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# Literature Abstracts

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## **Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty.**

Grover M, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, Brett S, Goldhill DR, Soni N. *Vox Sang.* 2006 Feb;90(2):105-12.

Chelsea and Westminster Hospital, London, UK.

**Background and Objectives** Red cell transfusion is commonly used in orthopaedic surgery. Evidence suggests that a restrictive transfusion strategy may be safe for most patients. However, concern has been raised over the risks of anaemia in those with ischaemic cardiac disease. Perioperative silent myocardial ischaemia (SMI) has a relatively high incidence in the elderly population undergoing elective surgery. This study used Holter monitoring to compare the effect of a restrictive and a liberal red cell transfusion strategy on the incidence of SMI in patients without signs or symptoms of ischaemic heart disease who were undergoing lower limb arthroplasty. **Materials and Methods** We performed a multicentre, controlled trial in which 260 patients undergoing elective hip and knee replacement surgery were enrolled and randomized to transfusion triggers that were either restrictive (8 g/dl) or liberal (10 g/dl). Participants were monitored with continuous ambulatory electrocardiogram (ECG) (Holter monitoring), preoperatively for 12 h and postoperatively for 72 h. The tapes were analysed for new ischaemia by technicians blinded to treatment. The total ischaemia time in minutes was divided by the recording time in hours and an ischaemic load in min/h was calculated. Haemoglobin levels were measured preoperatively, postoperatively in the recovery room, and on days one, three and five after surgery. **Results** The mean postoperative haemoglobin concentration was 9.87 g/dl in the restrictive group and 11.09 g/dl in the liberal group. In the restrictive group, 34% were transfused a total of 89 red cell units, and in the liberal group 43% were given a total of 119 red cell units. A postoperative episode of silent ischaemia was experienced by 21/109 (19%) patients in the restrictive group and by 26/109 (24%) patients in the liberal group [mean difference -4.6%; 95% confidence interval (CI): -15.5% to 6%,  $P = 0.41$ ]. There was no significant difference ( $P = 0.53$ ) between the overall ischaemic load in the restrictive group (median 0 min/h, range 0-4.18) and the liberal group (median 0

min/h, range 0-19.48). In those patients who did experience postoperative SMI, the mean ischaemic load was 0.48 min/h in the restrictive group and 1.51 min/h in the liberal group (ratio 0.32, 95% CI: 0.14-0.76,  $P = 0.011$ ). The median postoperative length of hospital stay in the restrictive group was 7.3 days [range 5-11; interquartile range (IQR) 6-8] compared with 7.5 days (range 5-13; IQR 7-8) in the liberal group. The numbers were not large enough to conclude equivalence. **Conclusions** In patients without preoperative evidence of myocardial ischaemia undergoing elective hip and knee replacement surgery, a restrictive transfusion strategy seems unlikely to be associated with an increased incidence of SMI. A proportion of these patients experience moderate SMI, regardless of the transfusion trigger. Use of a restrictive transfusion strategy did not increase length of hospital stay, and use of this strategy would lead to a significant reduction in red cell transfusion in orthopaedic surgery. Our data did not indicate any potential for harm in employing such a strategy in patients with no prior evidence of cardiac ischaemia who were undergoing elective orthopaedic surgery.

## **Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations.**

Ranucci M; Romitti F; Isgrò G; Cotza M; Brozzi S; Boncilli A; Ditta A. *Ann Thorac Surg.* 2005; 80(6):2213-20 (ISSN: 1552-6259)

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**BACKGROUND:** The degree of hemodilution during cardiopulmonary bypass has recently been identified as an independent risk factor for acute renal failure after cardiac operations. In this prospective observational study we have investigated the role of the lowest oxygen delivery, lowest hematocrit, and pump flow during cardiopulmonary bypass as possible risk factors for acute renal failure and renal dysfunction. **METHODS:** One thousand forty-eight consecutive patients undergoing coronary operations have been studied. For each patient we have recorded the lowest hematocrit on cardiopulmonary bypass, the correspondent lowest oxygen delivery, and the pump flow around the time of these determinations. The three variables have been explored in a multivariable model as possible risk factors for acute renal failure and postoperative serum creatinine levels increase. The role of

transfusions in determining acute renal failure was subsequently included in the model. RESULTS: The best predictor for acute renal failure and peak postoperative serum creatinine levels was the lowest oxygen delivery, with a critical value at 272 mL.min(-1).m(-2). The lowest hematocrit was an independent risk factor with a lowest predictive value at a cutoff of 26%. When corrected for the need for transfusions, only the lowest oxygen delivery remained an independent risk factor. CONCLUSIONS: A high degree of hemodilution during cardiopulmonary bypass is a risk factor for postoperative renal dysfunction; however, its detrimental effects may be reduced by increasing the oxygen delivery with an adequately increased pump flow.

#### **Low-prime system minimizes transfusions and hemodilution in coronary bypass.**

Beholz S, Zheng L, Rusche M, Kessler M, Konertz W. *Asian Cardiovasc Thorac Ann.* 2006 Feb;14(1):10-3.

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Standard heart-lung machines lead to substantial hemodilution with associated impaired organ function and increased need for blood transfusions. The aim of this study was to evaluate the effect of the new PRECiSe low prime volume system on perioperative myocardial damage, hemodilution, and transfusions. In a case-matched prospective study, 40 patients undergoing coronary artery bypass surgery using PRECiSe were compared with 40 patients on a standard heart-lung machine. In the PRECiSe group, the prime volume was significantly reduced, resulting in less hemodilution and transfusion requirements during and after extracorporeal circulation: only 10% of patients needed transfusions vs. 35% in the control group, with an average transfusion need of 0.16 vs. 1.25 units. There were no significant differences in perioperative cardiac-specific enzymes. The PRECiSe system was considered safe and effective for coronary artery bypass surgery.

#### **Effect of closed minimized cardiopulmonary bypass on cerebral tissue oxygenation and microembolization.**

Liebold A, Khosravi A, Westphal B, Skrabal C, Choi YH, Stamm C, Kaminski A, Alms A, Birken T, Zurakowski D, Steinhoff G. *J Thorac Cardiovasc Surg.* 2006 Feb;131(2):268-76. Epub 2006 Jan 18.

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OBJECTIVE: Coronary artery bypass grafting with cardiopulmonary bypass carries a risk for neurologic complications because of cerebral hypoperfusion and microembolization. The basic goals of a novel closed minimized extracorporeal circulation are to prevent excessive hemodilution and to avoid blood-air interface. The aim of this prospective randomized study was to determine the effect of using the minimized extracorporeal circulation system compared with open conventional extracorporeal circulation on cerebral tissue oxygenation

and microembolization. METHODS: Forty patients undergoing coronary artery bypass grafting (20 in each group) were continuously monitored for changes in cerebral oxygenated hemoglobin and tissue oxygenation index by using near-infrared spectroscopy. Total microembolic count and gaseous embolic count in both median cerebral arteries were monitored with multifrequency transcranial Doppler instrumentation. RESULTS: In the conventional extracorporeal circulation group there was a highly significant reduction in both cerebral oxygenated hemoglobin and tissue oxygenation index from the start to the end of cardiopulmonary bypass ( $P < .01$ ). The rate of decrease in cerebral oxygenated hemoglobin after aortic cannulation was faster in the conventional extracorporeal circulation group (F test = 9.03,  $P < .001$ ). No significant changes with respect to cerebral oxygenated hemoglobin or tissue oxygenation index occurred in the minimized extracorporeal circulation group, except at the beginning of rewarming ( $P < .01$ ). Total embolic count, as well as gaseous embolic count, in the left and right median cerebral arteries was significantly lower in the minimized extracorporeal circulation group (all  $P < .05$ ). Postoperative bleeding was greater ( $P < .05$ ) and the transfusion rate was higher ( $P < .05$ ) in the conventional extracorporeal circulation group. CONCLUSIONS: Use of closed minimized cardiopulmonary bypass compared with conventional open cardiopulmonary bypass preserves cerebral tissue oxygenation and reduces cerebral microembolization.

#### **Posttransplant off-pump coronary bypass and laser revascularization in a Jehovah's Witness.**

Gregoric ID, Nolen MT, Ksela J, Chandler LB, Messner GN, Cervera RD, Smart FW, Delgado RM 3rd, Frazier OH. *Tex Heart Inst J.* 2005;32(3):434-6.

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A 57-year-old man, who had received a heart transplant 14 years earlier, underwent coronary artery bypass grafting and transmyocardial laser revascularization for left main, left anterior descending, and circumflex coronary artery disease. The procedures were performed through a left thoracotomy incision without cardiopulmonary bypass. Because the patient was of the Jehovah's Witness faith, no blood or blood products were transfused.

