

Hematomorph EMQs

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EMQ 1

Options-Theme DLBCL Treatment

- A. CAR T-cell therapy
- B. Platinum-based salvage chemotherapy (R-ICE / R-DHAP)
- C. High-dose therapy with autologous stem cell transplant (HDT-ASCT)
- D. Polatuzumab vedotin + bendamustine + rituximab (Pola-BR)
- E. Tafasitamab + lenalidomide
- F. CD3×CD20 bispecific antibody (e.g. glofitamab / epcoritamab)
- G. Loncastuximab tesirine
- H. Palliative oral chemotherapy
- I. Involved-site radiotherapy (ISRT)
- J. R-GemOx
- K. Allogeneic stem cell transplant
- L. CAR-T bridging therapy followed by CAR-T infusion

Instructions

For each scenario, choose the single most appropriate next step in management.

Each option may be used once, more than once, or not at all.

1. A 52-year-old man with DLBCL (double-expressor: MYC/BCL2) achieved CR after Pola-R-CHP. He presents 7 months later with rapidly progressive lymphadenopathy, B symptoms, and LDH 3× ULN.

PET confirms widespread disease. He is ECOG 0, normal organ function. **Answer:**

2. A 60-year-old woman relapses 9 months after Pola-R-CHP with bulky abdominal disease-causing pain and early satiety. She is fit for CAR-T, but manufacturing time is expected to take 4–5 weeks, and disease is progressing rapidly. **Answer:**
3. A 64-year-old man relapses 4 years after R-CHOP. He receives 2 cycles of R-ICE, achieving a complete metabolic response on PET. He is otherwise fit, with preserved cardiac and renal function. **Answer:**
4. A 59-year-old woman relapses 2 years post R-CHOP. After 2 cycles of R-DHAP, PET shows progressive disease. She remains fit (ECOG 1). **Answer:**
5. An 80-year-old man relapses 6 months after R-CHOP. He has ischemic heart disease, CKD stage 3, and ECOG 2. He is not a candidate for CAR-T or intensive salvage chemotherapy. **Answer:**

Answers and Explanations

1 → A. CAR T-cell therapy

- Early relapse (<12 months) + aggressive biology
 - CAR-T superior to salvage + ASCT
-

2 → L. CAR-T bridging therapy followed by CAR-T infusion

- Key nuance: needs urgent disease control while awaiting CAR-T
 - Bridging (e.g. R-GemOx) → then CAR-T
-

3 → C. HDT-ASCT

- Late relapse + chemosensitive disease = transplant standard
-

4 → A. CAR T-cell therapy

- Platinum-refractory → do not proceed to ASCT
 - CAR-T indicated
-

5 → D. Pola-BR

- Unfit → Pola-BR is standard licensed option

EMQ 2

Options-Theme DLBCL Treatment

- A. CAR T-cell therapy
- B. Platinum-based salvage chemotherapy (R-ICE / R-DHAP)
- C. High-dose therapy with autologous stem cell transplant (HDT-ASCT)
- D. Polatuzumab vedotin + bendamustine + rituximab (Pola-BR)
- E. Tafasitamab + lenalidomide
- F. CD3×CD20 bispecific antibody (e.g. glofitamab / epcoritamab)
- G. Loncastuximab tesirine
- H. Palliative oral chemotherapy
- I. Involved-site radiotherapy (ISRT)
- J. R-GemOx
- K. Allogeneic stem cell transplant
- L. CAR-T bridging therapy followed by CAR-T infusion

Instructions

For each scenario, choose the single most appropriate next step in management.

Each option may be used once, more than once, or not at all.

1. A 67-year-old woman received: R-CHOP with partial response and R-GemOx with progression of disease. She is ECOG 1, with good organ function and motivated for further therapy.
2. A 78-year-old woman relapses 18 months after R-CHOP with bulky nodal disease and fatigue. She has ECOG 3, frailty, and recurrent hospital admissions.

3. A 61-year-old man received CAR T-cell therapy for refractory DLBCL and achieved CR. He now relapses 8 months later with nodal and extranodal disease. Performance status remains good.
4. A 70-year-old man previously treated with R-CHOP presents with isolated paraspinal mass causing early neurological symptoms. Imaging confirms single-site relapse.
5. A 43-year-old woman has received R-CHOP as 1st line, R-ICE followed by ASCT as second line and CAR T-cell therapy as third line. Her disease has relapsed again. She remains fit (ECOG 0), and a matched sibling donor is available.

Answers and Explanation

1 → A. CAR T-cell therapy

- ≥2 prior lines + fit → CAR-T standard
-

2 → H. Palliative oral chemotherapy

- Frailty dominates → symptom control focus
-

3 → F. CD3×CD20 bispecific antibody

- Post CAR-T relapse → bispecifics preferred emerging standard
-

4 → I. Involved-site radiotherapy (ISRT)

- Emergency local control → radiotherapy first
-

5 → K. Allogeneic stem cell transplant

- Young + multi-relapsed + donor → curative allo-SCT

EMQ 3

Theme: Inherited thrombophilia

Options

- A. Test for inherited thrombophilia
 - B. Do not test – results will not influence management
 - C. Test only if results will alter pregnancy management
 - D. Test for specific deficiency (Protein C/S)
 - E. Advise against oestrogen-containing therapy and testing
 - F. Defer testing until off anticoagulation
 - G. Test asymptomatic first-degree relatives selectively
 - H. Do not test – patient already in high-risk group
 - I. Test for antiphospholipid syndrome only
 - J. No inherited thrombophilia testing; investigate alternative causes
-

Instructions:

- **For each scenario, choose the single most appropriate next step in management.**
- **Each option may be used once, more than once, or not at all.**

Questions

Q1

A 34-year-old woman presents with a first episode of unprovoked proximal DVT. She is on long term anticoagulation and remains well. Her mother had a DVT at age 68 following surgery, and there is no other family history of thrombosis. She is keen to stop anticoagulation.

Q2

A 27-year-old woman, currently 9 weeks pregnant, is referred for thrombosis risk assessment. She is asymptomatic but reports that her brother had a pulmonary embolism at age 29 and was subsequently diagnosed with antithrombin deficiency. She has never been tested, and obstetric team has contacted you for this.

Q3

A 5-year-old child presents with rapidly progressive purpuric skin lesions, disseminated intravascular coagulation, and skin necrosis following a viral illness. There is no significant past medical history, but a sibling died in infancy with a similar presentation of unexplained coagulopathy.

Q4

A 36-year-old woman seeks contraceptive advice. She is otherwise well but reports a strong family history of venous thromboembolism: her father and two siblings all had unprovoked VTE before the age of 40. None of them have undergone thrombophilia testing. She is particularly keen to use the combined oral contraceptive pill for cycle control.

Q5

A 42-year-old man presents with abdominal pain and is found to have portal vein thrombosis on imaging. There are no clear provoking factors such as cirrhosis, malignancy, or recent surgery. Inherited thrombophilia screening is requested by the admitting team.

Answers & Explanations

Q1 → B. Do not test – results will not influence management

- Decision to stop anticoagulation depends on:
 - Provoked vs unprovoked event (Unprovoked events need lifelong anticoagulation)
 - Bleeding risk
 - Thrombophilia testing does not meaningfully refine recurrence risk here
-

Q2 → C. Test only if results will alter pregnancy management

- First-degree relative with high-risk thrombophilia (AT deficiency)
 - Positive result → ↑ LMWH intensity / closer monitoring
 - This is one of the few pregnancy scenarios where testing matters
-

Q3 → D. Test for specific deficiency (Protein C/S)

- Classic purpura fulminans → severe Protein C deficiency
 - Strong family history reinforces inherited severe deficiency
-

Q4 → E. Advise against oestrogen-containing therapy and testing

- Strong FH alone = contraindication
 - Negative test would not reduce risk sufficiently
 - Testing adds little value → avoid COCP regardless
-

Q5 → J. No inherited thrombophilia testing; investigate alternative causes

- Portal vein thrombosis → think:
 - Myeloproliferative neoplasm (e.g., JAK2 mutation)
 - Local intra-abdominal pathology
- Inherited thrombophilia testing = low yield

EMQ 4

Theme: Inherited thrombophilia

Options

- A. Test for inherited thrombophilia
 - B. Do not test – results will not influence management
 - C. Test only if results will alter pregnancy management
 - D. Test for specific deficiency (Protein C/S or Antithrombin)
 - E. Advise against oestrogen-containing therapy and testing
 - F. Defer testing until off anticoagulation
 - G. Test asymptomatic first-degree relatives selectively
 - H. Do not test – patient already in high-risk group
 - I. Test for antiphospholipid syndrome only
 - J. No inherited thrombophilia testing; investigate alternative causes
-

Instructions:

- **For each scenario, choose the single most appropriate next step in management.**
- **Each option may be used once, more than once, or not at all.**

Each Questions

Q1

A 30-year-old woman is referred to the haematology clinic following three consecutive first-trimester miscarriages. She has no personal or family

history of thrombosis. Her GP has requested a “full thrombophilia screen” including Protein C, Protein S, antithrombin, Factor V Leiden, and prothrombin gene mutation.

Q2

A 31-year-old asymptomatic man attends clinic because his sister was recently diagnosed with Protein S deficiency after an unprovoked DVT. There is no other family history of thrombosis. He wants to know whether testing would be useful for him, particularly in relation to long-haul travel and future surgery.

Q3

A 29-year-old woman is currently 20 weeks pregnant. She has a history of a previous unprovoked proximal DVT at age 25 and is already receiving prophylactic low molecular weight heparin. Her obstetrician queries whether thrombophilia testing should now be performed to refine her risk stratification for the remainder of pregnancy.

Q4

A 28-year-old woman is considering starting hormone replacement therapy for premature ovarian insufficiency. Her mother had a DVT at age 52 and was tested for thrombophilia with negative results. The patient asks whether she should undergo thrombophilia testing before starting HRT to ensure it is safe.

Q5

A 39-year-old man with a history of two unprovoked venous thromboembolic events is maintained on indefinite anticoagulation. He has never had thrombophilia testing. He asks whether testing should be performed now to better understand the cause of his condition.

Answers & Explanations

Q1 → I. Test for antiphospholipid syndrome only

- Recurrent miscarriage → APS is relevant

- Inherited thrombophilia's:
 - Weak/absent association
 - Not routinely recommended
-

Q2 → B. Do not test – results will not influence management

- Testing may not change anything
-

Q3 → D. Test for specific deficiency (Antithrombin)

Previous VTE → already qualifies for LMWH

- Protein C remains unchanged during pregnancy
 - Protein S goes down in Pregnancy
 - Anti thrombin goes down during third trimester and patient may need AT concentrate prior to delivery
-

Q4 → E. Advise against oestrogen-containing therapy and testing

- Family history alone increases risk
 - Even with:
 - Negative maternal thrombophilia testing
 - Key concept: **testing does not “clear” risk**
-

Q5 → B. Do not test – results will not influence management

- Often clinically unnecessary since already lifelong anticoagulation and testing will not change anything in management of this patient

EMQ 5

Theme: Granulocyte Transfusion

Options (Each option may be used once, more than once, or not at all)

- A. Start granulocyte transfusion immediately
- B. Do not give granulocytes – infection not refractory
- C. Not indicated – no expectation of neutrophil recovery
- D. Consider granulocytes after further optimisation
- E. Indicated due to neutrophil functional defect
- F. Not indicated – infection type inappropriate
- G. Needs MDT discussion with Microbiology and NHSBT about Prophylactic Granulocytes
- H. Seek specialist discussion but unlikely to proceed
- I. Contraindicated due to risk outweighing benefit
- J. Continue standard therapy without granulocytes

1.

A 46-year-old man with newly diagnosed AML is on day 14 following induction chemotherapy. His neutrophil count has been persistently $<0.1 \times 10^9/\text{L}$. He developed fever on day 5 and was started on piperacillin-tazobactam, escalated to meropenem and vancomycin due to persistent fevers. Liposomal amphotericin B was started 4 days ago. The treating team expects neutrophil recovery within 7–10 days. **Answer:**

2.

A 72-year-old woman with relapsed AML has declined further chemotherapy and is receiving best supportive care. She presents with neutropenic sepsis (ANC $0.2 \times 10^9/L$) and blood cultures grow ESBL-producing *E. coli*. She is started on meropenem and shows partial haemodynamic improvement after 48 hours, but remains febrile. The ICU team asks whether granulocyte transfusions may improve survival. **Answer:**

3.

A 28-year-old man with chronic granulomatous disease presents with fever, pleuritic chest pain, and multiple pulmonary nodules. He has a normal neutrophil count ($5.0 \times 10^9/L$), but oxidative burst testing confirms defective neutrophil function. Despite 7 days of appropriate antifungal and antibacterial therapy, he continues to deteriorate clinically with enlarging lesions on CT. **Answer:**

4.

A 61-year-old patient with MDS is receiving azacitidine. He develops neutropenia (ANC $0.4 \times 10^9/L$) and fever. Chest X-ray shows right lower lobe consolidation. He is started on IV antibiotics and improves clinically over 72 hours, with defervescence and improving inflammatory markers, although neutropenia persists. **Answer:**

5.

A 53-year-old woman undergoing consolidation chemotherapy for AML previously had invasive pulmonary aspergillosis during induction. She is now planned for further intensive chemotherapy. The team is concerned about recurrence of fungal infection during the upcoming period of expected prolonged neutropenia and considering Granulocytes as prophylaxis. **Answer:**

Answers and Explanations

1.

Answer: A. Start granulocyte transfusion immediately

Reason:

- ✓ Severe neutropenia
- ✓ Proven/probable invasive fungal infection

- ✓ Radiological progression despite therapy
- ✓ Recovery expected
- Meets *all* criteria

2.

Answer: C. Not indicated – no expectation of neutrophil recovery

Key trap:

Even with severe infection →

- ✗ No disease-modifying treatment planned
- ✗ No marrow recovery expected
- Not indicated

3.

Answer: E. Indicated due to neutrophil functional defect

Exam pearl:

- ✓ Functional defect = treat like neutropenia
- ✓ Infection refractory → indication

4.

Answer: B. Do not give granulocytes – infection not refractory

Trap:

- ✓ Neutropenia alone ≠ indication
- ✓ Infection responding → NO granulocytes

5.

Answer: G. Needs MDT discussion with Microbiology and NHSBT about Prophylactic Granulocytes

Subtle point:

- ✓ Not routine
- ✓ But acceptable in **selected high-risk cases after discussion in MDT**

EMQ 6

Theme: Granulocyte Transfusion

Options (Each option may be used once, more than once, or not at all)

- A. Start granulocyte transfusion immediately
- B. Do not give granulocytes – infection not refractory
- C. Not indicated – no expectation of neutrophil recovery
- D. Consider granulocytes after further optimisation
- E. Indicated due to neutrophil functional defect
- F. Not indicated – infection type inappropriate
- G. Needs MDT discussion with Microbiology and NHSBT about Prophylactic Granulocytes
- H. Seek specialist discussion (Microbiology). Too early for Granulocytes
- I. Contraindicated due to risk outweighing benefit
- J. Continue standard therapy without granulocytes

1

A 45-year-old man with ALL post-induction chemotherapy has persistent fever for 3 days. ANC is $0.2 \times 10^9/\text{L}$. Blood cultures are negative. CT scan is normal. He is on broad-spectrum antibiotics and antifungals empirically. The team is considering early granulocyte transfusion “to prevent deterioration.” **Answer:**

A 64-year-old man with AML post induction has persistent neutropenia (ANC $0.1 \times 10^9/L$) and worsening cellulitis with expanding erythema despite 4 days of appropriate IV antibiotics. Surgical review confirms progressive soft tissue infection. Neutrophil recovery is expected in ~5 days. **Answer:**

3

A 58-year-old woman with metastatic breast cancer develops chemotherapy-induced neutropenia (ANC $0.3 \times 10^9/L$) and influenza A infection confirmed on PCR. She has no evidence of bacterial or fungal co-infection but is febrile. **Answer:**

4

A 67-year-old patient with MDS has prolonged neutropenia and invasive fungal infection. He is not currently receiving treatment due to poor performance status, but the team is considering restarting azacitidine if infection improves. **Answer:**

5

A 50-year-old man with AML in remission develops febrile neutropenia (ANC $0.4 \times 10^9/L$) after chemotherapy. After 5 days of antibiotics, he is clinically stable but remains febrile. CT scan shows no focus, and cultures are negative. **Answer:**

Answers and Explanations:

1

Answer: J. Continue standard therapy without granulocytes

Important principle:

- ✗ No proven/probable infection
- ✗ Not refractory
- Too early

2

Answer: A. Start granulocyte transfusion immediately

- ✓ Bacterial infection
- ✓ Evidence of progression
- ✓ Refractory
- ✓ Recovery expected

3

Answer: F. Not indicated – infection type inappropriate

- ✓ Viral infection alone = NO

4

Answer: D. Consider granulocytes after further optimisation

Why difficult:

- ⚖ Borderline case
- ✓ Infection refractory
- ❓ Unclear treatment intent
- Needs MDT discussion

5

Answer: H. Seek specialist discussion (Microbiology). Too early for Granulocytes

Nuance:

- ✓ Persistent fever alone ≠ indication
- ✓ No documented infection
- Grey-zone → discuss but unlikely

EMQ 7

Theme: Waldenstrom

OPTIONS (Each option may be used once, more than once, or not at all)

- A. Immediate plasmapheresis
- B. Pre-emptive plasmapheresis prior to rituximab
- C. Observation only
- D. Rituximab monotherapy
- E. DRC (dexamethasone–rituximab–cyclophosphamide)
- F. Bendamustine–rituximab
- G. BTK inhibitor
- H. Bortezomib-based regimen
- I. Treat as high-grade lymphoma (e.g. R-CHOP)
- J. Intrathecal + CNS-penetrating chemotherapy

1.

A 72-year-old man presents with **blurred vision, headaches, and epistaxis**.
Investigations:

- Hb 88 g/L
- IgM 51 g/L
- Serum viscosity markedly elevated
- Fundoscopy: retinal vein engorgement

2.

A 70-year-old woman with newly diagnosed WM has:

- IgM 46 g/L
- Mild fatigue only
- No visual symptoms
- Planned for rituximab-based therapy

3.

A 79-year-old frail patient with WM has:

- Hb 94 g/L
- IgM 25 g/L
- No B symptoms
- ECOG 3

4.

A 67-year-old fit patient presents with:

- Hb 82 g/L
- Weight loss
- IgM 34 g/L
- Lymphadenopathy and splenomegaly

5.

A 75-year-old frail patient develops symptomatic anaemia due to WM:

- Hb 78 g/L
- IgM 28 g/L
- Multiple comorbidities

Answers and Explanations

1.

A 72-year-old man presents with **blurred vision, headaches, and epistaxis**. IgM 51 g/L, raised serum viscosity, retinal vein engorgement.

✅ **Answer: A. Immediate plasmapheresis**

Explanation:

This is **established hyperviscosity syndrome**:

- Visual symptoms + bleeding + fundoscopy changes
 - 👉 Plasmapheresis is **emergency first**, not chemo
 - 👉 IgM level supports but **clinical features drive decision**
-

2.

A 70-year-old woman with WM:

IgM 46 g/L, mild fatigue, no hyperviscosity. Planned for rituximab.

✅ **Answer: B. Pre-emptive plasmapheresis prior to rituximab**

Explanation:

- IgM >40 g/L → **high risk of IgM flare** with rituximab
 - Even without symptoms → **preventive plasmapheresis OR delay rituximab**
 - 👉 Classic guideline nuance frequently tested
-

3.

A 79-year-old frail patient:

Hb 94 g/L, IgM 25 g/L, no symptoms, ECOG 3.

✅ **Answer: C. Observation only**

Explanation:

- WM treatment is **symptom-driven**
 - Mild anaemia alone (Hb ~90s) without symptoms ≠ indication
 - 👉 Frailty reinforces conservative approach
-

4.

A 67-year-old fit patient:

Hb 82 g/L, weight loss, lymphadenopathy, IgM 34 g/L.

✅ **Answer: F. Bendamustine-rituximab**

Explanation:

- Symptomatic + fit → **chemoimmunotherapy**
- BR preferred for:

- Better depth of response
 - Bulky/systemic disease
 - 👉 DRC acceptable but less potent
-

5.

A 75-year-old frail patient with symptomatic anaemia (Hb 78 g/L), IgM 28 g/L.

✅ **Answer: D. Rituximab monotherapy**

Explanation:

- Frail → avoid combination chemo
- Rituximab alone acceptable despite:
 - Slower response
 - 👉 Balance **efficacy vs tolerability**

EMQ 8

Theme: Waldenstrom

OPTIONS (Each option may be used once, more than once, or not at all)

- A. Immediate plasmapheresis
- B. Pre-emptive plasmapheresis prior to rituximab
- C. Observation only
- D. Rituximab monotherapy
- E. DRC (dexamethasone–rituximab–cyclophosphamide)
- F. Bendamustine–rituximab
- G. BTK inhibitor
- H. Bortezomib-based regimen
- I. Treat as high-grade lymphoma
- J. Intrathecal/CNS-penetrating chemotherapy

1.

A 65-year-old patient with WM develops:

- Painful acrocyanosis
- Haemolytic anaemia
- DAT positive (C3 only)

Initially managed conservatively but becomes transfusion-dependent.

2.

A 60-year-old patient presents with:

- Rapidly enlarging lymph nodes
- High LDH
- B symptoms

Biopsy: diffuse large B-cell lymphoma

3.

A 63-year-old with WM develops:

- Confusion
- Ataxia
- Cranial nerve palsies

MRI: CNS infiltration

CSF: clonal lymphoplasmacytic cells

4.

A 61-year-old patient relapses 4 years after BR:

- Hb 90 g/L
 - IgM rising
 - Known MYD88 mutation
 - Baseline peripheral neuropathy
-

5.

A 58-year-old fit patient presents with:

- Bulky lymphadenopathy
- Rapid disease progression
- IgM 30 g/L

Answers and Explanations

1.

A 65-year-old with WM develops cold-induced haemolysis (DAT C3+), now transfusion-dependent.

✅ **Answer: F. Bendamustine–rituximab**

Explanation:

- Cold agglutinin disease secondary to WM
 - Now **clinically significant** → **treat clone**
 - BR superior to rituximab alone in severe disease
👉 Conservative measures only for mild disease
-

2.

A 60-year-old with rapidly enlarging nodes, high LDH, B symptoms. Biopsy: DLBCL.

✅ **Answer: I. Treat as high-grade lymphoma (R-CHOP)**

Explanation:

- **Histological transformation**
 - Treat as **de novo aggressive lymphoma**, not WM
👉 Very common exam pivot
-

3.

A 63-year-old develops confusion, ataxia, cranial nerve palsies. MRI + CSF confirm CNS involvement.

✅ **Answer: J. Intrathecal/CNS-penetrating chemotherapy**

Explanation:

- **Bing–Neel syndrome**
- Requires:
 - Intrathecal therapy

- CNS-penetrating systemic agents
 - 👉 NOT standard WM therapy
-

4.

A 61-year-old relapses 4 years post-BR, has neuropathy, MYD88 mutated.

✅ **Answer: G. BTK inhibitor**

Explanation:

- Standard relapse therapy
 - Neuropathy → avoid bortezomib
 - MYD88 mutation → predicts good response
 - 👉 Classic “best next line” question
-

5.

A 58-year-old fit patient with bulky, rapidly progressive disease, IgM 30 g/L.

✅ **Answer: F. Bendamustine–rituximab**

Explanation:

- Aggressive clinical behaviour (bulky/rapid)
 - need **deep, fast response**
- BR preferred over DRC or rituximab alone

EMQ 9

Theme: Inherited bone marrow failure syndromes

OPTIONS (Each option may be used once, more than once, or not at all)

- A. Fanconi anemia
- B. Dyskeratosis congenita
- C. Diamond–Blackfan anemia
- D. Shwachman–Diamond syndrome
- E. Severe congenital neutropenia
- F. Congenital amegakaryocytic thrombocytopenia
- G. GATA2 deficiency
- H. SAMD9/SAMD9L disorder
- I. MECOM-associated syndrome

Questions

Q1

An 8-year-old boy is referred with progressive pancytopenia. He has a history of being small for age with low birth weight. Examination reveals café-au-lait macules and microcephaly. His past history includes surgical repair of a tracheoesophageal fistula. Bone marrow is hypocellular.. **Answer:**

Q2

A 19-year-old man presents with fatigue and worsening cytopenias. He has a history of nail dystrophy since childhood and reticulated skin pigmentation over the neck and chest. He recently developed dysphagia and was found to have esophageal stenosis. HRCT shows early pulmonary fibrosis. Blood tests show macrocytosis and elevated HbF. **Answer:**

Q3

A 3-month-old infant is evaluated for severe anemia requiring repeated transfusions. There is no hepatosplenomegaly. Examination shows craniofacial abnormalities including hypertelorism and a flat nasal bridge. The thumbs are triphalangeal. Bone marrow shows paucity of erythroid precursors. **Answer:**

Q4

A 5-year-old child presents with recurrent chest infections, chronic diarrhea, and poor weight gain. There is a history of steatorrhea. Examination shows short stature and skeletal abnormalities. Blood tests reveal persistent neutropenia. **Answer:**

Q5

A neonate develops omphalitis within the first week of life, followed by recurrent severe bacterial infections. Serial full blood counts show profound neutropenia. Bone marrow examination demonstrates maturation arrest at the promyelocyte stage. **Answer:**

Q6

A full-term neonate presents with petechiae and severe thrombocytopenia at birth. There are no dysmorphic features. Bone marrow examination shows virtual absence of megakaryocytes. Over time, the child develops pancytopenia. **Answer:**

Q7

A 24-year-old woman presents with recurrent HPV infections and atypical mycobacterial disease. She has a history of chronic lower limb lymphedema. Blood tests show monocytopenia, neutropenia, and thrombocytopenia. Bone marrow shows dysplasia, and cytogenetics later reveal monosomy 7. **Answer:**

Answer:

Q1

An 8-year-old boy is referred with progressive pancytopenia. He has a history of being small for age with low birth weight. Examination reveals café-au-lait macules, microcephaly, and hypoplastic thumbs. His past history includes surgical repair of a tracheoesophageal fistula. Bone marrow is hypocellular. Chromosomal breakage testing with diepoxybutane shows marked instability.

👉 **Answer: A. Fanconi anemia**

Q2

A 19-year-old man presents with fatigue and worsening cytopenias. He has a history of nail dystrophy since childhood and reticulated skin pigmentation over the neck and chest. He recently developed dysphagia and was found to have esophageal stenosis. HRCT shows early pulmonary fibrosis. Blood tests show macrocytosis and elevated HbF. Telomere length analysis is markedly reduced.

👉 **Answer: B. Dyskeratosis congenita**

Q3

A 3-month-old infant is evaluated for severe anemia requiring repeated transfusions. There is no hepatosplenomegaly. Examination shows craniofacial abnormalities including hypertelorism and a flat nasal bridge. The thumbs are triphalangeal. Bone marrow shows paucity of erythroid precursors. MCV is elevated, and erythrocyte adenosine deaminase levels are raised.

👉 **Answer: C. Diamond-Blackfan anemia**

Q4

A 5-year-old child presents with recurrent chest infections, chronic diarrhea, and poor weight gain. There is a history of steatorrhea. Examination shows short stature and skeletal abnormalities. Blood tests reveal persistent neutropenia. Fecal elastase is low, and serum trypsinogen is reduced.

👉 **Answer: D. Shwachman-Diamond syndrome**

Q5

A neonate develops omphalitis within the first week of life, followed by recurrent severe bacterial infections. Serial full blood counts show profound neutropenia. Bone marrow examination demonstrates maturation arrest at the promyelocyte stage. Genetic testing reveals a mutation in ELANE.

👉 **Answer: E. Severe congenital neutropenia**

Q6

A full-term neonate presents with petechiae and severe thrombocytopenia at birth. There are no dysmorphic features. Bone marrow examination shows virtual absence of megakaryocytes. Over time, the child develops pancytopenia. Genetic testing identifies a mutation affecting thrombopoietin receptor signaling.

👉 **Answer: F. Congenital amegakaryocytic thrombocytopenia**

Q7

A 24-year-old woman presents with recurrent HPV infections and atypical mycobacterial disease. She has a history of chronic lower limb lymphedema. Blood tests show monocytopenia, neutropenia, and thrombocytopenia. Bone marrow shows dysplasia, and cytogenetics later reveal monosomy 7.

👉 **Answer: G. GATA2 deficiency**

EMQ 10

Theme: Inherited bone marrow failure syndromes Pathophysiology

OPTIONS (Each option may be used once, more than once, or not at all)

- A. Defective DNA interstrand crosslink repair leading to chromosomal instability
- B. Critically short telomeres causing stem cell exhaustion
- C. Haploinsufficiency of ribosomal proteins leading to p53 activation
- D. Endoplasmic reticulum stress impairing neutrophil maturation
- E. Defective thrombopoietin receptor signaling impairing megakaryopoiesis
- F. Transcription factor deficiency affecting hematopoietic stem cell maintenance
- G. Gain-of-function mutations causing growth restriction and cellular antiproliferation
- H. Clonal evolution with monosomy 7 leading to myelodysplasia
- I. Increased apoptosis of hematopoietic progenitors due to oxidative stress

Questions

Q1

A child presents with progressive pancytopenia and multiple congenital anomalies. Laboratory testing demonstrates increased chromosomal breakage when lymphocytes are exposed to diepoxybutane. Bone marrow shows hypocellularity. **Underlying Pathophysiology-Answer:**

Q2

A young adult presents with bone marrow failure, pulmonary fibrosis, and liver disease. Examination reveals nail dystrophy and abnormal skin pigmentation. The hematopoietic failure is primarily due to replicative senescence of stem cells. **Underlying Pathophysiology-Answer:**

Q3

An infant with severe macrocytic anemia. Bone marrow shows erythroid hypoplasia. Further studies demonstrate activation of p53 pathways leading to apoptosis of erythroid precursors. **Underlying Pathophysiology-Answer:**

Q4

A neonate presents with severe neutropenia and recurrent infections. Bone marrow examination shows maturation arrest at promyelocyte stage. **Underlying Pathophysiology-Answer:**

Q5

A newborn presents with severe thrombocytopenia and absent megakaryocytes in the bone marrow. Over time, the patient develops pancytopenia. **Underlying Pathophysiology-Answer:**

Q6

A young adult presents with recurrent infections, lymphedema, and cytopenias affecting multiple lineages. Bone marrow shows hypocellularity and dysplasia. **Underlying Pathophysiology-Answer:**

Answers:

Q1

A child presents with progressive pancytopenia and multiple congenital anomalies. Laboratory testing demonstrates increased chromosomal breakage when lymphocytes are exposed to diepoxybutane. Bone marrow shows hypocellularity. The underlying defect primarily affects a pathway responsible for repairing DNA damage caused by crosslinking agents.

👉 **Answer: A. Defective DNA interstrand crosslink repair leading to chromosomal instability**

Q2

A young adult presents with bone marrow failure, pulmonary fibrosis, and liver disease. Examination reveals nail dystrophy and abnormal skin pigmentation. Investigations show markedly reduced telomere length in leukocytes. The hematopoietic failure is primarily due to replicative senescence of stem cells.

👉 **Answer: B. Critically short telomeres causing stem cell exhaustion**

Q3

An infant with severe macrocytic anemia is found to have mutations in ribosomal protein genes. Bone marrow shows erythroid hypoplasia. Further studies demonstrate activation of p53 pathways leading to apoptosis of erythroid precursors.

👉 **Answer: C. Haploinsufficiency of ribosomal proteins leading to p53 activation**

Q4

A neonate presents with severe neutropenia and recurrent infections. Bone marrow examination shows maturation arrest at the promyelocyte stage. Genetic analysis reveals mutations affecting proteins involved in intracellular protein handling, resulting in cellular stress responses.

👉 **Answer: D. Endoplasmic reticulum stress impairing neutrophil maturation**

Q5

A newborn presents with severe thrombocytopenia and absent megakaryocytes in the bone marrow. Over time, the patient develops pancytopenia. Molecular studies show impaired signaling through a receptor critical for platelet production.

👉 **Answer: E. Defective thrombopoietin receptor signaling impairing megakaryopoiesis**

Q6

A young adult presents with recurrent infections, lymphedema, and cytopenias affecting multiple lineages. Bone marrow shows hypocellularity and dysplasia. Genetic testing reveals mutation in a gene encoding a zinc finger transcription factor essential for hematopoietic stem cell survival.

👉 **Answer: F. Transcription factor deficiency affecting hematopoietic stem cell maintenance**

EMQ 11 and 12

Theme: Inherited Bone Marrow Failure Syndrome

Options (Each option may be used once, more than once, or not at all)

- A. FANCA
 - B. FANCC
 - C. DKC1
 - D. TERT
 - E. RPS19
 - F. RPL11
 - G. SBDS
 - H. ELANE
 - I. MPL
 - J. GATA2
 - K. SAMD9
 - L. MECOM
-

Questions

Q1

An 8-year-old boy presents with progressive pancytopenia, short stature, and radial ray abnormalities. He has café-au-lait pigmentation and renal anomalies.

Bone marrow is hypocellular. Chromosomal breakage testing using diepoxybutane (DEB) is markedly increased.

Genetic testing confirms a mutation in the most commonly affected gene in this condition. **Answer:**

Q2

A 14-year-old male presents with progressive bone marrow failure. He has nail dystrophy, abnormal skin pigmentation, and oral leukoplakia.

Telomere length analysis shows severely shortened telomeres.

Family history reveals X-linked inheritance. **Answer:**

Q3

A 35-year-old woman presents with isolated pulmonary fibrosis and mild macrocytosis. She later develops thrombocytopenia.

Telomere length testing shows markedly shortened telomeres.

There is an autosomal dominant inheritance pattern across three generations. **Answer:**

Q4

A 6-month-old infant presents with transfusion-dependent anaemia.

- Hb: 55 g/L
- WBC and platelets: normal
- Bone marrow: absence of erythroid precursors

Erythrocyte adenosine deaminase (eADA) is elevated. **Answer:**

Q5

A 10-year-old child with Diamond–Blackfan anaemia develops additional skeletal abnormalities and cleft palate.

Genetic testing identifies a ribosomal protein gene associated with a higher risk of congenital anomalies compared to the most common DBA gene.

Answer:

Q6

A 4-year-old boy presents with recurrent infections, failure to thrive, and intermittent neutropenia.

- Low faecal elastase

- Low pancreatic isoamylase
- Bone marrow: hypocellular

Answer:

Q7

A neonate presents with severe congenital neutropenia and recurrent sepsis. Bone marrow shows maturation arrest at the promyelocyte stage.

Answer:

Q8

A 1-year-old child presents with severe thrombocytopenia since birth. Bone marrow shows absent megakaryocytes. Defect involves the thrombopoietin receptor pathway.

Answer:

Q9

A 25-year-old man presents with recurrent viral infections, extensive warts, and progressive cytopenias.

- Monocytopenia
- B-cell and NK-cell deficiency
- Progression to MDS with monosomy 7

Answer:

Q10

A 7-year-old child presents with growth restriction and cytopenias. Bone marrow is hypocellular. Cytogenetics reveal monosomy 7. Mutation associated with MIRAGE syndrome is identified.

Answer:

Q11

A neonate presents with severe thrombocytopenia and skeletal abnormalities (radioulnar synostosis).

Bone marrow shows reduced megakaryocytes.

No MPL mutation is identified.

Answer:

✓ **Answers with Explanations**

Q	Answer	Explanation
Q1	A. FANCA	Classic Fanconi anaemia phenotype (radial defects, café-au-lait, pancytopenia + DEB breakage). FANCA is the most common gene (~60–70%), making it the best answer over FANCC.
Q2	C. DKC1	Triad (skin, nails, leukoplakia) + very short telomeres + X-linked inheritance → Dyskeratosis congenita due to DKC1.
Q3	D. TERT	Adult-onset telomere disease (pulmonary fibrosis + cytopenias) with autosomal dominant inheritance strongly suggests TERT mutation.
Q4	E. RPS19	Pure red cell aplasia + ↑ eADA = Diamond–Blackfan anaemia. RPS19 is the most common mutated ribosomal protein gene.
Q5	F. RPL11	DBA with more congenital anomalies (craniofacial, thumb, cardiac) is classically linked to RPL11 (and RPL5) rather than RPS19.
Q6	G. SBDS	Neutropenia + pancreatic insufficiency (↓ elastase, isoamylase) = Shwachman–Diamond syndrome, caused by SBDS mutation.
Q7	H. ELANE	Severe congenital neutropenia with promyelocyte arrest is classic for ELANE mutation (formerly ELA2).
Q8	I. MPL	Absent megakaryocytes + severe thrombocytopenia = CAMT, caused by mutations in MPL (TPO receptor).

Q	Answer	Explanation
Q9	J. GATA2	MonoMAC phenotype (monocytes, B, NK ↓) + warts + MDS risk → hallmark of GATA2 deficiency.
Q10	K. SAMD9	MIRAGE syndrome + monosomy 7 is strongly associated with SAMD9 (or SAMD9L) mutations.
Q11	L. MECOM	CAMT-like picture but MPL negative + skeletal abnormalities (radioulnar synostosis) → classic for MECOM mutation.

High-Yield Exam Traps

- **FANCA vs FANCC** → always pick **FANCA** unless specified otherwise
- **DKC1 vs TERT** →
 - DKC1 = **X-linked + childhood + mucocutaneous triad**
 - TERT = **adult onset + pulmonary fibrosis**
- **RPS19 vs RPL11** →
 - RPS19 = most common
 - RPL11 = **more anomalies**
- **MPL vs MECOM** →
 - MPL = pure CAMT
 - MECOM = CAMT + **skeletal defects**
- **GATA2 vs SAMD9** →
 - GATA2 = immunodeficiency + warts
 - SAMD9 = **monosomy 7 + growth restriction (MIRAGE)**

EMQ 13 and 14

Theme: APS

Options (Each option may be used once, more than once, or not at all)

- A. Test full aPL panel (LA, aCL IgG/IgM, anti- β 2GPI) now
 - B. Do not test for aPL
 - C. Repeat aPL testing after ≥ 12 weeks
 - D. Defer LA testing due to anticoagulation interference
 - E. Defer LA testing due to recent thrombosis/acute phase
 - F. Perform DRVVT and LA-sensitive APTT
 - G. Perform mixing study and phospholipid neutralisation step
 - H. Start VKA (target INR 2.0–3.0) indefinitely
 - I. Increase VKA intensity (target INR 3.0–4.0)
 - J. Discuss switching DOAC to VKA
 - K. Add antiplatelet therapy to VKA
 - L. Use DAPT instead of anticoagulation
-

Questions

Q1

A 44-year-old woman presents with an unprovoked proximal DVT. She has a past history of migraine and one first-trimester miscarriage.

