A practical approach to desensitization and drug allergies for the practising general internist

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Conflict disclosures

• Algorithme Pharma: consultant
• Sanofi: fees received for a presentation on allergy to chemotherapy
• Nestlé: fees received for a presentation on food allergies
Plan

• Presentation of the different types of drug hypersensitivity reactions
  – Clinical presentation
  – Physiopathology
  – Diagnosis and management including drug desensitization and challenge procedures

• Beta-lactam allergy
  – Cross-reactivity

• ACEI-induced angioedema

• Aspirin allergy
Two general types of drug hypersensitivity reactions

• Immediate
  – ≤ 1 hour after the last dose
  – Accounts for a minority of reactions (5%)

• Non-immediate (delayed)
  – Occurs generally a few days after starting treatment
  – Accounts for the majority of reactions (95%)
Clinical case: immediate reaction

• Patient was admitted to the ICU after a sudden cardiac arrest
• Just prior to the arrest, he had his IV line flushed with a pre-filled saline syringe and developed within a minute
  – flushing, weakness, syncope, cardiac arrest
• Back to normal, after a brief resuscitation
• Strong clinical suspicion of anaphylaxis
  – What test would confirm anaphylaxis?
  – What caused the reaction?
IgE-mediated reaction (immediate)

Type I hypersensitivity reaction:
IgE-mediated
Immediate (<1 hour after intake)

Mast cell

Prior exposure is often not clinically evident

Histamine
Prostaglandines
Leucotrienes
Tryptase
Clinical case: immediate reaction

• Anaphylaxis confirmed:
  – Tryptase measured at 95 (normal less than 13.5ng/ml) in the hour following the reaction

• What caused the reaction?
  – The patient had noticed pruritus at sites where chlorhexidine/alcohol tampons were used for the last several months
  – The IV line was probably disinfected with a chlorhexidine/alcohol tampon just before it was flushed with saline
  – Positive skin prick test to chlorhexidine
  – Strict avoidance of chlorhexidine recommended and the patient was advised to wear a medic-alert bracelet
Diagnosis of IgE-mediated reactions

Skin prick test

Full concentration

Intradermal test

1/10 dilution in saline

Reading at 15 minutes
Diagnosis of IgE-mediated reactions

Drug challenge

1/10th

Full dose

30 minutes

1 hour surveillance
When is desensitization indicated for IgE-mediated reactions?

• Only indicated if there is no suitable alternatives
  – Chemotherapy (platins, taxanes, etc)
  – Monoclonal antibodies (infliximab, rituximab, etc)
  – Antibiotics (penicillin G to treat syphilis)

• High risk procedure at risk for anaphylaxis
  – Monitoring required

• Temporary phenomenon (patient remains allergic)
### Rapid desensitization

<table>
<thead>
<tr>
<th>1/100th dose</th>
<th>1/10th dose</th>
<th>Full dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="1/100th dose" /></td>
<td><img src="image2" alt="1/10th dose" /></td>
<td><img src="image3" alt="Full dose" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate (ml/h)</th>
<th>Rate (ml/h)</th>
<th>Rate (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 x 15min</td>
<td>5 x 15min</td>
<td>10 x 15min</td>
</tr>
<tr>
<td>5 x 15min</td>
<td>10 x 15min</td>
<td>20 x 15min</td>
</tr>
<tr>
<td>10 x 15min</td>
<td>20 x 15min</td>
<td>40 x 15min</td>
</tr>
<tr>
<td>20 x 15min</td>
<td>40 x 15min</td>
<td>80 x 2.9h</td>
</tr>
</tbody>
</table>
Clinical case: non-immediate reaction

• 60 years old diabetic man with cellulitis treated with piperacilline-tazobactam
• After 5 days of treatment, pruritic maculopapular rash
• Blood tests:
  – Eosinophilia: 1.2
  – C-reactive protein: 40
• Antibiotic changed to imipenem. Rash disappears within 7 days without desquamation.
• Should we confirm that the patient is allergic to piperacillin-tazobactam? What about cephalosporins?
Non-immediate reactions

• Large spectrum
• Type IV (T cell-mediated)
  – Maculopapular rash of varying severity
  – Fixed drug eruption
  – DRESS / SJS – TEN / AGEP
• Type II (antibody-mediated/cytotoxicity)
  – Hemolytic anemia
• Type III (immune complex-mediated)
  – Serum sickness
  – Cutaneous vasculitis (palpable purpura)
Type IV hypersensitivity reactions

