

## Literature Abstracts and Articles Update

From the Center for Bloodless Medicine and Surgery  
Children's Hospital Central California

*This update is designed as an aid to help healthcare professionals stay informed on the latest blood management healthcare developments. It is a way to see how people in the field of pediatric healthcare are preparing today for the challenges of a new era and beyond.*

*We hope that from time to time this monthly update will prove useful to you in keeping updated about all that is happening in the world of pediatric bloodless medicine and surgery.*

*Steve Cade – Coordinator*

### Recombinant Factor VIIa in Pediatric Patients

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Summary: To date, the majority of experience with recombinant factor VIIa (rFVIIa) has been in patients with hemophilia who developed auto-antibodies (inhibitors) against factor VIII. This paper examines the reported experiences with rFVIIa use in non-hemophiliac pediatric-aged patients and is based on a review of the literature as well as an evaluation of isolated case reports and case series. The literature contains reports on the successful use of rFVIIa in approximately 40 non-hemophiliac pediatric patients with acquired coagulation dysfunction of various etiologies as well as inherited disorders of platelet function. Although clinical experience is somewhat limited, no significant adverse effects have been noted in the pediatric-aged patient. Given its potential therapeutic impact, rFVIIa warrants further investigation in the pediatric population. As the reports in the literature illustrate, rFVIIa may be indicated in coagulopathic states to control active bleeding or as prophylaxis to correct coagulation function prior to an invasive procedure. rFVIIa may be considered when the coagulopathy does not respond to FFP, time constraints do not allow for blood typing, thawing and administration of FFP,

or there are concerns regarding the potential hemodynamic effects of FFP.

### The effect of amicar on perioperative blood loss in idiopathic scoliosis: the results of a prospective, randomized double-blind study.

*Florentino-Pineda I, Thompson GH, Poe-Kochert C, Huang RP, Haber LL, Blakemore LC. Spine. 2004 Feb 1;29(3):233-8. Division of Pediatric Anesthesiology, Rainbow Babies and Children's Hospital, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio 44106, USA.*

STUDY DESIGN: A prospective, randomized, double-blind Institutional Review Board-approved study evaluating the efficacy of Amicar (epsilon aminocaproic acid), an antifibrinolytic agent, in decreasing perioperative blood loss in idiopathic scoliosis. OBJECTIVES: To compare the perioperative (intraoperative and postoperative) blood loss and the need for autologous and homologous blood replacement in two groups of essentially identical patients undergoing a posterior spinal fusion for idiopathic scoliosis. SUMMARY OF BACKGROUND DATA: Reducing perioperative blood loss and the need for transfusion in patients undergoing spinal surgery is important to orthopedic surgeons. Recently, there has been interest in pharmacologic agents, particularly Amicar and Aprotinin, to assist in decreasing perioperative blood loss. In 2001, in a preliminary study, we

demonstrated that Amicar appeared to be effective in reducing perioperative blood loss in patients with idiopathic scoliosis undergoing a posterior spinal fusion and segmental spinal instrumentation. This was a study of 28 consecutive patients receiving Amicar compared to a historical control group of the 31 previous consecutive patients with the same study criteria. The current study was performed to confirm our preliminary findings. METHODS: We analyzed the perioperative blood loss of 36 patients with idiopathic scoliosis who were blindly randomized by the operating room pharmacy into an Amicar and control group. The criteria to be included in the study was the same as the preliminary study: diagnosis of idiopathic scoliosis, age at surgery 11 to 18 years, posterior spinal fusion and segmental spinal instrumentation only, autogenous iliac crest bone graft or homologous cancellous bone graft, and a signed agreement to participate in the study. The patients in both groups had the same anesthetic technique, intraoperative procedure, instrumentation, postoperative management, and standardized indications for transfusions. RESULTS: Before surgery, the patients in both groups were essentially identical. The distribution of patients and their results was not known until the completion of the study. Patients in the Amicar group demonstrated a statistically significant decrease in perioperative blood loss and the need for autologous blood transfusion. Interestingly, this decrease was predominantly in the postoperative suction drainage. This may be due to elevated fibrinogen levels induced by Amicar. The patients taking Amicar had no intraoperative or postoperative thromboembolic complications. CONCLUSIONS: The results of this study confirmed that the use of intraoperative Amicar is a safe, effective, and inexpensive method to significantly reduce perioperative blood loss in patients with idiopathic scoliosis undergoing posterior spinal fusion and segmental spinal instrumentation. The results have allowed us to reduce our recommendation for perioperative autologous blood donation, thereby further decreasing costs.

### The influence of a blood conserving device on anaemia in intensive care patients.

*MacIsaac CM, Presneill JJ, Boyce CA, Byron KL, Cade JF. Anaesth Intensive Care. 2003 Dec; 31(6):653-7. Intensive Care Unit, Royal Melbourne Hospital, Melbourne, Victoria.*

The contribution of iatrogenic blood loss through diagnostic testing to the anaemia of critical illness remains controversial. We measured the effect of an arterial line blood conservation device upon blood loss and anaemia in adult intensive care patients. This randomized controlled trial of 160 patients in a major

Intensive Care Unit (ICU) compared a blood conservation device (Venous Arterial Blood Management Protection Plus, VAMP Plus system, Baxter Healthcare) (VAMP group) to a standard arterial pressure line set attached to an arterial catheter (control group). The primary outcome measured was the change in haemoglobin concentration (Hb) during each patient's ICU admission and the volume of blood lost through diagnostic testing in ICU was also recorded. Both groups of 80 patients were matched for age, gender, severity of illness (APACHE II), baseline Hb on entry and ICU length of stay. Both groups had a similar (median [range]) change in Hb during ICU admission (VAMP-7 [-84 to +21] g/l; Control -4 [-67 to +40] g/l; P = 0.33). The VAMP patients lost significantly less blood for diagnostic testing while in ICU (VAMP 63 [0 to 787] ml; Control 133 [7 to 1227] ml; P = 0.001). We conclude that the VAMP Plus system significantly reduced iatrogenic blood loss in critically ill patients, but this reduction did not affect the fall in Hb that accompanies critical illness.

