Severe Cutaneous Adverse Drug Reactions:

John A. Oates Chair in Clinical Research
Professor of Medicine and Pharmacology
Professor or Pathology, Microbiology & Immunology
Vanderbilt University Medical Center

Severe Cutaneous Adverse Drug Reactions
Drug Hypersensitivity Reactions in 2021 – What should we know?
ACAAI 2021

Learning Objectives

• Understand definitions and classification
• Allergists contribution to prevention, recognition, early diagnosis, risk stratification and drug causality
• Show examples of what different SCAR phenotypes look like on differing skin pigmentation
• Acute management
• Short and long-term complications
• Implicated drugs(s): risk and causality assessment
• Future prospects
What is the Clinical Phenotype?


MODIFIABLE

CELLULAR TOXICITY: Aminoglycosides, fluoroquinolones, statins

Non-IgE mediated mast cell activation
Vancomycin, fluoroquinolone contrast, aspirin/NSAIDS

IgE or Antibody: Anaphylaxis, cytopenias, serum sickness

T-cell mediated: MPE, SCAR (DRESS, AGEP SJS/TEN), DILI, DIKI, HLA Class I restricted reactions – potentially preventable

MODIFIABLE

VARIABLE

WANES OVER TIME

HLA Class I restricted reactions – potentially preventable

Drawing out the Timeline for Each Drug is Critical

**Weeks**

- Benign Exanthem (MPE)
- FDE
- Serum sickness like reaction
- Drug-induced Interstitial Nephritis
- Drug-induced Liver Injury
- Drug Reaction with Eosinophilia & Systemic Symptoms
- Abacavir Hypersensitivity
- Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis
- Drug-induced Lupus or Vasculitis

*acute generalized exanthematous pustulosis*

A case of allopurinol TEN
Acute Generalized Exanthematous Pustulosis (AGEP)

- Fever
- Non-follicular rash appears like pustules on erythematous base
- Flexural folds
- Neutrophilic leukocytosis with mild eosinophilia
- Short latency
- Low morbidity and no mortality or relapse
- Typically drug and sometimes other (viral, brown recluse spider)

Distinct pathology with sub-corneal pustules and neutrophilic spongiosis, presence of eosinophils

AGEP Occurs Early (with some exceptions)

Pristinamycin
Aminopenicillins
Sulfa antimicrobials
Quinolones

Diltiazem
Hydroxychloroquine
Terbinafine

Sideroff et al Br J Derm 2007;157:989-96 (EuroSCAR) -97 cases AGEP 1009 controls
**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

- Fever
- Extensive rash (>50% BSA)
- Facial edema
- Absolute eosinophilia and atypical lymphocytes
- Organ involvement (hepatitis, nephritis, pneumonitis, myocarditis)
- 2-8 week latency
- Relapse, viral reactivation (HHV-6, EBV, CMV)
- 10% mortality
- Long-term morbidity (autoimmune sequelae, watch out to 5 years)
- HLA associations

Pathology is not necessarily distinct for DRESS and requires clinical correlation

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**Causes of DRESS in FAERS over time**

![Graph showing percentage of DRESS cases associated with Allopurinol, Vancomycin, Lamotrigine, Carbamazepine, and TMP-SMX in FAERS.](image)

*FDA Adverse event reporting system*
Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis (SJS/TEN)

- Prodromal symptoms
- Measured %BSA detached (<10% SJS; 10-30% overlap; >30% TEN)
- Organ involvement uncommon
- Non-drug related variants are SJS-like
- Latency 4-28 days
- Drug causes are not recurrent if drug & cross-reactive drugs avoided
- Average 15-20% mortality
- Long-term eye, strictures, mental health
- May be confused with erythema multiforme major, autoimmune bullous and generalized bullous fixed drug eruption
- Mainly drug related in adults (>80%) in children SJS-like illness can occur with prominent ocular surface and oral involvement with minimal skin involvement. Mycoplasma pneumoniae (MIRM) or a respiratory virus is sometimes implicated (RIME).
- Strong class I HLA associations but not for all drugs and across race/ethnicity

SJS Mimickers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SJS/TEN</th>
<th>EM</th>
<th>GIRD</th>
<th>FDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target lesions</td>
<td>Flat, atypical target lesions present</td>
<td>Typical or raised atypical target lesions</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blister and erosion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Distribution</td>
<td>Widespread</td>
<td>Mainly limbs or acral</td>
<td>Localized</td>
<td>No</td>
</tr>
<tr>
<td>Erosions of mucosa</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No or no</td>
</tr>
<tr>
<td>Recurrent history</td>
<td>Rare</td>
<td>Occasional</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Mortality depends on risk factors (SCORTEN)</td>
<td>Favorable</td>
<td>Generally favorable but associated with higher mortality with &gt;20% BSA involvement and in elderly</td>
<td>No</td>
</tr>
<tr>
<td>Etiology</td>
<td>Usually drug-induced</td>
<td>Suspected infection not drug</td>
<td>Usually drug-induced</td>
<td>No</td>
</tr>
</tbody>
</table>

SLN, Erythema multiforme major; GIRD, generalized bullous fixed drug eruption.

Vancomycin-induced linear IgA bullous disease
Treatment Considerations

DRESS
- Topical or Systemic Steroids
  - Steroid sparing (cyclosporine, mycophenolate)
- Chronic or relapse
- Steroid toxicity
- Supportive Care (eye, urogenital)
- Cyclosporine
- Etanercept
- Address chronic complications (eye, strictures, skin) - may need surgical or laser intervention

SJS/TEN
- Topical or Systemic Steroids
- Steroid sparing
- Monthly IV Ig
- Investigational targeted (JAK inhibitor etc)

AGEP
- Topical or Systemic Steroids
- Typically no relapse or chronic complications

VARIATION IN HLA AND DISEASE PROTECTION AND SUSCEPTIBILITY

# HLA Screening

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phenotype</th>
<th>Risk Allele</th>
<th>100% NPV</th>
<th>PPV</th>
<th>NNT</th>
<th>Screening Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Hypersensitivity</td>
<td>B*57:01</td>
<td>Yes</td>
<td>55%</td>
<td>13</td>
<td>Yes</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>DRESS/SJS/TEN</td>
<td>B*58:01</td>
<td>No</td>
<td>3%</td>
<td>250</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>SJS/TEN</td>
<td>B*15:02</td>
<td>No</td>
<td>3%</td>
<td>1000</td>
<td>Yes</td>
</tr>
<tr>
<td>Dapsone</td>
<td>DRESS/SJS/TEN</td>
<td>B*13:01</td>
<td>No</td>
<td>7.8%</td>
<td>84</td>
<td>Yes</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>DRESS</td>
<td>A*32:01</td>
<td>No</td>
<td>20%</td>
<td>75</td>
<td>Pre-emptive Diagnosis</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>SJS/TEN</td>
<td>C*04:01</td>
<td>potential</td>
<td>2.5%</td>
<td>200</td>
<td>Yes</td>
</tr>
</tbody>
</table>

