Bone marrow carcinosis and disseminated intravascular coagulation (DIC)

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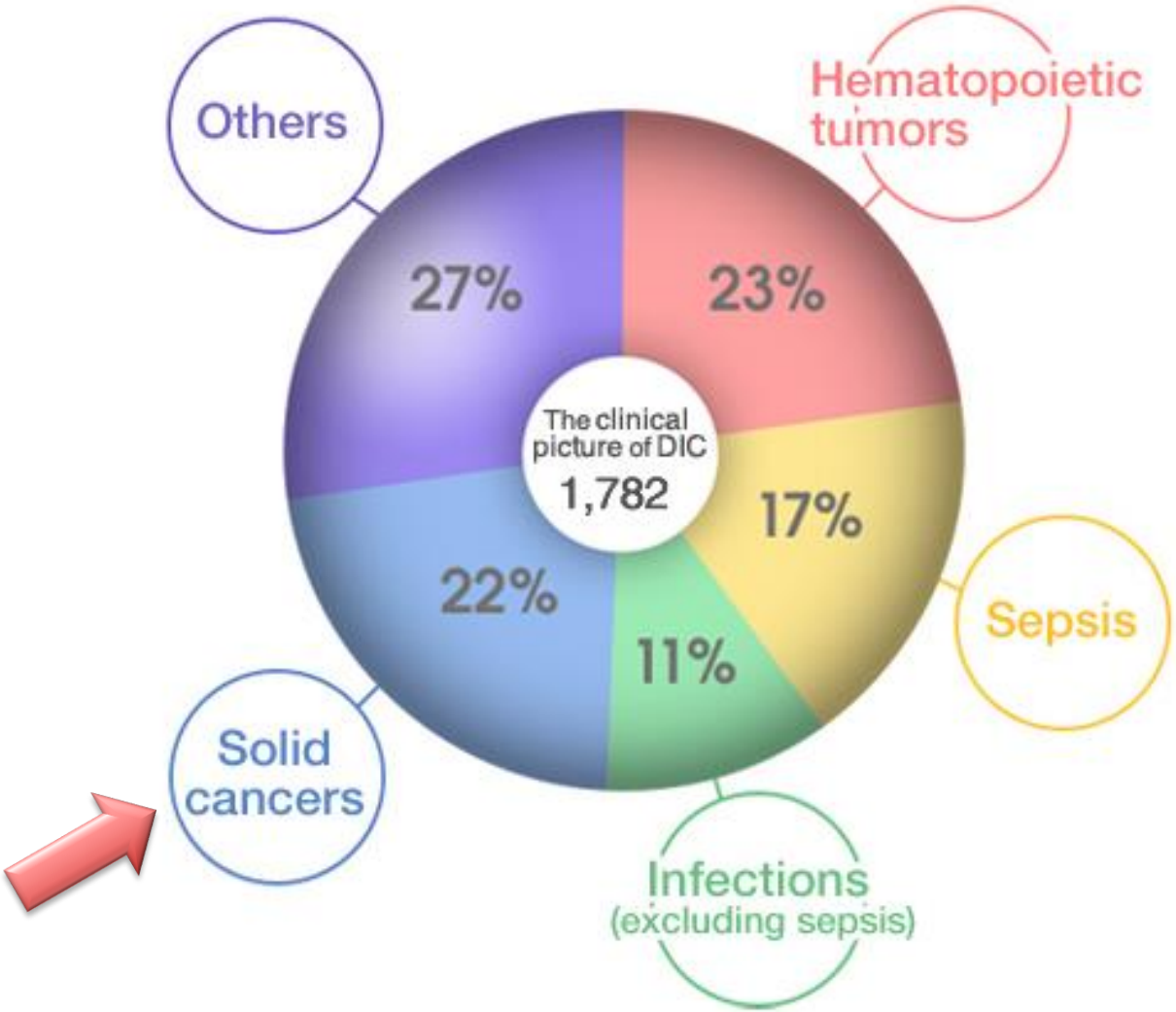
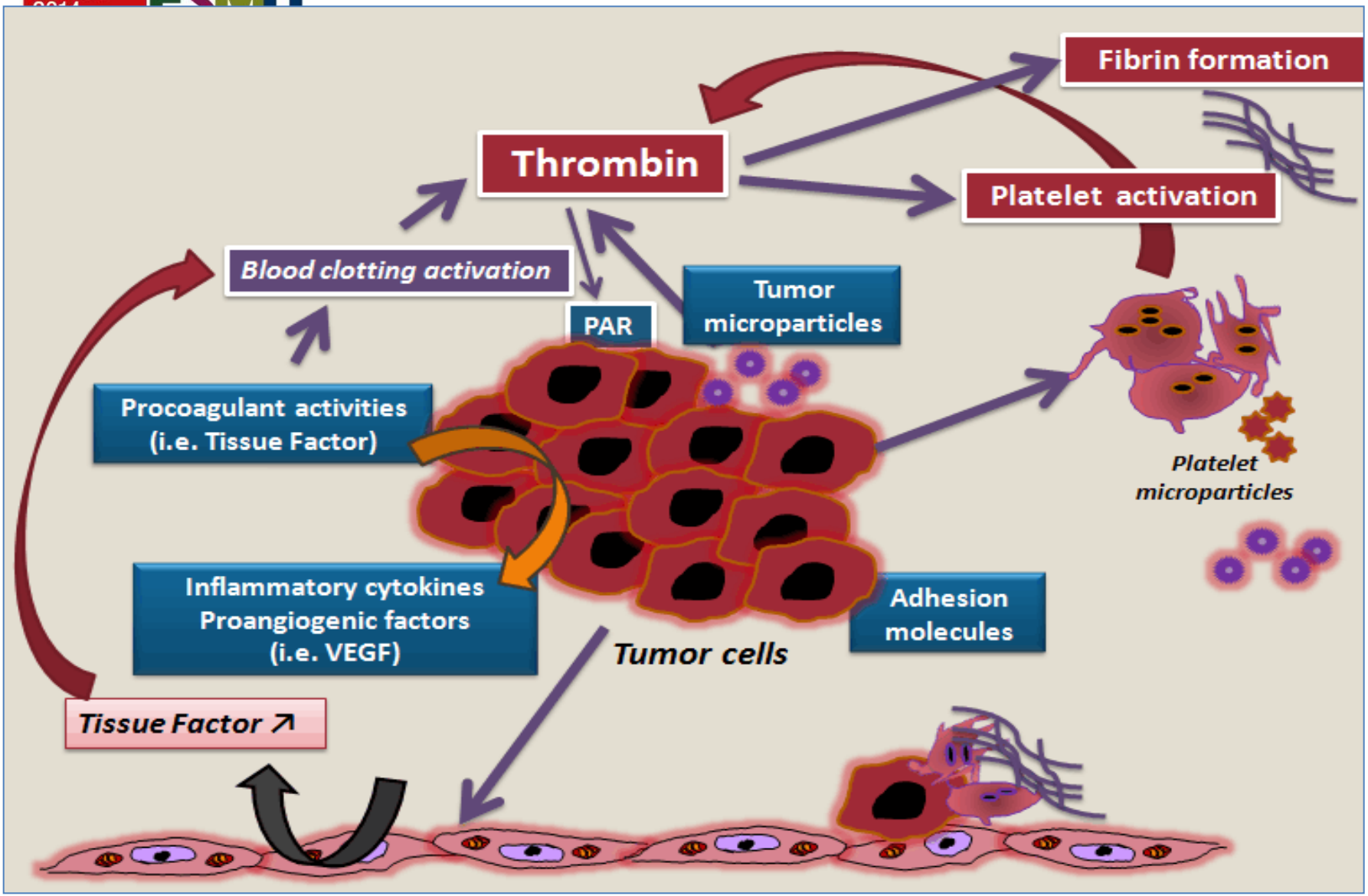
Thrombosis, DIC and cancer

