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Hypersensitivity to PEG-Asparaginase and Desensitization Strategies in Pediatric Acute Lymphoblastic Leukemia: A Narrative Review

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Abstract

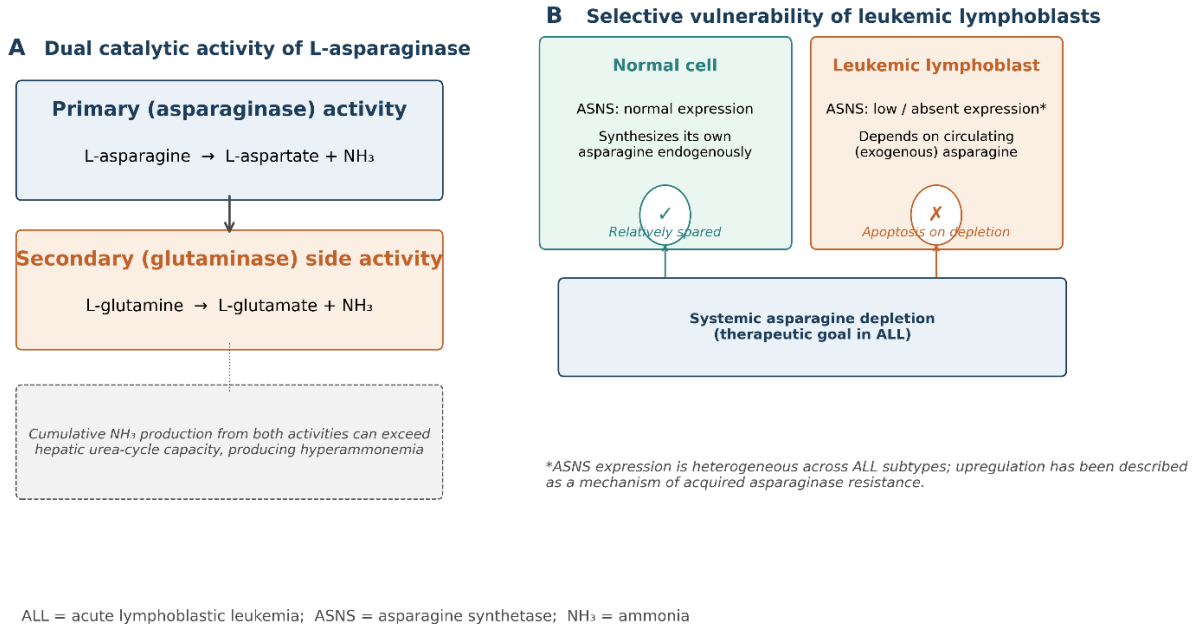
This narrative review synthesizes current evidence on incidence, the immunologic basis of hypersensitivity—including the recently clarified role of anti-PEG (rather than anti-protein) antibodies—genetic predisposition, differential diagnosis from asparaginase-associated hyperammonemia, therapeutic drug monitoring (TDM), and desensitization. Hypersensitivity to PEG-asparaginase is a frequent, clinically consequential complication of pediatric acute lymphoblastic leukemia therapy that can compromise treatment exposure and survival. Recombinant Erwinia asparaginase (crisantaspase) is now licensed in the United States (2021) and the European Union (2023) for hypersensitive patients; however, cost, reimbursement, and local availability continue to limit access in many settings. Therefore, strategies for the safe continuation of PEG-asparaginase remain clinically relevant for reasons other than supply shortages alone. Using Ponte di Legno Toxicity Working Group definitions, reactions are classified as clinical allergy, allergic-like reaction, or silent inactivation, each requiring a different response; TDM is central to making this distinction. Genetic susceptibility loci (HLA class II haplotypes, CNOT3, GRIA1) remain investigational, with moderate effect sizes and inconsistent replication, and are not yet suitable for clinical decision-making. An adapted multi-step desensitization protocol can preserve therapeutic enzyme activity in appropriately selected patients; however, tolerance is temporary and dose-specific and requires repeat TDM after every dose. **Conclusion.** A personalized, multidisciplinary approach—integrating TDM, realistic assessment of access to alternative formulations, and (where available) genetic data—is recommended to optimize treatment safety and antileukemic efficacy.

Key Words: Acute Lymphoblastic Leukemia ▪ PEG-Asparaginase ▪ Hypersensitivity ▪ Desensitization ▪ Therapeutic Drug Monitoring.

