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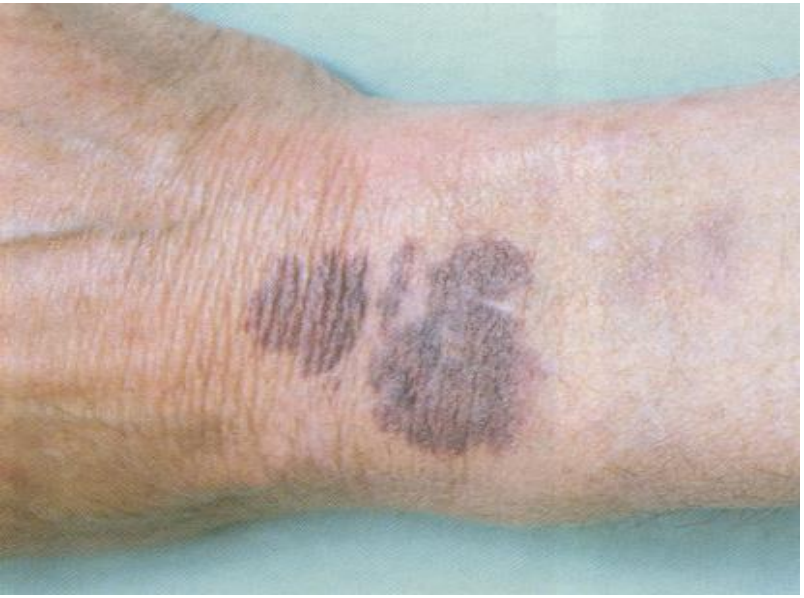
FACULTY OF NURSING SCIENCES

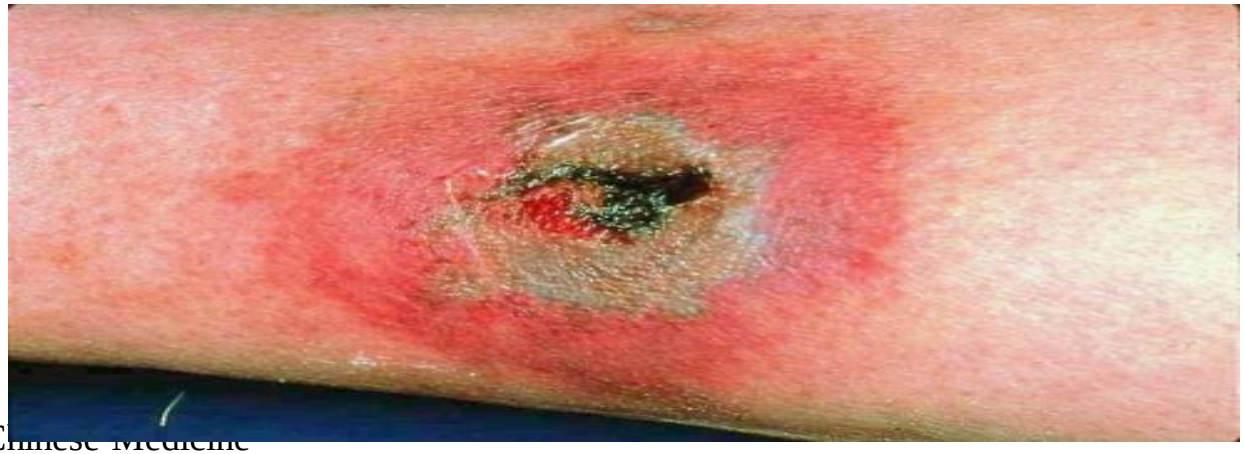
By- SUDHA BENJAMINI
Associate Professor
Faculty of Nursing

Disseminated intravascular coagulation (DIC)



INTRODUCTION

It is a Systemic process producing both thrombosis and hemorrhage. It is Also called consumption coagulopathy and defibrination syndrome. Its clinical manifestation may be widespread hemorrhage in acute, fulminant cases.



Definition

- "DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes.
- It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."

Scientific Subcommittee on DIC of ISTH, July , 2001

Disseminated Intravascular Coagulation (DIC)

- Is not a disease, but a complication of various disorders
- Conditions with activation of coagulation factors
- DIC should always be considered in critically ill

- Thrombin generation
- ↓
- Widespread microvascular thrombosis

- Secondary fibrinolysis
- ↓
- Platelets Consumption
- coagulation factors and inhibitors Consumption.

Thrombin generation, fibrinolysis and inhibition of fibrinolysis → thrombosis and/or bleeding

Causes Of DIC

- **Severe infections**
- **Trauma**
- **Organ destruction**
- **Malignancy**
- **Obstetric complications**
- **Vascular abnormalities**
- **Severe toxic or immunologic reactions**

Septicemia: bacterial, viral or fungal infections
Fractures : polytrauma, neurotrauma, fat embolism
Severe skin and soft tissue trauma
Severe burns
Major surgical interventions
Pancreatitis
Acute liver necrosis
Heat stroke
Metastatic cancer
Tumor necrosis
Amniotic fluid embolism
Placental abruption
Preeclampsia and eclampsia
Dead fetus syndrome
Giant hemangioma
Hereditary teleangiectasis
Large vascular aneurysms
Snake bites
Transfusion reactions
Transplant reactions
Invasive circulatory supportive devices (i.e. mechanical heart)
Extracorporal circulation

Factors Accelerating DIC

- Shock
- Acidosis
- Hypoxemia
- Stasis
- Dehydration
- Hyperthermia
- Chronic renal insufficiency
- Chronic hepatic insufficiency
- Malnutrition
- Impaired anti-coagulation activity
- Impaired fibrinolytic activity
- Phagocytic dysfunction

