

MADRAC *Bulletin*

For healthcare professionals only

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The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.



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DISCLAIMER

The MADRAC Bulletin is published by the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health (MOH), Malaysia. This publication is meant to provide updates on medication safety issues to health care professionals, and not as a substitute for clinical judgement. While reasonable care has been taken to verify the accuracy of the information at the time of publication, the NPRA shall not be held liable for any loss of whatsoever arising from the use or reliance on this publication. The opinions expressed in all articles are the authors' own and do not necessarily reflect the view of NPRA.

We would like to thank the Director General of Health, Malaysia for his permission to publish the case report articles.

Article Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).¹ The case reports presented in this section are intended to serve as a reminder of potential adverse events that healthcare providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not exhaustive but rather represents a selection of clinically relevant items that warrants dissemination..

Asparaginase-Associated Pancreatitis (AAP) in Paediatric Patients

By Azura Abdullah

Case Report 1¹

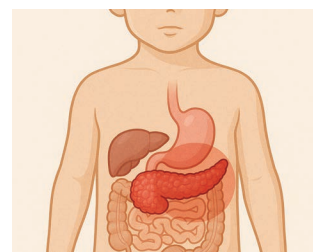
A 5-year old girl with underlying B-cell acute lymphoblastic leukaemia was admitted to the hospital for unresolved abdominal discomfort and inability to tolerate orally. This occurred 3 days after receiving her sixth dose of intramuscular (IM) L-asparaginase and 16 days after the first dose. She weighed 24 kg and was receiving a regimen of 4,400 IU administered every three days. Previously, after each dose she had experienced **abdominal discomfort** without vomiting, which was relieved with massage and oil application.

Upon admission, her amylase level was 882 U/L. She was diagnosed with **acute severe pancreatitis**, complicated by hypovolaemic shock and acute kidney injury (AKI), most likely secondary to asparaginase. IM asparaginase was withdrawn, and she was treated with intravenous (IV) metronidazole and cefotaxime. Her condition resolved within 1 week, with amylase level returning to the normal range (60 U/L). Considering that she was also taking other concomitant medication, the causality for this case has been assessed as *possible*.

Discussion

L-asparaginase is an enzyme-based chemotherapy used in the treatment of acute lymphoblastic leukaemia (ALL), the most common form of childhood cancer.²⁻⁴ It exerts its antineoplastic activity by depleting L-asparagine in the bloodstream, thereby starving leukaemic cells of a vital nutrient they cannot produce themselves. In Malaysia, there are currently no products containing L-asparaginase registered with the Drug Control Authority (DCA), and it is only available as a Special Approval Medicine (*Ubat Kelulusan Khas*, UKK).⁵

Asparaginase-associated pancreatitis (AAP) is defined as a sudden inflammation of the pancreatic parenchyma following asparaginase treatment.⁶ The diagnosis of acute pancreatitis requires at least two of the following diagnostic criteria: (1) *abdominal pain*, (2) *serum amylase or lipase levels ≥ 3 times the upper-normal limit*, and (3) *characteristic imaging findings (Figure 1)*.^{7,8}



*AI-generated image

AAP is a well-established toxicity of L-asparaginase, associated with considerable morbidity but generally low mortality.^{7,9} However, grade 3 or 4 cases often require discontinuation of asparaginase therapy, which may increase relapse risk and reduce event-free survival in children with ALL.^{6,7} Most cases of AAP are reversible and present with modest pancreatic oedema without severe complications. Nonetheless, acute complications—including pancreatic necrosis, hemorrhage, pseudocysts, and systemic inflammatory response syndrome (SIRS) requiring Intensive Care Unit (ICU) admission—can occur (*Figure 1*).⁸ Long-term sequelae may include morphological changes in the pancreas, recurrent painful episodes of pancreatitis, as well as gastrointestinal, endocrine and exocrine dysfunction.