# Skin & Patch Testing for SCAR

<table>
<thead>
<tr>
<th>REACTION TYPE</th>
<th>PATCH</th>
<th>INTRADERMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Drug Exanthem (MPE)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Abacavir hypersensitivity</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>DRESS</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>AGEP</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Drug-induced liver disease or any drug-induced organ disease</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fixed Drug Eruption</td>
<td><em>intralesional</em></td>
<td><em>intralesional</em></td>
</tr>
</tbody>
</table>

Validation of concentration is important

VANCOMYCIN DRESS

Diagnostic Clues
Vancomycin AGEP 2013

Skin and Patch Testing with AGEP Mimics the Acute Reaction
Integrated Approach to SCAR Diagnosis

*For DRESS suggest wait 6 months following diagnosis
*Consider ingestion challenge only if benefit outweighs risk

Copaescu, A, Frontiers in Pharmacology 2021

Rechallenge in setting of Tuberculosis

Lehloenya et al J Allerg Clin Immunol Practice 2020
Clinical Communications

Early high-dose intravenous corticosteroids rapidly arrest Stevens Johnson syndrome and drug reaction with eosinophilia and systemic symptoms recurrence on drug re-exposure

Rannakoe J, Lehloeny, MD,*, Thuraya Isaacs, MD,*, Tonderai Nyika, MD,*, Ashar Dhanani, MD,*, Lauren Knight, MD,*, Simon Veenstra, MD,*, and Jonny Peter, MD, PhD,*

Clinical Implications

- Single early infusion of corticosteroids rapidly and sustainably reverses cutaneous and systemic features of Stevens Johnson syndrome/tonic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms developing on re-exposure to the offending drug. These findings support the role of corticosteroids in these reactions and potentially improve the safety of drug rechallenge protocols.

Integrated Approaches to SCAR

Podium to Practice

- SCAR clinical phenotypes are T-cell mediated reactions that differ by key features such as acute clinical presentation, latency period and short and long-term morbidity and mortality
- Current clinical risk stratification enhanced by adjunctive testing techniques in the clinic to inform drug causality and are the mainstay of management to guide future drug avoidance and safety
- Newer research will support more advanced integrated approaches to prediction, prevention, early diagnosis and targeted therapies aiming to improve patient outcomes
Question 1

A 23-year-old woman develops acute onset of fever, sore eyes and sore mouth. She admits to taking ibuprofen and cold medication shortly after the onset of her symptoms and has now noticed a spreading rash with some blisters and approximately 2% body surface area detached. She has painful oral ulcers and crusting around her mouth. She also admits to starting on trimethoprim-sulfamethoxazole (TMP-SMX) for a urinary tract infection 1 week previously.

Which of the following represents the most likely scenario regarding the type of reaction and its cause?

A. This is likely SJS related to a respiratory virus (MIRM or RIME).
B. Ibuprofen is the most likely cause of this drug reaction and she should be advised to permanently avoid it.
C. The latency period and the clinical features are in keeping with DRESS associated with trimethoprim-sulfamethoxazole.
D. The clinical details here are less important and a skin biopsy is needed to make the diagnosis.
E. The time course and clinical features are in keeping with SJS associated with TMP-SMX and a skin biopsy would be helpful to differentiate other mimickers such as generalized bullous fixed drug eruption.**

Question 2

A 65-year-old man is started on ceftriaxone and vancomycin as empiric treatment for a suspected prosthetic joint infection which has been culture negative. Treatment is intended for 6 weeks. 3 weeks into treatment he develops fever and malaise and facial edema which is followed by a rash with edema and purpuric components covering >50% of his body surface. Bloodwork shows an absolute eosinophil count of 1.5 x 10^9/L and atypical lymphocytes on peripheral smear. Alanine aminotransferase is 3 x ULN at 120 IU/L. An extensive work-up including blood cultures and viral studies are negative. Skin biopsy is pending.

What is the most likely explanation for this reaction?

A. This is likely related to the underlying infection and the antibiotic treatment should be broadened.
B. Ceftriaxone is the likely cause and should be stopped with avoidance of all other penicillins and cephalosporins.
C. The most likely explanation is serum-sickness like reaction which in most cases can be treated through without event.
D. This is most likely DRESS due to vancomycin or ceftriaxone. Both drugs should be stopped immediately, the patient should be closely monitored for internal organ involvement and steroids should be considered. Only after 6 months has elapsed and patient is weaned off steroids should additional testing be considered.**
E. This reaction is most likely DRESS but it is really the skin biopsy that makes the diagnosis definitive and follow-up patch testing or skin testing will be the definitive way to ascertain drug causality.
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**SJS Foundation**

Dress syndrome.org

**Patients and Healthy Donors**

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**Thanks and Questions!**

Center for Drug Safety & Immunology
@vumc_cdsi_rsch
drugsafetyresearch@vumc.org
https://medsites.vumc.org/cdsi
Hypersensitivity Reactions to Beta-Lactams and NSAIDs

David A. Khan, MD
Professor of Medicine and Pediatrics
Allergy & Immunology Program Director

Disclosures

- No relevant disclosures
Objectives

- Be able to discuss key updates on allergy to penicillin, cephalosporin and other beta-lactams.
- Be able to discuss key updates on different NSAID hypersensitivity reactions.

Penicillin Allergy Updates

Testing
Delabeling Strategies
## Methods to Delabel Penicillin Allergy

<table>
<thead>
<tr>
<th>Setting</th>
<th>Method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong></td>
<td>Referral based skin test and challenge</td>
<td>With or without minor determinant mixture</td>
</tr>
<tr>
<td></td>
<td>Direct challenge</td>
<td>Low risk histories</td>
</tr>
<tr>
<td></td>
<td>Protocol driven</td>
<td>Allergy clinic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other clinics</td>
</tr>
<tr>
<td><strong>Inpatient</strong></td>
<td>Allergy consultation</td>
<td>Least efficient</td>
</tr>
<tr>
<td></td>
<td>Proactive testing protocol</td>
<td>Pharmacists or other healthcare providers</td>
</tr>
<tr>
<td></td>
<td>Intensive care unit testing</td>
<td>Skin testing</td>
</tr>
<tr>
<td></td>
<td>Emergency Department</td>
<td>Skin testing or direct challenge by non-allergy specialists or other healthcare providers</td>
</tr>
</tbody>
</table>


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## When to Skip Penicillin Skin Tests?

