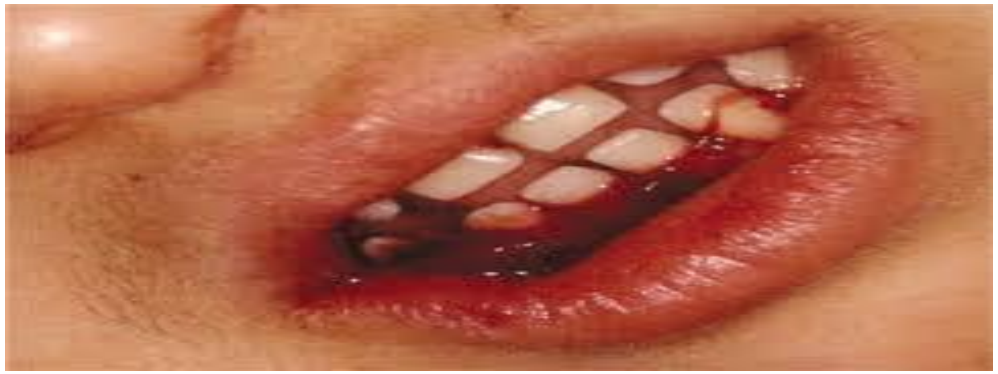
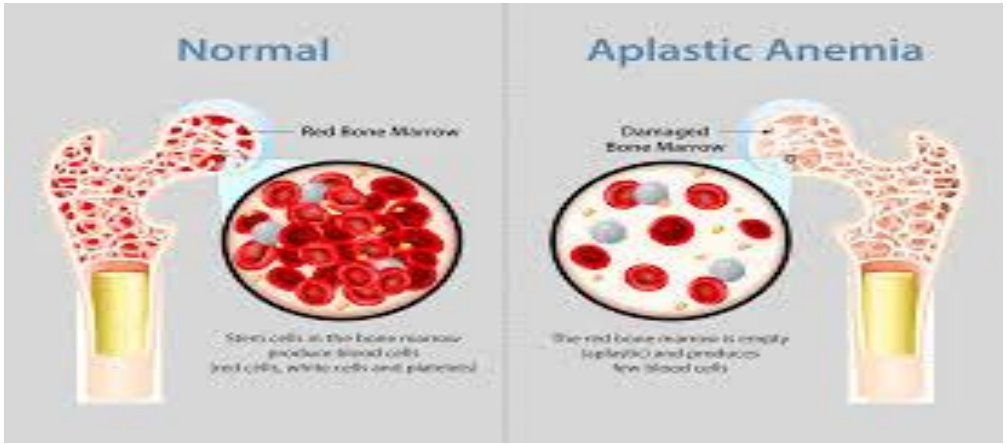
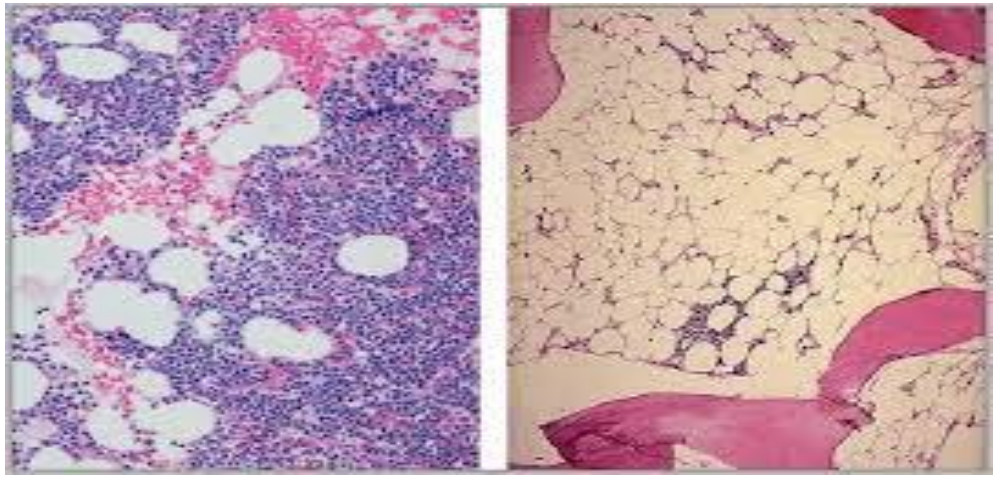
In the name of GOD

Aplastic Anemia in Children







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Articles

- American Society of Hematology(ASH) 2026, Guidelines for the Diagnosis and Management of Severe Acquired Aplastic Anemia .American Society of Hematology, **bloodadvances@hematology.org**.
- Comparable outcomes of HSCT up-front and after failure of IST in pediatric aplastic anemia in recent years .Felicia Andresen, Ayami Yoshi ,Peter Bader. **Blood advances .24 MARCH 2026 ,VOLUME 10, NUMBER 6**
- **Up-front Alternative donor HCT in severe aplastic anemia: gaps and opportunities to translate evidence into practice. Neel S. Bhatt, Azra Borogovac, Yvonne A. Efebera. Blood advances.9 SEPTEMBER 2025 • VOLUME 9, NUMBER 17**
- **Consensus for the treatment of Severe aplastic anaemia in children and adolescents**
  2023 . EWOG SAA
- **Haploidentical hematopoietic stem cell transplantation as a first-line treatment for paediatric severe aplastic anemia: a single-center research Meng Yuan. China. Int. J. Med. Sci. 2024, Vol. 2**

