**Module 1  
AA: The importance of early diagnosis and referrals to specialized centers of care**

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| **Thank you** | Thank you |

**Abbreviations**

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| **Abbreviation** | **Definition** |
| **AD** | Autosomal dominant |
| **ANA** | Antinuclear antibodies |
| **AR** | Autosomal recessive |
| **ATG** | Antithymocyte globulin |
| **AUSS** | Abdominal ultrasound scan |
| **BM** | Bone marrow |
| **BMF** | Bone marrow failure |
| **BSH** | British Society for Haematology |
| **CI** | Chief investigator |
| **CMV** | Cytomegalovirus |
| **CXR** | Chest X-ray |
| **DS** | Double-stranded |
| **EBV** | Epstein-Barr virus |
| **EHA** | European Hematology Association |
| **FBC** | Full blood count |
| **FA** | Fanconi anemia |
| **FISH** | Fluorescence in situ hybridization |
| **Hb** | Hemoglobin |
| **HIV** | Human immunodeficiency virus |
| **HLA** | Human leukocyte antigen |
| **HRCT** | High-resolution computed tomography |
| **HSCT** | Hematopoietic stem cell transplantation |
| **IST** | Immunosuppressive therapy |
| **LDH** | Lactate dehydrogenase |
| **LFT** | Liver function test |
| **MCV** | Mean corpuscular volume |
| **MDT** | Multidisciplinary team |
| **MDS** | Myelodysplastic syndrome |
| **NSAA** | Non-severe aplastic anemia |
| **PI** | Principal investigator |
| **PNH** | Paroxysmal nocturnal hemoglobinuria |
| **RBC** | Red blood cell |
| **SAA** | Severe aplastic anemia |
| **VSAA** | Very severe aplastic anemia |
| **WBC** | White blood cell |
| **WGS** | Whole genome sequencing |
| **XLR** | X-linked recessive |

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| **Chapter: Welcome** | **Sub-chapter:** **Welcome** |
| **Text** | **Graphic/Animation/Video** |
| {Title}: **Welcome**  {1} Welcome to this interactive module on the critical role of early diagnosis and timely referrals in Aplastic Anemia (AA). You'll explore why early detection is vital, the barriers to achieving it, and strategies to overcome them. Dive into real-world cases and actionable guidance to enhance your understanding and impact patient outcomes.  {2} This module will take approximately 15 minutes to complete.  When you see an underlined word, hover over it to learn more.  {footer} This activity is supported by an educational grant from Pfizer. The funder has had no input into the content. | [AA 2024 branding] |
| **Visual details** | |
| N/A | |
| **Interactivity/buttons** | |
| N/A | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
| Please **do not** show learning objective number  Please add the branding as a header if possible | |

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| **Chapter: Meet the expert** | **Sub-chapter:** **Meet the expert** |
| **Text** | **Graphic/Animation/Video** |
| {Title}: Meet the expert  {Balloon Title}: **Dr. Morag Griffin**  {Balloon text 1}: Consultant in Hematology, St. James University Teaching Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK  {Balloon text 2}: Dr. Morag Griffin is a joint clinical lead of the aplastic anemia and PNH service in Leeds (UK). She is also a clinical adviser to the Aplastic Anaemia Trust (UK) and a Member of the International PNH Interest Group (IPIG) and Severe Aplastic Anemia Working Party (SAAWP).  Dr. Griffin qualified in 2006 from Dundee University. She completed her hematology training in Sheffield and was awarded an MSc in medical leadership at the same time.  Dr. Griffin is active in clinical trials and has completed the EHA Clinical Research Training in Hematology (CRTH) program, serving as CI and PI for phase 1-3 trials in aplastic anemia and PNH.  {Button 1 label} Disclosures  {Button 1 text} **Consulting/speaker (symposium):** Alexion, Novartis, Omeros, Pfizer, Regen | [Morag picture] |
| **Visual details** | |
| {Title} headline 2  {Balloon} 7th option down under avatar option, large placeholder for medium on the left. Insert [Morag picture], as medium.  {Balloon title} Headline 4 bold,  {Balloon text 1} headline 5  {Balloon text 2} paragraph. | |
| **Interactivity/buttons** | |
| Add glossary entry for PNH, CI, PI, EHA.  Add {Button} underneath {Balloon} with disclosures. | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number.  Note abbreviation for PNH, CI, PI, EHA  Note bold in {button} text | |

