASA only or DAPT:

1. No intracranial bleeding: clopidogrel only- Consider VerifyNow testing. If PRU < 195 units, 1- 2 doses (AEU) of platelets, as platelet inventory allows. Otherwise, platelet transfusion (1-2 AEU) if adequate time has elapsed for partial drug/metabolite clearance- > 6 hours for clopidogrel and prasugrel; > 24 hours for ticagrelor.
2. Intracranial bleeding: (TBI) Platelet transfusion (1-2 AEU) if a neurosurgical intervention is about to be performed and adequate time has elapsed for partial drug/metabolite clearance- > 6 hours for clopidogrel and prasugrel; > 24 hours for ticagrelor.
   ICH with either subdural or intracerebral bleeding, platelet transfusion as above. Note subarachnoid hemorrhage: No platelet transfusion.

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Bloodless Medicine and Surgery and Patient Blood Management in Pediatrics: A Beacon of Hope in the Asian Continent

Bloodless medicine and surgery is a dynamic arena, where discovery, innovation, determination, courage and integrity thrive. The groundwork laid by countless pioneers has greatly contributed to improving and saving lives. One noteworthy example in pediatric medicine is the Blalock-Taussig (BT) procedure pioneered in 1944 by Alfred Blalock, MD, Helen Taussig, MD and Vivien Thomas, L.L.D.[1] The procedure marked the dawn of heart surgery and opened the door to performing invasive procedures in children with tetralogy of Fallot, thus giving hope to all patients with acquired heart diseases.1 It also set the stage to venture into bloodless medicine and surgery (BMS) and patient blood management (PBM) services in the pediatric population, whereby determined efforts, which may include going beyond popular opinion is crucial in bringing good outcomes and hope to many.

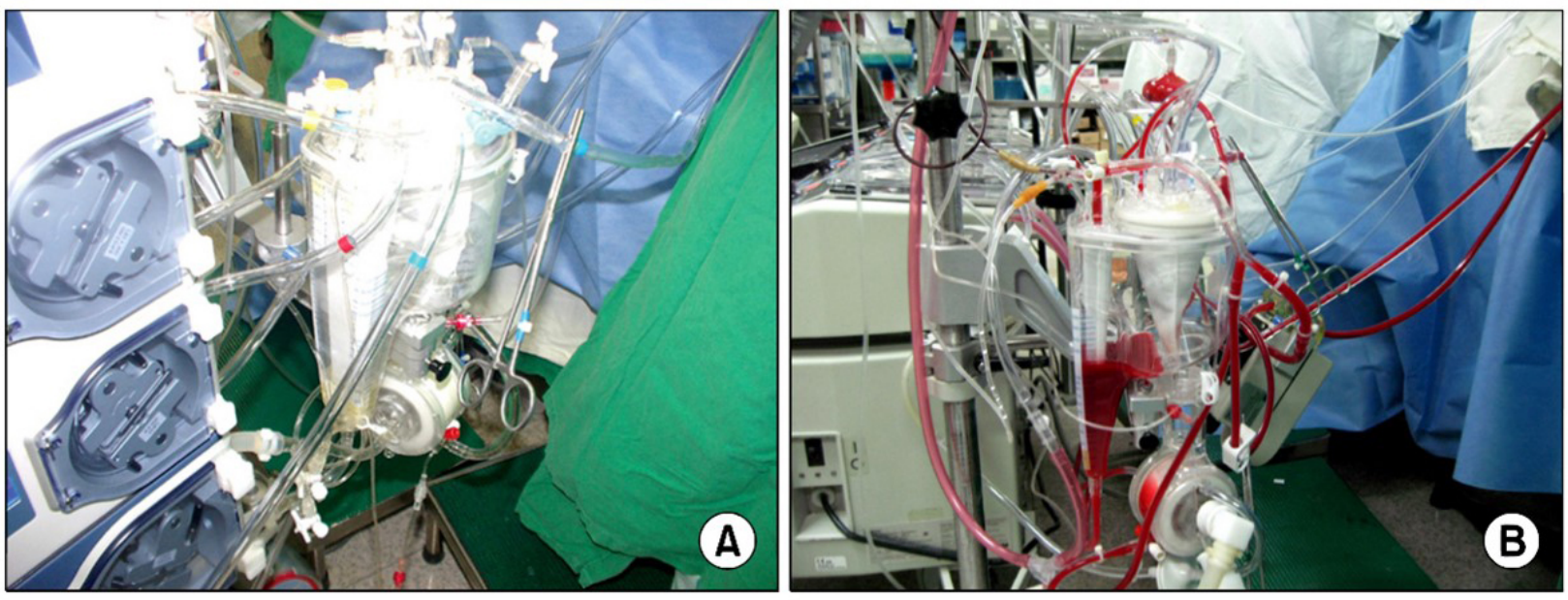
The following examples found in a few Asian countries illustrate how pioneers in BMS/PBM are helping children enjoy longer, healthier lives.

South Korea

South Korea has numerous advanced, well-established BMS/PBM centers. Its first center was established in Sejong General Hospital in Bucheon in 1986 under the direction of Lee JongHyun, MD, an experienced consultant, cardiac anesthetist, and pain specialist.

Among its many young patients was a 6-month-old, weighing 5 kg, with tetralogy of Fallot (TOF). In 2019, the infant underwent complete correction of the defects. The strategies crucial to surgery included: pre-operative intravenous iron and subcutaneous erythropoietin (EPO); skilled and meticulous surgery; and small priming volume for cardiopulmonary bypass (CPB) through mini-circuits. The strategies proved successful as the infant was discharged at post-operative day 7. [2]

Another example was a 2011 surgery for complex congenital heart disease in a boy less than 5 years old, weighing 15.1 kg. The child received a BT shunt at 1 month of age. Later he underwent right ventricular outflow tract reconstruction, right ventricular muscle partial removal, primary foramen suturing, arteriosus separation, and right pulmonary artery angioplasty using bovine pericardium. These were done without allogeneic blood transfusion (ABT). At 4 years and 10 months of age, he had conduit stenosis which required catheter replacement; his measured body surface area was 0.63 m2. Some of the strategies utilized pre-operative administration of EPO and iron to increase red blood cell mass, cell salvage modified ultrafiltration, and vacuum-assisted venous drainage to minimize circuit size and prime volume. [3]



(A) This heart-lung machine is used for minimized priming volume method. Note the vertical alignment of pump heads. (B) This heart-lung machine is used for conventional cardio-pulmonary method. Note the horizontal and ground based alignment of pump heads. (Picture reprinted from article originally appearing in Anesth Pain Med 2011; 6: 150~153)

