



RESEARCH ARTICLE OPEN ACCESS

Optimizing Asparaginase Treatment for Adolescent and Young Adult (AYA) Patients With Acute Lymphoblastic Leukemia: US Consensus Panel Recommendations

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Received: 17 July 2025 | **Revised:** 22 September 2025 | **Accepted:** 26 September 2025

Funding: This work was supported by the Jazz Pharmaceuticals.

Keywords: acute lymphoblastic leukemia | asparaginase | AYA

ABSTRACT

Asparaginase is an integral component of therapy for pediatric patients with acute lymphoblastic leukemia/lymphoblastic lymphoma. The success of asparaginase-containing regimens has led to trials of pediatric/pediatric-inspired regimens incorporating asparaginase for treating adolescent and young adult (AYA) and adult populations with acute lymphoblastic leukemia/lymphoblastic lymphoma. While treatment of AYA patients with these regimens is associated with improved clinical outcomes compared with adult-specific protocols, AYA patients face unique challenges with these treatments, further complicated by a rapidly evolving therapeutic landscape. In this article, we identify barriers and other feasibility issues associated with administering asparaginase-based treatment to AYA patients and provide recommendations from a consensus panel of experts to optimize AYA patient outcomes and experiences. Barriers identified include the limited access to clinical trials and specialized expertise in pediatric-inspired regimens for AYA patients compared with pediatric patients, the complex management of asparaginase toxicities, limited medical facilities and experienced staff to administer and manage pediatric-inspired regimens, and reduced AYA patient access/adherence to treatment due to lifestyle-related or psychosocial challenges. Recommendations are provided on addressing and managing these challenges to improve asparaginase-based treatment accessibility and safety in AYA patients, including specific recommendations for high-risk populations.

Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04817761): NCT04817761

1 | Introduction

Acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) is an aggressive hematological malignancy with

rising incidence among adolescent and young adult (AYA) patients (typically defined as aged 15–39 years [1]) [2]. While treatment advances have improved outcomes for pediatric patients [3], these gains have not been mirrored in AYA or adult

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populations [3–5]. Survival rates in ALL/LBL sharply decrease during adolescence and continue to decline into adulthood [6]. This steep drop in survival at approximately 18 years aligns with the transition from pediatric to adult treatment settings, suggesting that treatment approaches may play a critical role in the observed age-related disparities in outcomes. This highlights a critical need to optimize treatment strategies specifically for AYA patients, who historically have been treated on either a pediatric or an adult regimen (depending on referral patterns and the institution) and have shown better responses with pediatric-inspired regimens (PIRs) than with traditional adult protocols [2, 7–12].

Asparaginase, with its primary pharmacological effect based on the killing of leukemic cells by the depletion of plasma asparagine, is an important component of multi-agent regimens for patients with ALL/LBL [13]. The success of asparaginase-containing regimens in the treatment of pediatric patients with ALL/LBL, combined with poor outcomes associated with conventional cytotoxic regimens in adults, prompted trials of asparaginase-based treatments for AYA and adult populations. Data from studies in AYA patients with ALL/LBL, including single-arm trials with multiple doses of asparaginase such as the C10403 intergroup trial (conducted within the National Cancer Institute’s National Clinical Trials Network), have shown promising outcomes with PIRs [9, 11, 14–20]. The results of these studies have informed updates to the National Comprehensive Cancer Network guidelines and 2024 European LeukemiaNet recommendations for ALL management, which now advocate for PIRs in AYAs and adults with ALL/LBL [21, 22].

Despite encouraging evidence and recommendations for the treatment of AYA ALL/LBL with PIRs, the management of AYA patients presents a multitude of challenges. Compared to pediatric patients, AYAs face higher rates of asparaginase-related toxicities, partly due to increased body surface area and higher incidences of overweight/obesity status, and hence larger doses of asparaginase [23], but also because pediatric regimens are tailored to pediatric drug metabolism, which differs from that of AYAs [24]. The key toxicities include hepatotoxicity, pancreatitis, thrombosis, and hypersensitivity reactions, all of which can limit asparaginase use in some patients [25]. Furthermore, AYA patients often lack family support that pediatric patients receive, which may have a detrimental impact on their adherence to complex treatment programs as a consequence of logistical barriers, such as balancing clinic visits with work, study, and childcare obligations, as well as transportation difficulties [24, 26]. Financial and insurance challenges further impact access to comprehensive, sustained care, limiting the ability of many AYAs to complete and adhere to intensive treatment protocols [24, 27]. These challenges underscore the need to optimize asparaginase-based regimens for AYA patients with ALL/LBL to address barriers in both medical and practical aspects of care.

This article identifies barriers associated with asparaginase-based regimens in AYA patients and provides expert panel recommendations to address these challenges. By identifying and mitigating the specific obstacles that AYA patients face, we aim to provide a framework for more effective, accessible,

and sustained asparaginase-based therapy within this patient population.

2 | Methods

A modified two-round Delphi process was conducted between March and April 2024 to develop consensus recommendations for optimizing asparaginase-based therapy in AYA patients with ALL/LBL. The definition of AYA for the consensus recommendations is patients aged 15–39 years, consistent with the National Cancer Institute’s definition of AYAs [1]. The consensus panel included multidisciplinary healthcare providers (including physicians and pharmacists) from the United States (US), representing both pediatric and adult expertise in managing AYA ALL/LBL. Expert panel members were selected by the lead author based on their clinical experience treating AYA patients with asparaginase-based regimens and their publication record in this area. To ensure a comprehensive and multidisciplinary perspective, the panel intentionally included experts from academic institutions across diverse geographic regions within the US, encompassing both adult and pediatric leukemia specialists, along with a clinical pharmacist.

2.1 | Literature Search

A literature search (Table 1) was performed in November/December 2023 utilizing the US National Library of Medicine PubMed database to identify relevant English-language review articles published in the 10 years prior to November 1, 2023. Additional publications were identified through reference lists of pertinent review articles, ad hoc PubMed searches, and supplementary evidence from lead authors, including abstracts from recent conference proceedings.

