British Journal of Anaesthesia **109** (3): 376–81 (2012)
Advance Access publication 19 June 2012 · doi:10.1093/bja/aes186

BJA

CRITICAL CARE

Perioperative treatment algorithm for bleeding burn patients reduces allogeneic blood product requirements

E. Schaden[1], O. Kimberger[1], P. Kraincuk[1], D. M. Baron[1], P. G. Metnitz[1] and S. Kozek-Langenecker[2]*

[1] Department of Anaesthesia, General Intensive Care and Pain Control, Medical University of Vienna, Austria
[2] Department of Anaesthetics and Intensive Care, Evangelical Hospital Vienna, Austria

* Corresponding author. E-mail: sibylle.kozek@aon.at

Editor's key points

- Targeted treatment of bleeding appears to reduce requirements for allogeneic transfusion in trauma patients, but has not been studied in burn patients undergoing wound excision.
- A transfusion algorithm modified for burn excision surgery was evaluated prospectively in 30 patients randomized to a thromboelastometry-based algorithm or standard care.
- Cumulative use of allogeneic blood products was significantly reduced in the bleeding management algorithm group; further studies are needed to confirm this finding and investigate outcome measures.

Background. Surgical excision of burn wounds is often associated with severe bleeding. Timely and targeted correction of coagulopathy reduces transfusion requirements and improves survival in trauma victims. We hypothesized that rapid correction of coagulopathy after a treatment algorithm based on point-of-care viscoelastic coagulation testing would decrease allogeneic blood product transfusions during surgical excision of burn wounds.

Methods. Thirty consecutive patients undergoing surgical excision of burn wounds were enrolled into this prospective, randomized, controlled, single-centre study. In the control group, coagulation management was performed according to the clinicians' discretion. For the algorithm group, we standardized treatment based on the Austrian recommendation for the management of trauma-induced coagulopathy using point-of-care rotational thromboelastometry (ROTEM®). The main outcome parameter was the cumulative number of allogeneic blood units transfused on the day of surgery.

Results. The difference between the groups regarding the cumulative use of allogeneic blood products was highly significant with 3.0 (1.3–5.5) blood products in the algorithm group compared with 9.0 (6.0–12.3) in the control group [median (inter-quartile range); $P=0.002$]. No plasma was administered in the algorithm group compared with 5.0 (1.5–7.5) units overall in the control group ($P<0.001$). Fibrinogen concentrate administration was not significantly different between the groups ($P=0.89$). Tranexamic acid was not administered.

Conclusions. The significant reduction in allogeneic blood product requirements during surgical burn wound excision is a prospective proof of concept that a bleeding management algorithm based on thromboelastometry is efficacious. Hypofibrinogenaemia and hyperfibrinolysis are not significant pathomechanisms of bleeding in this setting and ROTEM® helps to avoid unnecessary interventions.

Keywords: blood, coagulation; fibrinogen; laboratory techniques and procedures, thrombelastography; wound and injuries, burns

Accepted for publication: 28 March 2012

Surgical excision of burn wounds is often associated with severe bleeding.[1] Despite multiple attempts to reduce this blood loss, patients still need large amounts of packed red blood cells (PRBC), fresh-frozen plasma (FFP), platelet concentrates, and coagulation factor concentrates such as prothrombin complex concentrate (PCC).[2–6] Each unit of allogeneic blood product worsens outcome of critically ill patients; increased infectious complications, multiple organ failure, respiratory distress syndrome might—at least in part—explain the outcome disadvantage after transfusions.[7–11] Reductions in blood loss and transfusion requirements might thus improve overall outcome and safety in bleeding patients. Timely and targeted correction of trauma-induced coagulopathy using coagulation factor concentrates has been shown to reduce transfusion requirements and improve survival,[12 13] but this treatment strategy has not yet been evaluated in burn victims. We hypothesized that rapid correction of coagulopathy would decrease allogeneic blood product transfusions during surgical excision of burn wounds. Accordingly, we designed a treatment algorithm based on point-of-care coagulation testing and prospectively compared blood product requirements with a control group.

