Antibiotic allergy in the Intensive Care

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Outline of talk

• True or false?
• Case example
• Types of drug allergy
• Testing methods available
• Using algorithms
• Approach to the patient with a stated allergy
• Useful resources
• Questions
True or false?

- If a patient has had anaphylaxis to a beta lactam antibiotic, they should avoid these for life?
  - False - specific IgE reduces with time and patients can become tolerant again to drugs they were once allergic to

- There is a 10% cross reactivity with regard to allergy between penicillins and cephalosporins
  - False - the cross reactivity is probably <1% and the 10% figure probably came about at a time that cephalosporins were contaminated with penicillins

- The best way to test for antibiotic drug allergy is by skin prick testing and intradermal testing?
  - True - blood tests are pretty useless
True or false...

- Allergy testing can be reliably performed for any antibiotic
  - False - best for penicillin, general anaesthetics and limited utility for most other drugs

- A negative skin prick test or intradermal test to penicillin means that a patient has the same risk of an IgE mediated reaction as someone not known to be allergic to penicillin
  - True - great test to exclude a penicillin allergy
Case 1

- 48 year old man admitted to ICU with recurrent aspiration pneumonia
- Was put on Tazocin earlier this year and apparently developed a mild but generalised erythematous rash (was able to tolerate the entire infusion as it wasn’t stopped)
  - Vague history in notes of possible hypotension and need for adrenaline, although patient history does not corroborate this
- Requires further antibiotics, ideally beta lactam based
  - In the ICU, how would you resolve this issue?
Case 2

- Elderly lady with multiple co-morbidities, including significant COPD presents with sepsis and respiratory failure

- CXR shows bilateral consolidation

- History of penicillin allergy 10 years ago with lip angioedema and urticaria following a course of Amoxicillin

- Patient has been intubated and put on a cephalosporin and moxifloxacin due to the penicillin allergy

- How do you approach the patient’s allergy?
Adverse drug reactions

- Adverse drug reactions are classified as either Type A (85-90%) of reactions or Type B (10-15%)

- Type A are predictable reactions that can occur in any individual depending on the properties of the drug

- Type B are the idiosyncratic reactions that are typical of hypersensitivity or immunological reactions to drugs
Gel and Coombs classification of drug reactions

- **Type I** – Immediate in onset; IgE and mast cell mediated
- **Type II** – mediated by IgG mediated cell destruction (usually delayed in onset)
- **Type III** – Delayed in onset and caused by IgG:Drug immune complex deposition and complement activation
- **Type IV** – delayed and T cell mediated
What can we test for?

• Important to remember that drug testing is aimed squarely at Type I reactions only

• Patch testing for cell mediated reactions (Type IV) are possible but only at very specialised centres

• Patients with a prior history of Stevens Johnson Syndrome/TEN, DRESS syndrome are not candidates for drug testing and should never be exposed to the culprit drug again
Penicillins

Cephalosporins

R1

6 - position

R1

7 - position

R3

3 - position

R-side chain (R-CONH-)

B-Lactam Ring

Thiazolidine ring

R-side chain (R-CONH-)

B-Lactam Ring

Dihydrothiazine ring

R2-side chain

EBMCONSULT®
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<td>Cefepime&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Cephalothin&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup> First generation cephalosporin  
<sup>b</sup> Second generation cephalosporin  
<sup>c</sup> Third generation cephalosporin  
<sup>d</sup> Fourth generation cephalosporin
Drug testing methods

• Specific IgE to drugs
  • available for penicilloyls, amoxicilloyl, benzylpenicilloyl, cefaclor
  • Pros: Patient can be on anti-histamines or other medications that interfere with skin tests
  • Cons: Poor sensitivity/specificity for detecting true allergy, turn around time can be a week or longer (usually batched)

• Skin prick tests (SPT) and intradermal testing (ID)
  • Addition of drugs to the skin (either on surface or as a bleb) and seeing if there is a wheal and flare response
Skin testing is fiddly...

