The below documents have kindly been made available by the faculty for individual study purposes:

Session: Diagnosing major allergic diseases in secondary care
Presentation: Drug allergy, Paul Whitaker, United Kingdom
Management of suspected drug allergy

Dr Paul Whitaker
Consultant Respiratory Physician
St James’s Hospital, Leeds, UK

St JAMES’S & SEACROFT
EAACI TF: In-vitro diagnosis of drug allergy
Definition of drug allergy

• Adverse reaction to a drug that clinically resembles allergy and a definite immunological response is demonstrated
UK epidemiology data

- 62,000 admissions a year admitted with an adverse drug reaction (ADR)
- 15% of hospital patients will experience an ADR
- Increase of 2.6 fold since 1998

- 10% of population penicillin allergic
  - Only 10% confirmed with full allergy work up

- Between 2005 and 2013 using National Reporting System
  - 18,079 events involving drug allergy
  - Most due to being given the drug when known allergy
  - 6 deaths, 19 severe harms
Who should be referred for allergy assessment?

- In the UK national guidelines recently written.

- Suggest referring
  - All patients with suspected anaphylaxis
  - All patients with severe reactions such as SJS and DRESS.
  - Patients with multiple drug allergies
  - Patients with a chronic disease with a high need for future drugs. For example a COPD patient.
What should be achieved during allergy assessment?

• Essential documentation
  o Generic and proprietary name and strength
  o Description/photo of reaction
  o Indication for the drug
  o Date and time of reaction
  o Number of doses before
  o Route of drug

• After allergy review
  o Diagnosis and which investigations
  o Drugs to avoid
  o Safe alternatives
Risk factors for drug allergy

**Drug Factors**
- Nature of the drug
- Route of administration (intravenous > oral)
- Repeated exposures

**Host Factors**
- Age (young adults)
- Gender (female > male)
- Co-existent illness (HIV significantly higher risk)
- Genetic polymorphisms
  - Abacavir and HLA B*5701
  - Carbamazepine and HLA B*1502
• Discovery of associations between HLA alleles and drug hypersensitivity represents an important advance

• Screening for HLA alleles during clinical practice effectively prevents reactions
  o Abacavir
  o Carbamazepine

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA Allele</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir</strong></td>
<td>HLA-B*5701</td>
<td>132</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flucloxacillin</strong></td>
<td>HLA-B*5701</td>
<td>72</td>
</tr>
<tr>
<td>DILI</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>HLA-B*1502</td>
<td>1000</td>
</tr>
<tr>
<td>SYS/TEN</td>
<td>(Chinese)</td>
<td></td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>HLA-A*3101</td>
<td>11</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>(Japanese)</td>
<td></td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>HLA-A*3101</td>
<td>30</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>(Caucasians)</td>
<td></td>
</tr>
<tr>
<td><strong>Lumiracoxib</strong></td>
<td>HLA-DRB1*1501</td>
<td></td>
</tr>
<tr>
<td>DILI</td>
<td>HLA-DOA1*0102</td>
<td></td>
</tr>
<tr>
<td><strong>Ximelagatran</strong></td>
<td>HLA-DRB1*0701</td>
<td></td>
</tr>
</tbody>
</table>

Mallal, 2008; Kindmark et al., 2008; Daly et al., 2009; Chung et al., 2004; McCormack et al., 2011; Singer et al., 2010; Spraggs et al., 2011
Classification

Timing of Reaction

• Immediate
  – < 1 hour
  – Recover in hours
  – Urticaria, anaphylaxis, angioedema