### Does prior transfusion worsen outcomes from infection in surgical patients?

*Hughes MG, Evans HL, Lightfoot L, Chong TW, Smith RL, Raymond DP, Pelletier SJ, Claridge JA, Pruett TL, Sawyer RG. Surg Infect (Larchmt). 2003 Winter; 4(4): 335-43. Department of Surgery, Surgical Infectious Disease Laboratory, University of Virginia, Charlottesville, Virginia 22908, USA. mgh6a@virginia.edu*

BACKGROUND: Controversy continues to exist regarding the immunomodulatory effects of cellular blood transfusions in the fields of oncology, transplantation, and infectious diseases. Numerous studies have correlated transfusion with hospital-acquired infection, but the impact of transfusion on infection-related mortality has not been addressed. The objective of this study was to determine the effect of transfusion on outcomes among infected surgical patients. METHODS: Data on all hospital-acquired infectious episodes among surgical intensive care unit and ward patients were collected prospectively over 39 months at a single university hospital. The relationships between prior transfusion (defined as the receipt of allogeneic red blood cells or platelets during the index hospitalization but prior to the development of infection) and over 100 variables were examined using univariate and multiple logistic regression analysis, with inclusion of a propensity score for prior transfusion to attempt to account for treatment selection bias. RESULTS: During the study period, 1,228 infectious episodes occurred; 641 were associated with the transfusion of packed red blood cells or platelets. Univariate analysis revealed that patients with those infectious

episodes following transfusion had higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (18.3 +/- 0.3 vs. 10.9 +/- 0.3,  $p < 0.0001$ ) and higher mortality (26.0% vs. 8.9%,  $p < 0.0001$ ). Those patients who died received a greater number of transfusions prior to infection than those who lived (7.7 +/- 0.8 vs. 4.5 +/- 0.3,  $p = 0.0002$ ). Multiple logistic regression analysis revealed that the propensity score for prior transfusion independently predicted mortality (odds ratio 9.45, 95% confidence interval 3.71-24.09,  $p < 0.001$ ), but that neither the presence or absence of transfusion (OR 0.89, 95% CI 0.54-1.46,  $p = 0.6$ ) nor the absolute number of units of red blood cells or platelets transfused (OR for red blood cells 1.00, 95% CI 0.98-1.02,  $p = 0.7$ ; OR for platelets 0.97, 95% CI 0.90-1.05,  $p = 0.5$ ) independently predicted mortality.

**CONCLUSIONS:** The transfusion of packed red blood cells or platelets prior to infection is associated with more severe disease among surgical patients, but once corrected for treatment selection bias does not appear to worsen outcomes from infection.

### The use of a fibrin tissue sealant during laparoscopic partial nephrectomy

*R.S. Pruthi, J. Chun and M. Richman BJU International Volume 93 Issue 6 Page 813 - April 2004 doi: 10.1111/j.1464-410X.2003.04742.x*

The use of a fibrin tissue sealant in laparoscopic partial nephrectomy is described by authors from Chapel Hill. They used it in 15 patients after electrocauterization and argon-beam coagulation; it was helpful in haemostasis and in preventing urinary leak. **OBJECTIVE** To assess the feasibility and efficacy of commercially available fibrin tissue sealant as a haemostatic agent and collecting-system sealant during hand-assisted laparoscopic partial nephrectomy (LPN). **PATIENTS AND METHODS** Fifteen consecutive patients underwent LPN for enhancing renal masses suspicious for renal cell carcinoma via a transperitoneal approach and with the use of a hand-assistance device. Monopolar electrocauterization and argon-beam coagulation were initially used to slow bleeding from the resection site. Through a laparoscopic applicator, Tisseel™ fibrin sealant (Baxter Inc., Deerfield, IL) was applied to the transected partial nephrectomy bed while the surgeon's hand maintained adequate compression and partial haemostasis. No further haemostatic measures were required in any patient; the patients were evaluated for acute and delayed bleeding or urinary extravasation. **RESULTS** In all cases electrocauterization and argon-beam coagulation followed by the application of Tisseel was successful in obtaining strict haemostasis of the surgical bed, with no evidence of bleeding during or after surgery on immediate and

extended follow-up. In addition, there was no evidence during or after surgery of any urinary leak. There were no immediate or delayed complications in any of the patients; a short-term outpatient follow-up (12-60 weeks) revealed no additional problems. **CONCLUSIONS** Conventional haemostatic measures of electrocauterization and argon-beam coagulation combined with commercial fibrin sealant allows successful haemostasis during LPN. In addition to haemostatic properties, fibrin sealants appear to have sealing properties that may help to prevent complications of urinary leakage by helping to seal or close the small defects in the urinary collecting system. The use of this compound may facilitate the ability of the urological laparoscopist during LPN.