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| **Chapter: Learning objectives** | **Sub-chapter:** **Learning objectives** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Learning objectives  {Text} After completing this module, you will be able to:   * Recognize the importance of achieving an accurate and timely diagnosis of aplastic anemia * Systematically exclude other bone marrow failure (BMF) disorders to diagnose aplastic anemia * Outline the role of supportive treatment and the multidisciplinary team (MDT) during the diagnostic process | Suggest PM to decide how to make this look visual |
| **Visual details** | |
| {Title} as headline  {text} top line paragraph, bullets as unordered list. | |
| **Interactivity/buttons** | |
| N/A | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
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| **Chapter: Preassessment questions** | **Sub-chapter: Preassessment question 1** |
| **Text** | |
| A 50-year-old patient with fatigue and repeated illness is found to be severely cytopenic after a full blood count (FBC). What is the best course of action while a diagnosis is being determined for this patient?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Immediately start looking for a transplant donor and start them on immunosuppressive therapy. |  | This is not the correct approach as a diagnosis should be confirmed by experienced physicians before treatment planning. | | Refer to an experienced center for further diagnostic tests and initiate supportive care. | This is the correct approach as it ensures an MDT, diagnosis-driven approach while starting the patient on appropriate supportive treatments. |  | | Suspect an inherited BMF disorder and insist on genetic testing. |  | Although an inherited BMF should not be ruled out, getting a BM biopsy should take priority. | | Prescribe prophylactic antimicrobial treatment and immediately administer a live influenza vaccine for winter. |  | Although supportive antimicrobial treatment is recommended for neutropenic individuals, the patient’s severe cytopenia needs to be investigated. Live vaccines should not be administered to patients with compromised immunity. | | |
| **Solution** | |
| DO NOT SHOW SOLUTION IN PREASSESSMENT  It is important for diagnosis and treatment to be managed by an MDT who have experience in aplastic anemia. Despite the patient's age, inherited BMF should not be ruled out, but the priority should be to investigate his severe cytopenia. Supportive antimicrobial treatment is recommended to prevent infection in neutropenic patients and inactive vaccination should be approached with caution **- live vaccines are contraindicated in immunocompromised patients**. Psychological support during diagnosis and referral to a local patient support group should also be considered. | |
| **References** | |
| [Kulasekararaj A, et al*. Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/) | |
| **Chapter: Preassessment questions** | |
| **Text** | |
| **Notes/Settings** | |
| Use drag and drop question (text to text) | |