- Accounts for more than 90% of all drug reactions
- Penicillins: 1-8%
- Sulfa: 2-4%
- Cephalosporines: 1%
- Fluoroquinolones: 1-2%
- Gentamicin: 1%
- Macrolid: <1%
- Tetracycllin: <1%
- Vancomycin: 6%
- Carbapenems: 1-2%

Reference:
Bigby. Arch Derm. 2001
Cavalcanti. Cochrane. 2010
Monographies: meropenem et imipenem
T cell-mediated reactions (type IV)

Eosinophils

1 to 10 days

CD4

CD8

UpToDate
A maculopapular rash is not necessarily an allergic reaction

• More than 100 patients with a benign maculopapular rash during a course of cephalosporin were evaluated
• Only 4.7% were found to be allergic
• Allergic reactions usually last longer than non-allergic rashes
  – 3.3 days for non-allergic vs 10 days for allergic reactions
• What can explain these findings:
  – Virus-induced rash
  – Rapid resolution of the drug allergy
Drug-induced eosinophilia is frequently benign

- Patients on IV antibiotics for a long period (median: 41 days)
- 25% had eosinophilia
  - Rash: 15% (vs 6%)
  - Renal injury: 15% (vs 10%)
  - Liver injury: 6% (vs 7%)
  - At least one feature: 30% (vs 21%)
  - DRESS (possible): 3% (vs 0%)
- Most patients with eosinophilia while on antibiotics do not develop an allergic reaction
- Close monitoring is recommended if eosinophilia develops
Diagnosis of a T cell-mediated reaction

Patch test

30% in petroleum jelly

Intradermal test

1/10th in saline

Reading at 48-72 hours
Diagnosis of a T cell-mediated reaction

Drug challenge

1/10th

Full dose

1 week

48-72 hours
Clinical case: delayed reaction

• Skin testing performed after the reaction resolved
• Intradermal testing to:
  – Penicillins
  – Cephalosporines
  – Carbapenems
  – Only piperacilline-tazobactam positive at 48H
• Conclusion: **selective allergy** to piperacilline-tazobactam. Can be treated with cephalosporines, carbapenems and even some penicillins (eg: amoxicilline)
Clinical case: severe reaction

45 years old woman HIV +
Took trimethoprim-sulfamethoxazole for 5 days to treat « bronchitis »
Asthenia, myalgias, fever and skin rash for 72 hours.
Liver injury
No eosinophilia

What is the diagnosis?
Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)

- Onset 5 to 28 days after starting the causal agent
- Fever and flu-like symptoms
- Treatment
  - Priority: skin and mucous membrane care
  - Transfer to burn unit
  - Uncertain benefit: IVIG, corticosteroids and cyclosporin
- Allergy testing not sensitive

Mucosal symptoms

Epidermal detachment

SJS: < 10%  TEN: > 30%

Creamer British J Dermatol 2016
Clinical case: severe reaction

• 50 years old woman treated with piperacilline-tazobactam for osteomyelitis
• After 2 weeks of treatment:
  – Fever
  – Maculopapular rash but no blisters or mucosal involvement
• Antibiotic changed to imipenem
• Transient improvement but 5 days later:
  – Recurrent fever and skin rash progresses
  – Acute kidney injury requiring dialysis
  – Eosinophilia
  – Lymphocytosis with atypical lymphocytes
• What is the diagnosis?
DRESS (drug reaction with eosinophilia and systemic symptoms)

- Onset often after prolonged treatment: 1-6 weeks
- Fever and asthenia
- Variable skin rash (often maculopapular) often with facial edema and purpura on the legs
- Diffuse lymphadenopathy
- Lymphopenia followed by lymphocytosis (with atypical lymphocytes)
- Eosinophilia
- Liver injury
- Kidney injury (interstitial nephritis)
- Lung involvement (pneumonitis)
- Other organs (heart, brain)
- Long-lasting and slow resolution over weeks/months

- Mortality: 2 to 10%
DRESS: treatment

• Stop every suspected drug
• Avoid starting new medication
  – Increased risk of reaction to unrelated drugs
• Corticosteroids with slow taper over 8 to 12 weeks
  – Risk of recurrent reaction if tapered too rapidly
DRESS: identification of the causal agent
# Red flags for severe type IV reactions

