Drug Allergy in the XXI Century
New Challenges and Outcomes
for Drug Desensitizations

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Disclosures

Schering Plough Consultant
Genentech: PI Xolair study
Merck Consultant: ADR Board
Complex Allergies XXI Century

- **Cancer patients** survive longer and are exposed to multiple chemotherapy treatments
- Patients with **chronic inflammatory diseases** (RA, IBD, Psoriasis) are repeatedly exposed to new monoclonal Abs and other biological agents
- **Cystic Fibrosis** patients live longer, have lung transplants
- Asthma patients sensitive to aspirin **Aspirin Exacerbated Respiratory Disease**
- **Pregesterone/estrogen** hypersensitivity (Progesterone Autoimmune Dermatitis)

**How to overcome IgE and non-IgE mediated hypersensitivity reactions?**

- **Avoidance:** life expectancy, quality of life
- **Substituting:** expensive, complications (antibiotic resistance)

**Desensitization:**
- no substitute
- life-threatening
- less efficacy
History of Desensitizations

O’Donovan WJ and Klorfajn I, JAMA 1946

30 yo soldier with severe skin infection after a wound, received **topical Penicillin** and developed a rash with lip and periorbital angioedema, a drop of PCN through skin puncture was positive and 15 min after 15 000 U of Penicillin IM he developed **hypotension** and wheezing.

**Questions:**

Whether a **penicillin-sensitive patient in immediate need** of treatment, having presented with **anaphylactic shock to a full dose**, can be **even temporarily** desensitized with administration of **small and increasing doses** of Penicillin at **short intervals**, so that **full therapeutic doses** can be started without delay. Whether a patient can be desensitized by **continuous administration of small doses** of Penicillin for a **longer period**.

30 patients with PCN allergy (ST positive) and life threatening infections, were desensitized using oral PCN q 15 min (5h). No deaths or anaphylaxis, ST negative.

**Sullivan TJ, 1982**

Penicillin desensitization of **15 pregnant women (ST positive ) with syphilis** using increasing doses of oral penicillin V over 3h45min

**Wendel GD, NEJM 1985**

12 patients ST positive to PCN- life threatening infections desensitized using **infusion of 10-fold increasing solutions of PCN** (0.0005 mg/ml to 500mg/ml) at 20 min intervals

**Borish L, 1987**
First Desensitization to carboplatin in Austria 2014

On Oct 18, 2013, at 4:11 PM, "M A" wrote:

Dear Mrs. Castells,

My mum (57 years of age) suffers from cervical cancer and just yesterday her second course of Paclitaxel+Carboplatin started after a break from the first course. In the first course she tolerated the therapy remarkably well, and it was also very efficient. Unfortunately, she suffered from hypersensitivity (flushing, tachycardia, pruritus on her scalp: 8th lifetime exposure) only a few minutes into her carboplatin infusion, and the treatment was immediately stopped. Her doctor said that he now wants to give only Paclitaxel and omit the Carboplatin, but I stumbled upon a paper (Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations) where you are suggesting desensitization. I understand you are probably very busy, and not familiar with all the details of my mum's case, but I hoped you could tell me if you would generally recommend doing a desensitization, if you practice desensitization in your hospital, if you have any experience to share that goes beyond the paper, and if you think there should be anything that needs to be pointed out specifically (such as risks).

I would be very grateful for your answer.

Yours sincerely,

M A

• On February 18 at 3:45PM “M A” wrote
• Dear Mrs. Castells,
• I wanted to let you know that we successfully applied your desensitization protocol with my mum. Since it apparently was the first time that such a desensitization was performed in Austria, the team was a little bit nervous in the beginning, and as a result some cortisol was also given.
• Anyway, we ironed out all those little "mistakes and it went smooth as silk.
• Also, the latest MRI results show that the tumor continued to respond remarkably well to the treatment, a reward that left everyone being even more excited about having successfully applied the protocol for the first time in this country.
• Right now, there's another chemo break, and then I guess we will start another cycle with desensitization.
• I wanted to tell you that everything went well, that the treatment still works, and that your research thus made a very big difference in my Mum's case. Thank you!!!
• Best Regards, M A
• PS.: You might have to be imaginative when it comes to me using medical vocabulary... I'm a technician, and for some of the medical terms I was basically guessing :-)

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Desensitization Type I

Desensitization Type IV

Rapidly (hours to days) inducing a state of temporary tolerance/tolerization to a drug to which a patient had presented a hypersensitivity reaction

AAAAI Drug Hypersensitivity Practice Parameters 2010
ENDA Desensitization Position Paper 2012
No desensitization for SJS/TEN/DRESS/AGEP!!!!!!

