FRCPath Mock Paper A

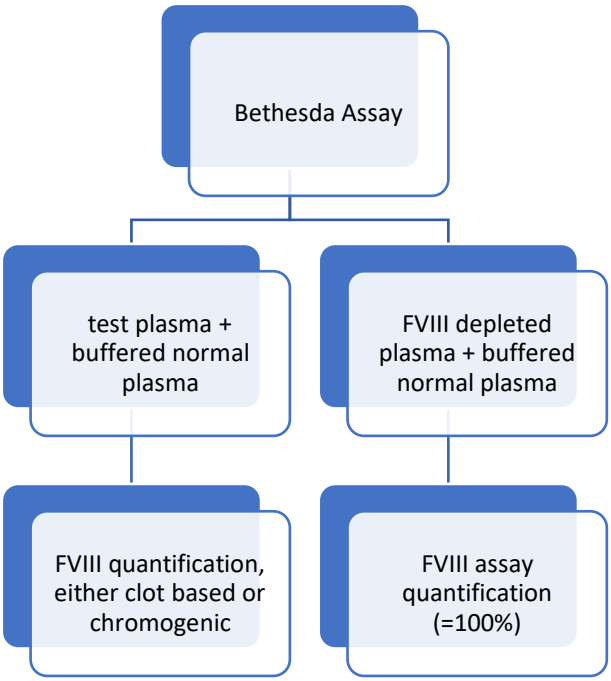
Marking scheme

Answer 1 Haemophilia and inhibitors

A. Patient is receiving 30units/Kg of FVIII and the invivo recovery 1 hr post-infusion is only 4%. This is poor recovery and suggestive of inhibitor development
B. Inhibitor detection and quantification
    i. Measurable FVIII levels 48hrs after last prophylactic dose: unlikely to be inhibitor
    ii. Inhibitor screen: Mixing studies with test and normal plasma with and without incubation

	APTT	APTT after 2hr incubation	Interpretation
Normal Plasma	Normal	normal	
Test Plasma	Prolonged	Prolonged	
Normal+ test plasma	Normal	prolonged	Indicative of time dependent inhibitor

    iii. Bethesda Assay (with Nijmegan modification) for quantification of inhibitor. Can be performed with both human and porcine FVIII



    iv. Half life studies: sensitive and especially useful for low titre inhibitor however difficult to perform due to repeated sampling and calculations. If half- life of FVIII is <7hours likely inhibitor
    v. ELISA for FVIII inhibitors

C. 1 Bethesda unit is the amount of inhibitor which will inactivate 50% of 1unit of FVIII in normal plasma after 120 minutes incubation at 37deg C.

b. Treatment options for haemophilia A inhibitors

i. Treatment of acute bleeding:
    a. FEIBA: 200units/kg in 2-4 divided doses
    b. rVIIa 90mcgkg 2hrly until haemostasis and then 6 hrly
    c. rPorcine FVIII
    d. high doses of FVIII: for low responding low titre inhibitor patients
ii. Emicizumab: bispecific antibody, given S/C
iii. Immune tolerance induction:
    a. Start immediately after inhibitor confirmation, irrespective of titre
    b. If inhibitor <10 BU, start 50units/kg alt days, monitor weekly and escalate if titres increase
    c. If inhibitor 10-200 BU, start 100units/kg/day escalate up to 200units/kg/day
    d. If inhibitor >200 BU, start at 200 units/kg/day
    e. May require CVC line, watch for infections, increase inhibitor levels
    f. Monitor inhibitors weekly increase to 200units/kg daily unless titres falling
    g. Rituximab, immunosuppression if no response after 6 months at highest dose. Seek specialist advice

c. New treatments for Haemophilia A & B

i. Long acting Factor VIII & IX
    a. Extended half-life recombinant FVIII and FIX are engineered either by linking them to PEG, Fc fragment of IgG or albumin. Increase half life by slowing the clearance.
    b. FVIII half life extended (Elocta, Adynovate) 1.5 times, 18-19 hrs, same bio-availability: Advantages prophylaxis can be give every 3-5 days (standard product- usually every 48-72hrs). Recombinant- no risk of TTI. Disadv: risk of inhibitors- similar to standard products, IV administration. May not be suitable for everyone. New technologies being tested to extend FVIII half life even further (37hrs: BIOV-001) being tested in animal models.
    c. FIX half-life extended: Alprolix (Fc-conjugate), Idelvion (Albumin), Refixia (PEG): extends half life to 80-90 hrs (std product 20-24hrs). Adv: Once weekly prophylaxis, better invivo recovery, no risk of TTI. Disad: inhibitor risk, anaphylaxis, IV adm

