



ICT 2023

28th International
Congress on Thrombosis

DIC a thrombotic microangiopathy in sepsis and COVID-19

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Declaration of Conflict Of Interest

I have no potential conflict of interest to report



Summary

- Introduction
- Disseminated intravascular coagulation
- Pathogenesis
- Clinical manifestations
- Diagnosis
- Management
- COVID-19
- Future



Introduction

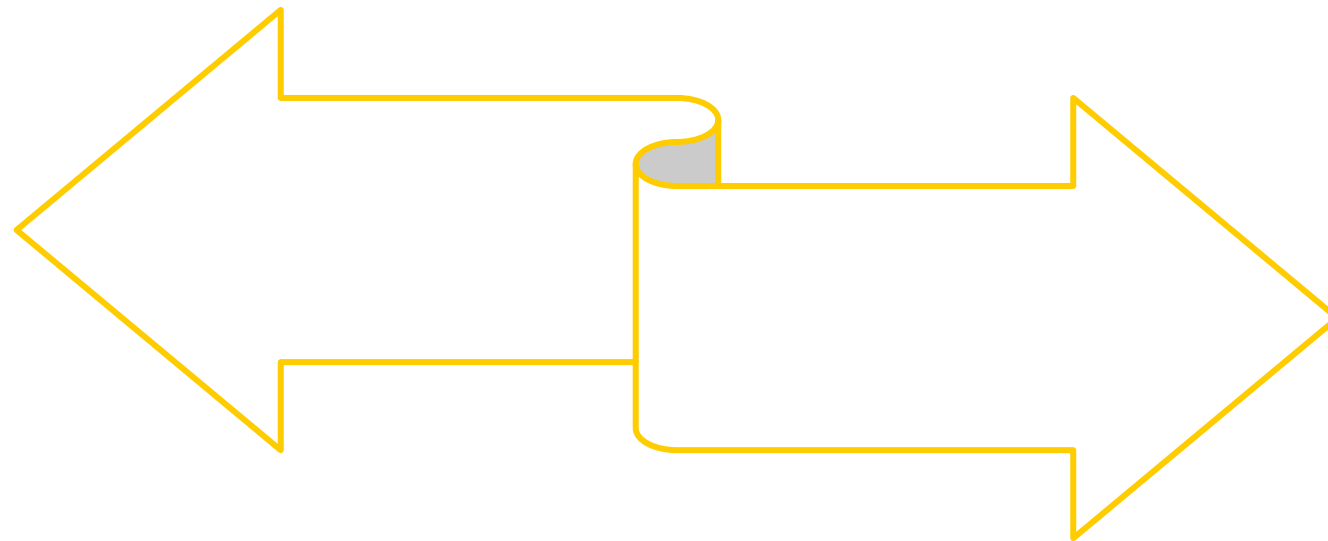
- Hemostasis is a fundamental host defense mechanism
- *Immunothrombosis*
- Excessive thromboinflammation leads to organ dysfunction

***Disseminated intravascular
coagulation***



Disseminated intravascular coagulation (DIC)

- Life-threatening syndrome
- Uncontrolled systemic activation of coagulation and suppression of fibrinolysis
- Thrombosis and consumption coagulopathy
- Organ dysfunction
- Multiple settings – **sepsis**, trauma, malignancy, obstetric complications, immunological reactions

