**Module 2  
Current treatment options for AA: benefits and potential complications**

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| **Chapters** | **Subchapters** |
| **Welcome** | [Welcome](#Welcome) |
| **Meet the experts** | [Meet the experts](#Meettheexpert) |
| **Learning objectives** | [Learning objectives](#LOs) |
| **Pre-assessment questions** | [Pre-assessment question 1](#PQ1) |
| [Pre-assessment question 2](#PQ2) |
| [Pre-assessment question 3](#PQ3) |
| **Introduction** | [Introduction](#Intro) |
| **When to initiate treatment** | [When to initiate treatment](#Whentoinit) |
| **Indications for HSCT** | [HLA-matched sibling bone marrow transplantation](#HLAmatched) |
| [Alternate up-front and second-line indications for HSCT](#AltHSCT) |
| **In module question** | [In module question](#InmodQ) |
| **Immunosuppressive therapy** | [IST: standard of care and how to improve immunosuppression](#ISTimprove) |
| **Treating refractory patients** | [Treating refractory patients](#refractory) |
| **Summary** | [Summary](#Summary) |
| **Post-assessment questions** | [Post-assessment question 1](#Post1) |
| [Post-assessment question 2](#Post2) |
| Post-assessment question 3 |
| **Thank you** | Thank you |

**Abbreviations**

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| **Abbreviation** | **Definition** |
| **ATG** | Antithymocyte globulin |
| **BM** | Bone marrow |
| **BMF** | Bone marrow failure |
| **BMT** | Bone marrow transplant |
| **BSH** | British Society of Haematology |
| **CBT** | Cord blood transplantation |
| **CIBMTR** | Center for International Blood and Marrow Transplant Research |
| **CSA** | Cyclosporine |
| **Cy** | Cyclophosphamide |
| **EBMT** | European Society for Blood and Marrow Transplantation |
| **G-CSF** | Granulocyte colony-stimulating factor |
| **GVHD** | Graft-versus-host syndrome |
| **HLA** | Human leukocyte antigen |
| **HSCT** | Hematopoietic stem cell transplant |
| **IBMF** | Inherited bone marrow failure |
| **IST** | Immunosuppressive therapy |
| **MSD** | Matched sibling donor |
| **MTX** | Methotrexate |
| **MUD** | Matched unrelated donor |
| **NSAA** | Non-severe aplastic anemia |
| **OL** | Open-label |
| **OS** | Overall survival |
| **PNH** | Paroxysmal nocturnal hemoglobinuria |
| **PTCy** | Posttransplant cyclophosphamide |
| **Ph2** | Phase 2 |
| **Ph3** | Phase 3 |
| **RCT** | Randomized controlled trial |
| **SAA** | Severe aplastic anemia |
| **TPO** | Thrombopoietin |
| **US FDA** | United States of America Food and Drug Administration |
| **VSAA** | Very severe aplastic anemia |
| **hATG** | Horse antithymocyte globulin |

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| **Chapter: Welcome** | **Sub-chapter: Welcome** |
| **Text** | **Graphic/Animation/Video** |
| {Title}: **Welcome**  {1} Welcome to this interactive module on the current treatment options for aplastic anemia (AA). You’ll explore the latest approaches to treatment through expert insights, engaging videos, and international guidelines. 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** | |
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| **Chapter: Meet the expert** | **Sub-chapter: Meet the expert** |
| **Text** | **Graphic/Animation/Video** |
| {Title}: Meet the expert  {Balloon Title}:Prof. Régis Peffault de Latour  {Balloon Subtitle} Hematology and Bone Marrow Transplant Department, Hôpital Saint-Louis, Paris, France  {Balloon text}: Régis Peffault de Latour received his MD degree from the University Paris – Lariboisière in 2003 and his PhD degree in Immunology from the Pasteur Institute in 2006, where he worked on regulatory T cells in graft versus host disease after hematopoietic stem cell transplantation.  He was trained in hematology at Paris Hospitals and did his post-doctoral fellowship at the Hematology Branch, National Institutes of Health, USA, from 2008 to 2010 on aplastic anemia and PNH.  Prof. Peffault de Latour obtained his tenure professorship position in 2014. He is currently the head of the Hematology and Bone Marrow Transplant Department, Hôpital Saint-Louis, Paris, France, since 2022. He is also responsible for the French reference center on aplastic anemia and PNH, as well as the French organization for rare hematological and immunological disorders. He is also the chair of the Severe Aplastic Anemia Working Party (SAAWP) of the European Blood and Marrow Transplantation (EBMT) group. His research interest focuses on bone marrow transplantation, BMF and PNH.  {Button 1 label} Disclosures  {Button 1 text} **Consulting/speaker (symposium):** Alexion, Apellis, Novartis, Pfizer.  **Research grant:** MSD, Novartis, Pfizer. | [Regis picture] |
| **Visual details** | |
| {Title} headline 2  {Balloon} 7th option down under avatar option, large placeholder for medium on the left. Insert [Regis picture], as medium. {Balloon title} Headline 4, {Balloon text} paragraph. | |
| **Interactivity/buttons** | |
| Add glossary entry for PNH, BMF  Add {Button} underneath {Balloon} with disclosures. | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number.  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:   * Integrate international guidelines to optimize treatment timing and improve patient outcomes. * Evaluate available resources, including donor options, to inform and implement effective treatment decisions. * Adapt treatment in consideration of individual patient factors, including age and refractory status. | Suggest PM to decide how to make this look visual |
| **Visual details** | |
| {Title} as headline  {text} top line paragraph, bullets as unordered list. | |
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| **References** | |
| N/A | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number. | |