Disseminated intravascular coagulation

- Systemic thrombo-haemorrhagic disorder
- Characteristic features:
  - activation of coagulation system
  - activation of fibrinolytic system
  - consumption of clotting factors
  - consumption of natural inhibitors
  - thrombocytopenia

Disseminated intravascular coagulation: characteristics

- Widespread activation of coagulation

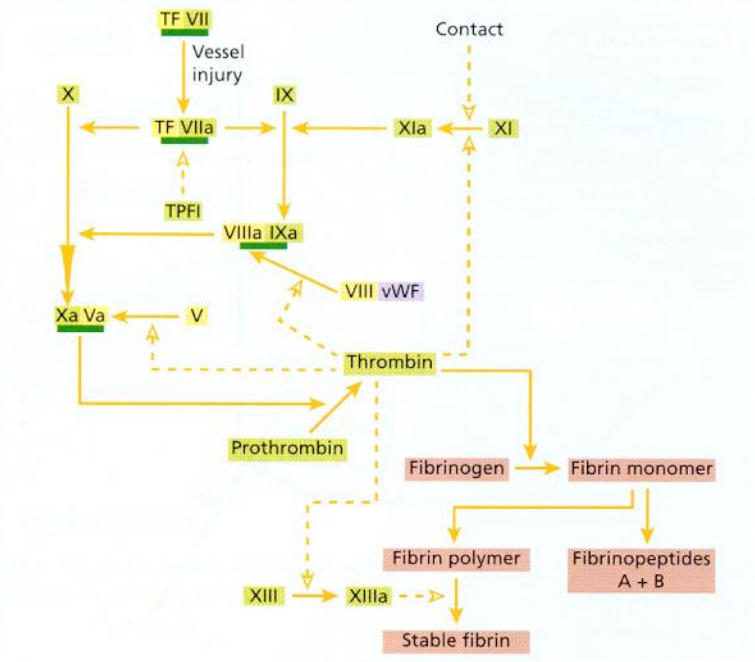
→ intravascular formation of fibrin

→ thrombotic occlusion of small vessels

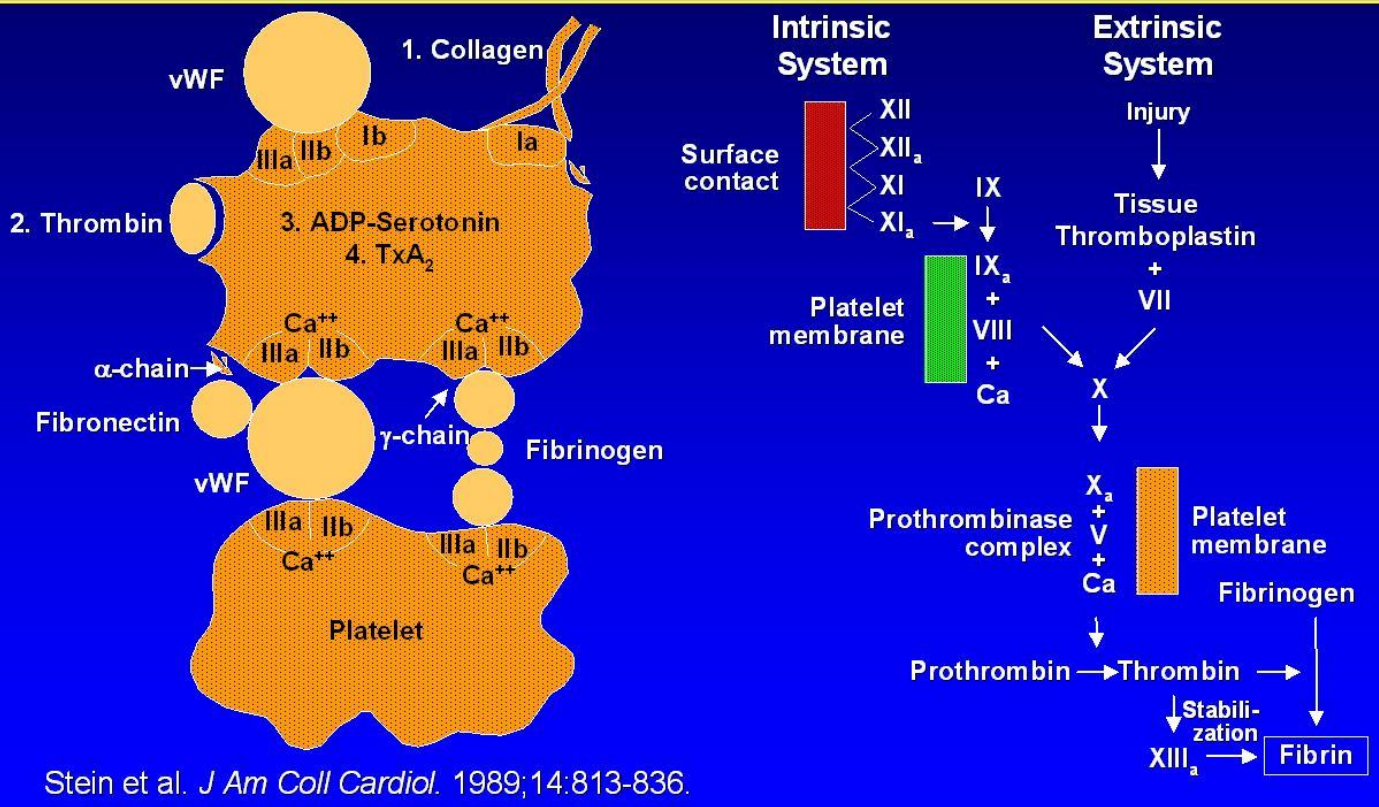
→ contributes to multiple organ failure in conjunction with haemodynamic and metabolic consequences

- Depletion of platelets and clotting factors

→ severe bleeding


TF VII
Vessel injury
Contact
X
IX
TF VIIa
XIa
XI
TPFI
VIIIa IXa
VIII vWF
Xa Va
V
Thrombin
Prothrombin
Fibrinogen
Fibrin monomer
Fibrin polymer
Fibrinopeptides A + B
XIII
XIIIa
Stable fibrin

Thrombosis: Platelets and the Coagulation System



Stein et al. *J Am Coll Cardiol.* 1989;14:813-836.

