CSL Behring

Controversies 1

Moderator: Dr. Juan Vicente Llau

Thursday, May 11, 2023 4pm – 5.30pm | Sevilla Room 3 + 4

1. CHRONIC LIVER DISEASE—HOW SHOULD I PERFORM BLEEDING AND THROMBOSIS PROPHYLAXIS?

Dr. Annabel Blasi

Cirrhosis patients present a "hemostatic rebalance" that provides them with hemostatic competence, which is translated into the same thrombin generation time, yet with a decrease in lysis. However, such hemostatic balance is fragile, and a small alteration may trigger both bleeding and thrombotic states.

Bleeding risk in cirrhosis patients basically depends on **three factors:**

1 PROCEDURE APPLIED

The most commonly observed bleeding is that related to portal hypertension, and not so much surgery or other invasive procedures[1,2]. However, there is currently no consensus between scientific societies on what procedures are high or low risk.

2 CHARACTERISTICS OF THE PATIENT

Fibrinogen and platelet levels have to be taken into account, although no cutoff points are currently defined. Other factors influencing hemostasis are the presence of kidney failure or infections.

3 OPERATOR SKILLS

Currently, there are no tools to properly assess the risk of bleeding and thrombosis in liver disease patients[3-5]. Nevertheless, the use of viscoelastics has been associated to a decrease in the use of blood products.

✕ PT/APTT: do not reflect the actual hemostatic competence of the patient
✕ Platelet count: only useful if levels are extremely low and with no established cutoff points
✕ Platelet function test: low value, since patients generally suffer from thrombocytopenia
✕ Fibrinogen: no set thresholds
✕ Fibrinolysis: not available in usual practice
✕ Bleeding time: does not predict risk
✕ Thrombin generation or thromboelastography: no set thresholds

RECOMENDATIONS FOUND IN EASL GUIDELINES, 2022:

Prophylaxis of bleeding

- Traditional or viscoelastic tests (VET) are not indicated to predict risk, but they may be used to assess severity or the hemostatic state, and guide management in case bleeding occurs during the procedure.
- Prophylactic plasma transfusion or using prothrombin complex concentrate to correct INR is not recommended. It must be noted that in patients with portal hypertension, each 100 ml of administered volume increase portal pressure by 1 mmHg, which in turn increases bleeding.
- Using platelet concentrate is not recommended if the count is > 50 x 10^9 or if it can be treated with local hemostasis. Platelet transfusion may be considered in high risk procedures in which local hemostasis is not possible, or if the count is < 20 x 10^9.
- Fibrinogen correction or routine use of tranexamic acid is not recommended.

Active bleeding

- VETs may prove useful to save on blood products, and they can be used when available.
- If hemostasis is achieved by decreasing portal hypertension in variceal bleeding, correcting hemostatic imbalances is not indicated.
- Routine use of tranexamic acid is not recommended, due to the higher risk of thrombotic events in cirrhosis patients.

ANTICOAGULATION IN CIRRHOSIS PATIENTS

Even though no evidence is available, standard thromboprophylaxis seems safe in cirrhosis patients:

✓ Direct Oral Anticoagulants (DOACs) in Child-Pugh A & B.

Treatment of deep vein thrombosis and pulmonary embolism:

✓ DOACs in Child-Pugh A and with caution in patients Child-Pugh B or CrCl < 30 ml/min. Antivitamin K & HBPM in Child-
✓ Pugh A & B
✓ HBPM in Child-Pugh C

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2. USE AND AVAILABILITY OF VISCOELASTIC TESTS. ARE THEY INDISPENSABLE? MULTIDISCIPLINARY CONSENSUS DOCUMENT

Dr. Sonia Mª Veiras del Río and Dr. Gabriel José Yanes

The use of VETs is part of the therapeutic arsenal in Spanish hospitals, both when caring for bleeding patients and in risk of thrombosis, more recently.

One of the projects promoted by the Hemostasis, Transfusion Medicine and Fluid Therapy section at SEDAR was a survey to get to know the degree of implementation of VETs in national hospitals, which reports a wide variability in the implementation and adherence to current guidelines[6].