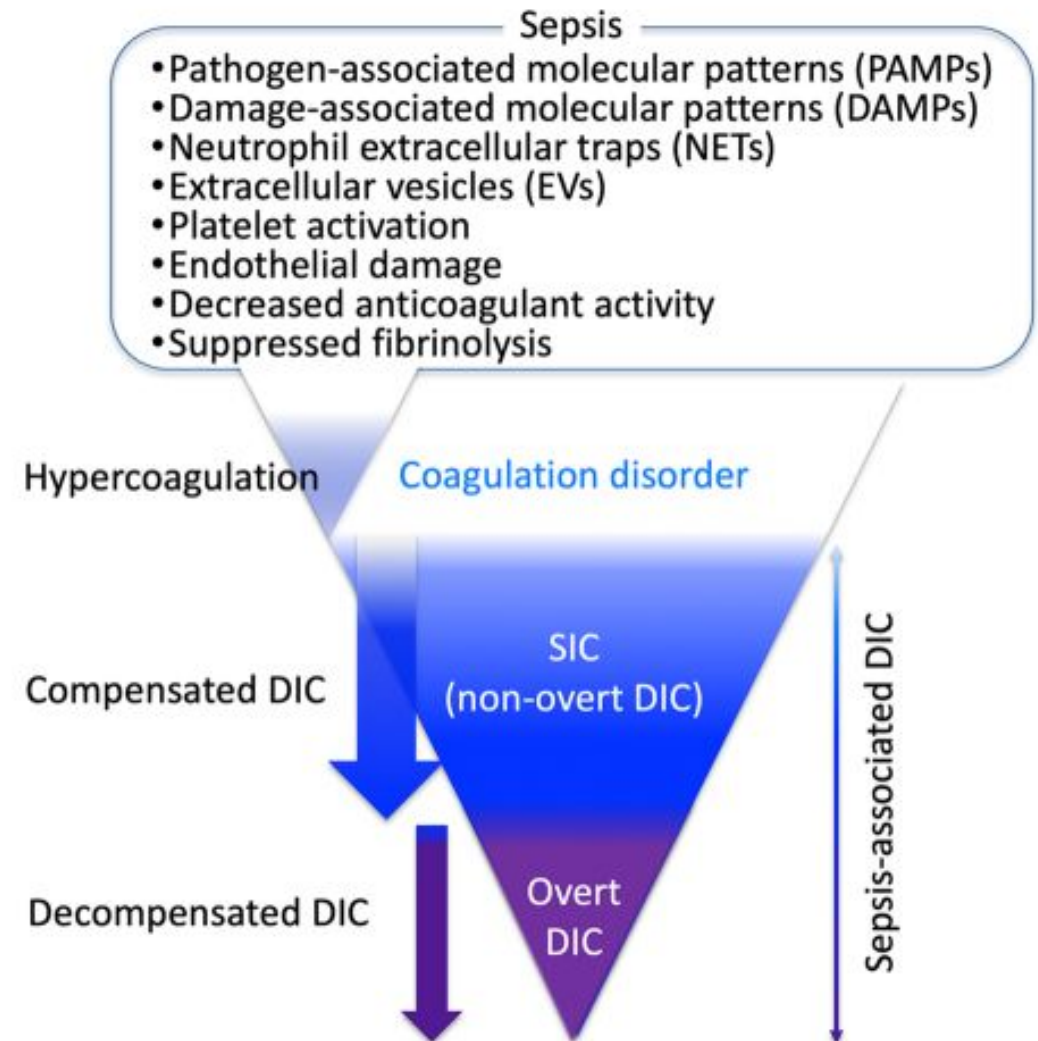




Disseminated intravascular coagulation (DIC)

Sepsis

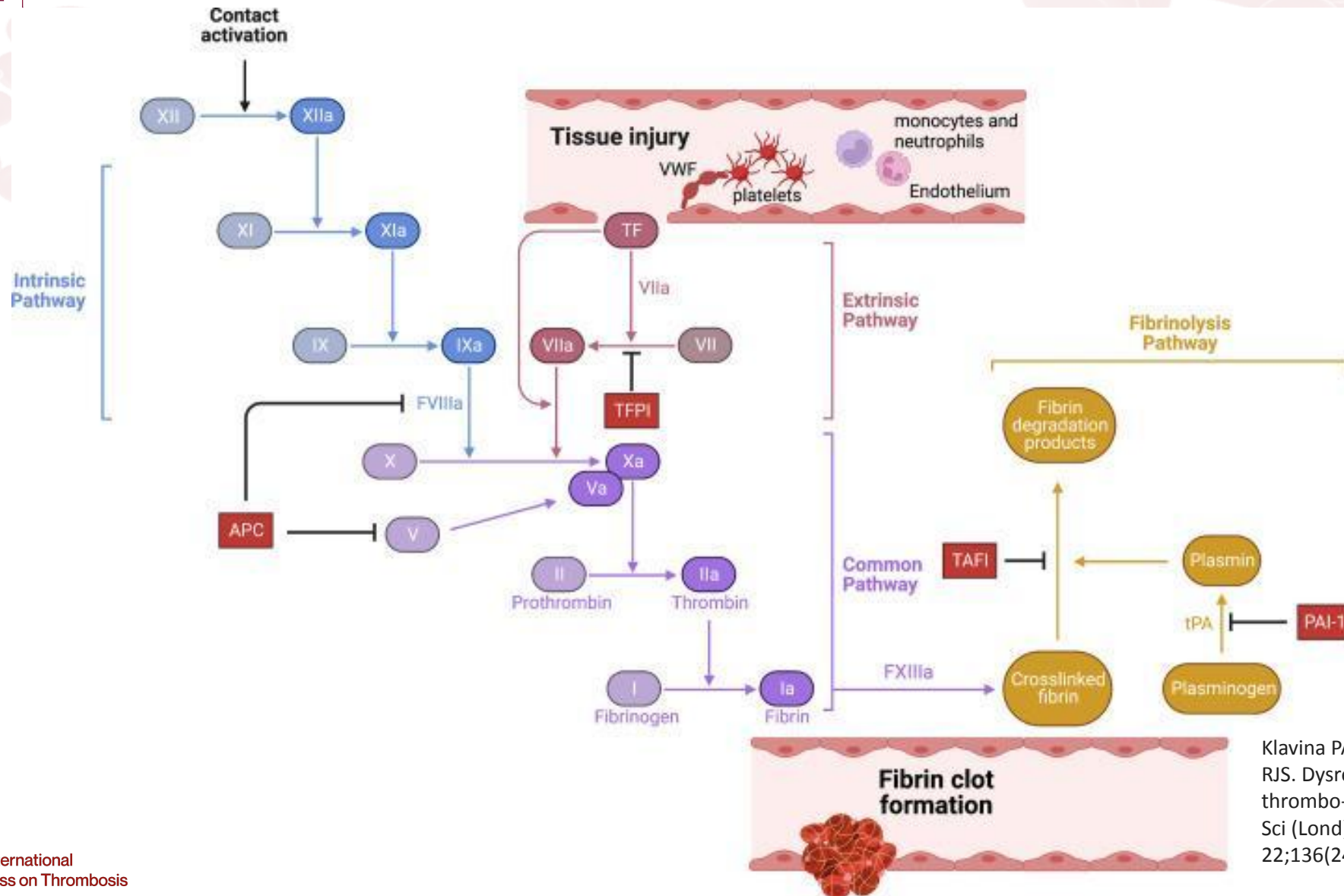
- Most frequent
- Thrombotic rather than hemorrhagic phenotype
- Dynamic process
- Higher mortality



Iba, T., Helms, J., Connors, J.M. et al. The pathophysiology, diagnosis, and management of sepsis-associated disseminated intravascular coagulation. *J Intensive Care* 11, 24 (2023).



