



Understanding the mechanisms in accelerated drug reactions

María J. Torres^a, Maria Salas^a, Adriana Ariza^b, and Tahia D. Fernández^b

Purpose of review

The purpose is to understand the underlying mechanisms of accelerated allergic reactions to drugs, defined here as reactions occurring between 1 and 24 h after drug intake.

Recent findings

Recent publications have shown that accelerated reactions are T cell-mediated, although an IgE mechanism cannot be ruled out in some cases.

Summary

Classification of allergic reactions to drugs is complex. Based on the time interval between drug administration and appearance of the clinical reaction, as well as the type of clinical symptoms, they can be classified as: immediate, typically appearing from less than 1 to 6 h after the last drug administration and nonimmediate, occurring at any time from 1 h after drug administration. Therefore, overlap exists in what the Levine classification defined as accelerated reactions, where clinical symptoms are mainly urticaria and less often exanthema and serum sickness-like reactions. The immunological mechanisms involved suggest that they are T cell-mediated reactions with a Th1 pattern, comprising increased production of IFN γ , TNF α , the chemokine CXCL9 and its corresponding receptor CXCR3. In most cases an IgE-mediated response is ruled out because of negative immediate skin test results, no detection of serum-specific IgE antibodies or tryptase, and no skin-secreted tryptase. However, an IgE-mediated response can be demonstrated in exceptional situations. Finally, serum sickness-like reactions have been reported as an immune complex-mediated accelerated reaction. However, the exact mechanism has not been confirmed.

Keywords

accelerated reactions, drug hypersensitivity, IgE, T lymphocytes

INTRODUCTION

Adverse reactions to drugs are defined by the WHO as 'any noxious, unintended and undesired effect of a drug that occurs at doses used for prevention, diagnosis or treatment' [1]. They constitute an important public health issue, causing 3–6% of hospital admissions and occurring in 10–15% of hospitalized patients [2,3]. Drug hypersensitivity reactions (DHR) are the most frequent type of adverse reactions [4].

CLASSIFICATION OF DRUG HYPERSENSITIVITY REACTIONS

The classification of DHR is still a matter of intense debate because of their heterogeneity in terms of drugs involved, clinical symptoms, and underlying mechanisms. The most common culprits are nonsteroidal anti-inflammatory drugs, betalactam antibiotics, nonbetalactam antibiotics, such as

fluoroquinolones and radiocontrast media [5]. The skin is the main organ affected, with drug reactions ranging from mild (e.g. urticaria/exanthema) to severe, such as toxic epidermal necrolysis.

Classically, DHRs are grouped according to the underlying mechanism. A first approach is to differentiate those with proven immunological mechanisms (allergic DHR) from those where these mechanisms cannot be proven (nonallergic DHR) [6]. Allergic DHR account for 6–10% of all adverse

^aAllergy Unit and ^bResearch Laboratory, IBIMA-Regional University Hospital of Malaga-UMA, Malaga, Spain

Correspondence to María J. Torres, Allergy Unit, IBIMA-Regional University Hospital of Malaga, Plaza del Hospital Civil. Pabellón 6, 1 planta, 29009 Malaga, Spain. Tel: +34 951290224; fax: +34 951290302; e-mail: mjtortresj@ibima.eu

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KEY POINTS

- Controversy exists in the clinical classification of drug allergy according to the time interval between drug administration and onset of symptoms and signs, particularly for accelerated reactions appearing between 1 and 24 h.
- The main clinical picture of accelerated reactions is urticaria, sometimes accompanied by angioedema. However, SSLR and exanthema can also appear. Anaphylaxis cannot be considered an accelerated reaction.
- Accelerated urticarial and exanthematous reactions are mediated by T cell-mediated mechanisms similar to those appearing in delayed reactions.
- Although rare, an IgE-mediated mechanism cannot be ruled out, especially for some urticarial reactions.
- The mechanisms involved in SSLR are still not well understood, and it is unclear whether they are mediated by immune complexes.

drug reactions [7] and were classified by Coombs and Gell [8] into four groups (Table 1):

- (1) Type I or immediate type, mediated by drug-specific IgE antibodies;
- (2) Type II, cytolytic or cytotoxic, mediated by drug-specific IgG or IgM antibodies;
- (3) Type III or immune complex, mediated by drug-specific IgG or IgM antibodies;
- (4) Type IV or delayed type, mediated by drug-specific T cells. This has been subclassified in other four types according to the mechanism involved [9]:
 - (a) Type IVa, mediated by Th1 lymphocytes, IFN γ , and monocytes.
 - (b) Type IVb, mediated by Th2 lymphocytes, IL-4, and eosinophils.
 - (c) Type IVc, cytotoxic response mediated by CD4⁺ and CD8⁺ lymphocytes.

