Haematology updates for GP

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Aims and Objectives

- Focus on non-malignant haematology
- How to Ix and Mx some common haematological conditions in primary care
- Practical tips
- Open, interactive talk

Talk overview

- Abnormal FBC
  - Anaemia, thrombocytopaenia, leucopaenia
- Anticoagulants: DOACs
- Bleeding disorders
- Thrombophilia
- Anything else you want to ask

Anaemia

- FBC
- Hb < 115 (females), Hb < 135 (males)
- MCV 80 -100
- Blood film

Anaemia investigations

- **Haematinics** – iron studies with CRP, B12, folate
- **Haemolysis screen**
  - Reticulocytes and blood film
  - DAT
  - Bilirubin, LDH, haptoglobins

Anaemia

- Ask about: bleeding, diet, drugs, surgery, family Hx
- Refer to Haematology if:
  - Persistent, unexplained anaemia
  - Haemolytic anaemia
  - Leucoerythroblastic picture or pancytopaenia
  - Not tolerating oral iron – refer for parenteral iron

Causes of Microcytic anaemia MCV < 76fl

1. Iron deficiency anaemia - IDA
2. Anaemia of chronic disease – AoCD
3. Thalassaemia

Iron studies and CRP

Ferritin < 15 = Iron Deficiency Anaemia

Ferritin > 15 - need full iron studies to interpret

Iron studies interpretation

IDA	AoCD
1. Serum Iron - Low/N	- Low/N
2. Transferrin - *High*	– *Low*/N
3. Saturation - Low	– Low/N
4. Ferritin – Low/N	–High/N

Normal ferritin (in particular with high CRP) doesn't exclude IDA!

Iron deficiency anaemia

TESTS

- Full blood count (FBC)
- Serum ferritin /iron studies/CRP
- Blood film
- Trial of oral iron therapy - assess response at 2 weeks, if no improvement - needs further tests!

Always Exclude blood loss!!

- blood loss : PV/ GI/ GU
- diet
- increased demands (toddlers/pregnant)
- malabsorption

Iron deficiency in pregnancy

– Hb < 110g/l in 1st trim

– Hb < 105 g/l in 2nd and 3rd trim

– Hb < 100g/l postpartum

Iron Replacement 100-200 mg elemental iron

Oral - one tablet a day/or alternate days on empty stomach, with glass of orange juice

- No need for higher doses as absorption is saturated/ increase side effects

Parenteral iron only in 2nd and 3rd trimester

Parenteral iron

Cautious if known allergic reaction/severe asthma/eczema. No test dose

Cosmofer – for inpatients

- 6 hs infusion/small risk of reaction

Ferinject – for outpatients

  - 15 min infusion/v small risk of reactions/ 1gm
  - Usually given as 2 infusions one week apart to deliver total dose
  - Risk of hypophosphataemia ! (check phosphate levels one week after infusion)

Anaemia of chronic disease
Functional anaemia

- Chronic inflammation/infection (6 weeks!) cancer/CKD/heart failure
- Common in hospitalised patients
- Cytokine-associated syndrome/complex
- Mechanism: impaired iron utilisation/lack Epo
- Diagnosed – by exclusion
  - normal MCV / Iron studies / ESR
- Rx - doesn't respond well to oral iron! (may respond to parenteral iron)
  - Epo/Blood Tx/Rx underlying cause

Macrocytic Anaemia
MCV > 100

- Causes
  - B12/folate deficiency
  - Alcohol/drugs
  - Liver disease
  - Hypothyroid
  - MDS
- Ix : B12/folate, LFTs, TFTs

B12 deficiency

- Causes:
  - Malabsorbtion
  - PA (IF ab positive, other ab APC non specific)
  - Diet – vegetarians/vegans
  - Elderly – atrophic gastritis, PPI
  - Metformin
  - COC/HRT
  - Pregnancy

Treatment of B12

- B12 injections as per BNF 1mg 3X week for 2 weeks , then ev 3 mo
  - Day 7-10 reticulocytosis
  - Watch for low K levels
  - Low dose oral B12 at 50 mcg as maintanance or if borderline levels in asymptomatic cases
  - Normal B12 levels but strong clinical suspicion of PA give a trial of B12

