ASH 2026 Guidelines for Frontline Management of Acute Lymphoblastic Leukemia in Adolescents and Young Adults (ALL in AYAs)

Visual Summary of Recommendations

Frontline Management of ALL in AYAs

Frontline Therapy | **CNS Prophylaxis** | **Consolidation** | **Managing Adverse Reactions**

Person-centered care and comprehensive psychosocial support throughout

Frontline Management and CNS Prophylaxis

AYAs with ALL

Recommends **pediatric inspired (asparaginase containing)** regimen ⊕⊕⊕○

Prophylaxis

VTE

Recommends against **routine use of cryoprecipitate replacement or UFH** for VTE prophylaxis ⊕○○○

AND

Hypersensitivity

Recommends **prophylactic premedication to prevent hypersensitivity** reaction ⊕○○○

Managing Adverse Reactions

Toxicity

Suggests **dose-capping and dose-reduction** to mitigate toxicities ⊕○○○

Use **therapeutic drug monitoring (TDM)** to ensure adequate asparaginase depletion

Hypersensitivity

Recommends switching to **Erwinia-based asparaginase** (over discontinuation) ⊕○○○

First Complete Remission

Suggests against **routine allo-HSCT** as consolidation ⊕○○○

CNS Prophylaxis
For AYAs with ALL *without CNS involvement at diagnosis:*

Suggests against **routine use of cranial irradiation** for CNS prophylaxis ⊕○○○

Suggests *either* **intrathecal methotrexate or triple intrathecal therapy** for CNS prophylaxis ⊕○○○

ALL: *Acute lymphoblastic leukemia;* ***Allo-HSCT:*** *Allogeneic hematopoietic stem cell transplantation;* ***AYAs:*** *Adolescents and young adults;* ***CNS:*** *Central nervous system;* ***UFH:*** *Unfractionated heparin;* ***VTE:*** *Venous thromboembolism*

Good Practice: *Good practice statements (GPS) are ungraded recommendations that reflect what the guideline panel considers to be an uncontested marker of good care. While not fully supported by systematic evidence, GPS are strong, actionable, and widely accepted as beneficial best practices.*

Definitions

Adolescents and young adults:	Age 15-39
Asparaginase:	Chemotherapy derived from bacteria, either E. coli or Erwinia chrysanthemi
Premedication:	Minimally, IV steroid premedication; may also include antihistamines and/or acetaminophen
Dose capping:	Max dose of 3750 IU
Dose reduction:	Weight-based dose of <2500 IU/m2 (under age 22) or <2000 IU/m2 (22 and older)
First complete remission:	Point at which, after initial treatment, no signs of leukemia detected in the bone marrow

Therapies for Specific Subsets

AYAs Receiving Frontline Therapy

B-cell

B-ALL
Suggests incorporating **blinatumomab** for those with morphologic remission (regardless of MRD). ⊕○○○

CD20+ B-ALL
Suggests addition of **rituximab** to standard chemotherapy ⊕○○○

T-cell

T-ALL
Suggests against the addition of **bortezomib** into regimens ⊕○○○

T-LBL/LLy
Suggests against the addition of **nelarabine** into regimens due to insufficient evidence showing efficacy in AYAs. ⊕○○○

ALL: *Acute lymphoblastic leukemia;* ***AYAs:*** *Adolescents and young adults;* ***B-ALL:*** *B-cell acute lymphoblastic leukemia;* ***MRD:*** *Minimal residual disease*
T-ALL: *T-cell acute lymphoblastic leukemia;* ***T-LBL/LLy:*** *T-cell lymphoblastic lymphoma*

Minimal Residual Disease

GOOD PRACTICE

Measurement of disease response using MRD is considered standard of care in AYAs with ALL for both prognostic value and, in some cases, determination of treatment intensity.