Stein B, Fuster V, Israel DH, et al. Platelet inhibitor agents in cardiovascular disease: an update. *J Am Coll Cardiol.* 1989;14:813–836.

Systemic activation of coagulation

Intravascular deposition of fibrin

Thrombosis of small and midsize vessels and organ failure

Depletion of platelets and coagulation factors

Bleeding

Symptoms And Sings

- Microvascular clot formation is the primary event in DIC
- Signs of organ dysfunction determine the clinical symptoms
- Indistinguishable from SIRS/Sepsis and MODS.
- Microclot formation → Organ failure
- Lung dysfunction

i. Acute pulmonary microembolism syndrome

ii. Late pulmonary microembolism syndrome → ARDS , Microatelectasis and capillary leakage

- Acute renal failure

i. Oligouria or anuria

ii. Microscopic or macroscopic hematuria

Symptoms And Sings

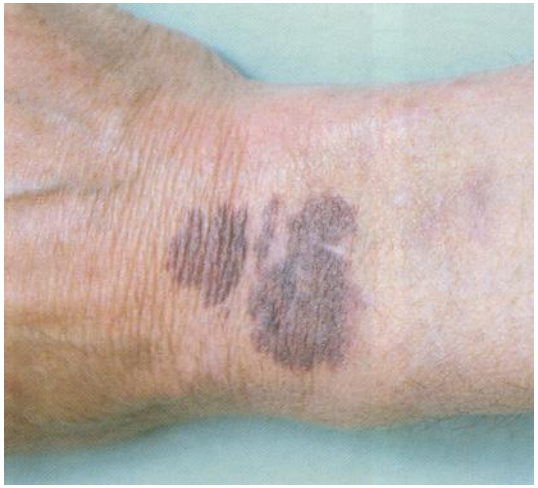
- Cerebral dysfunction :Confusion & Blurring of consciousness
- Dermal changes :microthrombosis / bleedings

i. Focal hemorrhagic necroses : face & peripheral extremities.

ii. Petechiae and/or ecchymoses.

- Additional symptoms can result from dysfunction of the liver, endocrine glands and other organs.

Skin Bruises



Associated Clinical Conditions

- Sepsis
- Trauma
  - Serious tissue injury
  - Fat embolism
- Cancer
- Obstetrical complications
- Vascular
  - Giant haemangioma
  - Aortic aneurysm
- Reaction to toxins
- Immunological disorders
  - Haemolytic transfusion reaction
  - Transplant rejection

DIC and Infectious Disease

- Severe sepsis is the most common clinical condition associated with DIC
- Bacterial infection
- Occurs in 30 - 50% of Gram -ve sepsis
  - Lipopolysaccharide (endotoxin)
- Gram positive sepsis
  - exotoxin (e.g. staphylococcal α-haemolysin)

DIC and severe trauma

- Especially seen after brain trauma
  - release of fat and phospholipid
- Cytokine activation
  - similar pattern to severe sepsis
- “Systemic inflammatory response syndrome” after trauma
  - 50 - 70% associated with DIC

DIC and Cancer

- Solid tumours
  - metastatic cancer 10 - 15%
- Haematological cancer
  - acute leukaemia 15%
- ‘Cancer pro-coagulant’: tissue factor
- Acute promyelocytic leukaemia
  - DIC and hyperfibrinolytic state

DIC and Obstetrical Disorders

- Abruptio placentae, amniotic fluid embolism, fetal death *in utero*, septic abortion
- 50% of cases
- Release of thromboplastin-like material
- Usually short-lived and self-limiting
- Pre-eclampsia (7%)

