Coagulopathy and plasma transfusion in critically ill patients
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Chapter 17

Summary and general discussion

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Introduction

The inflammatory response in critical illness simultaneously affects the coagulation system and the resulting coagulopathy frequently occurs among the critically ill. Activation of the coagulation system with enhanced thrombin generation is accompanied by attenuated fibrinolysis and reduced levels of anticoagulants. Altogether, this leads to a hypercoagulable state with the formation of (micro-) thrombi, impairing organ perfusion and thereby contributing to organ failure. However, as this state persists or occurs at a high rate, consumption of clotting factors and thrombocytes will result in deficiencies and hereby the hemostatic balance will shift to a hypocoagulable state with an increased bleeding tendency. As discussed in chapters 2 and 3, most clinically used coagulation assays (e.g. Prothrombin time (PT) and International Normalized Ratio (INR)) only reflect a part of the coagulation process and hereby they lack the ability to detect increased bleeding risk or a hypercoagulable state. In contrast, thromboelastography (TEG/ROTEM) assesses the whole process of clot formation and degradation and has the capability to also detect hypercoagulability and changes in fibrinolysis.

Despite the limited value of these conventional coagulation assays, increased PT value is the most common trigger to administer fresh frozen plasma (FFP) to critically ill patients. Indeed many patients are transfused with FFP during their stay at the intensive care unit. Of note, the effects of FFP administration on in vivo hemostatic potential of critically ill patients are largely unknown and whether its administration indeed reduces a presumed enhanced bleeding risk has not been established. Also, administration of FFP is not without risks as it can cause adverse events, of which the most important is (transfusion related) acute lung injury.

In this thesis, we studied the value of TEG/ROTEM to assess coagulation status in different critically ill patient populations. In addition we investigated the effects of prophylactic FFP transfusion in critically ill patients with a coagulopathy. We assessed effects of FFP on different tests that evaluate the coagulation system. Also, the effect of FFP on the occurrence of bleeding and lung injury was studied. In the last part of this thesis, the pathophysiology of transfusion related lung injury (TRALI) is studied in more detail. In addition, we tested two potential therapeutic strategies for TRALI in a murine model. Furthermore, we performed a systematic review and

Part I: Diagnosing coagulopathy in the critically ill: thromboelastometry

Summary of results
As described in chapter 2, TEG and ROTEM have been applied in different types of critically ill patients, including trauma, neurosurgical and post-cardiac arrest patients. Overall, evidence supporting the use of TEG/ROTEM to diagnose a hypo-coagulable state and hereby making an estimation of bleeding risk is limited. This also applies for the diagnosis of a hypercoagulable state and the risk assessment for development of multiple organ failure or thrombo-embolic complications. Main reasons for this low level of evidence are heterogeneity of the studies in design, use of different control groups, a lack of reference standards and variability in chosen endpoints.

In chapter 3, the available literature on the application of TEG/ROTEM in sepsis was systemically reviewed. Heterogeneity between studies was large and there was risk of bias. None of the studies performed an assessment of bleeding risk based on TEG/ROTEM results. With respect of diagnosing hypercoagulability, TEG/ROTEM showed to be valuable to discriminate between sepsis patients with and without disseminated intravascular coagulation (DIC). Interestingly, a hypocoagulable, but not a hypercoagulable profile, correlated with DIC in sepsis patients and was associated with more severe organ failure and excess mortality.

We additionally studied the value of ROTEM to predict outcome in trauma patients in chapter 4. Of the severely injured trauma patients 50% dies in the acute phase due to bleeding. While organ failure is the main reason for late mortality after trauma. Thereby, we hypothesized that late mortality in trauma may be related to a hypercoagulable profile as detected by ROTEM. In a large cohort of trauma patients, we determined whether ROTEM profiles were predictive for the occurrence of multiple organ failure and late mortality. Results indicated that early hypocoagulability was associated with more severe organ failure and higher mortality. Only 10% of the patients showed hypercoagulability early in trauma.
Finally, we assessed the correlation of ROTEM with conventional coagulation tests in a cohort of critically ill patients (chapter 7). Correlation with the INR was moderate, which underlines the finding in observational studies that INR is a bad predictor of bleeding risk. ROTEM correlated well with prothrombin levels, platelet count and fibrinogen. Again, ROTEM profiles were more hypocoagulable in patients with DIC compared to those without DIC and ROTEM parameters correlated strongly with ISTH DIC score. Hereby we confirmed the potential value of ROTEM to discriminate critically ill patients with and without DIC.

