

**VII corso Allergologia e Immunologia Pediatrica**

Benevento

23-25 Maggio 2013

**Eruzioni cutanee da farmaci: quando e come possiamo trovare una relazione? E se la sospettiamo, cosa facciamo?**

Guglielmo Scala

UOSD Allergologia

Loreto Crispi, Napoli

## **Drug trials in children: problems and the way forward**

*Conroy S, 2000, Br J Clin Pharmacol*

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**1968: disastro Talidomide**

**1996: task force British Pediatric Association per valutazione uso dei farmaci in pediatria**

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**Off-label fino al 90%**

- 
- a. dosi
  - b. gruppi di età
  - c. vie di somministrazione
  - d. indicazioni

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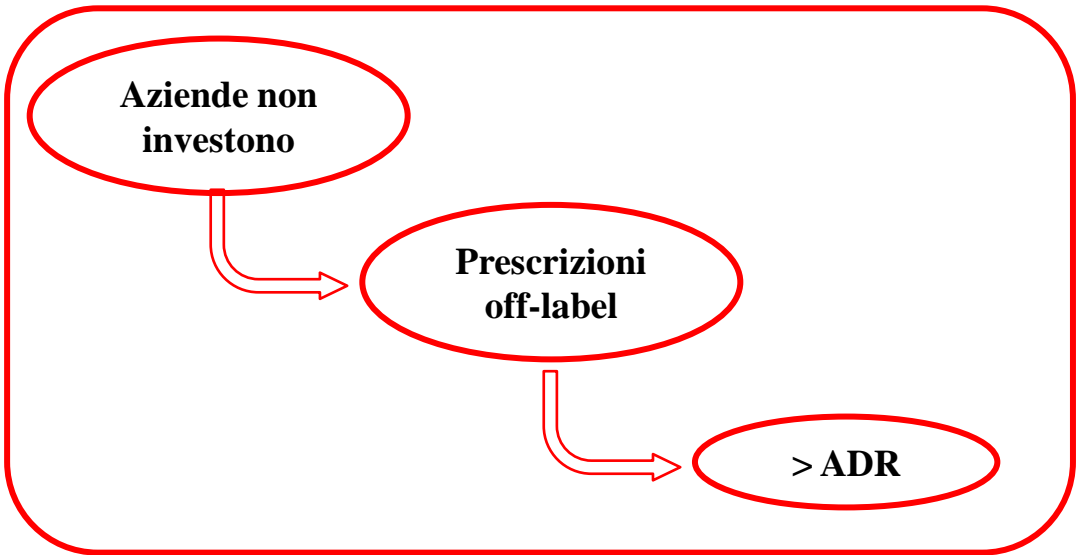
- a. dosi
- b. gruppi di età
- c. vie di somministrazione
- d. indicazioni

**Aziende non investono volentieri in studi pediatrici.**

- a. Numeri**
- b. Etica**
- c. Prelievi ematici**
- d. Consensi**

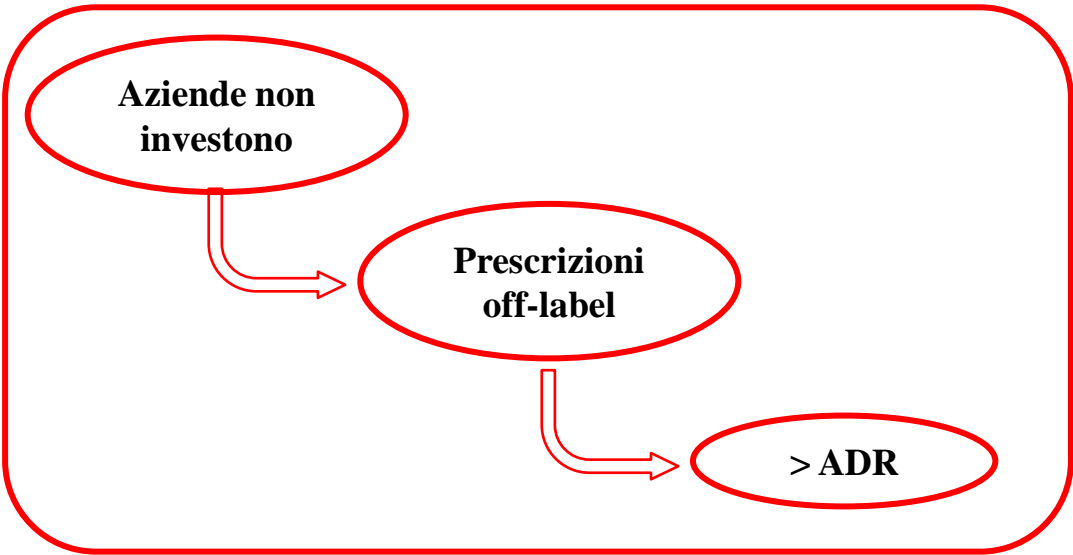
**Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study.**

*Turner S et al, 1999, Acta Paediatrica*

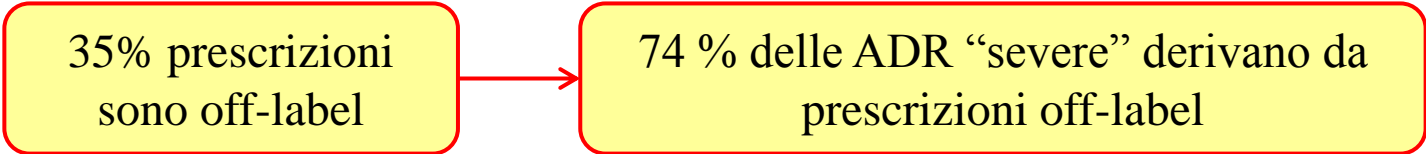


# Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study.

