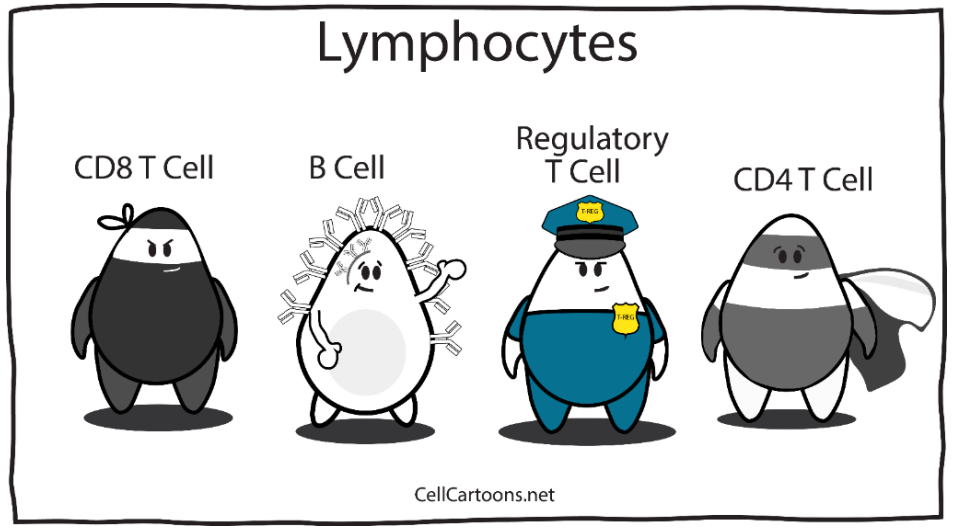
2024년 제 64차 알레르기 교육강좌

약물 알레르기, 진단과 검사의 최신 지견

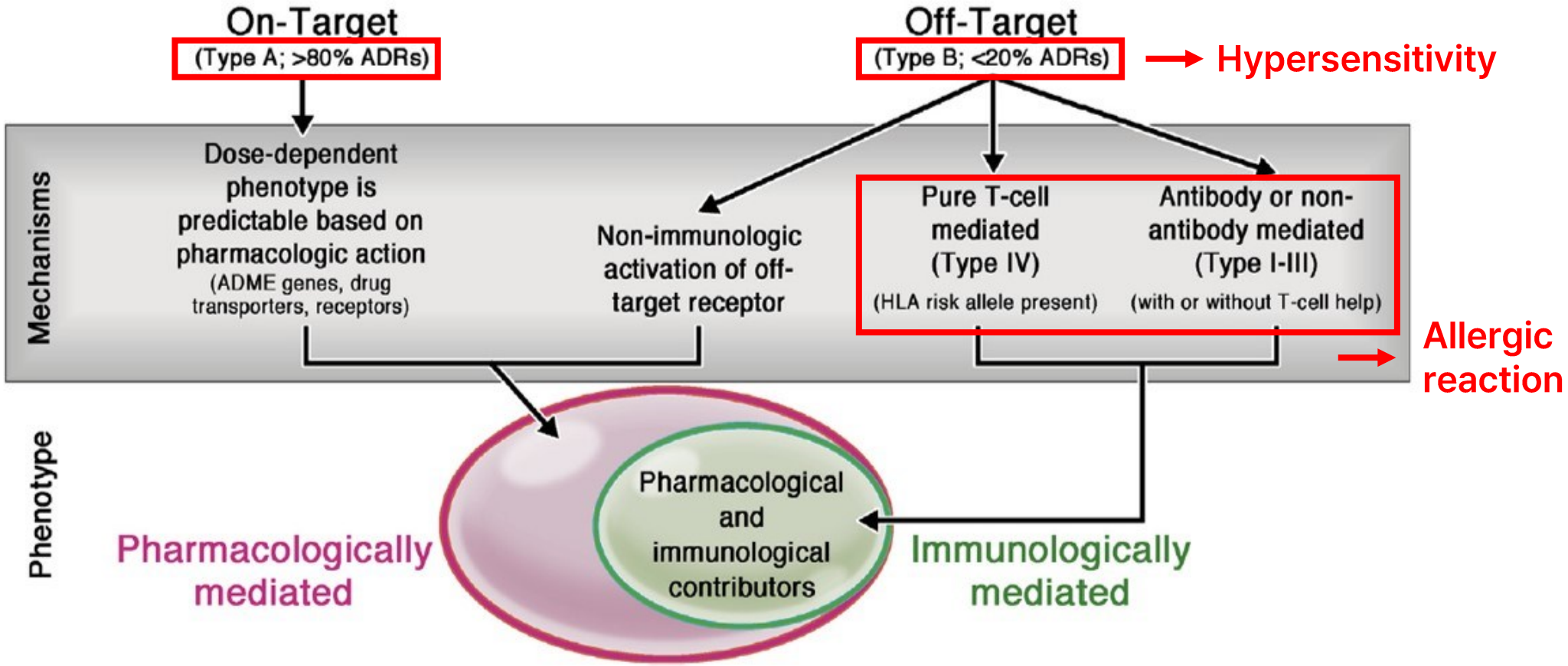
전남의대 알레르기내과 심다운

Adverse drug reaction

- Predictable (Type A)
  - Overdose (toxic)
  - Side effect
  - Secondary (indirect)
  - Drug-drug interaction
- Unpredictable (Type B)
  - Intolerance
  - Idiosyncrasy (pharmacogenetics)
  - Nonallergic (pseudoallergy)
  - Immunologic drug reaction (allergy)



Adverse drug reaction



J Allergy Clin Immunol 2015;136:219-35

Drug hypersensitivity reactions (DHR)

