Disseminated Intravascular Coagulation (DIC)

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Disclosures for

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ISTH™
International Society on Thrombosis and Haemostasis

Definition

- DIC is an acquired syndrome characterized by the **intravascular activation of coagulation** without a specific localization and arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.

Taylor FB Jr, et al. Thromb Haemost 2001;86:1327

Sepsis-Associated DIC and Mortality Rate

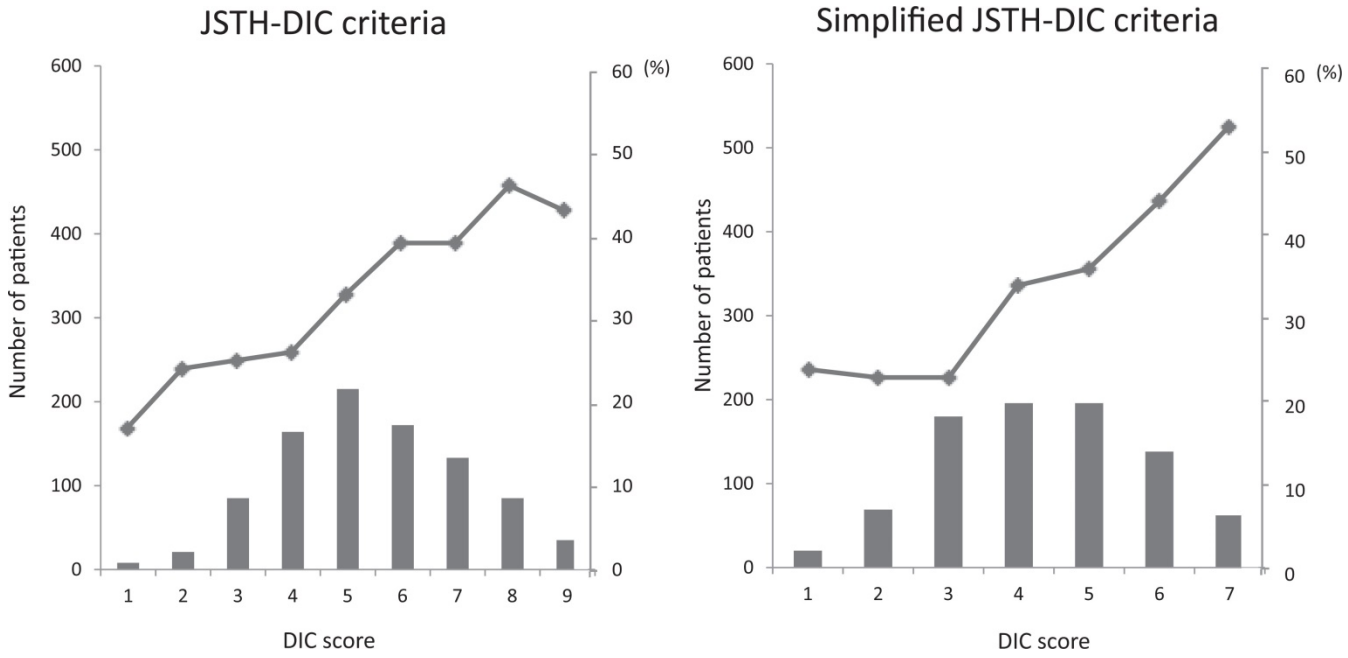
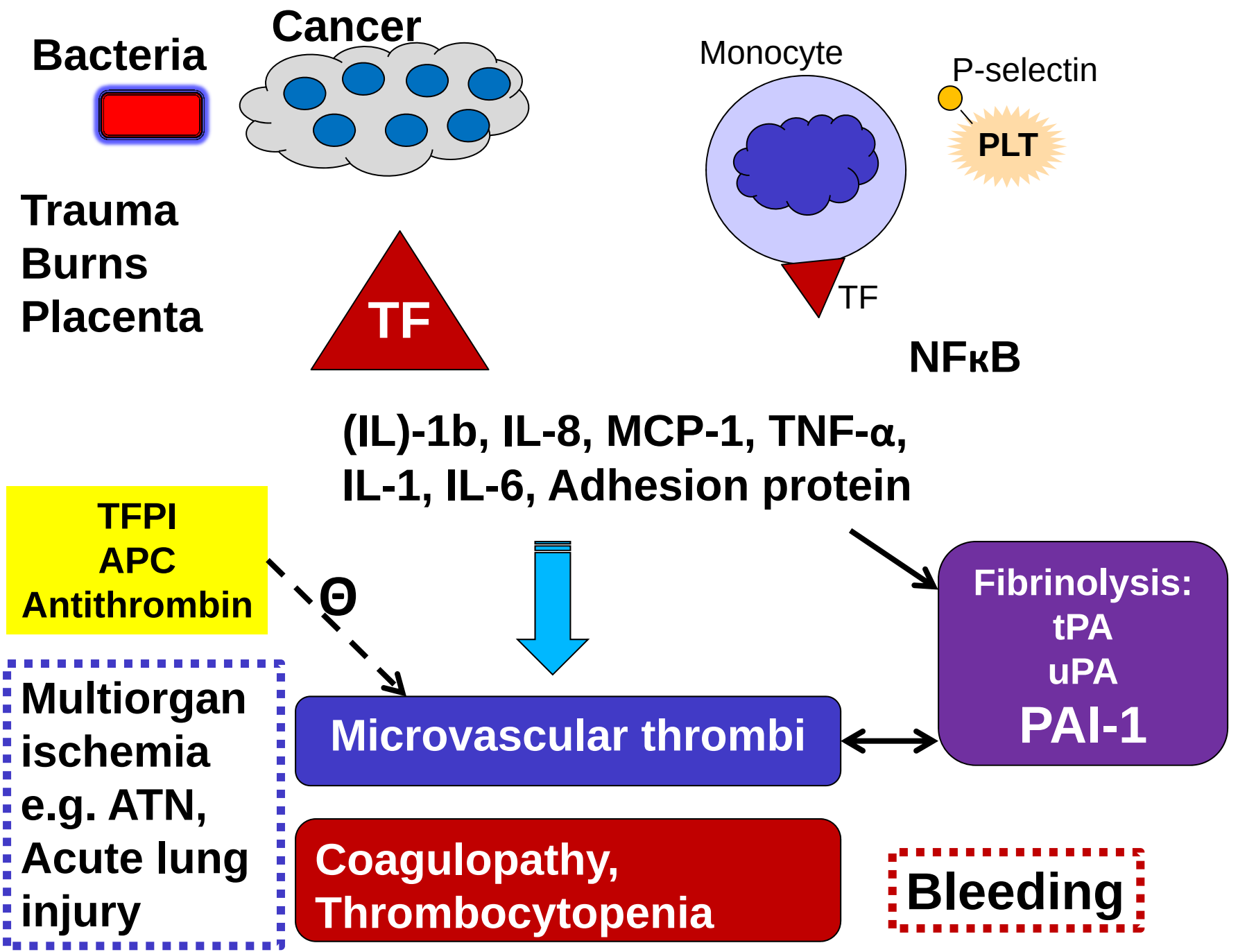