Japan

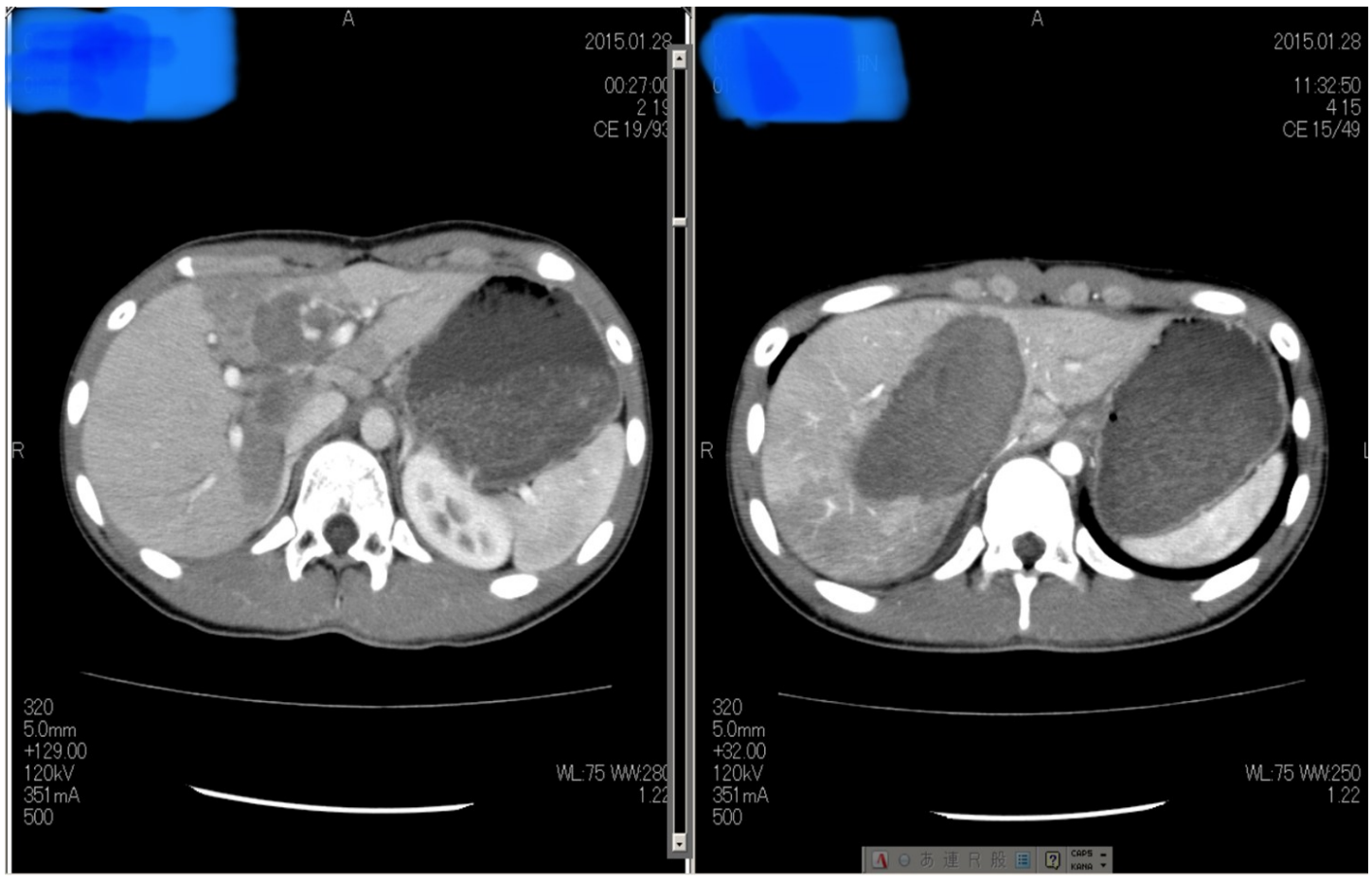
In October 2019, Japan hosted the 5th Asia-Pacific Society for Patient Blood Management (ASPBM) symposium, which promoted the benefits of PBM, along with support from fellow Asian colleagues and leaders from the Society for the Advancement of Patient Blood Management (SABM). While BMS/PBM is yet to take a strong hold in Japan, it has many skillful pioneers. Shunji Kawamoto, MD, an experienced surgeon and instructor of high-levelled hepatobiliary pancreatic surgery, has been practicing bloodless medicine and surgery since 1996.

It is a challenge for clinicians to comfortably operate without ABT, especially for major abdominal surgeries. Clinicians find it even more challenging when handling trauma cases.

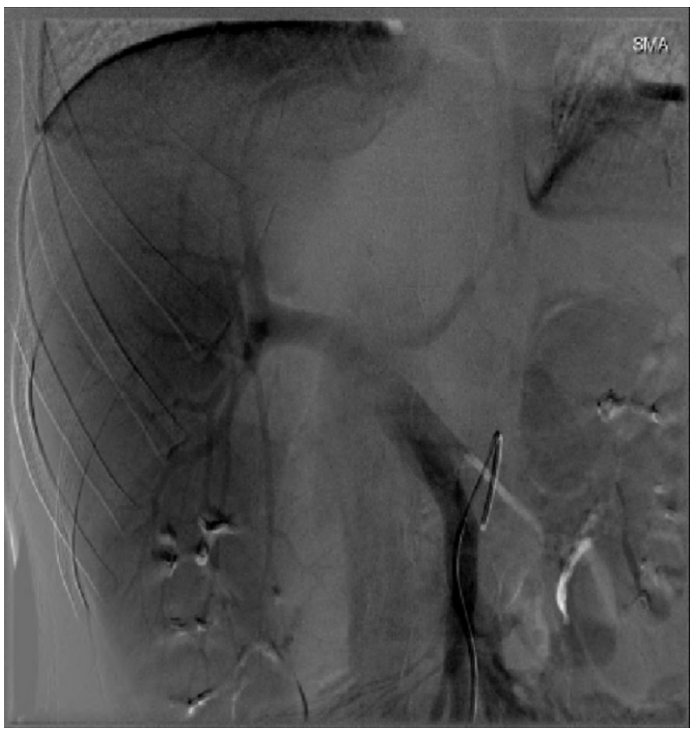
Bloodless Medicine and Surgery and Patient Blood Management in Pediatrics: A Beacon of Hope in the Asian Continent