Carbamazepine induced Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)  HLA genotyping
Questions

• **How safe are desensitization protocols?**
  
  Mechanisms
  
  In vivo Evidence

• **How effective** are desensitization protocols at treating infections, providing increased quality of life or improving survival?

• Are desensitizations **burdening** the costs of patient’s care?
Proposed Mechanisms for Antigen/IgE desensitizations

- Monomeric/Low antigen dose decrease cross-linking
- Inhibitory receptors
- Sub clinical mediators release
- Internalization of antigen/IgE/FceRIα
- Syk degradation
In Vitro Mast Cell Model Antigen/IgE desensitization

Desensitization to DNP-HSA

Rapid desensitization blocks the release of pre-formed mediators and calcium influx in a specific fashion

Sancho Serra et al 2011
Internalization may be impaired during rapid antigen desensitizations
Sancho Serra et al 2011

In vivo mouse model of DNP desensitization
Oka et al 2013

Syk is not decreased during desensitization
Zhao et al 2012
Principles of IgE Desensitization

1. Occurs at the membrane level
2. Starting dose, the time between the doses, the increments (X2) are critical to support the inhibitory state
3. It is specific
4. Can be maintained

Lee et al 2004
Current Understanding

- **High risk procedure**: requires the introduction of a potentially lethal medication to a highly sensitized patient.
- **Performed in critically ill patients**: survival depends on administration of a medication to which a patient has a previous history of a severe adverse reaction.
- **No alternative medications** are available or the alternatives (second and third line choices) have less demonstrated therapeutic value than first line treatment.
- It is a **temporary** phenomenon.
- **Antigen specific**, not IgE depleting, not hapten inhibition nor depletion of mast cell mediators.
- It is done by **repetitive increasing sub-optimal doses (suboptimal concentrations)** of the medication involved in the adverse reaction.
- Once desensitization is complete, the tolerization can be **maintained** by continuous administration of the medication.
Candidates for desensitization

- **IgE:** require repeated exposures
  - platins, antibiotics, iron, monoclonals

- **Non-IgE:** can occur upon first exposure
  - Taxenes
  - Monoclonals: Rituximab
  - Aspirin

**Type IV**
Hypersensitivity Reaction to Carboplatin

Anaphylactic IgE

- 49 year old female with ovarian cancer, treated with paclitaxel and carboplatin x 6 cycles (flushed, itchy last cycle)
- Recurrence 2 years later, restarted on paclitaxel and carboplatin
- 2nd infusion (8 exposure: 3-4g): flushed, itchy
- 3th infusion (9 exposure >4g): cramping, abdominal pain, flushing/pruritus, diffuse urticarial rash, SOB, hypotension, code
- Tryptase: 42ng/ml
  Skin test to carboplatin: positive 1 mg/ml

- Patients receiving >7 cycles of carboplatin have 27% of HSR, and 50% of those patients develop moderate to severe symptoms (anaphylaxis).

- BRCA mutation carriers have 10 fold increase in hypersensitivity (Moon 2013)

- Increased pre-medication (steroids) and re-infusion does not prevent HSR reactions.

- Cross-reactivity among platins is high.
Clinical Symptoms amendable to Rapid Desensitization
Type I hypersensitivity IgE/non IgE

- Cutaneous
- Cardiovascular
- Respiratory
- Throat Tightness
- Gastrointestinal
- Neurological/Muscular

Pain

- Carboplatin
- Paclitaxel
- Doxorubicin/Adriamycin
- Rituximab

Percentage of Patients (%)
Risk Stratification

**Low Risk (Out patient)**
- Mild reaction
- Grade 1–2 (skin +/- other organ)

**High Risk (MICU)**
- Pulmonary Disease (FEV1 < 1L)
- Cardiac Disease w/wo beta blockade
- Severe reaction: Grade 3
  intubation/hypotension/O2desaturation/
laryngeal edema/seizures/collapse