Thrombocytopaenia

- Platelet count < 135
- 1. Previous platelet count
- 2. Hx
  - Viral infect (IM, HIV, post-viral)
  - Drugs (Abs, NSAIDs, cardiac, antidepressants etc)
  - Alcohol/ chronic liver disease (hypersplenism)
  - Rarely; DIC, ITP, Autoimmune dis (SLE/RA)
  - Pregnancy - 5% have plat of 100
- Exam - bleeding, joints, splenomegaly
- Ix – blood film, U&E, LFTs, clotting, ANA/DAT/Lupus screen

  CRP, B12/folate, HIV/hepatitis

Alcohol Hx

Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.

Table 1. Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.*

Drug Category	Drugs Implicated in Five or More Reports	Other Drugs
Heparins	Unfractionated heparin, low-molecular-weight heparin	
Cinchona alkaloids	Quinine, quinidine	
Platelet inhibitors	Abciximab, eptifibatide, tirofiban	
Antirheumatic agents	Gold salts	D-penicillamine
Antimicrobial agents	Linezolid, rifampin, sulfonamides, vancomycin	
Sedatives and anticonvulsant agents	Carbamazepine, phenytoin, valproic acid	Diazepam
Histamine-receptor antagonists	Cimetidine	Ranitidine
Analgesic agents	Acetaminophen, diclofenac, naproxen	Ibuprofen
Diuretic agents	Chlorothiazide	Hydrochlorothiazide
Chemotherapeutic and immunosuppressant agents	Fludarabine, oxaliplatin	Cyclosporine, rituximab

* For a more extensive list, see Aster,[2] Warkentin,[12] and George et al.[13] and the University of Oklahoma Web site (http://moon.ouhsc.edu/jgeorge/DITP.html).

Aster RH, Bougie DW. N Engl J Med 2007;357:580-587.

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Thrombocytopaenia When to refer?

- Persistent at least 2 occasion 4-6 wk apart
- Hb/WCC abnormal
- Unexplained plat count < 100 or symptomatic
- Thrombocytoapenia in patients with Hx thrombosis
- Beware platelets clumps/laboratory artefacts/EDTA effect (1%)
  - Request FBC in citrate

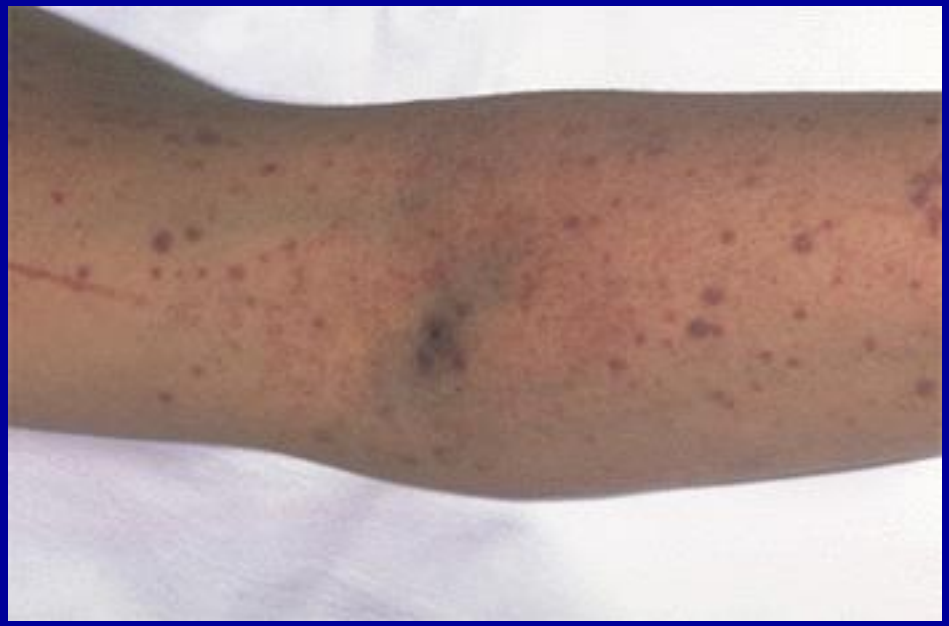
Thrombocytopaenia – urgent referral

- Platelet count < 50
- Plat count 50-100 with
  - Other cytopaenias (Hb <100, Neutrophils< 1)
  - Splenomegaly/lymphadenopathy
  - Pregnancy
  - Awaiting surgery

Plat count < 20 or active bleeding should be discussed with Haematologist on call!