**Discussion**

Despite the potential advantages of TEG/ROTEM over conventional coagulation assays, such as the possibility to diagnose hypercoagulability or DIC, application of TEG/ROTEM in critically ill patients has several limitations. First, reference values given by the manufacturer do not appear to discriminate between ‘normal’ and ‘a clinically relevant abnormal coagulation status’ in critically ill patients, when compared to conventional tests. Second, assays need to be further standardized and to date results of the two available assays (e.g. TEG and ROTEM) are not interchangeable. Thereby, a uniform definition of hyper- and hypocoagulability by viscoelastic tests is currently not available. These limitations preclude the incorporation of TEG and ROTEM into the standard diagnostic evaluation of critically ill patients with a suspected coagulopathy. However, as indicated in chapter 3 and confirmed in our small cohort described in chapter 7, TEG/ROTEM can be helpful in discriminating patients with and without DIC. Although a score to detect DIC using thromboelastometry which has been developed in a heterogeneous patient group [1] awaits validation in critically ill patients, this observation is promising as a potential advantage of an improved and facilitated diagnosis of DIC. Also, TEG/ROTEM diagnosed coagulopathies could be helpful for more tailor-made administration of future therapies that interfere with the coagulation system.

In addition to a potential diagnostic value, TEG/ROTEM results can be useful in prognostication of patients. In patients with sepsis, hypocoagulable profiles were associated with adverse outcomes. We also found that severely injured patients had more severe organ failure and excess mortality when they were hypocoagulable within the first 24 hours of admission. These findings are in line with results in a
large cohort of general intensive care patients, in whom a hypocoagulable profile at admission was also associated with an increased mortality [2]. One could argue that a hypocoagulable profile merely reflects severity of disease or injury. However, our results in trauma patients and the results of others in patients with sepsis [3] and the general intensive care population [2] showed that presence of hypocoagulability as detected by TEG/ROTEM was an independent risk factor for adverse outcome. These observations suggest that early activation of coagulation with reversal of hypocoagulability has potential beneficial effects. Indeed it has been demonstrated that enhanced coagulation during infection is functional, thereby preventing dissemination of bacteria [4]. In trauma patients, early hypercoagulability could be an evolutionary response to prevent exsanguination, as was also suggested by others who have reported similar observations [5]. We speculate that these beneficial effects are lost when activation of coagulation is overwhelming and/or persistent and results in consumption of coagulation factors and platelets with a subsequent hypocoagulable state, hereby explaining the observed association between hypocoagulability and adverse outcome. Overall, one may wonder whether hypocoagulopathy is a common pathway in the development of multiple organ failure or even death. This finding warrants further investigation.

In conclusion, TEG/ROTEM seems a promising tool to assess coagulation status in different types of critically ill patients, in particular those suspected to have DIC. However, further standardization, availability of reference values and uniform definitions are required before the technique can be implemented in standard clinical use at the intensive care unit. In addition, TEG/ROTEM has shown to be of additional value in the prognostication of critically ill and trauma patients. Further research is warranted to assess whether therapeutic strategies based on TEG/ROTEM profiles indeed improve patient outcomes and in general, the role of hypocoagulopathy in organ failure and dying.

