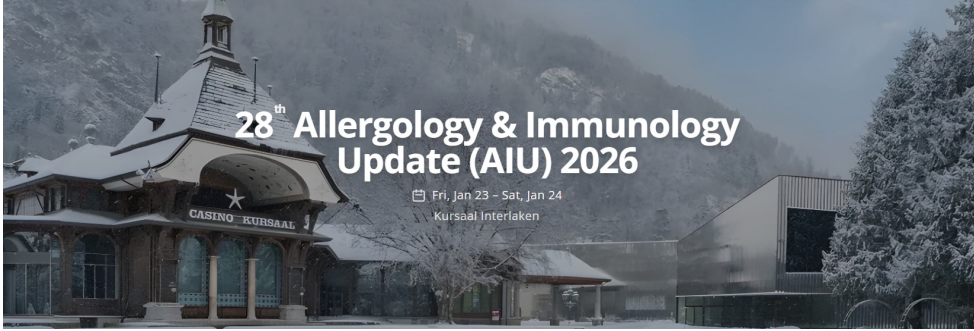


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28th Allergology & Immunology Update (AIU) 2026
 ☞ Fri, Jan 23 – Sat, Jan 24
 Kursaal Interlaken

In Vitro Assays for the Evaluation of Immediate and Delayed Reactions to Biologics and Chemotherapeutic agents

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Diagnosis of drug hypersensitivity reactions

The prevalence of drug hypersensitivity reactions (DHRs) is increasing

Higher consumption and heterogeneity of the pharmacological molecules for treating diseases (i.e. biological agents and chemotherapeutic drugs).

Label of HRs means the prescription of alternative non-first-line drugs and sometimes no alternative drug is available.

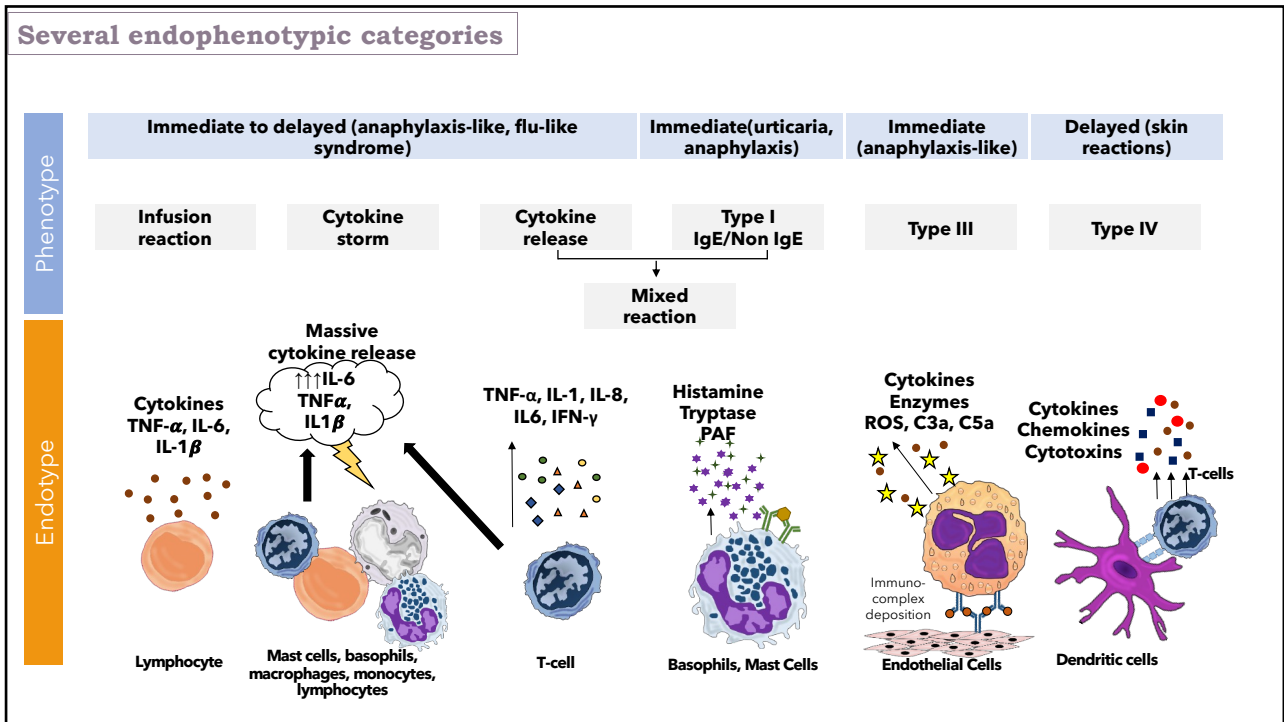
A significant percentage of patients with a suspicion of HRs to chemotherapeutics or biological agents are not truly allergic.