Case 1

A 23-year-old student presents to her GP with an ‘odd’ rash on her legs/arms



FBC:

- Hb 135 g/L
- WCC 7.9 x 10^9/L
- Platelets 11 x 10^9/L
  [135-400 x 10^9/L]

This is purpura

Diagnosis:
Idiopathic/Immune Thrombocytopaenic Purpua (ITP)

ITP mechanism

Increased peripheral destruction of platelets

– Mainly in spleen/RE system

AND

Decrease production of platelets due to reduced thrombopoietin (hormone made by the liver)

Treatment of ITP

- Platelets >20 x 10^9/L and no bleeding – may simply observe
- Platelets < 20 or higher but bleeding - start **1st line** Prednisolone 0.5mg/1mg per kg for 2 weeks and refer Haematology
  - Elderly 30 mg, max dose 60 mg
- Iv IG works more quickly…used in actively bleeding patients while waiting for steroids to work
- Response to steroids in 2/3 of patients/may take ~2-3 weeks to work
- If no response after 2 weeks taper down rapidly and stop after 6 weeks

Treatment of ITP

- **2nd line**

TPO (Thrombopoietin) Agonists

Romiplostim sc weekly

Eltrombopag po daily

Less used :

Rituximab

Other immunosuppressant drugs

Splenectomy

Neutropaenia (I)

- N < 2
- Hx
  - viral illness (IM, post-viral)
  - Racial/familial (N <1.3)
  - Drugs (stop if possible)
  - Chronic benign neutropaenia
  - Autoimmune disease
- Exam – any Infections/Splenomegaly
- Ix - blood film, ESR/CRP, B12/folate, ANA
  - ? HIV

Neutropaenia
When to refer?

- N < 1
- N 1 – 2 and anaemia/low platelets

If Neutrophils 1-2, patient well and no bacterial infect, Hb and plat normal

  - Monitor at 1 week, then at 1 month, if still abnormal then refer

Lymphopaenia
Lymph count < 1.5 x10

- Causes
  - 2.5% of normals < 1
  - Stress (illness), steroids
  - SLE/Hodgkin/renal failure
  - HIV
- Ix
  - viral and autoab screen
- Exam
  - LN, Hepato-splenomegaly

Lymphopaenia (II)

- Well, No LN, otherwise FBC normal
  - Repeat 3-4 weeks
- Not well, No LN, otherwise FBC normal
  - U&E, viral and autoab screen, HIV
- Persistent LN > 4 - 6 weeks - refer directly for Bx
  - Radiology USS guided Bx/ ENT/gen surgery
  - Do not refer to Haematology!!

DOACs

- Direct Oral Anticoagulants
  - Direct Thrombin inhibitors(anti IIa) Dabigatran
  - Direct Xa inhibitors (**Xaban**): Rivaro**xaban**, Api**xaban**, Edo**xaban**
- Equal or superior to warfarin both in effect and risk of bleeding
- Generally accepted lower risk of major bleeding vs warfarin
  - Lower risk ICH and death
  - Relative risk reduction for ICH ~ 60%
  - Possible lower risk for GI bleed vs warfarin

DOACs

- No randomised controlled trials comparing one DOACs with another (only observational studies)
- All trials DOACs vs warfarin
- Which anticoagulant to choose?
  - Patient assessment and preference
  - Risk of bleeding
  - Renal/hepatic function
  - drug interactions

DOACs

- NICE approved for AF and DVT prophylaxis and treatment (now including children)
- NOT licensed for
  - Prosthetic heart valve disease
  - Antiphospholipid syndrome
  - Pregnancy
  - Severe renal insufficiency (eGFR > 20)
  - No monitoring / ?role of clotting screen
  - Antidotes available

