Most patients tolerate penicillin administration despite history of non-anaphylactlc penicillin allergy: a systematic review and meta-analysis

Martha DesBiens MD1,2, Okechukwu Erinne MD2, Andrew Glick BS1, Saiganesh Ravikumar BA, BS3, Peter Scalia MSc2

1Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; 2The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, USA

Background

- True allergy to penicillin is rare, despite the high frequency with which it is reported.
- While around 10% of the US population report an allergy to penicillin, only 1% have a true type I hypersensitivity to this antibiotic class.
- Misrepresented allergy drives unnecessary use of alternative antibiotics, with profound impacts on clinical outcomes and antibiotic stewardship.
- Tolerance of penicillin administration in patients reporting allergy history, but at low risk for serious drug reactions is not well understood.
- We aim to estimate frequency of full tolerance of systemic drug challenge in patients with reported allergy to penicillin, with low risk of type I hypersensitivity or other serious drug reactions.

Methods

Study Eligibility and Data Collection:

- Clinical trials, observational studies, cross-sectional studies, quasi-experimental were considered
- Studies were included if they:
  - Evaluated participants with history of penicillin allergy
  - Reported outcomes of tolerance after systemic drug challenge
- Data were extracted by at least two independent reviewers
- Risk of bias was assessed with ECR1 tool

Analysis:

- We calculated the aggregate proportion of patients tolerating a systemic penicillin challenge using a Bayesian beta-binomial model. We included random effects for between-study variability and assumed a non-informative, or "flat" prior probability of penicillin tolerance (prior probability of tolerance = 0.5).

Results

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>Total n</th>
<th>Gender, %</th>
<th>Age range, years</th>
<th>Area of study, %</th>
<th>Allergy to PCN</th>
<th>Tolerance to PCN</th>
<th>% Tolerant</th>
<th>% Tolerant</th>
<th>% Tolerant</th>
<th>% Tolerant</th>
<th>% Tolerant</th>
<th>% Tolerant</th>
<th>% Tolerant</th>
<th>% Tolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiley, 2004</td>
<td>Prospective study</td>
<td>109</td>
<td>Male 60%</td>
<td>18-70</td>
<td>USA</td>
<td>23</td>
<td>29</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Holm, 2011</td>
<td>Prospective study</td>
<td>70</td>
<td>Female 55%</td>
<td>18-70</td>
<td>USA</td>
<td>9</td>
<td>14</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Macy, 2010</td>
<td>Prospective study</td>
<td>92</td>
<td>Female 65%</td>
<td>18-70</td>
<td>USA</td>
<td>10</td>
<td>17</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Forrest, 2001</td>
<td>Retrospective</td>
<td>100</td>
<td>Female 50%</td>
<td>18-70</td>
<td>USA</td>
<td>20</td>
<td>34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Macy, 2013</td>
<td>Prospective study</td>
<td>100</td>
<td>Male 50%</td>
<td>18-70</td>
<td>USA</td>
<td>20</td>
<td>34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Sundquist, 2017</td>
<td>Retrospective</td>
<td>250</td>
<td>Male 50%</td>
<td>18-70</td>
<td>USA</td>
<td>20</td>
<td>34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Romano, 2002</td>
<td>Prospective study</td>
<td>200</td>
<td>Female 50%</td>
<td>18-70</td>
<td>USA</td>
<td>20</td>
<td>34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Forrester, 2011</td>
<td>Retrospective</td>
<td>100</td>
<td>Male 50%</td>
<td>18-70</td>
<td>USA</td>
<td>20</td>
<td>34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Romano et al., 2002</td>
<td>Retrospective</td>
<td>200</td>
<td>Female 50%</td>
<td>18-70</td>
<td>USA</td>
<td>20</td>
<td>34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Pooled summary estimate of included studies suggests around 95% of patients reporting an allergy to penicillin, who are otherwise at low risk for serious drug reaction, will tolerate systemic administration of penicillin without any notable reaction. The presence of infection at the time of challenge is associated with lower odds of tolerance in our sample, suggesting a role for pre-empive allergy testing.

- This estimate adds to the previously accepted knowledge that at least 90% of patients reporting an allergy to penicillin are not truly allergic.
- Considering this impressive tolerance, formal evaluation of patients reporting an allergy to penicillin should be systematically performed, ideally pre-emptively.
- Studies evaluating individual patient and clinical characteristics associated with tolerance of penicillin challenge are needed to inform safe, systemic allergy assessment.

Limitations:

- Only studies with English language translations were included in this review
- Due to the nature of our research question, the majority of included articles are quasi-experimental, introducing potential for selection bias and attrition bias affecting internal validity of the included studies.

OR 0.64 (0.49, 0.84)

Differences in proportions is significant (2 (1, N=5002) = 10.29, p=0.001)