ALLERGY TO ANTIBIOTICS IN CHILDREN

how often is it real and how long it persists?

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DEFINITION

ANTIBIOTIC ALLERGY IN CHILDREN
Revised nomenclature in allergology
Johansson SGO, Allergy 2001, 2005

Clinical manifestations of hypersensitivity

Allergic*  Non allergic

IgE-dependent  Non IgE-dependent

* Proven immunological mechanism: antibodies and/or activated T lymphocytes directed against the drug or its metabolites
• Visible forms:

• Non visible forms:
  – Hepatitis, nephritis, pneumononitis…
  – Vasculitis
  – Cytopenia

Same clinical presentations as for adults
• **Mild severity:**
  – Isolated urticarias, most angio-œdemas
  – Most maculo-papular eruptions
  – Fixed drug eruptions

• **High severity:**
  – Anaphylaxis
  – TEN and Stevens-Johnson syndromes
  – DRESS/DIHS
  – Any organ involvement
ANTIBIOTIC ALLERGY IN CHILDREN

EPIDEMIOLOGY
Suspicion of drug allergy

Which is the real picture?

4.5-11.9% had drug allergy
(3 ± 5 out of 67)

Survey in a busy Porto children hospital

Gomes E et al., CEA 2008
Drug Allergy and Hypersensitivity Database

Bousquet PJ, Arnoux B, Demoly P, EAACI 2005

Total: 17.3% + out of 2734 tested from Sept 1996 to August 2004
Are there any epidemiological differences between children and adults?

✓ Amongst our 390 positive cases for beta-lactams, 48 were children (12.3%)

✓ 2 situations:
  - reaction during childhood tested in childhood (n=417 suspicions, 48 proven - 11.5%)
  - reaction during childhood tested in adulthood (n=205 suspicions, 26 proven - 12.7%)

✓ Compared to:
  - reaction during adulthood tested in adulthood (n=1410 suspicions, 329 proven - 23.3%)
Antibiotic consumption in Europe

Goosens, Lancet 2005
ANTIBIOTIC ALLERGY IN CHILDREN

β-LACTAMS

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY
**β-lactam structure**

<table>
<thead>
<tr>
<th>Penicillins</th>
<th>Cephalosporins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- β-lactam ring</td>
<td>1- β-lactam ring</td>
</tr>
<tr>
<td>2- thiazolidine ring</td>
<td>3- dihydrothiazine ring</td>
</tr>
</tbody>
</table>

- **Penams**: penicillins, tazobactam, sulbactam
- **Cephems**: cephalosporins
- **Oxapenams**: clavulanic acid
- **Carbapenems**: imipenem, meropenem, ertapenem…
- **Monobactams**: azthreonam
β-lactams are responsible for most suspicions of drug-induced eruptions.

33% of the urticarias and 43% of the maculo-papular eruptions of our DAHD®
Drug allergy: clinical presentation

• Quickly think about the possibility of a drug allergy

• Detail the type of lesions:
  - frequent polymorphism of drug induced cutaneous reactions ++ (photo)
  - look for organ involvement (liver enzymes, blood counts, renal parameters)

• Analyse the chronology: immediate, non immediate

• Eliminate a differential diagnosis

• Evaluate risk factors: severity, co-morbidities
Drug allergy, often difficult to prove

- Strategy to confirm the diagnosis includes:
  - anamnesis and physical examination
  - possibly followed by skin tests and laboratory tests
  - and ultimately drug provocation tests

- However:
  - clinical history is rarely reliable
  - skin tests are not all validated for all drugs
  - laboratory tests are not fully validated or available
  - drug provocation tests are dangerous
Clinical tools for drug allergy

✓ Clinical history:
- **standardised questionnaire:** Demoly et al. for EAACI-ENDA. Allergy 2001
- rarely 100% PPV

✓ Skin tests:
- **standardised:** Brockow et al. for EAACI-ENDA. Allergy 2002 and Barbaud et al. for ESCD. Contact Dermatitis 2002
- **best for β-lactams and a few other drugs:** Torres et al. Allergy 2003; Romano et al. Allergy 2004 and Mertes et al. JIACI 2005 for EAACI-ENDA

✓ Provocation tests:
- **standardised:** Aberer et al. for EAACI-ENDA. Allergy 2003
- **performed in more & more centers:** Torres et al. Allergy 2001;
If clinical history is anaphylactic

EAACI-ENDA. Allergy 2003, 2009

✓ Perform prick and ID tests
✓ 4-6 weeks after the reaction
✓ Predictive values are good:
  - For penicillins: 70% sensitivity and 97% specificity for prick and/or ID tests with 4 determinants
    Torres et al. Allergy 2001
  - For cephalosporins: 86% sensitivity for prick and/or ID tests with the culprit cephalosporin (alone for 2/3)
    Antunez et al. JACI 2006
✓ Precautions: AH1 and β-blockers (because of the risk of anaphylaxis during ST ≈ 2-8%)
✓ Followed by a DPT if ST are negative
β-lactam skin tests

For prick:
- Wheal larger than 3mm + erythema with a negative response to the control saline