- Definition
  - Adverse effects of drugs that clinically resemble allergic reactions
  - Drug allergies
    - DHRs for which a definite immunological mechanism (either drug specific antibody or T cell) is demonstrated

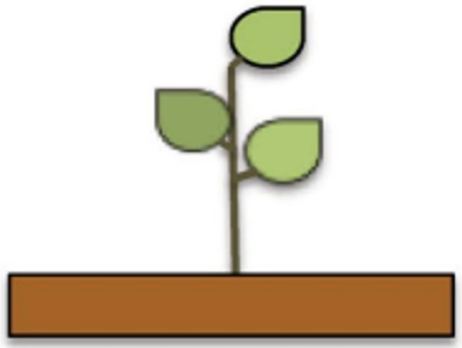
- Classification
  - Heterogenous
  - Clinically : immediate / nonimmediate
  - Mechanistically : allergic / nonallergic

Allergy. 2014;69:420-437

Aims of diagnostic tests

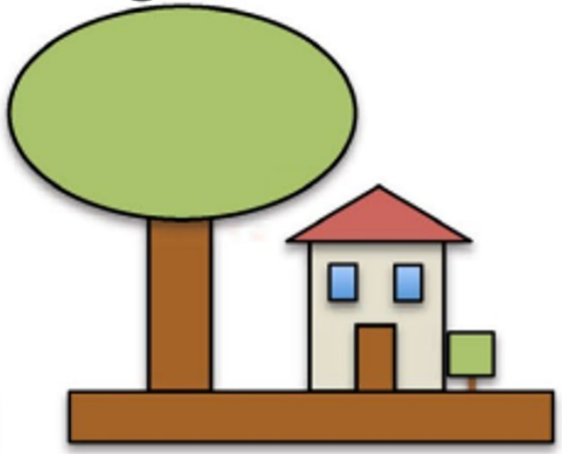
Allergy. 2024;79:565–579

Label acquisition



- 75% of penicillin allergy labels acquired in childhood by age 3
- Most labels are inaccurate

Labels persist and grow in significance



- 8% -25% of adults with penicillin allergy label
- Less than 5% of labeled are actually allergic
- Even true allergy may fade over time

Consequences of a label

- Pressure prescribing of 2nd and 3rd line antimicrobials
- Increased inappropriate antibiotic selection
- Increased mortality risk during cancer and infection treatment
- Delay the onset of appropriate

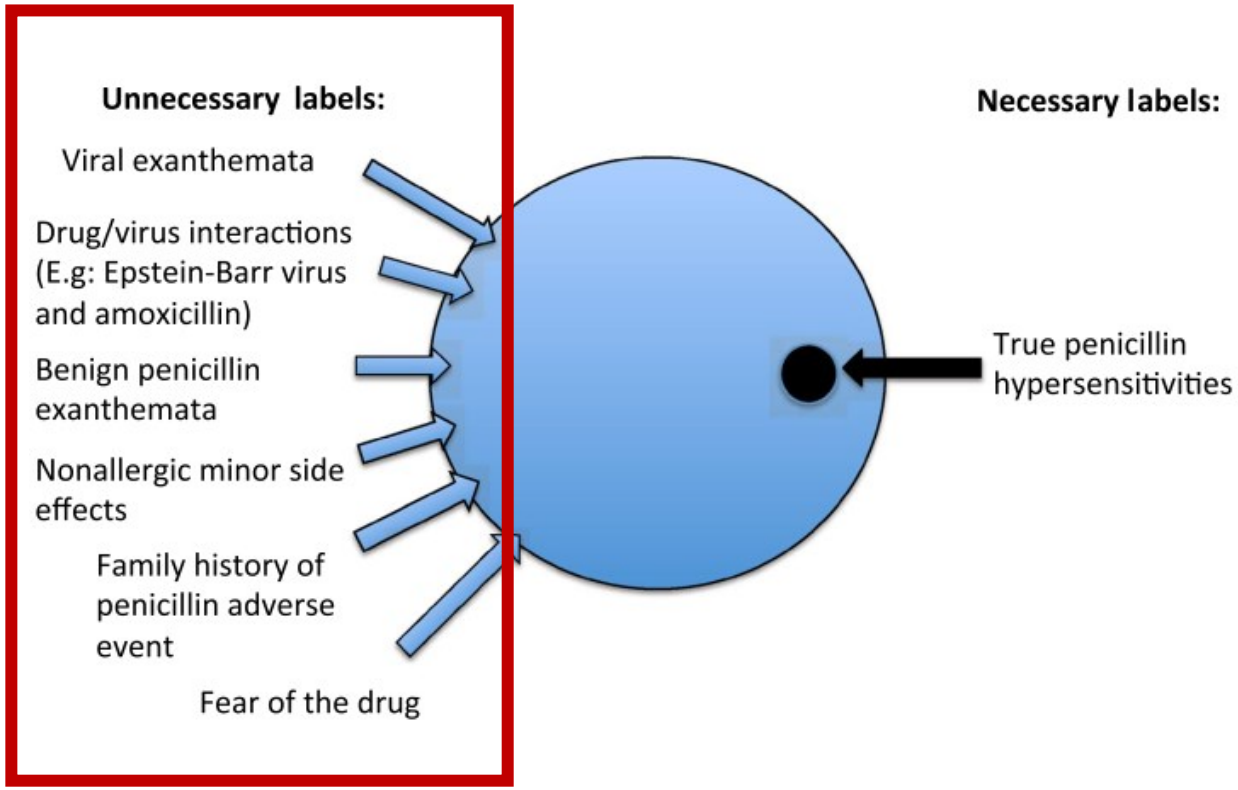
Testing/ removal of unnecessary label

- Cost-effective
- Patient reassured on safety
- Reduced expenses
- Avoidance of bad outcomes: treatment failures, surgical infections, multidrug resistant infections

