Bleeding news

Perioperative Considerations in Management of the Severely Bleeding Coagulopathic Patient

Gabor Erdoes, David Faraoni, Andreas Koster, Marie E Steiner, Kamrouz Ghadimi, Jerrold H Levy

PMID: 36862401 PMCID: PMC10373857 DOI: 10.1097/ALN.0000000000004520

Author of the comment: *Dra. Raquel Ferrandis Comes.* *Anesthesiology and Resuscitation. Hospital Universitari iPolitècnic La Fe, Valencia. Member of the SEDAR-COVID working group.*

The authors present an excellent review, going in great detail through the different aspects of bleeding in coagulopathy patients, and it should be read thoroughly. They study both general and specific aspects of 3 conditions encompassing the most complex situations, such as multiple trauma, extracorporeal circulation, or postpartum hemorrhage. All of them are multifactorial, with common pathophysiology, such as hypovolemia, coagulopathy, platelet dysfunction, or inflammatory response. Managing these situations includes assessing risks, using real-time coagulation tests, and transfusion therapies. However, it is equally relevant to identify high-risk procedures and patients in order to adapt preventive strategies.

Some pathophysiology details must be noted. Thus, during trauma, an unbalance emerges between pro- and anticoagulant factors, with an impact on platelet function, fibrinolysis, and immune response, leading to **trauma-induced coagulopathy**. This can be shown as hypocoagulability, evolving into a hypercoagulable state. Risk factors include age, anticoagulants, serious lesions, brain trauma, and systemic shock, among others. Also in heart surgery, **extracorporeal circulation** can bring about hemostatic activation and acquired coagulopathy, due to initial hemodilution, blood loss during surgery, tissue factor release, the activation of inflammatory response, and platelet depletion and their function. Regarding pregnant patients, **postpartum coagulopathy** may be connected to uterine atony, genital tract trauma, placental abruption, amniotic fluid embolism, among other causes, and it can lead to rapid deterioration if not properly managed.

The section on diagnosis is particularly interesting. The text offers a detailed overview of standard and advanced laboratory tests used in the assessment of perioperative hemostasis, underlining its significance in different clinical settings and highlighting the areas where further research is required. With regard to the preoperative assessment of the bleeding risk, it must be noted that laboratory tests do not always identify mild disorders in patients undergoing elective surgery. In fact, several national guides are in favor of using bleeding assessment tools instead of performing preoperative routine coagulation tests. However, the significance of specific tests–such as TTPa–must be noted in cases such as heart surgery with high-dose heparinization, specific tests to monitor the effect of oral anticoagulants and a qualitative assessment of inherited and acquired coagulation disorders. However, to get a quick and efficient assessment of the state of hemostatic competence,

Bleeding news

particularly in massive transfusion situations in heart surgery and serious trauma, the use of viscoelastic tests is referenced. Several systems are mentioned, such as ClotPro, Quantra, TEG® 6s, or ROTEM, each one of them with their own characteristics and benefits. The paper also reviews clinical trials researching the impact of transfusion algorithms based on viscoelastic tests on the reduction of the bleeding and the need for transfusions in heart surgery and trauma.

Another section deals with acquired coagulation disorders connected to the use of medication such as anticoagulants and antiplatelet drugs, particularly in patients undergoing urgent surgery. The residual effects of these drugs may help causing excessive bleeding in these patients, which may require the use of specific or non-specific reversing agents. Strategies such as hemofiltration or hemoadsorption are suggested to eliminate certain drugs, although they have not been validated in large clinical trials. In scheduled surgery, specific times are set for the suspension of these drugs, although their discontinuation should be assessed on an individual basis, taking into account thrombotic vs. hemorrhagic risk balance.

In terms of management, different strategies are described for treating microvascular bleeding and reverting coagulation anomalies in the described scenarios. Interestingly, viscoelastic tests are used to guide hemostatic resuscitation and the potential use of coagulation factor concentrates. In terms of general measures, a significant factor mentioned is inadvertent hypothermia, which may lead to coagulation enzyme deregulation, platelet dysfunction, fibrinolysis, endothelial lesion, and a worsening of results. Current recommendations suggest maintaining early normothermia in order to optimize coagulation and tackle metabolic acidosis and hypocalcemia associated to hemorrhage and coagulopathy. The use of antifibrinolytic agents is also recommended—despite the controversies on side effects—in situations where they have proven efficient to decrease mortality. Regarding the replenishment of volume and coagulation factors in cases of serious hemorrhage, the importance of a balanced hemostatic resuscitation is underlined. This involves the administration of coagulation factor concentrates (fibrinogen, prothrombin complex concentrate, factor XIII, factor VIIa) as potential alternatives to plasma or whole blood in cases of uncontrollable microvascular bleeding. However, using them outside the approved label poses a challenge in terms of efficacy and safety, particularly in connection to thromboembolic events, instead of efficiency in the specific replenishment of coagulation factors. Thus, the need for more clinical trials is stressed, in order to better define their role and optimal dosing in the management of uncontrollable bleeding.