### Role of Direct Challenge
Are Penicillin Skin Tests Needed in Children?

Original Investigation
Assessing the Diagnostic Properties of a Graded OralProvocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children


94% Passed challenge

Challenge Protocol: 10% dose then 20 min later 90% dose amoxicillin

All immediate and delayed reactions were mild (few cases of SSL reactions)
Penicillin Skin Testing Not Required for Most Children

<table>
<thead>
<tr>
<th>Consensus Based Statement (Draft)</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as maculopapular rashes and urticaria).</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Eligible for RCT: benign cutaneous only reactions

Age 5-17: reaction > 1 yr ago
Age ≥18: reaction > 10 yrs ago

3 reactions with challenge: benign rashes treated with antihistamines


<table>
<thead>
<tr>
<th>Consensus Based Statement (Draft)</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest that direct amoxicillin challenge be considered in adults with a history of distant and benign cutaneous reactions (such as maculopapular rashes and urticaria).</td>
<td>Conditional</td>
<td>Low</td>
</tr>
</tbody>
</table>
Development and Validation of a Penicillin Allergy Clinical Decision Rule


PEN-FAST Score=0, NPV of 99.4%
PEN-FAST Score=3, NPV of 96.3%
PEN-FAST Score < 3 excluded severe allergies

Immediate Hypersensitivity Reactions to Piperacillin-Tazobactam (TZP)

- TZP ST positive in 25/41 (61%)
  - 44% with SPT
  - 52% with positive ST had Grade 3 anaphylaxis
- 4/25 allergic patients were nurses with occupational exposure, all with anaphylaxis
66% selectively sensitized to TZP; 33% cross-sensitized to other PCN (rarely clavulanic acid)

Best Practice Advisory (BPA) Alert

Wallet Card

I am NOT allergic to Penicillin

Penicillin skin testing (prick and intradermal) followed by an oral Amoxicillin challenge was performed at Parkland on __________

RESULT: Negative (No Reaction)

Test performed by _______________________

---

TABLE II. Penicillin allergy relabel

<table>
<thead>
<tr>
<th>Initial labeled patients</th>
<th>N = 650</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with allergy relabel with QI interventions but before manual chart review (%)</td>
<td>84 (12.9)</td>
</tr>
<tr>
<td>Total number of relabels</td>
<td>107</td>
</tr>
<tr>
<td>Time to first relabel (average days ± SD)</td>
<td>273.8 ± 301</td>
</tr>
<tr>
<td>Time to second relabel (average days ± SD)</td>
<td>19.8 ± 47.1</td>
</tr>
<tr>
<td>Person adding penicillin allergy label back (%)</td>
<td></td>
</tr>
<tr>
<td>Registered nurse, LVN</td>
<td>63 (58.9)</td>
</tr>
<tr>
<td>Physicians/advanced practitioners</td>
<td>25 (23.6)</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>7 (6.6)</td>
</tr>
<tr>
<td>Medical assistant</td>
<td>7 (6.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>Relabel due to merging of EMR data</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Person removing allergy after relabel (%)</td>
<td></td>
</tr>
<tr>
<td>Registered nurse, LVN</td>
<td>13 (14.3)</td>
</tr>
<tr>
<td>Physicians/advanced practitioners</td>
<td>17 (18.7)</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>59 (64.8)</td>
</tr>
<tr>
<td>Medical assistant</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Patients with appropriate penicillin allergy relabel after QI interventions and manual chart review (%)</td>
<td>16 (2.5)</td>
</tr>
<tr>
<td>Itching/irritation</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
</tr>
<tr>
<td>Hives</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

Penicillin Allergy & Cross-Reactivity with Other Beta-Lactams

Cephalosporin Allergy is Largely Based on R1 Side Chain

- **Group 1**: Ceftriaxone, Cefotaxime, Cefepime, Cefpodoxime, Cefditoren (may cross-react with Groups 2&3)
- **Group 2**: Cefuroxime (may cross-react with groups 1&3)
- **Group 3**: Ceftazidime, aztreonam (may cross-react with groups 2&3)

1st Generation Cephalosporin Allergy and Aminopenicillin Structural Similarities

Group 4

- ampicillin
- cefaclor
- cephalaxin

Group 5

- amoxicillin
- cefadroxil
- cefprozil


- Caveats of systematic review
  - Almost all patients had confirmed aminopenicillin allergy (not penicillin allergy)
  - 89% studies from Europe (11% Canada)

If proven allergy to ampicillin:

risk of positive skin test to 1<sup>st</sup> /2<sup>nd</sup>gen aminopenicillin is 16%

risk of positive skin test to unrelated 2<sup>nd</sup>-4<sup>th</sup> generation is 2%


131 subjects
- 98.5% aminopenicillin allergy, 78% with anaphylaxis

130/131 had negative cefazolin/ceftibuten skin tests
- 1 subject (outlier) had positive skin tests to all PCN reagents, cephalosporins and carbapenems

129/130 agreed to cefazolin/ceftibuten challenges
- All 129 had negative challenges

Cefazolin and ceftibuten R1 groups disparate from aminopenicillins

Use of Cephalosporins in Penicillin Allergy

<table>
<thead>
<tr>
<th>Consensus Based Statement</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest that for patients with a history of an unverified non-anaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions.</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>We suggest that for patients with a history of anaphylaxis to penicillin, a non-cross-reactive cephalosporin can be administered without prior testing.</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Patients with DRESS or MPE to Penicillins should avoid other penicillins but may tolerate cephalosporins

In proven penicillin allergy
risk of reacting to carbapenem < 1%


Use of Carbapenems in Penicillin or Cephalosporin Allergy

<table>
<thead>
<tr>
<th>Consensus Based Statement</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without prior testing.</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Cephalosporin Allergy Updates

Cephalosporin Cross-Reactivity

- Most data suggest that at least 90% of cephalosporin allergy is due to R1 side chain
- Cephalosporin allergic patients typically tolerate other cephalosporins with disparate R1 side chains, especially if skin test negative
  - 102 cephalosporin allergic patients tolerated 326 challenges to skin test negative cephalosporins

### Alternative Cephalosporins with History of Cephalosporin Allergy

<table>
<thead>
<tr>
<th>Consensus Based Statement</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest for patients with <strong>non-anaphylactic cephalosporin allergy histories</strong>, direct challenges to cephalosporins with dissimilar side chains be performed to determine tolerance.</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>We suggest that for patients with <strong>anaphylactic cephalosporin allergy histories</strong>, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a non-identical R1 side chain.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
</tbody>
</table>