• Non-immediate
  – > 24 hours
  – Recover in days to weeks
  – Maculopapular rashes, fevers, bullous reactions, liver involvement, haemolysis
<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune reactant</strong></td>
<td>IgE</td>
<td>IgG</td>
<td>IgG</td>
<td>T_{H}1 cells</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>Soluble antigen</td>
<td>Cell- or matrix-associated antigen</td>
<td>Soluble antigen</td>
<td>T_{H}2 cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell-surface receptor</td>
<td>Soluble antigen</td>
<td>CTL</td>
</tr>
<tr>
<td><strong>Effector mechanism</strong></td>
<td>Mast-cell activation</td>
<td>Complement, FcR^+ cells (phagocytes, NK cells)</td>
<td>Antibody alters signaling</td>
<td>Complement, Phagocytes</td>
</tr>
<tr>
<td><strong>Example of hypersensitivity reaction</strong></td>
<td>Allergic rhinitis, asthma, systemic anaphylaxis</td>
<td>Some drug allergies (eg, penicillin)</td>
<td>Chronic urticaria (antibody against FcεR1α)</td>
<td>Serum sickness, Arthus reaction</td>
</tr>
</tbody>
</table>

![Gell-Coombs classification diagram](image-url)
Immediate reactions

- Urticaria
- Angioedema
- Rhinitis
- Bronchospasm
- Anaphylaxis
Immediate reaction on re-exposure

- Vascular leak
- Broncho-constriction
- Inflammation
- Tissue damage

- Biogenic amines (e.g., histamines)
- Lipid mediators (e.g., PAF, PGD$_2$, LTC$_4$)
- Cytokines (e.g., TNF)
- Lipid mediators (e.g., PAF, PGD$_2$, LTC$_4$)
- Enzymes (e.g., tryptase)

Activated mast cell (or basophil)
Non-immediate (T cell mediated)
Immune response following T cell activation

- Drug
- Antigen presenting cell
- MHC I & II
- TCR
- T-cell
- CD4+ T-cell
- CD8+ T-cell
- Perforin
- TNF-alpha
- IL-4
- IL-5
- IL-13
- IFN-\(\gamma\)
- IL-10
- MIP-1\(\beta\)

Tissue damage in skin

Th1/2 response

Cytotoxicity
Individual T cell response and immune mediators involved determine the type of reaction

<table>
<thead>
<tr>
<th>Category of Type IV reaction</th>
<th>Immune mediator</th>
<th>Cell type</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IVa</td>
<td>TH1 cells: IFN-γ and TNF-α</td>
<td>T cells, macrophages</td>
<td>Contact dermatitis, Tuberculin reaction</td>
</tr>
<tr>
<td>Type IVb</td>
<td>TH2 cells: IL-4, IL-5, IL-13</td>
<td>Eosinophils</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Type IVc</td>
<td>Cytotoxic T cells: Perforin, Granzyme B</td>
<td>T cells</td>
<td>Contact dermatitis, Maculopapular rash, Bullous eruptions (SJS, TEN)</td>
</tr>
<tr>
<td>Type IVd</td>
<td>T cells: GM-CSF, CXCL8, IL-8</td>
<td>Neutrophils</td>
<td>AGEP (Acute generalised exanthematous pustulosis)</td>
</tr>
</tbody>
</table>
Assessment

SKIN TESTING

HISTORY

SKIN TESTING

IN-VITRO TESTS

PROVOCATION TESTS

Skin Prick Tests

Patch Tests

Intradermal

IMMEDIATE
(IgE Mediated)

Specific IgE
Basophil activation tests

NON-IMMEDIATE
(T-cell mediated)

LTT
ELIspot
Investigating Hypersensitivity Reactions

**HISTORY**

- [Blank]
- [Blank]
- [Blank]
- [Blank]
# Drug Allergies

**Patient Name:** Shelley Taylor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>Nausea, Rash, AD</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Rash on legs - OK since 2005</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Rash, Gas, AD</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>(-)</td>
</tr>
<tr>
<td>Tazzarin</td>
<td>(-)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Rash on legs 2/19</td>
</tr>
</tbody>
</table>