### Influence of crystalloid and colloid replacement solutions on hemodynamic variables during acute normovolemic hemodilution.

*J Clin Anesth. 2004 Feb; 16(1): 11-7. Jones SB, Whitten CW, Monk TG. Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA.*

**STUDY OBJECTIVE:** To determine whether, in maintaining normovolemia during acute normovolemic hemodilution, replacement fluid choice influences intraoperative hemodynamic variables. **DESIGN:** Prospective, randomized, single-blinded study. **SETTING:** Operating room of a tertiary-care university hospital. **PATIENTS:** 40 adult, ASA physical status I, II, and III patients scheduled for acute normovolemic hemodilution during radical prostatectomy. **INTERVENTIONS:** Patients were randomly assigned to four replacement fluid groups to receive 1) Ringer's lactate, 2) 5% albumin, 3) 6% dextran 70, or 4) 6% hetastarch. A standardized general anesthetic was used, and patients underwent moderate hemodilution to a target hemoglobin of 9 gm/dL. **MEASUREMENTS:** Hemodynamic variables were recorded using standard monitors, 5-lead electrocardiography, radial arterial catheter, and pulmonary artery catheter. Red blood cell loss for the entire hospitalization was calculated. **MAIN RESULTS:** Demographic and clinical outcome data were similar among the groups. During acute normovolemic hemodilution, heart rate and pulmonary capillary wedge pressure were unchanged from baseline in all groups, but patients receiving Ringer's lactate or albumin had greater declines in mean arterial pressure at the end of acute normovolemic hemodilution. Cardiac and oxygen consumption indexes were stable during acute normovolemic hemodilution, but oxygen extraction increased. **CONCLUSIONS:** During hemodilution, anesthetized patients maintain whole body oxygenation by increasing oxygen extraction. The administration of hetastarch or dextran as

the replacement fluid during acute normovolemic hemodilution is associated with a more stable mean arterial pressure, but overall acute normovolemic hemodilution is well tolerated irrespective of the replacement fluid used.

### **Predictors of transfusion requirements for cardiac surgical procedures at a blood conservation center.**

*Ann Thorac Surg. 2004 Feb; 77(2): 626-34. Moskowitz DM, Klein JJ, Shander A, Cousineau KM, Goldweit RS, Bodian C, Perelman SI, Kang H, Fink DA, Rothman HC, Ergin MA. Department of Anesthesiology and Critical Care Medicine, Englewood Hospital and Medical Center, Englewood, New Jersey, USA. david.moskowitz@ehmc.com*

**BACKGROUND:** Previous studies defining perioperative risk factors for allogeneic transfusion requirements in cardiac surgery were limited to highly selected cardiac surgery populations or were associated with high transfusion rates. The purpose of this study was to determine perioperative risk factors and create a formula to predict transfusion requirements for major cardiac surgical procedures in a center that practices a multimodality approach to blood conservation. **METHODS:** We performed an observational study on 307 consecutive patients undergoing coronary artery bypass grafting, valve, and combined (coronary artery bypass grafting and valve) procedures. An equation was derived to estimate the risk of transfusion based on preoperative risk factors using multivariate analysis. In patients with a calculated probability of transfusion of at least 5%, intraoperative predictors of transfusion were identified by multivariate analysis. **RESULTS:** Thirty-five patients (11%) required intraoperative or postoperative allogeneic transfusions. Preoperative factors as independent predictors for transfusions included red blood cell mass, type of operation, urgency of operation, number of diseased vessels, serum creatinine of at least 1.3 mg/dL, and preoperative prothrombin time. Intraoperative factors included cardiopulmonary bypass time, three or fewer bypass grafts, lesser volume of acute normovolemic hemodilution removed, and total crystalloid infusion of at least 2,500 mL. The derived formula was applied to a validation cohort of 246 patients, and the observed transfusion rates conformed well to the predicted risks. **CONCLUSIONS:** A multimodality approach to blood conservation in cardiac surgery resulted in a low transfusion rate. Identifying patients' risks for transfusion should alter patient management perioperatively to decrease their transfusion rate and make more efficient use of blood resources.

### **Pharmacological alternatives to blood transfusion: what is new about?**

*Med Clin (Barc). 2004 Feb 21; 122(6): 231-6. [Article in Spanish] Paramo JA, Lecumberri R, Hernandez M, Rocha E. Servicio de Hematología. Clínica Universitaria de Navarra. Pamplona. Espana.*

Pharmacological approaches to reduce blood transfusion include the protease inhibitor aprotinin, lysine-analogue antifibrinolytics synthetic arginine-vasopressin derivatives (DDAVP) and recombinant factor VII (rFVIIa). These agents are known to prevent the need for blood after major surgery (cardiac, hepatic, and orthopaedic). Among the nonhemostatic agents erythropoietin (EPO) may be effective to reduce blood requirements in medical and surgical patients. Aprotinin is consistently effective in reducing blood transfusion in cardiac and hepatic surgical procedures, but there is little data to support its use in elective orthopaedic surgery. Antifibrinolytics show no evidence of efficacy in cardiac and hepatic surgery and its use is not warranted in orthopaedic surgery. Limited data suggest that DDAVP may be effective when a defect in platelet function is demonstrated. rFVIIa emerges as a promising haemostatic agent with proven benefit to reduce bleeding in haemophiliacs with inhibitors but might also be effective in patients with thrombocytopenia and thrombopathy, as well as in life-threatening hemorrhage in postsurgical patients. Ongoing studies will establish its role as a possible universal haemostatic agent. Hematopoietic cytokines, such as EPO, may have a place to avoid blood transfusion in a variety of clinical conditions, including cancer and critically ill patients.