2.2 | Development of Consensus Recommendations

Preliminary recommendations were based on the identified literature, combined with panel members’ clinical experience and expert opinion. The panel also considered data from a pilot patient survey study involving 17 AYA patients, recruited by a patient advocacy group, who self-confirmed a diagnosis of ALL/LBL and who were receiving ongoing (n = 4) or had completed asparaginase-based treatment (n = 13). The survey was conducted electronically via SurveyMonkey and included questions related to patients’ experience with asparaginase-based regimens and regarding tolerability across common

TABLE 1 | Literature search.

Search terms	“Asparaginase” AND (“Adolescent” OR “Young Adult”) AND (“ALL” OR “LBL”) AND (“Management,” “Outcomes,” “Toxicities,” “Side effects,” “Adverse events,” “Comorbidities,” “Relapsed B cell,” “Relapsed T cell,” OR “Dosing”)
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Abbreviations: ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma.

side effects, benefits/risks, quality of life, and advice to the care team. Detailed survey methodology and findings will be published separately.

The preliminary recommendations were circulated to the panel ahead of two premeeting assignments designed to foster independent reflection on the recommendations prior to group discussions. Panel members participated in two rounds of voting prior to two dedicated consensus meetings that were conducted in the form of virtual roundtable meetings. During this process, panel members provided feedback and proposed revisions to improve clarity and increase agreement for each statement. Each statement was anonymously rated by panel members using a 5-point Likert scale (from 0 = do not agree to 4 = very much agree). Statements with consistently low levels of consensus were excluded, while others were modified based on expert input. Ultimately, some statements were excluded, and several were consolidated to streamline the final set of recommendations.

3 | The Challenges Associated With Asparaginase-Based Treatment in AYA Patients and Consensus Recommendations for Optimized AYA Patient Outcomes

A systematic review and meta-analysis, published in 2012, of 11 comparative studies reporting results of 2489 AYA patients treated with either a PIR or conventional adult regimen demonstrated improved clinical outcomes with PIRs [28]. More recently, a number of single- and multi-center prospective and retrospective studies have established the safety and efficacy for PIRs in AYA patients with ALL/LBL [9, 11, 15–20]. Despite evidence supporting the use of PIRs for AYA patients with ALL/LBL, a recent retrospective analysis of US practices reported that 39% of AYA patients are still treated with an adult regimen [29]. This finding highlights that barriers remain with regard to initiating and implementing asparaginase-based treatments for the AYA population.

3.1 | Overcoming Barriers to Initiation and Use of Asparaginase-Based Regimens in AYA Patients

3.1.1 | Barrier 1: In Adult Treatment Settings, PIRs Are Not Always Considered or Offered for the Treatment of AYA Patients With ALL/LBL

Adult oncologists may lack familiarity with asparaginase treatment due to the lower prevalence of ALL/LBL in adult oncology compared to pediatrics [30], limiting their expertise in managing these malignancies. Additionally, they are typically most familiar with traditional cytotoxic chemotherapy and may be unaware of superior outcomes with PIRs compared with adult protocols [31–33]. This may lead adult ALL/LBL treaters to default to familiar adult regimens, resulting in some AYA patients not receiving a PIR despite evidence favoring its superiority to adult regimens [8, 31]. One regimen used exclusively in adults is hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), which differs fundamentally from PIRs in its structure and combination of cytotoxic drugs. Hyper-CVAD is more myelosuppressive, contains little to no asparaginase, and is typically

less complicated to administer than PIRs, which are multiple-phasic and risk-based regimens [31]. The absence of a randomized comparison of PIRs to hyper-CVAD may contribute to the uncertainty around the most appropriate treatment for these patients [31].

In addition to not being consistently considered for treatment with PIRs, AYA patients are often overlooked for clinical trial participation. Limited access to clinical trials remains a significant gap for the AYA population, potentially contributing to poorer outcomes compared with pediatric patients [24, 34]. Contributing factors may include a low referral rate of AYA patients to specialized institutions where trials are available ($\leq 50\%$ of AYA patients receive front-line treatment at specialized cancer centers) as well as psychosocial barriers that may hinder trial participation [27, 34–36].

3.1.1.1 | Recommendations. To overcome the challenge of PIRs not consistently considered or offered to AYA patients with ALL/LBL, we recommend that guidance be developed for identifying appropriate patients for asparaginase-based regimens. We also encourage more clinical trials in AYA patients, with strategies for increased enrollment of AYA patients (Table 2). With this in mind, we believe better dissemination of information regarding clinical trials to healthcare professionals/patients, including social media among other channels, would be beneficial.

3.1.2 | Barrier 2: Management of Asparaginase Toxicities Can Be Complex, Especially in AYA Patients With Comorbidities, Obesity, and/or Increased Age

Although asparaginases are non-myelosuppressive agents, they are associated with a unique toxicity profile unlike that of other chemotherapy drugs. As noted above, adverse events of interest include hepatotoxicity, pancreatitis, osteonecrosis, coagulopathies, and hypersensitivity reactions [14, 15, 37]. Toxicity management is complex, especially in AYA patients who frequently present with additional risk factors. Furthermore, the management of asparaginase-related toxicities in AYA patients may be especially challenging for treatment centers that see few ALL/LBL cases and lack extensive experience with asparaginase-based therapy.

In the AYA population, up to 30% of patients experience high-grade toxicities with asparaginase, and asparaginase toxicities at all grades are observed at higher rates in AYA compared with pediatric patients [15, 38–40]. Although concerns about toxicity have limited asparaginase use in AYAs [9, 14, 15, 39, 41], it has been demonstrated that with proactive management, these toxicities are often manageable, reversible, and generally free of long-term sequelae [37, 42]. Thus, broader adoption of asparaginase-based regimens to treat AYA patients with ALL/LBL is feasible with appropriate support.