**Future directives**

As stated above, to further establish the value of TEG/ROTEM in critically ill patients, validated universally accepted definitions of hyper- and hypocoagulability in relation to clinically relevant outcomes are necessary. As TEG/ROTEM based models have not been compared directly with the widely used ISTH DIC score, subsequently
further research can be done on the identification of patients with an increased bleeding tendency and in need for correction of their coagulopathy. In addition, it should be further explored in which patients a hypercoagulable state contributes to adverse events, such as thromboembolic complications, multiple organ failure or even (delayed) cerebral ischemia.

In sepsis patients, in addition to the abovementioned needs, further research into timing and changes of TEG/ROTEM profiles is highly needed, as activation of coagulation is a dynamic process. Currently, two observational prospective trials are being conducted (NCT00994877 and NCT00299949) on the value of TEG/ROTEM to diagnose DIC and to predict organ failure in sepsis. With regard to potential therapeutic value of viscoelastic test results, these tests might be of additional value to select specific patient populations who are likely to benefit from therapies aimed at intervention in the coagulation cascade during sepsis. To date, such therapies have failed to improve outcome and for activated protein C this can be partially contributed to bleeding complications related to the treatment [6]. Although it is tempting to speculate that viscoelastic testing might be helpful to improve patient selection for these therapies, coagulation disturbances in sepsis are complex and these tests do not take into account levels of anticoagulant proteins, being the main targets of studied interventions. Therefore, further research is warranted to elucidate whether there is a certain viscoelastic profile or a change over time in a profile that should trigger the institution of a therapy intervening in the coagulation cascade. Finally, if in the future viscoelastic testing would be used to select patients for anticoagulant therapy in sepsis, research should also focus on treatment targets. To date, data on viscoelastic testing and treatment effects of anticoagulant therapy for sepsis are extremely limited and it is questionable whether viscoelastic tests are sensitive enough to monitor treatment effects of such therapies.

Part II: Efficacy of plasma transfusion in critically ill patients

Summary of results
The second part of this thesis consisted of studies on the effectiveness of FFP transfusion in critically ill patients with a coagulopathy, as measured by INR in common everyday clinical practice. We performed a multicentre randomized clinical trial on the
effectiveness of FFP to prevent bleeding complications in critically ill patients with a coagulopathy and the need to undergo an intervention (TOPIC trial). As described in chapter 5, procedure related bleeding complications did not differ between both groups. However, due to slow inclusion rate, the trial was stopped early and non-inferiority of omitting FFP transfusion could not be demonstrated. Although the secondary endpoint, occurrence and severity of lung injury, did not differ between groups, patients who were transfused with FFP had longer duration of mechanical ventilation. This might by explained by the higher incidence of ventilator-associated pneumonia in patients transfused with FFP, however we cannot preclude that low numbers of patients have contributed to these differences. The other secondary endpoint was correction of INR in response to FFP transfusion. Of note, only half of patients corrected to an INR of <1.5, a value frequently reported to be a trigger for FFP transfusion in clinical practice.

In chapter 6 we investigated whether INR prolongation paralleled changes in other tests investigating hemostasis and evaluated the effects of FFP transfusion on these parameters. At baseline, patients indeed had reduced levels of individual coagulation factors, accompanied by a reduction of levels of anticoagulants. Also, onset of thrombin generation was impaired. Administration of FFP in a dose of 12 ml/kg resulted in an increase of individual factor levels, and levels of anticoagulants rose concomitantly. Thereby, thrombin generation remained nearly unaffected. Altogether, while conventional coagulation tests (INR and aPTT) improved in response to FFP because factor levels improved, FFP transfusion did not result in an altered hemostatic balance in these patients.

As discussed above, in chapter 7 we demonstrated that critically ill patients with DIC have more hypocoagulable ROTEM profiles compared to those without DIC. For the first time we describe the effect of FFP on ROTEM variables in critically ill patients with a coagulopathy. Indeed, administration of FFP slightly improved ROTEM extem and fibtem profiles. However, observed increments in our study were only small and the clinical significance of the observed improvement is questionable. Of note, effect of FFP did not differ between patients with and without DIC.

