













August 2024

NEWSLETTER



The summer season has been flying by, so I hope each of you has had at least a small amount of time to spend away from the hustle and bustle of work to enjoy family and friends. This past month allowed my husband and I to do just that, removing ourselves from the usual daily grind to enjoy a

lovely vacation visiting new places, exploring cultures, and learning history as part of a small group experience. Spending two weeks with such a group provides ample time to get to know one another. We heard personal and professional stories from the others on the trip, making new friends, some with whom we look forward to staying in touch. As part of the numerous conversations during tours, meals or downtime, there was something, however, that stuck me and actually gave me pause. Let me share.

As these get-to-know-you conversations go, questions regarding where you live, do you have family and what do you do for a living will typically come first. I noticed, when asked, that it was very easy for the group to understand my husband's role as an ophthalmologist. Whether in healthcare (there were 5 physicians and two nurses among the group) or as a layperson uninvolved with healthcare, everyone could relate to cataracts, contact lenses, Lasik and given the mean age of the group, the general frustration with presbyopia. But, when it came to my specialty as a pathologist, of course, much to my chagrin, most people seemed to think that being a pathologist implied the glamorized forensic pathologists on

those many TV shows. When asked about my role in healthcare, it was glaringly apparent that no one had heard of PBM and what a PBM clinician might actually do. Heads cocked a bit sideways, and the usual response was either "What is that?", "I have never heard of that!", or both rapidly in tandem. It became necessary to define PBM very clearly, emphasize the concept of Blood Health, and the importance of knowing and understanding blood as an organ. This ultimately was followed by "Oh, I must talk with my provider about this and know my numbers!". Perhaps you also have encountered this? Hats off to the eventual epiphany...

Although I was very glad that I was able to engage so many people and perhaps motivate them to pursue Blood Health and PBM in their personal care, it also spoke to the fact that these concepts and principles are still not out there as they need to be. It shows that our work at SABM and as PBM providers/administrators is not close to being done. We must continue to soldier on to bring this to all patients and patientsto-be. We must take every opportunity to explain PBM and Blood Health in a clear and consistent manner, to communicate as leaders in this field any chance we have.

As we wind down these next 2 months and move into Fall, I am looking forward to connecting at our SABM Annual Meeting in Phoenix. We can embrace the time together to learn, recharge, revitalize our mission and expand our SABM range. Our society may be small compared to others, but we are, indeed, mighty!

See you soon.

My best, Carolyn Burns, MD



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SABM NEWSLETTER AUGUST 2024 ISSUE

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SABM 2024 Newsletter Publication

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Consider submitting your future manuscripts in PBM for peer

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SABM Board of Directors © 2024 Society for the Advancement of Patient Blood Management 19 Mantua Road Mt. Royal, NJ 08061 USA Phone: (928) 551-6400 Fax: (856) 423-3420 EMAIL: info@sabm.org 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.

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- Have an article about some of the latest technology?
- Submitted an article to a journal for publication?

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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 <u>info@sabm.org</u>. Be sure to include your full name and details regarding the award, the recognition you received, or the publication citation.

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- Patient history and diagnosis
- Problem statement
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- Medical management
- Follow up
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- 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
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"PBM Rising"

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SABM 2024 Annual Meeting Phoenix, AZ September 12 – 14, 2024

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We are excited to invite you to join our SABM Annual Meeting September 12-14, 2024, in Phoenix, AZ, USA. The program will be rich with content that reinforces the clinical importance of Patient Blood Management (PBM), in line with the new Global Definition of PBM which emphasizes optimizing the care of our patients' own blood as a renewable and vital resource, with the goal of improving safety and outcomes. Presentations and content from global PBM experts will expand our comprehension of how PBM, an urgent international public health initiative, can be promoted and implemented, with critical social, economic, and clinical implications. By doing so, we can improve the lives of millions of people worldwide. Our target audience includes a range of multidisciplinary healthcare professionals, including but not limited to physicians, nurses, perfusionists, laboratorians, administrators, clinical quality and safety specialists, and patient advocates. There will be outstanding opportunities for collaboration, networking, and mentorship connections. Our meeting attendance reflects our diverse membership, and we warmly welcome you to join us. Registration will open soon.





Roberto Luiz da Silva, MD

Bone Marrow Transplantation (BMT) represents a highcomplexity treatment involving the administration of chemotherapeutic drugs at nearly lethal doses to the hematologic system, thereby inhibiting hematopoietic recovery. The primary goal of BMT is the eradication of underlying malignant

hematologic diseases and, in certain situations, the "reset" of the immune system in autoimmune diseases. The destruction of the hematopoietic system mainly occurs as a side effect of intensified chemotherapy and/or radiotherapy. Transplanted bone marrow or Hematopoietic Stem Cells (HSCs) then serve as a "reserve" in autologous BMT cases, while in allogeneic BMT, the intention is to replace diseased marrow (e.g., leukemia) with healthy marrow.

