JACI: In Practice
Year in Review:
Asthma and Drug Allergy

Michael Schatz, MD, MS
Editor-in-Chief, JACI: In Practice
Department of Allergy
Kaiser Permanente, San Diego
Disclosures

• Research grant; Contracted research
  • Merck
  • GlaxoSmithKline
  • AstraZeneca
Learning Objectives

• Examine and apply learnings from clinically impactful asthma articles published in the last year in JACI: *In Practice*

• Recognize controversies in beta lactam allergy management and understand the relevance of recent data on this subject published in the last year in JACI: *In Practice*

• Recognize controversies in the approach to patients with histories of reactions to radiographic contrast media and understand the implications of recent data on this subject published in the last year in JACI: *In Practice*
Asthma Topics for Today

- Co-morbidities
- Special populations
- Endotypes/phenotypes
- Non-pharmacologic management
- Pharmacologic management
Comorbidities in Difficult to Control Asthma

• Survey study of 2312 adults with a prescription for high dose ICS or oral corticosteroids
• 914 diagnosed with difficult-to-control asthma
• Co-morbidity diagnoses based on prescriptions or questionnaire responses
• 92% of patients with difficult-to-control asthma had at least one co-morbidity

Figure 2

The bar chart shows the percentage distribution of difficult-to-control asthma and not-difficult-to-control asthma based on the number of comorbidities. The x-axis represents the number of comorbidities, ranging from 0 to 6, and the y-axis represents the percentage, ranging from 0% to 35%. The chart indicates a statistically significant difference, with a P-value less than 0.01.
Figure 3

Comparison of comorbidities between difficult-to-control asthma and not-difficult-to-control asthma.

- Diabetes: 12.5% (difficult-to-control), 11.1% (not-difficult-to-control), *P* = 0.02, n.s.
- Obesity: 18.6% (difficult-to-control), 13.9% (not-difficult-to-control), *P* = 0.02
- Nasal polyps: 24.4% (difficult-to-control), 21.9% (not-difficult-to-control), n.s.
- Anxiety/Depression: 36.1% (difficult-to-control), 24.7% (not-difficult-to-control), *P* < 0.01
- Cardiovascular disease: 63.8% (difficult-to-control), 52.5% (not-difficult-to-control), *P* < 0.01
- GERD: 66.8% (difficult-to-control), 45.4% (not-difficult-to-control), *P* < 0.01
Anxiety, Depression, and Asthma Control: Changes After Standardized Treatment

- 3182 patients with moderate to severe asthma observed over 6 months of specialist treatment
- Diagnosis of anxiety and depression based on Hospital Anxiety and Depression Scale (HADS)
- Asthma control based on Asthma Control Test (ACT)
- Independent associations with asthma control
  - Anxiety (OR 0.20)
  - Depression (OR 0.34)
  - Lower FEV1 (OR 0.62)
## Longitudinal Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>24.2%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Depression</td>
<td>12.0%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Mean FEV1</td>
<td>81.6%</td>
<td>86.0%</td>
</tr>
<tr>
<td>Mean ACT</td>
<td>15.8</td>
<td>19.4</td>
</tr>
</tbody>
</table>
A Randomized, Double-Blind, Placebo-Controlled Trial of Escitalopram in Patients with Asthma and Major Depressive Disorder

- 12 week RCT of escitalopram (10 mg/day) in 139 outpatients with asthma and major depressive disorder
- Asthma severity stratified by oral corticosteroid use in the past 12 months (≥ 3 bursts)
- Depression severity stratified by Hamilton Rating Scale for Depression

Asthma Topics for Today

• Co-morbidities
• Special populations
• Endotypes/phenotypes
• Non-pharmacologic management
• Pharmacologic management
Asthma Morbidity, Comorbidities, and Modifiable Factors Among Older Adults

• Data from 14,076 patients ≥ 65 years of age with active asthma participating in the Behavioral Risk Factor Surveillance System Asthma Call-back Survey