ii. Emicizumab: a monoclonal bispecific antibody that substitutes for the function of factor VIII. Brings FIX and FX together obviating the need for FVIII cofactor activity for activation of FX. Can be administered subcutaneously, once every week to once every month, very effective in reducing ABR, used for prophylaxis in Haemophilia A with and without inhibitors, adults and children. No risk of inhibitor, risk of thrombotic microangiopathy if breakthrough bleeding treated with aPCC. 3mg /kg SC once weekly then once every fortnight and then 6mg/kg once monthly SC

iii. Gene Therapy: Trials using Adenovirus, engineered gene cassette with B-Domain depleted FVIII or FIX Padua gene. Mild transaminitis, managed with steroids, effective in raising FVIII and FIX levels on long-term basis. Has potential to turn a severe haemophilia A or B to milder disease without need for regular treatment. Long-term follow-up to ascertain longevity of response, anti-AAV antibodies, mutagenicity, oncogenicity.

iv. Developments in pipeline: Fitusiran- siRNA to inhibit Antithrombin; Concizumab-TFPI antibody. APC inhibitor also entering Phase1 studies.

Answer 2 i. Platelet refractoriness & management

Define Platelet refractoriness **4**

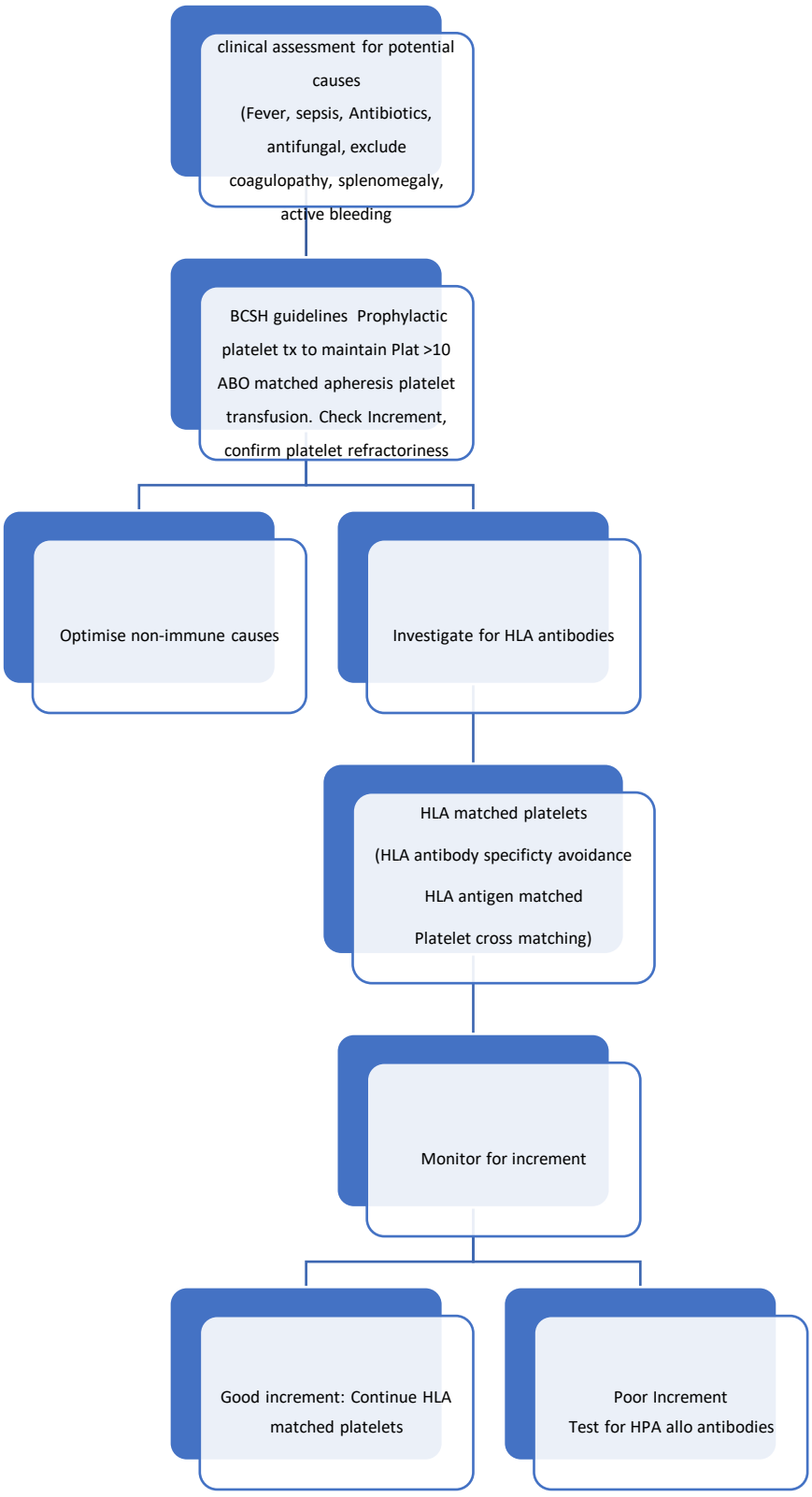
Platelet transfusion refractoriness is defined as the repeated failure to achieve satisfactory responses to platelet transfusions from random donors
There is lack of consensus in the literature with respect to which formula to use and which cut-offs are considered indicators of successful transfusion.
The most common formulae include:
1 The post-transfusion increment (PI),
2 The percentage platelet recovery,
3 The corrected count increment (CCI)
A PI of >10 9 109/l at 1 or 24 h is considered a successful transfusion to be consistent with the previous formulas, and if not attained, is a good indicator to suspect refractoriness

