

ORIGINAL PAPER

Drug allergy claims in children: from self-reporting to confirmed diagnosis

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Summary

Background Poorly documented self-reported drug allergy (DAll) is a frequent problem in daily clinical practice and has a considerable impact on prescription choices. The diagnostic work-up of drug hypersensitivity (DHs) allows a better classification of the reactions and provides patients with more reliable information and recommendations for future treatments. **Objective** To assess the prevalence of self-reported adverse drug reactions (ADRs) and DAll in a paediatric population and to investigate children reporting suspected DAll in order to achieve a firm diagnosis.

Design The first phase was based on a cross-sectional survey assessing the life occurrence of ADRs and self-reported DAll carried out at the outpatient clinic of a paediatric hospital. The second phase was based on the diagnostic work-up in children with parent-reported DAll, including detailed anamnesis and *in vitro* and *in vivo* investigations (skin and provocation tests).

Participants One thousand four hundred and twenty-six parents responded to the initial survey. Sixty of the 67 patients with reported DAll were evaluated at the allergy clinic.

Results The prevalences of self-reported ADRs and DAll were 10.2% and 6.0%, respectively. Most of the suspected allergic reactions were non-immediate cutaneous events attributable to β -lactam antibiotics and occurred in very young children. Thirty-nine of the 60 patients consulting for evaluation had a plausible clinical history and were recommended further investigation. DHs was diagnosed in three children only, based on positive responses in skin ($n = 1$) and oral provocation ($n = 2$) tests.

Conclusion ADRs are frequently reported in children, and many children are classified as having a DAll. After complete evaluation, only a few of these reactions can be attributed to DHs and DAll. Most of the patients (94% in this study) could actually tolerate the initially suspected drug.

Keywords children, diagnostic work-up, drug allergy, drug allergy survey, drug hypersensitivity

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Introduction

Adverse drug reactions (ADRs) were defined by the World Health Organization as a noxious and unintended response to a drug that occurs at a dose normally used in humans [1]. The nomenclature review committee of the World Allergy Organization recommended that the term 'drug allergy' (DAll) should be used only when a definite specific immunological mechanism is demonstrated. ADRs that clinically resemble an allergy but where a

specific immunological process is not proven should be classified as non-allergic hypersensitivity reactions [2].

Epidemiological data on DAll and drug hypersensitivity (DHs) are scarce. In a recent bibliographic review, the authors concluded that ADRs can affect 7% of the general population and up to 20% of hospitalized patients [3]. In paediatric populations, a meta-analysis by Impicciatore et al. [4] estimated an overall incidence of 9.53% in hospitalized children and of 1.46% in outpatients. It should be noted that most studies have assessed ADRs in

general, ignoring the underlying pathophysiological mechanism and relying only on the clinical history, without attempting to prove the relationship between drug intake and symptoms. In clinical practice, many patients who have experienced a drug reaction resembling allergy are frequently catalogued as being allergic to the drug, without any further investigation [5, 6], leading to frequent over-diagnosis of 'DAll/hypersensitivity'. However, most patients with suspected DAll have negative responses in skin and challenge tests. In a study in 898 patients with suspected drug-induced immediate-type hypersensitivity, only 241 of 1372 drug provocation tests (17.6%) were positive [7]. Misdiagnosis is an important issue, not only with regard to the possible undesirable consequences for the patients themselves but also regarding its negative impact at the socio-economical level [5, 6, 8, 9].

The diagnostic work-up for DHs is complex, time consuming and varies widely [10] despite the efforts made to harmonize procedures [11–13]. In general use, the diagnosis of DAll/hypersensitivity is based on a detailed clinical history, *in vitro* studies (validated for a few drugs

only), skin testing and provocation tests. However, the need for provocation tests with the suspected drug, especially in children, remains controversial [6, 13–15].