• One or more ED or urgent care visits reported by 10.6% of patients

• One or more asthma-related hospitalizations reported by 5.7% of patients
## Significant Relationships to Hospitalizations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>4.11</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.87</td>
</tr>
<tr>
<td>Depression</td>
<td>1.42</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.43</td>
</tr>
<tr>
<td><strong>Cost As A Barrier</strong></td>
<td></td>
</tr>
<tr>
<td>Primary care visits</td>
<td>3.07</td>
</tr>
<tr>
<td>Specialist visits</td>
<td>3.79</td>
</tr>
<tr>
<td>Unable to buy medication</td>
<td>2.76</td>
</tr>
<tr>
<td><strong>Home Environment</strong></td>
<td></td>
</tr>
<tr>
<td>Cockroaches seen</td>
<td>1.67</td>
</tr>
<tr>
<td>Mold seen or smelled</td>
<td>1.71</td>
</tr>
</tbody>
</table>
The Association of Maternal Asthma and Early Pregnancy Vitamin D with Risk of Preeclampsia: An Observation From VDAART

- 816 pregnant women
  - Asthma: 327
  - No asthma: 489

- Incidence of preeclampsia
  - Asthma: 8.9%
  - No asthma: 7.4%

- Asthma control measured by the Pregnancy Asthma Control Test and expressed as proportion of uncontrolled asthma months

- Adjusted for vitamin D level, there was a significant relationship between proportion of uncontrolled asthma months and the incidence of preeclampsia

Mirzakhani, et al. JACI: IP 2018; 6:600
Asthma Topics for Today

• Co-morbidities
• Special populations
• **Endotypes/phenotypes**
• Non-pharmacologic management
• Pharmacologic management
Identifying Patient Attitudinal Clusters Associated with Asthma Control: The European REALISE Survey

- Factor analysis of respondent data from 7930 patients from the REALISE study
- Survey captured common beliefs and attitudes toward asthma and its management
- Five clusters
  - Confident and self-managing
  - Confident and accepting of their asthma
  - Confident but dependent on others
  - Concerned by confident in their HCP
  - Not confident in themselves or their HCP

Van der Molen, et al. JACI: IP 2018; 962
## Relationship of Clusters to GINA-defined Asthma Control

<table>
<thead>
<tr>
<th>Cluster (n)</th>
<th>Controlled</th>
<th>Partially Controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confident and self managing (2044)</td>
<td>47.7%</td>
<td>41.9%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Confident and accepting (2782)</td>
<td>19.5%</td>
<td>50.0%</td>
<td>30.5%</td>
</tr>
<tr>
<td>Confident but dependent on others (442)</td>
<td>11.8%</td>
<td>40.7%</td>
<td>47.5%</td>
</tr>
<tr>
<td>Concerned but confident in their HCP</td>
<td>0.9%</td>
<td>12.9%</td>
<td>86.2%</td>
</tr>
<tr>
<td>Not confident in themselves or their HCP</td>
<td>2.1%</td>
<td>14.3%</td>
<td>83.5%</td>
</tr>
</tbody>
</table>
Type 2 Biomarkers and Prediction of Future Exacerbations and Lung Function Decline in Adult Asthma

• Cohort study of 212 patients from two cohort studies followed for at least 12 months
  • 177 randomly selected for the first cohort
  • 20 from the second cohort (on ICS and LABA)
  • 15 from both cohorts

• Time to severe exacerbation determined
  • Requiring corticosteroid as an inpatient or outpatient
  • 67 (32%) had at least one severe exacerbation
  • Adjusted for cohort and ICS use

Results and Conclusion

• Exacerbations
  • Inverse relationship with FENO
  • No significant relationship with peripheral eosinophil counts, serum IgE or serum periostin

• Lung function (FEV1) decline
  • Inverse relationship with peripheral eosinophil counts
  • No significant relationship with FENO, serum IgE or serum periostin

• Conclusions
  • The positive association between type 2 biomarkers and risk in patients with severe asthma may not extend to more general populations of patients with mild and moderate asthma
  • Non-type 2 asthma is associated with increased asthma risk in a broad asthma population
Asthma Topics for Today

