Beta-lactam hypersensitivity: Do geographical differences lead to different symptoms and management?

SOUTHERN EUROPE

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Malaga Regional University Hospital, Spain
BL ALLERGY AS A PUBLIC HEALTH PROBLEM

- Penicillin allergy is self-reported by 10-20% of the population
- They are more likely to be treated with broad-spectrum antibiotics, such as quinolones, vancomycin, and third-generation cephalosporins
- This is associated with antibiotic resistance and clinical complications (30.1% more vancomycin-resistant enterococcus, 23.4% more C difficile, and 14.1% more methicillin-resistant Staphylococcus aureus than control subjects)
- The average hospital stay for patients with penicillin “allergy” was 0.59 days longer than for control subjects
- Alternative second-line antibiotics are often more expensive
- Cost of penicillin allergic 17,849£ versus 9,831£ non-allergics
- The increase in treatment has been estimated in 273€/patient/day

Solensky R. JACI 2014
Macy E. JACI 2013
Satta G Clin Mol Allergy 2013
Sastre JACI 2012
CONFIRMED DIAGNOSIS ADULTS

N=4460

Doña I. JIACI 2012
• Skin testing was used by 74.7%, with only 71.4% having access to penicillin skin test reagents, and patch tests by 54.7%

Thong BY. WAO Journal 2011

• Skin testing was undertaken by 87% of respondents (17% SPT, 77% SPT and IDT if negative and 6% SPT and IDT in all cases)

• The drugs, doses and protocols for skin testing varied considerably

Richter AG. Clin Exp Allergy 2013
SKIN TESTING OVER TIME

PENICILLINS

Cross-reactions
Selective reactions

% skin test positive survival

CEPHALOSPORINS

Cross-reactions
Selective reactions

Cumulative proportion surviving

0 1 2 3 4 5 6

0 1 2 3 4 5 6

Time of negativization (month)

0 100 80 60 40 20 0

Blanca M. J Allergy Clin Immunol 1999

Romano A. Allergy 2014
BL ARE HAPTENS

A

B

Penicilloyl (BPO)

Cephalosporoyl (CPO)

Degradation Products

Torres MJ. Med Clin N Am 2010
BINDING SITES OF AX TO PROTEINS

Ariza A. J Proteomics 2012

0

0,5

AX biotinilate (mg/ml)

20

20

DIC

Estreptavidine-AlexaFluor488

Estreptavidine-DAPI

Ariza A. PLoS One 2014
CHEMICAL STRUCTURE

CARBAPENEMS

MONOBACTAMS

CLAVAMS

PENICILLINS

CEPHALOSPORINS

Ariza A et al. JIACI 2015
BETALACTAM CONSUMPTION IN SPAIN

AMOXICILLIN-CLAVULANIC

AMOXICILLIN
Consumption of broad- and narrow-spectrum penicillins in the community in 2012

*expressed as DDD per 1 000 inhabitants and per day

[Graph showing consumption levels across different countries]
## BL INVOLVED IN THE REACTION

### ITALY

<table>
<thead>
<tr>
<th>N</th>
<th>BL INVOLVED</th>
<th>REFERENCE</th>
</tr>
</thead>
</table>
| 212 | 66% Amoxicillin-CLV  
19% Amoxicillin  
11,8% other penicillins  
1,1% Penicillin V/BP  
2,2% Cephalosporin     | Gaeta F. JACI 2014 |

### FRANCE

<table>
<thead>
<tr>
<th>N</th>
<th>BL INVOLVED</th>
<th>REFERENCE</th>
</tr>
</thead>
</table>
| 142 | 68,3% Amoxicillin  
28,9% Cephalosporin  
3% Other penicillins          | Renaudin JM. Allergy 2013 |
| 201 | 45,1% Amoxicillin  
17,5% Cephalosporin  
20,2% Other penicillins      | Bousquet PJ. Clin Exp Allergy 2007 |
## BL INVOLVED IN THE REACTION

### DENMARK

<table>
<thead>
<tr>
<th>N</th>
<th>BL INVOLVED</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>45,4% Penicillin V/G</td>
<td>Borck JE. Int Arch Allergy Immunol 2011</td>
</tr>
<tr>
<td></td>
<td>36,4% Dicloxacillin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18,2% Pivampicillin</td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>46,9% Penicillin V/G</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20,4% Amoxicillin</td>
<td>Hjortlund J. Allergy 2013</td>
</tr>
<tr>
<td></td>
<td>15,3% Dicloxacillin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7,1% Ampicillin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4,1% Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8,2% UK penicillin</td>
<td></td>
</tr>
</tbody>
</table>