AYAs with MRD after 3+ months of frontline therapy

Recommends **a change in treatment approach** ⊕○○○

May include either

- **Immunotherapy**
- **Transplant**

AYAs: *Adolescents and young adults;* ***MRD:*** *Minimal residual disease*

Treatment for Ph+ ALL

Must receive CNS prophylaxis with intensive intrathecal chemotherapy

Suggests **reduced-intensity chemotherapy with TKI** over intensive chemotherapy with TKI, to induce remission ⊕○○○

This should be followed by post-remission therapy*:

- Intensive chemotherapy + TKI and/or
- Immunotherapy + TKI
- Consideration of allo-HSCT in first complete remission

**This recommendation may not be as applicable to the youngest AYA subgroup*

ALL: *Acute lymphoblastic leukemia;* ***Allo-HSCT:*** *Allogeneic hematopoietic stem cell transplantation;* ***CNS:*** *Central nervous system;* ***TKI:*** *Tyrosine kinase inhibitor*

Evidence Gaps

VTE Prophylaxis

There is insufficient evidence to issue a recommendation for or against routine VTE prophylaxis with LMWH, DOACs or AT replacement. There is also uncertainty in timing or duration of VTE prophylaxis (induction, consolidation, intensification), LMWH dosing, and AT replacement targets; risk models are needed to identify high-risk patients.

Asparaginase

The evidence is insufficient to issue a recommendation on resuming asparaginase therapy after a non-hypersensitivity asparaginase-related toxicity. There is also a lack of evidence comparing effects of desensitization versus alternative asparaginase products.

Additional Therapies

Current evidence is insufficient to issue a recommendation for or against the addition of the following therapies for specific subsets:

- Inotuzumab ozogamicin for AYAs with B-ALL receiving frontline therapy.
- Nelarabine for AYAs with T-ALL receiving frontline therapy.*
- Bortezomib for AYAs with T-LBL.**

** may provide benefit among non-ETP subtype, CNS3 disease, and/or others who receive a high-dose methotrexate-based interim maintenance regimen*
*** may provide benefit among youngest adolescents*

AT replacement: *Antithrombin replacement;* ***DOAC:*** *Direct oral anticoagulant;* ***LMWH:*** *Low molecular weight heparin;* ***T-ALL:*** *T-cell acute lymphoblastic leukemia;* ***T-LBL/LLy:*** *T-cell lymphoblastic lymphoma;* ***VTE:*** *Venous thromboembolism*

Psychosocial Care for AYAs

Good Practice Statements

Specialized Care
AYAs with ALL require person-centered and specialized healthcare.

Psychological Needs
Routinely assess psychosocial functioning and implement multidisciplinary psychosocial support from diagnosis and into survivorship.

Social Support
Assess existing social supports and encourage connection to supportive communities and resources as needed.

Financial Needs
Assess financial needs and encourage connection to institutional and/or regional financial counseling supports, resources, and organizations.

Goals of Care
Goals of care and end-of-life concepts should be addressed early in treatment and readdressed throughout treatment, particularly at transitional points during care (e.g., relapse).

Clinical Trials
Offer eligible AYAs enrollment in an appropriate clinical trial, as they are underrepresented in trials and have seen slower improvements in survival.

Palliative Care
Interdisciplinary and/or primary palliative care should be provided throughout treatment starting at the time of diagnosis.

Fertility
Multidisciplinary and comprehensive fertility consultation and care should be provided prior to diagnosis and throughout treatment and into survivorship.

Sexual Health
Sexual health and relevant identities should be discussed with each individual patient at diagnosis and through treatment and survivorship.

Developmental Needs
Deliver service flexibly in consideration of each patient's developmental needs, preferences, and goals for treatment.

Learn more about the ASH 2026 Clinical Practice Guidelines on ALL in AYAs at *hematology.org/ALLguidelines*

Recommendation Strength

	Recommends...	Recommends against...	Suggests...	Suggests against...
	INTERPRETATION OF STRONG RECOMMENDATIONS		INTERPRETATION OF CONDITIONAL RECOMMENDATIONS	
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.		Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.	
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.		Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.	
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.		Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision making is appropriate.	
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.		The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.	

Evidence Certainty

High Certainty	
⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate Certainty	
⊕⊕⊕○	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low Certainty	
⊕⊕○○	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low Certainty	
⊕○○○	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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