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prescrizioni	ADR
"corrette"	3.9 %
Off-label	6 %



## Drug trials in children: problems and the way forward

Conroy S, 2000, *Br J Clin Pharmacol*

*“Children have the same rights as adults to receive medicines that have been shown to be safe and effective.”*

Malattie esclusivamente pediatriche

trial pediatrici prima di adulti

Malattie prevalentemente pediatriche

trial precoci e paralleli

Malattie adulti e bambini a terapia note

trial precoci in pediatria

Malattie prevalentemente adulti

aggiungere bambini in fase III

Prima grande review metanalitica su pazienti adulti

ADR totali =

ADR motivo di ricovero ospedaliero + ADR intraospedaliera

<b>Motivo di ricovero</b>	<b>4.7 %</b>	
<b>ADR ospedaliera</b>	<b>10.9 %</b>	<b>(severe 2.1 %)</b>
<b>Totale:</b>	<b>15.1 %</b>	<b>(severe 6.7 %)</b>

Numeri relativi al 1994:

**2.216.000** pazienti ospedalizzati ebbero reazioni gravi  
**106.000** fatali (5 causa di morte)



**Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies**

*Impicciatore P et al, 2001, Br J Clin Pharmacol*

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Prima grande review metanalitica su pazienti pediatrici

Epidemiologia in età pediatrica:

Esaminati 17 studi tra il 1973 e il 2000

<b>Motivo di ricovero</b>	<b>2.09 %</b>	<b>(life-threatening: 39.3%)</b>
<b>ADR ospedaliera:</b>	<b>9.53 %</b>	<b>(severe: 12.29 %)</b>
<b>Outpatients:</b>	<b>1.46%</b>	

**Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies**

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<b>Outpatients:</b>	<b>1.46%</b>	

*“Whereas licensed drugs are monitored by spontaneous reporting, epidemiological surveys or surveillance systems, there is currently no similar process for monitoring and collecting information on ADRs due to unlicensed and off-label drug use.”*

*Revisione sistematica sulle ADR in pediatria,  
aggiornamento*

8 studi (6 in pazienti ospedalizzati) pubblicati tra il  
2001 e il 2007

<b>Motivo di ricovero</b>	<b>1.8 %</b>
<b>ADR ospedaliere</b>	<b>10.9 %</b>
<b>Outpatients</b>	<b>1.0 %</b>

***OR di ADR con farmaci off-label = 3.6***

# Adverse drug reactions in childhood: a review of prospective studies and safety alerts

*Clavenna A, Bonati M, 2009, Arch Dis Child*

**Table 1** Study characteristics

Country	Study period	Duration (months)	Population	Age (years)	System (% of ADRs)	Therapeutic class (% of ADRs)
<b>ADRs in hospitalised children</b>						
Norway <sup>12</sup>	1996	5	579	0–16	CNS (28), gastrointestinal (27), skin (11)	Anti-infective agents (9), anti-asthmatics (7), CNS drugs (7)
France <sup>17</sup>	1998	0.25	227	NR	Gastrointestinal (83), rash (17)	NR
Brazil <sup>18</sup>	2001	5	265	0–14	Skin (49), endocrine (15),	Anti-infective agents (53), systemic
Germa	<div style="background-color: yellow; padding: 10px; border: 1px solid black;"> <p style="font-size: 1.5em; margin: 0;">Sistemi coinvolti: cute, SNC, gastrointestinale</p> <p style="font-size: 1.5em; margin: 0;">Farmaci più coinvolti: antibiotici, FANS</p> </div>					
Germa						
Nigeria						
<b>ADRs leading to hospital admission</b>						
Norway <sup>12</sup>	1996	5	919	0–16	NR	NR
France <sup>17</sup>	1998	0.25	260	0–7	CNS (75), gastrointestinal (25)	CNS drugs (50), analgesics (50)
Sri Lanka <sup>22</sup>	2002	11	NR	NR	NR	NR
Nigeria <sup>21</sup>	2006	6	682	0–10	NR	NR
<b>ADRs in outpatient children</b>						
France <sup>17</sup>	1998	0.25	1192	0–4	Skin (50), general (25), gastrointestinal (25)	Antibiotics (75), vaccines (25)
France <sup>23</sup>	2000–1	4	1419	0–16	Gastrointestinal (40), skin (30), CNS (15)	Antibiotics (45), vaccines (15)

## A livello internazionale regna la confusione:

Agenzie	tosse	ASA	cefaclor	ceftriaxone	IS	Domper	Metocl	Halot.
Medwatch, USA	+			+				
Health, Canada								
EMA, Europa								
AFSSAPS, France				+	+			
AIFA, Italia	+	+	+	+		+	+	
BfArM, Germany				+				
AEMPS, Spagna								
MHRA, UK		+		+				+