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| **Chapter: Preassessment questions** | **Sub-chapter: Preassessment question 2** |
| **Text** | |
| Which of the following patients is most likely to have acquired AA rather than an inherited BMF syndrome?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Patient A: 25-year-old with pancytopenia, mild skeletal abnormalities, a family history of anemia, recently diagnosed with severe atopic dermatitis. |  | While this patient may have an inherited disorder, the presence of skeletal abnormalities and a family history of anemia make acquired aplastic anemia less likely. | | Patient B: 12-year-old with pancytopenia, café-au-lait spots, hypoplastic thumbs, and a sibling with similar features. |  | The clinical features in this patient, such as café-au-lait spots and hypoplastic thumbs, strongly suggest an inherited disorder, not acquired aplastic anemia. | | Patient C: 30-year-old with pancytopenia, macrocytic RBCs, and a family history of fatigue and anemia in multiple generations. |  | The macrocytic red blood cells and a strong family history of anemia make an inherited disorder more likely than acquired aplastic anemia. | | Patient D: 40-year-old with pancytopenia, normal physical exam findings, no family history, and recently started on azathioprine for their Crohn’s disease. | The absence of inherited syndrome markers and the presence of a clear environmental trigger (azathioprine) point to acquired aplastic anemia. |  | | |
| **Solution** | |
| DO NOT SHOW SOLUTION IN PREASSESSMENT  Acquired aplastic anemia is typically distinguished by pancytopenia without physical abnormalities or a family history of BMF syndromes. Patients A, B and C all have indicators of inherited disorders, while patient D does not and has a clear environmental trigger. | |
| **Interactivity/buttons** | |
| Add references button  Add glossary entries for BM, BMF, RBC | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
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| **Chapter: Preassessment questions** | **Sub-chapter: Preassessment question 3** |
| **Text** | |
| What is the best supportive treatment regimen for a pancytopenic patient with suspected AA whose diagnosis is yet to be determined?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Ideally supportive care should be delayed until a concrete diagnosis is made. |  | Supportive care should never be delayed, as early intervention prevents life-threatening complications. | | Initiate broad-spectrum antibiotics and corticosteroids, defer transfusions to minimize risks, and schedule vaccinations immediately. |  | Corticosteroids and immediate vaccinations are inappropriate, and transfusions should not be deferred. | | Start live vaccines to boost immunity, provide routine blood transfusions, and manage the patient independently without specialist involvement. |  | Live vaccines are contraindicated, and management without MDT involvement overlooks the complexity of care. | | Administer prophylactic antimicrobials and blood transfusions. Consider vaccination (avoiding live vaccines) and refer for psychological support. | This approach includes essential supportive care, adheres to vaccination guidelines, and involves MDT collaboration. |  | | |
| **Solution** | |
| DO NOT SHOW SOLUTION IN PREASSESSMENT  Supportive care during the diagnostic phase stabilizes the patient and prevents complications. Key measures include prophylactic antibiotic, antiviral and antifungal treatment for neutropenia, blood transfusions to manage severe anemia, avoiding live vaccines, and psychological support. MDT collaboration ensures comprehensive management, making **Option 4** the best choice. | |
| **Interactivity/buttons** | |
| Add references button  Add glossary entries for MDT | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
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| **Chapter: Introduction** | **Sub-chapter:** **Introduction** |
| **Text** | **Graphic/Animation/Video** |
| {Box} {text} **Aplastic Anemia (AA)** is a rare, immune-mediated disorder characterized by:   1. **Pancytopenia:** Reduced levels of all types of blood cells – RBCs, WBCs, and platelets 2. **Bone Marrow Failure (BMF):** The bone marrow loses its ability to produce new blood cells, with hypocellularity a common feature in AA histology   {Carousel Element 1} {Title} **Incidence** {text} Aplastic anemia has an overall incidence of:  **~2 cases per million people**  in Europe and US/Canada  {Carousel Element 2} {Title} **Variations in incidence**  {text 1}  AA is more common in Asia  {text 2}  and in those between the ages of 15–25 and over 60 years.  {Carousel Element 3}  {Expansion box element 1} {Title} **Categorization**   * Most cases are idiopathic (70–80%), whereas the remainder of AA cases are inherited and more common in children. * Disease severity is assessed using the Camitta Criteria   {Expansion box element 2}  {text} The most common clonal change in AA is the presence and progression of a PNH clone (40–60% patients) | [histology\_AA]  Severely hypocellular bone marrrow with very few erythroid and myeloid cells at any stage of differentiation suggesting features of aplastic anemia.  {caption} **Severely hypocellular bone marrow indicative of AA.**  [Severely hypocellular bone marrow with very few erythr | Open-i](https://openi.nlm.nih.gov/detailedresult?img=PMC3014810_CRIM2010-975039.001&query=Aplastic%20anaemia&it=xg&req=4&npos=3)  [incidence]    <https://www.flaticon.com/free-icon/people_2994337?term=population&related_id=2994337>  [far east]    {caption} **AA has higher incidence in asia.**  [https://www.flaticon.com/free-icon/map\_15304116?term=world+map&page=1&position=50&origin =search&related\_id=15304116](https://www.flaticon.com/free-icon/map_15304116?term=world+map&page=1&position=50&origin=search&related_id=15304116)  [biphasic\_incidence]    {caption} **Incidence of AA has biphasic peaks at 15–25 and 60+ years of age.**  [PNH clones in AA]    {caption} **Flow cytometry analysis of PNH clones in patients with AA.** Lack of specific glycosylphosphatidylinositol (GPI)-anchored proteins on neutrophils (CD24), monocytes (CD157) and red blood cells (CD235a and CD59) are indicative of PNH. Using reagents that bind to GPI-anchored proteins (FLAER) and specific fluorochromes (PE-A, Alexa-488-A, PE-Cy70A and FITC-A), the fluorescence intensity of PNH clones lacking these proteins will make them appear in distinct regions of the plot, highlighted by black square outlines. This data comes from the Leeds Teaching Hospitals NHS Trust (UK) flow cytometry labs, courtesy of Dr. Payne. |
| **Visual details** | |
| {Box text} first line paragraph, note bold words. Rest of text in ordered list – no full stops, note bold words. Add {medium} with [histology\_AA] underneath text.  {Carousel Element 1} {title} headline 4 bold, {text} paragraph, center aligned, use ‘highlighted’ formatting text which is highlighted, note bold words and differential spacing.  Add {medium} to the right of text, insert [biphasic\_incidence].  {Carousel Element 2} {title} headline 4 bold {text 1} paragraph, left-aligned. Add {medium} with [far east] image underneath the first line. Add {text 2} next with another {medium} insert [biphasic].  {Carousel Element 3} {Expansion box Element 1} {title} headline 4 bold {text} unordered list, left-aligned.  {Expansion box Element 2} {text} paragraph center aligned. Add {button} labelled “see more” with popup showing {medium} with [PNH clones in AA] image. Ensure the caption is easy to read as it is a hefty figure that probably needs explaining. | |
| **Interactivity/buttons** | |
| {Carousel Elements 1-3}  {Expansion box} within {Carousel Element 3}  Ensure [PNH clones in AA] is enlargeable.  Add {Button} for references at bottom left of section.  Add glossary entry: PNH, RBC, WBC | |
| **References** | |
| 1. [Vaht K, et al. *Haematologica* 2017;102(10):1683–1690.](https://pubmed.ncbi.nlm.nih.gov/28751565/) 2. [Papagiannopoulos C, et al. *Blood* 2022;140(Suppl 1):10774.](https://ashpublications.org/blood/article/140/Supplement%201/10774/490092/Severe-Aplastic-Anemia-A-Systematic-Literature) 3. [Issaragrisil S, et al. *Blood* 2006;107(4):1299–1307.](https://pubmed.ncbi.nlm.nih.gov/16254144/) 4. [Muir KR, et al. *Br J Haematol* 2003;123:906–914.](https://pubmed.ncbi.nlm.nih.gov/14632783/) 5. [Camitta BM, et al. *Blood* 1975;45(3):355–363.](https://pubmed.ncbi.nlm.nih.gov/779871/) 6. [Kulasekararaj A, et al. *Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/) | |
| **Notes/Settings** | |