Precise diagnosis for:

- ✓ **limiting or recommending** the use of some drugs.
- ✓ **limiting or recommending** desensitization performance.

Increasing the patient's survival.

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IgE-mediated IDHRs

Mast cells & basophils

Leukotrienes, Prostaglandins, Histamine, Tryptase

Phenotype	Endotype
Immediate urticaria, anaphylaxis, angioedema	<p>IgE-mediated mast cell and basophil activation and mediators release</p> <p>After 2nd exposure</p>

- ImmunoCAP sensitivity depends on the biologicals involved or severity:
 - Cetuximab (68-92%) and specificity from 90% to 92%.
 - Infliximab (26%) and a specificity of 90%.

Limitations and unmet needs:

- Tests for biologicals and chemotherapeutic drugs are not commercially available for diagnostic purposes.

de Las Vecillas L et al. (2023) Expert Opinion on Biological Therapy, 23:1, 61-72.
 Vultaggio A, et al. Int Arch Allergy Immunol 2012; 159:321-326.
 Puxeddu I et al. Clin Exp Rheumatol 2016; 34:129-132.
 van Schie KA et al. Ann Rheum Dis 2017; 76:1285-1288.
 Matucci A et al. Curr Opin Allergy Clin Immunol 2020, 20:346-351
 Yang B et al. Current Allergy and Asthma Reports (2023) 23:1-11
 Bavbek S et al. Allergy. 2022;77:39-54.

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Clinical aspect recommendations				
	Definition	Grade recommendation	Comments	Agreement
2.5. Opioids	Q32. We suggest the use of BAT for diagnosing opiate/opioid IDHRs.	Weak	Genuine opiate/opioid allergy is exceedingly rare. In contrast to nonspecific mediator release likely by occupation of the MRGPRX2 receptor.	Agree 11/12 92% Not agree 0/12 0% Abstention 1/12 8%
2.6. RCM	Q33. We suggest the use of BAT for diagnosis of IDHR to RCM.	Weak	BAT can be considered as a complementary tool and especially useful in cases with severe reaction where drug challenge is contraindicated.	Agree 11/12 92% Not agree 1/12 8% Abstention 0/12 0%
2.7. Chemotherapeutics	Q34. We suggest the use of BAT for diagnosing of hypersensitivity to chemotherapeutics	Weak	BAT might have a role not only in diagnosing but also as a predictor of severe reactions and monitoring rapid drug desensitization.	Agree 11/12 92% Not agree 0/12 0% Abstention 1/12 8%
2.8. Biological Agents	Q35. We suggest the use of BAT for diagnosing of hypersensitivity to biological agents	Weak	CD63 BAT can be helpful in evaluating hypersensitivity to biological agents, if no other diagnostic tests are available. BAT might have a role in monitoring rapid drug desensitization.	Agree 11/12 92% Not agree 0/12 0% Abstention 1/12 8%
2.9. NSAIDs	Q36. use of nona			Agree 11/12 92% Not agree 1/12 8% Abstention 0/12 0%
2.10. COVID Vaccine	Q37. use of (mRNA vaccines and vaccines not based on mRNA technology) in the diagnosis of patients with reaction to COVID-19 vaccine.	Strong	The possibility of positive results related with a past COVID-19 disease have to be taken into account ⁸⁸	Agree 12/12 100% Not agree 0/12 0% Abstention 0/12 0%
2.10. PEG containing drugs	Q38. We suggest to perform BAT with PEG in patients with suspected PEG allergy	Weak	It should be included a range of PEG molecular weight (>2.000 Da)	Agree 10/12 84% Not agree 1/12 8% Abstention 1/12 8%