Figure 5. The patient counts and mortality rates according to the categories of the original and simplified versions of Japanese Society on Thrombosis and Hemostasis (JSTH) disseminated intravascular coagulation (DIC) diagnostic criteria. The bar graph shows the number of patients in each category, and the line graph represents the mortality rate. The mortality rate increased linearly for scores of 3 to 7 and exceeded 30% based on the simplified JSTH-DIC score of 4.

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Clinical conditions most frequently complicated by DIC

Sepsis / severe infection	**Severe allergic / toxic reactions**
Trauma / Burn / Heat stroke	**Severe immunologic reactions** e.g., transfusion reaction
Malignancy: Solid tumors, Acute leukemia	**Obstetric conditions:** Amniotic fluid embolism Abruptio placentae HELLP syndrome Retained dead fetus
Vascular abnormalities: Kasabach-Merritt Syndrome Other vascular malformations Aortic aneurysms	


Bacteria
Cancer
Monocyte
P-selectin
PLT
Trauma
Burns
Placenta
TF
TF
NFκB
(IL)-1b, IL-8, MCP-1, TNF-α,
IL-1, IL-6, Adhesion protein
TFPI
APC
Antithrombin
Θ
Fibrinolysis:
tPA
uPA
PAI-1
Multiorgan
ischemia
e.g. ATN,
Acute lung
injury
Microvascular thrombi
Coagulopathy,
Thrombocytopenia
Bleeding

