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Patient Blood Management

The Pragmatic Solution for the Problems with Blood Transfusions

ALLOGENEIC erythrocyte transfusions are associated with increased mortality,[1] major adverse cardiac and noncardiac outcome,[2] and low output failure in cardiac surgery. Transfusion of allogeneic erythrocyte transfusions has also been found to be an independent factor increasing mortality in trauma, including traumatic brain injury,[3] burns,[4] liver transplantation, intensive care medicine,[5] and the treatment of acute coronary syndrome.[6] In addition, allogeneic erythrocyte, fresh frozen plasma, and platelet transfusions result in a several-fold increase in postoperative and nosocomial infections.[6,7] Furthermore, allogeneic erythrocyte, fresh frozen plasma, and platelet transfusions frequently cause transfusion-related acute lung injury,[6,8] which in itself again increases mortality, morbidity, and costs. Last but not least, costs of erythrocyte transfusions have been significantly underestimated, even when excluding the cost of treatment of these adverse outcomes or the prolonged intensive care and hospital stay related to erythrocyte transfusion.[9]

In the current issue of the Journal, Atzil *et al.*[10] alert us of another, potentially harmful effect of erythrocyte transfusions, namely the potential to promote tumor growth. In an established rat model of tumor growth, Atzil *et al.* demonstrate that transfusion of (the equivalent of) autologous and allogeneic erythrocytes increases lung retention of tumor cells several-fold. Interestingly, they could show that this effect is directly linked to the transfused erythrocytes and not related to the coadministration of leukocytes or soluble factors of the supernatant. The magnitude of tumor growth promotion was found to be dependent on storage duration, with erythrocytes stored for more than 9 days having a significantly more pronounced deleterious effect.

The reason for cancer progression after blood transfusion is unclear, and the article by Atzil *et al.* did not precisely elucidate the mechanisms involved. The perioperative period is characterized by numerous processes that can induce abrupt elevation of risk factors for the outbreak of preexisting micrometastases and the seeding of new metastases. Here, deterioration of erythrocytes as a result of storage is demonstrated as a major cause for the cancer-promoting effect. Atzil *et al.* mainly discuss the role of cellular immunity, particularly T cells and natural killer cells in controlling minimal residual tumor disease. It is hypothesized that transfused erythrocytes become targets to host immunocytes. These deteriorated erythrocytes will outnumber circulating tumor cells, and host immunocytes after erythrocyte transfusion may have a dramatically reduced chance to interact with residual tumor cells and eliminate them.

Nonimmune mechanisms may play an additional role in promoting cancer progression due to erythrocyte transfusion. Importantly, acute and chronic hypoxia might be the cause (anemia due to tumor-related blood loss) or consequence (quality of erythrocytes) of blood transfusion and may lead to different biology within a tumor. Therefore, blood transfusion may have a promoting effect on cancer progression, given many hypoxia-induced signaling responses, including transcription factor hypoxia-inducible factor 1 for angiogenesis, cell invasion, cell metabolism, and cell survival.[11] Interestingly, Tsai *et al.*[12] have recently shown that exchange transfusion with stored erythrocytes in their hamster window model reduced microvascular flow and functional capillary density by more than 50% of the level achieved with fresh erythrocytes. Moreover, tissue oxygen levels were 3.5 and 14.4 mmHg for stored and fresh erythrocytes, respectively. It is thus conceivable that the transfusion of stored erythrocytes may induce tissue hypoxia also in tumor tissue and, by consequence, result in tumor growth progression *via* the above nonimmune signaling pathways triggered by tissue hypoxia.[11] Further research is urgently needed to understand these mechanisms better and to improve patient treatment in the future.

The clinical epidemiologic and randomized trial evidence relating to transfusion being implicated in tumor recurrence remains controversial, but no reports suggest that transfusions are beneficial in this respect. Animal data as presented by Atzil *et al.*,[10] although not directly transferable to humans, further support a precautionary approach to blood transfusion.

This Editorial View accompanies the following article: Atzil S, Arad M, Glasner A, Abiri N, Avraham R, Greenfeld K, Rosenne E, Beilin B, Ben-Eliyahu S: Blood transfusion promotes cancer progression: A critical role for aged erythrocytes. ANESTHESIOLOGY 2008; 109:989–97.

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Considering all of the above major adverse sequelae of allogeneic erythrocyte transfusions, several questions need to be asked: First, do the benefits of allogeneic erythrocyte transfusion outweigh these negative aspects? Second, what are our responsibilities toward the patient, or what is the patient's role? Third, are we aware of the key factors determining the exposure of patients to erythrocyte transfusions? Fourth and most important, how can we drastically and sustainably reduce the use of allogeneic erythrocyte transfusion and improve the overall patient outcome? With recent evidence that the age of storage is also a factor adversely impacting efficacy and adverse outcomes, the case for avoiding or minimizing transfusion grows stronger.

The benefit of allogeneic erythrocyte transfusion has been shown in preterm infants,[13] and a benefit is presumed in massive bleeding due to trauma or surgery. Other (surgical) areas of benefit are unknown to these authors.