The current census of these tools indicates they are available in 88 hospitals throughout the country; 78 hospitals are represented in the survey, which means that this effort covers over 90% of hospitals

RESULTS FOUND:

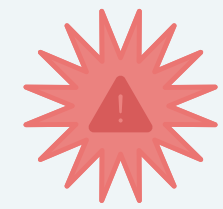
- ✓ Only a small percentage of Spanish hospitals have VETs available. In most cases, these are ROTEM.
- ✓ Most VETs are found in four Spanish regions (Catalonia, Madrid, Andalusia and Valencian Community), with a lower number in the remaining regions, probably due to a lower density of high complexity hospitals, among other causes.
- ✓ In a high percentage of cases, using VETs is not associated to the use of a treatment algorithm. These are the main.
- ✓ Scenarios in which they are used:

Cardiac surgery

- On demand (in most cases)
- Pre-exit from ECC
- Post-ECC

Liver transplant

- Baseline
- In anhepatic phase
- Post-reperfusion
- End of surgery



Trauma / Ortophedics

- On demand (in most cases) (guidelines recommend baseline determination)

- ✓ In all three scenarios, a VET-based follow-up is reported after surgery.
- ✓ Maximum firmness or maximum amplitude are the most commonly used parameters to assess the amplitude/firmness of the clot (although the literature backs the use of earlier indexes –A5 or A10-).
- ✓ In almost 20% of cases, VET parameters are corrected to normal ranges, even if there is no bleeding.

THE FOLLOWING ACTIONS MAY EMERGE FROM THE RESULTS FOUND:

Improving accessibility to VETs

Applying earlier indexes

Eradicating inadequate uses

Generating evidence in terms of cutoff points and determination time

In order to cover these objectives, a multidisciplinary document is being drafted (anesthesiology, laboratory, hematology) on the use of VET in clinical practice, aimed at physicians in any specialty who are involved in the management of VETs.

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Thursday, May 11, 2023 4pm – 5.30pm | Sevilla Room 3 + 4

3. PCC, FIBRINOGEN AND FXIII IN A MASSIVE BLEEDING-SEQUENTIAL OR SIMULTANEOUS?

Dr. Marta Barquero

It is important to pose **three key questions** when determining whether the administration of fibrinogen, prothrombin complex concentrate (PCC), and factor XIII should be performed simultaneously or sequentially:

The specific pathophysiology behind each scenario must be known, because the endothelial injury, hemostatic conditions, and mechanisms of coagulopathy will be different, even if the bleeding volume is the same. The administration of factors should be performed sequentially in case of bleeding and coagulopathy. At any rate, the first factor to fall will be fibrinogen, and then more slowly, platelets and coagulation factors.

Unlike the initial proposal of the hemostatic pyramid by K. Görglinger, in most recent algorithms, the order of administration of coagulation factors and platelets is inverted, or else left to the physician's judgment[7,8].

Currently, there are specific protocols to monitor coagulopathy in bleeding patients. Most of them are based on VETs, but also on more generally accessible and early parameters, such as gasometry, which may prove useful if access to other tools is limited[9].

Controversies associated to the administration of factor XIII:

- Doubts in pathophysiology
- Lack of relevant information
- Non-defined threshold
- Specific lab monitoring, not generally available 24/7
- Acute or more sustained administration: is one dose enough?

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Thursday, May 11, 2023 4pm – 5.30pm | Sevilla Room 3 + 4

4. MANAGEMENT OF ANTI-THROMBOSIS DRUGS IN ESAIC/ESRA GUIDELINE-SHOULD WE CHANGE OUR CLINICAL PRACTICE?

Dr. Raquel Ferrandis

The management of anti-thrombosis drugs to perform regional blocks is included in numerous clinical practice guidelines[10-14]. At a national level, there is a multidisciplinary consensus document on the perioperative management and anti-thrombosis treatment periprocedure[15].

The European guideline (signed by ESAIC and ESRA) to perform regional blocks in patients treated with anti-thrombosis drugs[16] has been published recently. It is a pragmatic consensus evidence-based document, aimed at reducing as much as possible the risk of bleeding (the risk of thrombosis is not assessed in this guideline).