Pathogenesis



Klavina PA, Leon G, Curtis AM, Preston RJS. Dysregulated haemostasis in thrombo-inflammatory disease. Clin Sci (Lond). 2022 Dec 22;136(24):1809-1829.



Pathogenesis

- Tissue factor overexpression
- Excessive thrombin generation
- Platelet activation
- Defective natural anticoagulant pathways
- Impaired fibrinolysis

***Thrombi
formation***

***Consumption
coagulopathy***

***Bleeding
diathesis***



Pathogenesis

- Monocytes and macrophages are the first-line responders to infection
- Activate neutrophils
- Upregulation of tissue factor
- Activation of coagulation cascade





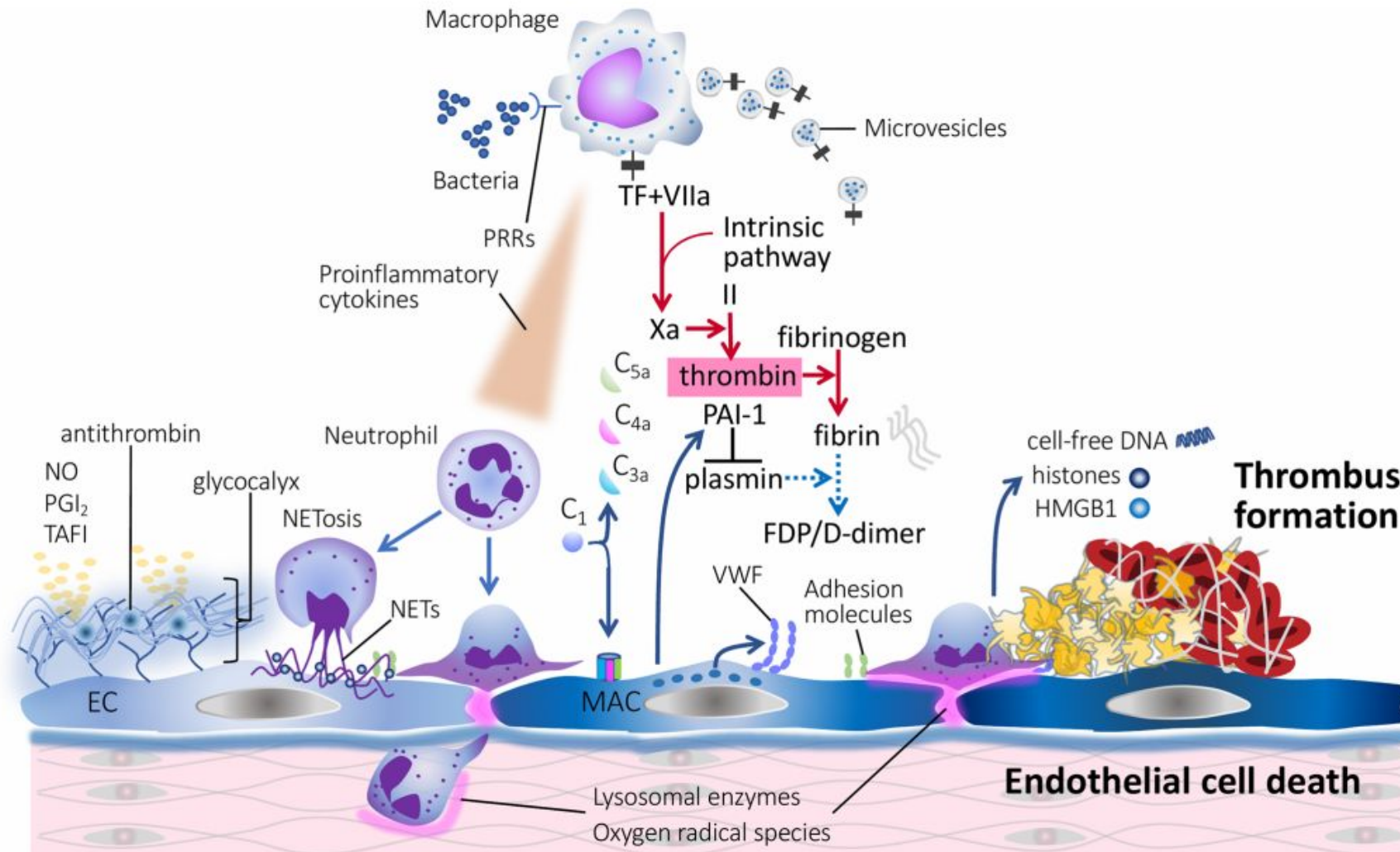
Pathogenesis

Derangement of endothelial function

- Activated polymorphonuclear neutrophils – proinflammatory mediators
- NETs
 - Eradicate invading pathogens
 - Change to procoagulant state
- Thrombin mediated endothelial damage
- Decreased activity of ACE2



Pathogenesis





Pathogenesis

Platelets

- Increased reactivity during sepsis
- PF4, VWF, procoagulant microvesicles
- Intravascular microthrombus formation
- Thrombocytopenia