We aimed to assess the prevalence of self-reported ADRs and DAll among outpatients from a children's hospital and to study the diagnostic value of a specialized DAll evaluation in children with parent-reported DAll.

Material and methods

Design of the study

This study included two phases, which are summarized in Fig. 1. The first was based on a cross-sectional survey of children attending the outpatient clinic of a children's hospital. This clinic sees around 86 000 patients/year, reporting different types of medical problems. This first phase lasted 4 months, from June to September 2005. The second phase, carried out in 2006, was based on a clinical evaluation that took place at the allergy clinic and included children whose parents reported suspected DAll.

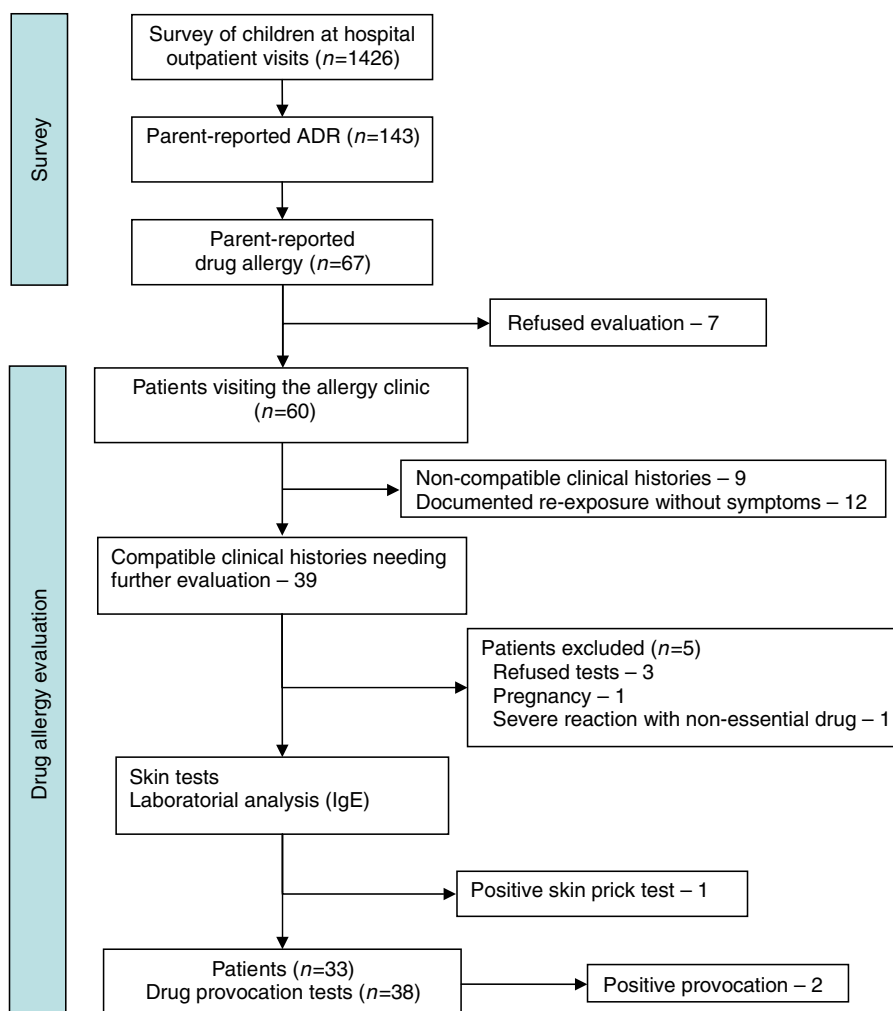


Fig. 1. Study flow chart.