One successful case took place in January 2015 at Fukuoka Tokushukai Hospital. A14-year-old boy sustained an injury to his liver when he fell off his bike and hit himself against its handle. He presented to the emergency room with abdominal pain, and the CAT scan revealed a hematoma in the left lobe of his liver. A repeat CAT scan showed that the hematoma was expanding and pressing on the right Glisson. His hemoglobin dropped from 13.5 g/dL on initial presentation to 11.6 g/dL on the next day. The BMS team ordered a CAT scan with contrast which revealed extravasation of the intrahepatic left portal vein, which was causing the hematoma and worsening anemia. [4]

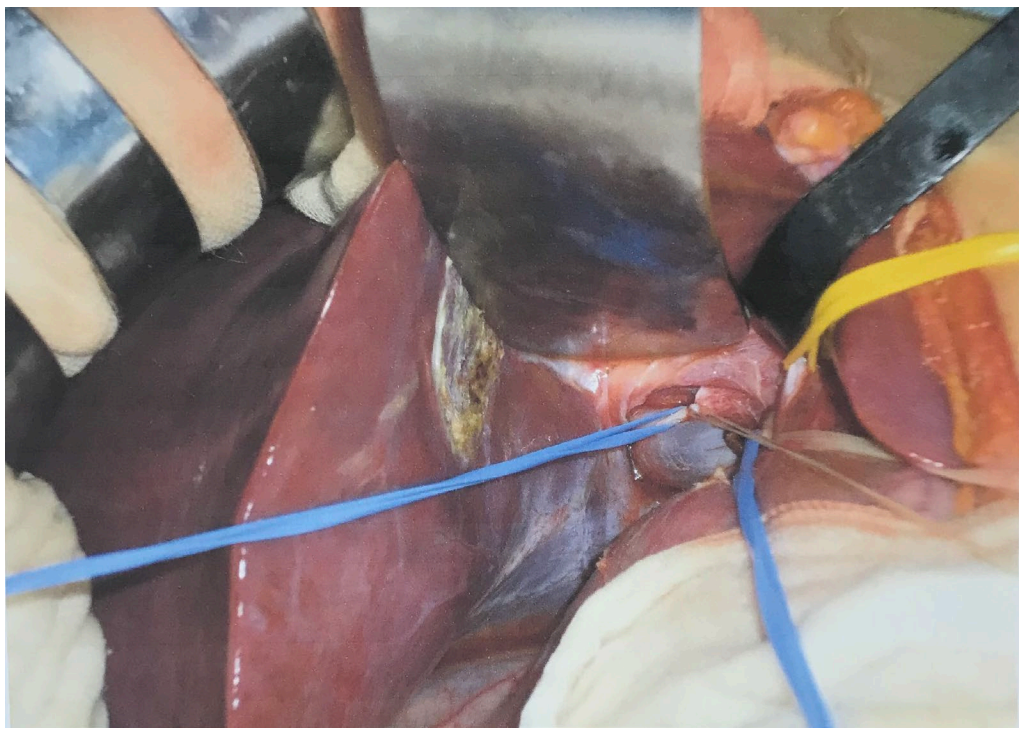
The patient promptly went into surgery, where celiotomy and ligation of the left portal vein staved off the inevitable rupture of the liver and massive abdominal bleeding, which would have been fatal. Using cell salvage, surgery began as the hepatic hilum was approached and the isolated left portal vein was ligated. Post-operative CAT scans showed ongoing reduction of the hematoma in his liver. Hemoglobin at post-operative day 10 was 12.4g/dL, and the patient has continued to do well. [4]



Expansion of bleed noted over few hours



Extravasation from left portal vein



Operative finding upon ligating the left portal vein.

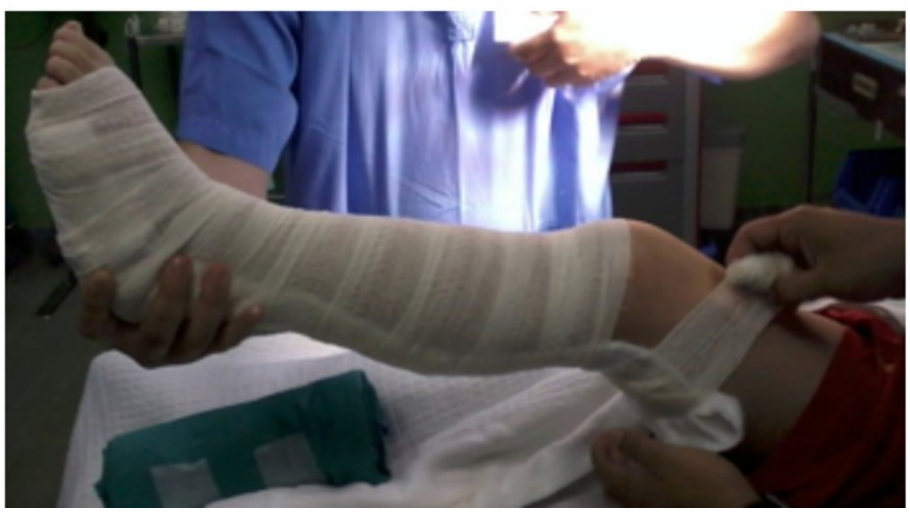
Bloodless Medicine and Surgery and Patient Blood Management in Pediatrics: A Beacon of Hope in the Asian Continent

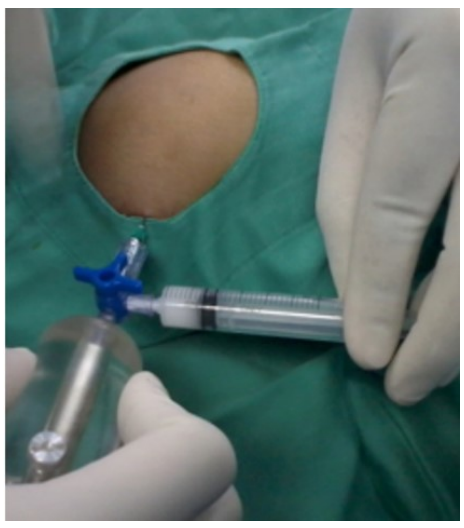
Malaysia

Malaysia's diversity is also seen in the country's variable acceptance of BMS/PBM—its BMS/PBM pioneers also come from various backgrounds. Among them are Pau Kiew Kong, MD, senior consultant cardiothoracic surgeon from the National Heart Institute and Jameela Sathar, MD, senior consultant hematologist at Ampang Hospital. Their determination allows adults and children to experience the superior benefits of BMS/PBM.