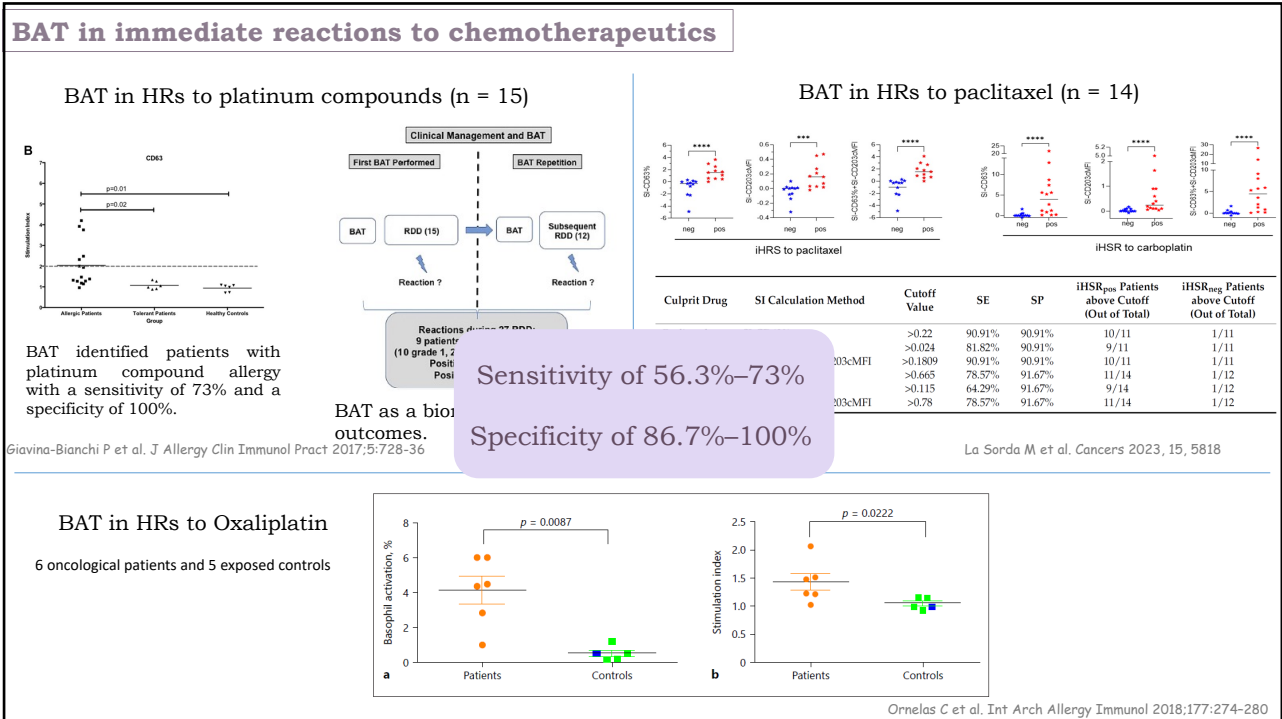
Q34-35. We recommend the use of BAT for diagnosing reactions to chemotherapeutics and biological agents.

Mayorga C et al. Allergy 2024 Mar;79(3):580-600.