In summary, given the increasing use of anticoagulant and antiplatelet drugs, the need for multimode management strategies is pointed out, integrating data from multiple tests and considering the complexity of the coagulopathy. Special stress is made on the importance of rigorous clinical trials, the implementation of management algorithms, and their validation in multi-center studies.

Bleeding news

Coagulation management and transfusion in massive postpartum hemorrhage. Review.

Christina Massoth, Manuel Wenk, Patrick Meybohm, Peter Kranke

PMID: 36815533 DOI: 10.1097/ACO.0000000000001258

Author of the comment: *Dra. Pilar Marcos.* *Intensive Care Medicine. Hospital Germans Trias i Pujol, Badalona, Barcelona.*

INTRODUCTION

Postpartum hemorrhage (PPH) is still the most common cause of maternal death. It has gone significantly down over the last 25 years, but it is still around 16-27%.

DEFINITION OF POSTPARTUM HEMORRHAGE (PPH)

It is defined by the **amount of blood loss**. The existing definitions are very heterogeneous (≥ 500 mL or ≥ 1000 mL or clinical signs of hypovolemia or depending on the mode of delivery).

PATHOPHYSIOLOGY OF PPH

The **late stages of pregnancy** entail a number of prothrombotic changes to prevent PPH: ↑ coagulation factors, mostly fibrinogen (3.7-6.2 g/dL) and ↓ fibrinolysis. In contrast, there is a somewhat low platelet count due to dilution caused by plasma expansion.

From a pathophysiological standpoint, **PPH is multifactorial, due to "the 4 Ts"**: uterine atony (**T**one), first trigger in 80% of cases, **T**issue (retention of conception products), **T**rauma (injuries in the delivery channel) and coagulation alterations (**T**hrombin). Furthermore, a number of factors favor it (multiparity, cesarean section, preeclampsia, and maternal age > 35).

It must be noted that early **coagulopathy due to a factor deficiency is highly uncommon in PPH**—except for cases of amniotic fluid embolism, placental abruption, preexisting.

GENERAL CONSIDERATIONS ON THE MANAGEMENT OF COAGULOPATHY

First, identifying the cause of bleeding and administering uterotonics. **Second**, treating **acidosis** (pH >7.2g/dL), **hypothermia** (>36.5°C), and **hypocalcemia** (>1.16mmol/L). Maintaining **Hb ≥ 8g/dL**, through a transfusion of packed red blood cells (PRBC) or autologous blood salvage (1C). Blood salvaging is mainly used in cesarean section deliveries.

Bleeding news

TRANEXAMIC ACID (TXA)

The effectiveness of TXA in the **treatment** of PPH was evidenced by the **WOMAN** clinical trial (2017), which showed a decrease in mortality due to bleeding. However, the **TRACES** clinical trial (2022) could to prove this. The purpose of this trial was to determine the optima dose of TXA (1g, 0.5g or placebo). It only proved a decrease of fibrinolysis with 1g of TXA.

The effectiveness of TXA in **prophylaxis** of PPH was evidenced by the TRAAP-2 trial (delivery by cesarean section, with a 100 mL decrease in bleeding!), but not by the TRAAP trial (vaginal delivery). This is why many guides do **not** recommend the **prophylactic** use of TXA.

TRANSFUSION

Generally speaking, it is recommended to maintain an **Hb of 7-9 g/dL and platelets of 75-100x10^9/L.**

The authors of this review recommend high transfusion ratios [4:4:1= CH:FFP (frozen fresh plasma):platelets] at the start of PPH. However, I believe **4:2:1** ratios may be considered, since factor loss is uncommon in the early stages of PPH.