Clinical Manifestations of DIC

Vary depending on Underlying disorder

Acute severe DIC

- Sepsis, major trauma, Obstetric, severe immunologic response
- Diffuse multiorgan bleeding, hemorrhagic necrosis, thrombi in small to medium/large blood vessels

Chronic DIC

- Malignancy, retained dead fetus, aneurysm
- Mucin-producing AdenoCA – venous thrombosis, NBTE → arterial embolism
- APL - bleeding

DIC in Infectious Disease

- Risk: immunocompromised, asplenia, newborns, (major trauma/active malignancy)
- Gram-negative bacteria e.g. *P. aeruginosa, E. coli, Proteus vulgaris*, Meningococcemia
- Gram-positive bacteria e.g. Streptococcus A toxic shock syndrome
- Others: virus (e.g. Dengue), malaria, fungi
- Vary from Lab abnormalities → severe DIC → Purpura fulminans

DIC in Trauma, Brain injury, Burns, Heat Stroke

- **Time interval** between Trauma and medical intervention (e.g. evacuation, resuscitation) correlates with development and magnitude of DIC … Rx:↓TF exposure, prevent shock
- **Trauma**: early phase – hyperfibrinolysis; later phase – hypercoagulable from ↑PAI-1
- **Head injury**: Lab DIC score predicts prognosis
- **Heat stroke**: endothelial cell damage, TF from heat-damaged tissues

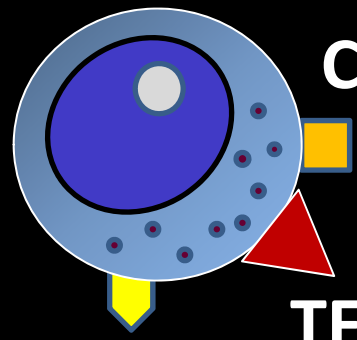
DIC in Obstetric Complications

- **Abruptio placentae**: 10% has DIC; risk: older multiparous, hypertension in pregnancy
- **Amniotic fluid embolism**: maternal mortality 26%; Pulmonary a. occlusion … anaphylactoid response/DIC … shock, convulsion … bleeding

DIC in Malignancy

- Risk: Tumor (mucin-producing, AL), Host (old age), Rx (chemo), Complication (sepsis)
- **TF** + FVIIa → IXa, Xa
- **Cancer procoagulant** (cysteine protease) → Xa
- P-,L-selectin interact with mucin→PLT thrombi
- APL (>90%) > AML (32%) > ALL (15-20%)

DIC in APL



Activate coagulation

Release IL-1β, TNF-α

↓Endothelial thrombomodulin

↓Protein C anticoagulant

DIC

Binds plasminogen and tPA

↑Plasmin

HyperFibrinolysis

Bleeding

DIC in Vascular Disorders

- **Aortic aneurysm** – TF in atherosclerotic plaque
  - 40% had ↑FDP, 4% had DIC
  - Risk of DIC: large, dissected, expand
- **Kasabach-Merritt**
  - giant cavernous hemangiomas → consume PLT and fibrinogen; tPA released from abnormal endothelium in tumor walls → hyperfibrinolysis

DIC with Liver Disease

- Severe liver disease → lab as DIC
  - ↓Coagulation factors
  - ↓Natural anticoagulants
  - ↓Clearance of IXa, Xa, XIa, tPA
  - Thrombocytopenia from hypersplenism, ↓TPO

DIC accompanies Liver Disease?

PRO

- ↓Half-life of radiolabeled fibrinogen (reversed with heparin)
- Failure of replacement Rx to significantly increase level of hemostatic factors
- ↑Markers of activation of coagulation

CON

- Microthrombi are found in only 2% of tissues from patients who die of liver dis.
- ↑Fibrinogen turnover is from extravascular accumulation

DIC with Liver Disease

Current thinking

- DIC is rare in liver disease
- Patients with liver disease are sensitive to triggers of DIC
  - ↓Synthetic capacity
  - Inability to clear activated clotting factors

Laboratory Findings in DIC

- **Low PLT**
  - <100 x 10^9/L : 50%-60% in critically ill patients, >80% in surgical or trauma patients
  - <50x 10^9/L : 10%-15% in critically ill patients
- **Prolonged PT or aPTT**: >95%
- **Factor VIII** – mostly elevated due to massive release of vWF from endothelium and as acute-phase protein

