ESTA PALESTRA NÃO PODERÁ SER REPRODUZIDA SEM A REFERÊNCIA DO AUTOR.

Atualizações em Coagulopatias

II Pós ASH/TANDEM/EBMT
XIV Jornada Cearense de Hematologia e Hemoterapia
7 a 10 de maio de 2014 - HEMOCE
Fortaleza-CE

Lindemberg da Costa Lima

II Pós ASH/TANDEM/EBMT
XIV Jornada Cearense de Hematologia e Hemoterapia
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Fortaleza-CE

DECLARAÇÃO DO POTENCIAL CONFLITO DE INTERESSE

- Palestrante: **Lindemberg da Costa Lima**
- Apresentação: **Atualização em Coagulopatias**

NENHUM CONFLITO DE INTERESSE

15/05/2014 11:59 Lindemberg da Costa Lima

Relevância médica

From: web, domínio público

"Disruptive innovation [1] is a powerful thing. In the midst of the Digital Revolution, analyst Clayton Christensen coined the term to describe the way businesses could have far-reaching, seismic effects on customers by employing emerging technologies. Just as email effectively killed the hand-stamped letter, the mobile device has changed the way we do everything from reading books to watching sports."

WFH President Alain Weill

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Relevância médica

The ASH Choosing Wisely® campaing: five hematologic tests and treatments to question.

Hematology Am Soc Hematol Edu Program, 2013;2013: 09-13

Choosing Wisely® is a medical stewardship and quality improvement initiative led by the American Board of Internal Medicine Foundation in collaboration with leading medical societies in the United States. The ASH is an active participant in the Choosing Wisely® project. Using an iterative process and an evidence-based method, ASH has identified 5 tests and treatments that in some circumstances are not well supported by evidence and which in certain cases involve a risk of adverse events and financial costs with low likelihood of benefit. The ASH Choosing Wisely® recommendations focus on avoiding liberal RBC transfusion, avoiding thrombophilia testing in adults in the setting of transient major thrombosis risk factors, avoiding inferior vena cava filter usage except in specified circumstances, avoiding the use of plasma or prothrombin complex concentrate in the nonemergent reversal of vitamin K antagonists, and limiting routine computed tomography surveillance after curative-intent treatment of non-Hodgkin lymphoma. We recommend that clinicians carefully consider anticipated benefits of the identified tests and treatments before performi

-***"impedir a política transfusional liberal para CH***
-impedir testes para trombofilia em adultos em situação transitória de risco para Trombose
-impedir uso de filtro de veia cava inferior, exceto em situações bem específicas
-impedir o uso de PFC e de Conc. Protrombínico na reversão não-emergencial de anti-Vit K
-limitar o uso rotineiro da TC na vigilância após tto (curative-intended) de Linfoma não-Hodgkin"

15/05/2014 11:59 Lindemberg da Costa Lima

WORLD THROMBOSIS DAY: IT'S HAPPENING!

Relevância médica

We are happy to announce that after years of planning, the ISTH will spearhead the launch of World Thrombosis Day in 2014. Our goal is not a one-time observance, but an annual event that brings together organizations and leaders passionately dedicated to reducing the terrible disease burden caused by thrombosis.

World Thrombosis Day will be observed annually on October 13 –

Rudolf Virchow's birthday- and the ISTH will be working with national and international thrombosis organizations, health advocates and partners in all corners of the world to foster public and professional educational activities to heighten awareness, spark action and ultimately save lives.

The need for World Thrombosis Day is clear: There is little public awareness of thrombosis as the common underlying mechanism of the three leading causes of cardiovascular death - heart attack, stroke, and venous thromboembolism (VTE). And in many locales health care professionals may not be doing all they should to correctly diagnose it, prevent it and appropriately treat patients.

13 de outubro – Dia Mundial da Trombose

https://www.isth.org/?WTD

isth

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Relevância médica

Congress on Controversies in Thrombosis and Hemostasis (CiTH) Berlin, Germany - October 30 - November 1, 2014

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Relevância médica

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Atualização em Coagulopatias

- Hemofilia

- TIC/Coagulopatia Trauma-induzida

- Trombose associada ao câncer

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Special Issue: Abstracts of the 7th Annual Congress of the European Association for Haemophilia and Allied Disorders, 26–28 February 2014, Brussels, Belgium

Haemophilia (2014), 20 (Suppl. 4), 1–3

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What will this new era hold? Some analysts see longer acting products that will alter and confront accepted methods of treatment; a potential redistribution of the existing products because of lower prices of recombinants, driven by companies having to look for new markets, with a related potential for surplus; and new players who will challenge the incumbents as they bring gene-transfer therapies and treatments to trial and begin to market them [2].