• Co-morbidities
• Special populations
• Endotypes/phenotypes
• Non-pharmacologic management
• Pharmacologic management
Sensitization and Exposure to Pets: The Effect on Asthma Morbidity in the US Population

• 5238 participants in the National Health and Nutrition Examination Survey 2005-6

• Exposure and sensitization determined
  • Dog
    • Exposure: 37.9% ownership; 36.0% high bedroom allergen level
    • Sensitization: 12.1 % of owners
  • Cat
    • Exposure: 27.5% ownership; 29.8% high bedroom allergen level
    • Sensitization: 13.9% of owners

• Outcomes
  • Current Asthma
  • Current Asthma and Attack in the Prior 12 months

Effects of Exercise and Diet in Nonobese Asthma Patients—A Randomized Controlled Trial

• 8 week RCT in 125 nonobese asthmatic patients aged 18-65 with Asthma Control Questionnaire > 1.0

• Interventions
  • Exercise
    • High intensity interval training
    • Indoor spinning bike session 3 times a week
  • Diet
    • High protein/low glycemic index
    • 5 group counselling sessions and 1 individual session
  • Both

Toennesen, et al. JACI: IP 2018; 6: 803
Figure 4

The figure shows a bar graph comparing miniAQLQ scores before (pre) and after (post) interventions for four groups: Exercise, Diet, Exercise+diet, and Control. The graph displays significant differences in post-intervention scores compared to pre-intervention scores, with the highest increase observed in the Exercise+diet group. The asterisks indicate statistical significance: *** for p < 0.001, * for p < 0.05.
Errors in the Use of Inhalers by Health Care Professionals: A Systematic Review

• Systematic review of published reports assessing the inhalation technique proficiency of Health Care Professionals (HCPs)
  • Pressurized metered dose inhalers (pMDI) with or without an inhalation chamber (IC)
  • Dry powder inhalers (DPI)
• Data extracted from 55 studies involving 6304 Health Care Professionals
• Early period (1975-1995) compared with late period (1996-2014)

Plaza, et al. JACI: IP 2018; 6: 987
Most Common Specific Errors

• pMDI
  • Not breathing out completely before inhalation (75%)
  • Lack of coordination (64%)
  • No breath hold (63%)

• DPI
  • Deficient preparation (89%)
  • Not breathing out completely before inhalation (79%)
  • No breath hold (76%)
Asthma Topics for Today

• Co-morbidities
• Special populations
• Endotypes/phenotypes
• Non-pharmacologic management
• Pharmacologic management
Step-Down Therapy for Asthma Well Controlled on Inhaled Corticosteroid and Long-Acting Beta-Agonist: A Randomized Clinical Trial

- 48 week RCT in 459 participants well-controlled for at least 3 months prior to enrollment (ACT ≥ 20) on medium dose ICS/LABA

- Interventions
  - No change
  - Reduced dose ICS/LABA
  - Stop LABA

- Primary outcome: Time to treatment failure (composite outcome)
  - Hospitalization or urgent medical visit for asthma
  - Systemic corticosteroids for asthma
  - Increase in controller or rescue therapy
  - Decline in lung function
  - Physician’s judgment

Rogers, et al. JACI: IP 2018; 6:633
Results

• Cumulative proportion of patients with treatment failure
  • No change: 26%
  • Reduced ICS/LABA: 28%
  • Stop LABA: 31%

• No significant differences in time to treatment failure between groups

• Stopping LABA was associated with a greater decline in lung function and more hospitalizations (five, all in group stopping LABA)
Tiotropium Attenuates Refractory Cough and Capsaicin Cough Reflex Sensitivity in Patients with Asthma

• 17 consecutive asthmatic patients (mean age 43 years, 13 women) with chronic cough in spite of ICS/LABA treatment
• Tiotropium (5µg/day) added for 4-8 weeks
• Outcomes
  • Cough severity (VAS)
  • Cough-specific QOL (Leicester Cough Questionnaire)
  • Asthma control (ACT)
  • Pulmonary function
  • Capsaicin cough reflex sensitivity