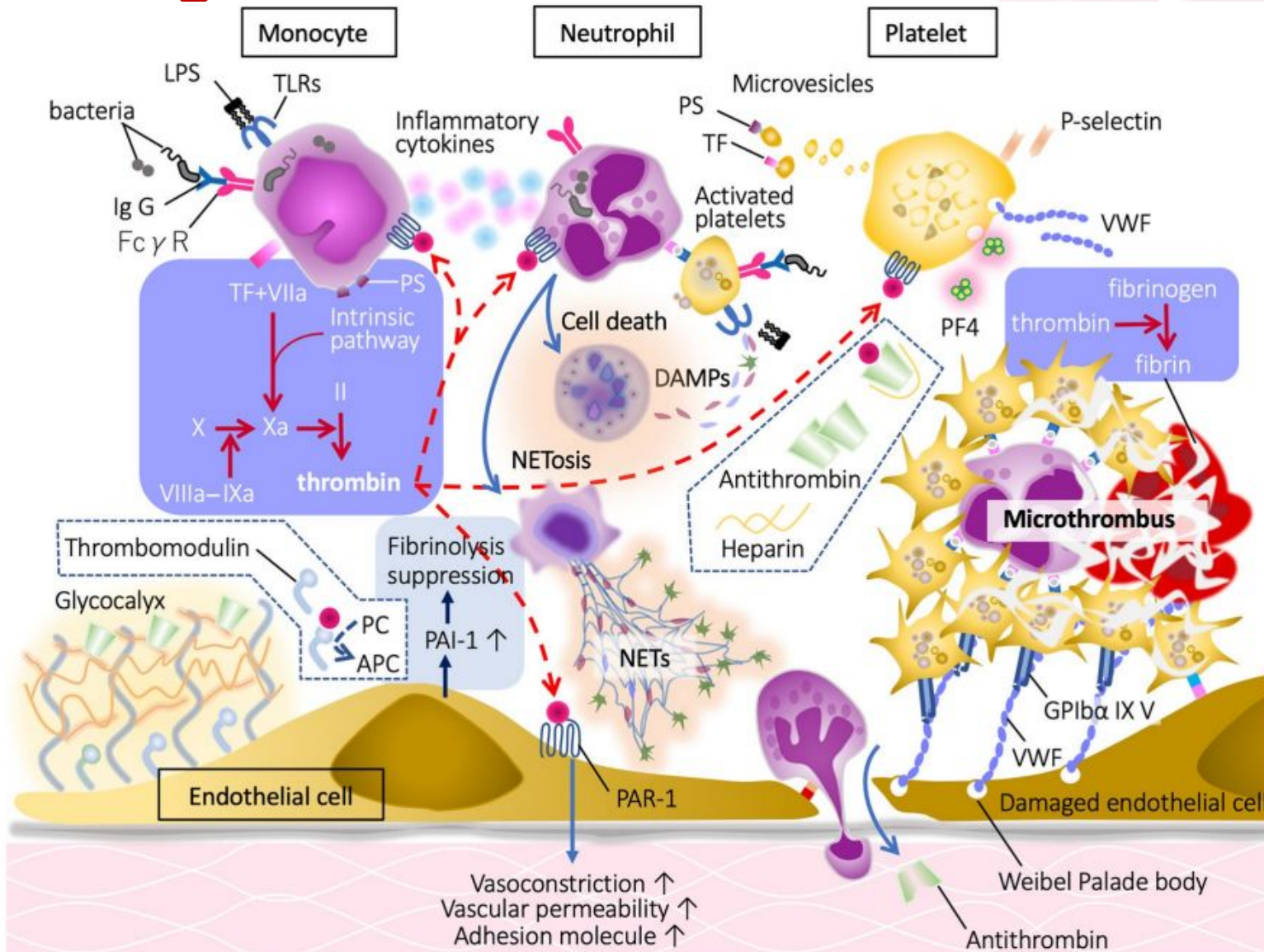
Pathogenesis

Anticoagulation dysregulation

- Increased PAI-1 production » fibrinolytic shutdown
- Decreased levels of protein C and antithrombin
- Fibrin degradation products
- Leakage with increased vascular permeability



Pathogenesis



Iba, T., Helms, J., Connors, J.M. et al. The pathophysiology, diagnosis, and management of sepsis-associated disseminated intravascular coagulation. *J Intensive Care* 11, 24 (2023).



Pathogenesis

***Widespread microthrombus
formation***



Clinical manifestations

- Thrombosis leading to tissue ischemia – small vessels
- Bleeding
- Organ dysfunction » thrombosis / hypoperfusion / hemorrhage
- Microangiopathic hemolytic anemia
- Laboratory abnormalities



Clinical manifestations

When to suspect

- Sepsis
- Organ dysfunction
- Thrombotic and / or bleeding complications
- Laboratory abnormalities – coagulation and platelets



Diagnosis

“Systemic activation of coagulation”

- Platelet count
- Prothrombin time
- Fibrinogen
- D-dimer

International Society of Thrombosis & Hemostasis (ISTH) DIC score

Test	0 points	1 point	2 points	3 points
INR, or, PT prolongation	INR \leq 1.3 <3 seconds	INR 1.3-1.7 3-6 seconds	INR >1.7 >6 seconds	
Fibrinogen	>100 mg/dL	<100 mg/dL		
D-dimer	<400 ng/dL		400-4,000 ng/ml	>4,000 ng/ml
Platelets	>100,000/ μ L	50,000-100,000/ μ L	<50,000/ μ L	

Interpretation of total score:

- **\geq 5 points:** Positive for DIC
- **<5 points:** Negative, but patients could still have "non-overt DIC" which could evolve into frank DIC. If there is ongoing concern for DIC, coagulation labs may be repeated in 12-24 hours.

