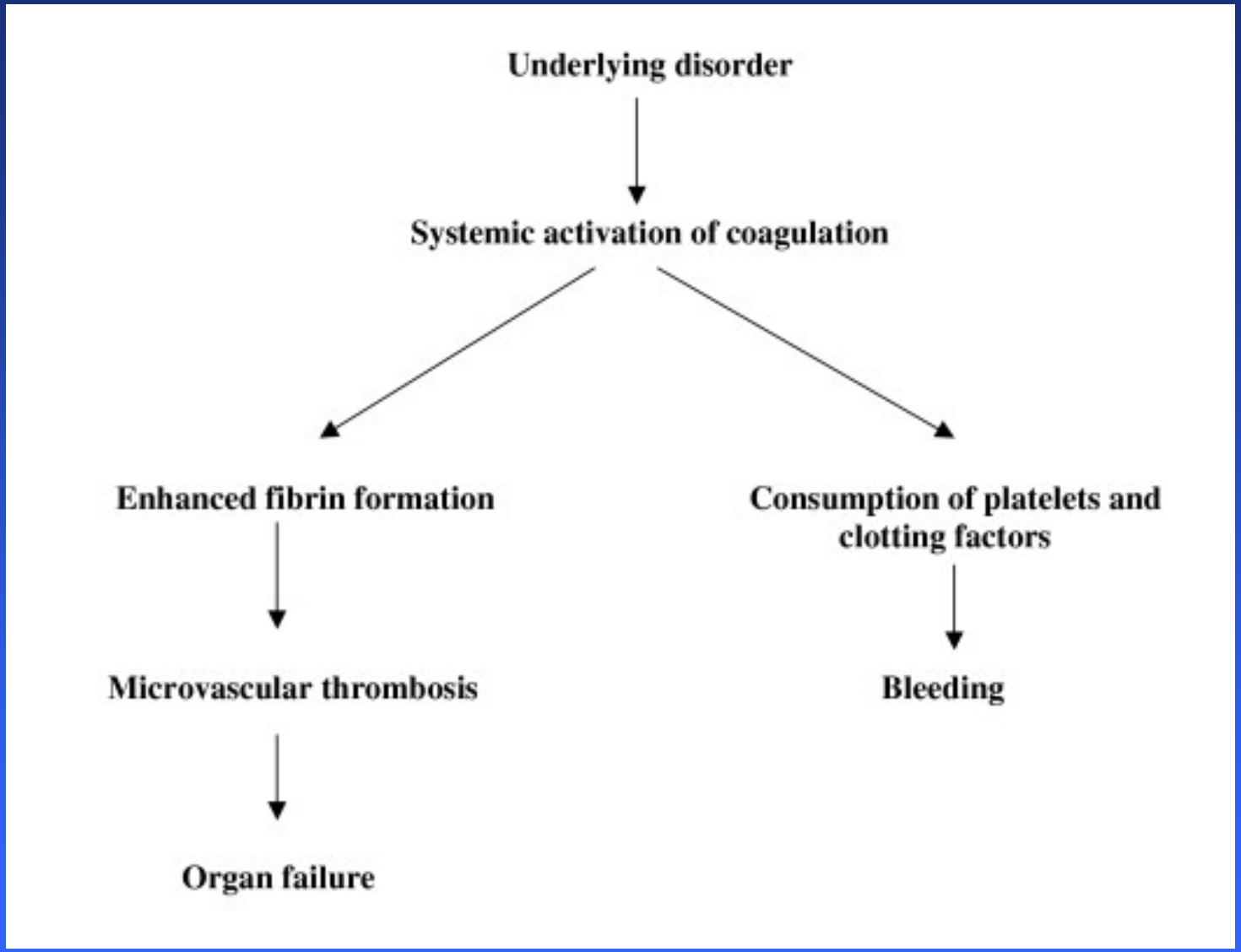
XXIV SISET – Master Classes
Abano Terme, 11 novembre 2016

Diagnosi e terapia della CID

Alessandro Squizzato

Centro di Ricerca 'Malattie Tromboemboliche e Terapie Antitrombotiche'

Dipartimento di Medicina Clinica e Sperimentale
Università dell'Insubria - Varese


Underlying disorder
Systemic activation of coagulation
Enhanced fibrin formation
Consumption of platelets and clotting factors
Microvascular thrombosis
Bleeding
Organ failure