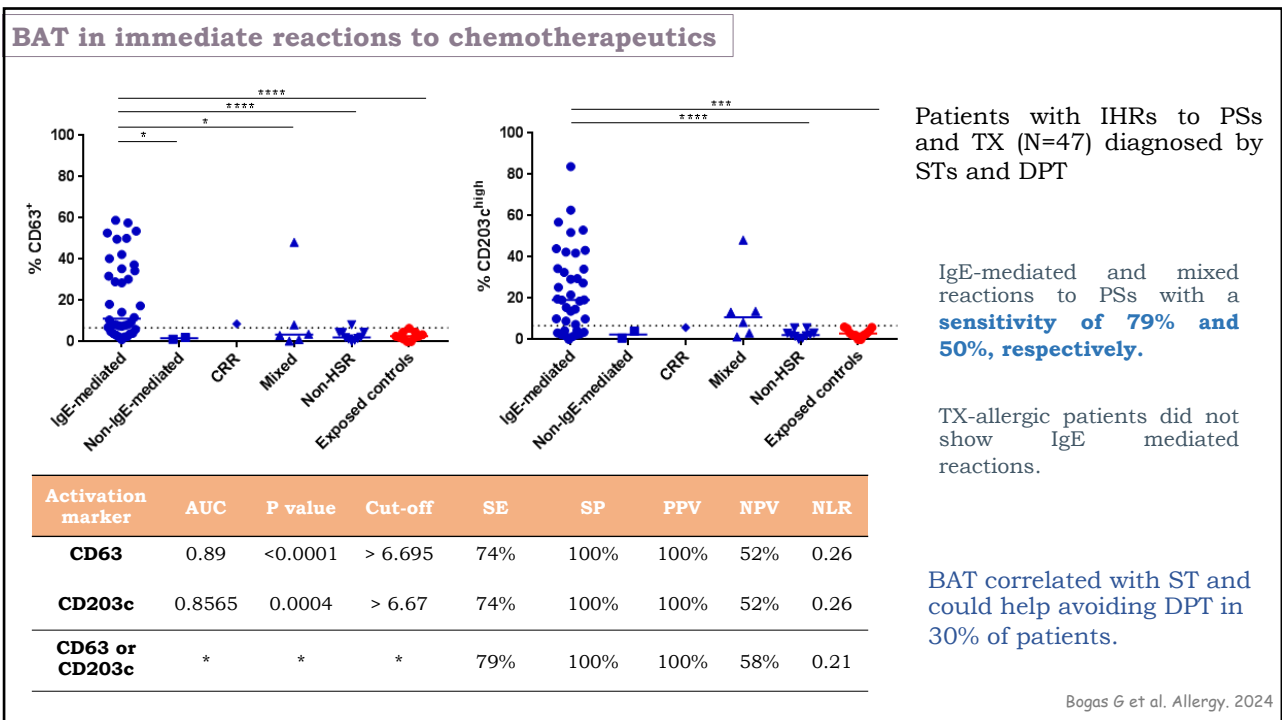
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Biomarkers for IgE-mediated reactions. BAT to biologicals	
<p>CD63 is elevated in patients with HR to rituximab <small>Piva,E.,et al. Am. J. Hematol. 2012 87,E130-E131. Michel S, et al. Allergy 2014; 69: 403-405.</small></p> <p>Gradual decrease of BAT positivity to adalimumab has been shown during rapid desensitization <small>Thevenot J et al. J Investig Allergol Clin Immunol. 2019;29(2):141-3.</small></p> <p>BAT may be positive even in skin testing negative as shown in etanercept and pertuzumab HRs. <small>de la Varga MR et al. Allergol Int.2017;66(2):357-9. & Gonzalez-de-Olano D et al. J Allergy Clin Immunol Pract. 2016;4(2):338-40.</small></p> <p>BAT has shown to be a promising tool for evaluating cetuximab HR taking into account that immunoassay for cetuximab-sIgE have a low positive predictive rate. <small>Iwamoto,T. et al . Cancer Medicine 2016; 5(6):1004-1012</small></p> <p>Additives present in the drug formulation can be the responsible for IgE-mediated HRs to biologicals (polysorbate).</p>	<p>Vultaggio A et al. Front. Immunol. 2021 12:765747. Vultaggio A et al. Curr Op Allergy Clin Immunol 2011, 11:262-268</p>

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IgG-mediated IDHRs

A % of patients: Unreactive responders (n=49), Non-reactive responders (n=11), Reactives (n=20), Controls (n=20). * indicates significance.

B Antibody level (µg/ml): Unreactive responders (n=49), Non-reactive responders (n=11), Reactives (n=20), Controls (n=20).

C Anti-omalizumab IgG (OD): Unreactive responders (n=49), Non-reactive responders (n=11), Reactives (n=20).

D OOI: Non isotype-specific ATI (solid line), IgE ATI (dashed line). X-axis: Baseline, Day of reaction, +7, +14, +21, +28 Days post reaction.

Montañez MI et al. Front Immunol. 2017 May 29;8:614.

Vultaggio A et al. Allergy 2010; 65: 657-661.

Phenotype	Endotype
Immediate urticaria, anaphylaxis, angioedema	IgG-mediated mast cell and basophil activation and mediators release After 2 nd exposure

Mayorga C et al. Allergy 2025. doi: 10.1111/all.16576

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Cytokine release reactions

Infusion reaction: Cytokines TNF- α , IL-6, IL-1 β

Cytokine storm: Massive cytokine release (IL-6, TNF- α , IL-1 β) from Mast cells, basophils, macrophages, monocytes, lymphocytes.

Cytokine release: TNF- α , IL-1, IL-8, IL-6, IFN- γ from T-cell.

