Risk estimation and management of coagulopathy in ICU patients in need of an invasive procedure

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Abstract
Coagulation abnormalities have a high prevalence in critically ill patients. The most commonly used tests to assess coagulation status include assessment of the platelet count, prothrombin time, fibrinogen and d-dimer. However, as these tests do not reflect in vivo haemostatic potential, their ability to assess a potential risk of bleeding is limited. Viscoelastic tests evaluate the whole process of clot formation and degradation, but their value in the assessment of bleeding risk remains to be established.

Despite their limitations, increased prothrombin time/international normalised ratio values or decreased platelet counts are the most important reasons to prophylactically administer plasma or platelets to critically ill patients prior to undergoing an invasive procedure. However, evidence that prophylactic correction of coagulation abnormalities prevents intervention-related bleeding complications is limited. In this narrative review, we discuss the assessment of bleeding risk and management of coagulopathy in critically ill patients in need of an invasive procedure. A practical recommendation is given.

Introduction
Coagulopathy has a high prevalence among critically ill patients,[1] and is the result of the derangement of both procoagulant and anticoagulant components of the coagulation system (figure 1).[2] The procoagulant elements include the endothelium, thrombocytes, individual coagulation factors and fibrinogen. The anticoagulant system includes proteins C and S and antithrombin. The third component of coagulation is the fibrinolytic system. The inflammatory response in critical illness results in activation of the coagulation system with enhanced thrombin generation, accompanied by attenuated fibrinolysis and reduced levels of anticoagulants. Altogether, this leads to a hypercoagulable state with the formation of (micro) thrombi, associated with impaired organ perfusion and subsequent organ failure. Ongoing coagulation processes during this hypercoagulable state result in consumption of clotting factors and thrombocytes, with ensuing deficiencies. Hereby, haemostatic balance will shift to a hypocoagulable state with an increased bleeding tendency. The most common causes of deranged coagulation in the critically ill are summarised in table 1.[2]

Assessment of coagulopathy in critically ill patients is a highly relevant clinical need; however, it is characterised by multiple limitations. The most commonly used tests, including platelet count and coagulation times, only reflect a limited part of the haemostatic process and thus cannot reliably predict potential bleeding risk.[3] The international normalised ratio (INR) was developed to monitor therapy with vitamin K antagonists as it reflects a deficiency of vitamin K dependent coagulation

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Thrombosis
- Increased levels of VWF
- Decreased levels of ADAMTS-13
- Increased levels of factor VIII
- Reduced proteins C and S and antithrombin
- Downregulation of thrombomodulin
- Reduced capacity of TFPI
- Impaired fibrinolysis (increased PAI-1 and TAFI)

Bleeding
- Thrombocytopenia
- Vitamin K deficiency
- Reduced levels of factors II, V, VII, IX, X, XI
- Reduced fibrinogen

Figure 1. Factors influencing the haemostatic balance in critically ill patients
ADAMTS-13 = a disintegrin and metalloproteinase with thrombospondin type 1, motif 13; PAI-1 = plasminogen activator inhibitor type I; TAFI = thrombin activatable fibrinolysis inhibitor; TFPI = tissue factor pathway inhibitor; VWF = von Willebrand factor
Table 1. Causes of coagulopathy in critically ill patients

<table>
<thead>
<tr>
<th>PT prolongation</th>
<th>Thrombocytopenia</th>
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<td>Sepsis</td>
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<td>DIC</td>
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<tr>
<td>Cardiac surgery</td>
<td>Extracorporeal circuits, Enlarged spleen, Drug-induced</td>
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<td>Blood loss</td>
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<tr>
<td>Multiple trauma</td>
<td>Multiple trauma</td>
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<tr>
<td>Major blood loss</td>
<td>Major blood loss</td>
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<tr>
<td>Decreased generation</td>
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<tr>
<td>Vitamin K deficiency</td>
<td>Bone marrow dysfunction</td>
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<td>Use of vitamin K antagonists</td>
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<tr>
<td>Renal failure</td>
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<td>Liver disease</td>
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Procedures were diverse and included kidney and liver biopsy, as well as abdominal and thoracic drainage. Results of this review were confirmed in two more recent observational studies of central venous catheter (CVC) insertion in patients with increased INR values.[16,17] In three studies evaluating the risk of chest tube placement in patients with coagulopathy, observed bleeding rates were low and not related to INR or PT values.[18-20] The same applies to patients undergoing percutaneous insertion of a tracheostomy.[21,22] Also, in trauma patients needing placement of an intracranial pressure monitor, INR was not predictive for the occurrence of bleeding complications.[23] These results are in line with a recent clinical trial in critically ill patients with coagulopathy, in which INR/PT values did not differ between patients with and without minor bleeding after undergoing an intervention.[14]