Case presentation : pancytopenia …

- Female , 10 y , 3 children in family , Sibling healthy
- Parents ; first degree relation ship
- CC : Seizure , no fever , CBC; low platelet ,then pancytopenia , low retic ,DEB test neg
- PE : Nl, just mild delay development
- BMA and BMB ; Hypocellular BM
- Several times plate transfusion and 2 times BT
- Suspicious PNH , On El thrombopag and levebel
- **Refer for Allo HSCT**

Case presentation

- **Evaluations in Mofid Children Hospital**
- CBC Pancytopenia , low retic , coombs neg
- BIO , LFT , KT , Virology , CVT , Ig : Nl . LDH , U -Acid : NL
- CXR ,SONO ,ECHO : NL
- PNH study RBC & WBC : Neg
- BMA : Mild hypocellular marrow , No dysplasia
- BMB ?? CD ??? Cytogenetic ???
- EBV PCR , IgG , IgM ,CMV…… PCR , Parvo PCR : neg
- HLA typing: pending

❑In admission : PC & Plate transfusion

Questions

- What is your diagnosis
- Do you have more recommendation for diagnosis ??
- What is your plan of treatment in this child ???

Severe Aplastic Anemia

- Severe aplastic anemia (SAA) is a rare hematological disorder characterized by **severe pancytopenia** and **markedly hypocellular bone marrow** (BM) without significant dysplasia.

- Most cases of **acquired SAA** are thought to be caused by **immune-mediated processes** leading to the rapid destruction of hematopoietic stem and progenitor cells.

Aplastic Anemia

- SAA was defined by :
- **BM cellularity of <25%**
- Decreased peripheral Blood counts in **at least 2 lineages** (that is,absolute neutrophil count [ANC] of <0.5 × 109/L, platelet count of <20 × 109/L
  And/ or absolute reticulocyte count of <60 × 109/L

- Very severe AA (VSAA) had to have an **ANC of <0.2 × 109/L.**

- **Non severe AA (NSAA) was characterized by cytopenias not fulfilling the definition of SAA.**

Pan cytopenia , Aplastic Anemia
Differential Diagnosis (DD)

- DD is very important in diagnosis of AA etiologies ??
  - **Especially inherited group & PID**

Aplastic Anemia

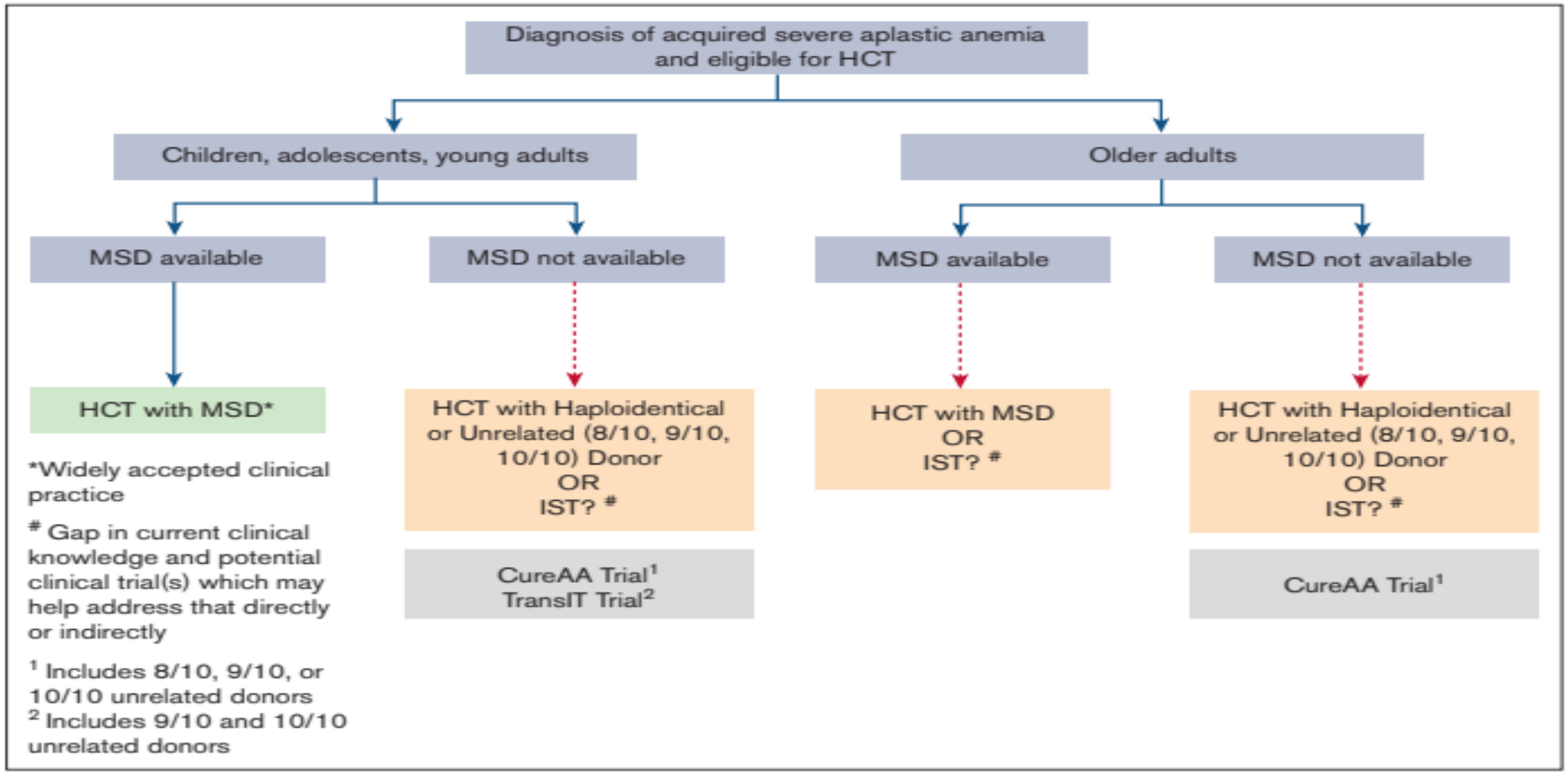
- The main treatment options for patients with SAA include allogeneic (HSCT) and (IST).
- Age is an important criteria …..