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| **Chapter: Pre-assessment questions** | **Sub-chapter: Pre-assessment question 1** | |
|  | **Graphic/Animation/Video** | |
|  | **[thanh\_profile\_1]**    **{Caption}** Meet Thanh. CBC, complete blood count; FA, Fanconi anemia; Hb, hemoglobin; PNH, paroxysmal nocturnal hemoglobinuria.  **[regis\_casevideo1]** | |
| {Title}Meet Thanh  {text}Thanh has been diagnosed with acquired AA. After checking his medical profile, what statement is TRUE for this case?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | A family genetic screening is necessary |  | That’s not quite right. Family genetic screening is not required in this case as Thanh has no relevant family history, his physical exam is normal and genetic testing so far has not been informative. Initiate treatment. | | Thanh has acquired AA – initiate treatment. | Correct! There is enough evidence to suggest a diagnosis of acquired AA – treatment initiation is recommended in this case. |  | | Dyserythropoiesis is atypical in this situation |  | That’s not quite right. Dyserythropoiesis is very common in AA and does not distinguish myelodysplastic syndrome from AA. | | Upfront allogeneic transplantation is mandatory |  | That’s not quite right. Upfront allogenic transplantation is not mandatory in all cases, but treatment should be initiated. | | The patient needs further investigations to make an accurate diagnosis. |  | That’s not quite right. There is enough evidence to initiate treatment. | | | |
| **Solution** | |
| DO NOT SHOW IN PRE-ASSESSMENT QUESTIONS  The diagnosis of acquired severe aplastic anemia (AA) is already established based on pancytopenia and bone marrow findings, with no indications of an inherited or secondary cause. Thus, the focus should now shift toward initiating appropriate treatment, as timing of treatment is critical to improving patient outcomes. | |
| **Visual details** | |
| {Title} Header 3  {text} paragraph, note bold words.  Insert 2 {medium} side by side, 1 with [thanh\_profile\_1] and the other with video of Regis talking through the case, ensure image is enlargeable and caption can be seen easily | |

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| **Chapter: Pre-assessment questions** | **Sub-chapter:** **Pre-assessment question 2** |
| **Text** | |
| |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Initiate the standard of care immunosuppressive therapy (IST) regimen of horse antithymocyte globulin (hATG) + cyclosporine A (CSA) + eltrombopag. |  | That’s not quite right. IST is the recommended first-line therapy in the absence of an available HLA-matched sibling donor, but Thanh’s worsening condition allows for the consideration of up-front transplantation using a haplo-identical family member. | | Proceed with a haplo-identical transplant using one of Thanh’s haplo-identical siblings as a donor. |  | That’s not quite right. First-line haplo-identical transplantation is not currently standard of care. | | Find an HLA-matched unrelated donor before proceeding with a bone marrow hematopoietic stem cell transplant (BM HSCT). |  | That’s not quite right. An unrelated matched transplant can be considered if a donor is immediately available, but due to the urgency of Thanh’s condition and the availability of a matched sibling, matched sibling transplantation would be preferred in this case. | | Strongly advise that Thanh’s HLA-matched sister would be the ideal candidate | Correct! An HLA-matched sibling is ideal, so it is advisable to try your best to facilitate a matched sibling transplant. |  |   Thanh refused vaccinations during the diagnosis stage of his disease and his condition has deteriorated; he recently got an infection and is now septic. He has an HLA-matched sister living abroad who may be unavailable as a donor, however, multiple haplo-identical family members have come forward and are ready to donate immediately. What is the most appropriate next step in managing Thanh’s treatment? | |
| **Solution** | |
| DO NOT SHOW IN PRE-ASSESSMENT QUESTIONS  Thanh is septic and needs urgent treatment. Immunosuppressive therapy (IST) may not improve Thanh’s condition if he is septic. Thanh’s HLA-matched sister as a donor would allow for first-line matched sibling HSCT, hence, it is recommended to strongly advise on this approach, as up-front haplo-identical transplantation is not the standard of care. | |

