Practice guideline for the therapeutic drug monitoring of asparaginase in acute lymphoblastic leukaemia

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Summary

Asparaginase is an essential therapeutic in the treatment of acute lymphoblastic leukaemia (ALL) in children and adults. Currently, there are three asparaginase products in clinical use: native *Escherichia coli* asparaginase, *Erwinia chrysanthemi* asparaginase and PEG-asparaginase. One of the important side effects is the occurrence of hypersensitivity reactions that can lead to inactivation of asparaginase with a negative impact on the outcome of the patient. Therapeutic drug monitoring (TDM) has proven to be a valuable tool to monitor asparaginase activity and detect decreased or absent activity at an early stage. Therefore, many contemporary paediatric ALL protocols include TDM of asparaginase as standard of care. In this report, the background of asparaginase hypersensitivity and silent inactivation is described and a practical flowchart regarding the use and TDM of PEG- and *Erwinia* asparaginase for patients with ALL is introduced.

Introduction

Asparaginases are potent anti-leukemic agents and therefore one of the key elements in treatment of acute lymphoblastic leukaemia (ALL) and non-Hodgkin lymphoma[1-5]. Asparaginase depletes the circulating pool of asparagine in the blood (Figure 1). Leukemic cells, in contrast to healthy cells, are not capable to produce their own asparagine as they lack asparagine synthetase. Due to shortage of asparagine, leukemic cells will undergo cell growth arrest and apoptosis[6].

Complete depletion of asparagine in the blood and cerebrospinal fluid (CSF) is attempted, but measurement of asparagine concentrations is not possible in clinical practice due to logistical and technical problems[9-11]. Currently, the measurement of asparaginase activity levels in serum remains the golden standard to assess asparaginase efficacy and an activity ≥100 IU/L is considered to be necessary for adequate asparagine depletion. This monitoring of asparaginase activity is often performed using the aspartic acid β-hydroxamate (AHA) test [11,12].

There are 3 main asparaginase products in clinical use with distinct pharmacokinetic and immunogenic characteristics (table 1)[12-17]. Two of them are derived from *E. coli* bacteria, a native product and a pegylated formulation (PEG-asparaginase), in which polyethylene glycol is covalently bound to the native *E. coli* asparaginase. The PEG-moiety prolongs the half-life of PEG-asparaginase, allowing dose regimens of 1 administration every 14 days, compared to at least twice weekly for the native *E. coli* product. The third asparaginase is produced from an *Erwinia chrysantemi* strain (*Erwinia* asparginase). The short half-life of *Erwinia* asparginase results in dose schedules of at least 3 times a week.

The non-human origin of asparaginase can induce hypersensitivity reactions. Some patients will develop clinically overt allergic reactions ranging from mild (grade 1) to life-threatening events (grade 4) according to the CTCAE v4.03 criteria (Table 2)[11]. Importantly, even grade 1 reactions can go along with inactivation of the asparaginase, due to neutralizing antibodies[11,12,19].

Other patients however develop neutralizing antibodies against asparaginase without overt allergy, so called silent inactivation. Finally, also allergic-like reactions without inactivation of asparaginase are described. They tend to occur late during the infusion.

Therapeutic drug monitoring (TDM) allows to make dose adjustments at suboptimal levels[11-13]. TDM is also essential to distinguish between a true allergy and an allergy-like reaction and it is the only way to detect silent inactivation[11,12,17,19]. In our Belgian TDM program we found allergic reactions to native *E. coli* asparaginase in 27% of patients, and silent inactivation in 6% (unpublished data). In patients treated with PEG-asparaginase, we found allergic reactions in 11% and silent inactivation in 5% of the patients [12]. The lower frequency of allergic reactions to PEG-asparaginase can be explained by the

shielding of immunogenic epitopes by the pegylation[14]. However, the PEG-molecule or the linker itself can also can give rise to hypersensitivity reactions[13]. During second-line therapy with *Erwinia* asparginase 7% of patients developed allergy and 2.5% silent inactivation[12] (Table 1).