- (d) Type IVd, characterized by the presence of neutrophils.

Levine [10] in 1996 classified allergic DHR into three types: immediate, accelerated, and delayed, based on the time interval between administration and symptom onset. Immediate reactions usually occur 2–20 min following drug administration, manifesting as urticaria or anaphylaxis; accelerated reactions occur after 2–48 h with urticaria being the main symptom, and delayed reactions occur after 72 h and are generally exanthematous reactions. This classification, originally proposed for penicillin allergy, was later generalized to other drugs. It was later simplified by Terrados *et al.* [11], and adopted by the European Network of Drug Allergy group, into two groups: immediate (those appearing within 1 h after drug administration) and nonimmediate (those appearing after 1 h) [12,13]. This classification has been widely used, and has mechanistic and diagnostic implications. The classification in immediate or nonimmediate reactions is based on drug challenge, which is the gold standard for diagnosing these patients. Moreover, immediate reactions are considered IgE-mediated and the diagnostic approach also includes skin test with immediate reading and in-vitro tests for detecting drug-specific IgE. In contrast, nonimmediate reactions are considered T cell-mediated and evaluation also includes skin test with delayed reading and in-vitro analysis of the specific T-cell response.

However, controversy exists regarding the use of this classification with an 'arbitrary' cut-off of 1 h, because immediate (IgE-mediated) reactions can appear up to 6 h (defined as 'late') and delayed (T cell-mediated) reactions can sometimes start after 8–12 h (defined as 'accelerated') [14,15]. Taking into account this controversy a new cut-off point has been proposed that divides reactions into immediate (less than 1 h to 6 h after the last drug administration) and nonimmediate (any time from 1 h after the initial drug administration) [16²²]. However, in

Table 1. Mechanisms and clinical examples of types of reaction according to Gell and Coombs classification

Type	Mechanism	Example
I	Specific IgE	Anaphylaxis
II	IgG or IgM	Hemolytic anemia
III	IgG or IgM	Serum sickness-like reaction
IV	A Th1 lymphocytes, IFN γ , and monocytes	Eczema
	B Th2 lymphocytes, IL-4, and eosinophils	Maculopapular exanthema, drug reaction eosinophilia systemic symptoms
	C CD4 ⁺ and CD8 ⁺ lymphocytes	Maculopapular exanthema, toxic epidermal necrolysis
	D Neutrophils	Acute generalized exanthematic pustulosis