3 bags 12 steps
4 bags 16 steps
# Skin Testing

## SKIN TEST ORDER

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug Name</th>
<th>Concentration</th>
<th>SPT</th>
<th>ID</th>
<th>ID</th>
<th>ID</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>Avastin*</td>
<td>25mg/ml</td>
<td></td>
<td>0.25mg/ml</td>
<td>2.5mg/ml</td>
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<tr>
<td></td>
<td>Carboplatin</td>
<td>10mg/ml</td>
<td></td>
<td>1mg/ml</td>
<td>10mg/ml</td>
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<tr>
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<td>Cisplatin</td>
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<td>0.1mg/ml</td>
<td>1mg/ml</td>
<td></td>
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<td>Cytoxan</td>
<td>10mg/ml</td>
<td></td>
<td>1mg/ml</td>
<td>10mg/ml</td>
<td></td>
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<tr>
<td></td>
<td>Oxaliplatin*</td>
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<td>0.5mg/ml</td>
<td>5mg/ml</td>
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<tr>
<td></td>
<td>Taxol*</td>
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<td>0.001mg/ml</td>
<td>0.01mg/ml</td>
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<tr>
<td>Biologics</td>
<td>Abatacept*</td>
<td>25 mg/ml</td>
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<td>0.025 mg/ml</td>
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<td>Etanecpt</td>
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<td>0.05 mg/ml</td>
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<td></td>
<td>Infliximab*</td>
<td>10 mg/ml</td>
<td></td>
<td>0.1 mg/ml</td>
<td>1 mg/ml</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>25 mg/ml</td>
<td></td>
<td>0.25 mg/ml</td>
<td>2.5 mg/ml</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Rebif</td>
<td>22mcg/ml</td>
<td></td>
<td>0.022mcg/ml</td>
<td>0.22 mcg/ml</td>
<td>2.2 mcg/ml</td>
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<tr>
<td></td>
<td>Rituximab*</td>
<td>10 mg/ml</td>
<td></td>
<td>0.01 mg/ml</td>
<td>0.1 mg/ml</td>
<td>1 mg/ml</td>
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<tr>
<td></td>
<td>Trastuzumab*</td>
<td>21 mg/ml</td>
<td></td>
<td>0.21 mg/ml</td>
<td>2.1 mg/ml</td>
<td>--</td>
</tr>
</tbody>
</table>

### Iron
- Ferrlecit*: SP: 12.5 mg/ml; ID: 0.0125 mg/ml, 0.125 mg/ml, 1.25 mg/ml
- (DO NOT TEST TO VENOFER)

### Antibiotics
- Hesterberg 2009
- Patil 2012
- Dioun 2013
In Vitro Platins Specific IgE

Caiado et al. 2013

<table>
<thead>
<tr>
<th>TABLE V. Results of carboplatin, oxaliplatin, and cisplatin sIgE: patients sensitive to carboplatin and oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crb-sensitive group</td>
</tr>
<tr>
<td>Grade of the initial reaction</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Patient no. 1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
</tr>
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</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

Note. Bold values represent positive results.
Cis, Cisplatin; Crb, carboplatin; ID, intradermal; ND, not done; Ox, oxaliplatin; sIgE, specific IgE; SPT, skin prick test.

Patients sensitized to oxaliplatin develop IgE against carboplatin and cisplatin.
Basophil Activation Test

CD 63

CD 203c

Negative Control

Carboplatin

Giavina-Bianchi P and Castells M 2014
Desensitization Protocols BWH

4-bag 16-step protocol (6.7h)

3-bag 12-step protocol (5.7h)

1/1000 1/100 1/10 Full dose

Rate (ml/h)

1

2

3

4

2.5 x 15min 2.5 x 15min 5 x 15min 5 x 15min

5 x 15min 5 x 15min 10 x 15min 10 x 15min

10 x 15min 10 x 15min 20 x 15min 20 x 15min

20 x 15min 20 x 15min 40 x 15min 40 x 15min

Rate (ml/h)

10 x 15min 10 x 15min 20 x 15min 20 x 15min

20 x 15min 20 x 15min 40 x 15min 40 x 15min

40 x 15min 80 x 2.9h

Picture from: http://www.safeinfusiontherapy.com
## Medication for Desensitization: Methotrexate