Methods

The study was performed at the intensive care unit for burn trauma of the General Hospital of Vienna, Austria, from February 2008 to October 2009. The institutional review board approved the study (no: 556/2007). All consecutive patients undergoing surgical excision of burn wounds were enrolled into this prospective, randomized, controlled, single-centre study. The surgical intervention was performed on the third day after burn trauma. Before surgical burn wound excision patients were enrolled and randomized into the algorithm group or the control group. The following data were documented: patient characteristic data, bleeding and thrombosis history, percentage of total body surface area burned (%TBSA), and abbreviated burn severity index (ABSI). The body core temperature (measured in the bladder) was registered before and after operation. Routine coagulation tests were performed in the hospital's central laboratory at least once before and after surgery. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level (Clauss method) were determined in citrated plasma using an automated coagulation analyser (STA-R Evolution, Stago, Asnieres, France). Platelet count was assessed in EDTA blood with a Sysmex XE-2100 cell counter (Sysmex, Kobe, Japan).

In the control group, coagulation management was performed according to the clinician's discretion and included administration of FFP, platelet concentrate, fibrinogen concentrate, PCC, and tranexamic acid according to clinical judgement based on expertise, impression of diffuse bleeding in the surgical field, and/or routine coagulation tests if deemed necessary.

Treatment in the algorithm group was standardized (Fig. 1) based on the recommendations for bleeding management in trauma-induced coagulopathy by the Austrian Task Force of Perioperative Coagulation.[14] These recommendations advocate point-of-care monitoring to guide correction of coagulopathy and of coagulation factor concentrates to permit fast optimization of haemostatic competence. In the present study, we used ROTEM® (TEM Innovations, Munich, Germany) for viscoelastic point-of-care coagulation testing as described previously.[15 16] The treatment algorithm was based on three commercially available tests (EXTEM®, FIBTEM®, and APTEM®). In brief, EXTEM® is a baseline test that uses recombinant tissue factor to activate coagulation (comparable with PT). The clotting time (CT) of EXTEM® gives information about the initial activation and dynamics of clot formation, thus allowing analysis of factor deficiencies.[17] The maximum clot firmness (MCF) of EXTEM® gives information about clot strength and stability, which is largely dependent on platelet count and fibrinogen function.[17] Clot strength 10 min after CT (A10) is available earlier than MCF and shows a high correlation to MCF.[18] In the FIBTEM® test, cytochalasin D, a platelet inhibitor, is added to the EXTEM® test. Hence, FIBTEM® MCF or A10 represents the contribution of fibrinogen to the clot strength.[17] A low FIBTEM® MCF or A10 is an indication for administration of fibrinogen concentrate, whereas a normal FIBTEM® MCF or A10 in the presence of a low EXTEM® MCF or A10 indicates the need for platelet substitution.[17]