Patel P et al. 2019 PMID 30991817



Diagnosis

“Systemic activation of coagulation”

- Platelet count
- Prothrombin time
- Fibrinogen
- D-dimer



***Consumption
coagulopathy***



***Diagnostic
delay***



Diagnosis

Sepsis-induced coagulopathy

- Organ dysfunction – SOFA score
- Platelets
- Prothrombin time / INR

Table 1. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO ₂ /FiO ₂ : > 400 SpO ₂ /FiO ₂ : > 302	PaO ₂ /FiO ₂ : < 400 SpO ₂ /FiO ₂ : < 302	PaO ₂ /FiO ₂ : < 300 SpO ₂ /FiO ₂ : < 221	PaO ₂ /FiO ₂ : < 200 SpO ₂ /FiO ₂ : < 142	PaO ₂ /FiO ₂ : < 100 SpO ₂ /FiO ₂ : < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP ≥ 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine > 15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x 10 ³ /mm ³)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6



Diagnosis

Sepsis-induced coagulopathy

- Organ dysfunction – SOFA score
- Platelets
- Prothrombin time / INR

***Earlier DIC
detection***

Sepsis Induced Coagulopathy (SIC) score

Test	0 points	1 point	2 points
INR	INR \leq 1.2	INR 1.2-1.4	INR $>$ 1.4
Platelets	$>$ 150,000/ μ L	100,000- 150,000/ μ L	$<$ 100,000/ μ L
SOFA score*	0	1	\geq 2

Interpretation of total score:

- \geq 4 points: Positive for SIC
- $<$ 4 points: Negative for SIC



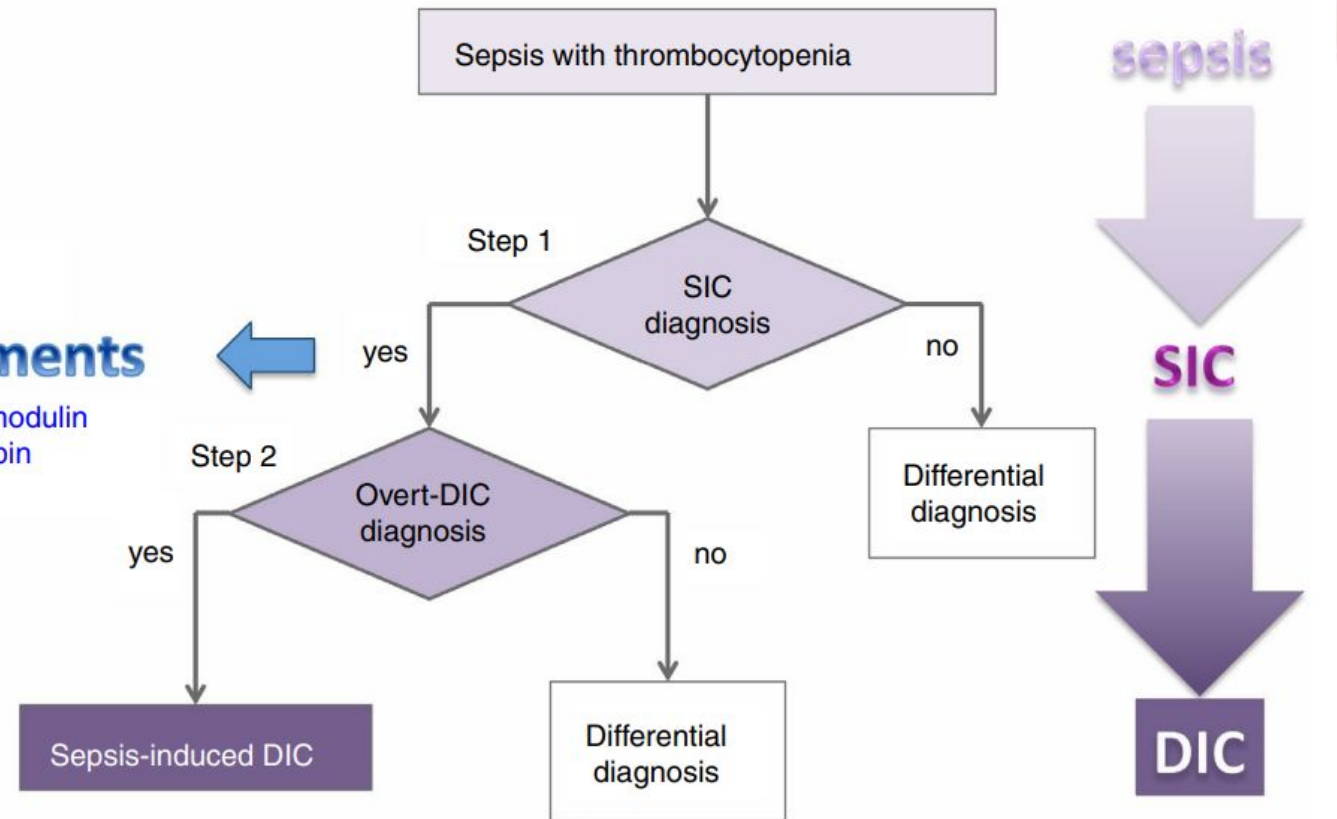
Diagnosis

Sepsis-induced coagulopathy

- Organ dysfunction – SOFA score
- Platelets
- Prothrombin time / INR

Consider
Treatments

Thrombomodulin
Antithrombin
Heparins



Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M; Scientific and Standardization Committee on DIC, and the Scientific and Standardization Committee on Perioperative and Critical Care of the International Society on Thrombosis and Haemostasis. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Thromb Haemost.* 2019 Nov;17(11):1989-1994.