Introduction

Asparaginase—a bacterial hydrolase obtained from Escherichia coli or from Dickeya dadantii (formerly classified as Erwinia chrysanthemi) (1) – is an essential component of modern treatment protocols for pediatric acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (2). It depletes circulating asparagine, on which leukemic lymphoblasts depend because of their characteristically low or absent expression of asparagine synthetase (ASNS), while normal cells synthesize asparagine endogenously and are relatively spared (Figure 1); ASNS expression is, however, heterogeneous across ALL subtypes, and its upregulation is a described mechanism of acquired resistance. Beyond this primary reaction, asparaginase also has a secondary glutaminase side-activity that contributes disproportionately to asparaginase-associated hyperammonemia (3, 4), discussed below.

Terminology for the available preparations is used inconsistently in the literature and is defined here at first use. Pegaspargase ("PEG-asparaginase") is E. coli asparaginase conjugated to polyethylene glycol (PEG) to prolong plasma half-life; calaspargase pegol is a related PEGylated E. coli-derived formulation with a more stable



ALL = acute lymphoblastic leukemia; ASNS = asparagine synthetase; NH_3 = ammonia

Figure 1. Dual catalytic activity of L-asparaginase and its clinical rationale in pediatric acute lymphoblastic leukemia. (A) L-asparaginase hydrolyzes L-asparagine to L-aspartate and ammonia (primary activity) and also hydrolyzes L-glutamine to L-glutamate and ammonia (secondary glutaminase activity); cumulative ammonia from both reactions can exceed hepatic urea-cycle capacity and produce hyperammonemia. (B) Leukemic lymphoblasts, which have low or absent asparagine synthetase (ASNS) expression, depend on exogenous asparagine and undergo apoptosis on its depletion, while normal cells synthesize asparagine endogenously and are relatively spared. ASNS expression is heterogeneous across ALL subtypes and its upregulation is a described resistance mechanism.

linker allowing a longer dosing interval; and crisantaspase is asparaginase derived from Dickeya dadantii, available as a native product and, since 2021–2023, as a recombinant product (JZP-458, marketed as Rylaze in the United States and Enrylaze in the European Union).

Despite its efficacy, asparaginase treatment is frequently complicated by hypersensitivity, which may force dose modification or discontinuation and thereby worsen outcomes. For many years the only licensed alternative for pegaspargase-hypersensitive patients was native crisantaspase, whose supply has been affected by recurring shortages (5, 6). This has changed: recombinant crisantaspase was approved by the US FDA in June 2021 and the European Commission in September 2023, on the basis of the pivotal AALL1931 study, specifically for patients with hypersensitivity or silent inactivation to E. coli-derived asparaginase (7-9). Even where recombinant crisantaspase is licensed, however, cost, reimbursement, and local supply arrangements mean many health systems cannot access it as readily as its licensing status suggests—so that strategies for safely continuing PEG-asparaginase remain clinically important, for a narrower reason than before.

This review synthesizes current evidence on PEG-asparaginase hypersensitivity: its immunologic basis (including anti-PEG immunogenicity), genetic predisposition, differential diagnosis, TDM, and desensitization, with emphasis on centers where access to alternatives is limited by cost or availability rather than licensing status. PubMed was searched (2008–June 2026; terms: asparaginase, pegaspargase, hypersensitivity, desensitization, anti-PEG antibod*, therapeutic drug monitoring, combined with acute lymphoblastic leukemia), supplemented by hand-searching of reference lists and Ponte di Legno Toxicity Working Group consensus statements; as a narrative rather than systematic review, selection prioritized clinical relevance over exhaustive coverage.

Hypersensitivity to PEG-asparaginase

Incidence and Clinical Features

Hypersensitivity reactions to PEG-asparaginase range from mild, self-limiting allergic manifestations (urticaria, erythema, pruritus) to severe, potentially life-threatening anaphylaxis, graded according to Common Terminology Criteria for Adverse Events (CTCAE); grade ≥3 denotes a reaction that is prolonged, recurs after initial improvement, or requires hospitalization for clinical sequelae, up to life-threatening anaphylaxis (grade 4) (10). Reported incidence rates vary considerably across studies, likely reflecting differences in route of administration, monitoring intensity, grading criteria, and patient populations (11-13).

In a cohort of 598 children enrolled in the St. Jude Children's Research Hospital Total XVI protocol, PEG-asparaginase caused significantly fewer allergic reactions than native L-asparaginase (13.5% vs. 41.2%); however, reactions to PEG-asparaginase were considerably more likely to be severe, with 71.6% reaching grade 3 or 4 compared with only 14.2% for native L-asparaginase. Furthermore, anti–L-asparaginase antibodies demonstrated a stronger inhibitory effect on asparaginase activity than anti–PEG-asparaginase antibodies (14).