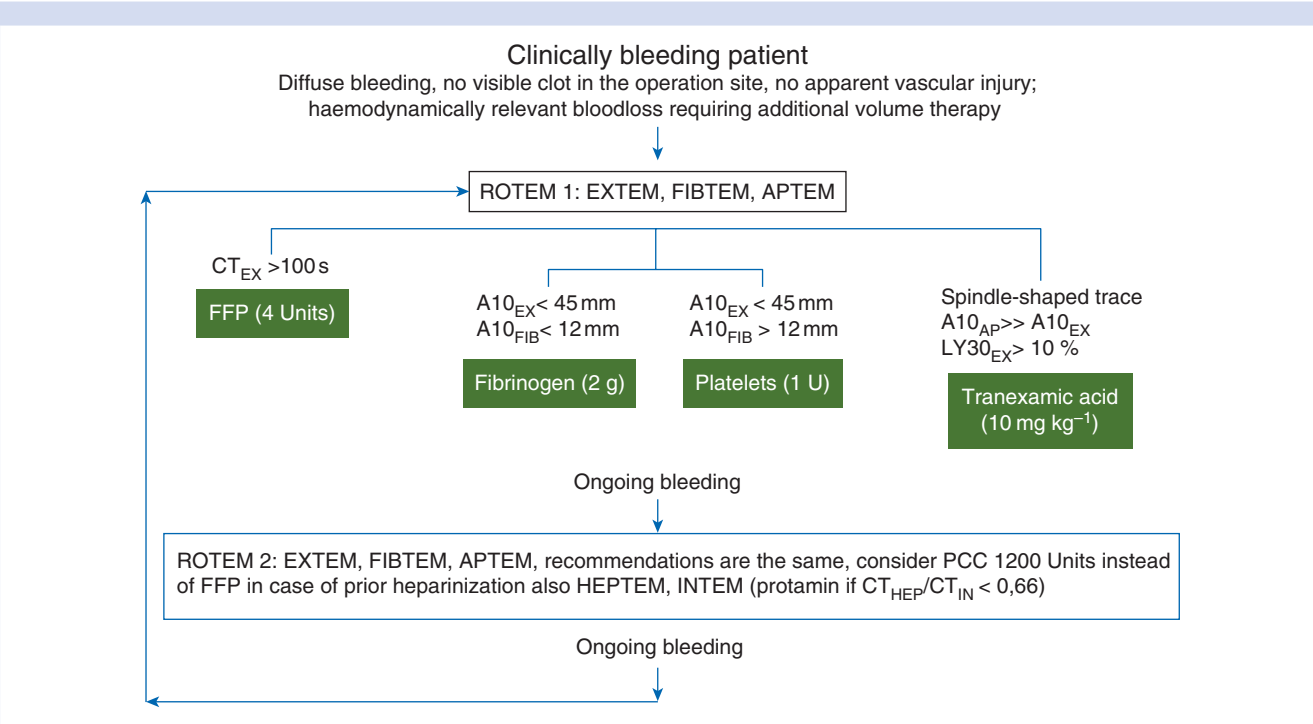

Fig 1 Treatment algorithm. CT, clotting time; A 10, amplitude 10 min after CT; LY, lysis index 30 min after CT; FFP, fresh-frozen plasma; PCC, prothrombin complex concentrate.

EXTEM® also allows the diagnosis of hyperfibrinolysis using the lysis index 30 min after CT (LY30). Quantitative assessment of fibrinolysis and estimation of the therapeutic benefit from antifibrinolytic agents are accomplished with the APTEM® test, in which aprotinin is added to the EXTEM® test. Improvement in prolonged CT and/or reduced MCF in the APTEM® compared with the EXTEM® indicates low-grade hyperfibrinolysis.[17]

Based on our previous experience with ROTEM® in burn patients,[19] threshold values for the three ROTEM® parameters used in the algorithm were slightly higher compared with those recommended for trauma patients.[12 14] In actively bleeding burn patients, a FIBTEM® A10 <12 mm triggered administration of 2 g fibrinogen concentrate (Haemocompletan® P, CSL Behring, Marburg, Germany). A FIBTEM® A10 >12 mm in the presence of an EXTEM® A10 <45 mm triggered transfusion of 1 unit of apheresis platelet concentrate. An EXTEM® CT >100 s triggered transfusion of 4 units of FFP. LY30 >10%, improvement of prolonged EXTEM® CT, and/or increased A10 in the APTEM® test triggered administration of 10 mg kg^{-1} tranexamic acid (Cyclokapron, Pfizer, Vienna, Austria). PCC was considered if EXTEM® CT remained >100 s in the ROTEM® control after FFP transfusions.

ROTEM® tests were performed using citrated whole blood before operation and intraoperatively in the operating theatre and after operation at the intensive care unit until the morning after surgery whenever clinically relevant bleeding occurred. Clinically relevant bleeding was defined as coagulopathic bleeding with diffuse oozing without clots in the surgical field or without a vascular lesion, or severe bleeding resulting in haemodynamic instability and requiring additional fluid therapy. All ROTEM® tests and quality control measurements were carried out according to the manufacturer's instructions.

Haemoglobin levels and haematocrit were assessed by blood gas analysis (BGA) in all patients before and after operation. BGA was performed at the point-of-care using a standard analyser (Radiometer Copenhagen®, Brønshøj, Denmark). In the algorithm group, BGA was determined whenever ROTEM® tests were analysed. In the control group, intraoperative BGA was left to the discretion of the attending anaesthesiologist. For all patients, a universal trigger for PRBC transfusion was defined at haemoglobin <8 g dl^{-1}.

The main outcome parameter was the cumulative number of allogeneic blood units (PRBC, FFP, and platelet concentrates) transfused on the day of the surgical excision of burn wounds. We hypothesized that transfusion of blood products is significantly reduced in the algorithm group. Secondary endpoints were the use of PRBC alone, FFP alone, platelet concentrate alone, fibrinogen concentrate, PCC, and tranexamic acid.

Statistical analysis

Under the assumption that a 50% reduction in total blood product use occurs in the algorithm group, a sample size of 12 patients per group was needed with an α-error of 0.05 and a power of 80%. Assuming a dropout rate of 25%, 30 patients were enrolled.

