Coagulation tests

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Disclosures

• None related to this talk.

• General disclosures:
  
  • Lecture fees from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol- Myers Squibb, MSD, Sysmex, and Pfizer.

  • Advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol- Myers Squibb.
Outline of talk: Coagulation tests

• Coagulation system

• Coagulation tests: why?, how?, when?
  • PT/INR
  • aPTT
  • ACT
  • Anti-Xa activity
  • Point-of-care testing: TEG & ROTEM
  • Evaluation of coagulation during treatment with NOACs

• Conclusions
Evaluating the coagulation system – why?

• Unexplained bleeding
• Pre- and perioperative testing
• Monitoring of anticoagulant treatment
• Research
Coagulation system: traditional concept

Intrinsic pathway
(aPTT)

XII
→ XI
→ XIIa
→ Xla

VIII
→ VIIIa
→ IXa

X
→ Xa

Prothrombin (II)
→ Thrombin (IIa)

VII
→ VIIa

Extrinsic pathway
(PT)

V
→ Va

Fibrinogen (I)
→ Fibrin clot

Protein S
Protein C

Antithrombin

Common pathway

Hvas AM, Grove EL, Kristensen SD
ESC Textbook of Intensive & Acute Cardiovascular Care, Oxford University Press, 2015
Coagulation system: *current* concept

Initiation → Amplification → Propagation

Modified from De Caterina et al, EHJ 2007.
Prothrombin time (PT) and INR

• PT measures the time [reference value: 11-13 seconds] it takes plasma to clot when exposed to tissue factor and reflects the ‘extrinsic’ and ‘common’ pathways of coagulation.

• International normalized ratio (INR) [ref: 0.8-1.2] = (PT-patient/PT-normal)^ISI

• **Clinical use:** bleeding, liver synthetic function, DIC, warfarin treatment.
Activated partial thromboplastin time (aPTT)

- The aPTT measures the time [ref: 25-35 seconds] it takes plasma to clot when exposed to substances that activate the contact factors - and assesses the ‘intrinsic’ and ‘common’ pathways of coagulation.

- No standardization.

- Clinical use: Bleeding, DIC, monitoring of unfractionated heparin.
Activated Clotting Time (ACT)

- The ACT measures the time [70-180 seconds, dependent on vendor] it takes whole blood (rather than plasma) to clot when exposed to an activator of the intrinsic pathway - and assesses both the ‘intrinsic’ and ‘common’ pathways of coagulation.

- **Clinical use**: adjusting heparin dosing before/during/shortly after procedures such as CABG, ECMO, PCI etc.
Antifactor Xa activity

- Unlike PT, INR, aPTT and ACT, the ‘anti-Xa’ is a *functional* assay measuring the degree of anticoagulation in units of enzymatic activity.

- **Clinical use**: evaluation of anticoagulant effect in selected patients at risk of accumulation during treatment with LMWH, fondaparinux etc.

- Most frequently used in obesity, pregnancy, reduced renal function.
Point-of-care testing: TEG & ROTEM

- **Point-of-care testing**: faster results to improve patient care.

- Thus meeting some of the limitations with frequently used ‘standard packages’ (e.g. platelet count, fibrinogen, aPTT & INR) – that only provide limited information about platelet function and do not predict bleeding risk.

- Thromboelastography (TEG) & rotational thromboelastometry (ROTEM) are global tests of haemostasis performed on *whole blood* and reflect platelet function and coagulation, showing kinetics of clot formation, strength, and dissolution – to manage bleeding and assess the response to interventions, e.g. during surgery.
Point-of-care testing: TEG & ROTEM
Non-vitamin K antagonist oral anticoagulants

- Routine *monitoring* is not recommended.
- ...but *measuring* the effect may be considered, in case of e.g.
  - Bleeding or thrombosis during treatment
  - Suspected overdose
  - Urgent surgery
  - Prior to thrombolysis

- Standard tests (PT/INR, aPTT, TT) are not recommended but may be used to rule out the presence of NOACs.
- Dabigatran: diluted Thrombin Time (e.g. Hemoclot®), Ecarin clotting time.
- Factor Xa-inhibitors: anti-Xa analyses.

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Conclusions

• There is no single global test available to adequately evaluate overall haemostasis: The right test for the right purpose!

• Ensure correct sample collection and handling

• Clotting times: PT/INR, aPTT, ACT.
• Functional assays: e.g. ‘anti-Xa’
• Dynamic whole blood assays: TEG & ROTOM
• NOACs: aim for specific tests, rather than standard clotting times

• All laboratory tests should be interpreted in a clinical context!
### Causes of prolonged PT and/or aPTT

<table>
<thead>
<tr>
<th>Test result</th>
<th>Causes of test result pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>Inherited</td>
<td>Factor VII deficiency</td>
</tr>
<tr>
<td>Acquired</td>
<td>Mild vitamin K deficiency</td>
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<tr>
<td></td>
<td>Liver disease</td>
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<tr>
<td></td>
<td>Warfarin administration*</td>
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<td></td>
<td>Acquired inhibitor of factor VII</td>
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<tr>
<td></td>
<td>Lupus anticoagulant (more commonly causes isolated prolonged aPTT; may be associated with thrombosis rather than bleeding)</td>
</tr>
<tr>
<td>Normal</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Inherited</td>
<td>Deficiency of factors VIII, IX, or XI</td>
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<tr>
<td></td>
<td>Deficiency of factor XII, prekallikrein, or HMW kininogen (not associated with a bleeding diathesis)</td>
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<td></td>
<td>von Willebrand disease (variable)</td>
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<tr>
<td>Acquired</td>
<td>Heparin administration*</td>
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<tr>
<td></td>
<td>Inhibitor of factors VIII, IX, XI, or XII</td>
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<tr>
<td></td>
<td>Acquired von Willebrand disease</td>
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<tr>
<td></td>
<td>Lupus anticoagulant (may be associated with thrombosis rather than bleeding)</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Inherited</td>
<td>Deficiency of prothrombin, fibrinogen, or factors V or X</td>
</tr>
<tr>
<td></td>
<td>Combined factor deficiencies</td>
</tr>
<tr>
<td>Acquired</td>
<td>Liver disease</td>
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<td></td>
<td>Disseminated intravascular coagulation</td>
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<td></td>
<td>Supratherapeutic doses of anticoagulants</td>
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<tr>
<td></td>
<td>Severe vitamin K deficiency</td>
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<td></td>
<td>Combined heparin and warfarin administration</td>
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<td></td>
<td>Direct thrombin inhibitor administration (eg, argatroban, dabigatran)*</td>
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<tr>
<td></td>
<td>Direct factor Xa inhibitor administration (eg, rivaroxaban, apixaban, edoxaban)</td>
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<td>Fondaparinux administration (slight prolongation)</td>
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<td></td>
<td>Inhibitor of prothrombin, fibrinogen, or factors V or X</td>
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<td></td>
<td>Primary amyloidosis-associated factor X deficiency</td>
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<td></td>
<td>Anticoagulant rodenticide poisoning</td>
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