#### **Off-pump repair of a giant pseudoaneurysm of a distal saphenous vein bypass graft.**

Couto WJ, Livesay JJ, Allam A. *Ann Thorac Surg.* 2005 Dec;80(6):2376-8.

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Pseudoaneurysm of a saphenous vein bypass graft is a rare occurrence after coronary artery bypass grafting but may have lethal consequences. We treated a giant pseudoaneurysm of a saphenous vein graft to the right coronary artery in an 80-year-old male Jehovah's Witness who had undergone coronary artery bypass grafting 4 and

a half years earlier. His history revealed a recurrent sternal wound infection. By using a venous patch to close the damaged graft, we were able to perform a successful surgical repair without the need for extracorporeal circulation.

### **Linear stapling of the short gastric vessels reduces blood loss and splenectomy at oesophageal and gastric surgery.**

Dowdall JF, McAnena OJ. *Surg Endosc.* 2006 Jan 19; [Epub ahead of print]

Department of Surgery, University College Hospital, New Castle, Galway, Ireland, omca@iol.ie.

**BACKGROUND:** Increased operative blood loss, blood transfusion and nontherapeutic splenectomy negatively influence postoperative morbidity and mortality following esophageal or gastric resection. A critical point at which blood loss and iatrogenic splenic injury occurs is at the time of division of the short gastric vessels. We examined the efficacy of using a laparoscopic linear cutting stapler (developed for minimal access surgery) to divide with the short gastric vessels at open surgery. **METHODS:** Fifty-six patients were included. In 28 consecutive patients the linear stapler was used when dividing the short gastric vessels. These were compared to 28 matched controls (short gastric vessels were divided between hemostats and ligated). In the two patient groups, patient age, body mass index, and preoperative hemoglobin levels were similar. **RESULTS:** Operation time, splenectomy rates, blood transfusion, and mean transfusion volume were all significantly reduced in the group where the stapler was used. **CONCLUSION:** Use of a linear cutting stapler reduced operation time, blood product use, and incidental splenectomy in patients undergoing radical open esophageal and gastric surgery.

### **Evaluation of wound healing after total knee arthroplasty in a randomized prospective trial comparing fondaparinux with enoxaparin.**

Bonneux IM, Bellemans J, Fabry G. *Knee.* 2005 Dec 29; [Epub ahead of print]

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**BACKGROUND:** Fondaparinux, a new synthetic pentasaccharide has proven to be a more potent thromboprophylactic drug compared to enoxaparin after major orthopaedic surgery. However, the safety of fondaparinux regarding wound healing has not yet been investigated. **METHODS:** We performed a single-centre prospective clinical trial, in which patients undergoing total knee arthroplasty or revision of at least one of the components of a previous knee arthroplasty were randomly assigned to thromboprophylaxis with fondaparinux or enoxaparin. The trial included 109 patients and wound discharge was compared. Secondary outcome measures were the amount of blood in the suction drain, postoperative transfusion rate, change in haemoglobin levels, haematocrit, intervention rate, time to regain flexion and rate of symptomatic thromboembolic events. **RESULTS:** 55 patients were treated with fondaparinux and 54 with enoxaparin. Base-line

characteristics were similar. In both groups wound dressings remained dry after five (5.17+/-2.5 and 5.19+/-3) days postoperatively. There were no significant differences in any of our outcome measures. **CONCLUSIONS:** We did not find any significant difference in wound healing with fondaparinux after major knee surgery. Post hoc analyses suggested the study should have had a sample size of 155 in each group. We believe this trial should be used as a pilot study for further investigations concerning the safety of thromboprophylaxis.

### **Management of patients with ectopic pregnancy with massive hemoperitoneum by laparoscopic surgery with intraoperative autologous blood transfusion.**

Takeda A, Manabe S, Mitsui T, Nakamura H. *J Minim Invasive Gynecol.* 2006 Jan;13(1):43-8.

Department of Obstetrics and Gynecology, Gifu Prefectural Tajimi Hospital, Tajimi, Gifu, Japan.

**STUDY OBJECTIVE:** To evaluate the feasibility and safety of surgical laparoscopy with intraoperative autologous blood transfusion for ectopic pregnancy with massive hemoperitoneum. **DESIGN:** Retrospective analysis (Canadian Task Force classification II-1). **SETTING:** Department of gynecology at a general hospital. **PATIENTS:** Seventeen consecutive patients with ectopic pregnancy with massive hemoperitoneum. **INTERVENTION:** Laparoscopic surgery with salvage device-based intraoperative autologous blood transfusion. **MEASUREMENTS AND MAIN RESULTS:** From January 2000 through June 2005, one hundred and twelve women with ectopic pregnancy (interstitial/cornual: 4; isthmic: 18; ampullary: 86; and ovarian: 4) were treated by laparoscopic surgery. Seventeen patients who demonstrated more than 501 g of intraabdominal bleeding were classified as having massive hemoperitoneum and retrospectively analyzed. Site of pregnancy in these 17 patients was interstitial/cornual: 3; isthmic: 5; ampullary: 7; and ovarian: 2. Except for two women with tubal abortion of ampullary pregnancy, all other patients had rupture at the pregnancy site. During laparoscopic surgery, blood pooled in the abdominal cavity was collected by an irrigation and aspiration procedure, and sent to an autologous blood-salvage device to make concentrated red blood cell solution. Processed blood was immediately transfused back to the patient through a leukocyte reduction filter. The mean amount of estimated intraabdominal bleeding, which was calculated by the difference between the volumes of aspirated and irrigated fluids, was 1362.1 +/- 491.4 g, and the mean volume of reinfused processed blood was 680.6 +/- 209.5 g. No patient received banked blood at any time. The degree of hemoperitoneum was well correlated with the shock index calculated by dividing the heart rate by systolic blood pressure at triage ( $r = 0.72$ ; 95% CI 0.37-0.89;  $p = .001$ ). In all cases of massive hemoperitoneum, there was no need for laparotomy conversion, and homologous blood transfusion was avoided. **CONCLUSIONS:** Even in women with ectopic pregnancy with massive hemoperitoneum, laparoscopic surgery can be safely conducted by experienced laparoscopists with intraoperative autologous

blood transfusion if hemodynamic stability is achieved by perioperative management.

**Five percent albumin for adult burn shock resuscitation: lack of effect on daily multiple organ dysfunction score.**

Cooper AB, Cohn SM, Zhang HS, Hanna K, Stewart TE, Slutsky AS; ALBUR Investigators. *Transfusion*. 2006 Jan;46(1):80-9.

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**BACKGROUND:** The effect of 5 percent human albumin on multiple organ dysfunction was investigated during the first 14 days of treatment to determine whether albumin resuscitation might benefit adult burn patients. **STUDY DESIGN AND METHODS:** Multicenter unblinded controlled trial with stratified block (two patients per block) randomization by center and mortality prediction at enrollment (high-risk stratum [predicted mortality, 50%-90%] and low-risk stratum [predicted mortality, <50%]). The primary outcome was the worst multiple organ dysfunction score (MODS), excluding the cardiovascular component, to Day 14. Eligible adults (>15 years) suffering from thermal injury not more than 12 hours before enrollment received fluid resuscitation with Ringer's lactate (n=23) or 5 percent human albumin plus Ringer's lactate (n=19) by protocol to achieve recommended (American Burn Association) resuscitation endpoints. **RESULTS:** Forty-two patients were randomly assigned. There were no significant differences (median [95% confidence intervals]) in age (36 [24-45] vs. 31 [25-39] years), burn size (39 [32-53] vs. 32 [26-34] total body surface area percentage), inhalation injury (n=12/19 vs. n=11/23), or baseline MODS (3 [1-5] vs. 1.5 [0-2]) between the treatment and control groups. In an intention-to-treat analysis, there was no significant difference between the treatment and control group in the lowest MODS from Day 0 to Day 14 (analysis of covariance, p=0.73). **CONCLUSION:** Treatment with 5 percent albumin from Day 0 to Day 14 does not decrease the burden of MODS in adult burn patients.

**The OxyArm: a supplemental oxygen delivery device.**

Futrell JW Jr, Moore JL. *Anesth Analg*. 2006 Feb;102(2):491-4.

Department of Anesthesiology, Cedars-Sinai Medical Center, Los Angeles, California, USA.

Facemasks and nasal cannulae are used to provide supplemental oxygen to patients in the postoperative period after general anesthesia. These devices are associated with several patient complications, including aspiration, hypercarbia, and mechanical trauma. A new device, the OxyArm, is designed to eliminate these problems. It is an "open oxygen" system that does not require physical contact with the patient's face. In this clinical study we evaluated the OxyArm in the immediate postoperative period. Sixty patients received supplemental oxygen via the OxyArm for the first 8 min after tracheal

extubation after general anesthesia. Oxygen saturation values were continuously recorded during 3 4-min time periods: 1) while breathing oxygen through an endotracheal tube before tracheal extubation, 2) while breathing oxygen delivered by the OxyArm at 4 L/min 4 min after tracheal extubation, and 3) while breathing oxygen delivered by the OxyArm at 2 L/min 8 min after tracheal extubation. There were no significant differences in oxygen saturation among the three time periods and no patient experienced an oxygen desaturation event less than 88%. Patients and clinicians praised the OxyArm for its comfort and ease of use, allowing nursing facial care without interrupting oxygen therapy. We conclude that the OxyArm delivers adequate levels of oxygen for most patients during the early postoperative period.