Phenotype	Endotype
Immediate urticaria, anaphylaxis, angioedema	CRRs After 1 st exposure

Cytokine release after activation of effector cells, (macrophages, basophils, mast cells, monocytes and lymphocytes)

Mayorga C et al. Allergy 2025. doi: 10.1111/all.16576
 Vultaggio A et al. Curr Op Allergy Clin Immunol 2011, 11:262-268
 Sala-Cunill A et al. Curr Opin Allergy Clin Immunol 2019, 19:439-446
 de Las Vecillas L et al. (2023) Expert Opinion on Biological Therapy, 23:1, 61-72,

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Mixed reactions

Phenotype


Cytokine release Type I IgE/Non IgE

↓

Mixed reaction


Endotype

TNF-α, IL-1, IL-8, IL6, IFN-γ



T-cell

Histamine
Tryptase
PAF



Basophils, Mast Cells

In patients presenting both **IgE-mediated and CRS-induced symptoms**.

They may occur in up to 20% of HSRs to biologics.

Biomarkers of both endotypes can be elevation of **IL-6 serum levels or increased serum tryptase, positive skin tests or positive sIgE**.

de Las Vecillas, L et al. (2023) Expert Opinion on Biological Therapy, 23:1, 61-72,

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Delayed hypersensitivity reactions

Biologics can be involved in delayed reactions (i.e. maculopapular rashes).

Also, severe cutaneous adverse reactions such as SJS, TEN, AGEP, and DRESS.

Serum sickness-like reactions have been reported during the treatment with biologics such as rituximab.

However, the exact utility of T-cell assays as a diagnostic tool for evaluating patients with delayed HSRs is currently undefined.

A. DHR

CD4&CD8 T-Lymphocytes

IFN-γ

Perforin

Granzyme B

Eotaxin

Th1

CD8

B. DRESS

Eosinophils

Th2

IL-13

IL-5

Th1

IFN-γ

TNF-α

T cell

C. AGEP

Neutrophils

CXCL8

IFN-γ

GM-CSF

IL-8 LL37

Th17

IL-17, IL-22, IFN-γ

D. SJS/TEN

Tissue damage

HMGB1

MMP9

Th1

Th17

Th22

CD8

IFN-γ

IL-17

NK

IFN-γ, Perforin, Granulysin

Granzyme B

Cytotoxic lymphocytes

Mayorga C et al. Allergy 2025. doi: 10.1111/all.16576

Mayorga C et al. Allergy 2025. doi: 10.1111/all.16576

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Delayed hypersensitivity reactions

Phenotype	Endotype	Biomarker & Evidence Level
Non-Immediate urticaria, MPE, DILs, SCARs	T-cell mediated	LTT 15,62,105,106 ELISPOT ^{64,107,108}

Uptaken and presentation of antigen presenting cells

Group	Healthy controls	Allergic patients
C-LTT	15	29.4
moDC-LTT	15	61.8
C-LTT+moDC-LTT	17.4	61.8

Fernandez-Santamaría R et al. Allergy. 2021;76:2123-2134.
Mayorga C et al. Allergy 2025. doi: 10.1111/all.16576

Mainly for BLs and anticonvulsants

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Desensitization of Drug Allergy

- Drug desensitization permits a safe reintroduction of the drugs needed for treating their diseases.

- The drug has a unique mechanism of action and is necessary or irreplaceable
- The alternative is less effective or associated to more adverse effects

Favourable individual RISK/BENEFIT evaluation

➔

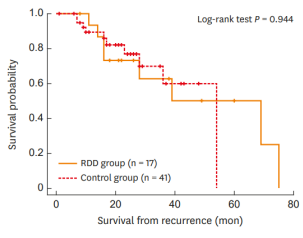
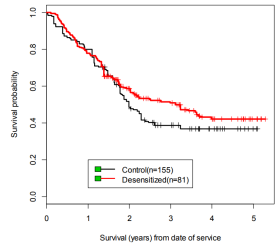
SCARs cannot be desensitized

Yang BC, Immunol Allergy Clin North Am 2022

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Desensitization of Drug Allergy

**Overall survival of the RDD group vs control group
(time from cancer recurrence to death)**

Park HK, Allergy Asthma Immunol Res 2020 Sloane D, J Allergy Clin Immunol Pract 2016

