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Incorporating the concept of overtransfusion into hemovigilance monitoring: An expert-based definition and criteria from the International HIT-OVER Forum

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What is an overtransfusion?

This concept may be defined as:

- OVERDOSE OF COMPONENTS
- INCORRECT COMPONENT
- UNNECESSARY ADMINISTRATION

Our Hemovigilance system is very thorough, but it does not include the concept of overtransfusion, focusing on the misses / near misses in the administration of blood components and in transfusion reactions.

Overtransfusion may have deleterious effects, including hypercoagulability, with may lead to thrombosis, alloimmunization, increased mortality, longer hospital stays, increased infection rates, and cardiovascular overload events.

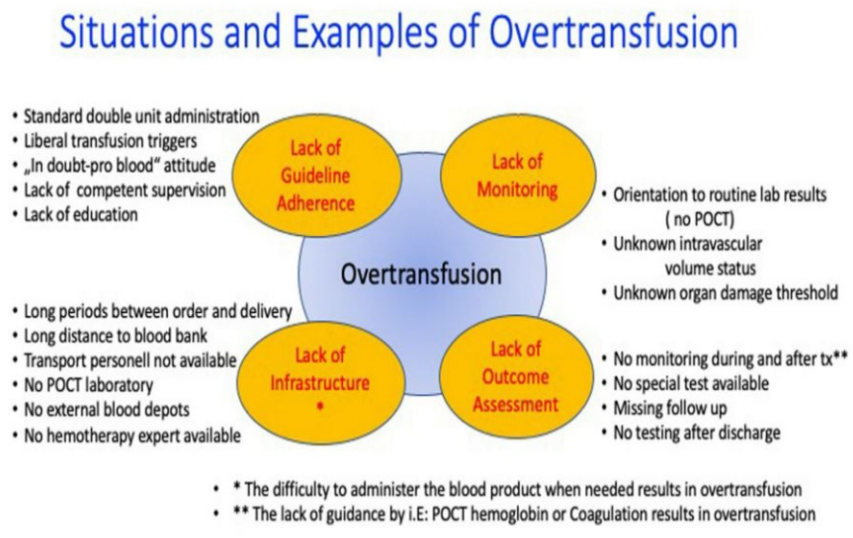

FIGURE 1 Situations and examples of overtransfusion. Overtransfusion is produced by the lack of guideline adherence, lack of monitoring, lack of infrastructure or structure, and lack of outcome assessment. POCT: point-of-care testing. [Color figure can be viewed at wileyonlinelibrary.com]

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There are four groups of reasons for overtransfusion:

1) Lack of adherence to clinical guidelines, which leads to attitudes such as “when in doubt, transfuse” and not considering transfusion thresholds.
2) Insufficient monitoring, meaning that the transfusion decision is frequently a “correction of analytical figures” and not necessarily beneficial for organ perfusion.
3) Hospital infrastructure hindering the immediate availability of blood components (blood bank far away, hospital attendant unavailable…)
4) Lack of auditing of post-transfusion outcomes.

In the 2023 NATA meeting, a working group was created to explore the concept of overtransfusion, with a literature review between 2000 and 2023, and the definition of overtransfusion was agreed as “the unnecessary or inadequate administration of blood products, incorrect component transfusion, overdose, administration of 2 units without proper monitoring, administration without clinical evidence”, separated into two divisions:

1) overtransfusion per se

2) overtransfusion-induced hypercoagulopathy

17,273 transfused subjects (articles published between 2011 and 2023 based on search keywords: overtransfusion, transfusion overdose, blood overdose, unnecessary transfusion…) with a mean overtransfusion rate of 46.99%.

The evolution of overtransfused patients is unclear due to heterogeneity and the lack of a control group.

If the discharge Hb levels are analysed as markers of appropriateness for CH, overtransfusion occurred in 20% of elective surgeries.

As examples of this search, the ***unnecessary use of FFP*** leads to an increase in surgical site infections, nosocomial infections, ARDS incidence, and longer hospital stays: for 100 ml of FFP… 0.38 more days in hospital.

Overtransfusion is an issue well beyond borders. As an example, in the United Kingdom, up to 45% of unnecessary packed red blood cells have been identified.

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Therefore, overtransfusion is defined as: The administration of a blood component not recommended in a specific clinical situation, or of multiple units when a single unit would do, or a dose that is inappropriately high for the patient's needs:

- In situations of controlled bleeding
- As a prophylactic treatment or with no evidence of improvement in vital signs
- Overcorrection
- With the potential to produce TRALIs, TACOs, transfusion associated dyspnea, alloimmunization, infection, transfusion reactions.