### Penicillin Administration with History of Cephalosporin Allergy

<table>
<thead>
<tr>
<th>Consensus Based Statement</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest against penicillin skin testing in patients with a history of non-anaphylactic cephalosporin allergy prior to administration of penicillin therapy.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>We suggest that in patients with a <strong>history of anaphylaxis to cephalosporins</strong>, <strong>penicillin skin testing and drug challenge should be performed</strong> prior to administration of penicillin therapy.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
</tbody>
</table>
19.6% of + DPT developed anaphylaxis

72% had anaphylactic histories

# Updates on NSAID Allergy

## Aspirin/NSAID Hypersensitivity Phenotypes

<table>
<thead>
<tr>
<th>Hypersensitivity Reaction</th>
<th>NSAID Cross-Reactivity</th>
<th>Onset</th>
<th>Clinical Features</th>
<th>Underlying Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin/NSAID Exacerbated Respiratory Disease (AERD/NERD)</td>
<td>Yes</td>
<td>Immediate</td>
<td>Naso-ocular Respiratory (GI, skin less often)</td>
<td>Asthma, nasal polyps</td>
<td>COX-1 Inhibition</td>
</tr>
<tr>
<td>Aspirin/NSAID Exacerbated Cutaneous Disease (AECD/NECD)</td>
<td>Yes</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>Chronic urticaria</td>
<td>COX-1 Inhibition</td>
</tr>
<tr>
<td>Multiple NSAID-Induced Urticaria/AE</td>
<td>Yes</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>None</td>
<td>COX-1 Inhibition ?</td>
</tr>
<tr>
<td>Single NSAID Induced Urticaria/AE/Anaphylaxis</td>
<td>No</td>
<td>Immediate</td>
<td>Urticaria/Angioedema Anaphylaxis</td>
<td>None</td>
<td>IgE mediated ?</td>
</tr>
<tr>
<td>Variable</td>
<td>Usually No</td>
<td>Delayed</td>
<td>FDE, SJS/TEN, MP exanthem, Hypersensitivity pneumonitis, aseptic meningitis</td>
<td>None</td>
<td>T cell mediated ?</td>
</tr>
</tbody>
</table>
## Selective COX-2 Inhibitors Generally Safe for All NSAID Reactions

<table>
<thead>
<tr>
<th>Consensus Based Statement</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest a <strong>selective COX-2 inhibitor</strong> may be used as an alternative analgesic in patients with any <strong>NSAID hypersensitivity phenotype</strong> when an NSAID is needed.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
</tbody>
</table>

### AERD

---


AERD Pathophysiology

- AERD has baseline abnormalities in prostaglandins and leukotrienes
- NSAIDs accentuate these differences and result in symptoms of AERD exacerbation
- Inflammatory signatures may differ amongst AERD patients
- Local antibody production may contribute

Acute Reactions to NSAIDs in AERD

- Occur within 30 minutes to 3 hours after ingestion of NSAID
- Naso-ocular symptoms
  - Nasal congestion, rhinorrhea, conjunctival injection
- Asthma symptoms
  - Dyspnea, wheeze, chest tightness, cough
- Less common symptoms
  - Urticaria/angioedema ~15%
  - GI symptoms: abdominal cramps, N/V
  - Hypotension very rare
Diagnosis of AERD by History

- Analysis of information of historical ASA/NSAID reactions in 243 patients undergoing oral aspirin challenge
  - Single reaction: 80% positive challenge
  - ≥ 2 reactions: 89% positive challenge
  - Severe reaction: 100% positive challenge
    - Severe: “poor response to albuterol and requirement for medical intervention up to intubation”
  - Hospitalization: 100% positive challenge


AERD Diagnosis

<table>
<thead>
<tr>
<th>Consensus Based Statement</th>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We suggest an oral aspirin challenge to confirm the diagnosis of AERD in cases of diagnostic uncertainty.</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology


Why Does Aspirin Therapy Work?

### TABLE V. Select aspirin desensitization protocols

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Oral aspirin</th>
<th>Intranasal ketorolac and oral aspirin</th>
<th>Oral aspirin</th>
<th>Oral aspirin</th>
<th>Oral aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-d protocols</td>
<td>1-d protocols</td>
<td>2-d protocols</td>
<td>1-d protocols</td>
<td>1-d protocols</td>
</tr>
<tr>
<td>Day 1</td>
<td>8:00 am</td>
<td>20-40 mg</td>
<td>1.26 mg ketorolac (1 spray)</td>
<td>20.25 mg</td>
<td>41 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td>8:30 am</td>
<td>2.52 mg ketorolac (2 sprays)</td>
<td></td>
<td>80 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9:00 am</td>
<td>5.04 mg ketorolac (4 sprays)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9:30 am</td>
<td>7.56 mg ketorolac (6 sprays)</td>
<td></td>
<td>40.5 mg</td>
<td>81 mg</td>
<td>160 mg</td>
</tr>
<tr>
<td></td>
<td>10:00 am</td>
<td>60 mg aspirin</td>
<td></td>
<td></td>
<td>160 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11:00 am</td>
<td>40-60 mg</td>
<td>81 mg</td>
<td>161 mg</td>
<td>325 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11:30 am</td>
<td>60 mg aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12:00 pm</td>
<td>Desensitization complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12:30 pm</td>
<td>162.5 mg</td>
<td>325 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:00 pm</td>
<td>Instructions and discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:00 pm</td>
<td>60-100 mg</td>
<td>325 mg</td>
<td>Desensitization complete</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3:00 pm</td>
<td>Desensitization complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3:30 pm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4:00 pm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4:30 pm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>5:00 pm</td>
<td>Instructions and discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8:00 am</td>
<td>100 mg</td>
<td>150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11:00 am</td>
<td>160 mg</td>
<td>325 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:00 pm</td>
<td>325 mg</td>
<td>Desensitization complete</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5:00 pm</td>
<td>Desensitization complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Actual time needed for the protocol to be completed may vary on the basis of severity of reaction and the time needed for recovery.