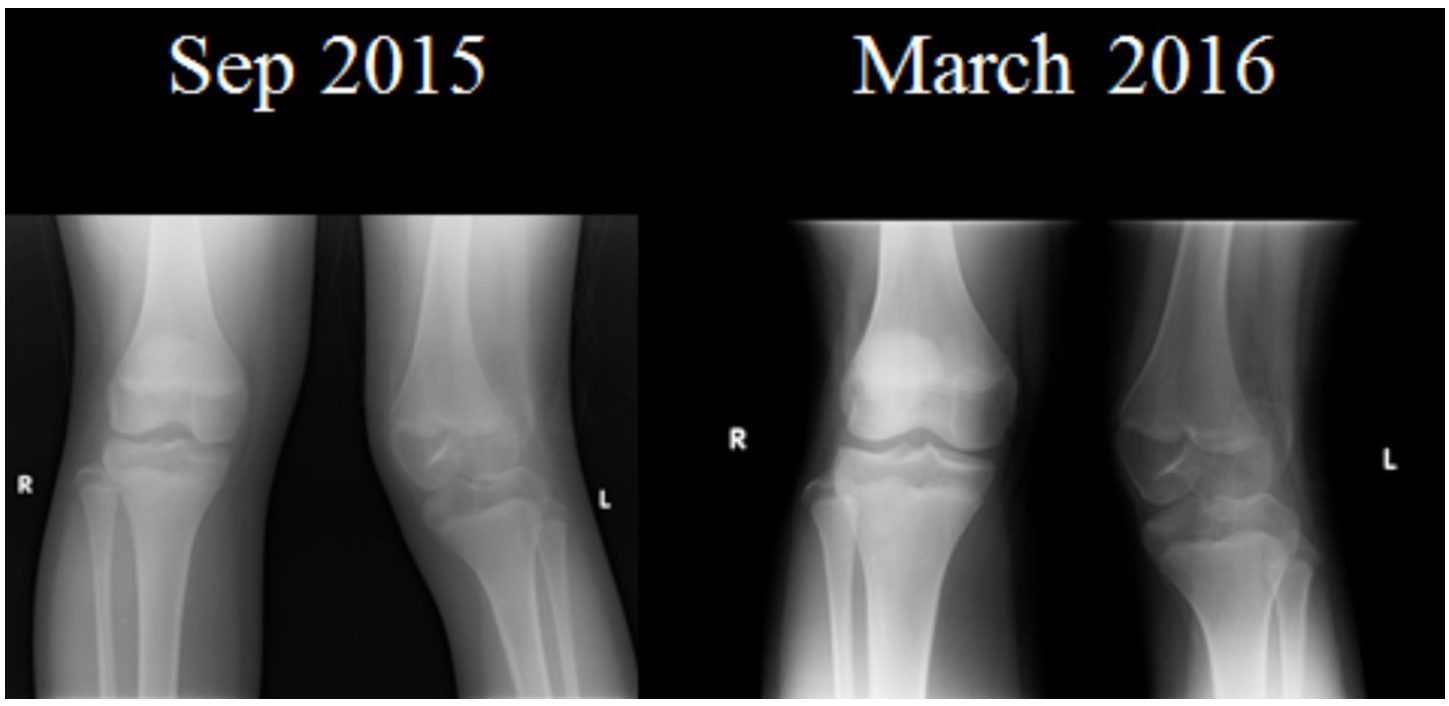
For example, a girl with a large ventricular septal defect was first seen in July 2018 at age 5 months. With a hemoglobin of 11.1 g/dL, she was started on oral iron and EPO, which raised the hemoglobin to 12.1 g/dL within a month. A year later in December 2019, she was ready for surgery. She was treated with oral iron and EPO during the four weeks prior to her procedure and reached a hemoglobin of 12.9 g/dL. Intraoperative strategies included meticulous surgery, using the smallest available circuits, and placing the CPB machine closer to the patient to reduce priming volume. Intraoperative and post-operative blood loss was minimal. At post-operative day 1, her hemoglobin was 9.6 g/dL due to hemodilution from CPB, but it improved after diuretics. She was discharged at post-operative day 4 with a hemoglobin of 11.2 g/dL and continued treatment with oral iron and folic acid for another 6 weeks. [5]

For children with hemophilia, a multidisciplinary team must be involved, as quality of life and minimal disability requires a long-term medical and surgical approach. Consider the case of a boy with severe hemophilia A. He had at least 5 intracranial bleeds between the ages of 4 months and 6 years. He was initially treated with on-demand Factor VIII replacement. In 2006, when he was 2.5 years old, he was diagnosed with having an inhibitor. He also had episodes of haemarrthrosis knees, iliopsoas haematoma, upper gastrointestinal bleed, and hematuria. All bleeds and procedures were treated with Factor VIIa coverage, but the chronic bleeds into joints left him with deformity and rendered him unable to walk. In 2012, radiosynovectomy was done to reduce bleeding into the joints. After subsequent immune tolerance induction, he was ready for definitive surgical correction. In 2015, he underwent a successful guided growth surgery, called percutaneous hemiepiphysiodesis, on the left distal femur. He was under the care of the hematology and the orthopaedic teams in Ampang hospital, led by visiting pediatric orthopaedic surgeon, Sharaf Ibrahim, MD, of Hospital University Kebangsaan Malaysia. [6]





Radiosynovectomy using radioisotope Yittrium 90. The procedure kills synovium, thus reducing bleeds.



Progress after growth guided surgery.

Bloodless Medicine and Surgery and Patient Blood Management in Pediatrics: A Beacon of Hope in the Asian Continent

Other Asian Countries

Some centers in Asia offer a beacon of hope to patients who must travel great distances to seek treatment without blood. One such place is the Mazumdar Shaw Cancer Center in Bangalore, India. A family from Tanzania moved to Bangalore in late 2018, to seek BMS treatment for their 4-year-old son. He was diagnosed with stage 4 abdominal cancer and underwent surgery in July 2019 with Sunil Bhat, MD, to remove the tumour. In September 2019, he received a bone marrow transplant; both procedures were performed without ABT and he recovered well. [7]

In the Philippines, when logistics and facilities cannot offer common BMS/ PBM treatments such as IV iron and/or EPO, patients are often treated by local BMS/PBM champions, such as Angelina Gapay, MD, senior consultant pediatric anaesthesiologist and Danilo Kuizon, MD, senior consultant interventional cardiologist. These two physicians have more than 20 years of experience providing treatment even where there are minimal resources.

