GUIDELINE ARTICLE

Recognition, prevention, and management of adverse events associated with asparaginase/pegaspargase treatment of acute lymphoblastic leukemia in adults: consensus of an expert panel

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Abstract

Asparaginase (ASNase)-based chemotherapy regimens significantly improve survival outcomes in children, adolescents and young adults (AYA), and even adults with acute lymphoblastic leukemia/lymphoma (ALL); however, the incidence and severity of ASNase-associated adverse events (AE) in adults may differ significantly from those reported in children. Strategies to mitigate, monitor for, and manage toxicities that allow adult ALL patients to receive full ASNase courses are needed. A representative 12-member panel of experts who treat AYA and adult ALL patients, incorporate ASNase into their treatment regimens, and conduct related research was assembled to consider opportunities to optimize the use of pediatric-inspired ALL regimens in these adult patients. Following 2 systematic biomedical literature searches from April 2009 through April 2024, a modified Delphi method was used to distill expert opinion into clinical statements that met a standardized definition of consensus. After 2 iterative Delphi method surveys, 23 statements met the standardized definition of consensus, whereas 19 statements did not. Five statements were merged to avoid redundancy. The clinical statements were grouped into 5 distinct categories: 1) hepatotoxicity; 2) hypersensitivity reactions; 3) thromboembolic and coagulopathy complications; 4) pancreatitis and metabolic complications; and 5) dosing. The intent of these statements is to provide health care providers with information that will help them mitigate, monitor for, and manage the most common and/or unique ASNase-induced AE in adult ALL patients, allowing these patients to receive more or all the planned ASNase doses and thereby improve outcomes.

Introduction

Although acute lymphoblastic leukemia/lymphoma (ALL) is most often considered a childhood cancer, almost half (47%) of ALL patients are 20 years or older.[1] Historically, survival rates in children with ALL were dismal (10-20%); however, with the development of intensive, multiagent chemotherapy regimens using asparaginase (ASNase) as a core component, the survival rates have risen sharply (up to 90%) over the past 50 years.[2,3]

The antileukemia effects of ASNase were first reported in the early 1960s, leading to US Food and Drug Administration (FDA) approval in 1978.[4,5] Because ALL cells are unable to produce their own asparagine, they depend on exogenous sources for survival.[6] Asparaginase hydrolyzes asparagine into ammonia and aspartate, selectively killing leukemic lymphoblasts by depleting serum asparagine, blocking protein synthesis, and reducing leukemic burden.[6,7]

Compared with children, adolescents and young adults (AYA) (age, 15-39 years) and adults (age, ≥40 years) with ALL exhibit consistently lower overall survival (OS) rates; the 5-year OS rates are 74% for AYA patients aged 15-19 years and approximately 50% for ages 20-39 years. These rates decline to 30-39% in adults, and are reported to be as low as 20% in patients aged 60 years or older.[8-10] These inferior outcomes in older patients may be related to an increased incidence of high-risk disease biology, lower frequency of favorable cytogenetics, poor tolerance to therapy, and a historically limited use of ASNase in adult protocols.[11-13] Several prospective study results demonstrated improved survival outcomes in the AYA and adult ALL populations receiving pediatric-inspired regimens. The improvement in survival is attributed to more extensive use of chemotherapy agents, including ASNase, compared with historic adult regimens.[14-16] Nevertheless, health care providers may be hesitant to prescribe pediatric-inspired regimens in AYA and adult patients because of ASNase-induced adverse events (AE), which may occur more frequently in these populations. For example, the risk of ASNase-associated hyperbilirubinemia, thrombosis, pancreatitis, and osteonecrosis (ON) have been shown to significantly increase with age (>10 years).[17] Other notable ASNase-associated toxicities include hypersensitivity reactions (HSR) / infusion-related reactions (IRR) and hypertriglyceridemia.[6,18] Adult patients who experience ASNase-related toxicities may require ASNase dose reductions, delays, or discontinuations, increasing the risk of relapse.[7,19] Retrospective analysis of large multi-institutional clinical trials has shown early discontinuation of ASNase therapy alone is associated with inferior outcomes.[20,21]

Recent improvements in drug purity, pegylation technology, flexibility in administration of pegasparaginase (PEG-ASNase), either by intramuscular (i.m.) or intravenous (i.v.) routes, and improved outcomes with ASNase in childhood ALL have renewed interest in incorporating ASNase into adult regimens.[22-24] Although toxicities may be more frequent or serious in AYA and adult populations, discontinuing ASNase or changing formulations may not be necessary; therefore, a comprehensive understanding of common toxicities, along with strategies for prevention and treatment, can better equip health care providers to provide optimal care for these patients.

A consensus panel of global leaders with expertise in managing adult ALL was convened to review strategies for mitigating and managing ASNase-associated toxicities in adult ALL patients with the intent of optimizing treatment outcomes. These consensus statements were developed as an update to the 2011 publication by Stock *et al.*,[25] utilizing a Delphi methodology to systematically achieve expert consensus among the authors regarding best practices for managing AE in AYA and adult patients receiving ASNase therapy. This approach ensures the strategies presented reflect current literature and the experiences gained since the 2011 publication by the expert panel on the topic.

Methods

A panel of global medical experts with diverse expertise was convened to review evidence regarding the mitigation, monitoring, and/or management of common AE associated with ASNase-based therapy in adult ALL patients. Using a modified Delphi method, the panel developed consensus statements to help clinicians identify and manage AE in this population. Consensus statements were developed in discrete, predetermined steps (Figure 1). Funding support was provided by Servier Pharmaceuticals, and medical writing assistance was provided by Syntaxx Communications. Methods are fully defined in the *Online Supplementary Appendix*.

Results

Using PubMed and Embase, 10 systematic reviews and review articles were identified in the stage 1 literature search, and 52 randomized controlled trials (RCT), case reports, and case series were identified in the stage 2 literature search (*Online Supplementary Table S4*). Each panelist reviewed the findings of both searches and identified these key gaps: hepatotoxicity, HSR/IRR, thromboembolic / coagulation complications, pancreatitis / metabolic complications, and dosing.

Forty-two clinical consensus statements were initially developed and assessed in the first Delphi survey. All panelists completed the survey. After the first iteration of the Delphi survey, 18 statements (43%) met the standardized defini-

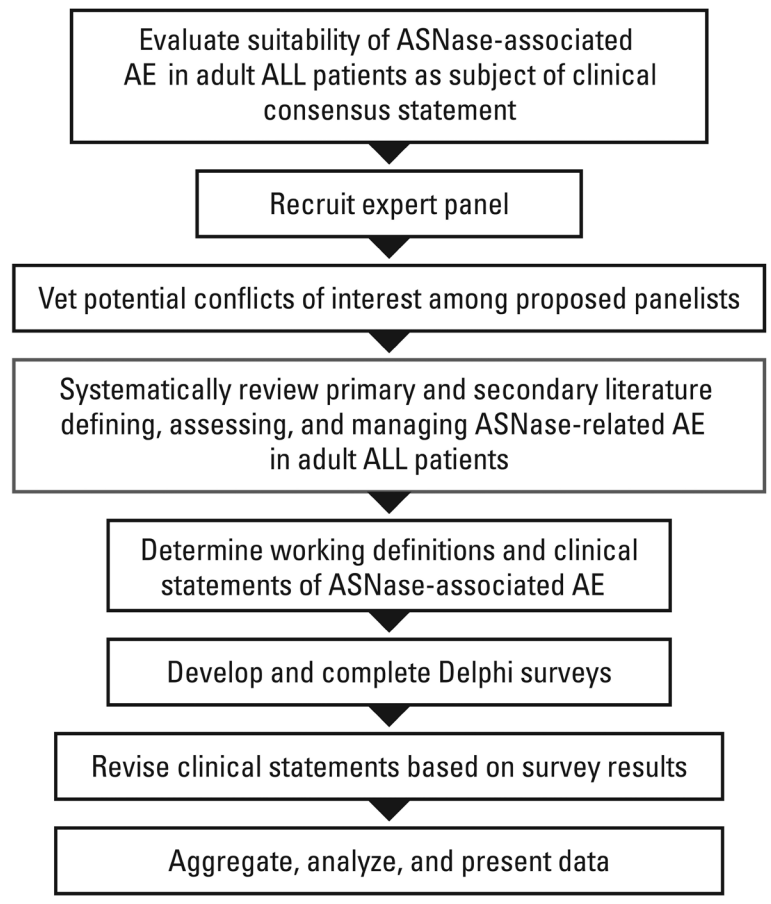

Figure 1. Predetermined steps for consensus statement development. AE: adverse event; ALL: acute lymphoblastic leukemia; ASNase: asparaginase.

tion of consensus, 10 statements (24%) met the criteria for near-consensus, and 14 statements (33%) met the criteria for no consensus. Five statements that reached consensus were merged because of redundancy. For statements not reaching consensus, statements were reworded / revised by the expert panelists and included in the second Delphi survey. After the second survey, 10 additional statements reached consensus. The 23 statements that reached consensus were organized into 5 subject areas. Tables 1-5 show the results of the Delphi survey for each gap identified. The consensus statements should be considered individually and are not presented in any order of preference.