Toxicities can range in severity, and the risk profile can vary widely across patients, particularly those with complicating factors; for example, increased age, body mass index $\geq 30 \text{ kg/m}^2$, and comorbid conditions such as diabetes and liver disease [41, 42]. Obesity (defined as a body mass index in the $>95\text{th}$ percentile for

TABLE 2 | Recommendations for overcoming barriers to initiation and use of asparaginase-based regimens in AYA patients with ALL/LBL.

Barrier	Recommendations	Agreement rating
Barrier 1: In adult treatment settings, PIRs are not always considered or offered for the treatment of AYA patients with ALL/LBL	Recommendation statement #1:	4.0
	Develop guidance for identifying appropriate patients for asparaginase-based regimens	4.0
	a. Based on comprehensive data and National Comprehensive Cancer Network recommendations, AYA patients with ALL/LBL should be referred to a center with an available clinical trial using a PIR for AYA patients and/or experience caring for AYA patients with ALL/LBL including administration of asparaginase-based, pediatric-inspired regimens	
	b. Evidence-based PIRs are recommended for AYA patients with Philadelphia chromosome negative (Ph-) B cell and T cell ALL/LBL. Adults with Ph-positive ALL/LBL should receive a tyrosine kinase inhibitor-based regimen, which do not typically include asparaginase	
	c. Asparaginase-based PIRs are favored over adult type (such as hyper-CVAD) in the AYA ALL/LBL population	
	Recommendation statement #2:	3.0
	Develop strategies for increased enrollment of AYA patients in clinical trials	4.0
	a. Increased/strategic dissemination of information to patients and healthcare professionals regarding available AYA clinical trial opportunities	
	b. Inclusion of AYA patients in clinical trial design	
	c. Reducing stringency of exclusion criteria and study visit burden to facilitate enrollment	
Barrier 2: Management of asparaginase toxicities can be complex, especially in AYA patients with comorbidities, obesity, and/or increased age	Recommendation statement #3:	4.0
	Foster more clinical trials in AYA patients	
	a. Include large community sites in multicenter and cooperative group studies for AYA patients with ALL/LBL	
	b. Encourage and support collaborative clinical trial development across pediatric and adult cooperative groups	
	Recommendation statement #1:	4.0
	Patients with increased risk factors for toxicities, such as higher age and those with obesity, should be identified. Dose reduction or capping dose to a maximum of 1 vial (3750 IU) of long-acting asparaginase may be considered for those patients	
	Recommendation statement #2:	3.6
	Facilitate engagement between experienced care teams and treating physicians to raise awareness of the data supporting long-term benefits of PIRs, educate on treatment toxicities and their management, and enable increased appropriate use	
	Recommendation statement #3:	4.0
	Conduct supportive care studies to identify effective preventive interventions that lead to improved asparaginase safety, particularly in high-risk populations (with obesity, older age, coexisting liver disease, history of thrombosis)	
Barrier 3: Limited medical facilities and experienced staff to support PIRs presents significant challenges in AYA ALL/LBL treatment	Recommendation statement #1:	3.9
	Following referral to a specialized ALL/LBL treatment center, pursue individualized strategies to support patients with barriers to care (e.g., specialized navigation and nursing support from trained teams, resources to support financial and travel burden, and/or collaborative care with institutions close to the patient's home)	

(Continues)

TABLE 2 | (Continued)

Barrier	Recommendations	Agreement rating
Barrier 4: Lifestyles and psychosocial aspects of the typical AYA patient often present challenges to accessing, adhering to, and completing asparaginase-based regimens	Recommendation statement #2: Develop collaborative treatment approaches between pediatric and adult oncology providers to leverage unique clinical experiences with the use of PIRs for AYA ALL/LBL	4.0
	Recommendation statement #3: Establish best practices in building a multidisciplinary infrastructure to provide ALL/LBL treatment in adult centers a. Provide training to care teams in asparaginase use, including toxicity management and supportive care b. Make adequate pharmacy arrangements to ensure asparaginase product accessibility (consider frequency of use, product indication, and shelf life of the various formulations)	4.0
	Recommendation statement #4 (patient-informed): Clearly communicate expectations of possible side effects, potential for experiencing multiple toxicities concurrently, and long-term risks when treating with a PIR. Reassure patients with open communications about the importance of promptly reporting toxicities, reversibility of toxicities, and the supportive care solutions and alternative therapies that enable regimen continuation	4.0
	Recommendation statement #1: In the absence of unacceptable toxicity, facilitating asparaginase continuation is critical, as patients who complete all asparaginase doses have better outcomes and lower rates of relapse than those who do not	4.0
	Recommendation statement #2: Consider developing AYA multidisciplinary clinics that address the “whole patient” and include a focus on unique psychosocial challenges that arise when treating AYA patients with ALL/LBL	3.9
	Recommendation statement #3 (patient-informed): Prepare and support AYA patients for potential disruption to everyday activities, such as missed work or school, during treatment with a PIR, and offer appropriate psychosocial resources	3.9
	Recommendation statement #4 (patient-informed): Facilitate AYA patient access to post-treatment and long-term survivorship support and/or counseling	4.0

Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; hyperCVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IU, International Units; LBL, lymphoblastic lymphoma; PIR, pediatric-inspired regimen.

age and weight) has been associated with inferior event-free survival, higher relapse rates, and an increased incidence of grade 3 or 4 adverse events in children and adolescents treated with pediatric protocols [18, 41, 42]. Therefore, tailored management strategies are required to mitigate risks and optimize treatment outcomes in these high-risk groups.

3.1.2.1 | Recommendations. To support successful treatment, we recommend a collaborative approach that includes consultation with experienced multidisciplinary care teams for AYA patients at increased risk of severe toxicity. In addition, further supportive care studies are essential to address specific needs within the AYA population (Table 2). Identifying high-risk patients early in treatment is critical to minimizing asparaginase-related toxicity. For patients at higher risk of adverse events, we recommend

considering strategies such as dose adjustments or dose capping (Table 2). Dose capping at a single vial (3750 international units [IU]) for pegaspargase is a common (but not evidence-based) clinical approach in this high-risk patient population (as used in CALGB 9511) [27, 43]. Other strategies include increased surveillance or delayed asparaginase administration during induction [41, 44, 45].

