ALLERGIA E INTOLLERANZE AI FARMACI

GB Pajno
UOS Allergologia pediatrica - Università di Messina

Bibliografia

Controversies in drug allergy: In vitro testing – Elsevier Enhanced Reader – January 2019

Important questions in drug allergy and hypersensitivity: consensus papers from the 2018 – WHO j - 2018

Controversies in drug allergy: consensus documents from the world experts – WHO j – 2018

Drug allergy – The journal o allergy and clinical immunology: in practice – may-june 2017

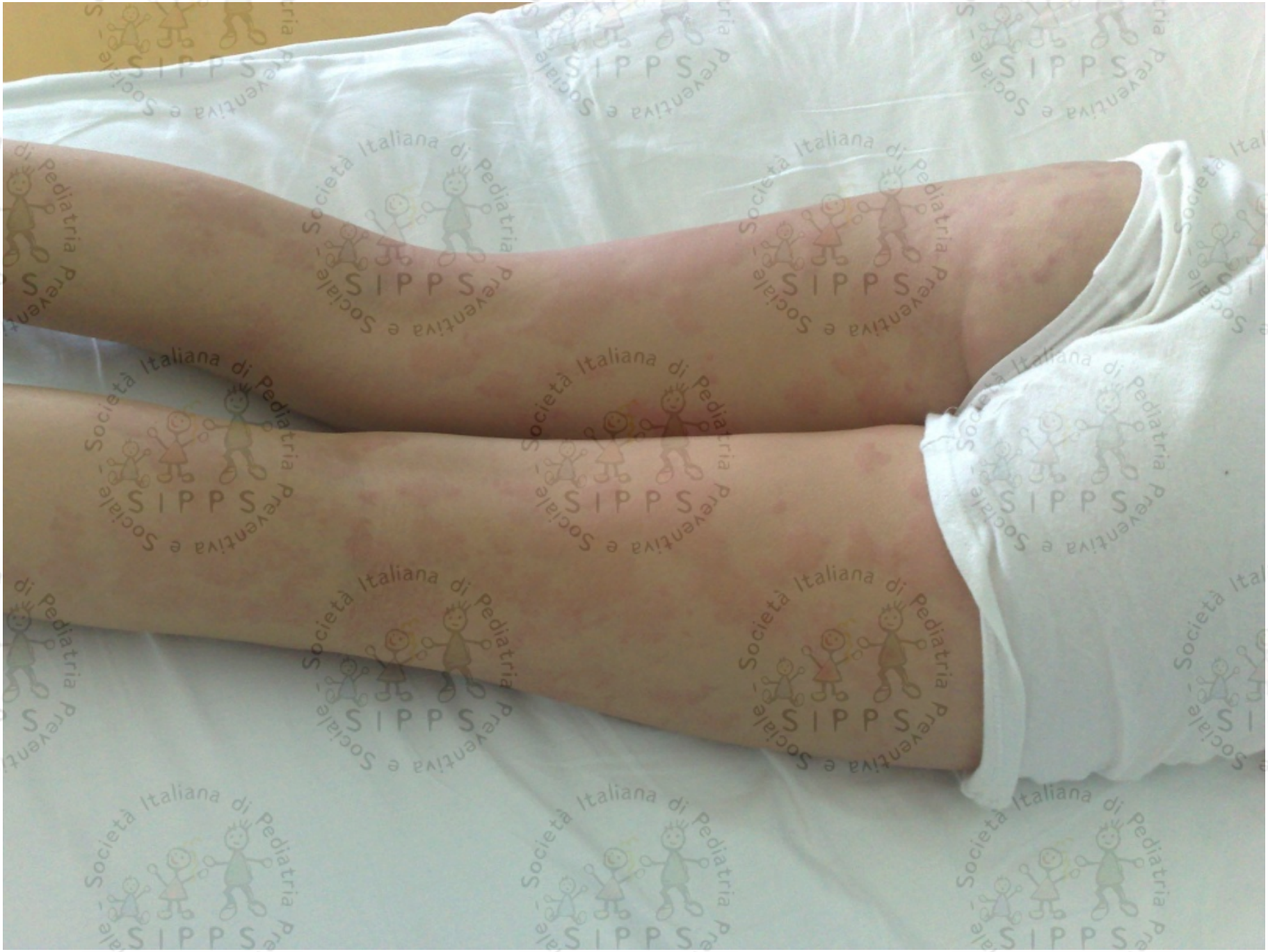
Antibiotic allergy – Lancet - 2019

Sommario

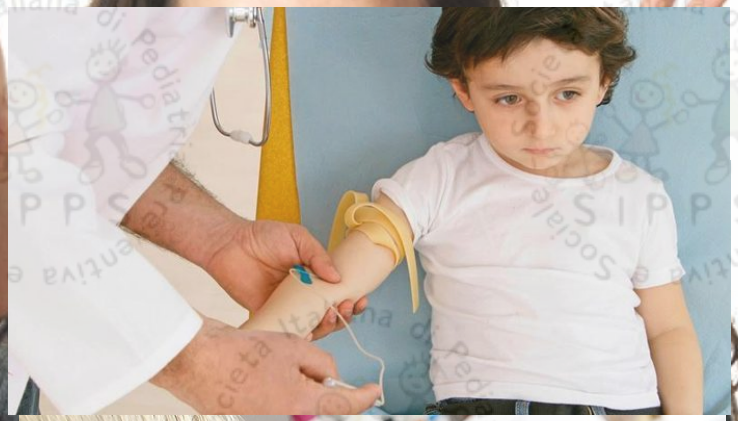
- *Quale è la reale prevalenza dell'allergia alimentare in età pediatrica?*

- *Qual'è la prevalenza delle allergie a farmaci? Quando sospettarla? Come comportarsi?*

- *Quali sono le conseguenze dei comportamenti cautelativi/astensionistici?*



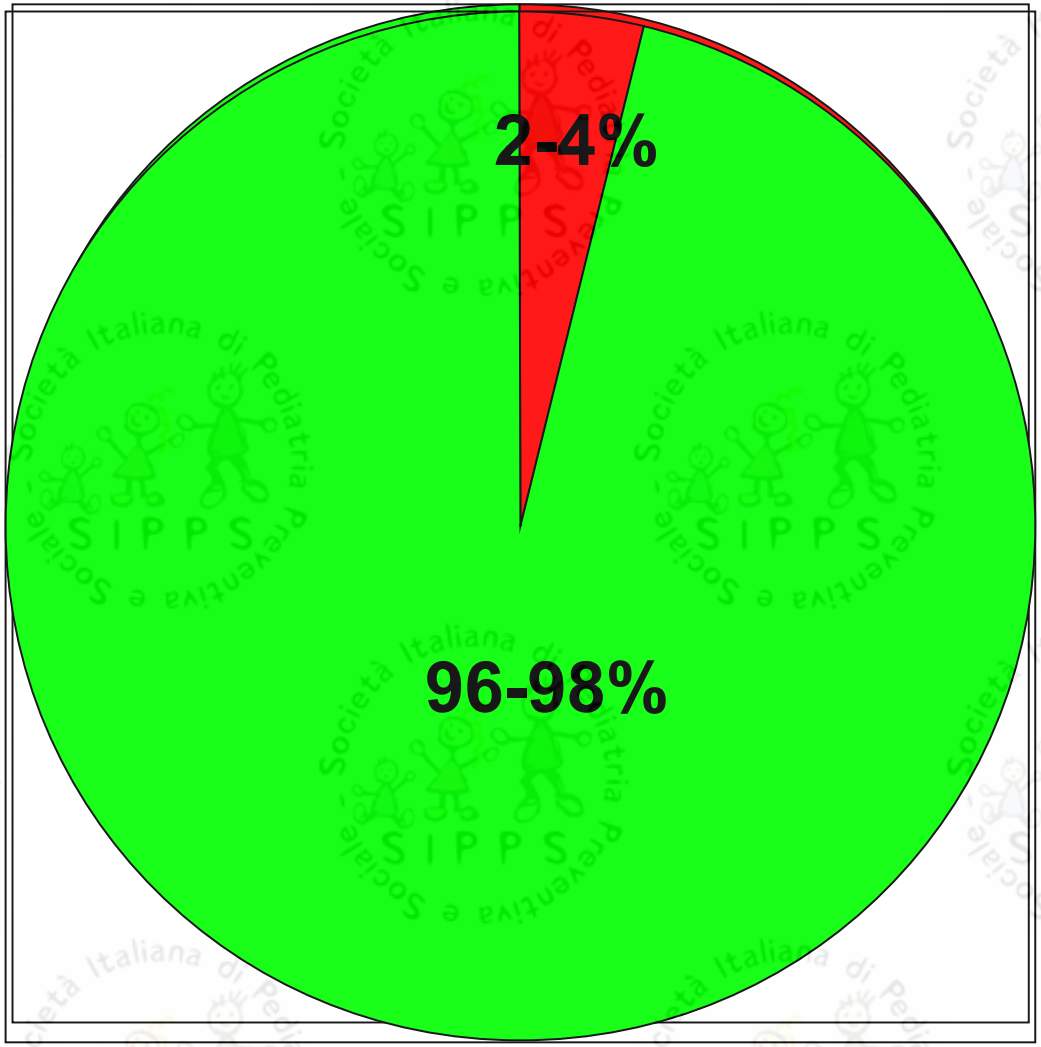
Ma insomma!
A qualcosa deve essere allergico!