- Patients with cancer have a 'Hypercoagulable state' (i.e., increased activation of blood coagulation), which predisposes to clotting complications.
- These complications span from localized thrombosis of large vessels to systemic manifestations, the most extreme form being the **disseminated intravascular coagulation (DIC)**.
- Finally, a specific presentation of cancer-related coagulopathy, often difficult to distinguish from DIC, is the thrombotic microangiopathic disease.

Underlying diseases in DIC patients



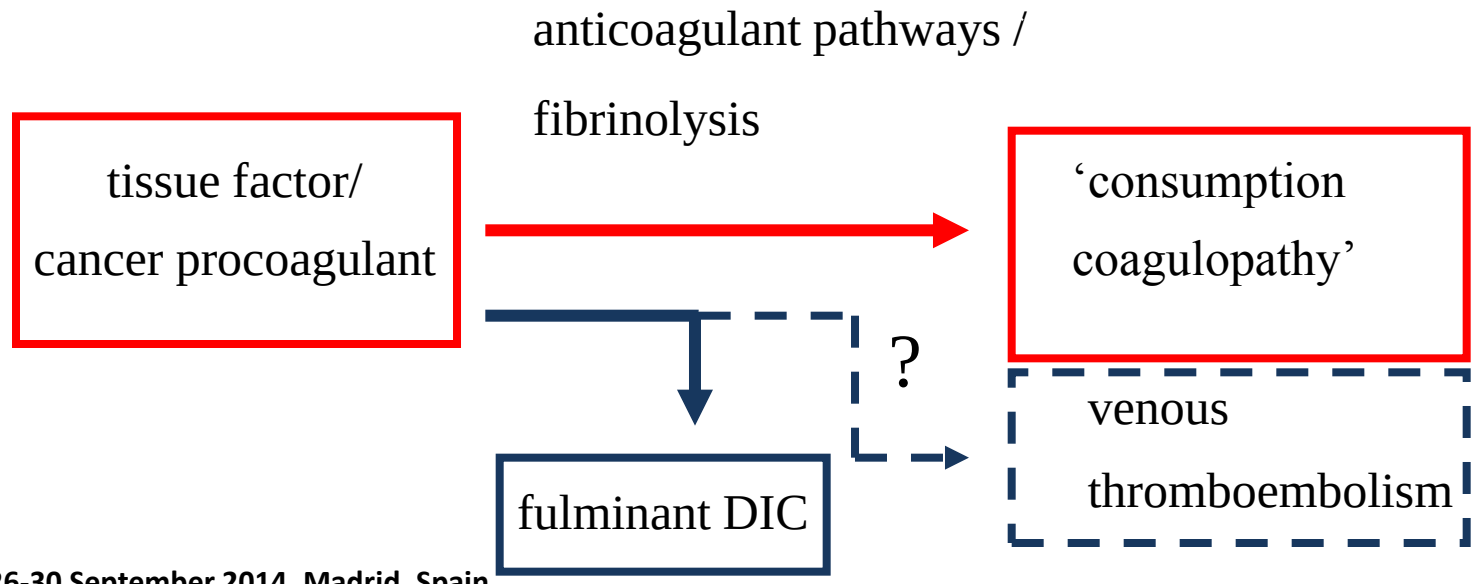
Nakagawa et al, 2014



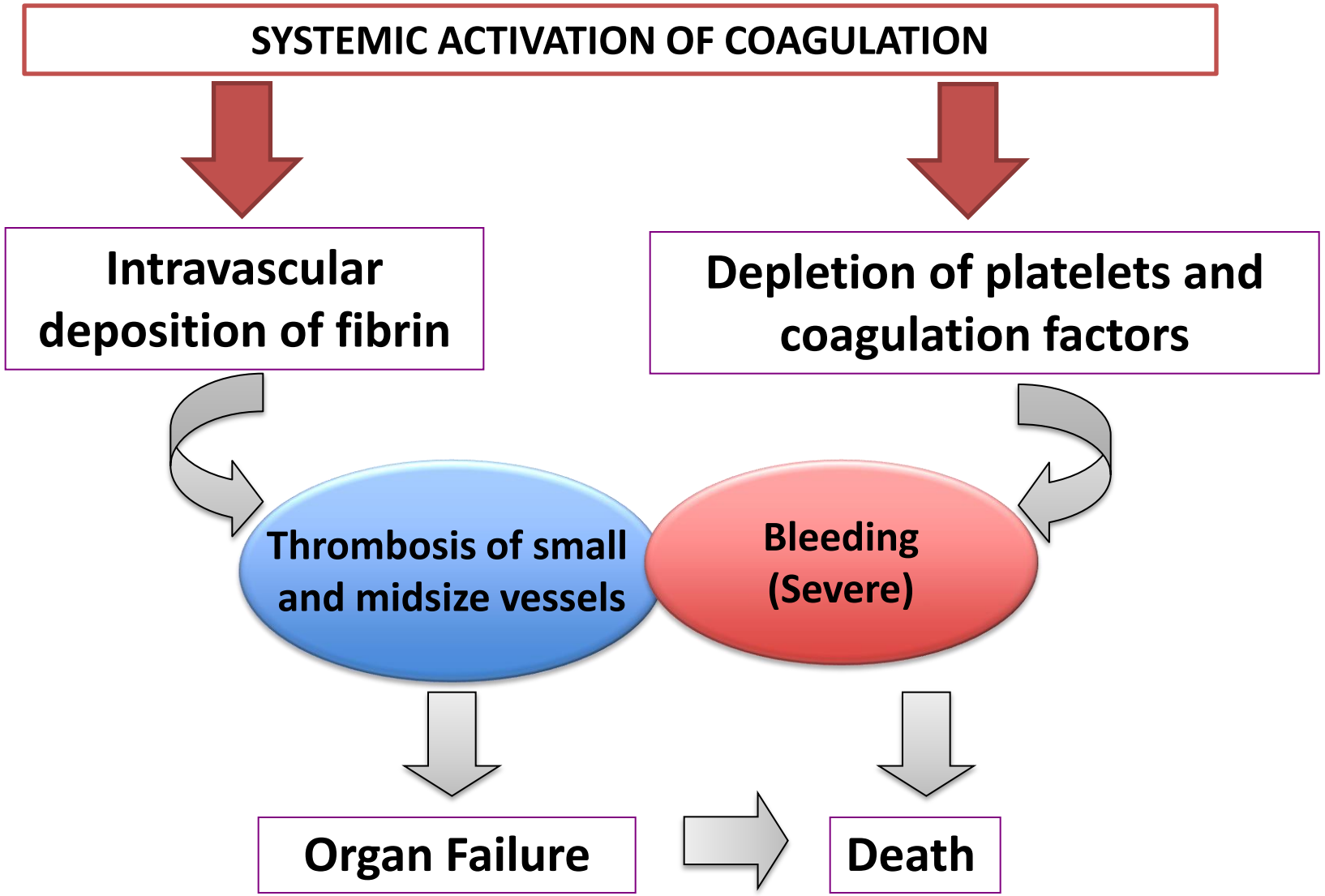
Falanga A, The Hematologist 2011

PATHOGENESIS OF CANCER COAGULOPATHY

- clear procoagulant stimulus
- thrombin generation is relatively contained by upregulation of physiologic anticoagulant pathways
- fibrin deposition is balanced by hyperfibrinolysis



The clinical picture of cancer coagulopathy