During the first phase, parents filled in a questionnaire [16] while waiting for an appointment with a specialist in allergy, paediatrics, physical rehabilitation, surgery, stomatology, ENT or psychiatry. They returned the questionnaire to the attending doctor who registered the children's main diagnosis. A consecutive sample of 200 questionnaires within each speciality was collected. The questionnaire assessed the life occurrence of ADRs and 'DAll'. Information about the reaction itself (the most serious event if several events occurred) was recorded, assessing the drug(s) involved, clinical manifestations and severity. The existence of a previous diagnosis of 'DAll' by a medical doctor was also evaluated. Children from phase 1 whose parents thought they had a 'DAll' were scheduled for an appointment at the DAll clinic.

In the second phase, a detailed clinical history was recorded and additional data were collected from the patient's hospital and personal health records. Next, the children with a clinical history compatible with DAll/hypersensitivity were proposed to continue the DAll evaluation, based on specific IgE determination for β -lactams, prick and intradermal (ID) skin testing for β -lactams, local anaesthetics and sulphonamides, and patch tests for all drugs if a delayed reaction was reported. Finally, a provocation test was performed if all the other investigations were inconclusive and if the provocation test was not contra-indicated. The ENDA guidelines on skin and drug provocation tests were carefully respected [12, 13]. Provocation tests were performed with the suspected culprit drug(s), administered at 30–60-min intervals until the administration of the full age/weight-adjusted single dose was achieved, reaching a total cumulative amount close to the usual age/weight-adjusted daily dose.

The survey was approved by the local ethical committee. Parents gave written informed consent for *in vivo* tests.

Statistical analysis

Frequency tables were created and standard descriptive techniques were used. The number of positive answers and valid percent values are shown, taking missing values into account. Statistical analysis was carried out with SPSS® v.14.

Results from the survey

Table 1 summarizes the demographic characteristics of the children included in the survey, the proportions of parent-reported ADRs and DAll and the reported existence of a previous diagnosis of 'DAll' by the paediatrician or family doctor (dxDA). The description of the ADRs of the children with parent-reported DAll is presented in Table 2. We found a 10.2% prevalence of self-reported ADRs, and 6.0% of the parents were convinced that their children

Table 1. Demographic characteristics of the studied population

	Total (n = 1426)	Parent-reported 'drug allergy' (n = 67)
Gender (M/F)	849/547*	41/26
Age mean $\pm$ SD (years)	7.3 $\pm$ 4.3	7.9 $\pm$ 4.0
ADRs, n (%) [†]	143 (10.2)	NA
Parent-reported DAll, n (%) [†]	67 (6.0)	NA
Medical diagnosis DAll, n (%) [†]	44 (3.9)	37 (88.1)

*Not reported in 30 (2.1%) of cases.

[†]Valid percent.

ADRs, adverse drug reactions; DAll, drug allergy; NA, not applicable.

Table 2. Description of adverse drug reactions (ADR) of children whose parents considered them to have a drug allergy

	Children with suspected 'drug allergy,' n (%) [*]
Age (years) when ADRs occurred	
≤ 2	23 (51)
3–5	12 (27)
6–10	9 (20)
≥ 10	1 (2)
Time to ADRs (h)	
≤ 1	13 (21)
> 1	48 (79)
Reported symptoms	
Cutaneous	41 (62)
Digestive	17 (26)
Respiratory	13 (20)
Other	4 (6)
Suspected drug	
NSAID	10 (18)
β -lactams	29 (52)
Other antibiotics	4 (7)
Other	13 (23)
Need medical care for ADRs	53 (83)

*Some data were missing; valid percentages are shown.

had a 'DAll'. The frequency of a previous medical diagnosis of 'DAll' was lower (3.9%). Self-reported allergy was not significantly different in boys and girls.

Most of the reactions in the group with self-reported DAll were non-immediate cutaneous reactions attributable to β -lactam antibiotics, and occurred before the age of 3. Most reactions were mild to moderately severe. Eighty-three percent of the parents had to seek medical advice at the time of the reaction, but only 47% of the reactions required a treatment with anti-allergic drugs and/or corticosteroids. The mean time elapsed from the reaction to the survey was 3.9 ± 3.1 years.