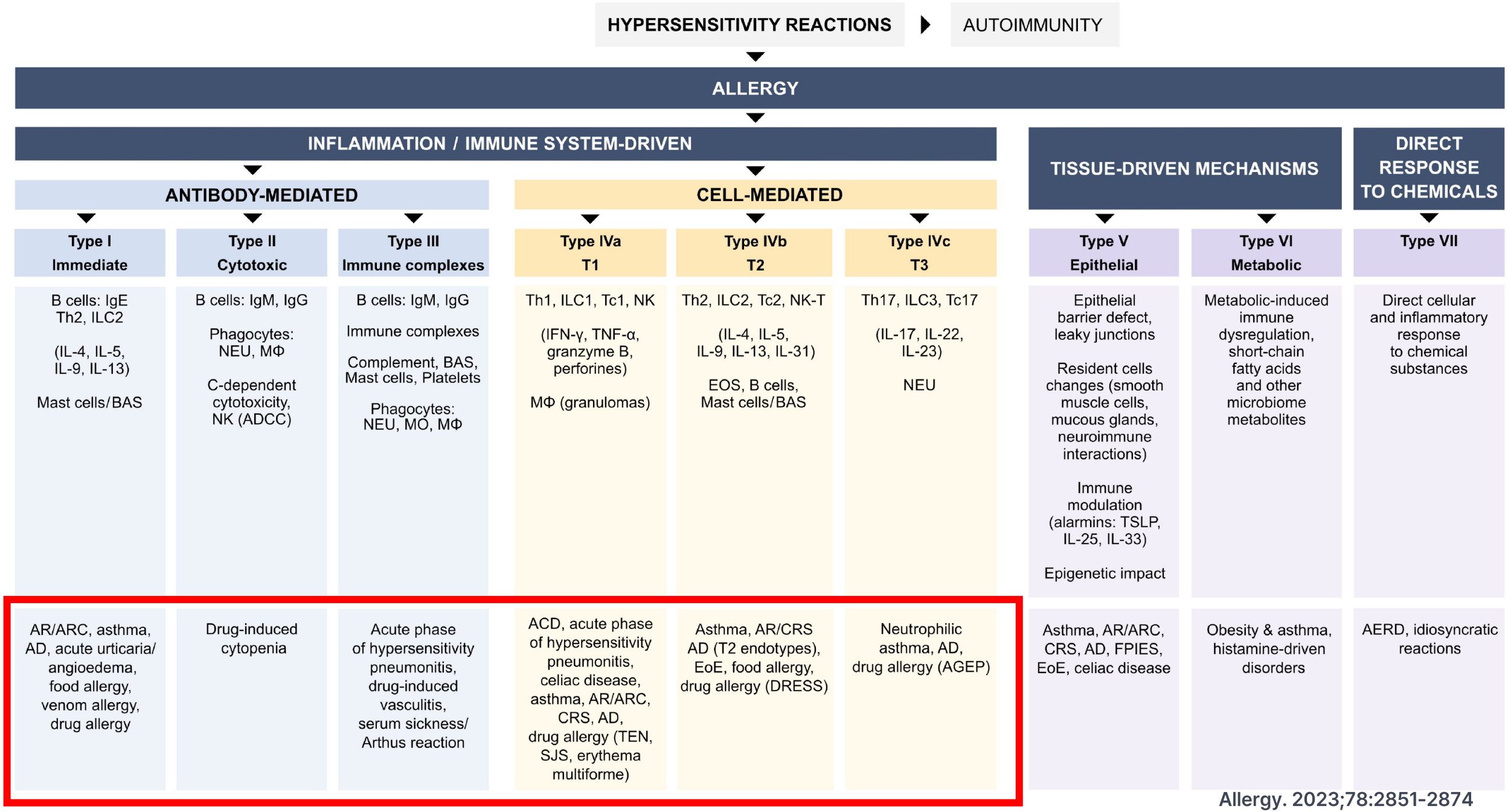
Allergy. 2020;75:273-288

Penicillin allergy label

- A label of penicillin allergy is common but most labeled patients are not allergic
- Penicillin is the most common reported drug allergy (8-25%)
- Rate of true penicillin allergy in patients reporting an allergy has declined to <2-5%



Allergy. 2020;75:273-288



Allergy. 2023;78:2851-2874

Pathogenesis and pathophysiology

- Allergic (Immunologic) DHRs
  - Antibodies
  - Activated T cells

- Non-allergic (nonimmune) DHRs
  - Nonspecific mast cell or basophil histamine release
  - Bradykinin accumulation
  - Complement activation
  - Alteration in arachidonate metabolism
  - The pharmacological action of certain substances inducing bronchospasm

Allergy. 2014;69:420-437

Pathogenesis and pathophysiology

- Immediate allergic DHRs
  - Specific IgE production after sensitization
  - IgE bind to the high-affinity FcεRI receptors on the surface of mast cells and basophils
  - Stimulating the release of preformed mediators (histamine, tryptase, some cytokines such as TNF-a)
  - Production of new mediators (leukotrienes, prostaglandins, kinins, other cytokines)

Allergy. 2014;69:420-437

Pathogenesis and pathophysiology

- Non-immediate (delayed) allergic DHRs
  - Actions of drug responsive T lymphocytes
  - Skin : most common targeted organ

  - Re-exposed to the antigen → activated to secrete cytokines that regulate the response and cytotoxins (perforin, granzymes, and granulysins) → produce tissue damage

Allergy. 2014;69:420-437

Clinical presentations

- Approach to the patients with suspected DHRs
  - A complete history of the drugs taken
    - Types, doses, duration
  - A detailed description of the symptoms and signs
    - Types, onset, localization, and evolution
  - A complete examination of the skin and the mucous membranes
    - Including the mouth, eyes, and genitals
  - The search for danger/severity signs
    - Clinical symptoms
    - Laboratory parameters

