542 Managing Hypersensitivity Reactions After Asparaginase Treatment: A Systematic Literature Review

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Background

- L-asparaginase (ASP) is an important component of multi-agent treatment regimens for acute lymphoblastic leukemia/lymphoblastic lymphoma[1,2]
  - However, hypersensitivity reactions (HSRs) to *Escherichia coli* (*E. coli*)-derived ASP are common, often lead to treatment discontinuation, and can lead to inferior clinical outcomes[1,3,4]
- Guidelines recommend switching to an immunologically distinct ASP formulation such as an *Erwinia chrysanthemi*-derived ASP, which has minimal cross-reactivity[5,6]
- From 2016 to 2021, quality and manufacturing issues have led to frequent and repeated global supply shortages of native *Erwinia* ASP, making transition to an *Erwinia* ASP challenging[7]
- Alternative practices such as administering premedication and rechallenging/desensitization with *E. coli* ASPs were explored to mitigate drug shortages and meet urgent patient needs[3,4]
  - However, there is limited understanding of the effectiveness of these practices

Objectives

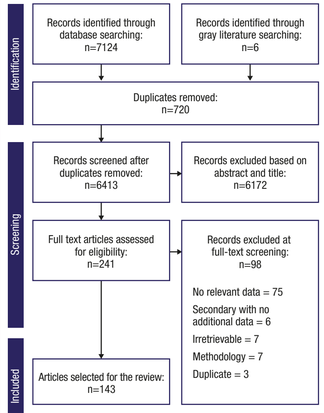
- A systematic literature review (SLR) was conducted to evaluate the prevalence of HSRs with different *E. coli* ASP formulations and summarize evidence on the effectiveness of alternative HSR management practices and current guideline recommendations

Methods

- Databases including PubMed, Embase, and the Cochrane library were searched from their inception to May 2023 to identify relevant studies reporting on HSRs and their management
  - The search was restricted to publications with abstracts and in humans only, and included several study designs such as randomized controlled trials (RCT), retrospective or prospective observational studies, and guidelines
  - The search strategy consisted of title/abstract key words and subject headings describing key concepts of "asparaginase" and "hypersensitivity"
  - The original search included congress abstracts published from 2010 to May 2023
  - Abstracts were screened independently by 2 researchers with discrepancies resolved by a project lead
- As pediatric patients (>1 month to <21.5 years old) transitioned from treatment with pegaspargase (PEG-ASP) to calaspargase pegol (CAL-PEG) beginning December 2022, a targeted search of recent congress abstracts was conducted after the original SLR was completed to capture recent data on CAL-PEG
- HSR rates defined as incidences for different ASP formulations were extracted from studies and summarized descriptively, including ranges, calculated weighted averages of studies with ≥100 patients (based on study sample sizes), and data on premedication and rechallenge/desensitization
- Other treatment variables including switching to other formulations and rechallenging with or without premedication were also extracted and summarized
- The quality of studies was assessed using the Cochrane Risk of Bias tool for RCTs and Downs and Black criteria for non-randomized trials[8,9]

Results

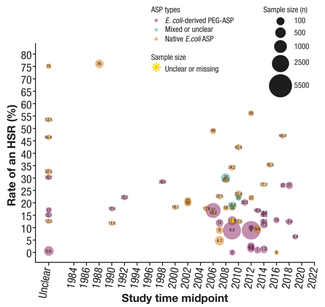
Figure 1. PRISMA Flow of Literature



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- The SLR identified 143 relevant articles selected for review, including guidelines, full-text publications, and abstracts, reporting a total of 141 nonduplicative studies
  - The different ASP types used for any line of treatment included 67 native *E. coli* ASP studies, 102 PEG-ASP studies, and 2 CAL-PEG studies
  - In addition, 4 relevant abstracts presented in 2024 were identified after the SLR was completed[10-13]

Figure 2. HSR Rates by Type of Asparaginase Received as First-Line Treatment[a]



[a]Included studies reporting all-grade or general HSR rates for first-line ASP treatment; studies on CAL-PEG were excluded as they reported grade-specific HSRs only.

ASP, asparaginase; CAL-PEG, calaspargase pegol; *E. coli*, *Escherichia coli*; HSR, hypersensitivity reaction; PEG-ASP, pegaspargase.