A systematic review and meta-analysis reported a higher incidence of hypersensitivity with intravenous (IV) compared to intramuscular (IM) administration (11), a finding corroborated by a large Children's Oncology Group (COG) analysis of 54,280 PEG-asparaginase doses (13). However, IV administration is now the preferred route in most contemporary protocols, as it is associated with lower rates of injection-site reactions and allows objective real-time monitoring. A multigroup meta-analysis by the Ponte di Legno Toxicity Working Group of 5,880 patients receiving PEG-asparaginase as first-line treatment found an overall hypersensitivity incidence of 2% during induction and 8% during post-induction therapy, with initiation of PEG-asparaginase in post-induction and a higher number of PEG-asparaginase-free intervals identified as risk factors (15); consistent with this, a subsequent randomized trial found that continuous, uninterrupted PEG-asparaginase dosing significantly reduced hypersensitivity reactions compared with an interrupted schedule (16).

Hypersensitivity reactions—particularly those leading to asparaginase discontinuation—have been associated with inferior event-free survival in pediatric ALL (6), a finding that underscores the critical importance of preserving adequate asparaginase exposure throughout treatment and that motivates the differential-diagnosis, monitoring, and desensitization strategies discussed below.

A Framework for Classifying Asparaginase Hypersensitivity

Reported incidence figures across studies are difficult to compare because they have historically used heterogeneous, often purely clinical definitions of "hypersensitivity." The Ponte di Legno Toxicity Working Group addressed this directly with a Delphi-consensus classification (17) that distinguishes three phenomena, summarized in Table 1: clinical allergy (symptoms of allergy, always accompanied by inactivated/undetectable asparaginase activity), allergic-like reaction (symptoms occurring with preserved enzyme activity), and silent inactivation (undetectable or sub-therapeutic enzyme activity without any clinical symptoms). Only the first and third categories reflect true immune-mediated neutralization of the drug; the second is not thought to reflect loss of drug exposure and, per Ponte di Legno guidance, does not by itself require a change in asparaginase formulation. Adopting this framework—rather than "hypersensitivity" as an undifferentiated clinical label—is essential for interpreting the TDM, genetic, and

Table 1. Ponte di Legno Toxicity Working Group Classification of Asparaginase hypersensitivity (17)

Category	Clinical symptoms	Asparaginase activity
Clinical allergy	Present	Undetectable / inactivated
Allergic-like reaction	Present	Preserved
Silent inactivation	Absent	Undetectable / inactivated

desensitization literature discussed in the remainder of this review, and we use it throughout.

Anti-PEG *antibodies* and the Immunogenicity of PEGylation

A dedicated discussion of anti-PEG immunogenicity is necessary for a review focused specifically on the PEGylated formulation, because the target of the immune response—and not merely its magnitude—differs from that seen with native asparaginase. Analysis of the St. Jude Total XVI cohort showed that for pegaspargase, anti-PEG antibodies, not anti-asparaginase (anti-protein) antibodies, were the predominant component (96%) of the antibody response, and that anti-PEG-ASP status was significantly associated with accelerated drug clearance (14). This contrasts with native (non-PEGylated) asparaginase, where the bacterial protein itself is the dominant epitope. This distinction has several practical implications:

- The Introduction's traditional claim that PEGylation "reduces immunogenicity" is only partly accurate: PEGylation reduces recognition of the bacterial protein backbone, but introduces a new immunogenic target (the PEG polymer itself) to which patients can form antibodies independently of any prior asparaginase exposure.
- Pre-existing anti-PEG antibodies—which can arise from prior exposure to other PEGylated therapeutics or from PEG-containing consumer products—provide a plausible mechanism for accelerated blood clearance and silent inactivation on first exposure to PEG-asparaginase, before any clinically apparent reaction has occurred.
- Because calaspargase pegol shares the same PEG moiety (conjugated via a different, more hydrolytically stable linker) attached to the same E. coli asparaginase backbone, anti-PEG antibodies generated against pegaspargase would be expected, on immunologic grounds, to cross-react with calaspargase pegol; this has direct implications for sequencing decisions when switching between the two PEGylated products.
- Whether desensitization—a technique developed for classical IgE-mediated protein and small-molecule allergens—can be expected to induce comparable temporary tolerance against a polymer epitope such as PEG is not established. This is a genuine gap in the literature rather than a settled question, and it is one of the areas we highlight under Future research perspectives, below.

Differential Diagnosis: Hyperammonemia versus Hypersensitivity

Hyperammonemia is a recognized adverse effect of asparaginase therapy and may clinically mimic hypersensitivity reactions, representing an important diagnostic challenge. As detailed in Figure 1, the mechanism involves both the primary asparaginase reaction and the enzyme's secondary glutaminase side-activity; with repeated asparaginase administrations, cumulative ammonia production may exceed hepatic urea cycle capacity, resulting in systemic hyperammonemia (3, 4).