---

**NSAID Exacerbated and Induced Cutaneous Disease**
### Aspirin/NSAID Hypersensitivity Phenotypes

<table>
<thead>
<tr>
<th>Hypersensitivity Reaction</th>
<th>NSAID Cross-Reactivity</th>
<th>Onset</th>
<th>Clinical Features</th>
<th>Underlying Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin/NSAID</td>
<td>Yes</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>Chronic urticaria</td>
<td>COX-1 Inhibition</td>
</tr>
<tr>
<td>Exacerbated Cutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease (AECD/NECD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple NSAID-Induced</td>
<td>Yes</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>None</td>
<td>COX-1 Inhibition ?</td>
</tr>
<tr>
<td>Urticaria/AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single NSAID Induced</td>
<td>No</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>None</td>
<td>IgE mediated ?</td>
</tr>
<tr>
<td>Urticaria/AE/Anaphylaxis</td>
<td></td>
<td></td>
<td>Anaphylaxis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dose of AH varied to get CSU controlled

+ NSAID Challenge \((-\text{AH})\)=69%
+ NSAID Challenge \((+\text{AH})\)=24%

**NSAID-Induced Urticaria/Angioedema: Determining Cross-Reactivity**

### Aspirin/NSAID Hypersensitivity Phenotypes

<table>
<thead>
<tr>
<th>Hypersensitivity Reaction</th>
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<th>Onset</th>
<th>Clinical Features</th>
<th>Underlying Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple</strong> NSAID-Induced Urticaria/AE</td>
<td>Yes</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>None</td>
<td>COX-1 Inhibition ?</td>
</tr>
<tr>
<td><strong>Single</strong> NSAID Induced Urticaria/AE/Anaphylaxis</td>
<td>No</td>
<td>Immediate</td>
<td>Urticaria/Angioedema</td>
<td>None</td>
<td>IgE mediated ?</td>
</tr>
</tbody>
</table>

**Consensus Based Statement**

For patients with NSAID-Induced Urticaria and Angioedema, we suggest an oral aspirin challenge to identify whether the reaction is COX-1 cross-reactive.

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditional</td>
<td>Low</td>
</tr>
</tbody>
</table>

---

**The Journal of Allergy and Clinical Immunology: In Practice**

Practical Guidance for the Evaluation and Management of Drug Hypersensitivity

An American Academy of Allergy, Asthma & Immunology Work Group Report

Presidential Initiative of Thomas A. Fleisher, MD, FAAAAI

Chief Editors:
Ana Douloul Biller, MD, FAAAAI
Alicia Banerji, MD, FAAAAI
Mariana C. Castells, MD, PhD, FAAAAI

JACI: In Practice Coordinating Editors:
David A. Khan, MD, FAAAAI
Michael Schatz, MD, MS, FAAAAI

Skin Testing Challenge Desensitization

Application of this supplement is supported by the American Academy of Allergy, Asthma & Immunology
Specific Drugs

Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs

Chief Editors: Ana Dioum Broyles, MD, Aleena Banerji, MD, and Mariana Castells, MD, PhD

Ana Dioum Broyles, MD\textsuperscript{a}, Aleena Banerji, MD\textsuperscript{b}, Sara Barmettler, MD\textsuperscript{c}, Catherine M. Biggs, MD\textsuperscript{d}, Kimberly Blumenthal, MD\textsuperscript{e}, Patrick J. Brennan, MD, PhD\textsuperscript{f}, Rebecca G. Breslow, MD\textsuperscript{g}, Knut Brockow, MD\textsuperscript{h}, Kathleen M. Buchheit, MD\textsuperscript{i}, Katherine N. Cahill, MD\textsuperscript{j}, Josefina Cernadas, MD, iPhD\textsuperscript{k}, Anca Mirela Chiriac, MD\textsuperscript{l}, Elena Crestani, MD, MS\textsuperscript{m}, Pascal Demoly, MD, PhD\textsuperscript{n}, Pascale Dewachter, MD, PhD\textsuperscript{o}, Meredith Dilley, MD\textsuperscript{p}, Jocelyn R. Farmer, MD, PhD\textsuperscript{q}, Dinah Foer, MD\textsuperscript{r}, Ari J. Fried, MD\textsuperscript{s}, Sarah L. Garon, MD\textsuperscript{t}, Matthew P. Giannetti, MD\textsuperscript{u}, David L. Hepner, MD, MPH\textsuperscript{v}, David I. Hong, MD\textsuperscript{w}, Joyce T. Hsu, MD\textsuperscript{x}, Parul H. Kothari, MD\textsuperscript{y}, Timothy Kyin, MD\textsuperscript{z}, Timothy Lax, MD\textsuperscript{aa}, Min Jung Lee, MD, MS\textsuperscript{ab}, Kathleen Lee-Sarwar, MD, MS\textsuperscript{ac}, Anice Liu, MD\textsuperscript{ad}, Stephanie Logsdon, MD\textsuperscript{ae}, Marger Louisias, MD, MPH\textsuperscript{af}, Andrew MacCinnitie, MD, PhD\textsuperscript{ag}, Michelle Maciag, MD\textsuperscript{ah}, Samantha Minnicozzi, MD\textsuperscript{ai}, Allison E. Norton, MD\textsuperscript{aj}, Iris M. Otani, MD\textsuperscript{ak}, Miguel Park, MD\textsuperscript{al}, Sarita Patil, MD\textsuperscript{am}, Elizabeth J. Phillips, MD\textsuperscript{an}, Matthew Picard, MD\textsuperscript{ao}, Craig D. Platt, MD, PhD\textsuperscript{ap}, Rima Rachid, MD\textsuperscript{aq}, Tito Rodriguez, MD\textsuperscript{ar}, Antonino Romano, MD\textsuperscript{as}, Cosby A. Stone, Jr., MD, MPH\textsuperscript{at}, Maria Jose Torres, MD, PhD\textsuperscript{au}, Miriam Verdú, MD\textsuperscript{av}, Alberta L. Wang, MD\textsuperscript{aw}, Paige Wickner, MD\textsuperscript{ax}, Anna R. Wolfson, MD\textsuperscript{ay}, Johnson T. Wong, MD\textsuperscript{az}, Christina Yee, MD, PhD\textsuperscript{ba}, Joseph Zhou, MD, PhD\textsuperscript{bb}, and Mariana Castells, MD, PhD\textsuperscript{bc} Boston, Mass; Vancouver and Montreal, Canada; Munich, Germany; Nashville, Tenn; Porto, Portugal; Montpellier and Paris, France; Chicago, Ill; Charlottesville, Va; Newport Beach, Pala Alto, and San Francisco, Calif; Cincinnati, Ohio; Al-Kuwait, Kuwait; Catania, Italy; Málaga and Cesta, Spain


Thank You

- Look for the Updated Drug Allergy Parameter in 2022!
Lessons From Drug-Induced Anaphylaxis – Can We Risk Stratify Patients With Drug Hypersensitivity?

