Multiple Drug Hypersensitivity

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UPDATE ON DRUG HYPERSENSITIVITY, Bern, March 23rd 2017
Definition
Multiple drug hypersensitivity (MDH)

MDH is a syndrome that develops as a consequence of massive T cell stimulations (exanthema, DRESS). It is characterized by drug hypersensitivity reactions to novel drugs.
Multiple drug hypersensitivity (MDH)

1. Does it exist?
2. Risk factors
3. Mechanism
4. Avoidance
**MDH: Definition/clinical course/DD**

**Acute T cell mediated drug hypersensitivity** (severe MPE, DRESS):

Cell infiltration into the skin and different organs

(liver>kidney> lung>heart ...);

activated lymphocytes

→ Stop of therapy  -  but some hyperreactivity persists
Clinical course of DHR & flare up reactions

Drug or drug combination

DRESS, severe exanthem, bullous IgA dermatosis, ........

Phase of hyperreactivity: flare up reactions

Weeks/months

activated lymphocytes

ACTIVATION

PASSIVE

ACTIVE

time
Clinical course of DHR & flare up reactions

**Drug or drug combination**

- **DRESS**, severe exanthem, bullous IgA dermatosis, ........

**Activation**

- Hyperreactivity

**Weeks/months**

**Time**

- Reappearance of symptoms (Exanthem, ALAT/AST, eosinophilia)
- Too rapid predisolone reduction
- **Viral** (HHV6, HSV, EBV, CMV..)
- **New drug**

**Activated lymphocytes**
Reappearance of DH symptoms

**Acute T cell mediated drug allergy** (severe MPE, DRESS)

→ Stop of therapy, but some hyperreactivity persists

→ **Reappearance** of symptoms within weeks (**flare up**)

* Second drug can be tolerated later; ST and LTT negative
Clinical course of MDH

1st drug or drug combination

DRESS, severe exanthenm, bullous IgA dermatosis, ........

2nd drug or drug combination

Exanthenm, DRESS, erythrodermia, agranulocytosis, fulminant hepatitis, necrotizing carditis, SJS/TEN.....

SJS/TEN are NOT risk diseases for MDH
Causes of MDH (1st & 2nd/3rd drug)

**First drug (n=31)**

5x: Amoxicillin

3x: Sulfasalazine (sulfapyridine/5-aminosalicylic acid), sulfamethoxazole/trimethoprim, phenytoin, carbamazepine, rifampicin, amoxicillin/clavulanic acid

2x: Lidocaine

1x: Vancomycin, allopurinol, escitalopram, metronidazole, ceftriaxone, cefepime, cefuroxime, piperacillin/tazobactam, isoniazid

**Follow up drugs (2-3rd DHR)**

2x Amoxicillin, sulfamethoxazole/trimethoprim, budesonide

1x phenytoin, lamotrigine, carbamazepine, triamzolam, amitriptyline, pantoprazole, rifampicin, clindamycin, metronidazole, sulfamethoxazole, ceftobiprole, ceftriaxone, ertapenem, penicillinG, piperacillin/tazobactam, vancomycin, levofloxacin, ciprofloxacin, zonisamid
Forms of MDH (n=31)

- **Sequential**
  - 2-8 weeks
  - N=11

- **Distant**
  - N=10
  - Each 1/3

- **Simultaneous (combination therapy)**
  - Activation/lymphoblasts
  - N=10
Risk factors for MDH

1. **Type of drug**: MDH often starts with a DRESS, which is a p-i stimulation. Drugs involved in DRESS are also involved in 1\textsuperscript{st} and later appearances of MDH: E.g. anti-epileptic medications, sulfonamide antibiotics, allopurinol, etc.

2. **High drug concentration and longer lasting therapy**: high daily drug doses; longer lasting treatment e.g. Joint infections, epilepsy,…

3. **Combination therapy**: DHR to both components of a fixed combination therapy like amoxicillin/clavulanic acid, cotrimoxazole (sulfamethoxazole/trimethoprim), sulfasalazine (sulfapyridine and 5-aminosalicylic acid), piperacillin/tazobactam; antituberculous therapy (INH, rifampicin, pyrazinamide, …)
Risk factors for MDH

1. **Type of drug**: drugs involved in DRESS are also involved in MDH. E.g. Anti-epileptic medications, sulfonamide antibiotics and allopurinol

2. **High drug concentration and longer lasting therapy**: high daily doses, often exceeding 1g/day.

3. **Combination therapy**: DHR to both components of a fixed combination therapy like
cotrimoxazole (sulfamethoxazole/trimethoprim ),
sulfasalazine (sulfapyridine and 5-aminosalicylic acid),
amoxicillin/clavulanic acid,
piperacillin/tazobactam;
antituberculous therapy (INH, rifampicin, pyrazinamide, ...)

Role of dose in DHR

What is the normal daily dose of a drug?