Discussion

Hepatotoxicity

Hepatotoxicity is the most common AE associated with ASNase therapy in adults, with high-grade (grades 3/4) hyperbilirubinemia and transaminase elevation occurring in approximately 18-30% of patients and 19% to more than 50% of patients, respectively (Table 6).[16,26-29] ASNase-associated hepatotoxicity is thought to result from depletion of asparagine pools within the liver, leading to impairment of mitochondrial oxidative pathways and accumulation of unoxidized fatty acids.[30,31] Despite a high incidence of hepatotoxicity, the associated morbidity is generally low, transitory, and without hepatic failure.[32] The panel reached consensus on 4 statements related to ASNase-associated hepatotoxicity in adults (Table 1).

Risk

Several factors have been shown to increase the risk of ASNase-associated hyperbilirubinemia[29,33,34] For example, older age has been associated with a risk of ASNase-associated hyperbilirubinemia.[33,35,36] The German Multicenter Study Group for Adult ALL (GMALL) analyzed 1,226 patients receiving induction therapy for ALL; grade 3/4 hyperbilirubinemia occurred in 17% of patients >45 years of age but in only 11% of the younger patients (*P*=0.005).[33] Similarly, the results of a phase II clinical trial (*clinicaltrials.gov identifier 01920737*) showed that adult patients (age, 40-60 years) were 4 times more likely to develop grade 3/4 hyperbilirubinemia than younger patients (age, 18-39 years) (44% *vs*. 10%, *P*=0.025).[35]

Higher body mass index (BMI) has also been associated with an increased risk of ASNase-associated hepatotoxicity.[26,33] In a small study of 51 patients, the development of high-grade hyperbilirubinemia (31.4%) and high-grade transaminase elevation (64.7%) was associated with a higher baseline BMI (27.8 kg/m^2 and 27.7 kg/m^2, respectively) than that of patients who did not develop these toxicities (25.2 kg/m^2).[26] Although these results did not reach statistical significance (*P*=0.055 for hyperbilirubinemia; *P*=0.065 for transaminase elevation), they did suggest a connection between higher BMI and increased hepatotoxicity.[26] This finding is supported by an analysis of patients treated in the GMALL study (N=1,226), in which patients with BMI >30 kg/m^2 experienced significantly higher rates of grade 3/4 hyperbilirubinemia during induction therapy than did patients with a lower BMI (<30 kg/m^2) (18% *vs*. 11%, *P*=0.04).[33]

The severity of ASNase-associated hepatotoxicity, in contrast to other ASNase-associated toxicities, appears to be dose-dependent; studies incorporating pediatric-inspired regimens have shown that adults receiving lower PEG-ASNase doses (1,000-2,000 IU/m^2) develop less hepatotoxicity than do adults receiving a standard pediatric dose (2,500 IU/m^2).[27,33,37] For example, the results of a retrospective analysis of 51 consecutively treated patients treated with at least one dose of PEG-ASNase (≤1,000 IU/m^2 PEG-reduced dose [PEG-RD]; [N=26] or >1,000 IU/m^2 PEG-standard dose [PEG-SD]; [N=25]) demonstrated a trend towards a lower prevalence of grade 3/4 hyperbilirubinemia in the PEG-RD group (23% *vs*. 44%, *P*=0.144), despite this group representing an older population (median age, 49 years; range, 19-76 years).[38] In the GMALL study, adult patients receiving 1,000 IU/m^2 had a significantly lower prevalence of grade 3/4 hyperbilirubinemia than adults receiving 2,000 IU/m^2 (10% *vs*. 16%, *P*=0.004).[33]

Table 1. Panel consensus vote: hepatotoxicity

	Mean rating	Outlier	N of panelists
Hyperbilirubinemia or transaminase elevation with previous ASNase doses is not an indication to omit subsequent doses of ASNase.	8.0	0	12
Delaying the start of subsequent cycles of chemotherapy is recommended for patients experiencing prolonged ASNase-induced hyperbilirubinemia; however, dose delays for patients with elevated transaminase levels are not routinely required.	8.0	1	12
Older age and obesity (BMI >30) increase the risk of ASNase-induced hyperbilirubinemia in adults. Study results suggest that reducing the ASNase dose may decrease the severity of hyperbilirubinemia without compromising efficacy in these vulnerable patients.	8.0	1	12
The results of small studies and case reports show L-carnitine accelerates the resolution of ASNase-induced hyperbilirubinemia. The treatment of ASNase-induced hyperbilirubinemia with intravenous L-carnitine (with or without vitamin B complex) is generally well tolerated.	7.0	1	12

ASNase: asparaginase; BMI: body mass index; L-carnitine: levocarnitine; N: number.

Prevention and treatment

Reducing or modifying the ASNase dose or using different drug-sequencing strategies may mitigate the risks of high-grade hyperbilirubinemia. Several studies assessing doses less than the US FDA–approved adult dosage (≤2,000 IU/m^2) have been shown to produce adequate depletion of asparagine and fewer hepatotoxicities in adult ALL patients.[39] Because high-grade hyperbilirubinemia can delay the administration of the next chemotherapy cycle in at-risk patients, a dose reduction to 1,000 to 1,500 IU/m^2 may be considered. In addition, drug sequencing to minimize overlapping toxicities, such as administering anthracyclines during the first three days and ASNase approximately two weeks later during induction therapy, may also reduce high-grade hepatotoxicity without adversely impacting outcomes. However, data regarding the number of ASNase dose delays, reductions, or discontinuations are limited.[27,35,40]

Animal studies, case reports, and small clinical studies assessing the use of mitochondrial co-factors, such as levocarnitine (L-carnitine), to prevent hepatoxicity in adult patients receiving ASNase have produced conflicting results.[41-44] A review of 52 patients (age, 10-40 years) who received L-carnitine prophylactically showed a risk reduction in the development of hyperbilirubinemia (direct bilirubin >3 mg/dL) but no effect on the development of severe transaminase elevation.[45] Conversely, a single-center, retrospective study of 25 adult ALL patients (age, 18-57 years) evaluated time to resolution of grade 3/4 hepatotoxicity with or without L-carnitine treatment.[31] In this study, L-carnitine was administered for a median of 11 days (range, 5-45 days), starting at a median of 6.5 days (range, 0-21 days) after the onset of hepatotoxicity; the investigators found no significant difference in median time to symptom resolution between the L-carnitine and control groups (27 *vs*. 11 days, *P*=0.08).[31] The panelists agreed that data to support the routine use of L-carnitine to prevent and/or lessen the severity or duration of hepatotoxicity are limited; however, given the low incidence of toxicity, the use of L-carnitine may be considered for high-risk patients. An ongoing phase III clinical trial conducted by the Children's Oncology Group (COG) is evaluating whether prophylactic L-carnitine reduces the development of high-grade ASNase-related hyperbilirubinemia.[46]

Rechallenge

Patients exhibiting grade 3/4 hyperbilirubinemia may be rechallenged with ASNase, because the risk of recurrence after its resolution is minimal.[16,26,35] A study of 51 adult patients (age, 18-57 years) demonstrated that, although high-grade hyperbilirubinemia and transaminase elevation occurred most frequently during first induction with PEG-ASNase, early occurrence did not predict recurrence in later cycles.[26] Another study of 39 patients (median age, 38 years; range, 20-60 years) showed high-grade hyperbilirubinemia occurred only after the first dose and almost never recurred with subsequent administration; 9 of the 10 patients experiencing grade 3/4 hyperbilirubinemia during the first induction phase were able to resume therapy at the dose and schedule outlined in the study protocol.[35] Although hepatotoxicity, regardless of grade, is not an indication to discontinue ASNase therapy, subsequent cycles of therapy may be delayed in patients with grade 3/4 hepatotoxicity until hyperbilirubinemia resolves to grade 1 or less and/or transaminase elevation resolves to grade 2 or less.[47] For patients at greater risk of hepatotoxicity (e.g., patients who are older, obese, or who are receiving higher doses of ASNase), ASNase dose reductions should be considered.[30]

Hypersensitivity reactions

ASNase is a bacterial enzyme with the potential to provoke an immune response that manifests as an apparent HSR reaction; symptoms can range from localized erythema and urticaria to systemic anaphylaxis. The panel reached consensus on 7 statements related to ASNase-associated hypersensitivity in adults (Table 2).

