Laboratory investigation in the Bleeding Patient

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Introduction

• Bleeding is common
• May consume significant resources
  – Crossmatched blood
• Lab results may be misinterpreted
• There is often an assumption that the cause is the abnormal blood tests
  – May be the other way round
• Investigation is mostly not in the lab!
Typical Case in EAU

- 52 year old male
- Presents to EAU with haematemesis
  - Fresh red blood
  - ‘toilet pan full’
What would we like to know from the lab tests?

• How much has he bled?
  – What volume has he lost
• Is he still bleeding?
• Where is he bleeding from?
• Does he have adequate clotting to stop the bleeding?
  – Is there a bleeding tendency
• Does he need blood component support?
How much blood has he lost?

• FBC
  – HB 130
  – Wbc 12
  – Plts 430

• But how do we interpret this?
Physiological factors

• Blood loss initially causes loss of circulating volume
• Volume is replaced initially by protein poor fluid influx
• And then by albumin containing extracellular fluid

• Restoration of blood volume after single bleed may take 20-60hrs (or more)
Blood volume and plasma protein changes following haemorrhage (in dogs)

– T Miller 1944
Change in HCT following bleed (in dogs)

- T Miller 1944
Other factors?

• When did the bleed start?
  – How long after the bleed is he presenting
• What was the Hb before the bleed?
• Have fluids been given?
  – How much?
  – When?
  – Often underestimated?
How much blood loss?

• Don’t know!
• Clinical picture will be more informative.

• What if significant anaemia?
  – Same factors need to be considered (esp fluids)
  – Must consider whether this may be a chronic
Look for signs of chronic anaemia

- Low MCV and MCH?
  - Suggestion of Fe deficiency?
  - Or anaemia of chronic disease

- High MCV
  - Suggestion of B12/Folate deficiency?
  - Or hypothyroidism?
  - Or haemolysis?
  - Or liver disease?
  - Or alcohol excess?
Is he still bleeding?

- Serial FBC’s?
  - Same factors need to be taken into account
- Reticulocyte count?
  - Rises after 3-5 days.
  - Peaks at 10 days following bleed.
Is his clotting adequate?

- Needs to be able to clot to plug the hole!
- Is there an underlying clotting problem?
- Has he used them all up?

- What is it that we need to measure?
Injury

TF/VIIa

IXa

IX

Prothrombin (II)

Thrombin (IIa)

X

Fibrinogen (I)

Fibrin monomer

Stable Fibrin

Plasminogen

Activator Inhibitors

Plasminogen Activators (TPA, urokinase)

Antiplasmins (α1 antitrypsin, α2 antiplasmin)

TFPI

ATIII (heparin)

Protein S

Protein C

Protein Ca

Red = Vitamin K dependant

= Activates

= Inhibits
Clotting tests?

• INR (or Prothrombin time)
  – Mostly dependent on ‘liver factors’
    • Factors II, VII, IX, X
  – Prolonged in
    • liver failure
    • Warfarin therapy
    • Factor VII deficiency
    • DIC/Consumption
• APTT
  – Sensitive to deficiencies in the ‘intrinsic pathway’
    • Factors XII, XI, X, VII, IX........II
  – Prolonged in:
    • Unfractionated heparin therapy
    • Haemophilia – FVIII, FIX deficiency
    • FXII, FXI deficiency
    • Antiphospholipid syndrome
    • Contact factor deficiencies..........
    • DIC/Consumption
• Fibrinogen?
  – Can't make a clot without Fibrinogen (Factor 1)!
  – Low in:
    • Congenital deficiency
    • DIC/Consumption

• But are you being given an actual fibrinogen level?
Derived versus measured Fibrinogen

• The fibrinogen level can be ‘derived’ from the rate of formation of the clot in the PT/INR test
  – Produced automatically by analysers
  – Rapid and cheap

• Can also be measured directly using functional assay – Clauss fibrinogen
  – More accurate
  – Especially when levels are low
Fibrinogen in the bleeding patient?

- Laboratory practice will vary
  - Clauss for all?
  - Screen with derived?
- Clauss should be used if level may be low
  - I.e. May need to replace
- Which result are you getting?
What about other anticoagulants?

- **LMWH**
  - Act mostly on FXa
  - Have no or little effect on routine clotting results
  - Can assay anti-Xa activity – not in emergency

- **NOACS/DOACS**
  - May not affect routine clotting at therapeutic levels
  - May get varying results with different reagents
• Dabigatran (direct thrombin inhibitor)
  – May affect the INR/APTT
  – Normal results may suggest a low level
  – Normal TT excludes residual effect
• Rivaroxaban (direct Xa inhibitor)
  – May affect the INR/APTT (not TT)
  – May have ‘prophylactic’ levels with normal results
• BUT – Only in labs where the sensitivity of their reagents has been confirmed
Interpreting Patient results (1)

- INR 10
- APTT 1.5
- Fibrinogen 4.5

- Disproportionate rise in INR
- Almost certainly on warfarin
Interpreting patient results (2)

- INR 1.0
- APTT 2.1
- Fib 3.8

- Isolated prolongation of APTT
- Is he on unfractionated heparin?
- Is he a haemophiliac?
- Does he have acquired haemophilia?
- Does he have anti-phospholipid syndrome?
- Does he have a clinically irrelevant factor deficiency
Interpreting patient results (3)

- INR 2.0
- APTT 1.8
- Fibrinogen 1.2

- Suggests consumption/DIC
Does Renal failure contribute?

• End stage renal disease
  – May have platelet dysfunction
  – Due to ‘uraemic toxins’

• Dialysis patients
  – Often use heparin

• New onset renal dysfunction
  – Are they on LMWH or a DOAC?
    • These are renal excreted
    • May be ‘supratherapeutic’
Conclusions/Take home messages

- Need to understand what question is being asked of the lab tests
- Hb may be a poor indicator of blood loss
- Clotting is a complex process
  - Lab tests are imperfect
- Effects of DOACS are hard to measure, and reagent dependent