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| **Chapter: Considerations in diagnosis of AA** | **Sub-chapter:** **Patient assessment and common indicators** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Patient assessment and common indicators  {text} There are a range of factors to consider when suspecting AA:  {Element 1: History}  {text} There are a range of factors within a patient’s history to consider when assessing for BMF disorder:  [patient history\_AA]  {Element 2: Clinical examination} {text} Look out for **dysmorphic features** such asshort stature, hypoplastic thumbs and early greying of hair.  These features can suggest a congenital or inherited cause of AA, or other inherited disorders.  {Element 3: Symptoms} {text}   * **Bleeding and petechiae:** Indicates low platelets * **Fatigue:** Gradual progression, especially in younger patients who may tolerate low hemoglobin * **Recurrent infections:** Indicates neutropenia * **Jaundice:** If linked with hepatitis | [patient history\_AA]    {Caption} **Patient history factors to consider.** |
| **Visual details** | |
| {title}headline 3 {text} paragraph  {Elements 1-3} Timeline  {Element 1} {text} paragraph, add medium underneath text, insert [patient history\_AA] | |
| **Interactivity/buttons** | |
| Ensure [patient history\_AA] is enlargeable.  Add glossary entry for BMF | |
| **References** | |
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| **Chapter: Considerations in diagnosis of AA** | **Sub-chapter:** **Inherited bone marrow failure disorders** |
| **Text** | **Graphic/Animation/Video** |
| {title} Inherited BMF disorders  {text}  BMF and cytopenia are common to a range of both inherited and non-inherited disorders. Below are the inherited BMF disorders and their features:  {table}   |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | **Inheritance pattern** | **BMF** | **Short telomeres?** | **Phenotypic features** | | Fanconi anemia (FA) | AR, XLR, AD | >90% | Yes | Café au lait spots  Short stature  Thumb abnormalities | | Dyskeratosis Congenita | XLR, AR | 80% | Yes | Skin pigmentation  Oral leukoplasia  Nail dystrophy  Premature grey hair  Lung and liver fibrosis | | Shwachman-Diamond | AR | 20% | Yes | Pancreatic insufficiency  Short stature  Thoracic abnormalities | | Diamond Blackfan anemia | AD, AR | Red cells aplasia, BM rare | Yes | Cleft palate  Microcephaly  Low hair line  Absent thumbs | |  |
| **Visual details** | |
| {title} headline 3  {text} paragraph  Up to PM to make the table look as clear, pretty and engaging as possible | |
| **Interactivity/buttons** | |
| Add glossary entries for BMF, AR, AD, XLR, BM  Add {Button} for references at bottom left of section. | |
| **References** | |
| [Kulasekararaj A, et al. *Br J Haematol* 2024;204(3):784–804.](https://onlinelibrary.wiley.com/doi/10.1111/bjh.19236) | |
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| **Chapter: Considerations in diagnosis of AA** | **Sub-chapter:** **Real-world evidence: Comorbidities and age at diagnosis** |
| **Text** | **Graphic/Animation/Video** |
| {title} Real-world evidence: Comorbidities and age at diagnosis  {text 1} Analysis of real-world data has found that certain comorbidities can influence the timing of AA diagnosis:  {text 2} Additionally, clinical trial populations more often include younger individuals, which may not reflect the real-world age distribution of AA.  Real-world evidence shows AA commonly affects patients aged **50–60 years and older**.  {balloon} This discrepancy highlights a **care gap in older patients** **with AA**, emphasizing the need for earlier referral, diagnosis, and appropriate treatment. | [Factors affecting diagnosis\_1]  Tooltip text: Click here to highlight co-morbidities to watch out for  Alt text: Comorbidities that can affect timing of AA diagnosis  [Factors affecting diagnosis\_2]    Tooltip text: Click here to see the original diagram  Alt text: Comorbidities that can affect timing of AA diagnosis  [Age at diagnosis\_AA]    [morag picture] |
| **Visual details** | |
| {title} headline 3  {text} paragraph  Add {Layered image} beneath, layer 1 insert [Factors affecting diagnosis\_1], layer 2 insert [Factors affecting diagnosis\_1]  {text 2} paragraph, note bold words. Insert {medium} underneath with [age at diagnosis\_AA].  Add {balloon} underneath, add text as paragraph, note bold words. Add [morag picture] as avatar for balloon. | |
| **Interactivity/buttons** | |
| {Layered image}  Add {Button} for references at bottom left of section. | |
| **References** | |
| [Scheinberg P, et al. *Presented at EHA 2024;* Madrid, Spain; June 13–16, 2024. Abstract PB2647 (publication only).](https://library.ehaweb.org/eha/2024/eha2024-congress/421440/phillip.scheinberg.analysis.of.real-world.data.to.identify.predictors.for.html)  [Vaht K, et al. *Haematologica* 2017;102(10):1683–1690.](https://pubmed.ncbi.nlm.nih.gov/28751565/) | |
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| **Chapter: Investigations informed by guidelines** | **Sub-chapter:** **Investigations required as per BSH guidelines** |
| **Text** | **Graphic/Animation/Video** |
| {title} Investigations required as per BSH guidelines  {text} A range of investigations are required for accurate and timely identification of AA. These are outlined in the latest British Society for Haematology (BSH) guidelines.  {Element 1} {title} Bloods  {Box 1} Baseline tests:   * FBC * Reticulocyte count * Blood film, hematinics, LFT’s   {Box 2} Virology:   * Hepatitis A/B/C * HIV * EBV * CMV * Parvovirus   {Box 3} Genetics:   * AI screen: ANA and DS DNA * PNH screen * Chromosome breakage: FA if patient <50 years old * Inherited BMF screen * HLA DR – HLA DR2 positivity is associated with better response to IST   {Element 2} {title} Radiology  {Text}   * CXR baseline; hands, forearms and feet if inherited BMF anticipated * HRCT if concerns about Dyskeratosis * AUSS: splenomegaly or abnormal kidneys could indicate alternate diagnosis   {Element 3} {title} Bone marrow  {Text}   * Aspirate, trephine, cytogenetics * FISH: chromosomes 5, 7, 8 and 13 * Myeloid panel   {Element 4} {title} Young patients  {Text}   * Telomeres * WGS | [RBCs]    [baseline\_icon]    [virus]    [genetics]    [radiology]    [bone marrow]    [young] |
| **Visual details** | |
| {title} headline 3  {text} paragraph, center aligned.  {Element 1} medium [RBCs], add 3 boxes side-by-side. Insert medium into each. [baseline\_icon] in left-most box, with {box 1} text. [virus] in center box, with {box 2} text. [genetics] in right-most box, with {box 3} text.  {Element 2} medium [radiology]  {Element 3} medium [bone marrow]  {Element 4} medium [young] | |
| **Interactivity/buttons** | |
| {Elements 1-4} Content selection  Add glossary entries for FBC, LFT, HIV, EBV, CMV, ANA, DS, PNH, FA, BMF, HLA DR, CXR, HRCT, AUSS, FISH, WGS, IST  Add references {button} in bottom left corner | |
| **References** | |
| [Kulasekararaj A, et al. *Br J Haematol* 2024;204(3):784–804.](https://onlinelibrary.wiley.com/doi/10.1111/bjh.19236) | |
| **Notes/Settings** | |
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| **Chapter: Test your knowledge** | **Sub-chapter: Patient case: Roberto** | |
| **Text** | | |
| {Title} **Patient case: Roberto**  {text}, Roberto is a 30-year-old professional rugby player. He attended his family doctor and was rapidly referred to his local hematologist. Roberto has:   * Noticed a reduction in his training abilities * Moderate alcohol intake; vegan diet   Roberto attended his family doctor, his FBC:   |  |  |  |  |  | | --- | --- | --- | --- | --- | | **Hb** | **WCC** | **Neutrophils** | **Platelets** | **MCV** | | 60 g/L | 1 x 109/L | 0.2 x 109/L | 20 x 109/L | 105 (NR 80–100) |   **Please rank the tests in order you would do them:** | | |
| **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answers (correct answer in green)** |
| (1) Additional blood tests – reticulocyte count, renal and liver function, LDH, blood film, hematinics, parvovirus | That is the correct order, well done!  This stepwise approach ensures that more common and less invasive diagnostic possibilities are addressed before proceeding to invasive procedures, aligning with best practice guidelines. Initial results will take less than 24 hours, thus, if a diagnosis is not reached, a stepwise approach with a bone marrow biopsy would be advised as the next test. | (1) Additional blood tests – reticulocyte count, renal and liver function, LDH, blood film, hematinics, parvovirus  (2) PNH screen  (3) BM biopsy |
| (2) PNH screen |
| (3) BM biopsy |
| **Solution** | | |
| Roberto is clearly cytopenic; however, AA is a rare condition. Dietary deficiencies, alcohol-related issues, and conditions like MDS or leukemia are more common causes of cytopenia. A logical, stepwise approach to diagnosis is essential to ensure accurate identification and timely management. | | |
| **Interactivity/buttons** | | |
| Add glossary entries for Hb, LDH, PNH, BM, MDS, FBC, MCV | | |
| **References** | | |
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| **Notes/Settings** | | |
| Use a drag and drop question type for this | | |