**Mathematical model for the estimation of hemodynamic and oxygenation variables by tissue spectroscopy.**

Kocsis L, Herman P, Eke A. *J Theor Biol*. 2006 Jan 10; [Epub ahead of print]

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This article presents a quasistatic, compartmental model of tissue-level hemodynamics and oxygenation that leads to a set of formulas, which is suitable to calculate important physiological variables from the mean tissue concentration and saturation of hemoglobin, measured by tissue spectroscopy. Dimensioned quantities are represented relative to their baseline value in the equations (relative value=perturbed/baseline). All model parameters are non-dimensional. The model is based and extends on a number of previous works: previous models of similar aim and scope are consolidated, and every critical assumptions and approximations are treated explicitly; extensions include for example the incorporation of the Fahraeus-effect and the separate estimation of the volume changes of the arterial and the venous compartments. The information content of spectroscopic data alone is shown to be valuable, but limited: the relative venous volume, the oxygen extraction fraction and the relative cellulovascular coupling (defined as the ratio of blood flow and oxygen consumption) can be calculated from these data, if the alterations in arterial blood volume are negligible. The number of variables estimated by the derived formulas can be increased if local blood flow is measured simultaneously: in this case, the relative arterial and venous volume and resistance, the oxygen extraction fraction, and the relative oxygen consumption can be determined. Given that this model considers arterial blood pressure, saturation and hematocrit as its inputs, when measured, the model becomes applicable in such conditions as hyper- or hypotension, hypoxic hypoxia, hemodilution and hemorrhage, where these variables do change. The estimation of the changes in arterial resistance can be applied to estimate the extent of an autoregulatory response.

**Massive transfusion coagulopathy.**

Levy JH. *Semin Hematol.* 2006 Jan;43(1 Suppl 1):S59-63.

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Coagulopathy following massive transfusion is a consequence of post-traumatic and surgical hemorrhage. Bleeding following massive transfusion can occur due to hypothermia, dilutional coagulopathy, platelet dysfunction, fibrinolysis, or hypofibrinogenemia. Transfusion of 15 to 20 units of blood products causes dilutional thrombocytopenia, and both antiplatelet agents (eg, clopidogrel [Plavix((R))], Sanofi, Bridgewater, NJ) and hemostatic inhibitors (eg, low-molecular-weight heparins, pentasaccharides, and direct thrombin inhibitors) are contributing factors to bleeding. Tests for platelet dysfunction are not readily available. Excessive fibrinolysis and low fibrinogen are also causes of bleeding in these patients. Currently, however, there are several agents that have been reported to be effective for the prophylaxis of hemorrhage in surgical patients, including aprotinin for cardiac surgery, orthopedic surgery, and hepatic transplantation, and the off-label use of recombinant activated factor VII (NovoSeven((R))), Novo Nordisk, Bagsvaerd, Denmark) as rescue therapy for life-threatening hemorrhage.

**Uterine artery embolization in the management of vaginal bleeding from cervical pregnancy: a case series.**

Trambert JJ, Einstein MH, Banks E, Frost A, Goldberg GL. *J Reprod Med.* 2005 Nov;50(11):844-50.

Department of Radiology, Montefiore Medical Center and Albert Einstein College of Medicine, New York, New York, USA. jtramber@montefiore.org

**OBJECTIVE:** To report our experience of selective embolotherapy in 8 consecutive patients with cervical pregnancy (CxP) presenting with vaginal bleeding. **STUDY DESIGN:** A total of 9 selective pelvic embolization procedures were performed on 8 patients with CxP, either as an emergency, for control of vaginal hemorrhage (2 patients), or on a nonemergency basis, for moderate vaginal bleeding (6 patients). One patient underwent 2 embolization procedures, once for each indication. **RESULTS:** Successful hemostasis was obtained in both emergency cases. In 3 of the nonemergency cases, the CxP rapidly resolved. In the 3 other nonemergency cases, elevated beta-human chorionic gonadotropin levels persisted, with a new episode of vaginal bleeding in 2 patients 2 and 4 weeks later, respectively; the bleeding resolved after the administration of methotrexate. Significant vaginal hemorrhage occurred 4 weeks later in the third patient and responded to repeat embolotherapy. One patient required a blood transfusion. The uterus was preserved in all 8 patients. One patient was lost to follow-up, but normal menses resumed in all 7 of the others; and 2 patients had subsequent successful pregnancies. **CONCLUSION:** Embolotherapy is effective in treating and

preventing vaginal hemorrhage associated with CxP while allowing uterine preservation. Along with methotrexate and other medical treatment of CxP, we recommend routine use of embolization in patients presenting with vaginal bleeding.

**Successful management of uterine incision hemorrhage in caesarean section with topical oxidized regenerated cellulose (Surgicel Nu Knit): a case report.**

Sharma JB, Malhotra M. *Arch Gynecol Obstet.* 2006 Jan 12;:1-2 [Epub ahead of print]

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**Introduction:** Uterine hemorrhage is a common problem at the time of caesarean section especially in a repeat caesarean section and when the operation is performed for placenta praevia. **Case report and discussion:** We present the case of a 28 year old woman undergoing a repeat emergency caesarean section for scar tenderness. She had excessive hemorrhage from the incision site that could not be controlled by traditional management including intravenous oxytocin and ergometrine, intramyometrial prostaglandin and local hemostatic sutures, but was successfully controlled with topical oxidized regenerated cellulose absorbable hemostat.

**Does aprotinin reduce blood loss in total hip arthroplasty?**

Petsatodis G, Samoladas E, Christodoulou A, Hatzokos I, Pournaras I. *Orthopedics.* 2006 Jan;29(1):75-7.

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This prospective randomized study examined the effects of aprotinin during total hip arthroplasty (THA). Fifty patients who were enrolled in the study received aprotinin or normal saline. Mean intraoperative blood loss was reduced from 1496 mL in the control group to 1073 mL in the aprotinin group. The mean transfusion unit was 1.56 in the aprotinin group and 3.8 in the control group.

**Aprotinin shows both hemostatic and antithrombotic effects during off-pump coronary artery bypass grafting.**

Poston RS; White C; Gu J; Brown J; Gammie J; Pierson RN; Lee A; Connerney I; Avari T; Christenson R; Tandy U; Griffith BP. *Ann Thorac Surg.* 2006; 81(1):104-10.

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**BACKGROUND:** Hemostatic drugs are widely thought to be unnecessary and potentially detrimental in off-pump coronary artery bypass graft surgery (OPCABG), despite well-established use in on-pump surgery. In a randomized, prospective OPCABG trial, we assessed efficacy and

safety of aprotinin through a comprehensive assessment of graft patency and hematologic function. **METHODS:** Sixty patients were randomly assigned to full-dose aprotinin or placebo. Heparin was titrated to a kaolin-based activated clotting time of greater than 300 seconds. Exclusionary criteria included creatinine greater than 2 mg/dL, conversion to on-pump CABG, and preoperative GPIIb/IIIa inhibition. Hematologic assessments were obtained preoperatively, at the end of surgery, and on days 1 and 3: mean platelet volume, thrombin generation (prothrombin fragment 1.2 assay), and aspirin resistance using a modified thrombelastography, whole blood aggregometry, 11-dehydro-thromboxane B2 levels, and flow cytometry. Thrombotic events were defined as postoperative myocardial infarction by electrocardiography or elevated troponin I, clinical stroke by examination and head computed tomography, and bypass graft failure by multichannel computed tomography angiography on day 5. **RESULTS:** Aprotinin was associated with a significant reduction in intraoperative and postoperative blood loss compared with placebo but had no effect on transfusion rates. Patients treated with aprotinin had significantly fewer thrombotic events (3% versus 23%,  $p < 0.05$ , Fisher's exact test) and less postoperative aspirin resistance (20% versus 46%, respectively,  $p < 0.05$ , Fisher's exact test). Postoperative prothrombin fragment 1.2 level was reduced by aprotinin use. **CONCLUSIONS:** Aprotinin reduced perioperative bleeding after OPCABG. Preserved aspirin sensitivity in the aprotinin group may explain the observed reduction in thrombotic events and might be related to the suppression of perioperative and transmyocardial thrombin formation.