The BMT was developed in the 60's as a life-changing treatment for leukemias and bone marrow aplasia. Significant advancements in histocompatibility system identification, immunosuppressants, chemotherapeutics, radiotherapy, infection control, and blood component transfusions, among other areas, were necessary to enable BMT. Substantial progress in the field has led to BMT being considered a viable treatment, widely utilized in many countries as the therapy of choice for hematologic, oncohematologic, and less frequently, immunodeficiency and autoimmune diseases. Nevertheless, BMT remains a treatment associated with considerable risk of mortality and comorbidities. Approximately 90,000 bone marrow transplants are performed worldwide annually, with 53% being autologous and 47% allogeneic.¹

In Brazil, in 2023, there were 4262 transplants recorded, with 1694 allogenic and 2568 autologous. Hematopoietic recovery usually occurs within about 10 to 24 days following the infusion of previously collected HSCs from the patient in autologous BMT, or from the donor in allogeneic BMT. Hence, the primordial side effect of the transplants is severe pancytopenia and its underlying effects, such as anemia, infections, and bleeding. The duration of the aplasia depends on a few variables, such as transplant type, conditioning intensity, donor type, cell source, and number of infused HSCs, among other factors. Therefore, early transfusion of red blood cells and platelets during the transplant's critical phase ensures patient safety, preventing severe anemia or bleeding. The protocol of blood transfusions is usually based on the numeric value of hemoglobin and platelets, keeping in consideration the patient's clinical status and the reference value of the institution. In this scenario, they are mainly prescribed prophylactically.

Questions regarding the relevance of blood transfusions in various medical circumstances were raised.² Until then, blood component transfusions were considered a therapeutic procedure completely incorporated in clinical practices, of relatively easy access, and recommended mainly based on laboratory results.

Several studies and meta-analyses have shown that liberal transfusions caused higher mortality and morbidity than restrictive transfusions.³ Other clinical situations, such as critical patients in Intensive Care Units, cardiac surgery, and others, demonstrate the safety and viability of restrictive transfusions.⁴ The advancement of this concept is the key to the development of what is called Patient Blood Management (PBM), since 2017 considered the new Standard of care.⁵ BMT is a therapy primarily used in patients with severe hematologic diseases. Even though the incorporation of PBM in hematological patients has started, the nature of hematologic diseases affects blood production and increases the chances of bleeding, causing the need for more transfusions. Introducing PBM in Bone Marrow transplants is a greater challenge than in scenarios where the hematopoietic system is functionally normal.⁶ Historically, BMT patients could require 5 to 20 units of red cells and platelets.

In 2020, data on 21 transplanted patients, including haploidentical cases, without the use of blood components in Brazil were published.⁷ These occurrences arose from the need for medical intervention for a specific group of patients who declined blood transfusions on account of religious beliefs. This demand generated the implementation of specific protocols, such as bleeding management, anemia tolerance, and restricting blood loss. These are the pillars of Patient Blood Management as we know it today.⁸ Thus, we can say that the first records of BMT without blood components were accomplished without the systematic implementation of PBM.

Our protocol is based on the following measures:

- Optimization of platelets and hemoglobin levels before the beginning of the conditioning
- Restriction of blood collection, using pediatric tubes
- Early Introduction of Hematopoietic Substrates and Hemostatic Control Agents such as Intravenous Iron, Vitamin B12, Folic Acid, Vitamin K, and Ascorbic Acid
- Early use of blood production stimulants: Erythropoietin, Eltrombopag and/or Romiplostim

In parallel to the advances that enabled the growth, safety, and efficacy of BMT, a paradigm shift in blood transfusion practice has occurred. The development of evidence-based medicine in the 90's resulted in the search for consistent evidence of effectiveness and safety in transfusions.

- Detection of early signs of bleeding for the use of tranexamic acid and epsilon aminocaproic
- Potent antiemetics measures and gastric protection
- Availability of therapeutic alternatives for coagulation factors (prothrombin complex concentrate, activated factor VII)
- Prepared multidisciplinary team trained to act in complications
- Adaptation of conditioning regimens according to the underlying disease, with preference for nonmyeloablative (NMA) and reduced-intensity (RIC) protocols in allogeneic BMT patients



Introduction:

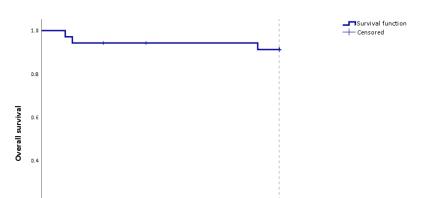
From October 2005 to March of 2024, there are records for 42 transplants corresponding to 35 patients. Five of the included patients with more than one transplant, two of them with 3 transplants, and three patients with 2 transplants. The clinical characteristics of the patients and the percentages of patients surviving at 100 days, 1 year, and 5 years, as well as survival curves and overall survival probabilities, will be presented in this article.

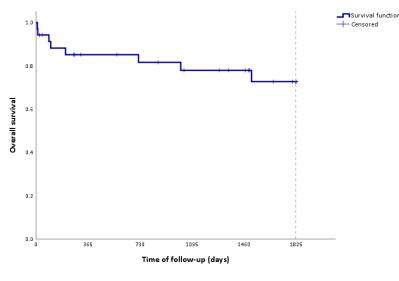
Demographics:

The median age was 44 years (2-71 years), 20 patients were female and 22 males. The transplants were recommended for the following: 1 Severe Aplastic Anemia, 1 Hereditary Immunodeficiencies, 6 Acute Myeloid Leukemia, 6 Hodgkin Lymphoma, 6 Non-Hodgkin Lymphoma, 15 Multiple Myeloma, and 3 Chronic Myeloid Leukemia. The types of transplants vary, 29 were autologous, 10 haploidentical, 2 allogeneic unrelated, and 1 allogeneic related. The median follow-up is 1365 (10 - 6305). Mortality rates at 100 days post-transplantation were 8.6%, increasing to 14.3% at one year and further to 22.9% at five years. The survival rate in 100 days was 91,2% 1 year was 85,2%, and in 5 years 72,7% (graphics 1 and 2). The causes of death within 100 days of the transplant were septic shock and systemic infection, after 100 days the causes of death were related to illness relapses.