She is started on apixaban.

Thrombophilia testing is requested by medical team on day 3 of admission. Blood sample shows:

- Prolonged APTT
- Positive DRVVT screen ratio
- Normal PT

No mixing or confirmatory studies are performed.

What is the most appropriate next step regarding APS testing?

Q2

A 39-year-old man presents with extensive iliofemoral DVT. No provoking factors are identified.

He is started on LMWH and warfarin.

Lupus anticoagulant testing is performed 5 days later upon medical team request while INR is 1.8 and anti-Xa level is therapeutic.

DRVVT is prolonged; mixing study shows incomplete correction.

What is the most appropriate interpretation/next step?

Q3

A 31-year-old woman with known SLE presents for pre-pregnancy counselling. She has no history of thrombosis but had two second-trimester miscarriages.

aPL testing shows:

- aCL IgG strongly positive
- anti- β 2GPI positive
- LA negative

What is required before confirming APS diagnosis?

Q4

A 52-year-old man presents with ischaemic stroke. He has no hypertension, diabetes, or hyperlipidaemia.

aPL testing is performed 10 days after the event while he is still hospitalised and systemically unwell.

LA is weakly positive

What is the most appropriate next step?

Q5

A 47-year-old woman with triple-positive APS presents with recurrent DVT while on warfarin with consistently therapeutic INR (2.3–2.7).

Adherence is confirmed. No malignancy identified.

What is the most appropriate management change?

Q6

A 36-year-old man with triple-positive APS and prior PE is treated with rivaroxaban by medical team.

He prefers DOAC due to lifestyle convenience.

He has had no recurrence over 18 months.

What is the most appropriate recommendation?

Q7

A 58-year-old woman with APS presents with acute ischaemic stroke.

She has a history of hypertension and smoking.

She is commenced on warfarin (INR target 2–3).

What additional therapy should be considered given her vascular risk profile?

Q8

A 62-year-old man with APS presents with stroke but has a recent intracranial haemorrhage making anticoagulation unsafe.

What is the most appropriate alternative strategy?

Q9

A 41-year-old man is referred for APS testing after a PE that occurred following prolonged immobilisation after a road traffic accident.

He has fully recovered and is otherwise well.

What is the most appropriate approach?

Q10

A 45-year-old woman with APS is planned for warfarin therapy.

Baseline PT is prolonged before starting anticoagulation.

What is the most appropriate action?

Answers

Q Answer

Q1 D. Defer LA testing due to anticoagulation interference

Q2 D. Defer LA testing due to anticoagulation interference

Q3 C. Repeat aPL testing after ≥ 12 weeks

Q4 E. Defer LA testing due to recent thrombosis/acute phase

Q5 I. Increase VKA intensity (target INR 3.0–4.0)

Q6 J. Switch DOAC to VKA

Q7 K. Add antiplatelet therapy to VKA

Q8 L. Use DAPT instead of anticoagulation

Q9 B. Do not test for aPL

Q10 H. Start VKA using alternative PT reagent

High-Level Explanations (FRCPath Depth)

Q1-Q2 (BIG TRAP)

- DOACs and LMWH **interfere with LA assays (especially DRVVT)**
 - Any result here is **unreliable** → **defer testing**
 - Classic exam trap: “*positive LA on anticoagulation*” = *ignore*
-

Q3

- APS diagnosis requires **persistent positivity ≥12 weeks**
 - Even strongly positive results **do NOT confirm APS on single test**
-

Q4

- Acute thrombosis + inflammation → **false-positive LA**
 - Must **repeat when stable (>3 months)**
-

Q5

- Recurrent thrombosis on therapeutic INR → **escalate intensity (INR 3–4)**
 - Not DOAC, not just adding antiplatelet alone
-

Q6

- **Triple-positive APS = DOAC contraindicated**
 - Even if stable → **recommend switching to VKA**
-

Q7

- Stroke + APS + vascular risk factors →
👉 **Add antiplatelet to VKA (careful risk-benefit)**
-

Q8

- If VKA contraindicated →
👉 **DAPT preferred over single antiplatelet**
-

Q9

- Clearly provoked VTE →
✗ Testing adds no value → **do not test**
-

Q10 (Subtle lab nuance)

- APS can **prolong baseline PT**
- Use **alternative PT reagent** before starting VKA
- Prevents **false INR interpretation**

EMQ 15 and 16

Theme: APS

Options (Each option may be used once, more than once, or not at all)

- A. Increase warfarin target INR to 3.0–4.0
 - B. Add low-dose aspirin while maintaining INR 2.0–3.0
 - C. Switch from DOAC to warfarin
 - D. Assess time in therapeutic range (TTR) and INR reliability
 - E. Add hydroxychloroquine
 - F. Refer to a specialist APS centre
 - G. Add rituximab
 - H. Switch to long-term therapeutic LMWH
 - I. Continue current management without change
 - J. Intensify cardiovascular risk management including statin
-

Scenario 1

A 35-year-old woman with a history of SLE presents with left leg swelling. She has known triple-positive APS (persistently positive lupus anticoagulant, anticardiolipin, and anti-β2GP1 antibodies). Two years ago, she had an unprovoked PE and was started on apixaban due to patient preference.

She is fully compliant. There are no provoking factors. Doppler confirms a new proximal DVT.

She is otherwise well, with stable renal function and no bleeding history.

Answer:

Scenario 2

A 48-year-old man with primary APS had a previous ischaemic stroke and is anticoagulated with warfarin (target INR 2.0–3.0). He now presents with a TIA.

On review:

- INR records show wide variability (range 1.5–3.4)
- TTR over 6 months: 42%
- No clear adherence issues
- Lupus anticoagulant strongly positive

Answer:

Scenario 3

A 56-year-old woman with APS (double positive) has a history of recurrent VTE. She is on warfarin with target INR 2.0–3.0, with excellent TTR (78%).

She now presents with a segmental PE confirmed on CTPA. She denies missed doses, and drug interactions have been excluded. **Answer:**

Scenario 4

A 43-year-old man with APS and prior arterial thrombosis is on warfarin (INR target 3.0–4.0) following a previous recurrence. He also takes low-dose aspirin.

He presents with digital ischaemia and imaging confirms new arterial thrombosis.

- TTR is excellent (>75%)
- Adherence confirmed
- No malignancy or additional thrombophilia

Answer:

Scenario 5

A 62-year-old man with APS and prior MI and DVT is stable on warfarin (INR 2.0–3.0). He has:

- LDL 4.2 mmol/L
- BP 158/92 mmHg
- Ongoing smoking (20 pack-years)

No recurrent thrombosis. **Answer:**

Scenario 6

A 45-year-old woman with triple-positive APS has had multiple thrombotic events despite:

- Warfarin (INR 3.0–4.0, TTR >75%)
- Aspirin
- Hydroxychloroquine

She now presents with another PE. Malignancy screen is negative. **Answer:**

Scenario 7

A 58-year-old man with APS develops recurrent thrombosis despite warfarin. He has:

- Highly unstable INRs despite adherence
- Difficulty attending monitoring clinics
- No contraindication to heparin

Answer:

Answers with Key Reasoning

1 → C. Switch from DOAC to warfarin

- High-risk APS (triple positive) + recurrence on DOAC
 - → DOACs **not recommended**
-

2 → D. Assess TTR and INR reliability

- Poor TTR (42%) → inadequate anticoagulation
- LA may interfere → must evaluate measurement reliability

3 → A. Increase INR target to 3.0–4.0

- Recurrence despite **good TTR at standard intensity**
- → escalate intensity

4 → E. Add hydroxychloroquine

- Refractory despite:
 - High-intensity VKA
 - Antiplatelet
- → immunomodulation next step

5 → J. Intensify cardiovascular risk management

- APS + thrombosis = **aggressive risk factor control mandatory**

6 → G. Add rituximab

- Fully refractory APS despite:
 - INR escalation
 - Aspirin
 - HCQ
- → rituximab considered

7 → H. Switch to long-term LMWH

- Unstable INR + practical issues
- → LMWH reasonable alternative

EMQ 17 and 18

Theme: Obstetric APS

Options (Each option may be used once, more than once, or not at all)

- A. Aspirin alone throughout pregnancy
 - B. Aspirin + prophylactic LMWH from positive pregnancy test
 - C. Therapeutic-dose LMWH throughout pregnancy
 - D. Switch from warfarin to LMWH immediately on confirmation of pregnancy
 - E. Continue warfarin until second trimester
 - F. Add hydroxychloroquine
 - G. Add prednisolone or IVIG
 - H. Refer to specialist obstetric–haematology centre
 - I. Continue LMWH for 6 weeks postpartum then reassess long-term anticoagulation
 - J. Continue warfarin during breastfeeding
 - K. Arrange uterine artery Doppler at 20–24 weeks with serial growth scans
 - L. Long-term low-dose aspirin only after pregnancy
-

Scenario 1

A 30-year-old woman with a history of three consecutive miscarriages at 9–11 weeks gestation is found to have persistently positive lupus anticoagulant and anticardiolipin antibodies. She has no prior thrombosis.

She presents at 5 weeks of gestation following spontaneous conception. She is otherwise well. **Answer:**

Scenario 2

A 34-year-old woman with known thrombotic APS (previous unprovoked DVT) is anticoagulated with warfarin. She presents having just discovered she is 6 weeks pregnant.

Her INR is 2.6. She is concerned about fetal safety. **Answer:**

Scenario 3

A 28-year-old woman with known obstetric APS is currently 20 weeks pregnant and on aspirin and prophylactic LMWH. Her pregnancy has been uncomplicated so far.

You are reviewing her routine antenatal care plan. **Answer:**

Scenario 4

A 37-year-old woman with obstetric APS has been treated with aspirin and prophylactic LMWH in two previous pregnancies but had:

- One fetal loss at 24 weeks
- One pregnancy complicated by severe pre-eclampsia and IUGR

She is now pregnant again at 8 weeks. **Answer:**

Scenario 5

A 40-year-old woman with thrombotic APS (previous PE) is switched from warfarin to therapeutic LMWH at 6 weeks gestation.

She asks about duration of anticoagulation after delivery. **Answer:**

Scenario 6

A 32-year-old woman with obstetric APS is on aspirin and prophylactic LMWH. At 26 weeks gestation, she develops a proximal DVT.

Scenario 7

A 29-year-old woman with obstetric APS has a successful pregnancy on aspirin and LMWH. She has no history of thrombosis.

She asks about long-term management after pregnancy.

Scenario 8

A 36-year-old woman with APS has had recurrent pregnancy losses despite aspirin and LMWH. She is now under review for further management.

Scenario 9

A 33-year-old woman with thrombotic APS has delivered successfully. She is breastfeeding and requires ongoing anticoagulation.

Scenario 10

A 35-year-old woman with APS and complex previous pregnancy complications is being managed in a district hospital. The team feels uncertain about escalation beyond standard therapy.

Answers with Explanations

1 → B. Aspirin + prophylactic LMWH

- Classic obstetric APS
 - Start combination therapy from positive pregnancy test
-

2 → D. Switch from warfarin to LMWH immediately

- Warfarin is teratogenic (especially early pregnancy)
 - Immediate switch required
-

3 → K. Uterine artery Doppler + serial growth scans

- Essential monitoring:
 - Placental insufficiency
 - IUGR
 - Pre-eclampsia risk
-

4 → F. Add hydroxychloroquine

- Refractory obstetric APS despite standard therapy
- HCQ increasingly used (case-by-case)

5 → I. Continue LMWH postpartum (≥6 weeks) and reassess

- Thrombotic APS → high-risk postpartum
- Requires prolonged anticoagulation

6 → C. Therapeutic LMWH

- Thrombosis during pregnancy → escalate to treatment dose
- Continue throughout pregnancy + postpartum

7 → L. Long-term low-dose aspirin

- Obstetric APS without thrombosis
- Consider long-term aspirin after risk assessment

8 → G. Add prednisolone or IVIG

- Refractory pregnancy complications
- Only case-by-case specialist decision

9 → J. Continue warfarin during breastfeeding

- Warfarin and LMWH are safe in breastfeeding

10 → H. Refer to specialist centre

- Complex APS → requires expert multidisciplinary input

 High-Yield Exam Pearls

- **Baseline treatment (VERY COMMON QUESTION):**
 - Obstetric APS → Aspirin + prophylactic LMWH
- **Thrombotic APS in pregnancy:**
 - Switch warfarin → LMWH immediately
 - Use therapeutic LMWH
- **Monitoring (often tested):**

- Uterine artery Doppler (20–24 weeks)
- Serial fetal growth scans

- **Escalation ladder in obstetric APS:**

1. Aspirin + LMWH
2. → Hydroxychloroquine
3. → Prednisolone / IVIG
4. → Specialist centre

- **Postpartum:**

- Minimum 6 weeks anticoagulation
- Assess need for long-term therapy

EMQ 19 and 20

Theme: CAPS in APS patients

Options (Each option may be used once, more than once, or not at all)

- A. Start intravenous unfractionated heparin (UFH) infusion
 - B. Monitor anticoagulation using anti-Xa levels rather than APTT
 - C. Start high-dose corticosteroids
 - D. Start IVIG
 - E. Initiate plasma exchange
 - F. Start rituximab
 - G. Identify and treat triggering factor (e.g. infection, surgery)
 - H. Multidisciplinary management including ICU + haematology
 - I. Switch to warfarin once stable
 - J. Consider LMWH prophylaxis only
 - K. No anticoagulation due to bleeding risk
-

Scenario 1

A 42-year-old woman with known triple-positive APS is admitted with acute confusion, hypoxia, and renal impairment.

Over 48 hours she develops:

- Bilateral pulmonary emboli
- Acute kidney injury (creatinine rising rapidly)
- Livedo reticularis and digital ischaemia
- Thrombocytopenia

Blood cultures are pending. CT shows multiple small infarcts in brain and kidneys.

She is transferred to the acute medical unit with suspected multi-organ failure. **Answer:**

Scenario 2

A 36-year-old man with APS develops abdominal pain, seizures, and worsening hypoxia after a recent abdominal surgery.

Imaging reveals:

- Hepatic infarcts
- Renal cortical infarction
- Pulmonary microthrombi

He is hypotensive and requires ICU admission. **Answer:**

Scenario 3

A 50-year-old woman with known APS presents with rapidly progressive multi-organ thrombosis affecting:

- Brain (multiple small infarcts)
- Lungs (segmental PE)
- Kidneys (renal infarction)

She is started on anticoagulation but deteriorates despite initial LMWH.

The team suspects catastrophic APS. **Answer:**

Scenario 4

A 44-year-old woman with APS develops CAPS following a recent chest infection.

She is started on UFH and steroids but continues to deteriorate with worsening renal function and thrombocytopenia.

The haematology team is contacted urgently. **Answer:**

Scenario 5

A 39-year-old man with CAPS is in ICU. He is already on:

- UFH infusion
- High-dose steroids
- IVIG
- Plasma exchange

Despite this, he develops worsening neurological deficits and new myocardial infarction. **Answer:**

Scenario 6

A 47-year-old woman with APS presents with CAPS triggered by sepsis following cholecystitis.

She is unstable, requiring vasopressors, and has evidence of:

- Microangiopathic thrombosis
- Multi-organ failure

Answer:

Scenario 7

A 41-year-old woman with CAPS shows no response to triple therapy after 5 days.

She continues to have:

- New thrombotic lesions
- Worsening platelet count
- Ongoing renal failure

Answer:

Scenario 8

A 35-year-old man with known APS is diagnosed with CAPS in ICU. He is receiving UFH, steroids, IVIG, and plasma exchange.

The ICU team asks about anticoagulation monitoring. **Answer:**

Scenario 9

A 52-year-old woman with CAPS is stabilising after aggressive therapy. The team is planning definitive ongoing management strategy. **Answer:**

Scenario 10

A 45-year-old man presents with suspected CAPS, but no trigger is immediately identified. The team is unsure of next step in evaluation.

Answer:

Answers with Explanations

1 → H. Multidisciplinary management including ICU + haematology

- CAPS = **life-threatening multi-organ thrombosis**
 - ICU + haematology + organ specialists essential early
-

2 → G. Identify and treat triggering factor

- CAPS is often triggered by:
 - Surgery
 - Infection
 - Malignancy
 - Treating trigger is **core part of management**
-

3 → A. Start IV unfractionated heparin

- First-line anticoagulation in CAPS:
 - UFH preferred (rapid titration, reversible)
-

4 → B. Monitor anti-Xa levels rather than APTT

- APTT unreliable in APS (lupus anticoagulant interference)
 - Anti-Xa preferred monitoring method
-

5 → F. Consider rituximab

- Refractory CAPS despite:

- UFH
 - Steroids
 - IVIG
 - Plasma exchange
 - → escalation to rituximab
-

6 → C. High-dose corticosteroids

- Part of **triple therapy standard CAPS management**
-

7 → F. Rituximab

- Failure of full triple therapy → immunomodulatory escalation
-

8 → B. Anti-Xa monitoring

- Key exam trap:
 - APTT unreliable due to lupus anticoagulant
 - Anti-Xa is correct
-

9 → H. Multidisciplinary specialist centre approach

- Ongoing CAPS management requires:
 - Specialist APS centre
 - Haematology + ICU + rheumatology input
-

10 → G. Identify and treat triggering factor

- Even if not obvious, always actively search:
 - Infection
 - Malignancy
 - Surgery
 - Drug triggers
-

Recognition

- APS + **multi-organ thrombosis + microvascular involvement + rapid deterioration**
 - Think CAPS early — do not wait
-

First-line treatment (“TRIPLE THERAPY”)

- UFH (IV)
 - High-dose steroids
 - IVIG and/or plasma exchange
-

Monitoring trap

- **APTT unreliable → anti-Xa required**
-

Always do simultaneously

- Treat trigger (infection/surgery/etc.)
 - ICU involvement early
-

Refractory disease

- Rituximab (specialist input required)

EMQ 21

Theme: Heparin monitoring and perioperative anticoagulation in APS/LA patients undergoing cardiac surgery

Options (Each option may be used once, more than once, or not at all)

- A. Measure baseline ACT pre-operatively
 - B. Use heparin anti-Xa monitoring during CPB
 - C. Use standard ACT targets without adjustment
 - D. Use patient-adjusted ACT based on baseline ACT
 - E. Post-operative Prophylactic LMWH
 - F. Post-operative thromboprophylaxis or treatment dose anticoagulation based on prior thrombosis history
 - G. Pre-operative warfarin continuation until surgery
 - H. Use APTT monitoring for heparin during CPB
 - I. No anticoagulation required post-operatively
 - J. Delay surgery due to APS
-

Scenario 1

A 68-year-old man with known lupus anticoagulant positivity (triple-positive APS) is scheduled for coronary artery bypass grafting (CABG).

He has a history of:

- Unprovoked DVT 5 years ago
- Currently on warfarin (stopped pre-operatively)

The cardiac anaesthesia team is concerned about heparin monitoring during CPB because baseline clotting tests are abnormal. **Answer:**

Scenario 2

A 55-year-old woman with known APS and positive LA is undergoing mitral valve replacement surgery requiring CPB.

Pre-operative work-up shows:

- Prolonged baseline ACT even before heparin
- Normal platelet count
- No bleeding history

The perfusion team asks how to best monitor intra-operative anticoagulation. **Answer:**

Scenario 3

A 60-year-old man with APS and previous PE is planned for CPB surgery.

The hospital laboratory has:

- No rapid anti-Xa availability during theatre
- Standard ACT monitoring available

The team is concerned about unreliable ACT due to LA. **Answer:**

Scenario 4

A 72-year-old woman with isolated lupus anticoagulant (no prior thrombosis) is undergoing elective cardiac bypass.

Pre-operative assessment shows:

- Baseline ACT already mildly prolonged
- No bleeding phenotype
- No prior anticoagulation

The surgical team requests a pre-operative anticoagulation plan. **Answer:**

Scenario 5

A 66-year-old woman with LA and no thrombosis history undergoes CPB surgery.

She is stable post-op and has no bleeding complications.

The team asks about long-term anticoagulation strategy.

Answer:

 Answers with Explanations

1 → B. Use heparin anti-Xa monitoring during CPB

- LA interferes with clot-based tests (ACT unreliable)
 - Anti-Xa = **preferred monitoring method**
-

2 → D. Use patient-adjusted ACT based on baseline ACT

- If ACT already prolonged at baseline
 - Must **individualise ACT target using pre-heparin value**
-

3 → D. Use patient-adjusted ACT based on baseline ACT

- No anti-Xa available → ACT still usable but must be **baseline-adjusted**
-

4 → A. Measure baseline ACT pre-operatively

- Essential first step:
 - Establish **reference ACT before heparin exposure**
 - Required for planning CPB anticoagulation
-

5 → E. Post-operative Prophylaxis LMWH

- LA without thrombosis history → prophylaxis only
-

 FRCPath HIGH-YIELD TAKE-HOME POINTS

 Why this is tricky in exams

- LA causes false prolongation of ACT/APTT
- Can lead to:

- under-heparinisation → thrombosis
 - over-heparinisation → bleeding
-

BEST MONITORING STRATEGY

1. Anti-Xa (preferred)
 2. If not available → baseline-adjusted ACT
-

MUST-DO PRE-OP STEP

- Always measure baseline ACT
-

POST-CPB PRINCIPLE

- Anticoagulation depends on:
 - prior thrombosis history
 - APS risk profile

EMQ 22 and 23

Theme: Primary Prevention & Risk Stratification in aPL Carriers

Options

- A. No pharmacological thromboprophylaxis; lifestyle advice only
 - B. Start low-dose aspirin (LDA)
 - C. Start hydroxychloroquine (HCQ)
 - D. LDA + HCQ
 - E. Thromboprophylaxis with LMWH in high-risk situation only
 - F. Long-term anticoagulation with warfarin
 - G. Avoid oestrogen-containing therapy; offer alternative contraception
 - H. Start statin therapy
 - I. Antenatal LMWH prophylaxis ± postnatal continuation
 - J. No intervention required at all
-

Scenarios

1.

A 32-year-old woman is incidentally found to have persistently positive lupus anticoagulant, anticardiolipin, and anti-β₂ glycoprotein I antibodies on repeat testing 12 weeks apart. She has no history of thrombosis, miscarriage, or autoimmune disease. She is a non-smoker with normal BMI and no cardiovascular risk factors.

2.

A 45-year-old man with persistently positive lupus anticoagulant (single positive) is asymptomatic but has hypertension, hyperlipidaemia, and is an active smoker. No prior thrombosis.

3.

A 29-year-old woman with triple-positive aPL is being evaluated pre-operatively before elective laparoscopic cholecystectomy. No previous thrombosis or obstetric history.

4.

A 38-year-old woman with persistently positive triple aPL is otherwise well but has a strong family history of autoimmune disease. She is keen to minimise her future thrombosis risk despite being asymptomatic.

5.

A 34-year-old asymptomatic woman with persistent aPL positivity (double positive) is planning pregnancy. No prior thrombosis or pregnancy complications.

6.

A 41-year-old woman with persistent aPL positivity asks about starting combined oral contraceptive pills for menstrual regulation. She has no thrombosis history.

7.

A 50-year-old man with persistent aPL positivity (single positive) is admitted for prolonged immobilisation following a spinal injury. No prior thrombosis.

8.

A 36-year-old woman with persistent aPL positivity is found to have elevated LDL cholesterol during cardiovascular risk assessment. She has no prior thrombosis.

Answers with Brief Explanations

1. → A

No routine LDA or HCQ in asymptomatic aPL carriers without additional risk factors.

2. → A

Still **no routine antiplatelet/HCQ**, but aggressive **risk factor modification** is key (hypertension, smoking, lipids).

3. → E

LMWH thromboprophylaxis in high-risk situations (surgery).

4. → C

Consider HCQ case-by-case in high-risk (triple-positive) individuals even if asymptomatic.

5. → I

Antenatal ± postnatal LMWH prophylaxis based on risk assessment.

6. → G

Avoid oestrogen-containing contraception due to thrombosis risk.

7. → E

Temporary LMWH prophylaxis during **immobility**.

8. → H

Treat cardiovascular risk factors → statins indicated.

EMQ 24 and 25

EMQ: Acute Transfusion Reactions – Complex Scenarios

Theme: Recognition and Management of Transfusion Reactions

Options

- A. Continue transfusion with paracetamol and close observation
 - B. Slow transfusion and give antihistamine
 - C. Stop transfusion and administer IM adrenaline immediately
 - D. Stop transfusion and send unit for urgent bacterial culture
 - E. Stop transfusion and perform full haemolytic reaction work-up
 - F. Continue transfusion as hypotension likely due to haemorrhage
 - G. Stop transfusion and arrange urgent chest X-ray
 - H. Stop transfusion, return unit, and urgently inform blood service
 - I. No further investigation required
 - J. Stop transfusion and switch to an alternative blood component
-

Questions

Q1

A 68-year-old man with myelodysplastic syndrome is receiving red cells for symptomatic anaemia (Hb 72 g/L).

After 20 minutes of transfusion he develops:

- Temperature rise from 36.8°C to 38.4°C
- Generalised pruritus with an erythematous rash

- Haemodynamically stable, no dyspnoea, no pain

The transfusion is temporarily stopped. Symptoms partially improve with antihistamine.

Q2

A 52-year-old woman with chemotherapy-induced thrombocytopenia is receiving platelets.

Within minutes she develops:

- Generalised urticaria
 - Facial flushing
 - No fever, no hypotension, no respiratory compromise
-

Q3

A 74-year-old man with urosepsis is transfused red cells for Hb 68 g/L. After 15 minutes:

- Temperature rises from 37.5°C to 39.6°C
- Severe rigors
- BP drops to 85/50 mmHg
- No rash

The unit appears slightly discoloured on inspection.

Q4

A 30-year-old trauma patient is undergoing massive transfusion following a road traffic accident.

During transfusion:

- BP drops from 110/70 to 75/45 mmHg
 - Ongoing heavy bleeding
 - No fever, rash, or respiratory symptoms
-

Q5

A 60-year-old man receiving red cells develops:

- Fever 39.3°C

- Severe lower back pain
 - Dark urine noted in catheter bag
 - Tachycardia
-

Q6

A 25-year-old woman with immune thrombocytopenia (platelets $18 \times 10^9/L$) is receiving platelets.

She suddenly develops:

- Wheeze
 - Stridor
 - Hypotension (BP 70/40 mmHg)
 - Periorbital swelling
-

Q7

A 67-year-old patient develops during transfusion:

- Temperature rise from 36.5°C to 38.1°C
 - No other symptoms
 - Observations otherwise normal
-

Q8

A 72-year-old patient with AML develops during platelet transfusion:

- Acute dyspnoea
 - Oxygen saturation 86% on air
 - No rash or urticaria
 - Bilateral crackles on auscultation
-

Q9

A 50-year-old patient develops:

- Isolated urticaria during transfusion
- Symptoms resolve fully after antihistamine
- No recurrence after restarting transfusion

Q10

A 63-year-old patient develops during transfusion:

- Fever 39°C (baseline 36.7°C)
- Rigors, nausea, vomiting
- Symptoms persist despite stopping transfusion

No hypotension initially, but clinical concern remains high.

Answers with Detailed Explanations

Q1 → B (Slow transfusion + antihistamine)

This is a **mixed mild febrile + allergic reaction**:

- Fever <39°C
- Rash/pruritus
- No systemic compromise

👉 Key principle:

Mild reactions **do not mandate stopping transfusion permanently**. Once symptoms improve:

- Restart at slower rate
 - Treat symptomatically
-

Q2 → B (Antihistamine + continue/slow transfusion)

Classic **isolated mild allergic reaction**:

- Urticaria only
- No systemic features

👉 Important nuance:

- No need for extensive investigation
 - Very common with platelet transfusions
-

Q3 → D (Stop + bacterial culture)

This is **severe febrile reaction with shock** → **suspect bacterial contamination**:

- Rapid onset
- High fever ($>39^{\circ}\text{C}$)
- Hypotension
- Rigors
- Abnormal unit appearance

👉 Why not haemolysis first?

- No haemoglobinuria/back pain
- Platelets/red cells both can transmit bacteria

👉 Action:

- Send unit + patient samples for culture urgently
-

Q4 → F (Continue transfusion – haemorrhage)

Critical exam trap ⚠️

👉 Hypotension during transfusion ≠ always reaction

Here:

- Clear ongoing bleeding
- No features of transfusion reaction

👉 Stopping transfusion could be fatal

Clinical judgement overrides protocol

Q5 → E (Haemolytic reaction work-up)

Classic **acute haemolytic transfusion reaction**:

- Fever
- Back pain
- Haemoglobinuria

👉 Mechanism:

- ABO incompatibility → intravascular haemolysis

👉 Requires:

- DAT
 - Repeat compatibility
 - LDH, bilirubin, haptoglobin
-

Q6 → C (IM adrenaline immediately)

This is **anaphylaxis**:

- Airway compromise (stridor)
- Hypotension
- Angioedema

👉 Key high-yield rule:

IM adrenaline is given EVEN in thrombocytopenia

👉 Do NOT delay for:

- IV access
 - Platelet count concerns
-

Q7 → A (Paracetamol + continue)

Mild febrile non-haemolytic reaction:

- Temp rise $<2^{\circ}\text{C}$ and $<39^{\circ}\text{C}$
- No other features

👉 Management:

- Symptomatic treatment
 - Continue transfusion
-

Q8 → G (Chest X-ray)

Respiratory reaction → think:

- TRALI
- TACO

👉 Key exam principle:

If respiratory symptoms WITHOUT allergy → MUST do CXR

👉 Differentiation (advanced):

- TRALI → non-cardiogenic
 - TACO → fluid overload
-

Q9 → I (No further investigation)

Resolved **mild allergic reaction**

👉 Important:

- No need for:
 - Repeat compatibility
 - Antibody testing

👉 Avoid over-investigation

Q10 → H (Return unit + inform blood service urgently)

Persistent severe febrile reaction:

- $\geq 39^{\circ}\text{C}$
- Systemic symptoms
- Not resolving

👉 Strong suspicion:

- Bacterial contamination
- Severe transfusion reaction

👉 Key step:

- **Notify blood service immediately**
→ Prevent harm to other recipients
-

High-Yield Exam Insights

- **Temperature $\geq 39^{\circ}\text{C}$ OR rise $\geq 2^{\circ}\text{C}$ + systemic features = RED FLAG**
- **Back pain + dark urine = haemolysis until proven otherwise**
- **Hypotension in bleeding $\neq$ transfusion reaction**
- **Anaphylaxis = IM adrenaline ALWAYS**
- **Respiratory symptoms → CXR mandatory**
- **Do not over-investigate mild allergic reactions**

EMQ 26 AND 27

Theme: Prevention and management of recurrent febrile and allergic transfusion reactions

Options

- A. Trial of premedication with oral paracetamol before transfusion
 - B. Trial of NSAIDs prior to transfusion (after risk assessment)
 - C. No prophylaxis; investigate alternative causes (e.g. drugs/latex)
 - D. Washed red cells/platelets for future transfusions
 - E. Routine antihistamine prophylaxis
 - F. Switch from apheresis platelets to pooled platelets (PAS)
 - G. Solvent-detergent-treated plasma
 - H. Measure serum IgA level
 - I. Transfuse standard components with enhanced monitoring
 - J. Discuss with allergy/immunology specialist
 - K. Transfuse urgently with standard components under close monitoring
 - L. Routine corticosteroid prophylaxis
-

Questions

Q1

A 70-year-old man with myelodysplastic syndrome requires regular red cell transfusions.

He has had **recurrent febrile reactions**:

- Temperature rises to ~38.5°C during transfusion
- Associated with chills but no hypotension or haemolysis
- Reactions persist despite slowing transfusion

He is otherwise stable and requires ongoing transfusion support.

Q2

A 62-year-old woman receiving platelet transfusions for AML develops:

- Recurrent rigors and chills
- Temperatures up to 38.8°C
- No allergic features

You are considering premedication strategies.

Q3

A 55-year-old patient continues to have:

- Recurrent febrile reactions (temp $\geq 39^{\circ}\text{C}$)
- Despite paracetamol premedication

No evidence of haemolysis or infection has been found.

Q4

A 40-year-old woman receiving platelet transfusions develops:

- Recurrent urticaria and itching
- No systemic symptoms
- Symptoms occur intermittently

She is also receiving multiple antibiotics.

Q5

A 67-year-old man with lymphoma develops:

- Recurrent moderate allergic reactions during **apheresis platelet transfusions**
- Urticaria, flushing, mild wheeze

- No hypotension
-

Q6

A 58-year-old patient undergoing plasma exchange develops:

- Recurrent allergic reactions to FFP
 - Urticaria and pruritus each time
-

Q7

A 45-year-old patient develops:

- Severe anaphylaxis during transfusion
- Hypotension, airway compromise

No clear cause identified (multiple drugs given peri-transfusion).

Q8

A 50-year-old patient has:

- Recurrent severe febrile reactions occurring **within 10–15 minutes** of starting transfusion
 - No haemolysis identified
-

Q9

A 60-year-old patient with **confirmed IgA deficiency (<0.07 g/L)** has:

- Previous anaphylactic reaction to transfusion
 - Now requires elective transfusion
-

Q10

A 72-year-old patient with known IgA deficiency:

- No prior transfusion reactions
 - Requires red cell transfusion
-

Q11

A 68-year-old patient with GI bleeding requires **urgent transfusion**.
He has a history of:

- Severe allergic transfusion reactions
 - Washed components are not immediately available
-
-

Answers with Detailed Explanations

Q1 → A (Paracetamol premedication)

This is **recurrent mild-moderate febrile non-haemolytic transfusion reaction (FNHTR)**.

👉 Key points:

- Temperature $<39^{\circ}\text{C}$
- No haemolysis/systemic instability
- Recurrent pattern

👉 First-line prevention:

- **Paracetamol 1 hour before transfusion**

👉 Why not washed components yet?

- Reserved for **failure of simple measures**
-

Q2 → B (NSAIDs if rigors predominant)

Here, **rigors/chills dominate** rather than just fever.

👉 Guideline nuance:

- NSAIDs may help **rigor-predominant reactions**
- Must assess:
 - Renal function
 - Bleeding risk

👉 This is a **subtle exam discriminator**

Q3 → D (Washed components)

Now we have:

- Persistent **moderate/severe febrile reactions**
- Failure of premedication

👉 Next escalation:

- **Washed red cells/platelets**

👉 Mechanism:

- Removes cytokines and plasma proteins
-

Q4 → C (No prophylaxis; exclude other causes)

Recurrent **mild allergic reactions**

👉 Critical exam point:

- **NO evidence for routine antihistamines or steroids**

👉 Must consider:

- Antibiotics
- Latex
- Other allergens

👉 Avoid unnecessary transfusion modifications

Q5 → F (Switch to pooled platelets)

Recurrent allergic reactions to **apheresis platelets**

👉 Strategy:

- Switch to **pooled platelets in PAS**

👉 Why?

- Lower plasma exposure
 - Reduced allergen load
-

Q6 → G (Solvent-detergent plasma)

Reactions specifically to **FFP**

👉 Best option:

- **SD plasma**

👉 Why?

- Standardised product
 - Reduced allergenic variability
-

Q7 → J (Refer to allergy/immunology)

Anaphylaxis with **uncertain cause**

👉 Important:

- Could be:
 - Blood component
 - Drug
 - Latex

👉 Requires specialist input:

- Identify causative agent
 - Guide future transfusions
-

Q8 → H (Measure IgA level)

Key red flag 🚩 :

- Severe reactions **within first 15 minutes**
- Recurrent

👉 Strong suspicion:

- **IgA deficiency with anti-IgA antibodies**

👉 Mandatory test:

- Serum IgA
-

Q9 → D (Washed components)

Confirmed IgA deficiency + prior reaction

👉 Management:

- **Washed components for elective transfusion**

👉 BUT:

- Do not delay life-saving transfusion (important nuance)
-

Q10 → I (Standard transfusion with monitoring)

IgA deficiency BUT:

- No prior reactions

👉 Management:

- **Standard components acceptable**
- Increase monitoring

👉 Avoid over-restriction

Q11 → K (Urgent transfusion under monitoring)

Life-threatening bleed + history of reactions

👉 Critical exam principle ⚠️:

Do NOT delay transfusion for ideal products

👉 Action:

- Transfuse standard components
 - In monitored setting
 - Resuscitation ready
-

High-Yield Exam Pearls

🔥 Prevention hierarchy (VERY examinable)

1. Mild febrile → Paracetamol
 2. Rigors → Consider NSAIDs
 3. Persistent/severe → Washed components
-

🔥 Allergic reactions

- Mild → **No routine prophylaxis**
- Moderate/severe →

- Washed products
 - Modify component (PAS, SD plasma)
-

IgA deficiency clues

- Anaphylaxis
 - Very early reactions (<15 min)
 - Recurrent severe reactions
-

Absolute rules

- **No routine steroids prophylaxis**
- **Do not delay life-saving transfusion**
- **Report all except mild reactions (MHRA/SHOT)**

EMQ 28

Theme: Diagnosis and Management of Congenital Dyserythropoietic Anaemia

Options

- A. CDA type I (CDAN1 mutation)
 - B. CDA type II (CDAN2 mutation)
 - C. CDA type III
 - D. Iron deficiency anaemia
 - E. β -thalassaemia major
 - F. Myelodysplastic syndrome (erythroid subtype)
 - G. Paroxysmal nocturnal haemoglobinuria
 - H. Hereditary spherocytosis
 - I. Aplastic anaemia
 - J. CDA type II with indication for splenectomy
-

Question 1

A male neonate born at 36 weeks is noted to have pallor and mild hepatosplenomegaly. Blood tests show Hb 85 g/L with macrocytosis. Over the first few months, he develops progressive anaemia requiring intermittent transfusions. Ferritin levels become elevated despite minimal transfusion exposure. Bone marrow examination shows erythroid hyperplasia with megaloblastoid changes, internuclear chromatin bridges, and binucleated erythroblasts.

What is the most likely diagnosis?

Question 2

A 24-year-old woman of Mediterranean origin presents with chronic mild anaemia and intermittent jaundice since adolescence. She reports a history of gallstones requiring cholecystectomy at age 19. Blood tests show Hb 98 g/L, mild reticulocytosis, and indirect hyperbilirubinaemia. Ferritin is mildly elevated. Bone marrow shows erythroid hyperplasia with binucleated erythroblasts.

Which is the most likely diagnosis?

Question 3

A 35-year-old man is referred for evaluation of unexplained anaemia. He has no iron overload and no history of transfusion. His father had a similar condition. Bone marrow demonstrates giant multinucleated erythroblasts with up to 10 nuclei per cell. There is no hepatosplenomegaly.

What is the most likely diagnosis?