### The Risk Associated with Aprotinin in Cardiac Surgery

Dennis T. Mangano, Ph.D., M.D., Iulia C. Tudor, Ph.D., Cynthia Dietzel, M.D., for the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation. *N Eng J Med* 2006; 354(4):353-365

**Background** The majority of patients undergoing surgical treatment for ST-elevation myocardial infarction receive antifibrinolytic therapy to limit blood loss. This approach appears counterintuitive to the accepted medical treatment of the same condition — namely, fibrinolysis to limit thrombosis. Despite this concern, no independent, large-scale safety assessment has been undertaken.

**Methods** In this observational study involving 4374 patients undergoing revascularization, we prospectively assessed three agents (aprotinin [1295 patients], aminocaproic acid [883], and tranexamic acid [822]) as compared with no agent (1374 patients) with regard to serious outcomes by propensity and multivariable methods. (Although aprotinin is a serine protease inhibitor, here we use the term antifibrinolytic therapy to include all three agents.)

**Results** In propensity-adjusted, multivariable logistic regression (C-index, 0.72), use of aprotinin was associated with a doubling in the risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery (odds ratio, 2.59; 95 percent confidence interval, 1.36 to 4.95) or primary surgery (odds ratio, 2.34; 95 percent confidence interval, 1.27 to 4.31). Similarly, use of

aprotinin in the latter group was associated with a 55 percent increase in the risk of myocardial infarction or heart failure ( $P < 0.001$ ) and a 181 percent increase in the risk of stroke or encephalopathy ( $P = 0.001$ ). Neither aminocaproic acid nor tranexamic acid was associated with an increased risk of renal, cardiac, or cerebral events. Adjustment according to propensity score for the use of any one of the three agents as compared with no agent yielded nearly identical findings. All the agents reduced blood loss.

**Conclusions** The association between aprotinin and serious end-organ damage indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

### A double-blind, placebo-controlled trial of epsilon-aminocaproic Acid for reducing blood loss in coronary artery bypass grafting surgery.

Kikura M, Levy JH, Tanaka KA, Ramsay JG. *J Am Coll Surg.* 2006 Feb;202(2):216-22. Epub 2005 Dec 19.

Department of Anesthesiology, Emory University School of Medicine, Emory University Hospital, The Emory Clinic, Atlanta, GA.

**BACKGROUND:** Epsilon-aminocaproic acid is a plasmin inhibitor that potentially reduces perioperative bleeding when administered prophylactically to cardiac surgery patients. To evaluate the efficacy of epsilon-aminocaproic acid, a prospective placebo-controlled trial was conducted in patients undergoing primary coronary artery bypass grafting surgery. **STUDY DESIGN:** One hundred patients were randomly assigned to receive either epsilon-aminocaproic acid (100 mg/kg before skin incision followed by 1 g/hour continuous infusion until chest closure, 10 g in cardiopulmonary bypass circuit) or placebo, and the efficacy of epsilon-aminocaproic acid was evaluated by the reduction in postoperative thoracic-drainage volume and in donor-blood transfusion up to postoperative day 12. **RESULTS:** Postoperative thoracic-drainage volume was significantly lower in the epsilon-aminocaproic acid group compared with the placebo group (epsilon-aminocaproic acid, 649 +/- 261mL; versus placebo, 940 +/- 626mL;  $p = 0.003$ ). There were no significant differences between the epsilon-aminocaproic acid and placebo groups in the percentage of patients requiring donor red blood cell transfusions (epsilon-aminocaproic acid, 24%; versus placebo, 18%;  $p = 0.62$ ) or in the number of units of donor red blood cells transfused (epsilon-aminocaproic acid, 2.2 +/- 0.8 U; versus placebo, 1.9 +/- 0.8 U;  $p = 0.29$ ). Epsilon-aminocaproic acid did not reduce the risk of donor red blood cell transfusions compared with placebo (odds ratio: 1.2, 95% confidence interval; 0.4 to 3.2,  $p = 0.63$ ). **CONCLUSIONS:** Prophylactic administration of epsilon-aminocaproic acid reduces postoperative thoracic-drainage volume by 30%, but it may not be potent enough to reduce the requirement and the risk for donor blood transfusion in cardiac surgery patients. This information is useful for deciding on a therapy for hemostasis in cardiac surgery.

**A randomized, double-blind, and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary artery bypass grafting.**

Santos AT, Kalil RA, Baumann C, Pereira JB, Nesralla IA. *Braz J Med Biol Res.* 2006 Jan;39(1):63-9. Epub 2005 Dec 15.

Cardiopulmonary bypass is frequently associated with excessive blood loss. Platelet dysfunction is the main cause of non-surgical bleeding after open-heart surgery. We randomized 65 patients in a double-blind fashion to receive tranexamic acid or placebo in order to determine whether antifibrinolytic therapy reduces chest tube drainage. The tranexamic acid group received an intravenous loading dose of 10 mg/kg, before the skin incision, followed by a continuous infusion of 1 mg kg<sup>-1</sup> h<sup>-1</sup> for 5 h. The placebo group received a bolus of normal saline solution and continuous infusion of normal saline for 5 h. Postoperative bleeding and fibrinolytic activity were assessed. Hematologic data, convulsive seizures, allogeneic transfusion, occurrence of myocardial infarction, mortality, allergic reactions, postoperative renal insufficiency, and reopening rate were also evaluated. The placebo group had a greater postoperative blood loss (median (25th to 75th percentile) 12 h after surgery (540 (350-750) vs 300 (250-455) mL,  $P = 0.001$ ). The placebo group also had greater blood loss 24 h after surgery (800 (520-1050) vs 500 (415-725) mL,  $P = 0.008$ ). There was a significant increase in plasma D-dimer levels after coronary artery bypass grafting only in patients of the placebo group, whereas no significant changes were observed in the group treated with tranexamic acid. The D-dimer levels were 1057 (1025-1100) microg/L in the placebo group and 520 (435-837) microg/L in the tranexamic acid group ( $P = 0.01$ ). We conclude that tranexamic acid effectively reduces postoperative bleeding and fibrinolysis in patients undergoing first-time coronary artery bypass grafting compared to placebo.

**Perioperative Parenteral Tranexamic Acid in Liver Tumor Resection: A Prospective Randomized Trial Toward a "Blood Transfusion"-Free Hepatectomy.**

Wu, Cheng-Chung; Ho, Wai-Meng; Cheng, Shao-Bin; Yeh, Dah-Cherng; Wen, Mei-Chin; Liu, Tse-Jia; P'eng, Fang-Ku. *Annals of Surgery.* 2006 February 243(2):173-180.

**Objective:** To examine the feasibility of a real "blood transfusion"-free hepatectomy in a large group of patients with liver tumors.

**Summary Background Data:** Bleeding control and blood transfusion remains problematic in liver resection. A real "blood transfusion"-free hepatectomy in a large group of patients has rarely been reported. The impact of tranexamic acid (TA), an antifibrinolytic agent, on blood transfusion in liver resection is unknown.

**Methods:** A prospective double-blind randomized trial was performed on elective liver tumor resections. In group A, TA 500 mg was intravenously administered just before operation followed by 250 mg, every 6 hours, for 3 days. In group B, only placebo was given. The patients' background, blood transfusion rates, and early

postoperative results in the 2 groups were compared. Factors that influenced blood requirement were analyzed. **Results:** There were 108 hepatectomies in group A and 106 hepatectomies in group B. The patients' backgrounds, operative procedures, and hepatectomy extent did not significantly differ between the 2 groups. Although the differences of the operative morbidity and postoperative stay were not significant, a significantly lower amount of operative blood loss, lower blood transfusion rate, shorter operative time, and lower hospital costs were found in group A patients. No patient in group A received blood transfusion. No hospital mortality occurred in either group. Tumor size and use of TA were independent factors that influenced blood transfusion.

**Conclusions:** Perioperative parenteral use of TA reduced the amount of operative blood loss and the need for blood transfusion in elective liver tumor resection. A real "blood transfusion"-free hepatectomy may be feasible with the assistance of parenteral TA.

**Treating coagulopathy in liver disease with plasma transfusions or recombinant factor VIIa: an evidence-based review.**

Ramsey G. *Best Pract Res Clin Haematol.* 2006 Mar;19(1):113-26.

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In severe liver disease, poor synthetic function leads to characteristic deficiencies in numerous coagulation factors, and plasma transfusions are frequently administered to treat or prevent bleeding. This chapter reviews the available English-language randomized controlled trials, evidence-based practice guidelines, and observational studies relevant to establishing criteria for plasma transfusions in liver disease. The alternatives of pathogen-inactivated plasmas and recombinant factor VIIa were also reviewed from this perspective. In current guidelines, plasma transfusions are justified when haemostasis is needed for bleeding or invasive procedures, and the prothrombin time (PT) or partial thromboplastin time (PTT) is >1.5 times normal (mid-normal or, for PTT, sometimes upper limit). Conversion of the PT to the International Normalized Ratio has not been validated in liver disease. Solvent-detergent or methylene-blue treatments alter various clotting factors, which might affect efficacy in liver disease. Recombinant factor VIIa improves laboratory clotting measurements, but reduction of bleeding is less well established to date.

