# Update on Blood and Iron


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### Massive Haemorrhage: Shock Trauma and Coagulopathy

Trauma has few benefits. But for the study of the response of the human's physiology to shock it provide a unique model to explain changes that have troubled clinicians for decades in understanding why patients continue to bleed when normally they do not.

If a patient has severe trauma defined by evidence of shock and ongoing, uncontrolled bleeding they have a 20% mortality, which increases to 40-50% if in addition they have a coagulopathy. They are 8 times more like to die in the next 24 hrs with a coagulopathy than not, and results from the PROPPR and PROMMTT [1]studies suggest that rapid resuscitation with fibrinogen rich blood products may reduce bleeding, improve short term survival, but not such that in hospital mortality is reduced.

The development of a coagulopathy has been recognised for many years since Cannon [2]recognised the delirious effect of resuscitation of patients with clear fluids in battlefield trauma. The dilutional coagulopathy does not explain the profound blockade in coagulation in shock. Evidence currently points to poorly perfused endothelium, stimulated by a hyper adrenergic sympathetic system exuding thrombomodulin and activated Protein C into the microcirculation.[3] This effects PAI-1 to promote fibrinolysis, inhibit FV and FVII to stimulate thrombin, and thus limit clot forming in the microcirculation. While this may preserve the organ if perfusion is re-established, the systemic effects of this are to induce non-surgical bleeding that increases mortality in the trauma patient.

Thus, and in tandem with this the previously intact glycocalyx is damaged. [4]When large crystalloid resuscitation fluids are used the protein and heparan matrix within the extra-endothelial layer loses its integrity. Fluid loss through the basement membranes increases, and he effectiveness of the circulation is impaired.[5]

Indicators of increased mortality using coagulation parameters show that they are the result of profound shock. Elevated Protein C levels, Syndactin-C levels (indicating glycocalyx destruction) and elevated adrenaline levels all are associated with abnormalities in coagulation parameters (INR, aPPT), and TEG abnormalities.[6] Similar changes in platelet aggregation occur.

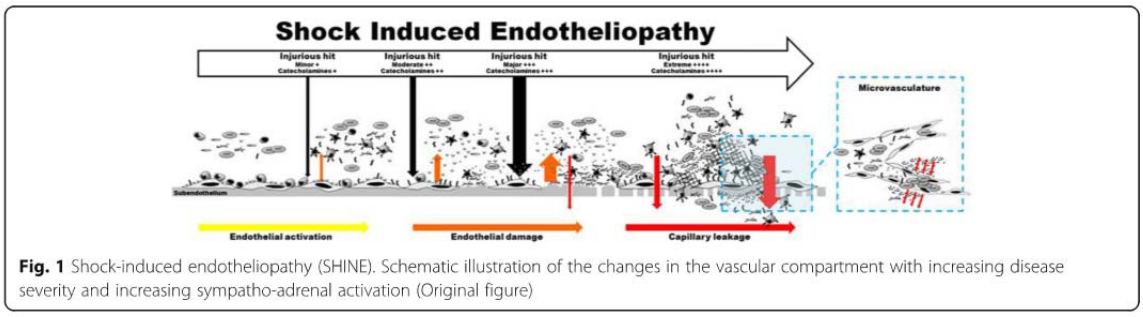



**Fig. 1** Shock-induced endotheliopathy (SHINE). Schematic illustration of the changes in the vascular compartment with increasing disease severity and increasing sympatho-adrenal activation (Original figure)