Not only the type of asparaginase will influence the occurrence of hypersensitivity reactions. The hypersensitivity risk increases also in later treatment phases (for example consolidation) and after asparaginase-free intervals[17].

Due to the longer half-life and favourable immunogenic profile, PEG-asparaginase is the first-line product in many contemporary childhood and adult ALL protocols[11-13,17]. *Erwinia* asparginase is the second line product of choice as it does not exhibit cross immunogenicity after hypersensitivity to *E. coli* products. The recent shortage and the high cost of *Erwinia* asparginase however necessitates a rational use of this product. Therefore, some attempt to continue PEG asparaginase after an allergic reaction by using premedication with antihistamines or corticosteroids. This can only be done in the context of TDM since premedication will mask the symptoms of the allergic reaction but does not avoid the generation of neutralizing antibodies[11].

In accordance with the consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation[11] and based on the prospective drug monitoring study performed in Belgium[12], we developed practical flow charts (Figure 2, Figure 3) for the administration and TDM of PEG- and *Erwinia* asparaginase in ALL patients.

Practical guideline for the use of asparaginase

1. **PEG-asparaginase (Figure 2)**

Patients without clinical allergic reaction after administration of PEG-asparaginase will undergo routine monitoring on day 7 ± 1 and day 14 ± 1 after administration. If the measured activity at both time points is ≥100 IU/L, adequate PEG-asparaginase activity has been achieved and therapy can be continued as planned.

A day 7 activity of <100 IU/L will be confirmed in the lab on a second testing and should be checked immediately on an additional patient sample. If the activity on the control sample is ≥100 IU/L, then monitoring on day 14 may be continued. However, if the control sample confirms activity <100 IU/L, especially if the value is <5 IU/L, silent inactivation is identified. This patient should be switched

immediately to *Erwinia* asparaginase with catch-up of the PEG-asparaginase dose at which inactivation occurred.

A good day 7 activity, but a day 14 activity <100 IU/L, may indicate silent inactivation as well. The presence of silent inactivation is very likely when there is no measurable activity on day 14. A suboptimal (near-threshold) level, on the other hand, may indicate accelerated clearance. It is up to the physician to decide on the best option for this patient in this situation: switching to *Erwinia* asparaginase in case of very low or no measurable activity (silent inactivation) or continuing, either or not with adjusting the dose or interval, in combination with enhanced monitoring (peak, day 7 and day 14 level).

In patients presenting any grade of allergic reaction at administration of PEG-asparaginase, an immediate level confirmation is advised if a substantial part of the dose is given.

If a reasonable dose has been administered, a peak sample should be taken. In case of activity <100 IU/L, especially if the value is <5 IU/L, inactivation is present. This patient should be switched immediately to *Erwinia* asparaginase and the PEG-asparaginase dose at which inactivation occurred needs to be caught up.

In allergic patients with peak asparaginase activity ≥100 IU/L, but with subsequent activity levels below 100 IU/L (especially when activity is below the lower limit of quantification), a neutralizing allergic reaction is very likely. These patients benefit from switching to *Erwinia* asparaginase with catch-up of the inactivated PEG-asparaginase dose.

Measured activities of ≥100 IU/L in peak, day 7 and day 14 samples from allergic patients indicate adequate PEG-asparaginase activity. These patients have an allergic-like reaction, to a component other than the asparaginase itself, such as the PEG-moiety or linker. In many cases, therapy can be continued as planned provided that administration is done with premedication and at a slower infusion rate, in combination with TDM.

For allergic reactions occurring after only a few drops have been administered, it is not possible to perform an activity measurement on a peak sample. In continuous dosing regimens, the trough activity after the previous administration can be informative. In discontinuous schedules, after a break, there is no trough activity level available before the administration. In this case, the physician should assess whether PEG-asparaginase can be re-administered after premedication and with enhanced TDM. If the allergic reaction is not too severe and patient is stable, one can try to give the remaining part of the dose after premedication with methyl-prednisolone and clemastine.