Allergy. 2014;69:420-437

Drug allergy

- Urticaria/ angioedema/ anaphylaxis

- Drug induced eosinophilia
- Drug rash
- Drug fever
- Fixed drug eruptions
- Serum sickness like reactions

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN)
- Acute generalized exanthematous pustulosis (AGEP)

Classification

- Immediate DHRs
  - Urticaria, angioedema
  - Rhinitis, conjunctivitis, bronchospasm
  - Gastrointestinal symptoms (nausea, vomiting, diarrhea)
  - Cardiovascular collapse

- Delayed DHRs
  - Variable cutaneous symptoms
    - Maculopapular eruptions, fixed drug eruptions, vasculitis, blistering diseases
  - Internal organs involvement
    - Hepatitis, renal failure, pneumonitis, anemia, neutropenia, and thrombocytopenia

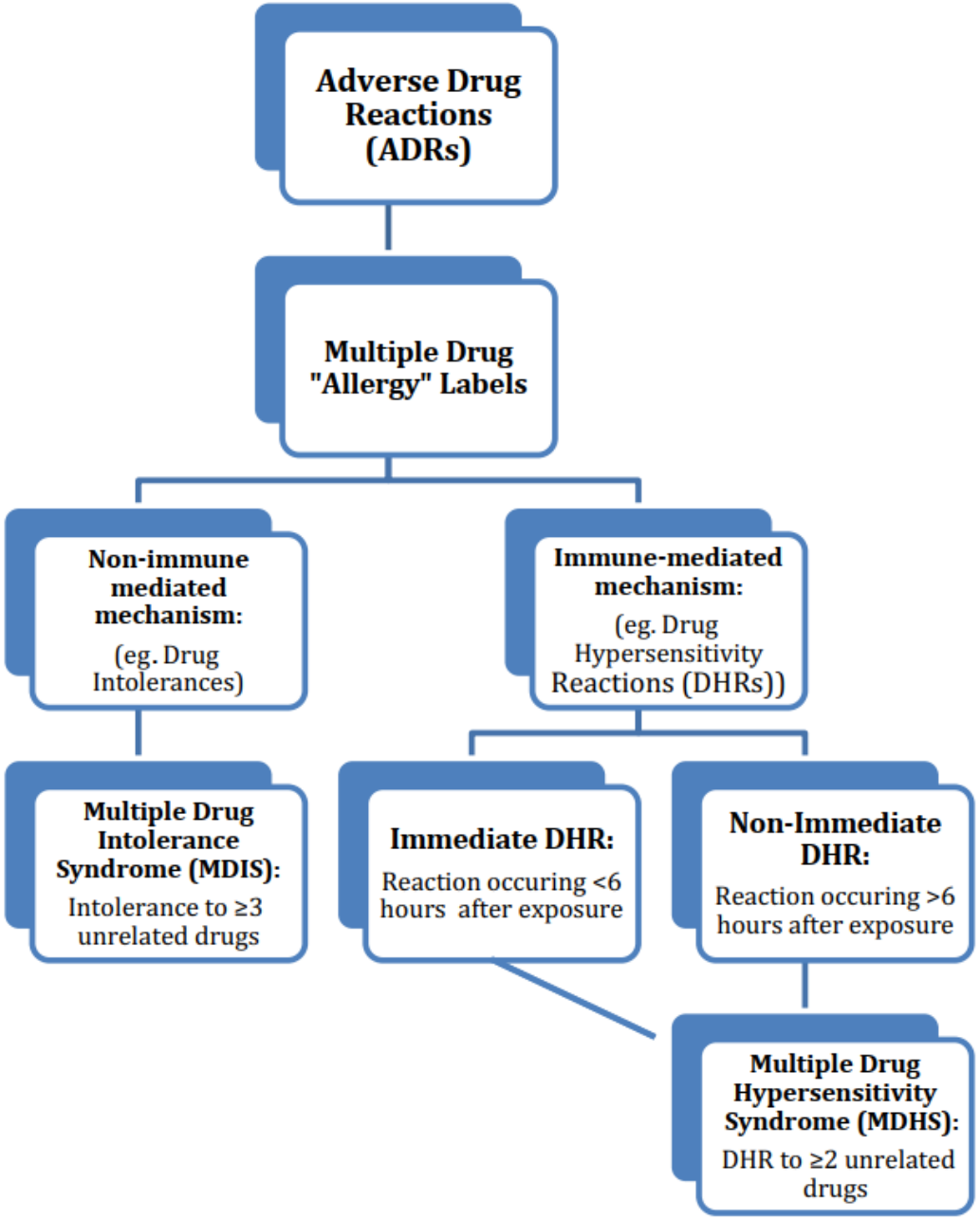
Allergy. 2014;69:420-437

Classification

- Multiple drug hypersensitivity syndrome
  - Allergic reactions to 2 or more unrelated drugs by immune-mediated mechanisms
  - Differential diagnosis
    - Cross-reactivity
    - Flare-up reactions
    - Multiple drug intolerance syndrome
  - T-cell activation by different compounds

Allergy. 2014;69:420-437

Clinical phenotypes for the patient with a history of multiple drug "allergies."