For IDT:
- 3mm change in the diameter of the initial wheal + flare and negative control reagent

5-8% systemic reactions during skin tests

Co-Minh JACI 2006
**β-lactam skin tests: reagents**

Brockow et al. for EAACI-ENDA. Allergy 2002
Torres et al. for EAACI-ENDA. Allergy 2003
Blanca et al. for EAACI-ENDA. Allergy 2009

1/100 or even less if shock, 1/10, pure

<table>
<thead>
<tr>
<th>REAGENTS</th>
<th>SUCCESSIVE DILUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicilloyl polylysine</td>
<td>undiluted (1.07 (10^{-2}) mM/l)</td>
</tr>
<tr>
<td>Minor determinant mixture</td>
<td>1/10, undiluted (1.05 mM/l)</td>
</tr>
<tr>
<td>Benzylpenicillin (PenG)</td>
<td>1000-2500, 10000-25000 U/ml</td>
</tr>
<tr>
<td>Amoxicillin, ampicillin</td>
<td>2-2.5, 20-25 mg/ml</td>
</tr>
<tr>
<td>Other penicillins</td>
<td>2-2.5, 20-25 mg/ml</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1-2 mg/ml</td>
</tr>
</tbody>
</table>
If clinical history is non immediate
Romano et al. *for EAACI-ENDA*. Allergy 2004
Blanca et al. *for EAACI-ENDA*. Allergy 2009

✔️ **Use patch tests 4-6 weeks after reaction**
   (reading at 20 min, D2, D3 and more with pulverized tablets 10-30% in petrolatum or 5% solution)

✔️ **Or late reading IDT** *(Se=40% for β-lactams)*

✔️ **Followed by a DPT if skin tests are negative and if the reaction was not severe:**
   - 1%, 10%, 100% of the therapeutic dose at 3-7 days of intervals
   - faster for other investigators
<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Score</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faint erythema only</td>
<td>? or +?</td>
<td>Doubtful reaction</td>
</tr>
<tr>
<td>Erythema, infiltration, possibly discrete papules</td>
<td>+</td>
<td>Weak positive reaction</td>
</tr>
<tr>
<td>Erythema, infiltration, papules, vesicles</td>
<td>+ +</td>
<td>Strong positive reaction</td>
</tr>
<tr>
<td>Intense erythema, infiltration, coalescing vesicles</td>
<td>+ + +</td>
<td>Extreme positive reaction</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>Negative reaction</td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td>Different irritant reactions</td>
</tr>
<tr>
<td>NT</td>
<td></td>
<td>Not tested</td>
</tr>
</tbody>
</table>

+++
Drug provocation tests

Search for alternative

Go around

Tolerance induction

Force

Provocation with suspected drug

Demonstrate

Aberer et al. Allergy 2003
DPT integrated in a step-wise approach

Aberer et al. Allergy 2003

✔️ After due consideration: only if other, less dangerous test methods do not allow relevant conclusions

✔️ Addressing the future needs of the patient

✔️ Under the highest safety conditions: intravenous access and intensive care room access, emergency treatment available, slow increase of doses…
Respect contra-indications
Aberer et al. Allergy 2003

- **Life-threatening immunocytotoxic reactions**: TEN, Stevens-Johnson, vasculitis, DRESS/DIHS, specific organ hypersensitivity (blood cytopenia, hepatitis, nephritis, pneumonitis)

- **Drug-induced autoimmune disease**: e.g. systemic lupus erythematosus, pemphigus vulgaris, bullous pemphigoid

- **Patients suffering from severe and/or unstable morbidity**

- **Pregnancy**

- **β-blockers and cardiovascular diseases** for immediate reactions
1218 patients with a compatible β-lactam hypersensitivity

257 confirmed
21.1%

78 positive skin tests
1040 negative skin tests
79 positive DPT
961 negative DPT
961 excluded
78.9%

Impact of PPL-MDM withdrawal?

15% + to PPL or MDM only

Work up of a patient with a suspicion of β-lactam allergy

Bousquet PJ et al., CEA 2007
Differences between children and adults

✓ Atanaskovic-Markovic M et al. PAI 2005: 682/1170 suspicions of IgE-dependent reactions = 58.3%
  Belgrade, Serbia and Montenegro; mean age: 7.6 yrs and time elapsed: 21.3 mths

✓ Hershkovich J et al. CEA 2009: 10/166 suspicions of IgE-dependent reactions = 6%
  Beer-Sheva, Israel (anaphylactic shocks excluded, no mean age nor time elapsed)

✓ Bousquet PJ et al. DAHD® 2009: 48/417 suspicions of all types of allergic reactions = 11.5%
  Montpellier, France; mean age: 6.6 yrs and time elapsed: 57.4 mths
Work up of a patient with a suspicion of β-lactam allergy

Bousquet PJ et al., CEA 2007

1218 patients with a compatible β-lactam hypersensitivity

178 positive skin tests

79 positive DPT

257 confirmed 21.1%

1040 negative skin tests

961 negative DPT

381 excluded 78.9%

How about biology?
Could specific IgE measurements help here?
Blanca M et al., Allergy 2001

