

Managing Coagulopathy in Intensive Care Setting

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Normal Haemostasis

- Primary Haemostasis
 - Vessels
 - Platelets
 - Von Willebrand Factor
- Coagulation
 - Clotting factors
 - In vivo vs In vitro

When Problem Occurs

- Quantitative more than qualitative
 - For examples, thrombocytopenia more common than platelets dysfunction
- Acquired more than congenital

Quantitative Problem

- Productive defect
- Increased consumption
- Loss
- Dilution
- Lysis
- Pool

Qualitative Problems

- Inhibitory
- Inactivation
- Functional

History: Rule out inherited defect or use of antithrombotic drugs.

Examination: Is bleeding general or local?

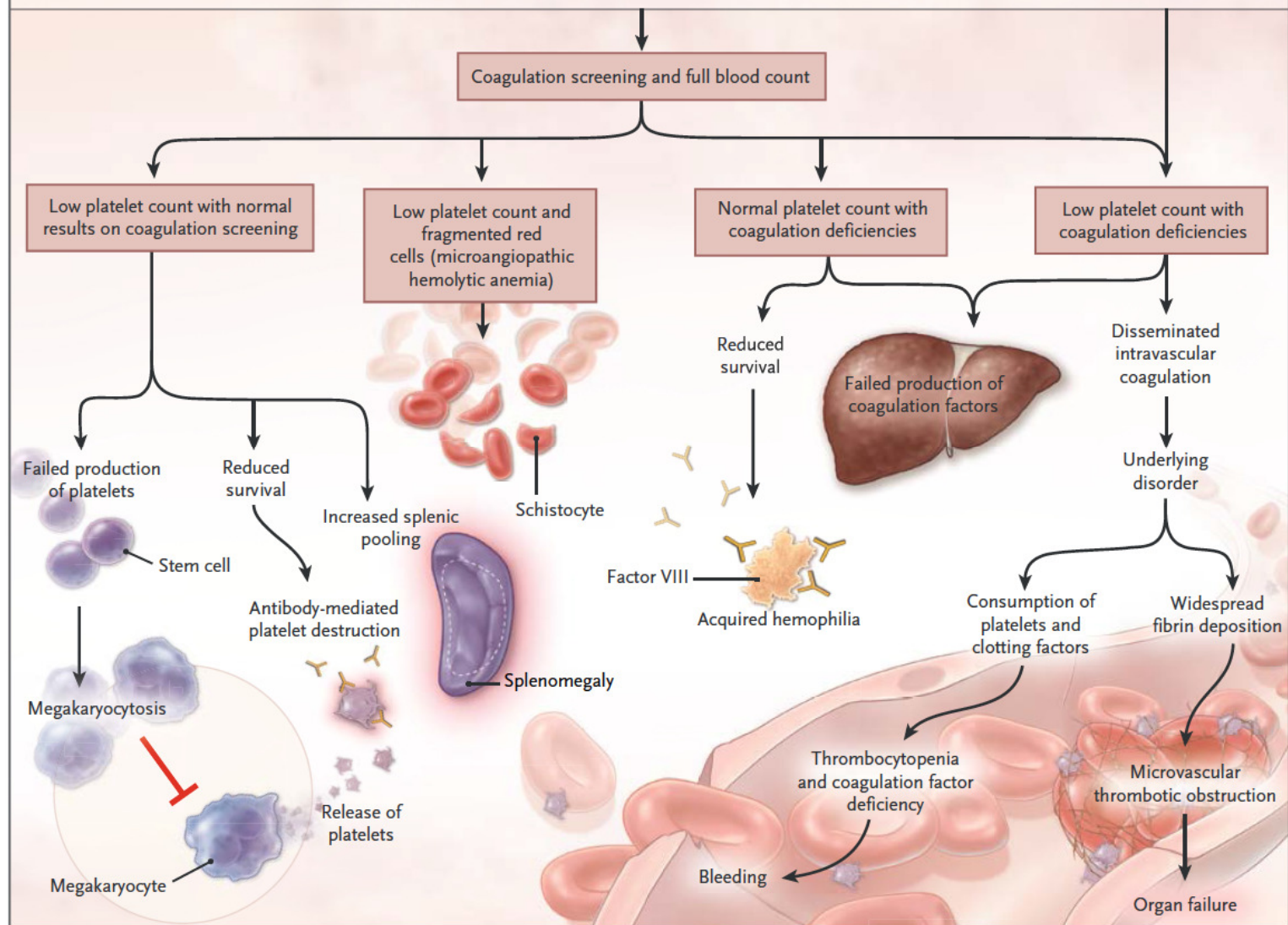


Figure 1. Causes of Bleeding among Patients in the ICU.

After the presence of inherited disorders and the use of antithrombotic drugs have been ruled out, the first major question ("Is the bleeding general or local?"), combined with a platelet count and coagulation screening, will assist in the identification of the pathogenesis of bleeding.

Table 1. Laboratory Findings in Various Platelet and Coagulation Disorders in the ICU.