A message from WFH President Alain Weill: Broad perspectives for a new era

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GOLD STANDARD OF CARE

In the past, the care of patients with hemophilia A was managed by the treatment of bleeds "on demand," but today the gold standard of care is primary prophylaxis

.[1,2] Primary prophylaxis is defined as continuous treatment started after the first joint bleed and before the age of 2 years or started before the age of 2 years in the absence of clinically evident joint bleeds. On-demand therapy is defined as treatment given when bleeding occurs. Episodic prophylaxis is defined as using factor replacement prior to an activity perceived likely to cause a bleed.

Primary prophylaxis injections are given 1-4 times per week, and many treaters aim to maintain factor levels above 1% to ensure bleed prevention.

[6] The goals of prophylactic care are to titrate FVIII to blood levels sufficient to prevent spontaneous bleeding as well as retain normal coagulation function after a trauma or accident.[2]

Tiede A, et al; Opar A. Coyle T and Goodman M.(2014)

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Numerous trials have demonstrated the benefits of prophylaxis in patients with hemophilia, including 2 randomized controlled trials, the Joint Outcomes Study (JOS) and the ESPRIT trial. The JOS was conducted in the United States and randomly assigned 65 young boys younger than 30 months with severe hemophilia A to regular infusions of rFVIII or to episodic treatment.[5] The primary endpoint in the study was incidence of bone or cartilage damage detected in ankles, knees, and elbows by radiography or MRI. At 6 years of age, 93% of those receiving prophylaxis had normal joint structure compared with only 55% of children receiving on-demand treatment ($P = .006$).
The Italian ESPRIT trial enrolled 45 children aged 1-7 years with severe hemophilia A and randomly assigned them to rFVIII (Recombinate® or Advate®) given as prophylaxis 3 times per week or on demand as needed until the bleeding completely resolved.[19] Children on prophylaxis had significantly fewer hemarthroses (0.20 vs 0.52 events per patient per month, $P < .02$) and fewer radiologic signs of arthropathy (29% vs 74%, $P < .05$).

This US study is one of many to show social benefits of bleed prevention. In a study involving 21 international hemophilia centers, patients who received prophylaxis had lower rates of absenteeism from work and school and also spent fewer days in the hospital.

[21] The impact of increased absenteeism and lesser academic achievement on the future social and economic development of children will almost undoubtedly be negative. In a study, which involved 84 adolescents and adults with hemophilia, prophylaxis reduced the average annual number of total bleeds (35.8 vs 4.2, $P < .01$), joint bleeds (32.4 vs 3.3, $P < .01$), and days lost from work and school (34.6 vs 3.0, $P < .01$).[22]

Tiede A, et al; Opar A. Coyle T and Goodman M.(2014)

INHIBITOR DEVELOPMENT

Approximately 15%-20% of children with hemophilia A and 30% of children with severe hemophilia A generate inhibitors, or antibodies, against therapeutically administered FVIII.

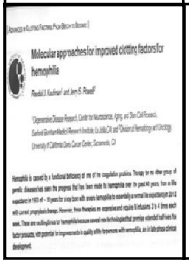
[2,29] Typically, patients develop inhibitors within the first 10-50 days of starting a treatment.

The presence of inhibitors markedly reduces the effectiveness of FVIII replacements, and patients with inhibitor titers more than 5 Bethesda units/mL will require bypassing agents.[44]

Tiede A, et al; Opar A. Coyle T and Goodman M.(2014)

Hematology Am Soc Hematol Edu Program, 2013;2013: 30-36

- **-Molecular approaches for improved clotting factors for hemophilia**


Molecular approaches for improved clotting factors for hemophilia

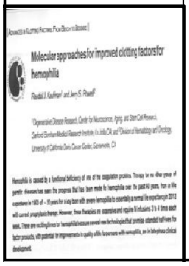
Novos produtos para suporte ao cuidado do Hemofiico:

- **Melhorar os parâmetros farmacocinéticos dos Fatores VIII, IX e VII: ↗ $T_{1/2}$ e ↙ clearence**

> eficiência terapêutica
< riscos adversos: formação de inibidor
otimizar relação custo-benefício
redistribuição equânime dos produtos no mundo

Hematology Am Soc Hematol Edu Program, 2013;2013: 30-36

-Molecular approaches for improved clotting factors for hemophilia


Molecular approaches for improved clotting factors for hemophilia

Novos produtos para suporte ao cuidado do Hemofiico:

- Melhorar os parâmetros farmacocinéticos dos Fatores VIII, IX e VII: ↗ $T_{1/2}$ e ↙ clearence

Técnicas de Biotecnologia

- **-PEGylation**
- **-Fusion protein**
- **-Novel FVIII molecules**
- **-Factor Xase complex mimetics**
- **-Inibition of antithrombotic pathways**
- **-Targeting antithrombin**