Laboratory Findings in DIC

Fibrinogen concentration

- Fib. is an acute-phase protein → ↑↑with inflammation
- Thus, Fib. level may remain normal for a long time despite ongoing consumption
- Sensitivity of low Fib. for Dx of DIC was 28%
- Hypofibrinogenemia only found in severe DIC

Laboratory Findings in DIC

Markers of fibrin generation and degradation

- **D-dimer** – sensitive but not specific
- Fibrin(ogen) degradation product (**FDP**) – metabolized in liver and cleared by kidney
- **Soluble fibrin** or fibrin monomer – theoretically useful, but no reliable quantitative test

Laboratory Findings in DIC

Endogenous coagulation inhibitors

- **Protein C, Antithrombin**
  - Reduced levels in 90% of DIC patients
  - Predictor of poor outcome and mortality

Laboratory Findings in DIC

Fibrinolytic markers

- Increased fibrinolytic activity
  - Plasma plasminogen and α2-antiplasmin : low levels may indicate consumption
  - Plasmin- α2-antiplasmin (PAP) complexes : increased
  - PAI-1 : often elevated and correlate with unfavorable outcome

Laboratory Findings in DIC

Point of care tests

- Thromboelastography (TEG), ROTEM
  - Use whole blood → global assessment of PLT function, coagulation, and fibrinolysis
  - Correlate with morbidity and mortality
  - May be overly sensitive to fibrinogen administration

Diagnostic Algorithm for Dx of Overt DIC

1. Presence of disorder associated with DIC: Yes→proceed
2. Score global coagulation test results

	0	1	2	3
Platelet count, $x10^9/L$	>100	<100	<50	
D-dimer or FDPs	≤ Upper limit of normal		> ULN but < 5x ULN	> 5x ULN
Prolonged PT, sec	< 3 sec	> 3 but < 6 sec	> 6 sec	
Fibrinogen level, mg/dL	> 100	< 100		

3. Calculate score: ≥5 overt DIC, <5 suggest non-overt DIC

Taylor FB Jr, et al. T & H 2001;86:1327

DIC Scoring Systems

	ISTH	JMHW	JAAM	CDSS
Underlying condition	Essential	0-1 point	Essential	0 – 2 points
Clinical symptom	-	Bleed, organ failure	SIRS	Bleed, organ dys-function, micro-circulatory disorder
PLT	0 – 2	0 – 3	0 – 2	0 – 2
FDP,D-dimer	0 – 3	0 – 3	0 – 3	0 – 3
Fibrinogen	0 – 1	0 – 2	-	0 – 1
PT	0 – 2	0 – 2	0 – 1	PT or APTT: 0 – 2
Dx, points	≥5	≥7	≥4	≥6 or 7

JMHW, Japanese Ministry of Health and welfare; JAAM, Japanese Association for Acute Medicine
CDSS, Chinese DIC Scoring System

DIC Score

- **ISTH**: Sensitivity 93%, Specificity 98%
- Related to the **mortality** in patients with sepsis.
- **Japanese** scoring system
  - Slightly higher sensitivity, probably from different population (more hematologic malignancies)
  - Simplified JSTH-DIC for Sepsis: with Antithrombin activity in score – sens. 80%, spec. 34%
- **Pregnancy** modified ISTH score of Erez, Clark : need more study

Treatment of DIC

SPECIFIC

- Sepsis: antibiotics, pus drainage
- Cancer: surgery, chemotherapy
- Abruptio placentae: uterus evacuation
- Aortic aneurysm: resection
- Trauma: debridement of crushed tissue

Treatment of DIC

SUPPORTIVE

- **Transfusion** if bleeding, requiring invasive procedure, at risk for bleeding