- HSCT :first-line treatment for children and adolescents with SAA with an available **HLA-matched sibling donor (MSD),** resulting in an excellent overall survival (OS) of >90% and event-free survival (EFS) of >85%.
- Many patients lack a suitable MSD , so receive IST consisting of (ATG) and cyclosporine A with an overall response rate and OS of ~50% to 70% and 90%, respectively.

Comparable outcomes of HSCT up-front and after failure of IST in pediatric aplastic anemia in recent years .Felicia Andresen, Ayami Yoshi ,Peter Bader. Blood advances .24 MARCH 2026 ,VOLUME 10, NUMBER 6

- Despite comparable OS of IST and MSD-HSCT, patients receiving IST are at risk for nonresponse, disease reoccurrence, and clonal evolution.
- Accordingly, EFS is significantly lower after IST than after MSD HSCT.
- Patients failing IST have an indication for a **second-line HSCT** from an HLA-matched unrelated donor (UD; MUD), which has historically resulted in a variable OS and EFS, mostly attributed to **graft failure (GF), graft-versus-host disease (GVHD), and infections.**
- More recent studies have reported **improved outcomes of HSCT using an MUD or haploidentical donor,** highlighting the potential role of alternative donor transplants in the treatment of SAA.

Current treatment paradigm in patients diagnosed with SAA: standard of care and gaps in knowledge. MSD, matched sibling donor. Blood advances .Sep 2025



Article 1:Comparable outcomes of HSCT up-front and after failure of IST in pediatric aplastic anemia in recent years .Felicia Andresen, Ayami Yoshi ,Peter Bader. Blood advances .24 MARCH 2026 ,VOLUME 10, NUMBER 6

- A comprehensive analysis of the outcomes of allogeneic HSCT in a consecutive cohort of **179 children and adolescents with SAA** registered in the European Working Group of SAA in Childhood (EWOG-SAA) 2010 registry.

- Compare the outcomes of pediatric patients with SAA
  - **up front hSCT**
  - **Or**
  - **HSCT after failure of IST**

Comparable outcomes of HSCT up-front and after failure of IST in pediatric aplastic anemia in recent years .Felicia Andresen, Ayami Yoshi ,Peter Bader. Blood advances .24 MARCH 2026 ,VOLUME 10, NUMBER 6

- The outcomes of 179 pediatric patients with (SAA)
- up-front (HSCT; n = 87) HSCT
- HSCT after failure of IS therapy (IST; n = 92).
- Median follow-up of 4.0 years (range, 0.2-10.7) after HSCT
- 161 patients were alive at last follow-up.
- The cumulative incidence of graft failure, grade 2 to 4 acute and chronic graft-versus-host disease (GVHD) was 10%, 18%, and 8%, respectively.
- 5 -vear (OS) and GVHD free.relapse/rejection-free survival (GRFS) were 89% and 79%, respectively

Comparable outcomes of HSCT up-front and after failure of IST in pediatric aplastic anemia in recent years .Felicia Andresen, Ayami Yoshi ,Peter Bader. Blood advances .24 MARCH 2026 ,VOLUME 10, NUMBER 6