Levi M. et al., Sem Thromb Hemost 2001

Cancers commonly associated with DIC

CLINICAL PARAMETER	CANCER TYPE
Acute DIC **(localized or systemic bleeding, echymosis)**	• Acute promyelocytic leukemia (APL) • Acute non-M3 myeloid leukemia (AML) • Acute lymphocytic leukemia (ALL) • **Prostate cancer** • Mucin-producing adenocarcinomas (e.g., pancreatic, gastrointestinal, ovary, thyroid, gallbladder) • Lymphoma (e.g., Stage IV, natural killer) • Chronic myelocytic leukemia (CML)
Chronic DIC **(Thrombosis)**	• Solid tumors (e.g., lung, breast, prostate, pancreatic cancer)

Saba H.I. et al. In: Cancer Treatment and Research 2009

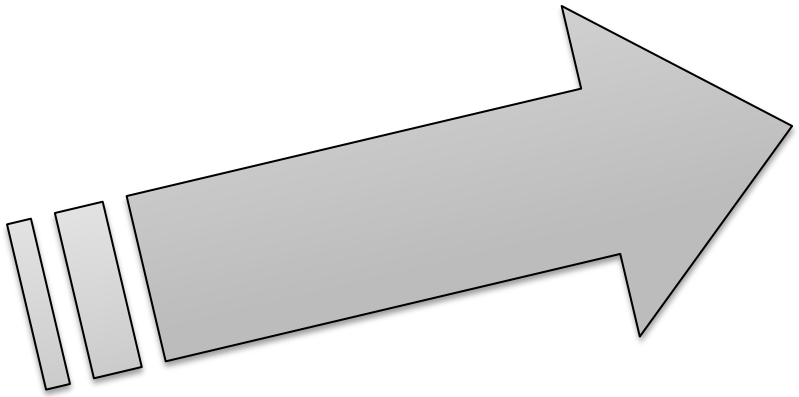
CLINICAL MANIFESTATIONS OF DIC

ACUTE DIC

HEMORRHAGE

MILD

-Petechiae
-Purpura
-Mucous membrane bleed
-Oozing from venipuncture



SEVERE

-Surgical wound bleeding
-Hemoptysis
-Hematuria
-Gastrointestinal bleeding
-Intracranial, deep tissue and intramuscolar bleeding