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| **Chapter: Pre-assessment questions** | **Sub-chapter: Pre-assessment question 3** |
| **Text** | **Graphic/Animation/Video** |
| Despite the situation, Thanh’s HLA-matched sister declined to donate. Thanh remains refractory to immunosuppresive therapy. What is the most appropriate next step in his management?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Initiate haplo-identical stem cell transplantation immediately to expedite treatment. |  | That’s not quite right. Haplo-identical transplantation can be considered, but would require additional testing, including karyotype analysis - this is not the immediate next step. | | Recommend splenectomy to improve hematologic recovery and reduce immune-mediated destruction. |  | That’s not quite right. Splenectomy is not typically indicated in aplastic anemia management and does not address the underlying cause of why Thanh is refractory. | | Proceed with a second course of immunosuppressive therapy targeting refractory aplastic anemia. |  | That’s not quite right. A second course of immunosuppressive therapy is generally not recommended after a failed previous IST and if the patient is young. | | Perform a marrow aspiration with karyotype analysis and re-evaluate for an inherited bone marrow failure syndrome while considering cord blood transplantation if necessary. | Correct! Chromosomal abnormalities or inherited BMF syndromes may have been missed initially, and cord blood transplantation is a viable treatment option in the absence of other donors in young patients. |  | | |
| **Solution** | |
| DO NOT SHOW IN PRE-ASSESSMENT QUESTIONS  The critical next steps here should be investigating the underlying cause of why Thanh is refractory – it may be due to an inherited disorder or clonal evolution. Bone marrow aspiration with karyotyping and further genetic investigations should be pursued. In the meantime, a cord blood transplant can be considered to help improve Thanh’s condition. Haplo-identical donor transplantation could be considered but not before karyotyping and additional analyses. A splenectomy is not appropriate in aplastic anemia and a second course of IST is not recommended after an unsuccessful bone marrow transplant. | |

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| **Chapter: Introduction** | **Sub-chapter: Introduction** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Treating Aplastic Anemia (AA)  {text} The treatment of AA is complex, with the patient journey varying significantly based on **age**, **comorbidities**, **donor availability**, and **initial treatment response**. | [guidelines\_treatment]  **{Caption}British Society of Heamatology (BSH)** **guidelines for the diagnosis and management of adult aplastic anemia.** \*For patients aged between 40 and 50 years, an individual patient assessment based on comorbidities, performance status, expertise of transplant center and rapid availability of sibling donor can be made to help decide whether to treat with first line immunosuppressive therapy (IST) or matched sibling donor (MSD) bone marrow (BM) hematopoietic stem cell transplant (HSCT). \*\*Within 8 weeks. IST, immunosuppressive therapy; MSD, matched sibling donor. |
| **Visual details** | |
| {Title} Header 3  {text} paragraph, note bold words  Insert {medium} with [guidelines\_treatment], ensure image is enlargeable and caption can be seen easily | |
| **Interactivity/buttons** | |
| Add references button 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). | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number. | |