<table>
<thead>
<tr>
<th>Target Dose (mg)</th>
<th>Standard volume per bag (ml)</th>
<th>Final rate of infusion (ml/hr)</th>
<th>Total mg of Methotrexate per 250 mL bag of D5W</th>
<th>Amount of bag infused (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full Therapeutic Dose (FTD) * Methotrexate 16.8 gram</td>
<td>iv</td>
</tr>
<tr>
<td>Solution 1</td>
<td>250 ml of D5W</td>
<td>0.034 mg/ml</td>
<td>16800.0</td>
<td></td>
</tr>
<tr>
<td>Solution 2</td>
<td>250 ml of D5W</td>
<td>0.672 mg/ml</td>
<td>168.000</td>
<td>9.38</td>
</tr>
<tr>
<td>Solution 3</td>
<td>250 ml of D5W</td>
<td>6.720 mg/ml</td>
<td>1680.000</td>
<td>18.75</td>
</tr>
<tr>
<td>Solution 4</td>
<td>250 ml of D5W</td>
<td>66.670 mg/ml</td>
<td>16667.385</td>
<td>250.00</td>
</tr>
</tbody>
</table>

*** PLEASE NOTE ***

The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are not completely infused.

<table>
<thead>
<tr>
<th>Step</th>
<th>Solution</th>
<th>Rate (ml/hr)</th>
<th>Time (min)</th>
<th>Volume infused per step (ml)</th>
<th>Dose administered with this step (mg)</th>
<th>Cumulative dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2.5</td>
<td>15</td>
<td>0.625</td>
<td>0.021</td>
<td>0.021</td>
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<tr>
<td>2</td>
<td>1</td>
<td>5</td>
<td>15</td>
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<td>0.042</td>
<td>0.063</td>
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<td>15</td>
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<td>0.084</td>
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<td>4</td>
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<td>20</td>
<td>15</td>
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<td>0.315</td>
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<td>2</td>
<td>2.5</td>
<td>15</td>
<td>0.625</td>
<td>0.420</td>
<td>0.735</td>
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<td>15</td>
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<td>3.255</td>
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<td>8</td>
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<td>20</td>
<td>15</td>
<td>5</td>
<td>3.360</td>
<td>6.615</td>
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<td>9</td>
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<td>5</td>
<td>15</td>
<td>1.25</td>
<td>8.400</td>
<td>15.015</td>
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<td>16.800</td>
<td>31.815</td>
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<td>11</td>
<td>3</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>33.600</td>
<td>65.415</td>
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<tr>
<td>12</td>
<td>3</td>
<td>40</td>
<td>15</td>
<td>10</td>
<td>67.200</td>
<td>132.615</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>10</td>
<td>15</td>
<td>2.5</td>
<td>166.674</td>
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<tr>
<td>14</td>
<td>4</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>333.348</td>
<td>632.637</td>
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<tr>
<td>15</td>
<td>4</td>
<td>40</td>
<td>15</td>
<td>10</td>
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<td>1299.332</td>
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<td>16</td>
<td>4</td>
<td>80</td>
<td>232.5</td>
<td>232.5</td>
<td>15500.668</td>
<td>16800.00</td>
</tr>
</tbody>
</table>

Total time (minutes) = \(45/0.5 = 90 \text{ mins}\)

RESUSCITATION: Verify availability of resuscitation cart and have the following medications at the bedside:

- Epinephrine (1:1000) 0.01mL/kg x 93 kg = 0.5 mL (max 0.5 mL/dose) IM x1
- Diphenhydramine 1 mg/kg x 93 kg = 50 mg (max 50 mg/dose) IV x1
- Methylprednisolone 2 mg/kg x 93 kg = 60 mg (max 60 mg/dose) IV x1
- Normal Saline Bolus 20 mL/kg x 93 kg = 1000 mL (max 1000 mL) IV x1
# Desensitization Protocols

## Table 2. Desensitization Protocol for Carboplatin

<table>
<thead>
<tr>
<th>Volume, mL</th>
<th>Infusion Time, min</th>
<th>Time Accumulated</th>
<th>Dose Administered, mg</th>
<th>Cumulative Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution A, 1/10000</td>
<td>50</td>
<td>15</td>
<td>15</td>
<td>0.03</td>
</tr>
<tr>
<td>Solution B, 1/1000</td>
<td>50</td>
<td>15</td>
<td>30</td>
<td>0.30</td>
</tr>
<tr>
<td>Solution C, 1/100</td>
<td>50</td>
<td>15</td>
<td>45</td>
<td>3.00</td>
</tr>
<tr>
<td>Solution D, 1/10</td>
<td>50</td>
<td>15</td>
<td>60</td>
<td>30.00</td>
</tr>
<tr>
<td>Solution E, 1/1</td>
<td>280</td>
<td>60</td>
<td>120</td>
<td>266.67</td>
</tr>
</tbody>
</table>