Question 4

A 17-year-old male presents with fatigue and abdominal fullness. He has a long-standing history of mild anaemia. Examination reveals severe splenomegaly. Labs show Hb 92 g/L, raised LDH, and indirect bilirubin. Ferritin is elevated. Bone marrow shows erythroid hyperplasia with binucleation and nuclear abnormalities. Genetic testing confirms a mutation on chromosome 20.

What is the most appropriate management option?

Question 5

A 5-year-old child presents with transfusion-dependent anaemia from early infancy. Examination reveals hepatosplenomegaly and growth delay. Ferritin is markedly elevated. Bone marrow shows erythroid hyperplasia with nuclear bridging. There is concern about progressive iron overload despite chelation.

Which condition best explains this presentation?

Question 6

A 28-year-old woman is referred with suspected haemolytic anaemia. She has mild anaemia and splenomegaly. Blood film shows anisopoikilocytosis but no spherocytes. Bone marrow demonstrates erythroid hyperplasia with binucleated erythroblasts. She reports recurrent jaundice and had gallstones removed previously. No significant family history.

Which diagnosis is most likely?

Question 7

A 40-year-old patient presents with anaemia and bone marrow erythroid dysplasia. There are multinuclear erythroid precursors. Cytogenetics reveal multiple abnormalities. There is no family history, and the patient has progressive cytopenias affecting other lineages.

What is the most likely diagnosis?

Answers and Explanations

Q1 → A. CDA type I

- Neonatal onset
 - Macrocytosis + iron overload early
 - Classic **internuclear chromatin bridges**
-

Q2 → B. CDA type II

- Most common CDA
 - Mediterranean association
 - **Binucleated erythroblasts + pseudo-Gaucher cells**
 - Gallstones common
-

Q3 → C. CDA type III

- Rare, autosomal dominant
 - **Giant multinucleated erythroblasts**
 - No iron overload
-

Q4 → J. CDA type II with indication for splenectomy

- CDA II with symptomatic splenomegaly
 - Splenectomy is a key management option in selected cases
-

Q5 → A. CDA type I

- Early severe disease
 - Iron overload disproportionate to transfusion
 - Growth delay + hepatosplenomegaly
-

Q6 → B. CDA type II

- Classic adult presentation
 - Mild haemolysis + gallstones
 - Binucleation on marrow
-

Q7 → F. Myelodysplastic syndrome (erythroid subtype)

- Multilineage cytopenia
- Clonal cytogenetic abnormalities
- Distinguishes from congenital causes

EMQ 29 and 30

Theme: Iron overload

Options:

- A. Calculate annual transfusional iron loading
 - B. Ferritin monitoring every 1–3 months
 - C. Baseline cardiac and liver MRI assessment
 - D. MRI with sedation
 - E. Routine interval MRI surveillance
 - F. Annual LVEF assessment (echo or MRI)
 - G. Liver MRI due to high liver iron burden
 - H. Liver MRI triggered by rising ferritin trend
 - I. Liver MRI (NTDT ferritin threshold >800 µg/L)
 - J. Baseline MRI (NTRIA ferritin >1000 µg/L)
 - K. Consider MRI (NTRIA ferritin >500 µg/L with clinical suspicion)
 - L. 6-monthly ultrasound for HCC surveillance
 - M. Liver fibrosis assessment (>40 years)
 - N. Early repeat MRI due to poor chelation compliance
 - O. No immediate MRI required
-

Questions:

Q1.

A 23-year-old man with transfusion-dependent β -thalassaemia major has been receiving 2–3 units of red cells every 3 weeks since childhood. He has recently transferred care from overseas and has no documented history of prior iron assessment. His ferritin is 2800 $\mu\text{g/L}$. He is asymptomatic, with normal ECG and echocardiography.

Answer:

Q2.

A 7-year-old child with transfusion-dependent anaemia has rising ferritin levels (900 $\rightarrow$ 1600 $\mu\text{g/L}$ over 6 months). Multiple attempts at MRI have failed due to distress and inability to remain still. There is concern regarding significant iron burden.

Answer:

Q3.

A 29-year-old woman with sickle cell disease is on regular top-up transfusions for stroke prevention. MRI liver iron concentration is reported as 17 mg/g dry weight. She has no cardiac symptoms and normal echocardiography.

Answer:

Q4.

A 31-year-old man with β -thalassaemia major on regular transfusions is well controlled on chelation. He has had prior MRI assessments demonstrating moderate hepatic iron and no cardiac involvement. You are planning ongoing surveillance.

Answer:

Q5.

A 26-year-old patient with transfusion-dependent anaemia has stable ferritin levels around 1100 $\mu\text{g/L}$ for the past year. He has had prior MRI showing mild iron overload. You are reviewing routine laboratory monitoring strategy.

Answer:

Q6.

A 34-year-old patient with sickle cell disease is managed with automated red cell exchange. Over 18 months, ferritin has gradually increased from 500 µg/L to 1200 µg/L. There is no prior MRI evidence of iron overload.

Answer:

Q7.

A 27-year-old woman with non-transfusion-dependent thalassaemia presents for baseline assessment. She has never received regular transfusions. Ferritin is 920 µg/L. She is asymptomatic.

Answer:

Q8.

A 36-year-old man with congenital sideroblastic anaemia (non-transfusion-related iron overload) has ferritin of 1150 µg/L. He has no prior iron assessment and minimal transfusion history.

Answer:

Q9.

A 44-year-old transfusion-dependent patient with a history of severe hepatic iron overload and previously treated hepatitis C infection is currently stable on chelation therapy. Ferritin is 700 µg/L.

Answer:

Q10.

A 15-year-old patient with transfusion-dependent thalassaemia has demonstrated poor adherence to iron chelation therapy over the past year. Ferritin has increased from 1500 µg/L to 3000 µg/L. His last MRI was 12 months ago.

Answer:

Answers:

Q1.

Answer: C. Baseline cardiac and liver MRI assessment

→ Key trigger: *never previously assessed despite long transfusion history*

Q2.

Answer: D. MRI with sedation

→ Young child + clinical suspicion of significant iron overload

Q3.

Answer: G. Cardiac MRI due to high liver iron burden

→ SCD-specific: cardiac MRI if LIC >15 mg/g

Q4.

Answer: E. Routine interval MRI surveillance

→ Regular longitudinal monitoring

Q5.

Answer: B. Ferritin monitoring every 1–3 months

→ Trend monitoring remains essential

Q6.

Answer: H. Liver MRI triggered by rising ferritin trend

→ Exchange patients → MRI guided by ferritin trend

Q7.

Answer: I. Liver MRI (NTDT ferritin threshold >800 µg/L)

→ NTDT threshold exceeded

Q8.

Answer: J. Baseline MRI (NTRIA ferritin >1000 µg/L)

→ NTRIA threshold

Q9.

Answer: L. 6-monthly ultrasound for HCC surveillance

→ Prior liver injury + iron overload

Q10.

Answer: N. Early repeat MRI due to poor chelation compliance

→ Compliance drives earlier reassessment

EMQ 31 and 32

Theme: Iron Overload

Options

- A. Start subcutaneous desferrioxamine (DFO)
 - B. Start deferasirox (DFX)
 - C. Start deferiprone (DFP)
 - D. Add deferiprone to desferrioxamine
 - E. Combination: deferasirox + desferrioxamine
 - F. Combination: deferiprone + deferasirox
 - G. Continue current therapy and monitor
 - H. Emergency IV continuous desferrioxamine infusion
 - I. Venesection
 - J. Reduce dose / avoid deferasirox due to renal impairment
 - K. Start iron chelation (indication met)
 - L. Intensify therapy due to cardiac iron overload
-

Scenarios

A 7-year-old boy with transfusion-dependent β -thalassaemia major has been receiving regular 3–4 weekly transfusions since infancy. He has now received approximately 14 transfusions. His serum ferritin has risen progressively over the past 6 months and is now 1150 $\mu\text{g/L}$ on two consecutive measurements. MRI liver iron concentration (LIC) is 4 mg/g dry weight. His parents express concern regarding adherence to prolonged subcutaneous infusions and strongly prefer an oral regimen. **Answer:**

2

A 4-year-old girl with β -thalassaemia major is reviewed in clinic. She has received regular transfusions since diagnosis at 9 months of age. Her ferritin is now 1400 $\mu\text{g/L}$. The team discusses starting subcutaneous desferrioxamine, but the family lives far from the hospital, has poor social support, and there are concerns about adherence to infusion-based therapy. No organ dysfunction is present. **Answer:**

3

A 26-year-old woman with non-transfusion-dependent thalassaemia (NTDT) is reviewed for fatigue. She has never received regular transfusions. Her ferritin is 870 $\mu\text{g/L}$, and MRI shows LIC of 6.2 mg/g dry weight. Cardiac T2* is normal. Liver function tests are within normal limits. **Answer:**

4

A 32-year-old man with sickle cell disease is on a chronic top-up transfusion programme for secondary stroke prevention. He has been transfused regularly for 5 years. His ferritin is 1900 $\mu\text{g/L}$, and LIC is 8 mg/g dry weight. Cardiac T2* is 28 ms. Renal and liver function are normal. **Answer:**

5

A 21-year-old woman with transfusion-dependent thalassaemia has been on deferasirox for 18 months at an adequate dose with excellent compliance. Despite this, her ferritin remains persistently elevated at 2600 $\mu\text{g/L}$, and MRI shows LIC of 9.5 mg/g dry weight. Cardiac T2* remains normal. There is no evidence of drug toxicity. **Answer:**

6

A 23-year-old man with β -thalassaemia major has been on deferasirox for several years with good adherence. His recent MRI shows cardiac T2* of 16

ms (previously 24 ms), while LVEF remains within normal limits. LIC is 7 mg/g dry weight. He is asymptomatic. **Answer:**

7

A 29-year-old woman with transfusion-dependent thalassaemia presents with progressive dyspnoea, orthopnoea, and reduced exercise tolerance over several weeks. Echocardiography shows LVEF of 48%. Cardiac MRI reveals T2* of 6 ms. She has been inconsistently compliant with oral chelation therapy in the past. **Answer:**

8

A 36-year-old man with TDT has been on deferasirox for iron overload. Over recent months, his creatinine has progressively increased, and his creatinine clearance is now 52 mL/min. Ferritin remains elevated at 1800 µg/L. There is no other identifiable cause for renal impairment. **Answer:**

9

A 42-year-old man with congenital sideroblastic anaemia (non-transfusion-dependent) is reviewed. His haemoglobin is stable at 138 g/L. Ferritin is 620 µg/L, and LIC is 5.5 mg/g dry weight. He has no history of transfusions and no organ dysfunction. **Answer:**

10

A 16-year-old adolescent with transfusion-dependent thalassaemia is on deferiprone monotherapy at 75 mg/kg/day in three divided doses. He reports good compliance. After 9 months of therapy, his ferritin remains elevated at 2100 µg/L with minimal downward trend. Neutrophil counts have remained stable. **Answer:**

Answers with Explanations

1 → B (Start deferasirox)

- TDT + >10–12 transfusions + ferritin >1000 → start chelation
 - Age >6 + preference for oral → **DFX appropriate first-line**
-

2 → B (Start deferasirox)

- <6 years → DFO standard
 - BUT adherence concerns → **early oral DFX justified**
👉 Exam trick: *real-world compliance overrides textbook*
-

3 → K (Start iron chelation)

- NTDT: ferritin >800 OR LIC >5 → both met
 - Question focuses on **indication threshold**
-

4 → K (Start iron chelation)

- SCD on **top-up transfusion** → **treat as TDT**
 - Ferritin high + LIC elevated → start chelation
-

5 → E (Combination: deferasirox + desferrioxamine)

- Persistent high LIC despite compliance → **monotherapy failure**
 - LIC >7 → intensification required
 - Add DFO to DFX
-

6 → L (Intensify therapy due to cardiac iron overload)

- T2* <20 ms = myocardial iron
 - Even if EF normal → **must intensify early**
👉 Prevent progression to heart failure
-

7 → H (Emergency IV continuous desferrioxamine infusion)

- LVEF ↓ + T2* <8 ms = **life-threatening cardiac iron**
 - Immediate IV DFO infusion
 - Add DFP later, but emergency step is DFO
-

8 → J (Reduce dose / avoid deferasirox)

- CrCl <60 mL/min → **DFX contraindicated**

- Requires dose reduction or discontinuation
-

9 → I (Venesection)

- NTRIA + adequate Hb + ferritin >500
 - Not transfusion dependent → **venesection preferred**
-

10 → C (Escalate deferiprone dose)

- DFP can be increased up to 100 mg/kg/day
 - Persistent ferritin → escalate before switching
-

Ultra-High Yield Exam Traps

- **Cardiac iron ≠ wait for symptoms** → act at $T2^* < 20$
- $T2 < 8 \text{ ms}$ = *emergency**, even if stable clinically
- **LIC > 7 mg/g** → intensify therapy
- **DFX contraindicated if CrCl < 60**
- **Best for cardiac iron:** deferiprone
- **Venesection only if Hb adequate + non-transfusion dependent**
- **Combination therapy = not first-line BUT essential in failure**

EMQ 33 and 34

Theme: Management of Mature T-cell Leukaemia's

Options (Each option may be used once, more than once, or not at all)

- A. Watch-and-wait (observation only)
 - B. Intravenous alemtuzumab
 - C. Alemtuzumab + purine analogue
 - D. Alemtuzumab re-treatment
 - E. Allogeneic HSCT
 - F. Autologous HSCT
 - G. Methotrexate (low-dose weekly)
 - H. Ciclosporin
 - I. Cyclophosphamide
 - J. Supportive therapy (G-CSF ± erythropoietin ± short steroids)
 - K. Alemtuzumab (for refractory LGLL)
 - L. Purine analogue (e.g. pentostatin) for refractory disease
-

Scenarios

1.

A 68-year-old man is incidentally found to have lymphocytosis (WBC $45 \times 10^9/L$) during routine testing. Flow cytometry confirms T-PLL. He is asymptomatic with no organomegaly, cytopenias, or B symptoms.

What is the most appropriate management?

2.

A 61-year-old woman presents with rapidly rising lymphocytosis, splenomegaly, and B symptoms. Diagnosis of T-PLL is confirmed. She is otherwise fit with no major comorbidities.

Best initial therapy?

3.

A 63-year-old man with T-PLL receives IV alemtuzumab. After 6 weeks, there is only minimal reduction in lymphocyte count, and bulky abdominal lymphadenopathy persists.

Next best step?

4.

A 55-year-old patient with T-PLL achieves complete remission after alemtuzumab. He is fit with a matched sibling donor available.

Best consolidation strategy?

5.

A 70-year-old patient with T-PLL achieves remission with alemtuzumab but is deemed high-risk for transplant-related mortality due to cardiac comorbidities.

Best consolidation option?

6.

A 66-year-old patient previously treated with alemtuzumab for T-PLL relapses after 9 months. Flow cytometry confirms persistent CD52 expression.

Best next management?

7.

A 72-year-old woman with LGLL is found incidentally to have neutrophils $1.2 \times 10^9/\text{L}$, Hb 120 g/L, platelets normal. She has no infections or symptoms.

Best management?

8.

A 69-year-old man with LGLL presents with severe neutropenia ($0.3 \times 10^9/\text{L}$) and recurrent bacterial infections. He also has longstanding rheumatoid arthritis.

Best first-line therapy?

9.

A 64-year-old patient with LGLL has transfusion-dependent anaemia and neutropenia. He is started on methotrexate but shows no response after 5 months.

Best next step?

10.

A 67-year-old patient with LGLL has failed methotrexate, ciclosporin, and cyclophosphamide. He remains transfusion-dependent with severe neutropenia.

Best next management?

Answers

1. **A** – Watch-and-wait
2. **B** – Intravenous alemtuzumab
3. **C** – Alemtuzumab + purine analogue
4. **E** – Allogeneic HSCT
5. **F** – Autologous HSCT
6. **D** – Alemtuzumab re-treatment
7. **A** – Watch-and-wait
8. **G** – Methotrexate (*RA association clue*)

9. **I** – Cyclophosphamide (*switch immunosuppressant*)
10. **K** – Alemtuzumab (refractory LGLL)

Answers with Explanations

1. → **A. Watch-and-wait**

This is **classic asymptomatic T-PLL**.

Despite being an aggressive disease biologically, treatment is **not started until symptomatic or progressive disease**.

Key trigger for treatment:

- B symptoms
- Organomegaly
- Rapid lymphocyte doubling
- Cytopenias

Exam trap: Don't treat based on diagnosis alone.

2. → **B. Intravenous alemtuzumab**

This patient has **symptomatic, active T-PLL**, so requires treatment.

Why alemtuzumab?

- Anti-CD52 monoclonal antibody
- **Gold-standard first-line therapy**
- High response rates compared to chemotherapy

Exam trap: CHOP-like regimens are ineffective → don't choose them.

3. → **C. Alemtuzumab + purine analogue**

This is **suboptimal response + bulky disease**.

Guideline logic:

- Poor/slow response → intensify therapy
- Add **purine analogue (e.g., pentostatin)**

Why?

- Synergistic cytotoxicity

- Overcomes resistance

Exam trigger phrase:

“Minimal response” / “bulky disease persists” → escalate

4. → E. Allogeneic HSCT

This is **first complete remission in a fit patient**.

Key concept:

- T-PLL is **not curable with alemtuzumab alone**
- **Allo-HSCT = only potentially curative option**

Why in CR1?

- Best outcomes when disease burden is lowest

Exam trap: Don't delay transplant until relapse.

5. → F. Autologous HSCT

Patient is **not fit for allo-HSCT**.

Logic:

- Auto-HSCT is **not curative**, but:
 - May prolong remission
 - Lower treatment-related mortality

Exam hierarchy:

- Allo-HSCT (preferred)
 - Auto-HSCT (if allo not feasible)
-

6. → D. Alemtuzumab re-treatment

Relapse after **>6 months + CD52 still expressed**

Why re-use alemtuzumab?

- Prior good response
- Target (CD52) still present

Key rule:

- **>6 months remission → reuse acceptable**

- **<6 months → likely resistance → avoid**
-

7. → A. Watch-and-wait

This is **asymptomatic LGLL**.

Even with mild neutropenia:

- No infections
- No transfusion requirement

→ **No treatment needed**

Exam trap: Don't treat numbers—treat symptoms.

8. → G. Methotrexate

This patient has:

- **Symptomatic neutropenia (infections)**
- **Rheumatoid arthritis**

Why methotrexate?

- Treats both **LGLL and RA**
- First-line immunosuppressive option

Exam pearl:

RA association → **methotrexate preferred**

9. → I. Cyclophosphamide

Failure of first-line methotrexate after **adequate trial (≥4 months)**.

Next step:

- Switch to **alternative immunosuppressive agent**

Options include:

- Cyclophosphamide
- Cyclosporin

Why cyclophosphamide here?

- Particularly effective in **cytopenias (e.g., PRCA)**

Exam trap: Don't escalate too early (<4 months).

10. → K. Alemtuzumab (refractory LGLL)

This is **triple failure of first-line immunosuppression**.

Next-line options:

- Alemtuzumab
- Purine analogues

Why alemtuzumab?

- Stronger immunosuppressive effect
- Used in **refractory disease**

EMQ 35 and 36

Theme: Complex Management of Peripheral T-cell Lymphomas

Options (Each option may be used once, more than once, or not at all)

- A. AZT + interferon- α
 - B. High-dose AZT + interferon- α
 - C. CHOP-like chemotherapy
 - D. CHOP-like chemotherapy + AZT/IFN- α
 - E. CHP + brentuximab vedotin (CHP-BV)
 - F. Allogeneic HSCT
 - G. Autologous HSCT
 - H. Brentuximab vedotin monotherapy
 - I. Multiagent salvage chemotherapy (non-cross-resistant)
 - J. CNS prophylaxis
 - K. Treat Strongyloides infection
 - L. AZT/IFN- α maintenance
 - M. Add integrase inhibitor (e.g. raltegravir)
 - N. Supportive care + antimicrobial prophylaxis only
-

Scenarios

1.

A 47-year-old man originally from Jamaica presents with a 6-month history of intermittent pruritic skin rash and mild fatigue. Examination shows scattered papular skin lesions and small-volume cervical lymphadenopathy. Blood tests reveal lymphocytosis (WBC $28 \times 10^9/L$) with atypical lymphocytes. Calcium is normal. LDH mildly elevated. Serology confirms HTLV-1 infection. Bone marrow shows involvement consistent with **chronic ATLL**. He has no B symptoms and no bulky disease.

What is the most appropriate initial management?

2.

A 62-year-old woman presents acutely unwell with confusion, dehydration, and bone pain. Blood tests show calcium 3.4 mmol/L, WBC $85 \times 10^9/L$ with circulating atypical lymphocytes, and deranged renal function. Imaging shows hepatosplenomegaly but no bulky nodal masses. HTLV-1 serology is positive, confirming **acute leukaemic ATLL**. After initial stabilisation, she remains fit for systemic therapy.

What is the most appropriate initial treatment?

3.

A 59-year-old man with acute ATLL is commenced on high-dose AZT/IFN- α . After 4 weeks, there is persistent lymphocytosis, worsening cytopenias, and progression of organomegaly. Repeat imaging confirms disease progression.

What is the most appropriate next step in management?

4.

A 53-year-old woman presents with rapidly enlarging lymph nodes, drenching night sweats, and weight loss. Imaging shows bulky mediastinal and abdominal lymphadenopathy (>10 cm). Biopsy confirms **lymphoma-type ATLL**, HTLV-1 positive. Performance status is good.

What is the most appropriate initial treatment?

5.

A 44-year-old man with acute ATLL achieves complete remission following systemic therapy. He has no significant comorbidities and has a matched sibling donor available. He is keen for definitive therapy.

What is the most appropriate next step?

6.

A 50-year-old woman with ATLL is planned for allogeneic HSCT following response to induction therapy. The transplant team discusses strategies to reduce the risk of viral transmission and infection of donor-derived lymphocytes by HTLV-1 during conditioning.

Which additional intervention should be considered?

7.

A 65-year-old man with newly diagnosed ATLL is being worked up prior to starting immunosuppressive therapy. Screening reveals positive serology for *Strongyloides stercoralis*. He has no gastrointestinal or respiratory symptoms.

What is the most appropriate management regarding this finding?

8.

A 57-year-old patient presents with widespread lymphadenopathy, fevers, and weight loss. Biopsy confirms **ALK-negative anaplastic large cell lymphoma (ALCL)** with strong CD30 expression. PET-CT shows stage III disease. He is otherwise fit with no major comorbidities.

What is the most appropriate first-line treatment?

9.

A 63-year-old patient with ALK-negative ALCL achieves complete metabolic remission following six cycles of CHP-BV. He has an IPI score of 3 and remains fit with good organ function.

What is the most appropriate next step in management?

10.

A 58-year-old patient with ALCL initially treated with CHP-BV achieved a complete remission lasting 10 months. He now presents with relapsed

disease confirmed on biopsy. He previously tolerated brentuximab well and had a deep initial response.

What is the most appropriate next treatment?

Answers with Explanations

1. → **A. AZT + interferon-α**

Indolent **chronic ATLL** → antiviral therapy is standard.

- No bulky disease or aggressive features
- Avoid chemotherapy

Exam trap: Skin involvement ≠ need for chemo

2. → **B. High-dose AZT + interferon-α**

Acute leukaemic ATLL + hypercalcaemia → aggressive disease.

- First-line = **high-dose AZT/IFN**
 - Controls viral-driven proliferation
-

3. → **C. CHOP-like chemotherapy**

Failure of antiviral therapy.

- Progression despite AZT/IFN → **switch to chemotherapy**

Key principle: escalate when non-responsive

4. → **D. CHOP-like chemotherapy + AZT/IFN-α**

Lymphoma-type + bulky disease

- Requires tumour debulking (CHOP)
 - Plus antiviral component
-

5. → **F. Allogeneic HSCT**

All eligible ATLL patients in remission → **allo-HSCT**

- Only curative approach

- Strong graft-versus-leukaemia effect
-

6. → M. Add integrase inhibitor (e.g. raltegravir)

Prevents **HTLV-1 infection of donor cells**

- Rare but high-yield exam point
-

7. → K. Treat Strongyloides infection

Must treat **even if asymptomatic**

- Prevents fatal hyperinfection during immunosuppression
-

8. → E. CHP + brentuximab vedotin (CHP-BV)

Standard first-line for ALCL

- CD30-targeted therapy
 - Superior to CHOP
-

9. → G. Autologous HSCT

High-risk ALCL in CR1

- IPI ≥ 2 → consolidate with **auto-HSCT**
-

10. → H. Brentuximab vedotin monotherapy

Relapse after good prior response

- Reuse BV is appropriate

Exam nuance:

- Short response → chemo
 - Good response → reuse BV
-

Final High-Yield Takeaways

- **ATLL = viral-driven → AZT/IFN backbone**
- **Aggressive ATLL ≠ always chemo first**
- **Allo-HSCT early if eligible**

- **Always treat Strongyloides**
- **ALCL = CD30 disease → brentuximab upfront**
- **Auto-HSCT in high-risk CR1**
- **Relapse strategy depends on prior response duration**

EMQ 37

Theme: Mature T/NK Cell Lymphomas

Options

- A. CHOP chemotherapy alone
- B. CHOP followed by involved-site radiotherapy (ISRT)
- C. CHOP followed by autologous stem cell transplant consolidation
- D. SMILE regimen + radiotherapy
- E. DDGP regimen
- F. Allogeneic stem cell transplant in first remission
- G. Allogeneic stem cell transplant in second remission
- H. High-dose methotrexate CNS prophylaxis
- I. Brentuximab vedotin + CHP
- J. AspaMetDex

Questions

1.

A 58-year-old man presents with generalized lymphadenopathy, drenching night sweats, pruritus, and weight loss. PET-CT shows extensive nodal disease above and below the diaphragm with splenic involvement. Lymph node biopsy shows peripheral T-cell lymphoma, NOS. CD30 expression is low. Bone marrow is uninvolved. Following 6 cycles of CHOP, PET confirms complete metabolic remission. He is fit with no major comorbidities.

What is the most appropriate next step?

2.

A 64-year-old woman presents with a solitary cervical lymph node enlargement. Biopsy confirms angioimmunoblastic T-cell lymphoma (AITL). PET-CT shows only localized cervical nodal involvement (Stage IA). She receives full-course CHOP and achieves complete remission on end-of-treatment PET.

What is the most appropriate consolidation strategy?

3.

A 46-year-old man of East Asian origin presents with nasal obstruction, epistaxis, and destructive midline palatal lesions. Biopsy confirms extranodal NK/T-cell lymphoma, nasal type. EBER ISH is strongly positive. PET-CT shows disease confined to the nasal cavity and local adjacent tissue only.

What is the most appropriate first-line treatment?

4.

A 39-year-old man presents with fever, hepatosplenomegaly, cytopenias, and rapidly progressive systemic illness. Bone marrow shows aggressive NK-cell leukaemia. EBV PCR is strongly positive. Performance status is good and organ function is preserved.

What is the most appropriate long-term management strategy after remission induction?

5.

A 61-year-old man with PTCL-NOS relapses 18 months after first-line CHOP and autologous transplant. He responds to salvage ICE chemotherapy and achieves second complete remission. He is otherwise fit and has an HLA-matched sibling donor.

What is the most appropriate next step?

Answers

1 → C. CHOP followed by autologous stem cell transplant consolidation

Explanation:

For PTCL-NOS in first complete remission, consolidation with high-dose therapy and auto-HSCT is recommended for fit patients due to poor long-term outcomes with chemotherapy alone.

2 → B. CHOP followed by involved-site radiotherapy (ISRT)

Explanation:

For localized early-stage PTCL/AITL, ISRT may be considered following full-course CHOP in responding patients.

3 → D. SMILE regimen + radiotherapy

Explanation:

Localized ENKTL requires non-anthracycline treatment with platinum and L-asparaginase-containing therapy combined with radiotherapy (>50 Gy).

4 → F. Allogeneic stem cell transplant in first remission

Explanation:

Aggressive NK-cell leukaemia is highly aggressive and requires intensive induction followed by allo-HSCT in first response.

5 → G. Allogeneic stem cell transplant in second remission

Explanation:

For relapsed PTCL responding to salvage therapy, allo-HSCT is preferred in second remission due to graft-versus-lymphoma effect.

EMQ 39 and 40

Theme: Diagnosis and Initial Management of Rare Aggressive T-cell Lymphomas

Options

- A. CHOP chemotherapy followed by consideration of autologous HSCT consolidation
- B. Intensive non-cross-resistant chemotherapy (e.g. NCRI/SNLG protocol) followed by BEAM-conditioned auto-HSCT
- C. Intensive non-anthracycline-based chemotherapy such as IVAC/ICE with early referral for allo-HSCT
- D. Immediate allogeneic HSCT without induction chemotherapy
- E. Brentuximab vedotin + CHP
- F. Watchful waiting with nutritional optimisation only
- G. Alemtuzumab monotherapy
- H. R-CHOP chemotherapy

- I. Surgical resection alone
 - J. High-dose methotrexate-based CNS-directed therapy
-

Questions

1.

A 52-year-old man presents with 6 months of weight loss, abdominal pain, chronic diarrhoea and severe hypoalbuminaemia. He has a long history of poorly controlled coeliac disease and poor adherence to a gluten-free diet. CT abdomen demonstrates jejunal wall thickening with mesenteric lymphadenopathy. Emergency laparotomy is performed following bowel perforation, and histology shows pleomorphic medium-to-large atypical lymphoid cells with marked inflammatory background. Immunophenotype: CD3+, CD7+, CD30 variable+, CD4-, CD8-, CD56-. EBER negative.

He is cachectic with ECOG PS 3 and requires TPN.

What is the most appropriate initial treatment?

2.

A 48-year-old woman with previously undiagnosed coeliac disease presents with recurrent abdominal pain, fevers, severe weight loss and small bowel obstruction. Resection specimen confirms enteropathy-associated T-cell lymphoma. Following nutritional rehabilitation and improvement in performance status, she is now ECOG 1 and PET shows residual metabolically active nodal disease.

She is otherwise fit with preserved cardiac and renal function.

What is the preferred treatment strategy?

3.

A 39-year-old Asian man presents with abdominal pain, acute intestinal perforation and B symptoms. Histology from ileal resection shows monomorphic medium-sized lymphoid infiltrate with marked epitheliotropism. Immunophenotype: CD3+, CD8+, CD56+, MATK+, TCR $\gamma\delta$ +, CD30 negative. There is no history of coeliac disease.

Diagnosis is confirmed as MEITL.

He is young and transplant eligible.

What is the most appropriate management?

4.

A 27-year-old man presents with fever, drenching night sweats and marked hepatosplenomegaly without lymphadenopathy. FBC shows Hb 92 g/L, platelets $58 \times 10^9/L$, WBC $3.1 \times 10^9/L$. Bone marrow biopsy shows sinusoidal infiltration by CD3+, CD2+, CD56+, TCR $\gamma\delta$ + lymphoid cells, CD4-, CD8-. Cytogenetics demonstrate isochromosome 7q.

Diagnosis is hepatosplenic T-cell lymphoma.

What is the best initial management?

5.

A 31-year-old woman with longstanding azathioprine exposure for Crohn disease develops fevers, hepatosplenomegaly and pancytopenia. PET shows diffuse marrow and splenic uptake but no significant nodal disease. Liver biopsy confirms hepatosplenic T-cell lymphoma.

She achieves partial remission after induction therapy.

What should be the next major management step?

6.

A 67-year-old frail man presents with perforated jejunal lymphoma on a background of refractory coeliac disease. Histology confirms EATL. He is severely malnourished, albumin 19 g/L, ECOG PS 4, and remains dependent on parenteral nutrition following surgery.

What is the most appropriate first-line approach?

7.

A 44-year-old man is diagnosed with MEITL after resection for bowel obstruction. He has recovered well post-operatively and is fit for intensive therapy. His consultant is considering standard CHOP because of familiarity and lower toxicity.

According to guideline-based management, which approach is preferred?

8.

A 29-year-old man with HSTL receives CHOP chemotherapy as initial therapy in a peripheral hospital before specialist review. Interim PET shows progressive splenic disease and worsening cytopenias.

What would have been the preferred first-line regimen?

9.

A 55-year-old woman with EATL receives 6 cycles of CHOP because of poor nutritional status at diagnosis. She achieves complete metabolic remission and is now significantly fitter.

For disease consolidation in an eligible patient, what should be considered?

10.

A 34-year-old man with newly diagnosed hepatosplenic T-cell lymphoma is reviewed in a tertiary lymphoma MDT. He is responding to ICE chemotherapy. No sibling donor is available, but unrelated donor search is underway.

What is the recommended transplantation strategy?

Answers with Explanations

Q Answer Explanation

- | | | |
|---|---|---|
| 1 | A | Frail EATL patients with poor PS and major nutritional deficits should receive initial CHOP rather than highly intensive regimens. Guideline specifically recommends CHOP particularly in impaired PS/nutritional compromise. |
| 2 | B | Fit EATL patients should be considered for intensification using non-cross-resistant regimens (e.g. NCRI/SNLG) followed by BEAM-conditioned autologous HSCT consolidation. |
| 3 | B | MEITL is managed similarly to EATL in transplant-eligible patients—intensive first-line therapy followed by auto-HSCT is preferred over standard CHOP alone. |
| 4 | C | HSTL requires intensive non-anthracycline regimens such as IVAC or ICE, not CHOP. Early transplant planning is essential due to aggressive disease biology. |

Q Answer Explanation

- 5 C Patients with HSTL who are potentially eligible should be referred early for allogeneic HSCT and consolidation allo-HSCT should be pursued if donor identified.
- 6 A Despite poor prognosis, frail EATL patients should usually start with CHOP rather than intensive regimens because treatment tolerance is limited.
- 7 B For fit MEITL patients, intensified chemotherapy followed by autologous HSCT is preferred; CHOP alone is generally inferior.
- 8 C HSTL should not receive CHOP first-line; preferred therapy is intensive non-anthracycline chemotherapy such as IVAC or ICE with transplant planning.
- 9 A After CHOP response in EATL, eligible patients should still be considered for consolidation with autologous HSCT.
- 10 C Consolidation with allogeneic HSCT is recommended in eligible HSTL patients after response induction, even using unrelated donor if suitable.

EMQ 38a

Theme: Relapsed/Refractory Disease and Special Situations

Options

- A. CNS prophylaxis using DLBCL risk assessment
 - B. PET-CT staging
 - C. EBER in situ hybridization
 - D. EBV DNA qPCR monitoring
 - E. Non-cross-resistant multiagent chemotherapy
 - F. Anthracycline-based therapy
 - G. Immediate radiotherapy alone
 - H. Brentuximab monotherapy
 - I. Observation only
 - J. Intrathecal methotrexate for all patients
-

Questions

1.

A 52-year-old woman presents with advanced-stage ENKTL involving the nasal cavity, skin, liver, and bone marrow. Histology confirms EBER positivity. The MDT is deciding systemic therapy.

Which treatment principle is most appropriate?

2.

A 67-year-old man presents with generalized lymphadenopathy and constitutional symptoms. PTCL-NOS is diagnosed. He also has testicular involvement and epidural extension causing back pain.

What additional management consideration is most appropriate?

3.

A 49-year-old woman presents with suspected ENKTL. The pathology team wants confirmation of EBV association directly within tumour cells.

Which investigation is most appropriate?

4.

A 57-year-old man with relapsed AITL after CHOP is being evaluated before second-line treatment. The MDT wants a regimen that avoids cross-resistance with prior therapy.

What is the best treatment principle?

5.

A 43-year-old patient with localized ENKTL is undergoing treatment. The MDT wishes to monitor treatment response using a circulating biomarker alongside imaging.

Which investigation is most appropriate?

Answers

1 → E. Non-cross-resistant multiagent chemotherapy

Explanation:

Advanced-stage ENKTL requires multiagent L-asparaginase-containing non-anthracycline therapy such as DDGP or SMILE.

2 → A. CNS prophylaxis using DLBCL risk assessment

Explanation:

CNS prophylaxis in PTCL should follow the same high-risk assessment principles used in DLBCL.

3 → C. EBER in situ hybridization

Explanation:

EBER ISH is essential for confirming EBV within tumour cells and is required for diagnosis of ENKTL.

4 → E. Non-cross-resistant multiagent chemotherapy

Explanation:

Relapsed PTCL should be treated with salvage regimens that are non-cross-resistant with prior CHOP.

5 → D. EBV DNA qPCR monitoring

Explanation:

Peripheral blood EBV DNA monitoring can act as a useful biomarker of treatment response in ENKTL.

EMQ 39 and 40

Theme: Diagnosis and Initial Management of Rare Aggressive T-cell Lymphomas

Options

- A. CHOP chemotherapy followed by consideration of autologous HSCT consolidation
- B. Intensive non-cross-resistant chemotherapy (e.g. NCRI/SNLG protocol) followed by BEAM-conditioned auto-HSCT
- C. Intensive non-anthracycline-based chemotherapy such as IVAC/ICE with early referral for allo-HSCT
- D. Immediate allogeneic HSCT without induction chemotherapy
- E. Brentuximab vedotin + CHP

- F. Watchful waiting with nutritional optimisation only
 - G. Alemtuzumab monotherapy
 - H. R-CHOP chemotherapy
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Q Answer Explanation

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| 1 | A | Frail EATL patients with poor PS and major nutritional deficits should receive initial CHOP rather than highly intensive regimens. Guideline specifically recommends CHOP particularly in impaired PS/nutritional compromise. |
| 2 | B | Fit EATL patients should be considered for intensification using non-cross-resistant regimens (e.g. NCRI/SNLG) followed by BEAM-conditioned autologous HSCT consolidation. |
| 3 | B | MEITL is managed similarly to EATL in transplant-eligible patients—intensive first-line therapy followed by auto-HSCT is preferred over standard CHOP alone. |
| 4 | C | HSTL requires intensive non-anthracycline regimens such as IVAC or ICE, not CHOP. Early transplant planning is essential due to aggressive disease biology. |

Q Answer Explanation

- 5 C Patients with HSTL who are potentially eligible should be referred early for allogeneic HSCT and consolidation allo-HSCT should be pursued if donor identified.
- 6 A Despite poor prognosis, frail EATL patients should usually start with CHOP rather than intensive regimens because treatment tolerance is limited.
- 7 B For fit MEITL patients, intensified chemotherapy followed by autologous HSCT is preferred; CHOP alone is generally inferior.
- 8 C HSTL should not receive CHOP first-line; preferred therapy is intensive non-anthracycline chemotherapy such as IVAC or ICE with transplant planning.
- 9 A After CHOP response in EATL, eligible patients should still be considered for consolidation with autologous HSCT.
- 10 C Consolidation with allogeneic HSCT is recommended in eligible HSTL patients after response induction, even using unrelated donor if suitable.

