CSL Behring

Update topics 2

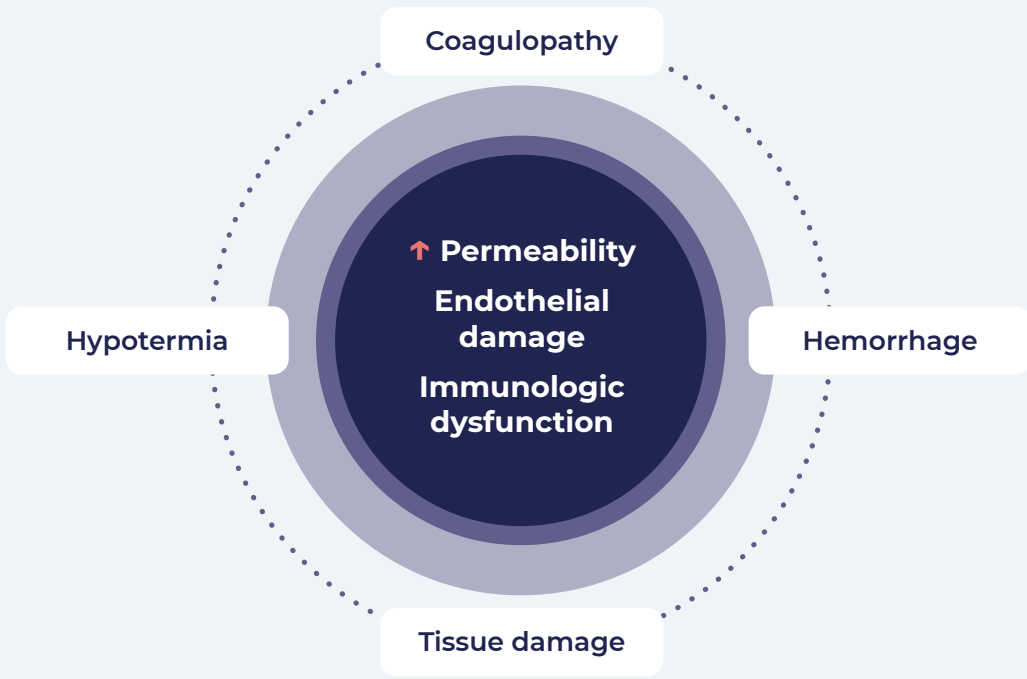
Moderator: Dr. Gabriel Yanes

Friday, May 12, 2023 11.39am – 1.30pm | Sevilla Room 3 + 4

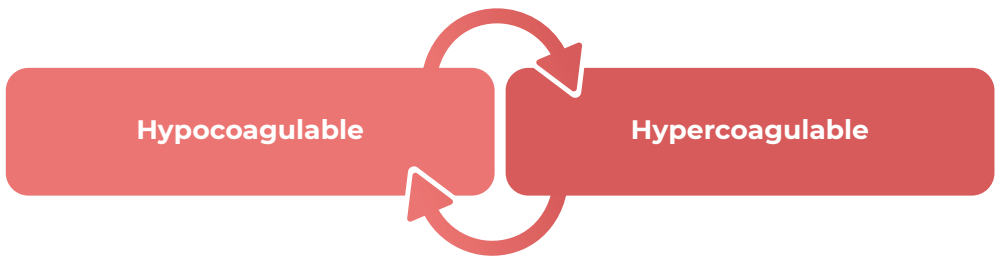
1. WHAT IS TRAUM-INDUCED COAGULOPATHY AND HOW TO TREAT IT?

Dr. Gontzal Tamayo

Trauma injuries are the main cause of death and disability among people under 45 in the EU[1]. Trauma-induced coagulopathy is common, but it is not presented in isolation: it coexists with hypovolemia, Hb decrease, severe systemic inflammation, endotheliopathy, and multiple tissue and organ alterations compromising function[2].