stipsi,
diarrea,
vomito,
dolori addominali,
disappetenza,
scarsa crescita,
prurito,
tosse,
strofulo e qualunque altro tipo di manifestazione cutanea,
forfora

Percezione di allergia

Reale prevalenza



Questionario SIAIP

L’allergia a farmaci e vaccini

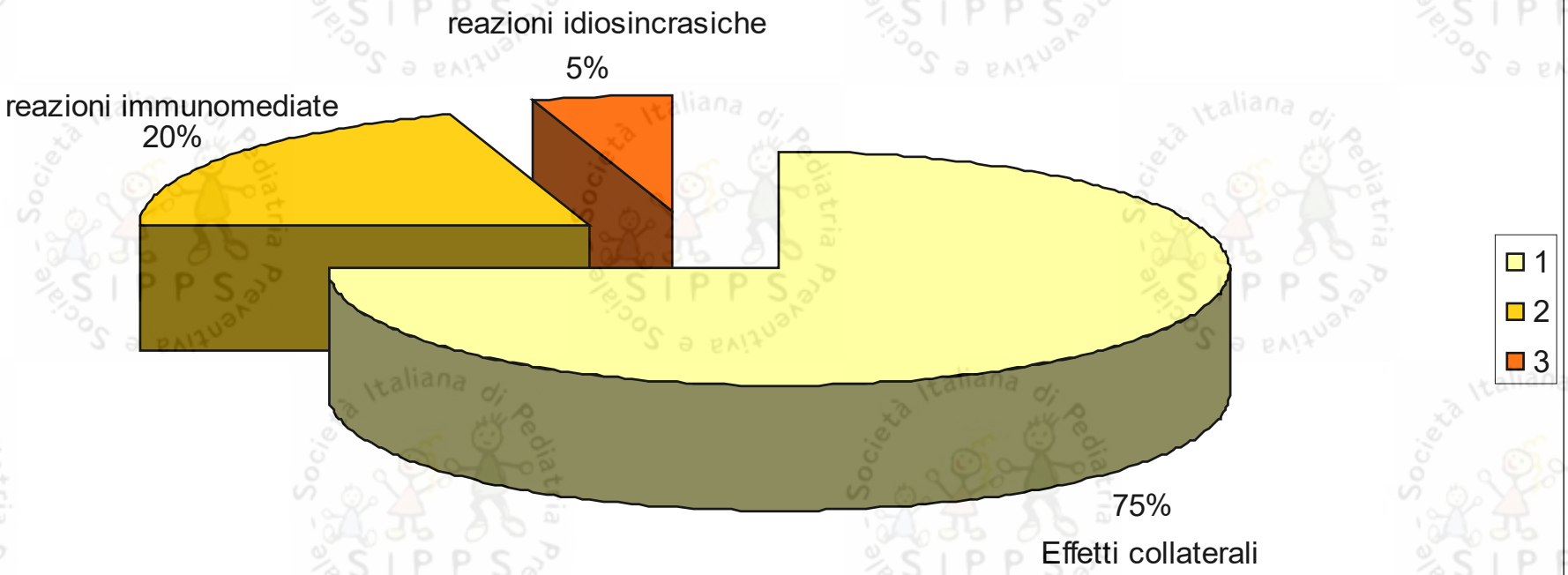
è ancor meno frequente dell’allergia alimentare e non andrebbe sopravvalutata…

Advers Drug Reaction

OMS

"tutte le conseguenze non terapeutiche di un farmaco, ad eccezione dei fallimenti terapeutici, degli avvelenamenti intenzionali o accidentali, degli errori di somministrazione e dell'abuso".

REAZIONI AVVERSE A FARMACI



BSACI guidelines for the managment of drug allergy
Clin. Exp. Allergy 2009; 39-43-61

Although antibiotic ADRs are commonly reported, immunologically mediated hypersensitivity is uncommon and true IgE-mediated antibiotic allergy is verified in only a small minority.

JAN 2019

REAZIONE	MANIFESTAZIONE CLINICA
I TIPO	orticaria/angiedema, broncospasmo, anafilassi
II TIPO	anemia emolitica
III TIPO	malattia da siero
IV TIPO	rush cutanei a insorgenza ritardata (morbilliformi, scarlattiniformi, Steven Johnson, eczemi da contatto)

secondo Gell e Coombs.

THE LANCET

	Mechanism	Presentation	Chronology or onset	Antibiotic examples	Diagnosis	Genetic (HLA) association[4]	Treatment	Antibiotic recommendations
Non-IgE-mediated*								
Flushing, itching, urticaria, and angio-oedema; occasionally presents like anaphylaxis	Direct mast-cell stimulation or basophil activation; MRGPRX2 implicated for certain direct mast-cell degranulators[5]	Cutaneous symptoms (most common), then respiratory symptoms (eg, wheezing), then cardiovascular symptoms (eg, hypotension)	Minutes to <1 h (typically during infusion)	Vancomycin or fluoroquinolones	History and physical exam; serum tryptase within 30 min to 1·5 h after reaction usually normal; drug challenge typically negative with lower dose (dose-dependent reaction)	..	Antihistamines alone typically suffice; epinephrine for those meeting anaphylaxis criteria; adjunctive treatment with corticosteroids and inhaled beta agonists as needed	Slow infusion or premedication with antihistamines or corticosteroids; use fewer associated drugs with similar mast-cell effects (eg, opioids)
Antibody-mediated								
IgE-mediated (type I HSR)								
Urticaria, angio-oedema, bronchospasm, and anaphylaxis	Mast-cell and basophil degranulation via IgE-crosslinking bound to the high-affinity IgE receptor (FceR1)[6]	Itching, palmar erythema, rhinitis, wheezing, urticaria, angio-oedema, or anaphylaxis	<1 h typical, but can be considered within 6 h of exposure	Penicillins or cephalosporins	History, physical exam, elevated serum tryptase (measured within 30 min to 1·5 h after reaction), skin testing, and drug challenge	..	Antihistamines; epinephrine for those meeting anaphylaxis criteria; adjunctive treatment with corticosteroids and inhaled beta agonists as needed	Desensitisation protocol for implicated drug(s); caution with use of drugs in the same class and and structurally related drugs which are potentially cross-reactive
IgG-mediated (type II HSR)								
Cytopenias	Antigen-antibody interactions; IgG and complement-mediated phagocytosis or cytotoxicity	Haemolytic anaemia, thrombocytopenia, or vasculitis	Often <72 h, but can be up to 15 days	Penicillins, cephalosporins, sulphonamides, dapsone, or rifampicin	History, physical exam, targeted laboratory evaluation, and biopsy as indicated	..	Corticosteroids, other immunosuppressants or immunomodulators	Avoidance of implicated drug(s); caution with use of same class and and structurally related drugs which are potentially cross-reactive
Serum sickness or serum sickness-like reaction (type III HSR)								
Serum sickness	High antibody titres and circulating immune-complexes; IgM or IgG and complement†	Fever, rash, or arthralgia; uncommon in adults	Days to weeks (typically 1–3 weeks)	Penicillin, amoxicillin, cefaclor, or trimethoprim-sulfamethoxazole	History, physical exam, and laboratory evaluation including differential blood count, sedimentation rate, C-reactive protein, total complement, C3, C4, urinalysis to assess for proteinuria, and skin biopsy	..	Antihistamines and corticosteroids (systemic for severe cases only)	Avoidance of implicated drug(s); caution with use of same class and and structurally related drugs which are potentially cross-reactive