PI = Post-transfusion platelet count - Pre-transfusion platelet count
The percentage platelet recovery (R) is calculated from the platelet increment 9 109/l (PI), the blood volume (BV) in litres and the platelet dose transfused X 10^{11} (PD):-
R (%) = (PI X BV)X100/ PD
A platelet recovery of about 67% in a stable patient indicates a successful transfusion, but the minimum platelet recovery to define a successful transfusion is considered as >30% at 1 h post-transfusion and >20% at 20–24 h
CCI (corrected count increment) X 10^9/l (CCI) is calculated from the PI, the body surface area of the patient in m2 (BSA) and the dose of platelets transfused X 10^{11} (PD):-

CCI = (PI X BSA)/ PD
A CCI of >7.5 X 10^9/l at 1 h and >4.5 X 10^9/l at 20–24 h is considered to be a successful transfusion
The TRAP study Platelets Study Group, 1997, defined platelet refractoriness as a 1-h CCI of <5 X 10^9/l on two sequential occasions

Causes of Platelet Refractoriness **4**

Immune	Non-Immune
Platelet alloantibodies HLA Antibodies HPA Antibodies ABO	Infection High Fever Antibiotic (Vancomycin) Antifungal (Amphotericin) Heparin DIC Splenomegaly Bleeding GVHD VOD
Platelet autoantibodies Drug dependent Ab Immune complex	


clinical assessment for potential causes
(Fever, sepsis, Antibiotics, antifungal, exclude coagulopathy, splenomegaly, active bleeding
BCSH guidelines Prophylactic platelet tx to maintain Plat >10
ABO matched apheresis platelet transfusion. Check Increment, confirm platelet refractoriness
Optimise non-immune causes
Investigate for HLA antibodies
HLA matched platelets
(HLA antibody specificty avoidance
HLA antigen matched
Platelet cross matching)
Monitor for increment
Good increment: Continue HLA matched platelets
Poor Increment
Test for HPA allo antibodies

2. ii **13**

Management of acute transfusion reaction: Suspect Incorrect Blood component transfusion

