# La Trasfusione massiva

*Patrizia Di Gregorio*

*Chieti  6 Maggio 2016*

Management of massive loss requires a quick concerted team effort by many medical and paramedical members. Understanding the complex pathophysiology of massive blood loss and its replacement is crucial to a successful outcome. **Recent evidence supports early use of coagulation factors to improve outcome.** Indian hospitals should formulate MTPs suited to their need and resources to improve survival in massive blood loss.

**Massive transfusion and massive transfusion protocol**
Vijaya Patil and Madhavi Shetmahajan
Indian J Anaesth. 2014 Sep-Oct; 58(5): 590–595.

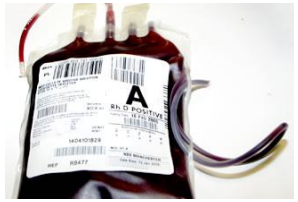
# IL RUOLO DEL TRASFUSIONISTA

SIMT

**consulente**

laboratorio

+



Preparazione emocomponenti

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Assegnazione di emocomponenti ed emoderivati

# SINDROME DA TRASFUSIONE MASSIVA (MBT)

- **Perdita pari all'intero volume ematico (TBV) in 24 ore (Pari all'infusione di 8-10 unità di emazie nell'adulto)**
- **Perdita superiore al 50% del volume ematico totale entro 3 ore**
- **Perdita ematica > 150 ml/min (adulto)**

# COMPLICATIONS OF MASSIVE TRANSFUSION (I)

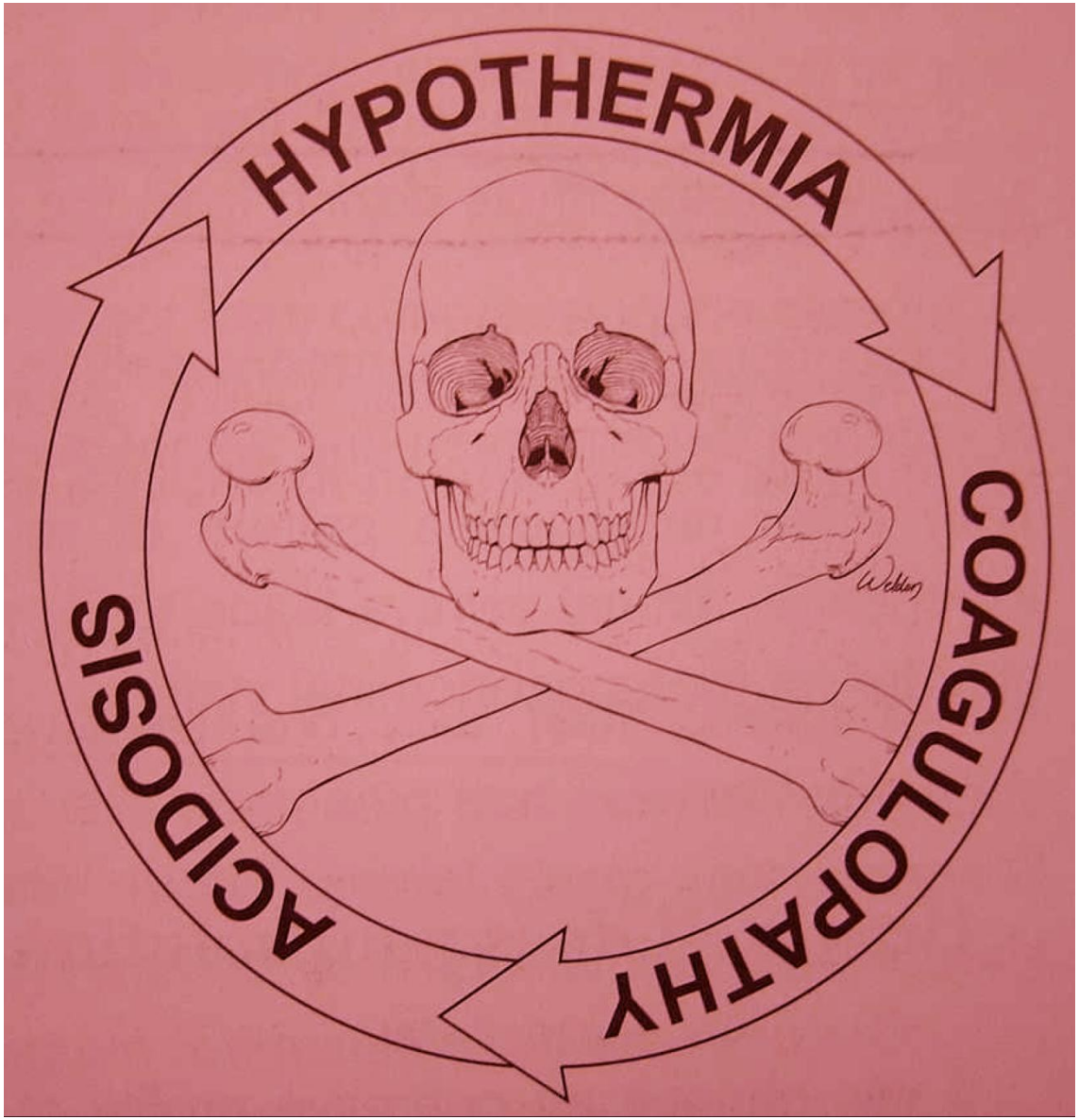
| | | |
|---|---|---|
| **Immediate** | **Problems secondary to volume resuscitation** | 1. Inadequate resuscitation<br>2. Overzealous resuscitation |
| | **Dilutional problems** | 1. Dilutional coagulopathy<br>2. Low colloid oncotic pressure giving rise to interstitial edema |
| | **Problems related to transfusion of large volume of stored blood** | 1. Citrate toxicity<br>2. Hyperkalaemia<br>3. Hypothermia<br>4. Hypomagnesemia<br>5. Acidosis |