Results of the specialized drug allergy evaluation

Among the 67 children whose parents thought they had a DAll, 60 (90%) came to the appointment at the DAll clinic.

After a detailed anamnesis and analysis of clinical records, it was possible to complete most of the data missing in the initial survey. Nine patients (15%) were considered as having well-known side-effects of medications not compatible with a diagnosis of DAll/hypersensitivity. Twelve other children (20%) had already tolerated subsequent treatments with the initially suspected drugs. The remaining 39 children (65%) had a compatible clinical history of DHs and required further evaluation. Three (5%) refused the diagnostic procedures, one 16-year-old girl was excluded because of an ongoing pregnancy, and another child was excluded because of an initial serious adverse reaction to a drug that was considered 'not important' (pirantel pamoato). Thus, 34 children (57%) agreed to proceed with diagnostic tests. Skin tests and/or specific IgE were carried out in 26 patients. Skin tests were performed with PPL and MDM (Kit DAP from Diater Laboratorios S.A., Madrid, Spain), amoxicillin 20 mg/mL, ampicillin 20 mg/mL, Penicillin G 10.000 IU/mL and cephalosporin 2 mg/mL for β -lactams, and a 2 mg/mL concentration was used for cotrimoxazole. Native drugs were used for patch tests. One patient, who had a clinical history of anaphylaxis and a positive ID test with ceftriaxone, underwent a provocation test with amoxicillin. In the 33 other children, 37 provocation tests were performed with the suspected drug(s). The drugs tested were β -lactams in 20 patients (59%) (eight amoxicillin, eight amoxicillin/clavulamic acid, two cefaclor, one cefatrizine, one cefixime) and analgesics, antipyretics and non-steroidal anti-inflammatory drugs in eight patients (23%) (six ibuprofen, two paracetamol). Non- β -lactam antibiotics were tested in six patients (one erythromycin, two clarithromycin, three cotrimoxazole), and other drugs (one lidocaine, one hydrocortisone, one acyclovir) in three patients. Most of the reactions reported in the children who underwent provocation tests were cutaneous (79%) and non-immediate (82%), occurring more than 1 h after the last exposure to the drug (Table 3). In six (18%) cases, the reaction involved more than one organ/system.

After complete evaluation, DHs was documented in only three of 34 patients (9%), including one patient with positive skin tests and two with positive provocation tests (Table 4). Among the 20 patients claiming allergy to β -lactams, only two (10%) were diagnosed as having allergic ($n = 1$) or non-allergic ($n = 1$) DHs.

Overall, from the 60 evaluated patients claiming 'DAll', only 39 (65%) had a plausible clinical history. Thirty-one of the 33 patients (94%) had a negative allergological work-up and could actually tolerate the suspected drug.

Discussion

This study supports the idea that a complete and careful diagnostic work-up is essential in order to classify ADRs as DHs.

The results from the survey indicate that ADRs occur frequently in children (8.7%), and that many children are classified as 'allergic', not only by their parents (46%) but also by healthcare professionals (31%). Previous studies in adults [3, 5, 9, 16–18] and children [3, 4, 19, 20] reported a similar prevalence of ADRs. However, these studies were not used to firmly demonstrate the diagnosis. It is largely believed that about one third of ADRs can be related to hypersensitivity [21], and the data from our survey on a first approach supported this idea. However, when a proper diagnostic work-up was carried out, hypersensitivity could be excluded in most patients and was uncovered in only three of 60 cases (5%). A careful examination of clinical records can help to discard the label of hypersensitivity in numerous patients [18, 22, 23]. This was the case in 21 of 60 (35%) children in our survey. The suspected drugs in our study were the same as those reported in other paediatric allergy clinics, and reflect prescribing patterns in children [6, 19, 20, 23–25]. Also, the clinical manifestations reported by the parents and healthcare professionals were similar to those reported by other groups [18, 19, 24, 26, 27]. The young age at the time of the reaction was unexpected, although it has been reported previously by other authors [28]. This particular result defies our current knowledge about DAll because, usually, more than one exposition is needed to develop sensitization and DAll. The female predominance found in most studies on ADRs and DHs in adult populations [28, 29] is not disclosed in most paediatric studies [24, 30].