### UK

<table>
<thead>
<tr>
<th>N</th>
<th>BL INVOLVED</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>44% BL</td>
<td>Richter A. J Clin Pathol 2011</td>
</tr>
<tr>
<td></td>
<td>20% Amoxicillin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14% Amoxicillin-CLV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8% Flucloxacillin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8% Penicillin V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2% Cephalosporin</td>
<td></td>
</tr>
</tbody>
</table>
DIAGNOSIS

CLINICAL HISTORY

SKIN TEST

IN VITRO TEST

DPT
**ICON ON DRUG ALLERGY**

- Standard procedures, trained staff and 4-6 weeks after the reaction
- Immediate reactions:
  - SPT is the initial screening due to its simplicity, rapidity, low cost, and high specificity
  - IDT are undertaken when SPT are negative. Compared to SPT, they provide an enhanced sensitivity for drug-specific IgE. They should be performed with the intravenously injectable form of the drug whenever possible
- Nonimmediate reactions:
  - PT and/or late-reading IDT should be performed

*Multicenter study* demonstrates significant differences in the methodology of IDT, in volumes injected and in resulting Pi sizes among centers

Demoly P et al. Allergy 2014

Barbaud A et al. (Data not published)
BENZYL-PENICILLIN DETERMINANTS

**BENZYL-PENICILLIN MAJOR DETERMINANTS**

- PENICILLOYL-POLY-L-LYSINE (PPL)
- BENZYL-PENICILLOYL-OCTA-L-LYSINE (BP-OL)

**BENZYL-PENICILLIN MINOR DETERMINANTS**

- BENZYL-PENICILLOIC ACID (BP)
- BENZYL-PENICILLOIC ACID (PO)

<table>
<thead>
<tr>
<th>Major determinants</th>
<th>Minor determinants</th>
<th>Commercialized products / Company</th>
<th>Commercialization date</th>
<th>Withdrawal date</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPL</td>
<td>-----</td>
<td>Pre-pen (PPL)</td>
<td>1974 (US)</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hollister-Stier (Spokane, WA, USA)</td>
<td>2009 (US, Canada)</td>
<td></td>
</tr>
<tr>
<td>PPL</td>
<td>BP, BPO, PO</td>
<td>Allergopen (MDM + PPL)</td>
<td>~1980</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>(MDM, mixture of minor determinants)</td>
<td>Allergopharma (Reinbek, Alemania)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPL</td>
<td>BP, BPO</td>
<td>DAP, Diagnostic Allergy Penicillin (MDM + PPL)</td>
<td>2004</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>(MDM)</td>
<td>Diater (Madrid, España)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP-OL</td>
<td>PO</td>
<td>DAP, Diagnostic Allergy Penicillin (MD + BP-OL)</td>
<td>2011</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>(MD, minor determinant)</td>
<td>Diater (Madrid, España)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ariza A et al. JIACI 2015
AMOXICILLIN DETERMINANTS

- Significant disagreement between EU and NA clinicians regarding AX concentration, but interestingly not of penicillin, penicilloate or penilloate
- AX solubility in water at pH 7 is 4 mg/mL. Thus, skin testing using 20 mg/mL of AX is an irritant because it requires a nonphysiologic pH to ensure AX solubility in solution.

The active pharmaceutical principle is the molecule of AX, which provides the antibiotic activity

Used for oral administration, has carboxylic acid functionality and cannot be easily dissolved in water. It is therefore impossible to reach a concentration of 20 mg/mL.

The injectable type is a sodium salt that can be easily dissolved at physiologic pH in water. In fact, 200 mg/mL is the concentration of AX allowed for parenteral use

Macy E. Clin Exp Allergy 2011
Montañez MI. J Allergy Clin immunol 2011
AMOXICILLIN DETERMINANTS

<table>
<thead>
<tr>
<th>METHOD</th>
<th>INJ AX</th>
<th>DIA AX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prick</td>
<td>24 (43.6%)</td>
<td>25 (45.9%)</td>
</tr>
<tr>
<td>ID</td>
<td>29 (52.7%)</td>
<td>28 (50.9%)</td>
</tr>
</tbody>
</table>