Condition	Prothrombin Time	Activated Partial-Thromboplastin Time	Fibrinogen Level	D-Dimer Level	Bleeding Time	Platelet Count	Findings on Blood Smear
Vitamin K deficiency or use of vitamin K antagonist	Prolonged	Normal or mildly prolonged	Normal	Unaffected	Unaffected	Unaffected	
Aspirin or thienopyridines	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Liver failure							
Early stage	Prolonged	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	
End stage	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	
Uremia	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Disseminated intravascular coagulation	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	Fragmented red cells
Thrombotic thrombocytopenic purpura	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Very low	Fragmented red cells
Hyperfibrinolysis	Prolonged	Prolonged	Low	Very high	Possibly prolonged	Unaffected	

IDEAL laboratory findings (only what is expected to see), patterns not always reproducible

Principles

- The first principle of the management of coagulopathies in critical care is to avoid the correction of laboratory abnormalities with blood components / products unless there is a clinical bleeding problem, a surgical procedure is required or both.
- If bleeding occurs, identify local factors; if bleeding general, identify underlying coagulation abnormalities.
- Don't let the vicious cycle of coagulopathy set in.

Common Scenarios

Current State-of-the-Art

- Major bleeding
- Haemostatic support for invasive procedures
- Disseminated Intravascular Coagulation
- Thrombocytopenia
- Bleeding associated with antithrombotic drug
- ECMO related coagulopathy

Major bleeding

- Massive transfusion
 - Replacement of one blood volume in 24 hours
 - Transfusion of > 4 RBC units within 1 hour when ongoing need is foreseeable
 - Replacement of 50% of total blood volume within 3 hours

Pathophysiology of Major Bleeding

- Cellular components in blood
 - RBC's
 - Rheological effect of RBC's on margination of platelets
 - RBC's modulates biochemical & functional responsiveness of activated platelets.
 - Platelets
 - Dilutional thrombocytopenia
 - Consumption
 - Acquired platelet dysfunction
 - No functional platelets in transfused RBC's
 - Coagulation factors
 - Dilutional
 - Consumption
 - Disseminated intravascular coagulation (D.I.C.)

Pathophysiology of Major Bleeding

○ Haemodilution

- Crystalloids & colloids
- Dilutional effect
- Some colloids may influence primary haemostasis & coagulation

○ Hypothermia

- Body temperature $<35^{\circ}\text{C}$
- Affects platelet function
- Slows coagulation
- Increases fibrinolysis

Trauma Transfusion

- Initial data from military setting; “automatically” related to hospital trauma setting, & even non-trauma setting (e.g., obstetric).
- Promulgation of early plasma / platelets transfusion at a higher ratios with reference to red cells to prevent the vicious cycle.
 - Supported by clinical observational study (PROMMTT study)
 - Favored by randomized clinical trials (PROPPR study)
- Time-varying ratios observed with greater ratio in the first 6 hours after injury associated with lower patient mortality (Efficient transfusion in the first few hours is important).
- Use of tranexamic acid as soon as possible (within 3 hours after injury) for trauma patients with bleeding or at risk for major bleedings (CRASH-2 trial).

QMH Trauma Transfusion Protocol: More than a ratio

- No enforcement in 1:1:1 package
- Provide alternative activation pathway, i.e., by *clinical decision*