## Clinical features:
- Asthenia
- Fever
- Facial edema
- Blister, bulla, pustules
- Epidermal detachment (ulcer)
- Desquamation
- Mucosal involvement
- Lymphadenopathy

## Laboratory features:
- Lymphopenia followed by **lymphocytosis**
- Liver injury
- Kidney injury
- Urinary eosinophilia
- Very high CRP (> 100) or ferritin (> 500)
History of penicillin allergy

• History of penicillin allergy:
  – Around 10% of the adult population

• Confirmed penicillin allergy (skin test +/- challenge):
  – Between 1 to 10% of the adult population with a history
  – Penicillin allergy resolves with time in most people:
    • Only 43% of penicillin allergic patients are still allergic 5 years later
    • Only 32% of cephalosporin allergic patients are still allergic 5 years later

1. Picard. JACI: In Practice 2013
2. Macy. JACI: In Practice 2013
3. Blanca. JACI 1999
4. Romano. Allergy. 2014
Use of alternative antibiotics

**TABLE IV.** Choice of alternative antibiotics in patients with a history of penicillin allergy and a first-line indication for treatment with beta-lactam antibiotics and associated costs

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No. of patients treated*</th>
<th>Days of treatment (total)</th>
<th>Estimated costs (CAD)†</th>
<th>Estimated additional costs (CAD)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>27</td>
<td>97</td>
<td>$11,640</td>
<td>$10,105</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>26</td>
<td>168</td>
<td>$7030</td>
<td>$4425</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>20</td>
<td>122</td>
<td>$4270</td>
<td>$1983</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>6</td>
<td>46</td>
<td>$2760</td>
<td>$2442</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
<td>84</td>
<td>$2444</td>
<td>$1142</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>8</td>
<td>41</td>
<td>$164</td>
<td>−$554</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>3</td>
<td>28</td>
<td>$1260</td>
<td>$1069</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1</td>
<td>5</td>
<td>$50</td>
<td>$15</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>1</td>
<td>5</td>
<td>$50</td>
<td>$43</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>1</td>
<td>2</td>
<td>$500</td>
<td>$200</td>
</tr>
<tr>
<td>Tigecyclin</td>
<td>1</td>
<td>3</td>
<td>$420</td>
<td>$369</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td>$21,114</td>
<td>$15,672</td>
</tr>
</tbody>
</table>

Additional cost 326.50$ per patient

Picard. JACI: In Practice 2013
Use of alternative antibiotics

Macy. JACI 2014

<table>
<thead>
<tr>
<th>TABLE III. Case and control demographics, health care use, and outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female subjects</strong></td>
</tr>
<tr>
<td>Cases with history of penicillin “allergy,” n = 36,583</td>
</tr>
<tr>
<td>1,071 (2.9)</td>
</tr>
<tr>
<td>1,686 (2.3)</td>
</tr>
<tr>
<td><strong>C. difficile prevalence, no. (%)</strong></td>
</tr>
<tr>
<td>+23.4%</td>
</tr>
<tr>
<td>Cases with no history of penicillin “allergy,” n = 73,166</td>
</tr>
<tr>
<td>960 (2.6)</td>
</tr>
<tr>
<td>1,631 (2.2)</td>
</tr>
<tr>
<td><strong>MRSA prevalence, no. (%)</strong></td>
</tr>
<tr>
<td>+14.1%</td>
</tr>
<tr>
<td>Cases with history of penicillin “allergy,” n = 36,583</td>
</tr>
<tr>
<td>234 (0.6)</td>
</tr>
<tr>
<td>337 (0.5)</td>
</tr>
<tr>
<td><strong>VRE prevalence, no. (%)</strong></td>
</tr>
<tr>
<td>+30.1%</td>
</tr>
</tbody>
</table>
Who should be referred for penicillin allergy evaluation?