EMQ 41

Theme: Heparin-Induced Thrombocytopenia (HIT)

Options

- A. Continue heparin and no further investigation required
- B. Stop heparin immediately and start alternative therapeutic anticoagulation
- C. Send PF4/heparin antibody test only and continue heparin
- D. Give prophylactic platelet transfusion
- E. Start warfarin immediately
- F. Calculate 4Ts pretest probability score

- G. Routine platelet monitoring not required
 - H. Repeat platelet count 24 hours after starting heparin
 - I. Switch from UFH to LMWH only
 - J. Observe only as thrombocytopenia is expected postoperatively
-

Questions

Scenario 1

A 68-year-old man is admitted with pulmonary embolism and started on intravenous unfractionated heparin (UFH) infusion. His baseline platelet count is $280 \times 10^9/\text{L}$. On Day 6 of treatment, his platelet count falls to $150 \times 10^9/\text{L}$. He also develops painful swelling of the right calf, and Doppler ultrasound confirms a new deep vein thrombosis.

What is the most appropriate next step?

Scenario 2

A 74-year-old woman undergoes total hip replacement surgery. She is receiving prophylactic low molecular weight heparin (LMWH). She has had no prior exposure to heparin. Her platelet count remains stable postoperatively and she has no symptoms of thrombosis.

What is the most appropriate recommendation regarding platelet monitoring?

Scenario 3

A 59-year-old man undergoes coronary artery bypass graft surgery requiring cardiopulmonary bypass. He received intraoperative UFH and is now receiving postoperative LMWH thromboprophylaxis. He had heparin exposure during coronary angiography 2 weeks earlier.

What is the most appropriate platelet monitoring strategy after restarting heparin?

Scenario 4

A 63-year-old intensive care patient on ECMO receives UFH infusion. On Day 5, platelet count falls from $210 \times 10^9/\text{L}$ to $165 \times 10^9/\text{L}$. There is no thrombosis, and no obvious alternative explanation. The clinician suspects possible HIT but the calculated 4Ts score is only 2.

What is the most appropriate next step?

Scenario 5

A 71-year-old medical inpatient is receiving therapeutic-dose subcutaneous UFH for extensive proximal DVT. On Day 7, platelet count falls from $320 \times 10^9/L$ to $210 \times 10^9/L$. There is no bleeding, but he develops erythematous painful skin lesions at the injection site.

What is the most appropriate immediate management?

Answers with Explanations

Scenario 1 → B. Stop heparin immediately and start alternative therapeutic anticoagulation

Explanation:

This is classic HIT:

- Platelet fall >30%
- Occurs between Days 4–14
- New thrombosis present (new DVT)
- Receiving UFH (higher risk)

If PTPS (4Ts) is ≥ 4 , guidelines recommend:

- stop all heparin immediately
- start alternative anticoagulation (e.g. argatroban, danaparoid, fondaparinux)

Do not wait for lab confirmation.

Scenario 2 → G. Routine platelet monitoring not required

Explanation:

Routine platelet monitoring is **not recommended** in:

- postoperative patients (except cardiopulmonary bypass patients)
- receiving LMWH

This patient is a standard postoperative orthopaedic patient on LMWH with no risk features.

Therefore routine monitoring is unnecessary.

Scenario 3 → H. Repeat platelet count 24 hours after starting heparin**Explanation:**

Patients with:

- recent heparin exposure within previous 100 days

and now restarting:

- any type of heparin

should have platelet count checked at **24 hours** because rapid-onset HIT may occur.

This is particularly important after cardiopulmonary bypass.

Scenario 4 → F. Calculate 4Ts pretest probability score**Explanation:**

Although the score is already low (≤ 3), ICU/ECMO patients are a special exception.

In such patients:

- HIT may still occur despite low PTPS
- laboratory testing may still be appropriate

However, the correct step in suspected HIT is always formal clinical assessment using PTPS first.

This guideline strongly recommends use of the 4Ts score.

Scenario 5 → B. Stop heparin immediately and start alternative therapeutic anticoagulation**Explanation:**

Skin lesions at heparin injection sites are a recognised manifestation of HIT.

Also present:

- 30% platelet fall
- timing Day 7
- therapeutic UFH exposure

This strongly suggests HIT.

Immediate management:

- stop heparin
- start non-heparin anticoagulant

Switching to LMWH is incorrect because HIT antibodies cross-react.

Warfarin should not be started initially due to risk of venous limb gangrene.

EMQ 42 and 43

Theme: Laboratory Diagnosis of HIT

Options

- A. HIT excluded; no further testing required
- B. Stop heparin and start alternative anticoagulation immediately
- C. Perform high-sensitivity IgG-specific anti-PF4 ELISA
- D. Perform serotonin release assay (functional platelet activation assay)
- E. Repeat sample using a fresh specimen for lateral flow assay
- F. Do not use PIFA alone for diagnosis

- G. Interpret positive ELISA result with 4Ts pretest probability score
 - H. Report optical density (OD) and assay-specific cut-off with result
 - I. Confirm donor platelet sensitivity before functional assay
 - J. Negative ELISA excludes HIT despite thrombocytopenia
-

Questions

Scenario 1

A 67-year-old man is admitted with NSTEMI and receives intravenous UFH. On Day 7, his platelet count falls from $310 \times 10^9/L$ to $145 \times 10^9/L$ and he develops acute femoral DVT. His 4Ts score is 7 (high probability). The laboratory requests the most appropriate first-line investigation for HIT.

What is the best next step?

Scenario 2

A 74-year-old ICU patient with severe sepsis is on UFH infusion for CRRT. Platelets fall from $220 \times 10^9/L$ to $180 \times 10^9/L$ on Day 5. No thrombosis is identified. The 4Ts score is 2 (low probability). A high-sensitivity IgG anti-PF4 ELISA returns negative.

What is the most appropriate interpretation?

Scenario 3

A 58-year-old woman develops thrombocytopenia after orthopedic surgery while receiving LMWH prophylaxis. A particle immunofiltration assay (PIFA) is positive, and the junior doctor documents “confirmed HIT.”

The consultant disagrees.

What is the most appropriate reason?

Scenario 4

A 69-year-old man with suspected HIT has a strongly positive anti-PF4 ELISA. The report simply states “positive” without giving the optical density (OD) value or assay threshold.

What should the laboratory ideally include in the report?

Scenario 5

A 61-year-old cardiac surgery patient develops thrombocytopenia and digital ischemia on Day 6 post-CABG. Anti-PF4 ELISA is positive with high OD and 4Ts score is high. The haematologist wants definitive confirmation before long-term management decisions.

Which test is most appropriate?

Scenario 6

A hospital introduces a rapid lateral flow assay for HIT screening. Several false-positive technical failures occur after samples stored overnight are tested.

What is the most appropriate corrective action?

Scenario 7

A 72-year-old woman with metastatic cancer develops thrombocytopenia while receiving therapeutic LMWH. Anti-PF4 ELISA is weakly positive, but her 4Ts score is only 2 and there is clear disseminated malignancy-associated DIC.

How should the ELISA result be interpreted?

Scenario 8

A specialist haemostasis laboratory is preparing to perform a functional platelet activation assay for suspected HIT confirmation.

Before using donor platelets, what must be ensured?

Scenario 9

A patient with suspected HIT has intermediate clinical probability. The anti-PF4 IgG ELISA is negative using a validated high-sensitivity assay.

What is the most appropriate conclusion?

Scenario 10

A trainee asks why laboratories should report numerical assay values rather than simply “positive” or “negative” for anti-PF4 testing.

What is the best explanation?

Answers with Explanations

Scenario 1 → C. Perform high-sensitivity IgG-specific anti-PF4 ELISA

Explanation

First-line laboratory investigation should be:

- high sensitivity (>95%)
- IgG-specific anti-PF4 ELISA

This is the recommended screening test.

Not all positive antibodies are pathogenic, so confirmation may later require functional testing.

Scenario 2 → J. Negative ELISA excludes HIT despite thrombocytopenia

Explanation

A negative high-sensitivity ELISA effectively excludes HIT.

Even in ICU patients, if the validated high-sensitivity assay is negative, HIT is highly unlikely.

Other causes of thrombocytopenia should be sought.

Scenario 3 → F. Do not use PIFA alone for diagnosis

Explanation

PIFA:

- should NOT be used in isolation
- has poor specificity

Diagnosis requires:

- pretest probability assessment
- preferably ELISA ± functional assay

A positive PIFA alone does not confirm HIT.

Scenario 4 → H. Report optical density (OD) and assay-specific cut-off with result

Explanation

Laboratory reports should include:

- assay cut-off
- actual OD value

Higher OD values correlate more strongly with true HIT and improve interpretation.

Simply stating “positive” is inadequate.

Scenario 5 → D. Perform serotonin release assay (functional platelet activation assay)

Explanation

When confirmation is required:

- functional platelet activation assays are gold standard

Examples include:

- serotonin release assay (SRA)
- heparin-induced platelet activation assay (HIPA)

These demonstrate inhibition with excess heparin.

Scenario 6 → E. Repeat sample using a fresh specimen for lateral flow assay

Explanation

Lateral flow assays should only be performed on:

- fresh samples

Stored samples increase technical failure and false results.

Fresh specimens reduce assay artefacts.

Scenario 7 → G. Interpret positive ELISA result with 4Ts pretest probability score

Explanation

Positive ELISA alone does not diagnose HIT.

Interpretation must consider:

- pretest clinical probability
- competing causes of thrombocytopenia

Low 4Ts + weak ELISA positivity usually argues against true HIT.

Scenario 8 → I. Confirm donor platelet sensitivity before functional assay

Explanation

Functional assays require donor platelets that are:

- responsive
- sensitive to HIT-positive material

Failure to confirm this may produce false-negative results.

This is an important laboratory quality requirement.

Scenario 9 → A. HIT excluded; no further testing required

Explanation

Negative high-sensitivity ELISA excludes HIT.

Further functional testing is unnecessary.

This is especially true when the assay sensitivity is validated.

Scenario 10 → The correct option: H/G principle → Stratification improves diagnostic accuracy

(Best matching option: **H**)

Explanation

Numerical values such as OD:

- improve specificity
- improve sensitivity
- improve negative predictive value

Strongly positive tests are more predictive of true HIT than weak positives.

Therefore laboratories should stratify numerical results rather than using binary reporting alone.

EMQ 44 and 45

Theme: Diagnosis and Management of HIT

Options

- A. Stop heparin and start argatroban
- B. Stop heparin and start fondaparinux
- C. Start warfarin immediately
- D. Perform PF4 IgG ELISA only
- E. Perform platelet activation assay with high-dose heparin inhibition and Fc receptor blockade
- F. Give IVIG 1 g/kg for 2 days

- G. Continue LMWH and repeat platelet count
 - H. Therapeutic anticoagulation for 3 months
 - I. Therapeutic anticoagulation for 4 weeks
 - J. Provide HIT alert card and clearly document diagnosis
 - K. Use DOAC once clinically stable
 - L. Plasma exchange (PE_x)
 - M. Suspect spontaneous HIT
 - N. Test for anti-PF4 antibodies using ELISA in suspected VITT-like syndrome
 - O. Delay treatment until confirmatory testing completed
-

Scenarios

1.

A 67-year-old man undergoes total hip replacement. Five days later he develops painful swelling of the left leg and acute dyspnoea. CTPA confirms pulmonary embolism and Doppler shows proximal DVT. Platelet count has fallen from $310 \times 10^9/L$ pre-operatively to $92 \times 10^9/L$. He has been receiving prophylactic LMWH since surgery.

There is no bleeding. Renal function is normal. The clinical team asks for the immediate next step in management.

2.

A 58-year-old woman with NSTEMI receives unfractionated heparin during PCI. Seven days later she develops digital ischaemia and platelet count falls from 280 to $74 \times 10^9/L$. HIT ELISA is strongly positive.

The medical registrar wishes to commence warfarin immediately because the patient will require long-term anticoagulation.

What is the most appropriate immediate management?

3.

A 45-year-old woman presents 10 days after laparoscopic cholecystectomy with abdominal pain and headache. CT demonstrates portal vein thrombosis and cerebral venous sinus thrombosis. Platelet count is $38 \times 10^9/L$.

She has had no exposure to heparin before or after surgery. D-dimer is markedly elevated. Fibrinogen is mildly reduced.

The haematologist suspects spontaneous HIT.

What is the most appropriate investigation?

4.

A 39-year-old man develops severe thrombocytopenia (platelets $22 \times 10^9/L$) and extensive lower limb DVT following a severe adenovirus respiratory infection 2 weeks earlier. No heparin exposure is documented.

The consultant suspects a VITT-like syndrome associated with anti-PF4 antibodies.

Which test is most appropriate initially?

5.

A 71-year-old woman with confirmed HIT develops progressive thrombosis despite therapeutic argatroban. Platelet count remains $18 \times 10^9/L$ and functional assay shows strong heparin-independent platelet activation.

She has extensive iliofemoral thrombosis and new adrenal haemorrhage.

What additional treatment is most appropriate?

6.

A 62-year-old dialysis patient develops thrombocytopenia 8 days after repeated heparin exposure during haemodialysis. Platelet count falls from 240 to $95 \times 10^9/L$. There is no thrombosis.

HIT is confirmed and heparin is stopped.

How long should therapeutic anticoagulation continue?

7.

A 54-year-old man with orthopaedic trauma develops HIT-associated PE after therapeutic UFH. Platelets recover after treatment with danaparoid. He is now clinically stable and wishes to avoid INR monitoring.

Which longer-term anticoagulant strategy is most appropriate?

8.

A 60-year-old woman with severe sepsis develops thrombocytopenia and bilateral adrenal vein thrombosis. She has not received heparin during this admission. Previous admission 3 months ago included LMWH prophylaxis only.

Platelet count is $44 \times 10^9/L$. The team suspects spontaneous HIT triggered by infection.

What should be suspected first?

9.

A patient with classical HIT-associated DVT has completed inpatient treatment and platelet count has normalised. He is ready for discharge.

Apart from anticoagulation, what additional important step should be taken to reduce future risk?

10.

A 50-year-old woman with severe autoimmune HIT presents with limb-threatening thrombosis and active gastrointestinal bleeding from peptic ulcer disease. Platelets are $15 \times 10^9/L$.

Therapeutic anticoagulation is considered unsafe because of major bleeding risk. Functional testing confirms strong platelet activation independent of heparin.

What additional therapy is most appropriate?

Answers with Explanation

1 → A. Stop heparin and start argatroban

Explanation:

This is classical HIT with thrombosis (HITT): platelet fall >50%, timing day 5–10, and new thrombosis.

Immediate treatment is:

- stop all heparin
- start a non-heparin anticoagulant

Argatroban is first-line and commonly preferred.

Do not delay treatment for confirmatory testing.

2 → A. Stop heparin and start argatroban

Explanation:

Warfarin must NOT be started immediately in acute HIT because:

- it can worsen thrombosis
- may precipitate venous limb gangrene due to protein C depletion

Warfarin should only be started after platelet recovery with bridging from a non-heparin anticoagulant.

3 → E. Perform platelet activation assay with high-dose heparin inhibition and Fc receptor blockade

Explanation:

This is suspected spontaneous HIT:

- thrombosis
- severe thrombocytopenia
- no recent heparin exposure
- post-surgical trigger

Diagnosis requires:

- platelet activation assay
- inhibition at 100 IU/mL heparin
- inhibition with Fc receptor-blocking monoclonal antibody

This is specifically recommended.

4 → N. Test for anti-PF4 antibodies using ELISA in suspected VITT-like syndrome**Explanation:**

VITT-like syndromes should be investigated initially using:
PF4 ELISA

This is preferred over rapid assays because ELISA is more sensitive for pathogenic anti-PF4 antibodies.

5 → F. Give IVIG 1 g/kg for 2 days**Explanation:**

This is severe autoimmune HIT with:

- heparin-independent platelet activation
- progressive thrombosis
- severe thrombocytopenia

Recommended treatment:

IVIG 1 g/kg for 2 days

IVIG blocks Fc-mediated platelet activation.

6 → I. Therapeutic anticoagulation for 4 weeks

Explanation:

Confirmed HIT WITHOUT thrombosis requires:
4 weeks therapeutic anticoagulation

If thrombosis were present, duration would be 3 months.

7 → K. Use DOAC once clinically stable**Explanation:**

DOACs are suggested for clinically stable HIT patients.

This is increasingly preferred when:

- platelet count recovered
- patient stable
- avoiding INR monitoring is desirable

Warfarin remains recommended traditionally, but DOACs are acceptable.

8 → M. Suspect spontaneous HIT**Explanation:**

Features strongly suggest spontaneous HIT:

- thrombosis
- thrombocytopenia
- no active heparin exposure
- infection trigger

Spontaneous HIT should especially be suspected after:

- surgery
 - infection
-

9 → J. Provide HIT alert card and clearly document diagnosis**Explanation:**

Future accidental heparin exposure can be dangerous.

Recommendations include:

- clear documentation in medical record

- provision of HIT alert card

This is commonly tested.

10 → L. Plasma exchange (PEX)

Explanation:

In severe HIT with:

- major bleeding preventing anticoagulation
- severe autoimmune platelet activation

Treatment with:

IVIg and/or Plasma Exchange (PEX)

is recommended.

Because anticoagulation is unsafe here, PEX is highly appropriate.

EMQ 46

Theme: HIT

Options

- A. Proceed with intraoperative unfractionated heparin (UFH) only, with non-heparin anticoagulation before and after surgery
- B. Use bivalirudin
- C. Delay surgery until PF4-heparin antibodies become negative
- D. Use argatroban

- E. Use citrate anticoagulation
 - F. Use danaparoid
 - G. Use plasma exchange (PEX) ± IVIG before essential heparin exposure
 - H. Use low molecular weight heparin (LMWH)
 - I. Perform a functional platelet activation assay for PF4-heparin antibodies
 - J. Use fondaparinux
-

Questions

Question 1

A 74-year-old man is scheduled for elective coronary artery bypass grafting (CABG) for severe left main stem coronary artery disease. He had confirmed HIT 14 months ago during treatment for postoperative pulmonary embolism following hip replacement surgery. At that time, he developed thrombocytopenia with platelet count falling from $280 \times 10^9/L$ to $62 \times 10^9/L$ and a new femoral DVT. HIT was confirmed by strongly positive anti-PF4 antibodies and a positive serotonin release assay.

He has now fully recovered. His platelet count is $245 \times 10^9/L$. Repeat anti-PF4 antibody ELISA is negative and functional assay is negative.

The cardiac surgeon asks which anticoagulant should be used during cardiopulmonary bypass.

What is the SINGLE BEST answer?

Question 2

A 61-year-old woman developed HIT 8 days ago while receiving UFH for NSTEMI. Her platelet count has fallen from $310 \times 10^9/L$ to $58 \times 10^9/L$ and she has developed a new radial artery thrombosis following arterial line insertion. HIT is confirmed with strongly positive PF4-heparin antibodies and a positive functional assay.

She develops recurrent chest pain with dynamic ECG changes and requires urgent coronary angiography with likely PCI.

Which is the SINGLE BEST anticoagulant for the procedure?

Question 3

A 69-year-old man requires urgent aortic valve replacement for infective endocarditis with severe acute regurgitation. He had confirmed HIT 3 weeks

ago during ICU admission for sepsis and remains strongly positive for platelet-activating PF4-heparin antibodies.

Cardiac surgery cannot be delayed due to worsening heart failure. Bivalirudin is not available in the hospital pharmacy.

What is the SINGLE BEST management option?

Question 4

A 58-year-old man in ICU with severe pancreatitis develops acute kidney injury requiring continuous renal replacement therapy (CRRT). Three days earlier he was diagnosed with HIT after developing thrombocytopenia and catheter-associated thrombosis while receiving UFH thromboprophylaxis.

Platelet count is currently $42 \times 10^9/L$ and HIT antibodies remain strongly positive.

What is the SINGLE BEST anticoagulation strategy for haemofiltration?

Question 5

A 76-year-old woman had HIT 18 months ago during treatment for pulmonary embolism. She now develops septic shock complicated by acute kidney injury requiring haemofiltration. Platelet count is normal and repeat PF4-heparin antibodies are negative.

The renal team asks whether standard heparin anticoagulation can be used for CRRT.

What is the SINGLE BEST answer?

Question 6

A 32-year-old woman who is 30 weeks pregnant develops painful swelling of the left leg. Doppler ultrasound confirms extensive proximal DVT. She had recently received LMWH thromboprophylaxis following emergency appendicectomy and now has thrombocytopenia with confirmed HIT.

Which is the SINGLE BEST treatment option?

Question 7

A 67-year-old man had confirmed HIT 5 weeks ago during treatment for unstable angina. He now requires elective mitral valve replacement for

severe symptomatic mitral regurgitation. Platelet count has recovered to normal but PF4-heparin antibody testing remains positive.

What is the SINGLE BEST next step?

Question 8

A 71-year-old man with a history of HIT 9 months ago is being assessed before elective CABG. The haematologist wishes to determine whether clinically significant platelet-activating antibodies are still present before deciding whether intraoperative UFH can be safely used.

Which is the SINGLE BEST investigation?

Answers and Explanations

Answer 1 → A. Proceed with intraoperative UFH only, with non-heparin anticoagulation before and after surgery

Explanation

Patients with a history of HIT who are now antibody negative (usually after >100 days) can safely receive intraoperative UFH for cardiac surgery because UFH remains the most validated anticoagulant for cardiopulmonary bypass.

However:

- preoperative anticoagulation should avoid UFH/LMWH
- postoperative anticoagulation should also use non-heparin agents

This is a classic FRCPATH favourite.

Answer 2 → B. Use bivalirudin

Explanation

This patient has active HIT (<100 days) with persistent platelet-activating antibodies and requires urgent PCI.

Guidelines recommend:

Bivalirudin

because:

- heparin must be avoided

- bivalirudin is well validated for PCI
 - it is the preferred agent in active HIT when urgent intervention cannot be delayed
-

Answer 3 → G. Use plasma exchange (PE_x) ± IVIG before essential heparin exposure

Explanation

This patient has recent HIT with positive antibodies and requires urgent cardiac surgery that cannot be delayed.

Preferred management:

Bivalirudin

But since it is unavailable:

Plasma exchange ± IVIG

is suggested to reduce antibody burden and allow essential heparin exposure during cardiopulmonary bypass.

This is a high-yield guideline point.

Answer 4 → D. Use argatroban

Explanation

In active HIT requiring haemofiltration:

Non-heparin anticoagulation is mandatory

Preferred options:

- argatroban
- danaparoid

Citrate alone is less suitable because active HIT requires systemic anticoagulation, not just circuit anticoagulation.

Answer 5 → D. Use argatroban

Explanation

Even in remote HIT, repeated heparin exposure during haemofiltration increases the risk of recurrent HIT.

Guidelines suggest:

- argatroban
- danaparoid
- citrate

rather than heparin.

Argatroban is the best answer among available options.

Answer 6 → F. Use danaparoid

Explanation

In pregnancy with HIT:

recommended alternatives include:

- argatroban
- danaparoid
- fondaparinux

Danaparoid is commonly preferred due to greater experience and safety data in pregnancy.

LMWH and UFH must be avoided.

Answer 7 → C. Delay surgery until PF4-heparin antibodies become negative

Explanation

This is recent HIT (<100 days).

If surgery is elective and can be delayed:

wait until antibodies become negative

because once antibody negative, standard intraoperative UFH can be used safely.

This is preferred over immediate alternative anticoagulation when feasible.

Answer 8 → I. Perform a functional platelet activation assay for PF4-heparin antibodies

Explanation

Before cardiac surgery in patients with previous HIT:

functional assays are preferred

because:

- ELISA may remain positive without clinical significance
- functional assays determine whether antibodies are platelet activating

This guides safe re-exposure to heparin.

Exam Pearl

HIT + Cardiac Surgery

Antibody negative (>100 days)

→ UFH intraoperatively acceptable

Antibody positive (<100 days)

→ Avoid heparin

Urgent surgery

→ Bivalirudin

If unavailable

→ PEx ± IVIG

EMQ 47 and 48

Theme: Blood Donation, Donor Eligibility, Component Processing and Blood Safety

Options

- A. Whole blood donation every 12 weeks
- B. Whole blood donation every 16 weeks
- C. Platelet donation every 2–4 weeks

- D. Plasma donation every 2 weeks
 - E. Minimum donor age 17 years
 - F. Minimum donor weight 50 kg
 - G. Female donor under 65 kg requires estimated blood volume calculation
 - H. Diversion pouch of first 20–30 mL
 - I. Male-only donor policy for FFP production
 - J. Platelet storage at 22°C with continuous agitation
 - K. Platelet shelf life of 7 days
 - L. Adult therapeutic dose of platelets $>240 \times 10^9$
 - M. Cryoprecipitate as major UK source of fibrinogen
 - N. Leucocyte depletion before component release
 - O. Donation Identification Number for traceability
-

Questions

Question 1

A 19-year-old female university student presents for her first blood donation. She weighs 54 kg and is otherwise healthy. Her haemoglobin is satisfactory and she wishes to proceed with donation. The donor nurse explains that additional safety assessment is required before proceeding because of her demographics.

Which is the SINGLE most appropriate next step?

Question 2

A 42-year-old regular male donor asks how often he is permitted to donate whole blood through the NHS Blood and Transplant service. He is fit, well, and has no medical contraindications.

Which is the correct recommendation?

Question 3

A consultant is reviewing bacterial contamination reduction strategies in blood collection. They ask which step specifically reduces the risk of contamination from skin flora introduced during venepuncture.

Which is the best answer?

Question 4

A hospital transfusion practitioner asks why fresh frozen plasma for routine transfusion support is preferentially produced from male donors rather than female donors.

What is the most appropriate explanation?

Question 5

A patient with massive obstetric haemorrhage develops severe hypofibrinogenaemia. The haematologist requests the blood product that is considered the principal source of fibrinogen replacement in the UK.

Which product is most appropriate?

Question 6

During a laboratory inspection, a trainee is asked how platelet concentrates should be stored to preserve function and viability.

Which is the correct answer?

Question 7

A patient with chemotherapy-induced thrombocytopenia requires one adult therapeutic dose of platelets.

Which statement best defines an adult therapeutic dose?

Question 8

A donor attends specifically for platelet apheresis donation and asks how frequently they may donate, assuming all intervals and counts remain acceptable.

Which is the best answer?

Question 9

During processing of whole blood donations, white blood cells are routinely removed prior to final release of blood components.

What is this process called?

Question 10

A blood transfusion laboratory must ensure full traceability of every donated unit from donor to recipient. Each donation is therefore assigned a specific unique number separate from the donor's personal donor ID.

What is this number called?

Answers with Explanations

Answer 1 — G

Female donor under 65 kg requires estimated blood volume calculation

Explanation

Female donors weighing less than 65 kg or aged under 21 years require estimated blood volume calculation to ensure that no more than 15% of total blood volume is donated. This reduces vasovagal risk and donor harm.

This candidate qualifies on BOTH criteria:

- female
- under 21 years
- under 65 kg

This is a common FRCPATH trap.

Answer 2 — A

Whole blood donation every 12 weeks

Explanation

Men may donate whole blood every 12 weeks.

Women donate every 16 weeks due to greater risk of iron deficiency.

This is a frequently tested factual recall area.

Answer 3 — H

Diversion pouch of first 20–30 mL

Explanation

The first 20–30 mL of donated blood is diverted into a separate pouch to remove:

- skin plug

- skin contaminants
- bacterial contamination risk

This significantly reduces transfusion-transmitted bacterial infection.

Answer 4 — I

Male-only donor policy for FFP production

Explanation

Female donors are more likely to have HLA and granulocyte antibodies (particularly after pregnancy), which increase the risk of:

TRALI

(Transfusion-Related Acute Lung Injury)

Therefore routine FFP production preferentially uses male donors.

Very common viva question.

Answer 5 — M

Cryoprecipitate as major UK source of fibrinogen

Explanation

Cryoprecipitate contains high concentrations of:

- fibrinogen
- factor VIII
- factor XIII
- vWF
- fibronectin

In the UK it is the principal source of fibrinogen replacement.

Massive haemorrhage + low fibrinogen = think cryoprecipitate.

Answer 6 — J

Platelet storage at 22°C with continuous agitation

Explanation

Platelets must be stored:

- at 22°C
- on a platelet agitator

This ensures:

- oxygenation
- platelet viability
- preserved function

Red cells are refrigerated; platelets are not.

Classic exam discriminator.

Answer 7 — L

Adult therapeutic dose $>240 \times 10^9$

Explanation

An adult therapeutic dose (ATD) of platelets should contain:

$>240 \times 10^9$ platelets

This may be provided by:

- pooled platelets
or
- apheresis platelets

Single apheresis may provide 2–3 ATDs.

Answer 8 — C

Platelet donation every 2–4 weeks

Explanation

Platelet donors are encouraged to donate every 2–4 weeks, with a maximum of:

24 donations per 12 months

This is commonly examined alongside whole blood intervals.

Answer 9 — N

Leucocyte depletion before component release

Explanation

Leucocyte depletion removes white cells from donations to:

- reduce febrile reactions
- reduce CMV transmission risk
- reduce alloimmunisation
- improve component quality

This is standard UK practice.

Answer 10 — O

Donation Identification Number for traceability

Explanation

Each donor has:

Donor ID

Each individual donation has:

Donation Identification Number (DIN)

DIN ensures:

- donor-to-recipient traceability
- haemovigilance
- recall capability
- regulatory compliance

Very important for MHRA and SHOT governance.

EMQ 49 and 50

Options

- A. Anti-D immunoglobulin within 72 hours
- B. Anti-D immunoglobulin 1500 IU after intraoperative cell salvage
- C. Additional anti-D dosing guided by fetomaternal haemorrhage estimation

- D. 20% Human Albumin Solution (HAS)
 - E. 4.5% / 5% Human Albumin Solution (HAS)
 - F. Intravenous Immunoglobulin (IVIg) replacement therapy
 - G. High-dose IVIg as immune modulation
 - H. Disease-specific immunoglobulin
 - I. No Albumin replacement required
 - J. Intramuscular normal immunoglobulin
-

Questions

Question 1

A 28-year-old primigravida woman at 30 weeks gestation is found to be RhD negative during routine antenatal screening. Her partner is RhD positive. She has had no previous pregnancies, no bleeding episodes, and fetal RhD genotyping has not been performed. Her pregnancy has been uncomplicated so far.

The obstetrician asks whether she should receive prophylaxis to reduce the risk of haemolytic disease of the fetus and newborn (HDFN).

What is the SINGLE most appropriate management?

Question 2

A 34-year-old RhD negative woman at 18 weeks gestation presents to the emergency department following abdominal trauma after a road traffic accident. Ultrasound confirms fetal viability and no placental abruption. She is otherwise stable.

The obstetric team requests advice regarding transfusion-related prophylaxis.

What is the SINGLE most appropriate next step?

Question 3

A 31-year-old RhD negative woman undergoes emergency Caesarean section for placental abruption. Significant haemorrhage occurs and intraoperative cell salvage is performed with reinfusion of salvaged blood. Cord blood testing confirms the newborn is RhD positive. She has no previous sensitisation.

What is the SINGLE most appropriate immediate management?

Question 4

Following the case above, the same patient has already received the recommended post-operative prophylaxis. The consultant asks what should happen next to ensure adequate protection.

What is the SINGLE most appropriate next step?

Question 5

A 67-year-old man with nephrotic syndrome presents with severe peripheral oedema and serum albumin of 18 g/L. He is haemodynamically stable with no evidence of acute blood loss or hypovolaemia. Renal physicians request plasma volume support.

Which is the SINGLE most appropriate blood product?

Question 6

A 75-year-old woman presents with septic shock secondary to perforated diverticulitis. She is hypotensive despite crystalloid resuscitation and requires urgent plasma volume expansion in the intensive care unit.

Which is the SINGLE most appropriate product?

Question 7

A junior doctor requests albumin infusion for a 79-year-old patient admitted with chronic frailty, poor oral intake and serum albumin of 24 g/L. There is no oedema, no nephrotic syndrome, no ascites and no evidence of intravascular depletion.

Which of these is an appropriate statement?

Question 8

A 42-year-old man with common variable immunodeficiency suffers recurrent severe bacterial sinopulmonary infections. Investigations confirm profound hypogammaglobulinaemia with markedly reduced IgG levels.

Which is the SINGLE most appropriate treatment?

Question 9

A 36-year-old woman with severe myasthenia gravis develops rapidly progressive bulbar weakness and respiratory compromise requiring HDU admission. Neurology requests urgent immunoglobulin treatment.

What is the SINGLE most appropriate therapy?

Question 10

A 24-year-old veterinary student sustains a high-risk dog bite while working abroad in a rabies-endemic region. She is incompletely vaccinated and presents for urgent prophylaxis.

Which is the SINGLE most appropriate product?

Answers with Explanations

Question 1 — Answer: A. Anti-D immunoglobulin within 72 hours

Explanation:

Routine anti-D prophylaxis is recommended for RhD negative pregnant women carrying a potentially RhD positive fetus to prevent maternal sensitisation and subsequent HDFN. Since fetal RhD genotyping has not been performed and the father is RhD positive, prophylaxis is indicated.

Question 2 — Answer: A. Anti-D immunoglobulin within 72 hours

Explanation:

Abdominal trauma during pregnancy is a sensitising event because fetomaternal haemorrhage may occur. Anti-D should ideally be administered within 72 hours, although some protection may still occur up to 10 days later.

Question 3 — Answer: B. Anti-D immunoglobulin 1500 IU after intraoperative cell salvage

Explanation:

Where intraoperative cell salvage is performed in an RhD negative woman without prior sensitisation and the baby is RhD positive, BSH recommends immediate administration of 1500 IU anti-D after reinfusion of salvaged cells.

This is a favourite FRCPATH exam detail.

Question 4 — Answer: C. Additional anti-D dosing guided by fetomaternal haemorrhage estimation

Explanation:

After the initial 1500 IU dose, a maternal sample should be checked within 45 minutes for fetomaternal haemorrhage quantification to determine whether further anti-D dosing is required.

Question 5 — Answer: D. 20% Human Albumin Solution (HAS)

Explanation:

20% HAS is used for hypoproteinaemia and oedema, particularly in nephrotic syndrome and chronic liver disease with ascites. This patient has nephrotic syndrome with severe oedema rather than acute volume depletion.

Question 6 — Answer: E. 4.5% / 5% Human Albumin Solution (HAS)

Explanation:

4.5–5% HAS is indicated for acute plasma volume replacement in hypovolaemic states such as septic shock when volume expansion is required.

Question 7 — Answer: I. No Albumin replacement required

Explanation:

This is a deliberate trap. Albumin should NOT be used simply to “correct” a low serum albumin level associated with chronic illness or frailty in the absence of a clinical indication such as nephrotic oedema, ascites or hypovolaemia.

Question 8 — Answer: F. Intravenous Immunoglobulin (IVIg) replacement therapy

Explanation:

Patients with severe antibody deficiency and recurrent infections require IVIg replacement therapy to restore protective IgG levels.

Classic indication: CVID.

Question 9 — Answer: G. High-dose IVIg as immune modulation

Explanation:

In autoimmune conditions such as myasthenia gravis, high-dose IVIg acts as an immune modulator rather than simple antibody replacement by reducing inflammatory immune responses.

Question 10 — Answer: H. Disease-specific immunoglobulin

Explanation:

Rabies exposure requires disease-specific immunoglobulin containing high titres of targeted antibodies for immediate passive immunity.

Other examples include tetanus immunoglobulin, hepatitis B immunoglobulin, and varicella-zoster immunoglobulin.

EMQ 51 and 52

Options

- A. Immediate issue O D negative red cells
- B. Immediate issue O D positive red cells
- C. Take crossmatch sample before first emergency unit
- D. Tranexamic acid (TXA) 1 g IV immediately
- E. Second dose TXA 1 g if bleeding persists after 30 min
- F. Early fibrinogen monitoring and replacement

- G. Intraoperative cell salvage (ICS)
 - H. ABO-incompatible platelets (low titre)
 - I. Anti-D immunoglobulin 1500 IU
 - J. Switch rapidly to group-specific blood
 - K. Platelet target $>75 \times 10^9/L$
 - L. Hb target 80 g/L
 - M. PT ratio target <1.5
 - N. Avoid delay waiting for age-specific components
 - O. Use leucodepletion filter for salvaged blood
-

Questions

Scenario 1

A 28-year-old woman presents with severe postpartum haemorrhage following emergency Caesarean section. Estimated blood loss is 1800 mL and ongoing. She is hypotensive and tachycardic. Blood group is unknown. Immediate emergency blood is required while the laboratory is preparing compatibility testing. She has not yet had a blood sample sent.

What is the SINGLE most important immediate laboratory-related action?

Scenario 2

A 34-year-old D negative woman undergoes Caesarean section complicated by placenta accreta and major haemorrhage. Cell salvage is used intraoperatively. The baby is confirmed O D positive. Salvaged blood is reinfused successfully.

Which additional treatment is essential?

Scenario 3

A 40-year-old trauma patient arrives after a road traffic collision with pelvic fractures and major haemorrhage. Blood group is unknown. Massive transfusion protocol is activated. The emergency department asks whether TXA should be given.

What is the most appropriate management?

Scenario 4

A 31-year-old woman develops severe postpartum haemorrhage after vaginal delivery due to uterine atony. TXA was given immediately on diagnosis. After

40 minutes, bleeding continues despite uterotonics and blood component support.

What is the next most appropriate action regarding antifibrinolytic therapy?

Scenario 5

A 5-year-old child weighing 18 kg undergoes emergency surgery for splenic rupture following trauma. Significant haemorrhage is ongoing. Paediatric red cells are temporarily unavailable.

What is the most appropriate immediate transfusion strategy?

Scenario 6

A 9-year-old child with major haemorrhage has received multiple transfusions. Laboratory results show:

Hb 82 g/L

Fibrinogen 1.2 g/L

Platelets $90 \times 10^9/L$

PT ratio 1.4

Which abnormality should be corrected most urgently?

Scenario 7

A woman aged 42 years presents with antepartum haemorrhage at 35 weeks gestation due to placental abruption. Blood loss is significant. Initial fibrinogen is 2.1 g/L.

Why is this fibrinogen result particularly concerning?

Scenario 8

A major trauma patient has already received 4 units of emergency O negative blood. Crossmatch sample taken on arrival confirms the patient is group A RhD positive.

What should happen next?

Scenario 9

A patient with catastrophic GI bleeding is receiving major haemorrhage support. A junior doctor asks whether TXA should routinely be administered because it is beneficial in all major bleeds.

What is the best response?

Scenario 10

A 7-year-old child with major haemorrhage remains haemodynamically unstable. Laboratory values show:

Hb 68 g/L

Platelets $62 \times 10^9/L$

Fibrinogen 1.8 g/L

PT ratio 1.3

Which therapeutic target is currently NOT achieved and requires urgent correction?

