ROYAL COLLEGE of PHYSICIANS of EDINBURGH

Evening Medical Update: Hints on Haematology
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This full blood count doesn't look right: leukaemias, lymphomas and the rest – Dr Neill Storrar

I am an ophthalmologist and in my line of work I come across cases of lymphomas within the orbit and eye. I often have to biopsy to establish a diagnosis, is LDH a useful test?

Helpful **if you know the patient has** lymphoma (it's a marker of activity, involved in disease activity) but VERY OFTEN normal especially if disease burden small. Would imagine that ocular lymphoma usually small volume so LDH unlikely to be elevated.

Is 'skeletal survey' still an investigation of value in myeloma?

Yes, so if you have someone with positive myeloma 'screen' (i.e. positive protein electrophoresis, bence jones or serum light chains) then worth requesting as it helps work out whether there's bone disease, the B of CRAB. If patient is 'CRAB' negative i.e. has none of those CRAB features then diagnosis more likely to be monoclonal gammopathy undetermined significance. More and more it's being superseded by whole body MRI and CT but only if your local service will offer that.

Where do leukaemoid reactions fit? And, how do they occur and how are they managed?

'leukaemoid reaction' really applies to a blood film / FBC result where many of the blood precursors usually confined to the marrow come into the blood. The typical story is someone who is extremely unwell e.g. Sepsis, major surgical emergencies etc. The white count is often high, but the person reporting blood film should be able to identify whether there is obvious cancer (i.e. blasts and other malignant cells)**.** If film doesn't' look like cancer and the patient has another clinical cause then usually just monitoring the FBC/film while the underlying problem is treated does the trick.

In the diagnosis of Myeloma, which test is more diagnostic between BM examination and serum protein electrophoresis as there is non-secretory type?

You're right that a very small proportion of myelomas do not secret any paraprotein or light chain - the 'screen' returns negative. In that case marrow is the definitive test. If you really think the patient has myeloma (e.g. otherwise unexplained lytic bone lesions, anaemia, malignant hypercalcaemia etc.) then a marrow will tell you one way or the other whether they have myeloma.

The alternative picture is much more common - the 'screening tests' are positive but no features of end organ damage (CRAB negative). Diagnosis more likely to be monoclonal gammopathy undetermined significance.

How would you distinguish between leukaemia and myelfibrosis? Would this be via BM biopsy?

Presumably you mean acute leukaemia? Both can present with pancytopenia, but the blood film should distinguish - in acute leukaemia's typically shows the classic blasts, whereas film in MF shows 'tear drop' red cells, 'nucleated red cells' and 'myelocytes' (precursors to neutrophils). Clinically, MF patients usually have a more subacute presentation, and splenomegaly is pretty typical, where is acute leukaemia often very short history and splenomegaly quite variable. MF also usually has a molecular abnormality in JAK2 / related mutations - this can usually be requested on peripheral blood if the presentation is suggestive of myelofibrosis. Bone marrow would be the definitive way to distinguish.

Is there a difference in the cut point for platelets transfusion between leukaemia and other causes such as ITP and sepsis? Is there any risk of transfusion if the patient has a high temperature?

Good question. In short, for marrow failures (particularly where cause is reversible) many centres transfuse routinely for anything less than 10 x10^9/L, with slightly higher thresholds if patient septic (20) or bleeding (30-50 depending on severity).

In ITP platelets don't last long (consumed by immune process) so only transfuse in critical/life threatening bleeding to buy you a few hours for other therapies to work i.e. immunosuppression, IVIG etc.
In sepsis would usually only transfuse if bleeding **and** platelets < around 50. Check coagulation here as this would make me suspicious of DIC> Rare for sepsis alone to cause platelet count to be lower than that so think of other causes and consult specialist advice.

DOACs: the fantasy versus the reality – Dr Kate Musgrave

What anticoagulation do you recommend for patients with high BMI (120kg and above) for AF patients and also use of sinthrome in accordance to patients with warfarin allergies where DOACs are not first line choice like CKDst4 patients etc.?
Thank you for your question. We have no clinical outcome data to support the use of DOACs in those weighing above 120kg. Having said this many clinicians, including myself, feel confident using them in higher bodyweights usually up to about 150kg. There is some interesting pharmacokinetic modelling data supporting this. Current ISTH guidance doesn't recommend this approach but we are expected an update a problem change to this soon.