ROLE OF VISCOELASTIC TESTS IN PPH

Validated to guide the administration of fibrinogen concentrate (FC). It should be administered when **FIBTEM A5 < 12 mm**, which is equivalent to fibrinogen < 2 g/L.

However, the value of EXTEM CT is not as validated to guide the administration of coagulation factors. The authors of this review recommend the administration of FFP (15-20 mL/Kg) when **EXTEM CT > 75 seconds.** I believe that the administration of prothrombin complex concentrate (PCC) may be considered instead of FFP, given it is faster and requires less volume, unless a pre-existing coagulopathy is suspected.

FIBRINOGEN

Low levels of fibrinogen are the most significant individual factor in the severity of PPH. Recent studies show that fibrinogen < 2 g/L implies a 12-fold increase in the odds of bleeding. The recommended dose of FC is 30-60 mg/Kg, considering that 0.5 g of fibrinogen increase the maximum clot strength in the viscoelastic test by 1 mm (patient weight: 70 Kg).

Bleeding news

FACTOR REPLACEMENT

The authors of this review advise against correcting coagulopathy with **PCC**, since there is little evidence in this context. However, sites in favor recommend doses of 20-30 UI/Kg and guiding the administration with a viscoelastic test.

The role of **factor XIII** is discussed as a clot stabilizer. Recent studies show that a decrease in its activity (< 50%) is connected to PPH. Therefore, some guides mention it may be administered in cases of massive bleeding (30 UI/Kg).

Recently, the European Medicines Agency has approved the administration of factor **VIIa** in PPH. They say it should be used on an individual basis, as a last resort (60-90 µg/Kg).

CONCLUSION

CORRECTION	ANTIFIBRINOLYTIC	DIAGNOSIS AND TRANSFUSION	TARGETS	REFRACTORY BLEEDING
Temp.>36.5 ºC pH > 7.2 Ca 2+ > 1.6 mmol/L Considering autologous transfusion	TXA 1 g	VISCOELASTIC test (VET) LABORATORY test (PL) 1st transfusion: 4:4:1 - 4:2:1 Following transfusions guided by VET and/or PL	Hb 7-9 g/dL Platelets 75-100x10^9/L Fibrinogen >2-2.5 g/L FIBTEM A5 > 12 mm EXTEM CT > 75 seg PT and/or aPTTP < 1.5 Factor XIII > 50%	Considering F VIIa

Bleeding news

Patient blood management guideline for adults with critical bleeding (guías australianas)

https://blood.gov.au/pbm-critical-bleeding

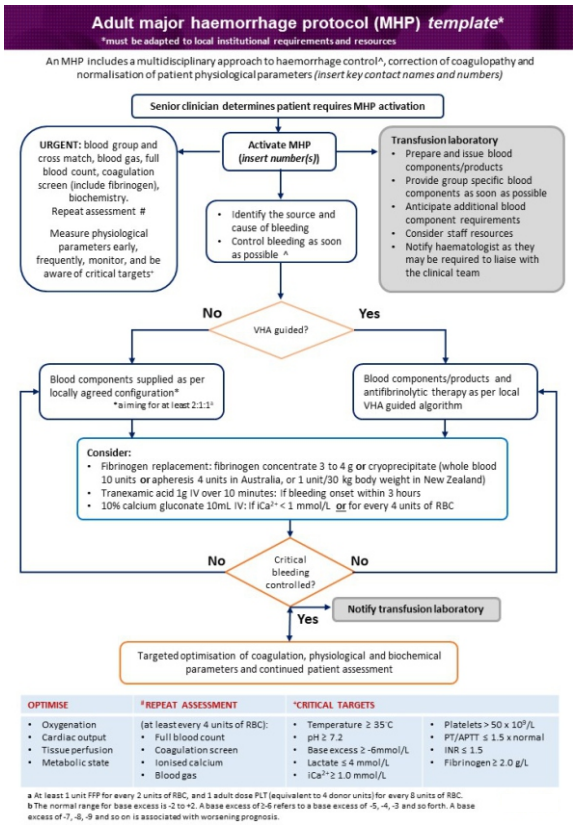
Author of the comment: *Dra. Sonia María Veiras.* *Hospital Clínico Universitario de Santiago de Compostela. Head of Section at the Anesthesia and Resuscitation Department. A Coruña Province.*