Data are displayed as median (inter-quartile range) unless otherwise specified. For univariate comparison of blood transfusion requirements between the groups, the Wilcoxon test was used. Owing to technical problems, ROTEM® could not be used in three patients of the algorithm group; these patients were treated like patients allocated to the control group. PASW Statistics 18.0 (IBM, Armonk, NY, USA) was used for statistical analysis, with $P<0.05$ considered statistically significant.

Results

Thirty consecutive patients were included in the study. Patient characteristics are shown in Table 1. No patient had known preexisting bleeding disorders or was taking antiplatelet and/or anticoagulant drugs before burn injury. Fourteen patients were included into the algorithm group and 16 into the control group. Groups were comparable with respect to age, sex, BMI, and severity of burn trauma (Table 1).

The difference between the groups in the cumulative use of allogeneic blood products was highly significant with 3.1 (2.2) blood products in the algorithm group compared with 10.2 (7.3) in the control group ($P=0.002$; Fig. 2).

Table 1 Characteristics of the study population. BMI, body mass index (kg m^{-2}, reference range 18.5–25); TBSA, total body surface area; ABSI, abbreviated burn severity index (reference range 2–18, probability of death for ABSI over 9 is >50%)

	Control group	Algorithm group	*P*-value
n	16	14	
Age (yr; median and range)	49.5 (26–83)	56 (17–87)	0.78
Male/female	9/7	9/5	0.47
BMI	25.7 (23.0–30.2)	27.9 (25.0–30.1)	0.89
% TBSA burned	40.0 (28.8–55.0)	35.0 (30.0–38.8)	0.61
ABSI	9.0 (8.0–11.0)	9.0 (7.3–9.0)	0.52

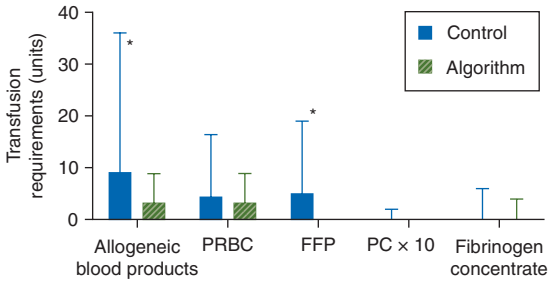

Fig 2 Transfusion requirements in the control and the algorithm group. Bar: median, whisker: range, *$P<0.05$ between the groups PRBC, packed red blood cells; FFP, fresh-frozen plasma; PC, platelet concentrate.

Table 2 Results of laboratory tests. PT, prothrombin time (%); aPTT, activated partial thromboplastin time (s); platelets (G litre^{-1}); fibrinogen measured with the Clauss method (mg dl^{-1}) and FIBTEM® (mm); Hb, haemoglobin (g dl^{-1})

	Control group	Algorithm group	*P*-value
PT preoperative	85.5 (77.3–103.3)	96.0 (82.8–112.8)	0.20
PT postoperative	68.0 (60.5–84.3)	70.5 (61.3–96.0)	0.60
aPTT preoperative	40.0 (36.0–43.3)	44.0 (41.0–48.0)	0.01
aPTT postoperative	41.0 (37.8–43.3)	43.5 (38.8–48.5)	0.45
Platelets preoperative	176.5 (107.0–275.0)	144.5 (105.3–233.8)	0.99
Platelets postoperative	131.0 (76.0–279.3)	125.5 (97.3–197.0)	0.68
Fibrinogen preoperative	527.0 (403.0–642.8)	669.0 (503.3–763.0)	0.09
Fibrinogen postoperative	311.0 (278.3–442.0)	494.5 (421.3–616.5)	0.12
FIBTEM® preoperative	26.5 (21.8–34.0)	33.0 (30.3–37.8)	0.15
FIBTEM® postoperative	17.5 (12.0–24.3)	24.0 (21.5–31.0)	0.09
Hb preoperative	10.6 (9.5–11.1)	11.0 (9.8–11.5)	0.40
Hb postoperative	10.2 (9.1–11.2)	10.0 (9.2–10.6)	0.94

In the algorithm group, 3.1 (2.1) units of PRBC were transfused (44 units overall) and 4.8 (3.0) units in the control group (76 units overall) ($P=0.12$).