Importantly, all patients with clinical allergic reactions will need intensified monitoring with a peak level, on day 7 ± 1 day and day 14 ± 1 day after administration.

2. *Erwinia* asparaginase (Figure 3)

Based on our TDM program results[12], we recommend to administer *Erwinia* asparaginase every other day and to monitor *Erwinia* asparaginase activity at day 2 (trough level).

If the measured trough activity is ≥100 IU/L, adequate activity has been achieved and *Erwinia* asparaginase therapy can be continued as planned.

Trough values <5 IU/L in the absence of an allergic reaction indicate silent inactivation of *Erwinia* asparaginase. After confirmation of absent activity, it is no longer appropriate to continue further administrations of *Erwinia* asparaginase as this may even lead to clinically evident allergic reactions at subsequent doses.

Large inter-individual differences in clearance of *Erwinia* asparaginase cause a proportion of patients to have suboptimal asparaginase activity, with levels between 5 IU/L and 100 IU/L. For these patients, it is recommended to switch to individualized dosing regimens based on activity measurements. This may involve increasing the dose, shortening the interval, or switching from intravenous to intramuscular administrations.

As with PEG-asparaginase, some patients may exhibit an allergic reaction after *Erwinia* asparaginase administration. In this case, too, it is advisable to determine a peak level, at least if a substantial part of the dose has been given. Peak activity <100 IU/L, especially if the value is <5 IU/L, points towards an allergy with inactivation. Further *Erwinia* asparaginase administrations are not useful anymore for these patients.

Allergic-like reactions are also seen after *Erwinia* asparaginase. In this situation, peak and day 2 levels remain ≥100 IU/L. Patients are able to continue *Erwinia* asparaginase after premedication. Prolongation of the infusion time is useful to attenuate the rapid formation of ammonia, which triggers some of the allergic-like symptoms, such as nausea, vomiting, dizziness and headache.

Conclusion

Based on our previous research we have developed a practical flowchart for the administration and TDM of PEG- and *Erwinia* asparaginase. Incorporation of real-time TDM in the daily practice allows to detect silent inactivation swiftly, and to distinguish between allergic reactions with neutralization of the asparaginase and allergic-like reactions with preserved activity. We recommend that all patients receiving asparaginase for the treatment of ALL should undergo TDM.

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Conflicts of interest

VM: participation in advisory boards of Servier, Jazz Pharmaceuticals and Clinigen, travel grants from Servier and Jazz Pharmaceuticals. TLM and BDM: travel grant from Jazz Pharmaceuticals

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Key messages

- PEG-asparaginase is the first-line and *Erwinia* asparaginase the second line asparaginase product in most contemporary childhood and adult ALL protocols.
- Hypersensitivity reactions, such as allergy and silent inactivation hamper the efficacy of asparaginase.
- Therapeutic drug monitoring (TDM) is essential to detect silent inactivation and to distinguish allergic-like reaction from real allergy.
- TDM allows to adapt dose or dosing interval in case of subtherapeutic levels.
- TDM of asparaginase should be standard of care for all patients treated for ALL.