In chapter 8 the effects of FFP on inflammation and endothelial host response is discussed. This sub-study of the TOPIC trial showed that patients in this cohort had generally mildly elevated cytokine levels. Contrary to the hypothesis that FFP
can induce lung injury and thereby may elicit an inflammatory response resembling ‘subclinical’ TRALI, FFP transfusion reduced systemic TNF-alpha levels. Other cytokine levels were unaffected by FFP. Markers of endothelial activation, factor VIII, von Willebrand factor and syndecan-1 all improved in response to FFP transfusion, suggesting a stabilizing effect of FFP on endothelial function.

The last chapter (9) of this part consisted of an evaluation of the TOPIC trial. As the trial was stopped early due to limited inclusion we surveyed participating clinicians to determine why the trial was difficult to conduct. We found that although most physicians expressed a need for more evidence on the prophylactic use of FFP in critically ill patients with a coagulopathy, they were reluctant to include patients in the TOPIC trial. The main reason was personal beliefs about the preferable transfusion strategy. Together with a short window of opportunity to obtain informed consent, we concluded that future trials on the efficacy of FFP might not be feasible, at least in the Netherlands.

Discussion

We carried out the first randomized controlled clinical trial on the efficacy of prophylactic FFP transfusion to prevent bleeding in coagulopathic ICU patients undergoing an invasive procedure. Although inclusion targets were not achieved, nevertheless, the study has several strengths. First, in contrast to other trials on the effectiveness of FFP in critically ill patients, we used the clinical relevant endpoint of procedure related bleeding. There was not even a trend towards a possible benefit. If anything, patients with FFP had more minor bleedings, which may suggest that most commonly performed invasive procedures can be safely carried out in critically ill patients with a coagulopathy.

Increased INR and PT are important triggers to administer FFP transfusion. This is based on the assumption that increased INR values are associated with enhanced bleeding risk and that FFP transfusion prevents bleeding by correcting the INR [7]. Indeed patients with an increased INR indeed had attenuated thrombin generation due to reduced levels of multiple coagulation factors. However, levels of anticoagulants were reduced concomitantly, suggesting an unaltered hemostatic balance. In addition, despite reduced factor levels, most ROTEM variables were within reference ranges and INR only correlated moderately with ROTEM. Of note, ROTEM
assesses the whole process of clot formation, while PT and INR only represent a part of it. These findings further confirm the limited value of PT and INR to assess in vivo coagulation status and predict bleeding risk. We believe that measuring PT and INR outside of the context to guide vitamin K antagonist therapy or to monitor the degree of liver failure, should not be done to assess risk of bleeding. Use of these tests should thereby be discouraged.

Transfusion of FFP resulted in an increase of both individual factor levels and levels of anticoagulant proteins, thereby suggesting that FFP transfusion fails to alter hemostatic balance. Indeed the response of patients with and without bleeding complications following FFP transfusion did not differ. Moreover, FFP failed to clearly improve thrombin generation or ROTEM profiles. These observations underline the lack of rationale in observational studies to administer FFP to ICU patients with an increased INR. The question whether FFP is beneficial in patients with a coagulopathy as diagnosed by other hemostatic tests, is not answered in this thesis. Of note, larger and earlier amounts of FFP improve outcome in observational studies of coagulopathic bleeding trauma patients, suggesting that FFP can increase hemostatic potential.

Besides effects on hemostasis, we found intriguing other effects of FFP. In experimental studies of hemorrhagic shock, it was shown that FFP prevented disruption of the endothelium and improved microvascular perfusion [8]. In our cohort we also observed beneficial effects of FFP administration on markers of endothelial function. The reduction of syndecan-1 levels in response to FFP was accompanied by attenuated levels of factor VIII and von Willebrand factor (vWF). As ADAMTS-13 levels increased, we postulate that the ADAMTS-13 present in administered FFPs reduces large vWF monomers. This is also the rationale of plasmapheresis in ADAMTS-13 deficiency. Presumably, this mechanism seems to also hold true for endothelial damage in the critically ill. Of note, levels of inflammatory cytokines remained unaltered or even improved in response to FFP transfusion. These observations are not in line with reports of associations between FFP transfusion and the occurrence of lung injury in critically ill patients [9,10]. However, antibody-containing plasma might have contributed to these observations. Although we did not assess antibody levels, FFP used in our trial was manufactured after institution of the policy to defer female donors for FFP preparation, a measure known to reduce the risk of lung injury after
transfusion. Thereby, the association of FFP with TRALI may be limited to antibody mediated lung injury, whereas administration of FFP might have beneficial effects in certain patient categories, not to correct coagulopathy, but to improve endothelial function. Further research is warranted to identify these patient categories, to assess the optimal dose and timing of FFP and to define outcome measures and treatment targets.