• 5-10mg
• 20-100mg
• 100-1000mg
• > 1000mg

Antihistamines: 5-180mg
Statin: 20-80mg
ACE inhibitors: 10-40mg
PGSH: 50mg->1600mg
High drug doses used in MDH-related combination therapy

**Combination therapy: often very high drug doses (grams!)**

*Cotrimoxazole*: sulfamethoxazole (800mg)/trimethoprim (160mg) – twice a day: 1.920mg/d

*Sulfasalazine*: 500mg sulfapyridine/5-aminosalicylic acid at 1.1 ratio – 2-4 times a day >2.000mg/d

*Amoxicillin/clavulanic acid*: amoxicillin (500mg) and clavulanic acid (125mg) – 2-3 times a day 1.875mg/d

*Piperacillin/tazobactam*: piperacillin [3g] and tazobactam [375mg] – 4 times a day 13.500mg/d

**Anti-tuberculous therapy: combination therapy of single drugs**

isoniazid (300mg), rifampicin (300mg), pyrazinamide (1500mg), and ethambutol (1,2g) or streptomycin (1g), once daily 4.300mg/d

All >>1g/d
Combination therapy as cause of MDH (1st & 2nd/3rd drug)

**First drug (n=31)**

5x: Amoxicillin

3x: Sulfasalazine (sulfapyridine/5-aminosalicylic acid), cotrimoxazole (sulfamethoxazole/trimethoprim), amoxicillin/clavulanic acid, phenytoin, carbamazepine, rifampicin

2x: Lidocaine

1x: Vancomycin, allopurinol, escitalopram, metronidazole, ceftriaxone, cefepime, cefuroxime, piperacillin/tazobactam, isoniazid

**Follow up drugs (2-3rd DHR)**

2x Amoxicillin, sulfamethoxazole/trimethoprim, budesonide

1x phenytoin, lamotrigine, carbamazepine, triamzolam, amitriptyline, pantoprazole, rifampicin, clindamycin, metronidazole, sulfamethoxazole, ceftobiprole, ceftriaxone, ertapenem, penicillinG, piperacillin/tazobactam, vancomycin, levofloxacin, ciprofloxacin, zonisamid
LTT results of combination therapy suggest a rather high double reactivity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>+ LTT/ (%)</th>
<th>+ LTT/ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 145</td>
<td>87 (63%)</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>co-trimoxazole (SMX/TRIM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 48</td>
<td>22 (46%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 25</td>
<td>7 (28%)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Salasalazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=10</td>
<td>6 (60%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>N= 228</td>
<td>122 (28-63%)</td>
<td>28 (0-32%)</td>
</tr>
</tbody>
</table>
LTT results of combination therapy suggest a rather high double reactivity

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>+ LTT/+%</th>
<th>+ LTT/+%</th>
<th>+ LTT/+%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/amoxicillin</td>
<td>87 (63%)</td>
<td>15 (11%)</td>
<td>43 (31%)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 145</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole (SMX/TRIM)</td>
<td>22 (46%)</td>
<td>21 (44%)</td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole sulfamethoxazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin/piperacillin &amp; tazobactam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>8 (32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salasalazine/Sulfapyridine</td>
<td>6 (60%)</td>
<td>0 (0%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Salasalazine/Sulfapyridine &amp; 5-ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n= 10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N= 228 122 (28-63%) 28 (0-32%) 78 (31-44%)

The reaction to one drug of the combination therapy facilitates the reactivity to the second drug.
Multiple drug hypersensitivity

*Does it exist?*

1. **Clinical course:** exazerbations of DHR-symptoms or appearance of new DHR after new drug

2. **Skin tests and LTT** to 2 or more drugs?

3. **cross-reactivity**?
Epicutaneous skin tests: positive to distinct drugs in T cell assay

Clinic:

1. DRESS after phenytoin;

Three months later:

2. Severe MPE and erythrodermia after amoxicillin

Reactive (48hr) to phenytoin and amoxicillin
A patient with DRESS and «multiple drug hypersensitivity» (4-8 weeks) was evaluated for a positive LTT to different drugs.

### Table: LTT Results

<table>
<thead>
<tr>
<th>Drugs</th>
<th>microg</th>
<th>Autol. Plasma SI</th>
<th>AB-Serum SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin RS</td>
<td>1</td>
<td>16.2</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>55.1</td>
<td>81.7</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>93.3</td>
<td>72.9</td>
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<tr>
<td></td>
<td>100</td>
<td>63.5</td>
<td>63.8</td>
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<tr>
<td>Lamotrigine RS</td>
<td>0.1</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.6</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>2.9</td>
<td>19.6</td>
</tr>
<tr>
<td>Pantoprazol RS</td>
<td>0.1</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2.0</td>
<td>1.0</td>
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<tr>
<td></td>
<td>10</td>
<td>1.1</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Ceftriaxon RS</td>
<td>1</td>
<td>3.3</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>78.3</td>
<td>36.8</td>
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<tr>
<td></td>
<td>100</td>
<td>82.1</td>
<td>32.3</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>67.7</td>
<td>35.8</td>
</tr>
<tr>
<td>Flucloxacillin RS</td>
<td>10</td>
<td>2.0</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>8.4</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>18.9</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>53.5</td>
<td>34.2</td>
</tr>
<tr>
<td>Vancomycin RS</td>
<td>1</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>2.0</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Xenetix RS</td>
<td>0.1</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Tetanus.pos. cptrol</td>
<td>1</td>
<td>63.6</td>
<td>93.0</td>
</tr>
<tr>
<td>Negative control (cpm)</td>
<td>-</td>
<td>450</td>
<td>607</td>
</tr>
</tbody>
</table>