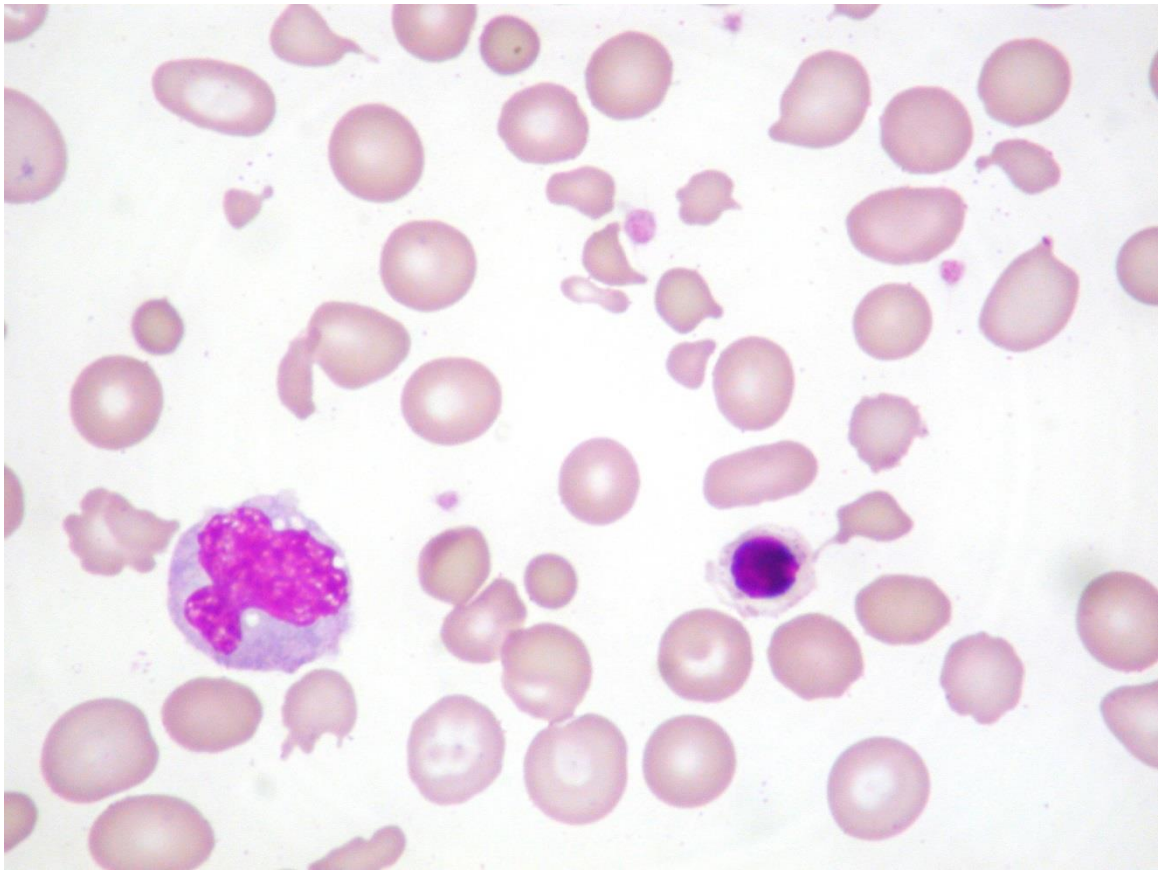
DIC and Giant Haemangioma

- Local activation of coagulation system → systemic depletion of locally consumed clotting factors and platelets
- Activated coagulation factors → reach systemic circulation → DIC
- Giant haemangioma 25%
- Large aortic aneurysm 0.5 - 1%

Microangiopathic haemolytic anaemia

- Peripheral blood picture:
  - Anaemia
  - Thrombocytopenia
  - Fragmented red cells (schistocytes)
- A feature common to several conditions:
  - DIC
  - Thrombotic thrombocytopenic purpura
  - Haemolytic Uraemic Syndrome

Disseminated intravascular coagulation



Pathogenesis of DIC

- Increased thrombin generation
- Depression of physiologic anticoagulation mechanism
- Delayed removal of fibrin due to impaired fibrinolysis

Thrombin generation

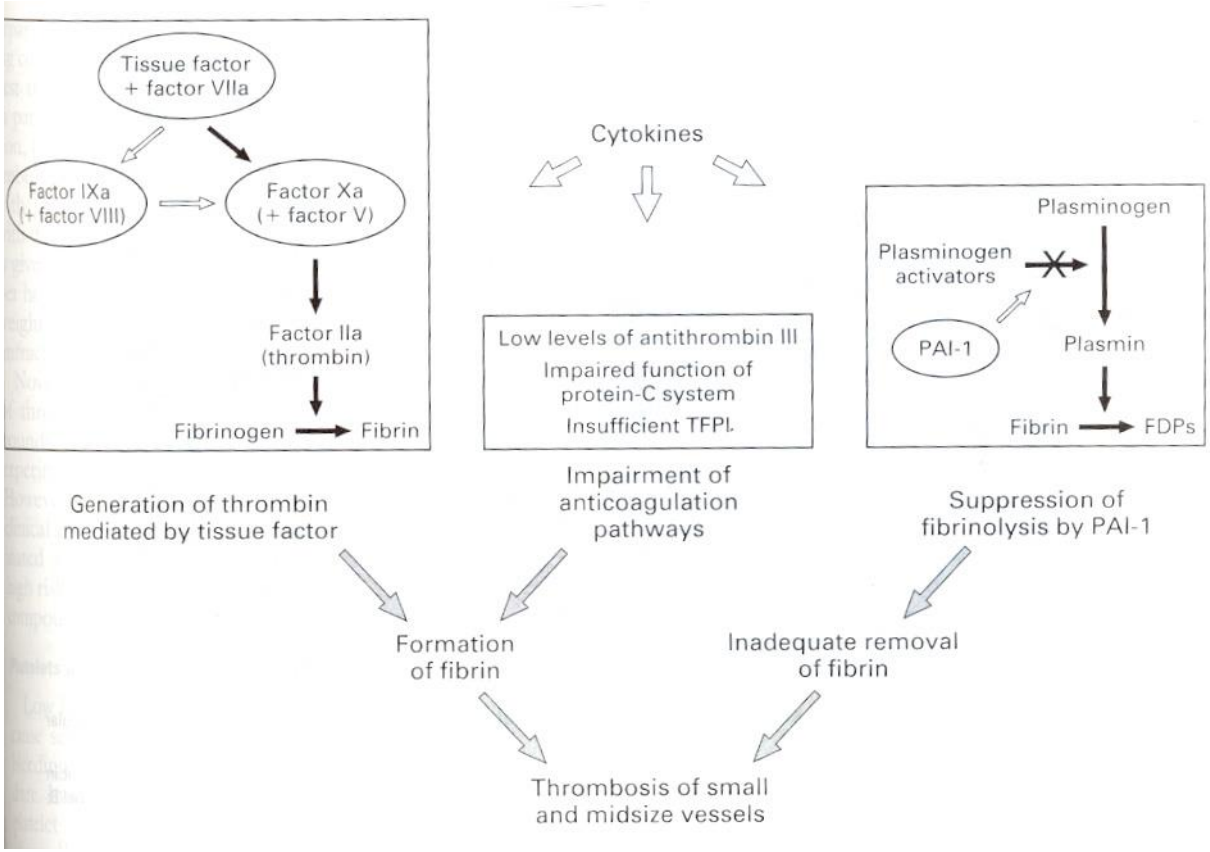
- Extrinsic pathway
- Tissue factor and factor VIIa