Fukumitsu, et al. JACI: IP 2018; 6: 1613
Results and Conclusions

• Improvement occurred in cough VAS, QOL, and ACT but not FEV1

• Changes in cough VAS correlated with changes in capsaicin sensitivity ($r = -0.58, p = .03$) and ACT scores ($r = -0.62, p = .02$) but not FEV1

• Tiotropium may alleviate asthmatic cough refractory to ICS/LABA by modulating cough reflex sensitivity but not through bronchodilation
Evaluation of Potential Continuation Rules for Mepolizumab Treatment of Severe Eosinophilic Asthma

• Post-hoc analysis from 2 placebo-controlled RCTs in 1192 patients with severe eosinophilic asthma
  • 2 or more exacerbations in the prior year
  • Blood eosinophils of ≥ 150 cells/µL at initiation or ≥ 300 cells/µL in the previous year

• Rules assessed at week 16
  • Reduction in blood eosinophils
  • Physician-rated response
  • FEV1 improvement
  • ACQ-5 score improvement
  • Exacerbations from baseline to week 16

• Long term assessment: exacerbations week 16 to end of study (week 32 or 52)

Gunsoy, et al. JACI: IP 2018; 6: 874
Results and Conclusion

- Nearly all patients failing to reduce blood eosinophil counts had counts ≤ 150 cells/µL at baseline.
- Patients not meeting continuation rules based on physician response, FEV1, and ACQ score still derived long-term benefit.
- For exacerbations, assessment at 16 weeks was premature for predicting future exacerbations.
- Treatment continuation should be reviewed based on long-term reduction in exacerbation frequency and/or oral corticosteroid dose.
Controversies in Drug Allergy

- International consensus meeting held at the 2018 AAAAI/WAO annual meeting
- Five topics covered and consensus articles published this month
  - Radiographic contrast media (RCM) reactions
  - Beta-lactam allergy
  - In vitro testing for drug allergy
  - Delayed hypersensitivity reactions to drugs
  - Institutional pathways for drug allergy
Controversies in Drug Allergy

• International consensus meeting held at the 2018 AAAAI/WAO annual meeting
• Five topics covered and consensus articles published this month
  • Radiographic contrast media (RCM) reactions
  • Beta-lactam allergy
  • In vitro testing for drug allergy
  • Delayed hypersensitivity reactions to drugs
  • Institutional pathways for drug allergy
Controversies in RCM Reactions

- Role of skin testing
- Value of switching agents
- Value of pre-treatment
Skin Testing for Suspected Iodinated Contrast Media Hypersensitivity

• Retrospective review of 597 patients evaluated after a hypersensitivity reaction to RCM
• Allergy Department of the University Hospital of Montpellier, France
• February, 2001 to September, 2014
• Premedication
  • Second generation H1-antihistamines twice a day for 48 hours before the examination
  • Generally advised only for patients with mast cell disorders or chronic urticaria and negative skin tests

Schrijvers, et al. JACI: IP 2018; 6:1246
## Challenges to negatively skin-tested RCM

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Initial Chronology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IHR</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>597</td>
<td>423 (70.9)</td>
</tr>
<tr>
<td>Re-exposed, n (%)</td>
<td>233 (39.0)</td>
<td>172 (40.6)</td>
</tr>
<tr>
<td>Tolerated, n (%)</td>
<td>217 (93.1)</td>
<td>162 (94.2)</td>
</tr>
<tr>
<td>Not tolerated, n (%)</td>
<td>16 (6.9)</td>
<td>10 (5.8)</td>
</tr>
</tbody>
</table>
## Challenges to negatively skin-tested RCM