Protocolized approach

Efficiency of delivery of blood component

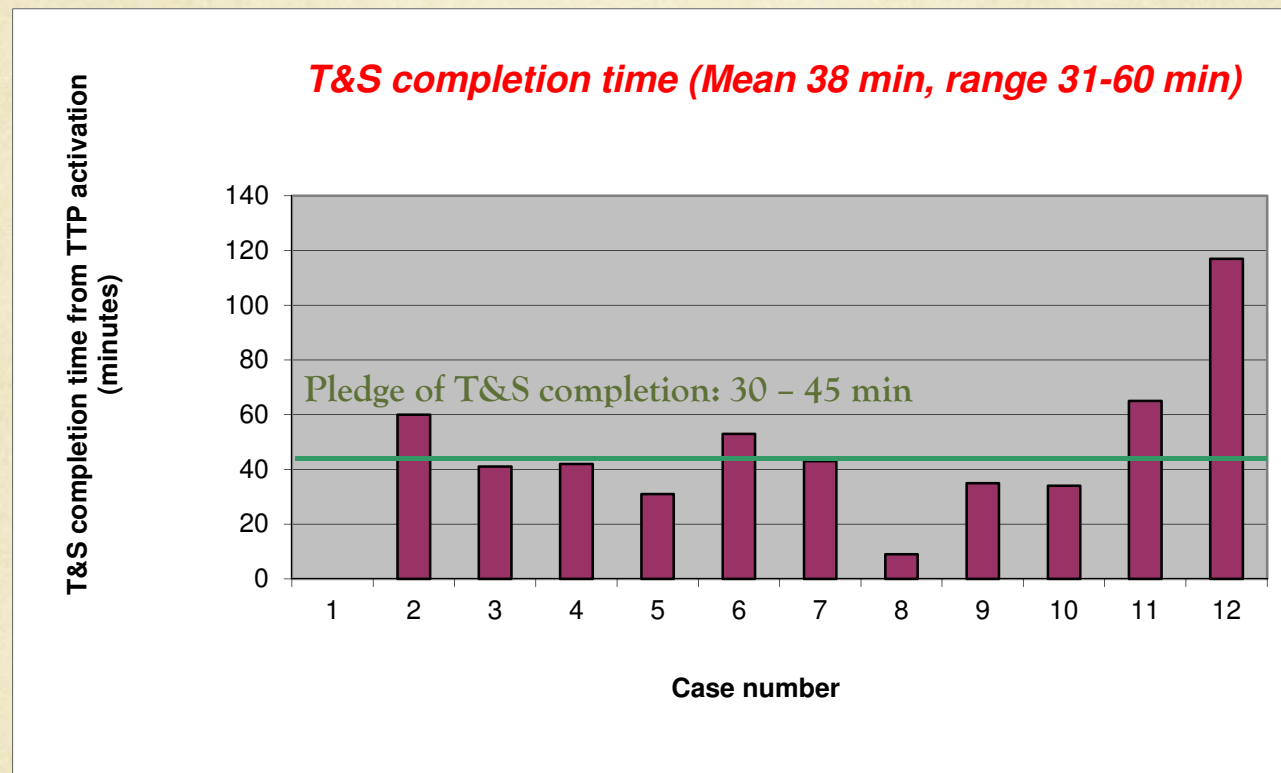
Effective communication

1. Portering system
 - Designated porter (*They are really fast!*)
 - Lift-holding by security
2. Special blood bank service pledges (*We are committed!*)



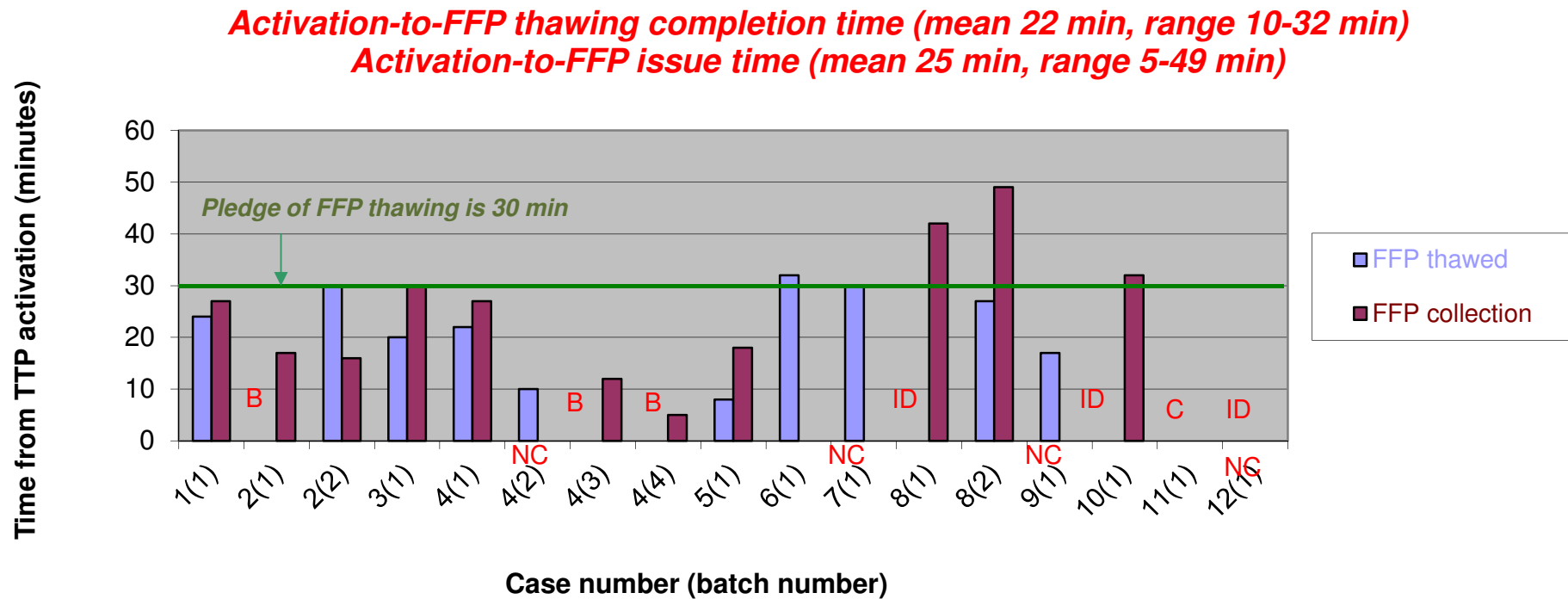
Central Porter Center designated phoneline: *6666*
Documenting the handover
Porter keep updated of the patient's transfer status

Activation-to-Type & Screen Completion time



Case 1 & 8: T&S sample arrived before activation
Case 11: Failed resuscitation at A&E
Case 12: Step down 2 minutes after activation
(All four cases were excluded for time study)

Activation-to-FFP Thawing Completion Time & Activation-to-FFP Issue Time



B = thawed component already available

C = cancel request

NC = not collected

ID = improper documentation

Restricted Transfusion for Acute GI Bleeding

- Patients with acute upper gastrointestinal bleeding who were treated with restrictive strategy ($<7\text{g/dl}$) had longer survival (6 weeks) and a lower rate of rebleeding than did those who were treated with liberal strategy ($<9\text{ g/dl}$)
- Transfusion may counteract the splanchnic vasoconstrictive response due to hypovolaemia, increase the splanchnic blood flow and pressure and impair the formation of blood clot.