Defects in coagulation inhibitors

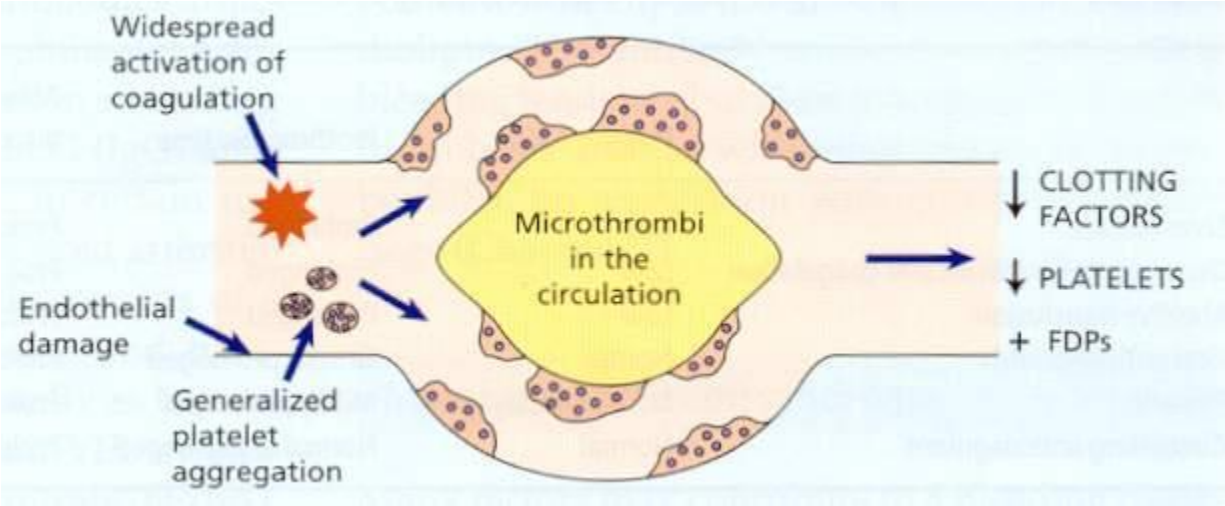
- ↓ antithrombin
  - ongoing coagulation
  - degradation by neutrophil elastase
  - impaired antithrombin synthesis
- Impairment of protein C system
  - impaired synthesis
  - cytokine mediated ↓ endothelial thrombomodulin
  - ↓ free protein S
- Insufficient tissue factor pathway inhibitor activity

Fibrinolytic defect

- ↑↑ plasminogen activator inhibitor type I


Tissue factor
+ factor VIIa
Factor IXa
(+ factor VIII)
Factor Xa
(+ factor V)
Factor IIa
(thrombin)
Fibrinogen
Fibrin
Cytokines
Low levels of antithrombin III
Impaired function of
protein-C system
Insufficient TFPI
Plasminogen
Plasminogen
activators
PAI-1
Plasmin
Fibrin
FDPs
Generation of thrombin
mediated by tissue factor
Impairment of
anticoagulation
pathways
Suppression of
fibrinolysis by PAI-1
Formation
of fibrin
Inadequate removal
of fibrin
Thrombosis of small
and midsize vessels