<table>
<thead>
<tr>
<th>Group</th>
<th>Skin Test (ST) Result</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ST Positive</td>
<td>ST negative</td>
<td>ST negative for Culprit RCM</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>80 (13.4 %)</td>
<td>517 (86.6 %)</td>
<td>125</td>
</tr>
<tr>
<td>Reexposed, n (%)</td>
<td>17 (21.2)</td>
<td>216 (41.8)</td>
<td>51 (69.7)**</td>
</tr>
<tr>
<td>Tolerated, n (%)</td>
<td>16 (94.1)</td>
<td>201 (93.1)</td>
<td>43 (84.3)</td>
</tr>
<tr>
<td>Not tolerated, n (%)</td>
<td>1 (5.9)*</td>
<td>15 (6.9)</td>
<td>8 (15.7)</td>
</tr>
</tbody>
</table>

* NIHR to RCM that caused initial NIHR with reported delayed positive skin test
** Reexposure to the *culprit RCM* was tolerated in 15/18 (83.3%) of patients
Cross-reactivity

• 54 patients with immediate skin test positive
  • 37 (68.5%) only 1 positive test
  • 17 (31.5%) cross reactivity (reactions to 2-5 of 10 tested agents)
    • Most observed for iopromide and iomeprol (41.1%)
    • Common side chain
Effect of Premedication*

<table>
<thead>
<tr>
<th>Premedication</th>
<th>Total</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n, %)</td>
<td>150 (100)</td>
<td>13 (8.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>31 (20.7)</td>
<td>7 (19.4)**</td>
</tr>
<tr>
<td>No</td>
<td>88 (58.7)</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>Not sure</td>
<td>31 (20.7)</td>
<td>2 (1.3)</td>
</tr>
</tbody>
</table>

* Based on patient report by phone or mail
**P = .01 compared to no premedication group
Iodinated Contrast Media Allergy in Patients Hospitalized for Investigation of Chest Pain

- Primary percutaneous coronary intervention (PCI) requires RCM injection
- 931 patients without prior RCM allergy
  - 2 reactions (0.2%)
- 32 patients with history of RCM allergy
  - Pretreatment: Prednisone 50 mg 13 and 7 hours before procedure; IV Promethazine 12.5 mg at the beginning of the procedure
  - 10 pre-treated: 1 reaction
  - 22 not pre-treated: 0 reactions

Topaz, et al. JACI: IP 2018; 6:2059
### Possible Approach to Patients with Prior Immediate RCM Reaction

<table>
<thead>
<tr>
<th>Culprit RCM Known</th>
<th>Skin Test RCM</th>
<th>Procedure RCM</th>
<th>Pre-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial skin test (ST)</td>
<td>Culprit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Additional RCM</td>
<td>ST negative RCM</td>
<td>?</td>
</tr>
<tr>
<td>Negative</td>
<td>-</td>
<td>Alternate RCM</td>
<td>Probable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culprit RCM Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial skin test (ST)</td>
<td>Panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td>ST negative RCM</td>
<td>?</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>Lowest osmolality RCM</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NIHR: Switch agents if known and pre-treatment
Controversies in Beta-Lactam Allergy

- Role of skin testing (versus direct challenge) and specific reagents
- Length of challenge (single dose versus multiple day) to rule out delayed reactions
- Cephalosporin cross-reactivity with penicillin and other cephalosporins
Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity

- 642 total patients
  - 435 (66.6%) children
  - 207 (33.4%) adults

- Skin tests (ID):
  - PPL
  - MDM
  - Amoxicillin
  - Penicillin G

- Challenge:
  - 1/10 usual single dose
  - 1 hour: full single dose
  - 4 more days: full daily dose

Confino-Cohen, et al. JACI: IP 2017; 660
Figure 1

"Penicillin allergy"

710

68 excluded:
Immediate reaction- 52
Cephalosporin allergy- 16

Non immediate reaction 642

First day graded challenge
617 (96.1)%*

Immediate reaction 9 (1.5%)

No immediate reaction 608 (98.5%)

First day late reaction 24 (4%)

No late reaction 584 (96%)

Home challenge 491 (76.4)%**

reaction 30 (6.1%)