(Table continues on next page)

THE LANCET
Volume 385 · Number 9970 · Pages 745–838 · February 28–March 6, 2015 www.thelancet.com

	Mechanism	Presentation	Chronology or onset	Antibiotic examples	Diagnosis	Genetic (HLA) association[4]	Treatment	Antibiotic recommendations
(Continued from previous page)								
Cell-mediated								
Primary single organ disease								
Acute interstitial nephritis‡	CD4 or monocyte immune injury to the renal tubulointerstitium	Rash, acute kidney injury, white cell casts in urinary sediment, peripheral blood eosinophilia, or eosinophiluria	3 days to 4 weeks	Semi-synthetic anti-staphylococcal penicillins (eg, nafcillin and oxacillin) fluoroquinolones, or rifampicin	History, physical exam, laboratory, urinalysis, and renal biopsy (severe cases)	..	Antihistamines, topical or systemic corticosteroids, and mycophenolate mofetil or cyclophosphamide (for renal failure not responsive to systemic corticosteroids)	Avoidance of implicated drug(s) and drugs in the same class advisable; limited data to support or negate cross-reactivity within same family (eg, cephalosporins often tolerated with semi-synthetic penicillin acute interstitial nephritis)
Drug-induced liver injury	CD4 then CD8 T-cell activation and FasL; TNF alpha and perforin to hepatocyte cell death	Transaminitis (cholestatic or mixed picture); hepatitis is the main presentation, but some cases are accompanied by rash, fever, or eosinophilia	From 5 days to 12 weeks (typically more than 4 weeks)	Amoxicillin–clavulanate, flucloxacillin, rifampicin, co-trimoxazole, nevirapine, efavirenz, nitrofurantoin,‡ or minocycline‡	History, physical exam, laboratory,§ and liver biopsy (severe cases)	HLA-B*57:01 (flucloxacillin) HLA-A*02:01; HLA-DRB1*15:01; HLA-DQB1*06:02 (amoxicillin–clavulanate) HLA-DRB1*01:01 and 01:02 (nevirapine)	Corticosteroids (after toxic or viral etiology excluded); antihistamines and topical corticosteroids (if concurrent rash)	Avoidance of implicated drug(s), drugs in same class, and structurally related drugs which are potentially cross-reactive
Isolated cutaneous disease¶								
Maculopapular rash	Eosinophilic inflammation (CD4 and Th2) via IL-4, IL-5, IL-13, or eotaxin (type IVb HSR)	Morbilliform rash, often with peripheral blood eosinophilia	Days to weeks (typically in second week of therapy)	Amoxicillin or sulphonamide antibiotics	History, physical exam, laboratory evaluation (eosinophilia, no organ involvement), and biopsy (severe cases only) with eosinophilic infiltrate in the dermis or variable non-specific picture	..	Antihistamines, topical corticosteroids, or systemic corticosteroids (severe cases only)	Repeat exposure to implicated drug(s) may not result in same reaction, especially after a period of unexposed time; cross-reactivity is less defined; data exists on a treat-through approach for patients requiring therapy who develop this hyper-sensitivity reaction with monitoring for signs of SCAR
Fixed drug eruption‖	Activated intraepidermal CD8 T cells release IFN gamma and cytotoxic granules	Erythematous or oedematous plaques of a round shape with gray or dusky center at same sites (often lip, tongue, face, or genitalia) with each exposure; burning and pain at involved sites	Days to weeks (within minutes on re-challenge)	Sulphonamide antibiotics or vancomycin	History, physical exam, biopsy with basal cell degeneration, pigmentary incontinence, dermal melanophages, patch testing (topical provocation), and drug challenge (systemic provocation)	..	Antihistamines, topical corticosteroids, or systemic corticosteroids (severe cases only)	Avoidance of implicated drug(s) advisable
Contact dermatitis or eczema**	Monocytic inflammation (Th1 and IFN gamma)	Erythema and oedema with vesicles or bullae**	Days to weeks	Bacitracin or ampicillin**	History, physical exam, biopsy (mixed superficial perivascular inflammation), patch testing, and drug challenge	..	Treatment similar to that for atopic dermatitis (mild cleansers, emollients, topical corticosteroids, and antihistamines) or systemic corticosteroids (severe cases only)	Avoidance of implicated drug(s) advisable

(Table continues on next page)

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	Mechanism	Presentation	Chronology or onset	Antibiotic examples	Diagnosis	Genetic (HLA) association[4]	Treatment	Antibiotic recommendations
(Continued from previous page)								
Systemic or multisystem disease[47,9]								
Drug reaction eosinophilia and systemic symptoms syndrome	CD4 (IL-4, IL-5, IL-13) and CD8 T cells implicated (release of TNF alpha and IFN gamma); primary dermal lymphocytic infiltrate	Fever, rash, peripheral blood eosinophilia, lymphadenopathy, or organ involvement (often liver or kidney)	2–6 weeks	Vancomycin, rifamycin, sulphonamide antibiotics, dapsone, or all β-lactam antibiotics	History, physical exam, laboratory (assessment of absolute eosinophil count and organ involvement), biopsy, clinical scoring RegiSCAR,†† causality assessment Naranjo,‡‡ and patch testing (may identify culprit)	HLA-B*13:01 (dapsone in southeast Asians); HLA-B*35:05 (nevirapine in southeast Asians); HLA-B*53:01 (raltegravir in African ancestry)	Immediate removal of drug; antihistamines or corticosteroids (severe cases only)	Avoidance of implicated drug(s), drugs in the same class, and structurally related drugs which are potentially cross-reactive
Abacavir hyper-sensitivity syndrome	CD8 T cells; non-covalent binding to floor of antigen blinding cleft with altered peptide repertoire of endogenous peptides bound to HLA-B*57:01	Fever, malaise, gastrointestinal or respiratory symptoms; rash is mild to moderate, present in 70% of patients, and occurs late	From days to 3 weeks (typically 1 week)	Abacavir (no other drugs to date cause identical syndrome)	History, physical exam, and patch test (to confirm culprit)	HLA-B*57:01 (screening is guideline-based therapy in developed world)	Immediate removal of drug	Avoidance of abacavir only
Stevens-Johnson syndrome and toxic epidermal necrolysis	CD8 cytotoxic T cells via perforin, granulysin, granzyme B, or FasL (keratinocyte death, type IVc HSR)	Rash with desquamation, mucosal lesions (mouth, eyes, genitals) with mucositis, or fever SJS: <10% BSA SJS–TEN overlap: 10–30% BSA TEN: >30% BSA	4 days to 4 weeks (for many antimicrobials shorter latency is typical)	Sulphonamide antimicrobials, nevirapine, antimycobacterials, macrolides, or quinolones	History (blistering rash with skin sloughing), physical exam (Nikolsky and Asboe-Hansen signs), skin biopsy with keratinocyte necrosis (from partial to full thickness) of the epidermis, and clinical scoring (SCORETEN,§§ ALDEN,¶¶ Naranjo‡‡)	HLA-C*04:01 (nevirapine in Africans)	Immediate removal of drug; aggressive supportive care in intensive care unit or burn unit setting; pulse corticosteroids, etanercept, or cyclosporine	Avoidance of implicated drug(s), drugs in the same class, and structurally related drugs which are potentially cross-reactive
Acute generalised exanthematous pustulosis	T cells via IL-8 and granulocyte-macrophage colony-stimulating factor (neutrophilic inflammation, type IVd HSR)	Acute pustular eruption characterised by widespread non-follicular sterile pustules with fever, facial oedema, or neutrophilia; 25% of patients have oral involvement	<48 h (typically within 24 h); longer latency for pristinamycin and hydroxychloroquine	Aminopenicillins, clindamycin, other β-lactams, fluoroquinolones, sulphonamides, pristinamycin, terbinafine, or hydroxychloroquine (anti-malarial)	History, physical exam, fever, laboratory evaluation showing neutrophilic leukocytosis with mild eosinophilia; skin biopsy (subcorneal pustules or intraepidermal pustules filled with neutrophils), and patch testing (to help identify culprit)	..	Immediate removal of drug, topical corticosteroids, or systemic corticosteroids (severe cases and widespread involvement)	Avoidance of implicated drug(s), drugs in the same class, and structurally related drugs which are potentially cross-reactive; drugs reintroduced may be guided by patch testing