Pathogenesis of DIC



Systemic activation of coagulation

Intravascular deposition of fibrin

Thrombosis of small and midsize vessels and organ failure

Depletion of platelets and coagulation factors

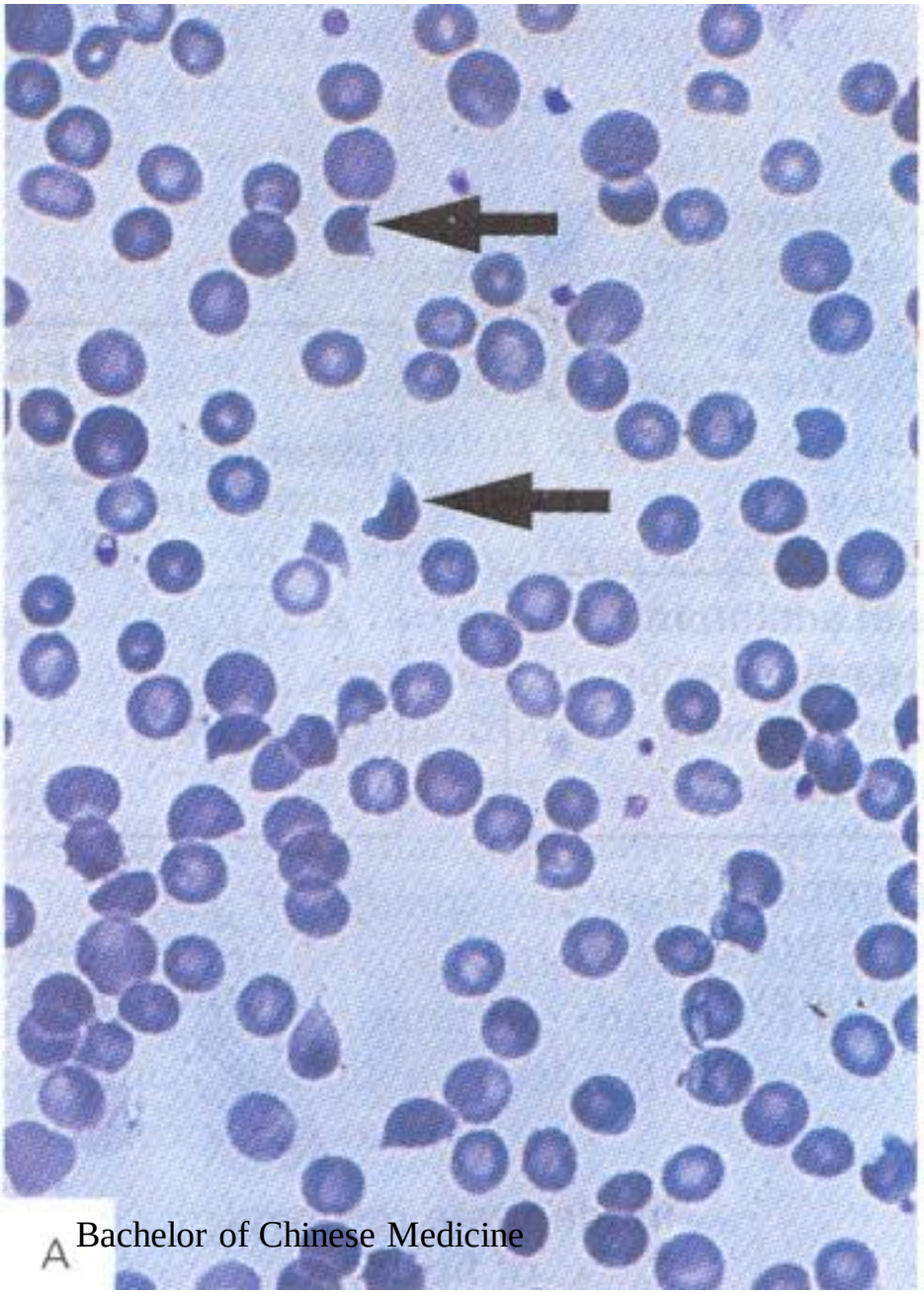
Bleeding

Diagnosis of DIC

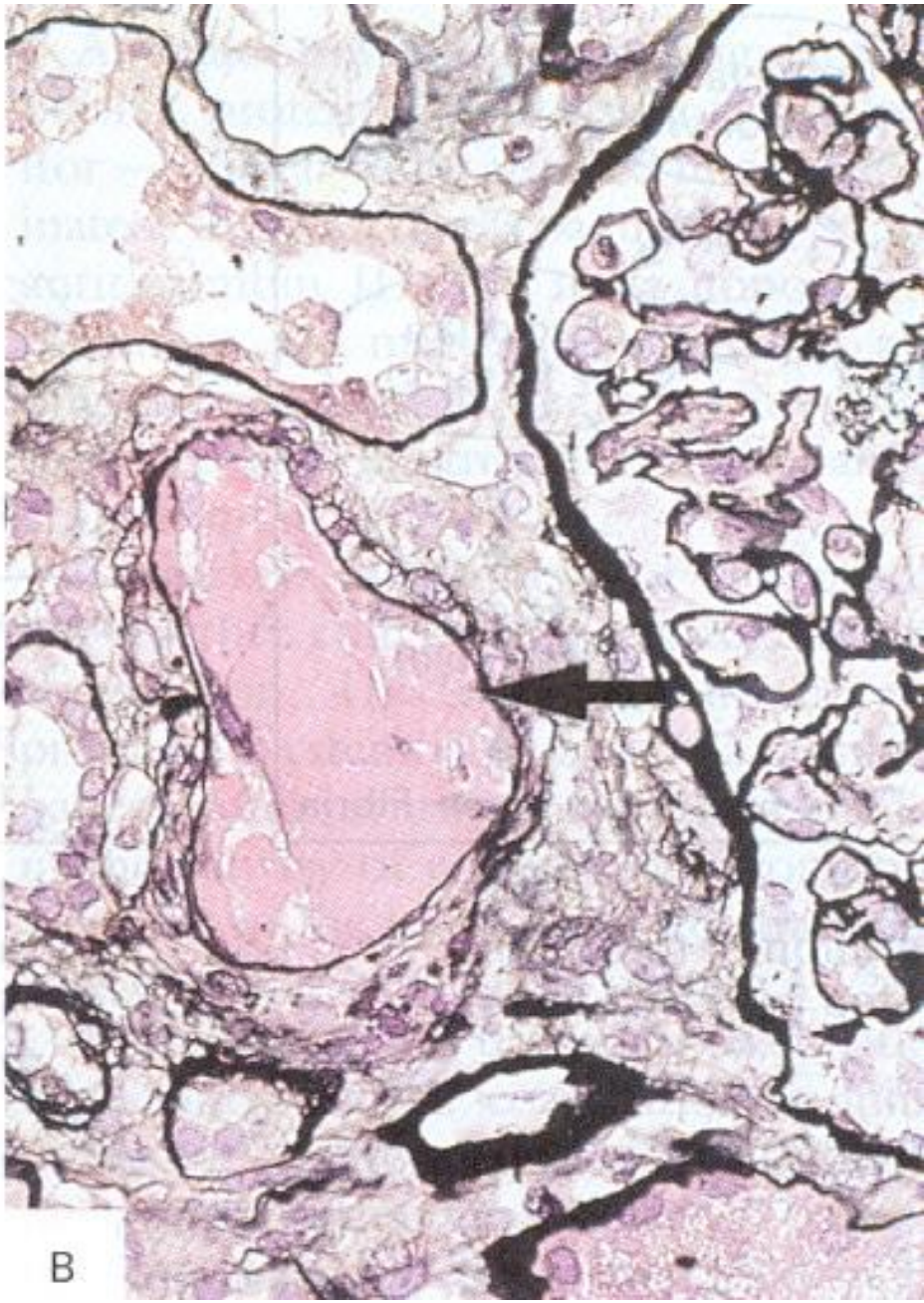
- Clinical setting
- Laboratory tests
- Criteria
  - Underlying disease known to be associated
  - Initial platelet count < 100 X 10^9/L, or rapid decline in platelet count
  - Prolongation of clotting times (PT & APTT)
  - Presence of fibrin degradation products
  - Low levels of coagulation inhibitors (e.g. antithrombin)
  - Low fibrinogen level in severe cases