Symptoms such as nausea, vomiting, rash, peripheral edema, and neurological changes may be common to both conditions, potentially leading to misclassification and inappropriate clinical decisions. Prompt measurement of serum ammonia, careful clinical assessment, and consideration of temporal relationships relative to asparaginase administration are essential for accurate differential diagnosis. Intradermal skin testing has limited predictive value in this setting, with both false-positive and false-negative results well documented, and a positive test does not reliably distinguish clinical allergy from allergic-like reaction or silent inactivation; an acutely elevated serum tryptase, when obtained within 1–2 hours of the reaction, can support a mast-cell/IgE-mediated mechanism but does not replace TDM for guiding subsequent management. Key distinguishing features are summarized in Table 2.

Table 2. Differential Diagnosis Between Peg-asparaginase Hypersensitivity and Asparaginase-associated Hyperammonemia

Feature	Hypersensitivity	Hyperammonemia
Onset	During/shortly after infusion	Variable; may be delayed
Skin manifestations	Common (urticaria, erythema)	Rare or absent
Respiratory symptoms	Possible (bronchospasm, dyspnoea)	Usually absent
Hemodynamic instability	Possible (anaphylaxis)	Rare
Gastrointestinal symptoms	Possible	Common (nausea, vomiting)
Neurological symptoms	Rare	Common (encephalopathy, altered consciousness)
Serum ammonia level	Usually normal; mild asymptomatic elevation can occur with asparaginase itself and does not alone indicate hyperammonemia syndrome	Elevated
Response to antihistamines/ corticosteroids	Usually good	Limited
Clinical implication	Discontinuation / switch / desensitization	Supportive care (hydration, lactulose, dietary protein restriction, nitrogen-scavenging agents such as sodium phenylbutyrate/benzoate, arginine, and, in severe cases, renal replacement therapy); asparaginase need not usually be permanently withdrawn

Genetic Predisposition

Accumulating evidence indicates that genetic factors contribute to inter-individual susceptibility to PEG-asparaginase hypersensitivity, although—as emphasized throughout this section—no genetic marker is currently validated for prospective clinical decision-making. A genome-wide association study (GWAS) in the NOPHO ALL2008 cohort identified a variant in the CNOT3 gene (rs73062673) associated with PEG-asparaginase allergy, together with independent signals in the HLA region near HLA-DQA1 and TAP2 (18). CNOT3 has been shown to regulate HLA transcription, providing a plausible biological link between this locus and the HLA associations described below. Separately, and using different cohorts and study designs, the HLA class II haplotype DRB1*07:01–DQA1*02:01–DQB1*02:02 has been associated with markedly increased hypersensitivity risk. This association was first described for HLA-DRB1*07:01 alone in patients of European ancestry treated with a mixture of native and PEGylated asparaginase (odds ratio 1.64 for hypersensitivity, 2.92 for anti-asparaginase antibodies) (19), refined to the specific three-locus haplotype in an independent cohort (odds ratio approximately 2–3 for the individual alleles) (20), and subsequently shown, in a GWAS restricted to hypersensitivity reactions specifically against the PEGylated preparation, to comprise the three top-associated alleles genome-wide (21). Collectively, these odds ratios—generally in the range of 1.6 to 3—indicate a real but moderate effect size, well short of the discriminative power needed for pre-treatment genotype-guided decisions; this qualification applies to all genetic associations discussed in this section, including those described below.

Rajić et al. reported that single-nucleotide polymorphisms in the GRIA1 gene—encoding the ionotropic glutamate receptor subunit GluA1, at a locus previously linked to asthma and atopy—are associated with increased risk of asparaginase hypersensitivity in a Slovenian cohort of children with ALL (22), a finding that had also been reported in the original discovery GWAS. This association has not, however, been consistently replicated: an independent Hungarian cohort found no association between the same GRIA1 variant and hypersensitivity to E. coli-derived asparaginase (20), and a more recent independent replication attempt in an Ethiopian cohort likewise found no association for GRIA1, CNOT3, or NFATC2 variants.

GRIA1 should therefore currently be regarded as a candidate rather than a confirmed susceptibility locus, and pharmacogenomic profiling for any of the loci discussed in this section remains investigational; its potential future role is prospective identification of high-risk patients, contingent on validation in larger and more diverse populations before any change to clinical practice.

Clinical Significance of Hypersensitivity

Beyond the survival association already noted, the pharmacodynamic rationale is worth making explicit: because sustained asparagine depletion throughout induction and consolidation—not merely peak drug exposure—is necessary for optimal antileukemic efficacy, any interruption of asparaginase therapy is potentially consequential, whether it arises from overt clinical allergy, from allergic-like reactions that prompt unnecessary discontinuation despite preserved enzyme activity, or from undetected silent inactivation.