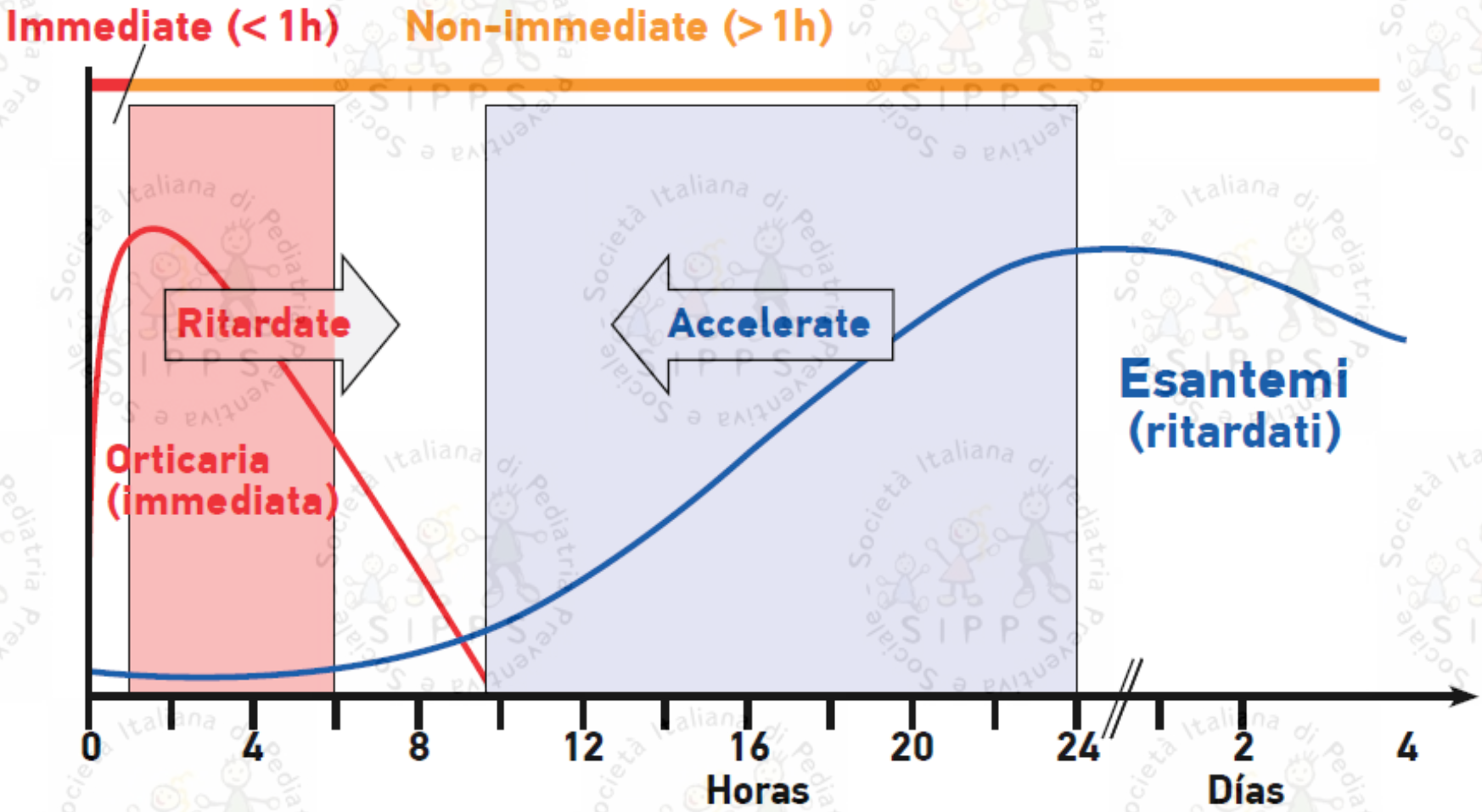
BSA=body surface area. C3=complement C3. C4=complement C4. FasL=Fas ligand (CD95). HSR=hypersensitivity reaction. IFN=interferon. IL=interleukin. MRGPRX2=MAS-related G-protein coupled receptor member X2. SCAR=severe cutaneous adverse reaction. SJS=Stevens-Johnson syndrome. TEN=toxic epidermal necrolysis. Th=T-helper cell. TNF=tumour necrosis factor. *Previously called pseudoallergic or anaphylactoid reactions. †Serum sickness reaction largely relates to interactions of large molecules (non-human protein) with antibodies and immune complex formation. Serum sickness-like reaction, associated with cefaclor and likely other small molecule antibiotics, does not involve immune complexes, so C3 and C4 are normal and nephritis is not observed. The drugs associated with serum sickness-like reaction from drug or reactive metabolites have an alternative, potentially directly toxic or T-cell-mediated mechanism. ‡Autoimmune drug-induced hepatitis. §Most autoimmune hepatitis is type 1 (96%). Drug-induced autoimmune hepatitis is often associated with antineutrophil antibody, anti-liver-kidney microsomal antibody, and anti-smooth muscle antibody (>1:80); however, these will often only be present acutely and not after drug withdrawal or clinical resolution. Drug-induced autoimmune hepatitis patients also have a polyclonal gammopathy, making IgG levels a useful laboratory evaluation with IgG >1·5 times the upper limit of normal. ¶All phenotypes present with itching and rash. ||Generalised bullous fixed drug eruption can be severe and associated with systemic features. **Can occasionally be more extensive (symmetrical drug-related intertriginous and flexural exanthem, formerly termed baboon syndrome), presenting with sharply demarcated erythema of buttock and inner thighs (in a V-shape). ††From the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples group. ‡‡An adverse drug reaction probability scale that can be used for any adverse drug reaction to assess causality. §§A score for severity of illness for toxic epidermal necrolysis. ¶¶An algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis.

Table: **Hypersensitivity reactions and clinical phenotypes**

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY 2014 EAACI

POSITION PAPER

International Consensus on drug allergy



Farmaci in causa: epidemiologia

Antibiotici:
- macrolidi
- **betalattamici**
  - **penicilline**
  - cefalosporine
- altro

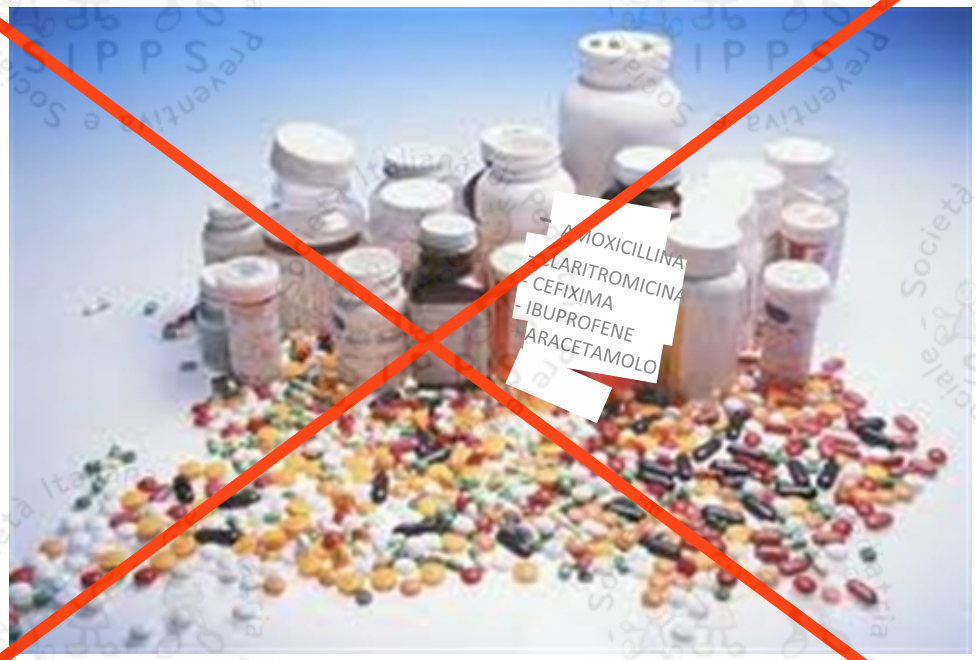
FANS:
- COX 2 inibitori
- **COX 1 inibitori**
- COX 3 inibitori