Pathophysiology of hypersensitivity reactions

Hypersensitivity reactions are an immune response that initiates development of anti-ASNase antibodies, which inactivate ASNase and reduce the clinical effectiveness of ASNase-containing regimens.

Clinical (or symptomatic) HSR to native *E. coli* ASNase (L-ASNase) usually occur in 10-30% of patients.[18,48] As reported in clinical trials, clinical HSR associated with PEG-ASNase appear to be less prevalent (3-24%), although they are more common when patients have been previously exposed to native L-ASNase.[18] In some patients, anti-ASNase antibodies develop without eliciting clinical symptoms, which is termed silent inactivation (see Silent Inactivation).

Three ASNase formulations have received FDA approval. *Erwinia*–derived ASNase (*Erwinia*-ASNase) is antigenically distinct from and demonstrates no cross-reactivity with the native *E. coli*–derived ASNase. Patients receiving an *E. coli*–derived ASNase who develop a clinical HSR, or silent inactivation, should be switched to an *Erwinia*-ASNase.[49] The prevalence of HSR among patients who switch to an *Erwinia*-ASNase is relatively low (3-33%); patients who switch to an *Erwinia*-ASNase and receive adequate dosing can achieve therapeutic ASNase activity levels.[50,51] Guidance for switching ASNase formulations is provided in *Guidance for Switching ASNase Formulations* (see below).

Polyethylene glycol (PEG) is prevalent in a wide variety of pharmaceutical, medicinal, industrial, cosmetic, and food products. Therefore, the prevalence of antibodies against PEG in patients receiving pegylated drugs, such as PEG-ASNase or calaspargase pegol (CAL-ASNase), has raised concerns about the presence of anti-PEG antibodies on the development of HSR and/or efficacy.[52] A study of children (N=701) and adults (N=188) with ALL showed 13.9% had

Table 2. Panel consensus vote: hypersensitivity

	Mean rating	Outlier	N of panelists
Distinguishing between grade 1 and 2 non-anaphylactic IRR and HSR is difficult because presenting symptoms may overlap; however, making this distinction is required to prevent unnecessary ASNase formulation changes. Symptom onset, clinical symptoms, and laboratory values (e.g., serum ASNase levels) can help differentiate between a non-allergic IRR and a true HSR.	9.0	0	12
True clinical or silent HSR to *E. coli*-derived ASNase warrant substitution with a non-cross-reactive formulation, such as *Erwinia*-derived ASNase; non-allergic IRR do not warrant a formulation substitution.	8.7	0	12
True ASNase HSR most frequently occur with the second or third ASNase dose and rarely with the first. First-dose reactions are typically non-allergic IRR.	8.2	1	12
For a true PEG-ASNase-associated HSR, patients may experience inferior outcomes unless all subsequent doses of PEG-ASNase, including the dose that caused the reaction, are replaced with *Erwinia*-derived ASNase.	8.0	0	12
The administration of premedications (e.g., corticosteroids, acetaminophen, H-1 or H-2 receptor blockers) 30-60 minutes before each dose of PEG-ASNase may decrease the risk and severity of IRR. Premedications do not prevent inactivation of ASNase caused by neutralizing antibodies and may only be combined with TDM to detect inactivation.	8.0	1	12
For a mild, non-HSR, interrupt or slow the infusion, administer additional premedication doses or supportive care if warranted, wait for symptoms to resolve, then resume the infusion at a reduced rate.	8.0	1	12
For patients who receive the majority of the planned ASNase doses, inadequate ASNase activity (<0.1 IU/mL) measured around day 7 and ASNase levels below the lower limit of quantification (the lowest value on the calibration curve) on day 14 confirm a diagnosis of a true clinical or silent HSR. Therapeutic ASNase levels (>l0.1 IU/mL) suggest a non-allergic reaction. In patients who have received only a small fraction of the intended ASNase dose, ASNase activity levels are not reliable for distinguishing these reactions.	7.0	0	12

ASNase: asparaginase; H: histamine; HSR: hypersensitivity reaction; IRR: infusion-related reaction; N: number; PEG-ASNase: pegylated-asparaginase; TDM: therapeutic drug monitoring.

anti-PEG immunoglobulin G (IgG) and 29.1% had anti-PEG immunoglobulin M (IgM) antibodies before administration of PEG-ASNase. Pre-existing antibodies reduced PEG-ASNase activity in a concentration-dependent manner, although not to the degree of inactivation, and were significantly associated with first exposure (grade 2) HSR (P<0.01).[53]

Differentiating allergic hypersensitivity reactions and non-allergic infusion-related reactions

While the Common Terminology Criteria for Adverse Events (CTCAE) categorizes HSR and non-allergic IRR as distinct entities,[54] their clinical symptoms overlap considerably[52] (Table 7). Distinguishing between HSR and IRR requires assessment of clinical symptoms, time to symptom onset, and, importantly, ASNase serum levels.

Hypersensitivity reactions require antibody development that can trigger histamine release from mast cells, inducing symptoms ranging from mild urticaria, dizziness, and respiratory symptoms to anaphylaxis. In contrast, IRR are not associated with antibody development; symptoms may result from a direct release of cytokines or histamine and/or sharp elevations in serum ammonia levels and include hyper- or hypotension, tachycardia, headache, confusion, flushing, local or diffuse erythema, nausea, vomiting, a sense of impending doom, tachypnea, and dyspnea.[47,55] For suspected anaphylactic reactions, clinicians should treat immediately according to institutional anaphylactic protocols (e.g., with epinephrine, antihistamines, and/or corticosteroids). For less severe or characteristic reactions, patients may continue the ASNase infusion after symptom resolution. True HSR virtually always lead to ASNase inactivation irrespective of reaction severity.

Time to symptom onset can also help distinguish between HSR and IRR, making close monitoring and accurate documentation of symptom onset critical. Clinical HSR are antibody-mediated and require prior ASNase exposure,[53] thus, they rarely occur during the initial treatment cycle. Anaphylactic reactions typically occur within several minutes of initiating an ASNase infusion (later if ASNase is administered intramuscularly). IRR, being non-antibody–mediated, often occur after initial exposure to ASNase.[56]

Therapeutic drug monitoring (TDM), particularly in patients receiving premedication(s) that can mask clinical symptoms indicating ASNase inactivation, may also help differentiate between HSR and IRR.[47] While the precise minimal ASNase activity level correlating with complete serum asparagine depletion is a subject of debate,[47] a trough serum ASNase level of greater than or equal to 0.1 IU/mL is generally accepted as the level required to achieve complete serum asparagine depletion, and would suggest an IRR rather than a true HSR.[49,56] Conversely, symptomatic patients with low enzyme activity (<0.1 IU/mL) are more likely to have

developed antibodies, suggesting a true clinical HSR, a particularly important consideration because patients who develop anti-ASNase antibodies are at risk of achieving significantly lower event-free survival (EFS) and OS times compared with patients who do not develop antibodies.[57-59] If symptoms do not clearly point to an HSR, measurement of ammonia levels may be informative. Sharp increases in serum ammonia resulting from rapid hydrolysis of asparagine can lead to hyperammonemia symptoms, including nausea, vomiting, headache, dizziness, lethargy, and rash, which are typically mild and transient.[56,60] However, accurate measurement of serum ammonia levels may be challenging because of residual ASNase activity *ex vivo* during sample acquisition and processing, even when samples are placed on ice.[61]