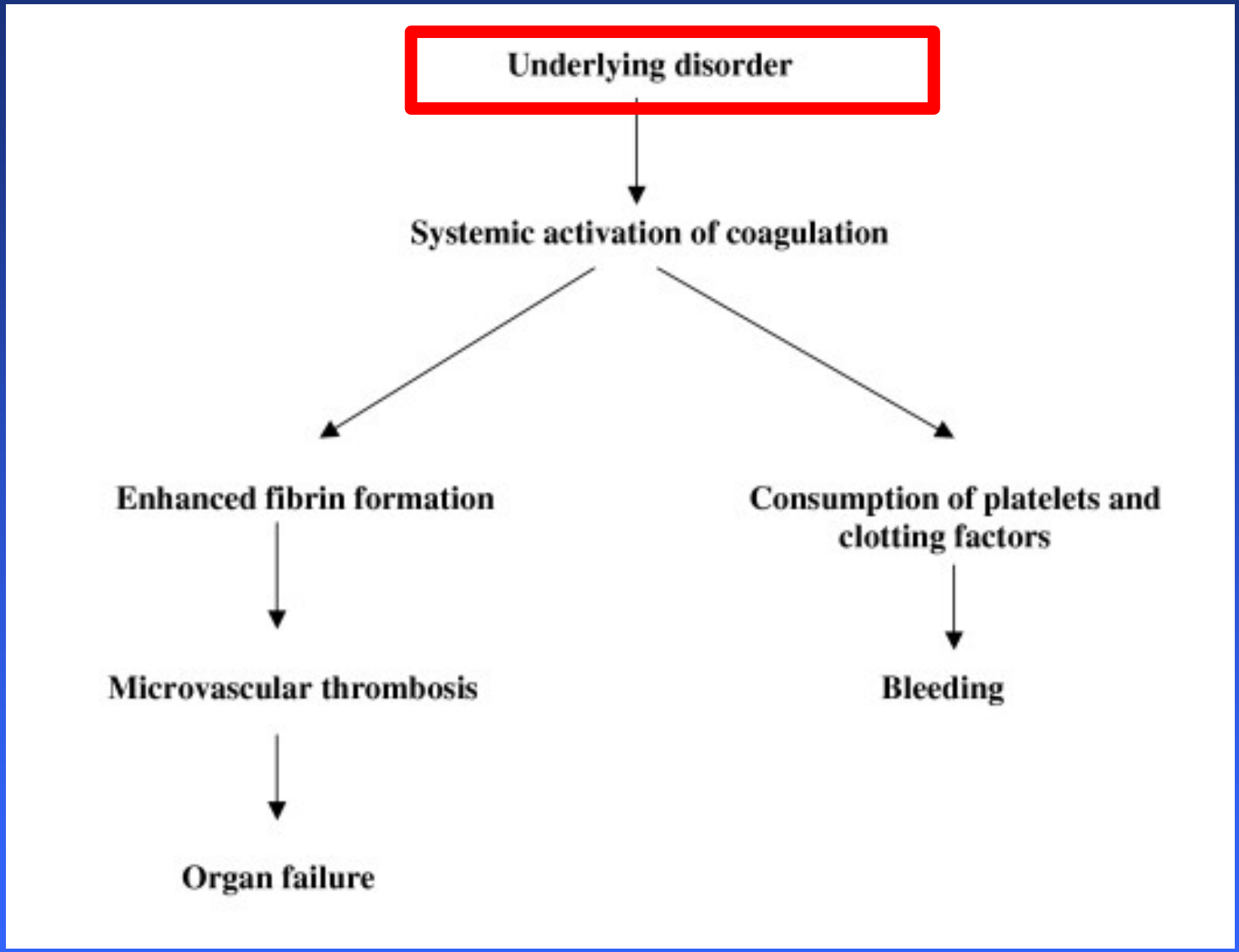
Quale terapia …?

1. Cura della patologia sottostante ?

2. Anticoagulante ??

3. Terapia di supporto ?

(previene e/o cura le ‘complicanze’)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Organ failure

Table 1 Differences in recommendations among three guidelines from BCSH, JSTH, and SISET and harmonized ISTH/SSC guidance

	BCSH	JSTH	SISET	ISTH/SSC
Scoring system for DIC	R; grade C	R[a]	R; grade C	R; high quality
Single test analysis for DIC	NR	NR[a]	NR; grade D	R high quality
Treatment of underlying disease	R; grade C	R; consensus	R; cornerstone	R; moderate quality
Platelet concentration	R; grade C	R; consensus	R; grade D	R; low quality
FFP	R; grade C	R; consensus	R; grade D	R; low quality
Fibrinogen, cryoprecipitate	R; grade C	Disregard	R; grade D	R; low quality
FVIIa	Disregard	Disregard	NR; grade D	NM
UFH (treatment)	R; grade C	R; level C	NR; grade D	R; low quality
UFH (prophylaxis for VTE)	R; grade A	Disregard	R	R; high quality
LMWH	Disregard	R; level B2	R; grade D	Preferred to UFH
Heparin sulfate	Disregard	R; level C		NM
Synthetic protease	Disregard	R; level B2	NR; grade D	NM
rhAPC	R; grade A	Disregard	R; grade D	Need for further Ed from RCT
AT	NR; grade A	R; B1	NR; grade D	Need for further Ed from RCT
rhTM	Disregard	Disregard	NR; grade B	Need for further Ed from RCT
Antifibrinolytic agents	R; grade C	NR; level D		R; low quality
Plasma exchange	Disregard	Disregard	NR; grade D	NM

R, recommendation; NR, not recommendation; R[a], suggestive recommendation; NM, not mention; Ed, evidence; FFP, fresh frozen plasma; PCC, FVIIa, activated coagulation factor VII; UFH, unfractionated heparin; LMWH, low molecular weight heparin; rh, recombinant human; APC, activated protein C; AT, antithrombin; TM, thrombomodulin; RCT, randomized control trial.