**Desensitization:**
- Shelley says she can have all antibiotics except Ceftriaxone.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Successful [Y/N]</th>
<th>Date</th>
<th>Reaction</th>
<th>If Not</th>
</tr>
</thead>
</table>
DRUG HYPERSENSITIVITY

INVESTIGATOR: Protocol No: __________________________
Name: __________________________ Center: __________________________
Address: __________________________ Tel/Fax/E-mail: __________________________

PATIENT: Date of protocol: __________________________
Name: __________________________ Date of birth: __________________________ Ager: __________________________
Weight: __________________________ cm Height: __________________________
Profession: __________________________ Origin: __________________________ Sex: M F
Riskgroups: Medical staff Pharmaceutical Industries Farmers Others/specify

CURRENT COMPLAINTS:

DRUG REACTION:
(Multiple boxes can be ticked; underline if necessary; chronology can be characterized with numbers)

● Cutaneous symptoms
  ○ Mucroepidermal exanthema
  ○ Maculopapular exanthema
  ○ Urticaria exanthema
  ○ ANGEL (Acute generalized exanthematous pustulosis)
  ○ Exanthematosis exanthematum multifforme
  ○ Urticarial exanthema
  ○ Erythema exudativum multiforme
  ○ Fixed drug exanthema
  ○ Purpura Thrombocyte count
  ○ Epidermolysis bullosa
  ○ Visceral organ involvement
  ○ Contact dermatitis
  ○ Topical cause
  ○ Haematogenous cause

● Constitutional factors
  ○ Fever
  ○ Hypotension
  ○ Collapse

● Evolution:
  ○ Intensity

GASTROINTESTINAL AND RESPIRATORY SYMPTOMS:

● Associated symptoms
  ○ Involvement of: Liver Kidney Others/specify
  ○ Fever: __________°C
  ○ Malaise
  ○ Pain/Feeling Location/c
  ○ Edema Location/c
  ○ Arthralgia Location/c
  ○ Lymphadenopathy
  ○ Other/specify

● Cardiovascular symptoms
  ○ Tachycardia Pulse rate: __________/min
  ○ Hypotension Blood pressure: __________mmHg
  ○ Collapse
  ○ Arrhythmia
  ○ Other/specify

● Psychic symptoms
  ○ Fear/Panic reaction
  ○ Vertigo

● Involvement of other organs

ENDA Questionnaire
Investigating Hypersensitivity Reactions

IMMEDIATE (IgE Mediated)
- Skin Prick Tests

HISTORY

SKIN TESTING

NON-IMMEDIATE (T-cell mediated)
- Patch Tests
- Intradermal
POSITION PAPER

Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper

K. Brockow¹, L. H. Garvey², W. Aberer³, M. Atanaskovic-Markovic⁴, A. Barbaud⁵, M. B. Bilo⁶, A. Bircher⁷, M. Blanca⁸, B. Bonadonna⁹, P. Campi¹⁰, E. Castro¹¹, J. R. Cernadas¹¹, A. M. Chiriac¹², P. Demoly¹², M. Grosber¹, J. Gooi¹³, C. Lombardo⁹, P. M. Mertes¹⁴, H. Mosbech², S. Nasser¹⁵, M. Pagani¹⁶, J. Ring¹, A. Romano¹⁷, K. Scherer⁷, B. Schnyder¹⁸, S. Testi¹⁰, M. Torres⁸, A. Trautmann¹⁹, I. Terreehorst²⁰ on behalf of the ENDA/EAACI Drug Allergy Interest Group
Skin Prick Testing

- Identify IgE mediated reaction (Sensitivity up to 70%)
- Maximal wheal after 15-20 minutes
- Positive (histamine) and negative (saline) controls
- Wheal 3mm greater than negative control considered positive
Allergy lost over time

- 5 year prospective study of IgE
- Amoxicillin SPT positive at baseline
  - 12/24 positive at 12/12
  - 6 positive at 36/12 (1 lost to follow up)
  - 0 positive at 60/12 (1 lost to follow up)


- T cell mediated reactions are much less likely to be lost
Intradermal Testing

- 0.02mls giving 5mm induration
- Readings at 24, 48, and 72 hours
- Infiltrated erythema greater than 5mm in diameter considered positive
Negative Skin Tests?