The discrepancy between alleged DAll and the demonstration of a presumable immunological mechanism behind reactions has also been found by other authors using similar diagnostic work-up protocols [6, 7, 18, 23, 31, 32]. It is important to notice that a positive provocation test can ascertain DHs but does not give any insight into the exact underlying mechanism of the reaction; thus, it does not allow the diagnosis of DAll.

Our study may have some limitations. First, we used the same 1-day drug provocation protocol for both immediate and non-immediate reactions. This has been done by others [7] with good results but it can be argued that in non-immediate DHs an oral provocation test may require a prolonged treatment in order to become positive and some authors propose a 5–7-day protocol. It should, however, be noted that the sensitivity of either protocols is still not known, comparative studies are lacking and so far we only have level C evidence for the use of these tests. Another important point is that 47% of the reactions fully investigated occurred more than 1 year before the appointment (data not shown). Several papers have demonstrated that sensitization decreases with time, especially IgE-mediated responses to β -lactams [33, 34], but this phenomenon seems less important in paediatric populations [30, 32]. Our results probably also reflect the fact that most of the reactions studied were non-immediate,

Table 3. Patients submitted to provocation tests: details on reactions and drugs involved

Patient	Number and type of reactions	Suspected drug/s	ST results	DPT results
1	2 IR Nausea/vomiting, generalized pruritus	Amox/Clav	Negative	Amox/Clav negative
2	1 IR Urticaria/angioedema	Amox/Clav Ceftriaxone	Negative	Amox/Clav negative
3	1 IR Anaphylaxis	Ceftriaxone	Positive ID test Ceftriaxone (2 mg/mL)	Amox negative
4	1 IR Brochospasm	Ibuprofen		Ibuprofen negative
5	1 IR Generalized erythema	Ibuprofen		Ibuprofen negative
6	1 IR and 1 NIR Periocular angioedema/urticaria	Ibuprofen		Ibuprofen negative
7	1 NIR Maculo-papular eruption	Erythromycin	Negative	Erythro negative
8	1 NIR Urticaria/angioedema	Clarithromycin	Negative	Clarithro negative
9	1 NIR Maculo-papular eruption	Clarithromycin	Negative	Clarithro negative
10	1 NIR Fixed drug eruption	Cotrimoxazol	Negative	Cotrimox positive (cumulative dose 480/96 mg)
11	1 NIR Maculo-papular eruption	Cotrimoxazol	Negative	Cotrimox negative
12	1 NIR Maculo-papular eruption	Cotrimoxazol	Negative	Cotrimox negative
13	1 NIR Maculo-papular eruption	Ibuprofen		Ibuprofen negative
14	1 NIR Maculo-papular eruption, rhinorea, ocular congestion	Ibuprofen		Ibuprofen negative
15	2 NIR Maculo-papular eruption	Paracetamol		Paracetamol negative
16	1 NIR Urticaria	Paracetamol Amoxicillin	Negative	Paracetamol and Amox negative
17	2 NIR Macular eruption and desquamation	Ibuprofen Amoxicillin Cefprozil	Negative	Ibuprofen negative Amox positive (cumulative dose 925 mg)
18	1 NIR Dyspnea, macular-papular eruption	Amoxicillin	Negative	Amox negative
19	1 NIR Pruritus, macular-papular eruption	Amoxicillin	Negative	Amox negative
20	2 NIR Maculo-papular eruption	Amoxicillin	Negative	Amox negative
21	1 NIR Generalized erythema and pruritus	Amoxicillin	Negative	Amox negative
22	2 NIR Urticaria	Amoxicillin	Negative	Amox negative
23	2 NIR Maculo-papular eruption	Amoxicillin Cefaclor	Negative	Amox and Cefaclor negative
24	1 NIR Dyspnea, nausea, vomiting	Cefaclor	Negative	Cefaclor negative