Recognition of event & Assessment of severity	Review TPR, BP, Urinary output, Oxygen saturation ABC and systemic clinical assessment STOP Transfusion Keep IV Access, fluid resuscitation Check Patient ID, compatibility label, issue date, expiry, documentation, inspect bag DO NOT DISCARD- return bag & giving set to Blood bank Severe TR confirmed, Possibilities include: • Incorrect Blood component (incorrect label, ID or suspect sampling error) • Anaphylaxis reaction (wheezing, stridor, rash, urticaria) • Bacterial contamination of blood component Call for help: ITU, renal team: pt may require inotropes, RRT
Resuscitating Patient	ABC, Oxygen Fluids IV antibiotics (bacterial contamination can present with similar symptoms If Anaphylaxis suspected: Adrenaline 0.5ml IM (1:1000) Hydrocortisone 200mg, Chlorpheniramine 10mg IM or IV Regular vitals monitoring, urine output Strict fluid balance chart
Investigations	FBC, UE, LFT, LDH, haptoglobin, lactate, urine for haemoglobin, PT, APTT, TT, Fibrinogen, Repeat sample for compatibility testing, DCT, Blood Culture. CXR when pt resuscitated, ABG
Specific Treatment	If indicated ITU for Ionotropic support, ventilation Renal: renal replacement therapy if renal failure Correction of coagulopathy if active bleeding
Documentation & Communication	Document clinical assessment & treatment interventions in pt records Inform Patient- relative- Duty of Candour Report to Lead transfusion consultant/nurse for further investigations Report to HTC Report to SHOT Report to MHRA- as per BSQR 2005 regulation
Future prevention	Root cause analysis of the event Review Trust transfusion policy Training and assessment of staff involved Incorporate IT checkpoints to minimise human error

3. a. Common causes of thrombocytopenia in pregnancy

Platelet count <150, ~5% pregnant women

Platelet Count <100, ~1% pregnant women

i. Gestational thrombocytopenia (75%): us 2n3-3rd trimester. Plat count usually >100, History, clinical examination, FBC, film, CS, UE, LFT if normal no further evaluation unless plat drops below 70. Resolves in 6-8 weeks post-partum. No neonatal thrombocytopenia

ii. Preeclampsia with severe features/ HELLP syndrome (20%)

iii. Immune Thrombocytopenia (1-4%)

iv. Acute fatty liver of pregnancy (<1%)

v. Others: APLS, DIC, TTP, Haematinic deficiency, Drug induced, Viral infections (HIV, CMV, EBV), SLE, Congenital, Type IIb VW Dis

3.b.

i. History and clinical assessment: Previous h/o thrombocytopenia, bleeding/bruising or thrombotic history, ongoing medication. h/o Auto-immune dis, possibility of viral infections. Family h/o thrombocytopenia, pre-eclampsia, bleeding disorder. O/E: Exclude HT, peripheral edema, splenomegaly, obvious bruising/bleeding, S/S active infection, Proteinuria,

ii. Plat count too low to be gestational and therefore requires investigations

   a. FBC & Blood film: to confirm thrombocytopenia, platelet clumping, abnormal platelet morphology, red cell fragmentation, primary BM pathology

   b. Coagulation Screen (PT, APTT, TT, Fibrinogen): will identify DIC, Type 2b VWD, APLS

   c. B12, Folate: to exclude severe folate, B12 def

   d. LFT, Albumin: to exclude Acute Fatty liver, preeclampsia

   e. Virology screen: exclude HIV, EBV, CMV

   f. If all above normal likely maternal ITP: diagnosis of exclusion

iii. Management:

   a. Treat the underlying cause

   b. If ITP confirmed: If plat count falls below 30 or bleeding problems: steroids or IVIG. Monitor for PIH and gestational diabetes. Splenectomy can be considered in 2nd trimester is steroid refractory or dependant. Avoid anti-D, though azathioprine can be considered. TPO agonist: not licensed.

   c. Preeclampsia, HELLP: prompt delivery if severe complications

iv. Epidural/spinal: can be given if platelet count >80 and stable. Caesarean section if platelet count >50. Avoid platelet transfusion unless major bleeding. Neonatal thrombocytopenia seen in around 25% of neonates. No correlation with maternal platelet count. No need for fetal sampling, avoid vacuum, midcavity forceps. Avoid IM injections if platelet count <50. Check FBC at birth and then for 3-5 days. Bleeding usually not a problem in neonates but if traumatic delivery and severe thrombocytopenia, steroids and IVIG