For example, a petite 7-year-old patient was admitted to the public hospital with dengue hemorrhagic fever. The patient bled down to a hemoglobin of 3.0 g/dL but was discharged because blood was not an option, and the hospital didn't offer BMS services. Another paediatrician stepped in to help the child, who was now experiencing failure symptoms. She was managed supportively, given oral iron daily and good nutrition, and improved after several days. [8]

Child suffering from cancer gets bloodless transplant

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Bengaluru: A cancer patient requiring bone marrow transplant can become a complicated case if he or she belongs to Jehovah's Witnesses denomination as blood transfusion is a taboo for the community even during life-threatening conditions.

However, a four-year-old

Four-year-old Ittai James Moshi from Tanzania, who was suffering from fourth stage abdominal cancer and belonged to Jehovah's Witnesses, underwent the transplant in last September and is recovering

for his treatment. "In way without blood transfu-

Newspaper article January 2020

These examples give a glimpse of how BMS/PBM is possible and beneficial, providing great potential for the pediatric population. Managing a child with anemia solely based on a number (i.e., transfusion trigger/ threshold) is actually a disservice to the child and family, as ABT is known to cause adverse outcomes for adults and children. "Do not just think of the number (Hb), but also the number of years ahead a child has" said Angelina Gapay, MD. These examples emphasize the need for careful planning, meticulous surgery, being alert to danger signs and promptly arresting any bleeding. Perhaps equally important are teamwork, innovation, respect, patience and persistence. As it is well known, these are valuable skill sets and qualities, much like what the predecessors who led the way in medicine had—something that should be pursued.

Contributor: Ananthi Krishnamoorthy, MD

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5. Case details courtesy of Pau K.K, M.D.
6. Case details courtesy of Sathar. J, M.D.
7. Times of India news article 16 January 2020
8. Case details courtesy of Gapay. A, M.D.

Transfusion-Free Liver Transplant
Keck Medical Center
University of Southern California
Los Angeles, CA, USA

There's an old English proverb that says: "Necessity is the mother of invention." In many cases, the primary force for innovation is an unmet need. At Keck Medical Center of USC, our approach to Transfusion-free Liver Transplants (TFLT) was born out of an unmet need that has continued to grow over time. Since the summer of 1999, we have been accepting referrals of patients who suffer from end-stage liver disease and have no other treatment alternatives except TFLT. From a foundation of meticulous surgical technique to minimize blood loss, we incorporate innovations in anesthesia and blood level augmentation to make transfusion-free surgery a safe option for these patients who are typically denied life-saving care. However, most of the medical community is unaware that TFLT is even an option for patients and even fewer understand the need for early referral to the transplant center that is crucial for a successful outcome. It is our hope that this article will elucidate some of the nuances in caring for this patient population and increase the number of patients referred for this life-saving operation.

It is important to understand that our selection criteria are more limiting than those utilized for transfusion-eligible patients, as some surgical challenges cannot be safely overcome without blood transfusions. Generally, TFLT requires patients to be earlier in the disease process (i.e. lower MELD score). Most patients will also require a medical regimen to augment their red blood cell levels and platelet counts prior to surgery. During surgery, we utilize acute normovolemic hemodilution (ANH), in which approximately four units of whole blood are drained into a closed system and replaced with colloid solution for the duration of the procedure. This technique allows us to minimize the number of red blood cells lost with each milliliter of bleeding and allows the anesthesiologist to quickly return the blood in the event of hemodynamically significant blood loss. There are a range of synthetic or fractionated blood product alternatives (i.e. albumin) that are individually reviewed with each patient prior to the procedure but generally must be accepted in order to safely proceed.

From 2005 to 2019, less than 30% of evaluated TF patients and less than 17% of all referred TF patients were accepted for listing. Our center received 118 referrals for TFLT. From these referrals, 36 patients were accepted for further evaluation. The most common reasons for denial at referral were complications of cirrhosis, such as ascites, peritonitis, encephalopathy, variceal bleed, to preclude safe TFLT. Of those evaluated, 20 patients were listed for LT, with 2 listed individuals dying prior to transplant. Twelve patients underwent LT, 10 were living donor LT with average MELD 20 at time of LT. Thus, early referral is highly recommended to improve the odds of TFLT. In reality, most transfusion-free patients with cirrhosis are not referred for transplant because of the mistaken belief that this surgery is unavailable. However, these data show that even referred patients are often referred after their disease has progressed beyond the point of safe transfusion-free transplant.

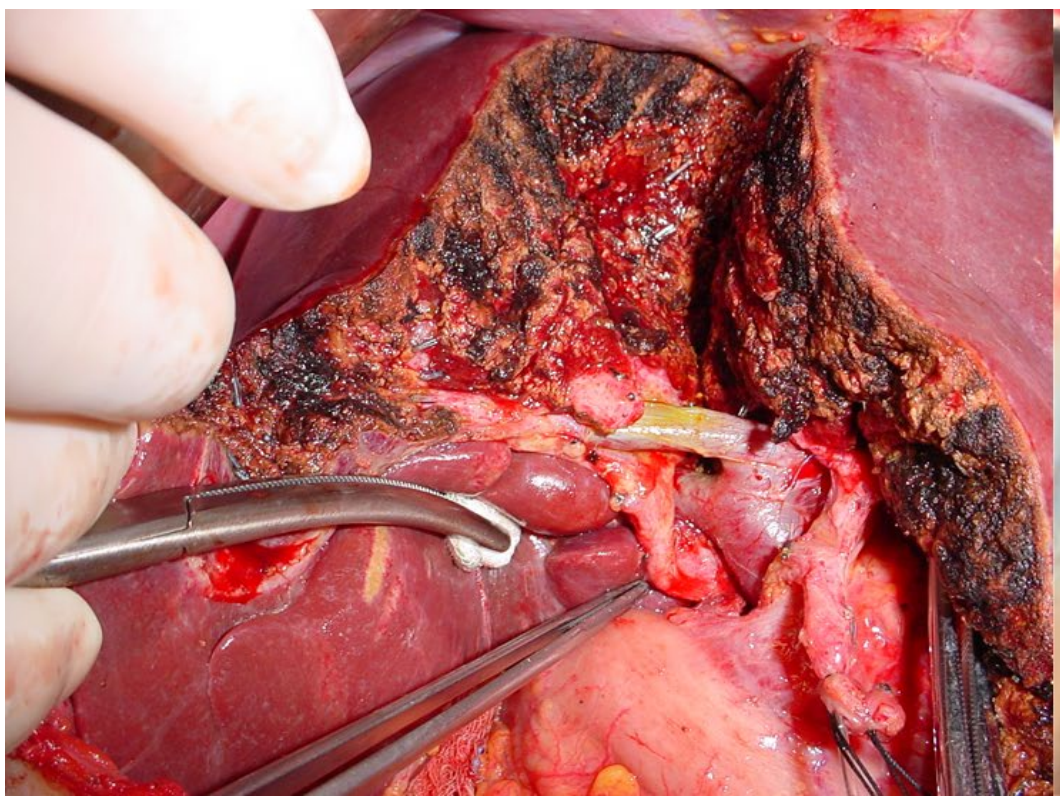


Figure 1A: Photo from a living donor surgery just before the liver is removed.