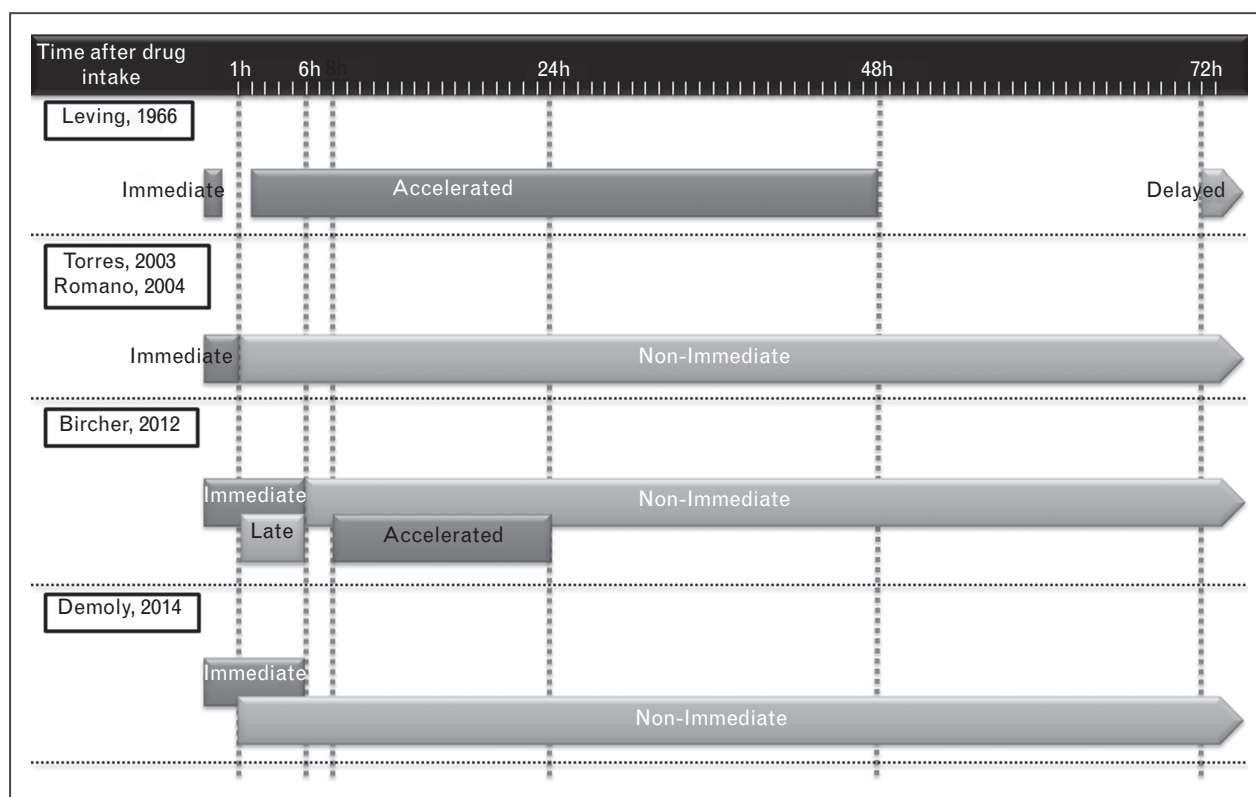


FIGURE 1. Time course of the different classifications from a clinical point of view, based on the clinical symptoms/signs and the time interval between drug administration and the development of the reaction, carried out by different authors from 1966 to 2014.

this last classification an overlap exists between immediate and nonimmediate reactions between 1 and 6 h.

Analysis of all these clinical classifications (Fig. 1) suggests that the main conflict between classifications occurs for reactions occurring from 1 to 24 h after drug administration, originally defined by Levine [10] as 'accelerated reactions'. This is important as a misclassification will hamper comparisons among studies, the understanding of the mechanisms involved, and the types of diagnostic tests to be used in evaluation and treatment of the reactions. The clinical symptoms and signs, and the underlying mechanisms of these accelerated reactions appearing from 1 to 24 h after drug administration will be the focus of this review.

CLINICAL SYMPTOMS OF ACCELERATED REACTIONS

The most frequent clinical symptom of accelerated reactions is urticaria [11,17], which comprises the appearance of intensely pruritic and pale wheals surrounded by erythematous flares that usually disappears within 24 h. It can be accompanied with angioedema, although this usually starts later. This

should be differentiated from urticarial vasculitis. There is no characteristic that can differentiate these cutaneous manifestations from those of immediate reactions [15].

Although the main feature of anaphylaxis is an acute onset of clinical symptoms, involving at least two organ systems together with skin and mucosal tissue [18], in some cases it can appear after 1 h [19,20]. However, this is extremely rare. Drug provocation with penicillin has shown that anaphylaxis appears more rapidly and at lower doses than urticaria, which appear after around 1 h [21]. Therefore, some patients initially classified as having immediate urticaria by clinical history had negative skin tests, showed an absence of in-vitro specific IgE antibodies and were drug provocation test positive after 1 h, suggesting they were accelerated reactions with a different underlying mechanism in contrast to the typical IgE-mediated immediate reactions [21]. In fact, in patients with perioperative allergic reactions to cephalosporins, those finally confirmed as having immediate allergy developed symptoms within 15 min following drug administration [22].

On the other hand, maculopapular exanthema (MPE) is a typical clinical symptom for delayed or nonimmediate reactions. However, an erythema

can start as early as 2 h after drug administration, and progress to the appearance of macules and papules after 24–48 h [15]. Therefore, using the onset of exanthema as the start of the allergic DHR, MPE can also be classified as accelerated.