• Historically studies demonstrated a >60% sensitivity with intradermal testing for non-immediate reactions to β-lactams

• However more recently studies dispute this:
  o Padial et al (Pediatrics 2008)
    2/22 intradermal positive
  o Romano et al (Clin Exp Allergy 2007)
    1/105 intradermal or patch positive
Skin Tests (n=50)

- 50 patients lymphocyte transformation test positive to piperacillin

- Intradermal
  - 4 patients have had positive to piperacillin at 48 hours
  - All 4 patients had SI on LTT >50

- Still do them as builds trust and rapport
SKIN TESTING IN-VITRO TESTS

IMMEDIATE (IgE Mediated)
- Specific IgE
- Basophil activation test (CD63)

NON-IMMEDIATE (T-cell mediated)
- LTT
- ELISPOT
Serum specific IgE

- Most available commercial method is the fluorooimmunoassay (FEIA) ImmunoCAP (Thermo-Fisher, Uppsala, Sweden)

- Limited range of drugs available
- Low sensitivity (50% at best with beta-lactams) although better in patients with anaphylaxis
- Some homemade assays perform better.

- Benefits are that it can be performed on stored samples and standardised assay.
Serum specific IgE

- Most available commercial method is the fluoroimmunoassay (FEIA) ImmunoCAP (Thermo-Fisher, Uppsala, Sweden)

- Limited range of drugs available
- Low sensitivity (50% at best with beta-lactams)
- Some homemade assays perform better.

- Benefits are that it can be performed on stored samples and standardised assay.
Basophil activation tests

- Based on flow cytometry and measuring activation markers (CD63 and CD203c)
- For injectable drugs and mimics *in-vivo* response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>22-55%</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>53%</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>92%</td>
</tr>
<tr>
<td>NMBA</td>
<td>64-85%</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>36-71%</td>
</tr>
</tbody>
</table>

- At present no standardised approach and variations between laboratories
Lymphocyte Transformation Test
Concentration range: 0.06-4 mM
No toxicity over that range
Piperacillin-specific lymphocyte responses detected prior to allergy diagnosis

<table>
<thead>
<tr>
<th>Allergic patients</th>
<th>LTT results (acute)</th>
<th>LTT results (retrospective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>Not performed</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>Not performed</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>Not performed</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>Not performed</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

RECRUITMENT SAMPLE

Course 1
ALLERGY DIAGNOSIS

RETROSPECTIVE SAMPLE

<table>
<thead>
<tr>
<th>Piperacillin (mM)</th>
<th>Proliferation (SI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Proliferation rate increases with increasing Piperacillin concentration.