3.1.3 | Barrier 3: Limited Medical Facilities and Experienced Staff to Support PIRs Presents Significant Challenges in AYA ALL/LBL Treatment

PIRs are often more complex to administer than adult protocols such as hyper-CVAD. For example, while hyper-CVAD involves

repeating the same two blocks of chemotherapy, PIRs typically include consolidation cycles that consist of a multitude of chemotherapy combinations in distinct blocks [9]. These blocks require careful planning and management, demanding a high level of clinic infrastructure and scheduling flexibility.

PIRs are typically designed for outpatient delivery, requiring frequent clinic visits for assessments and treatments. This model necessitates a well-developed clinic infrastructure, often exceeding the visit frequency for adult inpatient regimens [9]. However, many adult oncology centers lack facilities and specialized staff experience to provide intensive monitoring and timely management that PIRs require. Administering these complex regimens over several months requires experienced healthcare providers familiar with the unique demands of PIRs [9, 46, 47]. Understanding expected side effects, concurrent toxicities, and appropriate management strategies is essential for minimizing unnecessary interruptions or dose reductions. Inexperienced staff may misinterpret manageable biochemical toxicities (e.g., hyperbilirubinemia or hypertriglyceridemia) as severe, sometimes prompting early asparaginase discontinuation [37]. However, with proper recognition, prevention, and management, these toxicities are generally controllable and reversible, and as such, they should not necessitate the omission of asparaginase from treatment protocols [46].

Additional logistical challenges arise from financial and practical constraints associated with stocking asparaginase products for a relatively small AYA ALL/LBL population, particularly in adult centers where this treatment is less commonly used [14]. Furthermore, the differences between asparaginase formulations, each with specific indications, approved age ranges, dosing schedules, and administration routes (Table 3), may be a barrier to adopting PIRs, as awareness and education on these formulations may be lacking among pharmacists, nurses, and oncologists.

3.1.3.1 | Recommendations. To overcome these barriers, we recommend referring AYA patients to specialized ALL/LBL treatment centers and developing individualized strategies to support patients with barriers to care. Trained teams may offer specialized navigation and nursing support, as is often done in tertiary care children's hospitals, helping to alleviate financial and travel burdens or coordinating collaborative care with institutions closer to the patient's home (Table 2). For example, induction and possibly early consolidation intensive therapy could be initiated in a specialized ALL/LBL center before transitioning patients achieving remission to a center close to their home for subsequent consolidation cycles. In this approach, consistent communication between the local oncologist and the specialized center is essential to ensure continuity of care and to provide an optimized consultation for each patient.

Establishing open communication channels between institutions and fostering collaborative treatment models between pediatric and adult oncology providers is essential. Sharing clinical experiences across disciplines can help to leverage pediatric expertise in managing AYA ALL/LBL, enabling adult centers to more effectively integrate PIRs. Developing multidisciplinary infrastructure and establishing best practices will support optimized care for AYA patients treated in adult facilities (Table 2).

Providing staff with education on managing toxicity is vital to avoid the premature discontinuation of effective therapies. Building on this, it is crucial to communicate clearly with AYA patients on expected side effects, concurrent toxicities, and potential long-term risks associated with PIRs (Table 2). Addressing this gap in timely reporting of presumed toxicities and counseling of AYA patients may enhance adherence to asparaginase-based protocols, ultimately contributing to improved treatment outcomes.

3.1.4 | Barrier 4: Lifestyles and Psychosocial Aspects of the Typical AYA Patient Often Present Challenges to Accessing, Adhering to, and Completing Asparaginase-Based Regimens

Due to the transitional and dynamic nature of the life stage of the AYA population, multiple psychosocial and lifestyle issues contribute to difficulty following the scheduling demands of the PIRs for the treatment of ALL/LBL, with several studies showing that AYA patients adhere to and complete treatment at lower rates than pediatric patients [32, 48–50]. Early discontinuation of long-acting asparaginase is particularly prevalent and leads to a higher risk of relapse and inferior survival [32, 37].

The challenges in this population are multifaceted. AYA patients are often balancing academic pursuits, transitioning to independent living, establishing early careers, or managing young families. These demands can hinder treatment adherence by creating competing priorities and disrupting the ability to follow a rigorous treatment schedule. Practical barriers also add to these challenges, including inadequate access to reliable transportation, limited social support networks, and financial constraints that may restrict healthcare access or necessitate decisions between health expenses and other life costs [24, 26, 27, 31].

3.1.4.1 | Recommendations. To address these barriers, we recommend several approaches aimed at improving access to, adherence with, and completion of asparaginase-based regimens (Table 2). A key recommendation is to establish multidisciplinary AYA clinics to address the specific needs of this patient group throughout the prolonged duration of treatment. These clinics should ideally incorporate a comprehensive team of specialists, such as physicians, pharmacists, social workers, advanced practice providers, nurses, patient navigators, physical therapists, psychologists, dietitians, and integrative health practitioners, who can provide a coordinated and patient-centered approach. This multidisciplinary model is essential for delivering holistic care and managing the complex physical, emotional, and logistical challenges AYA patients often face. Furthermore, preparing AYA patients for potential disruptions to their everyday lives and equipping them with coping strategies may improve adherence. Practical support and resources should be integrated into their care plan to address not only treatment-related side effects but also the broader impact of the disease on education, career aspirations, and social relationships. These issues are particularly important given the prolonged duration of these treatments, during which many of these activities are put on hold. Additionally, post-treatment and long-term survivorship support is vital for AYA patients. Expanding community resources, including access to counseling and mental health support, has the potential to help patients reintegrate into their everyday lives after

TABLE 3 | Currently available asparaginase formulations.