NOAC dosing regimens

NOAC	Full dose	Reduced dose
Dabigatran[1]	150mg BD	110mg BD for patients aged 80 years or above or who receive concomitant verapamil. Also, for the following groups based on individual assessment of thromboembolic risk and risk of bleeding: •Patients aged 75-80 years •Patients with moderate renal impairment •Patients with gastritis, oesophagitis or gastro-oesophageal reflux •Other patients at increased risk of bleeding
Rivaroxaban[2]	20mg OD	15mg OD for patients with moderate or severe renal impairment (CrCl 15-49ml/min)
Apixaban[3]	5mg BD	2.5mg BD for patients with at least 2 of the following characteristics: •Age ≥80 years •Body weight ≤60 kg •Serum creatinine ≥1.5mg/dL (133 micromole/L) Or with severe renal impairment (CrCL 15-29ml/min)
Edoxaban[4]	60mg OD	30mg OD for patients with one or more of the following: •Moderate or severe renal impairment (CrCl 15-50ml/min) •Low body weight (≤60 kg) •Concomitant use of the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin or ketoconazole

BD = twice daily; OD = once daily; CrCl = creatinine clearance; P-gp = P-glycoprotein

; **4**

. Current versions of SPCs available online at:

http://www.medicines.org.uk/emc/

Pharmacology

	Dabigatran[1]	Rivaroxaban[2]	Apixaban[3]	Edoxaban[4]
Mode of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Half life	12-14 hours	5-9 hours (young) 11-13 hours (elderly)	12 hours	10-14 hours
Dosing	BD	OD	BD	OD
Metabolism	P-glycoprotein	CYP P450/P-glycoprotein	CYP P450/P-glycoprotein	CYP P450/P-glycoprotein
Excretion	80% Renal	33% Renal	27% Renal	50% Renal
Form	Hard capsule	Tablet	Tablet	Tablet

BD = twice daily; OD = once daily

; **4**

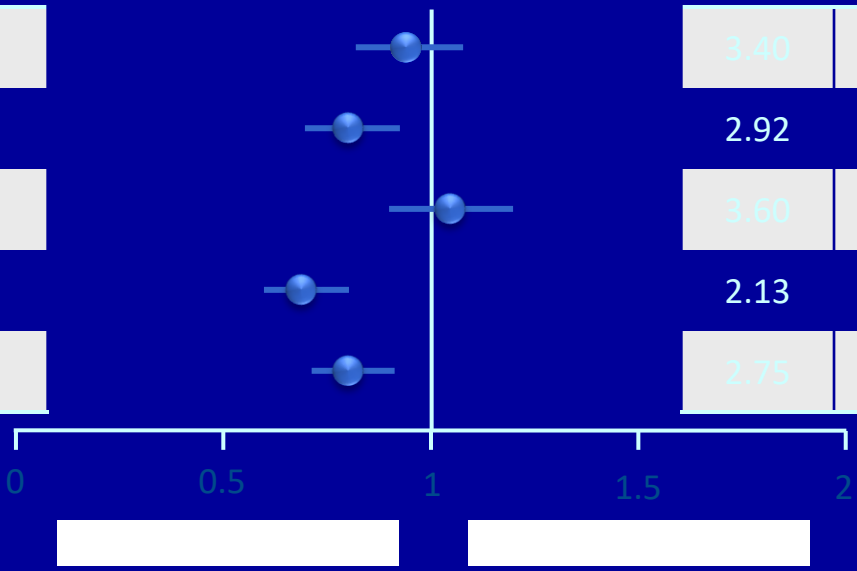
available online at: http://www.medicines.org.uk/emc/

;