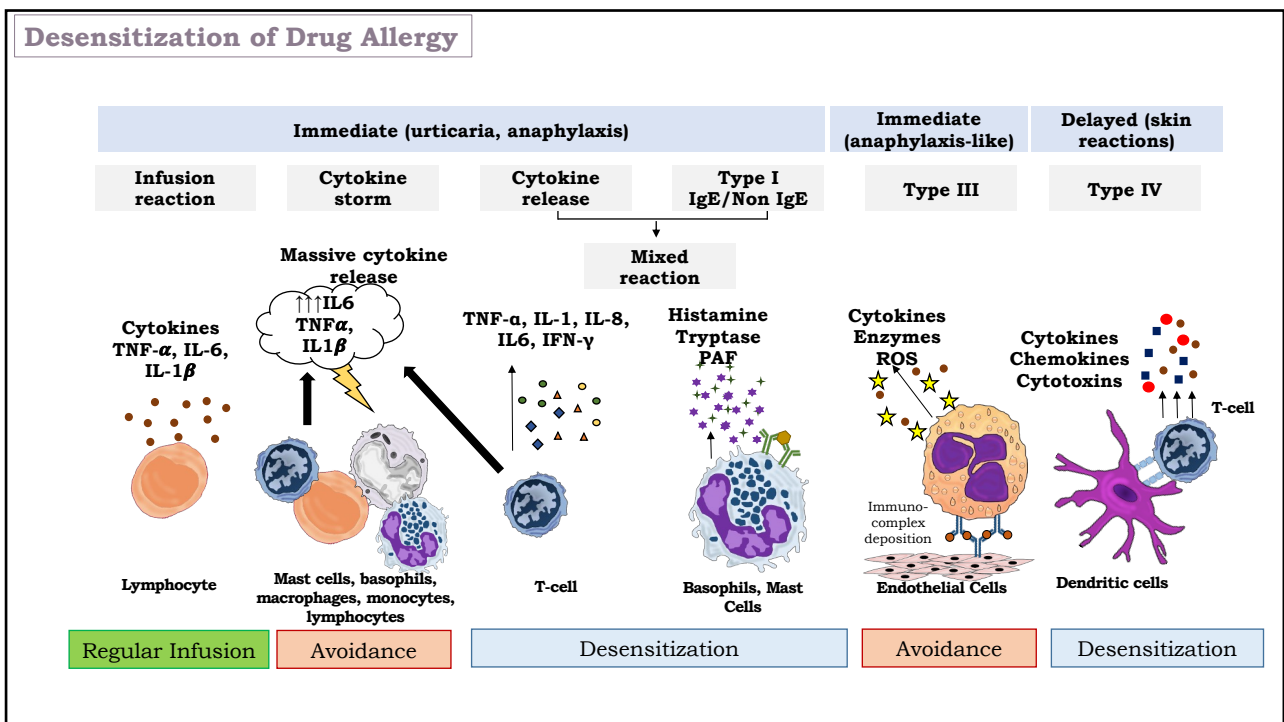
Costs for carboplatin -treated patients (primary and recurrent)

Patients and cost data	patients / encounters	age	total encounters	average (range) encounters/ patient	average cost*	total costs
Desensitized	171 / 146	62 (36-95)	532	3.1 (1 - 16)	\$6796	\$26,605
Control	186 / 170	57 (18-88)	592	3.2 (1 - 16)	\$9256	\$29,825