# Adverse drug reactions in childhood: a review of prospective studies and safety alerts

*Clavenna A, Bonati M, 2009, Arch Dis Child*

**Table 3** Warnings issued by the drug regulatory agencies in 2001–2007

Drug	ADR	Countries
ADHD drug products	Cardiovascular adverse events, neuropsychiatric symptoms	Ca, USA
Amiodarone iv	Potentially fatal and developmental side effects in neonates and infants	USA
Antidepressants	Increased risk of suicidal ideation	Ca, F, G, I, UK, USA
Aspirin	Reye's syndrome	I, UK
Atomoxetine	Increased risk of suicidal thinking in children and adolescents	Ca, G, UK, USA
Cefaclor	Severe allergic reactions	I
Ceftriaxone	Cases of fatal reactions with calcium-ceftriaxone precipitates in the lungs and kidneys in both term and premature neonates	USA, UK, F, G, I
Codeine (nursing mothers)	Risk of severe ADRs for infants with ultra-rapid metaboliser nursing mothers	I, UK, USA
Cough and cold medicines	Serious adverse events (death)	I, USA
Desmopressin (intranasal)	Severe hyponatremia and seizures	F, G, I, UK, USA
Dextroamphetamine	Sudden death in patient with cardiovascular diseases	Ca, USA
Dolasentron	ECG abnormalities (QTc prolongation)	I
Domperidone	Risk of extrapyramidal symptoms	I
Halothane	Increased risk of cardiac arrhythmias	UK
Immunostimulants	Benefit/risk profile unfavourable	F
Lamotrigine	Increased risk of potentially fatal rash in children	F, USA
Lopinavir/ritonavir	Accidental overdose	F, I, USA
Metoclopramide	Risk of extrapyramidal symptoms	F, I
NSAIDs	Septic shock in infants with chickenpox	F
Oprelvekin	Papilloedema (dose limiting side effect)	USA
Oseltamivir	Neuropsychiatric adverse events: suicidal ideation; delirium and abnormal behaviour leading to injury	Ca, F, I, USA
Palivizumab	Anaphylaxis	USA
Pemoline	Cardiovascular adverse events	USA
Promethazine	Respiratory depression, causing death in some children <2 years old	USA
Propofol	Increased number of deaths	Ca, USA
Somatropin	Fatalities reported in paediatric patients with Prader-Willi syndrome with severe obesity/history of respiratory impairment or sleep apnea/unidentified respiratory infection	USA
Topiramate	Oligohydrosis, hyperthermia	Ca, USA
Zonisamide	Increased risk of oligohydrosis and hyperthermia in children	USA

Ca, Canada; F, France; G, Germany; I, Italy; UK, United Kingdom; USA, United States of America.

Le allergie a farmaci sono quasi sempre auto-riferite

La diagnosi si basa sulla storia clinica riferita

Table 1. Demographic characteristics of the studied population

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

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

*Rebelo Gomes E, et al, 2007, Clin Exp Allergy*

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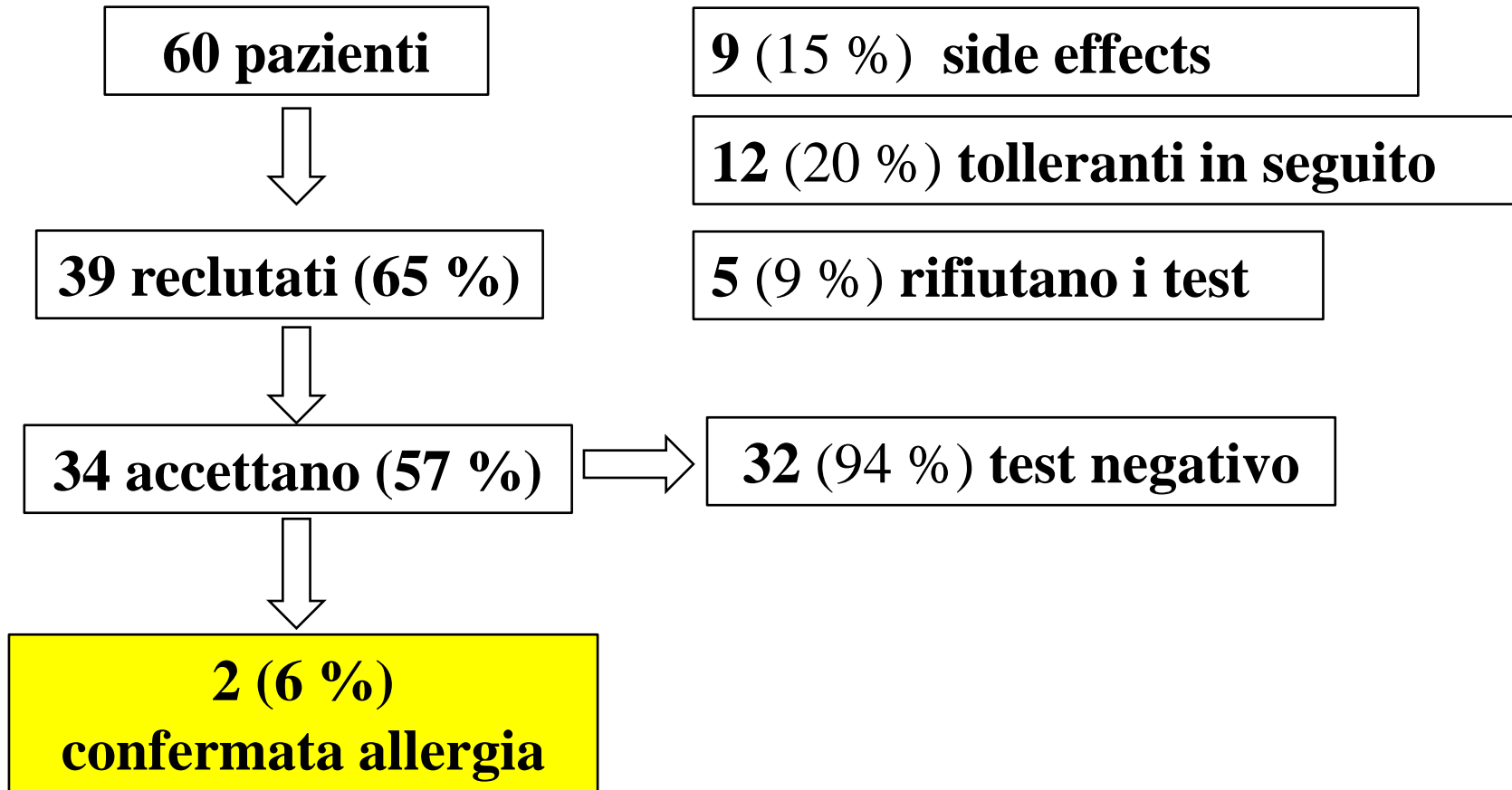
	Children with suspected 'drug allergy,' n (%) <sup>*</sup>
Age (years) when ADRs occurred	
≤ 2	23 (51)
3-5	12 (27)
6-10	9 (20)
≥ 10	1 (2)
Time to ADRs (h)	
≤ 1	13 (21)
> 1	48 (79)
Reported symptoms	
Cutaneous	41 (62)
Digestive	17 (26)
Respiratory	13 (20)
Other	4 (6)
Suspected drug	
NSAID	10 (18)
β-lactams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