# COMPLICATIONS OF MASSIVE TRANSFUSION (II)

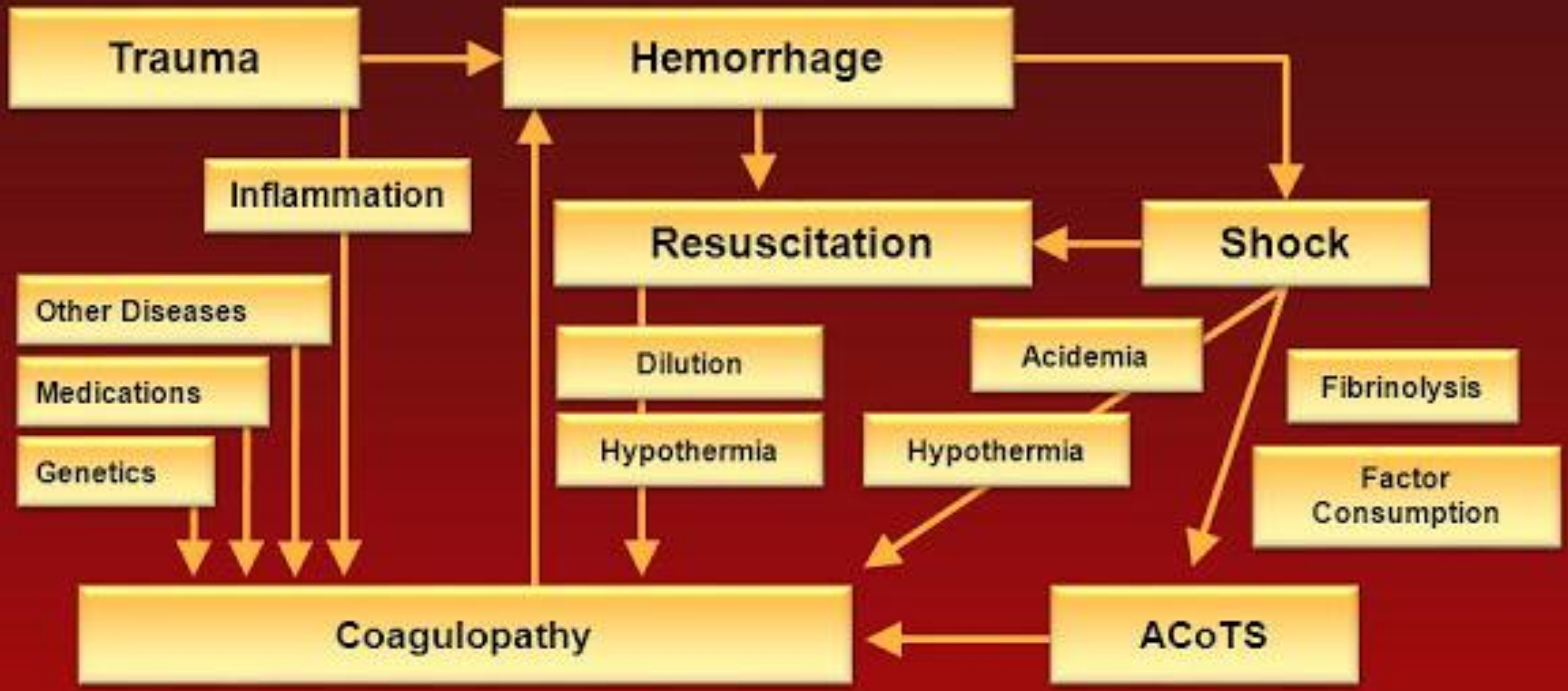
| | | |
|---|---|---|
| **Late complications** | **Respiratory failure** | Transfusion related acute lung injury (TRALI): The risk of TRALI increases with the number of allogenic blood and blood products transfused. The exact pathologic mechanisms of TRALI have not been clearly understood and both immunologic and nonimmunologic mechanisms have been suggested.<br>**TACO** |
| | **SIRS** | |
| | **Sepsis** | |
| | **Thrombotic complications** | |

# Trasfusione massiva e Coagulopatia

- Tipologia e volume dei liquidi infusi
- Anormalità emostatiche preesistenti
- Ipotermia
- Danno tissutale
- Shock ipovolemico
- DIC
- Iperfibrinolisi
- Alterazioni qualitative e quantitative delle piastrine


HYPOTHERMIA
COAGULOPATHY
ACIDOSIS

# Acute Coagulopathy of Trauma (ACOT)




Hess JR, et al. *J Trauma.* 2008;65:748-754.