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| **Chapter: Differential diagnoses for AA** | **Sub-chapter:** **Differential diagnoses for AA** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Differential diagnoses for AA  {text} Diagnosis of AA can be challenging due to overlap with other conditions.  {text 2} All results and patient cases should be discussed with an experienced center | [differential diagnosis]    {Caption} **AA in relation to other immune cytopenias.** Diagnostic and pathophysiologic overlaps are seen with PNH, MDS, and constitutional BMF syndromes. |
| **Visual details** | |
| {Title} Headline 3.  {Text} as paragraph underneath.  Insert {medium} as [differential diagnosis], ensure image is enlargeable and caption can be seen.  {text 2} as mark-up underneath image, center aligned. | |
| **Interactivity/buttons** | |
| Add glossary entries for PNH, MDS, BMF  Add references {button} in bottom left corner | |
| **References** | |
| [Young N. *N Engl J Med* 2018;379(17):1643–1656](https://www.nejm.org/doi/full/10.1056/NEJMra1413485). | |
| **Notes/Settings** | |
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| **Chapter: Pathogenic mechanisms of AA** | **Sub-chapter:** **Pathogenic mechanisms of AA** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Pathogenic mechanisms of AA  {text} AA pathology is complex and has multiple mechanisms.  {Element 1: Autoimmune} **Autoimmune mechanism**  Immune-mediated destruction of hematopoietic stem cells lead to BMF.  {Element 2: Direct injury} **Direct injury of the hematopoietic stem cell**  Damage to hematopoietic stem cells by **chemicals**, **radiation**, or certain **drugs** can lead to BMF.  {Element 3: Genetic} **Constitutional genetic defects**  Genetic defects such as FA, telomeropathies, and germline gene mutations can predispose an individual to AA. | [autoimmune disease]    [direct injury]    [genetic\_2] |
| **Visual details** | |
| {Title} Headline 3.  {Text} as paragraph underneath.  {Element 1} Title in bold, text in paragraph, add {medium} to the right of the text with [autoimmune disease]  {Element 2} Title in bold, text in paragraph, add {medium} to the left of the text with [direct injury]  {Element 3} Title in bold, text in paragraph, add {medium} to the right of the text with [genetic\_2] | |
| **Interactivity/buttons** | |
| {Elements 1-3} Tabs  Add glossary entry for BMF, FA  Add references {button} in bottom left corner | |
| **References** | |
| 1. [Kulasekararaj A, et al*. Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/) 2. [Uss AL, et al. *Stem Cells* 1997;15(Suppl. 2):299–303.](https://stemcellsjournals.onlinelibrary.wiley.com/doi/pdf/10.1002/stem.5530150739) 3. [Cheng Y, et al*. Front Endocrinol (Lausanne)* 2023;14:1064723.](https://europepmc.org/article/pmc/pmc9911543) 4. [Calado RT and Clé DV. *Hematology Am Soc Hematol Educ Program* 2017;(1):96–101.](https://pmc.ncbi.nlm.nih.gov/articles/PMC6142589/) 5. [Liu Y and Karlsson S. *Leukemia* 2024;38(1):1–9.](https://pmc.ncbi.nlm.nih.gov/articles/PMC10776401/) [Erratum in: *Leukemia*. 2024;38(1):228](https://pmc.ncbi.nlm.nih.gov/articles/PMC10776392/). | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number.  Note reference 5 has two links, one for original publication, other for corrections.  Note bold words. | |