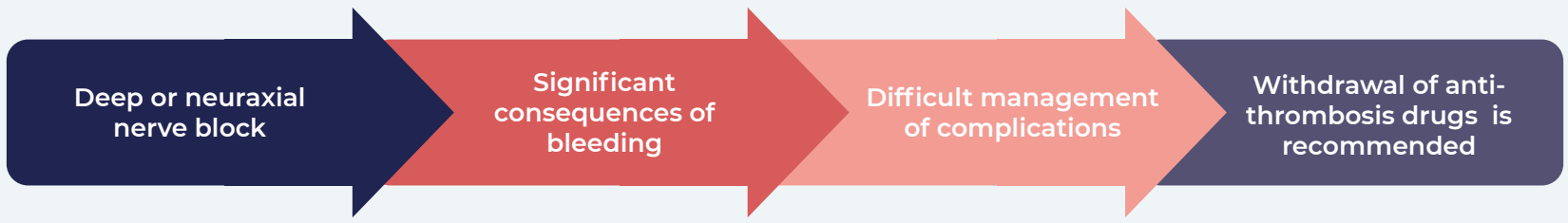
- **45 claims:**

57,5% with consensus > 90%

42,5% with consensus 75-90%

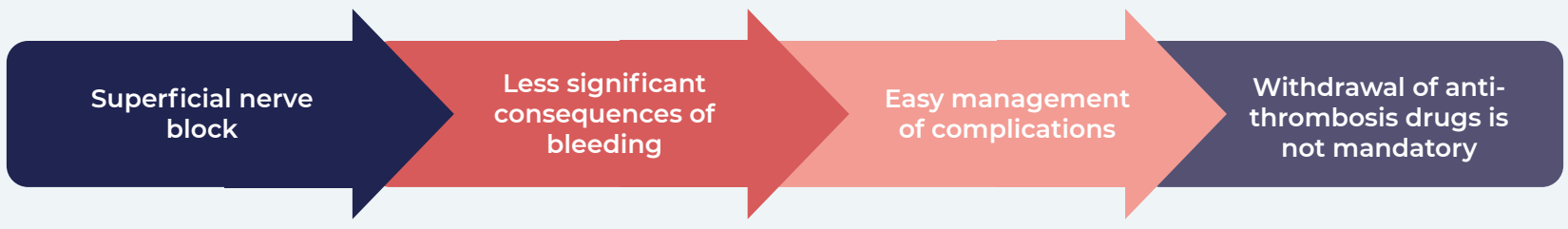
- **Many of the recommendations correspond to specific clinical situations. The evidence level in all of them is C, because this guideline covers situations with no evidence available.**
- **Categorization of blocks in two categories[16]:**

High risk:



- Acenocumarol: suspension time about 3 days for acenocumarol and search of normal INR (< 1.2).
- DOAC: low doses are considered for postoperative thromboprophylaxis. In patients with DOACs at high doses, a 72-hour is recommended, with no bridge therapy with HBPM. In patients with renal dysfunction (ClCr<30 ml/min for apixaban, rivaroxaban, edoxaban; ClCr<50 ml/min for dabigatran), a suspension time cannot be recommended, therefore specific monitoring is advised.
- Aspirin: does not require suspension in doses < 200 mg, which are considered low doses because there is no evidence with 300-400 mg.

Low risk:



- Currently, it is necessary to create local multidisciplinary protocols adapted to different scenarios.
- A thorough assessment of risks and the search for strategies to minimize them must be recorded in the clinical history of patients.

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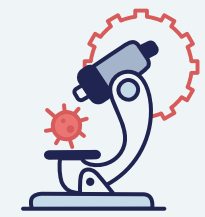
Projects 1

The two main **goals** of the **Fluid Therapy and Hemodynamic Monitoring Working Group** are:

Promoting continuous training



Promoting clinical research

Moderator: Dr. Ane Abad

Thursday, May 11, 2023 7pm – 8.30pm | Sevilla Room 3 + 4

1. TRAINING PROJECTS OF THE FLUID THERAPY AND HEMODINAMIC MONITORING WORKING GROUP. PLATAFORM, IFAD, E. UNIVERSITY

Dr. Patricia Galán Menéndez

In a wide survey carried out to assess prescription patterns and find out what physicians (1045 participants) know about fluid therapy in the operation room and ICU, it was found that the knowledge degree was below average in 56% of participants, and poor in 9.5%[1].

In Spain, during Fluid Day –an initiative promoted by the Hemostasis, Transfusion & Fluid Therapy section of SEDAR to assess the management of fluid therapy in our environment,– it was found that hemodynamic monitoring is limited, and it was performed in just 5% of patients during the perioperative period, and 10% in the postoperative period[2].

CURRENTLY, THE WORKING GROUP HAS FIVE ACTIVE TRAINING PROJECTS:

Edwars Hemodynamic University

- Platform offering training tools.
- In cooperation with the pharma industry.
- Online tutor support and training advice.
- Program aimed at young assistant doctors and residents.

Three update clinical sessions at the SEDAR campus

- 5 hemodynamic principles by Dr Pinsky (October 2022)
- From macrohemodynamics to microdynamics (May 2022)
- Hypotension manifest! (June 2022)

Fluid Therapy Guideline

- Physiology-based recommendation guideline.