Silent inactivation

Although overt clinical symptoms are often accompanied by antibodies to ASNase, patients can develop neutralizing anti-ASNase antibodies in the absence of clinical symptoms, which is known as subclinical hypersensitivity, or silent inactivation.[49] Silent inactivation is associated with reduced ASNase activity and may be linked to poor outcomes if not identified and managed early.[48,58,59] In patients receiving most of the planned ASNase doses, inadequate ASNase activity (<0.1 IU/mL at day 7 or less than the lower limit of quantification on day 14) confirms a diagnosis of silent inactivation.[49,56] Routinely monitoring nadir serum ASNase levels and changing the ASNase formulation in patients who develop silent inactivation have been recommended in various treatment protocols.[59] Figures 2 and 3 show representative treatment algorithms highlighting clinical signs and recognition of non-antibody-associated IRR, HSR, silent inactivation, and accelerated ASNase clearance.[56,62]

Premedication

The use of premedication (antihistamines and/or corticosteroids) can mitigate adverse clinical effects associated with HSR and IRR by stabilizing mast cells and preventing release of proinflammatory mediators,[63,64] although evidence regarding their efficacy remains mixed. The results of a retrospective study of ALL patients (N=46) receiving PEG-ASNase demonstrated that premedication with acetaminophen, diphenhydramine, and methylprednisolone reduced the number of grade 3/4 allergic reactions compared with patients receiving no premedication.[65] Similarly, in the prospective Cancer and Leukemia Group B (CALGB) 10403 study, a reduction in grade 3/4 HSR in AYA patients was noted after implementing a protocol amendment mandating premedication with acetaminophen, hydrocortisone, and diphenhydramine before each PEG-ASNase dose.[16] Conversely, the results of a larger retrospective analysis of 410 ALL patients (age, ≥1 year) receiving a PEG-ASNase-based regimen revealed that premedication with diphenhydramine and a glucocorticoid did not alter HSR incidence or severity.[66] This conflicting evidence underscores the complexity of managing ASNase-associated reactions. Importantly, although antihistamines and corticosteroids may reduce symptoms, they do not prevent antibody-mediated inactivation of ASNase activity and can mask clinically important signals of immune system activation; therefore, premedication should always be accompanied by TDM.[49] The recent introduction of B-cell directed immunotherapy (i.e., anti-CD20, anti-CD22, and CD19 targeted bispecific antibodies [blinatumomab] or CAR T-cell therapy) as part of the multi-drug regimen that includes ASNase in the first-line setting for ALL may impact on antibody production and antibody-mediated inactivation of ASNase.

Guidance for switching asparaginase formulations

Patients exhibiting a clinical HSR or silent inactivation to *E. coli*-derived ASNase should be switched to a non–*E. coli*-derived ASNase, such as an *Erwinia*-ASNase.[49] Unlike other oncology medications, for which allergic reactions can be managed by temporarily holding and restarting the drug with supportive care, ASNase requires a complete formulation change to maintain therapeutic efficacy. The transition may result in increased costs, heightened risk of hyperammonemia, and an additional burden to both patients and health care systems because of more frequent administration requirements. However, these challenges must be weighed against the necessity of maintaining adequate ASNase activity for optimal therapeutic outcomes. The approach to switching formulations should be guided by the reaction severity. For grade 1/2 HSR, monitoring of serum ASNase levels is recommended to identify ASNase inactivation prior to switching. However, in cases of grade 3 and higher HSR, immediate switching to another ASNase formulation is reasonable without first checking serum ASNase levels. Of note, when an HSR occurs immediately after ASNase administration and the infusion is stopped, TDM to determine presence of HSR is unreliable. For grade 1/2 HSR, practitioners should perform TDM after administration of the next ASNase dose. If TDM is unavailable, measuring ammonia levels during the next ASNase administration can provide alternative guidance. The *E. coli*-derived ASNase dose given immediately before HSR development should be replaced with an equivalent *Erwinia*-based ASNase dose, underscoring the importance of prompt identification and rapid initiation of the new formulation to minimize treatment delays. Table 8 provides detailed guidance for switching.

Thromboembolic and coagulation complications

Thromboembolic complications in ALL patients receiving ASNase, particularly in adults and among high-risk groups, are reported more frequently than bleeding events, which are rare.[30,67,68] Most ASNase-related thromboembolic events are effectively managed so that ALL patients can complete ASNase-based therapy.[30,69,70] Central nervous system thromboses, such as cerebral sinocavernous thrombosis

(CSVT), are rare but may cause serious morbidity, including long-term neurologic consequences, and, in some cases, can be fatal.[67,69,71] The panel reached consensus on 5 statements related to ASNase-induced thromboembolic and coagulation complications (Table 3).

Risk and therapeutic approach

ASNase therapy reduces serum levels of anticoagulant and procoagulant factors, which has prompted the prophylactic use of replacement therapies, such as fresh frozen plasma (FFP) and cryoprecipitate.[69] Studies have shown FFP and cryoprecipitate to be ineffective in maintaining hemostatic balance, perhaps because the incidence of ASNase-induced thrombosis outweighs the risk of bleeding in ALL patients.[69] Furthermore, FFP may increase serum asparagine levels, potentially negating the antileukemic

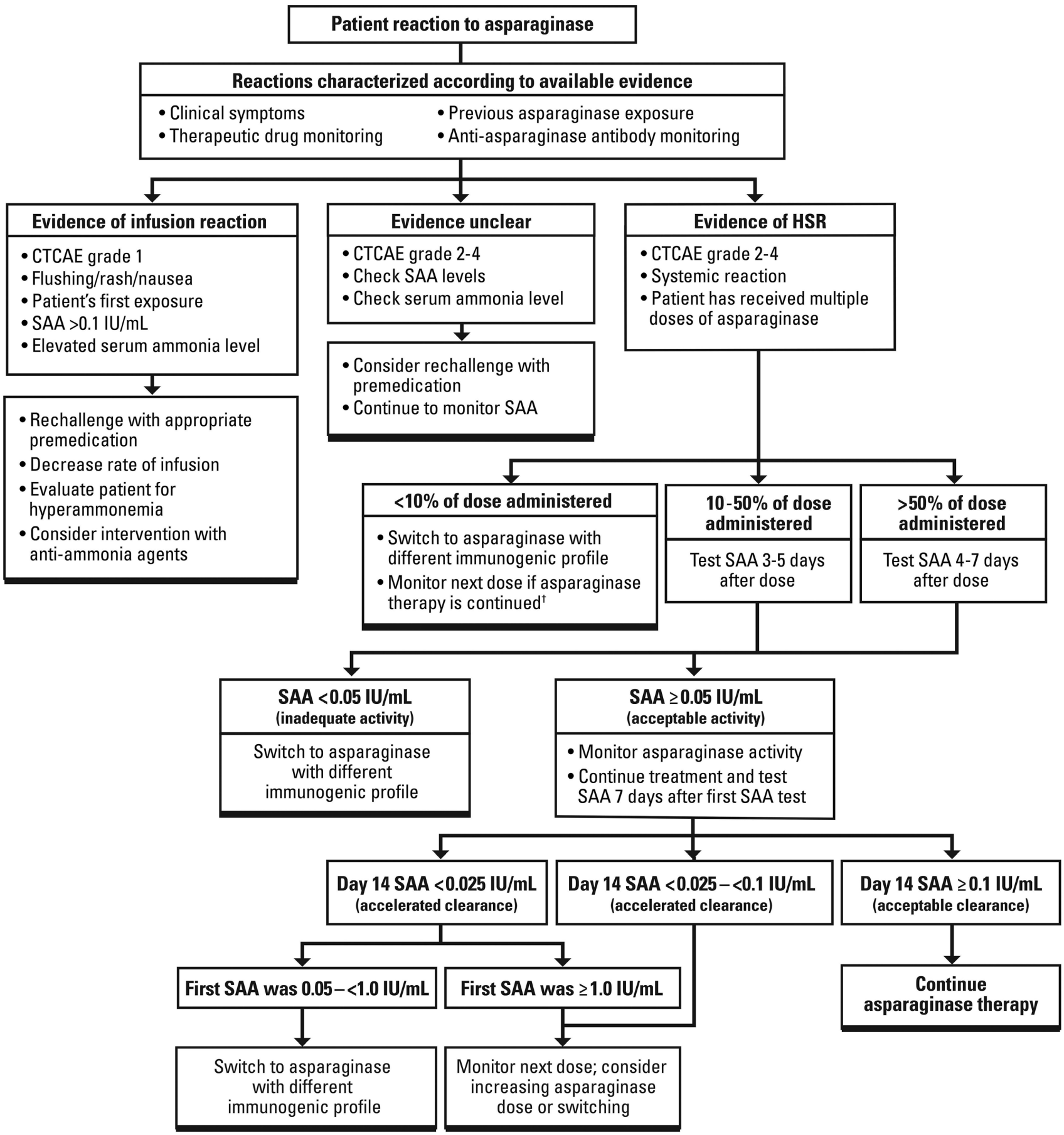

Figure 2. Treatment algorithm following reaction to asparaginase-based therapy. Adapted with permission from Bleyer *et al.*[62] CTCAE: Common Terminology Criteria for Adverse Events; HSR: hypersensitivity reaction; SAA: serum asparaginase activity.