Statistical Methods:

The qualitative variables were presented as absolute and relative frequencies. Mean, median, standard deviation, minimum, and maximum values were calculated for the follow-up time and age variables. Survival curves were constructed using the Kaplan-Meier method, and survival probabilities at 100 days and 5 years were presented. The analyses were performed using SPSS for Windows v.25 software.





Graphic 2: Survival rate in 5 years

Conclusion:

The recognition of PBM as a solid medical practice and its rising in international fields gives us the scientific base and utmost security for the treatment of patients that have restrictions in the use of blood components. Our experience and results, as it stands, corroborates that PBM should be considered, not only in situations of religious restrictions but within the general hematologic clinical context, including bone marrow transplantation, in line with WHO recommendations.

Contributors: Roberto Luiz da Silva, MD, et al.

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Graphic 1: Survival rate in 100 days

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Creation of a Web Application for Acute Normovolemic Hemodilution (ANH)



Tolentino S. Eduardo, MD

Considering the adverse effects associated with blood transfusions, the concept of Patient Blood Management (PBM) has emerged in the past years, and it is defined as a patient-centered, systematic and evidence-based approach to improve patient outcomes by managing

and preserving the patient's own blood, while promoting patient safety and empowerment. PBM shifts the focus from the traditional reactive transfusion of patients with allogeneic blood components to preventive measures, ultimately managing the patient's autologous blood more optimally, thereby reducing the use of blood transfusions, hospital length of stay, infectious and thromboembolic complications, as well as mortality and hospital costs.

PBM consists of a combination of medicines, equipment, and/or surgical techniques and it is used for: (1) increasing of hematopoiesis (formation of blood cells); (2) controlling the blood loss; and (3) maximizing the tolerance to anemia. Among the options available in PBM, the technique Acute Normovolemic Hemodilution (ANH) stands out, which has been studied in recent decades due to its benefits for patients with potential blood loss during surgery.

ANH is an option that can be individually considered to reduce blood transfusion. After anesthesia induction and before heparinization, a previously calculated amount of total blood volume is removed from the patient and temporarily stored at the bedside. Simultaneously, there is a replacement with sufficient volumes of crystalloid or colloid solutions to maintain intravascular volume. The consequent hemodilution reduces the patient's hemoglobin concentration throughout surgery, resulting in a lower amount of red blood cells lost during intraoperative hemorrhagic events. The autologous blood temporarily separated from the circulatory system is rich in red blood cells, platelets, and coagulation factors. Without the alterations related to prolonged storage time, it is returned to the patient after hemostasis, as needed.

A systematic review with meta-analysis of randomized clinical trials concluded that ANH reduces the use of blood transfusions. One of its main advantages is the intraoperative use without the need for long-term testing and storage. An adequate blood volume is collected and there is no more serious during pandemics such as that caused by COVID-19.

Although ANH is a safe, effective, and cost-effective technique, it is still relatively unknown and underutilized in medical practice. One way to disseminate a procedure in medical practice is by raising awareness by healthcare professionals through websites and smartphone and tablet applications, bringing them closer to continuing education and making updates on new medical techniques and technologies more accessible.

A study was conducted with the aim of developing a web application that would enable surgical teams to become familiar with and use the intraoperative Acute Normovolemic Hemodilution technique. This study was a Professional Master's project at the Federal University of São Paulo (Unifesp), approved by the Unifesp Research Ethics Committee under protocol number 5,556,610.

The study began with an extensive literature review, which initially found a total of 14,775 articles, which, after removing duplicates and applying exclusion criteria, resulted in a total of 58 articles. All articles were from the Pubmed/MEDLINE, LILACS and Cochrane databases and were used as a basis for the development of the web app. In parallel, the input of 10 experts in the technique were heard to guide the development of the web app, highlighting the most relevant information for the execution of the technique in practice, which is often not found in books or scientific articles. Subsequently, the content of the application was evaluated and reviewed by researchers and experts and then sent to the company for prototyping of the web app. Finally, the web app was submitted for evaluation by the target audience, consisting of 25 doctors with no experience with ANH, who evaluated the web app using the validated System Usability Scale (SUS) questionnaire, obtaining a score of 92.5, which is considered excellent usability.

The web application consists of thirteen main topics divided into tabs: "What is ANH?", "Why use the technique", "Indications", "Contraindications", "Regulation", "Public and private healthcare system", "Informed consent", "Materials", "Logistics", "About the technique", "The technique", "Technique in Jehovah's Witnesses", "Valuable tips",

significant blood loss intraoperatively, thus, ANH can achieve an acceptable hemoglobin concentration without the need for allogeneic transfusion.