J Allergy Clin Immuol Pract. 2020;8:1870-6

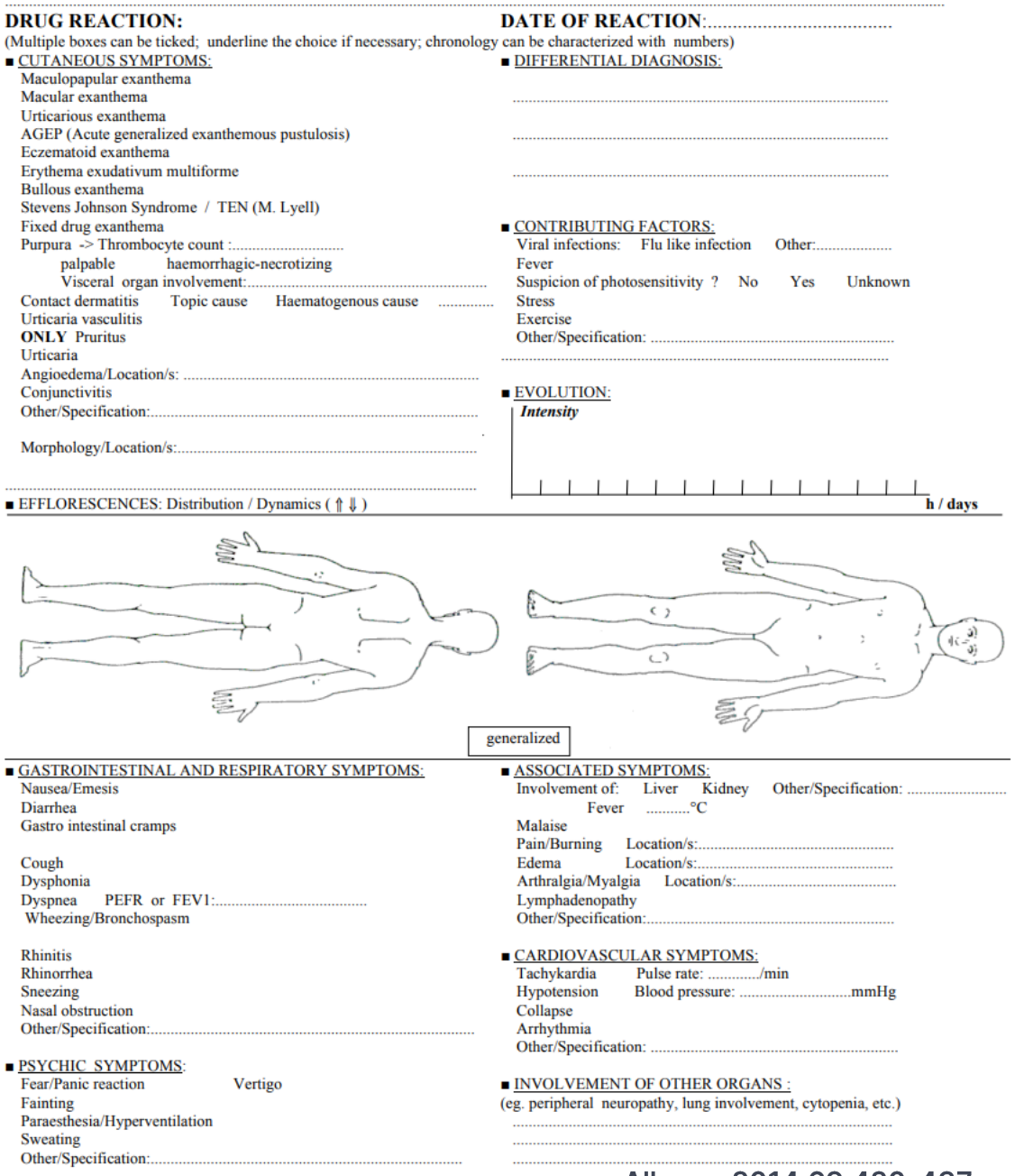
Points regarding DHR diagnosis

- A definitive diagnosis of a DHR
- Misclassification based on the DHR history alone
- The clinical tools allowing a definitive diagnosis
  - Clinical history, standardized skin tests, reliable in vitro tests, and drug challenge
- Properly performed in specialized centers
  - A reliable diagnosis is often possible and safe alternative medication can be administered
  - Screening subjects without a prior history of allergic drug reactions is not recommended

Allergy. 2014;69:420-437

Diagnosis

- Evaluation of the clinical history
  - The chronology of the symptoms
    - Previous exposure
    - Delay between the last dose and the onset of symptoms
    - Effect of stopping treatment
  - Drug history
    - Time of the reaction
    - Drugs of the same class taken since
  - Medical background
  - Photographs



DRUG REACTION: **DATE OF REACTION**:.....

(Multiple boxes can be ticked; underline the choice if necessary; chronology can be characterized with numbers)

■ CUTANEOUS SYMPTOMS:
Maculopapular exanthema
Macular exanthema
Urticarious exanthema
AGEP (Acute generalized exanthemous pustulosis)
Eczematoid exanthema
Erythema exudativum multiforme
Bullous exanthema
Stevens Johnson Syndrome / TEN (M. Lyell)
Fixed drug exanthema
Purpura -> Thrombocyte count :.....
palpable haemorrhagic-necrotizing
Visceral organ involvement:.....
Contact dermatitis Topic cause Haematogenous cause .....
Urticaria vasculitis
ONLY Pruritus
Urticaria
Angioedema/Location/s: .....
Conjunctivitis
Other/Specification:.....
Morphology/Location/s:.....

■ DIFFERENTIAL DIAGNOSIS:
.....
.....
.....

■ CONTRIBUTING FACTORS:
Viral infections: Flu like infection Other:.....
Fever
Suspicion of photosensitivity ? No Yes Unknown
Stress
Exercise
Other/Specification: .....
.....

■ EVOLUTION:
Intensity
h / days

■ EFFLORESCENCES: Distribution / Dynamics (⇑ ⇓)

generalized

■ GASTROINTESTINAL AND RESPIRATORY SYMPTOMS:
Nausea/Emesis
Diarrhea
Gastro intestinal cramps
Cough
Dysphonia
Dyspnea PEFR or FEV1:.....
Wheezing/Bronchospasm
Rhinitis
Rhinorrhea
Sneezing
Nasal obstruction
Other/Specification:.....