Johansson *et al. Critical Care* (2017) 21:25

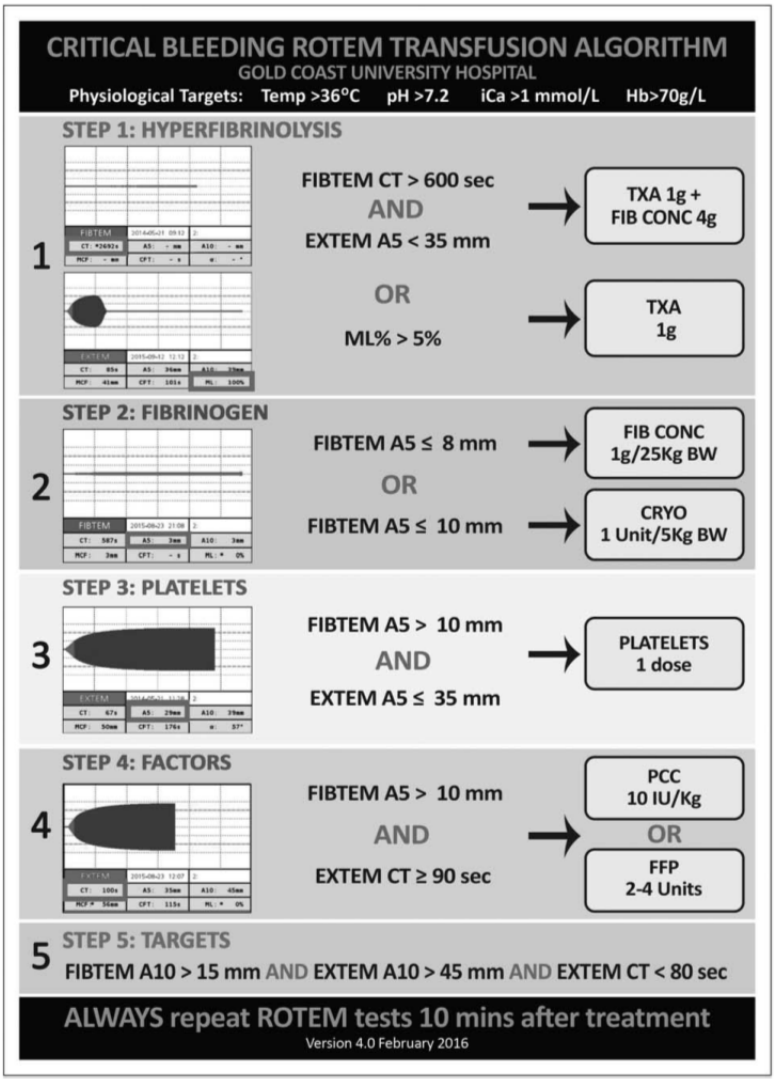
The resulting clinical problems are a patient in shock with bleeding from non-surgical wounds, that continues to bleed after the trauma pathology is fixed. This leads to abdominal compartment syndrome, Multisystem organ failure and death.

Empiric responses to this have been a rapid recognition of patients at risk, rapid transport to a definitive site of bleeding control (operating room or interventional radiology), damage control surgery, which involved rapid surgery limited to stopping bleeding, then stopping, Damage control resuscitation which involves limiting crystalloid, empiric use of Tranexamic acid at a dose of 15mg/kg bolus plus an infusion over 1 hrs, blood given in either a 1:1:1 fixed ratio, or targeted to a TEG or ROTEM, and sometimes permissive hypotension. Patients with persistent acidosis and hypothermia are managed in the ICU until stabilised before definitive trauma surgery

Together these bundles of care have reduced mortality form massive haemorrhage in trauma substantially.[7]

The question is where these lessons can be applied in other surgical areas. While the principles are logically applied to any surgery that includes shock and uncontrolled bleeding, in normal high blood loss surgery evidence is lacking to aggressive resuscitation along these lines. A warm, not shocked patient with limited tissue trauma behaves differently and focused therapy is more logical. In Cardiothoracic surgery, the effect of drugs that are anticoagulant and antiplatelet need to be specifically reversed rather an empirically treated.

The concept of Goal directed therapy where abnormalities are corrected only in bleeding patients has the advantage of focussing therapy on laboratory abnormalities. The most validated of these is using a TEG or ROTEM. It further allows treatment with less exposure to allogenic blood products, and less system waste. [8,9] But it usually needs specialist skills and a dedicated person controlling the resuscitation.



The question in the future is if we need to add a person to the team. There has usually been an airway specialist, should we add a bleeding specialist?