Table 3. Continued

Patient	Number and type of reactions	Suspected drug/s	ST results	DPT results
25	1 NIR Vomiting, diarrhoea, irritability, pruritus	Cefatrizine	Negative	Cefatrizine negative
26	2 NIR Maculo-papular eruption	Cefixime Amox/Clav	Negative	Cefixime and Amox/Clav negative
27	3 NIR Urticaria	Amox/Clav	Negative	Amox/Clav negative
28	1 NIR Nausea, diarrhoea, pruritus	Amox/Clav	Negative	Amox/Clav negative
29	1 NIR Facial oedema, flushing	Amox/Clav	Negative	Amox/Clav negative
30	1 NIR Macular-papular eruption	Amox/Clav	Negative	Amox/Clav negative
31	1 NIR Pruritus Macular-papular eruption	Amox/Clav	Negative	Amox/Clav negative
32	1 NIR Macular-papular eruption	Acyclovir	Negative	Acyclovir negative
33	1 NIR Localized oedema	Hydrocortisone	Negative	Hydrocortisone negative
34	1 NIR Localized oedema/swelling	Lidocaine	Negative	Lidocaine negative

ST, skin test; DPT, drug provocation test.

Table 4. Results from *in vivo* diagnostic procedures

Suspected drugs	Provocation test with culprit drug (n)	Positive tests (n)
β -lactams	20	2*
NSAIDs	8	0
Non- β -lactams antibiotics	6	1
Other drugs	3	0

*One patient with a positive skin ID test and another one with a positive provocation test.
ID, intradermal.

and that non-immediate reactions to drugs result less frequently than immediate reactions from allergic or non-allergic hypersensitivity [7, 14, 30]. Finally, it was impossible to fully investigate the 67 children with parent-reported DAll, because seven families refused the initial evaluation and five other children were excluded from the complete work-up protocol (Fig. 1).

Our results highlight the fact that epidemiological data on ADRs and DAll should be very carefully evaluated, because many ADRs are misdiagnosed as DHs reactions. This may be particularly important in children, who are frequently exposed to infectious agents capable of causing symptoms like wheezing, urticaria and maculopapular eruptions, which are also common features of DHs [35, 36]. Thus, it is important to point out that if 5.2% of the population believe to have some kind of DAll, healthcare

systems should be organized in order to fulfil the needs of the patients. Centres with trained professionals able to proceed with a full diagnostic evaluation, to confirm or discard DHs and to give recommendations for future treatments, are urgently needed because misdiagnosis of DAll leads to a considerable increase in health costs [8, 9, 18, 37], can put the patient at risk when taking less effective and/or more 'dangerous' drugs [5, 6, 8, 9, 37, 38], can lead to antibiotic resistance [37] and is a persistent cause of concern for patients and prescribing physicians who fear future reactions.

We can conclude that DHs is an important and prevalent problem that needs to be fully accessed in specialized centres as misdiagnosis is frequent. A complete investigation of clinical reports will allow professionals to provide patients with better and more reliable information and can help in the understanding of the pathophysiology of the reactions.

Implications for future research and organization of health care

The positive predictive value of questionnaires assessing DHs and allergy seems to be too low for use as tools for epidemiologic studies. This is also the case for pharmacovigilance algorithms in use [39, 40], emphasizing the need for an exhaustive diagnostic work-up including oral provocation tests. This indicates the need for trained

professionals and facilities to respond promptly to increasing solicitations. Studies focusing on the cost/benefit analysis of a full diagnostic work-up in suspected DAll as well as prospective work in larger series and cohort studies with a follow-up of investigated patients should be encouraged.

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