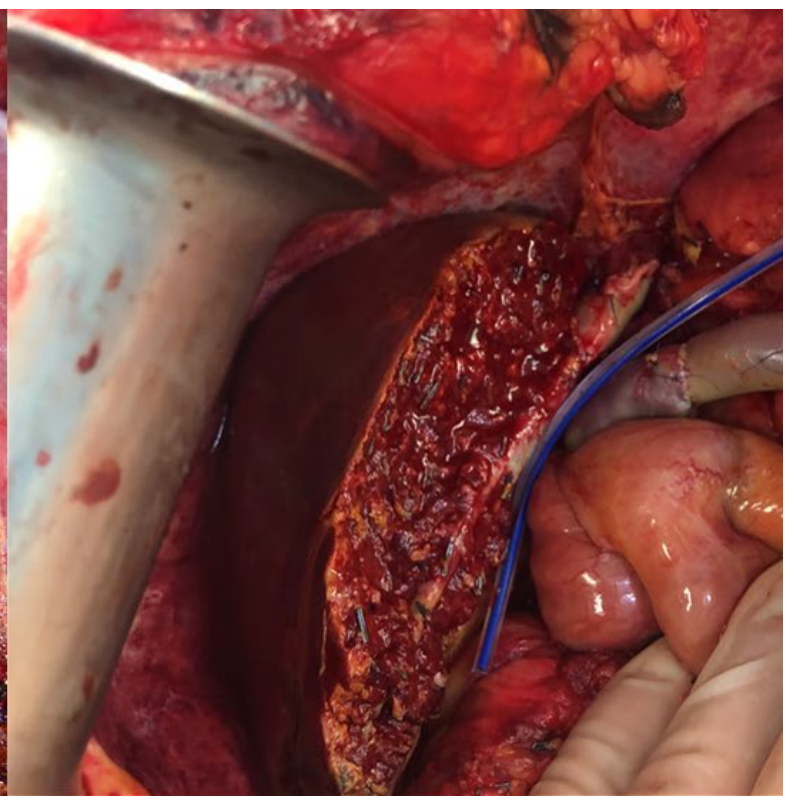


Figure 1B: Photo of a right lobe liver graft after implantation in a liver transplant recipient.

Both surgeries are offered without the need for blood transfusion at Keck Medical Center of USC.

Transfusion-Free Liver Transplant

After early referral, evaluation, listing, and transplant, our patients do well. To date, we have performed 40 TFLTs. Eleven transplants were performed with deceased donor allografts and 29 with living donor allografts. We have experienced two perioperative deaths in deceased donor LT recipients and two hepatic artery thrombosis amongst LDLT recipients requiring subsequent deceased donor liver re-transplant. We have demonstrated a 94%, 1-year post-operative survival, which are outcomes consistent with transfusion-eligible liver transplants recipients. Thus, we are confident in offering TFLT to the Jehovah's Witness community.

Organ shortage is common and rampant throughout the country, but the shortage is even more acute in our geographic region. Because of this trend, the patients competing for organs are higher acuity with worsening disease severity. Although it is possible to perform successful liver transplantation in extremely ill patients, it is nearly impossible in an individual who cannot accept transfusion of blood products. Thus, there is a growing gap between the disease severity (i.e. MELD score) of patients who can safely undergo TFLT and the MELD score in which a deceased donor organ would be available. Therefore, most patients will need to be able to identify a living donor in order to undergo a successful TFLT.