• Ideally, any patient with a history of penicillin allergy
  – It is best to perform skin testing and challenge when the patient is well and not in need of antibiotics

• Patients to prioritize for evaluation:
  – History of reaction to multiple antibiotics
  – Frequent need of antibiotics
  – Patients with a high likelihood of needing antibiotics in the near future
Cross-reactivity

Penicillin
  Amoxicilline

1\textsuperscript{st} generation
  Cefadroxil

2\textsuperscript{nd} generation
  Cefprozil

Sastre. Allergy 1996
Miranda J Allergy Clin Immunol 1996
Cross-reactivity

Penicillin
  Ampicilline

1\textsuperscript{st} generation
  Cephalexine

2\textsuperscript{nd} generation
  Cefaclor
Risk of cross-reactivity between beta-lactams

- Patients with confirmed penicillin allergy
- Carbapenems ≤ 1%
- Cephalosporines
  - 3rd generation: around 1%
  - 2nd generation: variable
    - Cefuroxime (IV): around 1%
    - Cefprozil (po): around 10-20%
    - Cefoxitin (po et IV): uncertain risk
  - 1st generation: variable
    - Cefazolin (IV): around 1-2%
    - Cefadroxil (po): around 10-20%
    - Cephalexine (po): around 10-20%
In urgent need, can a beta-lactam be given to a patient with a history of penicillin allergy?

- **Unconvincing history**
  - Isolated skin reaction
    - ≥10 yrs
    - <10 yrs
  - Anaphylaxis (no shock or intubation)
    - Serum sickness
    - Confirmed allergy
  - Anaphylaxis (shock or intubation)
    - Severe reaction (DRESS/SJS/TEN/AGEP)

- **Penicillins**
  - Cephalosporinases at risk
  - Cephalosporinases low risk
  - Carbapenems

- **Standard administration**
- **Drug challenge**
- **Avoid**
Clinical case: angioedema

• 50 years old man
  – Comes to the ER because of lip and tongue angioedema for 4 hours and growing
  – No urticaria, no pruritus
  – No difficulty breathing
  – 1st episode
  – On ramipril for 3 years

• What is the differential diagnosis?
Differential diagnosis

• ACEI-induced angioedema
• Idiopathic angioedema
  – Histamine-mediated (mast cell activation)
  – Bradykinin-mediated
• Acquired C1 inhibitor deficiency
• This is not an allergic reaction
Kinin system

- Pre-kallikrein
  - Factor XIIa
    - C1 INH
- Kallikrein
  - C1 INH
- Kininogen
- Bradykinin
  - ACE
  - DPPIV
- B2 receptor
  - (vessel wall)
How to treat?

• Antihistamine (H1)
• Corticosteroid
• If histamine-mediated, improvement with antihistamines and resolution in 1 to 2 days
• If bradykinin-mediated, no improvement with antihistamines and lasts 2 to 5 days
How to treat?

• If ACEI-induced angioedema and severe symptoms:
  • C1 inhibitor concentrate (Berinert)
    – Blocks bradykinin formation
    – 20 units/kg IV
    – Uncertain benefit/off label
  • Icatibant (firazyr)
    – B2 receptor blocker
    – 30mg SQ
    – Efficacy shown in a randomized trial
      • Resolution in 8 vs 27 hours (Bas. NEJM 2015)
    – Off label
What to do next?

- Avoid every ACEI
- Warn the patient that a recurrent angioedema attack may occur in the following weeks or months even if the ACEI has been stopped
- If recurrence, rule out C1 inhibitor deficiency by measuring C4 (during an attack), C1 inh antigenic level and C1 inh function
- ARA considered safe
  - Risk of recurrent reaction $\leq 10\%$
Clinical case

• 50 years old male
  – Acute coronary syndrome
  – Drug-eluting stent placed
  – Patient says he is allergic to aspirin
• What should we do?
What is the type of the allergic reaction?

• Many types:

• « Pseudo-allergic » (due to COX-1 inhibition)
  – Urticaria/angioedema with all NSAIDs
  – Urticaria/angioedema with all NSAIDs in a patient with chronic urticaria/angioedema
  – Aspirin-exacerbated respiratory disease (AERD): nasal polyps, asthma and reactivity to NSAIDs

  – Selective allergy to one NSAID (possibly IgE-mediated); almost never ASA
Clinical approach

AERD*

Premedication with:
- Montelukast
- Corticosteroid
- ICS/LABA

Any other type

No premedication

90 minutes between doses:
1. 40.5mg
2. 40.5mg
3. 81mg
4. 121.5mg
5. 202.5mg
6. 325mg

*May benefit from high dose ASA treatment (650mg bid)

Adapted from: Cook Curr Allergy Asthma Rep 2016
Questions?