Clinical trials have reported the incidence of AAP in 2–18% of patients receiving L-asparaginase therapy for ALL, with grade 3 or 4 occurring in 5–10% of patients.^{6,10} AAP typically occurs early during asparaginase treatment, with a median onset of about 4 weeks after the first dose and usually develops within 3 to 10 days after the last dose.⁷

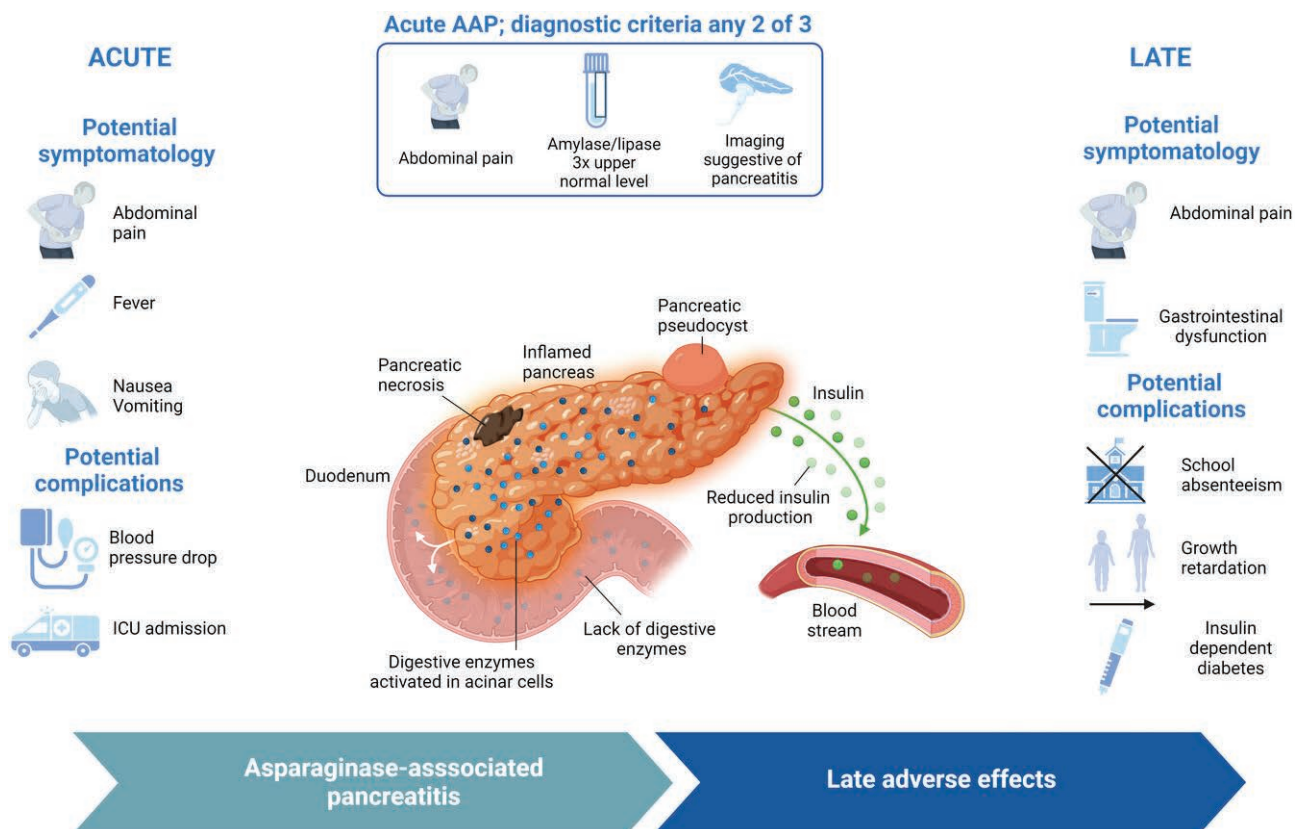


Figure 1. Symptoms and potential complications during and after asparaginase-associated pancreatitis.⁸

The precise pathophysiology of AAP remains unclear.^{7,11,12} One proposed mechanism involves the depletion of asparagine, impairing protein synthesis in organs with high protein turnover, such as the pancreas. Another hypothesis suggests that elevated calcium levels within the pancreatic acinar cells—due to the release of internal stores and increased extracellular calcium entry—can trigger the premature activation of trypsinogen into proteolytic trypsin. This process may lead to pancreatic autodigestion and subsequent acinar cell destruction.⁸ Genetic predisposition is also believed to contribute to the risk of developing AAP.^{6,7,11,12}

The management of AAP depends on disease severity and associated complications.^{6,7,9} Treatment is primarily supportive and includes fluid replacement, pain control, bowel rest, occasional parenteral nutrition, and often, hospital admission for close monitoring.⁷