Andrew White, MD FACAAI FAAAAI
AACAII 2021 – New Orleans
Scripps Clinic, San Diego

Scope of the problem

• Adults – one of the most common causes of anaphylaxis
• Hospitalized patients – 1:3000 patients (1)
• 35% of all anaphylaxis – medication related
• 58% of anaphylaxis deaths are medication related
• Fatal drug induced anaphylaxis – 1999-2001 – 0.27/million
  • 2008-2010 – 0.51/million (2)

1. Wood RA et al JACI 2014
2. Jerschow et al JACI 2014
Fatal drug induced anaphylaxis – by drug type

- UK – general anesthetics (neuromuscular agents)
- US, Korea, Canada, Australia – RCM might be higher rate of fatality
- NSAIDs much less likely to end in fatal anaphylaxis

Age

- Most fatalities >55 years old
- Association with black patients
- Comorbidities less clear (cardiovascular disease (71%), asthma/COPD (39%))

1. Jerschow et al JACI 2014
### TABLE I. Population-based data for rate of fatal anaphylaxis triggered by drugs

<table>
<thead>
<tr>
<th>Region</th>
<th>Data Source</th>
<th>Time period</th>
<th>Total deaths</th>
<th>Rate of fatal drug anaphylaxis (per million/year)</th>
<th>Age</th>
<th>Gender predominance</th>
<th>Leading causal drugs</th>
<th>Risk factors identified</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Australian Bureau of Statistics and National Coroners Information System</td>
<td>1997-2013</td>
<td>147 cases in total 84 (37%) triggered by drugs ICD code T88.6</td>
<td>1997: 0.05 2013: 0.13</td>
<td>Median 66 (IQR 52-73; range 26-84)</td>
<td>Male &gt; female</td>
<td>Antibiotics 43% General anesthetic 35% Radiocstim 18%</td>
<td>Age Cardiovascular disease 71% Known penicillin allergy 11% (33% of beta-lactam fatalities)</td>
<td>Mullins et al 2016</td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>Ontario Coroners’s database</td>
<td>1986-2011</td>
<td>92 total 16 (17%) drugs Conner mpn searched, ICD codes not used (0.04% of total anaphylaxis cases)</td>
<td>0.1</td>
<td>Mean 65 (range 39-86)</td>
<td>38% male</td>
<td>Antibiotics 44% Radiocstim 25%</td>
<td>Age Known allergy to the drug in 1 of 5 cases with data available (20%)</td>
<td>Xu et al 2014</td>
</tr>
<tr>
<td>France</td>
<td>French National Pharmacovigilance Database*</td>
<td>2000-2011</td>
<td>84 total 16 (17%) drugs Pharmacovigilance Database</td>
<td>Not calculated</td>
<td>Mean age 59</td>
<td>Male &gt; female</td>
<td>Not stated</td>
<td>Male gender Hypertension and cardiovascular comorbidities Obesity Beta-blocker use</td>
<td>Reiter et al 2014</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>National fatal anaphylaxis registry</td>
<td>1992-2012</td>
<td>479 total 263 (55% of total) ICD code T88.6</td>
<td>1992: 0.24 2012: 0.34</td>
<td>Median 58 (range 50-64)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Older age</td>
<td>Turner et al 2015</td>
</tr>
<tr>
<td>United States</td>
<td>National Center for Health Statistics MCID</td>
<td>1999-2010</td>
<td>2438 total 1446 (59% of total) ICD codes T78.2 or T88.6</td>
<td>1999: 0.27 2010: 0.51</td>
<td>Median 60 (IQR 47-73)</td>
<td>None</td>
<td>Antibiotics (mostly beta-lactams) Contrast agents Antithrombotic drugs</td>
<td>African American ethnicity Older age</td>
<td>Jerschow et al 2014</td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases; IQR, interquartile range; MCID, National Center for Health Statistics’ Multiple Cause of Death Data.
*Reported data were only on neurovascular blocking agents.

Turner P et al JACI:IP 2017
Direct Challenges

- **Non-immediate reactions – children**
  - 9 studies, DPT negative in 85-97%, only 1 case mild anaphylaxis (urticaria/vomiting)

- **Immediate reactions – children**
  - skipping skin testing – less predictive value but overall mostly negative challenges

- **Direct challenge in adults** –
  - 328 marine recruits direct challenge – 5 (1.5%) with acute objective (cutaneous only) and only 1 with globus only.
  - Kaiser San Diego – direct challenge (benign rash >12 months, benign somatic, or unknown) – 1/398 (0.3%) with acute onset oral challenge, 5 (1.3%) delayed rash
• 79 patients randomized to direct challenge – 3/79 positive (3.8%)
• 80 patients – PST – 10/80 positive (12.5%)
• No patients with a systemic reaction
• 3 failed oral challenges – cutaneous only, treated with oral antihistamines – no EPI

Mustafa et al JACI:IP 2019

Cephalosporins – structure matters

Touati et al JACI:IP 2021
### TABLE V. Cross-reactivity with penicillins in cephalosporin hypersensitive patients

<table>
<thead>
<tr>
<th>Groups</th>
<th>Percentage of cross-reactivity (Penicillin reagents)</th>
<th>Percentage of cross-reactivity (Ampicillin and/or amoxicillin only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Class 2</td>
<td>52</td>
<td>37.1</td>
</tr>
<tr>
<td>Class 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Class 4</td>
<td>3.8</td>
<td>0</td>
</tr>
</tbody>
</table>

Groups considering structural homology:
- Class 1: ceftriaxone, cefotaxime, cefepime, cefpodoxime, ceftazidime, cefixime, cefuroxime
- Class 2: cefaclor, cefalexin, cefadroxil, cefazolin
- Class 3: Cefaclor
- Class 4: cefalexin, cefotaxime, cefotiam, ceftriaxone.

### TABLE II. Risk stratification in the evaluation of beta-lactam allergy according to index reaction(s) adapted from EAACI guidelines

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Immediate vs nonimmediate</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>High&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Anaphylaxis, Immediate urticaria and/or angioedema</td>
</tr>
<tr>
<td></td>
<td>Nonimmediate</td>
<td>SCARs, Severe maculopapular exanthema (MPED), Systemic vasculitis, Serum sickness—like reaction, Organ involvement, Drug-induced autoimmune disease</td>
</tr>
<tr>
<td>Low&lt;sup&gt;-&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Isolated urticaria that did not require treatment, Isolated gastrointestinal symptoms (eg, nausea, diarrhea, vomiting), Local urticaria to parenteral administration</td>
</tr>
<tr>
<td></td>
<td>Nonimmediate</td>
<td>Contact dermatitis, Local reaction to intramuscular administration, Palmar exfoliative exanthema, Delayed-appearing urticaria, Nonsevere MPE</td>
</tr>
</tbody>
</table>

lammateo et al
JACI:IP 2021
Pediatric PCN algorithm

Drug hypersensitivity reaction

Benign*

Immediate (<1 hour after exposure)

Non-immediate (>1 hour after exposure)

Anaphylaxis

Skin tests (SPT, ID) +/- IgE

SCARs
Danger signals

Avoid culprit drug (if identified)