	Pegaspargase (ONCASPAR)	Calaspargase pegol-mknl (ASPARLAS)	Asparaginase <i>Erwinia chrysanthemi</i> (recombinant)-rywn (RYLAZE)
Indications	Pediatric ^a and adult patients with: • First-line ALL • ALL and hypersensitivity to asparaginase	ALL in pediatric and young adult patients aged 1 month to 21 years ^b	ALL and LBL in adult and pediatric patients 1 month or older who have developed hypersensitivity to <i>E. coli</i> -derived asparaginase
Mode of administration	Intramuscular or intravenous	Intravenous	Intramuscular
Half-life	Intramuscular: 5.73 days Intravenous: 5.3 days	13.4 days	0.76 days
Recommended dosing	Patients ≤ 21 years: 2500 IU/m ² Patients > 21 years: 2000 IU/m ²	2500 IU/m ²	25 and 50 mg/m ² (see the recommended interval)
Recommended interval	No more frequently than every 14 days	No more frequently than every 21 days	Every 48 h (25 mg/m ²) OR Three times a week (M/W/F: 25 mg/m ² on M morning and W morning, and 50 mg/m ² on F afternoon)

^aIn 2022, pegaspargase became unavailable to patients younger than 22 years in the US.

^bUse of calaspargase pegol in adults is being studied in the ongoing SPARK-ALL clinical trial (ClinicalTrials.gov ID: NCT04817761).

Abbreviations: ALL, acute lymphoblastic leukemia; *E. coli*, *Escherichia coli*; IU, International Units; LBL, lymphoblastic lymphoma; M/W/F, Monday, Wednesday; Friday; US, United States.

treatment and support sustained health outcomes. Establishing a pathway for ongoing survivorship care outside of specialized centers would benefit patients who may not have continuous access to the initial care team following the acute treatment phase.

3.2 | Monitoring for and Managing Asparaginase Toxicities in AYA Patients

Multiple literature reviews on asparaginase toxicities and guidelines for preventing, monitoring, and managing toxicities in the AYA population have been published in recent years [13–15, 25, 37, 38, 46, 51]. While an additional detailed discussion on monitoring for and managing asparaginase-based toxicities in AYA may be redundant, we have included recommendations on the management of common toxicities in Table 4, including hepatotoxicity, pancreatitis, thrombosis, hypersensitivity reactions, and metabolic and other toxicities (hypertriglyceridemia, hyperglycemia, hyperammonemia, nausea/vomiting, and osteonecrosis). The aim of these recommendations is to provide safe administration of the drug, education of healthcare professionals regarding when asparaginase can be continued despite the presence of side effects, and the monitoring and education of AYA patients.

3.3 | Optimizing Asparaginase Dosing in AYA ALL/LBL

3.3.1 | Long-Acting Asparaginase

Primary front-line asparaginases in the US for ALL/LBL are pegylated (long-acting) forms of *Escherichia coli* (*E. coli*)-derived asparaginase, such as pegaspargase and calaspargase pegol-mknl (CALPEG) [52, 53]. The difference in the linker

region contributes to a longer half-life (14–15 vs. 5.5–7 days) and extended shelf-life (~36 months vs. ~8 months) for CALPEG compared to pegaspargase [14, 25, 54]. In 2022, pegaspargase became unavailable to patients younger than 22 years in the US, leaving CALPEG as the only available long-acting asparaginase formulation for this population. The recommended dosing for long-acting asparaginases according to their respective labels is presented in Table 3. As CALPEG is approved for patients aged 1 month to 21 years, its use in the AYA population remains unclear [25]. However, a prospective trial evaluating its safety in adults aged ≥ 22 and < 55 years with newly diagnosed ALL is currently underway (NCT04817761) [55].

Optimizing asparaginase dosing in AYA ALL/LBL requires a balance between achieving therapeutic levels and managing adverse effects. Switching to alternative formulations (e.g., *E. coli*-derived to non-*E. coli*-derived asparaginase) in cases of hypersensitivity or silent inactivation (the absence of asparaginase activity after administration of drug without evidence of hypersensitivity reaction) can help maintain treatment efficacy. While the precise asparaginase activity level required for maximal efficacy remains undetermined, it has been suggested that serum asparaginase activity levels ≥ 0.1 IU/mL are required for therapeutic asparagine depletion [51, 56]. Future studies may determine the ideal therapeutic range for asparaginase trough levels in AYA patients and further define the role of alternative formulations in optimizing asparaginase therapy.

3.3.1.1 | Recommendations. The recommended dose of long-acting pegaspargase is 2000 IU/m² for patients > 21 years and 2500 IU/m² in patients ≤ 21 years (Table 3). However, based on current clinical evidence, our consensus is that a reduced pegaspargase dose of 1000 to < 2000 IU/

TABLE 4 | Recommendations for monitoring and managing asparaginase toxicities in AYA patients with ALL/LBL.