No reaction 461 (93.9%)

* Drug challenge was not preformed in 25 patients (Four with positive ST, 11 with equivocal ST and 10 with negative ST)

** Home challenge was not preformed in 93 patients (9 with positive ST, 35 with equivocal ST and 49 with negative ST)
Asthma, Family History of Drug Allergy, and Age Predict Amoxicillin Allergy in Children

- 133 children with immediate or non-immediate reactions
- *Prick test* to amoxicillin and penicillin G
- Oral Challenge:
  - Day 1 (20 min intervals):
    - 10% dose
    - 30% dose
    - 60% dose
  - Days 2 and 3: Full dose

Faitelson, et al. JACI: IP 2018; 1363
Results

• Skin tests were all negative
• Immediate reaction: 3 (2%)
• Non-immediate reaction: 7 (5%)
* $P < .05$. Older age at reaction significant as well.
Natural History of Benign Non-immediate Allergy to Beta-Lactams in Children: A Prospective Study in Re-treated Patients After a Positive and a Negative Provocation Test

• Children with history of benign non-immediate rash to BL
• No skin tests described
• Provocation Test (PT):
  • Day 1 (30 min interval):
    • 10% dose
    • 90% dose
    • 1 hour observation
  • Days 2 and 3: Full dose
• 180 children with initial negative PT received questionnaire
• 18 patients with initial positive PT had PT three years later

Tonson la Tour, et al. JACI: IP 2018; 6: 1321
Figure 1

Negative DPT
Questionnaires sent
n = 180

No reply
n = 8, 4.4 %

Questionnaire received back
n = 172, 95.6 %

No treatment
n = 50, 29 %

Re-treatment with
incriminated BL

Reactions
n = 4, 3.3 %

No reaction
n = 118, 96.7 %
Patients with Positive Initial PT (n = 18)

- Initial PT reactions
  - Immediate in 5 (28%)
  - Maculopapular eruption: 9 (56%)
  - Urticaria: 8 (40%)
  - Vomiting/asthenia: 1 (4%)

- Follow-up reactions
  - 2 reactions (“benign generalized urticaria”)
    - 1 hour and 4 hours after initial dose

- Follow-up call to 16 patients with negative follow-up PT
  - Subsequent treatment without reaction: 11 (68.8%)
  - 3 no-treatment
  - 2 could not be contacted
Efficacy and Safety of 5-Day Challenge for the Evaluation of Nonsevere Amoxicillin Allergy in Children

- 130 children with history of amoxicillin allergy (anaphylaxis, SCAR, and end-organ damage excluded)
  - Within 24 h: 26 (20%)
  - After 24 h: 99 (76.2%)
  - Unknown: 5 (3.8%)
- *Skin tests* performed but remain blinded
- **Challenge:**
  - Day 1 (30 minute intervals):
    - 1/100 dose
    - 1/10 dose
    - Full dose
  - Days 2-4: Full dose

Labrosse, et al. JACI: IP 2018; 6:1673
Figure 1

Patients screened
n=177

Patients included
n=130

Patients challenged
n=130 (100%)

Initial DPT +
n=3 (2.3%)
Stop challenge

Initial DPT –
n=127 (97.7%)

5-day DPT
n=127

DPT +
n=3 (2.3%)

DPT –
n=121 (93.1%)

Equivocal
n=3 (2.3%)

1 rechallenged: 1/1 DPT -
2 not rechallenged
Figure 2

DPT - (n=122)

- 114 reached (93.4%)
  - 75 ATB use (65.8%)
    - 39 no ATB use
    - 67 AXO use
    - 6 no AXO use
    - 2 uncertain if AXO used

- 5 other ATB chosen by MD (6.7%)
  - 1 refused because of fear of reaction (1.3%)
  - 3 re-sensitized (4.5%)
  - 5/5 would use AXO if needed
  - 2/2 would use AXO if needed