Answers with Explanation

1. Answer: C — Take crossmatch sample before first emergency unit

Explanation

Even in life-threatening haemorrhage requiring immediate uncrossmatched blood, a properly labelled crossmatch sample must be taken before the first emergency unit whenever possible. This allows rapid transition to group-specific blood and avoids prolonged use of universal donor units.

2. Answer: I — Anti-D immunoglobulin 1500 IU

Explanation

D negative women receiving salvaged blood after delivery of a D positive baby require a minimum dose of 1500 IU anti-D immunoglobulin to prevent Rh sensitisation. This is especially important after reinfusion of salvaged red cells.

3. Answer: D — Tranexamic acid (TXA) 1 g IV immediately

Explanation

TXA should be given as early as possible in traumatic major haemorrhage unless contraindicated. Evidence strongly supports reduced mortality when administered promptly in trauma patients.

4. Answer: E — Second dose TXA 1 g if bleeding persists after 30 min

Explanation

In obstetric haemorrhage, following the WOMAN trial recommendations, a second 1 g dose of TXA is indicated if bleeding persists after 30 minutes or recurs within 24 hours.

5. Answer: N — Avoid delay waiting for age-specific components

Explanation

In paediatric major haemorrhage, age-appropriate blood is preferred but treatment must not be delayed. The most appropriate available blood should be transfused immediately while age-specific components are arranged.

6. Answer: F — Early fibrinogen monitoring and replacement

Explanation

Fibrinogen is the earliest and most critical coagulation factor to fall in major haemorrhage, especially in paediatrics and obstetrics. A level of 1.2 g/L is below the therapeutic target (>1.5 g/L) and requires urgent correction.

7. Answer: F — Early fibrinogen monitoring and replacement

Explanation

Pregnancy normally increases fibrinogen levels to approximately 4–6 g/L at delivery. Therefore, a fibrinogen of 2.1 g/L in obstetric haemorrhage is relatively low and predicts severe bleeding risk despite appearing “normal” by non-pregnant standards.

8. Answer: J — Switch rapidly to group-specific blood

Explanation

Once a valid sample confirms ABO/Rh group, emergency O blood should be replaced rapidly by group-specific blood to preserve O negative stocks and improve blood inventory management.

9. Answer: TXA is not routinely beneficial in GI bleeding

Correct Option: D is NOT correct here

Explanation

Unlike trauma and obstetric haemorrhage, the HALT-IT trial showed that TXA did not reduce mortality in gastrointestinal bleeding. Therefore, routine TXA use in GI haemorrhage is not recommended.

10. Answer: K — Platelet target $>75 \times 10^9/L$

Explanation

In paediatric major haemorrhage:

- Hb target = 80 g/L
- Platelet target = $>75 \times 10^9/L$
- Fibrinogen >1.5 g/L
- PT ratio <1.5

This child has both low Hb and low platelets, but platelet count is specifically below the major haemorrhage target and requires urgent correction.

EMQ 53 and 54

Theme: AML

Options

- A. PML::RARA
 - B. RUNX1::RUNX1T1
 - C. CBFB::MYH11
 - D. KMT2A::MLLT3
 - E. DEK::NUP214
 - F. t(3;3)
 - G. AML with mutated NPM1
 - H. AML with CEBPA
 - I. AML with mutated TP53
 - J. AML with BCR::ABL1
-

Questions

Q1

A 34-year-old woman presents with menorrhagia, and rapidly worsening fatigue over 10 days. Examination reveals ecchymoses and mild fever but no significant lymphadenopathy. Laboratory tests show Hb 82 g/L, platelets $18 \times 10^9/L$, WBC $4.2 \times 10^9/L$, fibrinogen markedly reduced, prolonged PT/APTT, and very high D-dimer. Peripheral smear shows numerous abnormal hypergranular cells.

Which is the most likely diagnosis?

Q2

A 29-year-old man presents with recurrent chest infections and fatigue. Examination shows mild hepatosplenomegaly. Blood film demonstrates circulating blasts with large pink cytoplasmic granules and occasional Auer rods. Bone marrow shows myeloblasts with maturation and abnormal eosinophil precursors containing basophilic granules.

Which diagnosis is most likely?

Q3

A 48-year-old woman presents with marked leukocytosis, fever, and gingival hypertrophy. Bone marrow reveals acute monoblastic leukaemia. Flow cytometry shows CD33+, CD64+, CD14+, MPO weak+, HLA-DR+.

Which diagnosis is most likely?

Q4

A 56-year-old man presents with constitutional symptoms and severe thrombocytopenia. Examination reveals hepatosplenomegaly. Bone marrow shows multilineage dysplasia and blasts of 24%. Basophilia is present.

Which diagnosis is most likely?

Q5

A 63-year-old woman presents with fatigue and progressive cytopenias. Blood tests show Hb 79 g/L, WBC $3.1 \times 10^9/L$, platelets $42 \times 10^9/L$. Bone marrow reveals dysplastic megakaryocytes, 18% blasts, and marked thrombocytosis paradoxically present earlier in the disease course. Cytogenetics show chromosome 3q abnormality.

Most likely diagnosis?

Q6

A 45-year-old patient presents with fatigue and leukocytosis. Bone marrow shows 14% blasts with normal conventional cytogenetics. Molecular testing demonstrates an isolated NPM1 mutation. There is no FLT3-ITD. No other defining recurrent abnormality is detected.

Most likely diagnosis?

Q7

A 51-year-old patient has pancytopenia and marrow blasts of 12%. Molecular analysis reveals an in-frame bZIP mutation affecting. There is no history of antecedent MDS and cytogenetics are otherwise normal.

Most likely diagnosis?

Q8

A 70-year-old man with no prior haematological history presents with weight loss and severe pancytopenia. Bone marrow shows 15% blasts with complex karyotype including monosomy 5 and monosomy 7. Molecular testing demonstrates TP53 mutation with very high variant allele frequency.

Most likely diagnosis?

Q9

A 39-year-old patient presents with marked splenomegaly, high WBC count, and marrow blasts of 22%. Cytogenetics reveal t(9;22). Blasts are MPO positive and there is no convincing expression of lymphoid markers such as CD19, CD79a, or cytoplasmic CD3.

Most likely diagnosis?

Q10

A 27-year-old man presents with fatigue and recurrent infections. Peripheral blood shows blasts with large salmon-pink granules. Bone marrow reveals AML with maturation. CD19 aberrant expression is noted on flow cytometry.

Most likely diagnosis?

Answers with Explanation

Q1 → A. AML with t(15;17); PML::RARA

Explanation

Classic acute promyelocytic leukaemia (APL):

Key clues:

- DIC
- hypofibrinogenaemia
- promyelocytes
- faggot cells
- severe bleeding

Blast count does NOT need to be $\geq 20\%$.

This is a medical emergency requiring urgent ATRA.

Q2 → C. AML with inv(16)/t(16;16); CBFB::MYH11

Explanation

Classic clues:

- abnormal eosinophils
- AML with myelomonocytic differentiation
- core-binding factor AML

inv(16) is strongly associated with eosinophilia and favourable risk.

Q3 → D. AML with t(9;11); KMT2A::MLLT3

Explanation

Typical features:

- monoblastic/monocytic AML
- gingival hypertrophy
- 11q23 rearrangement

KMT2A rearrangements are high-yield in FRCPath.

Q4 → E. AML with t(6;9); DEK::NUP214

Explanation

Strong clues:

- basophilia
- multilineage dysplasia
- FLT3 mutation association
- poor prognosis

t(6;9) is strongly linked to FLT3 mutation.

Q5 → F. AML with inv(3)/t(3;3); GATA2, MECOM(EVI1)

Explanation

Classic features:

- thrombocytosis despite AML
- dysmegakaryopoiesis
- chromosome 3q abnormality
- MECOM/EVI1 activation

This carries very poor prognosis.

Q6 → G. AML with mutated NPM1

Explanation

NPM1-mutated AML is AML-defining even with blasts <20%.

This is a very common exam trap.

No 20% blast threshold required.

Q7 → H. AML with in-frame bZIP mutated CEBPA

Explanation

Updated classification now focuses on:

in-frame bZIP CEBPA mutation

—not simply biallelic mutation.

This is commonly tested in modern FRCPATH exams.

Q8 → I. AML with mutated TP53

Explanation

TP53-mutated AML often presents with:

- complex karyotype
- chromosome 5/7 abnormalities
- severe cytopenias
- poor prognosis

Can be classified with lower blast thresholds.

Q9 → J. AML with t(9;22); BCR::ABL1

Explanation

Important distinction:

This is AML with BCR::ABL1

—not MPAL because there are no lymphoid markers.

Very common viva trap.

Q10 → B. AML with t(8;21); RUNX1::RUNX1T1

Explanation

Typical clues:

- AML with maturation
- large salmon granules
- aberrant CD19 expression

This is a classic core-binding factor AML with favourable prognosis.

EMQ 55 AND 56

Options (each used once, more than once, or not at all):

- A. Pyruvate kinase deficiency
- B. Glucose-6-phosphate dehydrogenase deficiency
- C. Increased 2,3-bisphosphoglycerate
- D. Decreased oxygen affinity of haemoglobin

- E. Reticulocytosis masking enzyme deficiency
 - F. Heinz body formation
 - G. Echinocyte (burr cell) formation
 - H. Oxidative stress-induced hemolysis
 - I. ATP depletion in red cells
 - J. X-linked inheritance
-

Questions

Q1

A 24-year-old man of African ancestry presents with dark urine and jaundice 48 hours after starting trimethoprim-sulfamethoxazole. He reports similar episodes during childhood illnesses. Examination reveals mild scleral icterus but no splenomegaly. Hb is 95 g/L, reticulocytes are elevated, and LDH is raised. Blood film shows bite cells and blister cells.

Q2

A 17-year-old patient with a lifelong history of anemia presents with worsening fatigue. He has splenomegaly and gallstones. Hb is 85 g/L, reticulocytes are elevated. Blood film shows anisopoikilocytosis with numerous echinocytes. Enzyme assay reveals reduced pyruvate kinase activity.

Q3

A 28-year-old woman with chronic hemolytic anemia due to a glycolytic enzyme defect has relatively mild symptoms despite low hemoglobin levels. Laboratory testing shows elevated 2,3-BPG levels.

What is the main physiological adaptation explaining her relatively preserved exercise tolerance?

Q4

A 6-year-old child is investigated for chronic hemolysis. Initial enzyme assays for pyruvate kinase are within normal range. However, the reticulocyte count is markedly elevated. A repeat test after stabilization confirms enzyme deficiency.

Q5

A 35-year-old man with chronic hemolysis due to a glycolytic defect has a right-shifted oxygen dissociation curve on analysis.

What is the biochemical basis of this shift?

Q6

A 21-year-old male presents with acute hemolysis after eating fava beans. Family history reveals multiple affected male relatives on the maternal side. His sister is asymptomatic.

Q7

A patient with chronic nonspherocytic hemolytic anemia is found to have a deficiency in a key glycolytic enzyme. Red cells show reduced survival due to membrane rigidity and inability to maintain ion gradients.

What is the primary metabolic defect leading to hemolysis?

Q8

A peripheral blood smear from a patient with acute hemolysis shows inclusion bodies that stain with supravital dyes. These inclusions represent denatured hemoglobin due to oxidative damage.

Q9

A 30-year-old patient reports multiple episodes of jaundice triggered by infections and certain medications. Between episodes, hemoglobin levels are normal. No splenomegaly is noted.

Q10

A patient with pyruvate kinase deficiency is noted to have increased levels of 2,3-BPG. Despite anemia, oxygen delivery to tissues is relatively preserved.

What is the direct effect of increased 2,3-BPG on hemoglobin?

Answers

- 1 → **B. Glucose-6-phosphate dehydrogenase deficiency**
- 2 → **A. Pyruvate kinase deficiency**

- 3 → **D. Decreased oxygen affinity of haemoglobin**
 - 4 → **E. Reticulocytosis masking enzyme deficiency**
 - 5 → **C. Increased 2,3-bisphosphoglycerate**
 - 6 → **J. X-linked inheritance**
 - 7 → **I. ATP depletion in red cells**
 - 8 → **F. Heinz body formation**
 - 9 → **H. Oxidative stress-induced hemolysis**
 - 10 → **D. Decreased oxygen affinity of haemoglobin**
-

🔥 Why These Are Hard (Examiner Traps Explained)

Q1 trap

- No splenomegaly → pushes away from PK
 - Episodic + drug trigger → must recognise **oxidative hemolysis** → **G6PD**
-

Q2 trap

- Gallstones + chronic anemia → could be hereditary spherocytosis
 - BUT:
 - Echinocytes + enzyme defect → **PK deficiency**
-

Q3 vs Q5 (classic FRCPATH trick)

- Q3 asks **physiological effect** → answer = ↓ O₂ affinity
 - Q5 asks **biochemical cause** → answer = ↑ 2,3-BPG
 - 👉 They test if you separate **mechanism vs consequence**
-

Q4 (high-yield pitfall)

- Normal enzyme assay DOES NOT exclude disease
 - Reticulocytes = enzyme-rich → **false reassurance**
-

Q6

- Male + maternal lineage → **X-linked**
 - Classic G6PD inheritance pattern
-

Q7

- Core mechanism of PK deficiency:
 - ↓ ATP → membrane failure → hemolysis
 - 👉 examiners LOVE asking mechanism instead of diagnosis
-

Q8

- Don't confuse:
 - Heinz bodies = denatured Hb
 - Bite cells = consequence
 - 👉 question asks **what the inclusions are**
-

Q9

- Intermittent hemolysis = oxidative trigger
 - No chronic anemia → not PK
 - 👉 must pick **oxidative stress mechanism**
-

Q10

- Reinforces:
 - ↑ 2,3-BPG → ↓ Hb affinity → better tissue oxygenation
 - 👉 repeated concept = exam favourite
-

🧠 Ultra-High-Yield Memory Hooks

- **PK deficiency = “No ATP → cells collapse”**
- **G6PD = “Oxidative stress = crisis only”**
- **2,3-BPG = “Right shift = release oxygen”**
- **Retics = “Hide enzyme deficiency”**

EMQ 57 and 58

Theme: Haemoglobinopathies

Options (use once, more than once, or not at all):

- A. Sick cell trait (HbAS)
- B. Sick cell disease (HbSS)
- C. HbSC disease

- D. β -thalassaemia trait
 - E. β -thalassaemia major
 - F. $\delta\beta$ -thalassaemia
 - G. Hereditary persistence of fetal haemoglobin (HPFH)
 - H. HbE trait
 - I. HbE disease
 - J. HbD Punjab trait
 - K. HbC trait
 - L. HbH disease (α -thalassaemia)
 - M. Recent transfusion effect
 - N. Iron deficiency affecting HbA₂ interpretation
-

Questions

Q1

A 25-year-old man of West African origin is referred for pre-employment screening. He is asymptomatic with normal haemoglobin and mild microcytosis is absent. Family history is unremarkable.

HPLC shows:

- HbA 58%
- HbS 40%
- HbA₂ 2.5%
- HbF <1%

What is the most likely diagnosis?

Q2

A 3-year-old child presents with recurrent painful crises and dactylitis. Examination reveals mild splenomegaly.

HPLC shows:

- HbS 85%
- HbF 12%
- HbA₂ 3%
- HbA absent

What is the most likely diagnosis?

Q3

A 30-year-old woman undergoing antenatal screening is found to have a mild haemolytic picture. She is clinically well.

HPLC shows:

- HbA 52%
- HbC 43%
- HbA₂ 3%
- HbF <2%

What is the most likely diagnosis?

Q4

A 22-year-old woman is investigated for microcytic anaemia detected on routine blood testing. She has no significant symptoms.

FBC: low MCV, normal ferritin

HPLC shows:

- HbA 91%
- HbA₂ 5.6%
- HbF 1.2%

What is the most likely diagnosis?

Q5

A 1-year-old child of Mediterranean origin presents with failure to thrive, pallor, and hepatosplenomegaly. There is no history of transfusion.

HPLC shows:

- HbF 92%
- HbA absent
- HbA₂ 2%

What is the most likely diagnosis?

Q6

A 40-year-old asymptomatic man is incidentally found to have persistently elevated HbF during routine testing. His full blood count is normal, and there is a family history of similar findings without anaemia.

HPLC shows:

- HbA 70%
- HbF 28%
- HbA₂ normal

What is the most likely diagnosis?

Q7

A 28-year-old woman is referred for investigation of microcytosis. She reports fatigue.

FBC: low MCV

Ferritin: 6 µg/L (low)

HPLC shows:

- HbA 96%
- HbA₂ 2.9%
- HbF 1%

What is the most likely explanation for these findings?

Q8

A 35-year-old man of Southeast Asian origin is screened as part of a family study. He is asymptomatic.

HPLC shows:

- HbA 57%
- HbE 38%
- HbA₂ mildly elevated

What is the most likely diagnosis?

Q9

A 19-year-old patient presents with mild anaemia and occasional vaso-occlusive pain.

HPLC shows:

- HbS 45%
- HbC 45%
- HbF 8%
- HbA absent

What is the most likely diagnosis?

Q10

A 27-year-old man with known sickle cell disease presents for routine follow-up. He received a blood transfusion 3 weeks ago.

HPLC shows:

- HbA 35%
- HbS 40%
- HbF 20%
- HbA₂ 3%

What is the most likely explanation for this pattern?

Answers with Explanations

Q1 → A. Sickle cell trait (HbAS)

- HbA predominates with ~40% HbS
 - Normal HbA₂ excludes β -thalassaemia
 - Asymptomatic carrier state
-

Q2 → B. Sickle cell disease (HbSS)

- No HbA present
 - Predominantly HbS
 - Raised HbF (common in young children or hydroxycarbamide use)
-

Q3 → K. HbC trait

- HbA > HbC confirms trait
 - Typically asymptomatic or mild haemolysis
-

Q4 → D. β -thalassaemia trait

- Elevated HbA₂ (>3.5%) is diagnostic
 - Microcytosis with normal iron strongly supports this
-

Q5 → E. β -thalassaemia major

- Very high HbF with absent HbA
 - Severe clinical presentation in infancy
 - Classic pattern
-

Q6 → G. Hereditary persistence of fetal haemoglobin (HPFH)

- High HbF but **clinically silent**
 - Normal indices distinguish from $\delta\beta$ -thalassaemia
-

Q7 → N. Iron deficiency affecting HbA₂ interpretation

- HbA₂ not elevated despite microcytosis
 - Iron deficiency suppresses HbA₂ → can mask β -thal trait
-

Q8 → H. HbE trait

- HbE ~30–40% with remaining HbA
 - Common in Southeast Asian populations
 - Mild or no symptoms
-

Q9 → C. HbSC disease

- No HbA present
 - Roughly equal HbS and HbC
 - HbF mildly elevated
-

Q10 → M. Recent transfusion effect

- Presence of HbA in known HbSS patient
- Mixed pattern due to donor blood
- Always consider transfusion within last 3 months

EMQ 59 and 60

Theme: Perioperative Anticoagulation

Options

- A. Continue warfarin without interruption
 - B. Stop warfarin 5 days pre-op, no bridging
 - C. Stop warfarin 5 days pre-op + therapeutic LMWH bridging
 - D. Stop warfarin 5 days pre-op + prophylactic LMWH
 - E. Continue DOAC without interruption
 - F. Stop DOAC 24 hours pre-op
 - G. Stop DOAC 48–72 hours pre-op
 - H. Delay surgery
 - I. Warfarin reversal by PCC and Vitamin K
 - J. Restart anticoagulation 6–12 hours post-op at therapeutic dose
-

Questions

Q1

A 68-year-old man with **non-valvular AF**, CHA₂DS₂-VASc = 2, on warfarin, is scheduled for **elective inguinal hernia repair**.

Q2

A 75-year-old woman with **mechanical mitral valve** on warfarin requires **emergency hip fracture surgery**.

Q3

A 60-year-old man with AF on **apixaban**, normal renal function, undergoing **colonoscopy with polypectomy**.

Q4

A 72-year-old woman with **recent VTE (3 weeks ago)** on warfarin requires **elective cholecystectomy**.

Q5

A 66-year-old man with AF on **rivaroxaban**, CrCl 25 mL/min, scheduled for **major abdominal surgery**.

Q6

A 55-year-old woman on warfarin for **AF**, CHA₂DS₂-VASc = 1, undergoing **cataract surgery**.

Q7

A 70-year-old man with **mechanical aortic valve** on warfarin undergoing **elective knee replacement**.

Q8

A 64-year-old woman on **dabigatran**, normal renal function, undergoing **high bleeding risk neurosurgery**.

Q9

A 58-year-old man on warfarin for **unprovoked VTE 5 years ago**, now scheduled for **minor dermatological excision**.

Q10

A 77-year-old woman on warfarin for AF undergoes major surgery. Haemostasis is secure post-op. When should therapeutic anticoagulation be restarted?

Answers + Explanations

Q1 → B

Stop warfarin 5 days pre-op, no bridging

- Low-moderate thrombotic risk (CHA₂DS₂-VASc = 2)
 - No bridging needed per NICE/BSH guidance
 - Hernia repair = moderate bleeding risk
-

Q2 → I

Reversal by PCC and Vitamin K

- Mechanical **mitral** valve = **very high thrombotic risk**
 - Urgent surgery → need **rapid reversal**
-

Q3 → F

Stop DOAC 24 hours pre-op

- Apixaban + normal renal function
 - Procedure = **moderate bleeding risk**
 - 24 hours sufficient interruption
-

Q4 → C

Stop warfarin + therapeutic LMWH bridging

- VTE within **3 months** = **high risk**
 - Requires full bridging anticoagulation
-

Q5 → G

Stop DOAC 48–72 hours pre-op

- Rivaroxaban + **renal impairment (CrCl 25)**
 - Major surgery = high bleeding risk
 - Prolonged clearance → longer hold needed
-

Q6 → A

Continue warfarin without interruption

- Cataract surgery = **minimal bleeding risk**
 - Evidence supports continuing warfarin
-

Q7 → D

Stop warfarin + prophylactic LMWH

- Mechanical **aortic valve (low risk)**
 - Intermediate thrombotic risk
 - Prophylactic (not therapeutic) bridging acceptable
-

Q8 → G

Stop DOAC 48–72 hours pre-op

- Dabigatran + high bleeding risk (neurosurgery)

- Even with normal renal function → extended interruption
-

Q9 → A

Continue warfarin

- Minor skin procedure
 - Low bleeding risk → no interruption needed
-

Q10 → J

Restart anticoagulation 6–12 hours post-op (if haemostasis secure)

- Standard principle:
 - Early restart reduces thrombosis risk
 - Must balance bleeding → ensure haemostasis
-

Key Exam Pearls (High-Yield)

- **High thrombotic risk = bridge**
 - Mechanical mitral valve
 - VTE < 3 months
- **DOAC timing depends on:**
 - Renal function
 - Bleeding risk of surgery
- **Warfarin:**
 - Stop ~5 days pre-op
 - Bridge only if high risk
- **Minor procedures:**
 - Usually **continue anticoagulation**

EMQ 61

Theme: Inherited Platelet Disorders

- A. May–Hegglin anomaly
 - B. Sebastian syndrome
 - C. Fechtner syndrome
 - D. Epstein syndrome
 - E. Eckstein syndrome
 - F. Bernard–Soulier syndrome
 - G. Grey platelet syndrome
 - H. Giant platelet syndrome with velocardiofacial syndrome (22q11.2 deletion)
-

Questions (Select ONE best option for each scenario):

Q1.

A 24-year-old man is incidentally found to have thrombocytopenia on routine blood tests. Blood film shows giant platelets and Döhle-like leukocyte inclusions. Platelet function is otherwise normal. Genetic testing reveals an MYH9 mutation.

Q2.

A 19-year-old woman presents with hearing loss, cataracts, and proteinuria. Blood film shows granulocyte inclusions similar to those seen in Sebastian syndrome. Platelet count is low but function is near normal.

Q3.

A 32-year-old man has lifelong mild thrombocytopenia, nephritis, and progressive sensorineural deafness. Blood film shows Döhle-like bodies and giant platelets. Platelet aggregation studies are normal.

Q4.

A 27-year-old woman presents with bleeding gums and menorrhagia. Platelet aggregation studies show defective adhesion to von Willebrand factor. Platelets are large and dysfunctional. No leukocyte inclusions are seen.

Q5.

A 15-year-old boy has recurrent epistaxis and easy bruising. Blood film shows absence of alpha granules giving platelets a pale appearance. Platelet count is mildly reduced.

Q6.

A newborn is noted to have cyanotic congenital heart disease, hypocalcaemia, and facial dysmorphism. Platelets are large with reduced glycoprotein Ib/IX expression.

Q7.

A 40-year-old man presents with thrombocytopenia and nephritis. Blood film shows MYH9-related giant platelets, leukocyte inclusions, and cataracts. Unlike Sebastian syndrome, granulocyte inclusions are distinct in morphology.

Q8.

A 10-year-old child has mild bleeding symptoms. Blood film shows large platelets but no leukocyte inclusions. Platelet function is near normal. There is a family history of autosomal dominant thrombocytopenia.

✓ ANSWERS

1. **A — May-Hegglin anomaly**
 2. **B — Sebastian syndrome**
 3. **C — Fechtner syndrome**
 4. **F — Bernard-Soulier syndrome**
 5. **G — Grey platelet syndrome**
 6. **H — Giant platelet syndrome with velocardiofacial syndrome**
 7. **C — Fechtner syndrome**
 8. **E — Eckstein syndrome**
-

🧠 EXPLANATIONS**A. May-Hegglin anomaly**

- MYH9 mutation
- Giant platelets + Döhle-like inclusions in neutrophils
- Mild thrombocytopenia, usually normal function

- Classic entry point of MYH9-related disorders
-

B. Sebastian syndrome

- MYH9-related
 - Similar to May–Hegglin but **distinct granulocyte inclusions**
 - Mild thrombocytopenia
 - Near-normal platelet function
 - Often differentiated morphologically on blood film
-

C. Fechtner syndrome

- MYH9 mutation
 - Triad: thrombocytopenia + nephritis + deafness
 - May include cataracts
 - Leukocyte inclusions present but distinct
 - More systemic involvement than Sebastian
-

D. Epstein syndrome

- MYH9-related
 - Platelet dysfunction more prominent than inclusions
 - Nephritis + deafness present
 - **Key point: no granulocyte inclusions**
-

E. Eckstein syndrome

- Similar to Epstein syndrome but **platelet function is normal**
 - MYH9 mutation
 - Mild thrombocytopenia with large platelets
 - No leukocyte inclusions
-

F. Bernard–Soulier syndrome

- GpIb/IX deficiency

- Defective adhesion to von Willebrand factor
 - Giant platelets + severe bleeding tendency
 - **Ristocetin test abnormal**
-

G. Grey platelet syndrome

- Alpha granule deficiency
 - “Grey” appearance on blood film
 - Mild thrombocytopenia + bleeding tendency
 - Platelet aggregation defects due to absent granule contents
-

H. Giant platelet syndrome with velocardiofacial syndrome

- 22q11.2 deletion
- Congenital heart disease (conotruncal defects)
- Dysmorphism + hypocalcaemia
- Platelet abnormalities with large platelets and GpIb/IX issues

EMQ 62 and 63

Options

- A. APL
 - B. BPDCN
 - C. CMML
 - D. T-PLL
 - E. ATLL
 - F. T-LGL
 - G. NK-LGL
 - H. Hairy Cell Leukaemia
 - I. CLL
 - J. Mantle Cell Lymphoma
 - K. Follicular Lymphoma
 - L. Burkitt Lymphoma
 - M. DLBCL
 - N. Classical Hodgkin Lymphoma
 - O. Nodular Lymphocyte Predominant Hodgkin Lymphoma
 - P. Waldenström Macroglobulinaemia
 - Q. Splenic Marginal Zone Lymphoma
 - R. ALCL
 - S. PTCL-NOS
 - T. Sézary Syndrome
-

Questions

Q1

A 36-year-old woman presents with fatigue, spontaneous bruising, and gum bleeding. Blood tests show pancytopenia and prolonged PT/APTT with low fibrinogen. Blood film reveals abnormal promyelocytes with multiple Auer rods. Bone marrow aspirate shows hypergranular cells. Flow cytometry demonstrates CD45+, MPO+, CD33+, CD117+, with absence of CD34 and HLA-DR.

Q2

A 72-year-old man presents with marked lymphocytosis (WBC $180 \times 10^9/L$), weight loss, and massive splenomegaly. Peripheral blood shows medium-sized lymphoid cells with prominent nucleoli. Immunophenotyping reveals CD2+, CD3+, CD5+, strong CD7 expression, and bright CD52 positivity.

Q3

A 65-year-old presents with fatigue, night sweats, and splenomegaly. Bloods show persistent monocytosis ($2.5 \times 10^9/L$) over several months. Bone marrow demonstrates dysplasia in myeloid lineages. Flow cytometry shows CD11b+, CD13+, CD16+, with aberrant CD56 expression.

Q4

A 68-year-old asymptomatic male is found incidentally to have lymphocytosis. Blood film shows small mature lymphocytes and frequent smudge cells. Flow cytometry reveals CD19+, CD5+, CD23+, weak surface Ig, CD200+, and negative FMC7.

Q5

A 59-year-old man presents with fatigue, recurrent infections, and marked splenomegaly. Peripheral blood shows lymphoid cells with cytoplasmic projections. Bone marrow aspirate is difficult ("dry tap"). Immunophenotype: CD11c+, CD25+, CD103+, CD123+.

Q6

A 62-year-old woman presents with generalized lymphadenopathy. Excisional lymph node biopsy shows a nodular architecture. Flow cytometry reveals CD19+, CD20+, CD10+, BCL6+, and CD5 negative.

Q7

A 41-year-old patient presents with a rapidly enlarging abdominal mass and high LDH. Blood film is unremarkable. Biopsy shows a "starry sky" appearance. Immunophenotype: CD10+, CD20+, CD38++, CD43+, Ki-67 nearly 100%.

Q8

A 75-year-old presents with painless lymphadenopathy and B symptoms. Lymph node biopsy reveals large atypical cells. Immunophenotype: CD20+, CD10-, variable CD30 expression, high proliferation index.

Q9

A 28-year-old presents with cervical lymphadenopathy and fever. Lymph node biopsy shows Reed–Sternberg cells in a mixed inflammatory background. Immunophenotype: CD30+, CD15+, CD45–, CD20–.

Q10

A 61-year-old presents with generalized erythroderma, intense pruritus, and lymphadenopathy. Peripheral blood shows atypical cerebriform lymphocytes. Immunophenotype demonstrates CD3+, CD4+ T-cells with loss of CD7 and CD26.

✓ Answers with Explanations

Q1 → A. APL

DIC + promyelocytes + **CD34–, HLA-DR–** = classic.
This combo is one of the most tested immunophenotypes.

Q2 → D. T-PLL

Clues:

- Very high lymphocyte count
 - Prominent nucleoli
 - Strong CD7 and **CD52 positivity**
Distinguishes from other mature T-cell neoplasms.
-

Q3 → C. CMML

- Persistent monocytosis
 - Dysplasia
 - Aberrant CD56 → supports clonal disorder
-

Q4 → I. CLL

Classic:

- CD5+ B-cell
-

- CD23+
 - Weak Ig
 - CD200+
 - Smudge cells reinforce diagnosis
-

Q5 → H. Hairy Cell Leukaemia

- “Dry tap”
 - Splenomegaly
 - **CD11c, CD25, CD103, CD123 all positive** = textbook
-

Q6 → K. Follicular Lymphoma

- CD10+, BCL6+
 - CD5–
 - Nodular pattern
Classic germinal center tumor
-

Q7 → L. Burkitt Lymphoma

- Starry sky
 - Ki-67 ~100%
 - CD10+, CD38++
Aggressive, MYC-driven tumor
-

Q8 → M. DLBCL

- Large B cells
 - CD20+
 - High proliferation
 - Variable CD30 → can confuse with Hodgkin
-

Q9 → N. Classical Hodgkin Lymphoma

- CD30+, CD15+
- CD45–

- Reed–Sternberg cells = defining feature
-

Q10 → T. Sézary Syndrome

- Erythroderma
 - Circulating cerebriform cells
 - Loss of CD7/CD26 = key diagnostic clue
-

High-Yield Traps They Love

- **CD30 positivity**
 - Hodgkin vs ALCL → check CD15 & CD45
- **CD5+ B cells**
 - CLL vs Mantle → CD23 is decisive
- **T-cell neoplasms**
 - CD7 retained → T-PLL
 - CD7 lost → Sézary
- **Hairy cell markers**
 - All positive = classic
 - Missing CD25 → think variant (now removed here)

Theme: Cytogenetics & Molecular Abnormalities

Options (Each option may be used once, more than once, or not at all)

- A. t(8;21) – RUNX1-RUNX1T1
 - B. inv(16) / t(16;16) – CBFB-MYH11
 - C. t(15;17) – PML-RARA
 - D. t(9;22) – BCR-ABL1
 - E. t(11;14) – CCND1-IGH
 - F. t(14;18) – IGH-BCL2
 - G. t(8;14) – MYC-IGH
 - H. t(11;17) – PLZF-RARA
 - I. t(5;14) – IL3-IGH
 - J. t(4;14) – FGFR3-MMSET
-

Questions

Q1

A 32-year-old woman presents with fatigue, bruising, and gum bleeding. Blood film shows abnormal promyelocytes with multiple Auer rods. Coagulation profile reveals prolonged PT and low fibrinogen. Despite starting ATRA, there is minimal response.

Which translocation is most likely?

Q2

A 45-year-old man presents with leukocytosis and splenomegaly. Bone marrow shows granulocytic hyperplasia. Cytogenetics reveal a fusion gene leading to constitutive tyrosine kinase activity.

Which abnormality is responsible?

Q3

A 28-year-old patient presents with AML. Bone marrow shows blasts with abundant cytoplasm, Auer rods, and evidence of granulocytic maturation. There is good prognosis with standard chemotherapy.

Which translocation is most likely?

Q4

A 50-year-old patient presents with lymphadenopathy. Lymph node biopsy shows closely packed follicles lacking polarization. Cells express CD10, BCL6, and aberrant BCL2 positivity in germinal centres.

Which genetic abnormality explains this?

Q5

A 7-year-old boy presents with jaw swelling and rapidly enlarging abdominal mass. LDH is markedly elevated. Cytogenetics show translocation involving chromosome with immunoglobulin heavy chain locus.

What is the most likely translocation?

Q6

A 60-year-old male presents with hypercalcaemia, and bone pain. Serum protein electrophoresis reveals monoclonal spike. Cytogenetics show translocation involving FGFR3 and MMSET genes.

Which abnormality is most likely?

Q7

A 35-year-old woman presents with AML. Bone marrow shows abnormal eosinophils with basophilic granules and myelomonocytic features.

Which translocation corresponds to this?

Q8

A 68-year-old male presents with generalized lymphadenopathy. Lymph node biopsy shows small lymphocytes with irregular nuclei. SOX11 is positive.

Which translocation is most likely?

Q9

A 5-year-old child presents with marked eosinophilia and B-cell lymphoblastic leukaemia. Molecular analysis shows activation of IL-3 due to proximity to immunoglobulin heavy chain locus.

Which translocation is responsible?

✓ **Answers with Explanations**

Q1 → H. t(11;17) – PLZF-RARA

👉 Variant APL resistant to ATRA (key exam trap)

Q2 → D. t(9;22) – BCR-ABL1

👉 CML hallmark → constitutive tyrosine kinase → imatinib response

Q3 → A. t(8;21) – RUNX1-RUNX1T1

👉 AML with maturation → good prognosis

Q4 → F. t(14;18) – IGH-BCL2

👉 Follicular lymphoma → BCL2 overexpression prevents apoptosis

Q5 → G. t(8;14) – MYC-IGH

👉 Burkitt lymphoma → MYC activation → high proliferation

Q6 → J. t(4;14) – FGFR3-MMSET

👉 Poor prognosis myeloma subtype

Q7 → B. inv(16) – CBFB-MYH11

👉 AML with abnormal eosinophils → favourable prognosis

Q8 → E. t(11;14) – CCND1-IGH

👉 Mantle cell lymphoma → cyclin D1 overexpression

Q9 → I. t(5;14) – IL3-IGH

👉 Rare B-ALL with eosinophilia → classic exam question

 Exam Tips (High Yield)

- **APL variants (PLZF-RARA)** = ATRA resistant ⚠
- **inv(16) + t(8;21)** = favourable AML
- **t(4;14), t(14;16)** = poor myeloma prognosis
- **MYC translocations** = very high proliferation (Ki-67 ~100%)
- **IGH translocations** = common in B-cell malignancies

Theme: TLS

Options

Each option may be used once, more than once, or not at all.

- A. Oral allopurinol (standard dose)
- B. High-dose allopurinol (up to 800 mg/day)
- C. Febuxostat
- D. Aggressive IV hydration alone
- E. Fixed-dose rasburicase (3 mg stat)
- F. Weight-based rasburicase (0.2 mg/kg daily)
- G. Stop allopurinol and commence rasburicase
- H. Continue allopurinol and add rasburicase
- I. Emergency hyperkalaemia protocol
- J. IV calcium gluconate
- K. Withhold calcium replacement
- L. Initiate renal replacement therapy
- M. Sodium bicarbonate infusion
- N. Repeat uric acid with iced sample and interpret cautiously

10 SCENARIOS

Q1

A 41-year-old man presents with **abdominal distension, night sweats, and weight loss**. Imaging shows a **14 cm mesenteric mass**. Bloods:

- LDH: 6× ULN
- Uric acid: 410 µmol/L
- Creatinine: normal

Biopsy confirms **Burkitt lymphoma**. He is haemodynamically stable and planned for urgent chemotherapy within 12 hours.

He is drinking poorly due to nausea and has had minimal oral intake for 48 hours.

What is the most appropriate immediate management strategy?

Q2

A 72-year-old frail woman with **CKD stage 4 (eGFR 22 mL/min)** is diagnosed with **DLBCL** (bulky 11 cm mass, LDH 3× ULN).

She is started on pre-phase steroids and oral allopurinol.
24 hours later:

- Uric acid rises from 380 → 520 $\mu\text{mol/L}$
- Creatinine increases
- Potassium normal

She remains clinically stable.

What is the best next step?

Q3

A 59-year-old man with **CLL** is admitted for initiation of **venetoclax**.
Baseline:

- Lymph nodes 9 cm
- LDH 2× ULN
- Uric acid normal

Prophylaxis:

- Oral hydration + allopurinol

12 hours after first dose:

- Uric acid: 600 $\mu\text{mol/L}$
- Phosphate rising
- Creatinine mildly elevated

He is asymptomatic.

What is the most appropriate escalation?

