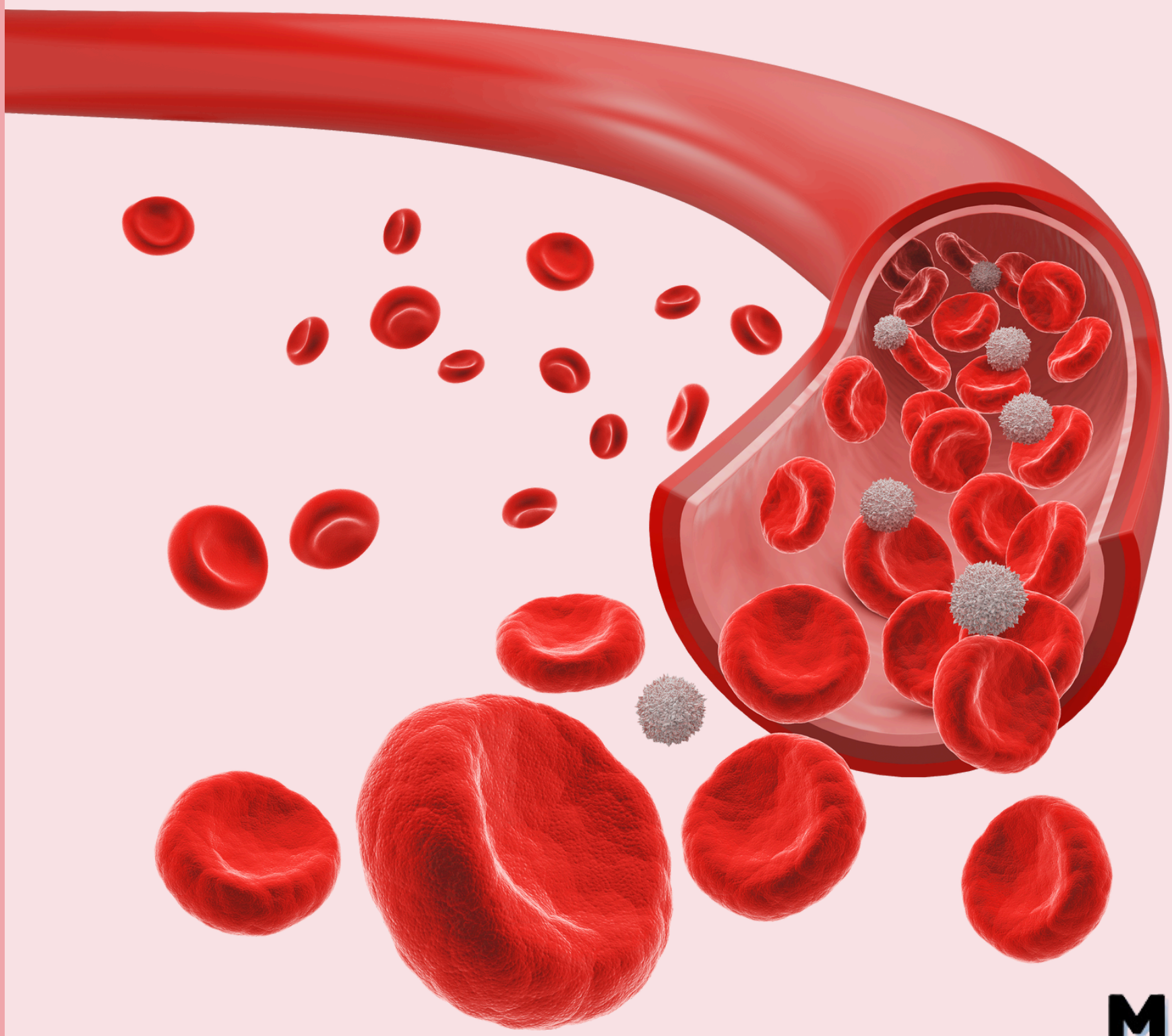
Matrix unlocked

HAEMOSTASIS 101:

MECHANISMS, PROFILES & COMMON DISORDERS



MUM IMs

Primary haemostasis

- **Initial response of the body to vascular injury**
- **Formation of a stable platelet plug around which a fibrin network can be built**