Therapeutic Drug Monitoring of Asparaginase Activity

Therapeutic drug monitoring (TDM) of asparaginase enzyme activity is an important tool for optimizing individualized treatment. A widely accepted therapeutic threshold is a nadir activity ≥0.1 IU/mL, and PEG-asparaginase has a prolonged half-life (approximately 5–7 days in asparaginase-naïve patients), enabling nadir activity measurements that reflect sustained drug exposure (23). Some debate persists regarding the optimal nadir threshold and the precise timing of sampling (commonly day 7 versus day 14 post-dose, or use of the lower limit of quantification rather than a fixed 0.1 IU/mL cut-off), and practice therefore varies somewhat between cooperative groups (15, 24).

In our setting, routine TDM has been implemented as an integral component of asparaginase management. Applying the Ponte di Legno framework above, it enables discrimination between clinical allergy, allergic-like reaction, and silent inactivation—a distinction that symptom-driven clinical evaluation alone cannot provide—and directly informs individualized dose adjustment or prompt switching of asparaginase formulations. Systematic use of TDM shifts clinical decision-making from symptom-driven responses toward evidence-based therapeutic optimization, thereby allowing more precise identification of patients who are appropriate candidates for desensitization while avoiding unnecessary or ineffective interventions (23, 24).

Desensitization to PEG-asparaginase

Rationale and Patient Selection

In clinical settings where alternative asparaginase formulations are unavailable or inaccessible—because of cost, reimbursement, or local supply, rather than the absence of a licensed product—desensitization represents a strategy for continuing PEG-asparaginase therapy in patients with confirmed clinical allergy (5, 25-27). Desensitization is based on the gradual administration of incrementally increasing doses or concentrations of the drug, with the aim of inducing temporary immunologic tolerance at the effector-cell level and thereby reducing the clinical expression of allergic reactions; whether this classical mast-cell desensitization model applies equally well to an anti-PEG (rather than anti-protein) antibody response is not established, as noted above.

Patient selection is a critical determinant of procedural safety and success and should be performed in a monitored clinical setting—typically a specialized oncology or intensive care unit—that allows continuous observation and immediate intervention. Close collaboration between the treating hematologist, an allergist, and, when necessary, an intensivist is strongly recommended. TDM should be integrated into the decision-making process: patients with confirmed silent inactivation are unlikely to benefit from desensitization and should instead be switched to an alternative formulation if accessible.

Desensitization has traditionally been reserved for patients without a prior history of life-threatening anaphylaxis, a more conservative threshold than is applied in desensitization practice for other drug classes (e.g., platinum agents, beta-lactams), where desensitization is used precisely in patients with severe IgE-mediated reactions. This more cautious approach in the asparaginase literature likely reflects the historical availability of an alternative formulation (native crisantaspase) for the most severe reactors, together with a comparatively limited evidence base in this specific population, rather than a demonstrated biological reason why severe reactors cannot be safely desensitized; as experience accumulates (25-28), including recent reports of successful desensitization to recombinant crisantaspase itself in patients who developed hypersensitivity to that product (28), this threshold may reasonably be expected to evolve, and institutions should weigh their own experience and resources rather than treat prior severe anaphylaxis as an absolute contraindication.

Premedication

Premedication is initiated 1–2 hours before the start of desensitization and typically includes an H1 antihistamine (e.g., diphenhydramine 1 mg/kg, maximum 50 mg IV), an H2 antihistamine (e.g., famotidine 0.5–1 mg/kg IV), and a corticosteroid (e.g., methylprednisolone 0.5–1 mg/kg IV, if not already administered as part of the chemotherapy protocol). H1 antihistamines are continued at regular intervals (every 4–6 hours) and H2 antihistamines every 12 hours throughout the desensitization procedure (5).

Routine premedication is not without controversy. Because antihistamines and corticosteroids can blunt or delay the clinical symptoms that would otherwise signal an evolving reaction, premedication carries a recognized risk of masking early hypersensitivity and allowing silent inactivation to pass clinically unrecognized during the procedure itself. For this reason, premedication should not be regarded as a substitute for TDM: a desensitization that proceeds without any clinical symptoms should still be confirmed, rather than assumed, to have delivered therapeutic enzyme activity.

Desensitization Protocols

Published protocols for PEG-asparaginase desensitization have generally adapted the standardized multi-step rapid drug desensitization framework originally developed for chemotherapy hypersensitivity (29), most often as a 12- or 13-step, three-solution intravenous protocol lasting approximately 6 hours (5, 25-27). Table 3 presents a representative step structure, expressed as a percentage of the total planned dose so that it can be applied regardless of the individual patient's target PEG-asparaginase dose; institutions adapting this framework should consult the primary protocols for exact solution preparation (5, 25, 29).