# Ipotermia

- ✓ Altera la funzionalità piastrinica
- ✓ Altera la funzionalità dei fattori coagulativi
- ✓ Aumenta la fibrinolisi ?
- ✓ La coagulopatia può essere non rilevata in quanto i test coagulativi vengono eseguiti a 37°

# COAGULOPATIA

**Il numero di UEC trasfuse nelle prime 12 ore correla in modo lineare con l'insorgenza di MOF**

- 0-5 → 8%
- 5-10 → 20%
- 11-15 → 32%
- 16-20 → 35%
- > 20 → 44%

**Malone DL J Trauma 2003: 898-905**

# COAGULOPATIA

nasce il concetto di **Damage Control Resuscitation**

**che descrive i criteri per la gestione della coagulopatia nei pazienti sottoposti a trasfusioni massive (MT)**

- **Infusione limitata di cristalloidi isotonici**
- **Uso aggressivo di PFC / EC / THAM e/o rFVIIa**

**Damage control resuscitation: directly addressing the early coagulopathy of trauma.**
**Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, Cox ED, Gehrke MJ, Beilman GJ, Schreiber M, Flaherty SF, Grathwohl KW, Spinella PC, Perkins JG, Beekley AC, McMullin NR, Park MS, Gonzalez EA, Wade CE, Dubick MA, Schwab CW, Moore FA, Champion HR, Hoyt DB, Hess JR.**
**J Trauma. 2007 Feb;62(2):307-10**

# Differenza della coagulopatia nel trauma e nella chirurgia elettiva

| | Chirurgia elettiva | Traumatismo |
|---|---|---|
| **Danno tissutale** | Controllato | Massivo ed incontrollato |
| **Inizio della trasfusione** | Tempestivo | Generalmente ritardato |
| **Volemia** | Normovolemia | Frequente shock e/o ipovolemia |
| **Temperatura** | Normotermia (?) | Frequente ipotermia |
| **Monitoraggio coagulazione** | Preventivo e contestuale | Ritardato |
| **Coagulopatia prevalente** | **Da diluizione** | **Da consumo** |

The coagulopathy of massive transfusion- *Hardy et al, Vox Sang, 2005*

# Emergenze emorragiche
## Criteri guida nella scelta dei test

- Lo screening di laboratorio deve basarsi su poche prove eseguibili in tempi brevi
- Il tempo massimo accettabile per l'esecuzione di un pannello di laboratorio completo ed utile per le emergenze non può essere superiore ai 30 minuti
- Tutti i test complicati che richiedono maggiore tempo non sono utili in sede diagnostica e per un primo approccio terapeutico

# Diagnosi della coagulopatia

- Test semplici nella esecuzione ed interpretazione
- Rapidi
- Capaci di discriminare le forme non solo manifeste ma anche quelle “latenti”
- Pannello uguale per tutte le tipologie di ospedale (tale condizione non è riservata solo alle grandi strutture ospedaliere)

# La tromboelastografia può essere di supporto?

# Cos'è la tromboelastografia?

- **Descritta per la prima volta da Hartet nel 1948**
- **Analisi sul sangue intero**
- **Proprietà fisiche del coagulo**
- **Funzionalità emostatica:**

