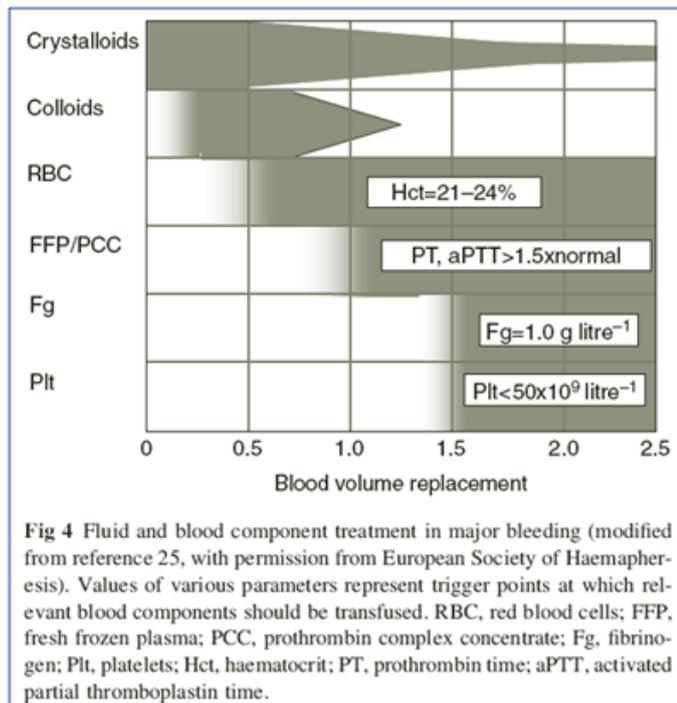


## Major Bleeding – Prevent Acidosis!

### Volume therapy and haemotherapy

Major bleeding up to massive bleeding, especially in trauma or polytrauma patients, is considered to be an extreme event with high mortality.

The currently accepted regimen of volume therapy or blood component therapy (Fig. 4, from Spahn DR and Rossaint R, BJA 2005; 95: 130-139) requires urgent revision: Not crystalloids at first, then colloids, then red blood cells (RBC) and then plasma (FFP), but first balanced colloids, then plasma (volume, coagulation factors, acidosis prevention) and then only fresh RBCs if the cHb falls below 5-7 g/dl.



### What is the role of acidosis in major bleeding?

1. In 8,000 polytrauma patients from 4 studies, a base deficit (BD, neg. base excess BE) of 15 mmol/l on admission to hospital predicts a later mortality of approx. 50 %, comparable with 3,300 trauma patients with blunt trauma or gunshot wound.
2. The two most important predictive factors of later mortality that can be influenced by the doctor, i. e. BD and prothrombin time (PT, Quick), exhibit – in addition to age, ISS (Injury Severity Score), GCS (Glasgow Coma Score) and injury pattern (head and extremities) – a highly significant correlation in 4,000 polytrauma patients: when the BD is approx. 15 mmol/l, the PT (Quick) is reduced to 50 %.
3. Trauma patients with massive transfusion develop coagulopathy depending on the level of BD. Patients who survived and those who died can be differentiated according to their mere BD, a BD of about 20 mmol/l limits survival.
4. The *in vitro* coagulation activity is strongly determined by the pH: activity was found to be reduced by half, when the pH was 7.20 (base deficit 12.5 mmol/l) and was found to be doubled when the pH was 7.60 (base excess 16.5 mmol/l).
5. Coagulopathy, metabolic acidosis and hypothermia are rightly regarded as a patient's "lethal triad".
6. Unlike *in vitro* findings, four animal experiments provide evidence that coagulopathy persists for another 12-18 hrs after treatment of acidosis.
7. Therefore, any acidosis is to be prevented during treatment of bleeding.

### What are the causes of acidosis?

1. Haemorrhagic shock as such provokes – as a result of blood loss and associated hypoxia – metabolic acidosis with an increase of BD and lactate concentration.
2. The volume replacement solutions available to date inevitably enhanced the existing acidosis via infusion and dilution acidosis.
3. Due to the production and storage of RBCs, fresh RBCs have a BD of 20 mmol/l and RBCs that are 20 days old have a BD of 40 mmol/l. Plasma (FFP), on the other hand, has a strong alkalinising effect due to its high citrate concentration.
4. The mean age of RBCs at the time of transfusion is about 20 days consistently worldwide. Thus, with any massive transfusion of as few as 3 RBCs (approx. 1 l), a patient receives 40 mmol H<sup>+</sup> ions, which is about the amount the kidney has to eliminate per day (50 mmol).
5. A massive transfusion causes metabolic acidosis with coagulopathy, the mere amount of RBCs transfused has an influence on mortality (8,500 patients from 3 studies), the influence of the age of the RBCs transfused is equally evident.