### **Can Policy Decisions in Transfusion Medicine Be Evidence-Based?**

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**Summary:** If the concept of evidence-based medicine were considered at a policy level, it would likely dictate that policy decisions be made on the basis of the best available research evidence. In transfusion medicine, however, decisions are based on a broader range of inputs, and the criteria for evaluating the

efficacy and/or cost-effectiveness of proposed interventions differ from those used in other areas. Reasons why policy decisions in transfusion medicine are often based on considerations other than solely the best available research evidence include public perceptions of transfusion as being an inherently "unsafe" intervention, public expectations with regard to transfusion safety, and proposals for applying the precautionary principle to transfusion medicine. In the authors' opinion, use of the precautionary principle may be justified in addressing transfusion risks that are viewed as "dread events," but this principle should not be applied indiscriminately to all transfusion risks.

### **Induction of megakaryocytopoiesis and thrombocytopoiesis by JTZ-132, a novel small molecule with thrombopoietin mimetic activities.**

*Blood. 2004 Mar 4 [Epub ahead of print] Inagaki K, Oda T, Naka Y, Shinkai H, Komatsu N, Iwamura H. Central Pharmaceutical Research Institute, Japan Tobacco Inc., Takatsuki, Osaka, Japan.*

We report in this paper that a novel small molecule, JTZ-132, induced growth and differentiation of megakaryocytic progenitor cells, and improved thrombocytopenia in myelosuppressed mice. JTZ-132 stimulated proliferation of UT-7/TPO cells, a cell line highly sensitive to thrombopoietin (TPO), and exhibited full efficacy comparable to TPO with an approximate EC50 value of 0.43 micro mol/L, whereas little proliferation was observed in a TPO-insensitive cell line, UT-7/EPO, and human carcinoma cell line, HCT116. Signal transduction studies revealed that JTZ-132 induced tyrosine phosphorylation of c-Mpl, JAK2 and STAT5 in UT-7/TPO cells as well as TPO. JTZ-132 increased the number of megakaryocyte-specific marker, CD61 and CD41-positive cells in cultures of mouse and human bone marrow cells, respectively, and the colony-forming unit megakaryocytes in mouse bone marrow cells. In vivo experiments in x-ray irradiation or busulfan-injection induced myelosuppressed mice demonstrated that subcutaneously injected JTZ-132 at 30 mg/kg showed significantly higher platelet number at nadir, and accelerated platelet recovery without affecting white blood cell number. These data suggest that JTZ-132 is a novel stimulator of megakaryocytopoiesis and thrombocytopoiesis in vitro and in vivo with TPO mimetic activities, and that it is useful for the treatment of thrombocytopenia.

### **Blood substitutes**

*Current Opinion in Anaesthesiology: Volume 17(2) April 2004 pp 139-143 Habib, Fahim A.;*

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Purpose of review: Risk of disease transmission and limitations in the ability to transfuse in the prehospital or combat setting have stimulated research in the field of oxygen therapeutics. Several products have completed safety trials and are presently undergoing investigation for their efficacy. In the near future, the clinician will likely employ these products in the management of a variety of patient populations. Though similar in their oxygen carrying capacity, each agent possesses distinct physiologic effects. Understanding of the benefits and shortcomings of the various compounds is essential in order to optimally utilize them in various clinical settings. This review provides an overview of recent developments in the field of oxygen therapeutics and highlights results of clinical trials. Recent findings: Modified hemoglobin solutions of human or bovine origin and perfluorochemical-based emulsions are in advanced stages of clinical testing. Bovine hemoglobin-based solutions have been associated with vascular reactivity, methemoglobin formation and development of antibodies. Larger safety trials are necessary before they can find widespread use. Polymerized human hemoglobin solutions have a favorable safety profile in early trials and have been effective as a resuscitation fluid in circumstances when red cells may be unavailable. Unfortunately, outdated human blood, the substrate for this product, is itself in short supply. Perfluorocarbons similarly reduce the need for allogeneic transfusion, but the need for high-inspired oxygen levels currently limits use. Recombinant, polymer-encapsulated and additional forms of chemically modified hemoglobins are being developed and are undergoing testing in animal models Summary: Oxygen carriers offer a viable alternative to allogeneic transfusion. All oxygen therapeutic agents are not clinically equivalent. Optimal utilization requires a thorough understanding of the therapeutic potentials and adverse effects of the solution being considered for use.