- Need experienced practitioners such as an Allergy CNC but medical practitioners and pharmacists can be trained to do this.
- Drugs need to made up fresh (major and minor determinants of penicillin, benzylpenicillin, ampicillin) and used mostly on the same day.
- Traditionally, skin prick tests are followed by intradermal tests, followed by an oral challenge (gold standard).
- Typically takes 3 hours.
- Numerous drugs interfere with testing: antihistamines, steroids, tricyclic antidepressants.
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<td>1/10</td>
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<td>Neat</td>
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<td>Minor determinant</td>
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<td>1/100</td>
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<td>1/10*</td>
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<td></td>
<td></td>
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<td>Neat*</td>
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<tr>
<td>Benzylpenicillin</td>
<td>10,000 Units /ml</td>
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<td></td>
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<td>1/10</td>
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<td>Neat</td>
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<td>Neat</td>
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<td>DRUG/AGENT</td>
<td>SPT</td>
<td>IDT</td>
<td>Published Maximum NIC</td>
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<td>(Reference Concentration, mg/mL)*</td>
<td>Initial</td>
<td>Maximum Non-irritant</td>
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ANZAAG
Australian & New Zealand Anaesthetists' Allergy Group
Test interpretation

• A positive test to a penicillin (either SPT or ID test) is highly suggestive that the patient has specific IgE against penicillin and should avoid these drugs.

• A negative test to a penicillin means that the patient has the same risk of an allergic reaction as someone not known to be allergic to penicillin.

• For many of the other drugs for which we can do testing, it’s difficult to be so certain - often a positive test is significant but a negative test may not necessarily exclude an allergy.
The holy grail….for an allergist

- Identify all patients in ICU with an allergy
- Use an algorithm to stratify identified patients into low/medium/high risk of allergy
- Challenge patients with low risk (either with full dose of drug or with a graded challenge)
- Skin testing for high risk groups and if negative, followed by a challenge
- Patients determined to be either non-allergic (most patients) or allergic (switch to alternative agents)
Penicillin / Cephalosporin Hypersensitivity Pathway

**Type II-IV HSR**
- Serum Sickness
- Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS / TEN)
- Acute Interstitial Nephritis (AIN)
- Drug Rash Eosinophilia with Systemic Symptoms (DRESS)
- Hemolytic Anemia
- Drug Fever

**Type I (IgE-mediated) HSR**
- Anaphylaxis
- Hypotension
- Angioedema
- Laryngeal edema
- Wheezing
- Hives / Urticaria
- OR
- **unknown reaction WITHOUT mucosal involvement, skin desquamation, or organ involvement**

**Mild Reaction**
- Minor rash (not hives)
- Maculopapular rash (mild Type IV HSR)
- Medical record lists allergy, but patient denies history of allergy

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Avoid using penicillin, cephalosporin, or carbapenem; use alternative agents by microbial coverage.

If penicillin or cephalosporin is clinically indicated, please involve the Infectious Disease or Allergy / Immunology services.

**Okay to use:**
- 3rd / 4th / 5th generation cephalosporin or carbapenem by **Test Dose Procedure**
- OR
- aztreonam
- OR
- alternative agent by microbial coverage
- OR
- If penicillin or 1st / 2nd generation cephalosporin is preferred, penicillin skin testing is indicated. Please call / contact Allergy / Immunology service.