Taken together, in critically ill patients undergoing an invasive procedure, PT or INR values are not predictive of the risk of bleeding. An explanation may be that the PT/INR provides information on only part of the coagulation process. Thereby, other than to detect or estimate the level of vitamin K deficiency, it is questionable whether PT/INR should be measured prior to invasive procedures.

Platelet count
Overall, studies on the predictive ability of platelet count to identify patients at risk of bleeding after invasive procedures are limited. In addition, probably not only the count but also the platelet function determines the risk of bleeding. Tests to determine platelet function are either cumbersome or not yet validated (such as the platelet function analyser, bleeding time and rotational thromboelastometry (ROTEM) with a multiplate functionality). Here, we will only discuss the platelet count.

In retrospective studies in patients undergoing tracheotomy or liver biopsy, an inverse relationship was found between the platelet count and risk of bleeding, although a specific threshold value could not be given.[24,25] Using multivariate modelling, a retrospective study in patients undergoing CVC placement suggested a cut-off level of a platelet count of less than 20,000 as an independent risk factor for bleeding.[26] In another single-centre study, bleeding outcomes were reported after placement of tunnelled CVCs using ultrasonography guidance.[27] During 344 procedures performed in patients with a platelet count less than 50,000, including 42 cases with a platelet count less than 25,000, no bleeding complications occurred. Of note, all practitioners in this study had extensive experience in image-guided catheter insertion, which limits the generalisation of these results to settings in which operators are less experienced.

Taken together, for commonly performed procedures on the ICU, there seems to be a relation between platelet count and risk of bleeding after a procedure, with a possible cut-off value of 20,000.

Value of haemostatic tests to predict bleeding following an invasive procedure in patients with critical illness-related coagulopathy

PT/INR
A review of 25 studies, performed in 2005, showed that an elevated INR was not predictive of periprocedural bleeding.
Viscoelastic tests

Both thromboelastography (TEG) and ROTEM have been applied in different critically ill patient populations, including trauma, neurosurgical and post-cardiac arrest patients. Overall, evidence supporting the use of TEG/ROTEM to diagnose a hypocoagulable state and thereby make an estimation of bleeding risk is limited. The main reasons for this low level of evidence are heterogeneity in the design of the studies, use of different control groups, a lack of reference standards and variability in chosen endpoints. A recent trial on the applicability of TEG in sepsis patients showed an association between low functional fibrinogen maximum amplitude and the development of bleeding. In addition, hypocoagulability according to the other TEG variables also showed a trend toward increased bleeding risk.

This promising observation needs further validation, with determination of cut-off values, before viscoelastic testing can be routinely used in clinical practice to identify patients with an increased bleeding risk.

Efficacy of blood products to correct critical illness-related coagulopathy and prevent bleeding complications

Plasma to correct PT/INR

The efficacy of plasma to correct INR is related to the pre-transfusion level of PT/INR (figure 2). If the INR is mildly prolonged, plasma is not very effective in correcting INR. Presumably, this effect is caused by the INR of the plasma product itself, which has a median INR of 1.1. However, it can be questioned whether a decrease in INR is related to a decrease in the risk of bleeding. Plasma replenishes a deficiency of coagulation factors but also contains anticoagulant proteins. Thereby, the net effect of plasma on thrombin generation was found to be negligible. The question of interest is not whether plasma corrects INR but whether plasma prevents bleeding. The efficacy of plasma to prevent bleeding in critically ill patients has been studied in a small clinical trial. However, both patients with active bleeding and patients without bleeding were included and the study had a variety of methodological flaws. We conducted a multicentre randomised clinical trial on the effectiveness of plasma to prevent bleeding complications in critically ill patients with coagulopathy and the need to undergo an intervention (TOPIC trial). Patients with an INR between 1.5 and 3.0 were randomised to receive a prophylactic dose of plasma (12 ml/kg) or not, before placement of a CVC, percutaneous tracheostomy, chest tube or abscess drainage. The primary outcome was occurrence of post-procedural bleeding complications. Due to the low inclusion rate and low incidence of major bleeding complications, the effect of fresh frozen plasma (FFP) on major bleeding could not be assessed. However, the combined outcome of major and minor bleeding complications did not differ between the groups.