No FFP was administered in the algorithm group compared with 5.0 (1.5–7.5) units in the control group (83 units overall; $P<0.001$; Fig. 2). Also no platelet concentrate was transfused in the algorithm group, whereas 4 units overall were applied in the control group ($P=0.12$). Fibrinogen concentrate administration was not significantly different with overall 8 g given in both groups ($P=0.89$). PCC and tranexamic acid were not administered in either group.

Results of coagulation tests and the mean fibrinogen and FIBTEM® A10 values measured before and after the surgical procedure are shown in Table 2.

Discussion

This is the first prospective, randomized, controlled trial in burn victims undergoing surgical burn wound excision showing a significant reduction in allogeneic blood product requirements using a standardized coagulation management algorithm. Increasing knowledge of the serious adverse effects of allogeneic blood products[7–11] and awareness of their limited availability and high costs triggered the urgent quest for strategies to reduce perioperative transfusion requirements. Among various therapeutic options, the concept of patient blood management has proved successful in elective surgical cases.[20–22] The three main goals of patient blood management are (i) correction of preoperative anaemia, (ii) reduction in perioperative blood loss by optimizing surgical technique and intraoperative haemostatic competence,[20 21] and (iii) increase in anaemia tolerance. Although preoperative optimization is not possible in emergency situations, at least anaemia tolerance and haemostatic coagulation management can be implemented during non-elective surgery. The present study confirms that the latter reduces patient exposure to allogeneic blood products in non-elective burn surgery.

In acute bleeding situations, predefined coagulation treatment protocols can facilitate decision-making comparable with the protocol for early goal-directed therapy in septic patients.[23] The management of massive bleeding after transfusion protocols has been found efficacious in patients undergoing cardiac surgery and liver transplantation and also in patients suffering polytrauma.[12 18 24–26] Our coagulation treatment was standardized by using a simple algorithm based on the results of point-of-care viscoelastic testing using ROTEM®.[27 28] A recent Cochrane analysis systematically assessed the benefits and harms of thrombelastography or ROTEM®-guided transfusion strategies in randomized trials of massively transfused patients.[27] The use of thrombelastography or ROTEM® showed no significant effect on overall mortality but significantly reduced blood loss and the proportion of patients requiring transfusion of PRBCs and FFP plus platelets.[27] We suggest that it is not simply the procedure of monitoring coagulation that improves outcome, but rather the rational therapeutic consequences based on timely viscoelastic monitoring that is especially sensitive for fibrinogen deficits and hyperfibrinolysis.[18 29 30] Interestingly, hyperfibrinolysis, which seems to be a relevant pathomechanism in bleeding after trauma,[31] was not observed in our burn trauma cohort. This finding is in line with our previous results on coagulation changes in the first 48 h after burn injury.[19] It appears that hyperfibrinolysis is not a leading mechanism for bleeding during surgical wound excision in burn patients. Accordingly, no patient received antifibrinolytic drugs in our study.

In severe bleeding, fibrinogen is the first haemostatic factor to reach critical levels and fibrinogen deficiency is suggested to be a relevant pathomechanism in trauma-related coagulopathy.[32] In burn patients, however, fibrinogen level and FIBTEM® MCF increase within 24 h after injury,[19] and we confirmed high baseline levels of fibrinogen before burn wound excision performed on the third day after burn injury. Therefore, in our algorithm, we chose an A10 of 12 mm as the trigger value for administration of fibrinogen concentrate, which is slightly higher compared with

threshold values empirically defined for trauma.[12 33] Interestingly, fibrinogen rarely decreased below the trigger value in our burn trauma cohort, overall fibrinogen concentrate requirements were moderate in both groups, and postoperative fibrinogen levels and FIBTEM® MCF were not different between the groups. It appears that fibrinogen deficiency is not a leading mechanism for bleeding in burn patients—at least if severe dilutional coagulopathy is avoided by an individualized and restrictive fluid management approach.[34]

Similarly, the standardized coagulation management algorithm never indicated the need for administration of PCC, FFP, or platelet concentrate. Despite the more restrictive use of procoagulant interventions compared with the control group, PRBC requirements were not significantly different in the algorithm group. The ROTEM®-based management algorithm prevented unnecessary procoagulant treatment in the algorithm group. Avoiding the use of FFP and platelet concentrates can have long-term outcome benefits for the individual patient and relevant cost-savings for the healthcare system. Taken together, a ROTEM®-based algorithm tailoring coagulation therapy to patient needs could increase the quality of care and safety in burn patients. Moreover, a normal ROTEM® trace can provide confidence in avoiding unnecessary therapy.