In conclusion, we cannot reject the hypothesis that FFP is unnecessary to prevent bleeding complications in critically ill patients with a coagulopathy, due to limited inclusion in the TOPIC trial. However, administration of FFP failed to alter the hemostatic balance in these patients and only marginally affected thrombin generation and thromboelastometry. Despite this lack of effect on coagulation status, administration of FFP might have beneficial effects on endothelial function. Further research is warranted to confirm and further explore this observation.

Future directives
Clinicians treating critically ill patients with a coagulopathy need a, preferably bedside, test that assesses coagulation status and identifies patients with an increased bleeding risk. Possibly the establishment of reference values for thromboelastometry for critically ill patients can contribute to the value of this test in the ICU population. However, studies on the use of thromboelastometry to assess bleeding risk are warranted first. Alternatively, it would be interesting to determine whether the use of thrombin generation tests in the clinical setting is feasible and contributes to improved assessment of patients with a coagulopathy.

If a patient indeed is hypocoagulable and has an enhanced bleeding risk, it is questionable whether a dose of 12 ml/kg FFP is sufficient to induce a more procoagulant state. However, results from audits indicate that use of higher doses of FFP is not deemed feasible in clinical practice. Also, despite the expressed need of more evidence on the use of FFP by many experts in the field, we believe that another randomized controlled trial on effectiveness of FFP in critically ill patients with a coagulopathy is not feasible, at least not in the Netherlands. An alternative option for further research is to assess whether patients with an increased bleeding risk could benefit from the administration of four factor prothrombin complex concentrate
or fibrinogen. These products require less volume and are not associated with the occurrence of lung injury.

In addition, it would be valuable to re-assess the bleeding risk of the most commonly performed procedures in the ICU, for example central venous catheter placement. Previous studies have already shown that procedure related bleeding complications are limited. However, the increasing use of ultrasound guided placement might have further reduced this risk, as was shown for pleural drainage [11]. Further confirmation of these observations could support clinicians to refrain from correction of a coagulopathy in case an intervention is necessary.

Finally, the observation that administration of FFP might have some beneficial effects on endothelial function needs to be further elucidated. Mechanisms of action and potential effects on clinical outcomes in different patient categories need to be further investigated. Of note, in addition to the lack of a pro-inflammatory effect of FFP there are also indications that administration of FFP is associated with enhanced risk of infectious complications in critically ill. All these observations need confirmation and to be studied in further detail before FFP can be suggested as a new therapeutic or resuscitation fluid for critically ill patients.

**Part III: Risks of transfusion in the critically ill: TRALI**

**Summary of results**

In the last part of this thesis we further investigated the problem of lung injury following transfusion. In chapter 10, an overview is given of risk factors for the onset of TRALI in critically ill patients. Main patient related risk factors are sepsis, shock, mechanical ventilation, cardiac surgery, the presence of a haematological malignancy and the need for massive transfusion. Blood product related risk factors consist of the presence of anti-leukocyte antibodies, bioactive response modifiers and the presence of the red cell storage lesion. Knowledge of these risk factors supports the ICU physician to take a more individualized approach in assessing the risk-benefit of the decision to transfuse a patient.