Finally, it is worth mentioning serum sickness-like reaction (SSLR), which although uncommon and mostly restricted to young children, has been typically considered as accelerated. SSLR is characterized by fever, macular and urticarial exanthemas, lymphadenopathy, polyarthralgia or polyarthritis, and sometimes peripheral oedema [23], appearing 6–8 h after drug administration [23]. An immune complex-mediated (type III) mechanism has been postulated [15], although it has not been appropriately investigated.

MECHANISMS OF ACCELERATED REACTIONS

The underlying mechanisms of accelerated reactions have not been clearly established. Some

studies [24–27] consider them as mediated by drug-specific IgE because of positive skin prick test and specific IgE determination in sera. However, most have considered them as T cell-mediated reactions [28,29,30^{***}]. Nevertheless, a few publications have analysed the mechanisms specifically involved in accelerated reactions [28,29,30^{***}] and SSLR [23,31–38,39^{*},40^{*},41]. In this review, information is also obtained from series of adult patients [24–29,30^{***},42,43] or children [23,35–38,39^{*},40^{*},41] with allergic DHR, including patients who developed drug reactions from 1 to 24 h after drug administration although not specifically classified as accelerated.

Specific studies on accelerated reactions

We could only find three publications that specifically evaluated the mechanisms involved in accelerated reactions [28,29,30^{***}]. All studies focused on skin reactions and concluded that they are mediated by a T-cell mechanism (Fig. 2a).

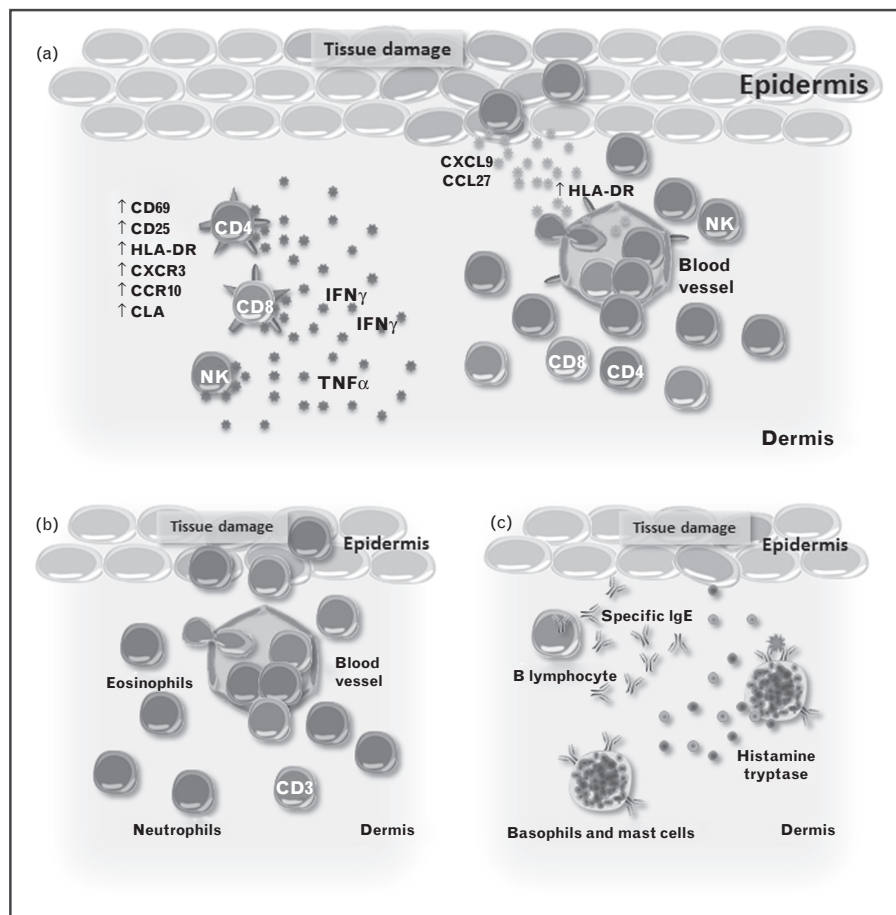


FIGURE 2. Mechanisms proposed to be involved in the development of accelerated reactions. (a) T cell-mediated mechanisms with the involvement of T lymphocytes and natural killer (NK) cells. (b) T cell-mediated mechanisms with the involvement of eosinophils and neutrophils. (c) IgE-mediated mechanisms.