THROMBOSIS

Concurrent signs of thrombosis (e.g. acral cyanosis and gangrene of extremities) can be present

CLINICAL MANIFESTATIONS OF DIC

CHRONIC OR COMPENSATED DIC

Thrombosis

Abnormalities of laboratory tests of clotting activation, alone

Local or diffuse Thrombosis (usually venous) ± mild signs of hemorrhage

Laboratory features of DIC in cancer patients

Laboratory Parameter	Acute DIC	Chronic DIC
Relative Platelet count	Low	Variable
Peripheral Smear RBC	Schistocytes	Schistocytes
PT, APTT, TT	Prolonged	Normal to mildly prolonged
Fibrinogen	Low	Normal to elevated
Factors V, VIII	Low	Normal
FDP	High	High
D-dimers	High	High
Prothrombin frag. F1+2	High	High
Proteins C and S	Low	Normal to low
Antithrombin	Low	Normal to low

Saba H.I. et al. In: Cancer Treatment and Research 2009, Chap. 9

DIFFERENTIAL DIAGNOSIS OF DIC

	CLINICAL FINDINGS	LABORATORY FINDINGS
DIC	• **Underlying clinical situation (cancer, sepsis …)** • **Haemorrhages and/or thrombosis** • **Shock**	• **Thrombocytopenia** • **↑ PT** • **↑ APTT** • **Positive D-dimer test** • **↓ Fibrinogen**
Thrombosis	• Venous thrombosis • Pulmonary embolism	• Increased platelet count • Positive D-dimer test
Anti-FVIII	• Haemorrhages	• ↑ APTT • ↓ FVIII • Elevated FVIII inhibitor level • Normal platelet count • PT normal • Fibrinogen normal
TTP	• Haemorrhages • Fever • Renal failure • Neurological abnormalities	• Thrombopenia • Normal D-dimer test • Microangiopathic haemolytic anaemia • ↑ LDH • Decreased ADAMTS13 activity

PT = prothrombin time, APT = activated partial thromboplastin time, TTP = thrombotic thrombocytopenia purpura, LDH = lactate dehydrogenase

De la Fouchardiere et al., The Journal of Medicine 2003

Prostate cancer and DIC

- Prostate cancer is one of the most common solid tumor in men and is the second cause of death from malignancy in men
- Bone metastasis is very frequent in this cancer; up to 90% of advanced prostatic cancer has skeletal metastasis
- Bone is the most common site of metastasis in this cancer and is responsible for inducing DIC even more than gastric and pancreatic cancer *(M. Forat Yazdi & G.Malekzadeh, Cent Eur J Urol, 2013).*

Incidence

- DIC incidence in prostate cancer was historically found to be close to 25%.
- More recently, this rate is reported to be 13 to 30%, but clinical signs of DIC are actually found in only 0.4 to 1.65% of patients with prostate cancer *(Ruffion et al., J Urol 2000)*.
- DIC is also reported as the first manifestation of an occult metastatic prostate cancer

Several clinical cases

«Prostate cancer with disseminated carcinomatosis of bone marrow initially presenting with disseminated intravascular coagulation syndrome: a case report.»
Minato N., et al. Hinyokika Kiyo, 2012

«Disseminated carcinomatosis of the bone marrow in two patients with prostate cancer»
Kato T., et al. Nihon Hinyokika Gakka Zasshi, 2011

«Prostatic adenocarcinoma revealed by disseminated intravascular coagulation and fibrinolysis»
Rabii R., et al. Ann Urol (Paris), 2002