**Okay to use:***
- 3rd / 4th / 5th generation cephalosporin as full dose
- OR
- penicillin or 1st / 2nd generation cephalosporin by **Test Dose Procedure**
- OR
- carbapenem

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**ALTERNATIVE AGENTS BY MICROBIAL COVERAGE:**
- **Gram positive coverage:** vancomycin, linezolid*, daptomycin*, clindamycin, doxycycline, sulfamethoxazole / trimethoprim
- **Gram negative coverage:** fluoroquinolones, sulfamethoxazole / trimethoprim, aminoglycosides, aztreonam*

**CEPHALOSPORINS BY GENERATION:**
- 1st: cephalexin / cefadroxil / cefazolin
- 2nd: cefoxitin / cefotaxim / cefuroxime
- 3rd: ceftriaxone / cefixime / cefotaxime / cefpodoxime / cefazidime
- 4th / 5th: cefepime / ceftresion

For complete pathway and decision support, visit:**
http://id.partners.org/allergy

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^ HSR: Hypersensitivity Reaction
* Infectious Disease approval required
** Access from Partners PC or while connected through secure Partners wi-fi (not phspiaquest)
Issues in ICU

- An accurate history from the patient may not be possible (intubated, sedated)

- Patients may be on medications (such as high dose steroids) that may affect drug testing

- Patients who have testing performed and had an allergy “de-labeled” may still report a drug allergy after being discharged from ICU! - report in IMJ 2016

- Recognising an allergic reaction may be more difficult in patients on inotropes already
Positives about drug testing in ICU

- Safest place in hospital to perform a drug challenge (with monitoring, 1:1 nursing)
- Bucket loads of broad spectrum antibiotics are being used (all appropriately, of course)
  - Can hopefully prevent the emergence of multi-resistant organisms by limiting use of broad spectrum antibiotics
- There may be scope in up-skilling a single person (nursing/medical/pharmacy) to do the testing within an ICU
Options in ICU with the drug allergic patient

• Easy option: Use an alternative class of antibiotics
  • Pros: Easy to implement, requires little fuss, no chance of patient being inadvertently exposed to drug
  • Cons: Use of alternate broad spectrum ABs may lead to emergence of drug resistant organisms; these drugs may be less effective than the “allergic” drug

• Consult your friendly allergist
  • If your hospital has one.....we are a rare breed
Options in the drug allergic patient

- More difficult options:
  - Follow an algorithm to determine if the patient really does have a drug allergy
    - if extremely unlikely, give drug directly
    - if low-moderate risk, give a graded drug challenge (1/100, 1/10, neat dose), separated by 30 min intervals
    - If high risk, drug testing should be done, followed by a challenge
  - Desensitise the patient to the drug
    - Pros: Protocols available for most commonly used drugs
    - Cons: Desensitisation only works whilst patient is on drug
    - Patient reverts to allergic status once drug is not being taken
Case 1

- 48 year old man admitted to ICU with recurrent aspiration pneumonia

- Was put on Tazocin earlier this year and apparently developed a mild but generalised erythematous rash (was able to tolerate the entire infusion as it wasn’t stopped)

- Vague history in notes of possible hypotension and need for adrenaline, although patient history does not corroborate this

- Requires further antibiotics, ideally beta lactam based

- In this case a graded challenge was performed, which the patient passed and the patient had the penicillin allergy removed
Case 2

- Elderly lady with multiple co-morbidities, including significant COPD presents with sepsis and respiratory failure
  - CXR shows bilateral consolidation
  - History of penicillin allergy 10 years ago with lip angioedema and urticaria following a course of Amoxicillin
  - Patient has been intubated and put on a cephalosporin and moxifloxacin due to the penicillin allergy
  - 10 years is at the cross roads; safest approach would be to skin test and if negative, challenge with a beta lactam antibiotic; alternative approach may be to give a graded challenge
Useful resources

- ANZAAG (Australia New Zealand Anaesthetic Allergy Group) - drug concentrations

- A proactive approach to Penicillin Allergy testing in Hospitalised patients - Chen et al, JACI 2016
  - [https://doi.org/10.1016/j.jaip.2016.09.045](https://doi.org/10.1016/j.jaip.2016.09.045)

- Tackling inpatient penicillin allergies: assessing tools for antimicrobial stewardship - Blumenthal et al, JACI, 2017
  - [http://dx.doi.org/10.1016/j.jaci.2017.02.005](http://dx.doi.org/10.1016/j.jaci.2017.02.005)