We did not use routine coagulation tests such as PT (or the International Normalized Ratio—INR) and aPTT in the treatment algorithm. This decision was based on the Cochrane analysis[27] and the updated European Guideline,[33] which recommends against the use of INR and aPTT alone to guide haemostatic therapy. INR and aPTT have static endpoints that provide no information about the quality of clot or dynamics of clot formation as obtained from the ROTEM®. Moreover, INR and aPTT are usually measured in plasma, excluding the pivotal role of platelets in the coagulation process, while ROTEM® is performed using whole blood.

Our study has several limitations, mainly due to the performance of the trial in a trauma population. First, there was a vital indication for surgery in all subjects such that none of the consecutive patients was excluded. However, as determined by a detailed bleeding history,[35] none of our subjects had preexisting coagulation disorders, platelet dysfunction, or both. The latter would have been undiagnosed in our algorithm because ROTEM® is not sensitive to platelet dysfunction.[36] Secondly, differences between the groups might have been smaller with more restrictive transfusion triggers. Thirdly, blood loss during and after surgery was not measured. In comparable studies for cardiac surgery, blood and fluids are collected in chest tubes and are accessible for quantification. Burn patients bleed into wound dressings and a large part of lost fluid is drained through so-called sand beds, making accurate measurement impossible. We refrained from using the surrogate parameter of calculated blood loss, as it has not been used for burn patients before and could be biased easily by capillary leak and oedema. Fourthly, subjects were observed only until the first postoperative morning; thrombotic complications occurring afterwards cannot be ruled out. Nevertheless, as severe burn injury has a high thrombotic risk *per se*, a distinction between a complication of the underlying disease and an adverse effect of a coagulation treatment algorithm in this sample size would be largely arbitrary. Finally, we used ROTEM® which is not sensitive for assessing deficiency in anticoagulant factors and endothelial integrity. Vascular damage leading to microvascular bleeding in burn trauma patients, however, cannot be diagnosed by any coagulation tests currently available.

In summary, this prospective randomized controlled trial showed a significant reduction in allogeneic blood product requirements in burn victims allocated to a ROTEM®-guided treatment algorithm during surgical burn wound excision. Hypofibrinogenaemia and hyperfibrinolysis were not significant pathomechanisms of bleeding in this setting, and ROTEM® might help avoid unnecessary interventions.

Declaration of interest

E.S. has received speaker's honoraria from Baxter and travel reimbursement from CSL Behring. SKL has received travel reimbursement and speaker's fees for lecturing from Biotest, Octapharma, Baxter, CSL Behring and TEM Innovations; travel reimbursement and honoraria for consulting at a Biotest advisory board; and an unrestricted educational grant for the e-learning platform www.perioperativebleeding.org from CSL Behring and TEM Innovations.

Funding

This study was funded by a project grant from the Österreichische Nationalbank (ÖNB 12688).

References

1 Sterling JP, Heimbach DM. Hemostasis in burn surgery—a review. *Burns* 2011; **37**: 559–65

2 Johansson PI, Eriksen K, Nielsen SL, Rojkjaer R, Alsbjorn B. Recombinant FVIIa decreases perioperative blood transfusion requirement in burn patient undergoing excision and skin grafting—results of a single centre pilot study. *Burns* 2007; **33**: 435–40

3 O'Mara MS, Hayetian F, Slater H, Goldfarb IW, Tolchin E, Caushaj PF. Results of a protocol of transfusion threshold and surgical technique on transfusion requirements in burn patients. *Burns* 2005; **13**: 558–61

4 Mzezewa S, Jönsson K, Aberg M, Sjöberg T, Salemark L. A prospective double blind randomized study comparing the need for blood transfusion with terlipressin or a placebo during early excision and grafting of burns. *Burns* 2004; **30**: 236–40

5 Gomez M, Logsetty S, Fish JS. Reduced blood loss during burn surgery. *J Burn Care Rehabil* 2001; **22**: 111–7

6 Cartotto R, Musgrave MA, Beveridge M, Fish J, Gomez M. Minimizing blood loss in burn surgery. *J Trauma* 2000; **49**: 1034–9