Because it is an autotransfusion, not involving different individuals and without prolonged blood storage, the technique can be an excellent intraoperative option for Jehovah's Witnesses and those with an absolute contraindication to allogeneic blood transfusion. Therefore, ANH technique may prove useful and feasible in the face of a shortage of blood and donors, as it uses the individual's own blood during surgery. It is also a valuable procedure in the face of the chronic scarcity of blood, which may be even "Formulas and calculators", "Evidence and benefits", and "Possible complications".

Acute Normovolemic Hemodilution

HNA HNA

Acute Normovolemic Hemodilution (ANH) is a medical technique of great importance and impact in the health sector. In this space, we will dive deeply into this technique, unraveling its mysteries and highlighting its main benefits.





The web application is available at <u>www.hna.app.br</u> for free and no prior registration is needed. The web app is in Portuguese but can be easily translated into any language Google using Translate the tool: type https://translate.google.com/ on your URL bar and follow these steps:

- 1. Select the Websites tab.
- 2. Choose a language to translate from on the left dropdown language list.
- 3. Select Detect language to let Google Translate automatically identify the language used on this website (Portuguese).
- 4. On the right dropdown language list, select the language you want the website to be translated into.
- 5. Type the URL (<u>www.hna.app.br</u>) in the Website field and click Enter.
- 6. The website will load in a new tab and take a couple of seconds to switch to the language you chose.

Although the web app has been developed for the Brazilian public, its recommendations and guidelines can be useful and adapted for any country. The authors of this web app expect that this new online tool can contribute to the popularization and use of ANH not only in Brazil but also in other countries, thus contributing to the implementation of PBM strategies around the world, as determined by the World Health Organization in its public health policy document.

Contributors: Tolentino S. Eduardo, MD; Quieregatto E. S. Paulo, MD; Montano-Pedroso Juan Carlos, MD

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Updated Protocol for Pharmacological Treatment of Anemia in Neonates and Children



Anemia affects a guarter of the world's population, with more than half of this clinical scenario being due to iron deficiency anemia (IDA). Anemia is most commonly found in children under 5 years of age, women, the elderly, and chronically Antonio Alceu dos Santos, MD ill patients, and it is the most prevalent of all morbidities, thus becoming a global public health problem. Despite economic development and scientific advancement in recent decades, there has been no significant reduction in the global prevalence of anemia.

increased arterial partial pressure of oxygen (PaO2) and Hb saturation after birth. For low birth weight (less than 1.500 g) and premature infants, the risk of developing anemia is exacerbated by the increased frequency of blood draws for tests, shorter red blood cell survival, lower iron reserves at birth, and reduced ability to regulate iron absorption by the gastrointestinal tract. Prolonged breastfeeding alone is also associated with IDA.

Childhood IDA, even in a high-income country, requires consistent implementation of national guidelines and education regarding nutritional deficiency. All newborns (NB) experience a decline in their hemoglobin (Hb) at birth due to

Anemia, with or without iron deficiency, is an independent predictor of higher morbidity and mortality. Early diagnosis and immediate treatment lead to reduced use of allogeneic blood transfusions and improved clinical outcomes, making it a modifiable risk factor for reducing mortality. The diagnosis of anemia in neonates and children, based on Hb values, age, and sex, is described in Table 1.



Age	Hb (g/dL)
6 months-5 years	<11.0
5-11 years	<11.5
11-14 years	<12.0
Women > 14 years	<12.0
Men > 14 years	<13.0

Table 1. Diagnosis of anemia according to hemoglobin (Hb) values, age, and sex

Extreme premature baby populations receive high volumes of blood transfusions. Correcting prematurity anemia through proper iron replacement and adding adjunctive therapy with erythropoietin (EPO) has been shown to reduce the use of allogeneic blood and, consequently, the adverse effects resulting from transfusion practice.

For preterm or low birth weight NB (1.000 - 1.500 g), the dose is 3 to 4 mg of elemental iron/kg/day (after 12 months, reduce to 1-2 mg/kg/day). Preterm NB or low birth weight (1.500 - 2.500 g) or term NB with adequate weight, the dose is 1 to 3 mg of elemental iron/kg/day. In children, the dose is 3 to 6 mg of elemental iron/kg/day [14-16]. If ferritin < 15ng/mL, administer IV iron (for example, iron sucrose at a dose of 20 mg/kg once a week, which corresponds to 2-3 mg/kg/day (maximum 100 mg for children up to 1 year).

EPO can act quickly and directly on the process of proliferation, differentiation, and maturation of red blood cells in the bone marrow. The literature presents several dosing regimens of EPO for the treatment of anemia in neonates and children. For example, EPO at a dose of 600-1.400 IU/kg/week (divided doses) or 200-300 IU/kg/day via IV or SC three times a week has been shown to be safe and effective in avoiding allogeneic blood transfusions. A prospective randomized clinical trial demonstrated that EPO at a dose of 500 IU/kg intravenously on alternate days for two weeks significantly reduced blood transfusions in premature babies and other complications such as necrotizing enterocolitis. Another successful dose suggestion used in extremely premature infants is the administration of EPO 1.000 IU/kg every 48 hours for 6 doses, followed by 400 IU/kg.