The first work published by Warrington *et al.* [28] described two patients who developed MPE within the first 24 h after the intake of penicillin. The analysis of the skin biopsy obtained during the acute reaction showed a dense-activated perivascular lymphoid infiltrate and epidermal changes, characteristic of a severe delayed hypersensitivity response. The infiltrate was mainly composed of CD4⁺ T cells with strong expression of human leukocyte antigen-D related (HLA-DR) by the vascular endothelium. In the infiltrate, there were no presence of B cells and the immunofluorescence analysis showed no evidence of any immune complex-mediated reaction. All these data support a Gell and Coombs type IV mechanism.

The second study, by Torres *et al.* [29] described 10 patients with accelerated urticaria appearing from 1 to 24 h after drug intake, and compared them with 46 patients with immediate ($N = 17$) or delayed ($N = 19$) allergic DHR. The analysis of different T-cell activation markers, CD69 (very early), CD25 (late) and HLA-DR (very late), in peripheral blood during the acute reaction phase showed an increase in CD69 and HLA-DR expressions in accelerated reactions compared with immediate reactions, and a similar level to delayed reactions. There was also an increase in CD25, similar to immediate reactions. In the assessment of cutaneous lymphocyte-associated antigen (CLA) expression involved in the trafficking of skin T-cell subpopulations to cutaneous sites of inflammation [44,45], no increase was detected in accelerated urticaria similar to those detected in delayed urticaria, indicating that although affecting the skin, this manifestation induces a weak cutaneous CLA⁺ T-cell infiltration. In this work, accelerated reactions were described, as suggested by others [28], as induced by a rapid T cell-mediated mechanism, leading to transient skin reactions that subsided rapidly.

The most recent work published by Gomez *et al.* [30^{***}] described three cases of accelerated reactions to amoxicillin, with typical manifestations of generalized erythema with systemic pruritus and angioedema. The involvement of T cells was studied in both peripheral blood and lesional skin. First, an immediate mechanism was excluded because of the negative results of immediate skin test, absence of serum-specific IgE antibodies, and the absence of an increase in tryptase during the acute response in both peripheral blood and skin biopsies. Analysis of the skin biopsies revealed a typical cell infiltrate with CD4⁺ and CD8⁺ T cells, natural killer (NK) cells and the expression of delayed activation (HLA-DR) marker. In this study, a Th1-mediated response was described, with an increased production of IFN γ and TNF α mainly in CD56⁺ cells,

no changes in IL-4 in peripheral blood and an increased expression of the chemokine receptor CXCR3. This receptor and its corresponding ligand CXCL9 were detected in the skin. Together with the increase in CLA, skin homing chemokine CCL27 and its receptor CCR10 in the skin biopsy, these data suggest T-cell trafficking to the skin. Similar data have been previously reported in drug exanthematous reactions [46]. Furthermore, a specific CD3⁺ T-lymphocyte proliferation against amoxicillin was demonstrated in the three patients studied. Therefore, these three works showed that accelerated reactions are mediated by T-cell mechanisms.

It is important to differentiate accelerated reactions induced by betalactams from those induced by other drugs like NSAIDs, proton pump inhibitors, etc. as in betalactam reactions the hapten hypothesis has been demonstrated with the IgE recognition of their antigenic determinants [47]. On the contrary, no antigenic determinant has been proposed in the case of the other drugs.

Specific studies on serum sickness-like reaction

The mechanisms involved in SSLR remain poorly understood (Fig. 2b), and although an immune complex-mediated mechanism has been proposed, the histopathology appears to be similar to urticaria. A mixed superficial to deep interstitial dermal inflammatory infiltrate with perivascular accumulations of lymphocytes and numerous neutrophils and eosinophils has been found [31,32]. Some studies [33–35] reported the presence of vasculitis, however, others did not [31]. Laboratory findings include a high erythrocyte sedimentation rate, and mild proteinuria or hematuria on urinalysis; however, these patients had normal complement levels and circulating immune complexes were absent [32,35,36].