Barrier	Recommendations	Agreement rating
Barrier 1: Monitoring for and managing hepatotoxicity	Recommendation statement #1: Adjust or avoid hepatically cleared medications and consider delaying the next cycle of therapy during periods of significant hyperbilirubinemia	3.5
	Recommendation statement #2: High-grade hepatotoxicity is not a contraindication for future use of asparaginase and does not reliably predict future occurrence	4.0
	Recommendation statement #3 (patient-informed): Educate patients that asparaginase used to treat ALL/LBL may result in abnormal hepatic laboratory values and jaundice, but generally this does not result in lasting liver injury as liver toxicity is reversible, and treatment discontinuation is not required	4.0
Barrier 2: Monitoring for and managing pancreatitis	Recommendation statement #1: Generally, asparaginase therapy should be discontinued following asparaginase-induced clinical pancreatitis in adults with ALL/LBL. Rechallenge may be cautiously considered in adolescent patients, depending on individual risk/benefit assessment and with acknowledgment of the risk of repeat pancreatitis	4.0
	Recommendation statement #2: Asparaginase should not be discontinued for chemical pancreatitis, defined as elevation of amylase and lipase in the absence of symptoms or imaging consistent with clinical pancreatitis	4.0
	Recommendation statement #3: Following asparaginase-induced clinical pancreatitis, no switching to another asparaginase formulation (such as <i>Erwinia</i> -derived) as pancreatic toxicity can occur with all formulations of asparaginase	4.0
	Recommendation statement #4: Practice vigilant monitoring of symptoms and educate providers regarding early recognition of potential clinical pancreatitis during asparaginase therapy. Initiate supportive treatment immediately upon development of symptoms	4.0
	Recommendation statement #5 (patient-focused): Educate patients and caregivers for the risk for asparaginase-associated pancreatitis. Advise monitoring for post-asparaginase abdominal pain (particularly that radiates to the back) and nausea/vomiting and prompt reporting of symptoms	4.0
Barrier 3: Monitoring for and managing thrombosis or bleeding	Recommendation statement #1: Asparaginase-associated thrombosis is not an indication to discontinue asparaginase therapy. For cavernous sinus thrombosis, risks and benefits should be weighed in the decision to continue asparaginase treatment	4.0
	Recommendation statement #2: With rare exceptions, resume asparaginase after VTE for patients who are clinically stabilized and treated with therapeutic anticoagulation. Continue anticoagulation at least until the completion of all doses of asparaginase treatment	4.0
	Recommendation statement #3: Consider preventive therapy for asparaginase-associated VTE for adolescent patients at high risk (e.g., with obesity, older adolescents), particularly when administering a regimen of continuous asparagine depletion. Data for preventive therapy in adults are lacking	3.9
	Recommendation statement #4: Low molecular weight heparin is recommended for the treatment of asparaginase-induced VTE. Direct oral anticoagulants also demonstrate some evidence of safety and efficacy	3.8

(Continues)

TABLE 4 | (Continued)

Barrier	Recommendations	Agreement rating
Barrier 4: Monitoring for and managing hypersensitivity reactions	Recommendation statement #5: It is not recommended to correct hypofibrinogenemia with cryoprecipitate or fresh frozen plasma during asparaginase therapy in the absence of clinically significant bleeding, as this practice may be associated with increased risk of VTE	4.0
	Recommendation statement #6 (patient-focused): Discuss the risk for asparaginase-associated thrombosis with patients and caregivers. Advise monitoring for shortness of breath or swelling of any limb and prompt reporting of symptoms. Reassure patients of recovery from thrombosis with continuous anticoagulation and inform that long-term harm due to asparaginase-associated thrombosis is rare	4.0
	Recommendation statement #1: If using premedication, monitor asparaginase activity with TDM after dosing (if > 10% of prescribed asparaginase administered) to confirm adequate drug activity, to differentiate the occurrence of a hypersensitivity reaction from an infusion reaction, or to reveal silent inactivation	3.9
	Recommendation statement #2: Consider routine premedication with hydrocortisone, acetaminophen, and antihistamine when administering long-acting asparaginases to potentially mitigate the occurrence of clinical hypersensitivity and infusion/injection reaction following asparaginase therapy. Use TDM when premedicating to ensure detection of silent inactivation	3.9
	Recommendation statement #3: Clinical hypersensitivity reaction should be treated with glucocorticoids and antihistamines, and epinephrine for anaphylaxis	4.0
	Recommendation statement #4: The occurrence of a hypersensitivity reaction or silent inactivation in patients with ALL/LBL treated with <i>E. coli</i> -derived asparaginase is an indication for switching to an <i>Erwinia</i> -derived asparaginase, ensuring continued asparaginase activity with the replacement of the most recent dose as soon as possible	4.0
	Recommendation statement #5 (patient-informed): Educate patients that hypersensitivity reactions to asparaginase vary in intensity and may be frightening, but rapid supportive management can successfully control symptoms, and alternative formulations allow for continuation of a safe and effective treatment	4.0
	Recommendation statement #1: Metabolic and other toxicities Asparaginase-induced hypertriglyceridemia is common and self-limited. Treatment of hypertriglyceridemia may be initiated depending on severity and patient situation, but its occurrence is not a contraindication to continuing asparaginase	4.0
	Consider insulin or other hypoglycemic medications for severe (grade 3/4) hyperglycemia Infusion reaction can result from hyperammonemia but does not necessitate a switch to an <i>Erwinia</i> -derived asparaginase Testing ammonia levels does not confirm adequate asparaginase activity or replace TDM Nausea and vomiting are common, possibly due to asparaginase-related hyperammonemia. Consider routine premedication with antiemetics	
	Recommendation statement #2: Osteonecrosis Maintain long-term awareness and educate AYA patients regarding the potential for asparaginase-associated osteonecrosis	4.0

(Continues)

TABLE 4 | (Continued)

Barrier	Recommendations	Agreement rating
	Recommendation statement #3 (patient-informed): Provide patients with antiemetics at the initiation of asparaginase, acknowledging that nausea and vomiting are common with ALL/LBL treatments and may temporarily impact daily life but are not expected to limit continuation of therapy Report late-onset, persistent joint pain (particularly large joints like knees and hips) to healthcare professional as a potential symptom of osteonecrosis	3.6

Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; *E. coli*, *Escherichia coli*; LBL, lymphoblastic lymphoma; TDM, therapeutic drug monitoring; VTE, venous thromboembolism.

m² or a maximum of 1 vial (3750IU) for young adults with ALL/LBL generally produces adequate asparaginase activity and may reduce the potential for certain toxicities (Tables 2 and 5). Lower pegylated asparaginase doses in adults aged 18–57 years have been demonstrated to adequately deplete asparagine and reduce toxicity in patients at risk [14, 57–59]. However, additional research is needed to further define the AYA population with the potential to benefit from dose reduction and capping [14, 25, 40, 41]. To ensure adequate asparaginase activity, therapeutic drug monitoring is recommended to identify patients with silent inactivation followed by switching these patients to other asparaginase formulations (see recommended practices in Table 5) [60]. While several clinical trials support using activity monitoring to identify silent inactivation, real-time dose adjustments of asparaginase remain less explored, making it challenging to differentiate the benefits of dose modulation from those gained through the detection and management of silent inactivation [60].