Powell, JS et al.Hematology Am Soc Hematol Edu Program, 2013;2013: 30-36

Protein	Name	Modification	Clinical status*	Reference(s)
Protein replacement strategies				
FVIII	wt FVIII	Pegylated liposomes	No increase in $T_{1/2}$; phase 3 completed	17, 18, 55
	N9-GP	Single 40 kDa PEG attached to 21 amino acid B-domain	Well-tolerated; in phase 3	31
	BAX855	~ 2 mol PEG/full-length FVIII	~ 1.5× increased $T_{1/2}$; in phase 1	29
	BAY94-9027	60 kDa PEG attached to single site in A3-domain	In phase 3	24, 38
	rFVIII-Fc	Fc/g fusion to rFVIII	~ 1.5-2× increased $T_{1/2}$; phase 3 completed	38, 56
	scFVIII	Single chain FVIII	~ 1.14× increased $T_{1/2}$	41
	rhFVIIIh-d	rFVIII manufactured in a human cell line	In clinical trials	44, 45
FIX	N9-GP	40 kDa PEG attached to activation peptide	5× increased $T_{1/2}$; phase 3 completed	33, 57
	Fc-FIX	Fc/g fusion protein to FIX	~ 3-4× increased $T_{1/2}$; phase 3 finished	37
	rFIX-FP	rFIX fusion to albumin	~ 5× increased $T_{1/2}$; in phase 3	39, 40
Bypassing strategies				
FVIIa	N7-GP	40 kDa attached to 1 glycan	Characterization stopped due to lack of effect	32
	rFVIIa-FP	hFVIIa fusion to albumin	~ 5× increased $T_{1/2}$ in clinical trials	38, 58
mAb	NB629 Xase mimetic	Bispecific mAb binds FIXa and FX	Preclinical	47
TFPI	mAb 2012	mAb binds TFPI kringle 2 to inhibit	Preclinical	48
	BAX499	Nucleic acid aptamer to inhibit TFPI	Characterization stopped	49
	BAX513	Sulfated polysaccharide	Characterization stopped	50
AT	ALN-AT3	siRNA targeting antithrombin 3	Preclinical	54

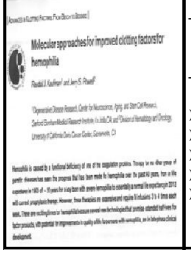
*Clinical status can be found at www.clinicaltrials.gov.

Impact of Bioengineering Strategies on rFVIII Half-Life

FVIII Therapy	Technology	Half-life
Octocog alfa (Advate®)	rFVIII processed without any blood-based additives	12 hours
Turoctocog alfa	rFVIII with truncated B-domain	12 hours
N8-GP	PEGylated turoctocog alfa converted to turoctocog alfa by thrombin at site of injury	19 hours
BIIB-031	rFVIII Fc fusion protein	19 hours
BAY-94-9027	PEGylated rFVIII	19 hours
CSL-627	Single-chain rFVIII	15 hours
BAX855	Full-length PEGylated rFVIII	18 hours

Tiede A, et al; Opar A. Coyle T and Goodman M.(2014)

Hematology Am Soc Hematol Edu Program, 2013;2013: 30-36


Molecular approaches for improved clotting factors for hemophilia

-Molecular approaches for improved clotting factors for hemophilia

Novos produtos para suporte ao cuidado do Hemofíico:

- Melhoram os parâmetros farmacocinéticos dos Fatores VIII, IX e VII: ↗ $T_{1/2}$ e ↙ clearence
- Promovem profilaxia primária mais eficiente:
  - **Maior aderência**
  - **Menor formação de inibidores**
  - **Menor hospitalização**
  - **Menor absentismo escolar/profissional**
  - **Melhor qualidade de vida**

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Pati, S et al.Hematology Am Soc Hematol Edu Program, 2013; 2013: 656/59

- **Optimal trauma resuscitation with plasma as the primary resuscittive fluid: the surgeon's perspective**

Trauma – principal causa de morte: 1 – 44a (USA)
> HIV-AIDS+Tuberculosis+Malária(Mundo)

Teoria do Grilo:

Tailândia: alimento
China – "bicho de estimação"
Brasil/USA – praga

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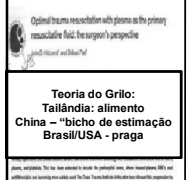

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- **Optimal trauma resuscitation with plasma as the primary resuscittive fluid: the surgeon's perspective**

-**I Guerra Mundial –** *uso de sangue diminui a mortalidade*

-**1979**(Counts,RB) **-** Não usar sangue/PFC: uso de cristalóide

Textbook Blood Transfusion in Clinical Medicine(2005):
"PFC não deve ser usado como expansor de volume"

-**Guerras recentes**-uso do PFC:CP:CH - (USA)
uso de hemoderivados:CH:CP (Europa)

Racional: politraumatizado grave, *endoteliopata*, súbito, por hipovolemia, hipoperfusão, hopoxemia e coagulopatia!