Linee Guida

Thrombosis Research xxx (2011) xxx–xxx

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Mini Review

Diagnosis and treatment of disseminated intravascular coagulation: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET)☆

Marcello Di Nisio [a,*], Francesco Baudo [b], Benilde Cosmi [c], Armando D'Angelo [d], Andrea De Gasperi [e], Alessandra Malato [f], Mario Schiavoni [g], Alessandro Squizzato [h]
on behalf of the Italian Society for Thrombosis and Haemostasis

[a] Department of Medicine and Aging, Centre for Aging Sciences (Ce.S.I.), "University G. D'Annunzio" Foundation, Chieti, Italy
[b] Department of Haematology, Niguarda Hospital, Milan, Italy
[c] Unit of Angiology and Coagulation Disorders "Marino Golinelli", Policlinic S. Orsola-Malpighi, Bologna, Italy
[d] Coagulation Service and Thrombosis Research Unit, San Raffaele Hospital IRCCS, Milan, Italy
[e] Department of Anaesthesiology and Intensive Care II, Niguarda Hospital, Milan, Italy
[f] Department of Haemostasis and Haematology, Policlinic P. Giaccone, Palermo, Italy
[g] Department of Internal Medicine, Thrombosis and Haemostasis Center, Scorrano-Lecce, Italy
[h] Research Center on Thromboembolic disorders and Antithrombotic Therapies, Department of Clinical Medicine, University of Insumbria, Varese, Italy

Patologia sottostante

controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

not been proved with randomised controlled trials

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Terapia anticoagulante

D Nei pazienti con sepsi con CID non si suggerisce l'uso dell'antitrombina

D Nelle pazienti ostetriche con CID non si suggerisce l'uso dell'antitrombina

D In pazienti epatopatici con CID non si suggerisce l'uso dell'antitrombina

---

D Nei pazienti con neoplasie ematologiche e CID non si suggerisce l'uso del dermatan solfato

Terapia anticoagulante

D Nei pazienti con sepsi, politraumatizzati, chirurgici, ostetriche, con neoplasie solide e CID non si suggerisce l'uso dell'eparina non frazionata ad esclusione della profilassi del tromboembolismo venoso nella CID senza sanguinamento

D Nei pazienti con sepsi, politraumatizzati, chirurgici, ostetriche, con neoplasie solide e CID non si suggerisce l'uso dell'eparina a basso peso molecolare ad esclusione della profilassi del tromboembolismo venoso nella CID senza sanguinamento

D Nei pazienti con anomalie vascolari o epatopatici con diagnosi di CID non si suggerisce l'uso dell'eparina non frazionata o dell' eparina a basso peso molecolare

D Nei pazienti con neoplasie solide, ostetriche, con ferita da arma da fuoco e CID non si suggerisce l'uso routinario del fattore VII attivato ricombinante in caso di emorragia

Terapia anticoagulante

D Nei pazienti con sepsi, chirurgici, con neoplasie solide o ematologiche e CID non si suggerisce l'uso del gabesato

D Nei pazienti con sepsi severa/shock settico con alto rischio di mortalità e APACHE II>25 (per EMEA almeno 2 organi compromessi) e CID si suggerisce l'uso della proteina C attivata ricombinante

D Nelle pazienti ostetriche e CID non si suggerisce l'uso della proteina C attivata

D Nei pazienti con sepsi e CID non si suggerisce l'uso della proteina C zimogeno

D Nei pazienti con sepsi o con neoplasie ematologiche e CID non si suggerisce il plasma exchange

Trombomodulina ricombinante

Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial.

Saito H, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N, Ohno R, Hirayama A, Matsuda T, Asakura H, Nakashima M, Aoki N.

J Thromb Haemost. 2007;5(1)

Trombomodulina ricombinante

A randomized, double-blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation.

Vincent JL, Ramesh MK, Ernest D, LaRosa SP, Pachl J, Aikawa N, Hoste E, Levy H, Hirman J, Levi M, Daga M, Kutsogiannis DJ, Crowther M, Bernard GR, Devriendt J, Puigserver JV, Blanzaco DU, Esmon CT, Parrillo JE, Guzzi L, Henderson SJ, Pothirat C, Mehta P, Fareed J, Talwar D, Tsuruta K, Gorelick KJ, Osawa Y, Kaul I.

Crit Care Med. 2013;41(9).

Quale terapia …
… cambia la prognosi ?