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| **Chapter: When to initiate treatment** | **Sub-chapter:** **When to initiate treatment** |
| **Text** | **Graphic/Animation/Video** |
| {Title} When to initiate treatment  {text 1} The decision to treat should be made based on **disease severity** according to the **Camitta criteria.**  {box 1}   * Treatment should be initiated in patients with **severe AA (SAA)** and **very severe AA (VSAA)** * Patients with moderate AA should be treated **only if they are receiving supportive transfusions** | [When to treat]  A diagram of a treatment procedure  Description automatically generated  **{Caption} Treatment initiation decision-making algorithm according to disease severity.** SAA, severe aplastic anemia; VSAA, very severe aplastic anemia. |
| **Visual details** | |
| {Title} heading 3  {Text} Paragraph, note bold words.  Add {Medium} underneath text with [When to treat]. Ensure caption is visible and image is enlargeable  {Box 1} variant 5 (with outline), margin to previous element (small). Add this underneath [When to treat] | |
| **Interactivity/buttons** | |
| Add ‘references’ button in bottom left of page | |
| **References** | |
| [Camitta BM, et al. *Blood* 1976;48:63–70.](https://www.sciencedirect.com/science/article/pii/S0006497120741534?via%3Dihub) | |
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| **Chapter: Indications for HSCT** | **Sub-chapter: HLA-matched sibling bone marrow transplantation** |
| **Text** | **Graphic/Animation/Video** |
| {Title} **HLA-matched sibling bone marrow transplantation**  {Accordion Element 1: Guidelines}  {text 1} Patients can be considered for first-line HLA-matched sibling donor (MSD)bone marrow (BM) hematopoietic stem cell transplant (HSCT), depending on the availability of a MSD, if they:   * Are less than 40 years old * Have no significant co-morbidities   {Accordion Element 2: Long term outcomes}  {text 2} A study of 61 patients with acquired SAA who underwent MSD HSCT (marrow / Cy-ATG / CSA + MTX) assessed overall survival (OS) and long-term complications:  {Accordion Element 3: Age limitation}  {text 3} European and global data have shown a strong age effect on survival of patients with AA who underwent MSD BM HSCT.  Survival for patients aged 40+ was nearly half that of younger patients, with significantly lower rates compared to those under 40: | [Treatment\_guidelines\_sibling\_HSCT]      **{Caption} For a patient under 40 years old, no comorbidities and an immediately available MSD, HSCT is recommended.** HSCT, hematopoietic stem cell transplant; Cy, cyclophosphamide; ATG, antithymocyte globulin; CSA, cyclosporine; MTX, methotrexate; hATG, horse ATG; UD, unrelated donor; BMT bone marrow transplant; IST, immunosuppressive therapy.  [sibling transplant procedure]    **{Caption} The standard procedure for MSD BM HSCT.** ATG, antithymocyte globulin; CSA, cyclosporin; Cy, cyclophosphamide; MTX, methotrexate.  [longterm\_sibling\_transplant chart]    **{Caption} 6-year probability of OS in acquired SAA patients who underwent MSD BM HSCT, adjusted for waiting time to transplantation.**  [longterm\_sibling\_transplant table]    **{Caption} Incidence of complications in those who underwent MSD BM HSCT (excluding infections).** CI, confidence interval; yr, year. –  [Age\_limitation\_sibling HSCT\_EBMT]    **{Caption} EBMT registry data: survival in patients with SAA who underwent first-line MSD BM HSCT.** EBMT, European Society for Blood and Marrow Transplantation; HLA, human leukocyte antigen; SAA, severe aplastic anemia.  [Age\_limitation\_sibling HSCT\_CIBMTR]    **{Caption} CIBMTR registry data - Survival in patients with SAA who underwent first-line MSD BM HSCT.** CIBMTR, Center for International Blood and Marrow Transplant Research; HLA, human leukocyte antigen; SAA, severe aplastic anemia. |
| **Visual details** | |
| {Title} headline 3  {Accordion element 1} add {text 1}, Paragraph, then unordered list, then paragraph again (note bold words). Next to this, insert {Medium} with [Treatment\_guidelines\_sibling\_HSCT]. Ensure Caption is visible and image enlargeable.  {Accordion element 2} {text 2} paragraph, center-aligned. Note bold words. Add 2 {medium} either side by side or one on top of the other, one with [longterm\_sibling\_transplant chart] and [longterm\_sibling\_transplant table]. Add button ‘Hear from the expert’ centre aligned and easily visible, with [regis\_sibling transplant\_explanation]  {Accordion element 3} {text 3} paragraph, center-aligned. Note bold words. Add 2 {medium} either side by side or one on top of the other, one with [Age\_limitation\_sibling HSCT\_CIBMTR] and [Age\_limitation\_sibling HSCT\_EBMT] | |
| **Interactivity/buttons** | |
| Add {Accordion} underneath title. Ensure ‘width based on length’ and ‘multiple elements can be open at the same time’ are **unchecked.**  Add {Carousel} within {Accordion Element 1}  Add button ‘Hear from the expert’ in bottom of {Accordion element 2}  Add ‘references’ button in bottom left of page  Add glossary entries for EBMT, HLA, HSCT, MSD, Cy, ATG, CSA, MTX, SAA, BM, OS | |
| **References** | |
| [Kulasekararaj A, et al. *Br J Haematol* 2024;204(3):784–804](https://onlinelibrary.wiley.com/doi/10.1111/bjh.19236).  [Konopacki J, et al. *Haematologica* 2012;97:710–716.](https://haematologica.org/article/view/6296)  [Bacigalupo A. *Blood* 2017;129:1428–1436.](https://www.sciencedirect.com/science/article/pii/S0006497120335886?via%3Dihub)  [Gupta V, et al. *Haematologica* 2010;95:2119-2125.](https://pmc.ncbi.nlm.nih.gov/articles/PMC2995571/) | |
| **Notes/Settings** | |
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| **Chapter: Indications for HSCT** | **Sub-chapter: Alternate up-front and second-line indications for HSCT** |
| **Text** | **Graphic/Animation/Video** |
| {text 1} If a patient with SAA/VSAA does not have an MSD or is >40 years old, IST is indicated as first-line therapy. HSCT using alternative donor sources can be considered in certain situations:  {Title} **Alternate up-front and second-line indications for HSCT**  {text 2} HSCT can be considered in the following cases:  **{Element 1: Up-front matched unrelated donor (MUD) HSCT}**  {Element 1 title} Up-front matched unrelated donor (MUD) HSCT  {Element 1 text} In adolescents and children with SAA/VSAA who meet the following criteria, an **up-front MUD HSCT** can be considered:   * No MSD * Multiple MUDs are available, and one can donate promptly * Patient requires urgent transplant due to severe/life-threatening sepsis   {Element 1 box} NOTE: This approach is **experimental** and mainly **pediatric** - RCTs comparing IST with MUD are unavailable.  **{Element 2: Second-line HSCT in refractory or relapsed patients}**  {Element 2 title} Second-line HSCT in refractory or relapsed patients  {Element 2 text} MUD HSCT is also indicated for patients with SAA **after failure of one IST course**:   * Patients should be less than 30 years old * Patients should be within their first year of diagnosis or treatment * Donor must be 10/10 (8/8 HLA-matched: HLA-A, -B, -C, -DRB1, -DQB1) with high-resolution typing   **{Element 3: Alternative donor options}**  {Element 3 title} Alternative donor options  {Element 3 text} When preferred donor options (MSD or MUD) are unavailable and a patient has failed to respond to IST, alternate donor options may be considered:   * 9/10 cord blood * Haplo-identical family donor * 9/10 MUD | [Regis\_matched unrelated donor transplant]  **{Caption}.**  [Treatment\_guidelines\_IST\_relapsed]    {caption} **For a patient who does not have an MSD or is >40 years old, first-line IST is indicated.** HSCT, hematopoietic stem cell transplant; Cy, cyclophosphamide; ATG, antithymocyte globulin; CSA, cyclosporine; MTX, methotrexate; hATG, horse ATG; UD, unrelated donor; BMT bone marrow transplant; IST, immunosuppressive therapy.  [MUD]    [Second line\_MUD HSCT]    [refractory\_relapsed\_algorithm]    **{Caption}** **MUD HSCT is also indicated for patients with SAA after failure of one IST course (after fulfilling criteria).** HSCT, hematopoietic stem cell transplant; IST, immunosuppressive therapy; MSD, matched sibling donor; MUD, matched unrelated donor.  [alternative donor options] |
| **Visual details** | |
| {text 1} at the top of the section as paragraph  Insert {medium underneath box} with [Treatment\_guidelines\_IST\_relapsed]  {Title} heading 3  {text 1} center aligned, paragraph  {element 1 title} heading 4  {element 1 text} paragraph then unordered list, note bold words. {Element 1 note} insert a box underneath text, variant 8 with blue ‘i’. Note bold words.  {element 2 title} heading 4  {element 2 text} paragraph then unordered list, note bold words. Add {medium} next to text with [refractory\_relapsed\_algorithm].  {element 3 title} heading 4  {element 3 text} paragraph then unordered list | |
| **Interactivity/buttons** | |
| Add {content selection} under {text}, center aligned.  Element 1 medium [MUD]  Element 2 medium [Second line\_MUD HSCT]  Element 3 medium [alternative donor options]  Add glossary entries for SAA, VSAA, HLA, HSCT, MUD, MSD, RCT, IST | |
| **References** | |
| [Kulasekararaj A, et al. *Br J Haematol* 2024;204(3):784–804](https://onlinelibrary.wiley.com/doi/10.1111/bjh.19236). | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number. | |