## Evidence supporting the use of PBM

### Improved outcomes and reduced costs with PBM – the Australian experience

The implementation of the world's first comprehensive health-system-wide PBM programme in Western Australia has reduced transfusion rates and improved patient and economic outcomes.[10] Prior to the implication of the programme, this Australian state already had one of the world's lowest RBC issuance rates; 31.8 per 1000 population in 2008-9, compared with rates in Germany, Denmark, the UK and the US of 57.3, 60.0, 36.3 and 48.8 per 1000 population, respectively. [10]
Patient and economic outcomes investigated over 6 years in 605,046 inpatient admissions at four major Western Australian adult tertiary care hospitals partaking in the PBM programme during the period 2008-14, revealed a 41% (RR 0.59; 95% CI 0.58-0.60, $p < 0.001$) decrease in units of RBCs, fresh-frozen plasma and platelet units transfused per 1000 discharges when baseline values were compared with end of study data (**Figure 5**). [10] During this period, the mean RBC pre-transfusion haemoglobin level decreased from 7.9 g/dL to 7.3 g/dL ($p < 0.001$) and the proportion of single-unit RBC transfusions increased from 33.33% to 63.69% ($p < 0.001$). There was a significant reduction in the proportion of elective surgical patients admitted with anaemia (20.81% vs 14.42%; $p = 0.001$), a 28% risk-adjusted reduction in hospital mortality (OR 0.72; 95% CI 0.67-0.77; $p < 0.001$), a 21% risk-adjusted reduction in hospital-acquired infections (OR 0.79; 95% CI 0.73-0.86), a 31% risk-adjusted reduction in acute myocardial infarction/stroke (0.5% vs 0.4%; OR 0.69; 95% CI 0.58-0.82; $p < 0.001$), and an adjusted 15% reduction in mean length of hospital stay (5.9 days vs 5.3 days; incidence RR 0.85; 95% CI 0.84-0.87; $p < 0.001$)

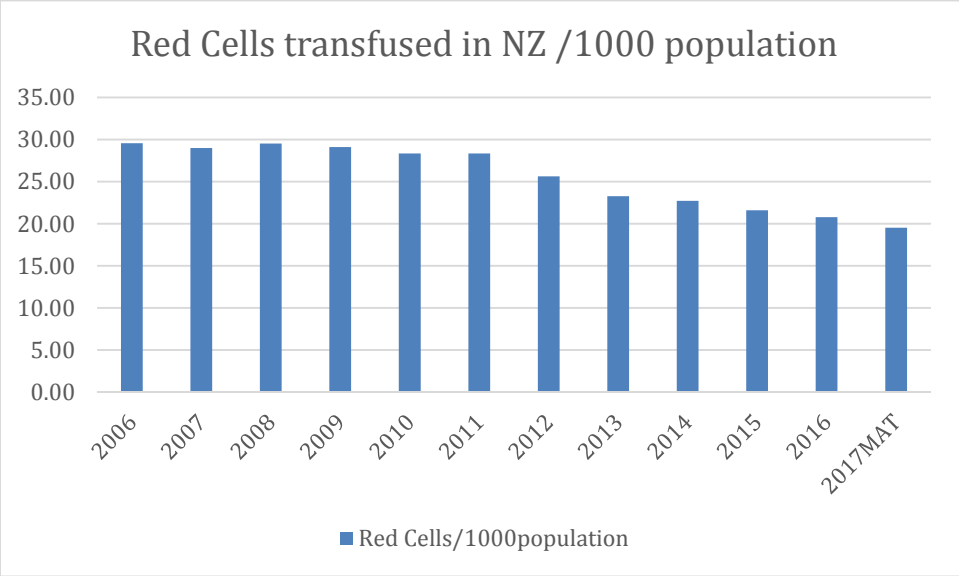
These reductions translated to a product-acquisition cost saving of AU$18,507,092 and an estimated activity-based saving of between AU$80 million and AU$100 million during the 6-year study period. The risk of all-cause emergency readmissions rose from 11.4% to 12.4% during the study period (OR 1.06; 95% CI 1.02-1.10; $p = 0.001$); this finding is contrary to the findings of other studies. [10]
The findings of the Western Australian study are consistent with those of smaller studies investigating the implementation of individual PBM strategies in selected patient groups.[24-30] A systematic review and meta-analysis of RCTs by Salpeter et al., demonstrated that trials with more restrictive transfusion thresholds demonstrate significantly reduced infection, cardiac events, rebleeding and mortality rates compared with those using less restrictive thresholds.[32] Furthermore, there are numerous risk-adjusted observational studies showing independent dose-dependent associations between RBC transfusion rates and increased morbidity and mortality.[10]