1. **Cura della patologia sottostante: SI !!**

2. **Anticoagulante: ??**

3. **Terapia di supporto …**
   (previene e/o cura le ‘complicanze’)

Terapia di supporto

D Nei pazienti con CID e sanguinamento in atto si suggerisce l'uso di terapia di supporto (trasfusione di piastrine, plasma, crioprecipitato)

D Nei pazienti con CID cronica o senza emorragia non si suggerisce l'uso di terapia di supporto (trasfusione di piastrine, plasma, crioprecipitato) indipendentemente dai risultati di test di laboratorio

Supportive management strategies for disseminated intravascular coagulation

An international consensus

Alessandro Squizzato[1]; Beverley J. Hunt[2]; Gary T. Kinasewitz[3]; Hideo Wada[4]; Hugo ten Cate[5]; Jecko Thachil[6]; Marcel Levi[7]; Vicente Vicente[8]; Armando D'Angelo[9]; Marcello Di Nisio[7,10]

[1]Research Center on Thromboembolic Disorders and Antithrombotic Therapies, Department of Clinical and Experimental Medicine, University of Insubria, Varese, Italy; [2]Department of Haematology, Pathology and Lupus, Guy's & St Thomas' NHS Foundation Trust, London, UK; [3]Pulmonary and Critical Care Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA; [4]Department of Molecular and Laboratory Medicine, Mie University School of Medicine, Mie, Japan; [5]Department of Internal Medicine and Cardiovascular Research Institute, Maastricht University Medical Center, Maastricht, The Netherlands; [6]Department of Haematology, Manchester Royal Infirmary, Manchester, UK; [7]Department of Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; [8]Division of Hematology and Clinical Oncology, Hospital Universitario Morales Meseguer, Murcia, Spain; [9]Coagulation Service and Thrombosis Research Unit, Scientific Institute San Raffaele, Milano, Italy; [10]Department of Medical, Oral, and Biotechnological Sciences, Università "G. D'Annunzio" of Chieti-Pescara, Chieti, Italy

Summary

The cornerstone of the management of disseminated intravascular coagulation (DIC) is the treatment of the underlying condition triggering the coagulopathy. However, a number of uncertainties remain over the optimal supportive treatment. The aim of this study was to provide tion and control groups. The experts' approach was heterogeneous, although there was consensus that supportive management should vary according to the underlying cause, clinical manifestations and severity of blood test abnormalities. Platelet transfusion should be given to maintain platelet count $>50\times10^9$/l in case of bleeding while a lower

Domande

1. How would you treat a patient with overt DIC, no bleeding, no thrombosis, and a treatable underlying disorder (i.e. pro-myelocitic leukemia; severe sepsis; pregnant complications)?

2. How would you treat a patient with overt DIC, minor bleeding (e.g. bruising, epistaxis), and an untreatable underlying disorder? Refer specifically to patients with an underlying metastatic solid cancer and specify: how long would you continue your treatment (in particular, plasma and/or Plt transfusion)?

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1	Gabexate and platelet transfusion for patients with pro-myelocitic leukemia; antithrombin for septic patients; gabexate for pregnant women
2	Prophylactic low-molecular weight heparin for all three conditions
3	For patients with pro-myelocitic leukemia, we use a Plt threshold of 50,000/mm3; below this threshold platelets are transfused. Furthermore, the hemoglobin level is maintained above 9 g/L, with a hematocrit of 30% to add to an optimal function of platelets. For septic patients, VTE prophylaxis with low molecular weight heparin, even in the existence of laboratory abnormalities. For pregnant women without an obvious clinical phenotype, prophylactic low molecular weight heparins will be administered during the bedbound period in the puerperium
4	For patients with pro-myelocitic leukemia, I would assess PT, aPTT, D-dimer and Plt count. In those with an overt DIC I would replace missing constituents and give LMWH to switch off the thrombotic drive due to TF; those with a primary hyperfibrinolytic state I would administer tranexamic acid. For septic patient, only monitoring unless a bleeding or thrombotic problem develop. For pregnant women, only monitoring unless there is bleeding or thrombosis. If the patient needs an epidural or spinal anesthetic, I would recommend against; in case of surgery, I would ensure adequate fibrinogen and platelet count
5	If the platelets counts is <30,000/mm3 or fibrinogen <150 mg/dL, Plt and cryoprecipate transfusion for all three conditions. After delivery (24-48 hours and without presence of bleeding), we consider starting anticoagulant prophylaxis with LMWH.
6	Tranexamic acid for patients with pro-myelocitic leukemia; FFP for pregnant women; and only monitoring for sepsis
7	For patients with pro-myelocitic leukemia, my treatment is based on the clinical presentation; if the patient has thrombotic presentation, I will commence intravenous heparin first due to the associated thrombocytopenia and high bleeding risk. If the patient has active bleeding, I will replace predominantly fibrinogen and platelets with laboratory markers to guide me. I will aim for lab values of fibrinogen >1.5 g/dl and platelets >

Table 4: Final recommendations.