Rate is expressed relative to the initial step-1 rate for generalizability; each step is administered for 15 minutes except the final step, which delivers the remaining dose at a constant rate. Total infusion time is approximately 5–6 hours. Steps 9–12 (solution 3) deliver more than 80% of the cumulative dose, consistent with published experience that most breakthrough reactions, when they occur, cluster in the final steps.

Three points deserve emphasis beyond the mechanics of the protocol itself. First, desensitization induces a temporary, dose-specific state of tolerance: it does not produce durable immune tolerance, must be repeated in full at each subsequent asparaginase administration, and is lost after a drug-free interval—so that a patient cannot skip the procedure for a "routine" dose simply because a prior desensitization succeeded. Second, because desensitization suppresses the clinical symptoms of hypersensitivity without necessarily preventing the underlying formation of neutralizing antibodies or accelerated clearance, TDM must be repeated after every single desensitized dose, not only at the time of initial patient selection; a clinically uneventful desensitization does not by itself confirm therapeutic drug exposure. Third, as discussed above, routine premedication—while standard

Table 3 Representative 12-step, 3-solution Desensitization Protocol Structure, Adapted for Peg-asparaginase from the Standardized Rapid Drug Desensitization Framework

Step	Solution	Concentration (fraction of target)	Rate (relative)	Duration (min)	Cumulative dose (%)
1	1	1:100	1×	15	0.01
2	1	1:100	2.5×	15	0.02
3	1	1:100	5×	15	0.04
4	1	1:100	10×	15	0.09
5	2	1:10	2.5×	15	0.22
6	2	1:10	5×	15	0.47
7	2	1:10	10×	15	0.97
8	2	1:10	20×	15	1.97
9	3	1:1 (full strength)	5×	15	4.47
10	3	1:1 (full strength)	10×	15	9.47
11	3	1:1 (full strength)	20×	15	19.47
12	3	1:1 (full strength)	40×	Remainder (~1 h)	100

practice—creates tension with this same monitoring principle, since it can mask the very symptoms that would otherwise prompt closer scrutiny of drug levels.

Patient Monitoring During Desensitization

Careful and continuous clinical monitoring is a critical safety component of any desensitization procedure. Throughout the protocol, patients should undergo real-time monitoring of vital signs—including heart rate, blood pressure, oxygen saturation, and respiratory rate. The clinical setting must allow for immediate recognition and management of adverse events. Emergency medications, including adrenaline (epinephrine), antihistamines, corticosteroids, and bronchodilators, must be immediately available at the bedside throughout the procedure.

Clinical Outcomes of Desensitization

Published clinical experience with PEG-asparaginase desensitization has yielded generally encouraging results, though the evidence base remains limited to small case series and single-institution retrospective cohorts. In the largest published series to date, hypersensitivity reactions during desensitization occurred in approximately 20% of treated patients; these reactions were predominantly mild to moderate in severity and manageable with standard supportive measures, rarely necessitating permanent discontinuation of therapy, and therapeutic asparaginase activity was preserved in approximately 70% of patients following successful desensitization (5). These figures derive from a single small retrospective series and should be interpreted as illustrative of feasibility rather than as precise, generalizable estimates of success or reaction rates.

Nonetheless, desensitization does not completely eliminate immunologic or pharmacokinetic complications. In a subset of patients, accelerated drug clearance or the development of neutralizing antibodies has been documented, resulting in reduced therapeutic exposure despite continued drug administration (5, 26). A more recent single-institution report found that desensitization compared favorably with alternative approaches on cost and resource utilization even after recombinant crisantaspase became commercially available, and that repeated cycles of desensitization appear feasible and generally safe when clinically indicated (27); notably, hypersensitivity

reactions requiring desensitization have also now been described against recombinant crisantaspase itself, indicating that the availability of a licensed alternative does not eliminate the clinical need for desensitization strategies, even if it changes the calculus of when they are preferred (28).

Limitations of Desensitization Strategies

Despite generally favorable outcomes, PEG-asparaginase desensitization is not universally successful and carries several important limitations. First, the development of neutralizing anti-asparaginase antibodies may occur even in patients who complete a desensitization protocol without overt clinical hypersensitivity, a distinction detectable only through TDM. Second, significant interindividual pharmacokinetic variability may result in subtherapeutic asparaginase activity even in the absence of identifiable immune-mediated inactivation. Third, desensitization protocols are resource-intensive and impose substantial organizational demands, requiring dedicated nursing and medical personnel, continuous monitoring equipment, and immediate access to emergency interventions—resources that may not be universally available (4, 12).