### **Recombinant factor VIIa as an antidote for anticoagulant treatment.**

*Levi M, Bijsterveld Nr N, Keller Tt T. Semin Hematol. 2004 Jan; 41(1 Suppl): 65-9.*

Increasing knowledge on the function of the hemostatic system in vivo and limitations of currently available anticoagulant agents have

led to the development of a new generation of anticoagulants. These new agents have a greater specificity towards activated coagulation pathways and factors and are presently being evaluated in clinical studies. The new generation anticoagulants include specific inhibitors of factor IIa (melagatran), factor Xa (pentasaccharides), and agents that interfere with tissue factor (TF) activity. A limitation of this new class of anticoagulants may be the lack of an appropriate strategy to reverse the effect if a bleeding event occurs. Recombinant factor VIIa (rFVIIa) is a potent prohemostatic agent and may represent an interesting option for consideration when an antidote is required. Indeed, rFVIIa has proven to be efficacious in the reversal of anticoagulant treatment with vitamin K antagonists. Studies in healthy subjects have also revealed that rFVIIa administration corrects coagulation time and can induce thrombin generation during anticoagulation with pentasaccharides or TF-inhibiting therapy. These results indicate that rFVIIa infusion results in a prohemostatic response *in vivo* in patients receiving treatment with factor Xa- or TF-specific anticoagulants. This suggests that rFVIIa may be a good candidate as an antidote for new anticoagulants in cases of (severe) bleeding or in patients scheduled for emergency surgery.

### Experiences with recombinant human factor VIIa in patients with thrombocytopenia.

*Goodnough LT. Semin Hematol. 2004 Jan; 41(1 Suppl): 25-9.*

In addition to its proven benefits in hemophilia, recombinant factor VIIa (rFVIIa), is predicted to be of benefit in other situations characterized by profuse bleeding and impaired thrombin generation, due to its ability to enhance thrombin generation on already activated platelets. This article reviews studies that have described the use of rFVIIa in a variety of clinical settings involving refractory hemorrhage. *Ex vivo* studies revealed that, at pharmacologic doses, rFVIIa significantly shortened the lag time of thrombin generation, resulting in the formation of more thrombin during the initial coagulation process. Anecdotal clinical reports describe how rFVIIa has been used to resolve serious bleeding in thrombocytopenic patients and a study showed how rFVIIa positively reduced bleeding time in 52% of bleeding wounds in patients with thrombocytopenia. It is concluded that rFVIIa has a potential role in patients with thrombocytopenia and clinical hemorrhage.

### Safety profile of recombinant factor VIIa.

*Roberts HR, Monroe DM 3rd, Hoffman M. Semin Hematol. 2004 Jan; 41(1 Suppl): 101-8.*

Recombinant factor VIIa (rFVIIa; NovoSeven(R), Novo Nordisk, Bagsvaerd, Denmark) has been used for many years in the successful management of bleeding episodes in patients with hemophilia and inhibitors. More recently, rFVIIa has also shown considerable success as a hemostatic agent in trauma and surgery patients without pre-existing coagulopathy. Despite extensive and varied usage of rFVIIa, the incidence of serious adverse events associated with its use is less than 1%; however, there remain concerns regarding the agent's potential to induce thrombosis. This paper will review the safety profile of rFVIIa by examining existing clinical evidence, and will demonstrate that the isolated thrombotic events reported following rFVIIa treatment are due primarily to an improvement in the coagulation mechanism rather than rFVIIa treatment *per se*. The demonstrated safety of rFVIIa is probably due to its localization to injured areas of the vascular tree by binding to tissue factor (TF) and activated platelets at the bleeding site, thus avoiding systemic activation of coagulation. Finally, those situations in which rFVIIa therapy may not be safe, such as disseminated intravascular coagulation (DIC) and sepsis, will also be discussed.

### Vascular biology-the role of tissue factor.

*Hathcock J. Semin Hematol. 2004 Jan; 41(1 Suppl): 30-4.*

It is well established that tissue factor (TF) is abundantly present in various extravascular tissues, in the adventitia of blood vessels, and in atheroma. Thus, in the event of plaque rupture or damage to the blood vessel wall, TF is readily exposed to flowing blood, allowing it to form a complex with circulating factor VIIa (FVIIa) in order to activate factor X (FX) both directly, and indirectly via factor IX (FIX). Platelets quickly adhere to the injured site, facilitating localized thrombin formation and subsequent fibrin production. With each new layer of platelets and fibrin that adheres to the injured surface, the exposed TF on the vessel wall, along with the localized circulating factors IX (FIXa) and X (FXa) that it generates, becomes increasingly isolated from the events near the surface of the growing thrombus. The physical blanketing of an injured surface by platelets and fibrin in addition to the release of platelet tissue factor pathway inhibitor (TFPI), prevents FIXa and FXa from diffusing more than a few tens of microns away from the vessel wall, far short of the 3 mm thickness needed for occlusive thrombosis. Thus an alternative FXa-generating mechanism must be involved that allows for the formation of prothrombinase activity far away from the

vessel wall near the front of a growing thrombus.

### Dosing with recombinant factor viia based on current evidence.

*Hedner U. Semin Hematol. 2004 Jan; 41(1 Suppl): 35-9.*

Recombinant factor VIIa (rFVIIa; NovoSeven(R), Novo Nordisk, Bagsvaerd, Denmark) induces hemostasis in patients with severe hemophilia and inhibitors, and has been found to control hemorrhage associated with severe trauma and surgery in patients with basically normal hemostatic mechanisms from the start. By enhancing the generation of thrombin on activated platelets, rFVIIa facilitates the formation of a tight, stable fibrin plug that is resistant to premature lysis. Clinical efficacy has been achieved with doses of rFVIIa much lower than originally proposed by in vitro models. Based on early clinical experiences, a dosing schedule of 90 to 120 microg/kg every 2 hours for the first 24 hours was recommended for serious bleeds and surgical cover. This schedule has been shown to induce and maintain hemostasis in 83% to 95% of serious bleeding episodes, and in 90% to 100% of major surgical cases. However, "mega" doses of rFVIIa may demonstrate greater efficacy in the treatment of joint bleeds, as they are more likely to evoke a full thrombin burst. Interpatient variation in recovery rates, clearance rates, and the ability to generate thrombin on the activated platelet surface may influence the efficacy of rFVIIa. Optimal doses may thus vary not only between hemophilia patients, but also between patients treated for other bleeding disorders.