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| **Chapter: In module question** | **Sub-chapter:** **In module question** |
| **Text** | |
| Match the patient with the best course of treatment.   |  |  |  | | --- | --- | --- | | **Answers (correct answers in green)** | **Correct answers** | **Answer Related Negative Feedback** | | Patient A: Relapsing very severe AA after immunosuppressive therapy, 30 years old, controlled type 1 diabetes, unrelated matched donor available. | Matched unrelated bone marrow transplant. |  | | Patient B: Severe AA, 12 years old, autism-spectrum disorder (ASD), matched sibling donor available. | Matched sibling bone marrow transplant. |  | | Patient C: Transfusion-dependent non-severe AA, 23 years old, matched sibling donor available. | Matched sibling bone marrow transplant. |  | | Patient D: Transfusion-independent non-severe AA, 89 years old, multi-organ failure. Matched sibling donor available. | Eltrombopag monotherapy with supportive care |  | | |
| **Solution** | |
| Patient A: This patient is relapsed and at the 30 years old threshold for matched unrelated bone marrow transplant  Patient B: This patient is young and matched sibling donor available: Matched sibling bone marrow transplant.  Patient C: This patient has transfusion-dependent non-severe AA which requires treatment. Bone marrow transplant should be considered for patients with moderate as well as severe AA, as moderate severity is not a reason to decrease the intensity of treatment.  Patient D: This patient is transfusion-independent AA does not require treatment. Follow up in 6 months. | |