Regarding coagulation, two phenotypes coexist in patients with multiple traumas: hypocoagulable, characterized by hyperfibrinolisis, and hypercoagulable, characterized instead by a prothrombotic and antifibrinolytic state[3].



The oscillation between both phenotypes is common, depending on the control of hemorrhage or the replacement of coagulation factors, among others. Both the hypocoagulable and the hypercoagulable phenotypes are associated to an increase in mortality.

An early detection of coagulopathy is required, and conventional or viscoelastic coagulation tests are recommended with the same level of evidence in trauma patients. Once the coagulopathy is detected, an early objective-guided therapy improves coagulation, increases survival, and reduces the use of blood products and hospital stays.

Therefore, management could be outlined as follows:

1 STOPPING THE HEMORRHAGE

2 CORRECTING HYPOTERMIA

3 CORRECTING HYPOCALCEMIA

- Target: 1.1-1.3 mmol/L

4 ADMINISTRATION OF TRANEXAMIC ACID

- 1 g as early as possible (within 3 hours of the trauma) + 1 g after 8 hours.

5 USE OF BLOOD PRODUCTS

- PFC:CH (1:2-1:1).
- Fibrinogen:CH (2g:4).
- Early platelets (1:1:1).
- PFC (10-20 ml/kg) after viscoelastic test, and never to correct hypofibrinogenemia.
- CCP, in no longer hypovolemic patients. Fibrinogen and FXIII should be monitored, and more should be administered if the levels are low.
- FXIII is a coagulation factor the activity of which is often reduced early in many severe trauma patients with coagulopathy, and so it is important to monitor and correct it[4,5].

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2. CONSISTENCY IN THE MANAGEMENT OF MASSIVE HEMORRHAGE BETWEEN THE LATEST EUROPEAN GUIDELINES AND THE HEMOMAS DOCUMENT?

Prof. Juan Vicente Llau Pitarch

Massive hemorrhage is a very significant cause of morbidity and mortality, modifiable and with a lot of room for improvement, and its management has changed in the last few years. In the last few months, European guidelines have been published on the management of perioperative massive hemorrhage, considering 13 scenarios and compiling 140 recommendations, including trauma patients[6,7].

At a national level, the HEMOMAS document has also been recently updated, and it will be published shortly. It contains 14 sections with 61 statements for practical use:

38 RECOMMENDATIONS

23 SUGGESTIONS

The **authors of HEMOMAS** approached the existence of the **ability to improve in five key aspects**:

1 EARLY IDENTIFICATION OF MASSIVE HEMORRHAGE

The time between the start of the bleeding and the hemorrhage control must be minimized.

The HEMOMAS document offers three recommendations focused on clinical criteria, as well as criteria for resuscitation and multiple traumas.

2 FLUID THERAPY FOLLOWING HYBRID RESUSCITATION

Hybrid resuscitation is based on:

1° Stopping hemorrhage, based on isotonic fluids

2° Tackling the hemodynamic objective, based on balanced fluids

3 USE OF BLOOD PRODUCTS AND PROTOCOLIZATION OF THE RESPONSE

HEMOMAS recommends an early administration of blood products, based on the concept of high ratio hemostatic resuscitation (PFC:CH at least 1:2). The application of massive transfusion protocols is recommended.

The early administration of fibrinogen (if hypofibrinogenemia is suspected) as fibrinogen concentrate, and not as frozen fresh plasma.

Using viscoelastic tests if they are available at the clinic; otherwise, monitoring should also be performed through conventional studies (actual situation in many Spanish sites).

4 DAMAGE CONTROL SURGERY

Depending on resource availability: surgery and interventional radiology

HEMOMAS recommends applying the concept “damage control surgery”, using hemostatic topics, and considering mechanical control measures.

5 PREVENTION OF COMPLICATIONS

HEMOMAS recommends preventing the “deadly pentad”:

Hypothermia	**Acidosis**	**Hypoxia**	**Hypocalcemia**	**Hyperglycemia**

In general, any action that may increase bleeding should be avoided, following protocols with permissive hypotension, restrictive fluid therapy, and early treatment of coagulopathy.