Diagnosis

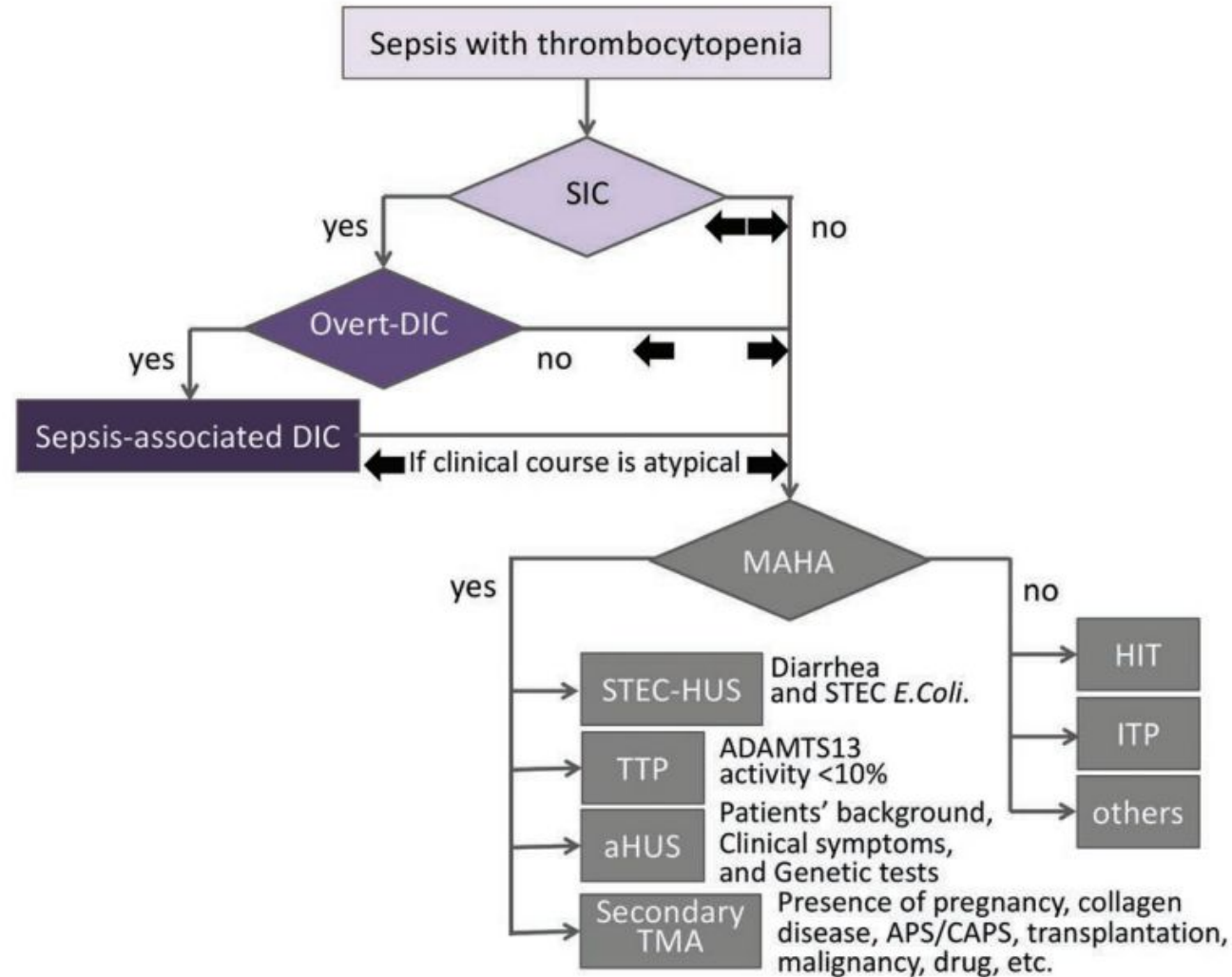
Sepsis-induced coagulopathy – benefits?