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| **Chapter: Immunosuppressive therapy** | **Sub-chapter: IST: standard of care and how to improve immunosuppression** |
| **Text** | **Graphic/Animation/Video** |
| {Title 1} IST: Standard of care and how to improve immunosuppression  {text 1} For the last 30 years, first-line standard IST for patients with AA has been   **horse antithymocyte globulin (hATG) + cyclosporine (CSA)**  {box 1}hATG and CSA-based IST is still indicated as first-line therapy for patients with NSAA who are transfusion-dependent, bleeding or encountering infections, as well as SAA and VSAA who are ineligible for MSD BM HSCT.  {text 2} Numerous studies have explored potential enhancements and modifications to the standard hATG + CSA regimen with limited success.  {Title 2} Thrombopoietin (TPO) receptor agonists  {text 3} Following the publication of the pivotal **RACE clinical trial**, amongst other trials, **eltrombopag** has been added to the standard of care first-line IST regimen in the latest BSH guidelines.  {Element 1: Eltrombopag}  The TPO-receptor agonist, eltrombopag, improves hematologic response rates and patient outcomes in:   * First-line IST for SAA/VSAA patients ineligible for HSCT * IST of refractory/relapsed patients   **Eltrombopag** is now approved by several global regulatory bodies (including US FDA) and is included in the latest BSH guidelines, to be used in combination with hATG + CSA  {Element 2: RACE trial}  The pivotal RACE trial was an investigator-driven, OL, Ph3 RCT which saw significant improvements in treatment response when eltrombopag was added to a standard IST regimen of hATG + CSA in patients with SAA.  {Element 3: Romiplostin}  Romiplostin is a **second-generation TPO-agonist** which has shown efficacy in high doses in refractory AA. It is not approved or routinely used in the US / Europe due to high dose requirements, but it has recently gained approval in Japan and Korea. | [Alterations to IST]    **{Caption} Enhancements and modifications to the standard of care IST regimen have had little success.** Studies in which hormonal (androgens) and corticosteroid modifications, replacement of ATG with varying doses of Cy, addition of other immunosuppressive agents and addition of G-CSF, have shown increased toxicities and little to no improvements in response and survival rates. ATG, antithymocyte globulin; CsA, Cyclosporine; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor.  [Treatment\_guidelines\_eltrombopag]    **{caption} Eltrombopag has been added to the standard of care first line IST regimen.** HSCT, hematopoietic stem cell transplant; Cy, cyclophosphamide; ATG, antithymocyte globulin; CSA, cyclosporine; MTX, methotrexate; hATG, horse ATG; UD, unrelated donor; BMT bone marrow transplant; IST, immunosuppressive therapy.  [RACE results chart]    {Caption} **Key efficacy endpoints from the RACE trial.**  Improved hematologic response: The complete response (CR) rate at 3 months was higher with eltrombopag (22%) compared to standard IST alone (10%), and the overall response (OR) rate at 6 months was 68% versus 41%, respectively. Faster time to response: Median time to first response was significantly shorter with eltrombopag (3.0 months) compared to IST alone (8.8 months). IST, immunosuppressive therapy. |
| **Visual details** | |
| {Title 1} Heading 3  {text 1} paragraph, note bold words  {box 1} added underneath  Add {separator} underneath.  Add {text 2} with {layered image} next to it. Sequential images of [Alterations to IST] to be shown as medium, ensure caption can be seen and if possible enlargeable.  Add {separator}  {Title 2} as header 3, with {text 3} as paragraph beneath, note bold words.  {Element 1} text as paragraph, then unordered list, then paragraph, note bold words. Add {Element 1 box} underneath with variant 5 (solid outline). Text center aligned and note bold words here as well.  {Element 2} Text to the left, insert {medium} to the right with [RACE results chart]. Ensure it is enlargeable, and caption is easily seen.  {Element 3} parargraph, note bold words | |
| **Interactivity/buttons** | |
| {Layered image}  {Elements 1-3} {Tabs}  Add references button in bottom left corner.  Add glossary entries for IST, hATG, CSA, NSAA, BSH, TPO, Cy, G-CSF, ATG, SAA, VSAA, HSCT, US FDA, BM, RCT, OL, Ph3, MSD | |
| **References** | |
| 1. [Champlin RE, et al. *Blood* 1985;66:184–188.](https://www.sciencedirect.com/science/article/pii/S0006497120825208?via%3Dihub) 2. [Marmont AM, et al. *Prog Clin Biol Res* 1984;148:271–287.](https://pubmed.ncbi.nlm.nih.gov/6379665/) 3. [Tisdale JF, et al. *Lancet* 2000;356:1554–1559.](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(00)03126-3/fulltext) 4. [Tisdale JF, et al. *Blood* 2002;100:4668–4670.](https://www.sciencedirect.com/science/article/pii/S0006497120536793?via%3Dihub) 5. [Scheinberg P, et al. *Blood* 2014;124:2820–2823.](https://ashpublications.org/blood/article/124/18/2820/33373/Moderate-dose-cyclophosphamide-for-severe-aplastic) 6. [Scheinberg P, et al. *Br J Haematol* 2006;133:606–611.](https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2141.2006.06085.x?sid=nlm%3Apubmed) 7. [Scheinberg P, et al. *Haematologica* 2009;94:348–354.](https://haematologica.org/article/view/5186) 8. [Locasciulli A, et al. *Haematologica* 2004;89:1054–1061.](https://pubmed.ncbi.nlm.nih.gov/15377466/) 9. Bussel JB, et al. *Drug Des Devel Ther.* 2021;15:2243–2268 | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number. | |

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| **Chapter: Treating refractory patients** | **Sub-chapter: Treating refractory patients** |
| **Text** | **Graphic/Animation/Video** |
| {Title} Treating refractory patients  {text} In the absence of an MSD, the best treatment for acquired AA patients refractory to IST is unclear:   * Alternative donor transplants can be considered in pediatric and young patients (<20 years old) with refractory AA. * Supportive care can still provide significant benefit in non-responders to IST   {Element 1: Cord blood transplantation}  {Title} Unrelated cord blood transplantation (CBT)  {text} Improved outcomes have established unrelated CBTas a viable option for refractory AA patients lacking a matched BM donor, with a Ph2 study presenting an **OS of 82% at 3 years**.  {Element 2: Haplo-identical transplantation and PTCy)  {Title} Haplo-identical transplantation and posttransplant cyclophosphamide (PTCy)  {text} Results from an EBMT report saw encouraging outcomes for patients who underwent haplo-identical transplantation and PTCy, with an **OS of 74% at 2 years.**  {Element 3: Supportive care} {Title} Supportive care for non-responders to IST  {Text} Advances in supportive care, especially the development of new antifungal agents, have significantly improved survival for:   * Refractory patients with AA * Non-responders to IST   Patients who declined or were ineligible for transplant or IST (e.g., due to age or other medical conditions). | [Cord blood transplantation]    **{Caption} Ph2 study on unrelated CBT outcomes in patients with idiopathic refractory SAA**. More than 80% of 26 patients undergoing unrelated CBT achieved neutrophil engraftment with full donor chimerism and survived beyond 3 years post-transplant, with a low incidence of both acute and chronic GVHD. CI, confidence interval; CumI, cumulative incidence; GVHD, graft-versus-host disease; cGVHD, chronic GVHD; OS, overall survival.  [Haplotransplantation]    **{Caption} EBMT report on haplo-identical transplantation and PTCy for treating AA patients.** 74% of 36 patients with AA survived past 2 years following haplo-identical transplantation with PTCy,. The sample was split between those with acquired SAA (n=32) and those with IBMF (n=4).  Cy, cyclophosphamide; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; IBMF, inherited bone marrow failure; SAA, severe aplastic anemia.  [Supportive care\_nonrespondersIST]    **{Caption} Survival for IST non-responders has improved between 1989 and 2008 due to newer antifungal agents and independent of HSCT. I**mprovement in survival is observed in group 3 (2002–2008), compared with survival in groups 1 (1989–1996) and 2 (1998–2002). Censoring for the long-term impact of HSCT (left) had minimal impact on survival when compared to uncensored data (right). Given that infection (particularly invasive fungal infection) is the dominant cause of mortality in SAA, improved antifungal therapy has likely driven this increase in survival for IST non-responders. |
| **Visual details** | |
| {Title} Heading 3  {text} paragraph, note bold words  {Element 1} {Title} heading 4, {text} paragraph, center aligned, note bold words. Add {medium} underneath with [Cord blood transplantation], ensure caption can be seen and image is enlargeable.  {Element 2} {Title} heading 4, {text} paragraph, center aligned, note bold words. Add {medium} underneath with [Haplotransplantation], ensure caption can be seen and image is enlargeable. | |
| **Interactivity/buttons** | |
| {Elements 1-2} accordion.  Add ‘references’ button in bottom left corner.  Add glossary entries for MSD, CBT, Ph2, EBMT, PTCy, GVHD, SAA, IBMF, IST, BM, OS | |
| **References** | |
| [Peffault de Latour R, et al. *Blood* 2018;132(7);750–754.](https://www.sciencedirect.com/science/article/pii/S0006497120319868)  [Prata PH, et al. *Bone Marrow Transplant.* 2020;55(6):1050–1058.](https://pubmed.ncbi.nlm.nih.gov/31844137/)  [Valdez JM, et al. *Clin Infect Dis 2*011;52(6):726–735.](https://pmc.ncbi.nlm.nih.gov/articles/PMC3106262/) | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number. | |

