Prolonged drug provocation with an initial full therapeutic dose to diagnose serum sickness-like reactions (SSLR) to β-lactams in children

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Προλονγεδ δρυγ προοσατιον ωιτη αν ινιτιαλ φυλλ τηεραπευτις δοσε το διαγνοσε σερυμ σιχκνεσσ-λικε ρεαχτιονς (ΣΣΛΡ) το β-λασταμς ιν χηιλδρεν

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SSLR =serum sickness-like reaction

DA= drug allergy

DPT = drug provocation test

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To the editor

Serum sickness-like reactions (SSLR) to β-lactams are non-immediate drug reactions affecting primarily children, mainly during the first 2 years of life.(1) This entity has been poorly investigated and its prevalence remains unknown.(2) SSLR is characterized by the presence of cutaneous signs and symptoms associated with arthritis/arthralgia. The skin manifestations might include erythematous macular, maculopapular exanthemas and urticaria which can evolve to purple lesions (figure 1). Fever is a common symptom present in as much as 40% of children.(3) Symptoms usually start 7 to 21 days after initial drug exposure.(4) Cefaclor was the most commonly incriminated drug, but other β-lactams, anti-inflammatory, anti-convulsants and other compounds, including biologicals and vaccines, have been reported.(5)

Although SSLR is a self-limiting disease, it is often considered as a severe drug reaction and strict avoidance of the offending and chemically related drugs without an allergy work-up is a common recommendation in clinical practice.(6) However, other causes, in particular viral or *Streptococcus* infections, have been reported. Since no clinical or laboratory findings differentiate SSLR from infectious exanthemas, a complete allergic study is necessary to confirm or exclude a drug reaction. Drug provocation test (DPT) without prior skin testing is a procedure that has been reported to be secure in children with benign exanthema/urticaria induced by drugs.(7)

Children with a history suggestive of SSLR to a β-lactam and an allergic study were included in 4 tertiary European pediatric allergy centers (Belgrade, Florence, Porto and Madrid) between 2008 and 2023. Skin involvement, including macular or maculopapular exanthems and urticaria, associated with arthritis/arthralgia were required for the diagnosis, with fever being an additional symptom. DPT to the culprit drug without prior skin testing was proposed to all parents. In all centers, an initial graded dose followed by a prolonged DPT was performed (up to 5 days in Serbia and Italy, up to 7 days in Portugal and Spain). Data on clinical manifestations and the results of the allergic work-up, including DPT to culprit or an alternative β-lactam, were analyzed.

A total of 218 children were evaluated between January 2008 and May 2023. The demographic data as well as further characteristics are summarized in Table 1. Two hundred and twelve (97.3%) children underwent a DPT (table 2). It was not performed in six cases due to parental refusal. In 187 (88.2%) children DPT was performed with the culprit drug, and in 25 (11.8%)

with an alternative β-lactam. The median latency between the index reaction and DTP was 4.5 (IQR 10).

Twenty (10.7%) cases had a positive DPT with the culprit drug. From these, 16 (76.2%) had exanthema/urticaria and arthritis, 3 (14.3%) isolated exanthema/urticaria, 1 (4.8%) exanthema/urticaria, angioedema, and arthritis and 1 (4.8%) exanthema/urticaria, arthritis, and fever. Only one child reacted to an alternative β-lactam with only exanthema/urticaria. None reacted to the first doses given during the graded challenge and no immediate reactivity was observed with subsequent doses. No severe reactions were observed, being all resolved with oral treatment. The presence of fever combined with skin symptoms

and arthritis/arthralgia during the index reaction was not associated with a higher risk for a positive DPT (p=0.36). No children reacted on the first day of challenge.

The diagnosis of SSLR is based on clinical symptoms as no specific biomarkers are currently available and diagnostic procedures are not well established. The absence of definite criteria for SSLR makes the diagnosis difficult and can lead to overdiagnosis of this entity. Indeed, distinguishing it from urticaria with angioedema, particularly localized at the joints might be difficult. In clinical practice, most of the patients developing symptoms of SSLR are considered to have a severe drug allergy (DA) and avoidance of the incriminated drug is recommended in the future. However, our results confirm that the clinical history and physical examination are not sufficient for the diagnosis of a DA in children with SSLR, highlighting the importance of an allergic study, particularly a diagnostic DPT. In fact, only a small proportion (10.7%) of the children included had a positive DPT to the culprit drug and no severe reaction occur in any DPT performed, pointing out that this procedure without prior skin testing is safe in children with a history of SSLR.