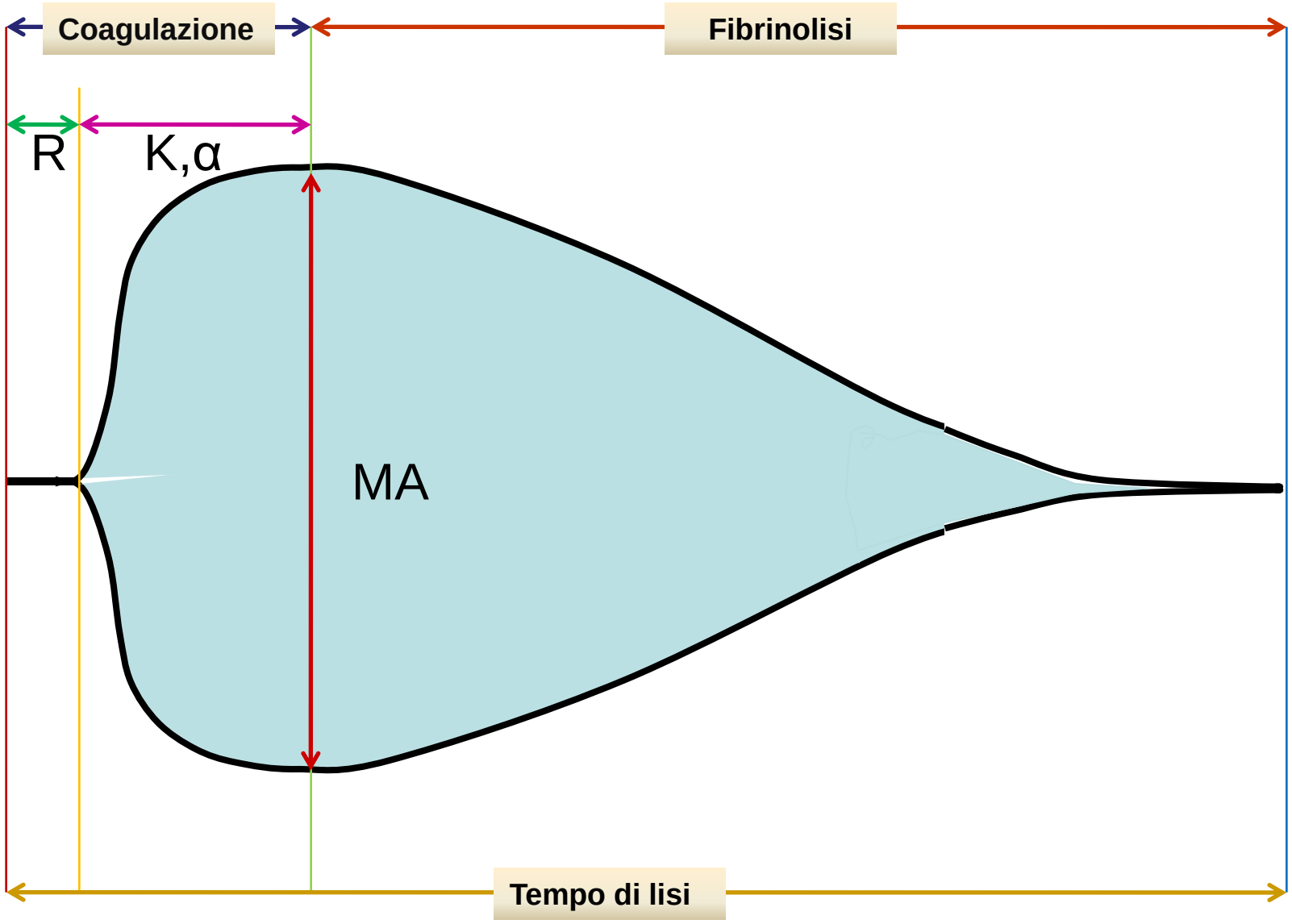
  **Componente cellulare**

  **Componente plasmatica (coagulativa e fibrinolitica)**

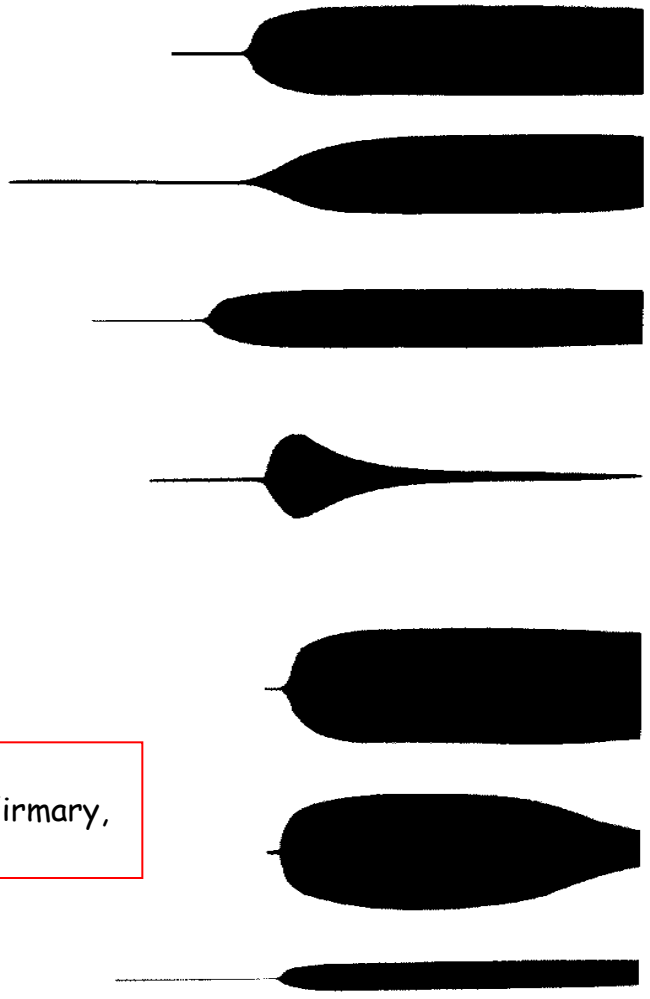
# La tecnologia


Tromboelastografo


ROTEM-Gamma


Coagulazione
Fibrinolisi
R
K,α
MA
Tempo di lisi

# THROMBOELATOGRAPHY
## *Qualitative analysis*



**Normal**
R;K;MA;Angle = Normal

**Anticoagulants/hemophilia**
Factor Deficiency
R;K = Prolonged;
MA;Angle = Decreased

**Platelet Blockers**
Thrombocytopenia/
Thrombocytopathy
R ~ Normal; K = Prolonged;
Angle ~ Normal
MA = Very Decreased

**Fibrinolysis (UK, SK or t-PA)**
Presence of t-PA
R ~ Normal;
MA = Continuous decrease
LY30 > 7.5%;
Ly60 > 15.0%

**Hypercoagubility**
R;K = Decreased;
MA;Angle = Increased

**D.I.C.**
**Stage 1**
Hypercoagulable state with
secondary fibrinolysis

**Stage 2**
Hypocoagulable state

Andrew Ronald
Aberdeen Royal Infirmary,
Aberdeen, UK

# Treatment protocol

| TEG VALUES | CLINICAL CAUSE | TREATMENT (SUGGESTED) |
|---|---|---|
| | factors | X 2 FFP or 8 ml/Kg |
| | rs | X 4 FFP or 16 ml/Kg |
| M | on | X 1 Platelet pool |
| MA l | tion | X 2 Platelet pool |
| LY30 at 7,5% or greaterwith C.I. less than 1,0 | Primary fibrinolysis | Antifibrinolytic (of choice) |
| LY30 at 7,5% or greaterwith C.I. greater than 3,0 | Secondary fibrinolysis | Anticoagulant (of choice) |
| R less than 3 mins, MA greater than 75 mm | Prothrombotic state | Anticoagulant (of choice) |

- measures % decrease in amplitude 30 minutes post-MA
- gives measure of degree fibrinolysis
- normal range
  - < 7.5% (nativ
  - < 7.5% (celite

Coagulation Index: linear combination of 4 parameters: R, K, α, and MA

*Sarah L-Haines (PhD) – University Hospital of south Manchester NHS Foundation Trust*


Haemoscope
Thrombelastograph
Analyzer


1
2
3
4


© Dennis Cox

# TEG Transfusion Algorithms

- Allow early intervention
- Rationalize use of blood component therapy
- Reduce inappropriate transfusion
- More objective clinical therapeutic approach to coagulopathy (avoids “carpet bombing”)
- The right patient gets the right component at the right time

# Le strategie terapeutiche

# Gli Emocomponenti

- **EC**
- **PFC**
- **CP**
- **Crioprecipitato**