### Recombinant factor VIIa in the treatment of bleeding.

*Midathada MV, Mehta P, Waner M, Fink LM. Am J Clin Pathol. 2004 Jan; 121(1): 124-37. Department of Hematology/Oncology, University of Arkansas for Medical Sciences, Little Rock, USA.*

Recombinant factor VIIa (rFVIIa) has become available for treating people with hemophilia with inhibitors who experience bleeding or require surgery. It has become apparent that rFVIIa is useful in controlling bleeding in a variety of clinical situations. This review attempts to collate and summarize the nonhemophilia applications of rFVIIa. The theoretical mechanism for the coagulation and hemostatic effects of rFVIIa are discussed. The dosage and clinical administration are described. The potential uses for patients with liver disease, anticoagulation-induced bleeding, surgery, thrombocytopenia, thrombasthenia, von Willebrand disease, and other bleeding disorders are reviewed. The use of rFVIIa is

evolving, and the indications, dosage, and precautions or contraindications need to be further described and defined. It is an expensive therapy and needs to be prescribed judiciously. This review is meant to be an introduction to this new hemostatic reagent. The uses for rFVIIa will evolve as more studies are published.

### Epoetin Beta: a review of its clinical use in the treatment of anaemia in patients with cancer.

*Cheer SM, Wagstaff AJ. Drugs. 2004; 64(3): 323-46. Adis International Limited, Auckland, New Zealand.*

Epoetin beta (NeoRecormon((R))) is a recombinant form of erythropoietin. It increases reticulocyte counts, haemoglobin (Hb) levels and haematocrit. Epoetin beta administered subcutaneously once weekly corrected anaemia and had equivalent efficacy to that of epoetin beta administered three times weekly in patients with haematological malignancies. Subcutaneous epoetin beta reduced transfusion requirements and increased Hb levels versus no treatment in patients with solid tumours and chemotherapy-induced anaemia in nonblind, randomised trials. Anaemia and quality of life were also improved, and blood transfusion requirements were reduced to a significantly greater extent than placebo or no treatment (with supportive blood transfusion) in patients with haematological malignancies. Most patients were receiving chemotherapy. Subcutaneous epoetin beta was well tolerated by patients with cancer; adverse events with the drug occurred with a similar incidence to those with placebo or no treatment (with supportive blood transfusion). Hypertension was relatively uncommon with epoetin beta in clinical trials. Patients with haematological malignancies and a baseline platelet count  $\geq 100 \times 10^9/L$ , Hb levels of  $\geq 9$  g/dL or lower erythropoietin levels have demonstrated better responses to epoetin beta than other patients in clinical trials. However, neither baseline erythropoietin level nor the observed to predicted ratio of erythropoietin levels correlated with the response to epoetin beta in patients with solid tumours and chemotherapy-induced anaemia. A decrease of  $< 1$  g/dL or an increase in Hb with epoetin beta during the first chemotherapy cycle indicated a low transfusion need in subsequent cycles in patients with ovarian carcinoma. In general, the efficacy of epoetin beta is not limited by tumour type. Response to the drug occurred irrespective of the nature (platinum- or nonplatinum-based) or presence of chemotherapy treatment in randomised trials. CONCLUSION: Epoetin beta has shown efficacy in the management of cancer-related anaemia in patients with haematological malignancies and of chemotherapy-induced anaemia in patients with solid tumours. Once-weekly administration

provides added convenience for patients and may be cost saving, although additional research into the potential pharmacoeconomic benefits of this regimen are required. The drug is well tolerated in patients with cancer and is associated with little injection-site pain when administered subcutaneously. Epoetin beta is an important option in the prevention of chemotherapy-induced anaemia, and a valid and valuable alternative to blood transfusion therapy for the treatment of cancer-related or chemotherapy-induced anaemia.

**Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients.**

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Systematic evaluations of anemia, thrombocytopenia, and coagulopathy are essential to identifying and managing their causes successfully. In all cases, clinicians should evaluate RBC measurements alongside WBC and platelet counts and WBC differentials. Multiple competing factors may coexist; certain factors affect RBCs independent of those that affect WBCs or platelets. Ideally, clinicians should examine the peripheral blood smear for morphologic features of RBCs, WBCs, and platelets that provide important clues to the cause of the patient's hematologic disorder. Thrombocytopenia arises from decreased platelet production, increased platelet destruction, or dilutional or distributional causes. Drug-induced thrombocytopenias present diagnostic challenges, because many medicines can cause thrombocytopenia and critically ill patients often receive multiple medications. If they suspect type II HIT, clinicians must promptly discontinue all heparin sources, including LMWHs, without awaiting laboratory confirmation, to avoid thrombotic sequelae. Because warfarin anticoagulation induces acquired protein C deficiency, thereby exacerbating the prothrombotic state of type II HIT, warfarin should be withheld until platelet counts increase to more than 100,000/microL and type II HIT is clearly resolving. The presence of a consumptive coagulopathy in the setting of thrombocytopenia supports a diagnosis of DIC, not TTP-HUS, and is demonstrated by decreasing serum fibrinogen levels, and increasing TTs, PTs, aPTTs, and fibrin degradation products. Increasing D-dimer, levels are the most specific DIC parameter and reflect fibrinolysis of cross-linked fibrin. Elevated PTs or a PTTs can result from the absence of factors or