1

Injury

Vessel wall is damaged

↓

Endothelium is breached → Release endothelin reflex → Transient vasoconstriction

↓

2

Exposure

↓ **[Secondary hemostasis]**

Collagen is exposed → Tissue factors (TF) are released → Thrombins are released

↓

3

Adhesion

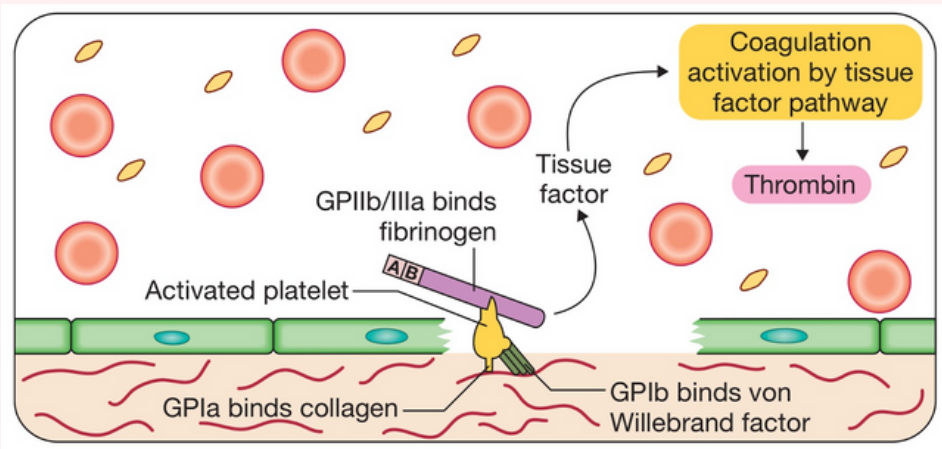
Platelets adhere to collagen via glycoprotein Ia (GPIa)

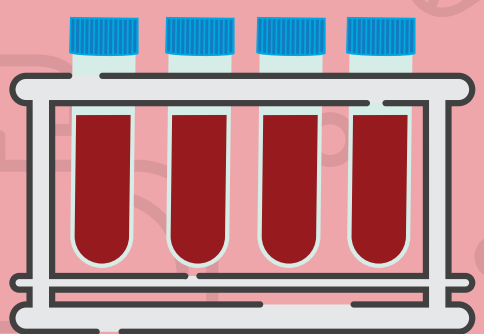
↓

Platelets bind von Willebrand factor (VWF) via GPIb

↓

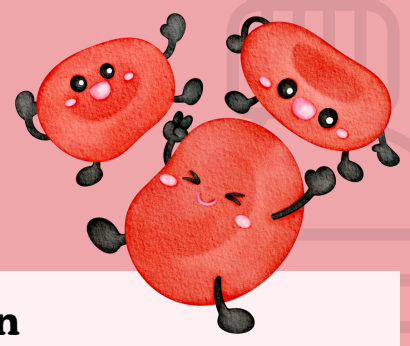
Platelets release Serotonin and Thromboxane A2 (TXA2) → Vasoconstriction





↑

4



Activation

Platelet releases Adenosine diphosphate (ADP)

↓

ADP causes conformational change in GPIIb/IIIa on platelets' surfaces

↓

Platelets bind fibrinogen

↓

5

Aggregation

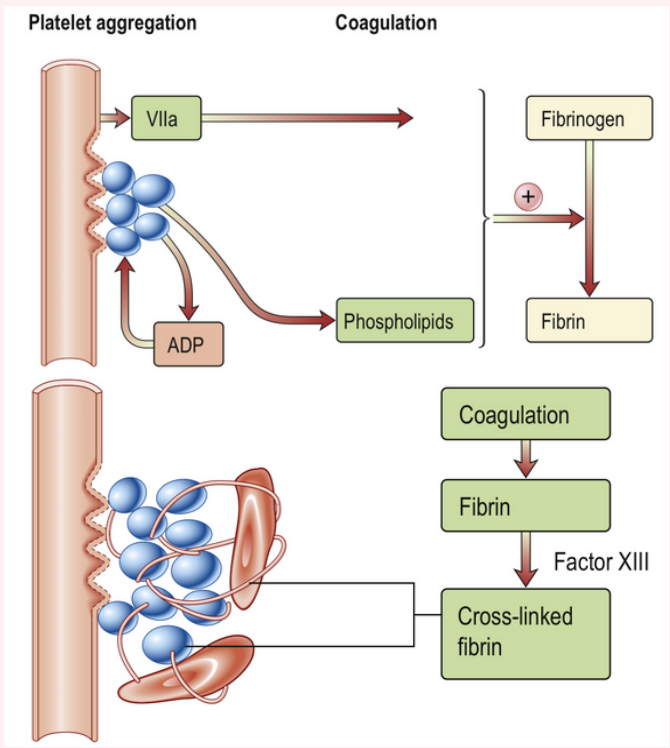
Fibrinogen forms a bridge between platelets