The decision to reintroduce asparaginase after an episode of AAP requires careful consideration, as follows:

- **For mild to moderate AAP (Grade 2 or 3)**, re-exposure may be considered once symptoms have resolved, pancreatic enzyme levels have normalised (<3 times the upper limit of normal), and imaging shows no complications.⁷ However, if a second episode of pancreatitis occurs after reintroduction, permanent discontinuation of asparaginase is recommended.^{6,9}
- **For severe AAP (Grade 3 or 4) lasting more than 72 hours or involving serious complications such as pseudocysts**, permanent discontinuation is warranted.^{6,7}

At the point of writing, the NPRA has received a total of 232 adverse drug reaction (ADR) reports comprising 426 events suspected to be associated with L-asparaginase treatment.¹ The most commonly reported events were pruritus (70 reports), urticaria (46), and rash (42). Cases of *pancreatitis* (2), *pancreatitis acute* (2), and *oedematous pancreatitis* (1) were reported in paediatric patients, including the case described above. Additionally, one case of *pancreatitis acute* was reported in an adult patient.

Globally, as of May 2025, the World Health Organization (WHO) ADR database, Vigibase, recorded a total of 868 cases with the Standardised MedDRA Query (SMQ) Narrow Term *acute pancreatitis* associated with L-asparaginase use, of which 557 were in patients aged 0 to 17 years old.^{13*}

***DISCLAIMER**

Vigibase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

Advice for Health Care Professionals

- **Be aware** of the risk of asparagine-associated pancreatitis (AAP), particularly in children with ALL.
- **Exercise caution** when initiating L-asparaginase treatment in patients with pancreatitis or a history of pancreatitis.
- **Perform** baseline and periodic monitoring of serum amylase and lipase during asparaginase treatment, especially during the first few weeks. Consider performing imaging if indicated.
- Educate patients to seek urgent medical care if they experience early symptoms of pancreatitis, such as abdominal pain, nausea, vomiting, or loss of appetite.
- If AAP is suspected, **promptly discontinue** L-asparaginase treatment and initiate appropriate management. **Assess** the severity of AAP and carefully consider the decision to reintroduce asparaginase.
- **Report** all ADRs suspected to be associated with the use of L-asparaginase-containing products to the NPRA.

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Features

Collaboration Early Planning for #MedSafetyWeek 2025: A United Effort for Safer Medicines

On 6 May 2025, the NPRA Pharmacovigilance Section hosted an initial discussion to kick off preparations for #MedSafetyWeek 2025 in Malaysia. This session brought together key stakeholders, including representatives from the Malaysian Pharmacists Society (MPS) and the Pharmaceutical Association of Malaysia (PhAMA) Pharmacovigilance Task Force (PVTf), to foster collaboration and develop a successful campaign.

#MedSafetyWeek is an annual global campaign involving about 100 countries, aiming to increase recognition and reporting of side effects. This year the campaign will run from 3 to 9 November 2025 with the theme “We can all help make medicines safer”. As 2025 marks the 10th anniversary of the campaign, this theme takes us back to the roots of #MedSafetyWeek to increase awareness among patients, carers and healthcare professionals.