- Patients with up-front HSCT /r (MSD) or ≥9/10 HLA- (MUD) both achieved an OS of 95%.
- OS ; superior in patients who received up-front HSCT than who received HSCT after failure of IST (up-front, 95% vs after IST failure, 83%)
- OS in the HSCT group after IST failure improved over time, resulting in comparable OS between up-front HSCT and HSCT after IST failure from 2015 **(97% vs 89%)**
- No difference in GRFS of MUD HSCT comparing patients who received a HSCT up front or after IST failure (up-front, 77% vs after IST failure, 76%)
- **Good transplant outcomes of a consecutive pediatric SAA cohort Although up-front HSCT from a readily available MUD is a viable option if an MSD is not available, HSCT after IST failure from a well matched unrelated donor also yields favorable outcomes**

Comparable outcomes of HSCT up-front and after failure of IST in pediatric aplastic anemia in recent years .Felicia Andresen, Ayami Yoshi ,Peter Bader. Blood advances .24 MARCH 2026 ,VOLUME 10, NUMBER 6

Risk factors ???

- Younger age at HSCT and the use of a well-matched UD ; improved OS in the post–IST failure SCT group.
- IST with : Hoarse ATG ;a better OS and GRFS compared with IST with Thymoglobulin.
- Although the use of **horse ATG in IST** has repeatedly been shown to result in superior outcomes and response rate of IST compared with rabbit ATG, **little is known about its impact on transplant outcomes.**
- In the **IST setting, rabbit ATG** ; longer-lasting and more potent immunosuppressive effect compared with horse ATG,resulting in a higher incidence of infectious complications such as the use of PbSC & positive CMV donor/recipient????

Multivariate analysis of variables predicting GRFS in 92 patients with SAA after HSCT after IST failure

	Relative Risk	95% CI	*P* value
Sex			
Female vs male	1.47	0.64-3.38	ns
Age at HSCT, y			
≥10 vs <10	1.58	0.88-14.60	ns
Year of HSCT			
<2015 vs 2015-2017	0.78	0.28-2.14	ns
<2015 vs ≥2018	3.57	0.88-14.60	.08
2015-2017 vs ≥2018	4.61	1.25-16.96	.02
Type of ATG used in IST			
Thymoglobulin vs Atgam	1.59	0.59-4.30	ns
Conditioning regimen			
Other regimens vs Flu/Cy	2.43	0.98-6.06	.06

ns, not significant.

Alternative donors :Haplo HSCT in AA of Children

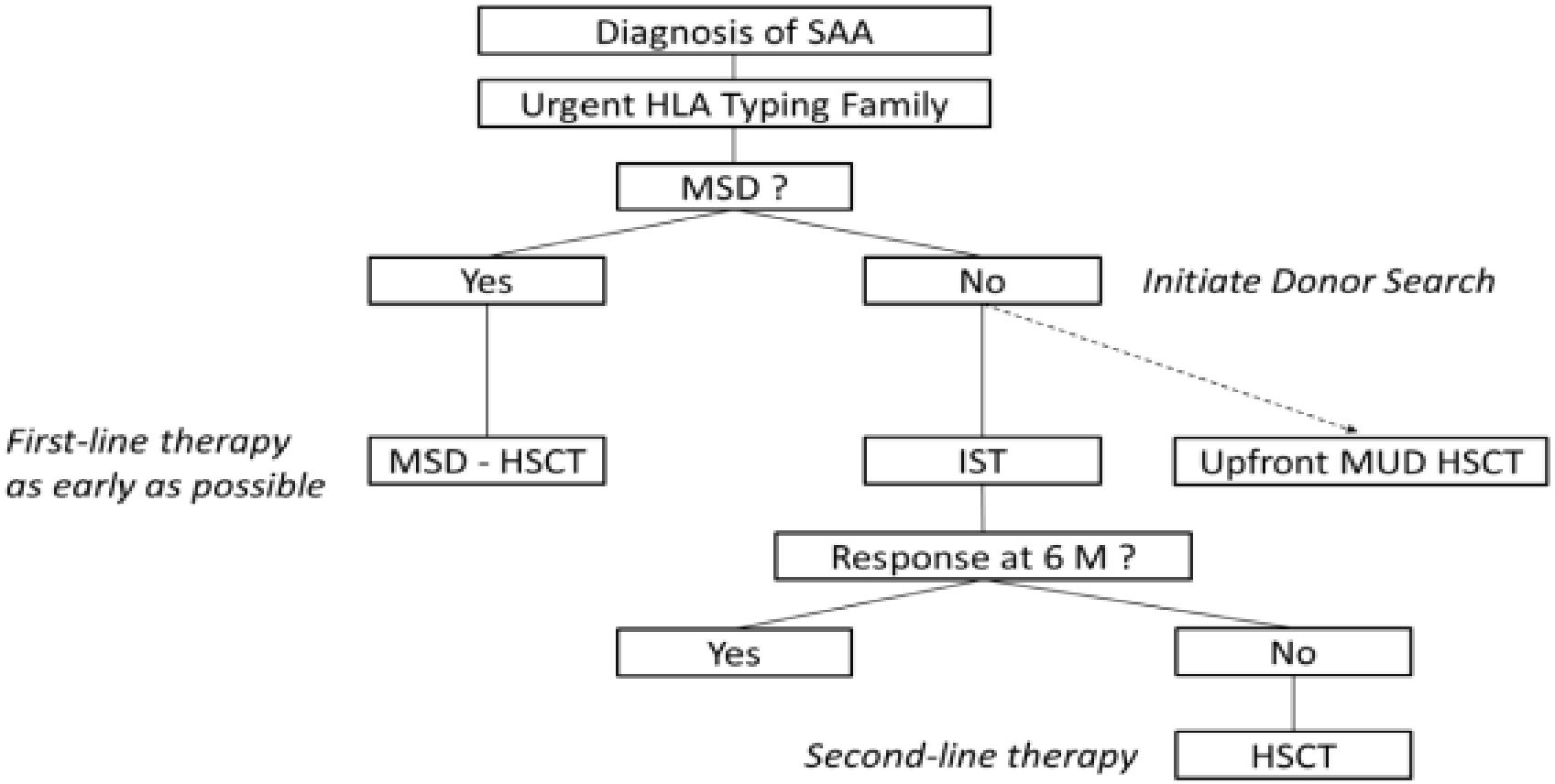
Up-front alternative donor HCT in severe aplastic anemia: gaps and opportunities to translate evidence into practice.Neel S. Bhatt, Azra Borogovac,Yvonne A. Efebera. Blood advances .9 SEP2025 • VOLUME 9, NUMBER 17