Counts RB et al. – Ann Surg. 1979;190(1):91-99
Borgman, MA et al–J Trauma,2007:63(4):805/13
Holcomb, JB et al - J Trauma,2007:62(2):307/10
Doran, CM et al - J Trauma,2010:69(2 Suppl):S64/8
Weiskopof,RB et al-Transfusion.2013:53(Suppl 1):1S-5S

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Teoria do Grilo
Tailândia - alimento
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Brasil/USA - praga

- **Optimal trauma resuscitation with plasma as the primary resuscittive fluid: the surgeon's perspective**

Tríade Letal:

Acidose

Coagulopatia Hipotermia

Racional: politraumatizado grave, *endoteliopata*, súbito, por hipovolemia, hipoperfusão, hipoxemia e coagulopatia!

Counts RB et al. – Ann Surg. 1979;190(1):91-99
Borgman, MA et al–J Trauma,2007:63(4):805/13
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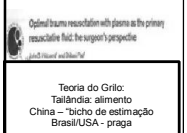
Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon's perspective

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Novos conceitos/novas práticas?:
(inovacção disruptiva)

-Endoteliopatia doTrauma – Vasopermeabilidade hipoxêmica

-Injúria Pulmonar Associada ao Cristalóide

-Reanimação Hemostática: hiperfibrinólise(CRASH-2)

-Reanimação Hemostática Tromboelastometria-guiada

-Cirurgia do Controle do Dano

-Reanimação Hipotensiva Permissiva

-Reanimação Hemostática Fármaco e Hemoderivados-induzida

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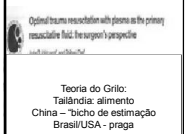
Pati, S et al.Hematology Am Soc Hematol Edu Program, 2013; 2013: 656/59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Special Issue: The THOR Network 2012 Remote Damage Control Resuscitation Symposium January 2013 - Transfusion
Volume 53, Issue Supplement S1 Pages 1S–149S
(Simpósio – Junho/2012 Bergen/Norway)

Estudos:

CRASH II e III
MATTER
PATCH
PROMMTT
PROPPR/Instituto do Trauma do Texas, Houston
(www.clinicltrials.gov identifier NCT01545232)

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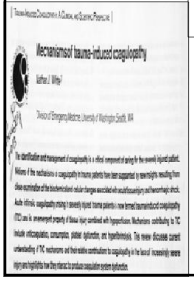
White, N.Hematology Am Soc Hematol Edu Program, 2013; 2013: 660/63


Mechanisms of trauma-induced coagulopathy

Mechanisms of Trauma-induced Coagulopathy

…"A coagulopatia aguda, […] do paciente politraumatizado,grave, agora denominada Coagulopatia Trauma-induzida(TIC),é um emergente estado clínico típico da lesão tecidual, combinada com hipoperfusão, consequência de uma complexa interação da coagulação com a inflamação e com a disfunção de células (endotélio, plaquetas e leucócitos)."

Mecanismos patofisiológicos:

1 – Anticoagulação

2 – Disfunção plaquetária

3 – Consumo de fibrinogênio e fibrinólise

4 - Choque hipovolêmico hemorrágico

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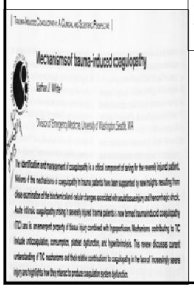
Mechanisms of Trauma-induced Coagulopathy

White, N.Hematology Am Soc Hematol Edu Program, 2013; 2013: 660/63

Mecanismos fisiopatogênicos:

1 – **Anticoagulação**
2 – Disfunção plaquetária
3 – Consumo de fibrinogênio e fibrinólise
4 - Choque hipovolêmico hemorrágico



Anticoagulação – INR/TTPA ↗ pré-reanimação:

Sistema Trombina-Trombomodulina-PCa ↗ ↗
Redução de atividade de Fator V e Fator VIII
Autoheparinização (glicocálix endotelial)
PDF/d-dímero ↗ - Hiperfibrinólise

-Brohi K et al. Acute traumatic coagulopathy . *J Trauma*. 2003;54(6):1127/30
-Gando, S. et al.*J Trauma*. 2009;67(2):381/383
-Ostrowski,SR et al.*J Trauma Acute Care Surg*. 2012;73(1):60-66