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding
N Engl J Med 2013; 368:11-21
- Trials on tranexamic acid in progress (HALT-IT)

Before Invasive Procedures

- There is no supportive evidence for the prophylactic use of FFP to correct abnormal results on coagulation screening
- Coagulation screening has no predictive value for later bleeding
- Generally, INR below 1.5 is considered safe
- Vitamin K deficiency should not be undertreated

DIC

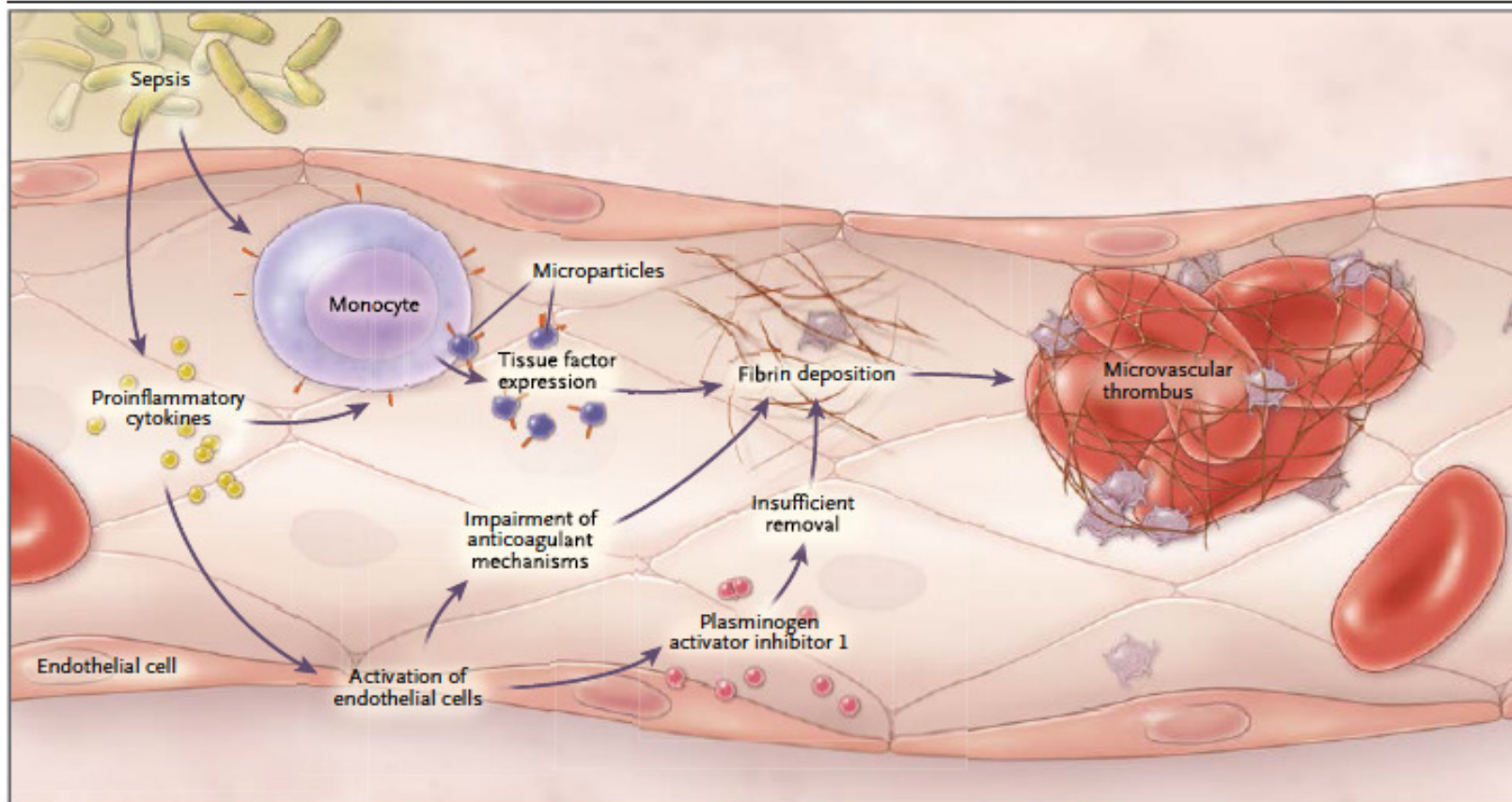


Figure 2. Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anticoagulant mechanisms and down-regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor.

To score or not to score

- Diagnosis of DIC should only be made in the right clinical context
- Its diagnosis makes little difference to the management strategy unless patient bleeds & transfusion support is the only option based on current evidence
- RCT on pharmacological doses of protein C, antithrombin & tissue pathway inhibitor showed discouraging results
- Antifibrinolytic contraindicated and heparin risky

Thrombocytopenia

- Rule out pseudothrombocytopenia.
- Often multifactorial in ICU setting.
- Urgent & life-threatening causes: HIT, TTP.
- Platelet refractoriness in patients at risk: CCI (corrected count increment) for diagnosis , HLA-matched platelets as treatment.
- Platelet transfusion trigger
 - Prophylactic vs Therapeutic
- Lowest threshold for prophylactic transfusion (mostly taken as $10 \times 10^9/L$), limited by the precision of platelet count generated by automated haematology analyzers.
- Autoimmune thrombocytopenic purpura is no longer a diagnosis of exclusion.