- Use of alternative donors: Haploidentical, mismatched, or matched unrelated donors, has previously been limited due to increased transplant-related morbidity, particularly (GVHD).
- HCTs have therefore been limited to young recipients and those with HLA-matched related donors
- Nevertheless, more recent advances in HCT, such as posttransplant cyclophosphamide for GVHD prophylaxis, have led to improved outcomes of HCT with alternative donors; however, alternative donor HCT remains underused as up-front therapy, in part because of limited multicenter trial data

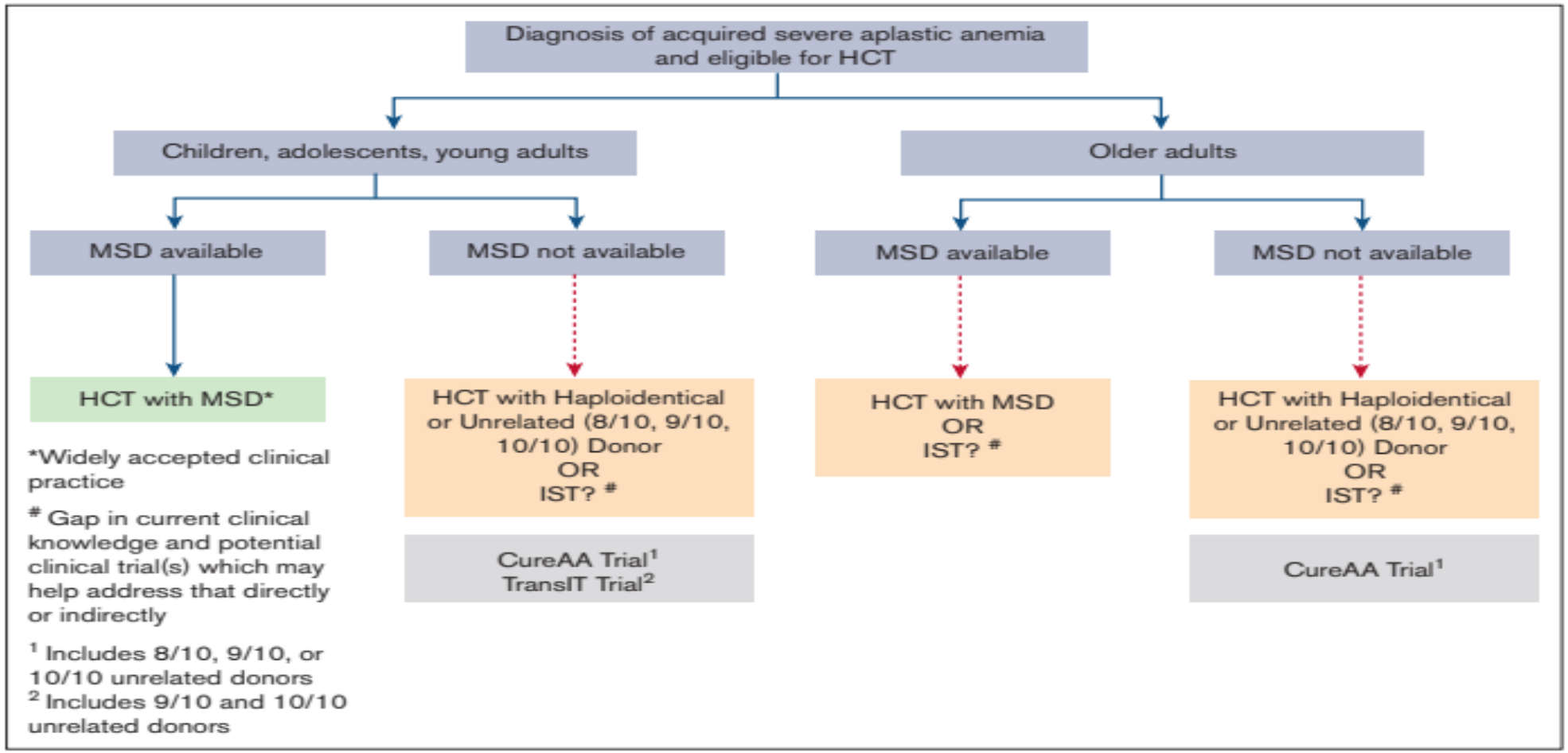
Haploidentical hematopoietic stem cell transplantation as a first-line treatment for paediatric severe aplastic anemia: a single-center research Meng Yuan.
China. Int. J. Med. Sci. 2024, Vol. 2