Toward a Clinical Decision Framework

The preceding sections point toward a structured, rather than uniform, approach to the patient who reacts to PEG-asparaginase (Figure 2). Three factors should jointly inform the choice between continuing the same formulation, switching to an Erwinia-derived product, and desensitization: (i)

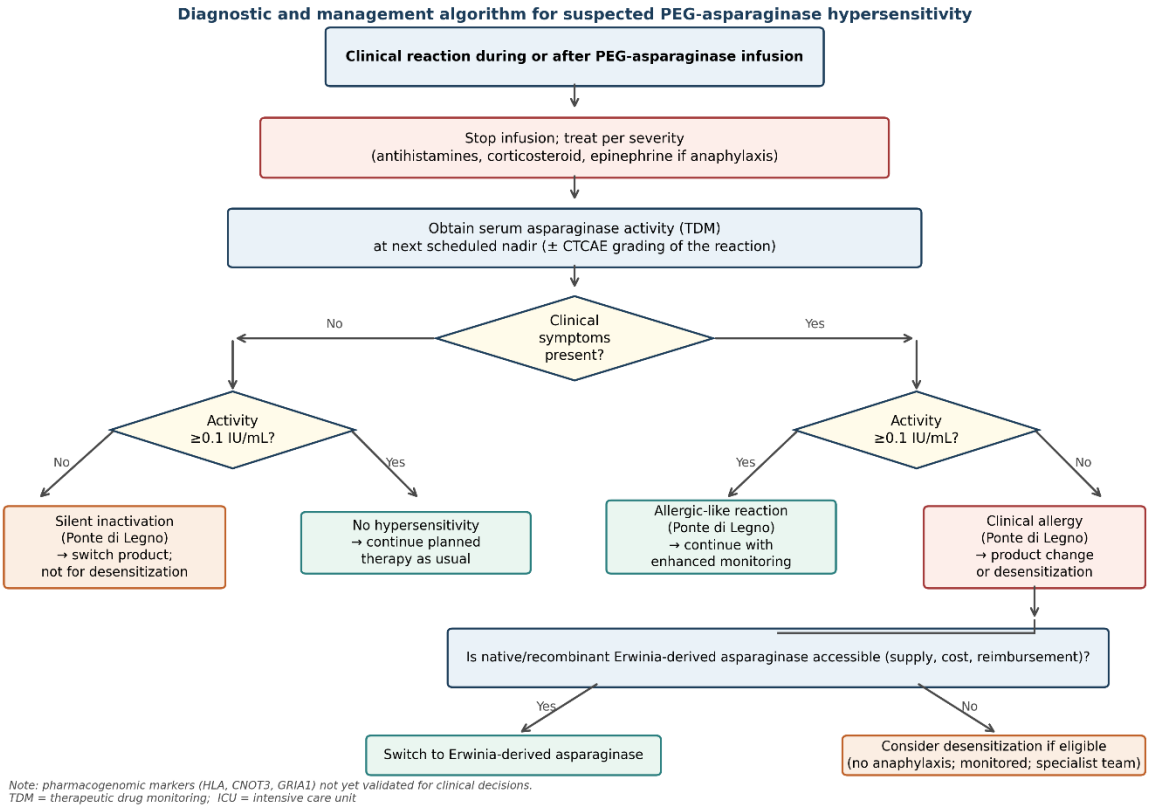


Figure 2. Practical diagnostic and management algorithm for suspected PEG-asparaginase hypersensitivity, integrating clinical assessment, the Ponte di Legno classification, therapeutic drug monitoring, and realistic assessment of access to Erwinia-derived alternatives. Pharmacogenomic markers are not included, as they are not yet validated for prospective clinical decision-making.

the Ponte di Legno classification of the reaction itself, established through TDM rather than clinical impression alone; (ii) realistic local access to native or recombinant crisantaspase, since licensing in a given jurisdiction does not guarantee affordable or timely supply; and (iii) institutional experience and monitoring capacity for the desensitization procedure. Discontinuing asparaginase altogether should generally be a last resort given its association with inferior survival (6), reserved for situations where neither product-switching nor desensitization is feasible or safe for the individual patient.

Discussion

PEG-asparaginase hypersensitivity remains one of the most challenging complications of pediatric ALL therapy, with the potential to compromise treatment exposure and adversely affect survival outcomes (6). This review highlights the multidimensional nature of this clinical problem, encompassing immunologic, pharmacokinetic, genetic, and organizational dimensions that cannot be addressed by a single uniform approach.

A central insight emerging from the literature is that clinical allergy, allergic-like reactions, silent inactivation, and asparaginase-associated hyperammonemia are distinct phenomena that overlap in their clinical presentation but differ fundamentally in their pathogenesis and management. Accurate differentiation among these conditions directly determines whether asparaginase should be discontinued, continued under desensitization, or addressed with supportive measures such as ammonia-lowering therapy (3, 4). TDM is an essential tool in this differentiation, enabling objective assessment of enzyme activity that symptom-driven clinical evaluation alone cannot provide (23, 24).