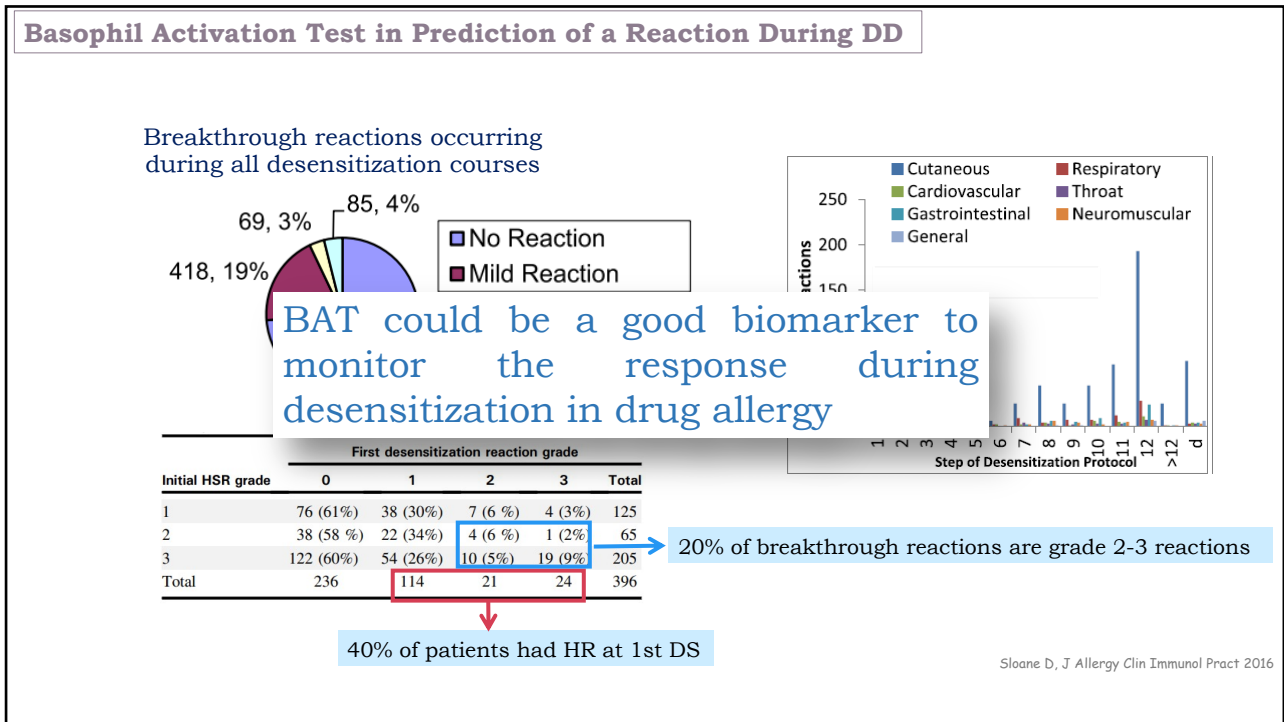
*significantly different between groups by t-test at p<0.0001

Sloane D, J Allergy Clin Immunol Pract 2016

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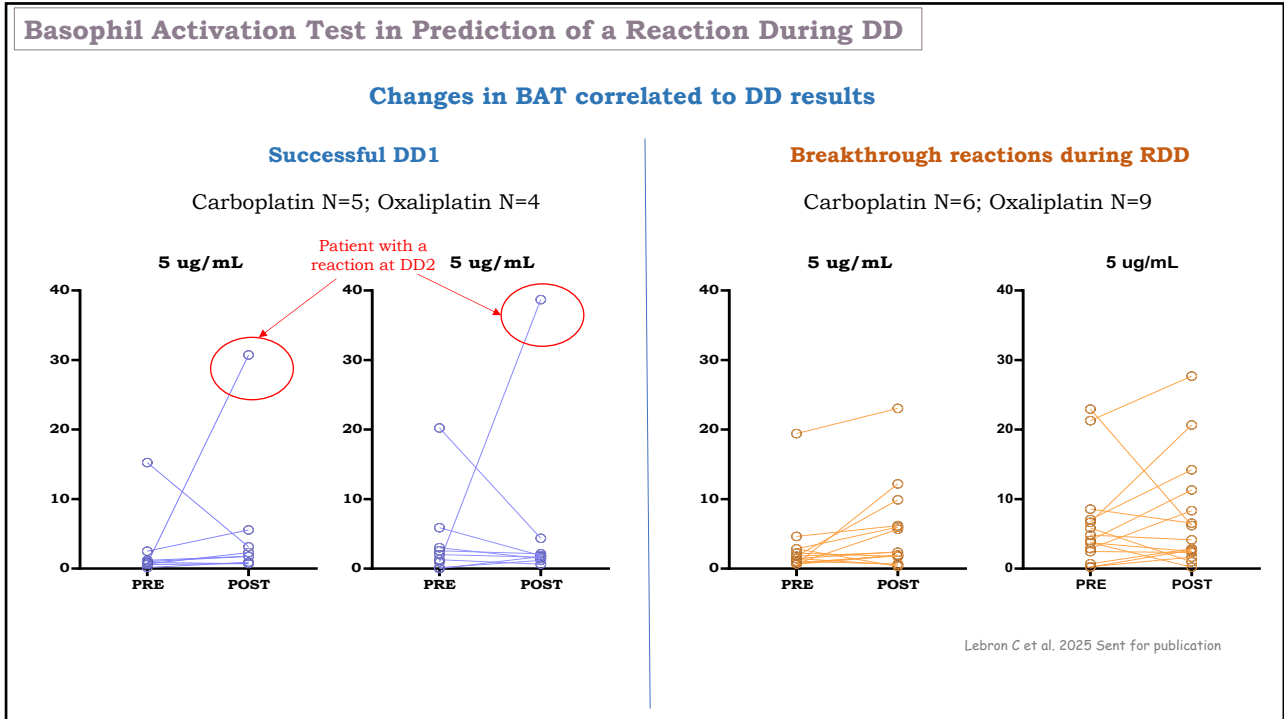
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Basophil Activation Test in Prediction of a Reaction During DD