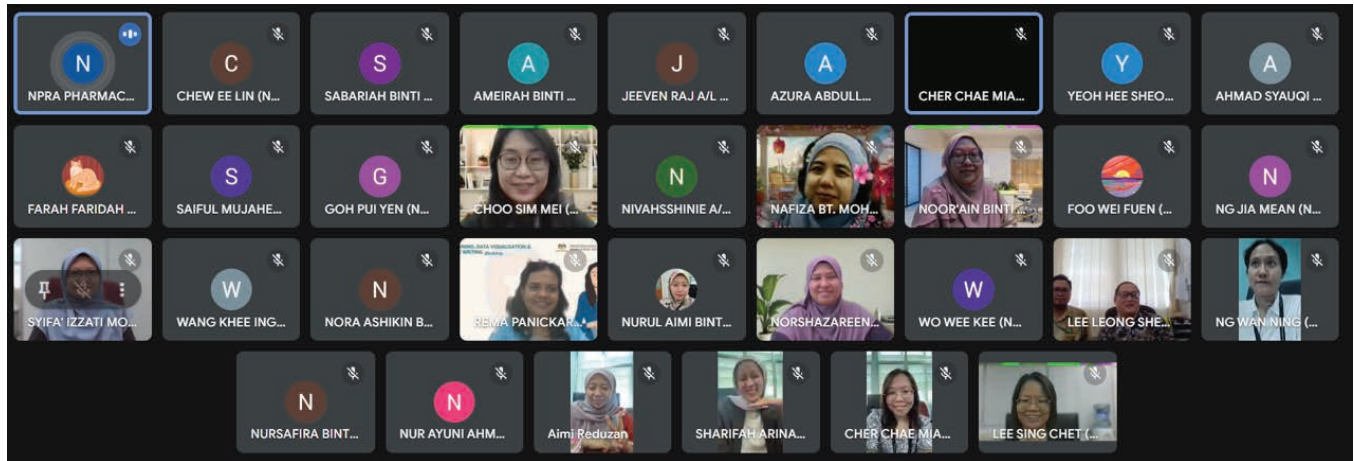
The NPRA kicked off the discussion by sharing plans for adapting international material and engaging stakeholders through coordinated activities. The PVTf then outlined their proposed educational initiatives and discussed media channels which could be utilised, while the MPS pledged to leverage its extensive network to amplify campaign messages through community pharmacies and social media.

The Malaysian #MedSafetyWeek Task Force has also been expanded this year to include Ministry of Health pharmacists representing each state, with the hope of further expanding the campaign outreach. This proactive collaboration sets the stage for a dynamic and inclusive #MedSafetyWeek 2025, reinforcing the shared commitment to improving medicine safety for all Malaysians.



Training Internal Workshop Highlights: Data Mining, Data Visualisation, and Article Writing

On 17 April 2025, the NPRA Pharmacovigilance Section conducted an engaging internal workshop on Data Mining, Data Visualisation, and Article Writing.

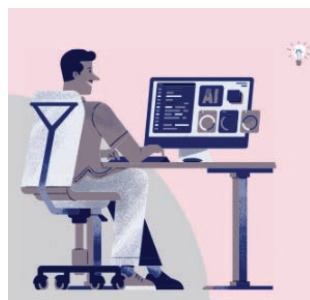


The first session offered a practical, hands-on experience in pharmacovigilance data management. Participants learned how to clean, map, transform, and mine data more efficiently using tools such as Excel formulas, pivot tables, and Power Query—essential skills for informed decision-making in regulatory work. The second session introduced participants to building data queries and retrieval using MedDRA (*Medical Dictionary for Regulatory Activities*).



Effective Data Communication

✓ puts **human** perspectives into complex data



The third session focused on crafting effective data visualisations, turning data into a compelling story. It covered key principles of effective visualisation, showing participants how to tailor visuals to different audiences and create engaging narratives using clear chart selection and thoughtful design practices.

Finally, the workshop explored the potential of AI-assisted tools in research and writing. The emphasis was on using these tools responsibly—as aids to search, review, summarise, and polish—while maintaining human oversight to ensure the integrity and clarity of published content.

What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts/DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts (SA)	SA Date	Directive Ref. No. [Date]
1	Azathioprine	Risk of Non-Cirrhotic Portal Hypertension (NCPH) / Portosinusoidal Vascular Disease (PVSD)	20-May-2025	-
2	Enoxaparin	Risk of Acute Generalised Exanthematous Pustulosis (AGEP)	21-May-2025	-
3	Isotretinoin	Risk of Sacroiliitis and Urethritis	26-May-2025	NPRA.600-1/9/13 (54) Jld.1 [05-May-2025]
4	Statins	[Updated] Risk of Inducing or Aggravating Myasthenia Gravis	27-May-2025	NPRA.600-1/9/13 (53) Jld.1 [05-May-2025]
5	Angiotensin II Receptor Blockers (ARBs)	Risk of Intestinal Angioedema	28-May-2025	-

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit www.npra.gov.my
2. Report ADR [as Healthcare Professional](#)
 - a) Choose [Online Reporting](#) or
 - b) Download the [ADR manual form](#) and submit the completed form via email or post:



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NPRA Safety Information Mailing List

To join the mailing list:



a) scan the QR code to complete the [subscription form](#), or



b) send an email with your details to fv@npra.gov.my

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