Series of adults with allergic drug hypersensitivity reaction

Although most reactions occurring between 1 and 24 h are labeled as T cell-mediated, there are some contradictory results that deserve our attention [24–27,42,43]. Regarding betalactam allergy, Hjordtund [24] found that from 235 cases with a non-immediate reaction (>1 h after drug intake), 12 had positive specific IgE *in vitro*, one had positive immediate skin prick test result, six had immediate positive intradermal test readings. For proton pump inhibitors, there are descriptions of patients with urticarial reactions from 1 to 3 h after drug administration and with positive skin tests to these drugs during immediate reading [25,26].

Finally, important information can be obtained by analysing series of patients with nonimmediate reactions to radiocontrast media, where 88% of the reactions appear in the first 24 h (in up to 16% from 1 to 6 h, up to 27% from 7 to 12 h, and up to 45% from 13 to 24 h) [27,42,43]. Differences can arise between the time intervals described in the clinical history and in the positive drug provocation test, with it generally being quicker in the drug provocation test [43]. Moreover, although in the three studies [27,42,43] skin tests (intradermal or patch testing) were mainly positive during delayed reading, there were two cases that were only positive in the immediate reading although the reaction occurred between 12 and 14 h [27].

These results indicate that although in most studies nonimmediate reactions seems to be T cell-mediated, in some cases an IgE-mediated mechanism cannot be ruled out (Fig. 2c). This may be explained by different reasons: the route of drug administration, with the latent interval being longer when the drug is administered orally; the possibility of reactions induced by drug metabolites rather than the parent drug; inconsistency of the clinical history [14,15]. The latter is probably the most common cause of confusion between immediate and accelerated reactions and the reason why for an accurate classification of allergic DHR, one needs to know not only the time interval but also a detailed description of the clinical symptoms and signs [48].

Series of children with allergic drug hypersensitivity reaction

In children, mechanisms involved in allergic DHR are similar to those appearing in adults [23,37,38,39,40,41]. In this age group, SSLR is a clinical picture that deserves special attention [23], as betalactams are the drugs most frequently implicated [37,38,39].

In one study [37] of 20 children with confirmed nonimmediate allergy to betalactams, seven of them had SSLR and all were diagnosed by a positive drug provocation test and negative skin test. In another large study [38], including 1430 children with a history of betalactam allergy, 23 had a suggestive clinical history of SSLR. A high percentage ($N=11$, 47.8%) was confirmed as SSLR: three by skin test (one of them on delayed reading), four by drug provocation test and four by clinical history alone. However, the mechanisms underlying the reactions were not fully evaluated [38].

The existence of SSLR in children with betalactam allergy has been questioned [39,41]. In fact, in cefaclor-induced SSLR, it has been suggested that a unique idiosyncratic mechanism involving hepatic

biotransformation of the parent drug with a defect in the metabolism of reactive intermediates rather than an immune-mediated hypersensitivity reaction is involved [41]. More recently, from the evaluation of 783 patients with a history of betalactam allergy, seven had a history of SSLR although six children tolerated betalactam administration and one of them was confirmed as having betalactam-induced MPE. Therefore in this study [39], no cases with a history of SSLR were finally confirmed.

CONCLUSION

Classification of allergic DHR is complex, especially for reactions appearing between 1 and 24 h after drug intake (accelerated reactions), and this may be different depending on the culprit drug. The underlying mechanism of accelerated reactions is not completely understood, although most are mediated by a T-cell mechanism. However, in some patients a specific IgE-mediated mechanism cannot be ruled out and SSLR must also be considered, especially for children.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Organization WH. International drug monitoring: the role of national centres. Report of a WHO meeting. World Health Organ Tech Rep Ser 1972; 498: 1–25.