the presence of inhibitors. Clinicians should suspect factor inhibitors when the prolonged PT or aPTT does not correct or only partially corrects following an immediate assay of a 1:1 mix of patient and normal plasma. In addition to factor inhibitors, antiphospholipid antibodies (e.g., lupus anticoagulant) can produce a prolonged aPTT that does not correct with normal plasma but is overcome by adding excess phospholipid or platelets. Paradoxically, a tendency to thrombosis, not bleeding, accompanies lupus anticoagulants and the antiphospholipid antibody syndrome. Transfusion of red blood cells, platelets, or plasma products is sometimes warranted, but clinicians must carefully weigh potential benefits against known risks. In critically ill patients, administering RBCs can enhance oxygen delivery to tissues. Among euvolemic patients who do not have ischemic heart disease, guidelines recommend a transfusion threshold of HGB levels in the range of 6.0 to 8.0 g/dL; patients who have HGB that is at least 10.0 g/dL are unlikely to benefit from blood transfusion. The use of rHuEPO to increase erythropoiesis offers an alternative to RBC transfusion, assuming normal, responsive progenitor cells and adequate iron, folate, and cobalamin stores. Future research should examine whether clinical outcomes from rHuEPO use in critically ill patients are important and cost-effective. Because platelets play an instrumental role in primary hemostasis, platelet transfusions are often important in managing patients who are bleeding or at risk of bleeding with thrombocytopenia or impaired platelet function. Platelet transfusions carry risks, and decisions to transfuse platelets must consider clinical circumstances. Most important, platelet transfusions are generally contraindicated if the underlying disorder is TTP or type II HIT, because platelet transfusion in these settings may fuel thrombosis and worsen clinical signs and symptoms. Plasma products can correct hemostasis when bleeding arises from malfunction, consumption, or underproduction of plasma coagulation proteins. Choice of plasma product for transfusion depends on clinical circumstances. FFP is the most commonly used plasma product to correct clotting factor deficiencies, particularly coagulopathies that are attributable to multiple clotting factor deficiency states as in liver disease, DIC, or warfarin anticoagulation. PCC or rFVIIa that is administered in small volumes may provide advantages over FFP when coagulopathies require quick reversal without risk of volume overload. Factor concentrates can replace specific factor deficiencies. Recombinant FVIIa bypasses inhibitors to factors VIII and IX and vWF. Use of rFVIIa in managing hemostatic abnormalities from severe liver dysfunction; extensive surgery, trauma, or bleeding; excessive warfarin anticoagulation; and certain platelet disorders requires further study to determine optimal and cost-effective dosing

regimens. Recombinant activated protein C reduces mortality from severe sepsis that is associated with organ dysfunction in adults who are at high risk for death (APACHE scores of at least 25). In severe sepsis, levels of protein C decrease, as do fibrinogen and platelet levels. Because of its anticoagulant effect, however, drotrecogin alfa may induce bleeding. Guidelines for drotrecogin alfa use must take into account bleeding risks.

### **The CRIT Study: Anemia and blood transfusion in the critically ill- Current clinical practice in the United States.**

*Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ. Crit Care Med. 2004 Jan; 32(1): 39-52.*

**SUMMARY:** **OBJECTIVE** To quantify the incidence of anemia and red blood cell (RBC) transfusion practice in critically ill patients and to examine the relationship of anemia and RBC transfusion to clinical outcomes. **DESIGN** Prospective, multiple center, observational cohort study of intensive care unit (ICU) patients in the United States. Enrollment period was from August 2000 to April 2001. Patients were enrolled within 48 hrs of ICU admission. Patient follow-up was for 30 days, hospital discharge, or death, whichever occurred first. **SETTING** A total of 284 ICUs (medical, surgical, or medical-surgical) in 213 hospitals participated in the study. **PATIENTS** A total of 4,892 patients were enrolled in the study. **MEASUREMENTS AND MAIN RESULTS** The mean hemoglobin level at baseline was 11.0 +/- 2.4 g/dL. Hemoglobin level decreased throughout the duration of the study. Overall, 44% of patients received one or more RBC units while in the ICU (mean, 4.6 +/- 4.9 units). The mean pretransfusion hemoglobin was 8.6 +/- 1.7 g/dL. The mean time to first ICU transfusion was 2.3 +/- 3.7 days. More RBC transfusions were given in study week 1; however, in subsequent weeks, subjects received one to two RBC units per week while in the ICU. The number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and an increase in mortality. Patients who received transfusions also had more total complications and were more likely to experience a complication. Baseline hemoglobin was related to the number of RBC transfusions, but it was not an independent predictor of length of stay or mortality. However, a nadir hemoglobin level of <9 g/dL was a predictor of increased mortality and length of stay. **CONCLUSIONS** Anemia is common in the critically ill and results in a large number of RBC transfusions. Transfusion practice has changed little during the past decade. The number of RBC units transfused is

an independent predictor of worse clinical outcome.