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

Rebello Gomes E, et al, 2007, Clin Exp Allergy

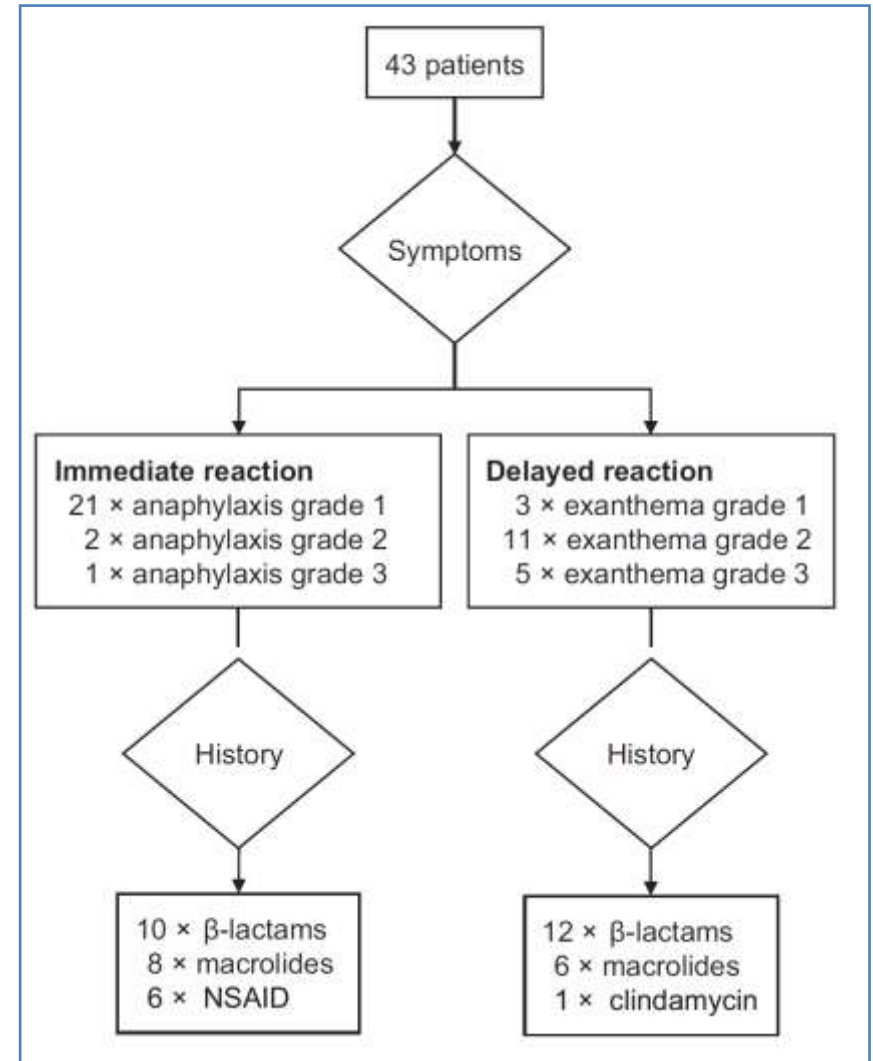


# Diagnosis of drug hypersensitivity in children and adolescents: Discrepancy between physician-based assessment and results of testing