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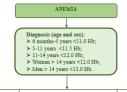
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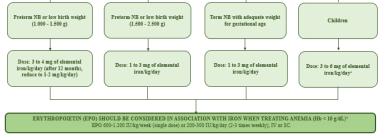
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children up to 1 year). ^b Check Hb after every 2 ^b hhreviations: EPO= er

Figure 1. Protocol for the diagnosis and treatment of anemia in neonates and children with iron and adjunctive therapy with EPO

Contributor: Antonio Alceu dos Santos, MD



In recent years, Brazil has experienced an increase in initiatives focused on Patient Blood Management (PBM), driven by a heightened awareness of the risks associated with blood transfusions. Concerns regarding infections, transfusion reactions, and immunomodulation have underscored the necessity for safer alternatives. Moreover, Brazil's healthcare system faces the challenge of maintaining an adequate and sustainable blood supply. Due to fluctuations in blood donations, the implementation of PBM practices has emerged as a strategic imperative to address these challenges. However, while there has been a noticeable increase in PBM discussions regarding its significance and potential benefits, the widespread adoption of PBM encounters significant obstacles, particularly concerning reimbursement and access to care.

A primary hurdle to the adoption of PBM in Brazil lies in the reluctance of health insurance providers, including the country's free public healthcare system (Sistema Único de Saúde or SUS), to cover the costs associated with PBM interventions. Many insurance plans categorize PBM procedures and treatments as non-standard, resulting in denial of coverage for patients seeking these treatments. Similarly, SUS may lack specific protocols or reimbursement mechanisms for PBM, rendering it inaccessible to patients reliant on government-funded healthcare services. Consequently, patients who stand to benefit from PBM interventions often find themselves in a precarious position, compelled to navigate complex bureaucratic processes or resort to legal action to secure coverage for PBM treatments. This necessity underscores systemic barriers and inequities within Brazil's healthcare system that impede access to innovative and evidence-based practices like PBM.

Furthermore, in Brazil, as in many other countries, healthcare professionals are expected to provide culturally competent care, accommodating the diverse values and beliefs of their patients. However, individuals from cultural minority groups or religious groups, such as Jehovah's Witnesses, may encounter challenges accessing care that aligns with their beliefs. This may necessitate legal intervention to ensure their preferences are respected within the healthcare system. These challenges highlight broader issues related to healthcare equity and patient rights in Brazil, emphasizing disparities in access to care based on insurance coverage, discrimination against minorities, and inadequate training of healthcare professionals on culturally competent and patientcentered care.

Nevertheless, PBM has reached significant milestones in Brazil. A recent ruling in a Civil Action initiated by the Federal Public Ministry has established a timeline for federal government-operated hospitals in the state of Rio de Janeiro to adjust their protocols, incorporating PBM strategies into perioperative care. Hospitals are required to enable patients to express their refusal of blood transfusions in hospital forms and documents. Additionally, Judge Souza Nery, of the São Paulo State Court of Appeals, in a preliminary decision, ensured the right of a patient to receive treatment without blood transfusions. The judge emphasized the need to respect the right to freedom of conscience and belief, as provided for in article 5, VI, of the Federal Constitution.

While the concept of PBM is gaining traction in Brazil, its widespread implementation is hindered by challenges related to reimbursement, access to care, and lack of PBM protocols and training. Addressing these barriers requires collaborative efforts from healthcare stakeholders, policymakers, and patient advocacy groups to raise awareness, promote policy reforms, and ensure equitable access to PBM interventions for all patients in Brazil.

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Spotlight on PBM Laboratory Testing: Review of Reticulocyte Parameters

What are reticulocytes and how are these measured?

Erythropoiesis is a process of proliferation and differentiation of the hematopoietic stem cell to mature red blood cell (RBC) (Figure 1). Numerous regulators are required for successful maturation, including erythropoietin, B12, folate and iron. Deficiency of any of these will cause impaired DNA synthesis that will lead to the apoptosis of erythroblasts and subsequently ineffective erythropoiesis. Reticulocytes represent immature red blood cells and are an indicator of erythropoiesis. After releasing into the peripheral bloodstream, they mature into RBCs within 1 to 2 days. The reticulocyte count is used to analyze the bone marrow activity or failure.



Most commonly, reticulocytes are measured as a percentage of the total number of RBCs in the blood sample. On peripheral smear, reticulocytes are recognized as nonnucleated cells with red to pale blue cytoplasm due to ribosomal RNA (visible with new methylene blue or Romanowsky stains), which lack central pallor and appear larger than mature erythrocyte. Normal range of reticulocytes is between 0.5% to 2.5% in adults and 2% to 6% in infants. Absolute reticulocyte count is a number of reticulocytes in a volume of blood (normal range is 50-100 x 109/L).1

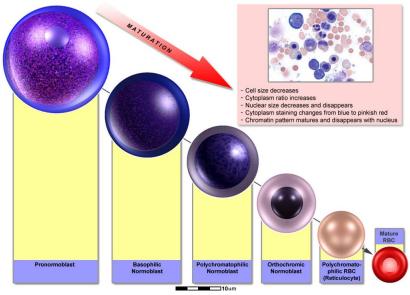


Figure 1. Erythroid maturation process Image from: <u>http://hematologyoutlines.com/atlas_topics/98.html</u>

What conditions are associated with changes in reticulocyte counts?

The reticulocyte count is a useful tool to assess the bone marrow's ability to increase RBC production in response to various types of anemia.