The challenge is… can we integrate overtransfusion in our hemovigilance?

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Early viscoelastometric guided fibrinogen replacement combined with escalation of clinical care reduces progression in postpartum haemorrhage: a comparison of outcomes from two prospective observational studies

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Haemostatic treatment in patients with postpartum haemorrhage (PPH) is still controversial, given the special characteristics of third-trimester pregnant women, including a significant increase in plasma fibrinogen levels, which in normal conditions is above 4 grams/litre. Thus, previous studies have shown that early treatment with fibrinogen, aimed at maintaining levels over 2 g/L, improves the outcomes and reduces the progression to massive bleeding in PPH patients.

The authors approach a comparison of 2 prospective studies in the same site, before and after the introduction of a set of measures for PPH management. This set of measures included the use of a quantitative blood loss method from the time of delivery, the administration of tranexamic acid when the estimated loss was at 1000 ml, and the use of the viscoelastic test (ROTEM). This allowed for management to go grom empirical or based on laboratory-based tests of coagulation to ROTEM-based, with a 2 g/L fibrinogen threshold, reducing the percentage of women progressing to massive PPH.

These improved outcomes result from a number of changes, including and early diagnosis of the coagulopathy and an early start of the treatment. In that regard, as already proven in other studies, clinical concern plays a major role, reinforced by the quantitative measurement of blood loss, triggering the alert and the start of PPH management. After such an alert, using a viscoelastic test as part of management and treatment guide leads to time savings and a global overview of the coagulopathy, which translates into a decrease/removal of fresh plasma in favour of fibrinogen replacement, by means of a concentrate.

The implementation of the viscoelastic test also meant an early management in patients with hypofibrinogenaemia (levels below 2 g/L) at the start of delivery, thus curbing the progression of PPH. As a matter of fact, none of the patients in the article progressed to massive bleeding.

This article is a clear example of how applying different evidence leads to an improved diagnosis, management and, consequently, outcome in complex situations such as PPH.

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CLINICAL INVESTIGATION: Association of hyperfibrinolysis with poor prognosis in refractory circulatory arrest: implications for extracorporeal cardiopulmonary resuscitation

Abakar Magomedov, Jan M Kruse, Daniel Zickler, Julius V Kunz, Roland Koerner, Sophie K Piper, Julian Kamhieh-Milz, Kai-Uwe Eckardt, Jens Nee

PMID: 39025778 PMCID: PMC11347786 DOI: 10.1016/j.bja.2024.05.034

EDITORIAL: Hyperfibrinolysis: potential guidance for decision-making to avoid futile extracorporeal cardiopulmonary resuscitation

Herbert Schöchl, Johannes Zipperle

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Out-of-hospital cardiorespiratory arrest (OHCA) is associated with a poor prognosis.

Resuscitation using extracorporeal membrane oxygenation (eCPR) is a potential treatment, although it is invasive, labour-intensive, and expensive, so we need to identify patients that may benefit from it. Even though it is known that OHCA with an extracardiac cause, non-defibrillation rhythms, and prolonged low or no-flow states are associated to a **worse neurological prognosis**, current clinical trials are not conclusive, and so further research is required to determine which patients can benefit from an eCPR.

In that regard, the authors of the commented editorial and research article suggest the analysis of **fibrinolysis** for that purpose. Thus, a clinical situation of **hyperfibrinolysis** may result from prolonged low or no-flow states and, therefore, bad prognosis. Moreover, this analysis can be performed easily and fast, by the bedside, using **point-of-care such as viscoelastic testing** (TEG® or ROTEM®, mostly).

But what would be the **pathophysiological driver of hyperfibrinolysis in the OHCA**? Low-flow states trigger thrombus formation in the microcirculation, which further aggravates tissue hypoxia. Hyperfibrinolysis would be an evolutionary response to survive, promoting an early lysis of the thrombus to maintain the blood flow and prevent hypoperfusion, even at the cost of increased bleeding. In other clinical situations, such as trauma-induced bleeding, almost 100% mortality has been reported when the image of the viscoelastic test has a diamond shape, which is clearest example of early hyperfibrinolysis.

Is there a **definition of fibrinolysis diagnosed using viscoelastic testing**? Although there is no universally

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accepted definition, hyperfibrinolysis is assumed with a lysis index of > 3% by TEG® or a maximum lysis (ML) ≥15 by ROTEM®. Currently, transfusional algorithms using ROTEM® allow for an early prediction of hyperfibrinolysis with the ROTEM® value of $A5_{EXT}$ (amplitude of EXTEM at 5 minutes) or $A10_{EXT}$ (amplitude of EXTEM at 10 minutes). Also, when diagnosed, the administration of tranexamic acid would be indicated.