HSR Rates With *E. coli* ASP

- Publications reported a wide range of HSR rates across studies and formulations
  - In studies with >100 patients, native *E. coli* ASP and PEG-ASP studies reported HSR rates of 5% to 56% (mean 28%; median 23.4%) and 1% to 33% (mean 8%; median 13%), respectively
  - Two randomized trials evaluated CAL-PEG: 1 trial reported post-induction grade ≥2 allergy in 17% of patients[14]; the other reported grade 1-4 allergy in 27% of patients during consolidation[15]
  - Three recent congress abstracts reported HSR rates with CAL-PEG at 4% (grade 3),[12] 38% (≥grade 3),[13] and 42% (≥grade 2)[10]

Table 1. Studies Comparing HSR Rates With and Without Universal Premedication

Study	Study Details	ASP as Primary Prevention	Number of ASP Doses	Premedication	HSR Rates	TDM	Significant Reduction in HSR From UPM
Cooper SL, et al. 2019[16,a]	• Single-institution • Pediatric/AYA • Historic cohort study (N=177)	PEG-ASP	With UPM: 68	• Diphenhydramine • H_2-receptor blocker • Hydrocortisone	7%	Yes	Yes RR 0.427 (95% CI: 0.27, 0.69) for UPM *P*=0.028
			Without UPM: 122	• None	17%		
Stock W, et al. 2019[17]	• AYA/adults • Consortia trial • (N=295)	PEG-ASP	With UPM: NR	• Acetaminophen • Hydrocortisone • Diphenhydramine	4%	NR	No statistical test performed
			Without UPM: NR	• None	10%		
Hughes C, et al. 2020[18,b]	• Single-institution • Pediatric historic cohort study (N=277)	PEG-ASP	With UPM: 94	• Diphenhydramine • Ranitidine	18%	NR	No *P*=0.56
			With UPM: 125	• Diphenhydramine • H_2-receptor blocker • Hydrocortisone • Saline piggyback	13%		
			Without UPM: 121	• None	12%		
Babcock KJ, et al. 2022[19]	• Single-institution • Pediatric/AYA, historic cohort study (N=38)	PEG-ASP	With UPM: 80	• Antihistamine • H_2-receptor blocker • Corticosteroid	6%	Yes	No *P*=1.0
			Without UPM: 50	• None	5%		
Fajardo A, et al. 2022[20]	• Single-institution, • Pediatric historic cohort study (N=107)	PEG-ASP	With UPM: 58	• Diphenhydramine • H_2-receptor blocker	17%	Yes	No *P*=0.25
			Without UPM: 49	• None	27%		

[a]Age was significantly higher in patients receiving UPM (11.3 vs 8 years, *P*=0.0006) and 13 patients received PEG-ASP both without and with premedication; [b]277 patients received at least 1 dose of PEG-ASP during the review period; some patients received PEG-ASP across multiple periods.

ASP, asparaginase; AYA, adolescent and young adults; CI, confidence interval; HSR, hypersensitivity reaction; NR, not reported; PEG-ASP, pegaspargase; RR, relative risk; TDM, therapeutic drug monitoring; UPM, universal premedication.

Existing Guideline Recommendations Regarding Premedication for HSR Management

- Five of the 7 guidelines identified in the SLR (eg, ASP management guidelines, single-center/institutional guidelines, and premedication/therapeutic drug monitoring protocol) recommended use of premedication to prevent HSRs[21-25]
  - Four guidelines specifically recommended premedication with therapeutic drug monitoring (TDM): 1 institutional,[21] 1 national,[24] European Society for Medical Oncology (ESMO),[23] and National Comprehensive Cancer Network Guidelines (NCCN Guidelines®)[25]
    - From the NCCN Guidelines: If anti-allergy premedication is used prior to PEG-ASP or *Erwinia* ASP administration, TDM using commercially available asparaginase activity assays is highly recommended
  - One institution guideline recommended premedication but did not include specific TDM requirements as they were being introduced into their institution at the time of writing[22]

Existing Guideline Recommendations Regarding Switching to Other ASPs

- Four guidelines recommended switching patients with grade 3/4 HSR to *Erwinia* ASP, and to rechallenge patients having grade 1/2 HSR with *E. coli*-derived PEG-ASP, preferably with premedication (2 institutional,[21,22] 1 national,[24] and NCCN Guidelines®[25])
- ESMO recommended the following[23]:
  - Switching patients who experience any grade 3/4 HSR or confirmed grade 1/2 HSR to *Erwinia* ASP