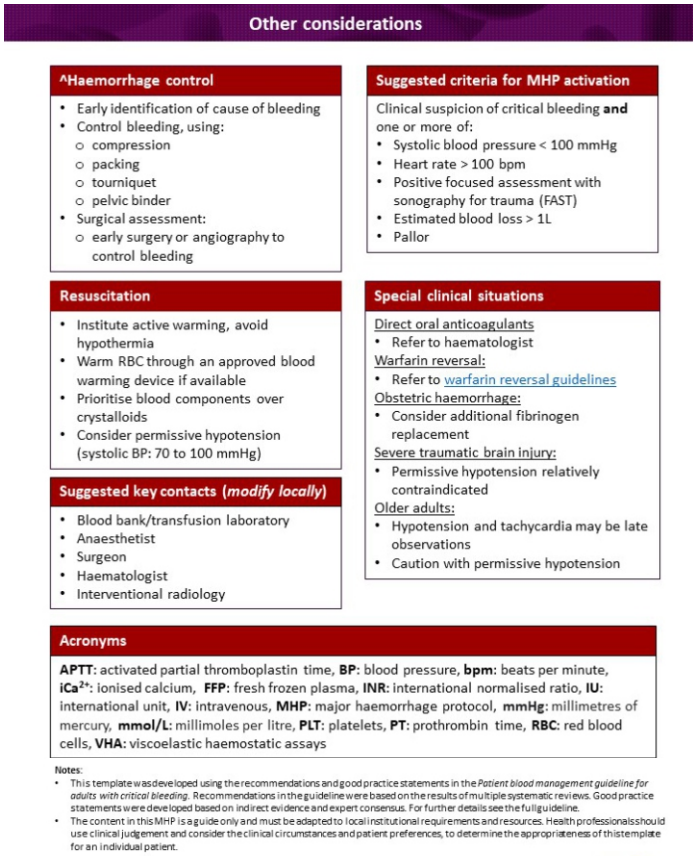
This document offers a specific simple guide for the management of critical bleeding.

There are plenty of massive hemorrhage management guides—European, American, advocated for by anesthesiologists, by intensivists, referred to specific bleeding scenarios, such as obstetric cases, multiple trauma, heart surgery, or liver transplant). Many of these documents are long and tedious, hard to read and summarize, which makes them less useful.

Australian guides are also a long document (185 pages) containing the arguments for each one of the recommendation.

At the same time, the Australian work group has published a summary of guides for quick reference.





Bleeding news

In summary, the document contains seven recommendations and eleven clinical best practice statements, depending on the level of existing evidence.

The recommendations, in a nutshell, are the following:

- Having a massive hemorrhage protocol in place at each site.
- Frequently measuring these parameters in the bleeding patient: temperature, acid-base status, ionized calcium, hemoglobin, platelet count, PT/INR, aPTT, fibrinogen.
- Transfusion ratio between PRBC, FFP and platelets not below 2:1:1 (a 1:1:1 ratio is even advocated for, although without the necessary evidence).
- At least 1 unit of FFP is recommended for each 2 PRBCs, and 1 unit of platelets for each 8 PRBCs.
- The group takes a stance against the routine use of recombinant activated factor VII, except for cases of factor VII or IX inhibitors, congenital deficiency of factor VII and Glanzmann thrombasthenia. In massive bleeding, recombinant FVII will be used as a last resort after using up other hemostatic measures.
- Early administration of tranexamic acid is recommended in trauma patients and in obstetric hemorrhage cases.

Best practice statements are agreements emerging from the working group that are considered to be beneficial but are lacking the evidence required to become recommendations:

- Identifying the cause of bleeding and early control of bleeding
- Temperature <35 °C, pH<7.2, Ca+2 <1 mmol, PT>1.5, INR>1.5, aPTT >1.5, fibrinogen <2 are considered critical physiological deterioration values.- the replacement of fibrinogen with 3-4 g of concentrate or else one unit of cryoprecipitate for each 30 kg of body weight, or the administration of 25-50 UI/kg of prothrombin complex concentrate (no evidence was found to make recommendations on the time of administration or the exact dose)
- The administration of PRBCs through fluid warmers
- The administration of isogroup blood products as soon as possible
- Stopping the activation of the massive hemorrhage protocol as soon as the critical hemorrhage is under control
- It is agreed that there is insufficient evidence to recommend using tranexamic acid in critical digestive bleeding
- Using viscoelastic tests to manage critical bleeding can be beneficial, as well as blood salvage (cell saver)