Five-day challenge
Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits

- Patients with history of “serious cutaneous reactions (excluding urticaria/angioedema), hepatitis, hemolytic anemia, or nephritis” excluded
- No recruits with this history
- 12 recruits refused to consent
- 402 recruits included in the study
- Skin tests with PPL and Penicillin G
  - 74 patients
  - All negative
Challenge Results (n = 402)

- Challenge with amoxicillin (250 mg orally)
- 5 with objective reactions (1.5%)
  - “All isolated cutaneous reactions except for 1, which included globus”
- Type of prior reactions
  - Rash: 2
  - Hives: 1
  - Unknown: 2
Consensus Approach Regarding Penicillin Testing

• Direct oral challenge in children with a history of delayed-onset benign cutaneous beta-lactam-associated adverse drug reactions (no anaphylactic signs and no signs of SCARS)
• Optimal length of challenge not defined
• Role of skin tests in other patients not defined
Current Kaiser San Diego Approach

• Direct Oral Amoxicillin Challenge
  • History of the following symptoms occurring more than 12 months previously
    • Any benign rash
    • GI symptoms
    • Headache only
    • Other benign somatic symptoms only
    • Unknown history

• Skin test first and challenge if negative
  • Reaction within 12 months
  • History of shortness of breath or symptoms of anaphylaxis

• No testing
  • Blistering rash involving ≥10% of body surface with skin loss
  • Hemolytic anemia
  • Nephritis
  • Hepatitis
Controversies in Beta-Lactam Allergy

• Role of skin testing (versus direct challenge) and specific reagents
• Length of challenge (single dose versus multiple day) to rule out delayed reactions
• **Cephalosporin cross-reactivity with penicillin and other cephalosporins**
Cross-Reactivity and Tolerability of Cephalosporins in Patients with IgE-Mediated Hypersensitivity to Penicillins

• 252 patients with 319 immediate reactions to penicillins

• Testing with cephalosporins
  • Aminocephalosporins (cephalexin, ceftazadine, cefadroxil)
  • Other (cefamandole, cefuroxime, ceftazadine, ceftriaxone, cefotaxime, cefepime)

• Challenge
  • Negative results for last 5: cefuroxime and ceftriaxone
  • Negative results for aminocephalosporins: cefaclor and cefadroxil as well
Results

• Skin Tests
  • 84 test positive to at least one cephalosporin
    • 68 (81%) only to aminocephalosporin
    • 11 (13%) only to other
    • 5 (6%) to both

• Challenge
  • 244 skin test negative to 5 other cephalosporins
    • No reaction to cefuroxime and ceftriaxone
  • 170 skin test negative to aminocephalosporins
    • 3 reactions to cefaclor (not challenged with cefadroxil)
    • 4 reactions to cefadroxil
Conclusions

- Cross-reactivity between penicillin and cephalosporins is mainly related to side chain similarity or identify.
- Patients with IgE-mediated hypersensitivity to penicillin could be treated with cephalosporins such as cefuroxime and ceftriaxone (that have side-chain determinants different from penicillin) if they are negative in pretreatment skin testing.
Use of Cephalosporins in Patients with Confirmed Penicillin Allergy

• My conclusions
  • Avoid aminoccephalosporins
  • Other cephalosporins likely to be safe
  • Need for pre-treatment cephalosporin skin testing not defined
Cross-reactivity in β-Lactam Allergy

• Reviewed 10 studies
• Concluded that cross-reactivity occurs rarely
• When cross-reactivity occurs, it is due to similarity in the R1 and R2 side chain

Zagusrsky and Pichichero. JACI: IP 2018; 6: 672
Chart Indicates identical side chains (gold or red), partial identity, similar side chains, and no structural similarities (blank)
Recommendations for Use of Alternate Cephalosporins in Patients with Cephalosporin Allergy

• Do not avoid all cephalosporins in patients with a history of a reaction to a specific cephalosporin
• Skin test alternative cephalosporin
• Choice of alternative
  • Based on lack of side chain similarity
  • More often based on specific clinical need
• If skin test negative, oral challenge (or IV challenge if needed and if patient hospitalized)