Disseminated intravascular coagulation

- Laboratory results:
  - Prolonged PT, APTT and TT
  - Reduced fibrinogen level
  - Increased D-Dimers
  - Thrombocytopenia
  - Microangiopathic changes in blood film



A



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Laboratory Diagnosis

Analysis	Early changes	Late changes
Platelets	↓/↓↓	↓↓↓
APTT	↑	↑↑↑
Fibrinogen	↓	↓↓↓
D-dimer	↑↑	↑↑↑
F:II,VII,X	↓	↓↓↓
Protein C	↓	↓↓↓
Anti-thrombin	↓	↓↓↓
TAT complex	↑↑	↑↑↑
Soluble fibrin	↑↑	↑↑↑

Diagnostic Algorithm for Overt DIC

- Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC? If yes: proceed; If no: do not use this algorithm.
- Order global coagulation tests (platelet count, PT, fibrinogen, soluble fibrin monomers or fibrin degradation products)
- Score global coagulation test results
- Calculate score

Scoring System For DIC

Risk assessment: Underlying disorder known to be associated with DIC	YES Continue Global coagulation tests	NO Stop
Platelet count (> 100 = 0, < 100 = 1, < 50 = 2)		
Soluble fibrin/D-dimer (no increase = 0), ↑ moderate increase: =2, ↑ ↑ strong increase = 3		
Prolongation of PT (<3 sec = 0; >3 -6 sec =1; >6 sec = 2)		
Fibrinogen level (> 1.0 g/l = 0; < 1.0 g/l = 1)		
Calculate score		

Calculated Score

- Patient scores is ≥5: compatible with overt DIC, (decompensated hemostasis) repeat scoring daily
- Patient scores is <5: suggestive (not affirmative) for non-overt DIC, repeat next 1-2 days

Taylor, Thromb Haemostas 2001;86:1327-1330

Algorithm for Diagnostic Sequence for Determining Non-overt DICK Non-overt DIC

1. Risk assessment:

Does the patient have an underlying disorder known to be associated with DIC? If yes: proceed ☐

2. General criteria ☐

Platelet count	>100 x 10^9/L = 0	<100 x 10^9/L =1	Rising = -1	Stable = 0	Falling = 1	Score
PT prolongation	< 3 s	> 3 s	Falling = -1	Stable = 0	Rising = 1	
Soluble fibrin or FDPs	Normal	Raised	Falling = -1	Stable = 0	Rising = 1	☐

3. Specific criteria ☐

Antithrombin	**Normal = -1**	**Low = 1**
Protein C	**Normal = -1**	**Low = 1** ☐
TAT complexes	**Normal = -1**	**High = 1** ☐

4. Calculate score

Management of DIC

- Treatment of underlying disorder
- Anticoagulants
  - low dose heparin
  - low molecular weight heparin
  - new thrombin inhibitors (ATIII independent)
  - useful for clinically overt thromboembolism or extensive deposition of fibrin

Management of DIC

- Platelets and Plasma
  - to treat bleeding tendency
  - to cover an invasive procedure for patients with a high risk of bleeding
- Clotting factor concentrates
  - overcomes large volumes of plasma
  - but not advocated because: 1) contains small amount of activated factors, and 2) DIC results in deficiency of multiple factors

General Treatment

- Treatment of underlying disorder
- Antibiotic treatment of infections
- Surgical debridement and drainage of infected foci
- Immobilization of fractures
- Evacuation of uterus in obstetric DIC

Supportive Treatment

- Supportive treatment of MODS
- Shock : fluids, catecholamines
- Hypoxemia : oxygen, mechanical ventilation
- Renal failure : diuretics, renal replacement therapy
- Severe anemia : blood transfusion

Hemostatic Therapy

- **Antithrombotic treatment**
- AT concentrate.
- Concurrent treatment with heparin should be avoided, heparin worsens thrombocytopenia
- **Fresh frozen plasma (FFP)** When bleeding; administer after antithrombin
- **Platelets :** severe thrombocytopenia + bleeding
- **Antifibrinolytic treatment** Should be avoided

Ayurvedic Herbal Treatment for Disseminated Intravascular Coagulation (DIC)

- The Ayurvedic herbal treatment of disseminated intravascular coagulation is aimed at treating the generalised inflammation process which commences in this condition. It is this inflammation which acts upon the arteries, veins, and the capillaries and results in a generalised bleeding and oozing in the entire body.

- The inflammatory process also gives rise to toxins which harm different vital organs and thereby cause multiple organ failure. Ayurvedic medicines are given to promptly treat the inflammation, to boost the immunity of the body, and to protect all the vital organs. Treatment is also given to treat the blood and blood vessels, so that harmful toxins and products of inflammation are swiftly removed from the body, usually through the urine. Treatment of the inflammation also treats fever as well as infection present in the body.