Seitz CS et al, 2011, *Ped Allergy Immunol*

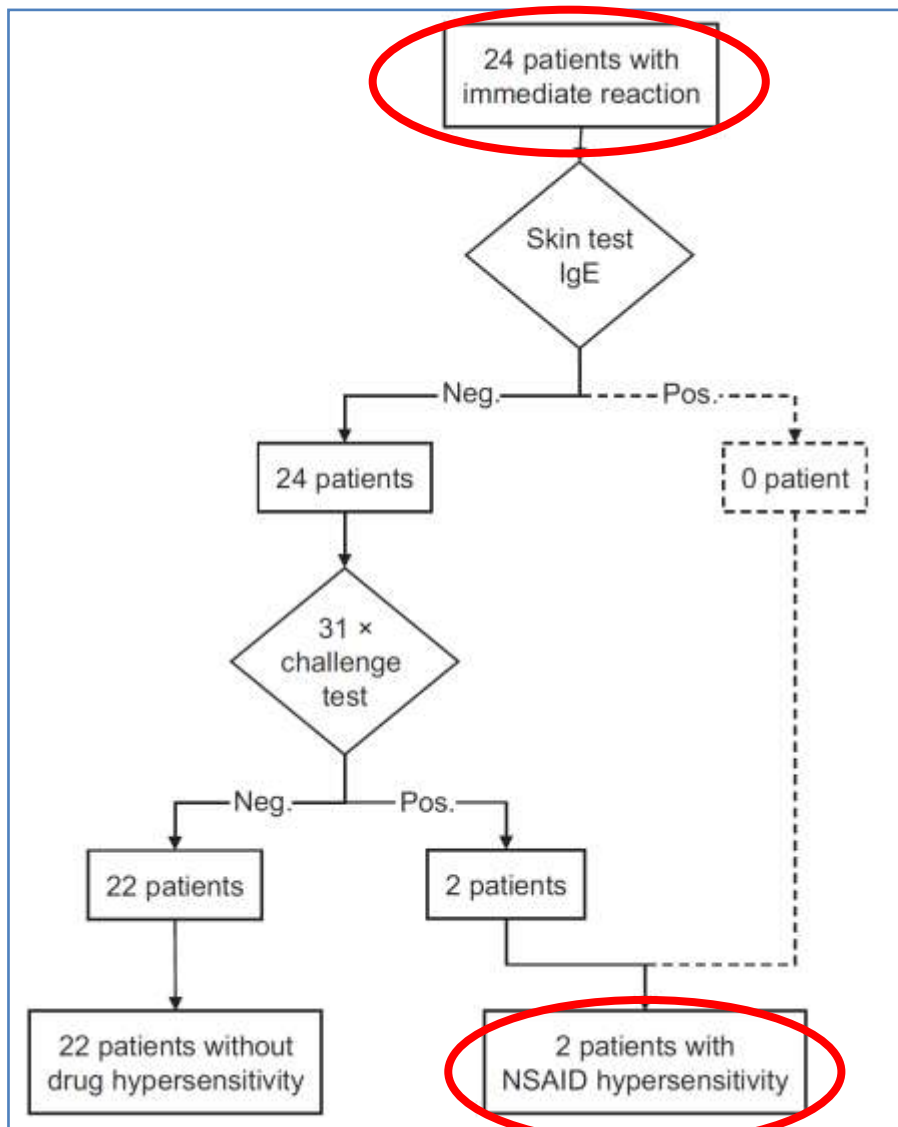
Abbiamo visto che le ADR self-reported si confermano nel 6 % dei casi.

Valutare l'efficacia delle diagnosi poste dai **medici** sulla base dei dati clinici.



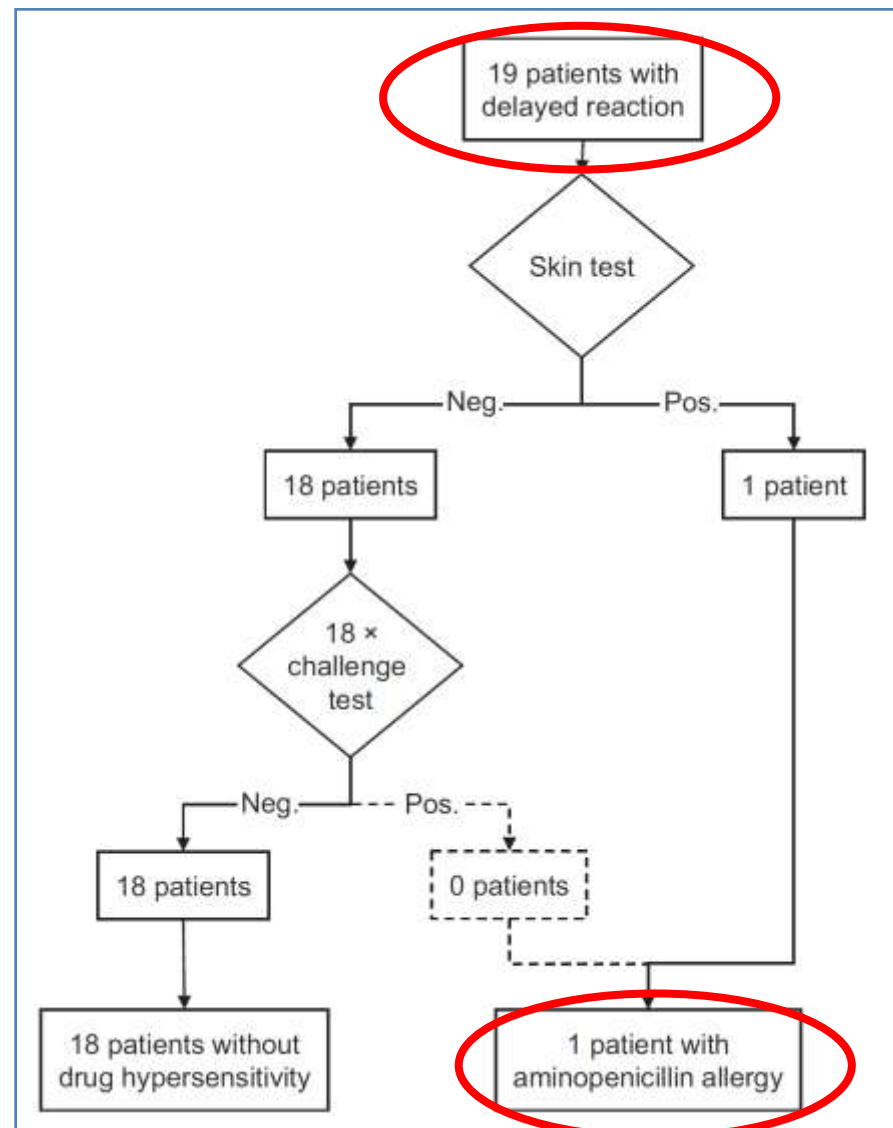
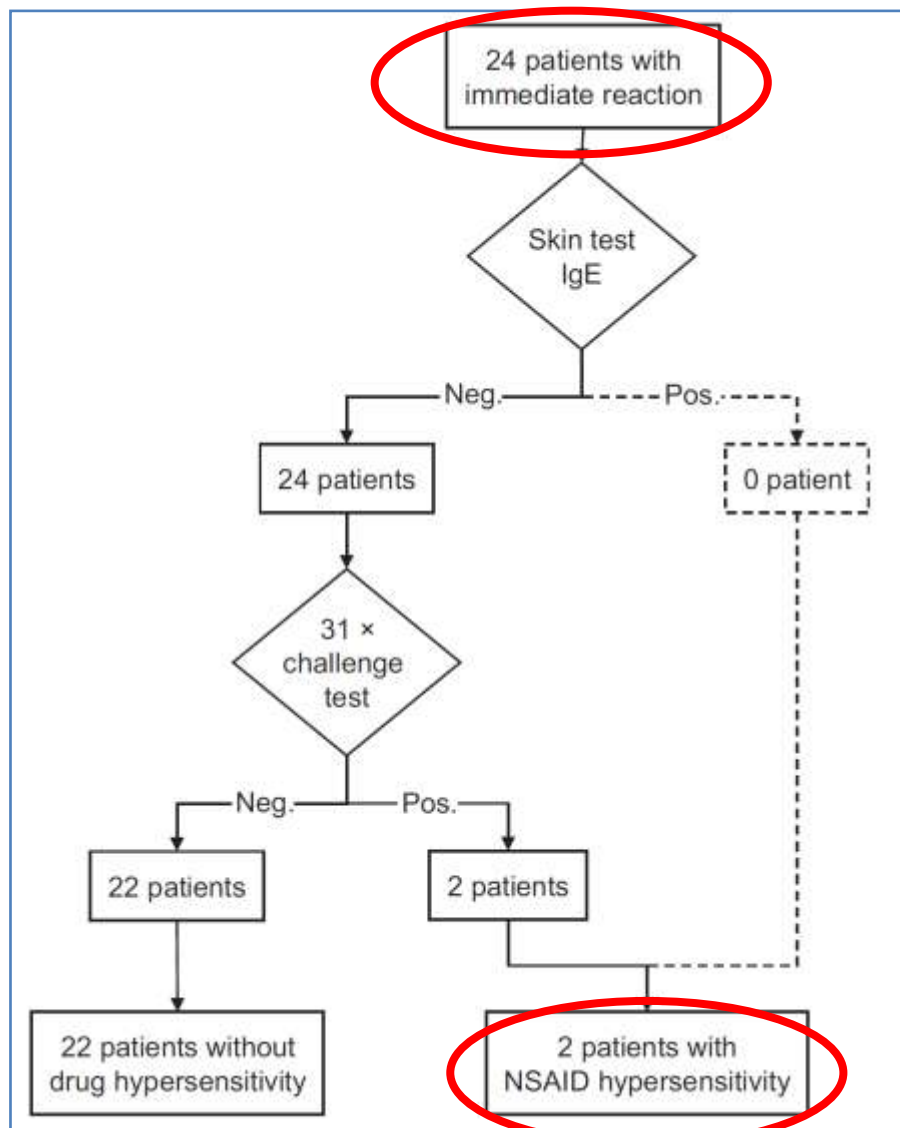
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# Diagnosis of drug hypersensitivity in children and adolescents: Discrepancy between physician-based assessment and results of testing