Table 4. Common Antithrombotic Agents, Mechanisms of Action, and Reversibility.

Agent	Mechanism of Action	Site of Clearance	Half-Life	Procedure for Immediate Reversal
Aspirin	Irreversible cyclooxygenase inhibitor		20 min but effect will persist for 5 days	Platelet transfusion; consider use of desmopressin
Clopidogrel, prasugrel, ticagrelor	P2Y ₁₂ antagonists	Hepatic	6 to 15 hr	Platelet transfusion
Unfractionated heparin	Indirect anti-Xa and anti-IIa effect; increases the action of antithrombin by factor of 10,000	Cellular and (at higher doses) renal	45–90 min	Protamine (at a dose of 1 mg) neutralizes 80–100 U unfractionated heparin
Low-molecular-weight heparin	Same as for unfractionated heparin but mainly anti-Xa effect	Renal	Approximately 4 hr, with variability among products	Protamine reverses 60% of effect; consider the use of recombinant activated factor VII if there is continued life-threatening bleeding and the time frame suggests there is residual effect
Danaparoid	A heparinoid with ratio of anti-Xa to anti-IIa of >20	Renal	24 hr	No specific antidote; plasmapheresis may be considered for critical bleeding
Fondaparinux	Synthetic pentasaccharide with indirect anti-Xa effect	Renal	17–20 hr	No specific antidote; use of recombinant activated factor VII should be considered for critical bleeding
Bivalirudin	Direct antithrombin effect	Proteolysis by thrombin (80%) with 20% renal excretion	25 min; 1 hr in renal failure	No specific antidote; hemodialysis, hemofiltration, or plasmapheresis may be considered for critical bleeding
Argatroban	Direct thrombin inhibitor	Hepatic	45 min	No specific antidote
Vitamin K antagonists (e.g., warfarin, phenprocoumon, acenocoumarol, phenindione)	Reduction in functional levels of vitamin K–dependent clotting factors (II, VII, IX, and X)	Hepatic	Varies according to drug, with phenprocoumon the longest and acenocoumarol the shortest	Intravenous vitamin K (1 to 5 mg) and prothrombin complex concentrate (25 to 50 U/kg); use of fresh frozen plasma only if prothrombin complex concentrate is not available
Dabigatran	A direct thrombin inhibitor	80% renal	13 hr (range, 11–22 hr); with creatinine clearance <30 ml/min, 22–35 hr	No specific antidote; use of oral activated charcoal if administered within 2 hr after receipt of drug; consider hemofiltration, hemodialysis; if life-threatening bleeding, consider prothrombin complex concentrate, activated prothrombin complex concentrate, and recombinant activated factor VII
Rivaroxaban, apixaban, edoxaban	Direct anti-Xa inhibition	Hepatic and renal	Rivaroxaban, 7–9 hr; apixaban, 9–14 hr	No specific antidote; if life-threatening bleeding, same as for dabigatran

When is laboratory monitoring for Target-Specific Oral Anticoagulant (TACO) indicated?

- To identify the mechanism of bleeding
- To detect overdose or drug accumulation
 - Renal impairment
 - Liver impairment
 - Elderly
- To determine the offset of activity
 - Pre-operative
 - Before thrombolysis for ischaemic stroke
- To monitor adherence
 - To distinguish treatment failure from non-adherence
- Clot-based assays for drug levels available for dabigatran & rivaroxaban