**Recombinant activated factor VIIa and hemostasis in critical care: a focus on trauma.**

Mohr AM, Holcomb JB, Dutton RP, Duranteau J. *Crit Care.* 2005;9 Suppl 5:S37-42. Epub 2005 Oct 7.

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In this article we describe the current use of recombinant

activated factor VII (rFVIIa; NovoSeven) in trauma patients. Emphasis is placed on current uses as defined by key studies, efficacy data, and safety data. Most published studies in trauma patients are retrospective case studies and reports, although an international, double-blind, randomized, controlled, phase II study has been conducted that reported on the efficacy of rFVIIa in reducing the amount of blood products transfused in blunt trauma patients. That study demonstrated the efficacy and safety profile of this hemostatic agent as compared with placebo as adjunctive therapy in the management of severe bleeding associated with trauma. Further prospective, randomized, and placebo-controlled clinical trials will yield more information on the role of rFVIIa in the management of traumatic bleeding.

### **Ultra-early Hemostatic Therapy for Acute Intracerebral Hemorrhage.**

Mayer SA, Rincon F. *Semin Hematol.* 2006 Jan;43(1 Suppl 1):S70-6.

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Intracerebral hemorrhage (ICH) is the least treatable form of stroke, and causes high mortality, severe disability, and a staggering economic burden. ICH accounts for 15% of stroke cases in the United States and Europe, and up to 30% in Asian populations. Computed tomography-based studies suggest that ICH growth within the first few hours of onset is common, and the principal cause of early neurological deterioration. Hematoma volume is also a well-established predictor of 30-day mortality. Intervention with ultra-early hemostatic therapy could minimize or prevent this early dynamic bleeding process, and might improve outcome. Recombinant activated factor VII (rFVIIa; NovoSeven((R)), Novo Nordisk, Bagsvaerd, Denmark) is approved for the treatment of bleeding in patients with hemophilia and inhibitors, but it may also promote hemostasis in patients with normal coagulation by acting locally at the bleeding site without activation of systemic coagulation. In a randomized, double-blind, placebo-controlled trial of 399 ICH patients treated with a single dose of 40, 80, or 160 mug/kg of rFVIIa or placebo within 4 hours of onset, subsequent hematoma growth was reduced by approximately 50% with rFVIIa. This was associated with a significant reduction (38%) in mortality, and improved functional outcomes among survivors. A phase III trial comparing 20 and 80 mug/kg rFVIIa with placebo is now in progress to confirm these results.

### **Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions.**

Steiner T, Rosand J, Diringer M. *Stroke.* 2006 Jan;37(1):256-62. Epub 2005 Dec 8.

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**BACKGROUND AND PURPOSE:** Life-threatening

intracranial hemorrhage, predominantly intracerebral hemorrhage (ICH), is the most serious complication of oral anticoagulant therapy (OAT), with mortality in excess of 50%. Early intervention focuses on rapid correction of coagulopathy in order to prevent continued bleeding. **SUMMARY OF REVIEW:** This article reviews the epidemiology of OAT-associated ICH (OAT-ICH), and current treatment options, with the aim of providing a framework for future studies of unresolved questions. A number of acute treatments are available, but all have a significant risk of inducing thrombosis and other side effects, and vary in their rapidity of effect: vitamin K (very slow response time), fresh frozen plasma (slow response time, large volume of fluid required, transfusion-related acute lung injury), prothrombin complex concentrates, and recombinant activated factor VII. Current practice is to administer a combination of vitamin K and either fresh frozen plasma or prothrombin complex concentrates; the occasional use of recombinant activated factor VII has been reported. No prospective study has addressed the efficacy of, or outcomes from, the use of these practices. **CONCLUSIONS:** Current management of OAT-ICH is varied and not based on evidence from randomized controlled trials. Well-designed clinical trials are essential if we are to identify the effective acute treatments for OAT-ICH that are urgently needed.

### **[In vitro generation of mature and functional human red blood cells: a model with multidisciplinary perspectives]**

[Article in French]

Douay L, Giarratana MC. *Bull Acad Natl Med.* 2005 May;189(5):903-13; discussion 914-5

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We describe a technical approach permitting massive expansion of CD34+ stem cells (up to 1.95 x 10(6)-fold) and their full ex vivo conversion into mature red blood cells (RBCs). This three-step protocol can be adapted to hematopoietic stem cells (HSC) of various origins. First, cell proliferation and erythroid differentiation are induced in serum-free media supplemented with stem cell factor, interleukin-3 and erythropoietin (Epo) for 8 days. The cells are then co-cultured with either the murine stromal cell line MS-5 or human mesenchymal cells for 3 days in the presence of Epo alone. Finally, all exogenous factors are withdrawn and the cells are incubated on a simple stroma for up to 10 days. The ex vivo microenvironment strongly influences both the terminal maturation of erythroid cells and hemoglobin (Hb) synthesis. Critically, in vitro-generated RBCs have all the characteristics of functional native adult RBCs in terms of their enzyme content, membrane deformability, and capacity to fix and release oxygen. In addition, their behavior in the murine NOD/SCID model mirrors that of native RBCs. This new concept of "cultured RBCs" (cRBC) has major implications for basic research on terminal erythropoiesis and for patient management. Currently, the potential yield of functional red cells is compatible with clinical

requirements, as several units of packed RBCs can be produced from a single donation. Importantly, infused cRBC would all have a life-span of about 120 days, whereas the mean half-life of normal donor RBCs is only 28 days. This would help to minimize the transfusion exposure of patients requiring regular treatment, thereby reducing the risk of iron overload and allo-immunization. The use of autologous CD34+ cells isolated from leukapheresis samples could be beneficial for patients who no longer tolerate allogeneic RBCs. This new method should also prove useful for analyzing the mechanisms of terminal erythropoiesis, including hemoglobin synthesis. Finally, it could provide a tool for investigating the lifecycle of blood parasites such as Plasmodium, the agent of malaria.

### [Intravenous iron in general surgery.]

[Article in Spanish]

Serrablo A, Urbieta E, Carcelen-Andres J, Ruiz J, Rodrigo J, Izuel M, Garcia-Erce J. *Cir Esp*. 2005 Sep;78(3):195-7.

Servicio de Cirugia. Hospital Universitario Miguel Servet. Zaragoza.

Preoperative anemia is the main cause of blood transfusion in surgical patients. In digestive surgery high blood loss and allogenic blood transfusion (ABT) are associated with serious adverse events and higher mortality. Consequently, we believe that intravenous iron administration is justified to correct perioperative anemia. We present the case of a woman with metastatic colorectal adenocarcinoma in whom intravenous iron administration avoided the use of ABT. Subsequently, the iron metabolism profile improved. This had previously corresponded to a mixed pattern of iron deficiency, that is, to the association of organic and functional iron deficiency.

### Recombinant human erythropoietin in a triplet pregnancy: a case report.

Lialios G, Kallitsaris A, Bourantas KL, Messinis IE. *J Reprod Med*. 2005 Nov;50(11):863-6.

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**BACKGROUND:** Women carrying triplets are at greater risk for both anemia, due to the increased demands of the developing fetuses, and peripartum hemorrhage. Jehovah's witnesses are a unique obstetric population since women of this faith refuse blood transfusion. **CASE:** A Jehovah's Witness with a triplet pregnancy was successfully administered recombinant human erythropoietin (rHuEpo), 200 IU/kg 3 times per week subcutaneously, in order to correct her peripartum anemia. No side effects were observed during rHuEpo therapy, and the patient delivered healthy triplets. **CONCLUSION:** rHuEpo can be safely administered, with a beneficial effect in pregnancy, and seems to be an effective option in

preventing transfusions as demonstrated in this case in a Jehovah's Witness.

### Recombinant human erythropoietin in the treatment of nonrenal anemia.

Heuser M, Ganser A. *Ann Hematol*. 2006 Feb;85(2):69-78. Epub 2005 Aug 3.

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Recombinant human erythropoietins (rhEPO) reliably increase hemoglobin levels in cancer patients experiencing chemotherapy-associated anemia. However, in patients with "anemia of cancer" not being treated with chemotherapy, rhEPO appears less effective. Recently, two studies have been broadly discussed which have raised concern on the concomitant use of erythropoietin and chemo- or radiation therapy in cancer patients. In addition, use of rhEPO is generally not considered cost-effective. Thus, the application of rhEPO should be limited to indications with proven clinical benefit. This review will provide an overview of the state of the art use of rhEPO in anemic patients and will discuss future developments.