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| **Chapter: Summary** | **Sub-chapter: Summary** |
| **Text** | **Graphic/Animation/Video** |
| {Title1} Summary  {title 2} **First-Line Treatment:**  {text 1}   * **Matched Sibling Donor (MSD):** Preferred for patients 40 years old or younger. * **Matched Unrelated Donor (MUD):** Experimental, primarily for pediatric patients. * **hATG + CSA + eltrombopag:** For other patients.   {title 3} **Refractory Patients:**  {text 2}   * **MUD:** Standard of care for patients 30 years old or younger. * **Alternative BMT:** Mainly for young patients (20 years or younger). * **Eltrombopag:** For other patients, if not used in first-line treatment. |  |
| **Visual details** | |
| {Title 1} heading 3  {Title 2} heading 6 {text 1} undordered list, note bold words  {title 3} heading 3  {text 2} unordered list, note bold words | |
| **Interactivity/buttons** | |
| Add glossary entries for hATG, CSA, BMT | |
| **References** | |
| N/A | |
| **Notes/Settings** | |
| Do not show learning objective or chapter number. | |

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| **Chapter: Post-assessment questions** | **Sub-chapter: Post-assessment question 1** | |
|  | **Graphic/Animation/Video** | |
|  | **[thanh\_profile\_1]**  **A screenshot of a phone  Description automatically generated**  **{Caption}** Meet Thanh. CBC, complete blood count; FA, Fanconi anemia; Hb, hemoglobin; PNH, paroxysmal nocturnal hemoglobinuria.  **[regis\_casevideo1]** | |
| {Title}Meet Thanh  {text}Thanh has been diagnosed with acquired AA. After checking his medical profile, what statement is TRUE for this case?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | A family genetic screening is necessary |  | That’s not quite right. Family genetic screening is not required in this case as Thanh has no relevant family history, his physical exam is normal and genetic testing so far has not been informative. Initiate treatment. | | Thanh has acquired AA – initiate treatment. | Correct! There is enough evidence to suggest a diagnosis of acquired AA – treatment initiation is recommended in this case. |  | | Dyserythropoiesis is atypical in this situation |  | That’s not quite right. Dyserythropoiesis is very common in AA and does not distinguish myelodysplastic syndrome from AA. | | Upfront allogeneic transplantation is mandatory |  | That’s not quite right. Upfront allogenic transplantation is not mandatory in all cases, but treatment should be initiated. | | The patient needs further investigations to make an accurate diagnosis. |  | That’s not quite right. There is enough evidence to initiate treatment. | | | |
| **Solution** | |
| The diagnosis of acquired severe aplastic anemia (AA) is already established based on pancytopenia and bone marrow findings, with no indications of an inherited or secondary cause. Thus, the focus should now shift toward initiating appropriate treatment, as timing of treatment is critical to improving patient outcomes. | |
| **Visual details** | |
| {Title} Header 3  {text} paragraph, note bold words.  Insert 2 {medium} side by side, 1 with [thanh\_profile\_1] and the other with video of Regis talking through the case, ensure image is enlargeable and caption can be seen easily | |
| **Chapter: Post-assessment questions** | **Sub-chapter: Post-assessment question 1** | |
|  | **Graphic/Animation/Video** | |
|  | **[thanh\_profile\_1]**  **A screenshot of a phone  Description automatically generated**  **{Caption}** Meet Thanh. CBC, complete blood count; FA, Fanconi anemia; Hb, hemoglobin; PNH, paroxysmal nocturnal hemoglobinuria.  **[regis\_casevideo1]** | |
| {Title}Meet Thanh  {text}Thanh has been diagnosed with acquired AA. After checking his medical profile, what statement is TRUE for this case?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | A family genetic screening is necessary |  | That’s not quite right. Family genetic screening is not required in this case as Thanh has no relevant family history, his physical exam is normal and genetic testing so far has not been informative. Initiate treatment. | | Thanh has acquired AA – initiate treatment. | Correct! There is enough evidence to suggest a diagnosis of acquired AA – treatment initiation is recommended in this case. |  | | Dyserythropoiesis is atypical in this situation |  | That’s not quite right. Dyserythropoiesis is very common in AA and does not distinguish myelodysplastic syndrome from AA. | | Upfront allogeneic transplantation is mandatory |  | That’s not quite right. Upfront allogenic transplantation is not mandatory in all cases, but treatment should be initiated. | | The patient needs further investigations to make an accurate diagnosis. |  | That’s not quite right. There is enough evidence to initiate treatment. | | | |
| **Solution** | |
| The diagnosis of acquired severe aplastic anemia (AA) is already established based on pancytopenia and bone marrow findings, with no indications of an inherited or secondary cause. Thus, the focus should now shift toward initiating appropriate treatment, as timing of treatment is critical to improving patient outcomes. | |