. Current versions of SPCs

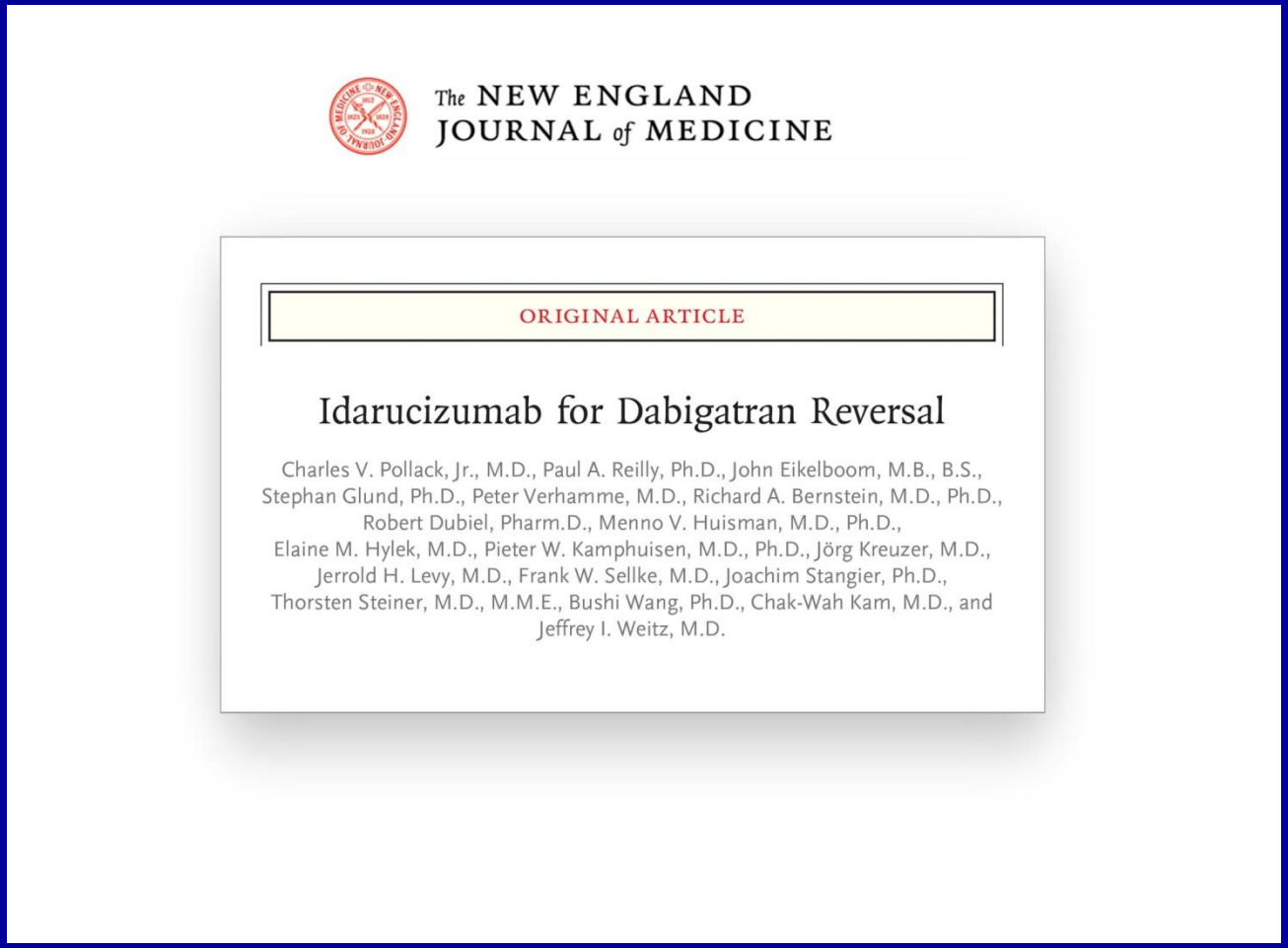
NOAC trial outcomes: Major bleeding versus warfarin

NOAC	Major bleeding %/yr	Warfarin %/yr	HR (95% CI)
Dabigatran 150 mg[1,3]	3.40	3.61	0.94 (0.82–1.08)
Dabigatran 110 mg[1,3]	2.92	3.61	0.80 (0.70–0.93)
Rivaroxaban[4]	3.60	3.40	1.04 (0.90–1.20)
Apixaban[5]	2.13	3.09	0.69 (0.60–0.80)
Edoxaban 60 mg*[6]	2.75	3.43	0.80 (0.71–0.91)



CI = confidence interval; HR = hazard ratio

DOACs - reversal



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ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

DOACs monitoring

- No routine monitoring required BUT
- DOACs do affect clotting screen
  - Prolonged PT – Xaban
  - Prolonged APTT – Dabigatran

  Always specify on request form for clotting screen or lupus anticoagulant if patient is on a DOAC (false positive!)
  - LA testing – DOAC removal – sample is sent to Addenbrookes

Bleeding

- 15 ys old girl with severe menorrhagia
- What blood tests do you request?