Anticonvulsivanti, anestetici, altri…

Percezione di Allergia

TREND
ALLERGIE

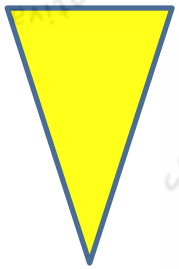
TREND
PERCEZIONE
DI
ESSERE ALLERGICI


- AMOXICILLINA
- CLARITROMICINA
- CEFIXIMA
- IBUPROFENE
- PARACETAMOLO

> 10.000 bambini

Per i genitori: 7,8% di ipersensibili ai farmaci

Per i medici allergologi: 1,16% di ipersensibili ai farmaci (il 14% degli screenati dai genitori)



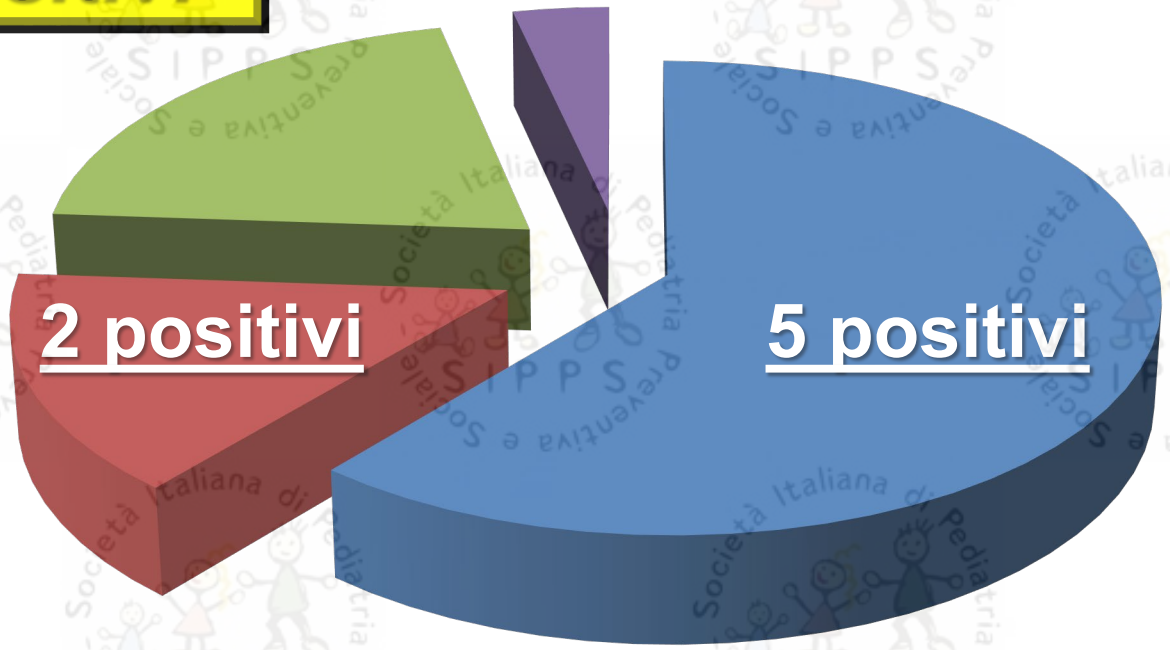
Dopo work-up diagnostico:

0,11 % di ipersensibili ai farmaci (6% degli screenati dai medici allergologi)

Pediatr Allergy Immunol. 2013 Mar

Casistica UOS Allergologia Pediatrica Università di Messina (2015-18)

6% di positivi

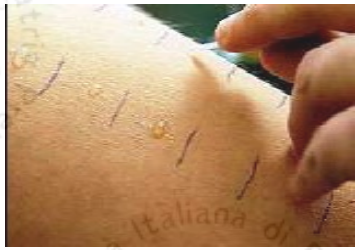


116 pazienti sottoposti a work-up :

- Betalattamici (69 pz.)
- Macrolidi (17 pz.)
- FANS o Paracetamolo (23 pz.)
- Anestetici (4 pz.)

Work-up diagnostico

- Storia clinica



- Test di provocazione

Diagnosi AA secondo EAACI Guidelines 2014

Anamnesi

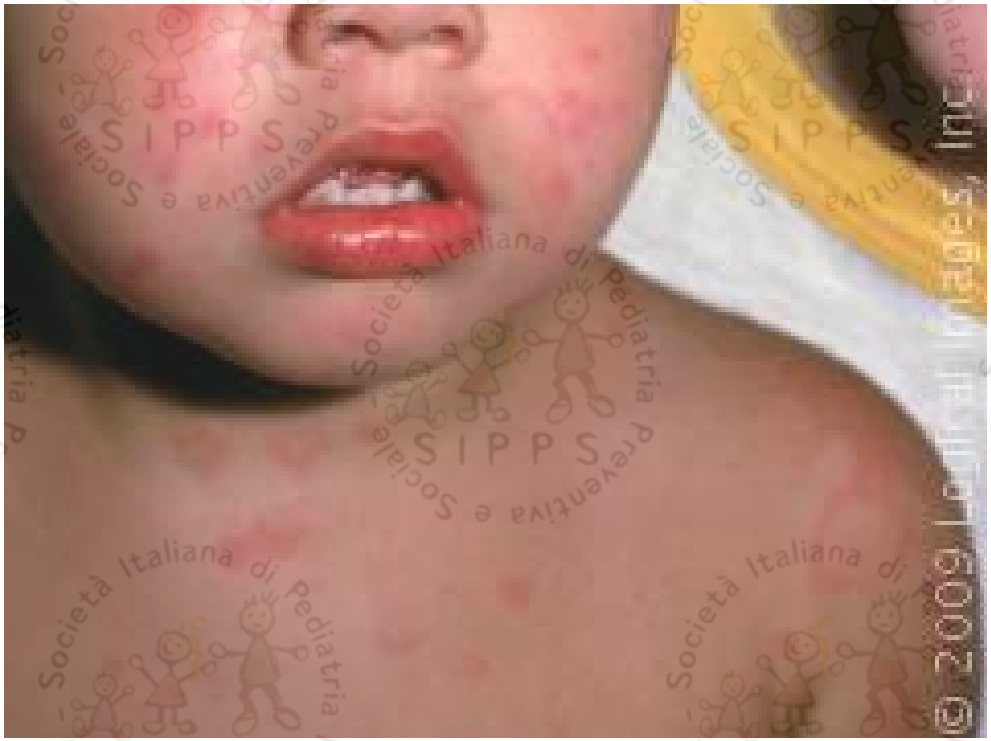
da choosing wisely (cose da fare) - SIAIP

- Ha mai avuto altre reazioni avverse a antibiotici?
- Era mai stato somministrato l'antibiotico incriminato o uno simile?
- Da quante dosi era iniziato il trattamento?
- Quando era stata somministrata l'ultima dose prima del riscontro della reazione?
- Quale è stata la via di somministrazione dell'antibiotico?
- Quali sono state le manifestazioni cliniche?
- Per quale motivo ha assunto l'antibiotico? Come stava il paziente?
- In quanto tempo e con quale eventuale trattamento si sono risolte?
- In seguito sono stati assunti ulteriori farmaci?