MADRID 2014 ESMO congress

Clinical and laboratory data of patients with prostate cancer and relapsing DIC

	EPISODE I				EPISODE II		EPISODE III
Physical examination	Extensive chest-wall ecchymosis Bleeding at venipuncture sites Gingival haemorrhage Epistaxis				No clinical signs		Epistaxis Gingival haemorrhage Pretibial ecchymoses Cerebromeningeal haemorrhage Death
Biological signs	17/09/02	19/09/02	20/09/02	25/09/02	18/12/02	23/12/02	06/02/03
Platelets	54,000	18,000	5,000	39,000	19,000	50,000	22,000
Fibrinogen	0.09	0.2	0.5	2.8	1.1	2.3	<0.1
PT (%)	20.7	30	32	78	70	81	21
APT (s)	60	57	52	31	54	32	49
D-dimer assay (ng/ml) n<500			>10,000		8912		5668
Treatment	Diethylstilbestrol diphosphate Blood and platelet transfusions Fibrinogen concentrates				Diethylstilbestrol diphosphate Heparin		Diethylstilbestrol diphosphate Heparin Blood and platelet transfusions

PT = prothrombin time, APT = activated partial thromboplastin time, Diethylstilbestrol diphosphate = Fosfestrol®, 1g/d 5d.

The scoring system of the Scientific and Standardization Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Hemostasis: a 5-year overview

The International Society on Thrombosis and Haemostasis (ISTH) Sub-Committee of the Scientific and Standardisation Committee (SSC) on Disseminated Intravascular Coagulation (DIC) proposed that the working definition of DIC be delineated into two phases.

Toh C.H. et al, JTH 2007

Scoring system: the disease is compatible with the appearance of DIC?

YES

NO: not use the score

Platelet count		Degradation products of fibrin		Prolonged prothrombin time		Fibrinogen level	
Value	Score	Value	Score	Value	Score	Value	Score
>100 X 10^9/l	0	N	0	<3 sec	0	>1 g/L	0
50 ÷ 100 X 10^9/l	1	↑	2	3-6 sec	1	<1 g/L	1
<50 X 10^9/l	2	↑↑	3	>6 sec	2		

≥ 5 Score **< 5**

compatible with overt DIC: repeat score daily

suggestive (not affirmative) for non-overt DIC: repeat next 1–2 days.

Toh C.H. et al, JTH 2007

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Diagnostic scores for disseminated intravascular coagulation

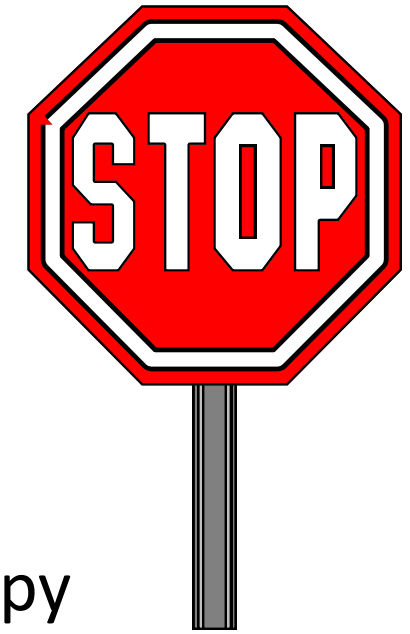
	ISTH	JMHW	JAAM	KSTH
Underlying disorder known to be associated with DIC	Required	1 point	0 points	0 points
Bleeding	0 points	No hematological malignancy: 1 point Hematological malignancy: 0 point	0 points	0 points
Thrombosis related organ failure	0 points	Present: 1 point; absent: 0 point	0 points	0 points
Systemic inflammatory response syndrome criteria	0 points	0 points	0-2: 0 points ≥3: 1 points	0 points
Prolonged thrombin time	<3 sec: 0 points ≥3 sec: 1 point ≥6 sec: 2 points	Prothrombin time ratio: <1.25: 0 points 1.25-1.67: 1 point ≥1.67: 2 points	Prothrombin time ratio <1.2: 0 points ≥1.2: 1 point	>3 sec: 1 point (or aPTT>5 sec: 1 point)
Fibrinogen level (g/L)	>1: 0 points ≤1: 1 point	>1.5: 0 points 1.0-1.5: 1 point ≤1: 2 points	≥3.5: 0 points <3.5: 1 point	<1.5: 1 point
Elevated fibrin related marker (e.g. soluble fibrin monomers, d-dimer)	No increase: 0 point Moderate increase: 2 points (D-dimer: increase ≤10 fold limit of normal) Marked increase: 3 points (>10 fold limit of normal)	Fibrin degradation product (μg/mL): <10: 0 point 10–20: 1 point 20–40: 2 points ≥40: 3 points	Fibrin/fibrinogen degradation products (mg/L) <10: 0 point ≥10 and <25: 1 point ≥25: 3 points	D-dimer increase: 1 point
Platelet count (x109/μL)	>100: 0 point ≤100: 1 point ≤50: 2 points	Patients with hematological malignancy: 0 points Patients without hematological malignancy: >120: 0 points 80–120: 1 point 50–80: 2 points ≤50: 3 points	≥120: 0 point ≥80 and <120 or >30% decrease within 24 hrs: 1 point <80 or >50% decrease within 24 hrs: 3 points	<100: 1 point
Total	DIC≥5 points No DIC <5 points	Patients with hematological malignancy:≥4 points No hematological malignancy: ≥7 points	DIC≥5 points No DIC <5 points	DIC≥3 points No DIC<3 points