Bleeding

- FBC and iron
- Clotting screen
- Factor 8 profile (Factor 8 and von Willebrand factor levels) - ? VWD
- Factor XI levels - ? FXI deficiency

- You can still have mild VWD/FXI deficiency with a normal clotting screen!

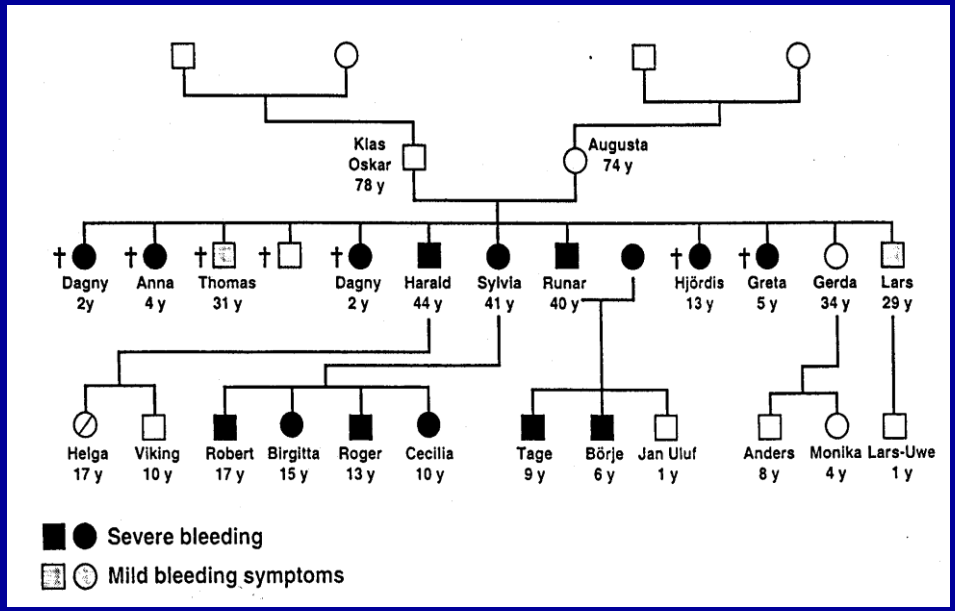
Von Willebrand disease

- The commonest inherited bleeding disorder (1% of population)
- Underdiagnosed
- Clinical bleeding:
  - mucocutaneous, brusing, epistaxis, dental surgery, menorrhagia, PPH

Menorrhagia clinic at RFH – 20% had VWD!

VWD- Historical perspective

- 1926 Dr Erik von Willebrand
- Bleeding disorder in 23 of 66 members of a family from Foglo (Äland Islands - Sweden)
- First patient: 5yr-old-girl who died aged 13 from uncontrollable uterine bleeding during her fourth menstruation



VWD – treatment

1. Tranexamic acid po 1 g tds for 5-7 days/PRN
   antifibrinolytic drug
   for all types mucosal/skin bleeding
   Avoid if haematuria

2. DDAVP 0.3 mcg/kg sc/iv/nasal spray for menorrhagia

3. VWF concentrate

Bleeding disorders

- Unexplained, prolonged, persistent bleeding
- Benign easy bruising
- Standardised Bleeding score if > 5 significant
- Think about ? NSAIDs, antiplatelets, anticoagulants

Bleeding disorders

- Tests:
  - FBC and film – platelet count/anaemia
  - Coagulation screen (PT, APTT) Fibrinogen – testing in 2ry care only!
  - No need for Ddimers
  - U&E, LFTs, autoimmune screen, paraprotein

Bleeding disorders Key points:

- family Hx of bleeding
- past Hx of beeding
- Comorbidities (renal/liver disease)
- drugs, alcohol
- diet/malnourished – vitamin K deficiency common!