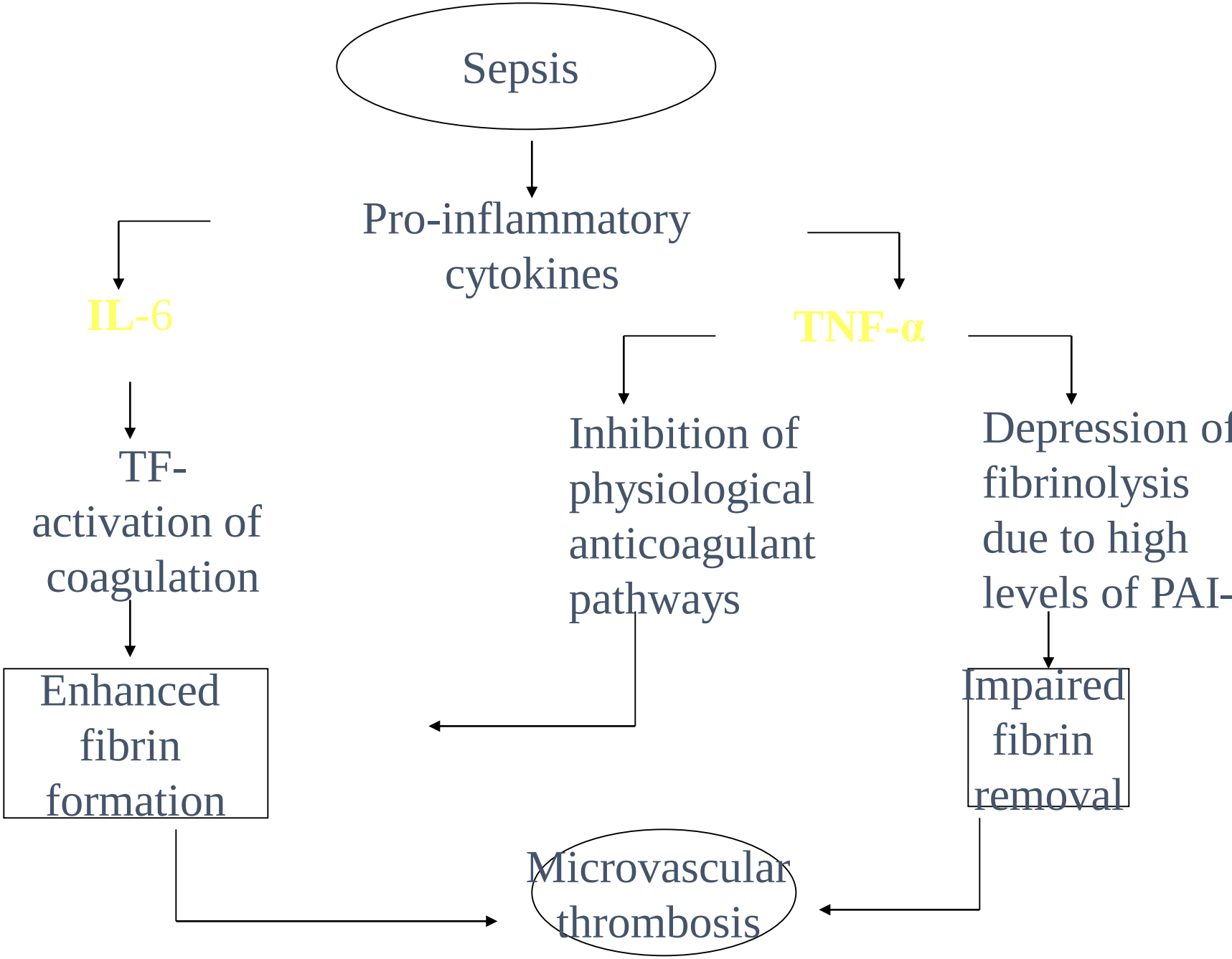
ATenative

- A quality antithrombin (AT)concentrate
- Loading dose for adult (70 kg) patient 2 x 1500 IU vials
- Follow up treatment based on measured AT levels
- Free from denatured AT (Hellstern et al, 1995)
- Two specific viral inactivation steps (SD + pasteurization)
- When treating DIC with AT ,heparin should be avoided due to high risk of bleeding comlications

Hoffmann et al, 2002

Biologic Markers in Measuring Non-overt DIC

- AT and TAT complexes (↑ procoagulation)
- E-selection and thrombomodulin (endothelial perturbation)
- FSPs or D-dimers (fibrinolysis)
- IL-6, TNF-α, IL-Iβ (cytokine and receptor upregulation)


Sepsis
Pro-inflammatory cytokines
IL-6
TNF-α
TF-activation of coagulation
Inhibition of physiological anticoagulant pathways
Depression of fibrinolysis due to high levels of PAI-
Enhanced fibrin formation
Impaired fibrin removal
Microvascular thrombosis

Practice Points

- DIC is not a disease entity on itself but is always associated to an underlying disease.
- There is no single laboratory test with adequate accuracy to establish the presence or absence of DIC.
- Most laboratory tests for DIC have a relatively high sensitivity but a low specificity
- A combination of tests may guide the clinician towards a confirmation or rejection of a diagnosis of DIC, *for example* following the recently established guidelines of the International Society of Thrombosis and Hemostasis.

Concentrates of coagulation inhibitors

- Antithrombin concentrate
  - reduces sepsis related mortality
  - improvement of DIC and organ function
- Supportive therapeutic option in severe DIC
- Drawback: expensive

Antifibrinolytic agents

- Generally not recommended
  - fibrinolysis is already impaired in DIC
  - may enhance fibrin deposition
- For bleeding in DIC associated with primary or secondary hyperfibrinolysis
  - e.g. acute promyelocytic leukaemia

New therapeutic options

- Nematode anticoagulant protein c2
  - specific inhibitor of tissue factor-VIIa-Xa complex
- Recombinant TFPI
- Protein C concentrate


THANK
YOU