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| **Chapter: Post-assessment questions** | **Sub-chapter: Post-assessment question 2** |
| **Text** | |
| |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Initiate the standard of care immunosuppressive therapy (IST) regimen of horse antithymocyte globulin (hATG) + cyclosporine A (CSA) + eltrombopag. |  | That’s not quite right. IST is the recommended first-line therapy in the absence of an available HLA-matched sibling donor, but Thanh’s worsening condition allows for the consideration of up-front transplantation using a haplo-identical family member. | | Proceed with a haplo-identical transplant using one of Thanh’s haplo-identical siblings as a donor. |  | That’s not quite right. First-line haplo-identical transplantation is not currently standard of care. | | Find an HLA-matched unrelated donor before proceeding with a bone marrow hematopoietic stem cell transplant (BM HSCT). |  | That’s not quite right. An unrelated matched transplant can be considered if a donor is immediately available, but due to the urgency of Thanh’s condition and the availability of a matched sibling, matched sibling transplantation would be preferred in this case. | | Strongly advise that Thanh’s HLA-matched sister would be the ideal candidate | Correct! An HLA-matched sibling is ideal, so it is advisable to try your best to facilitate a matched sibling transplant. |  |   Thanh refused vaccinations during the diagnosis stage of his disease and his condition has deteriorated; he recently got an infection and is now septic. He has an HLA-matched sister living abroad who may be unavailable as a donor, however, multiple haplo-identical family members have come forward and are ready to donate immediately. What is the most appropriate next step in managing Thanh’s treatment? | |
| **Solution** | |
| Thanh is septic and needs urgent treatment. Immunosuppressive therapy (IST) may not improve Thanh’s condition if he is septic. Thanh’s HLA-matched sister as a donor would allow for first-line matched sibling HSCT, hence, it is recommended to strongly advise on this approach, as up-front haplo-identical transplantation is not the standard of care. | |

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| **Chapter: Post-assessment questions** | **Sub-chapter: Post-assessment question 3** |
| **Text** | **Graphic/Animation/Video** |
| Despite the situation, Thanh’s HLA-matched sister declined to donate. Thanh remains refractory to immunosuppresive therapy. What is the most appropriate next step in his management?   |  |  |  | | --- | --- | --- | | **Answers (correct answer in green)** | **Answer Related Positive Feedback** | **Answer Related Negative Feedback** | | Initiate haplo-identical stem cell transplantation immediately to expedite treatment. |  | That’s not quite right. Haplo-identical transplantation can be considered, but would require additional testing, including karyotype analysis - this is not the immediate next step. | | Recommend splenectomy to improve hematologic recovery and reduce immune-mediated destruction. |  | That’s not quite right. Splenectomy is not typically indicated in aplastic anemia management and does not address the underlying cause of why Thanh is refractory. | | Proceed with a second course of immunosuppressive therapy targeting refractory aplastic anemia. |  | That’s not quite right. A second course of immunosuppressive therapy is generally not recommended after a failed previous IST and if the patient is young. | | Perform a marrow aspiration with karyotype analysis and re-evaluate for an inherited bone marrow failure syndrome while considering cord blood transplantation if necessary. | Correct! Chromosomal abnormalities or inherited BMF syndromes may have been missed initially, and cord blood transplantation is a viable treatment option in the absence of other donors in young patients. |  | | |
| **Solution** | |
| The critical next steps here should be investigating the underlying cause of why Thanh is refractory – it may be due to an inherited disorder or clonal evolution. Bone marrow aspiration with karyotyping and further genetic investigations should be pursued. In the meantime, a cord blood transplant can be considered to help improve Thanh’s condition. Haplo-identical donor transplantation could be considered but not before karyotyping and additional analyses. A splenectomy is not appropriate in aplastic anemia and a second course of IST is not recommended after an unsuccessful bone marrow transplant. | |