7 Bux J. Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. *Vox Sang* 2005; **89**: 1–10

8 Chaiwat O, Lang JD, Vavilala MS, *et al.* Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. *Anesthesiology* 2009; **110**: 351–60

9 Khan H, Belsher J, Yilmaz M, *et al.* Fresh frozen plasma and platelet transfusion are associated with development of acute lung injury in critically ill medical patients. *Chest* 2007; **131**: 1308–14

10 Sarani B, Dunkman J, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. *Crit Care Med* 2008; **36**: 1114–8

11 Watson GA, Sperry JL, Rosengart MR, *et al.* Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma* 2009; **67**: 221–7

12 Schöchl H, Nienaber U, Hofer G, *et al.* Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care* 2010; **14**: R55

13 Schöchl H, Nienaber U, Maegele M, *et al.* Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care* 2011; **15**: R83

14 Available from http://www.oegari.at/web_files/dateiarchiv/116/key messages management of TIC 2011.pdf (accessed June 2011)

15 Mallett SV, Cox DJA. Thrombelastography. *Br J Anaesth* 1992; **69**: 307–13

16 Luddington RJ. Thrombelastography/thromboelastometry. *Clin Lab Haematol* 2005; **27**: 81–90

17 Kozek-Langenecker S. Management of massive operative blood loss. *Minerva Anestesiol* 2007; **73**: 401–15

18 Roullet S, Pillot J, Freyburger G, *et al.* Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. *Br J Anaesth* 2010; **104**: 422–8

19 Schaden E, Hoerburger D, Hacker S, Kraincuk P, Baron DM, Kozek-Langenecker S. Fibrinogen function after severe burn injury. *Burns* 2012; **38**: 77–82

20 Gombotz H, Rehak PH, Shander A, Hofmann A. Blood use in elective surgery: the Austrian benchmark study. *Transfusion* 2007; **47**: 1468–80

21 Spahn DR, Moch H, Hofmann A, Isbister JP. Patient blood management: the pragmatic solution for the problems with blood transfusions. *Anesthesiology* 2008; **109**: 951–3

22 Available from http://www.nba.gov.au/guidelines/review.html (accessed August 2011)

23 Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368–77

24 Girdauskas E, Kempfert J, Kuntze T, *et al.* Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. *J Thorac Cardiovasc Surg* 2010; **140**: 1117–24

25 Rahe-Meyer N, Solomon C, Winterhalter M, *et al.* Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. *J Thorac Cardiovasc Surg* 2009; **138**: 694–702

26 Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirschke CG, Albes JM. Cost reduction of perioperative coagulation management in cardiac surgery: value of 'bedside' thrombelastography (ROTEM). *Eur J Cardiothorac Surg* 2007; **31**: 1052–7

27 Afshari A, Wikkelsø A, Brok J, Møller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database Syst Rev* 2011; **3**: CD007871

28 Kozek-Langenecker S, Sørensen B, Hess J, Spahn DR. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care* 2011; **15**: R239 (Epub ahead of print)

29 Solomon C, Pichlmaier U, Schoechl H, *et al.* Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. *Br J Anaesth* 2010; **104**: 555–62

30 Levrat A, Gros A, Rugeri L, *et al.* Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. *Br J Anaesth* 2008; **100**: 792–7

31 CRASH-2 Trial Collaborators, Shakur H, Roberts I, Bautista R, *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376**: 23–32

32 Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg* 1995; **81**: 360–5

33 Rossaint R, Bouillon B, Cerny V, *et al.* Management of bleeding following major trauma: an updated European guideline. *Crit Care* 2010; **14**: R52

34 Fodor L, Fodor A, Ramon Y, Shoshani O, Rissin Y, Ullmann Y. Controversies in fluid resuscitation for burn management: literature review and our experience. *Injury* 2006; **37**: 374–9

35 Pfanner G, Koscielny J, Pernerstorfer T, *et al.* Preoperative evaluation of the bleeding history. Recommendations of the working group on perioperative coagulation of the Austrian Society for Anaesthesia, Resuscitation and Intensive Care. *Anaesthesist* 2007; **56**: 604–11

36 Scharbert G, Auer A, Kozek-Langenecker S. Evaluation of the platelet mapping assay on rotational thromboelastometry ROTEM. *Platelets* 2009; **20**: 125–30