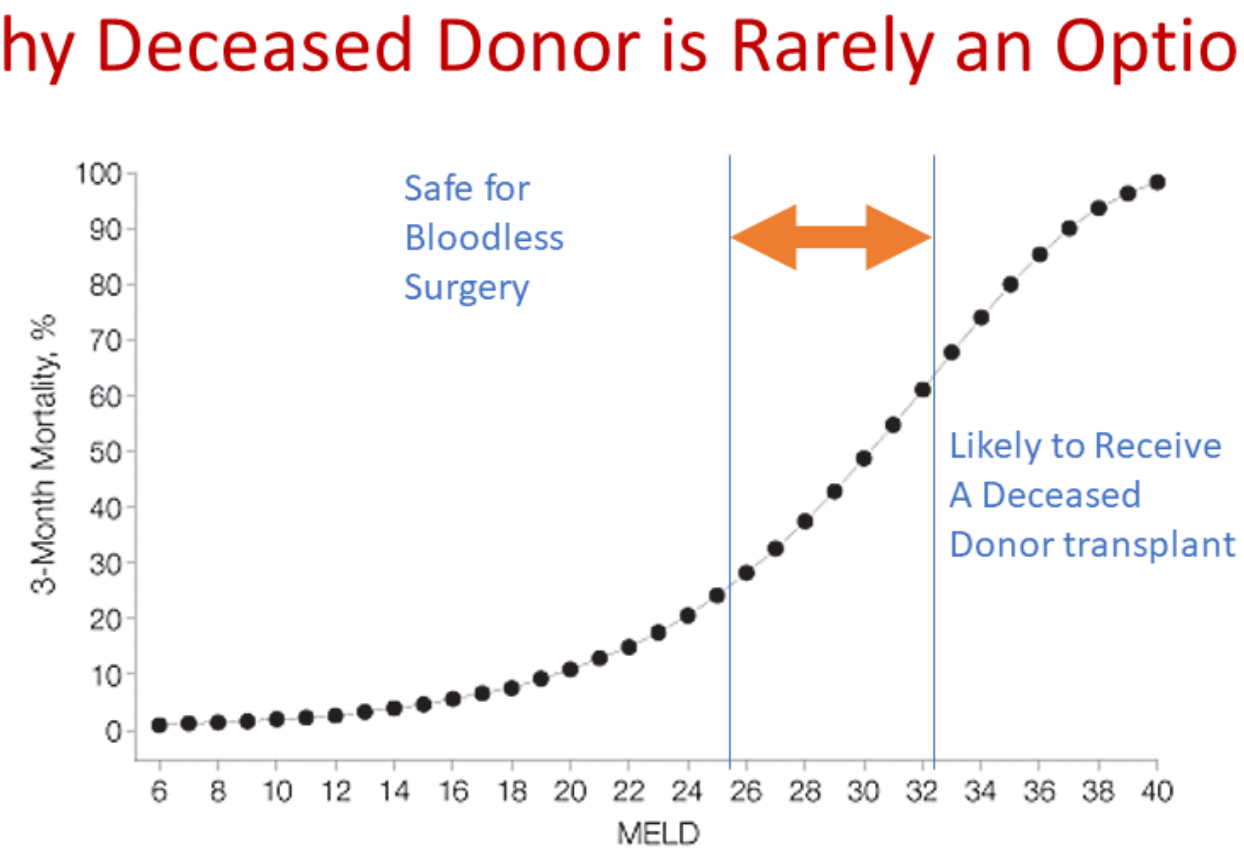


Figure 2: A graphic representation of the gap between patients who are safe to undergo transfusion free liver transplant and those who are likely to receive a deceased donor liver offer. Because of this trend, almost all transfusion free liver transplant recipients must undergo living donor liver transplant.

The dilemma for many transfusion-free recipients, especially those of the Jehovah's Witness faith, is identifying the most appropriate donor. Eligible donors are directed (known to the recipient), non-directed (anonymous to the recipient), transfusion-eligible, or transfusion-free. Over the long history of the program, we have successfully performed TFLT utilizing donors who are transfusion-free except during an eight-year hiatus from 2010 to 2018. During that time period, only donors who accepted blood products were deemed eligible. This limitation deterred transfusion-free recipients from undergoing LDLT and likely indirectly worsened waitlist mortality. Since most available or interested donors come from within the recipients' family, or within their community who are transfusion-free, access to LDLT improved after 2018 when we re-established the criteria for transfusion-free donors.

The oft-repeated phrase "knowledge is power" reminds us that only by spreading the knowledge of TFLT, do we have the power to save lives and offer hope in this otherwise desperate medical community.

Contributors: Helen Han, MD; Aaron Ahearn, MD; Yuri Genyk, MD; Jeffrey Kahn, MD; Randy Henderson

Patient Blood Management in Western Australia: History and Future Directions

In 2008 the Western Australia Department of Health initiated a five-year project to implement a comprehensive patient blood management (PBM) program. They did this to improve the safety and quality of patient care while reducing unnecessary costs. Interestingly at the time Western Australia had one of the lowest rates of blood units issued per capita in the developed world. Despite this, Western Australia proved to be the ideal starting point for this enormous project because of its rich history.

Early Beginnings

As early as the 1980s Prof. James Isbister identified the need for a paradigm shift in transfusion practice,[1,2] a bold call that proved to be incredibly insightful. Prof. Isbister later proposed the term PBM to identify the shift from a product focus to a patient focus, with transfusion not being the default treatment for anemia and blood loss.[3]

In 1990 Australia's first comprehensive blood conservation program at Fremantle Kaleeya Hospital in Perth, Western Australia was the practical application of Isbister's call for a paradigm shift.[4] At the time, this Program was one of only three in the world. It adopted a multidisciplinary multimodal perioperative approach which is now recommended as standard care in PBM.[5] This program resulted in substantial reductions in blood utilization with positive patient outcomes.[6] It attracted widespread interest with invitations locally, nationally and internationally to present outcomes and program implementation. A decade later there were over 200 of such hospital-based programs around the globe.[7]

The 2001 Review of the Australian Blood Banking and Plasma Product Sector (also known as the Stephen Review)[8] indicated that real clinician-led change was needed in hospitals. Its recommendations included the need for national safety and quality standards, hospital governance arrangements, engaging clinicians and developing guidelines, partnering with the Australian Council for Safety and Quality in Health Care, and practice in this area to be included in accreditation and national hemovigilance. The Stephen Review became a focal point for change and elements were effectively written into legislation that resulted in the formation of the National Blood Authority with the endorsement of all Australian governments.

The Western Australia State PBM Program (2008-2013)