Fluid News

- First meeting on fluid therapy and postIFAD hemodynamic monitoring (February 2023).

Training Platform on Fluid Therapy in Surgical Patients

- From September 2023
- In the SEDAR training space
- Modules: Basic principles, non-critical surgical patient, hemodynamic monitoring and control, CKD patient, critical patient, cardiac patient, patient with liver damage and patient with multiple trauma.

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Projects 1

Moderator: Dr. Ane Abad

Thursday, May 11, 2023 7pm – 8.30pm | Sevilla Room 3 + 4

3. RESEARCH PROJECTS BY THE FLUID THERAPY AND HEMODINAMIC MONITORING WORKING GROUP. HYT, BIGPACK2, NIMON

Dr. Paula Fernández Valdes-Bango

Research is a fundamental task in Anesthesiology departments, together with teaching and healthcare.

Between 2001 and 2015, under 20 articles on Anesthesiology per million of inhabitants were published in Spain, whereas in countries such as Austria or the Scandinavian countries, the figure was over 50. Furthermore, the average impact factor of Spanish publications is low[3].

Nevertheless, in a study showing a post-surgery mortality rate of 4%, it is found that in Spain many patients are recruited for large trials, in spite of the low publication rate[4].

The most important aspects research should focus on are:

Improving intraoperative quality of care

Reducing complications

Improving postoperative results

New ongoing studies researchers can take part in:

- BigpAK-2: Currently recruiting, open (RapNET ESAIC)

Multi-center international RCT
1302 patients with non-cardiac surgery admitted to the ICU or with high dependency

Goal:
Studying the impact of KDIGO measures in patients at high risk of acute kidney damage identified through urinary biomarkers

- HYT: Currently recruiting, open (RapNET ESAIC)

Multi-center international RCT
958 patients with abdominal major surgery

Goal:
Studying whether the hypotension prediction index (HPI) improves hemodynamic management and lowers the incidence of postoperative kidney failure

- niMON: Currently recruiting, open (SIAARTI)

Multi-center international RCT
1204 patients with moderate-risk surgery

Goal:
Assessing the impact of intraoperative monitoring of continuous vs. intermittent non-invasive blood pressure in myocardial and kidney injuries

- HeCoMo: Protocol in preparation, pending CEIC in Spain (ESICM)

Multi-center international observational trial
20-25 patients/center high-risk surgery

Goal:
Assessing the impact of intraoperative hemodynamic monitoring in complications and mortality

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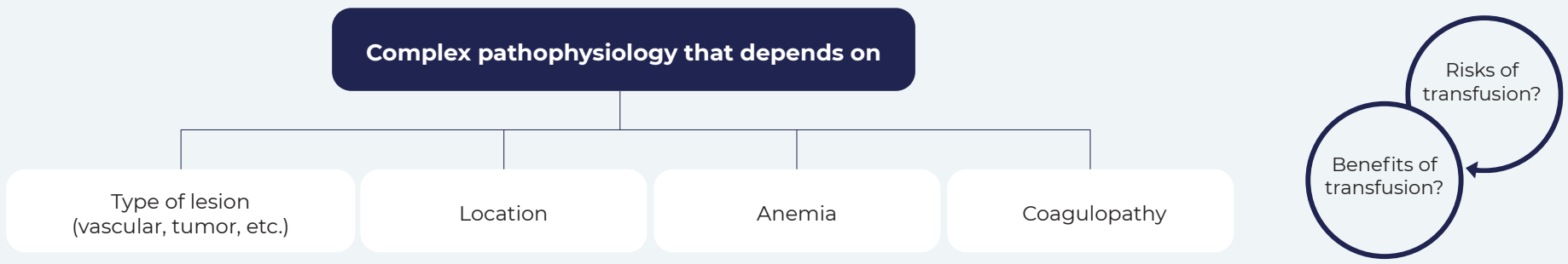
4. TRANSFUSIONAL SURVEY IN NEUROSURGERY. HOMOGENEOUS PRACTICE?

Dra. Paola Hurtado

Control and management of intracranial bleeding is vitally important in neurosurgery. Transfusion may be necessary in the context of neurosurgery.

Currently, there is no evidence-based consensus on how transfusion practice should be handled in neurosurgery.