### Stem cell mobilization by hyperbaric oxygen.

Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. *Am J Physiol Heart Circ Physiol*. 2005 Nov 18; [Epub ahead of print]

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We hypothesized that exposure to hyperbaric oxygen (HBO(2)) would mobilize stem/progenitor cells from the bone marrow by a nitric oxide (.NO) dependent mechanism. The population of CD34+ cells in the peripheral circulation of humans doubled in response to a single exposure to 2.0 atmospheres absolute (ATA) O2 for 2 hours. Over a course of twenty treatments, circulating CD34+ cells increased eight-fold, although the over-all circulating white cell count was not significantly increased. The number of colony-forming cells (CFCs) increased from 16 +/- 2 to 26 +/- 3 CFCs/100,000 monocytes plated. Elevations in CFCs were entirely due to the CD34+ sub-population, but increased cell growth only occurred in samples obtained immediately post-treatment. A high proportion of progeny cells express receptors for vascular endothelial growth factor-2 and for stromal derived growth factor. In mice, HBO2 increased circulating stem cell factor by 50%, increased the number of circulating cells expressing stem cell antigen-1 and CD34 by 3.4-fold, and doubled the number of CFCs. Bone marrow (.NO) concentration increased by 1008 +/- 255 nM in association with HBO2. Stem cell mobilization did not occur in knock out mice lacking genes for endothelial .NO synthase. Moreover, pre-treatment of wild type mice with a nitric

oxide ((.)NO) synthase inhibitor prevented the HBO<sub>2</sub>-induced elevation in stem cell factor and circulating stem cells. We conclude that HBO<sub>2</sub> mobilizes stem/progenitor cells by stimulating .NO synthesis.

### Randomized Trial of Anti-D Immunoglobulin versus Low-Dose Intravenous Immunoglobulin in the Treatment of Childhood Chronic Idiopathic Thrombocytopenic Purpura.

El Alfy MS, Mokhtar GM, El-Laboudy MA, Khalifa AS. *Acta Haematol.* 2006;115(1-2):46-52.

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**Background:** Chronic idiopathic (immune) thrombocytopenic purpura (ITP) develops in approximately 20% of children with acute ITP. Six years ago, low-dose intravenous immunoglobulin (IVIg) treatment of childhood ITP was started at the Pediatric Hematology Unit, Ain Shams University, while intravenous anti-D has been introduced in Egypt in 2001. **Objectives:** To assess the efficacy and safety of intravenous anti-D compared to low-dose IVIg in the treatment of children with chronic ITP. **Patients and Methods:** This randomized trial comprised 34 patients with chronic ITP (18 boys and 16 girls) with recurrent bleeding episodes. Median age of the patients was 6.5 years, duration of thrombocytopenia was >6 months, and platelet count (PC) was <30 x 10<sup>9</sup>/l (30 K). The patient cohort was divided into two subgroups: group A comprised 18 patients treated with anti-D in a dose of 50 mug/kg i.v. initially, and in 12 of them repeated doses (50 mug/kg) were given every 4 weeks, and group B consisted of 16 children who received IVIg in a dose of 250 mg/kg for 2 consecutive days. Bleeding manifestations, complete blood cell and reticulocyte counts were assessed at baseline and 3, 7, 14 and 28 days after infusion. **Results:** Clinically, more than 80% of the patients (82.3%) showed good control of bleeding. On day 3, 33.3% of group A versus 37.5% of group B, and on day 7: 66.6% of group A versus 75% of group B patients demonstrated a good response (PC >50 K and/or doubling of baseline PC). On days 14 and 21, no significant changes in PCs were observed between both groups. However, only 11.1% of group A and 12.5% of group B patients could maintain PC >100 K on day 28, while 38.8 versus 37.5% of group A and group B, respectively, still had PC >= double the initial count. The peak response to anti-D was noticed 7 and 14 days following infusion and to IVIg on days 3 and 7. Repeated doses of anti-D could maintain PC > 50 K (or > double the baseline PC) in 75% of patients 1 week after infusion, and in 60% of them by day 28, with good control of bleeding. Splenectomy was postponed and/or avoided in 4 (33.3%) patients on anti-D maintenance therapy who experienced recurrent severe bleeding episodes before starting therapy. The safety of anti-D was judged by the degree of intravascular hemolysis. The mean hemoglobin decrease was 0.8 +/- 0.4 g/dl; in 61.1% of patients the Hb level dropped but none of them experienced a drop of more than 3 g/dl or required transfusion. **Conclusion:** Both single intravenous anti-D and low-dose IVIg effectively increased PC in children with chronic ITP at risk of

bleeding or those with previous bleeding episodes. Repeated doses of anti-D could maintain PC above the critical values or double baseline counts in nearly two thirds of the patients showing good control of bleeding and may serve as an alternative to splenectomy in these patients.

### Salvage of focal cerebral ischemic damage by transfusion of high O<sub>2</sub>-affinity recombinant hemoglobin polymers in mouse.

Nemoto M, Mito T, Brinigar WS, Fronticelli C, Koehler RC. *J Appl Physiol.* 2006 Jan 19; [Epub ahead of print]

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Cell-free hemoglobin solutions with high oxygen affinity might be beneficial for selectively delivering oxygen to ischemic tissue. A recombinant hybrid hemoglobin molecule was designed using the human alpha-subunit and the bovine beta-subunit, with placement of surface cysteines to permit disulfide bond polymerization of the tetramers. The resulting protein generated from an *E. coli* expression system had a molecular weight > 1 MDa, a P50 of approximately 3 Torr, and a cooperativity of n = 1.0. Anesthetized mice were transfused during 2-h occlusion of the middle cerebral artery. Compared to transfusion with 5% albumin, cerebral infarct volume was reduced by 41% with transfusion of a 3% solution of the high oxygen-affinity hemoglobin polymer and by 50% with transfusion of a 6% solution of the polymer. Transfusion of a 6% solution of a 500-kDa polymer possessing a P50 of 17 Torr and a cooperativity of n = 2.0 resulted in a 66% reduction of infarct volume. These results indicate that cell-free Hb polymers with P50 values much lower than that of red blood cell hemoglobin are highly capable of salvaging ischemic brain. The assumption that the P50 of blood substitutes should be similar to that of blood might not be warranted when used during ischemic conditions.

### Recombinant hemoglobin betaG83C-F41Y.

Vasseur-Godbillon C, Sahu SC, Domingues E, Fablet C, Giovannelli JL, Tam TC, Ho NT, Ho C, Marden MC, Baudin-Creuzat V. *FEBS J.* 2006 Jan;273(1):230-41.

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We have engineered a stable octameric hemoglobin (Hb) of molecular mass 129 kDa, a dimer of recombinant hemoglobin (rHb betaG83C-F41Y) tetramers joined by disulfide bonds at the beta83 position. One of the major problems with oxygen carriers based on acellular hemoglobin solutions is vasoactivity, a limitation which may be overcome by increasing the molecular size of the carrier. The oxygen equilibrium curves showed that the octameric rHb betaG83C-F41Y exhibited an increased oxygen affinity and a decreased cooperativity. The CO rebinding kinetics, auto-oxidation kinetics, and size exclusion chromatography did not show the usual dependence on protein concentration, indicating that this octamer was stable and did not dissociate easily into tetramers or dimers at low concentration. These results were corroborated by the experiments with haptoglobin

showing no interaction between octameric rHb betaG83C-F41Y and haptoglobin, a plasma glycoprotein that binds the Hb dimers and permits their elimination from blood circulation. The lack of dimers could be explained if there are two disulfide bridges per octamer, which would be in agreement with the lack of reactivity of the additional cysteine residues. The kinetics of reduction of the disulfide bridge by reduced glutathione showed a rate of 1000 m(-1).h(-1) (observed time coefficient of 1 h at 1 mm glutathione) at 25 degrees C. Under air, the cysteines are oxidized and the disulfide bridge forms spontaneously; the kinetics of the tetramer to octamer reaction displayed a bimolecular reaction of time coefficient of 2 h at 11 microm Hb and 25 degrees C. In addition, the octameric rHb betaG83C-F41Y was resistant to potential reducing agents present in fresh plasma.

### The how and why of exocytic vesicles.

Greenwalt TJ. *Transfusion*. 2006 Jan;46(1):143-52.

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The purpose of this review is to draw the attention of general readers to the importance of cellular exocytic vesiculation as a normal mechanism of development and subsequent adjustment to changing conditions, focusing on red cell (RBC) vesiculation. Recent studies have emphasized the possible role of these microparticles as diagnostic and investigative tools. RBCs lose membrane, both in vivo and during ex vivo storage, by the blebbing of microvesicles from the tips of echinocytic spicules. Microvesicles shed by RBCs in vivo are rapidly removed by the reticuloendothelial system. During storage, this loss of membrane contributes to the storage lesion and the accumulation of the microvesicles are believed to be thrombogenic and thus to be clinically important.