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Mecanismos fisiopatogênicos:

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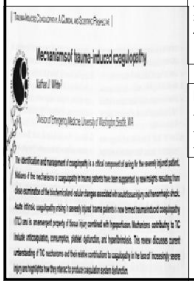

Disfunção plaquetária – *hipoagregação c/n Plt normal*
-Hipoagregante (ADP, Ác. Aracdônico, Colágeno…)
-Receptor Plaqueta P2T- > influxo de cálcio, inibe $P2T_{AdenylCiclase}$
-Inibição de múltiplos receptores Plt & Alteração do fluxo de Ca

-Solomon,C. et al. Platelet function following trauma[…] *J Thromb Haemost*. 2011;106(2):322-330
-Wohlauer, MV. et al.*J Am Coll Surg*. 2012;214(5):739-746
-Stansburyet al. *Transfusion*. 2013;53(4):783-789
-Kutcher, ME et al. *J Trauma Acute Care Surg*. 2012;73(1):13-19

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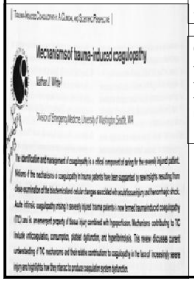

Consumo de fibrinogênio e fibrinólise – hiperfibrinólise
-hipofibrinogenemia tPA/plasmino-induzida
-ROTEM c/hipofibrinogenemia ∞ mortalidade
-↗ tPA, >d-dímero, complexo antiplasmina/plasmina, …
-↘PAI-1 induzido pelo sistema TBM/Proteína C ativada
+ elastase neutrofílica

-Rourke, C et al.Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost*. 2012;10(7):1342-1351
Raza I, et al. The incidence and magnitude of fibrinolitic activation in trauma patients. *J Thromb Haemost*. 2013;11(2):307-314
-Stansburyet al. *Transfusion*. 2013;53(4):783-789
-Levrat, A et al. Evaluation of tromboelastography for the diagnosis of hyperfibrinolysis in trauma patients. *Br J Anaesth*. 2008;100(6):792-797

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Mechanisms of Trauma-induced Coagulopathy

" ***Modern and future transfusion strategies are based on online bedside coagulation monitoring […]*** "

Theusinger

Mechanisms of Trauma-induced Coagulopathy

Advantages of Rotem in Trauma

Transfusion in trauma: why and how should we change our current practice?

O.M. Theusinger, D.R Spahn and M.T. Ganter

Institute of Anesthesiology, University Hospital and University of Zurich, Zurich, Switzerland

Current Opinion in Anaesthesiology 2009,22:305–312

Mechanisms of Trauma-induced Coagulopathy

Trauma, Hemorrhage, Mortality

Theusinger

"Hemorrhage is known to be a major cause of early death after injury and has been shown to be responsible for 30–40% of trauma mortalities." [1–3].

"Furthermore, hemorrhage with consecutive multiple transfusions has been shown to significantly worsen clinical outcomes" [4,5].

Mechanisms of Trauma-induced Coagulopathy

Transfusion in trauma: why and how should we change our current practice?
O.M. Theusinger, D.R Spahn and M.T. Ganter

"Traditionally, acute traumatic coagulopathy has been thought to be due to consumption of coagulation factors, dilution from intravenous fluid therapy, hypothermia and metabolic acidosis."

"It has recently been shown, however, that none of these factors is initially responsible for the acute traumatic coagulopathy. These factors become significant only in the later phase of traumatic coagulopathy." [Brohi,12, 13]

Mechanisms of Trauma-induced Coagulopathy

Referenced in Theursinger

12 Brohi K, Cohen MJ, Ganter MT, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma 2008; 64:1211–1217.

This study confirms that acute coagulopathy of trauma is associated with systemic hypoperfusion and is characterized by anticoagulation and hyperfibrinolysis. Thrombin binding to thrombomodulin activates protein C thereby inhibiting factor Va/VIIIa and consuming PAI-1 (derepression of fibrinolysis).

13 Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care 2007; 13:680–685.

The pathogenesis and problems of acute trauma bleeding including transfusion requirements, organ dysfunction and mortality are reviewed. Early treatment and recognition of coagulopathy has implications for the care of shocked patients and the management of massive transfusion.

Mechanisms of Trauma-induced Coagulopathy

Transfusion in trauma: why and how should we change our current practice?
O.M. Theusinger, D.R Spahn and M.T. Ganter

Studies by Brohi et al. [11–14] have described an early and previously unknown acute traumatic coagulopathy before any of the above-mentioned traditional causes of traumatic coagulopathy were present. It has been shown that tissue injury and hypoperfusion followed by the activation of the anticoagulation thrombomodulin protein C pathway plays the central role in the pathogenesis of acute traumatic coagulopathy. As a result of overt activation of protein C, acute traumatic coagulopathy is characterized by coagulopathy in conjunction with hyperfibrinolysis

Mechanisms of Trauma-induced Coagulopathy

Referenced in Thuersinger

11Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007; 245:812–818.