✓ FEIA Phadia CAP System®: c1 (PPL) and c6 (amoxicilloyl)
✓ Sensitivity = 42-74% and specificity = 96-100% in adults

<table>
<thead>
<tr>
<th>Immediate reactions</th>
<th>PPL</th>
<th>Amox</th>
<th>PPL or Amox</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ST to PPL or MDM</td>
<td>13/19</td>
<td>10/19</td>
<td>14/19 (74%)</td>
</tr>
<tr>
<td>+ST to Amox</td>
<td>3/29</td>
<td>12/29</td>
<td>12/29 (41%)</td>
</tr>
<tr>
<td>-ST+DPT</td>
<td>8/26</td>
<td>10/26</td>
<td>11/26 (42%)</td>
</tr>
</tbody>
</table>

| Non immediate reactions Controls     | 0/25    | 1/25    | 1/25 (4%)   |
|                                      | 1/30    | 0/30    | 1/30 (3%)   |
Basophil activation test in β-lactam allergy

Sanz M et al., Clin Exp Allergy 2002

✓ 58 adult patients with positive skin tests to β-lactams and 30 controls
✓ Ex vivo stimulation of blood cells
✓ CD63+, IgE+ cells
✓ Specificity = 93.3%
  Sensitivity = 50%
ELISA-spot in the diagnosis of amoxicillin-induced MPEs

A: 22 patch+ amox adults; B: 21 amox tolerants; C: 15 amox IgE+
Resensitization in children with suspected β-lactam allergy

✓ 166 children with suspected β-lactam allergy (150 for penicillins, 14 for penicillin + cephalosporins, and 2 cephalosporins).

✓ Only 10 children (6%) were positive in the initial evaluation (4 ST and 6 DPT).

✓ Second set of tests performed 1-5 months later in 98 children with a negative initial evaluation; only 2 children (2%) were resensitized (+ST).

✓ Follow-up survey of 71/96 patients, 59 (83%) had received β-lactams; only one had developed a minor eruption after subsequent exposure to amoxicillin (not retested).
Choosing in the same class is possible, but after skin testing

✓ **Penicillin-cephalosporin cross-reactivity: 0.5-10%**
  (via ß-lactam ring or side-chain, weak data in the literature - Pegler BMJ 2007; 0.3 to 24% in Atanaskovic-Markovic et al. PAI 2005)

✓ **Imipenem/cilastatin and meropenem** amongsts 112 and 104 adults and 108 children allergic to penicillins

  *All skin tests negative subjects who agreed to undergo imipenem/cilastatin and/or meropenem challenges tolerated them:*

  - 42 adults tolerated imipenem/cilastatin, 35 meropenem, and 68 both imipenem/cilastatin and meropenem - Romano NEJM 2006 and Ann Intern Med 2007
  - 107/108 penicillin ST+ children tolerated meropenem - Atanaskovic-Markovic et al. Allergy 2008 (one had +ST to meropenem)
β-lactam tolerance induction

- Indications are exceptional
- First, choose a β-lactam alternative under hospital surveillance

**Example of Penicillin G:** Vervloet, Pharmacia 2001
- 17 doses over 4 hrs
- from 100 U to 0.4 MU per os (doubling / 15 min)
- then 0.2, 0.4 and 0.8 MU SC (/ 15 min), then 1 MU IM

**Other example:** Moss, J Pediatr 1984
- 7 doses over 3 hrs
- $10^{-6} - 10^{-5} - 10^{-4} - 10^{-3} - 10^{-2} - 10^{-1} - 100\%$ of the therapeutic dose
- every 30 min
Conclusions

✓ β-lactam allergy diagnosis is possible and mainly clinical

✓ Drug allergy work up is safe in specialized settings

✓ Less than 25% of the suspicions are confirmed in general (less in children), 40-65% by skin testing, 35-60% by drug provocation

✓ Testing helps to find the culprit agent when several causes are possible and to guide the choice of future therapies (cross-reactivities)

✓ Further research is needed (mechanisms, biological diagnosis, cross-reactivities...)

![Chemical structure of a drug molecule]
ANTIBIOTIC ALLERGY IN CHILDREN

OTHER ANTIBIOTICS
Allergies to quinolones

- Contraindicated in young children
- 0.1 à 2% of treatments
- Symptoms often anaphylactic
- Probably IgE-dependent (IgE + 30/54, Manfredi JACI 2004)
- Skin tests not validated (false +)
- Provocation tests needed: 27%+ (Messaad Ann Intern Med 2004)
- Frequent cross-reactivities between quinolones and possibly quinoleins (Nivaquine, Lariam…)
- Tolerance induction is possible (cystic fibrosis)
General work up

- Is the antibiotic mandatory (case reports) ?
- If YES and immediate reaction: DPT (ST rarely efficient with a few exceptions)
- If YES and non urticarial non immediate reaction: patch tests then DPT if patch are negative
- If NO or if reaction was non immediate or very severe or if patch are positive: class exclusion
- If antibiotic is absolutely needed without any good alternatives and in the absence of contra-indications: tolerance induction