Not performed means that the lymphocyte proliferation test results were not available or performed.
<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
<th>Confirmed diagnosis</th>
<th>Culprit drugs</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PAPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 with range of reactions</td>
<td>102 patients with negative allergy workup</td>
<td>Yes</td>
<td>Mainly penicillin; however, also included sulphamethoxazole, carbamazepine, and phenytoin.</td>
<td>Sensitivity 78%</td>
<td>Specificity 85%</td>
<td>Nyfeler B. Clin Exp Allergy 1997; 27: 175-181.</td>
</tr>
<tr>
<td>19</td>
<td>28</td>
<td>Skin testing and history</td>
<td>Amoxicillin and penicillin G.</td>
<td>Sensitivity 57.9%</td>
<td>Specificity 92.8%</td>
<td>Luque Allergy 2001; 56: 611-618</td>
</tr>
<tr>
<td>12 patients with MPE</td>
<td>6</td>
<td>History alone</td>
<td>Penicillin and amoxicillin</td>
<td>Sensitivity 83%</td>
<td>Specificity 100%</td>
<td>Schnyder Clin Exp Allergy 2000; 30: 590-595</td>
</tr>
<tr>
<td>22 patients mainly with MPR</td>
<td>10</td>
<td>History alone</td>
<td>Antibiotics, anti-convulsants, and anti-hypertensives</td>
<td>Sensitivity 67%</td>
<td>Specificity 90%</td>
<td>Hari Clin Exp Allergy 2001; 31: 1398-1408</td>
</tr>
<tr>
<td>28 patients with mainly MPE</td>
<td>9</td>
<td>Skin testing and history</td>
<td>Piperacillin</td>
<td>Sensitivity 68%</td>
<td>Specificity 100%</td>
<td>Whitaker J Immunol 2011; 187: 200-211</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>History alone</td>
<td>Lamotrigine</td>
<td>Sensitivity 75%</td>
<td>Specificity 100%</td>
<td>Naisbitt JACI 2003; 111 (6): 1393-1403</td>
</tr>
<tr>
<td>95 patients with drug induced liver injury</td>
<td>156</td>
<td>History alone</td>
<td>Wide range of drugs including antibiotics, anti-convulsants, and analgesics.</td>
<td>Sensitivity 26%</td>
<td>Specificity 100%</td>
<td>Maria Gut 1997 41: 534-540</td>
</tr>
</tbody>
</table>
Lymphocyte transformation test

- Well established assay with wide experience, particularly with antibiotics and anti-epileptics

- Sensitivities vary between centres and drugs tested

- Better than skin testing; however, negative results have to be taken with caution

- For most drugs the reactive metabolite is not available

- Limited proliferation with CD8 positive T cells

- No information regarding effector response
  - Can be combined with flow cytometry to assess this
## Sulfamethoxazole metabolites

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>Allergic</th>
<th>Tolerant</th>
<th>Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMX</td>
<td></td>
<td>4/9 (44%)</td>
<td>0/2</td>
<td>0/4</td>
</tr>
<tr>
<td>HA - NO</td>
<td></td>
<td>5/9 (55.5%)</td>
<td>0/2</td>
<td>0/4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Only SMX</th>
<th>Only metabolites</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/6 (17%)</td>
<td>2/6 (33%)</td>
<td>3/6 (50%)</td>
</tr>
</tbody>
</table>
Enzyme-linked immunosorbent spot (ELISpot) assay

Determines the number of cells (even < 25 secreting cells per million) that produce and release target cytokines, such as IFN-γ, IL-5, or IL-13, and cytotoxic markers, such as perforin, granzyme B, and granulysin, after their activation by the incriminated drug.
ELISpot

- Simple assay with shorter incubation times than LTT (2 days vs 6 days) and no radioactive substances
- Allows assessment of the effector response
- Useful in severe reactions where granzyme B and granulysin play important role