### Reengineering transfusion and cellular therapy processes hospitalwide: ensuring the safe utilization of blood products.

Brooks JP. *Transfusion*. 2005; 45(4 Suppl):159S-71S

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Efforts to make blood transfusion as safe as possible have focused on making the blood in the bag as disease-free as possible. The results have been dramatic, and the costs have been correspondingly high. Although blood services will have to continue to deal with emerging pathogens, efforts to reduce the transfusion of infectious agents presently posing a risk will require high incremental costs and result in only improvements of a small magnitude. The other aspect of safe blood transfusion, the actual transfusion process performed primarily in hospitals, has been accorded considerably less interest. We should turn our attention to enhancing overall blood safety by focusing on improving the process of blood transfusion. Errors involving patient, specimen, and blood product

identification put transfused patients at risk, increasing the mortality risk for some. Solutions that could improve the transfusion process are discussed as a focus of this article.

### Detection of West Nile virus in the Mexican blood supply.

Sanchez-Guerrero SA, Romero-Estrella S, Rodriguez-Ruiz A, Infante-Ramirez L, Gomez A, Villanueva-Vidales E, Garcia-Torres M, Dominguez AM, Vazquez JA, Calderon ED, Valiente-Banuet L, Linnen JM, Broulik A, Harel W, Marin Y Lopez RA. *Transfusion*. 2006 Jan;46(1):111-7.

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**BACKGROUND:** West Nile virus (WNV) is the etiologic agent of an emerging disease in the Western Hemisphere that can be transmitted to humans by blood transfusion. WNV first appeared in the United States in 1999, in Canada in 2001, and in Mexico in 2002. The aim of this nationwide study was to determine the prevalence of WNV in blood donors in Mexico as a first step in preventing its transfusion-associated transmission. **STUDY DESIGN AND METHODS:** In July and August 2004, a total of 3856 fresh plasma specimens collected from each state's center for blood transfusion in 29 of 31 Mexican states were screened with an investigational WNV assay (Procleix, (R) Gen-Probe Inc. and Chiron Corp.), a nucleic acid test based on transcription-mediated amplification (TMA). Reactive specimens were confirmed with a second TMA-based test, the alternative WNV assay (Gen-Probe), and with WNV capture enzyme-linked immunosorbent assays (ELISAs) for detection of immunoglobulin M (IgM) and IgG antibodies. In addition, 3714 frozen plasma samples collected in 2002 and 2003 were similarly tested. **RESULTS:** One of 3856 fresh samples from an asymptomatic donor from Chihuahua was reactive by both TMA-based tests and IgM ELISA, suggesting a recently acquired infection. The observed percentage of viremic donors blood donors was 0.03 percent. Results from frozen samples were not included in the prevalence calculation and none were TMA-reactive for WNV. **CONCLUSIONS:** WNV is present in the Mexican blood supply and measures should be taken to reduce the risk of transfusion transmission.

### [Post-transfusion parasite transmission: do the present controls fit with the EU directive?]

Garraud O ; Elghouzzi MH. *Transfus Clin Biol*. 2005; 12(3):275-85

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Blood transfusion has become extremely safe regarding the transmission of infectious pathogens, some of them having been responsible for mostly severe complications and a certain loss of confidence from practitioners and patients over the last decades. This may result from the

strict observance of ethical principles, of a better medical selection of donors, of technical steps for preparing and qualifying blood components for therapeutic use. The transfusion systems--which vary in their constitution and missions depending on the countries or even regions--have imposed themselves strict security rules and guidelines in industrialized countries. Further, governmental sanitary authorities have set up additional surveillance systems to make the transfusion systems the safest as possible. In addition, the Council of Europe has edicted directives to redefine guidelines to the preparation, use and quality assurance of blood products, that are mandatory in countries of the European Community. Regarding the infectious risks, most recommendations have focused more on the bacterial (immediate) and the viral (mostly delayed) risks than on the parasitic risks because these risks are not only less frequent in industrialized countries, but also far less well known and even much more complex. However, because travel habits and immigrations are increasing fast, most transfusion systems or blood banks must revisit their practices and controls towards hemoparasite transmission by blood transfusion. This review aims at discussing the present controls set up in most industrialized countries and particularly in Europe regarding the risk of post-transfusion transmission of hemoparasites, and the robustness of such controls as well as how these controls may be secured by the European Directive.

#### **Clinical perspectives of emerging pathogens in bleeding disorders.**

Ludlam CA, Powderly WG, Bozzette S, Diamond M, Koerper MA, Kulkarni R, Ritchie B, Siegel J, Simmonds P, Stanley S, Tapper ML, von Depka M. *Lancet*. 2006 Jan 21;367(9506):252-61.

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As a result of immunological and nucleic-acid screening of plasma donations for transfusion-transmissible viruses, and the incorporation of viral reduction processes during plasma fractionation, coagulation-factor concentrates (CFC) are now judged safe in terms of many known infectious agents, including hepatitis B and C viruses, HIV, and human T-cell lymphotropic virus. However, emerging pathogens could pose future threats, particularly those with blood-borne stages that are resistant to viral-inactivation steps in the manufacturing process, such as non-lipid-coated viruses. As outlined in this Review, better understanding of infectious diseases allows challenges from newly described agents of potential concern in the future to be anticipated, but the processes of zoonotic transmission and genetic selection or modification ensure that plasma-derived products will continue to be subject to infectious concerns. Manufacturers of plasma-derived CFC have addressed the issue of emerging infectious agents by developing recombinant products that limit the need for human plasma during production. Such recombinant products have extended the safety profile of their predecessors by ensuring that all reagents used for cell culture, purification steps, and stabilisation and storage buffers are completely independent of human plasma.

#### **Risks of transmission of variant Creutzfeldt-Jakob disease by blood transfusion.**

Peden AH, Ritchie DL, Ironside JW. *Folia Neuropathol*. 2005;43(4):271-8.

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Variante Creutzfeldt-Jakob disease (vCJD) was first identified in 1996 in the UK, and results from human exposure to the bovine spongiform encephalopathy (BSE) agent. vCJD has subsequently been identified in 10 additional countries, and numbers continue to increase in the UK. Unlike other human prion diseases, infectivity and the disease-associated form of the prion protein are readily detected in lymphoid tissues in vCJD. In experimental BSE infection in a sheep model, infectivity has been transmitted by blood transfusion from asymptomatic infected animals to normal recipient animals, indicating that infectivity is present in blood during the incubation period. Recently, two cases of apparent iatrogenic vCJD infection by blood transfusion from asymptomatic donors who subsequently died from vCJD have been reported from the UK. The first case resulted in clinical illness identical to other cases of vCJD, while the second case was an asymptomatic infection detected at autopsy. Sensitive means of detection of disease-associated prion protein in the blood are required in order to be employed for screening purposes, both individually at the time of blood donation, and to help ascertain future numbers of vCJD cases in the UK and beyond.

#### **Immunization to minor histocompatibility antigens on transfused RBCs through crosspriming into recipient MHC class I pathways.**

Zimring JC, Hair GA, Deshpande SS, Horan JT. *Blood*. 2006 Jan 1;107(1):187-9. Epub 2005 Aug 25.

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Increased rates of graft rejection after bone marrow transplantation (BMT) are observed in patients whose illnesses--such as sickle cell disease, thalassemia, and aplastic anemia--necessitate chronic transfusion before BMT. Because BM transplants in these patients are routinely HLA matched, any immunization responsible for increased rejection is likely against minor histocompatibility antigens (mHAs). It has been assumed that contaminating leukocytes in red blood cell (RBC) units are the main sources of immunization to mHAs. However, in this report, we demonstrate that antigens on donor RBCs are presented in the major histocompatibility complex (MHC) class I pathway of recipient antigen-presenting cells, resulting in activation and expansion of recipient CD8+ T cells specific for donor mHAs. Given that human hematopoietic progenitor cells express many of the

known mHAs, this observation provides a mechanism by which chronic transfusion of even stringently leukoreduced RBCs may result in sufficient mHA immunization to increase the frequency of BMT rejection.

### **Malaria and blood transfusion.**

Kitchen AD, Chiodini PL. *Vox Sang.* 2006 Feb;90(2):77-84.

National Blood Service, London, UK.