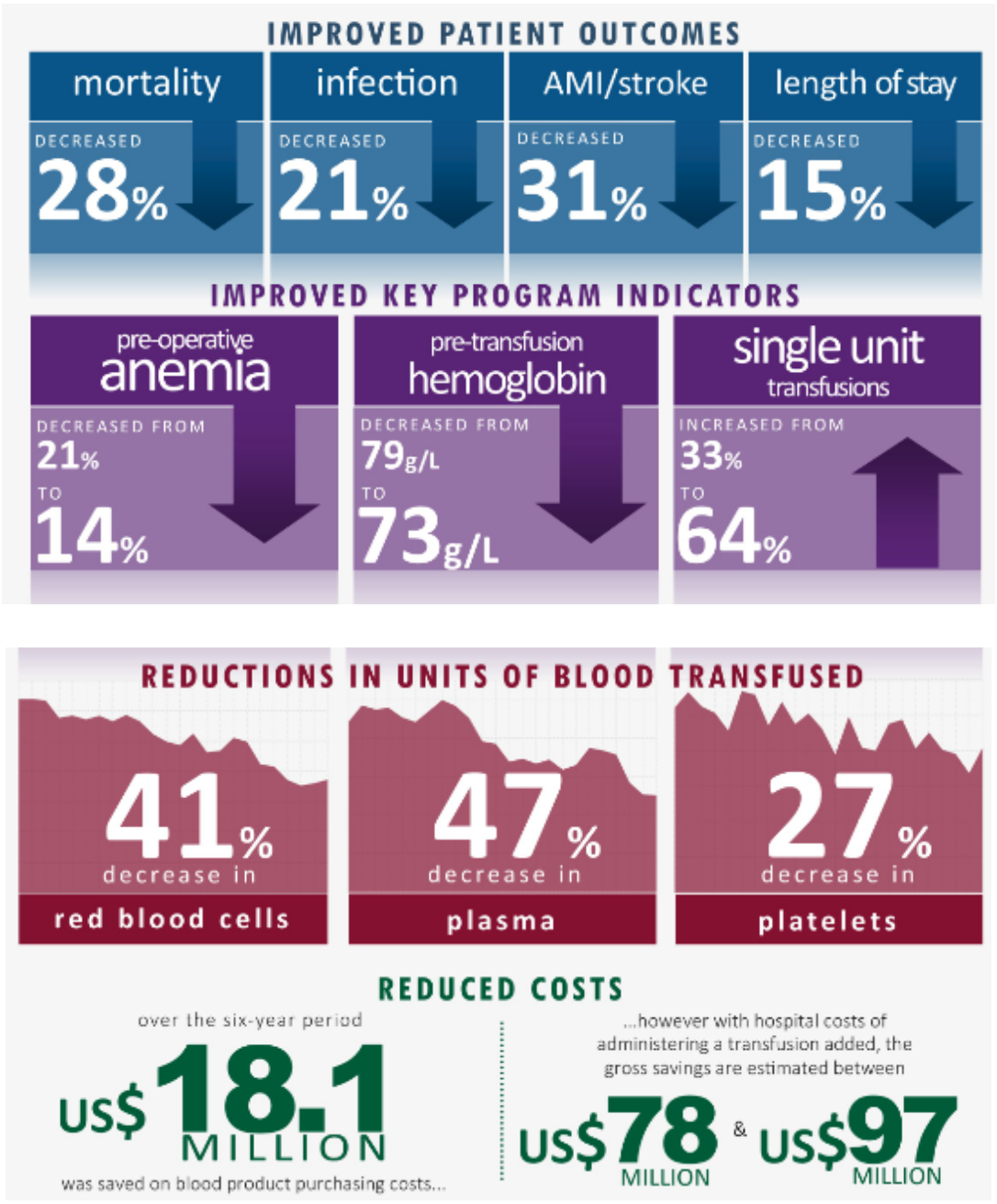
In this context and building on the Fremantle Kaleeya Hospital Program experience and lessons from hospital-based international programs, in 2007 the Western Australia State Health Executive Forum (SHEF) funded the design of the world's first sustainable health-system-wide PBM Program with the aim of improving patient outcomes while reducing costs.[9]

When implementation commenced, Western Australia had the lowest red blood cell (RBC) transfusion rate (issuance per capita) in the developed world. However, total RBC, fresh frozen plasma and platelet units issued to the State were increasing and, based on historical data, projected age distribution, and population and activity increases, it was projected to keep increasing.[9] This had substantial supply and cost implications.[10,11] Additionally, a large body of literature was emerging demonstrating transfusion as a dose-dependent risk factor for adverse patient outcomes.[12,13] Studies also showed that the establishment of hospital-based PBM programs resulted in improved outcomes and reduced costs.[4,14]

With visiting international PBM faculty present, the WA Program was announced to a local 71-member multidisciplinary Clinical Reference Group assembled to secure clinical engagement and leadership.15 With that, multiple implementation strategies commenced, including change (culture change) management.16 At the time, an editorial appeared in the journal Transfusion stating, *"the Government of Western Australia is to be congratulated for realizing the urgency of the matter and their subsequent decision to sustainably implement patient blood management. By their decision and initiative, they are leading the world in the battle against unnecessary erythrocyte transfusions and their burden—financially and in terms of morbidity and mortality."* [17]

In the same year, the National Blood Authority (Australia) commenced project management of developing the world's first evidence-based PBM guidelines.[18] These Guidelines contained an evidence-based recommendation that *"Health-care services should establish a multidisciplinary, multimodal perioperative patient blood management program."*[19] Commenting on these guidelines, authors of an article published in *Transfusion Medicine Reviews* stated, *"This, together with the Western Australian implementation of PBM within its public sector, has made Australia a model for other nations to follow."* [20]

Patient Blood Management in Western Australia: History and Future Directions



Outcomes associated with the Western Australia PBM Program

Did The WA PBM Program Work?

The results of the WA PBM Program were published in 2017, the largest study to date investigating the clinical and economic impact of a PBM program.[16] The study showed that the Program was associated with reduced mortality, hospital acquired complications, hospital length of stay, and transfusion utilisation. Product-acquisition cost savings were US $18 million and an estimated US $78 to 97 million in activity-based product cost savings. The accompanying editorial stated, *"The Western Australia Department of Health should be congratulated for their courageous and visionary decision 10 years ago to support this state-wide PBM program and the local champions for implementing the program for many years. With the current achievements, this program is clearly number one worldwide and as such has set new standards."*[21]

An upward trend in blood issuance rates to the state from 2003-04 was arrested with implementation of the Program and, with the exception of 2016-17, has decreased since, indicating that the culture change generated by the WA PBM Program has been sustained, something anecdotally confirmed by some senior consultants.

Members from the WA PBM Group (from left to right): Angie Monk, Kylie Symons, Kevin Trentino, Hamish Mace, Linda Campbell

Patient Blood Management in Western Australia: History and Future Directions

Birth of the Western Australia Patient Blood Management Group

The initial five-year investment from the Western Australia Department of Health came to an end in 2013, however a number of clinical champions and hospital-based PBM programs remained. These champions needed a forum to share innovations between hospitals and health systems, and it was clear Western Australia needed a group to accommodate the growing requests from organizations across the globe interested in visiting and learning from the Western Australia experience. To fill this gap the Western Australian PBM Group was formed in 2019. The group consists of a steering committee of 12 professionals representing surgery, anaesthesia, nursing, general practice, general medicine, intensive care, haematology, research and data analytics. The group has five themes: Advocacy, Data & Research, Education & Training, Health Service & Benchmarking, and Primary Care, and is part of the Faculty of Health and Medical Sciences at the University of Western Australia. This group provides an important teaching and research role in Western Australia and continues to partner with national and international organizations interested in PBM.

2019 CTEC Conference: PBM – Perioperative and Beyond, featuring presentations from Shannon Farmer, Jeffrey Hamdorf, Axel Hofmann, Wendy Erber, Pradeep Jayasuriya, Simon Towler and other members from the group.

The Western Australian PBM Group Steering Committee: Prof. Jeffrey Hamdorf (Chair), Dr Shannon Farmer, Ms. Angie Monk, Ms. Linda Campbell, Ms. Kylie Symons, Dr Hamish Mace, Mr Kevin Trentino, Dr Simon Towler, Dr Susan Pen, Dr Cameron Gent, Dr Nolan McDonnell, Dr Michael Leahy

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