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

Atualizações em Coagulopatias

DECLARAÇÃO DO POTENCIAL CONFLITO DE INTERESSE

• Palestrante: Lindemberg da Costa Lima
• Apresentação: Atualização em Coagulopatias

NENHUM CONFLITO DE INTERESSE
"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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"Impedir a política transfusional liberal para CIV
Impedir teste para trombfilia nos adultos em situação transitória de risco para Trombose
-Interromper uso de filtro de vena cava inferior, exceto em situações bem específicas
-Interromper uso de PCV e de Conc. Protrombínicos na reversão não-urgencial de anti-VK
-Deixar à somente da TF do cateter após o diagnóstico positivo de trombose não-hospitalar"

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WORLD THROMBOSIS DAY: IT’S HAPPENING!

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
Relevância médica

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

Relevância médica

Atualização em Coagulopatias
- Hemofília
- TIC/Coagulopatia Trauma-induzida
- Trombose associada ao câncer
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].

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

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.

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 incident [2].

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. The primary endpoint in the study was incidence of bone or cartilage damage detected in ankles, knees, and elbows by radiographs in patients 6-9 years of age. 52% of those receiving prophylaxis had normal joint structure compared with only 18% of children receiving on-demand therapy [5].

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 is well-documented to be negative. In a study, which enrolled 44 adolescents and young adults with hemophilia, prophylaxis reduced the percentage of missed school days by 83% [21]. In another study [21], children on prophylaxis had significantly fewer hemorrhages (33 vs 0.3 events per patient per month, P < .05) and fewer radiologic signs of arthropathy (29% vs 76%, P = .03).

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.

Reference: 2, 9

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]

### Impact of Bioengineering Strategies on rFVIII Half-Life

<table>
<thead>
<tr>
<th>FVIII Therapy</th>
<th>Technology</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octocog alfa (Advate®)</td>
<td>rFVIII processed without any blood-based additives</td>
<td>12 hours</td>
</tr>
<tr>
<td>Turoctocog alfa</td>
<td>rFVIII with truncated B-domain</td>
<td>12 hours</td>
</tr>
<tr>
<td>NB-GP</td>
<td>PEGylated turoctocog alfa</td>
<td>19 hours</td>
</tr>
<tr>
<td>BIB-031-rFVIII Fc fusion protein</td>
<td>19 hours</td>
<td></td>
</tr>
<tr>
<td>BAV-94-9027</td>
<td>PEGylated FVIII</td>
<td>19 hours</td>
</tr>
<tr>
<td>CSL-627 Single-chain rFVIII</td>
<td>15 hours</td>
<td></td>
</tr>
<tr>
<td>BAX855 Full-length PEGylated rFVIII</td>
<td>18 hours</td>
<td></td>
</tr>
</tbody>
</table>


### Molecular approaches for improved clotting factors for hemophilia

Novos produtos para suporte ao cuidado do Hemofílico:

- Melhoram os parâmetros farmacocinéticos dos Fatores VIII, IX e VII: $\frac{T_{1/2}}{T_{max}}$ e clearance
- Promovem profilaxia primária mais eficiente:
  - Maior aderência
  - Menor formação de inibidores
  - Menor hospitalização
  - Menor absentismo escolar/profissional
  - Melhor qualidade de vida
• Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon’s perspective

Triade Lethal:

Acidose
Coagulopatia
Hipotermia

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

Doran, CM et al. – J Trauma.2010;69(2 Suppl 1):S64–8

• Optimal trauma resuscitation with plasma as the primary resuscitative fluid: the surgeon’s perspective

Novos conceitos/novas práticas?:

- Endoteliopatia do Trauma – Vasopermeabilidade hipoxêmica
- Injúria Pulmonar Associada ao Cristalóide
- Reanimação Hemostática: hiperfibrinólise (CRASH-II)
- Reanimação Hemostática Tromboelastometria-guiada
- Cirurgia do Controle do Dano
- Reanimação Hipotensiva Permissiva
- Reanimação Hemostática Fármaco e Hemosiderados-induzida

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
PROMMTT
PROPPR
Instituto do Trauma do Texas, Houston
(www.clinicltrials.gov identifier NCT01545232)