Consider skin tests (ID, patch) to identify the culprit drugs when multiple drugs are co-administered

DPT for drugs with low index of suspicion

Immediate DPT or DPT after negative skin tests** in DCUs

Non-immediate DPT Start in consultation

1 therapeutic dose

Or Graded (10-90% therapeutic dose)

DPT with the culprit drug

Graded, in DCUs

Iammatteo et al
JACI:IP 2021

Side effects (e.g., GI upset, headache, yeast infection)

OR

Family history

only of penicillin allergy

Side effects (e.g., urticarial cutaneous reaction (e.g., isolated pruritus or mild delayed maculopapular exanthem)*)

OR

Mild unknown reaction >10 years prior that did not require treatment or emergency medical attention*

Mild non-urticarial cutaneous reaction

Potential IgE-mediated reaction** without features of anaphylaxis

Anaphylaxis ***

OR

Prior positive penicillin ST ***

OR

Recurrent reactions to β-lactams***

SCARs

OR

Danger Signals

Low Risk

Deliberal; no need for ST or challenge

Direct oral 2-step graded challenge

Intermediate Risk

Penicillin ST followed by oral graded challenge, if negative

High Risk

Avoid beta lactams

Iammatteo et al

JACI:IP 2021
Introduction

- Rapid expansion of cancer therapeutics has been associated with a concomitant increase in infusion reactions
- All biologics have the potential to induce immunogenicity
  - Degree of humanization, pattern of glycosylation, episodic administration
Infusion Reaction: Timing and Risk Factors

- Usually occur during or within a few hours of drug infusion
- Most commonly occur with the first or second drug administration, but can occur at any time despite preventive measures
- Generally, more common in the following settings:
  - Intravenous vs. oral or intraperitoneal
  - After multiple cycles of certain agents
  - In patients with a prior infusion reaction to a drug of the same chemical class
  - A history of multiple drug allergies

Incidence of Infusion or Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Overall</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>2% - 30%</td>
<td>2-5%</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>15-20%, dependent on tumor type</td>
<td>3%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>5-12%</td>
<td>2%</td>
</tr>
<tr>
<td>Eloxatin</td>
<td>15-33%</td>
<td>2-3%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>41%</td>
<td>2%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>77% First infusion, 30% fourth infusion, 14% eighth infusion</td>
<td>10%</td>
</tr>
</tbody>
</table>

Vogel, CJON 2010
Decrease the Risk of a Subsequent Reaction

- Premedication
  - can help prevent or reduce the severity of infusion reactions
  - anaphylaxis is generally not prevented by premedication
  - steroids, antihistamines
  - derived empirically rather than established through randomized trials
- Slowed infusion rates
- Desensitization
Carboplatin Hypersensitivity: Overview

- Ovarian cancer is the most fatal gynecologic malignancy
  - Majority of patients will develop recurrent ovarian cancer
  - Repeat treatment with carboplatin is frequently recommended

- Increased risk of hypersensitivity reaction with repeated exposure
  - 1% with 6 or less exposures to carboplatin
  - Approximately 25-30% with 7 or more exposure

Symptoms of Carboplatin HSRs

<table>
<thead>
<tr>
<th>Immediate reactions</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>13.8</td>
</tr>
<tr>
<td>Throat tightness</td>
<td>5</td>
<td>11.2</td>
</tr>
<tr>
<td>Tongue swelling</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>11</td>
<td>28.9</td>
</tr>
<tr>
<td>Tachycardia/tachypnea</td>
<td>5</td>
<td>7.9</td>
</tr>
<tr>
<td>Blood pressure alterations</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3</td>
<td>7.1</td>
</tr>
<tr>
<td>Dizziness/Headache</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11</td>
<td>28.9</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Vasovagal symptoms</td>
<td>8</td>
<td>21.1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>14</td>
<td>36.8</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>14</td>
<td>36.8</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Upper/lower Swelling</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Auras</td>
<td>30</td>
<td>78.9</td>
</tr>
<tr>
<td>Erythema/hypertension</td>
<td>23</td>
<td>60.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>21</td>
<td>53.3</td>
</tr>
<tr>
<td>Urticaria</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>Pulsar erythema</td>
<td>19</td>
<td>50.0</td>
</tr>
<tr>
<td>Delayed reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>23</td>
<td>60.5</td>
</tr>
<tr>
<td>Rob</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Erythema</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Combined cutaneous reactions</td>
<td>9</td>
<td>23.7</td>
</tr>
</tbody>
</table>

Skin Testing for Platinum Agents

- Skin testing for platinum agents well-validated
  - Skin prick (epicutaneous) testing: 10 mg/mL
  - Intradermal testing: 1 mg/mL, 5 mg/mL*
- Patient must not receive anti-histamines for 5 days prior and should hold beta-blockers
- Patient has results same day

Understanding the value of skin testing

- 98-99% positive predictive value

Carboplatin Desensitization is Safe and Effective

- >5000 successful desensitizations at Mass General Brigham
- Majority tolerated without any reactions

Novel One-Bag Desensitization Protocol

Doxiliplatin 120 mg/24 mL was reconstituted with 200 mL of 5% dextrose in water and the concentration of the solution was 0.5385 mg/mL.

Dose (mg) = Rate (mL/h) × time (h) × concentration (mg/mL)

*5% dextrose in water was infused as a side stream at a rate of 10 mL/h
Why is “Desensitization” Successful?

Management of Reactions during Desensitization

[Diagram showing cumulative drug concentration vs. dose with thresholds for anaphylaxis and desensitization.

Reference:
Castells. Front Immunol 2017

[Flowchart showing management of reactions with steps:
- Hold infusion
- Severe HSR
- EPINEPHRINE IM
- Glucocorticoid Crystallloid
- Mild-moderate HSR
- H1/H2 blockade
- Flush
- Throat tightening
- Bronchospasm
- Aspirin
- Montelukast
- Glucocorticoid
- Inhaled β-agonist
- When symptoms have resolved, resume protocol at the point where the reaction occurred

Reference:
Brennan et al. JACI 2009]
Understanding the Value of Skin Testing

- 98-99% positive predictive value
- False negative rates as high as 8.5% with carboplatin

Timing of Skin Testing in Relation to HSR Critical

**Skin Testing: Less than 6 Weeks from HSR**

- Less than or equal to 6 weeks
- Hymenoptera data suggests period of "anergy" for 4-6 weeks after HSR

---

**Skin Testing: 6 Weeks to 6 Months**

Carboplatin ST results potentially most predictive between 6 weeks and 6 months
Skin Testing: Greater than 6 Months from HSR

- ST is more likely to convert if > 6 months from HSR
  - Hesterberg et al. 75% (6/8) ST converted
  - Patil et al. 79% (11/14) ST converted