# Rationale for massive transfusion protocol

**Aggressive management of injury-associated coagulopathy has been promoted in recent years in massive blood loss. Studies have shown improved survival using higher ratio of FFP to RBC transfusion as compared to the conventional approach. Transfusing fresh whole blood would seem ideal but the time required to conduct safety tests on blood is long enough to cause significant depletion of coagulation factors. Therefore, administering RBCs, coagulation factors and platelets together maintains the physiological constitution of blood and prevents deficits of one or more constituents.**

Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, et al. Massive transfusion protocols: The role of aggressive resuscitation versus product ratio in mortality reduction. J Am Coll Surg. 2009;209:198–205.

# Rationale for massive transfusion protocol

**Massive transfusion protocols are activated by a clinician in response to massive bleeding. Generally this is activated after transfusion of 4-10 units. MTPs have a predefined ratio of RBCs, FFP/cryoprecipitate and platelets units (random donor platelets) in each pack (e.g. 1:1:1 or 2:1:1 ratio) for transfusion. Once the patient is in the protocol, the blood bank ensures rapid and timely delivery of all blood components together to facilitate resuscitation. This reduces dependency on laboratory testing during the acute resuscitation phase and decreases the need for communication between the blood bank, laboratory and physician.**

O'Keeffe T, Refaai M, Tchorz K, Forestner JE, Sarode R. A massive transfusion protocol to decrease blood component use and costs. Arch Surg. 2008;143:686–90.

# Limitations of massive transfusion protocols

1. Not standardised: The trigger for initiating the protocol as well as the optimum ratio of RBC: FFP: Platelets is controversial. Therefore practice varies from centre to centre.
2. Wastage: If MTP is triggered for a nonmassive blood loss situation, it may lead to wastage of blood products.

**Massive transfusion and massive transfusion protocol**
Vijaya Patil and Madhavi Shetmahajan
Indian J Anaesth. 2014 Sep-Oct; 58(5): 590–595.

CMAJ* 2013 Jul 15.

**Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory-results-guided transfusion in patientswith severe trauma: a randomized feasibility trial**

Nascimento B, Callum J, Tien H, Rubenfeld G, Pinto R, Lin Y, Rizoli S.

* Canadian Medical Association Journal

# Scopo dello studio

Controllato randomizzato per valutare la fattibilità del protocollo 1:1:1 e il suo effetto sulla mortalità e le complicanze nei pazienti con trauma grave

Sono stati osservati 78 pazienti ricoverati in un centro traumatologico tra luglio 2009 e ottobre 2011.