■ PSYCHIC SYMPTOMS:
Fear/Panic reaction Vertigo
Fainting
Paraesthesia/Hyperventilation
Sweating
Other/Specification:.....

■ ASSOCIATED SYMPTOMS:
Involvement of: Liver Kidney Other/Specification: .....
Fever .....°C
Malaise
Pain/Burning Location/s:.....
Edema Location/s:.....
Arthralgia/Myalgia Location/s:.....
Lymphadenopathy
Other/Specification:.....

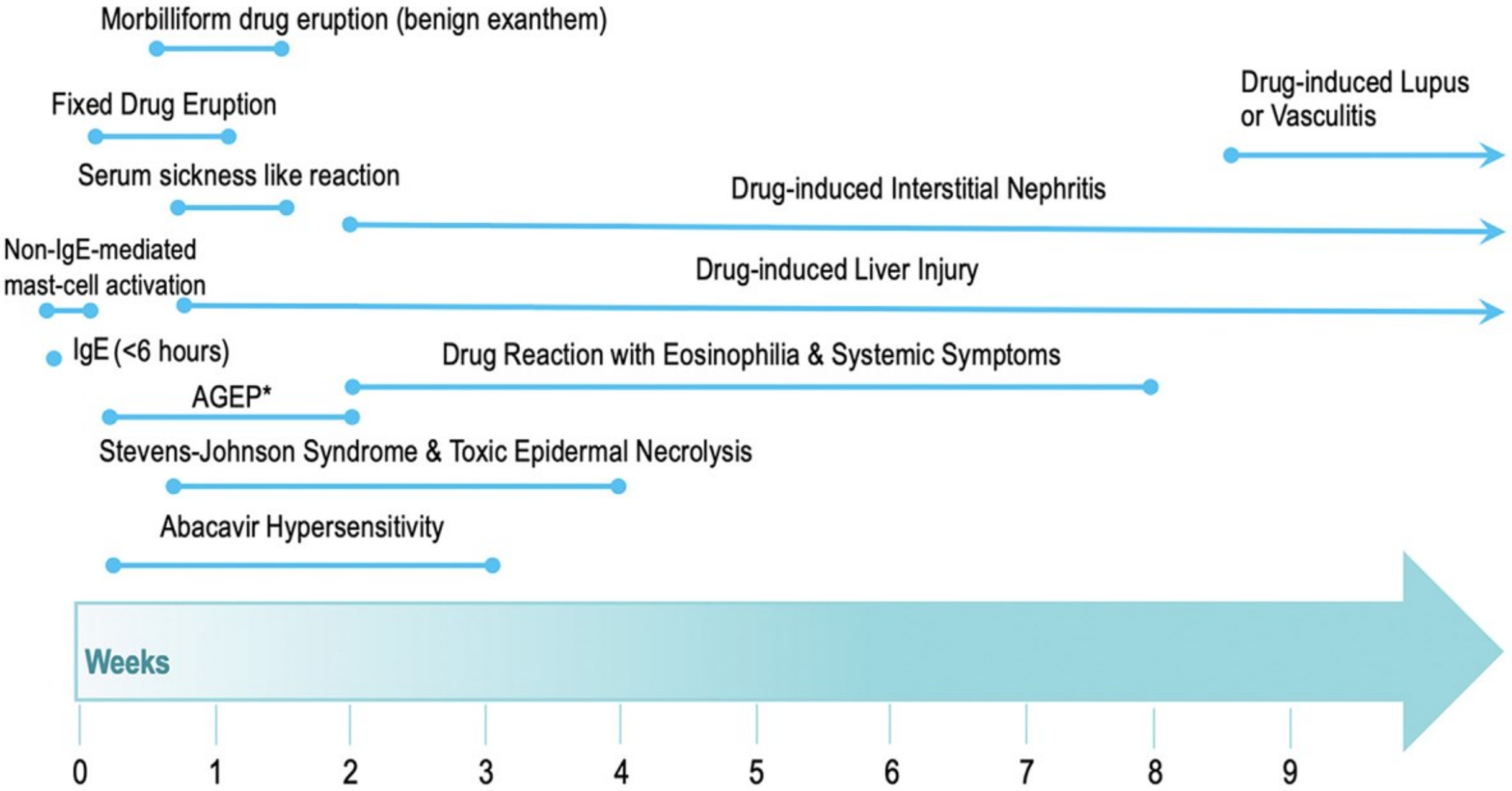
■ CARDIOVASCULAR SYMPTOMS:
Tachykardia Pulse rate: ...../min
Hypotension Blood pressure: .....mmHg
Collapse
Arrhythmia
Other/Specification: .....

■ INVOLVEMENT OF OTHER ORGANS :
(eg. peripheral neuropathy, lung involvement, cytopenia, etc.)
.....
.....
.....