- MRD-HSCT is the first-line therapy for children with SAA, while it is not easy to find a compatible donor due to the Chinese one-child policy.
- China: Single child ,limited donor in BMT bank , long time search for MURD…. & IST has a high recurrence rate, a risk of clonal transformation.
  Haplo-HSCT, as a first-line treatment
- **Prospective study (2006-2021) of 210 patients with AA who received HSCT or IST in Beijing Children's Hospital.**
- 3- and 5-year cumulative FFS rates were both 85.3% in the first-line Haplo-HSCT group and 67.5% and 66.2% in the first-line IST group (P = 0.033).
- Haplo-HSCT can be a first-line treatment for paediatric SAA.

Consensus for the treatment of Severe aplastic anaemia in children and adolescents 2023 . EWOG SAA



Current treatment paradigm in patients diagnosed with SAA: standard of care and gaps in knowledge. MSD, matched sibling donor. Blood advances .Sep 2025



GCSF And EPAG In Children with SAA, Consensus for the treatment of Severe aplastic anaemia in children and adolescents 2023 . EWOG SAA

- IS therapy in SAA: Cyclospurine + Hoarse ATG

- **G-CSF :** only an ANC < 0.5 x 109 /l at day 1 of IST at a dose of 5 µg/kg/day sc or iv
- pegylated G-CSF has not been evaluated in this setting , No recommendation
- If response (ANC > 0.5 x 109 /l) at day 28 (or at any later time point) the dose is tapered by giving it every second day, every third day etc.
- If the WBC decreases again to 0.5 x 109 /l, the original dose of 5 µg/kg is restarted.
- G-CSF dose > 5 µg/kg/day is not recommended.
- **All patients should be off G-CSF therapy by day 60.**

- Patients with an ANC ≥ 0.5 x 109 /l at day 1 who subsequently develop severe neutropenia should not receive G-CSF.

GCSF And EPAG In Children with SAA, Consensus for the treatment of Severe aplastic anaemia in children and adolescents 2023 . EWOG SAA

- EPAG：**Current available data do not support the addition of EPAG to IST in children with treatment-naïve SAA as general standard of care.**
-
- **If use : protocol , day 1 instead of day 14 and for 6 mo**

American Society of Hematology 2026 Guidelines for the Diagnosis and Management of Severe Acquired Aplastic Anemia(SAA)

- The panel agreed on 33 recommendations & 4 good practice Statements addressing the use of diagnostic tests, treatment strategies and supportive care.

- Additional recommendations covered the incorporation of Eltrombopag into immunosuppressive regimens and the use of antimicrobial prophylaxis in high-risk patients.

American Society of Hematology 2026 Guidelines for the Diagnosis and Management of Severe Acquired Aplastic Anemia(SAAA)

- **Good Practice Statement 1.** Clinicians should obtain detailed information of exposures,family history, medications, infections, and other potential acquired causes of aplastic anemia in patients with persistent unexplained pancytopenia
- **Good Practice Statement 2.** Clinicians should perform **a BMA & BMB for patients with unexplained pancytopenia**
- **Good Practice Statement 3.** Clinicians should perform **germline genetic testing** for patients with clinical features suggestive of a germline-inherited blood disorder
- **Good Practice Statement 4.** Clinicians should perform **HLA testing** as soon as possible for patients with severe or very severe aplastic anemia who are eligible for hematopoietic cell transplantation

Diagnostic tests at the time of diagnosis *(PNH) clone testing*

- **Recommendation 1.** For patients under 20 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests PNH clone testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 2.** For patients between 20 and 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests PNH clone testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 3.** For patients over 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests PNH clone testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 4.** For patients that are **refractory to immunosuppressive therapy (IST)** with severe or very severe aplastic anemia, the ASH guideline panel suggests PNH clone testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects

Somatic mutations testing

- **Recommendation 5.** For patients under 20 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests somatic mutations testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects
- **Recommendation 6.** For patients between 20 and 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests somatic mutations testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects
- **Recommendation 7.** For patients over 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests somatic mutations testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects
- **Recommendation 8.** For patients that are refractory to immunosuppressive therapy (IST) with severe or very severe aplastic anemia, the ASH guideline panel suggests somatic mutations testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects

Telomere length testing

- **Recommendation 9.** For patients **under 20 years old** with severe or very severe aplastic anemia, the
- ASH guideline panel suggests conducting telomere length (TL) testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects
- **Recommendation 10.** For patients between 20 and 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests conducting telomere length (TL) testing over no testing
- **Recommendation 11.** For patients over 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests conducting telomere length (TL) testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects
- **Recommendation 12.** For patients that are refractory to immunosuppressive therapy (IST) with severe or very severe aplastic anemia, the ASH guideline panel suggests conducting telomere length (TL) testing over no testing (conditional recommendation, based on very low certainty in the evidence of the effects).

Frontline therapy

Hematopoietic cell transplant (HCT) with a matched sibling donor vs. Immunosuppressive Therapy (IST)

- **Recommendation 13.** For patients under 20 years old with severe or very severe aplastic anemiawho have a matched sibling donor available, the ASH guideline panel suggests a hematopoietic cell transplant (HCT) over immunosuppressive therapy (IST) (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 14.** For patients between 20-40 years old with severe or very severe aplastic anemia who have a matched sibling donor available, the ASH guideline panel suggests a hematopoietic cell transplant (HCT) over immunosuppressive therapy (IST) (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 15.** For patients **over 40 years old with severe or very severe aplastic anemia** who have a matched sibling donor available, the ASH guideline panel suggests immunosuppressive therapy (IST) over hematopoietic cell transplant (HCT) (conditional recommendation, based on very low certainty in the evidence of the effects

Hematopoietic cell transplant (HCT) with a matched unrelated donor vs. Immunosuppressive Therapy (IST)

- **Recommendation 16.** For patients under 20 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests **either matched unrelated (HCT) or (IST)** (conditional recommendation, based on very low certainty in the evidence of the effects
- **Recommendation 17.** For patients between 20 and 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests **either matched unrelated (HCT) or (IST)** (conditional recommendation, based on very low certainty in the evidence of the effects
- **Recommendation 18.** For patients **over 40 years** old with severe or very severe aplastic anemia, the ASH guideline panel suggests **(IST) over matched unrelated (HCT)** (conditional recommendation, based on very low certainty in the evidence of the effects

Hematopoietic cell transplant (HCT) with a haploidentical donor vs. Immunosuppressive Therapy (IST)

- **Recommendation 19**. For patients under 20 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests (IST) over haploidentical (HCT) (conditional recommendation, based on very low certainty in the evidence of the Effects

- **Recommendation 20.** For patients between 20 and 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests immunosuppressive therapy (IST) over haploidentical (HCT) (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 21.** For patients over 40 years old with severe or very severe aplastic anemia, the ASH guideline panel suggests (IST) over haplo identical hematopoietic cell transplant (HCT) (conditional recommendation, based on very low certainty in the evidence of the effects

Use of eltrombopag as a part of immunosuppressive therapy

- **Recommendation 22.** For adults with severe or very severe aplastic anemia undergoing immunosuppressive therapy (IST), the ASH guideline panel suggests the addition of eltrombopag (conditional recommendation, based on low certainty in the evidence of the effects
- **Recommendation 23.** For children with severe or very severe aplastic anemia undergoing (IST), the ASH guideline panel suggests the addition of Eltrombopag (conditional recommendation, based on low certainty in the evidence of the effects

Second line therapy, *Refractory*

- **Recommendation 24.** For patients under 40 years old with severe or very severe aplastic anemia with **no response** to an initial course of (IST), the ASH guideline panel suggests (HCT) over second anti-thymocyte globulin-based therapy (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 25.** For patients between 40 and 60 years old with severe or very severe aplastic anemia with **no response** to an initial course of immunosuppressive therapy (IST), the ASH guideline suggests (HCT) over second ATG -based therapy (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 26.** For patients over 60 years old with severe or very severe AA and no response to an initial course (IST), the ASH guideline panel suggests either (HCT) or a second anti-thymocyte globulin- based therapy (conditional recommendation, based on very low certainty in the evidence of the effects

Relapse

- **Recommendation 27.**
- For patients under 40 years old with severe or very severe aplastic anemia/VSAA who respond to a first course of immunosuppressive therapy (IST) but subsequently relapse, the ASH Guideline panel suggests **either (HCT) or a second ATG -based therapy** (conditional recommendation, based on very low certainty in the evidence of the effects

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- **Recommendation 28.** For patients between 40 and 60 years old with severe or very severe aplastic anemia who respond to a first course of i (IST) but subsequently relapse,the ASH guideline panel suggests either (HCT) or a second antithymocyte globulin-based therapy (conditional recommendation, based on very low certainty in the evidence of the effects