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 hiperperfusão, 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
### Mechanisms of Trauma-induced Coagulopathy

**Mecanismos fisiopatogênicos:**

1. **Anticoagulação**
   - Inibição de vários receptores de ativação do fator de fibrinólise

2. **Disfunção plaquetária**
   - Redução de atividade do Fator V e Factor VIII
   - Autoheparinização (glicoxil endotelial)
   - PDFII-dímero
   - Hiperfibrinólise

### Anticoagulação → INR/TPP, pré-reanimação:

- Sistema Trombina-Trombolitica-PCs
- Redução de atividade de Fator V e Factor VIII
- Autoheparinização (glicoxil endotelial)
- PDFII-dímero
- Hiperfibrinólise

**Referências:**

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### Mechanisms of Trauma-induced Coagulopathy

**Mecanismos fisiopatogênicos:**

1. **Anticoagulação**
2. **Disfunção plaquetária**
3. **Consumo de fibrinogênio e fibrinólise**
4. **Disfunção plaquetária**

**Disfunção plaquetária → hipoagregação e/ou PI normal**

- Hipoagregante (ADP, AC, Aracnoides, Colágeno...)
- Receptor Plaquetas P2Y₉ → influxo de cálcio, inibe P2Y₁₁
- Inibição de múltiplos receptores PI & Alteração do fluxo do Ca²⁺

**Referências:**

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### Mechanisms of Trauma-induced Coagulopathy

**Mecanismos fisiopatogênicos:**

1. **Anticoagulação**
2. **Disfunção plaquetária**
3. **Consumo de fibrinogênio e fibrinólise**
4. **Disfunção plaquetária**

**Consumo de fibrinogênio e fibrinólise → hiperfibrinólise**

- ROTEM chofibrinogênema = mortalidade
- [PI, P1, dímeros, complexo antifibrinogênio/plasma, ...]
- [PIA-1 induto pelo sistema TMBProteína C ativada
  + elastase neutrofílica]

**Referências:**

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

Theusinger

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

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].
“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 Thuesinger


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.


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

Thuesinger

“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 - Thuesinger

“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.”
Lindemberg da Costa Lima

Mechanisms of Trauma-induced Coagulopathy

Referenced in Theusinger


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 approximately 20% 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, Petra Innerhofer, and Wolfgang Schobersberger.


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

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**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

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**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

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**Guideline for Blood Product Use**

<table>
<thead>
<tr>
<th>Mechanisms of Trauma-induced Coagulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal TEG</td>
</tr>
<tr>
<td>Prolonged R time</td>
</tr>
<tr>
<td>Transfuse 4 units FFP</td>
</tr>
<tr>
<td>Decrease Maximum Amplitude</td>
</tr>
<tr>
<td>Transfuse 2-4 units Whole Blood</td>
</tr>
<tr>
<td>Prolonged K time or Decrease a-Angle</td>
</tr>
<tr>
<td>Transfuse 4 units FFP then 4 units Cryoprecipitate Consider rVIIa if abnml after above</td>
</tr>
<tr>
<td>Increase LY30</td>
</tr>
<tr>
<td>Amicar 5gm IV load over 1 hour then 1 gm/hr until LY normal</td>
</tr>
</tbody>
</table>

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**Postinjury Coagulopathy Management**

**Mechanisms of Trauma-induced Coagulopathy**
Mechanisms of Trauma-induced Coagulopathy

CRASH - 2

The Lancet, Volume 376, Issue 9734, Pages 23 - 32, 3 July 2010
Dewan Y1, Komolafe EO, Mejia-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.

CRASH-3


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, Mejia-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.
<table>
<thead>
<tr>
<th>CRASH-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critics:</strong> Mark Walsh MD 1,2 and Bradon Fritz BS 1,2</td>
</tr>
<tr>
<td>1 Memorial Hospital of South Bend, South Bend, IN 46601 2 Indiana University School of Medicine South Bend, IN 46637</td>
</tr>
<tr>
<td>CRASH-2 trial has several limitations, 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 between 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!</td>
</tr>
</tbody>
</table>
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.

Obrigado!