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ha poi tollerato Cefpodoxime e Ceftriaxone

# Skin manifestations of drug allergy

*Ardner-Jones MR et al, 2011, Br J Clin Pharmacol*

(A) Type of hypersensitivity	Immune effector mechanisms	Clinical manifestations relevant to drug hypersensitivity
<b>Type 1</b> Immediate or anaphylactic	IgE bound to surface of mast cells or basophils. Antigen-binding causes mast cell degranulation, release of histamine and other mediators.	Urticaria, asthma, anaphylaxis
<b>Type 2</b> Cytotoxic	Antigenic determinants on cell surfaces are targets for antibodies, may be IgG or IgM. The antibodies damage cells/tissues by activating complement, or by binding to cells through Fcγ receptors, they activate cytotoxic killing, e.g. by K cells.	Pemphigus, Blood cell penias: haemolytic anaemia, neutropenia, thrombocytopenia
<b>Type 3</b> Immune complex	Circulating immune complexes are deposited in vascular beds or on tissue surfaces. Complement is activated, neutrophils attracted and their products damage tissues.	Vasculitis - hypersensitivity vasculitis, Henoch-Schonlein purpura
<b>Type 4</b> Delayed type, T cell mediated	Effector T lymphocytes, may be CD4 <sup>+</sup> or CD8 <sup>+</sup> , producing different patterns of cytokines and/or cytotoxic factors.	Many clinical patterns sub-categorized in Table 1B

(B)	Immune mediators	Inflammation characterized by:	Clinical pattern
<b>Type 4a</b>	Th1/Tc1 cells: IFN-γ, TNFα	T cells, macrophages	Contact dermatitis, Tuberculin reaction
<b>Type 4b</b>	Th2 cells: IL-4/-13 IL-5	Eosinophils	Maculopapular rash, Exanthemata with eosinophilia
<b>Type 4c</b>	Cytotoxic T cells: Perforin Granzyme B	T cells Keratinocyte apoptosis	Contact dermatitis, maculopapular rash, drug-induced exanthemata, Bullous eruptions (SJS.TEN)
<b>Type 4d</b>	T cells: CXCL8 GM-CSF	Neutrophils	AGEP (Acute generalized exanthematous pustulosis)