- Early recognition
- Easy access information
- Timing for therapy

- TMAs
- Not to predict outcomes



Diagnosis

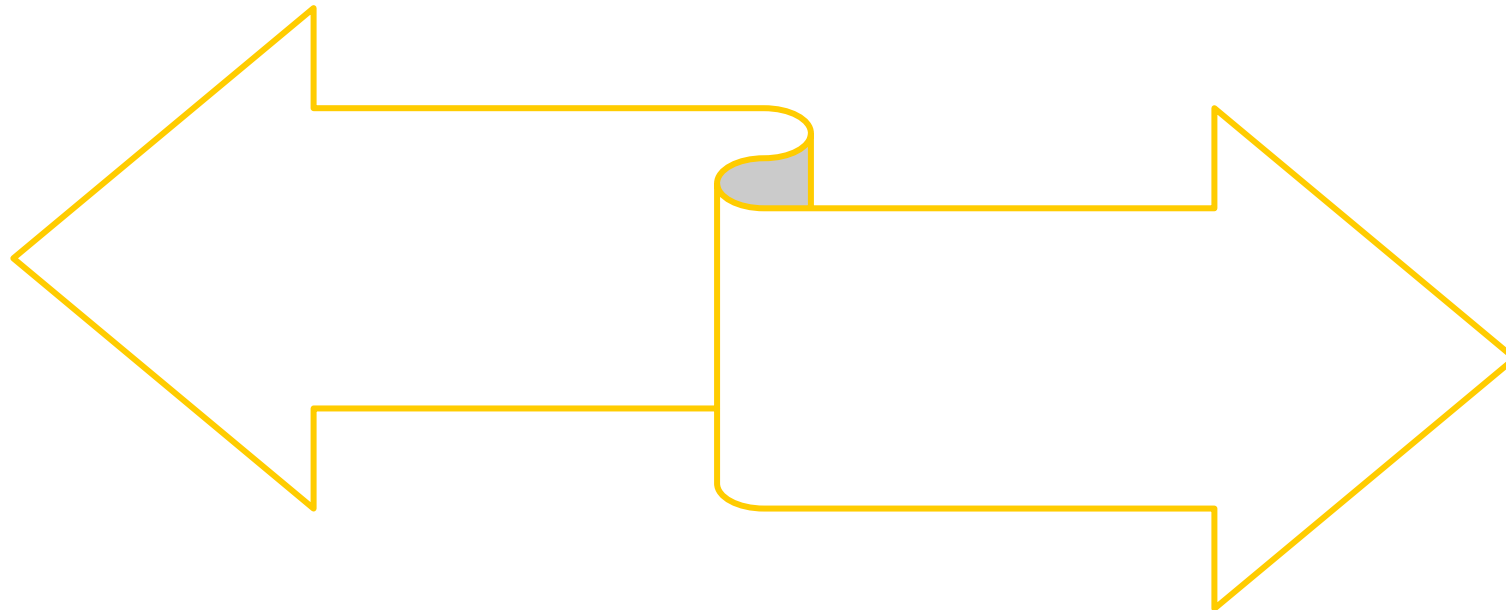


Iba T, Levi M, Levy JH. Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation. *Semin Thromb Hemost.* 2020 Feb;46(1):89-95.



Management

- Lack of specific therapeutic options
- Treatment of the underlying infection
- Supportive measures





Management

- Antiplatelets
- Heparins
- Recombinant thrombomodulin
- Antithrombin

No current anticoagulant as yet demonstrated efficacy

Fu et al. *BMC Anesthesiology* (2022) 22:28
<https://doi.org/10.1186/s12871-021-01545-w>

BMC Anesthesiology

RESEARCH

Open Access

Unfractionated heparin improves the clinical efficacy in adult sepsis patients: a systematic review and meta-analysis



Sifeng Fu, Sihan Yu, Liang Wang, Xiaochun Ma and Xu Li*

Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy
The SCARLET Randomized Clinical Trial

Jean-Louis Vincent, MD, PhD¹; Bruno Francois, MD²; Igor Zabolotskikh, MD, PhD³; [et al](#)

» [Author Affiliations](#) | [Article Information](#)

JAMA. 2019;321(20):1993-2002. doi:10.1001/jama.2019.5358



Management

If severe bleeding or invasive procedures

- Platelet transfusion
- Red blood cell transfusion
- FFP / Prothrombin complex concentrates / cryoprecipitate
- Fibrinogen
- Vitamin K

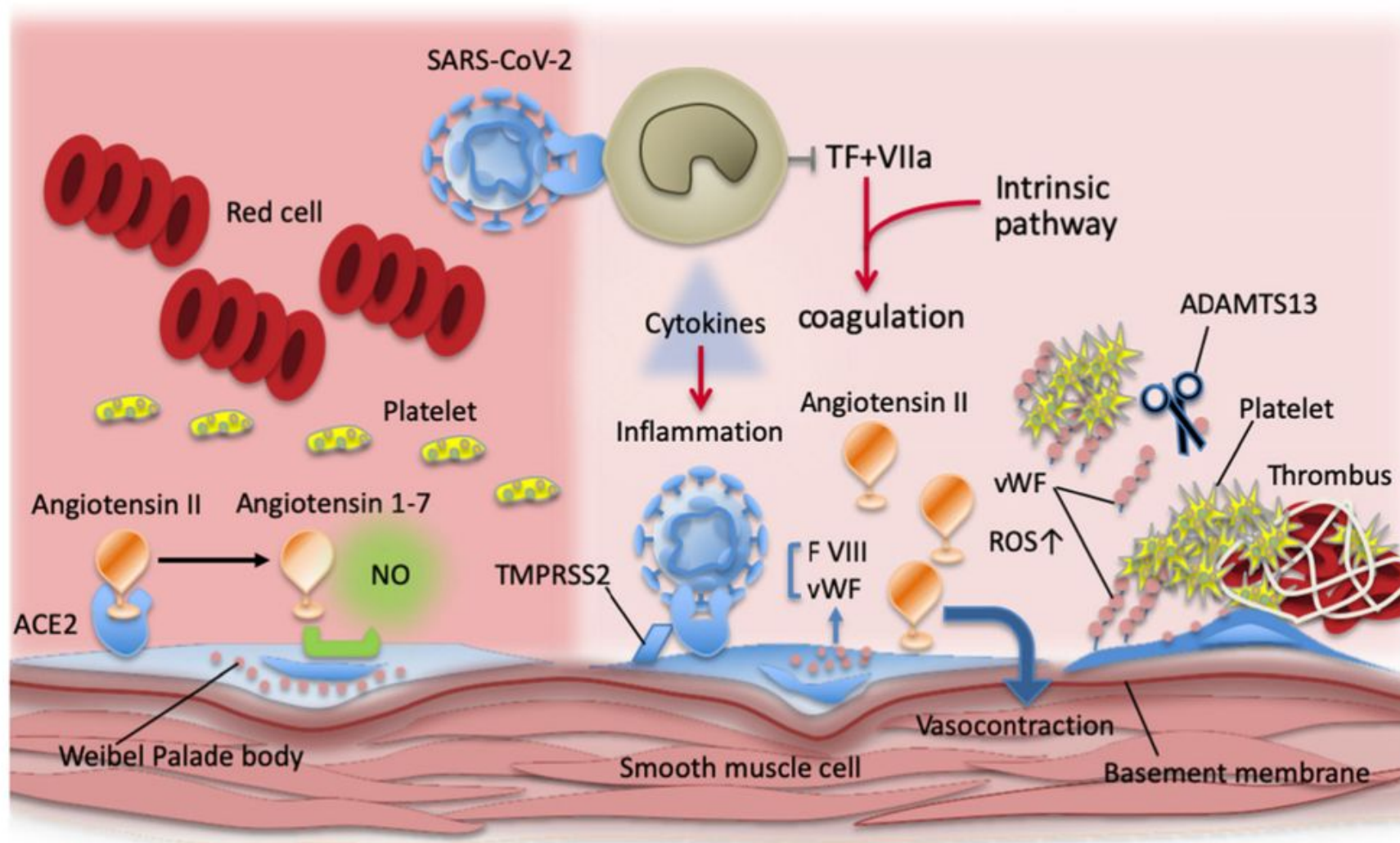


COVID-19

- Thrombotic events - VTE
- Higher mortality if SIC or DIC
- Immunothrombosis
- SARS-CoV-2 invasion with endothelial injury – ACE2
- Inflammatory cell infiltration in lung tissue
- IL-1 β , IL6