Q4

A 36-year-old patient with **T-ALL (WCC $180 \times 10^9/\text{L}$)** develops 6 hours after starting steroids:

- K^+ 6.6 mmol/L
- ECG: peaked T waves
- Uric acid: 520 $\mu\text{mol/L}$

He is drowsy but rousable.

What is the immediate priority in management?

Q5

A 65-year-old man with **AML** develops confirmed TLS:

- Uric acid: 780 $\mu\text{mol/L}$
- Creatinine rising
- Phosphate 2.3 mmol/L

He has been on allopurinol for 48 hours.

What is the most appropriate urate-lowering strategy NOW?

Q6

A 54-year-old patient with TLS is receiving rasburicase.
Repeat bloods show:

- Uric acid: 90 $\mu\text{mol/L}$ (previously 700)
- Phosphate rising
- Creatinine worsening

The sample was transported routinely (not on ice).

Clinically, the patient is deteriorating.

What is the most appropriate interpretation/action?

Q7

A 68-year-old man with TLS has:

- Calcium: 1.7 mmol/L
- Phosphate: 2.6 mmol/L
- No neuromuscular or cardiac symptoms

The junior doctor is concerned and suggests correction.

What is the most appropriate management?

Q8

A 61-year-old woman with TLS develops:

- Severe muscle cramps

- Carpopedal spasm
- QT prolongation

Biochemistry:

- Calcium 1.65 mmol/L
- Phosphate 2.4 mmol/L

What is the most appropriate immediate treatment?

Q9

A 70-year-old patient with refractory TLS despite hydration and rasburicase has:

- Potassium 6.4 mmol/L (persistent)
- Phosphate rising
- Creatinine doubling
- Oliguria

He is becoming fluid overloaded.

What is the most appropriate next step?

Q10

A 48-year-old man with high-grade lymphoma and TLS is being managed on the ward. A junior doctor proposes:

“We should alkalinise the urine to prevent uric acid crystallisation.”

The patient already has:

- Hyperphosphataemia
- Hypocalcaemia

What is the best response?

ANSWERS WITH DEEP EXPLANATIONS

Q1 → E. Fixed-dose rasburicase (3 mg stat)

Why this is hard:

- You must integrate:

- Burkitt (very high risk)
- Bulky disease + high LDH
- Poor oral intake (limits oral hydration)

Key reasoning:

- This is **high-risk TLS** → **needs rasburicase upfront**
- Oral strategies are insufficient
- IV hydration alone is inadequate

👉 Early rasburicase is a **patient safety priority**

Q2 → G. Stop allopurinol and commence rasburicase

Trap:

- Already on “appropriate prophylaxis”

But:

- Rising urate + AKI = **failure of prophylaxis**
- CKD → higher risk of rapid deterioration

👉 Switch to rasburicase

👉 Continuing allopurinol is ineffective here

Q3 → G. Stop allopurinol and commence rasburicase

Key nuance:

- CLL normally low risk
- Venetoclax → **high-risk biology**

This is evolving TLS:

- Rising urate + phosphate + creatinine

👉 Escalate to rasburicase immediately

Q4 → I. Emergency hyperkalaemia protocol

Classic prioritisation question

Even though TLS is present:

👉 **Hyperkalaemia with ECG changes = immediate threat to life**

Treat first:

- Calcium, insulin-glucose, etc.

TLS-specific therapy comes after stabilisation.

Q5 → G. Stop allopurinol and commence rasburicase

Why not F immediately?

- In many UK protocols:
 - Start rasburicase (fixed or weight-based depending on context)
- The key tested concept:
👉 **Allopurinol must be stopped**

Because:

- It blocks new urate formation
 - Does NOT reduce existing urate
-

Q6 → N. Repeat uric acid with iced sample and interpret cautiously

Very high-yield lab trap

Rasburicase:

- Continues breaking down uric acid **in vitro**
- Leads to **false low levels**

👉 Result may be misleading

👉 Clinical deterioration overrides lab value

Q7 → K. Withhold calcium replacement

Key principle:

- Asymptomatic hypocalcaemia → DO NOT treat

Because:

- High phosphate → calcium-phosphate precipitation
 - Can worsen renal failure
-

Q8 → J. IV calcium gluconate

Contrast with Q7

Now:

- Symptomatic (tetany + ECG changes)

👉 Must treat

But:

- Aim = symptom control, not full correction
-

Q9 → L. Initiate renal replacement therapy

Integrated decision point

Features:

- Refractory hyperkalaemia
- Rising creatinine
- Fluid overload
- Oliguria

👉 Meets **multiple dialysis criteria**

Q10 → M. Sodium bicarbonate infusion

Correct interpretation: this is **WRONG** practice

Best answer = recognising:

👉 This should NOT be done

Reason:

- Increases calcium-phosphate precipitation
- No longer recommended

EMQ 68 and 69

Options

- A. No transfusion required
 - B. Simple transfusion (top up)
 - C. Exchange transfusion
 - D. Either simple or exchange transfusion depending on severity
 - E. Avoid transfusion unless life-threatening anaemia
 - F. Urgent red cell exchange within hours
 - G. Chronic transfusion programme
 - H. Emergency transfusion followed by ICU support
 - I. Supportive management only
 - J. Pre-operative transfusion optimisation
 - K. Automated exchange transfusion
 - L. Manual exchange transfusion
 - M. Transfusion contraindicated
 - N. Immediate neurology-led stroke protocol plus exchange transfusion
 - O. Observation and repeat haemoglobin assessment
-

Questions

1.

A 19-year-old woman with HbSS disease presents with worsening fatigue and dizziness following a recent parvovirus infection. Examination shows pallor but no splenomegaly. Hb has fallen from 8.5 g/dL to 3.9 g/dL with a markedly low reticulocyte count. She is haemodynamically stable with no respiratory symptoms.

What is the most appropriate transfusion strategy?

2.

A 7-year-old boy with HbSS disease is brought to hospital with abdominal distension, lethargy, and tachycardia. Examination reveals a rapidly enlarging spleen. Hb is 4.8 g/dL (baseline 8.2 g/dL) with reticulocytosis. Blood pressure is borderline low.

What is the most appropriate transfusion strategy?

3.

A 25-year-old man with sickle cell disease develops severe chest pain, hypoxia, fever, and bilateral pulmonary infiltrates on chest imaging. Oxygen

saturation remains 84% despite supplemental oxygen. Hb is close to baseline at 8.0 g/dL.

What is the most appropriate transfusion strategy?

4.

A 30-year-old woman with HbSS disease suddenly develops right-sided weakness and expressive dysphasia. CT head excludes haemorrhage. Symptoms began 2 hours earlier. Hb is 7.9 g/dL.

What is the most appropriate transfusion strategy?

5.

A 33-year-old man with sickle cell disease develops severe sepsis secondary to pneumococcal bacteraemia. He becomes hypotensive and requires ICU admission. Laboratory tests demonstrate rising lactate and worsening hypoxia.

What is the most appropriate transfusion strategy?

6.

A 14-year-old girl with HbSC disease is scheduled for elective laparoscopic cholecystectomy. She has a history of recurrent vaso-occlusive crises but is clinically stable at present.

What is the most appropriate transfusion strategy?

7.

A 27-year-old pregnant woman with HbSS disease presents at 28 weeks gestation with recurrent painful crises requiring multiple admissions. Fetal growth restriction has also been identified on ultrasound.

What is the most appropriate transfusion strategy?

8.

A 22-year-old man with sickle cell disease develops progressive jaundice, tender hepatomegaly, worsening liver function tests, and coagulopathy. Bilirubin is markedly elevated and there is evidence of acute liver failure.

What is the most appropriate transfusion strategy?

9.

A 24-year-old woman with sickle cell disease develops dark urine and severe anaemia 10 days after receiving a blood transfusion. Hb falls to 4.5 g/dL. Antibody testing suggests delayed haemolytic transfusion reaction. She is stable without cardiovascular compromise.

What is the most appropriate transfusion strategy?

10.

A 9-year-old child with HbSS disease undergoes transcranial Doppler screening which demonstrates persistently elevated cerebral blood flow velocities associated with high future stroke risk. The child has never had a stroke.

What is the most appropriate transfusion strategy?

Answers with Explanations

Q Answer Explanation

- | | | |
|---|----------|---|
| 1 | B | This is aplastic crisis , classically due to parvovirus B19. Severe anaemia with reticulocytopenia is treated with simple transfusion . |
| 2 | B | Acute splenic sequestration causes rapid pooling of blood in the spleen with hypovolaemia and severe anaemia. Initial treatment is simple transfusion . |
| 3 | D | Acute chest syndrome (ACS) may require either simple or exchange transfusion depending on severity. Severe hypoxia and extensive infiltrates strongly favour exchange, but ACS overall falls into the “simple or exchange” category. |
| 4 | C | Acute stroke or neurological deficit in sickle cell disease is an indication for urgent exchange transfusion to rapidly reduce HbS concentration. |
| 5 | C | Severe sepsis with organ dysfunction in sickle cell disease is treated with exchange transfusion because reducing HbS improves oxygen delivery and rheology. |
| 6 | C | HbSC patients undergoing elective low- or medium-risk surgery are recommended to receive exchange transfusion . |

Q Answer Explanation

- 7 **D** Pregnancy with recurrent crises and fetal risk may require **simple or exchange transfusion**, depending on severity and multidisciplinary assessment.
- 8 **C** Acute intrahepatic cholestasis is a severe, life-threatening hepatic complication requiring urgent **exchange transfusion**.
- 9 **E** In delayed haemolytic transfusion reaction, further transfusion may worsen haemolysis and should generally be avoided unless anaemia is life-threatening.
- 10 **D** Primary stroke prevention in children with abnormal transcranial Doppler findings may use either **simple or exchange transfusion**.

EMQ 70 and 71

Options

- A. Immediate simple (top-up) transfusion
 - B. Urgent red cell exchange transfusion
 - C. Incentive spirometry and aggressive analgesia only
 - D. Broad-spectrum antibiotics including atypical cover
 - E. Transfer to intensive care for ventilatory support
 - F. Pulmonary embolism should be considered and investigated
 - G. Rib infarction leading to hypoventilation
 - H. Fluid overload causing worsening hypoxia
 - I. Delayed haemolytic transfusion reaction
 - J. Hydroxycarbamide for secondary prevention
 - K. Regular transfusion programme for secondary prevention
 - L. Acute respiratory distress syndrome (ARDS)
 - M. Bronchodilator therapy
 - N. Urgent arterial blood gas analysis on room air
 - O. No transfusion currently indicated
 - P. Pre-operative exchange transfusion
 - Q. Mycoplasma pneumoniae infection
 - R. Opioid-induced hypoventilation
-

Questions

Question 1

A 24-year-old man with HbSS disease is admitted with severe lumbar spine and bilateral rib pain. He has a history of previous ACS and is on intermittent hydroxycarbamide with poor adherence. On admission his oxygen saturation is 97% on air and chest examination is normal. He receives repeated IV morphine boluses overnight.

Twelve hours later he becomes increasingly drowsy. Respiratory rate is 8/min, oxygen saturation falls to 91% on room air, and nursing staff note shallow breathing. Chest X-ray shows only minimal bibasal atelectatic change without focal consolidation. Arterial blood gas demonstrates rising pCO₂.

Which is the SINGLE most likely precipitating factor?

Question 2

A 31-year-old pregnant woman with HbSS disease at 30 weeks' gestation is admitted with painful crisis involving the thoracic spine and chest wall. Initial observations are stable. Over the next 18 hours she develops fever 38.6°C, tachycardia, productive cough and oxygen saturation of 93% on air. Chest X-ray demonstrates a new right lower lobe infiltrate. Haemoglobin has fallen from a baseline of 86 g/L to 67 g/L.

She remains haemodynamically stable with no evidence of respiratory failure.

What is the MOST appropriate transfusion strategy?

Question 3

A 22-year-old woman with HbSS disease presents with painful crisis. She has severe pleuritic chest pain in a "T-shirt distribution." Initial chest X-ray is normal. Six hours later she develops worsening tachypnoea, fever 38.4°C, oxygen saturation 89% despite 15 L oxygen, and diffuse bilateral pulmonary infiltrates involving three lobes.

Arterial blood gas on room air earlier showed PaO₂ 61 mmHg.

What is the MOST appropriate immediate management?

Question 4

A 27-year-old man with HbSC disease develops ACS following femoral surgery performed under general anaesthesia. He becomes febrile with bilateral basal crackles and oxygen saturation 92% on air. Chest radiograph shows patchy bibasal infiltrates.

His haemoglobin is 111 g/L, close to baseline.

What is the MOST appropriate next step regarding transfusion?

Question 5

A 19-year-old student with HbSS disease is admitted with fever, dry cough, headache, and progressive breathlessness. Chest X-ray demonstrates bilateral patchy infiltrates. Blood cultures are negative. CRP is markedly elevated. There is associated mild haemolysis and reticulocytosis.

Several university classmates recently experienced atypical pneumonia.

Which underlying trigger is MOST likely?

Question 6

A 35-year-old man with HbSS disease is admitted with severe vaso-occlusive crisis. He receives large volumes of intravenous crystalloid over 24 hours. Subsequently he develops worsening oxygen requirements, bibasal crackles, elevated jugular venous pressure, and chest X-ray showing diffuse pulmonary shadowing.

Echocardiography demonstrates preserved ventricular function.

What is the MOST likely contributor to his respiratory deterioration?

Question 7

A 29-year-old woman with recurrent ACS episodes has had three hospital admissions in the past year requiring transfusion support. She is now clinically stable following recovery from another episode. She asks about strategies to reduce future ACS risk.

Which is the MOST evidence-based long-term disease-modifying therapy?

Question 8

A 26-year-old man with HbSS disease and previous splenectomy is admitted with ACS. Despite maximal oxygen therapy, oxygen saturation remains 84%. Arterial blood gas reveals PaO₂ 54 mmHg and rising pCO₂. He becomes increasingly exhausted with worsening work of breathing.

What is the MOST appropriate next step?

Question 9

A 33-year-old woman with HbSS disease is admitted with painful crisis involving ribs and upper abdomen. She has severe pleuritic pain causing shallow respirations but no fever or infiltrates initially. Oxygen saturation is 95% on air.

The haematology consultant emphasises a non-pharmacological intervention to reduce risk of progression to ACS.

Which is the MOST appropriate intervention?

Question 10

A 37-year-old man with HbSS disease presents five days after receiving transfusion support for ACS. He develops recurrent fever, worsening anaemia, dark urine, and increasing pain. Haemoglobin falls from 92 g/L post-transfusion to 51 g/L. LDH and bilirubin are markedly elevated. Repeat chest imaging shows no major progression of infiltrates.

Direct antiglobulin test is weakly positive.

What is the MOST likely diagnosis?

Answers and Explanations**Question 1****Answer**

R. Opioid-induced hypoventilation

Explanation

This patient demonstrates opioid-related respiratory depression causing hypoventilation and early ACS physiology. Excessive opioid sedation is a recognised precipitant of ACS because shallow breathing promotes atelectasis, hypoxia, and pulmonary sickling. The elevated pCO₂ strongly supports hypoventilation rather than isolated infection. Rib pain also contributes through splinting of the diaphragm.

Candidates must recognise that ACS may develop during treatment of painful crisis and may initially present subtly before radiographic infiltrates become obvious.

Question 2

Answer

A. Immediate simple (top-up) transfusion

Explanation

This patient has early ACS with falling haemoglobin and new infiltrate but without severe hypoxaemia or rapid deterioration. Guidelines recommend early top-up transfusion in stable patients with evolving ACS, especially where Hb is falling significantly below baseline.

The aim is to improve oxygen-carrying capacity and reduce HbS concentration while avoiding hyperviscosity. Post-transfusion Hb should generally not exceed 100 g/L.

Exchange transfusion is reserved for severe or rapidly progressive disease.

Question 3

Answer

B. Urgent red cell exchange transfusion

Explanation

This patient has severe ACS with multi-lobar involvement and significant hypoxaemia. Indications for exchange transfusion include:

- Rapid clinical deterioration
- Multi-lobar infiltrates
- Oxygen saturation below 90%
- Severe hypoxaemia ($\text{PaO}_2 < 70$ mmHg)

Exchange transfusion rapidly lowers HbS percentage and improves oxygen delivery while avoiding excessive viscosity.

Simple transfusion alone would be inadequate in severe progressive disease.

Question 4

Answer

B. Urgent red cell exchange transfusion

Explanation

In HbSC disease, baseline haemoglobin is often relatively high. Simple transfusion risks hyperviscosity and may worsen vaso-occlusion. Because this patient already has haemoglobin above 90 g/L, exchange transfusion is preferred if transfusion support is required.

Anaesthesia and post-operative hypoventilation are major risk factors for ACS.

This scenario tests understanding that transfusion decisions depend not only on severity but also baseline haemoglobin and viscosity risk.

Question 5

Answer

Q. *Mycoplasma pneumoniae* infection

Explanation

Mycoplasma pneumoniae is a well-recognised trigger for ACS, particularly in younger patients. ACS frequently has infectious precipitants, including atypical organisms.

The combination of dry cough, bilateral infiltrates, epidemiological exposure, and negative routine cultures strongly supports atypical pneumonia.

Management requires antibiotics with atypical cover, such as macrolides.

Question 6

Answer

H. Fluid overload causing worsening hypoxia

Explanation

Careful fluid balance is essential in ACS management. Excessive IV fluids may worsen pulmonary oedema and impair oxygenation. Patients with SCD are particularly vulnerable because endothelial injury and pulmonary inflammation already impair gas exchange.

This case highlights an important exam principle: overhydration can worsen ACS and respiratory failure.

Question 7

Answer

J. Hydroxycarbamide for secondary prevention

Explanation

Hydroxycarbamide reduces frequency of ACS by increasing HbF levels, reducing sickling, and decreasing vaso-occlusive events.

Guidelines recommend consideration of hydroxycarbamide after ACS because recurrent episodes are associated with increased mortality and chronic lung disease.

Although regular transfusion programmes may also reduce recurrence, hydroxycarbamide is the most established first-line disease-modifying therapy for many patients.

Question 8

Answer

E. Transfer to intensive care for ventilatory support

Explanation

This patient has impending respiratory failure. ICU involvement is indicated for:

- Persistent oxygen saturation below 90% despite maximal oxygen
- PaO₂ <60 mmHg
- Rising pCO₂
- Rapid clinical deterioration
- Exhaustion or respiratory fatigue

ACS can progress rapidly to ARDS and multi-organ failure. Early critical care involvement improves outcomes.

Question 9

Answer

C. Incentive spirometry and aggressive analgesia only

Explanation

Incentive spirometry reduces atelectasis and progression to ACS by improving lung expansion and ventilation. Rib infarction and splinting predispose to alveolar collapse and pulmonary sickling.

Question 10

I. Delayed haemolytic transfusion reaction

Why?

Key clues in the scenario:

- Recent transfusion for ACS
- Recurrent fever and pain after transfusion

- Marked fall in Hb after initial post-transfusion rise
- Dark urine (haemoglobinuria)
- Raised LDH and bilirubin
- Weakly positive DAT

This is classic for **Delayed Haemolytic Transfusion Reaction (DHTR)** in sickle cell disease.

Important FRCPATH point

EMQ 72 AND 73

Theme: Diagnosis, Risk Stratification and Management of ET

Options

- A. Reactive thrombocytosis secondary to iron deficiency
 - B. Triple-negative ET
 - C. CALR-mutated ET
 - D. JAK2 V617F-positive ET
 - E. MPL-mutated ET
 - F. Hydroxycarbamide
 - G. Pegylated interferon-alpha
 - H. Anagrelide
 - I. Aspirin alone with observation
 - J. Bone marrow biopsy and extended molecular testing
 - K. Busulfan
 - L. Essential thrombocythaemia in pregnancy requiring LMWH and interferon
 - M. Idiopathic thrombocytosis of undetermined significance (ITUS)
 - N. Clonal thrombocytosis of undetermined significance (CTUS)
 - O. Post-ET myelofibrotic transformation
-

Questions

Question 1

A 33-year-old woman is referred with persistent thrombocytosis identified during investigation for headaches and erythromelalgia. Platelet count is $980 \times 10^9/L$, Hb 118 g/L and WBC $7.5 \times 10^9/L$. She has no cardiovascular risk factors and no previous thrombosis. Ferritin and CRP are normal. JAK2 V617F mutation is absent. Bone marrow examination demonstrates marked megakaryocytic proliferation with large hyperlobated “staghorn” megakaryocytes and minimal reticulin fibrosis. Molecular analysis reveals a type 1 CALR mutation.

Which is the SINGLE most likely diagnosis?

Question 2

A 71-year-old man with hypertension, diabetes mellitus and prior NSTEMI is found to have a platelet count of $670 \times 10^9/L$. Hb is 152 g/L and WBC $14 \times 10^9/L$. He reports aquagenic pruritus and transient visual disturbance. JAK2 V617F mutation is detected. Bone marrow demonstrates megakaryocytic proliferation without significant fibrosis.

Which molecular subtype is MOST associated with increased thrombotic risk and later transformation to polycythaemia vera?

Question 3

A 42-year-old female presents with platelet count $520 \times 10^9/\text{L}$ discovered incidentally during pre-operative assessment. Hb 82 g/L, MCV 68 fL and ferritin 5 $\mu\text{g}/\text{L}$. CRP normal. Blood film shows hypochromic microcytic red cells and thrombocytosis. JAK2, CALR and MPL mutations are negative.

What is the MOST likely explanation for the thrombocytosis?

Question 4

A 29-year-old woman with known ET presents at 10 weeks' gestation. She has a prior history of first trimester miscarriage and a previous splanchnic vein thrombosis. Platelet count is $850 \times 10^9/\text{L}$. She is currently taking hydroxycarbamide.

What is the MOST appropriate management?

Question 5

A 58-year-old man with ET was commenced on hydroxycarbamide 4 years ago after an ischaemic stroke. Platelet count is now well controlled at $390 \times 10^9/\text{L}$. However, he develops painful non-healing ulcers over both ankles. There is no evidence of venous insufficiency or vasculitis.

What is the MOST appropriate next treatment?

Question 6

A 76-year-old frail woman with ET has progressive thrombocytosis despite intolerance to hydroxycarbamide and pegylated interferon. She has severe osteoarthritis, limited mobility and mild dementia. Platelet count is $1450 \times 10^9/\text{L}$. Bone marrow shows no transformation.

Which cytoreductive therapy is MOST appropriate?

Question 7

A 36-year-old woman has persistent platelet counts between $470\text{--}520 \times 10^9/\text{L}$ for 4 years. She is asymptomatic. No cardiovascular risk factors are present. Ferritin, CRP and autoimmune screen are normal.

JAK2/CALR/MPL testing and extended myeloid NGS panel are negative. Bone marrow demonstrates no megakaryocyte atypia and no fibrosis.

According to proposed BSH terminology, what is the MOST appropriate classification?

Question 8

A 64-year-old man presents with constitutional symptoms, drenching night sweats and weight loss. He has longstanding ET diagnosed 15 years previously. Examination reveals splenomegaly 8 cm below the costal margin. Hb 89 g/L, WBC $22 \times 10^9/L$ and platelets $210 \times 10^9/L$. Blood film demonstrates tear drop poikilocytes and a leucoerythroblastic picture. Bone marrow aspirate is dry tap.

What is the MOST likely diagnosis?

Question 9

A 47-year-old female with ET is commenced on second-line therapy after hydroxycarbamide intolerance. Two years later, repeat marrow biopsy demonstrates progressive reticulin fibrosis. She remains on aspirin. The treating haematologist notes that the chosen agent is recognised to increase risk of myelofibrotic transformation compared with hydroxycarbamide.

Which treatment was MOST likely prescribed?

Question 10

A 52-year-old woman has platelet count persistently around $780 \times 10^9/L$. JAK2/CALR/MPL testing is negative. Bone marrow shows atypical megakaryocytic proliferation consistent with ET morphology. Extended molecular testing demonstrates a pathogenic ASXL1 mutation. She has no thrombosis history but does have hypertension and hypercholesterolaemia.

According to proposed BSH terminology, which category BEST fits this patient?

Answers and Explanations

Question 1

Answer: C. CALR-mutated ET

Explanation

This patient fulfils WHO criteria for ET:

- Platelets $>450 \times 10^9/L$
- Characteristic megakaryocytes
- Exclusion of other myeloid neoplasms
- Presence of CALR mutation

CALR-mutated ET typically presents in:

- Younger patients
- Higher platelet counts
- Lower thrombotic risk
- Higher long-term risk of myelofibrotic transformation

The absence of JAK2 and presence of CALR strongly support this subtype.

Question 2

Answer: D. JAK2 V617F-positive ET

Explanation

JAK2-positive ET is associated with:

- Older age
- Higher Hb and WBC
- Increased arterial and venous thrombosis
- Increased likelihood of transformation to PV

This patient has classical JAK2-associated clinical features:

- Aquagenic pruritus
 - Leukocytosis
 - Thrombotic vascular symptoms
 - Cardiovascular comorbidity
-

Question 3

Answer: A. Reactive thrombocytosis secondary to iron deficiency

Explanation

Iron deficiency is one of the commonest causes of reactive thrombocytosis.

Supporting features:

- Microcytic anaemia
- Very low ferritin
- Lack of clonal mutation
- No marrow evidence of ET

Reactive thrombocytosis accounts for ~80% of thrombocytosis cases overall.

Question 4

Answer: L. Essential thrombocythaemia in pregnancy requiring LMWH and interferon

Explanation

This is high-risk ET in pregnancy because of:

- Previous thrombosis
- Prior pregnancy morbidity
- Significant thrombocytosis

Management:

- Stop hydroxycarbamide (teratogenic)
- Start interferon-alpha
- Aspirin
- Early LMWH prophylaxis
- Close fetal monitoring

Pegylated interferon is preferred cytoreduction during pregnancy.

Question 5

Answer: G. Pegylated interferon-alpha

Explanation

Hydroxycarbamide causes:

- Painful leg ulcers
- Poor wound healing

This represents hydroxycarbamide intolerance.

Pegylated interferon is appropriate second-line therapy, particularly in younger patients. It may also achieve molecular responses over time.

Question 6

Answer: K. Busulfan

Explanation

Busulfan is generally reserved for:

- Elderly patients
- Frail patients
- Those intolerant of standard therapies

Although leukemogenic potential exists, it may be reasonable in selected elderly individuals where long-term transformation risk is less relevant than symptom control.

Question 7

Answer: M. Idiopathic thrombocytosis of undetermined significance (ITUS)

Explanation

ITUS is defined by:

- Persistent thrombocytosis
- No clonal marker
- No megakaryocyte atypia

This patient lacks:

- Molecular abnormalities
- Histological atypia

Therefore she does not meet criteria for ET.

Question 8

Answer: O. Post-ET myelofibrotic transformation

Explanation

Features strongly suggesting secondary myelofibrosis:

- Constitutional symptoms
- Splenomegaly
- Anaemia
- Tear drop cells
- Leucoerythroblastic blood film
- Dry tap marrow

This represents progression of ET to post-ET myelofibrosis.

Question 9

Answer: H. Anagrelide

Explanation

The PT-1 trial demonstrated:

- Hydroxycarbamide superior to anagrelide
- Increased fibrotic progression with anagrelide

Patients on anagrelide require periodic marrow reassessment because of this risk.

Question 10

Answer: Triple-negative ET with clonal markers

Explanation

This patient has:

- No JAK2/CALR/MPL mutation
- Histological ET morphology
- Presence of another clonal mutation (ASXL1)

Therefore this fits:

“Triple-negative ET with clonal markers”

This proposed BSH category includes:

- Megakaryocyte atypia
- Additional clonal mutation identified by NGS

These patients may carry higher-risk molecular features.

EMQ 74 and 75

Theme: Acute Myeloid Leukaemia (AML)

Options

- A. DA 3+7 plus Gemtuzumab Ozogamicin (GO)
 - B. DA 3+10 plus Midostaurin
 - C. CPX-351 (Vyxeos)
 - D. FLAG-IDA
 - E. ATRA + Arsenic Trioxide
 - F. ATRA + Idarubicin (AIDA)
 - G. Allogeneic stem cell transplantation in CR1
 - H. Gilteritinib
 - I. Quizartinib
 - J. Azacitidine + Donor Lymphocyte Infusion (DLI)
 - K. HiDAC consolidation alone
 - L. Hydroxycarbamide cytoreduction followed by induction
 - M. Supportive/palliative management
 - N. Enasidenib
 - O. Ivosidenib
-

Questions

Question 1

A 34-year-old man presents with fatigue, gum hypertrophy, and easy bruising. Blood tests show Hb 72 g/L, WBC $42 \times 10^9/L$, platelets $28 \times 10^9/L$. Bone marrow confirms AML with t(8;21). Flow cytometry demonstrates strong CD33 expression. FLT3 mutation testing is negative and NPM1 is wild type. After induction chemotherapy, MRD assessment demonstrates a >3-log reduction in RUNX1-RUNX1T1 transcript level.

What is the SINGLE most appropriate initial management strategy?

Question 2

A 51-year-old woman presents with fever, mucosal bleeding, and pancytopenia. Blood film shows abnormal promyelocytes with Auer rods.

Coagulation profile demonstrates disseminated intravascular coagulation. WBC is $4 \times 10^9/L$. FISH confirms t(15;17).

What is the SINGLE best treatment approach?

Question 3

A 63-year-old man with previous MDS treated conservatively develops worsening cytopenias and circulating blasts. Bone marrow demonstrates AML with multilineage dysplasia. Cytogenetics reveal monosomy 7 and del(5q). He is fit for intensive treatment.

What is the SINGLE most appropriate induction regimen?

Question 4

A 46-year-old woman is diagnosed with AML. Molecular analysis reveals FLT3-ITD mutation with high allelic ratio and NPM1 wild type disease. She achieves CR after induction therapy.

What is the SINGLE most appropriate additional treatment consideration to improve long-term survival?

Question 5

A 58-year-old patient with AML receives two cycles of intensive induction chemotherapy. Repeat marrow demonstrates persistent 18% blasts with minimal reduction from baseline disease burden. Cytogenetics demonstrate complex karyotype with TP53 mutation.

What is the SINGLE most appropriate next management option?

Question 6

A 39-year-old woman with low-risk APML treated with ATRA and arsenic trioxide develops dyspnoea, pulmonary infiltrates, fever, rapid weight gain, hypotension, and acute kidney injury during induction.

What is the MOST likely complication?

Question 7

A 49-year-old man previously treated for FLT3-ITD AML relapses 10 months after achieving remission. He is fit for salvage therapy and has no major comorbidities. Molecular testing again confirms FLT3-ITD positivity.

What is the SINGLE best salvage treatment option?

Question 8

A 66-year-old woman relapses 18 months after allogeneic stem cell transplantation for AML. Bone marrow shows 12% blasts. Donor chimerism is declining. She is unfit for intensive chemotherapy but has good performance status.

What is the SINGLE most appropriate management option?

Question 9

A 29-year-old man with AML has NPM1 mutation and low allelic ratio FLT3-ITD. Following two induction cycles, RT-qPCR demonstrates less than 3-log reduction in NPM1 MRD transcript.

What is the SINGLE most appropriate next management strategy?

Question 10

A 72-year-old frail man presents with AML evolving from CMML. He has severe COPD, poor functional status, recurrent infections, and significant cardiac impairment. Cytogenetics show complex abnormalities and TP53 mutation.

What is the SINGLE most appropriate management strategy?

Answers and Explanations

Question 1

Answer: A — DA 3+7 plus Gemtuzumab Ozogamicin (GO)

Explanation

This patient has favourable-risk core-binding factor AML with t(8;21). CD33 positivity makes him an ideal candidate for addition of GO to standard daunorubicin/cytarabine induction. GO improves survival in favourable/intermediate-risk CD33-positive AML. A >3-log MRD reduction indicates good response and transplant is not routinely indicated in CR1.

High-yield points:

- t(8;21) = favourable-risk AML
- GO particularly useful in CD33-positive favourable-risk AML

- Good MRD response reduces need for allogeneic SCT
-

Question 2

Answer: E — ATRA + Arsenic Trioxide

Explanation

This patient has low-risk acute promyelocytic leukaemia (APML/APL) because WBC is $<10 \times 10^9/L$. Standard treatment is immediate initiation of ATRA plus arsenic trioxide.

Key point: ATRA should be started immediately when APML is suspected, even before confirmation, due to risk of fatal DIC.

Why not AIDA? AIDA (ATRA + idarubicin) is generally reserved for high-risk APML with WBC $>10 \times 10^9/L$.

Question 3

Answer: C — CPX-351 (Vyxeos)

Explanation

This patient has AML with myelodysplasia-related changes (AML-MRC) arising from previous MDS and adverse cytogenetics (-7/del5q). CPX-351 is specifically indicated for:

- Therapy-related AML
- AML evolving from MDS/CMML
- AML-MRC cytogenetic abnormalities

CPX-351 has demonstrated superior survival compared with conventional DA chemotherapy in this subgroup.

Question 4

Answer: G — Allogeneic stem cell transplantation in CR1

Explanation

FLT3-ITD high allelic ratio with wild-type NPM1 confers adverse prognosis and high relapse risk. Even if remission is achieved, consolidation with allogeneic SCT in CR1 is usually recommended.

High-yield transplant indications:

- FLT3-ITD high + NPM1 wild type

- Adverse cytogenetics
 - MRD positivity
 - Secondary AML
 - Poor induction response
-

Question 5

Answer: D — FLAG-IDA

Explanation

This patient has primary refractory AML with persistent blasts after two induction cycles. FLAG-IDA is a standard intensive salvage regimen used to achieve remission and bridge to transplant.

Poor prognostic markers include:

- TP53 mutation
- Complex karyotype
- Failure after two induction cycles
- Persistent high blast burden

These patients should be discussed early with transplant teams.

Question 6

Answer: Differentiation syndrome

Explanation

Differentiation syndrome is a life-threatening complication associated with ATRA and arsenic therapy in APML.

Typical features:

- Fever
- Pulmonary infiltrates
- Dyspnoea
- Hypotension
- Weight gain
- Renal impairment
- Pleural/pericardial effusions

Management:

- Immediate dexamethasone
 - Temporarily withhold ATRA/ATO if severe
 - Aggressive supportive care
-

Question 7

Answer: H — Gilteritinib

Explanation

Gilteritinib is the preferred salvage therapy for relapsed FLT3-mutated AML (both FLT3-ITD and TKD mutations).

Advantages:

- Superior overall survival compared with standard salvage chemotherapy
- Better toxicity profile
- Useful bridge to transplant

Quizartinib only targets FLT3-ITD, whereas gilteritinib targets both ITD and TKD mutations.

Question 8

Answer: J — Azacitidine + Donor Lymphocyte Infusion (DLI)

Explanation

Relapse after allogeneic SCT carries poor prognosis. In patients unfit for intensive chemotherapy, azacitidine combined with DLI is an effective and relatively well-tolerated strategy.

DLI is most effective in:

- Low disease burden
- Molecular relapse
- Gradual relapse

High blast burden predicts poor DLI response.

Question 9

Answer: G — Allogeneic stem cell transplantation in CR1

Explanation

Although NPM1 mutation with low-ratio FLT3-ITD is usually favourable risk, poor MRD response (<3-log reduction after cycle 2) significantly increases relapse risk.

MRD positivity overrides otherwise favourable genetics and strongly supports consideration of allo-SCT in CR1.

Important viva pearl: MRD is one of the strongest prognostic factors in AML management.

Question 10

Answer: M — Supportive/palliative management

Explanation

This patient has multiple poor prognostic features:

- Advanced age
- Frailty
- Significant comorbidities
- Secondary AML
- TP53 mutation
- Complex cytogenetics

The risks of intensive chemotherapy outweigh benefits. Focus should therefore be on:

- Symptom control
- Transfusion support
- Infection management
- Quality of life
- Goals-of-care discussion

Low-intensity therapy may occasionally be considered, but supportive management is most appropriate in this scenario.

Ultra-High-Yield FRCPath Pearls

- t(15;17) → ATRA immediately
- GO used in CD33+ favourable/intermediate AML

- Midostaurin for FLT3-mutated AML only
- CPX-351 for AML-MRC/therapy-related AML
- MRD positivity may override favourable cytogenetics
- FLAG-IDA = standard salvage regimen
- Gilteritinib = best salvage for relapsed FLT3-mutated AML
- Allo-SCT is the most powerful anti-leukaemic strategy for high-risk AML
- TP53 mutation = very poor prognosis
- Differentiation syndrome is a medical emergency

EMQ 76 and 77

CMML EMQs – FRCPath Haematology

OPTIONS

- A. Hydroxyurea
 - B. Azacitidine
 - C. Decitabine + venetoclax
 - D. Allogeneic stem cell transplantation
 - E. Ruxolitinib
 - F. Watch and wait
 - G. Erythropoietin-stimulating agent
 - H. Tagraxofusp
 - I. Acute monocytic AML
 - J. Oligomonocytic CMML
 - K. CMML-1, dysplastic type
 - L. CMML-2, proliferative type
 - M. Reactive monocytosis
 - N. VEXAS syndrome-associated CMML
 - O. CPSSmol high-risk disease
 - P. SF3B1-mutated CMML with ring sideroblasts
 - Q. Therapy-related CMML
 - R. HMA failure with clonal evolution
 - S. Hyperleukocytic CMML crisis
 - T. CMML with marrow fibrosis
-

QUESTIONS

1

A 74-year-old man presents with progressive fatigue and transfusion-dependent anaemia. Hb is 7.9 g/dL, WBC $8 \times 10^9/L$, platelets $110 \times 10^9/L$, monocytes $2.1 \times 10^9/L$. Bone marrow shows multilineage dysplasia with 3% blasts. Cytogenetics normal. NGS reveals TET2 and SRSF2 mutations only. Serum EPO is 45 IU/L. He is asymptomatic otherwise and has no splenomegaly.

2

A 68-year-old woman has persistent monocytosis of $0.8 \times 10^9/L$ for 8 months. WBC $9 \times 10^9/L$. Flow cytometry shows 96% classical monocytes (CD14+/CD16-). Bone marrow reveals dysplasia and 2% blasts. NGS shows ASXL1 and TET2 mutations.

3

A 59-year-old male presents with:

- WBC $48 \times 10^9/L$
- Monocytes $12 \times 10^9/L$
- Massive splenomegaly
- Weight loss and night sweats
- BM blasts 4%
- NRAS mutation
- Complex karyotype absent

He develops increasing dyspnoea and confusion.

4

A 71-year-old patient with CMML develops:

- WBC $22 \times 10^9/L$
- Persistent fever
- Weight loss
- Painful splenomegaly
- Severe constitutional symptoms
- Platelets $85 \times 10^9/L$

Bone marrow blasts are 3%.