## Diagnosis and management of drug hypersensitivity reactions

*Romano A et al, 2011, J Allergy Clin Immunol*

Reazioni Immediate

Entro 1 ora

- Orticaria acuta
- Angioedema
- Rinite
- Broncospasmo
- Shock anafilattico

Reazioni Ritardate

Oltre 1 ora

- Eruzioni Maculopapulari
- Orticaria ritardata

# Cutaneous Reactions to Drugs in Children

*Segal AR et al, Pediatrics, 2007*



Orticaria dermatografica





Angioedema da Farmaci





## Cutaneous Reactions to Drugs in Children

*Segal AR et al, Pediatrics, 2007*



Esantema maculopapulare

## Cutaneous Reactions to Drugs in Children

*Segal AR et al, Pediatrics, 2007*



Reazione morbilliforme



**REAZIONI ESANTEMATICHE DA FARMACI**





**ERITEMA FISSO DA FARMACI**



Eritema polimorfo





ERITEMA POLIMORFO



DIAGNOSI

ANAMNESI

*TEST IN VITRO E/O IN VIVO*

TEST DI PROVOCAZIONE



## Schema di anamnesi

- 1. Qual è il nome del farmaco?**
- 2. Qual'era la situazione clinica per cui il farmaco è stato assunto?**
- 3. Che segni e sintomi ha avuto durante la reazione?**
- 4. Dopo quanto tempo è insorta dall'assunzione del farmaco?**
- 5. Ha assunto altri farmaci e con quali modalità?**
- 6. Dopo quanto tempo dalla sospensione del farmaco il problema si è risolto?**
- 7. Da allora ha più assunto quel farmaco o farmaci simili?**
- 8. Ha mai avuto sintomi simili senza aver assunto farmaci?**

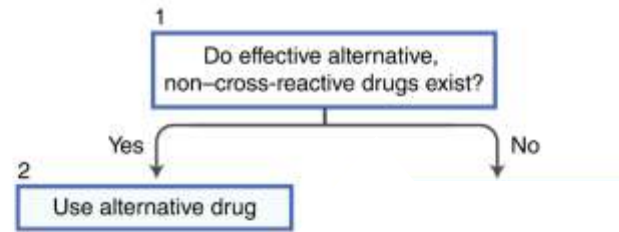


**TABLE I.** Diagnostic tests of hypersensitivity reactions to drugs

Type of reaction	Type of tests	
Immediate	<i>In vitro</i>	Specific IgE assays
		Flow cytometric BATs
	<i>In vivo</i>	Skin tests
		Provocation tests
Nonimmediate	<i>In vitro</i>	LTTs or LATs
		ELISPOT assays for analysis of antigen-specific, cytokine-producing cells
	<i>In vivo</i>	Delayed-reading intradermal tests
		Patch tests
		Provocation tests

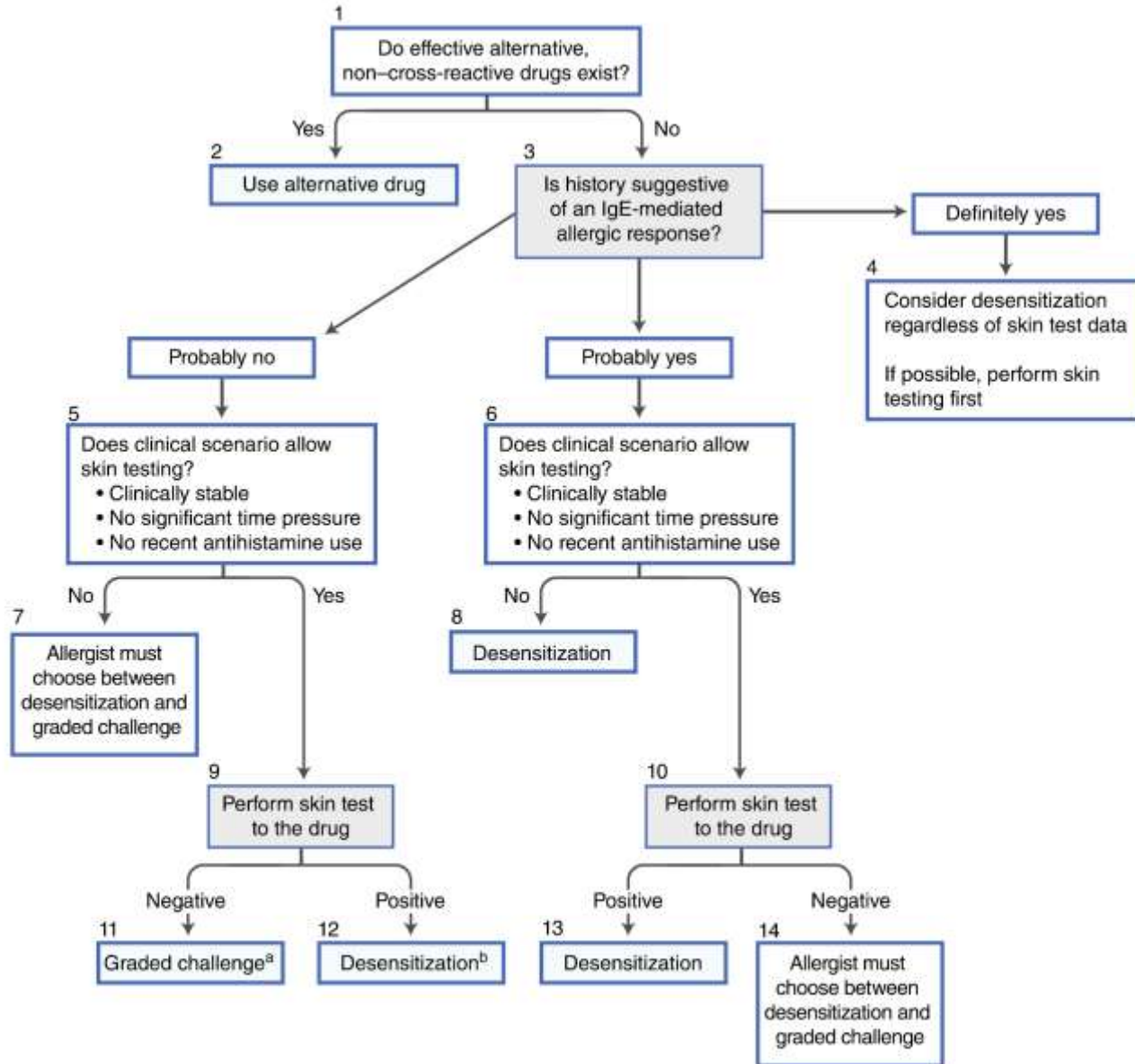
# Management of Multiple Drug Allergies in Children