This study shows for the first time that tissue injury and hypoperfusion followed by the activation of the anticoagulation thrombomodulin protein C pathway plays the central role in the pathogenesis of acute traumatic coagulopathy.

14 Cohen MJ, Brohi K, Ganter MT, et al. Early coagulopathy after traumatic brain injury/TBI: the role of hypoperfusion and the protein C pathway. J Trauma 2007; 63:1254–1261.

The study shows that TBI alone does not cause early coagulopathy, but must be coupled with hypoperfusion to lead to coagulation derangements, associated with the activation of the protein C pathway. This finding has implications for the treatment of coagulopathy after severe TBI.

Mechanisms of Trauma-induced Coagulopathy

Trauma – aPC Clinically Significant

Theusinger

"The activation of the thrombomodulin protein C pathway has clinical significance;

high thrombomodulin and low protein C plasma levels were associated with increased mortality, blood transfusion requirements, acute renal injury, and reduced ventilator-free days early after trauma"
[11–14].

Mechanisms of Trauma-induced Coagulopathy

Prothrombin Complex Concentrate - Theusinger

"Bruce and Nokes [66]
recently demonstrated that the use of PCCs in trauma patients leads to a considerable reduction in the
use of blood products (FFP, RBCs and cryoprecipitate) and that survival improved and bleeding stopped earlier."

"Therefore, PCCs might have a place in control of trauma related bleeding, although this indication is currently off label."

Mechanisms of Trauma-induced Coagulopathy

Referenced in Theusinger

66 **Bruce D, Nokes TJ. Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: experience in a large tertiary hospital. Crit Care 2008; 12:R105.**

This study emphasizes the value of PCC in reversing the effects of oral anticoagulant therapy in bleeding patients.

It also demonstrates the potential value of PCC in controlling the bleeding in patients undergoing cardiac and other surgical procedures.

Mechanisms of Trauma-induced Coagulopathy

Algorithms – reduce blood products

"algorithm incorporates information obtained from the patient's history, clinical presentation and routine coagulation laboratory and bedside viscoelastic coagulation tests."

"in the first 6 months after implementation of the algorithm, the use of FFP dropped by approximately 50% and RBCs as well as platelet administration decreased by approximately20% each."

Mechanisms of Trauma-induced Coagulopathy

Conclusion - Theusinger

"Modern and future transfusion strategies are based on online bedside coagulation monitoring with specific goal-directed administration of antifibrinolytics, coagulation factors, RBCs, FFP and platelets to optimize coagulation early.

This improves the patient's outcome, minimizes the patient's exposure to blood products and reduces costs."

Mechanisms of Trauma-induced Coagulopathy

Purpose of Review: **"New insights TIC - POC devices – New concepts Managing Massive Blood Loss"**

Time for changing coagulation management in trauma-related massive bleeding

Dietmar Fries[a], Petra Innerhofer[b] and Wolfgang Schobersberger[c]

Current Opinion in Anaesthesiology 2009, 22:267–274

Department of General and Surgical Critical Care Medicine, Innsbruck Medical University, Department of Anaesthesiology and Critical Care Medicine, Medical University Innsbruck and cInstitute for Sports Medicine, Alpine Medicine and Health Tourism (ISAG), Innsbruck and Hall, Innsbruck, Austria

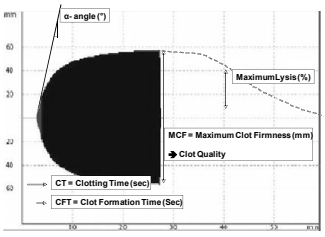
Mechanisms of Trauma-induced Coagulopathy

Recent Findings

- **Trauma – aPC Pathway leads to Fibrinolytic Potential**
- **Widespread use of Viscoelastic devices, (Rotem) highlights importance of Fibrinogen contribution to Clot Firmness**
- **Clot Firmness a precondition to cessation of bleeding**
- **Growing evidence – Targeted therapy, coagulation factor concentrates, guided by Viscoelastic measurements, (Rotem)**
- **Enables effective correction of Severe Coagulopathy**

Mechanisms of Trauma-induced Coagulopathy

Thromboelastometry:



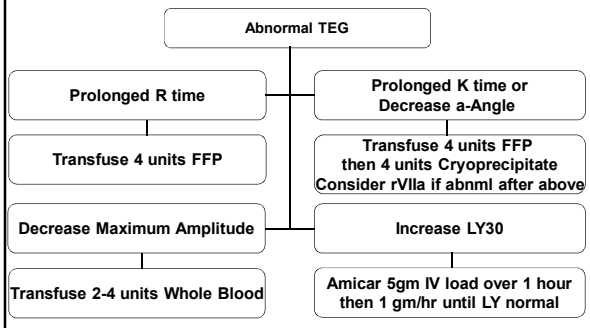
- Based on whole blood analysis
- Typical reaction curves
- Numerical data for many phases of hemostasis
- Abnormal results clearly indicated
- Clot firmness = Quality of clot
- +/-15 minutes
- POC/Point Of Care Device

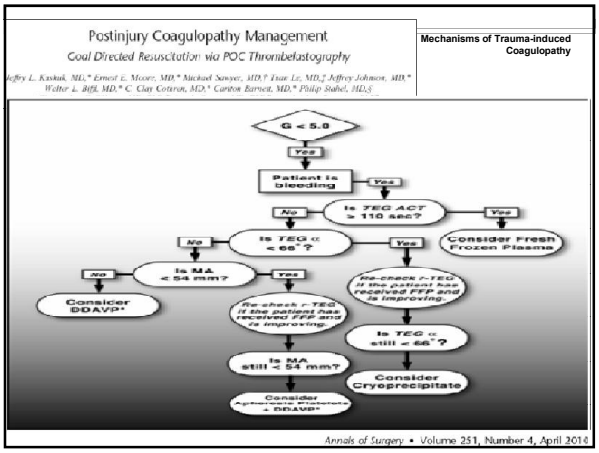
Summary

Tromboelastometria no Tauma

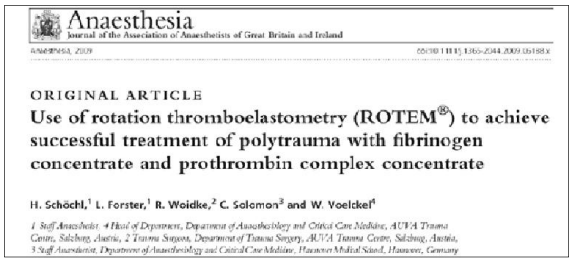
- Hemorrhage is the enemy (early)
- Hypercoagulability is the enemy (late)
- Diagnosis: time consuming and confusing
- ROTEM Delta and TEG
- "Whole blood coagulation measurement"
- Fast
- One test
- Easily repeatable
- It's what you want-clot measurement

Guideline for Blood Product Use





Mechanisms of Trauma-induced Coagulopathy



Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

ORIGINAL ARTICLE

Use of rotation thromboelastometry (ROTEM®) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate

H. Schöchl,[1] L. Forster,[1] R. Woidke,[2] C. Solomon[3] and W. Voelckel[4]

1 Staff Anaesthetist 4 Head of Department, Department of Anaesthesiology and Critical Care Medicine, AUVA Trauma Centre, Salzburg, Austria, 2 Trauma Surgeon, Department of Trauma Surgery, AUVA Trauma Centre, Salzburg, Austria, 3 Staff Anaesthetist, Department of Anaesthesiology and Critical Care Medicine, Hannover Medical School, Hannover, Germany

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Mechanisms of Trauma-induced Coagulopathy

CRASH - 2

The Lancet, Volume 376, Issue 9734, Pages 23 - 32, 3 July 2010
Dewan Y1, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H; CRASH-3 Collaborators.

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

Ácido Traexâmico 1g, EV, *in bolus*, na admissão
e 1g de 8/8 horas, dose de manutenção.

Interpretation
Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

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Mechanisms of Trauma-induced Coagulopathy

CRASH-3

Trials. 2012 Jun 21;13:87. doi: 10.1186/1745-6215-13-87.

CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial.
Dewan Y1, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H; CRASH-3 Collaborators.

Ácido Traexâmico 1g, EV, *in bolus*, na admissão
e 1g de 8/8 horas, dose de manutenção.

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Mechanisms of Trauma-induced Coagulopathy

CRASH-2

Críticas:

Mark Walsh MD 1,2 and Braxton Fritz BS 1,2
1:Memorial Hospital of South Bend, South Bend, IN 46601 2:Indiana University School of Medicine Sou
the University of Notre Dame campus, South Bend, IN 46617