SIAIP
Società Italiana di Allergologia e Immunologia Pediatrica


OF
OF


Vomiting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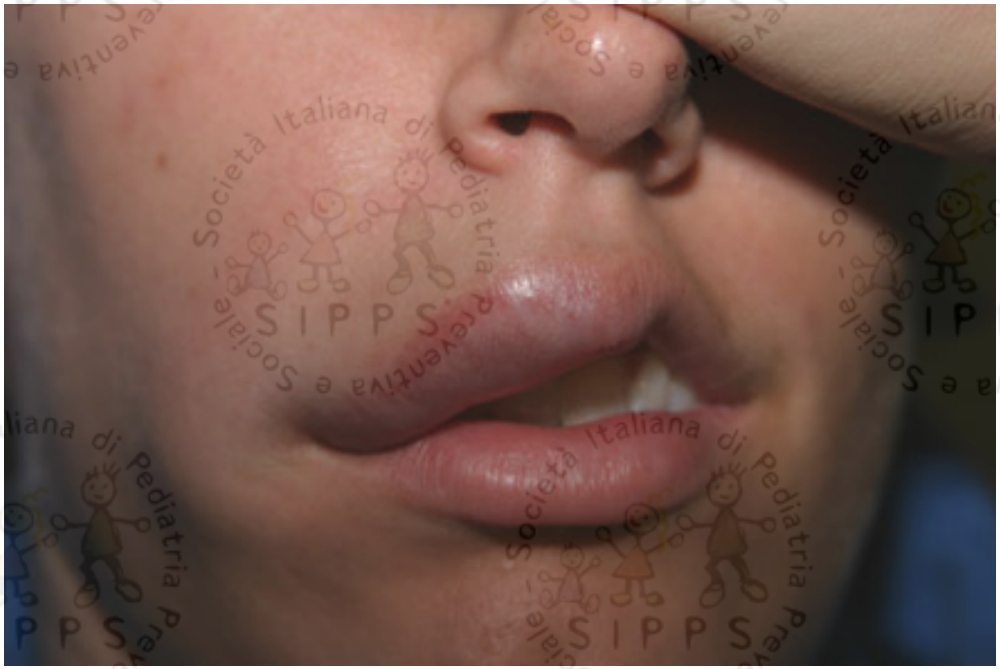
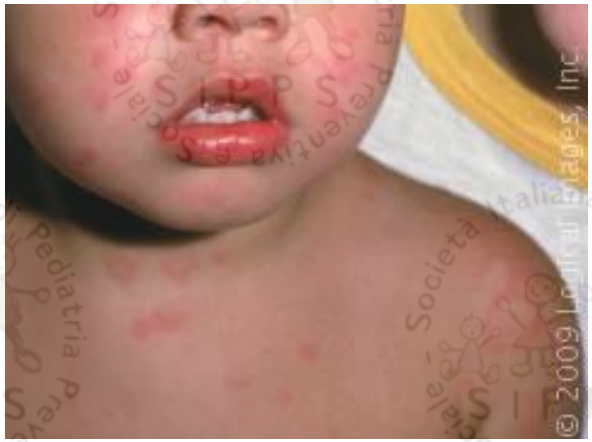
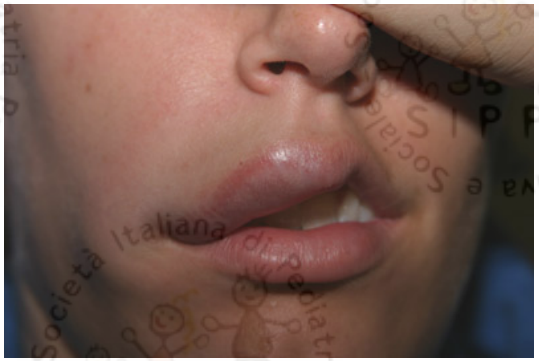
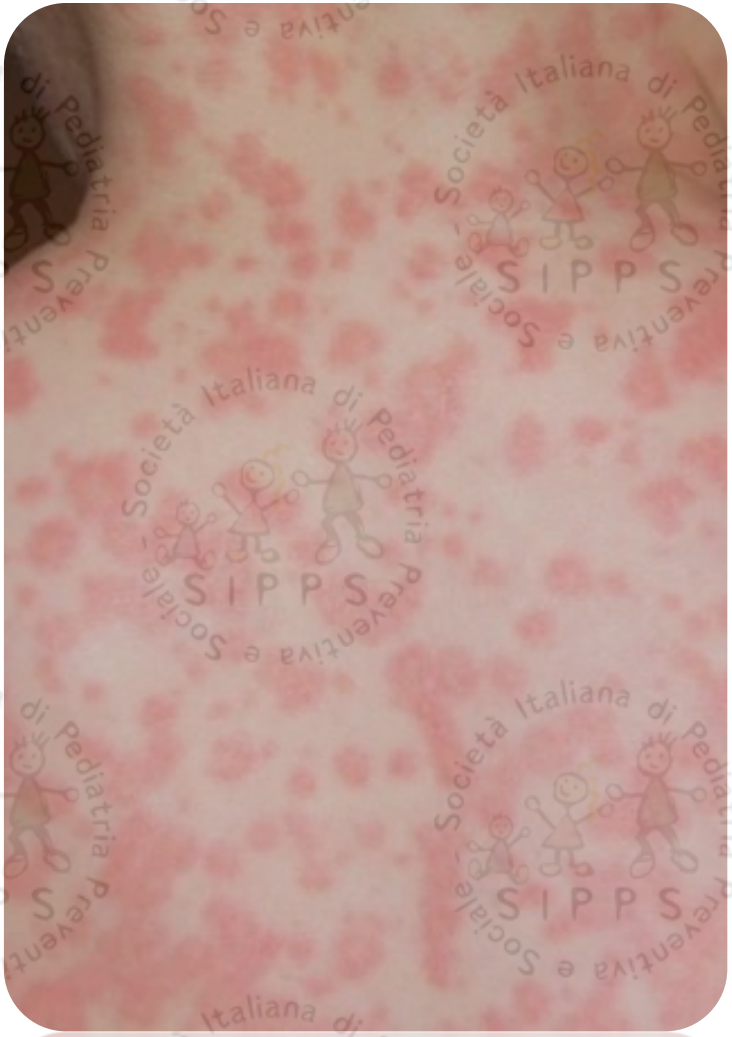



© 2009 Laurie Images, Inc.