Table 2. Desensitization Outcomes With PEG-ASP and CAL-PEG

Study	Study Details	Initial ASP	Rechallenge or Switch Details	Number of Patients Rechallenged	Desensitization Success Rate[a]
Fry J, et al. 2024[10]	• Single-center study • Pediatric patients with ALL/LBL	CAL-PEG	• CAL-PEG rechallenge with desensitization and premedication	10	30%
Matherne M. 2024[11]	• Single-center study • Pediatric patients with ALL	CAL-PEG	• CAL-PEG rechallenge with desensitization	4	20%
August KJ, et al. 2020[26]	• Retrospective study in 2 centers • Children and AYA patients with ALL	PEG-ASP	• PEG-ASP	9	100%
Farooki S, et al. 2019[27]	• Case series • Pediatric patients with ALL	PEG-ASP	• PEG-ASP with premedication and desensitization	3	100%
Swanson HD, et al. 2020[28]	• Single-center study • Pediatric and AYA patients with ALL	PEG-ASP	• PEG-ASP with premedication and desensitization	8	88%
August KJ, et al. 2022[29]	• Single-center study • Pediatric patients with ALL/LBL	PEG-ASP	• PEG-ASP rechallenge with desensitization	21	81%
Cecconello DK, et al. 2022[30]	• Case study • Children and adolescents (5-13) years with ALL	PEG-ASP	• PEG-ASP with desensitization and premedication	4	75%
Sorge C, et al. 2015[31]	• Retrospective observational study • Children with ALL treated between 2012 and 2014	PEG-ASP	• PEG-ASP with premedication and desensitization	3	75%
Verma A, et al. 2019[32]	• Case series • Children and AYA (3-19 years) with ALL or LBL	PEG-ASP	• PEG-ASP with premedication and desensitization	10	70%
Cramer J, et al. 2022[33]	• Single-center retrospective study • Children and AYA (2-22 years) with ALL or LBL treated between 2019 and 2020	PEG-ASP	• PEG-ASP rechallenge with premedication and desensitization	15	60%
Gilje EA, et al. 2023[34]	• Retrospective observational study • Pediatric patients with ALL	PEG-ASP	• PEG-ASP rechallenge with desensitization	8	13%
Dara C, et al. 2021[35]	• Multicenter study • Patients with ALL or NK T-cell lymphoma	PEG-ASP	• PEG-ASP with same premedication and desensitization	4	No results

[a]Success was defined as completing ASP treatment without recurrent HSR and/or achieving therapeutic SAA level if SAA was measured.

ALL, acute lymphoblastic leukemia; ASP, asparaginase; AYA, adolescent and young adults; CAL-PEG, calaspargase pegol; HSR, hypersensitivity reaction; LBL, lymphoblastic lymphoma; NK, natural killer; PEG-ASP, pegaspargase; SAA, serum asparaginase activity.

Desensitization Protocols and Outcomes

- The SLR and the recent abstract search identified 21 reports including observational studies, case reports, and case series manuscripts on desensitization: 10 on PEG-ASP, 6 on *E. coli* ASP, 2 on CAL-PEG, and 3 on unspecified ASP
- There was no consensus or guideline on desensitization protocols
  - One case study involved a 10-step, 185-minute desensitization regimen[36] while 1 observational study and 1 case study adopted differing protocols involving 12 steps[37,38]
- Studies exploring the effectiveness of desensitization did not show consistent results
- Of 17 reports with ≥2 patients, 11 reported failure rates of ≥25%; notably, 2 studies reported desensitization with CAL-PEG, however, the success rate was <25% in both studies

Impact of Premedication on HSR Rates

- Premedication (defined as ≥1 agent administered before or with ASP to prevent HSRs in each study) has become common practice
- A total of 21 studies on universal premedication were identified from 2006 to 2022
  - Five compared HSR rates with and without universal premedication[16-19]
    - Three studies showed no statistically significant difference on HSR rates[18-20]; 1 study showed a numerical reduction without statistical tests,[17] and 1 study showed a statistically significant reduction in HSR rates with universal premedication[16]

Conclusions

- HSRs are common with ASP, with varying prevalence across ASP formulations and protocols
- This SLR suggests increasing use of premedication with the use of TDM, despite insufficient evidence on its effectiveness
- Large studies on desensitization are lacking, most being case studies/series showing variable rates of success
- A meta-analysis is being explored to further evaluate HSR rates and treatment strategies by addressing the heterogenous nature of the studies identified in this SLR; 2 studies involving desensitization with CAL-PEG reported success rates of <25%

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