**SI = \( \frac{cpm\ with\ drug}{cpm\ without\ drug\ (control)} \)**

Positive SI > 2 (3)
MDH is not due to cross-reactivity

Data: Dr. Dean Naisbitt, University of Liverpool, GB

**Patient with epilepsy and DRESS:** Each T cell clone was reactive to only one drug! MDH is due to multiple sensitizations….
Pathomechanism

1. The initial reaction is T cell mediated
   - Skin tests and LTT are frequently positive
   - No cross-reactivity of drug specific T cell clones

2. T cell stimulation occurs via p-i, which can can result in allo-like stimulations (gvhd)

3. The T cell stimulation persists in spite of stopping the drug!
   - strong activation for weeks: CD71, CD38, HLA-DR↑
   - smoldering activation for years: CD4^+CD25^{dim}, CD38^+ & PD-1^+

like in chronic virus infections or chronic graft versus host disease
Pathomechanism

In MDH, the activation of T cells becomes permanent, like in a chronic virus infection or chronic gvh disease.

In “normal” DH, no permanent activation measurable.

CD71, CD38, HLA-DR↑

CD4+CD25+dim, CD38+, PD-1+

MDH

An acute DHR becomes a chronic condition/disease?

What keeps the T cell stimulated?

Daubner B et al, Allergy 2012 Jan;67(1):58-66
1) A drug binds to the HLA itself: This changes the HLA-peptide configuration (e.g. HLA-B*57:01 plus abacavir → ~B*58:01).

2) The \{drug-HLA\} complex elicits a massive, polyclonal T cell stimulation like in an acute gvh. Such reactions go along with

3) breaking of tolerance and consequently autoimmunity/autoinflammation.

**Drug hypersensitivity: a gvh like immune reaction!**
MDH pathomechanism

Massive activation +
  T cells +
  p-i +
  Allo-immune model of DH +
  Phenotype of chronic gvhd

MDH: possibly related to an auto-reactivity after drug-induced «allo»-reactivity: break of self tolerance after allo; similar to chronic gvhd
Possible measures to avoid flare up reactions and further DHR and MDH

- **Avoid** severe T cell reactions (DRESS, ...)
- **restrict the use of drugs** in patients with ongoing severe DHR (mainly DRESS) as much as possible; do not start therapy in an ongoing eosinophilia....
- if new drugs are essential, choose drugs which can be given at **lower dose** (<50mg/d) and are **not** DRESS elicitors
- **Replace antipyretics** by physical measures (e.g. wet compresses instead of acetaminophen)
- **Use antibiotics only for therapy, not for prophylaxis**; monitor closely!
Possible measures to avoid flare up reactions and further DHR*

- **Suppress the immune stimulation**
  by corticosteroid therapy (oral or i.v. prednisolone is normally tolerated). For example, 0.3 - 1 mg/kg per day of prednisolone equivalent for >2 - >>7days, followed by a stepwise reduction.

- **Monitor eosinophilia and lymphocyte activation**, *****

- **create a therapy free interval** for days to weeks.

* Based on clinical experience, and the risk factors described in the text;  e.g. patients with DRESS

** fatal cases show that eosinophilia might persists in spite of high steroid therapy

***The standard values of lymphoblasts differ from lab to lab. A substantial decrease should be noted.
26yr, f, acne

1 DRESS with lymphadenopathy, exanthema, DILI

20.9. → 18.10. 26.10  10.11.

2 eosinophilic pneumonia

(Partial?) remission, Eo:0,34
No skin symptoms

26.10  10.11. 1.12.

CRP 130mg/ml
Eosinophil 0,54G

The new symptoms were suspected to be due bacterial pneumonia.

Cave: No tests made; interpretation!

3 necrotizing eosino. myocarditis

16.12./17.12. + 2.1.

Mino
cyclin

Prednisolon

Piperacillin/Tazobactam 13.5g
Levofloxacin 1g/d

50mg/d

50mg/d

Pred

Heart transpl

Levo
Multiple drug hypersensitivity

*It exists*

- *It is rare*
  - \( \approx 0.6\% \) of sensitized
  - Ca. 10\% of DRESS

Is a drug induced *disease*, similar to chronic GVHD

Is *iatrogenic* and potentially *fatal*, with definable risk factors (drugs, dose, duration..)

Many questions are still open.....
Some recommendations «make sense», but need to be validated
Thank you very much

http://www.adr-ac.ch/de/10-jahre-adr-ac/handouts/