Gasteminza 2011
11 women mild to moderate HSR

## Table 2. Ramon y Cajal University Hospital rapid desensitization protocol for a total dose of 200 mg of oxaliplatin (diluted in 250 ml of 5% glucose) originally meant to be infused in 2 h at a 125 ml/h rate

<table>
<thead>
<tr>
<th>Total dose</th>
<th>200 mg</th>
<th>Solution concentration</th>
<th>Total dose in each solution (mg)</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution A</td>
<td>250 ml</td>
<td>0.016 mg/ml</td>
<td>4.0</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Solution B</td>
<td>250 ml</td>
<td>0.160 mg/ml</td>
<td>40.0</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Solution C</td>
<td>250 ml</td>
<td>0.677 mg/ml</td>
<td>169.2</td>
<td>Oxaliplatin</td>
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</table>

<table>
<thead>
<tr>
<th>Step</th>
<th>Solution</th>
<th>Rate (ml/h)</th>
<th>Administered volume (ml)</th>
<th>Time (min)</th>
<th>Administered dose (mg)</th>
<th>Cumulative dose infused (mg)</th>
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<tr>
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<td>7</td>
<td>B</td>
<td>200</td>
<td>50</td>
<td>15</td>
<td>4.0</td>
<td>6.8</td>
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<td>400</td>
<td>100</td>
<td>15</td>
<td>8.0</td>
<td>14.8</td>
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<td>9</td>
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<td>88</td>
<td>22</td>
<td>15</td>
<td>16.0</td>
<td>30.0</td>
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<tr>
<td>10</td>
<td>C</td>
<td>125</td>
<td>250</td>
<td>120</td>
<td>200.0</td>
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</tbody>
</table>

Madrigal-Burgaleta 2013,
189 IV desensitization 23 patients
Premedications for desensitization

Chemotherapy Premedications

- Opiods
- Muscle Relaxants
- Anti-emetics
- Bronchodilators
- Steroids
- NSAIDS
- 5LO and Leukotriene R2 blockers
- H2 anti-histamine
- H1 anti-histamine

Monoclonals Premedications

- Opiods
- Muscle Relaxants
- Anti-emetics
- Bronchodilators
- Steroids
- NSAIDS
- 5LO and Leukotriene R2 blockers
- H2 anti-histamine
- H1 anti-histamine

Breslow et al 2013
Castells et al submitted 2014
Safety of Rapid Desensitizations 413 cases

94 % of cases with mild or no reactions

No Deaths

Mild Reaction: 27%
(111/413)

Severe Reaction: 6%
(24/413)
2 epinephrines

No Reaction: 67%
(278/413)

2177 cases submitted 2014
96 % mild, 4% severe, no deaths

Castells et al. JACI 2008
Adverse Reaction to Paclitaxel:

• 54 year old female with ovarian cancer.
• Within few minutes of Paclitaxel first infusion she presented flushing, given more pre-medications and continued the infusion.
• Within few minutes of second infusion she presented severe flushing, SOB with decreased O2 saturation, nausea, hypotension and severe lower abdomen and back pain.
• Re-infusion with a slower rate and increasing steroid pre-medications did not help.
• Switching to Docetaxel (without cremophor) induced the same reaction.
Taxenes Hypersensitivity
Piccard M and Castells M 2014

Pain

Taxane moiety
- Paclitaxel
- Docetaxel
- Cabazitaxel

Solvent
- Cremophor EL
- Polysorbate 80

IgG

IgE

C3a
C5a

Direct action

Mast cell/Basophil

Mediators
- LTC4
- PGD2
- Histamine
- Tryptase
Taxene Hypersensitivity Reactions

**Immediate-type**

**Delayed-type**

**Severe (e.g., SJS/TEN, pneumonitis)**

**Avoidance**

**Non-severe (e.g., non-blistering, non-desquamative skin eruption)**

**Skin testing**

**Negative**

**Mild or delayed-type**

**Challenge**

**Reaction**

**No reaction**

**Regular infusion**

**Moderate**

Depending on physician and patient comfort and severity of grade 2 reaction

**Severe**

**Desensitization**

**Positive**

Piccard M and Castells M 2014
Adverse Reaction to Rituximab
Anaphylactic : IgE / non-IgE