-CRASH-2 trial has several limitation, mainly based upon the lack of a defined requirement for the use of TXA (no bleeding) and the small sample size of truly sick (hypotensive, shock-y) patients
-CRASH-2 also does not adequately show a clinically significant outcome: no transfusion reduction, no clinically relevant mortality benefit (i.e. 0.8% absolute reduction in "death caused by bleeding"….)
-The MATTERS showed: 1) A true benefit for the use of TXA (NNT was 1:7 in the MATTERs trial while the NNT was 1:67 in the CRASH-2 trial); 2) a relative reduction in mortality of 6.7 %; and 3) a HIGHER risk for thromboembolic events!! (something strangely missing from the CRASH-2 trial…..)
-The PATCH trial should be able to bridge the gap btw the CRASH-2 limitations and the use in the general trauma population (unlike MATTERS trial and military use)
-TEG/ROTEM may not be the best at detecting fibrinolysis, but it is certainly the best we have!
-It is better to question literature instead of taking a "government funded, highly publicized" study for absolute truth (lessons from NASCIS advocating methylprednisolone for spinal cord injuries)

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Mechanisms of Trauma-induced Coagulopathy

MATTERs

Ácido Traexâmico 1g, EV, *in bolus*, na admissão
e 1g de 8/8 horas, *dose de manutenção*.

The more applicable and useful study is the **Military Application Of Tranexamic Acid for Trauma Emergency Resuscitation study (MATTERs)** (3,4) which evaluated those patients who clearly needed an anti-fibrinolytic. In this study those military trauma patients who needed at least a unit of blood were divided into TXA or no TXA arms. Unlike the subtle CRASH-2 benefit, the MATTERs results were striking. The number needed to treat (NNT) was 1:7 in the MATTERs trial while the NNT was 1:67 in the CRASH-2 trial. The relative reduction in mortality was a very subtle 1.5 percent in the CRASH-2 trial and the mechanism for survival remains unclear in this trial since half of the CRASH-2 trial patients did not receive blood. The relative reduction in mortality was 6.7 % in the MATTERs trial and those who received TXA received less blood products. In the CRASH-2 trial TXA patients received the same amount of blood as those who did not receive the drug. (1) **The question remains, why include patients who probably will not need blood products into a trial that tests the ability of TXA to reduce blood product use?**

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Mechanisms of Trauma-induced Coagulopathy

PATCH

Ácido Traexâmico 1g, EV, *in bolus*,.

Derek Sifford refers to the **Prehospital Treatment of Acute Traumatic Coagulopathy and Hemorrhage (PATCH) trial** from the Alfred Trauma Center in Australia as a study that will help clarify practical and mechanistic questions regarding the use of TXA in trauma resuscitation.(5) The PATCH trial from Melbourne uses criteria that select out hypotensive patients who will probably need blood products based on a 7 point numeric system called the COAST criteria. **Most of the patients from this trial will have blood pressures less than 100mmHg and have well documented and significant pelvic and or abdominal injury.** One of the stated reasons to perform the PATCH trial is that the results of the CRASH-2 trial may not be applicable to the economically developed countries where patients are treated more quickly. Even the authors of the PATCH trial found the CRASH-2 trial problematic and as justification for their study they address the same points that Napolitano et al. delineated. The PATCH authors note that: **"Thrombotic complications were reported very rarely in the CRASH-2 study (PE, 0.7% of all patients; DVT, 0.4%),(1) probably because they were not actively sought in many of the participating hospitals. In contrast, the MATTERs study showed that rates of PE and DVT among patients who received TXA were, respectively, 9 and 12 times the rates among those who did not." (3,5)**

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Hematology Am Soc Hematol Edu Program, 2013;2013: 684/91

• Cancer-associated thrombosis

Thromboprophylaxis in Cancer Patients: Needs Rethink
Janis C. Kelly - May 08, 2014
J Clin Oncol. Published online May 5, 2014
A new multicenter study in the United States has found that use of thromboprophylaxis in hospitalized cancer patients is now much higher (74%) than has been previously reported, but it also found that many of these patients were at low risk, and about a third of the patients receiving anticoagulation had contraindications.

| Updates in Aggressive Thrombotic Disease |

Cancer-associated thrombosis

Gregory C. Connolly[1] and Charles W. Francis[1]

[1]James P. Wilmot Cancer Center and Department of Medicine, University of Rochester, Rochester, NY

Cancer-associated thrombosis accounts for almost one-fifth of all cases of venous thromboembolism (VTE) and is a leading cause of death, morbidity, delays in care, and increased costs. Our understanding of risk factors for cancer-associated thrombosis has expanded in recent years, and investigators have begun to use biomarkers and clinical prediction models to identify those cancer patients at greatest risk for VTE. The Khorana Risk Model, which is based on easily obtained biomarkers and clinical factors, has now been validated in several studies. Recent clinical trials of prophylaxis and treatment of VTE in cancer patients are reviewed here. In addition, consensus guidelines and expert opinion regarding management of VTE in specific challenging situations are presented.

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Obrigado!

2014 ASH Annual Meeting & Exposition
December 6-9, 2014
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