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| **Chapter: Reaching a diagnosis** | **Sub-chapter:** **The multidisciplinary team (MDT) role in a diagnostic-driven approach** |
| **Text** | **Graphic/Animation/Video** |
| {Title} The multidisciplinary team (MDT) role in a diagnostic-driven approach  {text} Effective diagnosis of AA relies on an **expert-led MDT** to:   * Collate results and achieve as early a diagnosis as possible * Develop an effective treatment plan * Share expert advice in cases of diagnostic uncertainty or suspected inherited BMF syndrome   {box} {text} AA is a rare disease—patients should be diagnosed and managed in **experienced centers** by physicians **with expertise in AA**. | [MDT collaboration]    {caption} **MDT collaboration in AA diagnosis.** |
| **Visual details** | |
| {Title} Headline 3  {text} paragraph then unordered list.  Add medium underneath with [MDT\_collaboration]  {box} underneath with paragraph text. First variant with ‘I’ icon in top left, choose box color based on branding and box icon should be ‘attention’. | |
| **Interactivity/buttons** | |
| Add glossary entries for BMF, MDT | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number.  Note bold words | |

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| **Chapter: Reaching a diagnosis** | **Sub-chapter:** **AA diagnostic criteria** |
| **Text** | **Graphic/Animation/Video** |
| {Title} AA diagnostic criteria  {text} The latest **BSH guidelines** classify adult AA by severity according to the Camitta criteria:  {Element 1: Non-severe AA}  {text}  Patients not fulfilling the criteria for severe or very severe aplastic anemia are classified as **non-severe AA**  {Element 2: Severe AA}  {text}  A diagnosis of **severe AA** is classified as:  {box 1} BM cellularity of <25%, or 25–50% with <30% residual hematopoietic cells  {box 2} **Two** of the following:   1. neutrophils <0.5 x 109/L 2. platelets < 20 x 109/L 3. reticulocytes <60 x 109/L   {Element 3: Very-severe AA}  {text}  **Very severe AA**  Same criteria as for severe AA with the addition of neutrophils <0.2 x 109/L | [AA\_severity]    {caption} **AA diagnosis by severity.** |
| **Visual details** | |
| {title} headline 3  {text} center aligned at the top  Add {medium} with [AA\_severity]  {Accordion} to the right of medium. (If possible) it would look great If individual accordion boxes could match the color on the medium.  {Element 1 text} paragraph  {Element 2 text} paragraph, add two boxes below text and insert {box 1} text as paragraph and {box 2} text as paragraph with ordered list.  {Element 3 text} paragraph | |
| **Interactivity/buttons** | |
| {Elements 1-3} accordion, display setting ‘width based on text length’ OFF.  Add a link on word ‘guidelines’ to the reference, as well as a references button in bottom right corner.  Add glossary entries for BSH, BM  Note superscript 9 for blood counts  Note bold words | |
| **References** | |
| [Kulasekararaj A, et al*. Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/) | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number.  Note bold words | |