- **Recommendation 29.** For patients over 60 years old with severe or very severe aplastic anemia who **responds to a first course** of (IST) but subsequently relapse, the ASH guideline panel suggests a second ATG -based therapy **over hematopoietic cell transplant** (HCT) (conditional recommendation, based on very low certainty in the evidence of the effects

Timing of second line of treatment

- **Recommendation 30.** For patients with severe aplastic anemia who do not respond to immunosuppressive therapy (IST), the ASH guideline panel suggests initiating a second-line treatment no later than 6 MO after ATG administration (conditional recommendation based on very low certainty in the evidence of the effects

- **Recommendation 31.** For patients with very severe aplastic anemia who do not respond to immunosuppressive therapy (IST), the ASH guideline panel suggests initiating a second-line treatment no later than 6 after ATG administration (conditional recommendation based on very low certainty in the evidence of the effects

REMARK

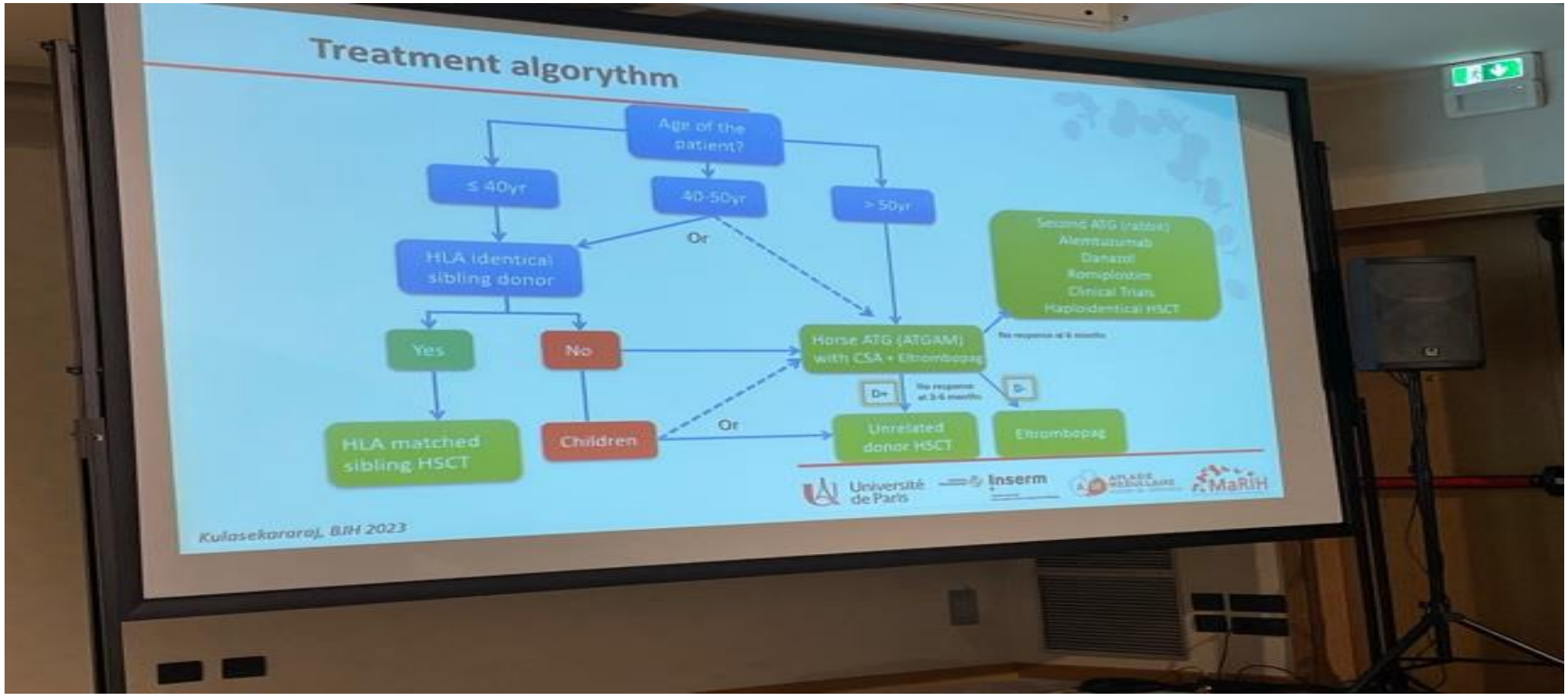
- Although some individuals with very severe aplastic anemia/ VSAA may respond to IST after 3 months, the severity of cytopenias and increased risk of adverse outcomes in this population may warrant an earlier decision to initiate second-line treatment

Medical Management *Antimicrobial prophylaxis*

- **Recommendation 32.** For patients with SAA with a neutrophil count < 500 per µl, the ASH guideline panel suggests mold-active antifungal prophylaxis (conditional recommendation based on very low certainty in the evidence of the effects

- **Recommendation 33.** For patients with severe aplastic anemia with a neutrophil count < 500 per µl, the ASH guideline panel suggests **AB prophylaxis** (conditional recommendation based on very low certainty in the evidence of the effects

SAA :Treatment Algorythm



Thank YOU