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

Northern Europe

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Disclosure

In relation to this presentation, I declare that there are no conflicts of interest.

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## Pubmed search 14. april 2016

<table>
<thead>
<tr>
<th>Penicillin hypersensitivity</th>
<th>Beta-lactam hypersensitivity</th>
<th>Country</th>
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<tr>
<td>37</td>
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<td>91</td>
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<td>Italy</td>
</tr>
<tr>
<td>164</td>
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<td>Spain</td>
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</table>
Guidelines

• ICON Drug Allergy (2014)
• ENDA guidelines/EAACI position papers
  – Update Beta-lactam hypersensitivity (2009)
  – Drug provocation (2003), (2015 allergen provocation)
  – Skin test concentrations (2013)

Very few participants from Northern Europe...
Beta lactam hypersensitivity in Northern Europe

• Geographical differences
  – Variable resources available in allergology
  – Antibiotic usage, prescription patterns
  – Population (cultural differences, genetic factors)

Differences in
• Symptoms
  – Severity (anaphylaxis), immediate/delayed

• Investigations/management
  – IgE, Skin testing, provocation
  – Following ENDA guidelines
  – Children vs adults
Retrospective case series analysis of penicillin allergy testing in a UK specialist regional allergy clinic


EAACI β-lactam testing protocols require significant staffing and clinic space with an initial clinic appointment and potentially two further appointments for skin testing and then DPT. An

EAACI also recommends performing DPT in patients with non-immediate reactions with increasing doses over 3 weeks, a policy that would have major resource implications for UK NHS specialist allergy services.
Antibiotic prescription patterns

Brauer R et al

PHARMACOEPIEMIOLOGY AND DRUG SAFETY 2016; 25(Suppl. 1): 11–20

- CPRD (UK)
- THIN (UK)
- BIFAP (Spain)
- Bavarian Claims Database (Germany)
- Mondriaan NPCRD (The Netherlands)
- Mondriaan AHC (The Netherlands)
- DKMA (Denmark)
Prescriptions penicillins


Figure 3: Outpatient use of penicillins (JOIC) in 26 European countries in 2002 in descending order of narrow spectrum penicillins
Figure 1. Outpatient use of cephalosporins in 25 European countries in 2003. The use of the fourth-generation cephalosporins is minimal. For Iceland total data are used; for Poland 2002 data are used.
Prevalence beta-lactam (penicillin) hypersensitivity - self reported

• Borch JE et al *Basic and clinical toxicology and pharmacology* 2006
  – 3642 Danish inpatients screened for suspected penicillinallergy. If suspected, allergy investigation was offered. 96/3642 (2.6%) had suspected penicillinallergy

• Salden OAE et al *Family practice* 2015
  – 163/8288 (2%) Dutch patients in primary care reported beta-lactam allergy

• Kerr JR *BR journal Clin pract* 1994
  – 21/271 (7.7%) inpatients with infections needing consultation with a microbiologist reported allergy to penicillin.
Hjortlund et al one week oral challenge with penicillin in diagnosis of penicillin allergy. Acta derm venereol 2012

• Allergy Centre, Odense Universitetshospital Denmark 2007-2009
• 405 patients. Penicillin culprit drug in 72%
• Modified ENDA guidelines
  – Specific IgE (PenV and G, AMP, AX) in all patients
  – SPT with Pen G, AMP, AX + culprit
  – IDT Pen G, AMP
  – Single oral challenge
  – One week oral Penicillin V treatment
• Allergy centre, Odense, Denmark 2010-2011
  – 452 referred with suspected penicillin allergy. 342 patients included (24.3% declined)
• Presenting symptoms:
  – Urticaria and/or angioedema 39.5%
  – Unclassified rash 52.6%
  – Anaphylaxis 3.2%
• Culprit drugs
  – PenV/G 55%, AX 9.6%, AMP 7%, DX 11.4%, unknown 18.4%
• Modified ENDA protocol like previous study
  – Only 3 positive SPT/IDT to PPL and MDM, all also positive to Penicillin G
  – 60% of positive IDT were delayed (mainly AMP)
  – IDT with delayed reading more sensitive than patch test
  – Patients more likely to test positive if history of urticaria/angioedema/anaphylaxis
In total 98/342 tested positive (28.7%)

- Specific IgE 19 patients (5.6%)
- Skin test 35 patients (10.2%)
- Iv challenge 4 patients (1.2%)
- Single dose challenge 7 patients (2%)
- Prolonged 7 day oral challenge 39 patients (11.4%)
Anaphylaxis – a rarer presentation in beta-lactam hypersensitivity in Denmark?