What should be the patient's role in deciding whether he or she is prepared to have a blood transfusion when alternatives are available? From a legal perspective, if there was not a medical indication for a blood transfusion and a patient sustained an adverse outcome, the law is quite clear. A patient with an adverse outcome taking legal action against a doctor who did not warn about these risks and offer transfusion alternatives would have a strong case to present to the court. Such a case would be decided on the balance of probabilities, the plaintiff only needing to convince a court that the alleged negligent act (the avoidable transfusion) was associated with the injurious outcome with a probability, *i.e.*, greater than 50% chance, of being causative, and would not have occurred in the absence of the blood transfusion. This is different from the scientific uses of probability definitions, where the probability threshold that the scientific method demands is greater than 95%. A strong case can be supported that all patients receiving or likely to receive a blood transfusion should be informed of risks of an adverse outcome beyond those that are traditionally included in informed consent.

What are the key factors determining the exposure of patients to erythrocyte transfusions? The most significant predictors of allogeneic erythrocyte transfusions are a low preoperative erythrocyte mass or hemoglobin level, a high perioperative surgical erythrocyte loss, and the hospital where a patient is being treated.[14] Being aware of these simple facts allows designing a pragmatic solution, namely patient blood management.

Patient blood management comprises three main elements: (1) correction of a low preoperative erythrocyte mass or preoperative anemia, (2) minimizing perioperative erythrocyte loss, and (3) using minimal (*i.e.*, low) hemoglobin-based transfusion triggers. In the presence of clinical uncertainty, the default position has been to administer a blood transfusion; this is not usually the case with other therapies. Blood transfusion is an inherently hazardous and costly therapy that should only be prescribed when there is evidence for patient benefit outweighing the potential for harm. The accumulating evidence for allogeneic blood transfusion being implicated as a risk factor for poorer clinical outcomes challenges this medical dogma demanding a more precautionary approach.

Preoperative anemia is frequent in elective orthopedic surgery (20–35%),[15] cardiac surgery (25–37%),[2] and gastrointestinal surgery (up to 75%) and increases with age. A high percentage of these anemic patients can be treated preoperatively with (intravenous) iron and erythropoietin.[15] Perioperative blood loss can be reduced with blood-sparing surgical techniques,[16] maintenance of normothermia, low central venous pressure in liver surgery, cell salvage and retransfusion, use of antifibrinolytics,[17] and avoidance of factor XIII deficiency in cancer surgery.[18] Low hemoglobin–based transfusion triggers are well tolerated even by high-risk patients, including those with severe coronary artery disease.[16]

Therefore, patient blood management is neither science fiction nor rocket science. Patient blood management is possible today and needs to be implemented urgently in our hospitals. The hypothesis is allowed and justified that patient blood management will decrease the use of allogeneic erythrocyte transfusion and its cost and adverse sequelae significantly.

The Department of Health of the Government of Western Australia recently acknowledged patient blood management as an evidence-based patient-focused medical and surgical concept, being in full compliance with the Australian Council on Healthcare Standards, and decided to implement it as a standard of care statewide between 2008 and 2012. The decision of the executives of the Western Australian public health system to support the paradigm shift from behavior-based transfusion practice to patient blood management is based on whole series of reasons. The main ones can be grouped into five major categories: (1) Ethics: Informed consent over patient blood management, combined with the foremost principle *primum non nocere*, leads to new preferences not only for patients but also for physicians. (2) Evidence-based medicine: The growing knowledge of transfusion limitations and adverse outcomes demands discontinuation of unreflected transfusion habits and prescription routines. (3) Economics: True costs of erythrocyte transfusions are currently estimated to be two to four times the product costs or up to 5% of Western Australia's total public healthcare budget. (4) Demographics: Blood shortages are to be expected because of an overaging population, actual and potential donor deferrals, loss of altruism, and wide variations in transfusion practice. (5) Legal aspects: In developed countries, during the acquired immunodeficiency syndrome crisis, high-ranking health officials were criminally indicted for blood safety

concerns and charged with poisoning, manslaughter, professional negligence leading to death, inflicting bodily harm, and even murder.[19] In civil cases and out-of-court settlements, payments in compensation to victims in Ireland reached volumes equaling 15–20 times the purchasing volume of the annual national blood supply.

Therefore, 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.

Donat R. Spahn, M.D., F.R.C.A.,* Holger Moch, M.D.,† Axel Hofmann, M.E.,‡ James P. Isbister, M.B., F.R.A.C.P.§
*Institute of Anesthesiology, University Hospital Zürich, Zürich, Switzerland. donat.spahn@usz.ch. †Institute of Surgical Pathology, Department of Pathology, University Hospital Zurich, Zurich, Switzerland. ‡Medical Society for Blood Management, Laxenburg, Austria. §Department of Haematology, University of Sydney, Royal North Shore Hospital of Sydney, St. Leonards, New South Wales, Australia.

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