1. Patient with DIC, without bleeding or thrombosis (i. e. non-overt / non-symptomatic type), with a treatable underlying disorder	
Recommendation	In a patient with overt DIC, without bleeding or thrombosis, and with a treatable underlying disorder, there was consensus that physicians should provide an individualised supportive strategy according to the underlying condition triggering the coagulopathy. In DIC patients with acute promyelocytic leukaemia, we suggest prophylactic platelet transfusion to maintain a platelet level at least above 20×10^9/l; in severe sepsis, we suggest prophylactic dose of LMWH and prophylactic platelet transfusion to maintain a platelet level at least above 20×10^9/l; in DIC secondary to pregnancy complication, we suggest prophylactic dose of LMWH, in particular during the post-partum period, and prophylactic platelet transfusion to maintain a platelet level at least above 20×10^9/l.
2. Patient with overt DIC, minor bleeding, and an untreatable underlying disorder	
Recommendation	Haemostatic transfusion support with blood products should be given for a limited period of time to a patient with DIC, minor bleeding and an underlying untreatable disorder. In particular, we suggest to continue with platelet transfusion till bleeding cease and to maintain a platelet level at least above 20×10^9/l.
3. Platelet count in patient with overt DIC	
Recommendation	A platelet count $>50 \times 10^9$/l is suggested in all DIC patients with an active major bleeding. In non-bleeding patients, the trigger for platelet transfusion is between 20 and 30×10^9/l.
4. Duration of VTE prophylaxis in patient with overt DIC	
Recommendation	Pharmacological VTE prophylaxis should be stopped in case of bleeding or when platelet count is less than 30×10^9/l and/or PT ratio is more than 1.5 and/or aPTT ratio is more than 1.5 and/or fibrinogen level <1 g/l.
5. Acute DVT and/or PE in patient with overt DIC and concomitant bleeding	
Recommendation	We suggest the use of a retrievable IVC filter in DIC patients with acute VTE and concomitant bleeding. When bleeding has ceased, risks and benefits of starting anticoagulation should be assessed daily through the close monitoring of the patient's clinical status, laboratory tests and treatment of the underlying condition.

Domande

3. **Do you always try to achieve Plt levels > 50,000 / mm^3 ?**

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Squizzato et al. Haemostatic and antithrombotic management of DIC

Domande

4. In case you start pharmacological VTE prophylaxis, when do you consider to stop it (when the patient bleeds, when Plts are low (please indicate a cut-off), when PT e/o aPTT are prolonged (please indicate a cut-off), or a combination of these conditions)?

5. How would you treat an acute DVT and/or PE in patients with overt DIC and concomitant bleeding? Do you consider an inferior vena cava filter?

Table 4: Final recommendations.

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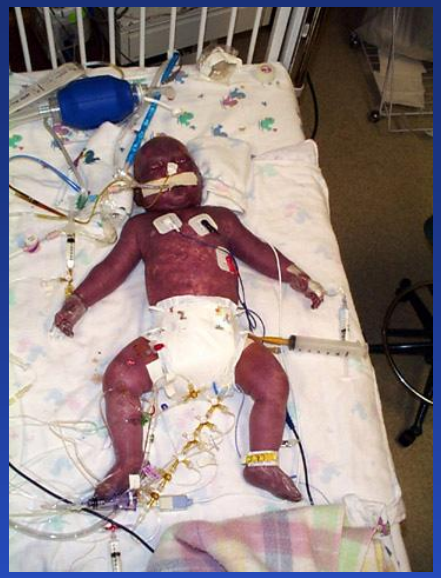
Squizzato et al. Haemostatic and antithrombotic management of DIC

CONCLUSIONI – parte 1

Death
Is
Coming



1. **Non esiste la DIC ‘idiopatica’**

2. **Prognosi riservata ‘per definizione’**

3. **Rapida diagnosi e cura della patologia sottostante**

CONCLUSIONI- parte 2 (molto personali)

Table 1 Clinical conditions that may be associated with overt DIC

- sepsis/severe infection (any micro-organism)
- trauma (e.g. polytrauma, neurotrauma, fat embolism)
- organ destruction (e.g. severe pancreatitis)
- malignancy
  - solid tumors
  - myeloproliferative/lymphoproliferative malignancies
- obstetrical calamities
  - amniotic fluid embolism
  - abruptio placentae
- vascular abnormalities
  - Kasabach-Merrit Syndrome
  - large vascular aneurysms