• Anaphylaxis - suspected penicillin reactions
  – Hjortlund Acta derm venereol 2012  9/405  (2.2%)
  – Hjortlund Allergy 2013  11/342  (3.2%)
  – Fransson unpublished  65/1913  (3.4%)

• Anaphylaxis – provocation positive patients
  – Hjortlund Allergy 2013 n=342  0/98  (0)
  – Fransson unpublished n=1913  1/211  (0.5%)
  – Holm AAIR 2011 n=580  0/14  (0)
Allergy Clinic, Gentofte Hospital Denmark

• No routine skin testing in suspected drug hypersensitivity

• Skin testing before drug provocation in high risk patients only
  – anaphylaxis, perioperative reactions, severe comorbidity, positive specific IgE, elevated tryptase

• If performed, then with culprit drug and titrated IDT starting with dilute concentrations (1/1000)
Allergy Clinic, Gentofte Hospital Denmark

• Provocation not performed when hx of severe delayed skin reactions or in pregnancy
• Provocation titrated in high risk patients
  – Iv access and 1/100, 1/10, 1/1
• Prolonged provocation in all patients with negative provocation and no clear hx of reaction on first tablet
  – 3-10 day depending on timing of initial reaction
• Positive test leads to testing with relevant alternative
Figure 1. Investigation algorithm for drug allergy in Gentofte Hospital Allergy Clinic.
Allergy Clinic, Gentofte Hospital Denmark

- Study of 1913 drug provocations during 2010-2014 in penicillin seronegative patients
  - Provocation with culprit drug if known
  - If not known for beta-lactam test with penicillin V
- 211/1913 (11%) tested positive
- Only 43/211 (20.4%) were positive after first dose
- Only 1/211 (0.5%) had anaphylaxis on provocation
Figure 2. Total Drug Provocation Tests
n=1913

Penicillin V
n=1141 (59.6%)

Penicillin G
n=15 (0.7%)

Aminopenicillins
n=269 (14.1%)

Other penicillins
n=165 (8.6%)

Cephalosporins
n=21 (1.1%)

Other antibiotics
n=165 (8.6%)

Analgesics
n=59 (3.1%)

Local anaesthetics
n=33 (1.7%)

Other drugs
n=45 (2.3%)
Figure 3. Positive Drug Provocation Tests
n=211 (11%)

- Penicillin V  n=68 (32.2%)
- Penicillin G  n=0 (0%)
- Aminopenicillins  n=79 (37.4%)
- Other penicillins  n=20 (9.5%)
- Cephalosporins  n=1 (0.5%)
- Other antibiotics  n=30 (14.2%)
- Analgesics  n=7 (3.3%)
- Local anaesthetics  n=0 (0%)
- Other drugs  n=6 (2.8%)

Fransson S et al submitted
Figure 5. First dose vs prolonged provocation

- Positive DPT on first dose (20.4%)
- Positive prolonged DPT (79.6%)
Results - prolonged provocation and concordance with history

<table>
<thead>
<tr>
<th>Initial reaction</th>
<th>DPT positive IR</th>
<th>DPT positive NIR 2-24 hours</th>
<th>DPT positive NIR 2-3 days</th>
<th>DPT positive NIR &gt;3 days</th>
<th>DPT positive NIR after treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2-24 hours</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>2-3days</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>&gt;3 days</td>
<td>10</td>
<td>9</td>
<td>17</td>
<td>29</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>After treatment</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td>5</td>
<td>23</td>
<td>44</td>
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<tr>
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<td>2</td>
<td>1</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Total</td>
<td>43</td>
<td>30</td>
<td>42</td>
<td>47</td>
<td>49</td>
<td>211</td>
</tr>
</tbody>
</table>

Concordance: 20.9% 16.7% 21.4% 61.7% 46.9%

Table 2. The time interval from first dose to the reaction at the initial reaction and drug provocation test (DPT).

Recall most reliable for reactions occurring > 3 days after initiation of treatment
Fig. 4. Management of child presenting with a suspected allergic reaction to a beta-lactam antibiotic. Children with SJS, EM, AGEP, TEN and DRESS should not be tested. Avoid proceeding directly to challenge if details of the clinical history are not well documented.
Gomes ER et al Allergy 2016
Drug hypersensitivity in children report from EAACI task force
Conclusions

Northern Europe

• Information about beta-lactam hypersensitivity lacking in the literature

• Differences in prescription patterns
  – Mainly narrow spectrum penicillins
  – Very few cephalosporins

• Differences in presentation?
  – Anaphylaxis rare presentation
  – Prolonged challenge reveals more delayed reactions
Conclusions

Northern Europe

• Differences in investigation
  – Common algorithm for immediate and delayed reactions in Denmark, including specific IgE and prolonged provocation
  – More focus on culprit drug in Denmark
    • Crossreactivity important - but if no reaction to culprit drug no need for further investigations

– Call for optimization of algorithms
  • Highest safety and correct outcome with the least resources
  • More focus on individual risk evaluation when choosing investigation strategy
"Drug allergy is a matter for collaboration, not competition"

M. Blanca, opening lecture DHM7 Malaga 2016
Beta-lactam hypersensitivity – geographical differences

Do geographical differences lead to different symptoms and management?