Presentavano ipotensione ed emorragie e per i quali si attendeva che avrebbero abbisognato di trasfusione massiva

**40** pazienti sono stati randomizzati verso un protocollo trasfusionale a rapporto **fisso (1:1:1)**

**38** (controllo) sono stati sottoposti ad un regime trasfusionale basato sui valori degli esami di laboratorio.

# Risultati

La mortalità a 28 giorni e il numero di giorni liberi della sindrome da distress respiratorio acuto erano statisticamente simili tra i gruppi .

# Conclusioni

Il protocollo trasfusionale a rapporto fisso è fattibile, ma è stato associato ad un aumento di spreco di plasma. Sono necessari studi più ampi e randomizzati per valutare l'efficacia di un tale protocollo nella cura del trauma .

- Complesso protrombinico

Da preferire il “4 fattori” (II,VII,IX,X+Prot.C e S), indicato nei pazienti in terapia anticoagulante (TAO/NAO)

- Fattore VII attivato

Registrato solo per Emofilici con inibitori, M.di Glanzmann refrattari, Carenza di VII) pertanto il suo impiego sarebbe off label

In altri casi solo esperienze limitate ed aneddotiche

# Il FIBRINOGENO

# Potential value of pharmacological protocols in trauma

Herbert Schöchl, Christoph J. Schlimp, and Wolfgang Voelckel

www.co-anesthesiology.com Volume 26 Number 00 Month 2013

## CONCLUSION

***It remains unclear whether the theragnostic approach can improve outcomes such as morbidity. However, it has been clearly established that coagulation factor concentrates allow rapid and targeted supplementation of procoagulants, and that the administration of fibrinogen concentrate in cases of TIC effectively treats early and critical fibrinogen depletion. Thus, fibrinogen concentrate holds significant advantages in both safety and speed of administration over FFP transfusion for supplementation of fibrinogen. Results from large randomized controlled trials show that early administration of TXA should be an integral step in all trauma resuscitation protocols.***

**It may be that focused restitution of fibrinogen levels with a fibrinogen concentrate is more efficient and efficacious than the use of cryoprecipitate or other blood products. Although it is unlikely that fibrinogen will be a magic bullet, it may be an excellent adjunct to blood component replacement.**

**Is fibrinogen the answer to coagulopathy after massive transfusions?**

Samuel A Tisherman[1]

Crit Care. 2010; 14(3): 154.

Transfusion. 2013 Jan;53 Suppl 1:91S-95S. doi: 10.1111/trf.12041.

**The early use of fibrinogen, prothrombin complex concentrate, and recombinant-activated factor VIIa in massive bleeding.**

Fries D.

**RESULTS:**

Paradigms are actively changing and there is still shortage of data. However, there is increasing experience and evidence that "target controlled algorithms" using point-of-care monitoring devices and coagulation factor concentrates are more effective compared to transfusion of fresh frozen plasma, independently of the individual clinical situation.

**CONCLUSION:**

Future treatment of coagulopathy associated with massive bleeding can be based on an individualized point-of-care guided rational use of coagulation factor concentrates such as fibrinogen, prothrombin complex concentrate, and recombinant factor VIIa. The timely and rational use of coagulation factor concentrates may be more efficacious and safer than ratio-driven use of transfusion packages of allogeneic blood products.

# Fibrinogen dosing recommendations in published algorithms

| Reference | Clinical setting | Trigger for administering fibrinogen concentrate | Fibrinogen dose |
|---|---|---|---|
| 66 | Cardiac surgery | Using conventional laboratory measures: <200 mg/dL (<2 g/L) | 25 mg/kg |
| | | <150 mg/dL (<1.5 g/L) | 50 mg/kg |
| | | Using POC: EXTEM A10 <40 mm and FIBTEM A10 <8 mm | 25 mg/kg |
| | | EXTEM A10 <40 mm and FIBTEM A10 <6 mm | 50 mg/kg |
| | | EXTEM A10 <40 mm and FIBTEM A10 <4 mm | 75 mg/kg |
| | | EXTEM A10 <30 mm and FIBTEM A10 <4 mm | 75 mg/kg + 2 [illegible] g |
| 74 | Trauma | FIBTEM CA10 <7 mm | 2-6 g |
| | | EXTEM CA10 <30 mm | 6-8 g and PCC 20-30 U/kg BW |
| 100 | Liver transplantation | Massive diffuse bleeding and EXTEM MCF <25 mm | Fibrinogen concentrate,* PC and PCC |
| | | EXTEM MCF <35 mm and FIBTEM MCF <8 mm | 25 mg/kg (or cryoprecipitate); 50 mg/kg if FIBTEM MCF <4 mm |
| | | EXTEM MCF <45 mm and FIBTEM MCF <8 mm | 25 mg/kg (or cryoprecipitate); 50 mg/kg if FIBTEM MCF <4 mm |