COVID-19





COVID-19

- Increased fibrinogen levels
- Increased D-dimer levels
- PT, aPTT and platelets – mild changes
- DIC in later stages

≠ SIC & DIC



COVID-19

Pulmonary intravascular coagulopathy (PIC)

- diffuse pulmonary immunothrombosis

Item	DIC diagnostic criteria			
	ISTH	JAAM	SIC	PIC
Underlying disease	0 point	0 point	0 point	NA
Platelet count ($\times 10^9/L$)	50–100: 1 point < 50: 2 points	≤ 120 or $> 30\%$ reduction/24 h: 1 point < 80 or $> 50\%$ reduction/24 h: 3 points	100–150: 1 point < 100: 2 points	Normal or slight decrease
Fibrin-related marker	FDP, D-dimer, SF Moderate increase: 2 points Strong increase: 3 points	FDP ($\mu g/mL$) ≥ 10 but < 25 : 1 point ≥ 25 : 3 points	None	Increase in D-dimer levels
Fibrinogen (g/L)	< 1: 1 point	None	None	Normal or a slight increase
PT	Prolonged PT (s) 3–6: 1 point > 6: 2 points	PT ratio ≥ 1.2 : 1 point	PT ratio 1.2–1.4: 1 point > 1.4: 2 points	Normal or a slight increase
Others	NA	SIRS score ≥ 3 : 1 point	Four items SOFA* = 1: 1 point ≥ 2 : 2 points	NA
Diagnosis	≥ 5 points	≥ 4 points	≥ 4 points (coagulopathy)	NA

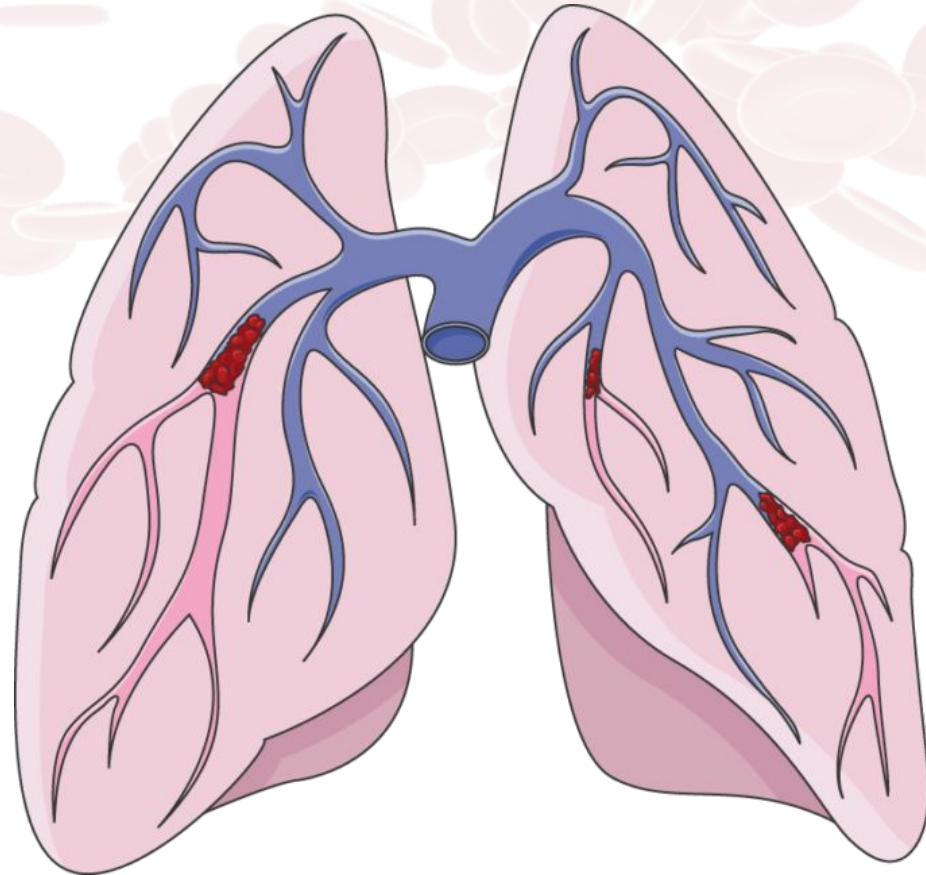
Wang Z, Gao X, Miao H, Ma X, Ding R. Understanding COVID-19-associated coagulopathy: From PIC to SIC or DIC. J Intensive Med. 2021 Mar 27;1(1):35-41.



COVID-19

Pulmonary arterial thrombosis

- Localized immunothrombosis
- Localized thrombi





Future

- Sepsis and DIC are complex syndromes
- Better understanding of the pathology and pathobiology
- Better biomarkers - vascular endothelium
- Role of point-of-care tests
- Better treatment options



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