↓ **[Secondary hemostasis]**

Platelet plug is formed → coagulation cascade

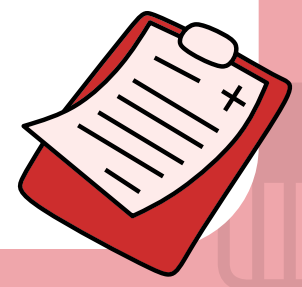
↓

Stops bleeding temporarily



Secondary haemostasis

- Sequential activation of procoagulant proteins (coagulation cascade)
- Conversion of soluble fibrinogen to fibrin through thrombin
- Coagulation factors are synthesised by liver
- Active forms are denoted as ‘a’



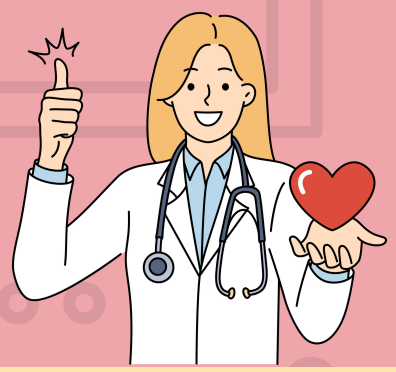
INTRINSIC PATHWAY

Surface Contact

Factor XII → Factor XIIa

Factor XI → Factor XIa

Factor IX → Factor IXa



COMMON PATHWAY

EXTRINSIC PATHWAY

Tissue damage

Factor VIIa ← Factor VII

Factor X

Tissue factor

APTT

PT

Factor VIII

Carrier protein: VWF

Factor Xa

Factor XIII

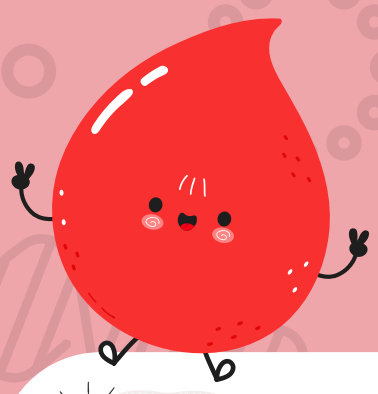
2 Prothrombin → Thrombin

5

Factor XIIIa

TT

1 Fibrinogen → Fibrin → Stable fibrin clot



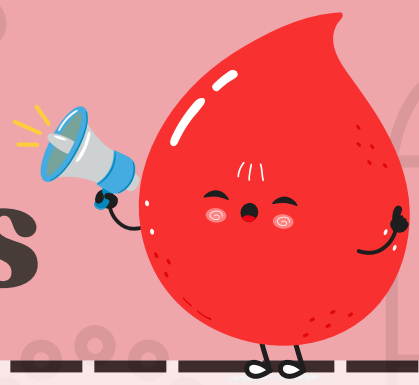
REMEMBER:

- **Common pathway: Factors of 10 = 5, 2, 1**
- **Extrinsic pathway: 7**
- **Intrinsic pathway: 12 to 8 (except 10)**

Natural anticoagulation

- Antithrombin → mainly inhibit thrombin (factor IIa) and factor Xa
- Protein C and Protein S → inhibit factor VIIIa and factor Va

