

Importance of Specific IgE/Total IgE Ratio in Disambiguating Amoxicillin Allergy Diagnosis in a Real-Life Setting

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Dear Editor,

Allergic reaction to β -lactams antibiotics is the most frequent cause of Adverse Drug Reaction (ADR) mediated by immunological mechanisms [1]. In clinical practice, the evaluation of β -lactam-specific IgE levels is instrumental in the establishment of the diagnosis of ADR [2]. Drug-specific IgE titres rise 3–4 weeks upon exposure and decline over time [3].

Assessment of circulating drug-specific IgE is often done using the RAST-CAP system. The specificity of this test was assessed to range between 83.3 and 100%, with a 0.35 kU/L threshold, but the sensitivity was estimated to range only from 12.5 to 25% [4]. However, a 0.1 kU/L threshold is currently considered acceptable, increasing the sensitivity but possibly reducing the specificity [5].

The test-positive predictive value might also be influenced by the total serum IgE. Indeed, 2 different pools of IgE molecules exist: (i) IgE molecules bound on the mast-cell and basophil surface via the interaction with the high affinity receptor Fc ϵ RI and (ii) the unbound IgE molecules that circulate freely in plasma [6]. It was recently proposed that the ratio β -lactam-specific IgE/total IgE might be

an additional parameter to consider in the ADR diagnostic process [7]. In particular, an elevated drug-specific IgE/total IgE ratio might reflect high levels of drug-specific IgE on mast-cells and basophils, thereby increasing the probability of adverse reaction upon drug administration. Thus, the authors propose the use of a 0.002 threshold for the ratio drug-specific IgE/total IgE. A positive predictive value of 95% is achieved if the ratio is ≥ 0.002 , whereas it diminishes significantly if the ratio is < 0.002 [7].

Here we describe 6 cases of suspected ADR to amoxicillin (AMX). We used the 0.002 amoxicilloyl-specific IgE/total IgE ratio to clarify the clinical diagnosis in a real-life setting.

The patients (1 men and 5 women; mean of age 38.6 ± 16.3 ; all from Southern Italy) were referred to our Clinic for a suspected (although ambiguous) immediate ADR to AMX. Five patients had been treated with AMX alone and one with AMX-Clavulanic Acid (CLV). Five out of 6 had experienced the adverse reaction more than 6 months before the clinical assessment and no other concomitant medications were given (Table 1).

In all patients, the amoxicilloyl-specific IgE levels (CAP System) were slightly above the current threshold limit (0.1 kU/L; Fig. 1a). Considering the possible decline of drug-specific IgE [3], these results could have been interpreted as positive. We also evaluated the penicilloyl-G, cefaclor, penicilloyl-V, and ampicillin-specific IgE (Fig. 1b). Notably, in all patients the total IgE levels were above the usually accepted threshold limit of 100 kU/L and in 4 of them were remarkably high (Fig. 1c).

As proposed [7], we calculated the amoxicilloyl-specific IgE/total IgE ratio. This ratio was below 0.002 in all the patients (Fig. 1d). Thus, we hypothesized that the amoxicilloyl-specific IgE levels in these patients were not reliable. To further corroborate this finding, we also evaluated the *Ambrosia elatior*-specific IgE in 2 patients with total IgE $> 1,000$ kU/L and their levels were above the 0.1 kU/L threshold. Clearly false positives, since *A. elatior* pollen is not detectable in Southern Italy (data not shown; moreover in 5 AMX-tolerant con-