3.3.2 | Short-Acting Asparaginase

The only currently available short-acting asparaginase formulation in the US is *Erwinia chrysanthemi* (recombinant)-rywn, which is antigenically distinct from *E. coli*-derived asparaginase forms and has a distinct immunogenicity profile [61]. A phase 2/3 Children's Oncology Group AALL1931 study of *Erwinia chrysanthemi* (recombinant)-rywn in ALL/LBL patients following hypersensitivity or silent inactivation to long-acting (pegylated) *E. coli*-derived asparaginase demonstrated efficacy with the approved dosing regimens based on observed and population pharmacokinetic modeling data and a safety profile consistent with other asparaginase products [62]. This underscores another unique aspect of asparaginase-based treatment: in most cases, allergic reactions to chemotherapy generally lead to changes in supportive care, such as slowing the infusion rate, administering aggressive premedication, or discontinuing the problematic drug. However, with asparaginase, a switch to an alternative agent within the same class is necessary.

3.3.2.1 | Recommendations. Our consensus recommendation is that *Erwinia*-derived asparaginase should be used as a substitute for *E. coli*-derived asparaginase in patients who experience silent inactivation or clinical hypersensitivity, and replacement with recombinant *Erwinia*-derived asparaginase should be based on the intended duration of asparaginase activity (Table 5), which differs across protocols.

For short-acting asparaginase formulations, we were unable to develop recommendations for dose-capping, therapeutic drug monitoring-based dose adjustments, or premedication due to limited evidence. Further studies are needed to support future guidance in these areas.

4 | Future Directions

Asparaginase-based regimens, known for high cure rates in pediatric ALL/LBL, are increasingly being recommended for AYA/adult patients as a promising alternative to adult-type regimens [21, 22]. However, barriers to their adoption and successful completion persist in this population, with discontinuation of asparaginase or truncation of dosing resulting in inferior patient outcomes [32].

While contemporary reviews are limited to recommendations for overcoming toxicity-related barriers secondary to asparaginase, this consensus review offers a comprehensive approach to address challenges that AYA patients with ALL/LBL encounter throughout their treatment journey. It highlights institutional and psychological barriers to asparaginase use, and provides actionable recommendations for providers and institutions, areas often overlooked in more traditional, systematic research.

Much work is still needed to optimize asparaginase treatment for AYA patients. In particular, as a panel we believe that future directions should focus on education and awareness among healthcare providers, enhanced collaboration and interactions, localized and coordinated care, increasing AYA enrollment in clinical trials, and addressing additional risk factors for toxicities. Effective education and awareness programs would help to equip healthcare providers, particularly those unfamiliar with asparaginase regimens, with the knowledge needed to administer and manage these therapies. Clear responsibilities should be defined for expert treaters and specialized institutions in educating general oncologists and primary care providers who may encounter AYA ALL/LBL patients.

To facilitate optimized care for AYA patients, interaction and collaboration between pediatric and adult healthcare centers is vital. Furthermore, multidisciplinary teams including, but not limited to, physicians, pharmacists, advanced practice providers, and nurses should engage with patients and their families to provide a holistic understanding of treatment options and associated risks. This approach would ensure that asparaginase-based therapy is not only introduced effectively but also supported

TABLE 5 | Recommendations for optimizing asparaginase dosing in AYA patients with ALL/LBL.

Topic	Recommendations	Agreement rating
Long-acting asparaginase (pegaspargase and calaspargase pegol)	Recommendation statement #1: A reduced pegaspargase dose of 1000 to < 2000 IU/m ² or maximum of 1 vial (3750 IU) for young adults with ALL/LBL (compared with the standard 2500 IU/m ² in patients ≤ 21 years) generally produces adequate asparaginase activity and may reduce potential for toxicity	3.8
	Recommendation statement #2: Capping long-acting asparaginase dose to a maximum of 1 vial (3750 IU) in select AYA populations (patients with obesity, young adults) undergoing ALL/LBL therapy is an acceptable practice to mitigate toxicity	3.9
	Recommendation statement #3: The long-acting asparaginase formulations have different half-lives and dosing intervals and are not interchangeable at the same dose and frequency	4.0
	Recommendation statement #4: Perform TDM routinely between 7 and 14 days following administration of a long-acting asparaginase in patients receiving premedication to detect silent inactivation and, in the event of a possible hypersensitivity reaction, to differentiate from an infusion reaction. Asparaginase activity ≥ 0.1 IU/mL is currently accepted as standard for the nadir serum asparaginase activity level that is considered sufficient to deplete serum amino acid asparagine. Asparaginase activity below that threshold is an indication for switching to an <i>Erwinia</i> -derived asparaginase	3.5
	Recommendation statement #5: WHO should receive TDM All patients receiving premedication and undergoing therapy with <i>E. coli</i> -based long-acting asparaginase to assess for silent inactivation Any patient who develops a clinical infusion reaction in order to identify a hypersensitivity/allergic reaction that may be indicative of inactivation and receives ≥ 50% of intended dose • If patient receives between 10% and 50%, check earlier between day 3 and 5	3.5
	Recommendation statement #6: HOW to test Specimens can be sent to one of multiple commercial laboratories for measurement of nadir serum asparaginase activity levels Turnaround times are generally ≤ 1 day from sample receipt but may take up to a week to report based on individual site logistics CPT Code: 82657 Detection of neutralizing antibodies is not part of standard TDM testing for asparaginase activity	4.0
	Recommendation statement #7: WHAT to do with results For levels < 0.1 IU/mL, switch from long-acting asparaginase to short-acting asparaginase (recombinant <i>Erwinia</i>), preferably as soon as possible following the most recent dose • Substitute the <i>E. coli</i> asparaginase dose that caused hypersensitivity and all subsequent doses	4.0
Short-acting recombinant <i>Erwinia</i> asparaginase	Recommendation statement #1: Replacement with recombinant <i>Erwinia</i> -derived asparaginase should be based on intended duration of asparaginase activity - If intended duration is 2 weeks (e.g., pegaspargase), the long-acting asparaginase is substituted by 7 doses of IM recombinant <i>Erwinia</i>-derived asparaginase if administered every 48 h or by 6 doses if administered M/W/F 25/25/50 mg/m² - If intended duration is 3 weeks (e.g., calaspargase pegol), the long-acting asparaginase is substituted by 11 doses of IM recombinant <i>Erwinia</i>-derived asparaginase if administered every 48 h or by 9 doses if administered M/W/F 25/25/50 mg/m² <i>Erwinia</i>-derived asparaginase should replace the long-acting asparaginase dose that was associated with hypersensitivity and subsequent doses	4.0