The heterogeneity of published desensitization protocols, outcome measures, and patient populations limits the strength of available evidence (5, 25-27). Most data derive from small retrospective cohorts with variable definitions of hypersensitivity, inconsistent use of TDM, and limited assessment of long-term leukemia outcomes. While collectively demonstrating feasibility and procedural safety, these reports do not allow definitive conclusions regarding optimal patient selection, comparative effectiveness against switching to recombinant crisantaspase, or the impact of desensitization on event-free survival. Desensitization should therefore be regarded as a conditional and context-dependent strategy, and the choice between desensitization and product-switching—now that a licensed Erwinia-derived alternative exists—warrants explicit, case-by-case discussion rather than being framed as a default dictated by supply shortage alone.

Emerging data on genetic susceptibility offer a promising direction for future risk stratification (18-22), but, as detailed above, effect sizes are moderate, the GRIA1 association in particular has not replicated consistently, and no locus is presently suitable for genotype-informed clinical decisions; these markers should currently be regarded as research tools rather than decision aids. Practical and organizational factors remain critically important: successful implementation requires multidisciplinary collaboration, continuous monitoring, and immediate access to emergency interventions (12, 25). Centralizing asparaginase-related complications management in experienced centers and developing clear protocols for safe referral when local capacity is insufficient are recommended.

Future Research Perspectives

Several questions raised in this review remain open and merit dedicated study. First, whether desensitization—a technique validated for IgE-mediated protein and hapten allergens—achieves comparable, mechanistically similar tolerance against a PEG-antibody-mediated reaction is not established and would benefit from mechanistic (e.g., basophil activation, mast-cell) studies specific to PEG-asparaginase. Second, standardized, prospectively validated anti-PEG and anti-asparaginase antibody assays, applied consistently across cooperative groups, would allow more direct comparison of incidence and outcome data than is

currently possible. Third, prospective, adequately powered validation of the genetic associations summarized above—ideally in diverse populations, given that most cohorts to date have been of predominantly European ancestry—is needed before any of these markers could support pretreatment risk stratification. Fourth, comparative studies of desensitization versus switching to recombinant crisantaspase, incorporating cost-effectiveness and long-term leukemia outcomes rather than short-term feasibility alone, are needed now that both strategies are simultaneously available in some health systems. Finally, prospective registries applying the Ponte di Legno classification uniformly would allow the field to move beyond the heterogeneous, retrospective case series that currently constitute most of the evidence base for desensitization.

Conclusion

PEG-asparaginase hypersensitivity is a clinically consequential complication of pediatric ALL therapy that requires accurate diagnosis and individualized management. The integration of clinical assessment (using the Ponte di Legno framework), therapeutic drug monitoring, and—where available—genetic data enables precise differentiation between clinical allergy, allergic-like reaction, silent inactivation, and asparaginase-associated hyperammonemia, each of which demands a different clinical response. Desensitization represents a clinically valuable, though inherently limited and temporary, strategy for preserving asparaginase exposure in patients with confirmed clinical allergy when alternative formulations are unavailable or inaccessible. A personalized, multidisciplinary approach—guided by TDM, careful patient selection, realistic assessment of access to Erwinia-derived alternatives, and institutional expertise—is recommended. Future advances in immunogenetic risk stratification, in standardized anti-PEG antibody testing, and in comparative outcome data against the newly available recombinant crisantaspase will be essential to further improve safety and efficacy in this vulnerable patient population.

What Is Already Known on This Topic

PEG-asparaginase hypersensitivity is a frequent and clinically important complication of pediatric ALL therapy, associated with inferior survival when it leads to treatment discontinuation. Desensitization protocols have been described in small case series and retrospective cohorts, and genetic susceptibility loci—including HLA haplotypes, CNOT3, and GRIA1 variants—have been identified through pharmacogenomic studies. Therapeutic drug monitoring enables differentiation between clinical hypersensitivity and silent inactivation of asparaginase.

What This Review Adds

This narrative review provides a clinically oriented synthesis that, beyond epidemiology, pathogenesis, genetic risk factors, differential diagnosis, TDM, and desensitization strategies, explicitly addresses three issues not previously integrated in a single framework: the changed regulatory landscape following approval of recombinant crisantaspase and its implications for how the clinical problem should now be framed; the specific role of anti-PEG (rather than anti-protein) antibodies in pegaspargase hypersensitivity and its practical consequences; and the Ponte di Legno consensus classification as an organizing framework for interpreting the heterogeneous existing literature. It also provides a representative, generalizable desensitization protocol table and a practical diagnostic and management algorithm intended for direct clinical use.

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