As for benign skin manifestations, the high rate of negative DPT might be explained by the high incidence of infections, viral in particular, in the pediatric population, that mimic DA.(7,8) In fact, infections can cause skin exanthemas, angioedema, fever and arthralgia. (4,7) Viruses have also been shown to play an important role as co-factors in DA, not reproducible upon further exposures to the drug. This has been shown for severe cutaneous adverse reactions (SCAR), but also in patients developing a skin rash while under aminopenicillin treatment with an underlying Epstein-Barr virus (EBV) infection.(9,10) In our study, serologic study was performed in 113 children (51.6%) showing during the index reaction a positive IgM for adenovirus in 42.4%, for*Mycoplasma Pneumoniae* in 39.4% and in one case to 3 different viruses (EBV, *Cytomegalovirus* and Human Herpes Virus-6).

The protocol used for DPT varies between countries and centers and is generally not standardized. In a recent study, Delli Colli et al. performed a DPT in 75 children with a history of SSLR to β-lactams and 2.7% of them had an immediate reaction during a graded 1-day challenge.(3) In our study, none of the 21 children with a positive DPT experienced an immediate reaction. Based on our findings and the fact that no severe immediate reactions have been observed in both studies, we suggest that DPT with an initial full therapeutic dose can be considered useful and secure in children with a clinical history suggestive for SSLR. A graded challenge, that is more time consuming and associated with higher medical costs, could be avoided.

In the study by Delli-Colli et al., 25% of children with a negative 1-day challenge experienced a mild reaction on subsequent curses of the culprit drug suggesting that a 1-day challenge might be insufficient to diagnose DA.(3) In our study, a prolonged protocol led to a higher DPT positivity rate (10.7% versus 6.7% in study by the Delli Colli et al.) and might indicate a higher sensitivity of our procedure. Most children with a positive DPT reacted at day 5 and based on these, a 5-days protocol seems appropriate to identify children with an underlying DA. Two children in Portugal undergoing a 7-days DPT did react after the 5^{th} day. However, increasing the length of DPT to identify only few more patients who develop a rather benign reaction is always debatable.

The latency between the index reaction and the DPT still needs to be determined. Although the mean interval was 12.6 months (SD 24.8) when considering all centers together, the mean interval in the Serbian population was 5.3 (SD 8.6) months without a significative difference in DPT positivity, suggesting that DPT might be performed as soon as 6 months after index reaction.

Our data suggest that DPT with an initial full dose is a safe procedure in children with a history of SSLR and that a prolonged DPT seems necessary to increase its sensitivity.

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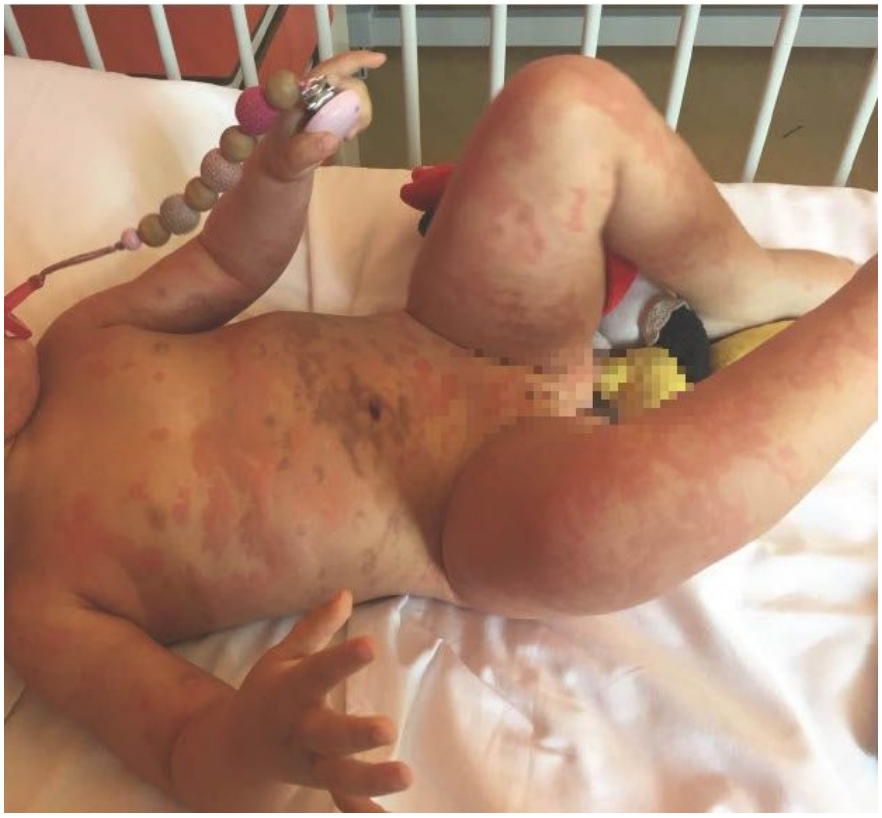

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