ASH® CLINICAL PRACTICE GUIDELINES

Diagnosis and Management of Severe and Very Severe Acquired Aplastic Anemia

An Educational Slide Set

American Society of Hematology 2026 guidelines for diagnosis and management of severe and very severe acquired aplastic anemia

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ASH Clinical Practice Guidelines on Aplastic Anemia (AA)

1. Diagnosis of AA
2. Frontline therapy
3. Second Line Therapy for Relapsed or Refractory AA
4. Timing of Second Line Therapy
5. Antimicrobial Prophylaxis for patients with AA
6. Use of Eltrombopag in Immunosuppressive Therapy (IST)

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How were these guidelines developed?

PANEL FORMATION

Guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology)
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

37 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

Example: PICO question

"Should somatic mutation testing should be performed versus not performed in patients with severe or very severe aplastic anemia?"

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

How patients and clinicians should use these recommendations

	STRONG Recommendation		CONDITIONAL Recommendation	
	"The panel recommends…"	"The panel recommends against…"	"The panel suggests…"	"The panel suggests against…"
				
For patients	Most individuals would want the intervention.		A majority would want the intervention, but many would not.	
For clinicians	Most individuals should receive the intervention.		Different choices will be appropriate for different patients, depending on their values and preferences. Use **shared decision making**.	

Objectives

1. Describe recommendation for the addition of eltrombopag to immunosuppressive therapy (IST) in children with severe or very severe AA
2. Describe recommendation for timing of second-line treatment for individuals who do not respond to IST
3. Describe recommendation for matched unrelated donor (MUD) hematopoietic cell transplant (HCT) as front-line therapy in individuals ≤40 years old with severe or very severe AA

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Aplastic Anemia: Introduction

- Aplastic anemia (AA) is rare
  - Incidence ranges from 1.5 to 7 cases per million per year
- AA affects both children and adults
- Characterized by acquired bone marrow failure and pancytopenia
- Approach to diagnostic work-up and treatment remains heterogenous

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About this guideline

- Addresses diagnostic work-up, therapy selection and management
- Intended to guide individuals with AA, caregivers, and clinicians on diagnostic work-up and management of AA in children and adults
- Systematically reviewed and analyzed data using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology

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Case 1: Management of a child with new diagnosis of severe AA

- 4-year-old previously healthy boy presented to the ED with vomiting, diarrhea, petechiae and fever
- Complete blood count (CBC) notable for WBC 0.88 x 10^3/µL, Hemoglobin 5.9 g/dL, platelet 6 x 10^3/µL, absolute reticulocyte count (ARC) 7.1 x 10^3/µL and absolute neutrophil count (ANC) 0.13 x 10^3/µL
- Medication exposure/history: None
- Family history: unremarkable
- Physical examination: Petechiae on lower extremities, otherwise unremarkable

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Case 1: Management of a child with new diagnosis of severe AA

Additional Labs

- Peripheral smear and bone marrow (BM) flow cytometry: No blasts
- BM Biopsy and aspirate: markedly hypocellular marrow (<5% cellularity) with trilineage hypoplasia
- FISH MDS/Myeloid panel: negative
- PNH by flow cytometry: not detected
- Chromosome breakage analysis: negative with diepoxybutane (DEB) assay
- Telomere length: normal
- **Diagnosis: very severe acquired AA**

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This child has very severe AA.

He does not have HLA matched sibling donor (MSD). Therefore, plan is to start IST.

What would be the best recommended IST regimen?

A. Anti-thymocyte globulin (ATG) + Cyclosporine ONLY
B. ATG + Cyclosporine + intravenous immunoglobulin (IVIG)
C. ATG + Cyclosporine + Eltrombopag
D. ATG + Cyclosporine + Romiplostim

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Recommendation

- The ASH guideline panel ***suggests*** the addition of eltrombopag to IST for children with severe or very severe AA *(conditional recommendation, based on low certainty of evidence of the effects)*

•For this analysis, randomized and non-randomized trial data were pooled, which showed:

- IST + eltrombopag may be associated with earlier responses and improved complete response
- Sensitivity analyses, including meta-regression, showed that the effects of eltrombopag are independent of age, suggesting the benefit extends across all age groups

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Case 1, continued:

- The patient proceeded with IST plus eltrombopag
- About 14 weeks after initiation of therapy, he remains cytopenic and requires transfusion support once a week:
  - CBC: WBC 4.13 x 10^3/µL, Hemoglobin 7.6 g/dL, platelet 8 x 10^3/µL, ARC 67.1 x 10^3/µL and ANC 0.54 x 10^3/µL
- He is otherwise clinically stable with no signs of infection

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This child continues to have cytopenias with ongoing transfusion needs at week 14.

How long would you wait to consider second-line treatment for this patient?

A. Do not wait, initiate second-line treatment now
B. Consider starting second-line treatment no later than 4 months of follow-up
C. Consider starting second-line treatment no later than 6 months of follow-up
D. Consider starting second-line treatment no later than 12 months of follow up

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Recommendation

- The ASH guideline panel ***suggests*** initiating second-line treatment no later than six months of follow-up for patients with severe and very severe AA who do not respond to IST *(conditional recommendation, based on very low certainty of evidence of the effects)*

- Guideline panel considered that initiating a second line of treatment before six months, compared to after six months, may offer a net benefit, as the response curve tends to plateau beyond that point
- Preparing for a second-line treatment, especially HCT, requires time and coordination; therefore, early identification of non-responders may contribute to better outcomes

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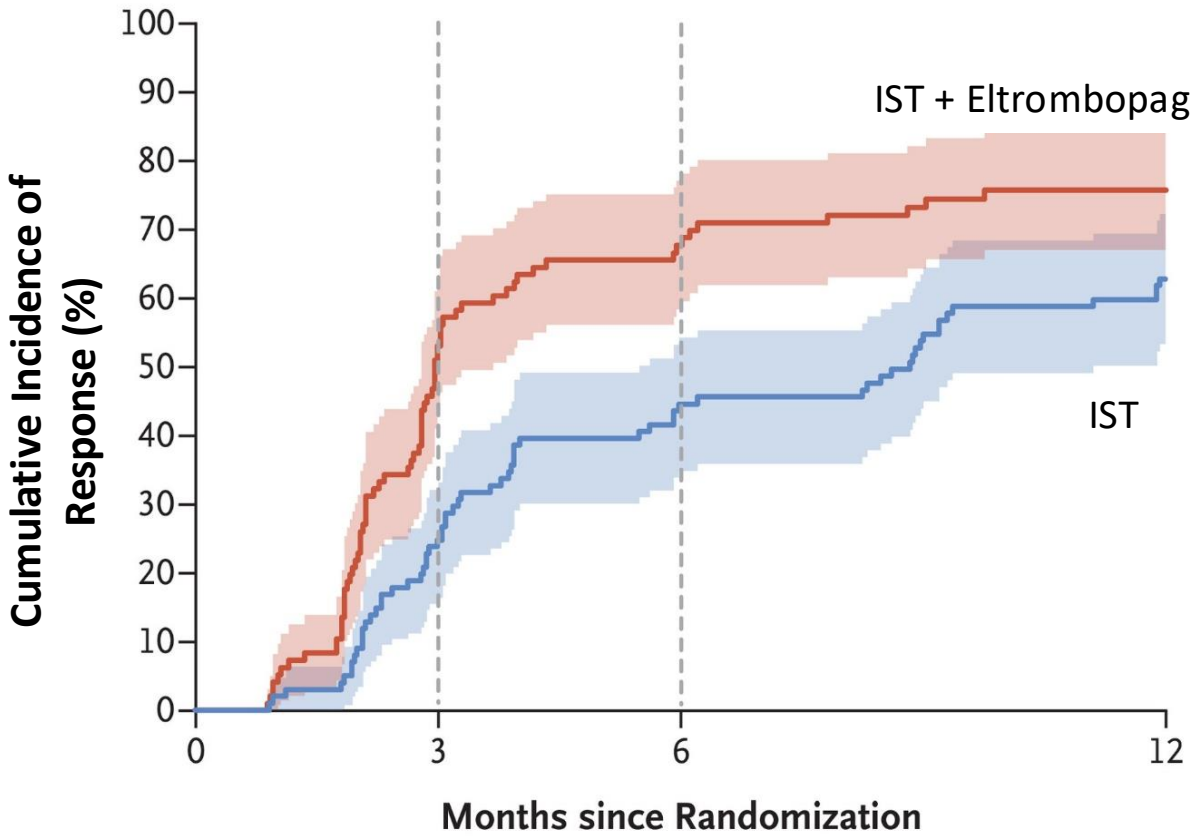
Rationale