- Promising results but more studies needed
- Likely that will be used with two or more cytokines or in combination with other assays.
- **Patient cohort:** Six patients with clinically well-defined flucloxacillin-mediated liver injury
- **Pilot study:**
  - LTT
  - *negative in all patients*
  - IFN-gamma ELIspot
  - *positive in 5/6 patients*
<table>
<thead>
<tr>
<th>Method</th>
<th>Patients</th>
<th>Controls</th>
<th>Confirmed diagnosis</th>
<th>Culprit drugs</th>
<th>Drugs tested</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
<th>PAPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTT and ELISPOT</td>
<td>43 patients with acute reactions (including 7 with DRESS and 8 with SJS/TEN)</td>
<td>14</td>
<td>History and confirmatory histology</td>
<td>Wide range, mainly antibiotics and anti-convulsants</td>
<td>Sensitivity 83% Specificity 95%</td>
<td>Combination of LTT and IFNγ/IL-4 ELISpot.</td>
<td>Polak Br J Derm 2013; 168: 539-549.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow cytometry and ELISA</td>
<td>19 with range of reactions including some SJS/TEN</td>
<td>10</td>
<td>History alone</td>
<td>Mainly antibiotics</td>
<td>Sensitivity of flow cytometry 75% Specificity of ELISA 79% Specificity 100% for both</td>
<td>Intracellular IL-5 and IFN-γ, was investigated with flow cytometry. IL-2, IL-5, and IFN-γ with ELISA.</td>
<td>Martin Allergy 2010; 65: 32-39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD69 upregulation</td>
<td>15 LTT positive patients</td>
<td>5</td>
<td>LTT positive</td>
<td>Range of drugs and reactions</td>
<td>Sensitivity 100% Specificity 100%</td>
<td>Pre-selected population already known to be LTT positive</td>
<td>Beeler, Allergy, 2008; 63; 181-188.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination of Granzyme-B/Granulysin ELISpot and Interferon-γ production.</td>
<td>15 patients with SJS/TEN</td>
<td>18</td>
<td>History alone</td>
<td>Range of drugs including carbamazepine and lamotrigine</td>
<td>Sensitivity 80% Specificity 95%</td>
<td>LTT only positive in 4/15 (27%)</td>
<td>Porebski, Clin Exp Allergy 2013; 43: 1027-1037</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Investigating Hypersensitivity Reactions

1. HISTORY
2. SKIN TESTING
3. IN-VITRO TESTS
4. PROVOCATION TESTS
Drug Provocation Tests

- Skin and *in-vitro* testing remains poor in general

- DPTs are the gold standard, 94-98% who tolerated DPT have no problems with future courses

- Not to be used when investigating severe skin reactions or organ involvement

- Risk of re-sensitisation and patient anxiety
- Time consuming and can be dangerous
- Tolerance during clinical stability can be different to future exposures
Patient 1

- 69 year old female with COPD
- Admitted to hospital with pneumonia
- Given IV amoxicillin and clarithromycin
  - Within 15 mins developed hypotension (70/40mmHg), wheeze, and urticaria
  - Tryptase level not taken
  - Full recovery with adrenaline and steroids
  - Treated with quinolone and labelled as “amoxicillin and clarithromycin allergy”
- Referred as a year later her GP felt treatment options were restricted
• SPT –ve to amoxicillin and clarithromycin
• DPT –ve to amoxicillin and clarithromycin

• Daughter reported that seemed to happen after the “bag of liquid put in”

• Strongly SPT positive to gelofusin

• Diagnosis: Colloid allergy. No restrictions on antibiotics.
Patient 2

- 23 year old lady with Cystic Fibrosis
- FEV1 25%
- Chronic *Pseudomonas* infection
- Previous reaction to ceftazidime.

- Now rash with piperacilltin after 2 days.
- On a previous course slight rash on day 13.
Lymphocytic perivascular dermatitis
• SPT –ve
• ID test –ve at 48 and 72 hours

• LTT +ve to piperacillin (SI 9)

• LTT –ve to meropenem and aztreonam

• Tolerated DPT to meropenem and aztreonam

• Conclusion: T cell mediated reaction to piperacillin but able to receive meropenem and aztreonam safely.
Clones are drug specific

- **Piperacillin clone 1**
- **Meropenem clone 1**
- **Aztreonam clone 1**

**Proliferation (cpm x 10^3)**

- **Concentration (mM)**: 0, 0.1, 1, 2, 5, 10
- **Proliferation (cpm x 10^3)**: 0, 5000, 10000, 15000, 20000, 25000

**Legend**:
- Black: Piperacillin
- Gray: Meropenem
- Dark gray: Aztreonam
Conclusion

- Tests remain suboptimal and DPT gold standard
- Combination testing and better standardised assays will be step forward
- New drug classes, such as biologics, bringing new challenges.