### What are the consequences for diagnostics, especially POC?

The correlations between acid-base balance and coagulation and fibrinolysis are to be extended to diagnostics.

- The example of hypothermia, i.e. reduced patient temperature, is used to describe the state of the art: The coagulation function of a patient with a body temperature of 32 instead of 37 °C is reduced by approximately 50 % due to the mere hypothermia. If coagulations diagnostics were performed, e.g. by thromboelastography (TEG) with 37 °C, an erroneous result would be generated, because the blood sample of the hypothermic patient, which is related to normal temperature in the instrument, would mimic a normal coagulation status. Therefore, the patient temperature can nowadays be set in point of care instruments for TEG.
- The same statement is true for the patient's acid-base balance, defined by their pH in connection with the BE (or BD, mmol/l) as well as the carbon dioxide partial pressure (pCO<sub>2</sub>, mmHg) of their blood. If the coagulations diagnostics are performed in such a way that changes of the pH or BE level are offset during diagnostics (e.g. by using buffered reagents) or that changes of the pH are admitted (if the pH of a sample, e.g., increases due to alkalosis as a consequence of CO<sub>2</sub> loss), a coagulopathy caused by acidosis cannot be detected any longer. Therefore, especially the POC diagnostics have to be improved. This is true for preanalytics as well as for the actual diagnostics. All possible changes of pH, BE and pCO<sub>2</sub> are to be prevented if the current coagulation diagnostics are to be performed correctly.

### Why is a new treatment regimen required for major bleeding?

It seems that the strategy which consists in treating massive bleeding by massive transfusion reaches an impasse: The patient's existing metabolic acidosis causes coagulopathy. Massive transfusion with the commonly used 20-day-old RBCs increases this acidosis and thus coagulopathy. The metabolic acidosis which is typical for trauma patients should be prevented and not accepted and/or should be treated, because once it has developed, it is responsible for the bleeding risk over many hours.

A massive transfusion reduces the efficacy of rFVIIa (NovoSeven), especially since old RBC maintain acidosis. If rFVIIa is to be used at all, it should be administered prior to the administration of RBC and not, as recommended, as "ultima ratio" (e.g. after the 8<sup>th</sup> unit of RBC).

Since the coagulation activity strongly depends on the pH, it can be assumed that fibrinolysis and products modifying fibrinolysis, e.g. aprotinin or tranexamic acid, are influenced by the BD as well.

### How could a new treatment regimen for major bleeding look like?

Volume therapy does not start with a crystalloidal but a colloidal solution, the solution being – importantly – a balanced isotonic solution, i.e. not modifying the electrolyte and acid-base status (e.g. HES 130/0.4 with  $BE_{pot} \sim 0$  mmol/l), the permissive haemodilution being accepted up to a cHb of approx. 7.5 g/dl.

Then fresh frozen plasma (FFP) or lyophilised plasma is given for volume replacement, coagulation factors, and prophylactic acidosis treatment.

If the cHb falls below 5-7 g/dl and signs of hypoxia occur (tachycardia, ECG changes, increase of BD and lactate), RBCs are indicated, which should be as fresh as possible.

rFVIIa can be used reasonably only if no appreciable metabolic acidosis was present at any time of treatment. This holds – with reservations – also true for products modifying fibrinolysis and all types of coagulation factors.

#### Treatment regimen for major bleeding

##### 1. Volume therapy

Permissive isovolaemic haemodilution up to a cHb of 7.5 g/dl with balanced colloidal volume replacement (e.g. HES 130/0.4 with  $BE_{pot} \sim 0$  mmol/l): prevention of infusion acidosis and thus coagulopathy.

##### 2. Volume therapy and coagulation therapy

Fresh frozen (FFP) or lyophilised plasma (especially lyophilised autoplasm): volume, coagulation factors, prophylaxis of acidosis (citrate).

##### 3. Coagulation therapy

Fibrinogen, coagulation factors, rFVIIa, aprotinin, tranexamic acid, etc. but only without metabolic acidosis.

##### 4. Haemotherapy

RBCs that are as fresh as possible when the cHb falls to less than 5-7 g/dl and there are signs of hypoxia (ECG, BE, lactate) even though a  $FIO_2$  of 1.0 was confirmed.

If the patient has his own "autoplasm" (lyophilised autologous plasma, one DIN-A4 bag in letter format with a weight of approximately 75 g per litre, stored at room temperature), treatment can be extremely simplified and optimised, in many cases the administration of RBC may possibly even be refrained from completely.

There is impressive evidence from 5,000 patients of the trauma register of the German Society for Trauma Surgery (DGU), that the marked reduction of RBC administration led to a reduced mortality of polytrauma patients.

The quoted figures and literature can be found under [Volumen und Hämotherapie bei Massiv-Blutung](#).