We further elucidated the inflammatory changes in TRALI and in particular the contribution of damage associated molecular patterns (DAMPs). DAMPs ligate with the receptor for advanced glycation end products (RAGE), which is expressed on
type I alveolar cells, endothelium and neutrophils. Both high-mobility group box 1 (HMGB1) and S100A12 are DAMPs that have been shown to contribute to inflammatory insults in the lung. We studied their contribution to the inflammatory response in 14 cardiac surgery patients that developed TRALI (chapter 11). These patients were matched with transfused and non-transfused controls without lung injury. Although specific DAMPs including HMGB1 and sRAGE did not differ between groups, there was a trend towards higher levels of early DAMP S100A12 in patients who developed TRALI. S100A12 levels were associated with prolonged cardiopulmonary bypass, pulmonary inflammation, prolonged ventilation and hypoxemia. Hereby S100A12 may mediate the priming phase of acute lung injury in cardiac surgery patients who develop TRALI.

Although the pathophysiology of TRALI is not fully elucidated, various preventive measures to reduce the risk of TRALI have been studied and implemented by blood supplying facilities across Europe and Northern America. An overview of TRALI prevention strategies is given in chapter 12 and in chapter 13 specific measures to prevent immune-mediated TRALI are discussed. The most striking TRALI prevention measure has been the deferral of females from donating plasma. However, evidence that the deferral of all female plasma donors indeed reduces TRALI incidence is mainly gathered in studies with a before-after design. In order to further strengthen evidence for low TRALI risk donor strategies, we performed a systematic review and meta-analysis (chapter 14). This meta-analysis made clear that the implementation of low risk TRALI plasma donor strategies indeed reduced onset of TRALI (OR 0.61 95%CI 0.42-0.88). The effect was most clear in patients with an increased risk to develop TRALI (OR 0.51 95%CI 0.29-0.90), while effects in general patient populations showed a similar non-significant trend (OR 0.66 95%CI 0.40-1.09).

Despite preventive measures TRALI still occurs, in particular in high-risk populations such as critically ill patients. To date no therapeutic strategies are available. Therefore we studied the effects of two potential therapeutic strategies in a mouse model of TRALI. First, effects of corticosteroids were assessed. Despite an attenuated IL-6 host response, administration of methylprednisolone failed to prevent the development of lung injury in this ‘two hit’ murine TRALI model (chapter 15). We also assessed the effect of administration of C1-inhibitor in the same TRALI model (chapter 16). We confirmed that induction of TRALI resulted in activation of
the complement system, demonstrated by increased BALF levels of C3a and C5a. Administration of C1-inhibitor reduced pulmonary levels of C3a and improved lung injury scores. However, C5a and inflammatory cytokines levels were unaffected by C1-inhibitor.

**Discussion**

In particular critically ill patients are at increased risk to develop TRALI. In these patients, some factors can be modified in order to reduce susceptibility for TRALI. Mechanical ventilation with injurious tidal volumes aggravate TRALI in a mouse model [12] and contributes to adverse outcome in patients with lung injury [13]. In addition, fluid restrictive management has been shown to improve outcomes in patients with acute lung injury [14]. Considering the similarities between acute lung injury and TRALI, it seems reasonable that these strategies also have beneficial effects in reducing TRALI risk. However, as most patient related risk factors can not be modified, the key point remains an adequate assessment of whether a patient is really likely to benefit from the administration of a blood product.

Blood products also harbour risk factors for the development of a TRALI reaction. Anti-leukocyte antibodies are indisputably associated with the occurrence of TRALI, moreover the presence of anti-neutrophil antibodies (HNA-3a and 5b) is associated with a more severe course of TRALI [15]. To prevent antibody mediated TRALI, important preventive measures have been implemented in the past decade. The deferral of female or antibody harbouring donors from donating FFP has resulted in a significant reduction of TRALI risk, in particular in at risk populations. This policy was shown to be feasible without interfering with adequate plasma supply. However, immune mediated TRALI can also result from platelet transfusion and deferral of all female or antibody harbouring donors will hamper adequate supply. Alternative measures to prevent platelet related antibody mediated TRALI could be the resuspension of platelets in male plasma or the addition of platelet additive solution, although these measures have not been widely adopted yet. Finally, occurrence of non-immune mediated TRALI is unaffected by abovementioned measures. Evidence regarding the contribution of prolonged storage of red blood cells and resulting accumulation of bioactive substances with neutrophil priming capacity to the occurrence of TRALI is conflicting [16,17]. These opposing results are probably
not only affected by storage time, but also by storage conditions and remaining plasma content in implicated products. However, to date no evidence is available whether specific measures regarding preparation and storage of blood products indeed affect TRALI risk.