This is why a **Transfusion survey in neurosurgery** was promoted, with the following goal:

Obtaining information to assess the current status of Patient Blood Management (PBM) in adult patients undergoing scheduled or urgent cranial surgery

It was done through an online questionnaire, among physicians from Anesthesiology and Resuscitation in Spain, between June and October, 2022. Several areas of interest were covered:

- Pre-anesthetic visit
- Preoperative assessment of hemostasis
- Monitoring of hemostasis/coagulation
- Peri- and post-operative use of drugs and blood products.

Main results

65% Absence of correction protocol of **preoperative anemia**

20% Assessment of peri-operative state

82% < 3 weeks to surgery

91% Routine blood reserve

Routine blood reserve for all patients is not a cost-effective measure, and it should only be done with high-risk patients[5].

76% Acceptable platelet limit **100 000/mcL** to scheduled craniotomy

Transfusion threshold:

- < 100 000 in **34%**
- Platelets + algorithm Rotem/TEG in **27%**
- < 75 000 in **20%**

78% Verbalization of the chances of bleeding during the routine *check-list*

Identifying patients at a high risk of bleeding in the pre-operative setting allows the implementation of multidisciplinary measures[6].

65% Rotem/TEG **vs.** **19%** classic post-operative test with signs of bleeding

Lack of evidence in neurosurgery, but not in other fields of use for TEG.

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Thursday, May 11, 2023 7pm – 8.30pm | Sevilla Room 3 + 4

7. GUÍA SETS/SEDAR

Dr. Maria José Colomina

The latest version of the *National Guideline of the Transfusion of Blood Products and Plasma Derivatives* was published by the Spanish Society of Blood Transfusion and Cell Therapy (SETS) in 2015[7]. Therefore, SEDAR, together with SETS, starts the process for the publication of a new guideline with up-to-date information on transfusion practice, to facilitate clinical decision-making to all specialists involved. The goal is to obtain an agile, easily-transportable document that can be published.

Systematic Review

Gathering evidence and recommendations from other already published documents, with a short-term horizon (2016-2022). For that purpose, relevant useful documents will be used:

- Educational modules on clinical use of blood, published by the WHO[8]
- Transfusion handbook by JPAC[9]
- Systematic review by the clinical transfusion medicine committee at AABB[10]
- Guidelines from the Birtish society[11]

Relevant article selection

- Meta-analysis
- Cochrane indications
- RCT
- Controlled observational studies, mainly prospective with a high N

Grading of recommendations using GRADE

Assessment of evidence strength and quality

Drafting of modules

- Perioperative transfusion
- Massive hemorrhage
- Transfusion in intensive care
- Transfusion in special situations
- Implementation of PBM in the hospital setting

Publication in 2024

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Symposium CSL Behring

Moderator: Dr. Maria José Colomina

Thursday, May 11, 2023 5.30pm – 6.30pm | Sevilla Room 2

1. GASTROINTESTINAL (GI) BLEEDING: EVALUATION, STABILIZATION, AND RISK FACTORS

Dr. José Aguiar

In 2020, the manuscript *Interventional Algorithm in Gastrointestinal Bleeding-An Expert Consensus Multimodal Approach Based on a Multidisciplinary Team* was published. The document offers a collection of algorithms to manage gastrointestinal bleeding, based on a literature review and the experience of 14 Portuguese experts making up a multidisciplinary working group[1].

The work was published in the *Clinical and Applied Thrombosis/Hemostasis* journal, and the author advocate the adaptation of the recommendations to each individual situation and clinical scenario, to the experience and expertise of the physicians, and to the resources available in the setting.

The document provides a hands-on approach on the following items:

1 ASSESSMENT

Why is the patient bleeding and what can we do to stabilize them and control risk factors?

- **Signs of bleeding**
  - sometimes may be subtle
- **Clinical history**
  - Previous episodes of gastrointestinal bleeding
  - Gastrointestinal disease
  - Gastrointestinal surgery
  - Endoscopy
  - Radiotherapy
  - Other
- **Management of different comorbidities**
  - Cirrhosis, portal hypertension
  - Chronic kidney disease
  - Cardiovascular disease

2 MANAGEMENT OF ANTICOAGULATION/ANTIAGGREGATION

Criteria for discontinuation and/or use of antidotes or FXa inhibitors.