• 38 yo male with non-Hodgkin lymphoma

• 1st infusion of rituximab : 15 min

• Severe itching, nausea, dizziness, SOB, hypotension, collapse

• Skin test : negative
Monoclonals Evaluation for Desensitization

Methods:
One hundred five rapid desensitizations were performed in 23 patients with a standardized 12-step, 6-hour protocol. Our approach to patient evaluation before desensitization is described. The severity, characteristics, and timing of both initial HSRs and HSRs during desensitization were determined by means of retrospective review of medical records. After a reaction during desensitization, patient-specific protocol modifications were made before each subsequent desensitization.
Step at which reactions occur during monoclonal AB desensitization

Severities of the reactions during desensitizations over multiple desensitizations

Progesterone/Estrogen Hypersensitivity

• 32 yo fashion writer who had used plan B X2 (0.75mg of levonorgestrel) starts presenting severe facial and anterior chest rash, pruritic, starting 1 week before menstrual period and lasting 7-10 days

• Reactions increased in severity during the next 12 months and included SOB, wheezing and hypotension

• After multiple ER visits and severe facial disfiguring, the patient is fired from her job and started on steroids, lupron and develops osteopenia and osteoporosis
Autoimmune progesterone dermatitis Clinical presentation and management with progesterone desensitization for successful in vitro fertilization  Prieto-Garcia et al 2011
Recognition of hypersensitivity to estrogens and progesterone: catamenial anaphylaxis to infertility
Mechanisms of sensitization (IVF, plan B) and reactions (IgE to type IV) are not completely understood
Diagnosis: skin testing (reagents and interpretation difficult)
Desensitization protocols have induced reversal of infertility and decreased symptoms
### Aspirin Exacerbated Respiratory Disease

**What is it?**

- Classic triad:
  - Asthma
  - Nasal polyps
  - Aspirin-sensitivity

**What is it not?**

- Not IgE-mediated allergy to aspirin
- Not Mendelian inheritance
- Not childhood disease
Aspirin Desensitization

Simon and Stevenson JACI 2003
Macy et al Practice Paper Annals 2007

• No skin test or blood test
• Oral challenges/Inhalation challenges : Lysine-ASA
• Universal cross-reactivity with all non-specific NSAIDS but not with COX-2 specific inhibitors
  - starting dose 3-40 mg, doubling every 90 min to 3 hours
  - threshold: once crossed the patient is desensitized
  - Montelukast shift the reaction to the upper airway only, Zileuton can block the provoking dose
  - Some patients cannot be desensitized and present non urticarial skin lesions and severe GI symptoms

Cahill and Laidlaw 2014
Cysteinyi leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes

Tanya M. Laclaw, Molly S. Kidset, Neil Bhattacharyya, Wei Xing, Shiliang Shen, Ginger L. Milne, Mariana C. Castells, Heng Chhay and Joshua A. Boyce
Cefepime Desensitization in Cystic Fibrosis

FEV1 0.5L (40%)

Legere et al 2009

Volumes of desensitization bags need to match the volume of the non-desensitized antibiotic
Tolerance after multiple desensitizations?
Drug with Successful Desensitization Protocols
intravenous, oral, subcutaneous, intraperitoneal

• Platins: carboplatin, cisplatin, oxaliplatin
• Taxenes: paclitaxel, docetaxel, Abraxene
• Monoclonals:
  • Rituximab, Trastuzumab, Cituximab, Tocilizumab
  • TNFa: ertanercept, adalimumab, infliximab
  • Bevacizumab,
  • Ofatumumab,
  • Alemtuzumab
• Antibiotics: beta lactams including cephalosporins, sulfonamides,
  • vancomycin
• Enzymes: laronidase
• Iron: sodium ferric gluconate
• Aspirin
Survival and costs of chemotherapy desensitizations in ovarian cancer treated with carboplatin

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Desens Ovarian</th>
<th>Variance</th>
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<tbody>
<tr>
<td>Total Direct Cost</td>
<td>$9,426,162</td>
<td>$3,884,355</td>
<td></td>
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<tr>
<td>MRN</td>
<td>354</td>
<td>146</td>
<td></td>
</tr>
<tr>
<td>Total # Encounters (IP and ATO)</td>
<td>1,061</td>
<td>507</td>
<td></td>
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<tr>
<td>Avg. # Encounters/MRN</td>
<td>3.0</td>
<td>3.5</td>
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<tr>
<td>Avg. Direct Cost/Encounter</td>
<td>$8,884</td>
<td>$7,661</td>
<td>-14%</td>
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<tr>
<td>Avg. Direct Cost/MRN</td>
<td>$26,628</td>
<td>$26,665</td>
<td>0%</td>
</tr>
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</table>

The costs for the control patients were the same as for the costs for carboplatin desensitized patients. Preliminary data indicates that survival is similar or better in desensitized patients.