The transmission of malaria by blood transfusion was one of the first recorded incidents of transfusion-transmitted infection. Although a number of different infections have been reported to be transmitted by transfusion since then, on a global scale malaria remains one of the most common transfusion-transmitted infections. Transfusion-transmitted malaria can have serious consequences, as infection with *Plasmodium falciparum* may prove rapidly fatal. Ensuring that, in non-endemic countries, the blood supply is free from malaria is problematical, especially as travel to malarious areas is increasing and there is some spread of the disease into new areas, as well as a resurgence of malaria in areas where previously it had been eradicated. In non-endemic countries, donor deferral can be effective, but clear guidelines are needed. In endemic countries the problem is far greater as the majority of donors may be potentially infected with malaria parasites. In both situations, the simple deferral of donors may be wasteful and can eventually erode the donor base. Thus, other strategies are needed to ensure safety with sufficiency. However, the screening of donations for evidence of malaria is not without its problems. Although the examination of blood films is still the basis for diagnosing acute malaria, in most situations it is not sufficiently sensitive for blood bank screening. In non-endemic countries, donor deferral in combination with screening for specific antimalarial immunoglobulin provides an effective means of minimizing the risk of transmission. In endemic countries, more specific donor questioning, consideration of seasonal variation and geographical distribution may help to identify the population of donors who are most likely to be infected. In addition, the administration of antimalarials to transfusion recipients may help to prevent transmission. Nonetheless, no matter what strategy is adopted, it is likely that cases of transfusion-transmitted malaria may still occur, so malaria must always be considered in any patient with a febrile illness post-transfusion.

### **Perioperative blood transfusions for the recurrence of colorectal cancer.**

Amato A, Pescatori M. *Cochrane Database Syst Rev.* 2006 Jan 25;(1):CD005033.

**BACKGROUND:** The improvement of renal allograft survival by pre-transplantation transfusions alerted the medical community to the potential detrimental effect of transfusions in patients being treated for cancer.

**OBJECTIVES:** The present meta-analysis aims to evaluate the role of perioperative blood transfusions (PBT) on colorectal cancer recurrence. This is accomplished by validating the results of a previously published meta-

analysis (Amato 1998); and by updating it to December 2004. **SEARCH STRATEGY:** Published papers were retrieved using Medline, EMBASE, the Cochrane Library, controlled trials web-based registries, or the CCG Trial Database. The search strategy used was: {colon OR rectal OR colorectal} WITH {cancer OR tumor OR neoplasm} AND transfusion. The tendency not to publish negative trials was balanced by inspecting the proceedings of international congresses. **SELECTION CRITERIA:** Patients undergoing curative resection of colorectal cancer (classified either as Dukes stages A-C, Astler-Coller stages A-C2, or TNM stages T1-3a/N0-1/M0) were included if they had received any amount of blood products within one month of surgery. Excluded were patients with distant metastases at surgery, and studies with short follow-up or with no data. **DATA COLLECTION AND ANALYSIS:** A specific form was developed for data collection. Data extraction was cross-checked, using the most recent publication in case of repetitive ones. Papers' quality was ranked using the method by Evans and Pollock. Odds ratios (OR, with 95% confidence intervals) were computed for each study, and pooled estimates were generated by RevMan (version 4.2). When available, data were stratified for risk factors of cancer recurrence. **MAIN RESULTS:** The findings of the 1998 meta-analysis were confirmed, with small variations in some estimates. Updating it through December 2004 led to the identification of 237 references. Two-hundred and one of them were excluded because they analyzed survival (n=22), were repetitive (n=26), letters/reviews (n=66) or had no data (n=87). Thirty-six studies on 12,127 patients were included: 23 showed a detrimental effect of PBT; 22 used also multivariable analyses, and 14 found PBT to be an independent prognostic factor. Pooled estimates of PBT effect on colorectal cancer recurrence yielded overall OR of 1.42 (95% CI, 1.20 to 1.67) against transfused patients in randomized controlled studies. Stratified meta-analyses confirmed these findings, also when stratifying patients by site and stage of disease. The PBT effect was observed regardless of timing, type, and in a dose-related fashion, although heterogeneity was detected. Data on surgical techniques was not available for further analysis. **AUTHORS' CONCLUSIONS:** This updated meta-analysis confirms the previous findings. All analyses support the hypothesis that PBT have a detrimental effect on the recurrence of curable colorectal cancers. However, since heterogeneity was detected and conclusions on the effect of surgical technique could not be drawn, a causal relationship cannot still be claimed. Carefully restricted indications for PBT seems necessary.

### **Transfusion increases the risk of postoperative infection after cardiovascular surgery.**

Banbury MK, Brizzio ME, Rajeswaran J, Lytle BW, Blackstone EH. *J Am Coll Surg.* 2006 Jan;202(1):131-8. Epub 2005 Nov 10.

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**BACKGROUND:** Because of the immunomodulatory effects of transfusion, we attempted to identify factors associated with blood product use and determine the association of transfusion quantity with postoperative

infection. **STUDY DESIGN:** We studied total perioperative transfusion of blood products for 15,592 cardiovascular operations performed from July 1998 to May 2003. Infection end points were septicemia/bacteremia (n=351, 2.2%) and superficial (n=353, 2.3%) and deep (n=212, 1.4%) sternal wound infections. Factors associated with blood product administration were used to form balancing scores to adjust for differences in patient characteristics among those receiving and not receiving blood products. **RESULTS:** Fifty-five percent of patients received packed red blood cells (RBC), 21% received platelets, 13% got fresh frozen plasma (FFP), and 3% got cryoprecipitate. Factors associated with RBC use included older age, female gender, higher New York Heart Association class, lower hematocrit, reoperation, and longer cardiopulmonary bypass time—all indicative of higher-risk patients. The more RBC units transfused, the higher was the occurrence of septicemia/bacteremia ( $p < 0.0001$ ) and superficial ( $p=0.0007$ ) and deep ( $p < 0.0001$ ) sternal wound infection. Use of FFP (septicemia/bacteremia) and platelets (septicemia/bacteremia and deep sternal wound infection) mitigated against this association only slightly. **CONCLUSIONS:** Blood products tended to be used in the sickest patients. But after accounting for this, risk of infection increased incrementally with each unit of blood transfused. Although cause and effect cannot be established, results suggested that blood product transfusion is an independent risk factor for postoperative infection in cardiac surgical patients, blood products are more likely to be used in the sickest patients, and no amount of blood loss treated by transfusion is innocuous.

#### **[Toward zero mortality in liver resection. Presentation of 200 consecutive cases.]**

[Article in Spanish]

Robles R, Marin C, Fernandez JA, Ramirez P, Sanchez-Bueno F, Morales D, Lujan JA, Abellan B, Ramirez M, Cascales P, Perez D, Parrilla P. *Cir Esp.* 2005 Jul;78(1):19-27.

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**INTRODUCTION.** Liver resection (LR) morbidity and mortality rates have dropped in recent decades. Mortality is now below 5% and morbidity is less than 30%. Our objective was to present a series of 200 LRs without mortality and to analyze the factors that may be related to complications. **Patients and method.** Between January 1996 and October 2003, 200 LRs were performed in 177 patients. The most common indication was liver metastases in 123 patients (61.5%), primary malignant liver tumors in 27 patients (13.5%), bile duct tumors in 27 patients (13.5%) and benign disease in 23 patients (11.5%). Fifty-one percent of the resections were performed under hemihepatic vascular control and 49% were resections of central segments, segmentary and atypical resections. We studied the association between morbidity and age, sex, previous comorbidity, liver status, indication for surgery, number of resections, major and

minor resections, resection extended to other organs, type of vascular occlusion, transfusion requirements, operating time, length of hospital stay and experience of the surgical team. **RESULTS.** There was no postoperative mortality. The morbidity rate was 17.5% (35 patients) and the most common complications were biliary (8%). Morbidity was related to transfusion (transfused patients presented more complications) ( $P < .001$ ). Transfusion was greater in major resections, the first 100 resections and prolonged operations. Among the segmentary resections the Pringle maneuver reduced transfusion requirements but this difference was not statistically significant. Morbidity decreased in the second 100 resections, without significant differences. **CONCLUSION.** LRs can be performed with low mortality and morbidity. Biliary complications and blood transfusion should be avoided whenever possible.

#### **Consenting to blood: what do patients remember?**

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We sought to characterize the consent process for transfusion and determine its impact on patients' knowledge and level of comfort with receiving blood. We identified all adult patients who had received blood transfusion at a tertiary care centre over 3 months. Patients who were discharged each received a survey that assessed their (1) recall of the consent process, (2) recall of information conveyed, (3) assessment of the discussion's understandability and (4) perceived knowledge of as well as comfort level with transfusion as a result of the discussion. Overall, 80% of respondents recalled discussing and signing an informed consent. Information was mostly conveyed by attending physicians (35%) and consent obtained in the patient's hospital room (38%) or the preadmission clinic (19%). Although the majority recalled the consent process, many did not recall the discussion of specific transfusion risks or alternatives to donor blood (88%). Although the majority felt the discussion was at least somewhat understandable (77%), only 35% felt better informed and more comfortable with accepting blood. Despite implementation of written informed consent for transfusion, patients' recollection and understanding of risks and alternatives remain poor. This suggests the need for improving risk communication.