- No response The absence of an appropriate bone marrow compensation that can be seen in hypochromic anemia (including iron-deficiency anemia, sideroblastic anemia or anemia of chronic disease), aplastic anemia, nutritional deficiency (B12 or folate) or myelodysplasia.
- Response When the bone marrow responds adequately, the reticulocyte count will be high. This includes acute or chronic blood loss and hemolytic anemia.² An example this may be seen when patients with iron deficiency anemia is treated with IV iron doses, providing the bone marrow with means to increase RBC production with repletion of IV iron.

Reticulocyte Index (RI) = [% reticulocyte count x Patient hematocrit (Hct)] / 45 (normal Hct).

Reticulocyte index <2% indicates inadequate response of the bone marrow, while >3% is considered sufficient response.

Reticulocyte Production Index (RPI) = RI x (1/reticulocyte maturation time).

Maturation time is different based on hematocrit results (1.0 if HCT >36, 1.5 if HCT is 26-35, 2.0 if HCT is 16-25, 2.5 if HCT is <15).

Similarly to RI, RPI of <2 suggests inadequate bone marrow response and >3 is consistent with normal bone marrow response.³

What is the Immature Reticulocyte Fraction (IRF)?

The term Immature Reticulocyte Fraction (IRF) was introduced to indicate the less mature portion of reticulocytes. This fraction encompasses young reticulocytes with elevated RNA content. These reticulocytes are distinguished by their larger size and increased RNA levels. Emerging as one of the newer parameters in automated hematology analyzers, IRF serves as a sensitive indicator of erythropoiesis.⁴

- Reticulocytes are juvenile RBCs that develop a network or granules upon exposure to certain supravital stains. These structures consist of aggregated rough endoplasmic reticulum accompanied by polyribosomes.⁴
- The immature reticulocyte fraction (IRF) represents a new reticulocyte parameter on automated hematology analyzers. It evaluates the maturity level of reticulocytes in circulation by quantifying the fraction that displays the highest intensity of RNA staining.⁵

What is the clinical utility of IRF in patient blood management?

- The clinical significance of IRF has been described across various conditions. These include its role in diagnosing anemia, distinguishing between hypoproliferative, ineffective, or hemolytic types, and monitoring treatment efficacy.
- IRF aids in assessing transfusion requirements, monitoring renal transplant engraftment linked to

What is corrected reticulocyte count?

In clinical scenario of anemia, the bone marrow will release reticulocytes prematurely into the bloodstream. These premature reticulocytes (also called "shift reticulocytes") will continue to circulate in the peripheral blood for a longer period of time than those reticulocytes released under normal circumstances. In addition, the decrease in RBCs due to anemia will automatically increase reticulocyte count as it is measured as a percentage of RBCs. Therefore, corrected count such as reticulocyte index (RI) or reticulocyte production index (RPI) is necessary to reliably evaluate if increased erythropoiesis in the bone marrow has begun. Erythropoietin (EPO) production, detecting hemorrhages or hemolysis, and evaluating the necessity for RBC transfusions in patients with anemia.⁵

What is the hemoglobin content of reticulocytes (Ret-Hb) compared to a regular hemoglobin (Hb) test?

- The hemoglobin (Hb) reflects total hemoglobin in all measured circulating red blood cells.
- Since mature red blood cells have a lifespan of around 120 days, they aren't the most sensitive indicators of hemoglobin (Hb) synthesis.



- The hemoglobin content of reticulocytes (Ret-Hb) can provide a more current reflection of Hb synthesis status.
- Additionally, iron, a key component of Hb, is essential for nearly all cells in the body, with about 70% stored in the reticuloendothelial system. Assuming normal hematopoiesis, Hb-ret serves as a valuable tool for assessing acute iron metabolism, as Hb synthesis is influenced by iron intake.⁶

What are clinical applications of Reticulocyte Hemoglobin content testing in patient blood management?

- The CHr (Reticulocyte Hemoglobin Content) serves as an effective screening tool for detecting iron status early, offering convenience for both healthcare providers and patients. Research indicates that changes in reticulocytes due to reduced iron stores are observed before alterations in erythrocyte indices, particularly evident in female athletes with high rates of latent iron deficiency.
- CHr holds significance in screening special/high-risk populations like neonates, where iron deficiency can lead

to developmental deficits. By detecting inadequate iron levels before anemia develops, potential adverse effects can be prevented.

- In clinical practice, CHr's direct correlation with iron deficiency severity is important for treatment and the subsequent need for additional iron therapy.
- CHr may also aid in differentiating hematologic conditions such as iron deficiency anemia and β-thalassemia trait, offering a simpler and more precise approach compared to traditional diagnostic methods.

Take-Home Points

- Reticulocyte counts and index are commonly used markers to assess bone marrow's response to increase RBC production in response to acute or ongoing anemia.
- While the IRF and CHr may not be readily available universally across all laboratory systems, their clinical significance and role in patient blood management may support and promote their use to guide clinicians to effectively diagnose and treat anemia.