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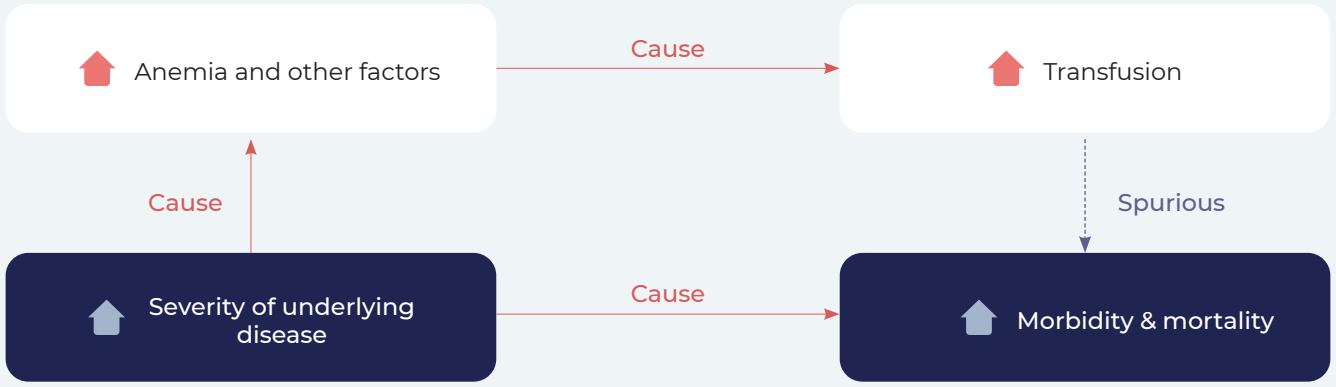
3. THE EFFECTIVENESS OF RED BLOOD CELL TRANSFUSION IN NON-BLEEDING PATIENTS. ANY EVIDENCE? HEMATOLOGIST PERSPECTIVE

Dr. Arturo Pereira

Currently there is an expert consensus on the effectiveness of red blood transfusion, but it is not backed by a high level of evidence. The likelihood of carrying out such trials is zero, because it would mean leaving half the patients without a transfusion. Given the lack of clinical trials, the available evidence comes from cohort observational studies, hemovigilance data, and comparative clinical trials with restrictive and liberal policies.

In the last 15 years, over 200 studies have been published, and the goal of most of them is not to assess the efficacy, but the appearance of adverse effects; given the kind of question asked, some end up establishing a causal relationship between transfusion and morbidity and mortality.

Mortality associated to transfusions is around 1-2 / million units of red blood cells[8,9].
Mortality associated to delays in transfusion is around 5,6 / million units of red blood cells[10].



The reason for such correlation is the existence of multiple confusion factors, and generally speaking, what is really associated to mortality is the severity in each patient.

Limitations of trials on transfusion upper thresholds, even though they are prestigious and published in high-impact journals:

- They take into account hemoglobin values as an exclusive criterion to decide to make a transfusion; in clinical practice there are multiple factors also determining decision-making.
- Hemoglobin is not the perfect indicator for the O2 transport capacity. Other indicators, such as cardiovascular adaptation, may be more decisive.
- These trials have a low statistical power, and the existing differences are probably not detectable.
- The heterogeneity of the investigational product contributes to the observed result variability.

For all these reasons, clinical guidelines should reflect all the uncertainty and leave leeway for good clinical judgment.

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4. TRANEXAMIC ACID FOR EVERYTHING?

Dr. Ane Abad Motos

Using tranexamic acid is one of the interventions in transfusion medicine more strongly backed by clinical evidence. The publication of the POISE-3 study concluded that using tranexamic acid reduced the relative risk of bleeding and transfusions in major surgeries.

Tranexamic acid is an effective cheap safe treatment vs. transfusion, but evidence supports its use in certain scenarios and not others.