properties of ASNase.[69,72]

Prophylaxis and treatment

Studies assessing thromboprophylactic strategies in adult patients receiving ASNase have produced conflicting results.[73] For example, Grace and colleagues[74] assessed the effect of implementing a prophylactic anticoagulation protocol for thromboembolic events or deaths in adult patients receiving pediatric-inspired ALL protocols. With a median follow-up of 52 months, patients receiving prophylactic anticoagulation experienced fewer thromboembolic events than patients not receiving prophylaxis, and no deaths were attributed to thromboembolic events or anticoagulation therapy. Paradoxically, Orvain and colleagues[72] reported a significant increase in the occurrence of thromboembolic events in patients who received prophylactic heparin; because of methodological concerns, the investigators cautioned that generalization of this observation is limited. Thromboprophylaxis could be protocol dependent, particularly those protocols incorporating frequent or intensified ASNase administration (e.g., DCFI Consortium regimens). The potential benefit of thromboprophylaxis in children

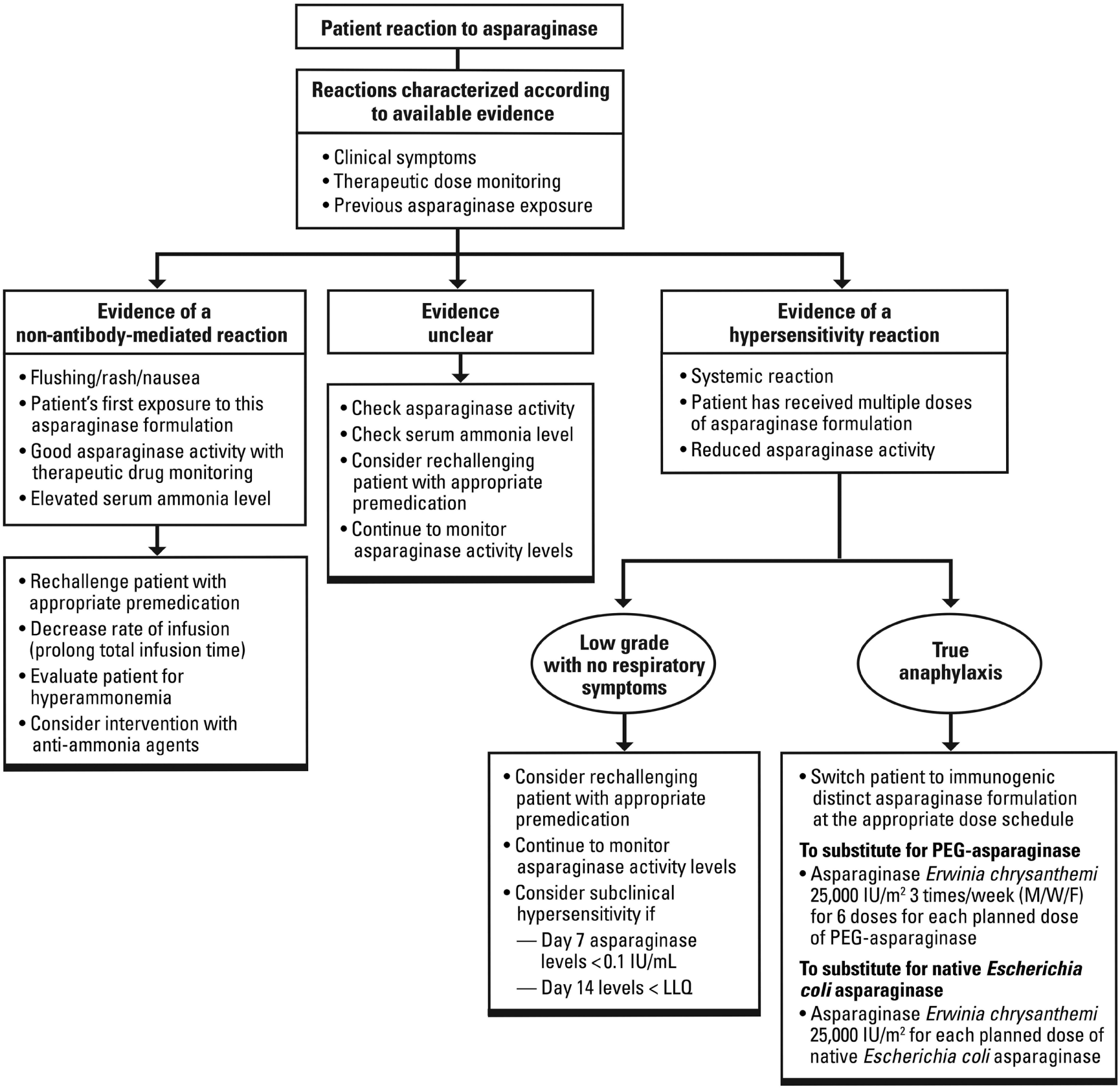

Figure 3. Clinical pathway to classification and management of adverse events to asparaginase. Adapted with permission from Burke *et al.*[56] LLQ: lower limits of quantification; M/W/F: Monday / Wednesday / Friday; PEG: pegylated.

Table 3. Panel consensus vote: thromboembolic and coagulation complications.

	Mean rating	Outlier	N of panelists
The standard of care for treating ASNase-induced thromboembolic complications is therapeutic anticoagulation; initiate anticoagulation per standard guidelines for specific venous thromboembolic events and continue throughout ASNase treatment.	8.6	0	12
In adults, the clinical utility of replacing AT during ASNase therapy to prevent thrombosis is of uncertain benefit and based on limited data.	8.5	0	12
The prophylactic administration of cryoprecipitate in patients receiving ASNase may increase the risk of thrombosis. The administration of cryoprecipitate should be limited to patients with active bleeding and not based solely on fibrinogen levels.	8.5	0	12
ASNase-induced thromboembolism, including CSVT, is not a contraindication for future ASNase dosing. With appropriate anticoagulation and resolution of symptoms, ASNase administration may be resumed in patients who experience these complications. Permanent discontinuation of ASNase for CNS thrombosis is reasonable when the risk of recurrent thrombosis is considered to outweigh that of leukemic relapse.	8.0	1	12
Data recommending routine thromboprophylaxis in adult ALL patients receiving ASNase are limited; however, it may be considered for patients at increased risk of thrombosis or who require frequent or intensified ASNase administration (e.g., DFCI Consortium regimens).	7.8	1	12

ALL: acute lymphoblastic leukemia/lymphoma; ASNase: asparaginase; AT: antithrombin; CNS: central nervous system; CSVT: cerebral sinocavernous thrombosis; DFCI: Dana-Farber Cancer Institute; N: number.

Table 4. Panel consensus vote: pancreatitis and metabolic complications.

	Mean rating	Outlier	N of panelists
Hypertriglyceridemia has been associated with ASNase therapy and is self-limiting. Because no clear association between ASNase-induced hypertriglyceridemia and pancreatitis has emerged, permanent discontinuation of ASNase in patients with hypertriglyceridemia is not warranted.	8.8	0	12
ASNase has been associated with an increased risk of ON. The mechanism for ON is unclear, but it may result from a pharmacokinetic/pharmacodynamic interaction with corticosteroids that increases exposure to corticosteroids.	8.3	0	12
For adults with symptomatic (clinical) and/or image-verified pancreatitis, permanent discontinuation of any ASNase formulation is reasonable because of high recurrence rates; however, ASNase can be safely administered to patients who develop chemical pancreatitis.	8.0	0	12

ASNase: asparaginase; N: number; ON: osteonecrosis.

remains inconclusive, despite the availability of RCT results. In the THROMBOTECT trial, which compared low molecular-weight heparin (LMWH), enoxaparin, or activity-adapted antithrombin (AT) with unfractionated heparin (UFH) as thromboprophylaxis during ALL induction chemotherapy, thromboembolic events occurred in 4.4% of all participants, with significantly lower rates in the enoxaparin (3.5%) and AT (1.9%) groups compared with the UFH (8%) group.[75] Importantly, no differences in hemorrhagic events, which was the primary safety outcome, were reported.[75] The international phase III PREVAPIX-ALL study compared prophylactic apixaban *versus* no anticoagulation therapy in children during induction therapy.[76] The investigators reported a 12% prevalence of thromboembolic events in the apixaban group *versus* 18% in the control group (P=0.08); the reduced prevalence was primarily attributed to increased incidence of non-fatal, asymptomatic deep vein thrombotic events in the control group.[76] Because of the conflicting and limited data to support routine thromboprophylaxis, the panelists agreed that routine thromboprophylaxis in adults may not be needed but should be considered in patients at increased risk of thrombosis.