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thrombin generati
severity of DIC. A
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helpful in establi
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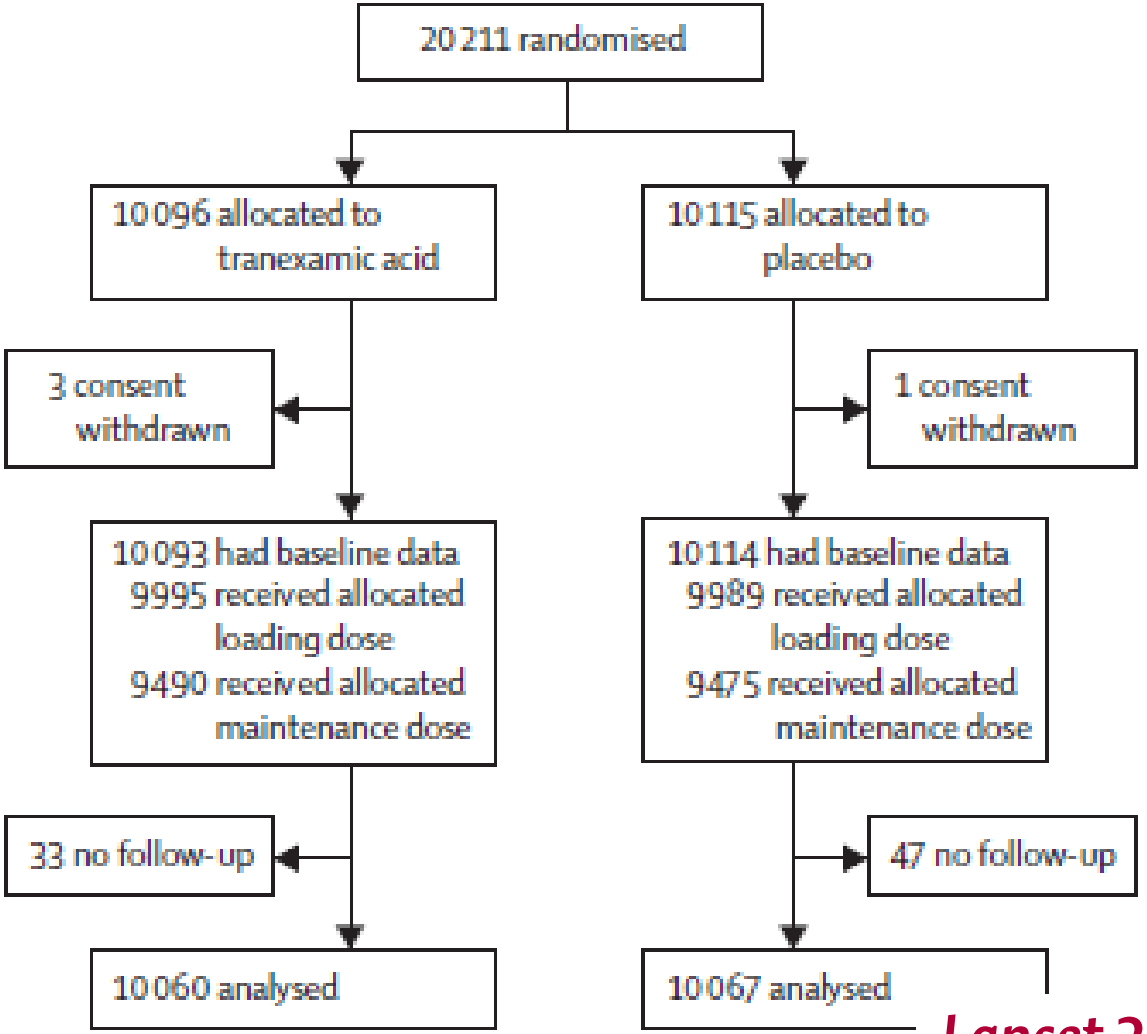
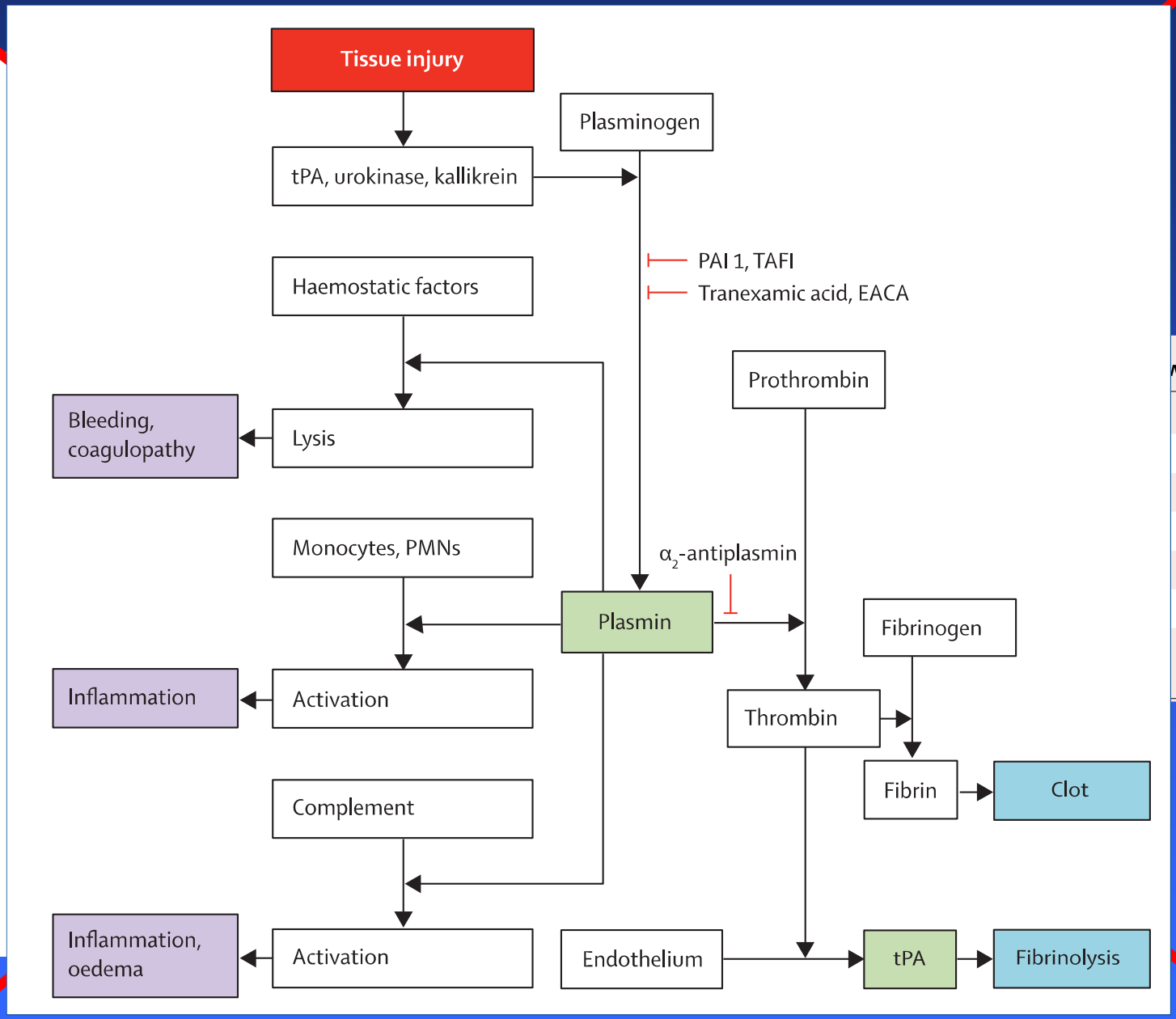
ciently sensitive.
5. In considering mc
these tests have gr
hemostatic activat