5

A 63-year-old woman with prior breast cancer treated with chemotherapy 8 years ago presents with:

- Monocytosis $3.5 \times 10^9/L$
- Hb 8.8 g/dL
- Platelets $60 \times 10^9/L$
- Complex karyotype including chromosome 7 abnormality
- ASXL1 mutation
- BM blasts 8%

6

A 66-year-old man has:

- WBC $11 \times 10^9/L$
- Monocytes $2 \times 10^9/L$
- Ring sideroblasts 22%
- SF3B1 mutation
- BM blasts 2%
- No splenomegaly

7

A 61-year-old fit patient has:

- WBC $18 \times 10^9/L$
- BM blasts 11%
- Peripheral blasts 8%
- RUNX1 and SETBP1 mutations
- Transfusion dependence
- Complex cytogenetics

CPSSmol score categorizes him as high risk.

8

A 75-year-old woman with CMML treated with azacitidine for 10 months develops:

- Rising monocyte count
- New RUNX1 mutation
- Increasing VAF of ASXL1
- Peripheral blasts increase from 2% to 9%

9

A 70-year-old man presents with:

- Persistent monocytosis $4 \times 10^9/L$
 - Macrocytic anaemia
 - Marrow fibrosis MF-2
 - Splenomegaly
 - JAK2 V617F mutation
 - Constitutional symptoms
-

10

A 73-year-old man is referred with:

- Monocytes $2.5 \times 10^9/L$
- Fever and elevated CRP
- Recent pneumonia
- No dysplasia
- Normal cytogenetics
- NGS negative
- Monocyte repartitioning not suggestive of CMML

Counts normalize after antibiotic therapy.

ANSWERS WITH EXPLANATIONS

Q1

Answer: G. Erythropoietin-stimulating agent

Explanation

This is lower-risk dysplastic CMML with symptomatic anaemia and low endogenous EPO level. ESA therapy is appropriate first-line supportive treatment. There is no current indication for HMA or transplant because:

- low blast percentage
 - absence of proliferative features
 - no constitutional symptoms
 - no high-risk molecular abnormalities.
-

Q 2

Answer: J. Oligomonocytic CMML

Explanation

WHO/ICC classifications recognize oligomonocytic CMML when:

- monocytes are between $0.5-1.0 \times 10^9/L$
- clonality is demonstrated
- dysplasia is present.

The monocyte repartitioning pattern strongly supports CMML over reactive monocytosis.

Q 3

Answer: S. Hyperleukocytic CMML crisis

Explanation

This patient has proliferative CMML complicated by symptomatic hyperleukocytosis causing leukostasis symptoms (dyspnoea and confusion). Immediate cytoreduction is required. NRAS mutation supports proliferative/aggressive biology.

Q 4

Answer: E. Ruxolitinib

Explanation

Ruxolitinib may improve:

- constitutional symptoms
- inflammatory manifestations
- splenomegaly

in proliferative CMML. Cytopenias are important toxicities.

Q 5

Answer: Q. Therapy-related CMML

Explanation

Prior chemotherapy exposure plus:

- chromosome 7 abnormality

- cytopenias
- ASXL1 mutation
- excess blasts

strongly support therapy-related CMML, which usually carries poor-risk biology.

Q 6

Answer: P. SF3B1-mutated CMML with ring sideroblasts

Explanation

This subgroup resembles MDS/MPN with SF3B1 mutation and ring sideroblasts. It generally has:

- lower proliferative burden
 - fewer aggressive features
 - relatively favourable prognosis.
-

Q 7

Answer: D. Allogeneic stem cell transplantation

Explanation

This patient has:

- CMML-2
- high-risk CPSSmol disease
- adverse mutations (RUNX1, SETBP1)
- proliferative disease
- transfusion dependence

Allogeneic SCT is the only curative option and should be pursued early in a fit patient.

Q 8

Answer: R. HMA failure with clonal evolution

Explanation

This demonstrates disease progression despite azacitidine:

- increasing blasts
- acquisition of new mutations
- rising VAFs

These findings indicate clonal evolution and aggressive biology. Prognosis is poor.

Q 9

Answer: T. CMML with marrow fibrosis

Explanation

Marrow fibrosis in CMML is associated with:

- proliferative phenotype
- splenomegaly
- constitutional symptoms
- poorer prognosis

and can clinically mimic myeloproliferative neoplasms.

Q 10

Answer: M. Reactive monocytosis

Explanation

Features supporting reactive monocytosis include:

- transient monocytosis
- infection-related presentation
- absence of dysplasia
- negative molecular studies
- normalization after treatment

This is an important differential diagnosis in CMML assessment.

EMQ 78 and 79

Theme: Investigation and Management of Antiphospholipid Syndrome (APS)

Options

- A. Triple-positive antiphospholipid syndrome
 - B. Catastrophic antiphospholipid syndrome (CAPS)
 - C. Direct oral anticoagulant interference causing false-positive lupus anticoagulant
 - D. Warfarin with target INR 2.0–3.0
 - E. Warfarin with target INR 3.0–4.0
 - F. Dual antiplatelet therapy
 - G. Repeat antiphospholipid antibody testing after ≥ 12 weeks
 - H. Lupus anticoagulant testing should be deferred
 - I. Anti-phosphatidylserine/prothrombin antibody testing
 - J. Addition of antiplatelet therapy to warfarin
 - K. Activated charcoal product for DOAC removal
 - L. Pregnancy-associated APS
 - M. APS-associated thrombocytopenia
 - N. Venous thrombosis provoked by major transient risk factor
 - O. DRVVT and lupus anticoagulant-sensitive APTT
 - P. Chromogenic factor X assay
 - Q. Long-term anticoagulation not indicated
 - R. Repeat testing unnecessary because diagnosis already confirmed
 - S. Warfarin should replace rivaroxaban
 - T. Microvascular APS nephropathy
-

Questions

Question 1

A 34-year-old woman presents with a left middle cerebral artery infarct. She has no hypertension, diabetes or hyperlipidaemia. MRI confirms acute ischaemic stroke. Thrombophilia testing demonstrates persistent lupus anticoagulant positivity, high-titre IgG anticardiolipin antibodies and high-titre anti- $\beta 2$ glycoprotein-I antibodies detected 14 weeks apart. She had a miscarriage at 13 weeks gestation 3 years previously. She was initially anticoagulated with rivaroxaban by the stroke team.

Which is the SINGLE most appropriate next management step?

Question 2

A 41-year-old man develops portal vein thrombosis without cirrhosis or malignancy. Lupus anticoagulant testing is requested while he is receiving

therapeutic rivaroxaban. DRVVT screening ratio is prolonged and confirm ratio corrects. The anti-Xa assay confirms therapeutic rivaroxaban levels.

What is the MOST likely explanation for the laboratory findings?

Question 3

A 29-year-old woman with systemic lupus erythematosus presents at 24 weeks gestation with hypertension, proteinuria and fetal growth restriction. She has persistent lupus anticoagulant positivity and prior history of three miscarriages before 10 weeks gestation.

Which diagnosis BEST fits this clinical picture?

Question 4

A 57-year-old man with APS develops recurrent DVT despite therapeutic warfarin with stable INR 2.5. He is fully compliant. He has persistent triple-positive antibodies and no malignancy.

What is the MOST appropriate long-term anticoagulation strategy according to current BSH guidance?

Question 5

A 46-year-old woman with APS is monitored using point-of-care INR testing. Several results are markedly discordant compared with laboratory INR values. Baseline PT before anticoagulation had been prolonged because of lupus anticoagulant interference.

Which laboratory investigation would be MOST useful to assess adequacy of anticoagulation?

Question 6

A 39-year-old woman develops renal impairment, thrombocytopenia, pulmonary haemorrhage and confusion over 48 hours. Laboratory investigations demonstrate microangiopathic haemolytic anaemia and persistent triple-positive antiphospholipid antibodies.

Which diagnosis is MOST likely?

Question 7

A 51-year-old man presents with provoked proximal DVT 5 days after major colorectal surgery. There is no previous thrombosis, autoimmune disease or obstetric history. The surgical team requests APS testing.

What is the MOST appropriate recommendation?

Question 8

A coagulation laboratory is validating lupus anticoagulant testing. The consultant wants to ensure the minimum recommended assay combination for detecting lupus anticoagulant in non-anticoagulated patients.

Which combination is MOST appropriate?

Question 9

A 48-year-old woman with APS-associated stroke remains event-free on warfarin INR 2.5 for 3 years. She subsequently develops worsening carotid atherosclerosis and poorly controlled diabetes mellitus.

What additional treatment strategy should be considered?

Question 10

A 37-year-old man with recurrent venous thrombosis has persistent lupus anticoagulant positivity but negative anticardiolipin and anti- β_2 glycoprotein-I antibodies. He asks whether APS can be diagnosed now or whether additional laboratory confirmation is required. Initial positive testing was performed 4 weeks ago.

What is the MOST appropriate next step?

Answers and Explanations

Question 1

Answer: S. Warfarin should replace rivaroxaban

Explanation

This patient has:

- arterial thrombosis (stroke)
- obstetric morbidity

- persistent triple-positive APS

Current BSH guidance recommends:

- avoidance of DOACs in triple-positive APS
- especially avoidance in arterial APS/stroke

Warfarin is preferred.

Question 2

Answer: C. Direct oral anticoagulant interference causing false-positive lupus anticoagulant

Explanation

Rivaroxaban commonly interferes with DRVVT assays and may produce:

- false-positive lupus anticoagulant results
- particularly prolonged DRVVT screening tests

Testing should ideally occur off anticoagulation or at trough levels.

Question 3

Answer: L. Pregnancy-associated APS

Explanation

This patient fulfils obstetric APS criteria:

- recurrent miscarriages
- placental insufficiency
- severe pre-eclampsia features
- persistent aPL positivity

APS causes placental dysfunction through:

- complement activation
 - inflammation
 - thrombosis.
-

Question 4

Answer: E. Warfarin with target INR 3.0–4.0

Explanation

As per BSH Guidelines

Question 5

Answer: P. Chromogenic factor X assay

Explanation

Lupus anticoagulants may interfere with PT/INR assays causing unreliable INR measurements.

Chromogenic factor X assays:

- avoid phospholipid interference
 - better reflect warfarin effect in APS.
-

Question 6

Answer: B. Catastrophic antiphospholipid syndrome (CAPS)

Explanation

CAPS is characterized by:

- rapid multiorgan failure
- microvascular thrombosis
- thrombocytopenia
- MAHA
- pulmonary and renal involvement

It is rare but life-threatening.

Question 7

Answer: Q. Long-term anticoagulation not indicated

Explanation

Major surgery is a strong transient provoking factor.

Routine APS testing is NOT recommended after:

- major surgery-associated VTE
- immobilisation-associated VTE

- active cancer-associated VTE

because APS is less likely to alter management.

Question 8

Answer: O. DRVVT and lupus anticoagulant-sensitive APTT

Explanation

BSH guidance recommends:

- two assays of different principles

Standard approach:

- DRVVT
- LA-sensitive APTT

for lupus anticoagulant detection.

Question 9

Answer: J. Addition of antiplatelet therapy to warfarin

Explanation

In APS-associated stroke patients with:

- additional vascular risk factors
- low bleeding risk

addition of antiplatelet therapy to VKA may be considered.

Question 10

Answer: G. Repeat antiphospholipid antibody testing after ≥ 12 weeks

Explanation

APS diagnosis requires persistence of antibodies:
 ≥ 12 weeks

A single positive test is **insufficient for diagnosis**.

EMQ 80 and 81

Option List

- A. Brentuximab vedotin monotherapy
 - B. Brentuximab vedotin + bendamustine
 - C. Brentuximab vedotin + nivolumab
 - D. Brentuximab vedotin maintenance post-ASCT
 - E. GDP chemotherapy
 - F. High-dose therapy with autologous stem cell transplantation (ASCT)
 - G. Immediate allogeneic stem cell transplantation
 - H. Nivolumab monotherapy
 - I. Observation only
 - J. Pembrolizumab-GVD
 - K. Peripheral neuropathy is a major toxicity of BV maintenance
 - L. PET-negative status before ASCT predicts superior progression-free survival
 - M. Palliative vinblastine
 - N. PD-1 inhibitors increase risk of GVHD before allogeneic SCT
 - O. Radiotherapy alone
 - P. Switch to alternative salvage regimen
 - Q. CD30 CAR-T therapy
 - R. Pembrolizumab superior to BV for quality of life
 - S. Allogeneic SCT is generally reserved for ASCT failure
 - T. Pembro-GVD achieves very high complete metabolic remission rates
-

Questions

Question 1

A 28-year-old man with advanced-stage classical Hodgkin lymphoma was initially treated with escalated BEACOPP and achieved complete metabolic remission. Nine months later he develops recurrent mediastinal and para-aortic disease with B symptoms. PET-CT confirms FDG-avid relapse and biopsy reconfirms classical Hodgkin lymphoma.

He receives two cycles of GDP chemotherapy. Interim PET demonstrates persistent Deauville 5 uptake in the mediastinum. ECOG performance status is 0 and cardiac, renal, and pulmonary function remain normal.

What is the SINGLE most appropriate next step?

Question 2

A 34-year-old woman with primary refractory classical Hodgkin lymphoma receives pembrolizumab-GVD as second-line therapy. After three cycles she achieves complete metabolic remission on PET-CT with Deauville score 2.

She has no major comorbidities and stem cells have been successfully harvested.

What is the most appropriate next management step?

Question 3

A 67-year-old man with relapsed Hodgkin lymphoma underwent ASCT 3 years previously. He now presents with disseminated nodal and extranodal relapse. ECOG performance status is 2. He has painful diabetic neuropathy, impaired left ventricular systolic function, and chronic kidney disease stage 3.

He wishes to avoid further intensive therapy and prioritises symptom relief and outpatient-based treatment.

What is the most appropriate management option?

Question 4

A 22-year-old woman relapses 18 months after abbreviated frontline therapy for stage IIA favourable-risk Hodgkin lymphoma. Disease is confined to a single cervical nodal region without extranodal involvement. PET-CT demonstrates localised disease that can be completely encompassed within an involved-site radiotherapy field.

What is the most appropriate treatment option?

Question 5

A 30-year-old man with relapsed Hodgkin lymphoma undergoes salvage chemotherapy followed by ASCT. Pre-transplant PET remained Deauville 4 despite salvage therapy, although disease burden reduced substantially. Engraftment is uncomplicated.

Which post-transplant strategy is most evidence-based for reducing subsequent relapse risk?

Question 6

A 40-year-old woman undergoing discussion regarding ASCT asks about the prognostic significance of PET imaging before transplant. Her consultant explains that modern treatment strategies aim to achieve complete metabolic remission prior to ASCT whenever possible.

Which statement best reflects current evidence?

Question 7

A 31-year-old man with multiply relapsed Hodgkin lymphoma undergoes matched unrelated donor allogeneic SCT after previous treatment with nivolumab. The transplant physician discusses complications associated with prior checkpoint inhibitor exposure.

Which complication risk is specifically increased?

Question 8

A 52-year-old patient receives brentuximab vedotin maintenance after ASCT because of high-risk relapsed disease with residual PET positivity before transplant.

Which adverse effect most commonly limits treatment delivery?

Question 9

A 25-year-old woman with relapsed Hodgkin lymphoma receives pembrolizumab-GVD salvage therapy. Her consultant explains that recent studies have demonstrated particularly impressive complete metabolic remission rates with this regimen compared with historical chemotherapy approaches.

Which statement best describes this regimen?

Question 10

A 19-year-old man with heavily pre-treated Hodgkin lymphoma has progressed after BV, nivolumab, ASCT, and allogeneic SCT. He is enrolled into a clinical trial using genetically modified T cells directed against CD30-expressing Reed–Sternberg cells.

Which therapeutic modality is being described?

Answers and Explanations

Question 1

Answer: P. Switch to alternative salvage regimen

Explanation

Persistent PET positivity after first salvage therapy predicts significantly inferior progression-free survival after ASCT. Current practice aims for PET negativity before transplant whenever feasible. Therefore, switching to an alternative salvage regimen is preferred before proceeding to ASCT.

Question 2

Answer: F. High-dose therapy with autologous stem cell transplantation (ASCT)

Explanation

Although pembrolizumab-GVD achieves very high remission rates, ASCT remains the standard consolidation strategy for fit patients with chemosensitive relapsed/refractory Hodgkin lymphoma.

Question 3

Answer: M. Palliative vinblastine

Explanation

This patient is elderly, comorbid, previously transplanted, and unsuitable for intensive therapy. Palliative low-intensity therapy such as vinblastine may provide symptom control with acceptable tolerability.

Question 4

Answer: O. Radiotherapy alone

Explanation

Selected patients with localised, low-risk relapse may achieve durable remission with radiotherapy alone, especially where disease is confined and suitable for involved-site radiotherapy.

Question 5

Answer: D. Brentuximab vedotin maintenance post-ASCT

Explanation

The AETHERA study demonstrated improved progression-free survival with BV maintenance after ASCT in high-risk patients, particularly those with residual PET positivity or early relapse.

Question 6

Answer: L. PET-negative status before ASCT predicts superior progression-free survival

Explanation

Pre-ASCT PET status is among the strongest prognostic markers:

- PET-negative patients have markedly superior PFS
 - PET-positive patients have substantially higher relapse risk
-

Question 7

Answer: N. PD-1 inhibitors increase risk of GVHD before allogeneic SCT

Explanation

Checkpoint inhibitor exposure prior to allogeneic transplantation is associated with increased risk of acute graft-versus-host disease due to immune activation.

Question 8

Answer: K. Peripheral neuropathy is a major toxicity of BV maintenance

Explanation

Peripheral neuropathy is the principal toxicity associated with BV maintenance and commonly necessitates dose modification or discontinuation.

Question 9

Answer: T. Pembro-GVD achieves very high complete metabolic remission rates

Explanation

Pembrolizumab-GVD has demonstrated exceptionally high PET-negative remission rates in relapsed Hodgkin lymphoma and represents one of the most promising modern salvage regimens.

Question 10

Answer: Q. CD30 CAR-T therapy

Explanation

CD30 CAR-T therapy is an investigational cellular immunotherapy approach showing promising response rates in heavily pre-treated relapsed/refractory Hodgkin lymphoma.

EMQ 82 and 83

Splanchnic Vein Thrombosis (SVT)

Options

- A. Acute portal vein thrombosis
 - B. Chronic portal vein thrombosis with portal cavernoma
 - C. Budd–Chiari syndrome
 - D. Acute mesenteric vein thrombosis
 - E. Splenic vein thrombosis
 - F. Myeloproliferative neoplasm-associated SVT
 - G. Paroxysmal nocturnal haemoglobinuria (PNH)
 - H. Cirrhosis-associated portal vein thrombosis
 - I. Antiphospholipid syndrome-associated SVT
 - J. Intestinal infarction secondary to SVT
 - K. JAK2 V617F mutation-associated SVT
 - L. Factor V Leiden-associated SVT
 - M. DOAC-associated management strategy
 - N. LMWH preferred strategy
 - O. Indefinite anticoagulation indicated
-

Questions

Question 1

A 42-year-old woman presents with progressive abdominal distension, right upper quadrant pain and tender hepatomegaly. She recently started the oral contraceptive pill. Examination reveals ascites and mild jaundice. Doppler ultrasound demonstrates absent hepatic venous flow. Liver biopsy shows centrilobular congestion.

Which is the SINGLE BEST diagnosis?

Question 2

A 61-year-old man with longstanding alcohol-related cirrhosis undergoes surveillance ultrasound which demonstrates partial thrombosis of the portal vein. He has large oesophageal varices on endoscopy and platelet count is $48 \times 10^9/L$. He has no abdominal pain.

Which is the MOST appropriate anticoagulation strategy initially?

Question 3

A 36-year-old man presents with severe central abdominal pain out of proportion to examination findings. CT abdomen demonstrates thrombosis

of the superior mesenteric vein with bowel wall oedema and early pneumatosis intestinalis.

What is the MOST likely complication developing?

Question 4

A 29-year-old woman presents with acute abdominal pain two weeks postpartum. Imaging confirms portal vein thrombosis extending into the splenic vein. Blood counts show Hb 175 g/L, WBC $14 \times 10^9/L$ and platelets $620 \times 10^9/L$. JAK2 V617F mutation is positive.

What is the MOST likely underlying prothrombotic disorder?

Question 5

A 48-year-old man with haemolytic anaemia develops hepatic vein thrombosis. Flow cytometry demonstrates absence of CD55 and CD59 on granulocytes.

What is the MOST likely underlying diagnosis?

Question 6

A 55-year-old woman presents with upper gastrointestinal bleeding due to gastric varices. CT imaging reveals isolated thrombosis of the splenic vein secondary to chronic pancreatitis.

Which is the SINGLE BEST diagnosis?

Question 7

A 40-year-old woman with no liver disease develops acute portal vein thrombosis after abdominal sepsis. She is treated with LMWH followed by warfarin. Repeat imaging at 9 months demonstrates complete recanalisation and no persistent risk factor is identified.

What is the MOST appropriate duration of anticoagulation?

Question 8

A 63-year-old man with non-cirrhotic portal vein thrombosis is found to carry antiphospholipid antibodies and has a prior history of lower limb DVT. He has no active bleeding and renal function is normal.

What is the MOST appropriate long-term management strategy?

Question 9

A 58-year-old man with Child-Pugh C cirrhosis develops symptomatic portal vein thrombosis. He has thrombocytopenia and previous variceal bleeding.

Which anticoagulant approach is considered SAFEST according to practical guideline-based management?

Question 10

A 34-year-old woman presents with chronic abdominal discomfort and splenomegaly. Imaging demonstrates cavernous transformation of the portal vein with extensive periportal collateral vessels.

Which is the SINGLE BEST diagnosis?

Answers and Explanations

Question 1

Answer: C. Budd–Chiari syndrome

Explanation

Budd–Chiari syndrome is hepatic venous outflow obstruction. Typical findings:

- Hepatomegaly
- Ascites
- RUQ pain
- Hepatic vein obstruction on Doppler
- OCP use is an important risk factor

Histology classically shows centrilobular congestion.

Question 2

Answer: N. LMWH preferred strategy

Explanation

In cirrhosis with:

- Large varices
- Thrombocytopenia
- High bleeding risk

LMWH is generally preferred initially. DOACs are used cautiously, especially in advanced cirrhosis. Varices should ideally be treated before anticoagulation.

Child-Pugh B/C disease favours LMWH over DOACs.

Question 3

Answer: J. Intestinal infarction secondary to SVT

Explanation

Acute mesenteric vein thrombosis may progress to bowel infarction.

Features suggesting evolving intestinal infarction:

- Severe pain out of proportion
- Pneumatosis intestinalis
- Bowel wall oedema
- Metabolic acidosis
- Peritonism

This is a surgical emergency.

Question 4

Answer: F. Myeloproliferative neoplasm-associated SVT

Explanation

SVT is strongly associated with MPNs, especially:

- Polycythaemia vera
- Essential thrombocythaemia

Clues:

- Raised Hb
- Thrombocytosis
- JAK2 positivity

SVT may be the first presentation of occult MPN.

Question 5

Answer: G. Paroxysmal nocturnal haemoglobinuria (PNH)

Explanation

PNH is highly associated with unusual-site thrombosis including:

- Hepatic veins
- Portal veins
- Cerebral veins

Loss of CD55/CD59 is diagnostic.

Budd–Chiari syndrome is a classic thrombotic manifestation of PNH.

Question 6

Answer: E. Splenic vein thrombosis

Explanation

Splenic vein thrombosis classically occurs in:

- Chronic pancreatitis
- Pancreatic malignancy

It causes:

- Left-sided portal hypertension
 - Gastric varices
 - Upper GI bleeding
-

Question 7

Answer: N. LMWH preferred strategy

Explanation

The question asks about finite anticoagulation after transient provoked SVT.

For transient provoking factors:

- 6–12 months anticoagulation is reasonable

This patient had:

- Abdominal sepsis (transient trigger)

- Complete recanalisation
- No persistent thrombophilia

Thus indefinite anticoagulation is not mandatory.

Question 8

Answer: O. Indefinite anticoagulation indicated

Explanation

Indications for indefinite anticoagulation in SVT include:

- Antiphospholipid syndrome
- Persistent thrombophilia
- Previous VTE
- Unprovoked SVT
- MPN/PNH

This patient has APS and prior DVT, conferring high recurrence risk.

Question 9

Answer: N. LMWH preferred strategy

Explanation

Child-Pugh C cirrhosis carries:

- High bleeding risk
- Altered DOAC metabolism
- Variceal risk

Practical guidance:

- LMWH safest option
- Avoid DOACs if possible
- Warfarin difficult due to unstable INR

This reflects current expert-based practice.

Question 10

Answer: B. Chronic portal vein thrombosis with portal cavernoma

Explanation

Portal cavernoma refers to:

- Cavernous transformation of the portal vein
- Multiple periportal collateral veins
- Chronic portal vein obstruction

Typical manifestations:

- Splenomegaly
- Portal hypertension
- Varices
- Chronic abdominal symptoms

EMQ 84 AND 85

Theme: Measurable Residual Disease (MRD) Monitoring in AML

Options

- A. qPCR for NPM1 mutation
 - B. qPCR for RUNX1::RUNX1T1
 - C. qPCR for CBFB::MYH11
 - D. qPCR for PML::RARA
 - E. Multiparameter flow cytometry (MFC)
 - F. FLT3-ITD ultra-high sensitivity NGS
 - G. Bone marrow (BM) preferred over peripheral blood (PB)
 - H. Peripheral blood (PB) acceptable if blasts $\geq 20\%$
 - I. MRD monitoring not routinely recommended after 2 cycles
 - J. Post-allogeneic transplant MRD surveillance
-

Questions

1.

A 42-year-old woman with AML has a mutation in NPM1 without FLT3-ITD. The clinician wants the most appropriate MRD assay during remission monitoring.

2.

A patient with AML carrying RUNX1::RUNX1T1 fusion achieves morphological remission after induction therapy. Which MRD technique is preferred?

3.

A 29-year-old patient with acute promyelocytic leukaemia (APL) requires molecular MRD follow-up after completion of therapy.

4.

A patient with AML has FLT3-ITD and NPM1 mutation. The laboratory wants the most sensitive assay for FLT3 MRD assessment.

5.

A clinician asks whether peripheral blood can be used instead of bone marrow for MRD assessment in AML when blasts at diagnosis were markedly elevated ($>20\%$).

6.

A patient with AML has no validated molecular marker available. Which MRD modality is most appropriate?

7.

A patient with CBFB::MYH11 AML is in complete remission. Which MRD assay should be used for longitudinal monitoring?

8.

A patient with PML::RARA-positive APL asks whether MRD testing is recommended after two cycles of treatment before HCT.

9.

A patient undergoes allogeneic stem cell transplantation for AML with high-risk molecular features. What is the key MRD strategy after transplant?

10.

A clinician requests the preferred specimen type for AML MRD monitoring because of higher sensitivity and reliability.

Answers and Explanations

Q Answer Explanation

- | | | |
|---|---|--|
| 1 | A | NPM1-mutated AML is best monitored using highly sensitive quantitative PCR assays targeting the NPM1 transcript. |
| 2 | B | RUNX1::RUNX1T1 AML has a validated molecular target suitable for qPCR MRD monitoring. |
| 3 | D | PML::RARA transcripts in APL are monitored using qPCR, which is highly sensitive and clinically validated. |
| 4 | F | FLT3-ITD ultra-high sensitivity NGS provides superior detection of low-level residual disease. |
| 5 | H | Peripheral blood may be acceptable for MRD assessment when blasts at diagnosis were $\geq 20\%$, though BM is generally more sensitive. |
| 6 | E | Multiparameter flow cytometry is useful when no validated molecular marker is available. |
| 7 | C | CBFB::MYH11 is a core-binding factor AML abnormality monitored effectively using qPCR. |
| 8 | I | In APL, MRD monitoring after two cycles before HCT is generally not routinely recommended according to ELN guidance. |

Q Answer Explanation

- 9 J High-risk AML patients require MRD surveillance after allogeneic transplantation to detect impending relapse early.
- 10 G Bone marrow is generally preferred because it provides greater sensitivity for AML MRD detection than peripheral blood.
-

High-Yield FRCPATH Pearls

- qPCR is preferred for validated molecular targets such as:
 - NPM1
 - RUNX1::RUNX1T1
 - CBFB::MYH11
 - PML::RARA
- MFC is useful when no molecular marker exists.
- Bone marrow is usually more sensitive than peripheral blood for MRD detection.
- FLT3-ITD UHS-NGS is emerging as a highly sensitive MRD tool.
- MRD positivity after therapy or transplant predicts:
 - Increased relapse risk
 - Poorer survival
 - Potential need for therapeutic escalation

EMQ 86 and 87

EMQ Theme

Managing transfusion investigations in patients receiving monoclonal antibody therapies

Option List

- A. Perform testing using DTT-treated reagent red cells
 - B. Provide K-negative red cells unless patient is known to be K-positive
 - C. Refer sample to NHSBT Red Cell Immunohaematology laboratory
 - D. Use Capture methodology
 - E. Extended red cell genotyping
 - F. Group O red cells for transfusion
 - G. Perform alloadsorption studies
 - H. Inform transfusion laboratory before therapy commences
 - I. Use a different monoclonal anti-IgG reagent
 - J. Match red cells for Rh and K antigens
 - K. Patient should carry alert card for 6 months after therapy
 - L. Routine antibody screen without modification
 - M. Emergency transfusion only out of hours
 - N. Direct antiglobulin test (DAT) prior to therapy
 - O. Extended phenotype matching despite unresolved serology
-

Questions

Question 1

A 69-year-old man with relapsed multiple myeloma is due to commence daratumumab therapy. He received transfusion support 2 weeks ago. The transfusion laboratory wishes to establish a comprehensive antigen profile before treatment begins. Which is the SINGLE most appropriate investigation?

Question 2

A patient receiving isatuximab demonstrates panreactivity on indirect antiglobulin testing. The transfusion scientist wishes to minimise anti-CD38 interference during antibody screening. Which is the BEST approach?

Question 3

A 74-year-old woman receiving magrolimab develops severe anaemia requiring urgent transfusion. Her ABO group cannot be conclusively determined due to interference in serological testing. Which transfusion strategy is MOST appropriate?

Question 4

A patient on anti-CD47 therapy has persistent panagglutination despite routine investigations. The laboratory wants to identify underlying alloantibodies while avoiding interference from therapeutic antibody. Which investigation is MOST appropriate?

Question 5

A patient treated with daratumumab requires elective transfusion support. Antibody screening has been performed using modified methodology. Which blood selection policy is MOST appropriate?

Question 6

A transfusion practitioner is counselling a patient about to commence anti-CD38 therapy. What is the MOST important practical recommendation to minimise delays during future admissions?

Question 7

A patient previously transfused within the last month is about to commence anti-CD38 therapy. Extended serological profiling is required, but phenotyping may be unreliable. Which investigation is MOST appropriate?

Question 8

A patient on magrolimab has unresolved serology despite alloadsorption studies. The local laboratory lacks specialised methods for further evaluation. What is the MOST appropriate next step?

Question 9

A patient receiving monoclonal antibody therapy requires transfusion overnight for life-threatening haemorrhage. The local laboratory contacts the regional RCI service. Which statement BEST reflects NHSBT guidance regarding out-of-hours investigations?

Question 10

A patient with multiple myeloma completed daratumumab therapy 4 months ago and presents to another hospital requiring urgent surgery. The patient informs staff using a wallet card indicating prior treatment. Why is continued alerting necessary?

Answers and Explanations

Q Answer Explanation

- 1 **E** Recently transfused patients may have unreliable phenotyping due to donor red cells. NHSBT guidance recommends **genotyping** if transfused within the previous month.

Q Answer Explanation

- 2 **A** Anti-CD38 therapies interfere with indirect antiglobulin testing. DTT-treated reagent cells are recommended to remove CD38 interference during antibody screening.
- 3 **F** Anti-CD47 therapies can interfere with ABO determination. When ABO grouping cannot be resolved, **group O red cells** may be required.
- 4 **G** NHSBT guidance states that alloadsorption studies may permit antibody detection and identification in patients with panagglutination caused by anti-CD47 therapy.
- 5 **J** Patients receiving anti-CD38 therapies should receive red cells matched for Rh and K antigens in addition to any identified alloantibodies.
- 6 **K** Patients should carry an alert card for up to 6 months after therapy because monoclonal antibody interference may persist and affect compatibility testing.
- 7 **E** Recent transfusion invalidates reliable phenotyping; therefore extended red cell genotyping is preferred before therapy commences.
- 8 **D** NHSBT guidance recommends onward referral for investigation using Capture methodology when routine serology remains unresolved.
- 9 **M** NHSBT guidance states that out-of-hours investigations and crossmatching are generally not routinely performed except in emergencies.
- 10 **K** Monoclonal antibody-induced serological interference may persist for up to 6 months after treatment cessation; therefore patients should continue carrying alert documentation.

Additional Viva-Level Pearls for FRCPATH Candidates

- Anti-CD38 therapies primarily interfere with **IAT-based compatibility testing** because CD38 is weakly expressed on reagent red cells.
- DTT treatment destroys CD38 antigen but also denatures **Kell antigens**, which is why K-negative blood is usually required.
- Anti-CD47 therapies may produce broader serological interference affecting both forward and reverse grouping.

- Early communication between haematology teams and transfusion laboratories is a recurrent examinable governance point.
- Genotyping is preferred over phenotyping in recently transfused patients because donor cells may mask recipient antigen expression.
- Examiners commonly ask candidates to discuss **pre-treatment baseline testing** before commencing monoclonal antibody therapy.

EMQ 88 and 89

Theme: Inherited and Acquired Platelet Function Disorders

Options

- A. Bernard–Soulier syndrome
 - B. Glanzmann thrombasthenia
 - C. Scott syndrome
 - D. Wiskott–Aldrich syndrome
 - E. Hermansky–Pudlak syndrome
 - F. Chediak–Higashi syndrome
 - G. Gray platelet syndrome
 - H. Paris–Trousseau syndrome
 - I. Aspirin-induced platelet dysfunction
 - J. BTK inhibitor-associated platelet dysfunction
 - K. SSRI-induced platelet dysfunction
 - L. Platelet dysfunction secondary to paraproteinaemia
 - M. Platelet dysfunction due to myelodysplastic syndrome
 - N. Platelet dysfunction due to acute leukaemia
-

Questions

Scenario 1

A 14-year-old boy presents with lifelong epistaxis and gum bleeding. Platelet count is $40 \times 10^9/\text{L}$. Blood film demonstrates very large platelets. Platelet aggregation studies show normal aggregation responses but markedly reduced ristocetin-induced agglutination that fails to correct with patient plasma.

Which diagnosis is most likely?

Scenario 2

A 7-year-old child has severe mucocutaneous bleeding since infancy. Platelet count is normal. Aggregation studies demonstrate absent responses to ADP, collagen and adrenaline, but normal response to ristocetin.

Which diagnosis is most likely?

Scenario 3

A 21-year-old woman has excessive bleeding after dental extraction despite normal platelet count and normal aggregation studies. Flow cytometry demonstrates failure of activated platelets to externalize phosphatidylserine.

Which diagnosis is most likely?

Scenario 4

A 5-year-old boy is referred with recurrent bacterial infections, severe eczema and thrombocytopenia. Blood film reveals unusually small platelets.

Which diagnosis is most likely?

Scenario 5

A young adult presents with easy bruising and recurrent epistaxis. Examination reveals oculocutaneous albinism. Platelet electron microscopy demonstrates absence of dense granules.

Which diagnosis is most likely?

Scenario 6

A child develops recurrent pyogenic infections and partial albinism. Peripheral blood film shows giant cytoplasmic granules in neutrophils. Platelet dysfunction contributes to a bleeding tendency.

Which diagnosis is most likely?

Scenario 7

A 32-year-old woman has lifelong bruising and menorrhagia. Platelet count is mildly reduced. Blood film demonstrates large pale-gray appearing platelets lacking normal granularity.

Which diagnosis is most likely?

Scenario 8

A neonate with developmental delay and congenital anomalies develops thrombocytopenia. Blood film demonstrates giant platelets with abnormal α -granule morphology.

Which diagnosis is most likely?

Scenario 9

A 74-year-old man with Waldenström macroglobulinaemia develops spontaneous bruising. Platelet count is normal. Aggregation studies demonstrate impaired platelet function due to circulating IgM paraprotein coating platelet membranes.

Which diagnosis is most likely?

Scenario 10

A 68-year-old man with chronic lymphocytic leukaemia is receiving treatment with ibrutinib. He develops troublesome epistaxis and bruising despite a normal platelet count. Coagulation studies are normal.

Which diagnosis is most likely?

Answers and Explanations

Scenario Answer

- | | |
|----|---|
| 1 | A |
| 2 | B |
| 3 | C |
| 4 | D |
| 5 | E |
| 6 | F |
| 7 | G |
| 8 | H |
| 9 | L |
| 10 | J |
-

Detailed Explanations

Scenario 1 → Bernard–Soulier Syndrome (A)

Key clues:

- Macrothrombocytopenia

- Giant platelets
- Defective ristocetin response

Pathophysiology:

Deficiency of the **GPIb-IX-V complex**, the platelet receptor for **von Willebrand factor (vWF)**. Platelets cannot adhere normally to damaged endothelium.

Scenario 2 → Glanzmann Thrombasthenia (B)

Key clues:

- Normal platelet count
- Severe mucocutaneous bleeding
- Absent aggregation with ADP, collagen and adrenaline
- Normal ristocetin response

Pathophysiology:

Defect in **GPIIb/IIIa (α IIb β 3 integrin)** causing failure of fibrinogen-mediated platelet aggregation.

Scenario 3 → Scott Syndrome (C)

Key clues:

- Normal platelet aggregation
- Significant bleeding
- Failure of phosphatidylserine exposure

Pathophysiology:

Platelets cannot expose negatively charged phospholipid surfaces required for assembly of tenase and prothrombinase complexes.

Scenario 4 → Wiskott–Aldrich Syndrome (D)

Key clues:

- Eczema
- Immunodeficiency
- Thrombocytopenia
- Small platelets

Pathophysiology:

Mutation in the **WAS gene** affecting cytoskeletal organization of haematopoietic cells.

Classic FRCPATH pearl:

"Small platelets = Wiskott–Aldrich until proven otherwise."

Scenario 5 → Hermansky–Pudlak Syndrome (E)**Key clues:**

- Oculocutaneous albinism
- Dense granule deficiency

Pathophysiology:

Defective lysosome-related organelle biogenesis causing absent platelet dense bodies.

Scenario 6 → Chediak–Higashi Syndrome (F)**Key clues:**

- Partial albinism
- Recurrent infections
- Giant granules in neutrophils

Pathophysiology:

LYST gene mutation causing abnormal lysosomal trafficking.

Exam Pearl: Giant granules in neutrophils are highly characteristic.

