Supplementary Online Content


Table 1. Hypersensitivity reaction types
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Figure 1. NIAID/FAAN Anaphylaxis Criteria
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This supplementary material has been provided by the authors to give readers additional information about their work.
### Table S1. Hypersensitivity reaction types.¹

<table>
<thead>
<tr>
<th>Immune mediator</th>
<th>Type I/Immediate</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV/Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Drug antigen binds and crosslinks IgE on allergic cells, which results in degranulation.</td>
<td>Drug antigen-specific IgG binds antigen on the cell surface or matrix and activated phagocytic cells.</td>
<td>Drug antigen-specific IgG binds to soluble antigen forming immune-complexes that activate complement and phagocytic cells.</td>
<td>Drug antigen-specific T lymphocyte receptors bind to drug antigens and activates T lymphocytes with effector cells including macrophages, eosinophils and/or cytotoxic T lymphocytes</td>
</tr>
<tr>
<td><strong>Timing of onset</strong></td>
<td>Minutes to hours</td>
<td>Days to weeks</td>
<td>Days to weeks</td>
<td>Days to weeks</td>
</tr>
<tr>
<td><strong>HSRs</strong></td>
<td>Anaphylaxis</td>
<td>Hemolytic anemia</td>
<td>Serum sickness</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>Thrombocytopenia</td>
<td>Drug fever</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td><strong>Testing/verification methods possible</strong></td>
<td>Tryptase (acutely)</td>
<td>Reaction-specific (e.g., Coombs testing for hemolytic anemia)</td>
<td>Complement levels</td>
<td>Prolonged drug challenges</td>
</tr>
<tr>
<td></td>
<td>Skin testing</td>
<td>Drug challenge</td>
<td></td>
<td>Patch testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Delayed intradermal testing</td>
</tr>
</tbody>
</table>

Abbreviations: Ig, Immunoglobulin; HSR, hypersensitivity reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis
Table S2. Cephalosporin cross-reactivity, by R1 groups*

<table>
<thead>
<tr>
<th>Common amino R1 group</th>
<th>Common methoxyimino R1 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Cefotaxime</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Cefuroxime</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Cefepime</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Ceftazidime</td>
</tr>
<tr>
<td></td>
<td>Cefpodoxime</td>
</tr>
</tbody>
</table>

*Beta-lactam antibiotics have shared beta-lactam rings and may have R1 (6/7 position) and/or R2 (3 position) side chains that can be structurally identical or similar. Cross reactivity appears highest for beta-lactams that share identical R1 side chains. More comprehensive cephalosporin cross-reactivity matrices may be used if avoiding identical and similar structures at both side chain locations is desired.

Figure S1. NIAID/FAAN Anaphylaxis Criteria. This is a visual representation of the anaphylaxis definition from the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network. Anaphylaxis to penicillins and other beta-lactam antibiotics occurs from immediate hypersensitivity (IgE-mediated). Anaphylaxis should be promptly treated with epinephrine, supportive care, and adjunctive antihistamines, corticosteroids, and albuterol, as indicated by patient symptoms (Toolkit E).

Figure S2a
To perform percutaneous skin testing, a drop of allergen is placed on the skin. A 1 mm calibrated lancet is used to puncture the skin to incorporate the allergen; either by pressing down and “scooping” or by pressing down and twisting. To perform intradermal skin testing, a 25 gauge or smaller intradermal needle is loaded with 0.02 cc of allergen. Hold the needle at a 5 to 15 degree angle to the skin. The needle is then inserted into skin dermis and allergen injected to form a bleb under the skin.

Figure S2b
Penicillin skin testing (PST) includes percutaneous (i.e., skin-prick testing) testing followed by intradermal skin testing if skin-prick is negative. It is often performed prior to a drug challenge to reduce the number of serious acute-onset challenge reactions. At a minimum, skin testing uses the major antigenic determinant, benzylpenicilloyl polylysine injection (PPL). Allergists often skin test with additional reagents, including diluted penicillin G (10,000 units/mL for prick testing and intradermal testing), minor determinants penilloate and penicilloate, and/or ampicillin. For generalist adoption, we recommend using PPL and diluted Penicillin G. The entire test takes less than 45 minutes.

The first panel demonstrates the two steps of PST in a skin test positive patient. The test is shown using major determinant (labeled “PPL”), and diluted penicillin G (labeled “PCN”), 10,000 units/mL for the skin prick and 1 intradermal testing. The test is performed using a positive control (histamine phosphate 1.0 mg/mL) and a negative control (normal saline). The first step, a percutaneous or skin prick test, uses a skin prick-puncture device to prick the skin. The test is
read after 15 minutes. The patient shown here has a negative skin-prick test for penicillin allergy. The intradermal step places 0.02 mL of each reagent intradermally and the test is read after 15 minutes. A positive result for both tests is a wheal of at least 5 mm with flare greater than wheal when read at 15 minutes. The patient has a positive skin test to penicillin given the wheal and flare to major determinant (PPL).

The second panel demonstrates indeterminate skin testing situations. The photo on the left does not have a positive histamine response, which results in uninterpretable PPL and PCN. This can happen because of medications (e.g., antihistamines, tricyclic antidepressants) or patient condition (e.g., inpatient, elderly, immunocompromised). The photo on the right is also uninterpretable because the negative control is positive (i.e., there is a positive saline response), which may result from dermatographism.

Acute onset of an illness (minutes to several hours) with involvement of:

- Skin and/or mucosa
- Pruritus
- Flushing
- Hives
- Angioedema

And either

- Respiratory compromise
  - Dyspnea
  - Wheeze-bronchospasm
  - ↓ Peak expiratory flow
  - Stridor
  - Hypoxemia

Or

- ↓ BP or end-organ dysfunction
  - Collapse
  - Syncope
  - Incontinence

Anaphylaxis is likely when any one of the three criteria is fulfilled:

2 or more of the following that occur rapidly after exposure to a likely allergen for that patient:

- Skin and/or mucosa
- Pruritus
- Flushing
- Hives
- Angioedema

Respiratory compromise

- Dyspnea
- Wheeze-bronchospasm
- ↓ Peak expiratory flow
- Stridor
- Hypoxemia

↓ BP or end-organ dysfunction

- Collapse
- Syncope
- Incontinence

Persistent GI Symptoms

- Vomiting
- Crampy Abdominal Pain
- Diarrhea

After exposure to known allergen for that patient (minutes to several hours):

↓ BP
Figure S2A

<table>
<thead>
<tr>
<th>Percutaneous</th>
<th>Intradermal</th>
</tr>
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Figure S2B

- **Patient with a positive penicillin skin test**
- **Positive Intradermal Test**
- **Histamine Not Reactive**
- **Saline Reactive**

Negative Percutaneous Test  Positive Intradermal Test  Histamine Not Reactive  Saline Reactive