Because ASNase reduces AT levels and AT can delay thrombin generation, AT replacement therapy has been studied as a thromboembolic preventive strategy.[39,69] Chen and colleagues[77] conducted a retrospective analysis of patients (N=75) receiving an ASNase-based ALL regimen who did and did not receive AT prophylaxis, and reported no significant difference in the occurrence of thromboembolic events between groups. Although not powered to show efficacy, a larger clinical study conducted by Orvain and colleagues[72] reported no significant difference in the occurrence of thromboembolic events between patients (N=784) receiving or not receiving prophylactic AT supplementation.[72] Because clinical data have reported: 1) similar thrombosis recurrence rates in patients who received AT and patients who did not; 2) significant discrepancies in AT administration schedule cut-offs and target levels; and 3) the absence of supportive data in RCT, the panelists agreed that current data do not support the routine use of AT prophylaxis to prevent thrombosis during concomitant ASNase therapy.[69] Although evidence-based guidelines for treating ASNase-induced thrombosis are lacking, several study results have reported successful treatment with standard anticoagu-

lant therapies, most commonly, LMWH and, more recently, direct oral anticoagulants (DOAC).[30,68,69,76] If possible, antithrombotic treatment should continue until all doses of PEG-ASNase have been administered.[30,69] To date, studies investigating universal thromboprophylaxis strategies have yielded sub-optimal results; ongoing research using validated risk prediction models is underway to identify patients who would and would not benefit from intensified thromboprophylaxis in this setting.[78]

Rechallenge

Although the results of several case studies have reported recurrent thrombosis in patients receiving ASNase, recent results show successful rechallenge of ASNase in patients who developed thrombosis in an earlier cycle.[71] For example, Aldoss and colleagues[29] assessed adult patients receiving a pediatric-inspired ALL regimen; patients who experienced a thromboembolic event were able to continue ASNase treatment without recurrence. Furthermore, Grace and colleagues[70] reported that most patients (77%) who had ASNase therapy withheld for several weeks while receiving anticoagulant therapy successfully restarted ASNase therapy, with 70% receiving at least 85% of their intended doses.[70] Skipper and colleagues[79] evaluated patients who developed CSVT while receiving ASNase-based ALL therapy and showed that re-exposure to ASNase with concomitant anticoagulation could be administered safely.

Because the risk of ALL relapse from early discontinuation of ASNase therapy outweighs the risk of recurrent thrombotic complications, the panelists agreed that continuing ASNase treatment with concurrent antithrombotic therapy is reasonable.[30,80]

Pancreatic and metabolic complications

ASNase-associated hypertriglyceridemia, and other metabolic complications are associated with a low mortality rate and are often reversible; pancreatitis, however, can result in significant morbidity and even death.[81-83] Regarding pancreatic/metabolic complications, 3 statements reached objective clinical consensus (Table 4).

Pancreatitis

Pancreatitis, a well-documented toxicity of ASNase treatment, is more likely to occur in older patients.[30,80,81,84-86] The dosage and route, origin, and type of ASNase do not seem to affect the risk of developing ASNase-associated pancreatitis; however, the intensity of and prolonged exposure to ASNase does increase the risk.[2,84-87] An increased risk of pancreatitis has also been observed in children with

Table 5. Panel consensus vote: dosing.

	Mean rating	Outlier	N of panelists
TDM of ASNase enzymatic activity detects silent inactivation, reduces masking of inactivation associated with premedications, may help distinguish true HSR from IRR, and could be used to ensure adequate dosing in patients receiving reduced doses of ASNase. A serum ASNase level ≥0.1 IU/mL detected 14 days after ASNase administration is generally considered therapeutic, because it sufficiently depletes the asparagine amino acid.	8.2	1	12
Dose capping of PEG-ASNase at 3,750 IU (1 vial) to mitigate toxicity is routine in adult patients, although data to support this approach are limited.	8.0	0	12
A reduction in the pediatric dose of PEG-ASNase (from 2,500 IU/m^2 to 1,000-2,000 IU/m^2) adequately depletes serum asparagine for 14 days or longer in adult patients with ALL.	8.0	1	12
For older adult patients and adults with increased BMI (>30 mg/m^2) more likely to experience ASNase-related toxicities, including hyperbilirubinemia, thrombosis, and death, ASNase dose reduction may be considered.	7.0	1	12

ALL: acute lymphoblastic leukemia; ASNase: asparaginase; AT: antithrombin; BMI: body mass index; HSR: hypersensitivity reaction; IRR: infusion-related reaction; PEG-ASNase: pegylated-asparaginase; TDM: therapeutic drug monitoring.

Table 6. Incidence of grade 3/4 hyperbilirubinemia and transaminase elevation in select studies.[7]

Study	≥Grade 3 transaminase elevation, N (%)	≥Grade 3 hyperbilirubinemia, N (%)
CALGB 10403	ALT: 158 (53.6) AST: 98 (33.2)	77 (26.1) -
DFCI	AST or ALT: 20 (22)	10 (11)
NOPHO2008	NR	5 (2.4)
UKALL14	ALT: 10 (14) AST: 4 (5)	17 (23) -

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CALGB: Cancer and Leukemia Group B; DFCI: Dana-Faber Cancer Institute; N: number of patients; NOPHO: Nordic Society of Paediatric Haematology; NR: not reported; UKALL14: United Kingdom Acute Lymphoblastic Leukemia 14 Trial.

a genetic predisposition, particularly children with genes that prolong trypsin activity or cause premature trypsin activation in the pancreas (e.g., *PRSS1*, *PRSS2*, *CPA2*, *RGS6*, *ULK2*).[83,86,88]

Chemical (or laboratory) pancreatitis occurs when serum lipase and amylase levels are elevated in asymptomatic patients.[30,89] ASNase therapy may be continued in these patients but with close laboratory monitoring.[30,47,89] Chemical pancreatitis has not been linked to long-term sequelae.[80] Conversely, clinical pancreatitis, with a reported incidence of 2-18%, occurs in patients who develop clinical symptoms (e.g., abdominal pain, nausea, vomiting) along with elevated serum lipase or amylase levels with or without image verification.[30,81,85] Administration of supportive care (e.g., intravenous hydration, analgesics and/or antibiotics, and, if needed, nasogastric decompression) should be initiated as soon as clinical pancreatitis signs and symptoms are observed.[30] Generally, these patients should not be rechallenged with ASNase because of high recurrence rates of pancreatitis (up to 63%), unless the risk of relapse is greater than the risk of recurrent pancreatitis.[30,80,85]

Osteonecrosis

Osteonecrosis usually manifests later in an ASNase course, often after maintenance therapy has been completed. The prevalence ranges from 1.6% to 45% in patients receiving ASNase and concomitant corticosteroids, primarily dexamethasone.[2,90,91] The risk of developing ON appears to be related to age, corticosteroid use, hyperlipidemia, and ASNase enzymatic activity levels. For example, Valtis and colleagues[91] showed that patients under 30 years of age had a significantly higher risk of ON (5-year cumulative prevalence of 21%) than patients 30-50 years of age (5-year cumulative prevalence of 8%; P=0.005).[91] The COG AALL0232 study, which included 3,154 patients (age, 1-30 years), showed higher rates of ON in patients aged ten years or older; a higher 5-year cumulative prevalence of ON was observed with dexamethasone compared with prednisone during induction therapy (24.3±2.3% *vs.* 15.9±2.0%, respectively, P=0.001).[92] Finally, Lynggaard and colleagues[87] evaluated ASNase enzymatic activity levels and the risk of ASNase-associated toxicities in children and reported an increased risk of ON in patients with elevated ASNase enzymatic activity levels (HR 1.36 per 100 IU/L increase in ASNase levels; P=0.02). Although the mechanism of ASNase-associated ON has not been clearly defined, the panelists agreed that an interaction between ASNase and corticosteroids plays a significant role.