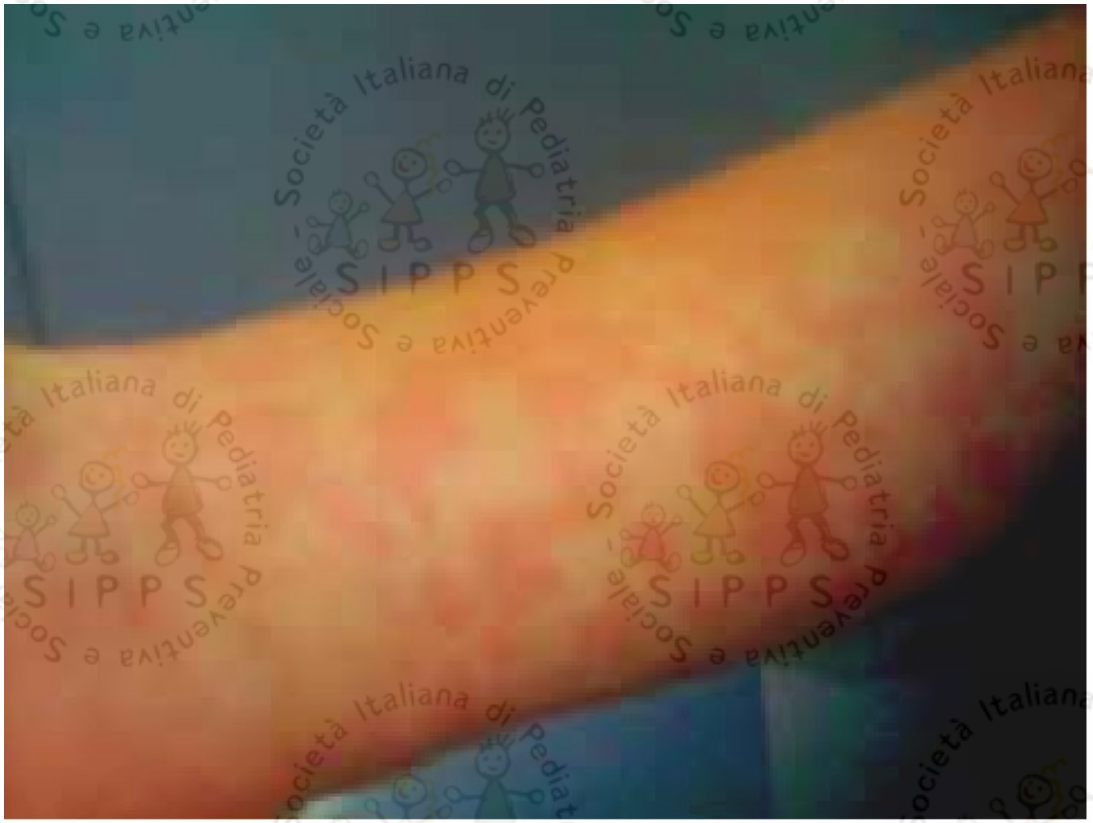
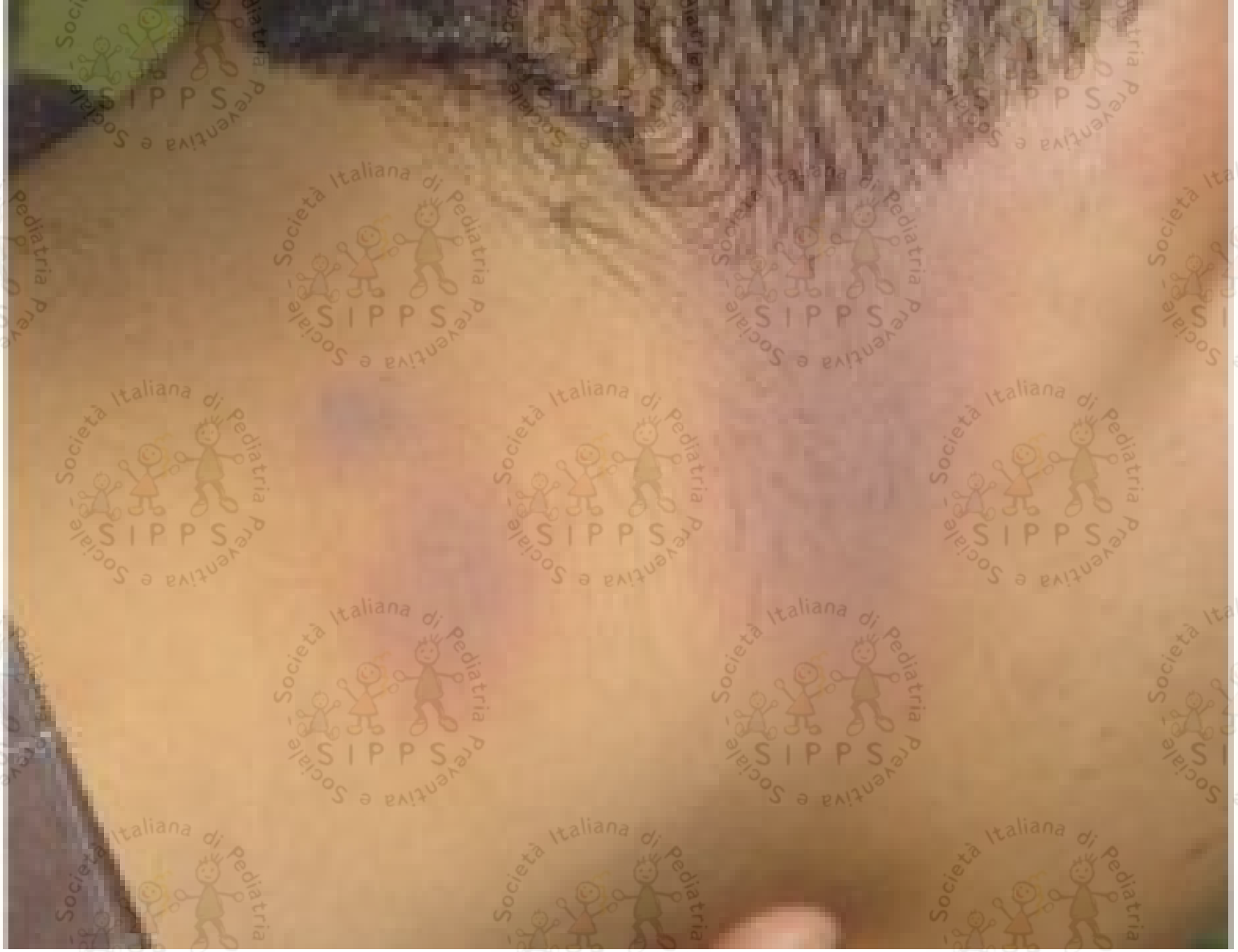


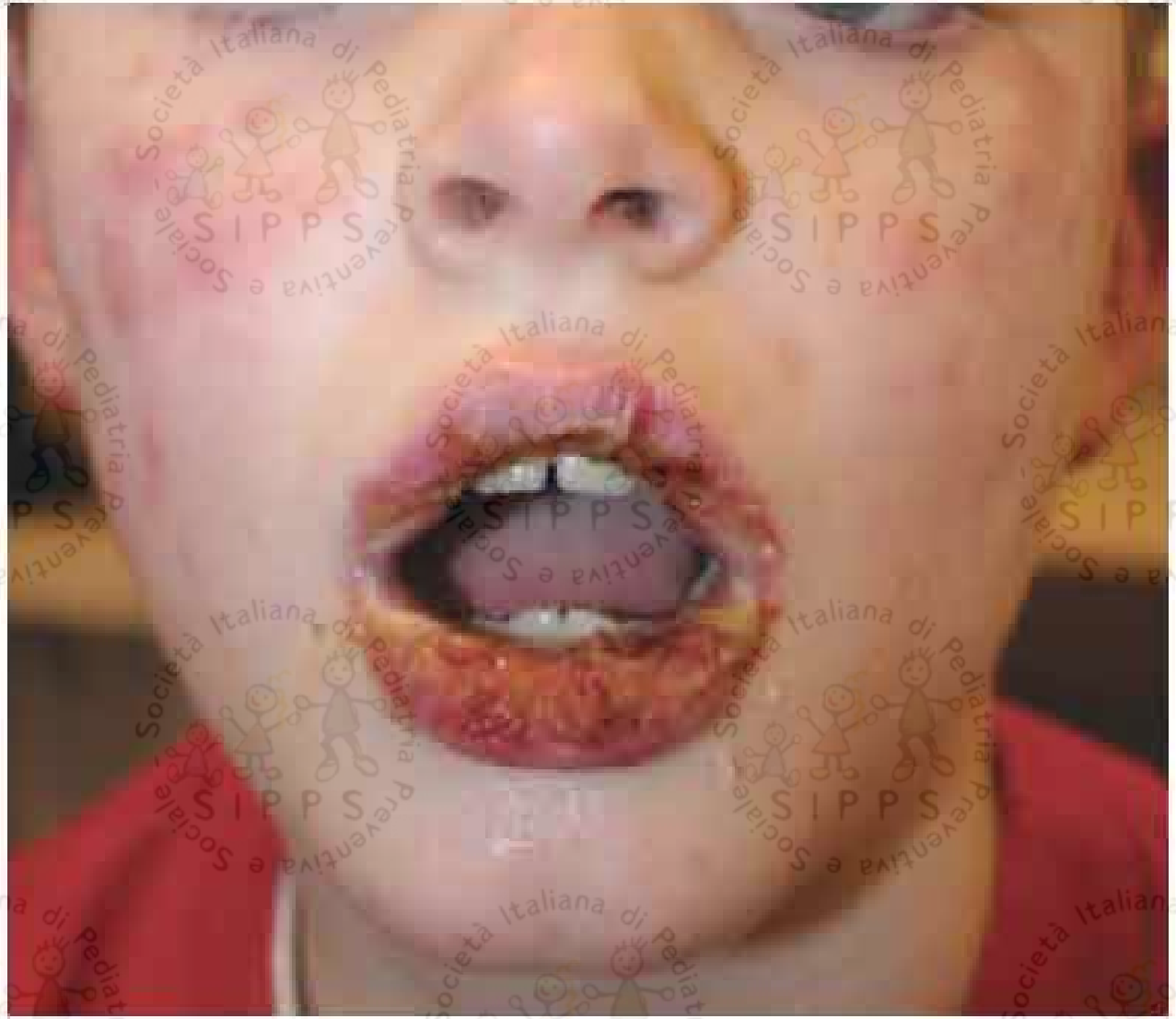
Fig. 1. Reazione cutanea in paziente affetto da mononucleosi infettiva in erronea terapia con amoxicillina + acido clavulanico.