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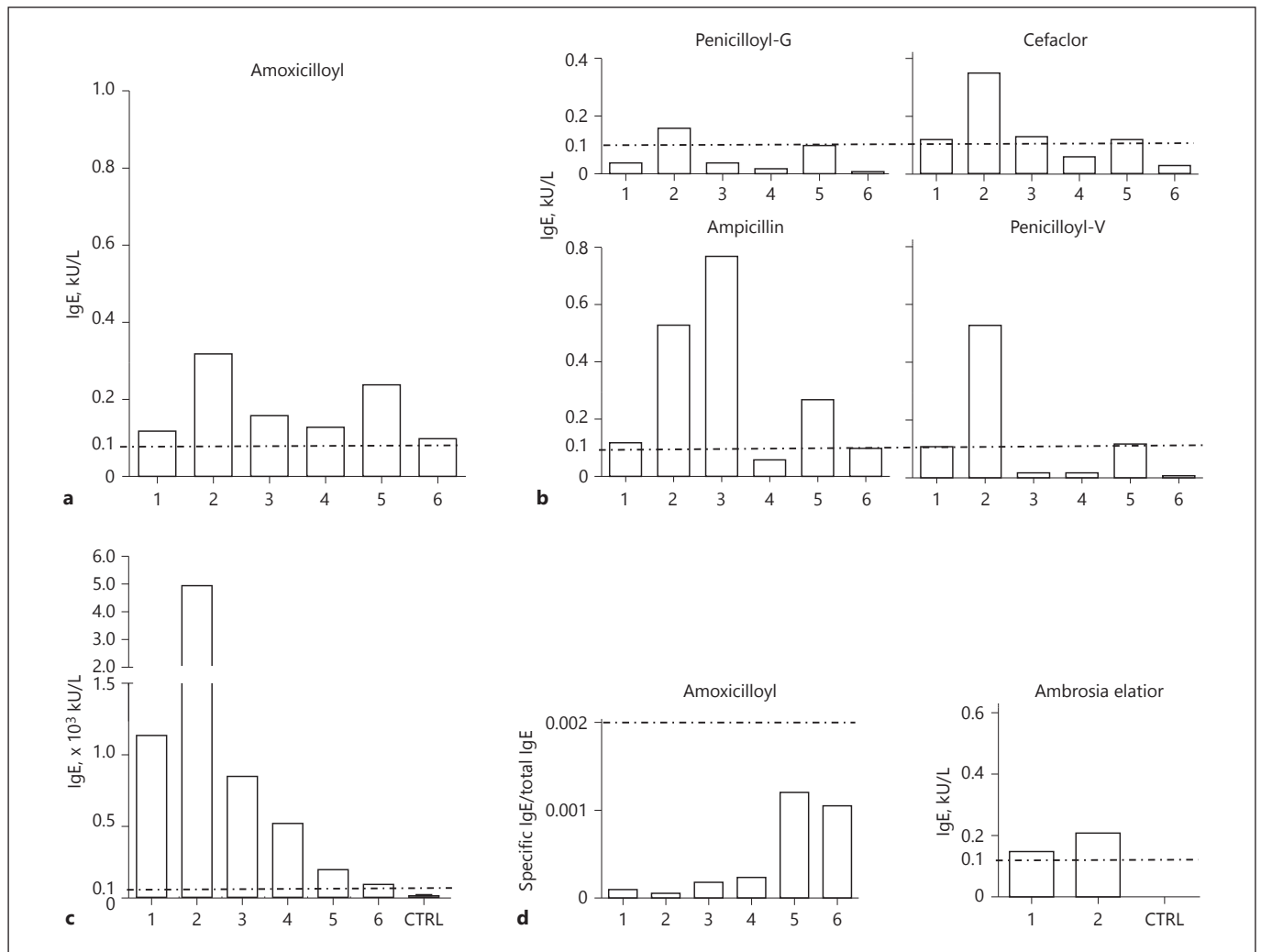


Fig. 1. **a** Serum levels of amoxicilloyl-specific IgE. **b** Serum levels of (from upper left, clockwise) penicilloyl-G, cefaclor, penicilloyl-V and ampicillin. **c** Serum levels of total IgE. **d** Amoxicilloyl-specific IgE/total IgE ratio. **e** Serum levels of Ambrosia elatior-specific IgE. Dashed horizontal lines represent 0.10 kU/L threshold (**a**, **b** and **e**), 100 kU/L and 0.002 ratio (**d**). On the x-axis, patients 1–6 as in Table 1. CTRL, Controls were AMX-tolerant healthy volunteers.