Fibrinolysis



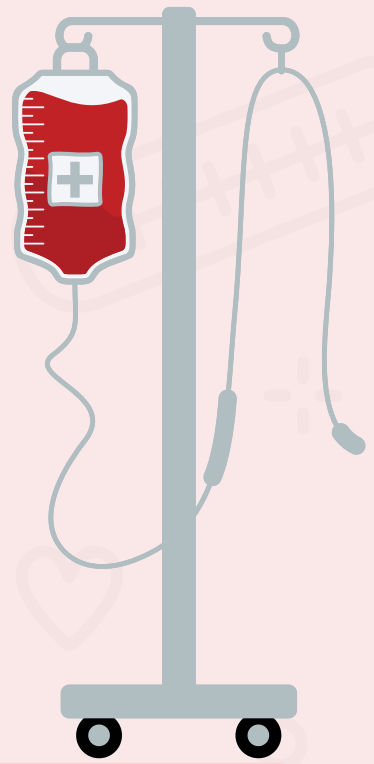
Plasminogen

Activators
Tissue plasminogen activator (t-PA)

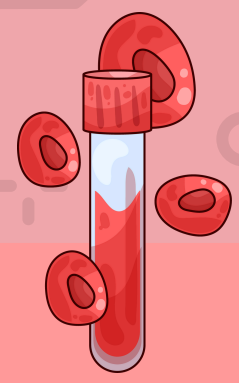
Plasmin

Fibrin (Fibrinogen)

Fibrin (fibrinogen) degradation products (FDPs) e.g. D-dimer



Coagulation profile



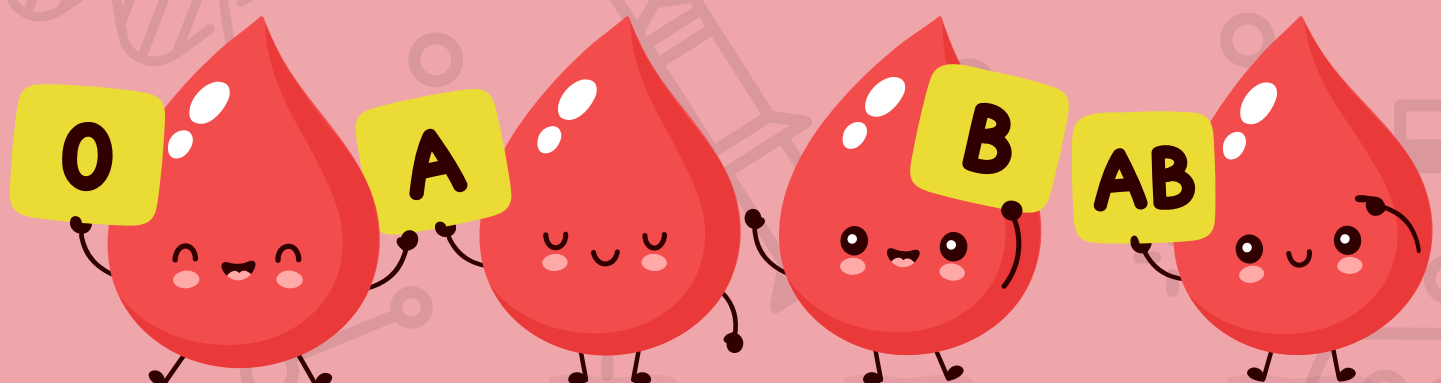
Parameter	Explanation

Activated partial thromboplastin time (APTT)	• Assess intrinsic pathway
	• Prolonged in coagulation factor deficiency of 30% or below
	• Artefactual prolongation may be due to:
	  ◦ Presence of heparin or a direct oral anticoagulant
	  ◦ Difficult or slow collection
	  ◦ Incorrect volume of blood
	  ◦ Delay in mixing
	  ◦ Suboptimal specimen storage
	  ◦ Prolonged interval between collection and testing

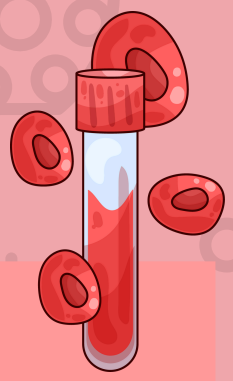
Prothrombin time (PT)	Assess extrinsic pathway