Rivista di Immunologia e Allergologia Pediatrica

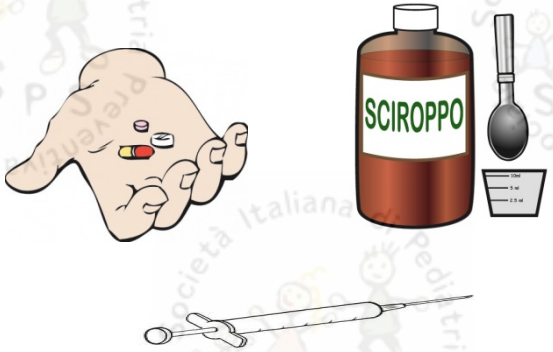
05•06/2012 • 32–42



Da Medico & Bambino Gennaio 2008



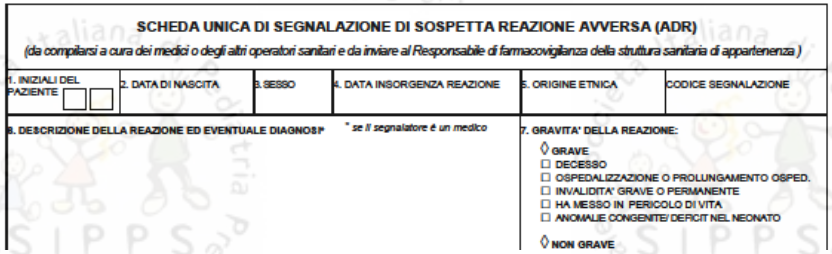
Fattori di rischio per allergia ai farmaci



LEGATI Al PAZIENTE:
Età/sesso
Concomitanti patologie
Atopia?

LEGATI AL FARMACO:
Capacità immunogena
Durata e frequenza
Via di somministrazione

Scheda AIFA



SCHEDA UNICA DI SEGNALAZIONE DI SOSPETTA REAZIONE AVVERSA (ADR)

(da compilarsi a cura dei medici o degli altri operatori sanitari e da inviare al Responsabile di farmacovigilanza della struttura sanitaria di appartenenza)

1. INIZIALI DEL PAZIENTE ☐☐	2. DATA DI NASCITA	3. SESSO	4. DATA INSORGENZA REAZIONE	5. ORIGINE ETNICA	CODICE SEGNALAZIONE

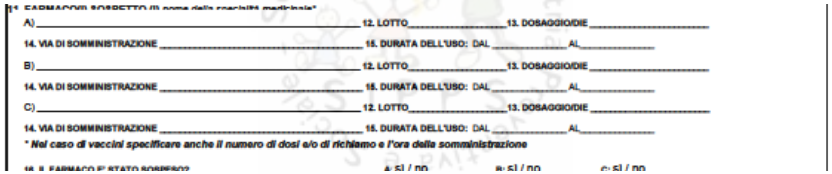
8. DESCRIZIONE DELLA REAZIONE ED EVENTUALE DIAGNOSI* — * se il segnalatore è un medico

7. GRAVITA' DELLA REAZIONE:

◊ GRAVE
- ☐ DECESSO
- ☐ OSPEDALIZZAZIONE O PROLUNGAMENTO OSPED.
- ☐ INVALIDITA' GRAVE O PERMANENTE
- ☐ HA MESSO IN PERICOLO DI VITA
- ☐ ANOMALIE CONGENITE/ DEFICIT NEL NEONATO

◊ NON GRAVE

FAX 092521918 – 0922407273 giuseppe.bellavia@aspag.it



A) _____ 12. LOTTO_____ 13. DOSAGGIO/DIE _____

14. VIA DI SOMMINISTRAZIONE _____ 15. DURATA DELL'USO: DAL _____ AL_____

B) _____ 12. LOTTO_____ 13. DOSAGGIO/DIE _____

14. VIA DI SOMMINISTRAZIONE _____ 15. DURATA DELL'USO: DAL _____ AL_____

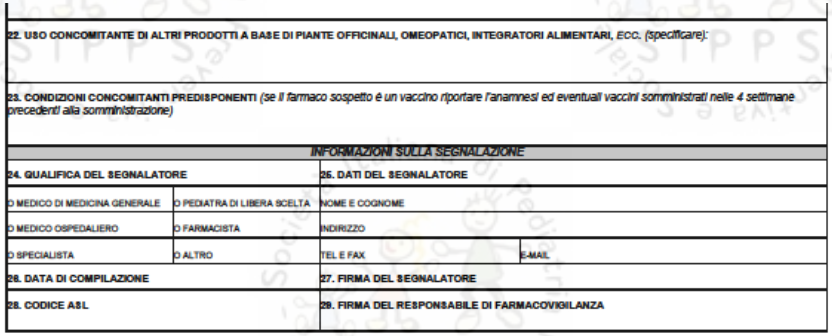
C) _____ 12. LOTTO_____ 13. DOSAGGIO/DIE _____

14. VIA DI SOMMINISTRAZIONE _____ 15. DURATA DELL'USO: DAL _____ AL_____

** Nel caso di vaccini specificare anche il numero di dosi e/o di richiamo e l'ora della somministrazione*

o direttamente online sul sito www.vigifarmaco.it

seguendo la procedura guidata.



22. USO CONCOMITANTE DI ALTRI PRODOTTI A BASE DI PIANTE OFFICINALI, OMEOPATICI, INTEGRATORI ALIMENTARI, *Ecc. (specificare):*

23. CONDIZIONI CONCOMITANTI PREDISPONENTI *(se il farmaco sospetto è un vaccino riportare l'anamnesi ed eventuali vaccini somministrati nelle 4 settimane precedenti alla somministrazione)*

INFORMAZIONI SULLA SEGNALAZIONE

24. QUALIFICA DEL SEGNALATORE		25. DATI DEL SEGNALATORE	
○ MEDICO DI MEDICINA GENERALE	○ PEDIATRA DI LIBERA SCELTA	NOME E COGNOME	
○ MEDICO OSPEDALIERO	○ FARMACISTA	INDIRIZZO	
○ SPECIALISTA	○ ALTRO	TEL E FAX	E-MAIL
26. DATA DI COMPILAZIONE		27. FIRMA DEL SEGNALATORE	
28. CODICE ASL		29. FIRMA DEL RESPONSABILE DI FARMACOVIGILANZA	

Farmaco alternativo: quale?

I scelta

II scelta

Cause di mancata prescrizione di farmaci di I scelta

Conseguenze della mancata prescrizione di farmaci di I scelta

ragionamento etiologico

efficacia subottimale

costi aumentati

screening anamnestico se sospetta RAF

aumento delle assenze

informazione della famiglia

•presunta inefficacia del precedente trattamento.

•volontà di compiacere la famiglia nella richiesta di un farmaco meno scomodo per n. dosi e via di somministrazione

•presunta pregressa reazione avversa a farmaco.

Bibliografia:
Romano A et al. J Allergy Clin Immunol Pract. 2014.
European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). 2013.

Clavenna A et al. Arch Dis Child. 2011.

CONSIDERAZIONI CONCLUSIVE

Le reazioni avverse ai farmaci in pediatria sono fortemente sovrastimate

Il paracetamolo (e l'ibuprofene) sono i più sicuri tra gli antipiretici /analgesici

Le cross-reazioni tra gli antibiotici betalattamici non sono frequenti

Le allergie ai macrolidi sono molto rare e ancor meno le cross-reazioni

L'amoxi (o l'amoxiclav) costituiscono le molecole di I scelta nelle infezioni respiratorie

La via orale è la più sicura (la via intramuscolare non offre reali vantaggi farmacologici)

Evitare i cocktail di farmaci e tendere a preferire i farmaci più conosciuti (prima scelta)

Se in base a quanto ci siamo detti non siete tranquilli, più che proscrivere definitivamente il farmaco, pensate a un successivo TPO in ambiente protetto

GRAZIE