2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; 356:1255–1259.
 3. Thong BY, Leong KP, Tang CY, *et al.* Drug allergy in a general hospital: results of a novel prospective inpatient reporting system. *Ann Allergy Asthma Immunol* 2003; 90:342–347.
 4. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. *Textbook of adverse drug reactions*. Oxford: Oxford University Press; 1977.
 5. Dona I, Blanca-Lopez N, Torres MJ, *et al.* Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol* 2012; 22:363–371.
 6. Johansson SG, Bieber T, Dahl R, *et al.* Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113:832–836.
 7. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 2005; 5:309–316.
 8. Gell PGH, Coombs RRA. *Clinical aspects of immunology*. Oxford: Blackwell; 1963.
 9. Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003; 139:683–693.
 10. Levine BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *N Engl J Med* 1966; 275:1115–1125.
 11. Terrados S, Blanca M, Garcia J, *et al.* Nonimmediate reactions to betalactams: prevalence and role of the different penicillins. *Allergy* 1995; 50:563–567.
 12. Torres MJ, Blanca M, Fernandez J, *et al.* Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; 58:961–972.
 13. Romano A, Blanca M, Torres MJ, *et al.* Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy* 2004; 59:1153–1160.
 14. Bircher AJ, Scherer Hofmeier K. Drug hypersensitivity reactions: inconsistency in the use of the classification of immediate and nonimmediate reactions. *J Allergy Clin Immunol* 2012; 129:263–264.
 15. Bircher AJ, Scherer K. Delayed cutaneous manifestations of drug hypersensitivity. *Med Clin North Am* 2010; 94:711–725.
 16. Demoly P, Adkinson NF, Brockow K, *et al.* International Consensus on drug allergy. *Allergy* 2014; 69:420–437.
- In the manuscript, it is considered the difficulty on classification of drug allergy, especially in those reactions appearing from 1 to 6 h, where an overlapping exist. They considered the importance of the clinical symptoms together with the time interval between drug administration and drug reaction.
17. Atanaskovic-Markovic M, Gaeta F, Medjo B, *et al.* Nonimmediate hypersensitivity reactions to beta-lactam antibiotics in children: our 10-year experience in allergy work-up. *Pediatr Allergy Immunol* 2016; DOI: 10.1111/pai.12565 [Epub ahead of print]
 18. Sampson HA, Munoz-Furlong A, Campbell RL, *et al.* Second symposium on the definition and management of anaphylaxis: summary report: second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391–397.
 19. Limsuwan T, Demoly P. Acute symptoms of drug hypersensitivity (urticaria, angioedema, anaphylaxis, anaphylactic shock). *Med Clin North Am* 2010; 94:691–710.
 20. Blanca-López N, Pérez-Sánchez N, Agúndez J, *et al.* Allergic reactions to metamizole: immediate and delayed responses. *Int Arch Allergy Immunol* 2016 (in press).
 21. Torres MJ, Mayorga C, Leyva L, *et al.* Controlled administration of penicillin to patients with a positive history but negative skin and specific serum IgE tests. *Clin Exp Allergy* 2002; 32:270–276.
 22. Christiansen IS, Kroigaard M, Mosbech H, *et al.* Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; 45:807–814.
- In this manuscript, authors confirmed that the shorter the interval between drug administration and development of symptoms (less than 15 min), the higher the possibility of confirming an immediate drug allergic reaction.
23. Vial T, Pont J, Pham E, *et al.* Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother* 1992; 26:910–914.
 24. Hjortlund J, Mortz CG, Skov PS, *et al.* Diagnosis of penicillin allergy revisited: the value of case history, skin testing, specific IgE and prolonged challenge. *Allergy* 2013; 68:1057–1064.
 25. Bose S, Guyer A, Long A, *et al.* Evaluation and management of hypersensitivity to proton pump inhibitors. *Ann Allergy Asthma Immunol* 2013; 111:452–457.
 26. Sobrevia Elfau MT, Garces Sotillos M, Ferrer Claveria L, *et al.* Study of cross-reactivity between proton pump inhibitors. *J Investig Allergol Clin Immunol* 2010; 20:157–161.