Figures

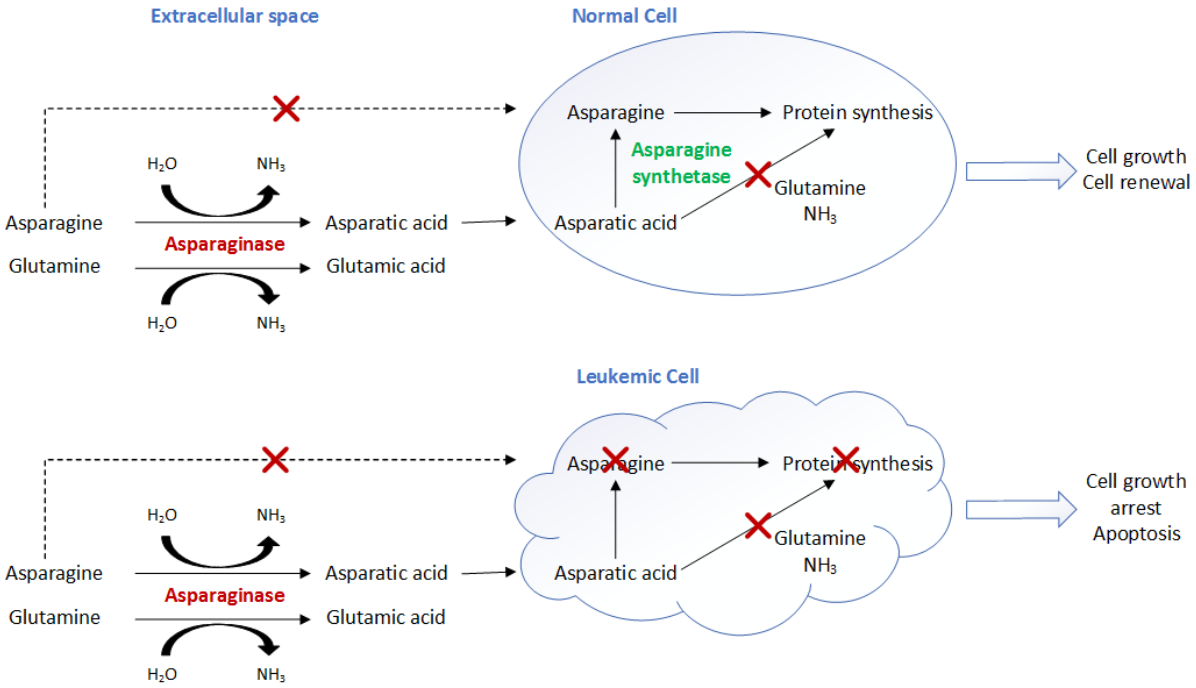


Figure 1: Mechanism of action of asparaginase in normal and leukemic cells.