Allergy. 2014;69:420-437

Type	Type of immune response	Pathophysiology	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Anaphylactic shock Angioedema Urticaria Bronchospasm	Within 1 to 6 h after the last intake of the drug
II	IgG and complement	IgG and complement-dependent cytotoxicity	Cytopenia	5–15 days after the start of the eliciting drug
III	IgM or IgG and complement or FcR	Deposition of immune complexes	Serum sickness Urticaria Vasculitis	7–8 days for serum sickness/urticaria 7–21 days after the start of the eliciting drug for vasculitis
IVa	Th1 (IFN-γ)	Monocytic inflammation	Eczema	1–21 days after the start of the eliciting drug
IVb	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculopapular exanthema, DRESS	1 to several days after the start of the eliciting drug for MPE 2–6 weeks after the start of the eliciting drug for DRESS
IVc	Cytotoxic T cells (perforin, granzyme B, FasL)	Keratinocyte death mediated by CD4 or CD8	Maculopapular exanthema, SJS/TEN, pustular exanthema	1–2 days after the start of the eliciting drug for fixed drug eruption 4–28 days after the start of the eliciting drug for SJS/TEN
IVd	T cells (IL-8/CXCL8)	Neutrophilic inflammation	Acute generalized exanthematous pustulosis	Typically 1–2 days after the start of the eliciting drug (but could be longer)

Allergy. 2014;69:420-437



J Allergy Clin Immunol. 2022;150:1333-1393

Skin tests

- Should follow standard procedures
- Should be performed by trained staff
- Should be performed 4–6 weeks after the reaction
- Depending on the suspected pathomechanism of the DHR
  - Skin prick test, intradermal test, patch test, intradermal test with delayed reading
- Sensitivity and predictive values
  - Good : Beta-lactam antibiotics, muscle relaxants and heparins
  - Moderate to low : most other drug

Allergy. 2014;69:420-437

Skin tests

- Nonirritating test concentrations

DRUG	SPT	IDT	PT
Penicilloyl-poly-L-lysine	5×10^{-5} mM	5×10^{-5} mM	NA
Minor determinant mixture	2×10^{-2} mM	2×10^{-2} mM	NA
Benzylpenicillin	10.000 UI	10.000 UI	5%
Amoxicillin	20 mg/ml	20 mg/ml	5%
Ampicillin	20 mg/ml	20 mg/ml	5%
Cephalosporins	2 mg/ml	2 mg/ml	5%

Drug or drug class	SPT	IDT	Patch
Anticoagulants			
Heparins*	Undiluted	1/10 diluted	Undiluted
Heparinoids†	Undiluted	1/10 diluted	Undiluted
Platinum salts			
Carboplatin	10 mg/ml	1 mg/ml	NA
Oxaliplatin	1 mg/ml	0.1 mg/ml	NA
Cisplatin	1 mg/ml	0.1 mg/ml	NA
NSAIDs			
Pyrazolones‡	Powder	0.1 mg/ml	10%
Coxibs§	Powder		10%
Other NSAIDs¶	Powder	0.1 mg/ml	10%
Biologicals			
Adalimumab	50 mg/ml	50 mg/ml	Undiluted
Etanercept	25 mg/ml	5 mg/ml	NA
Infliximab	10 mg/ml	10 mg/ml	NA
Omalizumab	1.25 µg/ml	1.25 µg/ml	NA
Others			
Local anaesthetics	Undiluted	1/10 diluted	Undiluted
Iodinated contrast media	Undiluted	1/10 diluted	Undiluted
Gadolinium chélates	Undiluted	1/10 diluted	NA

TABLE XIII. Immediate hypersensitivity cephalosporin skin testing[119,265,266]

	Cefazolin*	Cefuroxime†	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime‡
Step 1: Epicutaneous (prick/puncture)	200 mg/mL	90 mg/mL	100 mg/mL	100 mg/mL	100 mg/mL	2 mg/mL
Step 2:§ Intradermal	2.0 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	2 mg/mL
Step 3: Intradermal	20 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	2 mg/mL

ted

J Allergy Clin Immunol. 2022;150:1333-1393
Allergy. 2013;68:702-12

Skin tests

- Testing procedures for delayed HSRs

	Delayed intradermal	Patch testing*
Volume injected or vehicle	0.02-0.05 mL	Petrolatum, water, or alternative soluble vehicle
Drug concentration and preparation	Limited to drugs available in sterile preparation Highest nonirritating concentration	10% and 30% of trade product 1% and 10% of pure substance Highest nonirritating concentration
Performance of test†	6 weeks to 6 months after complete healing of reaction 6 months following DRESS reactions 4 weeks after discontinuation of systemic steroids (>10 mg prednisone equivalent) or other immunosuppressants	At least 6 weeks to 6 months after complete healing of reaction 6 months following DRESS reactions 4 weeks after discontinuation of systemic steroids (>10 mg prednisone equivalent) or other immunosuppressants
Criteria for delayed positivity	Any obvious induration at 24 h[8]‡	24-72 h infiltrated erythema as per international contact dermatitis guidelines[113] Patch removal at 48 h with further reading at 96 h and 7 d[113]
Site	Volar aspect of the forearm§ Non–sun-exposed if possible	Flat part of the back Upper arm is alternative Ideal areas are non–sun-exposed
Negative control	Saline	Petrolatum or vehicle
Positive control specific for delayed response	None	None

J Allergy Clin Immunol. 2022;150:1333-1393

• Intradermal test for SCAR

HLA B62 as a possible risk factor for drug reaction with eosinophilia and systemic symptoms to piperacillin/ tazobactam

Krzysztof Rutkowski, MD, MRCP[a],
Craig Taylor, PhD, FRCPath[b], and Annette Wagner, MD[c]

TABLE I. Clinical characteristics and laboratory investigations

					Laboratory investigations						
Age (y) & sex	Indication for PT	Onset (day of course)	T (°C)	Skin	Neu (× 10^9/L)	Lym (× 10^9/L)	ALT (U/L)	Plt (× 10^9 L)	Eos (× 10^9/L) (maximum on day)	IDT: size (mm) and delay (h)	RegiScar score
61, F	Perforated sigmoid	31	39.2	Severe MPR	13.08	2.76	27	490	2.68 (9)	9 × 10; 24	7: definite
29, M	Osteomyelitis	18	39.7	Severe MPR trunk	1.85	0.59	30	222	1.64 (20)	7; 10	4: probable
54, F	Infection after wrist surgery	4 post course	39.8	Severe MPR; facial angioedema	4.21	1.03	39	320	0.9 (3)	Not read at 24 h	4: probable
12, M	Chemotherapy for medulloblastoma	14	40	Severe MPR	2.37	1.20	1099	30	0.79 (11)	(+); 24	6: definite
69, F	Esophageal perforation	18	38.3	Severe MPR	8.88	2.8	52	329	1.47 (8)	(+); 24	5: probable
53, M	Infected calcaneal fracture	25	39.8	Severe MPR; generalized angioedema	0.1	0.41	212	213	2.6 (14)	(+); 24 (central blister)	8: definite