ECMO related coagulopathy

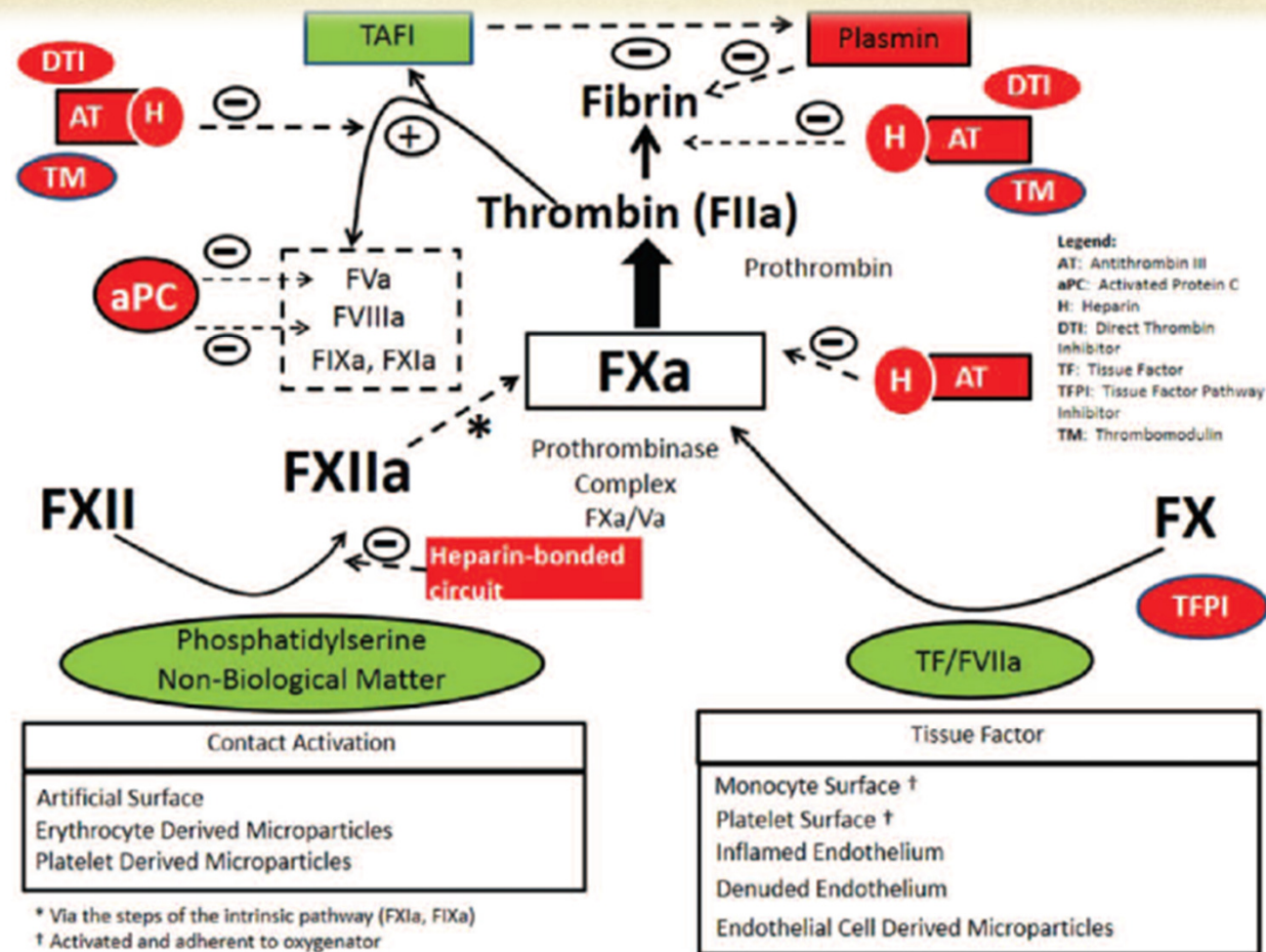
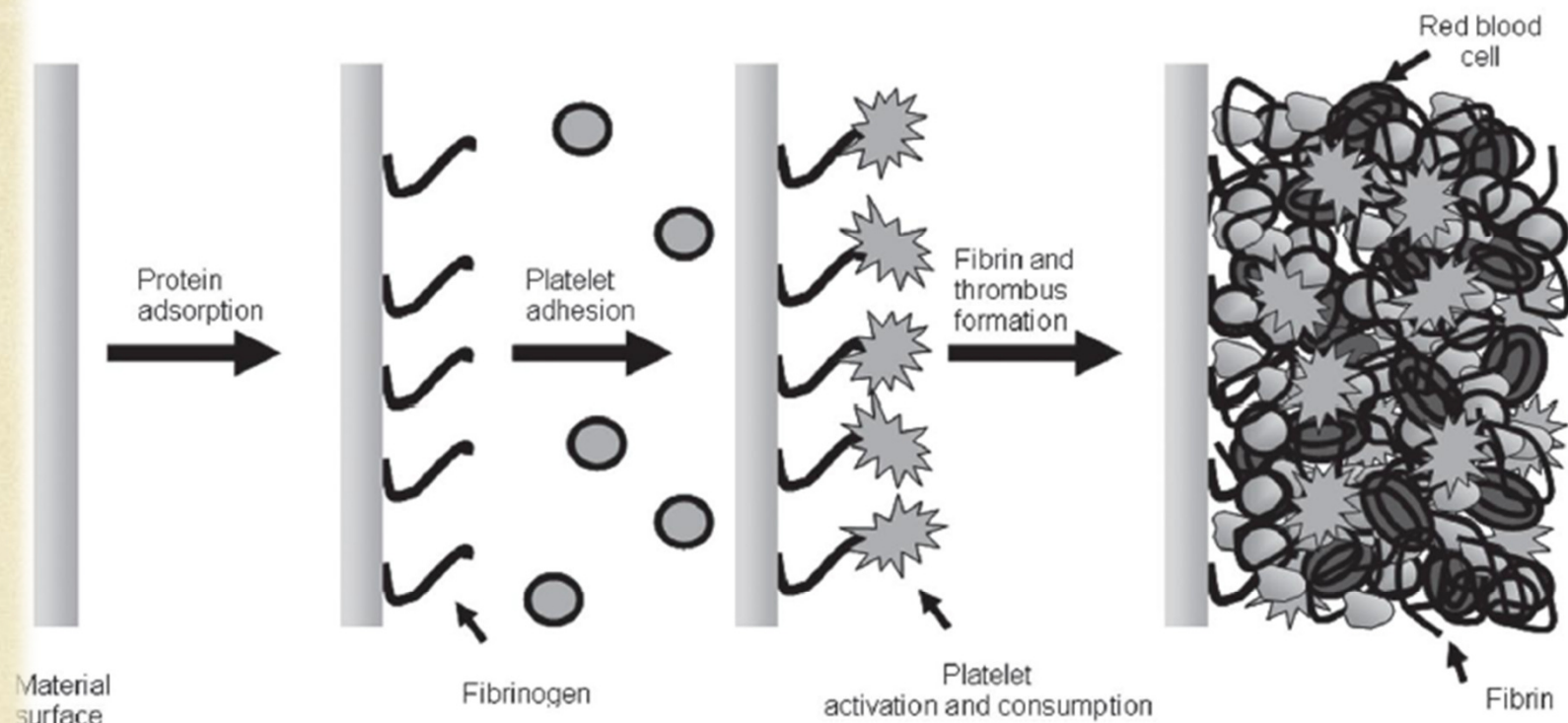