Hypertriglyceridemia

Hypertriglyceridemia caused by ASNase therapy is transient and typically resolves after completion of ASNase therapy, despite a reported incidence of grade 3/4 hypertriglyceridemia in more than 50% of patients.[2,30,35,80,93] The results of clinical trials, case reports, systematic reviews and meta-analyses, which have included children and adolescents with ALL, have reported no clear association between hypertriglyceridemia and pancreatitis.[29,93-95] Therefore, the panelists agreed that dose modifications or discontinuation of ASNase in patients who develop hypertriglyceridemia is not warranted. If high-grade hypertriglyceridemia persists, fibrates are often prescribed to manage persistent hypertriglyceridemia;[93] interestingly, fibrates have the added advantage of preventing interference with biochemical test measurements - serum triglyceride levels greater than 1,000 mg/dL can clog laboratory devices.[30]

Table 7. Common symptoms of hypersensitivity and infusion-related reactions by body system.

Body system	Hypersensitivity reaction	Infusion-related reaction
Cardiovascular	Chest pain, palpitations, hypotension, tachycardia, bradycardia, arrhythmia, edema, ischemia or infection, cardiac arrest	Hypertension, hypotension, tachycardia
CNS	Dizziness, loss of consciousness	Headache (throbbing), confusion, loss of consciousness
Dermatologic	Pruritus, urticaria, local or diffuse erythema, conjunctival erythema, tearing, angioedema	Flushing, rash, diffuse erythema
Endocrine	Diaphoresis, fever, generalized feeling of warmth	Rigors, fever
GI	Nausea, vomiting, metallic taste, diarrhea, abdominal cramping, bloating	Nausea, vomiting
Genitourinary	Renal impairment	Incontinence, uterine cramping, pelvic pain
Musculoskeletal	Arthralgias, myalgias, tumor pain, hypotonia	Fatigue, hypotonia
Psychiatric	Anxiety, sense of impending doom	Anxiety, sense of impending doom
Respiratory	Cough, dyspnea, nasal congestion, rhinitis, sneezing, hoarseness, wheezing, chest tightness, hypoxemia, bronchospasms, reduced pulmonary expiratory flow, oropharyngeal or laryngeal edema, stridor, pulmonary infiltrates, cyanosis, acute respiratory distress syndrome	Dyspnea, tachypnea

CNS: central nervous system; GI: gastrointestinal.

Dosing

The optimal dose and frequency of PEG-ASNase for adults has yet to be clearly defined.[80] Effective asparagine depletion is associated with improved outcomes; therefore, ensuring consistent asparagine depletion is imperative.[14] The panel reached consensus on 4 statements related to ASNase-associated dosing in adults (Table 5).

Dosing and pharmacokinetics

The FDA-approved dose of PEG-ASNase in adults (age, >21 years) is 2,000 IU/m^2 rather than the 2,500 IU/m^2 dose commonly used in children (≤21 years old).[24] This decision was based on studies showing that lower PEG-ASNase doses (i.e., doses <2,500 IU/m^2) could achieve optimal asparagine depletion (i.e., ASNase enzymatic activity levels ≥0.1 IU/mL) in adult ALL patients.[28,39,96] For example, Lanvers-Kaminsky and colleagues[96] evaluated PEG-ASNase 500 IU/m^2 or 1,000 IU/m^2 during both induction and consolidation treatment phases; therapeutic ASNase levels were achieved at day 14 in 25% and 77% of patients, respectively, during induction, and in 59% and 96% of patients, respectively, during consolidation. Additionally, Patel and colleagues[28] showed a single dose of PEG-ASNase 1,000 IU/m^2 achieved therapeutic levels in 42 of 49 patients (86%) 14 days after administration. The panelists agreed that when initiating therapy for adult ALL patients, doses of 1,000 IU/m^2 to 2,000 IU/m^2 consistently produced therapeutic ASNase levels. However, an accepted algorithm to guide dose reductions or adjustments based on TDM is not available.

Empiric dose capping

Several studies have implemented dose capping (with a single 3,750 IU vial) as a strategy to reduce toxicities, especially in obese adult patients.[2,97,98] Baek and colleagues[97] compared toxicity rates between patients receiving dose-capped (N=28) *versus* non-capped (N=29) PEG-ASNase. Although not statistically significant, fewer all-grade and grade 3/4 AE and a lower rate of recurrent toxicities with rechallenge were observed in the dose-capped group. Conversely, the results of a retrospective study showed no significant differences in toxicity rates between patients who received a dose greater than 3,750 IU compared with patients receiving a flat dose of 3,750 IU or lower. Grade 3/4 toxicities were equal, and no differences were noted in the incidence of hepatotoxicity, pancreatitis, or thrombosis between the 2 groups.[89] While dose capping has become common practice, current clinical data may not support the hypothesis of fewer toxicities with a capped dose.[89]

Therapeutic drug monitoring and dosing

Therapeutic drug monitoring (i.e., ASNase enzymatic activity) is used to ensure optimal asparagine depletion, diagnose a clinical or silent HSR, and/or to distinguish between HSR and IRR.[49,99,100] While TDM is not routinely used to determine individualized dosing, it is recommended in patients receiving premedication to detect decreased ASNase activity or silent inactivation.[30,49] Checking for antibodies is unreliable because they are often not inactivating and monitoring asparagine levels for depletion is not practical in routine clinical practice. For further discussion of silent inactivation and TDM, please refer to *Hypersensitivity reactions* (see above).

The minimal ASNase enzymatic activity level necessary for complete serum asparagine depletion is currently under debate; target therapeutic levels ranging from as low as 0.02 IU/mL to as high as 0.4 IU/mL have been suggested.[39,47,49,100] In 2016, an expert panel conducted and published a comprehensive review about ASNase enzymatic activity level and asparagine depletion,[49] and concluded that a level of ≥0.1 IU/mL remains the target to achieve appropriate asparagine depletion.[49] A representative algorithm to guide TDM in patients receiving PEG-ASNase is shown in Figure 4.

Dose reduction in patients at high risk of toxicity

The incidence of ASNase-associated toxicities, such as hyperbilirubinemia or thrombosis, and death are potentially higher in older and obese (BMI > 30kg/m^2) patients; therefore, several studies have evaluated the benefits of PEG-ASNase dose reductions to decrease the incidence of toxicities in these populations. Derman and colleagues[38] reported that reduced PEG-ASNase doses (i.e., ≤1,000 IU/m^2) resulted in fewer grade 3/4 toxicities in patients with

Table 8. Recommended duration and dosing to replace long-acting ASNase dose.

ASNase regimen to be replaced	Replacement options		
	Erwinia chrysanthemi[102]	Recombinant *Erwinia chrysanthemi*[103]	
	-	Dosing option 1: 25 mg/m^2 IM every 48 hr	Dosing option 2: 25 mg/m^2 IM on Monday and Wednesday 50 mg/m^2 IM on Friday
2-wk PEG-ASNase coverage[24]	25,000 IU/m^2 3 times/wk for 6 doses for each planned PEG-ASNase dose	Replace 1 dose of PEG-ASNase with 7 doses	Replace 1 dose of PEG-ASNase with 6 doses
3-wk calaspargase coverage[104a]	-	Replace 1 dose of calaspargase with 11 doses	Replace 1 dose of calaspargase with 9 doses

ASNase: asparaginase; hr: hours; IM: intramuscularly; PEG-ASNase: pegylated-asparaginase; wk: week. aCalaspargase is approved by the US Food and Drug Administration only for patients ≤21 years of age.