Of note, it can be argued whether a dose of 12 ml/kg FFP is sufficient to induce a more procoagulant state. However, results from audits indicate that the use of higher doses of FFP is not deemed feasible in clinical practice. Another randomised controlled trial on effectiveness of prophylactic plasma in critically ill patients with coagulopathy is not feasible, at least not in the Netherlands. Although outside of the scope of this review as it concerns another patient population, it may be worth mentioning the efficacy of prophylactic plasma in cardiac surgery. In a meta-analysis of 14 trials, plasma was shown to decrease INR, but not prevent bleeding. These findings are in accordance with results in the critically ill.

In addition to a lack of evidence on effectiveness, there may be detrimental effects of plasma. In critically ill patients, plasma transfusion was shown to be an independent risk factor for the occurrence of lung injury and was associated with an increased ICU length of stay. Also, transfusion of FFP has been linked to occurrence of infectious complications. Several guidelines address the correction of increased PT or INR values. A clinical practice guideline from the American Association of Blood Banks (AABB) states that the use of plasma in patients undergoing surgery or other invasive procedures in the absence of bleeding is not recommended. The panel based this recommendation on the available evidence in 2010, including a trend toward increased risk of death in this patient population and the known risks of transfusion-related acute lung injury with plasma transfusion. However, other guidelines do recommend to correct an INR of more than 1.5 to prevent bleeding in the case of surgery or invasive procedures. An overview of different guidelines published in 2008 confirmed the variation in recommendations regarding the correction of increased INR values in patients without bleeding.

The Dutch guideline on transfusion (CBO) recommends considering plasma transfusion in patients with disseminated intravascular coagulation and the need to undergo an intervention. Since then, however, more data on the absence of efficacy of plasma to improve coagulation status and reduce risk of bleeding have emerged.
Taken together, prophylactic administration of plasma to patients with an increased PT/INR is not recommended. 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 contain only procoagulant proteins, require less volume and are not associated with the occurrence of lung injury. Their safety in terms of inducing a thromboembolic event has not, however, been addressed.

**Platelets**

The TOPPS trial randomised haematology patients to the use of prophylactic platelet transfusion versus no use of prophylactic platelet transfusion.\[32\] The trial showed that the use of prophylactic platelet transfusion decreased the proportion of patients with bleeding. However, this trial was performed in haematology patients and did not concern invasive procedures. In a retrospective study in critically ill patients undergoing chest tube insertion, platelet transfusion was not associated with a decrease in bleeding events.\[19\] In patients undergoing CVC placement, platelet transfusion did not reduce the incidence of bleeding.\[26\] Of note, as the incidence of bleeding is low, the number of patients may have been too low to show a beneficial effect. Also, platelet function is not taken into account. In the critically ill, platelet function may be compromised due to the use of aspirin or the presence of renal failure. Lastly, platelet dose is not studied. During critical illness, platelet refractoriness can be a problem.

A guideline on management of disseminated intravascular coagulation published in 2008 suggests to administer platelets to patients undergoing an invasive procedure at a platelet count less than 50 × 10^9/l. These recommendations are based on expert opinion or on observational data. A recently published AABB guideline suggests to give prophylactic platelet transfusion to patients undergoing CVC placement at a platelet count of less than 20 × 10^9/l and to patients undergoing lumbar puncture at a platelet count less than 50 × 10^9/l. These recommendations are based on low to very low quality evidence.\[24\] Currently, the PACER trial is ongoing, in which patients with a platelet count between 10 and 50 × 10^9/l in need of a CVC are randomised to receive either prophylactic transfusion of platelets pooled from five donors or no transfusion.