- RACE trial demonstrated that the majority of individuals in both the IST-alone and IST plus eltrombopag groups achieved responses by month 6

Peffault de Latour R, et al. N Engl J Med. 2022. PMID: 34986284.

Additional remarks

- Even though some individuals with very severe AA may respond to IST after three months, individuals with severe cytopenias may warrant earlier decision to initiate second-line treatment
  - Severe and prolonged neutropenia increase the risk of life-threatening infections
  - Response assessment at three months for patients with very severe AA may help identify those who have not achieved adequate hematologic improvement and who may benefit from earlier salvage therapy

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Case 1: Conclusion

- At 6 months follow-up, patient underwent IST-response assessment and determined he was a non-responder
  - Require transfusion support 3-4 times per month
  - CBC: WBC 4.1 x 10^3/µL, Hemoglobin 7.1 g/dL, platelet 9 x 10^3/µL, ARC 65.4 x 10^3/µL and ANC 0.55 x 10^3/µL
- As this patient did not have MSD and matched unrelated donor (MUD), he was referred for a haploidentical donor HCT

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Case 1: Summary

The ASH guideline panel suggests the addition of eltrombopag to IST for children with severe or very severe AA

- This is a conditional recommendation because most studies in the meta-analysis were non-randomized trials

The ASH guideline panel suggests initiating second-line treatment no later than six months of follow-up for patients who do not respond to IST

- Individuals with very severe AA may be at increased risk of adverse outcomes so this population may warrant earlier decision to initiate second-line treatment

Future areas of study:

- Additional randomized clinical trials to evaluate the outcomes of adding of eltrombopag to IST
- Long-term studies to characterize the risks of relapse and clonal evolution associated with eltrombopag
- Studies investigating the optimal timing for initiation and the ideal duration of eltrombopag
- Further research to determine the optimal time for initiating second-line treatment

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Case 2: Matched unrelated donor HCT vs. IST as front-line therapy

- 23-year-old, previously healthy female presented to the ED with syncope
  - History notable for new-onset petechiae for the past 2-3 weeks
- CBC notable for WBC 1.54 x 10^3/µL, Hemoglobin 6.5 g/dL, platelet 9 x 10^3/µL, ARC 21 x 10^3/µL and ANC 0.26 x 10^3/µL
- Medication history/exposure: None
- Family history: unremarkable
- Physical Examination: heart rate of 105 bpm, BP 120/66 mm Hg, tachycardia without murmur, bruises and petechiae on lower extremities; remaining exam normal

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Case 2: Matched unrelated donor HCT vs IST as front-line therapy

Additional Labs

- Peripheral smear and bone marrow (BM) flow cytometry: No blasts
- BM Biopsy and aspirate: markedly hypocellular marrow (<10% cellularity) with trilineage hypoplasia
- FISH MDS/Myeloid panel: negative
- Somatic mutation panel: negative
- PNH by flow cytometry: PNH clone with neutrophils (2.9%), monocytes (9.1%) and RBC (0.69%)
- Chromosome breakage analysis: negative by DEB assay
- Telomere length: normal

Diagnosis: **Severe AA**

Patient has no matched sibling donor (MSD) but has multiple matched unrelated donor (MUD) available. She is clinically stable with no infections.

What would you recommend for front-line therapy?