- Prolonged PT – give trial vit K 10 mg po for 10 days then repeat clotting

Thrombophilia

- predisposition to develop VTE
- 50% of patients presenting with VTE have thrombophilia defect
- 1-2 /1000 population /year get VTE
- 6% of UK population genetic defect
- Risk factors
  - Environmental
    immobility/surgery/COCP/travel/malignancy
  - Inherited
  - Acquired

Risk Factors

- A history of DVT or PE
- Family history of VTE
- Acute Infection
- Malignancy
- Age > 75 years
- Congestive heart failure
- Paraproteinaemia
- Behcet's disease
- Nephrotic syndrome
- Polycythaemia
- PNH
- High dose oestrogen therapy
- Obsesity (BMI > 25)
- Stroke
- Prolonged immobility > 4 days
- Acute or chronic lung disease
- Inflammatory bowel disease
- Shock
- Hyper homocysteinaemia
- Dysfibrinogenaemia
- Myeloproliferative disorders
- Sepsis < 1 month
- Heparin induced thrombocytopenia
- Congenital or acquired thrombrophilia
- Varicose Veins

When to suspect Familial Thrombophilia

- Strong FH of VTE
- 1st VTE early age (<40ys)
- Unusual site (cerebral, mesentery)
- During pregnancy/COCP–hormone related
- Spontaneous without environmental, acquired factors
- Recurrent VTE

Thrombophilia testing

- When to test?
  - Idiopathic 1st VTE in young (< 50ys)
  - Unusual site
  - Recurrent in non-cancer patients
  - Secondary VTE in young lady on OCP/HRT/pregnant
- Why?
  - Prevent recurrence – indefinite anticoagulation
  - Family testing - to offer thromboprophylaxis

Thrombophilia PTS screen

- Inherited factors
  - AT deficiency
  - Protein C and S deficiency
  - Factor V Leiden (low APCR ratio)
  - PGM
- Acquired
  - Lupus ac and antibodies (ACA/antib2GPI)
  - More common!

Absence of defect does not mean absence of risk!

Thrombophilia defects

- FVL
  - 5-10 % Caucasians
  - Risk VTE 8x (heterozygous)
  - 80x homozygous
- PGM
  - 2% of UK population
  - Risk VTE 2-3 x
- Protein C/S affects 1: 5000
- AT - rare
  - 50% risk VTE before age 50 and in pregnancy

Problems with PTS testing I

- Widespread availability of tests - overuse
- Clinical utility – usually no influence on clinical management of individual case
- Patients selection difficult
  - Who? when? why?
- Extended family testing ?

Problems with PTS testing II

- Cost effectiveness ?
  - Test 2 mil women to prevent one death from OCP – related PE per year
- Accuracy of tests
  - NEQAS - significant difficulties/errors/variability
- Interpretation: over or under diagnosis
- Misleading advice - false reassurance, anxiety, lifestyle decisions
- Evidence is changing – move away from testing/only in very selective cases

Q1

- Young lady wants to start OCP
- No personal Hx of clots
- Mother had a DVT post-op

- ? Needs Thrombophilia screen

A1

- NO
- Only request PTS if known hereditary defect in family i.e. mother had been tested and is positive

NO universal screening

need to screen 2 mil women to prevent one death form COCP - related PE per year

Q2

- 70 ys lady , IHD, COPD
- Presents with a PE

- Q: Request thrombophilia screen?

A2

- NO
- age 70
- Comorbidites – likely provoked event?
- Consider test for lupus screen only

Q3

- 28 ys old lady
- Three consecutive miscarriages

- Q: request thrombophilia screen?

A3

- YES
- PTS and Lupus screen and antibodies

- Role Aspirin and Clexane

Q4

- 70 ys old
- Smoker, NIDDM
- Presented with stroke

- Q: request thrombophilia screen?

A4

- NO need for PTS
- Consider Lupus screen only
- Apart from Lupus screen there is no clear evidence on role of thrombophilia defects in arterial events

Thrombophilia screen Conclusion

- Testing for hereditary thrombophilia generally does not alter clinical management
- Most important risk factors for recurrence are previous personal Hx of VTE and family Hx of VTE
- Testing for thrombophilia has a very limited role

Thank you

- Any questions?