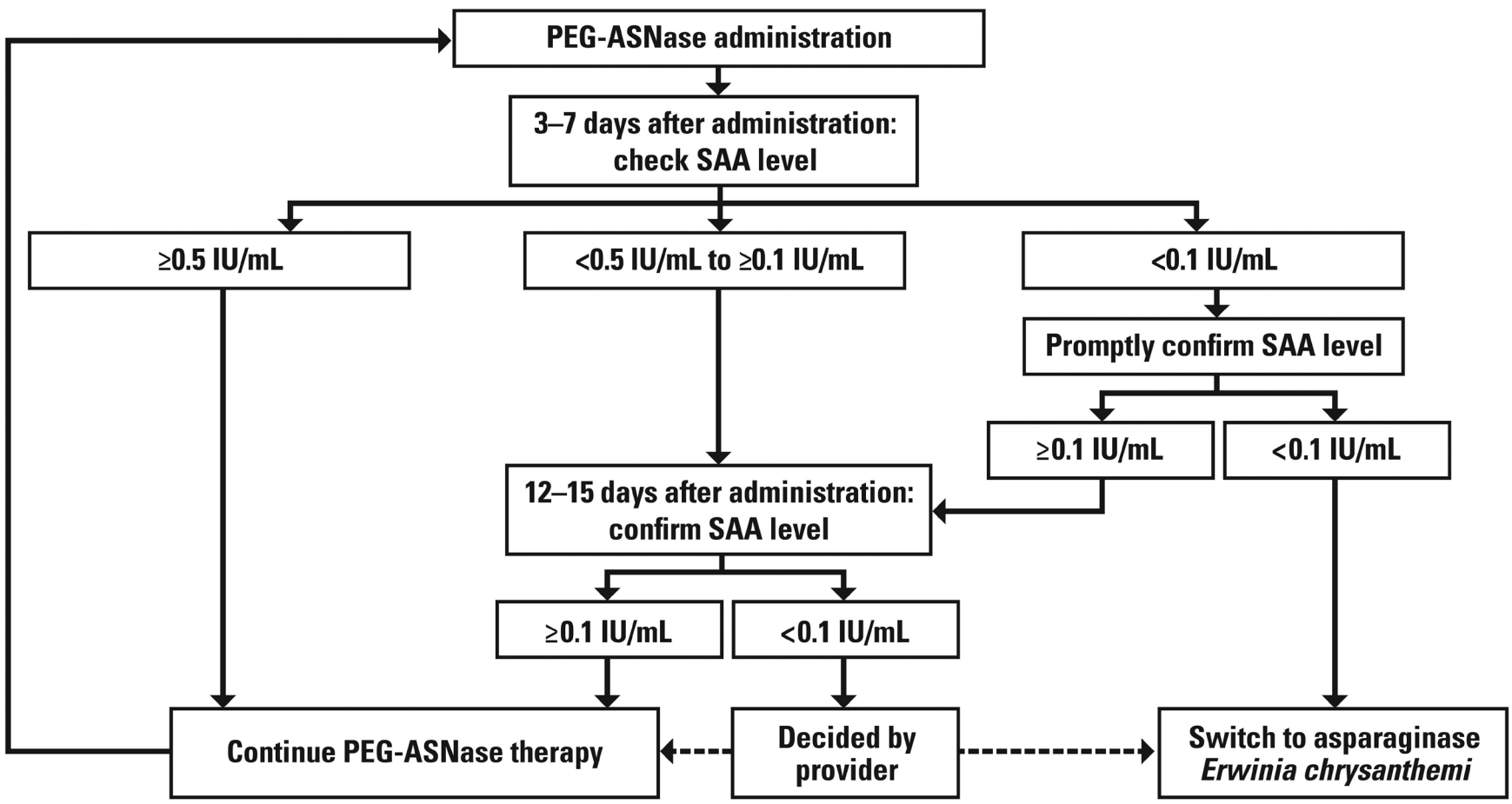

Figure 4. Pegylated asparaginase therapeutic drug monitoring algorithm. Adapted with permission from Douer.[19] PEG-ASNase: pegylated asparaginase; SAA: serum asparaginase activity.

a BMI of 25 kg/m^2 or greater and patients older than 40 years. In a retrospective review by Daley and colleagues[101] of 60 patients 40 years of age or older (median, 53 years), most patients 60 years and older (N=20) received a reduced dose (1,000 IU/m^2 [N=15] and 500 IU/m^2 [N=2]), whereas all but 2 patients aged 40 to 59 years received PEG-ASNase 2,000 IU/m^2. The younger cohort that received the higher dose experienced more grade 3/4 hyperbilirubinemia and hypertriglyceridemia, suggesting that reduced doses of PEG-ASNase in older patients (e.g., ≥60 years) would allow more doses to be administered while maintaining safety and the manageability of toxicities.[101]

Because of the lack of a generally accepted algorithm to guide routine TDM testing and TDM-directed dosing, the number of patients who do not achieve the target ASNase activity level when receiving lower doses of ASNase remains unknown.

Conclusions

Although survival rates have risen dramatically for AYA and adult patients receiving pediatric-inspired chemotherapy regimens containing multiple doses of ASNase compared with standard chemotherapy regimens containing no or less ASNase, there is still a reluctance to prescribing PEG-ASNase in adult ALL patients. This hesitancy may be related to: 1) a higher incidence and/or severity of PEG-ASNase–related AE in adults (compared with children); and 2) medical oncologists not being familiar with using ASNase in the treatment of adult ALL patients (as ALL is rarely diagnosed in adults).

Despite a higher incidence and, in some cases, higher grade of AE or AE not commonly observed in children, these toxicities are usually reversible and manageable, and may not warrant dose reductions, delays, or discontinuations. However, dose reductions to <2,000 IU/m^2 may be considered to reduce toxicity risk in high-risk populations (i.e., older patients, patients with high BMI, hepatosteatosis) without jeopardizing efficacy in the vast majority of patients. Because maintenance of ASNase therapeutic serum levels is required to maximize clinical outcomes, creating strategies that maximize the dose intensity of these treatment regimens is important. These consensus statements represent an update to the 2011 publication by Stock *et al.*,[25] employing a Delphi methodology to systematically achieve expert consensus on best practices for managing AE in AYA and adult patients receiving ASNase therapy. By combining evidence-based findings with current expert opinion, the strategies provided aim to guide clinical practice and improve patient outcomes. Implementing these strategies will help health care providers, especially providers unfamiliar with using pediatric-inspired ALL regimens, to manage AE and optimize treatment outcomes.

Disclosures

EC is a paid consultant for Servier Pharmaceuticals, and sits on the Advisory Boards of Jazz Pharmaceuticals and

KiTE Pharmaceuticals. MRL is a paid consultant for Servier Pharmaceuticals Novartis, has received research funding from and sits on the Advisory Board of AbbVie, and sits on the Advisory Boards of Jazz Pharmaceuticals and Pfizer. HA is a paid consultant for Servier Pharmaceuticals. IA is a paid consultant for Servier Pharmaceuticals, Amgen, and Pfizer, sits on the Advisory Boards of Jazz Pharmaceuticals, Takeda Pharmaceuticals, Pfizer, KiTE Pharmaceuticals, Wugen, and Syndax Pharmaceuticals, and has received research support from AbbVie and MacroGenics. PWB is a paid consultant for Servier Pharmaceuticals, and has received research funding from Takeda. RDC is a paid consultant for and has received research funding from Servier Pharmaceuticals, has received research funding from and sits on the Advisory Boards of Amgen, KiTE Pharmaceuticals, and Pfizer, has received research funding from Incyte and Vanda Pharmaceuticals, sits on the Advisory Board of Jazz Pharmaceuticals, sits on the Advisory Board of Autolus Therapeutics and is member of their data review committee, and is a member of the data review committee of Pepromene Bio. SEK is a paid consultant for Servier Pharmaceuticals and Jazz Pharmaceuticals. AJP is a paid consultant for and sits on the Advisory Board and Speakers Bureau of Servier Pharmaceuticals, is a paid consultant for Pfizer, Sanofi Adventis, and AbbVie, and sits on the Advisory Board of Rigel Pharmaceuticals. CUR is a paid consultant for Servier Pharmaceuticals. KS is a paid consultant for and sits on the Speakers Bureau of Servier Pharmaceuticals, is a paid consultant for, has received research funding from, sits on the Speakers Bureau, and holds stocks in Novo Nordisk, and sits on the Speakers Bureau and Advisory Boards of Jazz Pharmaceuticals, Illumina, and Amgen. JW is a paid consultant for and has received research funding from Servier Pharmaceuticals, and has received research funding from Amgen. DD is a paid consultant for and sits on the Speakers Bureau of Servier Pharmaceuticals, sits on the Speakers Bureau of Amgen, and is a paid consultant for Jazz Pharmaceuticals.

Contributions

EC was the panel chairperson and wrote the manuscript. MRL and DD were the panel co-chairpersons and wrote the manuscript. HA, IA, PWB, RDC, SEK, AJP, CUR, KS and JW were panel members and wrote the manuscript.

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