(Continues)

TABLE 5 | (Continued)

Topic	Recommendations	Agreement rating
	Recommendation statement #2: For short-acting asparaginase formulations, the panel can make no recommendations for dose-capping, TDM-based dose adjustments, or premedication due to limited evidence Note: Short-acting <i>E. coli</i> derived asparaginase formulation is no longer available in the US.	3.9

Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; CPT, Current Procedural Terminology; *E. coli*, *Escherichia coli*; IM, intramuscular; IU, International Units; LBL, lymphoblastic lymphoma; M/W/F, Monday, Wednesday, Friday; TDM, therapeutic drug monitoring; US United States.

through comprehensive communication between care teams, patients, and their families.

Recognizing that the centralized nature of some treatment protocols may pose logistical challenges, particularly for AYA patients, there is a need for strategies that would permit treatment administration and care management closer to patients' homes to improve adherence and ease logistical challenges.

Clinical trial participation remains limited for AYA patients [63]. To address this, coordinated efforts among the National Cancer Treatment Network, the National Community Oncology Research Program, and the Food and Drug Administration are essential to address and eliminate barriers to enrollment [63]. Targeted initiatives to support community oncologists in prioritizing AYA trial participation, as well as streamlined trial referral systems, could help to improve trial enrollment for AYA patients [63, 64].

While this consensus article focuses on managing key toxicity risks associated with asparaginase, we recognize that there are additional risk factors, such as ethnicity (principally Hispanic) and genetic variants, that may impact outcomes and which warrant further study for tailored supportive care interventions [25].

Recently, a significant barrier to optimal asparaginase delivery in AYA patients stems from the unproven perception that front-line immunotherapy avoids the need for asparaginase in ALL regimens. However, we recommend that asparaginase should not be omitted solely due to the early incorporation of immunotherapy. Studies demonstrating the benefit of front-line blinatumomab in pediatric and AYA patients have utilized asparaginase-based regimens, as exemplified by the ECOG-ACRIN E1910 trial (particularly in patients <55 years who received more asparaginase), AALL1731, and Interfant-06 + blinatumomab [65–67]. In contrast, the benefit of blinatumomab in regimens with limited or no asparaginase exposure remains less clear, as observed in ECOG-ACRIN E1910 for older patients (≥55 years) and mini-Hyper-CVD plus inotuzumab ozogamicin (InO) ± blinatumomab [65, 68]. The early use of InO in AYA-directed regimens also presents uncertainties. While the AALL1732 study did not show a significant increase in sinusoidal obstruction syndrome, both the AALL1732 and A041501 studies reported higher rates of infectious complications among patients receiving InO [69, 70]. These observations underscore the importance of maintaining asparaginase as a key component of AYA ALL treatment, even in the era of novel immunotherapies.

5 | Conclusions

Overall, this consensus outlines a framework for healthcare professionals managing AYA patients with ALL/LBL, providing recommendations on the effective use of asparaginase-based regimens. By identifying the key barriers and recommending strategies for optimal treatment delivery, we highlight the critical role of asparaginase-based regimens in not only improving clinical outcomes but also enhancing the overall treatment experience for AYA patients.

Author Contributions

All authors contributed to the conception, writing, and review of this article. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgments

Under the direction of the authors, Angharad Morgan, PhD, CMPP, of CMC Connect, a division of IPG Health Medical Communications, provided medical writing support, which was funded by Jazz Pharmaceuticals in accordance with Good Publication Practice (GPP 2022) guidelines. Jazz Pharmaceuticals reviewed the manuscript for factual accuracy. Although Jazz Pharmaceuticals was involved in the review of the manuscript, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in the *American Journal of Hematology* were made by the authors independently.

The authors acknowledge the Interactive Forums Inc. staff for designing the methodology and moderating the panel, the Elephants and Tea advocacy group for assisting with the patient survey, and the patients who participated in the survey.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

I.A. reports advisory board participation for Acentage, Adaptive, Amgen, Autolus, Jazz Pharmaceuticals, Kite, Pfizer, Syndax, and Takeda; consulting for Amgen, Jazz Pharmaceuticals, Pfizer, and Takeda; and research support from AbbVie, Jazz Pharmaceuticals, and MacroGenics. A.A. reports consulting and participation in advisory boards, speakers' bureau participation, and research funding from Jazz Pharmaceuticals. R.D.C. reports research funding from Amgen, Incyte, Kite Pharma/Gilead, Merck, Pfizer, Servier, and Vanda Pharmaceuticals; consultancy/honoraria from Autolus, Amgen, Jazz Pharmaceuticals, Kite Pharma/Gilead, and Pfizer; and membership on a board or advisory committee for Autolus and PeproMene Bio. His spouse was employed by

and owned stock in Seagen. E.K.C. reports consulting and participation in advisory boards for Jazz Pharmaceuticals and Servier. M.R.L. reports research support (institutional) from AbbVie and Novartis as well as advisory board participation (ad hoc) with Jazz Pharmaceuticals, Kite Pharma/Gilead, Novartis, and Pfizer. L.D.M. reports consulting and participation in advisory boards with Jazz Pharmaceuticals and Servier as well as speakers' bureau participation with Jazz Pharmaceuticals. E.O. reports consulting with Jazz Pharmaceuticals. D.D. reports speakers' bureau participation with Amgen and Servier as well as consulting with Jazz Pharmaceuticals and Servier.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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