Although DOACs are preferred anticoagulant by many physicians, Warfarin is still the drug of choice in some indications e.g. AF with valvular heart disease and antiphospholipid. What would be your choice of anticoagulant in the above two indications?
Thank you for your questions. I don't treat AF with valvular heart disease so I'm probably not best placed to comment. With regards to antiphospholipid syndrome there is data to show that patients who are 'triple positive' (this means they have evidence of lupus anticoagulant, anti-cardiolipin Ab, anti-beta2 glycoprotein Ab measured raised on two readings at least 3 months apart) warfarin is superior to DOACs. In these patients I always use warfarin. In patients who are 'single positive' have only one of the above markers of antiphospholipid syndrome I tend to offer a DOAC. In those who have two markers I tend to suggest warfarin. In all cases I explain to the patients that the evidence at the moment is that warfarin is superior but we don't have enough data outside of triple positivity.

What about the use of all the reversal agents for warfarin during major bleeds (prothrombin complex concentrate, vitamin K, FFP, etc.) to reverse bleeds involving the DOACs?
Thank you for your question. Prothrombin complex concentrate shouldn't be considered a reversal agent for DOACs. It is something that supports coagulation but is not an 'antidote'. Praxbind reverses dabigatran and andexanet reverses the Xa inhibitors. Andexanet is unfortunately less effective that praxabind, it has recently been approved by NICE in the UK but just for GI bleeding because it has not been shown to affect outcomes in intracranially bleeding. Vitamin K has no effect on the DOACs because they do not work through this mechanism, it can be useful if you suspect that the patient has an underlying vitamin K deficiency but probably won't work in the acute setting. FFP is also not a reversal agent for warfarin, you need huge volumes to make a small impact so it is no longer used for reversal.

If there was the immediate need for urgent surgery for a patient on DOAC and levels measured are high (or if unable to measure due to unavailability) what would be the approach given DOAC should be withheld 2 or 3 days prior to surgery?

Thank you for your question. If the surgery could not be delayed I would advocate treatment as for bleeding. So reverse the DOAC if possible (praxabind for dabigatran). Tranexamic acid 1g IV if there is no recent history of MI or haematuria. Prothrombin complex concentrate should not be considered a reversal agent for the Xa inhibitors but some places do give it to support coagulation in this setting. It is best to review your local policy and discuss with the surgeon, it is something that could be held back until necessary as it does come with a thrombotic risk. Ensure platelet count and fibrinogen levels are optimised. Simply measures such as IV fluids to help maintain a good urine output also helps clear the DOAC.

For DOAC monitoring, do we just check factor 10 level?

Thank you for your question. For the Xa inhibitor drugs (apixaban, rivaroxaban, edoxaban) the drug levels assays are basically based upon the measurement of anti-Factor Xa. This is not the same for dabigatran that is a direct thrombin inhibitor.

What specific test can we use to monitor the DOAC and what would we see as deranged that we would need to speak to the Haematologist?

Thank you for your question. In general, we should not be monitoring the DOACs, the therapeutic range is wide and very variable between individuals. Depending upon the assay used by your local laboratory the range that is considered therapeutic may also vary a little. There are a few circumstances where levels can be helpful but in general, they are best measured after discussion with your local haematology team. The times I would consider measuring a DOAC level would be if a patient needed emergency surgery, renal failure and at the extremes of body weight but usually I try to avoid it.

You mentioned tranexamic acid does not increase clotting, however, it is still listed as a side effect in the BNF, and the HALF-IT trial looking at TXA in Upper GI bleeds suggested an increase in the number of VTE events in patients who received TXA, what is your view on this?

I am confident that tranexamic acid does not cause thrombosis multiple large scale studies and meta-analyses have shown no increase (https://jamanetwork.com/journals/jamasurgery/article-abstract/2778639?resultClick=1). These have included data post orthopaedic surgery and post-partum (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30638-4/fulltext)both very prothrombotic states. The HALT-IT trial showed that a tranexamic acid infusion did not improve outcome from GI bleeding, this is also a prothrombotic state. As the outcome was not improved I don't think this trial alone is sufficient to change my opinion. HALT-IT was also not powered to look at VTE, it's also hard to justify that a DVT that's occurs 27 days post an infusion of tranexamic acid is still related to it. Thank you for this question though it is an interesting one.