Figure 3. Schematic of the process of thrombin generation occurring during extracorporeal membrane oxygenation with the procoagulant stimuli (green background), competing with natural (red background, black border) or pharmacological anticoagulants. AT = antithrombin III; aPC = activated protein C; H = heparin; DTI = direct thrombin inhibitor; TF = tissue factor; TFPI = tissue factor pathway inhibitor; TM = thrombomodulin.



Reynolds MM. The artificial endothelium. Organogenesis 2011; 7: 42-9

Monitoring of anticoagulation

- ACT 180-220 sec
 - Affected by hypothermia & haemodilution
 - Closest to in vivo state, including other non-plasma components
- APTT may be off scale at the therapeutic range, depending on sensitivity of APTT reagent
- Anti-Xa assay
 - So called therapeutic range (intercenter variation)
 - Affected by plasma colorimetric
 - When high in face of a normal ACT, suspicious of heparin resistance > check AT level
 - Not practical for continuous monitoring

Laboratory tests

- Haemoglobin
- Platelet count
- Coagulation screening
 - Prothrombin time (PT)
 - Activated partial thromboplastin time (APTT)
 - Fibrinogen
 - D-dimers
- Other laboratory tests: ABG/RFT/LFT

Limitations of laboratory tests

- **Haemoglobin** may not reflect the extent of blood loss & the effect of haemodilution.
- **Platelet count** does not reflect platelet dysfunction acquired during tissue trauma & hypothermia.
- **PT/APTT** may not reflect *in vivo* function of the clotting factors during hypothermia.
- Increased **D-dimers** may or may not reflect disseminated intravascular coagulation (D.I.C.).
- **Limitation** of conventional laboratory parameters to guide transfusion therapy

Idealistic Guide for Transfusion Therapy

- Fast TAT – Certainly **NOT** PT/APTT
- Assay better reflect in vivo coagulation state
- Protocolized (Standardized), with proven benefit by clinical trials, preferably RCT

Coagulation screen predicts poorly levels of coagulation factors

Table I. PT and aPTT ratios of patients during the study.

	All patients, median (range)	In retrospect FFP not required, median (range)	In retrospect FFP required, median (range)
PT ratio	1·8 (1·4–20)	1·6 (1·4–1·9)	2·2 (1·5–20)
aPTT ratio	1·8 (1·1–10)	1·4 (1·1–2·8)	2·2 (1·2–10)

The median and range of the ratio of PT and aPTT, expressed as patient time divided by the mid-point of the normal range, are shown. Patients who, after retrospective analysis of coagulation factor results, had not required FFP are shown separately from those that had.

Retrospective analysis of the individual coagulation factor levels of patients (using the threshold of 30 IU/dl and 1 g/l for fibrinogen) showed that 10 of the 22 patients had not required FFP replacement (nine patients had no coagulation factor levels below 30 IU/dl and one patient had only a decreased level of factor XII).

Exploring the Global Assay

Table 1

Comparison global haemostasis assays.

Haemostasis test	Summary	Time		Detection			α 2M	WB	POC	Ref
		F	C	EA	T	V				
Thromboplastin generation test	Mixing test.	+	-	-	-	-	-	-	-	[8]
Two-stage prothrombin assay	Laborious, sub-sampling of plasma required to determine clotting time as endpoint in fibrinogen solution.	-	(+)	+/-	-	-	-	-	-	[9,10]
Chromogenic thrombin generation	Defibrinated plasma required since fibrin formation disturbs chromogenic registration.	-	+	+	-	-	++	-	-	[11]
Fluorescent thrombin generation	Generated signal interferes no longer with fibrin formation, but is adsorbed by plasma components (inner filter effect).	-	+	+	-	-	+	+/-	+/-	[22]
Overall hemostasis assay (OHP)	Monitors fibrin formation and lysis and reveals information about clot structure. OHP starts with a fixed amount of thrombin.	-	+	-	+	-	-	-	-	[33,34]
Clot formation And Lysis assay (CloFAL)	As OHP but starts coagulation with TF	-	+	-	+	-	-	-	-	[35]
Thromboelastography (TEG)	Registers viscoelastic changes by detection of movement in a rotating cup. TEG provides haemostatic status within 30 min.	-	+	-	-	+	-	+	+	[37,38]
Rotational thrombo-elastometry (ROTEM)	Monitors viscoelasticity by registration of impedance of the rotation on a pin and provides haemostatic status within 30 min.	-	+	-	-	+	-	+	+	[37,38]
Euglobulin clot lysis time assay (ECLT)	Measures fibrinolysis of fibrin clot by visual inspection after incubation with a fixed amount of thrombin	+	-	-	+	-	-	-	-	[49]
Global fibrinolytic capacity (GFC)	Measures fibrinolytic degradation products by ELISA after incubation with a fixed amount of thrombin.	+	-	-	-	-	-	+/-	-	[51]
Simultaneous TG and PG (STP)	Measures simultaneous TG and PG in two separate wells with AMC-based substrates for both TG and PG.	-	+	+	-	-	+/-	+/-	+/-	[52]
Novel Haemostasis Assay (NHA)	Simultaneous TG and PG assay, measures in a single well with AMC- and rhodamine-based substrates, allows interaction between coagulation and fibrinolysis.	-	+	+	-	-	+/-	+/-	+/-	[53]
Electrochemical thrombin generation	Registers electrochemical TG in whole blood. Prevents problems with fibrin formation, color of sample	-	+	+	-	-	+/-	+	+	[85]