Table 1. Clinical characteristics of the patients

Patient	Age	Gender	Culprit drug	Symptoms	Time of onset	Time of screening ^a	Associated sensitizations ^b	Autoimmunity ^c	Re-exposure	Cause of administration
1	25	M	AMX	Urticaria/Angioedema	<1 h	>6 months	Yes	Yes	No	Tonsillitis
2	40	F	AMX	Angioedema	<1 h	>6 months	No	No	Yes	Flu
3	16	F	AMX	Generalized pruritus with tightness of the throat	<1 h	>6 months	Yes	No	No	Tonsillitis
4	39	F	AMX/CLV	Urticaria	<1 h	>6 months	Yes	Yes	Yes	Surgery treatment
5	52	F	AMX	Urticaria/angioedema	<1 h	>6 months	Yes	Yes	Yes	Toothache
6	60	F	AMX	Urticaria	<1 h	<6 months	No	Yes	Yes	Toothache

^a From AMX suspected reaction.

^b Confirmed by a positive skin test to inhalant and/or food allergens.

^c Confirmed by either autologous serum skin test or anti-thyroglobulin, anti-thyroperoxidase antibodies or anti-nuclear antibody assessment.

AMX, amoxicillin; CLV, clavulanic acid.

trols *Ambrosia*-specific circulating IgE were undetectable; Fig. 1c–e). This latter observation supported the idea that the results obtained for AMX could also be considered false positives.

To validate this hypothesis, we performed an oral provocation test (OPT) with AMX (1,000 mg in 4 steps, 30 min apart). All the patients tolerated the OPT. Moreover, the drug was administered for 3 consecutive days, following the OPT (1,000 mg, once daily; sustained OPT). No adverse reactions were observed, thus excluding the possible AMX hypersensitivity that could have been suspected formerly. Moreover, 4 of the patients were re-exposed to AMX more than 4 weeks after the OPT and had no adverse reactions.

In clinical practice, the diagnosis of ADR can be difficult, mainly when the clinical history of ADR is unclear. The evaluation of specific IgE levels in these cases is particularly valuable.

If the levels of drug-specific IgE are above the threshold limit, normally an OPT is not recommended due to the possible occurrence of severe adverse reactions. However, in the cases reported, we proved in a real-life setting that the values of circulating specific IgE are not trustworthy when the specific/total IgE ratio falls

below 0.002. In fact, our patients tolerated the AMX-OPT even though all of them reported a clinical history that could have been related to drug hypersensitivity to this drug. These observations suggest that indeed the measurement of total IgE levels in the context of AMX allergy matters. Only one of the 6 patients analyzed at the time of the adverse reaction was treated with AMX-CLV (#4). Thus, as CLV accounts for around 30% of allergic reactions to the AMX-CLV combination, CLV might have also been regarded as the culprit drug [8]. However, when spontaneously re-exposed, this patient tolerated the association AMX-CLV, ruling out a possible CLV involvement.

Nearly all the patients reported urticaria-angioedema episodes (Table 1). However, urticaria-angioedema can also be due to other underlying conditions. Indeed, 4 patients had either circulating auto-antibodies or a positive autologous serum skin test (Table 1). In fact, the presence of autoimmunity and, in particular, of thyroid-specific autoantibodies has been related to the occurrence of chronic spontaneous urticaria [9]. Therefore, the symptoms associated to AMX exposure could have been caused by an underlying autoimmune disorder. Moreover, patients undergoing anti-

infectious treatments can develop urticaria-like skin manifestations unrelated to drug-hypersensitivity [10].

In conclusion, the cases reported show that the ratio between amoxicilloyl-specific IgE/total IgE (threshold 0.002) might be a useful parameter to rule out false positives. Indeed, a high ratio most probably reflects a larger FcεRI-bound pool of IgE, thereby predicting cell activation in sensitized patients [7]. We propose that total IgE levels should be always assessed when amoxicilloyl-specific IgE are evaluated. Moreover, urticaria can be a misleading symptom in the context of infections treated with AMX and other concomitant causes of ambiguity should also be routinely assessed, such as autoimmunity.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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