### **Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery.**

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**BACKGROUND:** Using algorithms based on point of care coagulation tests can decrease blood loss and blood component transfusion after cardiac surgery. We wished to test the hypothesis that a management algorithm based on near-patient tests would reduce blood loss and blood component use after routine coronary artery surgery with cardiopulmonary bypass when compared with an algorithm based on routine laboratory assays or with clinical judgement. **METHODS:** Patients (n=102) undergoing elective coronary artery surgery with cardiac bypass were randomized into two groups. In the point of care group, the management algorithm was based on information provided by three devices, the Hepcon((R)), thromboelastography and the PFA-100((R)) platelet function analyser. Management in the laboratory test group depended on rapidly available laboratory clotting tests and transfusion of haemostatic blood components only if specific criteria were met. Blood loss and transfusion was compared between these two groups and with a retrospective case-control group (n=108), in which management of bleeding had been according to the clinician's discretion. **RESULTS:** All three groups had similar median blood losses. The transfusion of packed red blood cells (PRBCs) and blood components was greater in the clinician discretion group (P<0.05) but there was no difference in the transfusion of PRBCs and blood components between the two algorithm-guided groups. **CONCLUSION:** Following algorithms based on point of care tests or on structured clinical practice with standard laboratory tests does not decrease blood loss, but reduces the transfusion of PRBCs and blood components after routine cardiac surgery, when compared with clinician discretion. Cardiac surgery services should use transfusion guidelines based on laboratory-guided algorithms, and the possible benefits of point of care testing should be tested against this standard.

## The combination of platelet-enriched autologous plasma with bovine collagen and thrombin decreases the need for multiple blood transfusions in trauma patients with retroperitoneal bleeding.

Bochicchio G, Dunne J, Bochicchio K, Scalea T. *J Trauma*. 2004 Jan;56(1):76-9.

**SUMMARY:** OBJECTIVES Bleeding from blunt and penetrating retroperitoneal injuries during operative exploration are often difficult to control surgically and can be associated with significant blood loss. Our goals were to evaluate and compare the efficacy of a topical autologous platelet-enriched plasma combined with bovine collagen and thrombin (PCT) to Gelfoam/thrombin (G/T) in relation to hemostatic control/blood transfusion (BTx) requirements and subsequent outcome. METHODS Prospective data were collected on all patients who underwent operative exploration for retroperitoneal injuries in which either PCT or G/T was applied with or without packing over a 2.5-year period. Patients were stratified by age, gender, mechanism of injury, preoperative international normalized ratio, pH, hematocrit, intraoperative blood loss, and BTx requirements. Subsequent BTx requirements were calculated within 48 hours of the surgical procedure. Outcome was measured by intensive care unit and hospital length of stay and mortality.

**RESULTS** A total of 78 patients met study criteria. Patients who received G/T had a significantly greater number of early postoperative transfusions ( $p < 0.001$ ) and a longer hospital ( $p < 0.001$ ) and intensive care unit length of stay ( $p < 0.007$ ). There was no difference in mortality.

**CONCLUSION** PCT is a rapidly available topical hemostat that is associated with a significant decrease in the need for postoperative blood transfusions and intensive care unit and hospital length of stay. A randomized prospective trial to confirm these results is warranted.

## Emerging infectious threats to the blood supply.

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During the past 15 years, it has become clear that new agents and new strains of existing agents continue to emerge worldwide as protagonists of infectious disease. These

emerging agents pose threats not only to the general human population but also to recipients of blood transfusions. Indeed, the modern era of blood safety perhaps began with the recognition of HIV as an emerging agent transmissible by blood transfusion. Today, emerging infectious agents that pose a threat to the blood supply are not limited to viruses, but include bacterial, protozoan, and prion agents. Preventing the transmission of these new agents by blood transfusion is often problematic, as the available tools may be inadequate. It is certain, however, that new agents will continue to emerge as threats to blood safety and these agents are likely to require novel approaches to prevent their transmission.

## Autoantibody formation after alloimmunization: are blood transfusions a risk factor for autoimmune hemolytic anemia?

Young PP, Uzieblo A, Trulock E, Lublin DM, Goodnough LT. *Transfusion* 2004 Jan;44(1):67-72

**BACKGROUND:** The development of RBC autoantibodies resulting from or associated with allogeneic blood transfusions (i.e., RBC autoimmunization) is not a well-recognized complication of RBC transfusions.

**STUDY DESIGN AND METHODS:** T: he presentation, laboratory evaluation, clinical course, and management of two patients whose autoimmune hemolytic anemia followed allogeneic blood transfusion and occurred in association with the development of one or more alloantibodies is described. A retrospective analysis was performed of our blood-bank records over 1 year to determine the frequency of RBC autoimmunization associated with alloimmunization.

**RESULTS:** Out of 2618 patients who had a positive DAT or IAT, 121 were identified with RBC autoantibodies; 41 of these patients had both allo- and autoantibodies to RBC antigens, whereas the remainder, 80, had only autoantibodies. At least 34 percent (12/41) of these patients (none with hemoglobinopathy) developed their autoantibodies in temporal association with alloimmunization after recent blood transfusion(s).

**CONCLUSION:** RBC autoimmunization and the development of autoimmune hemolytic anemia should be recognized as a complication of allogeneic blood transfusion. The need for additional blood transfusion was successfully avoided in one patient by treatment with recombinant human EPO and corticosteroid therapy. Once RBC autoimmunization is identified, subsequent management should incorporate a strategy that minimizes subsequent exposure to allogeneic blood.



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