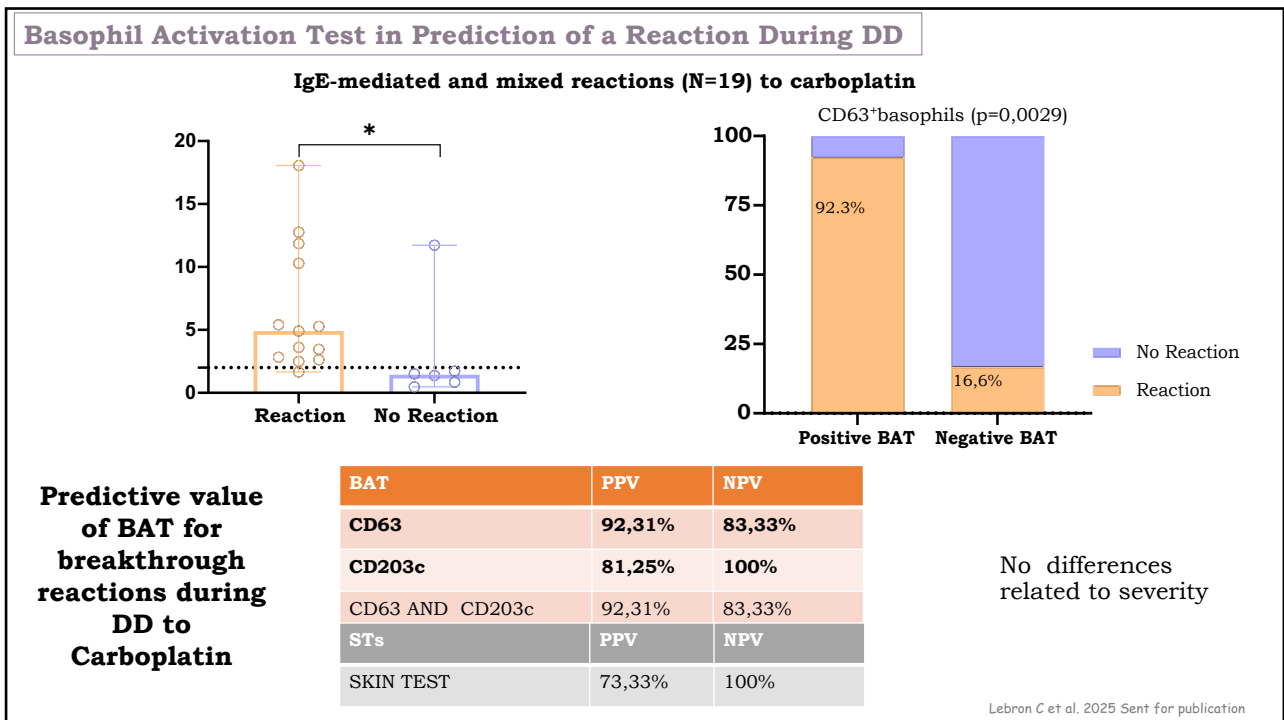
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Mayorga C et al. Allergy 2024 Mar;79(3):580-600.

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Take-home messages

DHRs can be produced by a wide array of mechanisms.

Identifying the cause of hypersensitivity is crucial not only for future prescription to the patient but also for finding therapeutic targets to block specific pathways.

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Take-home messages

- In vitro tests are safe and valuable diagnostic in DHR.
- Different tests and biomarkers for defining endotypes only few of them in **Clinical validity/utility phase**:
 - sIgE and BAT for IgE and mixed reactions
 - IL6 for CRRs and mixed reactions
 - LTT in delayed reactions

BAT is a useful tool for predicting the response during DD:

- i. BAT positivity predict **risk of reactions** during DD.
- ii. BAT may enable the **safe reintroduction** of the culprit drug (with appropriate rate or using premedication) through desensitization.

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