### The European Union follows suit

In April 2017, the European Commission announced the publication of two PBM guides recommending PBM as the standard of care for the European Union.[30] The guides were modelled on the "impressive results" of the Western Australian PBM programme. Furthermore, the World Health Organisation has endorsed and promoted PBM and it is widely accepted as current best practice.[32]

### Local experience

'Blood as a gift' has been an ongoing initiative in NZ at Auckland City Hospital since 2010. The initiative was developed with the mission of introducing and embedding blood management principles and practice, in an aim to improve patient blood safety and reduce unnecessary transfusions. Between October 2010 and December 2013, the initiative improved the utilisation of RBC units, with an overall reduction of approx. 18% in mean consumption. In addition to the associated financial savings, there was a significant time saving for both patients and staff.




**The status of PBM in NZ**

There are a number of subtle differences between NZ, Australia and other counties with regard to PBM. The costs of blood products are borne by the District Health Boards, unlike federally paid products in Australia. It may be that micromanagement of the effective use of NZ blood products have always lead to more rational use. Saying that, audits in the ADHB in 2003 showed 20% of prescribed red cells had no logical indication on modern criteria (as in the NBA guidelines), and a program to encourage better transfusion practice lead to a 17% reduction in use. Similar programs with the use of fresh frozen plasma, platelets and group and antibody screens have led to reduced use. In fact in absolute terms, FFP use in 2017 is 50% of that in 2005, and red cell use has been dropping in the last four years, despite an increasing population and more complex surgery. While the more restricted use of blood products are logical in anaemic patients, or those with deranged coagulation screens, but not bleeding, the use of a MTP has lead to reduced deaths due to exsanguination. This paradoxically is associated to a more liberal delivery of coagulation factors (predominantly fibrinogen dominant) to the patient rapidly. As these products are usually frozen, early thawing often leads to waste. The key to using these products wisely is to understand the indications for the activation of the MTP, use rapid assays (often the thromboelastogram [TEG]) to diagnose coagulopathy, and to stop the MTP at the correct time. Alternative approaches with a goal directed approach that differs in not following the empiric formula of an MTP are also being investigated.
The development of the NBA guidelines involved collaboration with NZ and Australian groups, and the endorsement of them by Colleges in Anaesthesia, Critical Care, Surgery and Haematology. They are relevant to NZ practice.

**The optimal timing of iron treatment**

Oral iron still should be the first drug used in treating iron deficiency. In patients tolerant of the side effects, and with intact gastrointestinal absorption, replacement is near equivalent to a single bolus of IV Iron. Unfortunately many of the patients presenting with low ferritins have a body deficit of iron of >1G. With daily absorption of oral iron approx. 5mg, replacement will take 2-3 months. Thus with a patient intolerant to oral iron, poor absorption due to elevated hepcidin, and surgery within the next month, the place of IV Iron has become better defined. Modern preparations have a low side effect profile, unlike the older dextran preparations. They are able to be given as an undiluted slow IV injection in GPs' surgeries, and are effective. Peak elevations in haemoglobin are in the 2-4 week period, dependent of the nature of the deficiency, and the degree of concomitant bleeding. Post-operative oral iron has very limited absorption.