Scenario 7 → Gray Platelet Syndrome (G)**Key clues:**

- Large gray platelets
- α -granule deficiency

Pathophysiology:

Defective formation or packaging of α -granules leading to pale platelets on blood film.

Scenario 8 → Paris–Trousseau Syndrome (H)**Key clues:**

- Congenital syndrome
- Macrothrombocytopenia
- Abnormal α -granules

Pathophysiology:

Associated with chromosome 11q deletion syndrome and abnormal megakaryocyte maturation.

Scenario 9 → Platelet Dysfunction Secondary to Paraproteinaemia (L)

Key clues:

- Waldenström macroglobulinaemia
- Normal platelet count
- Acquired platelet dysfunction

Pathophysiology:

Monoclonal paraproteins coat platelet surfaces and interfere with normal receptor function.

Scenario 10 → BTK Inhibitor-Associated Platelet Dysfunction (J)

Key clues:

- Ibrutinib therapy
- Normal platelet count
- Mucocutaneous bleeding

Pathophysiology:

BTK inhibition impairs signalling downstream of collagen receptors, reducing platelet activation and aggregation.

Important FRCPATH Point:

Bleeding may occur even when platelet counts and coagulation tests are normal.

High-Yield FRCPATH Memory Table

Disorder	Defect	Platelet Count	Characteristic Finding
Bernard-Soulier	GPIb	↓	Giant platelets

Disorder	Defect	Platelet Count	Characteristic Finding
Glanzmann	GPIIb/IIIa	Normal	Absent aggregation
Scott	Phosphatidylserine exposure	Normal	Defective coagulation complex assembly
Wiskott–Aldrich	WAS protein	↓	Small platelets
Hermansky–Pudlak	Dense granules	Usually normal	Albinism
Chediak–Higashi	Lysosomal trafficking	Variable	Giant neutrophil granules
Gray Platelet Syndrome	α-granules	Mild ↓	Gray platelets
Paris–Trousseau	α-granule abnormality	↓	Congenital macrothrombocytopenia
Aspirin	COX-1 inhibition	Normal	Prolonged bleeding
BTKi	Signalling defect	Normal	Bruising/epistaxis

EMQ 90 and 91

Theme: Diagnosis and investigation of haemoglobinopathies.

Options

- A. β -thalassaemia trait
 - B. α^0 -thalassaemia trait
 - C. Homozygous α^+ -thalassaemia
 - D. $\delta\beta$ -thalassaemia trait
 - E. Hereditary persistence of fetal haemoglobin (HPFH)
 - F. Hb E trait
 - G. Hb Lepore trait
 - H. Hb S/ β^0 -thalassaemia
 - I. Hb SC disease
 - J. Further DNA analysis required
 - K. Repeat testing after iron repletion
 - L. Test biological father immediately
 - M. Newborn likely to have β -thalassaemia major/TDT
 - N. Emergency sickle screening requires confirmatory testing
 - O. Hb H disease
-

Question 1

A 10-week pregnant woman of Pakistani origin is referred following routine antenatal screening. Her FBC shows Hb 112 g/L, MCV 66 fL, MCH 20 pg. Ferritin is normal. HPLC demonstrates HbA 94.2%, HbA₂ 5.8%, HbF 0.9%. No variant peak is identified.

What is the most likely diagnosis?

Question 2

A 12-week pregnant woman from Thailand has Hb 109 g/L, MCV 68 fL, MCH 21 pg. HbA₂ is 2.3% and HbF 0.8%. No abnormal haemoglobin is detected. Her partner is also Thai with MCH 22 pg.

What is the most appropriate next step?

Question 3

A healthy 25-year-old Greek woman undergoes preconceptual screening. Hb is 125 g/L, MCV 84 fL, MCH 28 pg. HbA₂ is 4.3% and HbF 0.7%.

What is the most likely diagnosis?

Question 4

A pregnant woman from Nigeria has Hb 116 g/L, MCV 78 fL, MCH 25 pg. HbA₂ is 2.5%. HbF is 7.2%. No abnormal haemoglobin is detected.

What is the most likely diagnosis?

Question 5

A 23-year-old woman has Hb 132 g/L, MCV 86 fL, MCH 29 pg. HbA₂ is 2.5%. HbF is 18%. Family study shows similar findings in her father and grandmother. No anaemia is present.

What is the most likely diagnosis?

Question 6

A pregnant woman of Vietnamese origin has Hb 108 g/L, MCV 67 fL, MCH 22 pg. HPLC shows a peak in the HbA₂ window measuring 16%. HbF is normal.

What is the most likely diagnosis?

Question 7

A newborn screening sample shows Hb F only with no detectable Hb A. The baby is clinically well.

What is the most likely interpretation?

Question 8

A 35-year-old man from Ghana is scheduled for emergency laparotomy. A sickle solubility test is positive. No previous records are available.

What is the most appropriate laboratory action?

Question 9

A 32-year-old woman from Cyprus has Hb 121 g/L, MCV 64 fL, MCH 21 pg, HbA₂ 2.1%, HbF 0.7%. Brilliant cresyl blue staining demonstrates numerous HbH inclusion bodies in approximately 5% of erythrocytes.

What is the most likely diagnosis?

Question 10

A 21-year-old woman is referred following newborn screening of her infant. The infant's screen suggests Hb FS. Maternal testing demonstrates HbA 0%, HbS 49%, HbC 48%, HbF 3%.

What is the mother's diagnosis?

ANSWERS AND EXPLANATIONS

Q Answer

1 A

2 J

3 A

4 D

5 E

6 F

7 M

8 N

9 O

10 I

Explanations

Question 1 → A. β -thalassaemia trait

Microcytosis with MCH <27 pg and HbA₂ >3.5% is diagnostic of β -thalassaemia trait.

Question 2 → J. Further DNA analysis required

This woman has marked microcytosis with normal HbA₂ and both parents originate from a region where α^0 -thalassaemia is common. Molecular testing is required to assess risk of Hb Bart's hydrops fetalis.

Question 3 → A. β -thalassaemia trait

Normal indices do not exclude mild β -thalassaemia. HbA₂ >4% is highly suggestive and should trigger partner testing in reproductive settings.

Question 4 → D. $\delta\beta$ -thalassaemia trait

MCH <27 pg with HbF ≥5% and normal HbA₂ strongly suggests $\delta\beta$ -thalassaemia trait.

Question 5 → E. HPFH

Persistently elevated HbF (>10%) with normal red cell indices and dominant inheritance pattern indicates HPFH.

Question 6 → F. Hb E trait

An apparent HbA₂ >15% on HPLC should strongly suggest Hb E trait because Hb E co-elutes in the A₂ window.

Question 7 → M. Newborn likely to have β -thalassaemia major/TDT

Absence of HbA on newborn screening requires urgent follow-up for β -thalassaemia major or severe β -globin synthesis disorders.

Question 8 → N. Emergency sickle screening requires confirmatory testing

A positive sickle solubility test confirms presence of HbS but cannot distinguish trait from disease. Definitive testing by HPLC or CE is mandatory.

Question 9 → O. Hb H disease

Golf-ball inclusions in approximately 5% of red cells after supravital staining are characteristic of Hb H disease.

Question 10 → I. Hb SC disease

The maternal haemoglobin pattern demonstrates approximately equal HbS and HbC with no HbA, diagnostic of HbSC disease.

EMQ 92 and 93

Theme

For each clinical scenario, select the single most appropriate treatment from the option list below. Each option may be used once, more than once, or not at all.

Options

- A. Prothrombin Complex Concentrate (PCC)
 - B. Recombinant activated factor VII (NovoSeven®)
 - C. FEIBA® (Activated Prothrombin Complex Concentrate)
 - D. Fresh Frozen Plasma (FFP)
 - E. Vitamin K
 - F. Obizur® (Recombinant Porcine FVIII) and Steroids
 - G. Voncento® (VWF/FVIII concentrate)
 - H. Factor VIII concentrate
 - I. Cryoprecipitate
 - J. Von Willebrand factor concentrate
 - K. Platelet transfusion
 - L. Tranexamic acid
 - M. Obizur® (Recombinant Porcine FVIII)
-

Question 1

A 74-year-old man with atrial fibrillation is admitted following a fall. CT brain demonstrates a large acute subdural haematoma with midline shift. He is taking warfarin and his INR is 5.8. Neurosurgeons plan emergency decompression within 1 hour. The blood bank has sufficient blood products available. Immediate correction of coagulopathy is required.

Most appropriate treatment?

Question 2

A 69-year-old woman develops haematuria three days after commencing broad-spectrum antibiotics for cholangitis. She has been receiving warfarin for a mechanical mitral valve. INR is 8.5. She is haemodynamically stable and there is no life-threatening bleeding. Warfarin is withheld.

Most appropriate treatment?

Question 3

A 23-year-old man with severe haemophilia A develops a painful swollen knee after a football injury. Baseline FVIII <1%. He has never developed inhibitors and current status is negative as well. Joint aspiration is not required.

Most appropriate treatment?

Question 4

A 31-year-old man with severe haemophilia A presents with a spontaneous iliopsoas bleed. He is known to have a high-titre FVIII inhibitor (>20 BU). Previous treatment with FVIII concentrate produced no increment in FVIII levels.

Most appropriate treatment?

Question 5

A 76-year-old woman presents with rapidly enlarging thigh and retroperitoneal haematomas. Laboratory investigations show:

- APTT 110 seconds
- PT normal
- Mixing study fails to correct
- FVIII activity <1%
- FVIII inhibitor 80 BU

She has no previous personal or family history of bleeding.

Most appropriate treatment?

Question 6

A 54-year-old man with decompensated liver cirrhosis develops diffuse bleeding from a central venous catheter insertion site. PT and APTT are markedly prolonged. Fibrinogen level is 0.7 g/L.

Most appropriate treatment?

Question 7

A 16-year-old girl with type 3 von Willebrand disease presents with severe menorrhagia causing symptomatic anaemia. Previous desmopressin trials were ineffective.

Most appropriate treatment?

Question 8

A 68-year-old man undergoes emergency laparotomy for perforated diverticulitis. He develops massive surgical bleeding. Laboratory testing demonstrates:

- Platelets $180 \times 10^9/L$
- PT 13 seconds
- APTT 32 seconds
- Fibrinogen 0.6 g/L

Massive transfusion protocol is underway.

Most appropriate treatment?

Question 9

A 57-year-old man taking rivaroxaban for recurrent venous thromboembolism presents with gastrointestinal haemorrhage. He is shocked and requires emergency endoscopy. Specific anti-Xa reversal agents are unavailable.

Most appropriate treatment?

Question 10

A 42-year-old woman develops persistent oozing following extensive dental extractions. Full blood count, PT, APTT, fibrinogen and platelet function studies are normal. Bleeding is predominantly mucosal and local measures have failed.

Most appropriate treatment?

Answers

Question Answer

- | | |
|---|----------------------------|
| 1 | A. PCC |
| 2 | E. Vitamin K |
| 3 | H. Factor VIII concentrate |

Question Answer

- | | |
|----|--------------------------------------|
| 4 | B. NovoSeven® |
| 5 | F. Obizur® and Steroids |
| 6 | I. Cryoprecipitate |
| 7 | G. Voncento® (VWF/FVIII concentrate) |
| 8 | I. Cryoprecipitate |
| 9 | A. PCC |
| 10 | L. Tranexamic acid |
-

Higher-Level Discussion Points for FRCPath

PCC

- First-line urgent reversal of warfarin-associated major bleeding.
- Increasing off-label use in factor Xa inhibitor bleeding when specific antidotes unavailable.

NovoSeven®

- Bypassing agent.
- Particularly useful in haemophilia with inhibitors.
- Thrombotic risk important examination point.

FEIBA®

- Alternative bypassing agent in inhibitor patients.
- Often discussed alongside NovoSeven in inhibitor management.

Obizur®

- Recombinant porcine FVIII.
- Preferred haemostatic therapy in severe acquired haemophilia A.

Voncento®

- Contains both VWF and FVIII.
- Preferred for severe VWD when DDAVP ineffective or contraindicated.

Cryoprecipitate

- Rich source of fibrinogen, FVIII, VWF, FXIII.

- Used primarily for hypofibrinogenaemia.

Tranexamic Acid

- Antifibrinolytic.
- Particularly useful for mucosal bleeding, dental procedures, epistaxis, menorrhagia, and adjunctive therapy in haemophilia and VWD.

EMQ 94

Option List

Choose the **single best answer** for each scenario.

- A. Proceed with blood transfusion immediately
 - B. Respect the patient's refusal and continue bloodless management
 - C. Seek consent from relatives before transfusing
 - D. Refer to the High Court for a specific issue order
 - E. Review and follow the patient's Advance Decision document
 - F. Administer transfusion because refusal may result in death
 - G. Optimize haemoglobin with iron and/or erythropoietin before surgery
 - H. Transfer care to another willing clinician if unable to accept treatment limitations
-

Question 1

A 58-year-old Jehovah's Witness is scheduled for elective colorectal surgery in six weeks. His haemoglobin is 95 g/L due to iron deficiency anaemia. He refuses all major blood components but is willing to consider erythropoietin and intravenous iron. The surgeon believes the operation can safely be delayed.

What is the **most appropriate next step**?

Question 2

A 42-year-old Jehovah's Witness presents with severe gastrointestinal bleeding. She is conscious, competent, and produces a signed Advance Decision refusing red cells, platelets, plasma, and cryoprecipitate even if her life is at risk. Her haemoglobin is rapidly falling.

What is the **most appropriate action**?

Question 3

A 67-year-old unconscious man is brought to the emergency department following a road traffic collision. He is exsanguinating and requires immediate surgery. Family members state that he was a Jehovah's Witness, but no Advance Decision or refusal document can be located despite urgent efforts.

What is the **most appropriate action**?

Question 4

A 14-year-old Jehovah's Witness with acute leukaemia requires an urgent transfusion to prevent imminent death. Both parents refuse consent. The child also states that he does not want blood. There is sufficient time before deterioration to obtain legal advice.

What is the **most appropriate next step**?

Question 5

A consultant anaesthetist is asked to participate in a high-risk elective vascular procedure on a competent Jehovah's Witness patient. The patient refuses all blood products and the anaesthetist feels unable to provide care under those restrictions because of the anticipated bleeding risk.

What is the **most appropriate action**?

Answers and Explanations

Question Answer

- | | |
|---|----------|
| 1 | G |
| 2 | B |
| 3 | A |
| 4 | D |
| 5 | H |
-

Question 1 — Answer G

Optimize haemoglobin with iron and/or erythropoietin before surgery.

For elective surgery, the guideline emphasizes correction of anaemia before the procedure. Iron deficiency should be treated, and erythropoietin may be considered when appropriate. Delaying surgery to improve haemoglobin can reduce perioperative risk and the likelihood of transfusion.

Question 2 — Answer B

Respect the patient's refusal and continue bloodless management.

A competent adult has an absolute legal right to refuse blood transfusion, even if refusal may result in death. A valid Advance Decision is legally

binding and must be respected. Administering blood against her wishes could constitute battery.

Question 3 — Answer A

Proceed with blood transfusion immediately.

The patient is unconscious and no valid Advance Decision is available. In such circumstances, clinicians must act in the patient's best interests. The guideline states that blood transfusion may be given if there is no evidence of a valid refusal.

Why not C? Relatives cannot legally consent to or refuse treatment on behalf of a competent adult who lacks capacity in this situation.

Question 4 — Answer D

Refer to the High Court for a specific issue order.

Although parents and even a mature child may refuse transfusion, courts can override refusal when necessary to protect the child's welfare. When time permits, legal advice should be sought and the Trust should apply to the High Court for authorization of treatment.

Key principle: The child's best interests are the court's paramount consideration.

Question 5 — Answer H

Transfer care to another willing clinician if unable to accept treatment limitations.

The guideline specifically states that in elective situations, a surgeon or anaesthetist may decline to manage a patient who refuses blood if they feel unable to comply with those wishes. However, they should arrange referral to a suitable colleague willing to provide care within the patient's treatment preferences.

High-Yield Exam Pearls

- ✓ Competent adults can refuse blood even if death is likely.
- ✓ A valid Advance Decision is legally binding.
- ✓ Relatives cannot override an adult's refusal.
- ✓ If no Advance Decision exists and the patient is unconscious, act in the patient's best interests.

- ✓ Children are different: courts may authorize transfusion despite parental or child refusal.
- ✓ Elective surgery requires early planning, anaemia optimization, and documentation of accepted/refused products.
- ✓ Clinicians uncomfortable with treatment restrictions may refer elective cases to another willing clinician.

EMQ 95 and 96

High-Dose Methotrexate (HD-MTX) Toxicity, Prevention and Management

Instructions

For Questions 1–10, select the **single BEST answer** from the option list below. Each option may be used once, more than once, or not at all.

Option List

- A. Acyclovir
 - B. Co-trimoxazole
 - C. Ciprofloxacin
 - D. Meropenem
 - E. Omeprazole
 - F. Trimethoprim
 - G. Sodium bicarbonate hydration and urine alkalinisation
 - H. Calcium folinate (folinic acid) rescue
 - I. Glucarpidase
 - J. Monitoring methotrexate plasma concentrations
 - K. NSAIDs
 - L. Delaying methotrexate administration pending consultant review
-

Question 1

A 12-year-old boy with osteosarcoma is admitted for a scheduled 12 g/m² methotrexate infusion. During clerking, the SHO notes that he has developed significant oral ulceration over the preceding 48 hours and reports worsening abdominal discomfort. Blood results are satisfactory and renal function is normal. The chemotherapy chart is otherwise complete.

What is the **most appropriate immediate action**?

Question 2

A 7-year-old child with ALL is due to receive HD-MTX tomorrow morning. During admission review, the registrar discovers that the patient has continued receiving Pneumocystis prophylaxis until the morning of admission despite protocol instructions.

Which medication is most concerning in this situation?

Question 3

A 15-year-old patient receives HD-MTX. Twenty-four hours later, methotrexate concentrations remain significantly above protocol thresholds despite appropriate urine output and normal creatinine. The oncology consultant decides that rescue therapy should begin immediately to minimise toxicity to healthy tissues.

Which intervention is indicated?

Question 4

A 10-year-old patient is admitted overnight for HD-MTX. The nursing staff ask why intravenous fluids containing bicarbonate are commenced before chemotherapy administration.

What is the principal reason for this intervention?

Question 5

A patient receiving HD-MTX develops delayed clearance with rising creatinine and persistently elevated methotrexate concentrations. Despite intensified folinic acid rescue and hydration, methotrexate levels remain dangerously high.

Which treatment directly accelerates methotrexate breakdown through an alternative elimination pathway?

Question 6

A 14-year-old patient receiving HD-MTX develops neutropenic sepsis 48 hours after treatment. The medical team wishes to initiate broad-spectrum intravenous antibiotics.

Which option is preferred according to the safety guidance presented?

Question 7

A patient receiving HD-MTX complains of musculoskeletal pain. A junior doctor prescribes ibuprofen. During pharmacist review, the prescription is immediately stopped.

Which option best explains this concern?

Question 8

A patient receiving HD-MTX develops delayed clearance. Medication reconciliation reveals a long-standing prescription for a gastric acid suppressant.

Which drug is specifically highlighted as potentially reducing methotrexate clearance and therefore requiring review?

Question 9

A child receives HD-MTX and subsequently develops severe renal impairment. Rescue treatment is administered successfully. The pharmacist reminds the team that folinic acid therapy must continue despite this intervention because methotrexate redistribution can occur after treatment.

Which intervention was most likely administered?

Question 10

A consultant reviews a patient receiving HD-MTX. Urine pH remains >7 , hydration is adequate, folinic acid has been administered correctly, and no interacting medications are present. The consultant now needs the key investigation that will guide subsequent rescue therapy adjustments and determine when treatment can safely stop.

What is the most appropriate answer?

Answers and Explanations

Q Answer

- 1 L
- 2 B
- 3 H
- 4 G
- 5 I
- 6 D
- 7 K
- 8 E
- 9 I

Q Answer

10 J

Q1 — Answer: L. Delaying methotrexate administration pending consultant review

The presentation emphasises checking for **mucositis and abdominal tenderness** before HD-MTX. Significant findings may necessitate delaying treatment and discussing the case with the consultant. Proceeding despite active mucosal toxicity may increase complications.

Q2 — Answer: B. Co-trimoxazole

Co-trimoxazole increases methotrexate exposure and should be stopped before HD-MTX administration. In ALL protocols, it is commonly withheld at least 24 hours before treatment.

Why not F?

Trimethoprim is also problematic, but the scenario specifically describes continuation of Pneumocystis prophylaxis, which is most commonly co-trimoxazole.

Q3 — Answer: H. Calcium folinate (folinic acid) rescue

Folinic acid rescue is the standard protective therapy started after HD-MTX administration to reduce toxicity in normal tissues. Dosing is adjusted according to methotrexate concentrations and renal function.

Q4 — Answer: G. Sodium bicarbonate hydration and urine alkalinisation

Methotrexate and its metabolites may precipitate within renal tubules. Alkalinising urine to a pH >7 reduces precipitation and helps prevent nephrotoxicity while promoting elimination.

Q5 — Answer: I. Glucarpidase (Voraxaze)

Glucarpidase hydrolyses extracellular methotrexate into inactive metabolites that can be cleared independently of renal function. It is reserved for severe toxicity or markedly delayed clearance.

Q6 — Answer: D. Meropenem

Penicillins can reduce methotrexate excretion and increase toxicity. The presentation specifically recommends substituting piperacillin/tazobactam with meropenem in patients currently receiving or clearing methotrexate.

Q7 — Answer: K. NSAIDs

NSAIDs reduce renal elimination of methotrexate and can markedly increase toxicity. Severe toxicity and even fatal outcomes have been reported; therefore they should generally be avoided.

Q8 — Answer: E. Omeprazole

PPIs such as omeprazole, lansoprazole and esomeprazole may reduce methotrexate clearance. Although evidence is less robust than for some other interactions, they should be reviewed carefully.

Q9 — Answer: I. Glucarpidase (Voraxaze)

Even after glucarpidase administration, intracellular methotrexate can redistribute into plasma. Therefore folinic acid rescue must continue and should be separated from glucarpidase administration by at least four hours.

Q10 — Answer: J. Monitoring methotrexate plasma concentrations

Serial methotrexate levels are central to management. They determine:

- Whether clearance is occurring appropriately
- Whether folinic acid dose escalation is required
- Whether glucarpidase should be considered
- When rescue therapy can be safely discontinued

Without methotrexate level monitoring, safe HD-MTX management is impossible.

EMQ 97

Theme: ALL Risk Stratification and Management Decisions

Options

- A. Continue allocated induction and commence Imatinib from Day 15
 - B. Transfer to Induction C on Day 15
 - C. Proceed directly to Blinatumomab consolidation at Week 6
 - D. Proceed to Extended Induction (Hemi-1B)
 - E. Allocate to Standard-Risk pathway following Blinatumomab
 - F. Allocate to High-Risk pathway following Blinatumomab
 - G. Classify as Blinatumomab Failure
 - H. Consider allogeneic stem cell transplantation
 - I. Manage according to Down Syndrome pathway (Induction D)
 - J. Patient is not eligible for treatment under the UKALL 2025 Blinatumomab guideline
-

Questions

Question 1

An 11-year-old boy presents with precursor B-cell ALL. Initial WCC is $82 \times 10^9/\text{L}$. CNS examination is normal and diagnostic CSF is CNS1. Cytogenetic analysis demonstrates an ABL-class fusion identified on Day 15. Day 15 MRD is 0.8%. Day 29 MRD is 0.03%. There is no evidence of testicular disease. The patient remains clinically well and achieves complete morphological remission.

Which is the single most appropriate management decision at the point the genetic result becomes available?

Question 2

A 7-year-old girl presents with precursor B-cell ALL. Initial WCC is $12 \times 10^9/\text{L}$. She commences Induction A. On Day 15, FISH identifies iAMP21. Bone marrow morphology demonstrates good response and Day 15 MRD is 0.2%. There is no CNS involvement.

Which is the single most appropriate protocol-directed action?

Question 3

A 14-year-old boy with newly diagnosed BCP-ALL has a presenting WCC of $63 \times 10^9/L$. Cytogenetics are unremarkable. Day 15 MRD is 0.6%. At the end of induction, MRD is reported as 7.4%. Bone marrow morphology confirms persistence of disease below the threshold of overt relapse. CNS status remains negative.

Which is the single most appropriate next treatment step?

Question 4

A 9-year-old girl with NCI standard-risk BCP-ALL has no CNS disease, no high-risk cytogenetics, and Day 15 MRD $<0.01\%$. End-induction MRD is undetectable. Following the first cycle of Blinatumomab, both flow cytometry and molecular assays demonstrate complete MRD negativity below assay detection limits.

Which is the most appropriate post-Blinatumomab risk assignment?

Question 5

A 13-year-old boy initially presents with WCC $45 \times 10^9/L$ and CNS1 disease. Cytogenetics show no recognised high-risk abnormalities. Day 15 MRD is 0.2%. End-induction MRD is 0.03%, and he proceeds to Blinatumomab. Following cycle 1, bone marrow MRD is 0.12% by validated flow cytometry. Repeat testing confirms the result.

Which is the most appropriate classification under the guideline?

Answers and Explanations

Question 1

Answer: A — Continue allocated induction and commence Imatinib from Day 15

Explanation

ABL-class fusions are treated differently from other high-risk genetic lesions. Identification of an ABL-class fusion does not mandate transfer to Induction C or the High-Risk pathway at that stage. Instead, Imatinib is introduced from Day 15 (or as soon as the result becomes available) while the patient continues the originally allocated induction regimen.

A common FRCPATH trap is confusing ABL-class fusions with iAMP21, KMT2A rearrangements, near-haploidy or low hypodiploidy.

Question 2

Answer: B — Transfer to Induction C on Day 15

Explanation

iAMP21 is one of the recognised high-risk cytogenetic abnormalities. Patients who initially appear NCI Standard Risk and commence Induction A must transfer to Induction C when iAMP21 is identified.

The key issue here is that treatment modification is driven by the genetic abnormality rather than MRD response.

Question 3

Answer: D — Proceed to Extended Induction (Hemi-1B)

Explanation

End-induction MRD $\geq 5\%$ constitutes Induction Failure under UKALL 2025.

Patients with induction failure do not proceed directly to Blinatumomab. Instead, they receive Extended Induction (Hemi-1B). Subsequent therapy depends upon response after this additional phase.

A frequent examination pitfall is prematurely escalating to transplant before assessing response to Hemi-1B and Blinatumomab.

Question 4

Answer: E — Allocate to Standard-Risk pathway following Blinatumomab

Explanation

The patient satisfies all Standard-Risk criteria:

- Age < 16 years
- No CNS disease
- No high-risk genetics
- Day 15 MRD $< 5\%$
- Compatible ALLTogether-1 SR/IR-L characteristics
- Undetectable MRD after Blinatumomab cycle 1

Failure to achieve MRD negativity after Blinatumomab would have resulted in High-Risk allocation.

Question 5

Answer: G — Classify as Blinatumomab Failure

Explanation

Blinatumomab Failure is defined by any of:

- MRD $\geq 0.1\%$ after cycle 1
- MRD $\geq 0.01\%$ after cycle 2
- ≥ 1 -log increase in MRD during treatment

This patient's MRD of 0.12% after cycle 1 exceeds the 0.1% threshold and therefore fulfills the definition of Blinatumomab Failure.

Such patients leave the standard guideline pathway and require consideration of alternative strategies, including transplant and potentially CAR-T-cell therapy depending on disease burden and clinical circumstances.

EMQ 98

Theme: Management of Relapsed Acute Lymphoblastic Leukaemia (ALL)

Option List

Each option may be used once, more than once, or not at all.

- A. Blinatumomab followed by HSCT
 - B. CAR-T cell therapy assessment
 - C. Standard-risk chemotherapy pathway without HSCT
 - D. Imatinib in addition to relapse therapy
 - E. Cranial radiotherapy during maintenance
 - F. National MDT discussion only
 - G. Bilateral orchidectomy
 - H. Second cycle of blinatumomab
 - I. Proceed directly to HSCT
 - J. Continue induction chemotherapy to Day 29
-

Scenario 1

A 9-year-old boy with precursor B-ALL relapses 18 months after diagnosis while still receiving maintenance therapy. Cytogenetics demonstrate an iAMP21 abnormality. Following induction, marrow MRD is undetectable after one cycle of blinatumomab.

What is the most appropriate next step?

Scenario 2

A 14-year-old girl experiences a first relapse of precursor B-ALL 4 years after completing frontline therapy. She has no adverse cytogenetic abnormalities. Bone marrow relapse responds well to induction and MRD becomes negative after blinatumomab.

Which treatment pathway is most appropriate?

Scenario 3

A 12-year-old boy with relapsed precursor B-ALL has an ABL1 fusion identified at relapse. He is commencing relapse chemotherapy.

What additional treatment should be started?

Scenario 4

A 17-year-old patient with high-risk marrow relapse receives induction and subsequently one cycle of blinatumomab. End-of-cycle MRD is 0.05%.

What is the most appropriate next treatment?

Scenario 5

A 15-year-old girl with high-risk marrow relapse has persistent marrow disease of 2% by flow cytometry at Day 29 of induction chemotherapy.

What is the most appropriate management?

Answers and Explanations

Scenario Answer

- | | |
|---|---|
| 1 | I |
| 2 | C |
| 3 | D |
| 4 | H |
| 5 | B |
-

Scenario 1 → I. Proceed directly to HSCT

This patient is high risk because:

- Relapse occurred during therapy.
- iAMP21 is a high-risk cytogenetic abnormality.

The UK guideline recommends that patients who achieve MRD-negative remission after the first cycle of blinatumomab should proceed to HSCT as soon as feasible rather than receive additional blinatumomab.

Scenario 2 → C. Standard-risk chemotherapy pathway without HSCT

This is:

- A late relapse (>6 months after completion of therapy).
- No high-risk genetics.

Therefore she belongs to the standard-risk group. Current UK guidance aims to avoid HSCT in most standard-risk patients and uses blinatumomab followed by delayed intensification and maintenance chemotherapy.

Scenario 3 → D. Imatinib in addition to relapse therapy

Patients with ABL-class fusions (ABL1, ABL2, PDGFRA, PDGFRB, CSF1R) should receive a tyrosine kinase inhibitor from the start of relapse treatment.

Imatinib is the standard first-line TKI unless a second-generation agent has previously been required.

Scenario 4 → H. Second cycle of blinatumomab

Following Cycle 1:

- MRD <0.01% → HSCT.
- MRD 0.01–0.1% → Second cycle of blinatumomab.
- MRD ≥0.1% → Refractory disease; discuss CAR-T.

This patient's MRD is 0.05%, therefore a second cycle of blinatumomab is indicated.

Scenario 5 → B. CAR-T cell therapy assessment

Patients with:

- MRD ≥1% at Day 29 induction,
- Persistent significant disease after induction,

are considered poor responders and should be discussed urgently for CAR-T cell therapy assessment via the National Leukaemia MDT.

These patients have poor outcomes with conventional chemotherapy and HSCT alone.

Key FRCPATH Pearls

- Relapse during treatment = High Risk.
- iAMP21, KMT2A rearrangement, TCF3-HLF, TCF3-PBX1, low hypodiploidy = High Risk regardless of timing.
- MRD <0.01% after first blinatumomab → HSCT.

- MRD 0.01–0.1% → second blinatumomab cycle.
- MRD $\geq 0.1\%$ after blinatumomab → consider CAR-T.
- ABL-class fusions → add imatinib.
- Most standard-risk late relapses no longer proceed routinely to HSCT.

EMQ 99 and 100

Theme: Paediatric & Neonatal Transfusion Medicine

Options

- A. Delayed cord clamping
 - B. Exchange blood transfusion (EBT)
 - C. Fetal blood sampling (FBS)
 - D. Intrauterine red cell transfusion (IUT)
 - E. Intrauterine platelet transfusion
 - F. Neonatal red cell transfusion 15 mL/kg
 - G. Neonatal platelet transfusion threshold $25 \times 10^9/L$
 - H. IVIg and maternal steroids during pregnancy
 - I. Fresh (<5 day old) irradiated red cells transfused through a blood warmer
 - J. Paedipack red cell transfusion
 - K. Restrictive red cell transfusion threshold (Hb 70 g/L)
 - L. Cryoprecipitate
 - M. Fresh frozen plasma (FFP)
 - N. Protein C replacement (with FFP initially)
 - O. Washed platelets in platelet suspension medium
 - P. Extended red cell phenotyping/genotyping
 - Q. Cell salvage
 - R. Solvent-detergent plasma
 - S. Methylene blue-treated plasma
 - T. Monitor for late anaemia due to suppression of erythropoiesis
-

Questions

Question 1

A 28-week fetus develops severe anaemia due to maternal anti-K antibodies. MCA peak systolic velocity is markedly elevated. The fetus is hydropic. The obstetric team wishes to prolong the pregnancy until term if possible.

Which is the SINGLE most appropriate intervention?

Question 2

A neonate delivered following multiple antenatal transfusions for severe RhD haemolytic disease has a stable haemoglobin at birth. Three weeks later the baby develops worsening anaemia with a low reticulocyte count and minimal evidence of haemolysis.

What is the most likely management principle?

Question 3

A mother previously delivered a baby with severe neonatal alloimmune thrombocytopenia (NAIT) complicated by intracranial haemorrhage. During a subsequent pregnancy the fetus is considered high risk for recurrent disease.

What is the preferred first-line antenatal strategy?

Question 4

A term neonate with anti-D haemolytic disease has rapidly rising bilirubin despite intensive phototherapy and IVIg. The bilirubin level is approaching the threshold associated with kernicterus.

What is the most appropriate next intervention?

Question 5

A 900 g premature infant in NICU has a platelet count of $22 \times 10^9/L$. There is no evidence of bleeding and cranial ultrasound is normal.

Which management strategy is supported by current evidence?

Question 6

A 3-day-old infant develops severe neonatal sepsis complicated by necrotising enterocolitis. Following transfusion, unexpected haemolysis occurs. T-activation is suspected.

Which blood component modification would be most appropriate if platelet support is required?

Question 7

A 2.5 kg neonate requires emergency surgery for gastroschisis. The surgical team anticipates transfusion exceeding one blood volume over several hours.

Which blood product specification is most appropriate?

Question 8

A child with sickle cell disease is expected to require lifelong transfusion support. The haematologist wishes to minimise future alloimmunisation and transfusion complications.

Which intervention should be instituted early?

Question 9

A 7-year-old child in PICU with severe bacterial pneumonia has an Hb of 72 g/L. The child is haemodynamically stable, ventilated and not actively bleeding.

What is the most evidence-based transfusion strategy?

Question 10

A newborn presents on day 1 with rapidly progressive skin necrosis, disseminated intravascular coagulation and a strong family history of neonatal deaths shortly after birth. Severe congenital protein C deficiency is suspected.

What is the most urgent treatment?

Answers and Explanations

Q Answer

1 D

2 T

3 H

4 B

5 G

6 O

7 I

8 P

9 K

10 N

Q1 — D. Intrauterine Red Cell Transfusion (IUT)

This fetus has severe anaemia secondary to maternal anti-K alloimmunisation. Elevated MCA PSV is the preferred non-invasive method

of diagnosing significant fetal anaemia. Red cell IUT is the treatment of choice and aims for a fetal haematocrit around 0.45 while allowing continuation of pregnancy until approximately 37–38 weeks.

Q2 — T. Monitor for Late Anaemia Due to Suppression of Erythropoiesis

Neonates who undergo multiple IUTs commonly develop late anaemia weeks after birth because transfused donor red cells suppress neonatal erythropoiesis. The low reticulocyte count and lack of haemolysis point toward marrow suppression rather than ongoing HDN.

Q3 — H. IVIg and Maternal Steroids During Pregnancy

The majority of severe NAIT is due to anti-HPA-1a antibodies. Current practice is to treat the mother with IVIg ± corticosteroids antenatally to reduce fetal thrombocytopenia and avoid invasive procedures such as fetal platelet transfusions whenever possible.

Q4 — B. Exchange Blood Transfusion (EBT)

Exchange transfusion is indicated when bilirubin rises despite maximal phototherapy and IVIg. EBT removes bilirubin, maternal antibodies and antibody-coated red cells, thereby preventing bilirubin encephalopathy.

Q5 — G. Neonatal Platelet Transfusion Threshold $25 \times 10^9/L$

The PLANET-2 trial demonstrated that liberal platelet transfusion strategies resulted in higher rates of death and major bleeding than restrictive approaches. A non-bleeding neonate is generally transfused only when the platelet count falls below approximately $25 \times 10^9/L$.

Q6 — O. Washed Platelets in Platelet Suspension Medium

T-activation occurs when bacterial neuraminidase exposes the T cryptantigen on neonatal red cells. Naturally occurring anti-T antibodies in donor plasma can worsen haemolysis. Plasma reduction by using washed platelets suspended in platelet additive solution is preferred.

Q7 — I. Fresh (<5 Day Old) Irradiated Red Cells Through a Blood Warmer

Large-volume neonatal transfusions are associated with risks of hyperkalaemia and hypothermia. Guidance recommends red cells less than

5 days old, transfused within 24 hours of irradiation and administered through a blood warmer.

Q8 — P. Extended Red Cell Phenotyping/Genotyping

Children expected to receive chronic transfusions (e.g., sickle cell disease, thalassaemia, aplastic anaemia) should undergo extended antigen typing/genotyping early. This reduces alloimmunisation and facilitates provision of compatible blood in the future.

Q9 — K. Restrictive Red Cell Transfusion Threshold (Hb 70 g/L)

The TRIPICU study demonstrated that a restrictive transfusion threshold of 70 g/L in stable critically ill children reduced blood use without increasing adverse outcomes. A stable child with Hb 72 g/L would not routinely require transfusion.

Q10 — N. Protein C Replacement (with FFP Initially)

Neonatal purpura fulminans is a haematological emergency typically caused by severe congenital protein C deficiency. Immediate replacement with FFP is required while specific protein C concentrate is arranged. Delay in treatment can be fatal.

Bonus FRCPATH-Level Pearls

1. Anti-K HDN often causes severe fetal anaemia with relatively less hyperbilirubinaemia because it suppresses erythropoiesis.
2. MCA PSV has largely replaced invasive fetal blood sampling for diagnosis of fetal anaemia.
3. PLANET-2 is a favourite exam topic because the results were counterintuitive (more platelet transfusions caused worse outcomes).
4. Late anaemia after IUT is usually due to marrow suppression, whereas early anaemia is more likely due to persistent maternal antibody-mediated haemolysis.
5. T-activation is classically associated with NEC and pneumococcal infection.
6. Major neonatal transfusion: think hyperkalaemia, hypothermia and citrate toxicity.

7. Exchange transfusion removes only ~50% of circulating bilirubin even though it replaces 85–90% of red cells in a double-volume exchange.