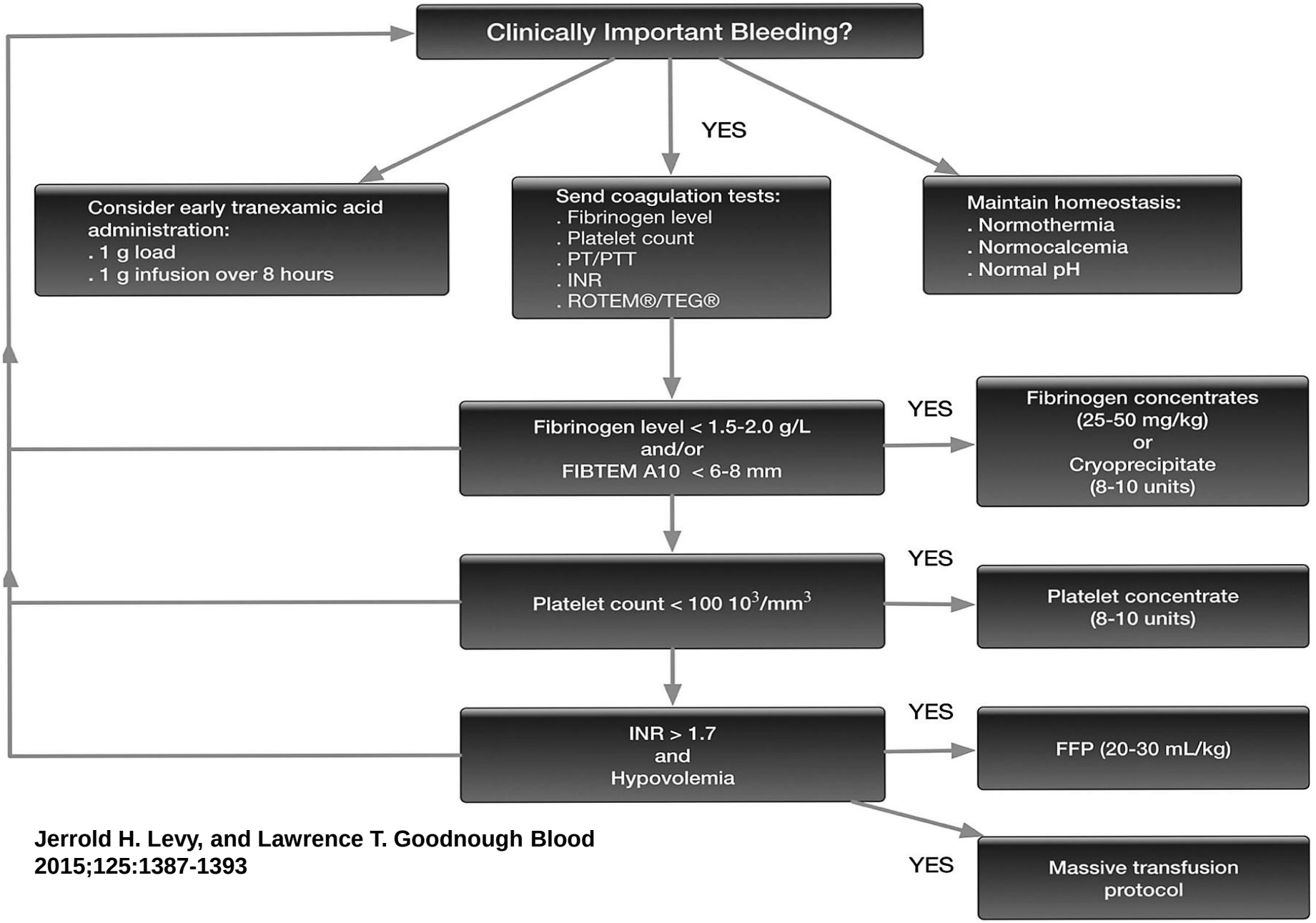
tissue factor-activated clotting test based on ROTEM

clot amplitude on ROTEM after 10 minutes

bodyweight

***How I use fibrinogen replacement therapy in acquired bleeding***
Jerrold H. Levy[1,2] and
Lawrence T. Goodnough[3,4]

# Fibrinogen algorithm




**Jerrold H. Levy, and Lawrence T. Goodnough Blood 2015;125:1387-1393**

**Fibrinogen is a critical hemostatic protein required for both prevention and treatment of bleeding. Fibrinogen levels can best be repleted with either cryoprecipitate (containing fibrinogen, factorVIII, von Willebrand factor, and FXIII) or a commercial fibrinogen concentrate. An increasing number of studies have examined the role of fibrinogen as a therapeutic target, for its use in acquired coagulopathies. Therapy in the bleeding patient should be multimodal to include repletion of other coagulation proteins, antifibrinolytic agents, and blood products including platelets and RBCs as needed.**

**Fibrinogen concentrate represents an important option for treating coagulopathic bleeding, allowing reduction of allogeneic bloodproduct transfusion. Further multicenter studies in a variety of clinical settings are needed to determine optimal dosing strategies and target thresholds for fibrinogen therapy.**

How I use fibrinogen replacement therapy in acquired bleeding

Jerrold H. Levy and Lawrence T. Goodnough (2015)