How can we **classify the post-CPR neurological prognosis**? Using the Cerebral Performance Category (CPC): CPC 1-2 (good prognosis) and CPC 3-5 (bad prognosis).

CPC 1: Complete recovery or mild disability.

CPC 2: Moderate disability, but independent for daily-life activities.

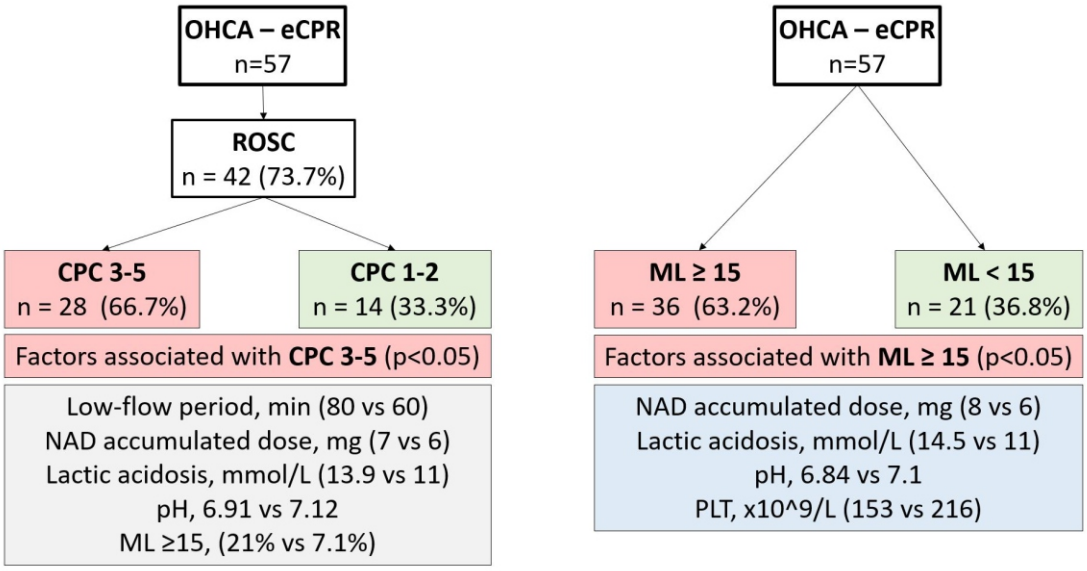
CPC 3: Severe disability. Dependent for daily-life activities.

CPC 4: Persistent vegetative state.

CPC 5: Death.

Magomedov et al. analyzed the lysis state of the clot in 57 patients with OHCA that were treated using eCPR, at the time of hospital admission. They observed that:

A) Factors related to poor neurological prognosis (CPC 3-5) and factors related to hyperfibrinolysis:



OHCA: Out-of-Hospital Cardiorespiratory Arrest; eCPR: Extracorporeal Cardiopulmonary Resuscitation; ROSC: Return of Spontaneous Circulation; CPC: Cerebral Performance Category; NAD: Noradrenaline; PLT: Platelets

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As can be seen, the authors did not find any connection between the existence of hyperfibrinolysis and the low-flow state time (72.5 min in patients with ML ≥15, and 70 min in patients with ML<15). Most likely, this is due to small sample size.

B) Predictors of a poor neurological prognosis (CPC 3-5):

- **Lactic acidosis**, with an AUC of 0.78 (95% CI: 0.63-0.89).
- Transfusional algorithms using ROTEM® are early predictors of hyperfibrinolysis with the $A5_{EXT}$ or $A10_{EXT}$ value. This study show a connection between **$A5_{EXT}$** and **$A10_{EXT}$** with CPC 3-5, with an AUC of 0.76 (95% CI: 0.63-0.89) and 0.79 (95% CI: 0.62-0.9), respectively.
- Given the strong connection between lactic acidosis and ML, they analyzed the connection between **$A5_{EXT}$ / Lactate**, improving the AUC up to 0.89 (95% CI: 0.8-1).

In conclusion, the hypothesis that hyperfibrinolysis may be related to the low or no-flow time in OHCA clearly deserves a multi-centre analysis.

The connection between **$A5_{EXT}$ / Lactate** on admission may be yet another tool, and a fast predictor of an unfavourable neurological outcome (CPC 3-5) in a patient with OHCA for which an eCPR is considered on admission. It may also help optimizing the indication of this invasive, expensive therapy.