Test	How its measured	Interpretation
Reticulocyte Count	Percentage of the total number of RBCs	Normal range is 0.5% to 2.5%.
		Levels <0.5 - insufficient bone
		marrow compensation, levels >2.5
		% are consistent with adequate
		response.
Absolute Reticulocyte Count		Normal range 50-100 x 10 ⁹ /L. <50
	Number of reticulocytes in a volume of blood	x10 ⁹ /L – poor bone marrow
		response, >100 x x10 ⁹ /L –
		overproduction in the bone
		marrow.
Reticulocyte Index	[% reticulocyte count x Patient hematocrit (Hct)] / 45 (normal Hct).	<2% - inadequate bone marrow
		response, >3% - sufficient
		response
Reticulocyte Production Index	RI x (1/reticulocyte maturation time)	<2 - inadequate bone marrow
		response, >3 - sufficient response
Immature Reticulocyte Fraction	Immature reticulocytes/ total number of reticulocytes	2.3 - 15.9 %
		Increased- adequate erythroid
		response to anemia.
		Decreased - decreased
		erythropoietic activity
Hemoglobin Content of	Product of the cellular volume x	Normal: 28-36 pg
Reticulocytes	cellular Hb concentration	Decreased - Acute Iron deficiency

Table 1. Summary of tests

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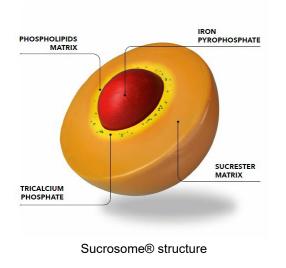
Patient Blood Management (PBM) is a systematic, evidencebased, patient-centered approach to improve patient outcomes by managing and preserving the patient's own blood, while promoting patient safety and empowerment. The main objectives of PBM are the improvement of clinical outcomes, prevention of avoidable transfusion and the reduction of management costs.

Individuals should have their hemoglobin levels checked at least 2 weeks before surgery, and before taking intravenous iron medicines it is recommended to consider firstly the use of oral iron supplement.

Cardiac surgery is known to be associated with a high risk of perioperative blood loss and allogeneic blood transfusions due to the invasiveness of the procedures. PBM in cardiac surgery contributes to the maintenance of perioperative hemostasis and the minimization of bleeding, which reduce blood transfusion requirements.

Preoperative iron supplementation may reduce transfusion requirements in patients undergoing cardiac surgery. However, supplementation of the conventional oral iron formulations may cause some common side effects, such as abdominal pain, bloating, diarrhea and constipation.

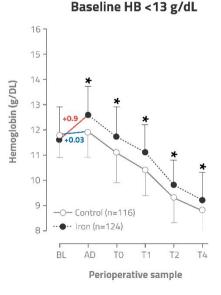
An excellent alternative to conventional oral iron supplement is represented by Sucrosomial® Iron, designed and patented exclusively by PharmaNutra. This innovative formulation consists of iron pyrophosphate protected by a matrix of phospholipids and sucrose esters of fatty acids. Each of these elements take part in a single structure, called Sucrosome® (Figure below).



Several scientific studies confirm the effectiveness of Sucrosomial® Iron supplementation in many clinical settings, where iron deficiency is frequently present, for example: gastroenterology, gynecology, nephrology, cardiology and also in PBM.

A study titled "Benefits of pre-operative oral Sucrosomial® iron supplementation in cardiac surgery: influence of patient's baseline hemoglobin and gender", published in the journal *Blood Transfusion* in 2022, was conducted by Dr. Luca P. Welter of Cardiac Surgery of the European Hospital in Rome (Italy). This publication is a retrospective analysis and involved 594 patients who were candidates for elective cardiac surgery, with the aim of evaluating the effectiveness of Sucrosomial® Iron in improving the concentration of hemoglobin before surgery, compared to the control group.

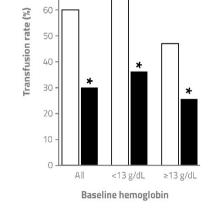
Individuals were divided into two groups; the first group (n=309) received Sucrosomial® Iron for 30 days at a dosage of 60 mg of iron per day, while the second group (n=285) received no treatment (control group).



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Control

Sucrosomial® iron, marketed with the range of SiderAL® food supplements, has a different absorption profile from common iron products, thus avoiding the mineral coming into contact with the gastrointestinal mucosa; this means that it has a higher absorption rate, allowing a faster increase of hemoglobin levels. The innovation of Sucrosomial® technology is characterized by an excellent tolerability and it allows the iron intake at any time during the day (with or away from meals), for long periods of time, and prevents any discomfort or limitations commonly associated with iron intake.





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The results showed in the above graphs that the group of subjects with basal hemoglobin value inferior to 13 g/dL supplemented with Sucrosomial® Iron, had a 0.9 g/dL increase basal of hemoglobin the day before surgery compared to the control group; and also showed a decreased need for allogeneic transfusions.

When is the right time to start a PBM protocol when surgery is scheduled?

Approximately 4 weeks before surgery is a sufficient period to prepare for the physiological hemoglobin loss that normally occurs post-operation.

Nowadays, many hospitals have adopted a PBM protocol using SiderAL® products, with the dosage tailored to the hemoglobin levels of each individual patient.

For example, if a patient has hemoglobin levels between 8-10 g/dL, it is essential to quickly restore these to physiological levels by administering 4 capsules of SiderAL® Forte per day for one week. After this initial period, the dosage should be reduced to 1 capsule per day for the remaining 3 weeks before surgery.