Although preventive measures have reduced TRALI incidence, once TRALI occurs morbidity and mortality is considerable. Therefore therapeutic strategies are highly warranted. Corticosteroids are anecdotally used in patients with TRALI and in ARDS use of corticosteroids reduces mortality [18]. As ARDS and TRALI show pathophysiological similarities, we hypothesized that corticosteroids could attenuate a TRALI reaction. However, in a murine ‘two hit’ TRALI model, methylprednisolone failed to attenuate occurrence of lung injury, despite a systemic and pulmonary reduction of IL-6 levels. Possible explanations for an absence of effect could be suboptimal timing of methylprednisolone administration and contribution of inflammatory pathways to a TRALI reaction that are steroid independent, for example complement activation. Therefore, we also evaluated the effect of C1-inhibitor in TRALI. In line with others, we indeed demonstrated complement activation in TRALI. Although administration of C1-inhibitor reduced C3a levels, C5a levels remained unaffected, as were cytokine levels. We speculate that routes that are independent from C1-esterase, such as the alternative route and routes that activate coagulation, contribute to persisting high C5a levels and subsequent inflammation.

In conclusion, critically ill patients carry an increased risk to develop TRALI, but implementation of strategies to reduce TRALI risk of plasma containing blood products by blood supplying facilities, have significantly attenuated TRALI risk. However, therapeutic strategies are still warranted, as these measures do not prevent all TRALI cases. Experimental evidence does not support the use of corticosteroids for the treatment of TRALI. Also, effectiveness of the administration of C1-inhibitor could not be demonstrated. Further understanding of TRALI pathophysiology and the role complement activation is warranted before more targeted therapeutic strategies can be developed.

**Future directives**

Although the implementation of preventive measures has reduced TRALI incidence, there are still several issues that need to be addressed for future prevention of
TRALI. First universal use of the consensus definition is highly warranted, hereby donors implicated in TRALI can be identified. In addition, guidelines on donor deferral and antibody screening are warranted. Also, standardization of HLA and HNA tests to screen donors is needed. Further research has to elucidate whether storage conditions and duration indeed affect occurrence of TRALI. Results of a trial comparing fresh blood with standard transfusion care in critically ill patients are expected within a year. With regard to plasma products, no TRALI cases have been reported with the use of pooled plasma and it has been successfully used for years in Scandinavian countries. Also, the Netherlands will change to pooled plasma instead of FFP this year. Whether this change indeed results in a further reduction of plasma associated TRALI cases, including in high-risk patients such as critically ill, will become clear in the near future. Finally, additional evidence on other factors or substances within blood products that contribute to adverse reactions, in particular in patients at risk, will help to develop a more tailored transfusion policy for critically ill patients. Also clinicians’ awareness about the risk and benefits of transfusion of blood products needs to be improved, as many audits have shown high rates of inappropriate use of blood products. A restrictive transfusion policy has shown to be safe and advantageous in different types of critically ill patients [19-21]. However, at least in the Netherlands, this evidence has not yet been incorporated in clinical guidelines or become routine practice in daily care. In addition, as discussed previously, inappropriate use of plasma products is also still high [22]. Therefore, improved knowledge and awareness among clinicians will hopefully contribute to reduced inappropriate use of blood products, with a concomitant reduction in undesired side effects and costs. The implementation of computer-supported decision making is a promising tool in this perspective.
References