Torres MJ. Clin Exp Allergy 2011
# Skin Test Sensitivity

<table>
<thead>
<tr>
<th>N</th>
<th>Reagents</th>
<th>Sensitivity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>PPL/MDM/BP/AX</td>
<td>72%</td>
<td>Blanca-Lopez N et al. Allergy 2015</td>
</tr>
<tr>
<td>29</td>
<td>PPL/MDM</td>
<td>72.4%</td>
<td>Celik G. Int Arch Allergy Immunol 2012</td>
</tr>
<tr>
<td>50</td>
<td>PPL/MDM/AX</td>
<td>57%</td>
<td>Richter A. J Clin Pathol 2011</td>
</tr>
<tr>
<td>52</td>
<td>PPL/MDM/BP/AX</td>
<td>67.31%</td>
<td>Antico A. In Arch All Appl Immunol 2011</td>
</tr>
<tr>
<td>257</td>
<td>PPL/MDM/BP/AX</td>
<td>69%</td>
<td>Bousquet PJ. Clin Exp Allergy 2008</td>
</tr>
<tr>
<td>290</td>
<td>PPL/MDM/BP/AX</td>
<td>70%</td>
<td>Torres MJ. Allergy 2001</td>
</tr>
</tbody>
</table>
SKIN TESTS SENSITIVITY

Doña I. JIACI 2012

Barrionuevo E et al. (not published)
SKIN TESTS WITH A PANEL OF HAPTENS

Barrionuevo E et al. (not published)
**SELECTIVE REACTIONS TO CLAVULANIC**

- **Group A**: Skin test (+) to PPL/MDM (N=5; 9%).
- **Group B**: Skin test (+) to AX and good tolerance to BP (N=34; 62%)
- **Group C**: Skin test (+) to CLV and good tolerance to BP/AX (N=16; 29%)

Torres MJ et al. J Allergy Clin Immunol 2010
SELECTIVE REACTIONS TO AX AND CLAV

History suggestive of immediate reaction after intake of AX or AX-CLAV

- Prick/ID PPL/MDM
  - DPT PG/PV

- Prick or ID AX
  - Selective to AX N=40

- Prick and ID AX
  - DPT AX
  - Prick or ID CLAV
  - Selective to CLAV N=11

0/11 Repositivization to BP/PV/AX

NON ALLERGIC

Blanca-Lopez N et al. Allergy 2015
ST SENSITIVITY IN NON IMMEDIATE

- Lower than in immediate reactions
- IDT has higher sensitivity than PT
- Great variations from 2.6% to 37.8%
- Piperacillin in CF the percentage of ST + is 14%

Whitaker P. J Immunol 2011
Padial A. Clin Exp Allergy 2008

Romano A, et al. Allergy 2010

![Graph showing percentage of ST positive for Culprit, MDM, and PPL with N=157]
DRUG PROVOCATION TEST

Clinical Setting

- 1/100 therapeutical dose
  - 30 min
  - 3d-1w later

- 1/10 therapeutical dose
  - 30 min
  - 3d-1w later

- Full therapeutical dose
  - 30 min
  - 3d-1w later

Home 2 days
Home 7 days
How long?????

N=118 patients from France, Italy and Portugal were re-exposed to the negative BL

N=9 reported non-severe NI reactions (5 urticaria, 3 exanthema, 1 UN).

Figures probably over-stimated (5 not re-evaluated)

NPV 94.1% (29.8-98.3)

Demoly P. Allergy 2010
### SEVEN DAYS PROTOCOL

<table>
<thead>
<tr>
<th></th>
<th>BP/PV</th>
<th>CULPRIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1d</td>
<td>7d</td>
</tr>
<tr>
<td>IMMEDIATE</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>NON IMMEDIATE</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

- **SYMPTOMS:** 52.6% rash, 39.5% Urt/Ang, 3.2% anaf, 3.8% others
- **BL INVOLVED:** BP/PV 55%, DX 11.4%, AX 9.6%, AMP 7%, UN 18.4%.
- **TIME INTERVAL:** Immediate 10.5%, Non-immediate 68.7%, not classified 20.8%.

Hjortlund J. Allergy 2013
CONCLUSIONS

There are many factors that can influence differences in BL allergy diagnosis:

- BL Consumption
- Health system organization, waiting lists, availability of skin tests reagents, and drug provocation tests
- Classification of reactions
- Diagnostic tests interpretations
- Genetics