Timing of ST is Important in Evaluation of Platin Reactions

- Patients who present < 6 weeks or >6 months from initial HSR to ST evaluation were at higher risk of having an initial false negative skin test
- Repeat skin testing is important in management
Utility of Repeat ST in Risk Stratification after Carboplatin HSR

- Platin risk stratification protocol is safe and effective in distinguishing allergic from non-allergic patients
- Identifying non-allergic patients after presumed HSR avoids unnecessary desensitization

Delabeling Patients from Allergy to Chemotherapy and Biologics using Drug Provocation

Vázquez-Revuelta et al., JACI IP 2021
Docetaxel and Paclitaxel Infusion Reactions

- Reactions are primarily due to polysorbate 80 (docetaxel) or cremophor (paclitaxel)
- Occur in 30% of patients decreasing to <4% with premedication
- Reactions are dose- and rate-dependent and most often occur within the first few min of the 1st or 2nd infusions
- Symptoms include dyspnea, hypotension, bronchospasm, urticarial and erythematous rash
  - Clinical presentations similar to IgE mediated reactions

Management of Paclitaxel Infusion Reactions

- Slowed infusions
- Increase premedications
- Mixed experience with skin testing
- Desensitization safe and successful
- Risk stratification
  - Allow patients to safely receive paclitaxel
  - Reduce the number of unnecessary desensitizations
Risk Stratification Algorithm: Taxol Hypersensitivity

Otani et al., J Allergy Clin Immunol Pract 2017

Rate of Reactions to Biologics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Overall reactions</th>
<th>HSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (Rituxan®) IV</td>
<td>CD20</td>
<td>77% (first infusion) (52)</td>
<td>5-10% (53)</td>
</tr>
<tr>
<td>Otelumab (Arcema®) IV</td>
<td>CD20</td>
<td>44% (first infusion) (54)</td>
<td>2% (55)</td>
</tr>
<tr>
<td>Ocinutzumab (Ozlyva®) IV</td>
<td>CD20</td>
<td>67% (combination therapy) (55)</td>
<td>[58]</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®) IV</td>
<td>HER-2</td>
<td>40% (mild; first infusion) (59)</td>
<td>0.6-0.6% (60)</td>
</tr>
<tr>
<td>Celoximab (Eribux®) IV</td>
<td>EGFR</td>
<td>15-21% (61)</td>
<td>1.1-5% (62-68)</td>
</tr>
<tr>
<td>Toclizumab (Actemra®) IV</td>
<td>IL-6 receptor</td>
<td>7-8% (69)</td>
<td>0.1-0.7% (88)</td>
</tr>
<tr>
<td>Infliximab (Remicade®) IV</td>
<td>TNF-α</td>
<td>5-15% (69)</td>
<td>1%* (69)</td>
</tr>
<tr>
<td>Etanercept (Enbrel®) SC</td>
<td>TNF-α</td>
<td>15-37% (70)</td>
<td>&lt;2% (70)</td>
</tr>
<tr>
<td>Adalimumab (Humira®) SC</td>
<td>TNF-α</td>
<td>20% (71)</td>
<td>1% (71)</td>
</tr>
<tr>
<td>Golimumab (Simponi®) SC</td>
<td>TNF-α</td>
<td>4-20% (72,73)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®) SC</td>
<td>TNF-α</td>
<td>0.6-4.5% (74,75)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Brentuximab (Ad cetin®) IV</td>
<td>CD30</td>
<td>12% (76)</td>
<td>[77-79]</td>
</tr>
<tr>
<td>Bevacizumab (Avastin®) IV</td>
<td>VEGF-A</td>
<td>&lt;3% (80)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Omalizumab (Xolair®) SC</td>
<td>IgE</td>
<td>45% (81)</td>
<td>0.9-0.2% (81,82)</td>
</tr>
</tbody>
</table>

*<p > 0.05
Mechanism of Reactions to Biologics is Variable

Hypersensitivity Reaction to mAbs Precision Medicine Approach

<table>
<thead>
<tr>
<th>Initial HSR Frequency</th>
<th>Phenotype</th>
<th>Endotypes</th>
<th>Biomarkers</th>
<th>Desensitization HSR Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>63%</td>
<td>Mixed Reactions</td>
<td>Cytokine Release</td>
<td>Histamine, Tryptase, TNF-α, IL-6, IL-8, IL-4, IL-10</td>
<td>32%</td>
</tr>
<tr>
<td>21%</td>
<td>Type I IgE non-IgE</td>
<td></td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>13%</td>
<td></td>
<td></td>
<td></td>
<td>52%</td>
</tr>
<tr>
<td>3%</td>
<td></td>
<td>Type IV</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>50-20%</td>
<td>Infusion Reaction</td>
<td></td>
<td></td>
<td>Regulate infusion with prednisolone</td>
</tr>
</tbody>
</table>

Isabwe et al. Journal of Allergy and Clinical Immunology
Volume 142 Issue 1 Pages 159-170.e2 (July 2018)

Skin Testing to Biologics: Non-Irritating Skin Testing Concentrations

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Suggested skin testing concentrations for mAbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPT (mg/mL)</td>
<td>IDT (mg/mL)</td>
</tr>
<tr>
<td>Abatacept [17]</td>
<td>25</td>
</tr>
<tr>
<td>Adalimumab [12]</td>
<td>40</td>
</tr>
<tr>
<td>Bivalirudin [13]</td>
<td>NA</td>
</tr>
<tr>
<td>Cetuximab [11]</td>
<td>5</td>
</tr>
<tr>
<td>Erametrex [22]</td>
<td>50</td>
</tr>
<tr>
<td>Infliximab [13]</td>
<td>10</td>
</tr>
<tr>
<td>Omalizumab [17]</td>
<td>125</td>
</tr>
<tr>
<td>Pertuzumab [11]</td>
<td>1.6</td>
</tr>
<tr>
<td>Rituximab [12]</td>
<td>10</td>
</tr>
<tr>
<td>Tecelizumab [18]</td>
<td>20</td>
</tr>
<tr>
<td>Trastuzumab [18]</td>
<td>21</td>
</tr>
</tbody>
</table>

1. Akarsu et al., Curr Treat Options Allergy, 2020
2. Isabwe et al., Journal of Allergy and Clinical Immunology
Volume 142 Issue 1 Pages 159-170.e2 (July 2018)
Risk Stratification with Biologics: Rituximab as a Model

Take Home Points

- Reactions to chemotherapeutics and biologics have impact on patient outcomes
- Skin testing, challenges, risk stratification and desensitization can play an important role in allowing patients to continue first-line therapy safely
- Important to identify patients that have true allergy vs. those that can continue drug without desensitization