3 RESUSCITATION IN SEVERE BLEEDING

Recommendations are provided on the following aspects:

- **Goals to consider in hemodynamic stabilization**
  - Hemodynamic
  - Therapeutic
  - Laboratory
  - Transfusion
- **Bad prognosis factors**
  - Involve alert signs

4 DIAGNOSTIC/THERAPEUTIC APPROACH DEPENDING ON THE SUSPECTED LOCATION OF THE BLEEDING

- **Upper gastrointestinal tract**
  - Variceal
    - Empirical treatment
    - Endoscopy
  - Non-variceal
    - Endoscopy
    - Empirical treatment
- **Middle gastrointestinal tract**
  - Angiography by tomography
  - Capsule endoscopy
- **Lower gastrointestinal tract**
  - Angiography by tomography
  - Endoscopy of the lower gastrointestinal tract

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Moderator: Dr. Maria José Colomina

Thursday, May 11, 2023 5.30pm – 6.30pm | Sevilla Room 2

2. MANAGEMENT OF COAGULOPATHY IN GI BLEEDING

Dr. Manuela Gomes

Before starting to manage the coagulopathy, the following factors must be considered:

- Concomitant medication
- Comorbidities, with a special focus on liver disease:
  - Whether there is variceal bleeding (cirrhotic patient with portal hypertension) ➡ limiting the administration of fluids so as not to make portal hypertension worse.

Massive bleeding is defined as the volume of blood lost, the pace of bleeding, and the number of transfused blood units. Depending on the severity of the bleeding, the concomitant administration of certain drugs may be necessary, or the administration of several doses[1].

The authors of the consensus document suggest:

1 **TRANSFUSION OF RED BLOOD CELLS** if Hb is < 7 g/dL (< 8 g/dL if there is cardiac disease) with the following target values:

7-9 g/dL

8-10 g/dL in case of cardiac disease

2 **TRANEXAMIC ACID** if there is evidence of fibrinolysis (confirmation by ROTEM)

- In gastrointestinal bleeding, tranexamic acid decreases mortality, but not rebleeding.

3 **FIBRINOGEN** is a deficiency is suspected (confirmation by ROTEM)

- Levels < 1.5-2 g/L and/or loss of ≥ 1-1.5 L and bleeding persists.

4 **PLATELET CONCENTRATE** if there is thrombocytopenia:

- Bleeding in the upper gastrointestinal tract and liver disease with active bleeding, and count < 50 x 109/L or viscoelastic test.

5 **DESMOPRESSIN** if there is active bleeding in patients with uremia and altered kidney function, or in patients with antiplatelet therapy.

6 **PROTHROMBIN COMPLEX / VITAMIN K / FROZEN FRESH PLASMA** if a deficiency in other coagulation factors is suspected (thrombin formation deficiency).

7 **FROZEN FRESH PLASMA** if there is variceal bleeding and suspected FV deficiency.

8 **FROZEN FRESH PLASMA / FXIII** in other types of bleeding and suspected FXIII deficiency (clot instability not related to hyperfibrinolysis).

9 **rFVII** in patients in which the above has been corrected but are still experiencing life-threatening bleeding.

Although unusual, treatment changes may have to be introduced in certain clinical situations, and coagulation must be assessed after each specific therapeutic episode.

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Moderator: Dr. Maria José Colomina

Thursday, May 11, 2023 5.30pm – 6.30pm | Sevilla Room 2

3. PBM IN GI BLEEDING

Dr. Manuel Quintana

The concept of patient *blood management* (PBM) is much wider than optimizing the use of blood products: not only the use of blood products has to be improved (product-centered approach), but also any health-related results (patient-centered approach):

Optimizing bleeding management

Optimizing the management of hemostasis and coagulopathy

Minimizing the contribution of blood products

In case of gastrointestinal bleeding[2]

- An estimated 15-20% of red blood cell transfusions are performed inadequately.
- The characteristics of patients are highly heterogeneous: comorbidities, medication, risk factors, etc.
- These are 'pseudo-surgical' patients, and as such, go through pre-, peri-, and post-operative moments.
- Anemia can be due to a combination of a chronic factor and an acute one (easier to identify).
- The transfusion of large volumes can lead to an increase in portal hypertension and make the bleeding worse.