If the hemoglobin levels are between 10-12 g/dL it is advisable to use 2 capsules per day of SiderAL® Forte for 2-3 consecutive weeks, and then reduce to 1 capsule per day for the time remaining to surgery.

Iron supplementation is strongly recommended even when hemoglobin levels are within the normal range; in such cases, taking one capsule per day of SiderAL® Forte for 4 weeks would be sufficient.

If the 4-week iron supplementation period before surgery cannot be adhered to, this can be compensated by increasing the daily iron dosage, taking high doses of SiderAL® Forte (up to 4 capsules per day) for the entire required period.

After surgery, iron supplementation should be administered to accelerate the recovery of blood values and alleviate symptoms related to iron deficiency.

In conclusion, it is recommended to adopt a PBM protocol in cardiac surgery which is a critical approach that enhances patient care by minimizing unnecessary transfusions and optimizing overall blood management. By integrating these strategies, healthcare providers can improve surgical outcomes, reduce complications, and provide high-quality care to patients undergoing cardiac procedures.

Sucrosomial® Iron supplementation is confirmed as a safe, well tolerated, and a cost-effective strategy to increase preoperative hemoglobin and decrease transfusion requirements in surgeries.

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NATA Scientific Newsletter Literature Updates

Berenger JB, *et al.* **Prophylactic versus restrictive platelet transfusion strategy in patients with haematological malignancies in the ICU setting, a propensity-score analysis.** *J Crit Care* 2024;83:154817. PubMed: <u>https://www.ncbi.nlm.nih.gov/pubmed/38805833</u>

Population: Patients >18 years old with haematological malignancy admitted to the ICU with thrombocytopenia <20 G/L between 2018 and 2021

Intervention: We assessed whether restrictive PT compared to prophylactic strategy could apply in ICU. Patients were

classified in 2 groups according transfusion strategy applied during the first 3 days comparing prophylactic or restrictive transfusion. The restrictive transfusion strategy did not transfuse platelets in the absence of a grade \geq 2 bleeding, despite platelet count <20 G/L.

Control: Use of a prophylactic transfusion strategy, also known as preemptive or liberal PC transfusion, consisted of transfusion when the platelet count was below 20 G/L in the absence of bleeding. Platelet transfusion could be performed for curative purposes if the patient had a significant bleeding



or at the discretion of intensivist to support an invasive procedure.

Outcomes: Restrictive strategy did not result in higher grade ≥ 2 bleeding. Transfusion efficiency was low with similar

number of days with platelet <10 or < 20 G/L regardless of strategy. Platelet transfusion strategy was not associated with 28-day mortality. Platelet nadir <5G/L was associated with day-28 mortality with HR = 1.882 [1.011-3.055], p = 0.046.

Dorken-Gallastegi A, *et al.* Whole blood and blood component resuscitation in trauma: interaction and association with mortality. *Ann Surg* 2024; May 6 [Online ahead of print]. PubMed:

https://www.ncbi.nlm.nih.gov/pubmed/38708894

Population: Adult trauma patients with a shock index >1 who received ≥4 combined units of red blood cells (RBC) or WB within 4 hours across 501 United States trauma centers were included using the American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) database

Intervention: Comparison of Component therapy with WB resuscitation including the associations between: WB resuscitation and mortality, WB to total transfusion volume

ratio (WB:TTV) and mortality, balanced blood component transfusion in the setting of combined WB and component resuscitation and mortality were evaluated with multivariable analysis.

Control: 9,391 patients treated with standard of care balanced blood resuscitation (versus 2,884 receiving whole blood)

Outcomes: WB resuscitation, higher WB:TTV ratios, and balanced blood component transfusion in conjunction with WB were associated with lower mortality in trauma patients presenting in shock requiring 4 units of RBC and/or WB transfusion within 4 hours of arrival

de Lloyd LJ, *et al.* Early viscoelastometric guided fibrinogen replacement combined with escalation of clinical care reduces progression in postpartum haemorrhage: a comparison of outcomes from two prospective observational studies. *Int J Obstet Anesth* 2024;59:104209. PubMed:

https://www.ncbi.nlm.nih.gov/pubmed/38788302

Population: This paper compares outcomes from two observational studies of postpartum haemorrhage (PPH) in the same institution, before and after practice changed from fixed ratio empirical transfusion of coagulation products with laboratory coagulation testing to VHA-guided fibrinogen replacement incorporated into an enhanced PPH care bundle was empirical or based on laboratory tests of coagulation. In Study Two, QBL started at delivery and VHA was used to guide fibrinogen replacement if FIBTEM A5 was <12 mm (Claus fibrinogen ≤ 2 g/L) or to withhold coagulation products if FIBTEM A5 was >12 mm.

Control: Standard of care laboratory based fibrinogen replacement

Outcomes: Improved PPH outcomes were observed in Study Two, with rates of measured blood loss \geq 2500 mL, \geq 4 units red blood cell (RBC) transfusion, fresh frozen plasma transfusion and \geq 8 units of any blood product transfusion all reduced (P < 0.01). Clinically significant improvements occurred in women with fibrinogen \leq 2 g/L at study entry, where the proportion of women who received \geq 4 units RBC

Intervention: In Study One, QBL started once PPH was identified, and resuscitation with coagulation blood products

transfusion fell from 67% in Study One to 0% in Study Two (P = 0.0007).





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