Treatment of DIC

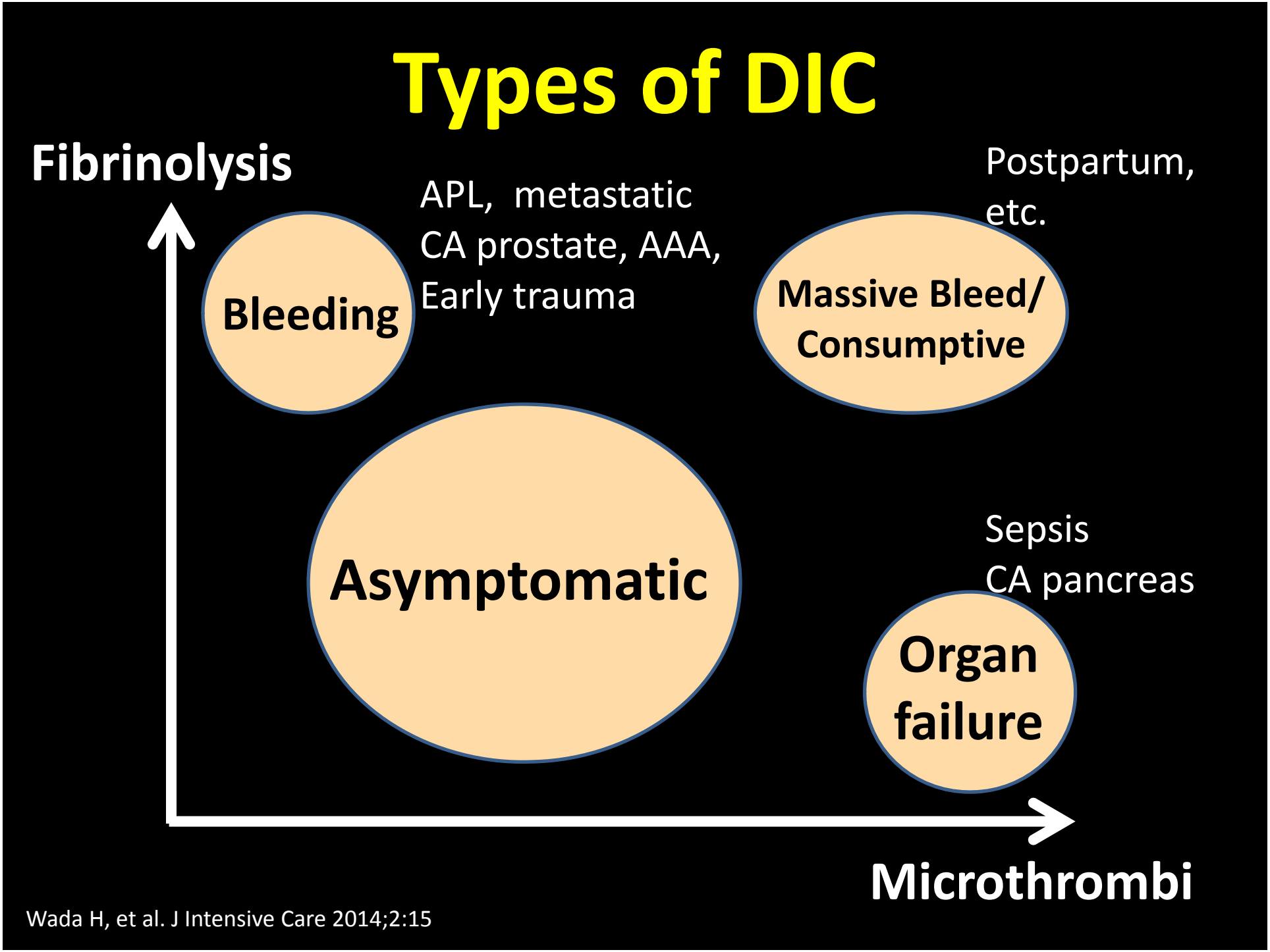
SUPPORTIVE

- Transfusion
- **Heparin**: purpura fulminans, before surgery in chronic DIC (e.g. Aortic aneurysm), digital gangrene, failure of intensive transfusion to improve excessive bleeding

Treatment of DIC

SUPPORTIVE

- Transfusion
- Heparin
- **Tranexamic acid** in selected cases with refractory bleeding from primary **hyperfibrinolysis** e.g. metastatic CA prostate, APL, giant cavernous hemangioma, heat stroke, acute coagulopathy of trauma, massive postpartum hemorrhage



Wada H, et al. J Intensive Care 2014;2:15

Criteria for Dx of DIC with Enhanced Fibrinolysis

1. Prerequisite: TAT ≥20 ug/L and PIC ≥10 ug/L
2. Lab findings – at least 2 of followings:
   1. FDP ≥80 ug/mL
   2. Fibrinogen <100 mg/dL
   3. Increased FDP/D-dimer ratio
3. Reference findings – more severe bleeding is likely with the following findings:
   1. Decreased platelet count (<50,000/uL)
   2. Decreased α2PI activity (<50%)

PIC, plasmin-α2 plasmin inhibitor complex

Asakura H. J Intensive Care 2014;2:20