The document *Indications and hemoglobin thresholds for red blood cell transfusion and iron replacement in adults with gastrointestinal bleeding: An algorithm proposed by gastroenterologists and patient blood management experts*[2] is based on **three clear ideas**:

Need of a protocol to manage anemia and iron deficiency in GI bleeding

Red blood cell transfusion restrictive model (1-unit policy)

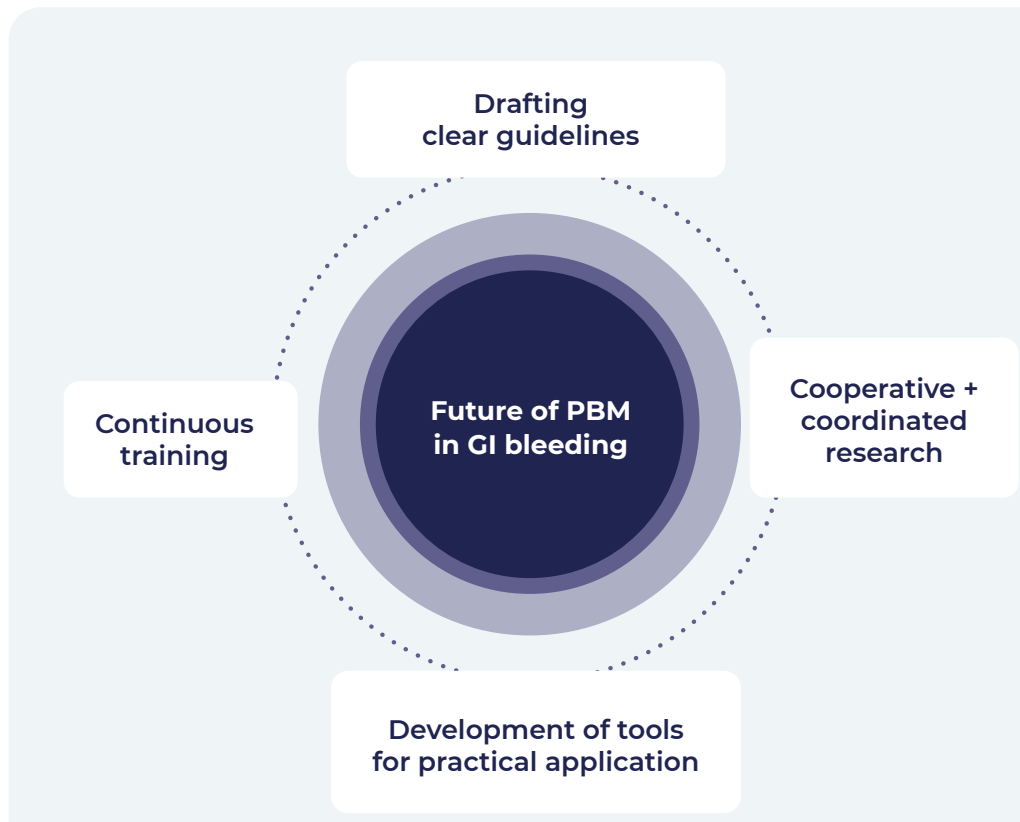
Safe effective use of intravenous iron

Relevant points included in the publication:

- Algorithm om the consideration of risk factors and organic dysfunction. It considers the possibility of a transfusion together with the administration of iron
- Indication of viscoelastic tests in the management of the coagulopathy, exclusively in patients with hemorrhagic shock.
- Use of tranexamic acid, fibrinogen, and prothrombin complex in specific cases in which this is indicated, not as a routine.

Relevant resources for the implementation of a PBM in gastrointestinal bleeding

- Human and material resources: On-duty endoscopist, liver hemodynamic laboratory, massive transfusion protocol, interventional radiology, etc.
- Reference documentation, ideally based on clinical cases.
- Relationship with control and regulatory institutions
- Institutional support