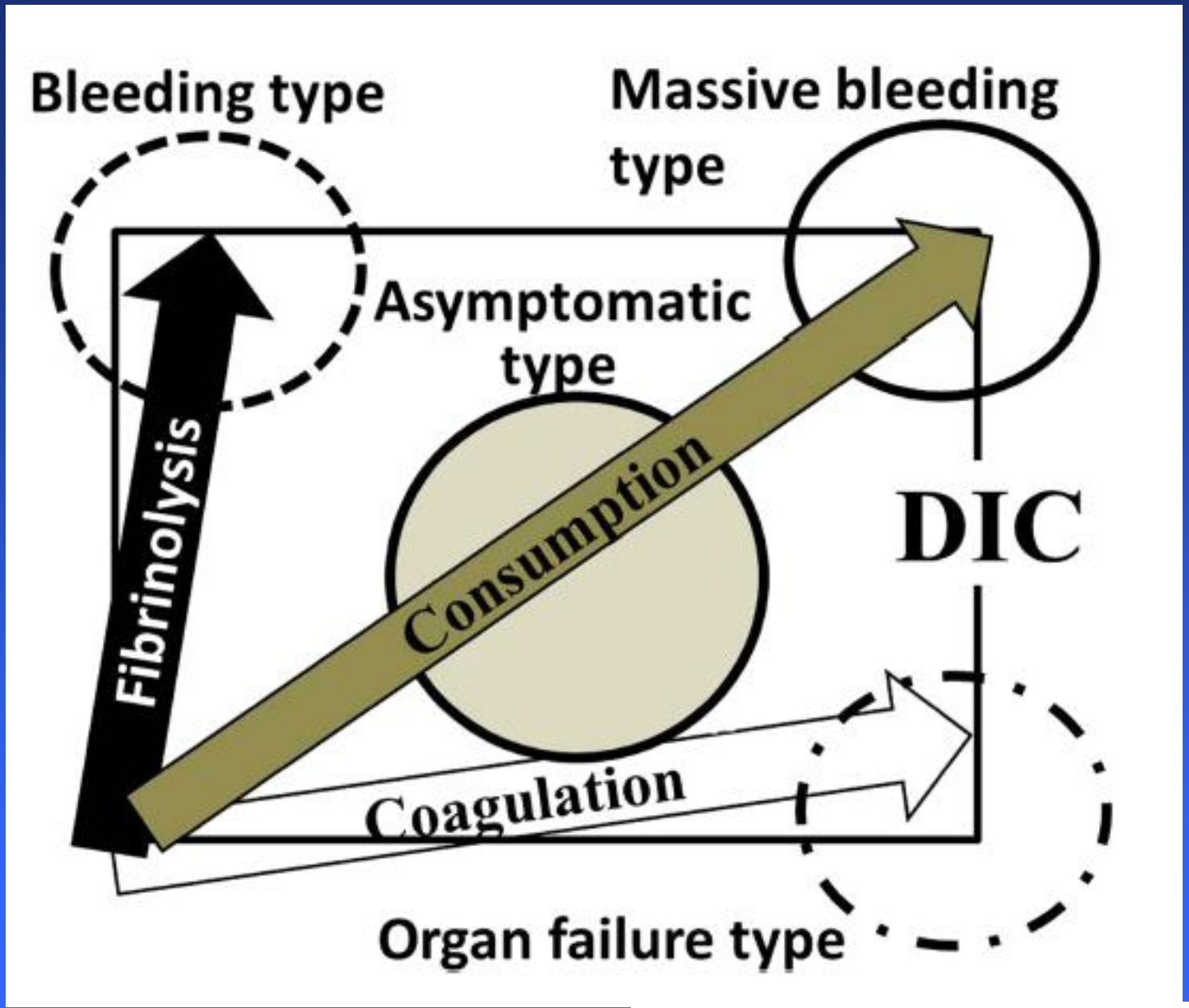
Diapositiva ‘rubata’ a Paolo Severgnini

CRASH-2



Lancet 2010; 376: 23–32


Tissue injury
Plasminogen
tPA, urokinase, kallikrein
PAI 1, TAFI
Tranexamic acid, EACA
Haemostatic factors
Prothrombin
Bleeding, coagulopathy
Lysis
Monocytes, PMNs
α2-antiplasmin
Plasmin
Fibrinogen
Inflammation
Activation
Thrombin
Fibrin
Clot
Complement
Inflammation, oedema
Activation
Endothelium
tPA
Fibrinolysis

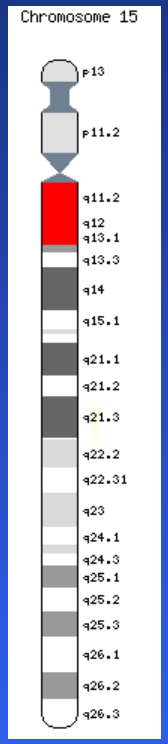


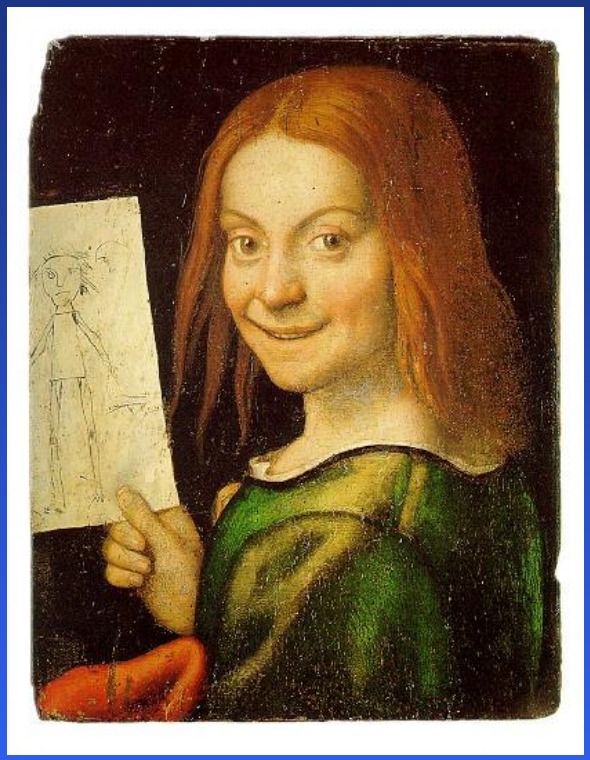
Wada *et al. Journal of Intensive Care* 2014, **2**:15

DIC: disease-induced coagulopathy

1. TIC: trauma-induced coagulopathy
2. SIC: sepsis-induced coagulopathy
3. CIC: cancer-induced coagulopathy
4. LIC: leukemia-induced coagulopathy
5. AIC: aneurysm-induced coagulopathy
6. …

Squizzato®





The Angelman Syndrome

1965, Verona

"Boy with a Puppet" or "A child with a drawing" by
Giovanni Francesco Caroto, Castelvecchio Museum, Verona
Italy

”I may not speak, but I have much to say”

The ‘Angel’ Pietro

Table 1. Laboratory Findings in Various Platelet and Coagulation Disorders in the ICU.

Condition	Prothrombin Time	Activated Partial-Thromboplastin Time	Fibrinogen Level	D-Dimer Level	Bleeding Time	Platelet Count	Findings on Blood Smear
Vitamin K deficiency or use of vitamin K antagonist	Prolonged	Normal or mildly prolonged	Normal	Unaffected	Unaffected	Unaffected	
Aspirin or thienopyridines	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Liver failure							
Early stage	Prolonged	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	
End stage	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	
Uremia	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Disseminated intravascular coagulation	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	Fragmented red cells
Thrombotic thrombocytopenic purpura	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Very low	Fragmented red cells
Hyperfibrinolysis	Prolonged	Prolonged	Low	Very high	Possibly prolonged	Unaffected	

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