 27. Brockow K, Romano A, Aberer W, *et al.* Skin testing in patients with hypersensitivity reactions to iodinated contrast media: a European multicenter study. *Allergy* 2009; 64:234–241.
 28. Warrington RJ, Silviu-Dan F, Magro C. Accelerated cell-mediated immune reactions in penicillin allergy. *J Allergy Clin Immunol* 1993; 92:626–628.
 29. Torres MJ, Mayorga C, Fernandez TD, *et al.* T cell assessment in allergic drug reactions during the acute phase according to the time of occurrence. *Int J Immunopathol Pharmacol* 2006; 19:119–130.
 30. Gomez E, Blanca-Lopez N, Salas M, *et al.* Induction of accelerated reactions to amoxicillin by T-cell effector mechanisms. *Ann Allergy Asthma Immunol* 2013; 110:267–273.
- The first manuscript that clearly establishes that accelerated reactions are mediated by a T-cell mechanism, with no involvement of IgE. The mechanisms underlying these reactions are the same that those previously described for delayed reactions.
31. Tolpinrud WL, Bunick CG, King BA. Serum sicknesslike reaction: histopathology and case report. *J Am Acad Dermatol* 2011; 65:e83–e85.
 32. Aujero MP, Brooks S, Li N, *et al.* Severe serum sickness-like type III reaction to insulin detemir. *J Am Acad Dermatol* 2011; 64:e127–128.
 33. Yerushalmi J, Zvulunov A, Halevy S. Serum sickness-like reactions. *Cutis* 2002; 69:395–397.
 34. Swanson JK, English JC 3rd. Serum sickness-like reaction to pamabrom. *J Drugs Dermatol* 2006; 5:284–286.
 35. Mathur AN, Mathes EF. Urticaria mimickers in children. *Dermatol Ther* 2013; 26:467–475.
 36. Misirliloglu ED, Duman H, Ozmen S, *et al.* Serum sickness-like reaction in children due to cefditoren. *Pediatr Dermatol* 2012; 29:327–328.
 37. Blanca-Lopez N, Zapatero L, Alonso E, *et al.* Skin testing and drug provocation in the diagnosis of nonimmediate reactions to aminopenicillins in children. *Allergy* 2009; 64:229–233.
 38. Ponvert C, Perrin Y, Bados-Albiero A, *et al.* Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol* 2011; 22:411–418.
 39. Zambonino MA, Corzo JL, Munoz C, *et al.* Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol* 2014; 25:80–87.
- In this study, it is established that patients that originally reported SSLR developed symptoms only affecting the skin when a drug provocation test was performed. Therefore these authors questioned the existence of SSLR.
40. Gomes ER, Brockow K, Kuyucu S, *et al.* Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy* 2016; 71:149–161.
- In this review, authors described the SSLR as a typical clinical picture that appear especially in children.
41. Kearns GL, Wheeler JG, Childress SH, *et al.* Serum sickness-like reactions to cefaclor: role of hepatic metabolism and individual susceptibility. *J Pediatr* 1994; 125:805–811.
 42. Hasdenteufel F, Waton J, Cordebar V, *et al.* Delayed hypersensitivity reactions caused by iodixanol: an assessment of cross-reactivity in 22 patients. *J Allergy Clin Immunol* 2011; 128:1356–1357.
 43. Torres MJ, Gomez F, Dona I, *et al.* Diagnostic evaluation of patients with nonimmediate cutaneous hypersensitivity reactions to iodinated contrast media. *Allergy* 2012; 67:929–935.
 44. Picker LJ, Treer JR, Ferguson-Darnell B, *et al.* Control of lymphocyte recirculation in man. II. Differential regulation of the cutaneous lymphocyte-associated antigen, a tissue-selective homing receptor for skin-homing T cells. *J Immunol* 1993; 150:1122–1136.
 45. Blanca M, Torres MJ, Leyva L, *et al.* Expression of the skin-homing receptor in peripheral blood lymphocytes from subjects with nonimmediate cutaneous allergic drug reactions. *Allergy* 2000; 55:998–1004.
 46. Fernandez TD, Mayorga C, Torres MJ, *et al.* Cytokine and chemokine expression in the skin from patients with maculopapular exanthema to drugs. *Allergy* 2008; 63:712–719.
 47. Ariza A, Barriónuevo E, Mayorga C, *et al.* IgE to penicillins with different specificities can be identified by a multi-epitope macromolecule: bihaptenic penicillin structures and IgE specificities. *J Immunol Methods* 2014; 406:43–50.
 48. Seitz CS, Brocker EB, Trautmann A. Diagnosis of drug hypersensitivity in children and adolescents: discrepancy between physician-based assessment and results of testing. *Pediatr Allergy Immunol* 2011; 22:405–410.