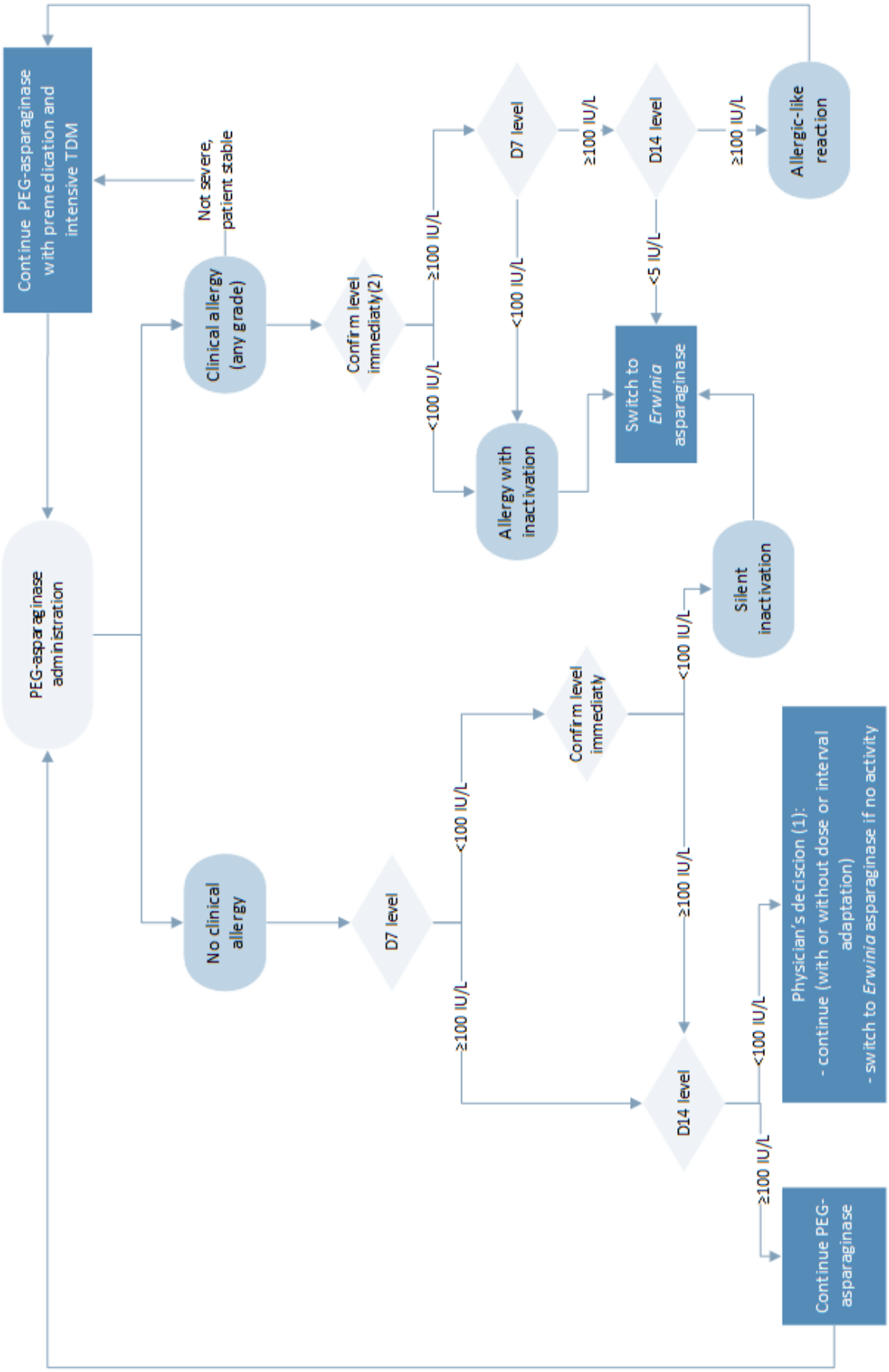
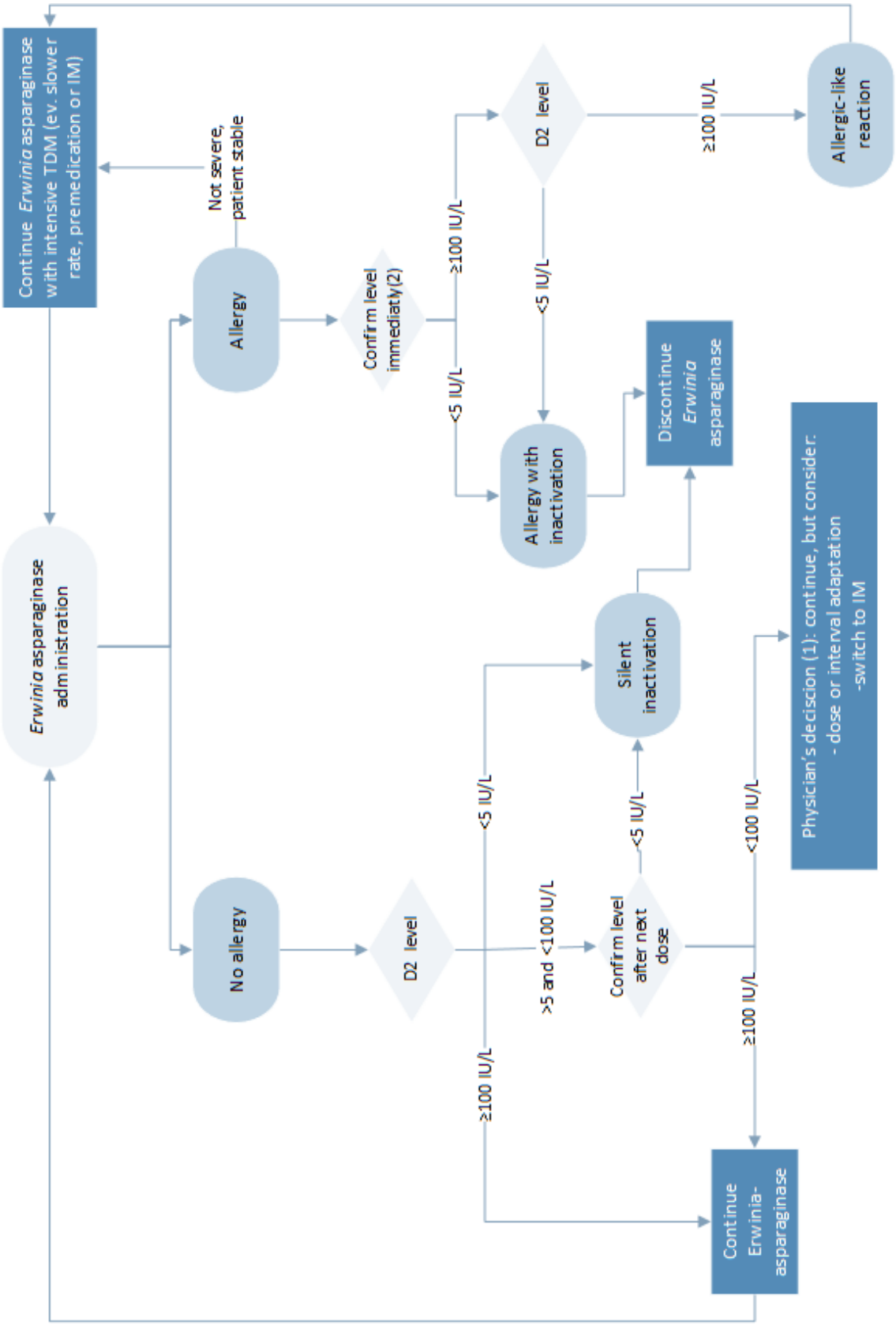