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| **Chapter: Test your knowledge!** | **Sub-chapter: Diagnosis classification** |
| **Text** | |
| Following a BM biopsy, another FBC and additional reticulocyte count test, results have come back for Roberto. How would you diagnose him according to the 2024 BSH guidelines for aplastic anemia (AA) in adults?   |  |  | | --- | --- | | **Roberto** | | | **BM,** % | 23 | | **N,** /L | 0.1 × 10⁹ | | **PL,** /L | 20 × 10⁹ | | **R,** /L | 50 × 10⁹ |  |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Non-severe AA (NSAA) |  | That’s not right. Roberto would be diagnosed with VSAA as he fulfils the criteria for SAA **and** has a neutrophil count lower than 20 × 10⁹ which indicates VSAA. | | Severe AA (SAA) |  | That’s not right. Roberto would be diagnosed with VSAA as he fulfils the criteria for SAA **and** has a neutrophil count lower than 20 × 10⁹ which indicates VSAA. | | Very Severe AA (VSAA) | Well done. You correctly diagnosed Roberto with VSAA as he fulfils the criteria for SAA **and** has a neutrophil count lower than 20 × 10⁹ which indicates VSAA. |  | | |
| **Solution** | |
| Roberto meets the criteria for VSAA due to BM cellularity <25% (23%), platelets at the threshold of 20 x 10⁹/L, and neutrophils <0.2 x 10⁹/L (0.1 x 10⁹/L). | |
| **Interactivity/buttons** | |
| Add link to guidelines/criteria on word ‘guidelines’ in question. Also add a ‘guidelines’ button somewhere visible.  Add glossary entries for NSAA, SAA, VSAA, BM, FBC | |
| **References** | |
| [Kulasekararaj A, et al*. Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/)  [Link to severity criteria within guidelines](https://onlinelibrary.wiley.com/doi/10.1111/bjh.19236#:~:text=Criteria%20used%20to,SAA%20or%20VSAA) | |
| **Notes/Settings** | |
| Use drag and drop question (text to text) | |

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| **Chapter: Reaching a diagnosis** | **Sub-chapter:** **Supportive care** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Supportive care  {text} **Supportive care** should be commenced while a diagnosis is being determined.  {Element 1} {text} To mitigate infection risk **in patients with a neutrophil count below 0.5 × 10⁹/L,** initiate prophylactic:  {Element 2}  {title} Transfusions  {text}   * Transfusionsshould be irradiated for patients undergoing ATG or HSCT * Iron overload should be monitored and managed as needed   {Element 3}  {title} Vaccinations  {text}   * Avoid live vaccines * Inactive vaccinations may be given after thoroughly considering and balancing risk vs. benefit   Post-transplantation AA patients should follow standard post-transplantation guidelines for vaccine administration | [anti3]    [irradiated\_blood]    [vaccination] |
| **Visual details** | |
| {title} headline 3  {text} paragraph  {Element 1} add paragraph center aligned. add {medium} with [anti3] underneath  {Element 2} add box, variant 6 down with picture option. Select [irradiated blood] as medium. Aligned left, 2:10. Add {title} as headline 3. {text} as unordered list. Left aligned  {Element 3} {title} as headline 4, {text} unordered list left aligned. Insert {medium} to the right with [vaccination]. | |
| **Interactivity/buttons** | |
| {elements 1-3} carousel. Display settings – animation: fade.  Add references button in bottom left  Add glossary entry ATG, HSCT | |
| **References** | |
| [Kulasekararaj A, et al*. Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/) | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number.  Note superscript 9 for blood counts  Note bold words | |

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| **Chapter: Summary** | **Sub-chapter:** **Summary** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Summary  {text}   * Aplastic anemia is a rare BMF disorder with diverse mechanisms and overlapping features, requiring nuanced diagnosis and treatment * Whilst there is a biphasic peak, it is increasingly common in the elderly.. * Patients should be treated in an experienced center * Early diagnosis of patients enables early treatment commencement. * Signposting to patient support groups and psychological support is essential. | [pathogenic mechanisms prism]    {Caption} **AA pathogenic mechanisms.** HSCT, hematopoietic stem cell transplant; TPO, thrombopoietin receptor agonist. |
| **Visual details** | |
| {title} headline 3  {text} paragraph  Add media section underneath with [pathogenic mechanisms prisms] | |
| **Interactivity/buttons** | |
| N/A | |
| **References** | |
| 1. [Kulasekararaj A, et al*. Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/) 2. [Uss AL, et al. *Stem Cells* 1997;15(Suppl. 2):299–303.](https://stemcellsjournals.onlinelibrary.wiley.com/doi/pdf/10.1002/stem.5530150739) 3. [Cheng Y, et al*. Front Endocrinol (Lausanne)* 2023;14:1064723.](https://europepmc.org/article/pmc/pmc9911543) 4. [Calado RT and Clé DV. *Hematology Am Soc Hematol Educ Program* 2017;(1):96–101.](https://pmc.ncbi.nlm.nih.gov/articles/PMC6142589/) 5. [Liu Y and Karlsson S. *Leukemia* 2024;38(1):1–9.](https://pmc.ncbi.nlm.nih.gov/articles/PMC10776401/) [Erratum in: *Leukemia*. 2024;38(1):228](https://pmc.ncbi.nlm.nih.gov/articles/PMC10776392/). | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number. | |