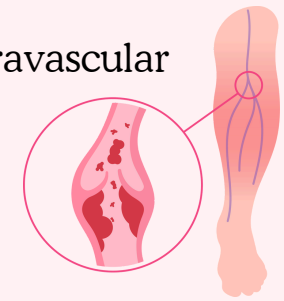
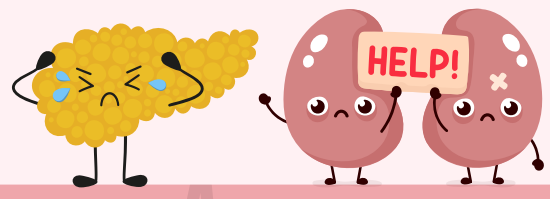
International normalised ratio (INR)	• Commonly adjusted according to the formula:
	  ◦ INR = (Patient PT/Mean normal PT) ^ ISI
	  ◦ ISI: international sensitivity index of the thromboplastin
	• Assesses the therapeutic effect of coumarin anticoagulants, including warfarin

Prolongation of both APTT and PT: factor X, V, II or I (fibrinogen) deficiency in common pathway or global coagulation factor deficiency



Coagulation profile



Parameter	Explanation
Fibrinogen 	 • Low levels ◦ Reduced production (Liver disease) ◦ Increased consumption (Fibrinolysis), levels are elevated in an acute phase response • High levels ◦ Acute phase response of inflammation 
Thrombin time	Prolonged in fibrinogen deficiency
Fibrin-degradation products/ D Dimer 	Elevated in venous thromboembolism and Disseminated Intravascular Coagulation (DIC)  Causes of DIC:  **REMEMBER: STOP Making New Thrombi**  **S**: Sepsis, Snake bite (rattlesnake) **T**: Trauma **O**: Obstetric complications (placental abruption, amniotic fluid embolism) **P**: Pancreatitis (acute) **M**: Malignancy **N**: Nephrotic syndrome **T**: Transfusion  
Full blood count: Platelet count	Thrombocytopenia or thrombocytosis 
Bleeding time (BT) 	• Time to stop bleeding after a standardised incision • Historically assess platelet function ◦ Now platelet function is measured by aggregation in response to various agonists

Common conditions

Conditions	BT	PT/INR	APTT
Haemophilia A X-linked disorder causing lack of factor VIII with normal VWF	=	=	↑
Von Willebrand's disease Most common inherited bleeding disorder with deficiency or abnormalities of VWF causing impaired platelet adhesion and factor VIII deficiency	↑	=	↑/=
Vitamin K deficiency Lack of γ-carboxylation on factor II, VII, IX, X, and Protein C and S	=	↑	↑
DIC Systemic activation of coagulation causing widespread fibrin deposition in blood vessels, leading to thrombosis and multiorgan failure • ↓ Platelet count • ↑ D-dimer • ↓ Fibrinogen	↑	↑	↑

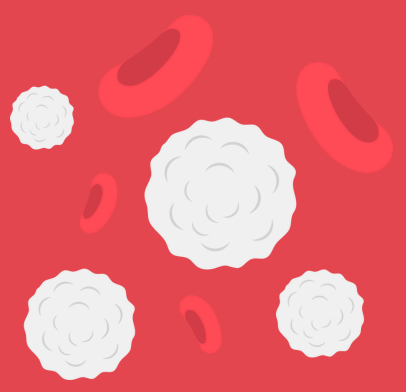
PT goes first!

Factor VII has the shortest half-life (4–6 h)

--> So in warfarin use, vitamin K deficiency, or liver disease, PT is prolonged before aPTT

Mixing test

- Differentiation between coagulation factor deficiency and inhibitor
- Based on the ability / inability of normal plasma to correct prolonged APTT (or PT) of patient's plasma
    - 50:50 mixture

	**Haemophilia (Factor deficiency)**	**Coagulation inhibitor (e.g., lupus anticoagulant, factor VIII inhibitor)**
Mechanism	Deficiency of clotting factor (VIII in Hem A, IX in Hem B)	Antibody or inhibitor interferes with clotting factor activity
Baseline APTT	Prolonged	Prolonged
Mixing test (patient plasma + normal plasma)	**APTT corrects to normal** (because normal plasma supplies missing factor)	**APTT does not correct** (inhibitor in patient plasma inactivates normal plasma factors)

References

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