Yes		No	
Trauma[a][11]	• ↓ mortality • ↓ mortality by bleeding	Gastrointestinal bleeding[12]	• = mortality • ↑ convulsions • ↑ venous thrombotic events
Cardiac surgery[13]	• ↓ need of transfusion • ↓ Resurgery due to bleeding • = mortality by thrombotic events • ↑ convulsions[b]	Prevention of bleeding by C-section[c][14]	• ↓ bleeding over 1 L oor need of transfusion • = secondary clinical results related to hemorrhage
Postpartum hemorrhagea[a][15]	• = mortality • ↓ mortality by bleeding		
Traumatic brain injuryo[a][16]	• ↓ mortality by trauma		
Surgical bleeding[17]	• ↓ bleeding and transfusion • = thrombotic events		

[a] Administered within the first 3 hours posttrauma or postpartum.
[b] Probably due to the doses administered at the beginning of the trial, higher than the current ones.
[c] The difference in the estimated bleeding between both groups was 100 mL. A doubt remains as to whether tranexamic acid may be administered at the start of surgery.

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5. ERYTHROPOIETIN ANALOGUES IN PBM, A PRACTICAL APPROACH

Dr. Salvador Payán

As a result of the appearance of thromboembolic and cardiovascular events (although at those times Hb thresholds over 12 g/dL were applied), erythropoietin has had a very negative reputation until now.

Currently, recommendations state that it should be offered to patients with anemia associated to chemotherapy, which is being administered for non-healing purposes and Hb values < 10 g/dL[18].

Inflammatory anemia produces a dysfunction in the synthesis of erythropoietin, as well as iron sequestration in macrophages and a decrease in the intestinal absorption of iron. In renal anemia and inflammatory anemia, the relationship between the observed EPO and the expected EPO must be taken into account, and if it drops below 0.8, it means that treatment with EPO may be effective.

What about perioperative anemia?

The use of erythropoietin in surgery is completely different from its chronic use for anemia[18-20]:

It does not increase the risk of thromboembolic events

It does not increase mortality

It reduces the number of transfusions

It increases pre- and postoperative hemoglobin

In Spain there are two formulations with an indication in patients with non-ferropenic anemia (Hb 10-13 g/dL) before major orthopedic surgery: alpha and theta.

Recommendations included in guidelines:

Recommendations	Degree
Pre- or perioperative administration of rHuEPO in moderate anemia and risk of bleeding in scheduled orthopedic surgery[21]	1A
Administration of rHuEPO in anemic patients undergoing major surgery[21]	2A
Administration with or without iron in patients with non-ferropenic anemia undergoing major surgery[22].	2A
Administration in the preoperative treatment of anemia—it must be administered with iron and considering postoperative prophylactic treatment of thromboembolism*[23]	

* The prophylaxis of thromboembolism responds to a statistically non-significant increase of risk in critical patients, but not in surgery.

When should it be administered?

KIDNEY FUNCTION	FERRITIN (ng/ml) < 30	FERRITIN (ng/ml) 30-100	FERRITIN (ng/ml) > 100	TRANSFERRIN SATURATION INDEX
Normal	**FERROPENIC** ANEMIA Fe	**FERROPENIC** ANEMIA + INFLAMMATORY Fe + EPO	INFLAMMATORY ANEMIA EPO + Fe	< 20%
Normal		Other causes	Other causes	≥ 20%
Chronic Kidney Disease	**FERROPENIC** ANEMIA + **RENAL** Fe + EPO	**FERROPENIC** ANEMIA + INFLAMMATORY + **RENAL** Fe + EPO	INFLAMMATORY ANEMIA + **RENAL** EPO + Fe	< 20%
Chronic Kidney Disease		**RENAL** ANEMIA EPO + Fe	**RENAL** ANEMIA EPO + Fe	≥ 20%

How should it be administered?

SC or IV path

300 UI/kg

21, 14, 7 days before surgery and the same day of surgery

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