A. No therapy, observation only
B. IST plus eltrombopag as front-line therapy
C. MUD HCT as front-line therapy
D. Haploidentical donor HCT as front-line therapy

Both are reasonable options

Recommendation

- The ASH guideline panel ***suggests*** either matched unrelated donor HCT or IST for patients under 20 years of age and those between 20 and 40 years old with severe or very severe AA *(conditional recommendation, based on very low certainty of evidence of the effects)*

- IST is the standard front-line therapy for individuals <40 years old who lacks MSD
  - IST is associated with high rate of treatment failure (~20-30%), relapses (~30%) and clonal evolution
- Outcomes of up-front MUD HCT have markedly improved in recent decades due to:
  - Advancement in high-resolution HLA typing
  - Improved conditioning regimens
  - Improved supportive care

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Rationale

- MUD HCT for individuals under 20 years old may be associated with:
  - Moderate decrease in mortality (66 fewer per 1,000, 95% CI: 129 fewer to 85 more)
  - Large decrease in treatment failure (417 fewer per 1,000, 95% CI: 456 fewer to 333 fewer)
  - Large increase in complete response (364 more per 1,000, 95% CI: 11 more to 1,000 more)
- In individuals aged 20-40 years, MUD HCT may be associated with an increase in mortality (176 more per 1,000; 95% CI: 92 fewer to 1,000 more), BUT the evidence for this age group is very limited

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Recommendation

- Studies informing these recommendations are based on
  - Non-randomized, small cohort studies
  - Population consisting mostly of children
- Decision to pursue MUD HCT versus IST as front-line treatment should be guided by:
  - Patient's clinical status
  - Availability of and access to a suitable donor
  - Resource availability, including cost
  - Patient and caregiver preference
- MUD may be less readily available than MSD, and prolonged neutropenia increases the risk of life-threatening infections

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Case 2: Conclusion

- Other than requiring platelet transfusion once every other week, she remains clinically stable
- After a thorough discussion weighing the risks and benefits of MUD HCT versus IST, the patient elected to proceed with MUD HCT
- The patient was referred for MUD HCT

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Case 2: Summary

- Outcomes of MUD HCT have significantly improved with possibility of similar results to the MSD HCT
- The benefit of MUD HCT compared to IST is the cure of AA and prevent the possibility of clonal evolution
- HCT carries the risk of GVHD, infection, infertility and organ toxicity
- Studies informing these recommendations are from non-randomized, small cohort studies
- Decision to pursue MUD HCT versus IST as frontline therapy should consider patient's clinical status, resource availability, and patient's preference

Future areas of study:

- Randomized clinical trial comparing outcomes of MUD HCT versus IST in **both** adults and children with severe AA
- Long-term safety data on MUD HCT for AA

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Other guideline recommendations that were not covered in this presentation

For these topics, conditional recommendations were made based on very low certainty of evidence

- Diagnostic testing
- Front-line therapy including MSD HCT and haploidentical donor HCT
- Second-line therapy after IST failure
- Antimicrobial prophylaxis

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Future Priorities for Research

In addition to the research priorities listed on slides 21 and 29, the following areas require further investigation:

- Comparative studies evaluating the effectiveness of antimicrobial prophylaxis
- Determination of the optimal duration of antimicrobial prophylaxis
- Identification of ideal treatment options for patients with relapsed or refractory AA following IST
- Outcomes of alternative donor HCT as front-line therapy for **both** adults and children

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In Summary: Back to our Objectives

1. Describe recommendation for the addition of eltrombopag to immunosuppressive therapy (IST) in children with severe or very severe AA
   - ✓ Addition of eltrombopag to IST is suggested for children with severe or very severe AA
2. Describe recommendation for timing of second-line treatment for individuals who do not respond to IST
   - ✓ ASH guideline panel suggests initiating second-line treatment no later than six months of follow-up if there is no response
3. Describe recommendation for matched unrelated donor (MUD) hematopoietic cell transplant (HCT) as front-line therapy in individuals ≤40 years old with severe or very severe AA
   - ✓ Either MUD HCT or IST is suggested for individuals ≤40 years old with severe of very severe AA

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Acknowledgements

- ASH guideline panel team members
- Evidence synthesis team

See more about the **ASH AA guidelines** at hematology.org/aplasticanemia

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