## Implementing PBM in NZ

The implementation of a PBM strategy in NZ has started, but has much promise to reduce further unnecessary blood transfusions, and consider reducing wastage. This has put considerable pressure of the New Zealand Blood Service (NZBS), who is adapting their donor population to meet the product demands of more fractionated products (IVIG, Prothrombinex®, albumin and possible fibrinogen concentrate) and reduced FFP and red cell use. We do not have a well-funded overarching body like the NBA in NZ, but we do have an effective network of committed clinicians, mainly through blood transfusion committees to introduce systems to reduce variance in blood transfusion practices. We also need to ensure the public, who are the donors and recipients of blood at the same time, believe the decisions we make on their behalf are well founded in fact, and are not wasteful.

The recently developed 'Simplified International Recommendations for the Implementation of Patient Blood Management' which include a series of simple cost-effective, best-practice, feasible and evidence-based measures, is a useful resource aimed at enabling any hospital to reduce both anaemia prevalence on the day of surgery or intervention and anaemia-related unnecessary transfusion in surgical and medical patients.

## Educational resources on PBM

BloodSafe eLearning Australia has excellent online courses relating to PBM and clinical transfusion practice for health professionals. https://bloodsafelearning.org.au
The National Blood Authority provides a range of online tools to aid in the implementation of the PBM Guidelines at a heath provider level. https://www.blood.gov.au/implementing-pbm

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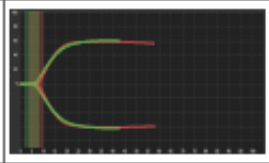
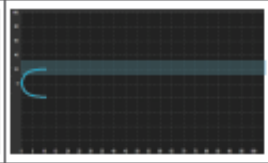
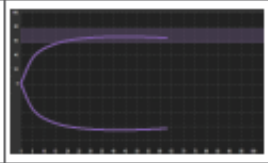
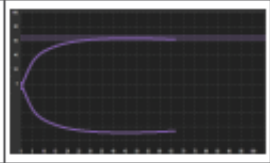
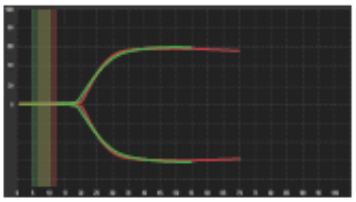
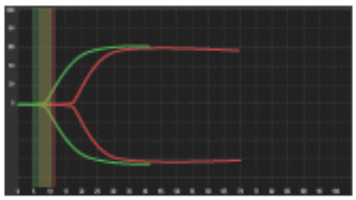
# TEG® 6s Deficiency Assessment

| | Clot Rate | Clot Strength | Clot Strength | Clot Stability |
|---|---|---|---|---|
| Hemostatic Component | Coagulation factors & heparin | Fibrin clot | Platelet & fibrin clot | Fibrinolysis |
| Test - Parameter | CK / CKH - R | CFF - MA | CRT - MA | CRT - LY30 |
| Normal Tracings<br>*Shaded Reference Ranges for illustration only* |  |  |  |  |
| Reference Ranges | 4.6 - 9.1 min | 15 - 32 mm | 52 - 70 mm | 0.0 - 2.2% |
| Hypocoaguable | ↑ $R_{CK}$ (min) | ↓ $MA_{CFF}$ (mm) | ↓ $MA_{CRT}$ (mm) | ↑ $LY30_{CRT}$ (%) |
| Hypercoaguable | ↓ $R_{CK}$ (min) | ↑ $MA_{CFF}$ (mm) | ↑ $MA_{CRT}$ (mm) | N/A |