Abbreviations in Table 1. F, fixed time point measurement; C, continuous measurement; EA, enzyme activity; T, turbidity; V, viscoelasticity; α 2M, residual α 2M conversion by thrombin; WB, whole blood; POC, point-of-care measurement.

TEG/ROTEM

- TEG: Cup rotates/ROTEM: Pin rotates
- Movement transmitted to tracing recorded as curves & pre-defined parameters
- A real time continuous assessment
- Standardization
 - Reference range
 - Validation of protocol for guided transfusion

Summary of evidence for TE-guided transfusion therapy

- Supportive evidence
 - Reduction of incidence and volume of FFP transfusion in cardiac surgery*
 - Reduction of incidence of platelet transfusion in cardiac surgery*
 - Reduce the amount of bleeding in massive transfusion**
- Uncertain evidence**
 - Effect on mortality
 - Effect on morbidity
 - Effect on length of hospital / ICU stay

**Cochrane Database Syst Rev. 2011 Mar 16;(3)

* Patient Blood Management: Module 2: Perioperative, National Blood Authority, 2012

How Accurate

[Diagnostic Test Accuracy Review]

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding

Harriet Hunt^{1,2}, Simon Stanworth^{3,4}, Nicola Curry⁵, Tom Woolley⁶, Chris Cooper¹, Obioha Ukoumunne², Zhivko Zhelev⁷, Chris Hyde¹

Authors' conclusions

We found no evidence on the accuracy of TEG and very little evidence on the accuracy of ROTEM. The value of accuracy estimates are considerably undermined by the small number of included studies, and concerns about risk of bias relating to the index test and the reference standard. We are unable to offer advice on the use of global measures of haemostatic function for trauma based on the evidence on test accuracy identified in this systematic review. This evidence strongly suggests that at present these tests should only be used for research. We consider more thoroughly what this research could be in the Discussion section.

Role of POC assay in perioperative bleeding

5.1.7 Are patient outcomes improved by algorithms that incorporate coagulation monitoring for perioperative haemostatic management?

Long turnaround times may preclude the use of some tests in emergency situations. Even in the absence of definitive evidence, implementation of POC assays appears rational if the alternative is haemostatic management guided by clinical judgement alone.^{119,120} A prospective study recently demonstrated superior turnaround times, and quality of assessment, with POC monitoring compared with PT and aPTT.³¹ Transfusion algorithms incorporating POC coagulation monitoring are effective in reducing blood loss, reducing exposure to allogeneic blood products and improving the safety and cost-effectiveness of haemostatic therapy in cardiac surgery.^{121,129,144}

Cont'd

Perioperative coagulation monitoring is beneficial only if the results contribute to clinically effective decisions. Patients with similar conditions may receive different treatments if protocols and triggers for coagulation management are not in place.¹⁴⁵ In a study of transfusion triggers used for bleeding management in OLT patients, substantial variability was observed in transfused quantities of FFP, platelets and cryoprecipitate when different monitoring assays were used.¹¹⁵ The authors concluded that further studies would be required to determine optimal monitoring procedures for guiding haemostatic intervention.

Future Laboratory Service Development

○ Efficiency

- Satellite blood bank (Operating Theatre Blood Transaction System)
- Pre-thawed plasma
- Just next door (Hot Floor & Rapid Response Lab Concept)
- Expansion of test repertoire: Global assay, POCT
- T&S turnaround time

○ Safety

- Transfusion safety: Patient identification (Policies in place)
- Pre-operative optimization of haemostasis
- Post-operative monitoring to identify patients at risk

Conclusion

- Coagulopathy in ICU setting is **complex** and often **multifactorial**.
- Always consider the **clinical context**.
- **Conventional laboratory tests** are **valuable** to guide subsequent investigations.
- **Limitations** of conventional laboratory tests should be acknowledged.
- **Absence of robust evidence** from clinical trials to guide the management of acquired bleeding disorders is very striking & the need of studies to address gaps that currently exists.
- **Emerging role of global assay** to guide transfusion therapy.