# Management of bleeding and coagulopathy following major trauma: an updated European guideline

*Critical Care 2013,* ***17:R76***

- *Recommendation 1*

**We recommend that the time elapsed between injury and operation be minimised for patients in need of urgent surgical bleeding control. (Grade 1A)**

- *Recommendation 5*

**We recommend that patients presenting with haemorrhagic shock and an identified source of bleeding undergo an immediate bleeding control procedure unless initial resuscitation measures are successful. (Grade 1B)**

- *Recommendation 10*

**We do not recommend the use of single Hct measurements as an isolated laboratory marker for bleeding. (Grade 1B)**

- *Recommendation 14*

**We recommend that fluid therapy be initiated in the hypotensive bleeding trauma patient. (Grade 1A)**

**We recommend that crystalloids be applied initially to treat the hypotensive bleeding trauma patient. (Grade 1B)**

**We recommend that hypotonic solutions such as Ringer's lactate be avoided in patients with severe head trauma. (Grade 1C)**

**If colloids are administered, we recommend use within the prescribed limits for each solution. (Grade 1B)**

**We suggest that hypertonic solutions during initial treatment be used, but demonstrate no advantage compared to crystalloids or colloids in blunt trauma and TBI. (Grade 2B)**

**We suggest the use of hypertonic solutions in hemodynamically unstable patients with penetrating torso trauma. (Grade 2C)**

- *Recommendation 16*

**We recommend early application of measures to reduce heat loss and warm the hypothermic patient in order to achieve and maintain normothermia. (Grade 1C)**

**We suggest that hypothermia at 33-35ºC for ≥48 h be applied in patients with TBI once bleeding from other sources has been controlled. (Grade 2C)**

- *Recommendation 17*

**We recommend a target haemoglobin (Hb) of 7 to 9 g/dl. (Grade 1C)**

- *Recommendation 23*

**We recommend that monitoring and measures to support coagulation be initiated as early as possible. (Grade 1C)**

- ***Recommendation 24***

**We recommend that tranexamic acid be administered as early as possible to the trauma patient who is bleeding or at risk of significant haemorrhage at a loading dose of 1 g infused over 10 min, followed by an intravenous infusion of 1 g over 8 h. (Grade 1A)**

**We recommend that tranexamic acid be administered to the bleeding trauma patient within 3 h after injury. (Grade 1B)**

**We suggest that protocols for the management of bleeding patients consider administration of the first dose of tranexamic acid en route to the hospital. (Grade 2C)**

*Recommendation 26*

- **We recommend the initial administration of plasma [fresh frozen plasma (FFP) or pathogen-inactivated plasma] (Grade 1B) or fibrinogen (Grade 1C) in patients with massive bleeding. If further plasma is administered, we suggest an optimal plasma:red blood cell ratio of at least 1:2. (Grade 2C)**
- **We recommend that plasma transfusion be avoided in patients without substantial bleeding. (Grade 1B)**

*Recommendation 27*

- **We recommend treatment with fibrinogen concentrate or cryoprecipitate in the continuing management of the patient if significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5-2.0 g/l. (Grade 1C)**
- **We suggest an initial fibrinogen concentrate dose of 3-4 g or 50 mg/kg of cryoprecipitate, which is approximately equivalent to 15-20 singe donor units in a 70 kg adult. Repeat doses may be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels. (Grade 2C)**

*Recommendation 28*

- **We recommend that platelets be administered to maintain a platelet count above 50 × 109/l. (Grade 1C)**
- **We suggest maintenance of a platelet count above 100 × 109/l in patients with ongoing bleeding and/or TBI. (Grade 2C)**
- **We suggest an initial dose of 4-8 single platelet units or one aphaeresis pack. (Grade 2C)**

*Recommendation 31*

- **We recommend the early use of prothrombin complex concentrate (PCC) for the emergency reversal of vitamin K-dependent oral anticoagulants. (Grade 1B)**
- **If a concentrate-based goal-directed strategy is applied, we suggest that PCC be administered in the bleeding patient with thromboelastometric evidence of delayed coagulation initiation. (Grade 2C)**

*Recommendation 32*

- **We suggest the measurement of substrate-specific anti-factor Xa activity in patients treated or suspected of being treated with oral anti-factor Xa agents such as rivaroxaban, apixaban or edoxaban. (Grade 2C)**
- **If bleeding is life-threatening, we suggest reversal of rivaroxaban, apixaban and endoxaban with high-dose (25-50 U/kg) PCC. (Grade 2C)**
- **We do not suggest the administration of PCC in patients treated or suspected of being treated with oral direct thrombin inhibitors such as dabigatran. (Grade 2B)**

*Recommendation 33*

- **We suggest that the use of recombinant activated coagulation factor VII (rFVIIa) be considered if major bleeding and traumatic coagulopathy persist despite standard attempts to control bleeding and best-practice use of conventional haemostatic measures. (Grade 2C)**
- **We do not suggest the use of rFVIIa in patients with intracerebral haemorrhage caused by isolated head trauma. (Grade 2C)**

CHIRURGO ANESTESISTA TRASFUSIONISTA