Figure 2: Algorithm for the administrations and TDM of PEG-asparaginase.

(1) Physician's decision based on activity levels, clinical context, regimen and route of administration applied. (2) If substantial part of the dose is given.



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224 Figure 3: Algorithm for the administrations and TDM of *Erwinia* asparaginase.

225 (1) Physician's decision based on activity levels, clinical context, regimen and route of administration
226 applied. (2) if substantial part of the dose is given. IM: intramuscularly.

Tables

	Half-life	Dose schedule	Hypersensitivity
Native *E. coli* asparaginase	1.28 ± 0.35 days	Every 3th day or 2x/week	Up to 75% of patients
PEG- asparaginase	5.73 ± 3.24 days	Every 2 weeks	3-30% of patients
Native *Erwinia* asparaginase	0.65 ± 0.13 days	Every 2nd day or 3x/week	3-33% of patients

Table 1: Pharmacokinetic and immunogenic properties of the three main asparaginase formulations used in frontline ALL[12-17].

Allergic reaction	
A disorder characterized by an adverse local or general response from exposure to an allergen	
Grade 1	transient flushing or rash, drug fever <38°C; intervention not indicated
Grade 2	intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hours
Grade 3	prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
Grade 4	life-threatening consequences; urgent intervention indicated

Anaphylaxis	
A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response Clinically, it presents with breathing difficultly, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death	
Grade 3	symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4	life-threatening consequences; urgent intervention indicated

Table 2: Common Terminology Criteria for Adverse Events (CTCAE) classification version 4.03 for allergic reactions and anaphylaxis.