*Dioun AF, 2011, Curr Allergy Asthma Rep*



# Management of Multiple Drug Allergies in Children

*Dioun AF, 2011, Curr Allergy Asthma Rep*



## Diagnosing multiple drug hypersensitivity in children

Marina Atanaskovic -Markovic , Romano A et al, 2012, *Ped Allergy Immunol*

**928 bambini con storia di ADR**

**292 con storia di MDH**

### Manifestations

#### Immediate

**Urticaria** 37 (6.1)

Angioedema 28 (4.6)

Urticaria-angioedema 12 (2)

Anaphylaxis 3 (0.5)

#### Non-immediate

**Urticaria** 280 (46.2)

**Maculopapular rash** 172 (28.4)

Urticaria-angioedema 54 (8.9)

Angioedema 14 (2.3)

Fixed drug eruption 4 (0.6)

Stevens-Johnson 2 (0.3)

syndrome

# Diagnosing multiple drug hypersensitivity in children

Marina Atanaskovic -Markovic , Romano A et al, 2012, Ped Allergy Immunol

**928 bambini con storia di ADR**

**292 con storia di MDH**

**69 (24,7 %) confermata ADR singola**  
**7 (2.5 %) confermata MDH**

## Manifestations

<b>Immediate</b>	<b>Urticaria</b>	<b>37 (6.1)</b>
	Angioedema	28 (4.6)
	Urticaria-angioedema	12 (2)
	Anaphylaxis	3 (0.5)
<b>Non-immediate</b>	<b>Urticaria</b>	<b>280 (46.2)</b>
	<b>Maculopapular rash</b>	<b>172 (28.4)</b>
	Urticaria-angioedema	54 (8.9)
	Angioedema	14 (2.3)
	Fixed drug eruption	4 (0.6)
	Stevens-Johnson syndrome	2 (0.3)

## Diagnosing multiple drug hypersensitivity in children

Marina Atanaskovic -Markovic , Romano A et al, 2012, *Ped Allergy Immunol*

**Table 3** Children with MDH to different drugs given simultaneously

Patient/Gender	Age (years)	Clinical manifestations	Time	Responsible drugs	Patch tests	Intradermal tests	DPTs
1/M	10	Delayed-appearing urticaria-angioedema	3 h	Erythromycin	neg	neg	Urticaria/12 h
		Maculopapular rash	3 h	Ibuprofen	np	np	Urticaria-angioedema/2 h
		Maculopapular rash	5 h	Lamotrigine	pos	np	np
2/F	6	Maculopapular rash	6 h	Cephalexin	neg	neg	Maculopapular rash/24 h
		Maculopapular rash	6 h	Phenobarbital	pos	np	np

**Table 4** Children with MDH to different drugs given sequentially

Patient/Gender	Age (years)	Clinical manifestations	Time	Responsible drugs	Time interval	Patch tests	Skin tests	DPTs
1/M	10	Anaphylaxis	10 min	Fentanyl	2 month	np	pos	np
		Anaphylaxis	5 min	Methylprednisolone		np	pos	np
2/F	10	Delayed-appearing urticaria	4 h	Benzyl-penicillin		neg	neg	Urticaria/2 h
		Fixed drug eruption	12 h	Cotrimoxazole	2 year	pos	np	np
3/F	13	Maculopapular rash	10 h	Cephalexin	1 year	neg	neg	Maculopapular rash/6 h
		Angioedema	15 min	Ibuprofen		np	np	Angioedema/10 min
4/M	6	Maculopapular rash	4 h	Phenobarbital	2 year	pos	np	np
		Urticaria	30 min	Amoxicillin		np	pos	np
5/F	9	Stevens-Johnson syndrome	10 h	Ceftriaxone	2 year	pos	np	np
		Delayed-appearing urticaria	3 h	Ibuprofen		np	np	Urticaria/24 h

*Non amo le conclusioni, uno parla, parla e poi.  
Questa presentazione è già una conclusione, tutta quanta.*

*Però, se proprio devo... allora:*

- 1. Ricordiamoci che le ADR esistono!*
- 2. Sono molto rare ma non eccezionali.*
- 3. I sintomi sono spessissimo cutanei, immediati o ritardati.*
- 4. Attenzione all'uso di farmaci off-label.*
- 5. Raccogliamo la storia con molta pignoleria.*
- 6. Non accontentiamoci di una storia per quanto plausibile per etichettare un paziente "allergico alle medicine".*



U.O.S.D. Allergologia  
Loreto Crispi  
Napoli

**W A C I** 2013 - 1

**Workshop  
Allergologico  
Continuo  
Interdisciplinare**



S.M. di Loreto - Crispi

- *Anna Ciccarelli*
- *Claudia Calabrò*

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**DERMATITE ALLERGICA DA CONTATTO DA FARMACI**