Castells et al 2014
Outcomes Desensitizations XXI Century

- **Safety** is outstanding: thousands of cases with no deaths
- **Drug efficacy** is maintained:
  - Cancer patients have similar or better **life expectancy**
  - Chronic inflammatory diseases patients have
    - increased **quality of life**
  - Cystic Fibrosis patients undergo effective **clean ups**
  - Aspirin intolerant patients can **smell and decrease**
    - **polyp surgeries** and steroid usage
  - Progesterone/estrogen allergic patients can **conceive**
- **Costs** are **not superior** to standard treatments
Challenges Desensitizations

- **Service**: there is a need that can be serviced specifically by allergy/immunology (CPT coding, 2 night rule)

- **Education**: understand the mechanism of reactions (Type I, III, IV) and of the symptoms and management of hypersensitivity and anaphylaxis (skin testing, tryptase)
  - fellows/allergists
  - nurses
  - pharmacists

- **Research**
  - Clinical: diagnostic tools, improved customized protocols, pre-medication regimes
  - Basic: molecular basis of inhibitory mechanism(s)
Survival of ovarian cancer carboplatin desensitized patients compared to age and time of diagnosis matched non allergic carboplatin treated patients

Castells et al submitted 2014
Growth of BWH Desensitization Program

Growth of Desensitization Program

- 2007: 358
- 2008: 510
- 2009: 570
- 2010: 772
- 2011: 925
- 2012: 947

Year

Number of Desensitizations
Drug Hypersensitivity and Desensitization Center

Desensitization Program

The Adverse Drug Reaction and Desensitization Program serves patients with a specific drug allergy and provides the opportunity to receive the first line treatment that is essential to their medical care. Desensitization refers to a method of administering a medication to which patients are allergic. This program is headed by Mariana Castells, MD, PhD, who pioneered this form of interventional allergy management. The program has performed several thousand desensitizations since its inception in 1995 and has supported several clinical studies, which have led to the publication of multiple original articles, review articles, and book chapters.

About Us

For general information about the program.

For Patients
For additional patient information.

For Medical Professionals
For additional medical professionals information.

Our Desensitization Team
Profiles of the physicians on the Desensitization team.

BWH DFCI Quality Improvement Award
Partners in Excellence Award
2004-2008-2012
Nursing, Pharmacy, Medical Specialties, Allergy/Immunology
Desensitization Information for Medical Professionals

Guidelines for Outside Desensitizations

1. Patients can only be evaluated as candidates for desensitizations by an allergist.
2. A risk assessment is necessary for each patient who needs desensitization: high risk patients have either a life threatening initial reaction with hypotension and/or desaturation, have cardiac risk and/or are on beta blockers, have low FEV1 < 80%.
3. All high risk patients need to be placed in the Medical Intensive Care Unit for their desensitization.
4. Non high risk patients can be done in an outpatient infusion center with a 1:1 nurse to patient ratio and an attending allergist for care.
5. An allergist has to order the desensitization protocol and needs a consent from the patient at each desensitization.
6. The desensitization protocol needs to be explained to the nurse and pharmacist prior to desensitization.
7. The allergist needs to have a face to face interaction with the patient on the day of the desensitization, do a history, a physical exam and reassess the risk during desensitization. He/she needs to be at the site when the first dose is administered.
8. The allergist needs to be available during the entire desensitization at less than 3 minute distance from the desensitization site and come to the site if there is a reaction. Communication with the nurses needs to be immediate and cell phone contact is preferred.
9. Instructions are given to the nurses in writing regarding treatment for reactions but the allergist is responsible for the orders and once a reaction has occurred he/she needs to see the patient and assess if the desensitizational can be continued.
2013: USA, Portugal, Spain, Canada, Hawaii, Brazil, Argentina, Chile, Israel, Mexico, Austria, Switzerland, Germany, France, South Korea, Thailand, Singapore, India
Drug Hypersensivity and Desensitization Center

Research: Mentxu Sancho, Pedro Giavina-Bianchi, Matthieu Piccard, Joana Caiado
Coordinator: Cristina Badawi  NP: Donna Lynch