**Blood products to correct abnormal viscoelastic test results**

Most data on correcting coagulation abnormalities detected by viscoelastic tests are gathered from actively bleeding patients, mainly in the setting of trauma and cardiothoracic surgery.\[55,56\] In critically ill patients, different ROTEM and TEG patterns have been observed including hypercoagulable and hypocoagulable traces and attenuated fibrinolysis.\[11,28\] Correction of a hypercoagulable state in patients with sepsis has only been evaluated as a sub-study of a trial on the effectiveness of antithrombin administration. No effect on hypercoagulability was observed.\[57\] In a mixed population of critically ill patients with coagulopathy (defined as INR >1.5), transfusion of plasma slightly improved ROTEM EXTEM and FIBTEM profiles. Observed increments were only small and the clinical significance of the observed improvement is questionable, as no effect on bleeding was detected.\[14\] Taken together, it is too premature to use ROTEM or TEG as a guide to correct coagulopathy and prevent bleeding in critically ill patients.

In the guidelines, the use of viscoelastic tests to monitor coagulopathies is only addressed in the setting of massive bleeding. In the European Guideline on the management of bleeding and coagulopathy following trauma, the use of viscoelastic tests to monitor coagulation is a Class 1C recommendation.\[58\] However, no exact thresholds for the transfusion of blood components are defined, mainly due to lack of agreement between experts and the lack of high-quality data. The UK National Institute for Health and Care Excellence recommends the use of viscoelastic tests, specifically TEG and ROTEM, in cardiac surgery, but suggests they are only used as a research tool in trauma and obstetrics.\[39\] Nevertheless, the trend appears to be an increased use of these devices as standard management during major haemorrhage. To date, ROTEM and TEG are not incorporated in the guidelines on prophylactic use of blood products to decrease bleeding risk in critically ill patients.

**Practical recommendation**

Based on current evidence, we make the following recommendations for the assessment of bleeding risk and correction of coagulopathies in critically ill patients. We have chosen to report our recommendations as proposed by the American College of Chest Physicians; the strength of any recommendation depends on the trade-off between the benefits and the risks and burdens, and the quality of the evidence.\[60\]

1. Assessment of bleeding risk following an invasive procedure:
   a. The use of PT/INR is recommended to monitor or detect a deficiency of vitamin K dependent coagulation factors but not to assess bleeding risk (Grade 1C; strong recommendation, low-quality evidence).
   b. It is recommended to measure platelet count prior to an invasive procedure (Grade 1C; strong recommendation, low-quality evidence).

2. Management of coagulopathy prior to an invasive procedure:
   a. In patients not using vitamin K antagonists, correction of increased PT or INR values with FFP is not recommended (Grade 1B, strong recommendation, moderate quality evidence).
b. In patients using vitamin K antagonists, increased PT/INR values should be corrected by administration of factor concentrate (Grade 1C; strong recommendation, low-quality evidence).

c. Correction of low platelet count with platelet transfusion is recommended at a level of 20 x 10^9/l for CVC insertion and 50 x 10^9/l for diagnostic lumber puncture (Grade 2C, weak recommendation, low quality of evidence).

3. The use of viscoelastic tests to assess bleeding risk in critically ill patients is recommended for research purposes only as it requires standardisation and determination of cut-off values (Grade 2C, weak recommendation, low quality of evidence).

**Conclusion**

Despite the high prevalence of coagulopathies in critically ill patients, there is currently no test available to reliably assess bleeding risk in these patients. Observational data suggest that insertion of CVCs, percutaneous tracheotomy and thoracocentesis can be carried out with a low risk of bleeding complications. Low platelet counts are associated with increased bleeding risk and correction of platelet counts below 20,000 should be considered in patients needing to undergo an intervention. Assessment of PT/INR does not predict bleeding risk and correction of increased PT/INR values with plasma is not recommended. To date there are insufficient data to support the use of viscoelastic tests to assess bleeding risk.

**Disclosure**

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**References**

Op de 1e dag wordt de basale echocardiografie behandeld volgens de principes van de R(apid) A(ssessment) by C(ardiac) E(cho).

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