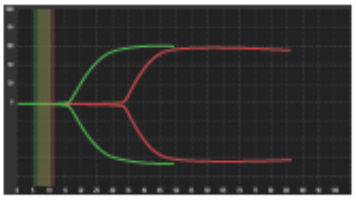
## Clot rate



Factor Deficiency

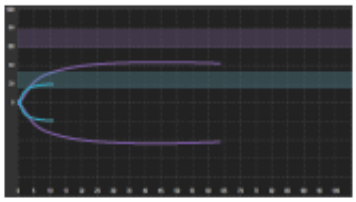


Heparin Effect

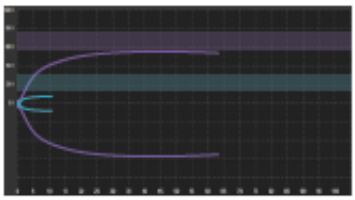


Factor Deficiency & Heparin Effect

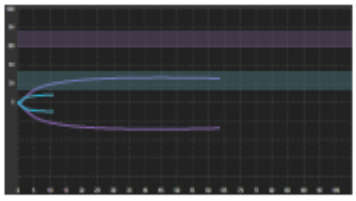
## Clot strength



Platelet Deficiency

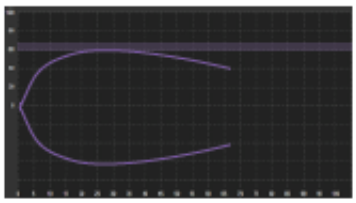


Fibrinogen Deficiency

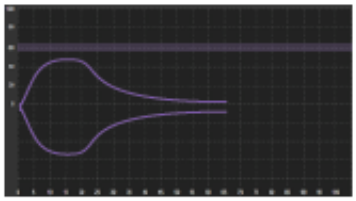


Platelet & Fibrinogen Deficiency

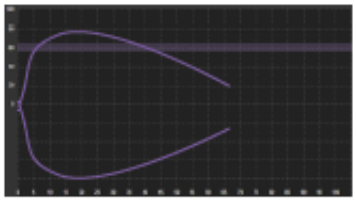
## Clot stability



Hyperfibrinolysis



Primary Fibrinolysis



Secondary Fibrinolysis

Shaded reference ranges are shown for illustrative purposes only

CK - R reference range

CKH - R reference range

CFF - MA reference range

CRT - MA reference range

CRT - LY reference range

Results from the TEG 6s analyzer should not be the sole basis for a patient diagnosis, but should be evaluated together with the patient's medical history, the clinical picture and, if necessary, other coagulation tests.



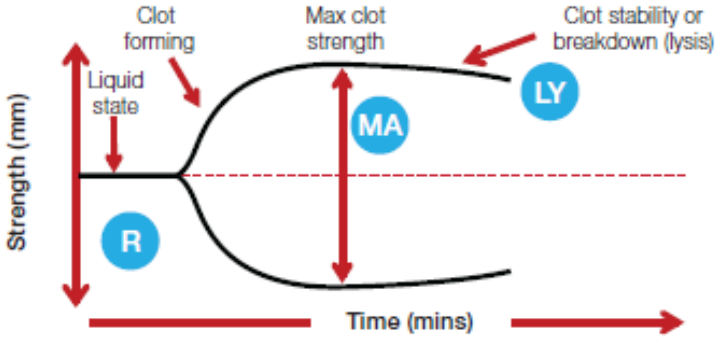
HAEMONETICS®

# TEG® 6s Deficiency Assessment

## TEG tracing results

Thromboelastography measures clot strength over time, providing information relative to:

- Clot rate (rate R, in mins)
- Clot strength (Maximum Amplitude MA, in mm)
- Clot stability (LYsis LY30, as a %)




## Viewing cartridge results

The TEG 6s analyzer runs four tests simultaneously, providing the most specific and timely information.

The greatest sensitivity to clotting factors and heparin is achieved with the R parameter of the CK and CKH tests.

Clot strength is most rapidly assessed with the MA parameter of the CRT test, while CFF isolates fibrinogen conribution.


## Deficiency assessment guide

Results from the TEG 6s analyzer should not be the sole basis for a patient diagnosis, but should be evaluated together with the patient's medical history, the clinical picture and, if necessary, other coagulation tests.

| Test | Parameter | Deficiency |
|---|---|---|
| CK | ↑ R | Clotting factors * |
| CKH | R < CK-R | Heparin effect |
| CFF | ↓ MA | Fibrinogen |
| CRT | ↓ MA | Platelets ** |
| CRT | ↑ LY30 | Fibrinolysis |

* In presence of heparin (CK-R > CKH-R) refer to CKH-R for adequacy of clotting factors
** If CFF-MA normal

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