Di Nisio M., et al Thromb. Res. 2012

Therapeutic options

Treatment of DIC

- **<u>Stop the triggering process</u>**
  - *The only proven treatment!*
- Supportive therapy
- No specific treatments
  - Plasma and platelet substitution therapy
  - Anticoagulants
  - Physiologic coagulation inhibitors



Potential therapeutics for DIC

Agent and rationale	Comment
The Heparins	
If thrombosis is a risk or a problem, then inhibiting thrombin's action seems plausible	No randomized controlled trials published. Venous thromboembolism prophylaxis is ICU standard and seems rational. Heparin may worsen bleeding if used with ATIII therapy. If using heparin for therapy, do not use PTT to monitor; use heparin levels.
Antithrombin III	
ATIII is consumed in nearly all reports of DIC. Bolstering its level might increase clearance of thrombin	Large KyberSept[13] trial showed no benefit yet increased bleeding when used with low-dose heparin. In septic DIC and in patients not receiving heparin, ATIII reduced mortality 15%.[14] A systematic review[15] of three studies gives odds ratio of 0.65 for DIC septic patients not receiving heparin. ATIII infusions decreased mortality by 25% in a group of 32 burn patients with DIC features.[16]
Human Activated Protein C (APC)	
Theoretically inhibits thrombin generation mostly at microvascular level. By decreasing WBC release of tumor necrosis factor-alpha (TNFα), APC may also be anti-inflammatory	Aoki et al[11] compared APC to heparin, finding increased bleeding in heparin group and decreased bleeding with APC group compared with bleeding at study entry but no effect on multiorgan dysfunction syndrome with either. Their battery of coagulation studies all improved, APC greater than heparin, but no difference in complete recovery from DIC. Death rate was 20% in APC group and 40% in heparin group.
Drotrecogin Alfa (DrotAA) (recombinant activated ProC)	
Rationale similar to human APC	Generally used in sepsis independent of DIC. DrotAA decreased mortality (risk ratio [RR] 0.71 in overt DIC and RR of 0.81 in non-overt DIC) in PROWESS study[10] with trend to more bleeding but less overt thrombosis.
Activated Recombinant Human Factor VII (rhFVIIa)	
Typically used as a final option to increase production of thrombin in hemorrhaging patient resistant to all other efforts	If circulating thrombin is thought to be a major culprit, rhFVIIa could be dangerous to administer in DIC. In order to work, thrombin must be able to be generated so might be expected to not work in massive heparin overdosage or in situations having no fibrinogen and/or platelets. Several small case series[17-19] suggest possible efficacy in patients with DIC.
Recombinant Human Soluble Thrombomodulin (ART-123)	
Thrombomodulin (TM) is an endothelial-bound sink for circulating thrombin.	Aoki's group[20] compared infusion of ART-123 against low-dose heparin infusion in DIC from cancer or infection. ART-123 compared to heparin gave better improvements in coagulation tests and clinical bleeding yet no significant decrease in mortality. Side effects fewer with ART-123 than with heparin infusion

Kitchens C.S, American Society of Hematology 2009

Summary

- DIC is a syndrome characterized systemic intravascular coagulation
- Coagulation is the initial event and the extent of intravascular thrombosis has the greatest impact on morbidity and mortality
- Important link between inflammation and coagulation
- Morbidity and mortality remain high
- ***The only proven treatment is reversal or control of the underlying cause***