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| **Chapter: Postassessment questions** | **Sub-chapter: Postassessment question 1** |
| **Text** | |
| A 50-year-old patient with fatigue and repeated illness is found to be severely cytopenic after a full blood count (FBC). What is the best course of action while a diagnosis is being determined for this patient?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Immediately start looking for a transplant donor and start them on immunosuppressive therapy. |  | This is not the correct approach as a diagnosis should be confirmed by experienced physicians before treatment planning. | | Refer to an experienced center for BM biopsy and initiate supportive care. | This is the correct approach as it ensures an MDT, diagnosis-driven approach while starting the patient on appropriate supportive treatments. |  | | Suspect an inherited BMF disorder and insist on genetic testing. |  | Although an inherited BMF should not be ruled out, getting a BM biopsy should take priority. | | Prescribe prophylactic antimicrobial treatment and immediately administer a live influenza vaccine for winter. |  | Although supportive antimicrobial treatment is recommended for neutropenic individuals, the patient’s severe cytopenia needs to be investigated. Live vaccines should not be administered to patients with compromised immunity. | | |
| **Solution** | |
| It is important for diagnosis and treatment to be managed by an MDT who have experience in aplastic anemia. Despite the patient's age, inherited BMF should not be ruled out, but a BM biopsy but priority should be a priority to investigate severe cytopenia. Supportive antimicrobial treatment is recommended to prevent infection in neutropenic patients and inactive vaccination should be approached with caution **- live vaccines are contraindicated in immunocompromised patients**. Psychological support during diagnosis and referral to a local patient support group should also be considered. | |
| **Interactivity/buttons** | |
| Add references button  Add glossary entries for BM, BMF, MDT | |
| **References** | |
| [Kulasekararaj A, et al*. Br J Haematol* 2024;204(3):784–804.](https://pubmed.ncbi.nlm.nih.gov/38247114/) | |
| **Notes/Settings** | |
| Use drag and drop question (text to text) | |

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| **Chapter: Preassessment questions** | **Sub-chapter: Postassessment question 2** |
| **Text** | |
| Which of the following patients is most likely to have acquired AA rather than an inherited BMF syndrome?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Patient A: 25-year-old with pancytopenia, mild skeletal abnormalities, a family history of anemia, recently diagnosed with severe atopic dermatitis. |  | While this patient may have an inherited disorder, the presence of skeletal abnormalities and a family history of anemia make acquired aplastic anemia less likely. | | Patient B: 12-year-old with pancytopenia, café-au-lait spots, hypoplastic thumbs, and a sibling with similar features. |  | The clinical features in this patient, such as café-au-lait spots and hypoplastic thumbs, strongly suggest an inherited disorder, not acquired aplastic anemia. | | Patient C: 30-year-old with pancytopenia, macrocytic RBCs, and a family history of fatigue and anemia in multiple generations. |  | The macrocytic red blood cells and a strong family history of anemia make an inherited disorder more likely than acquired aplastic anemia. | | Patient D: 40-year-old with pancytopenia, normal physical exam findings, no family history, and recently started on azathioprine for their Crohn’s disease. | The absence of inherited syndrome markers and the presence of a clear environmental trigger (azathioprine) point to acquired aplastic anemia. |  | | |
| **Solution** | |
| Acquired aplastic anemia is typically distinguished by pancytopenia without physical abnormalities or a family history of BMF syndromes. Patients A, B and C all have indicators of inherited disorders, while patient D does not and has a clear environmental trigger. | |
| **Interactivity/buttons** | |
| Add references button  Add glossary entries for BM, BMF, RBC | |
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| **Chapter: Preassessment questions** | **Sub-chapter: Postassessment question 3** |
| **Text** | |
| What is the best supportive treatment regimen for a pancytopenic patient with suspected AA whose diagnosis is yet to be determined?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Ideally supportive care should be delayed until a concrete diagnosis is made. |  | Supportive care should never be delayed, as early intervention prevents life-threatening complications. | | Initiate broad-spectrum antibiotics and corticosteroids, defer transfusions to minimize risks, and schedule vaccinations immediately. |  | Corticosteroids and immediate vaccinations are inappropriate, and transfusions should not be deferred. | | Start live vaccines to boost immunity, provide routine blood transfusions, and manage the patient independently without specialist involvement. |  | Live vaccines are contraindicated, and management without MDT involvement overlooks the complexity of care. | | Administer prophylactic antimicrobials and blood transfusions. Consider vaccination (avoiding live vaccines) and refer for psychological support. | This approach includes essential supportive care, adheres to vaccination guidelines, and involves MDT collaboration. |  | | |
| **Solution** | |
| Supportive care during the diagnostic phase stabilizes the patient and prevents complications. Key measures include prophylactic antibiotic, antiviral and antifungal treatment for neutropenia, blood transfusions to manage severe anemia, avoiding live vaccines, and psychological support. MDT collaboration ensures comprehensive management, making **Option 4** the best choice. | |
| **Interactivity/buttons** | |
| Add references button  Add glossary entries for BM, BMF, RBC | |
| **References** | |
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