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CSL Behring

Update topics 2

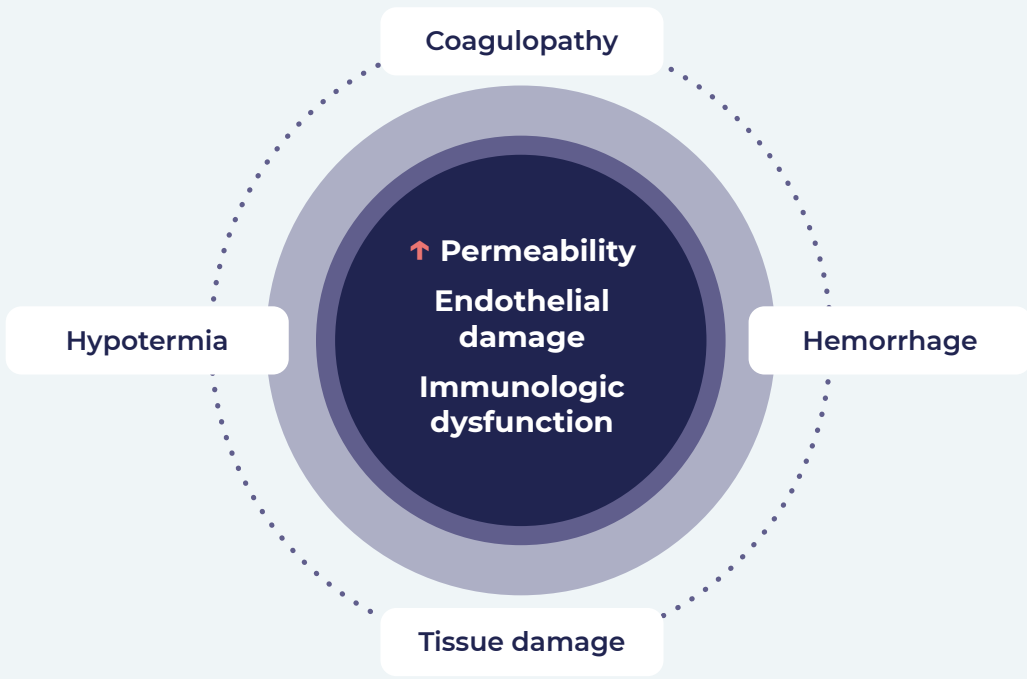
Moderator: Dr. Gabriel Yanes

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

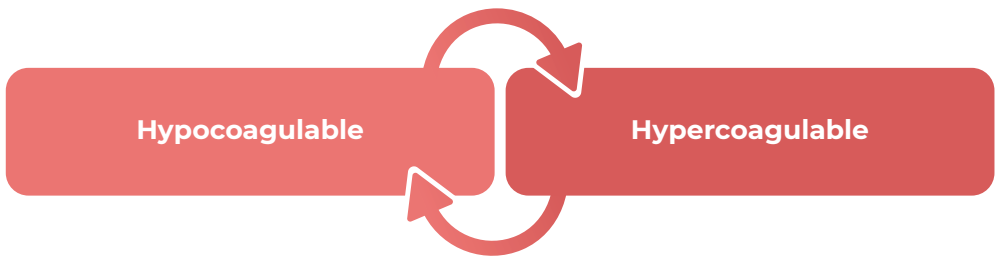
1. WHAT IS TRAUM-INDUCED COAGULOPATHY AND HOW TO TREAT IT?

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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Update Topics 2

Moderator: Dr. Gabriel Yanes

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

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.

Update topics 2

Moderator: Dr. Gabriel Yanes

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

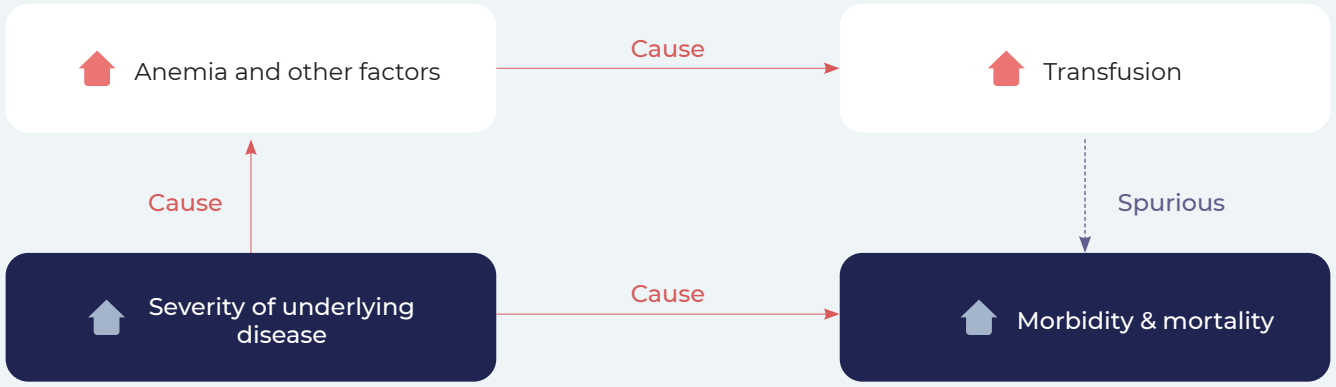
3. THE EFFECTIVENESS OF RED BLOOD CELL TRANSFUSION IN NON-BLEEDING PATIENTS. ANY EVIDENCE? HEMATOLOGIST PERSPECTIVE

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.

Update topics 2

Moderator: Dr. Gabriel Yanes

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

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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Update topics 2

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

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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