DRESS Syndrome due to benzylpenicillin with cross-reactivity to amoxicillin

Timothy J. Watts, MRCP[a],
Philip H. Li, MRes (Med), MRCP[a,b], and
Rubaiyat Haque, FRCP[a]

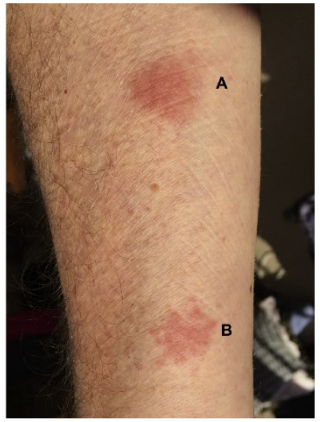


FIGURE 1. Positive delayed intradermal tests at D4 to (**A**) benzylpenicillin and (**B**) amoxicillin with focal papules, induration, and infiltrated erythema.

ORIGINAL ARTICLE

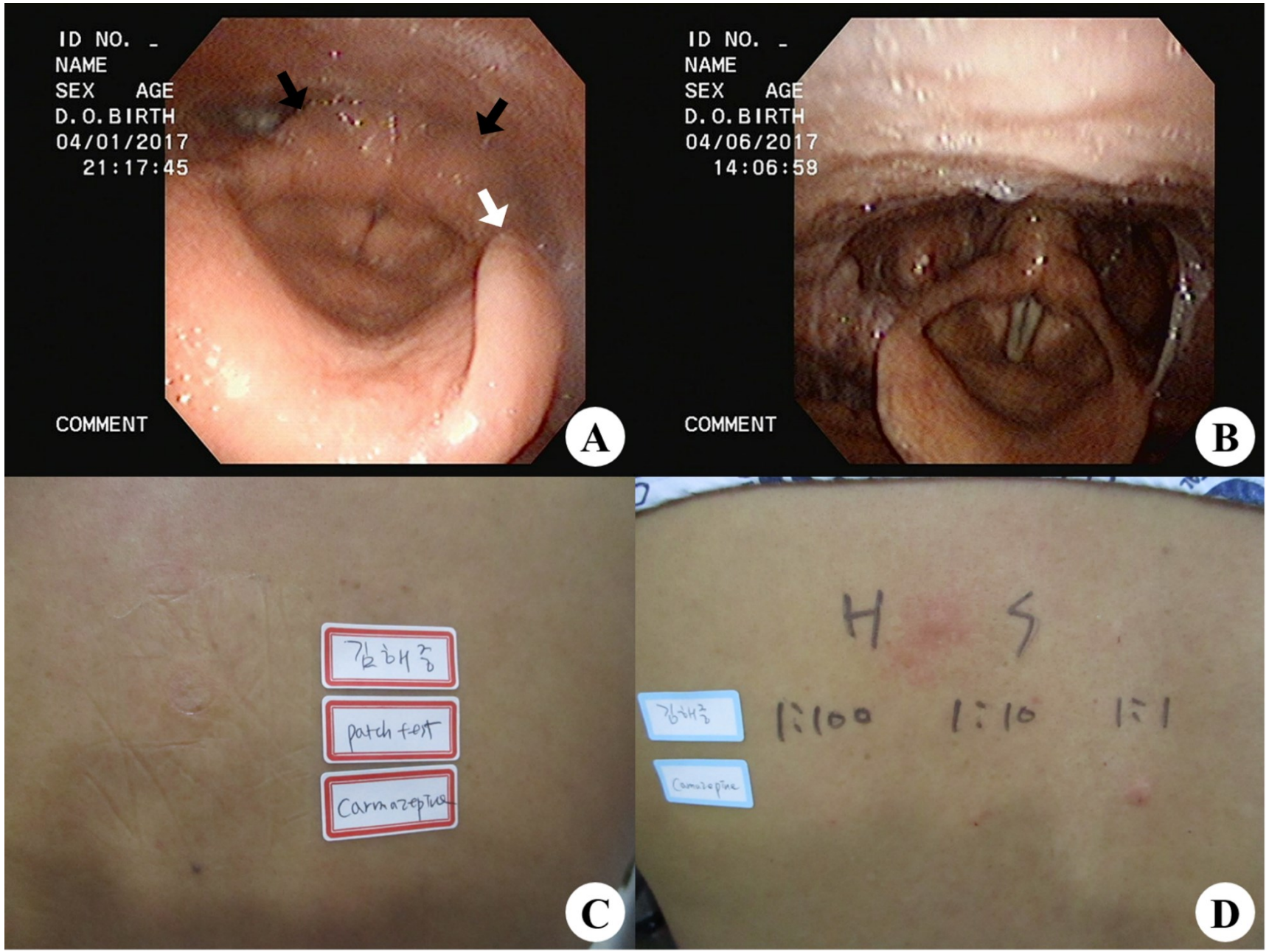
Piperacillin-Induced DRESS: Distinguishing Features Observed in a Clinical and Allergy Study of 8 Patients

R Cabañas,*[1,5] O Calderón,*[1] E Ramírez,[2,5] A Fiandor,[1,5] N Prior,[1,5] T Caballero,[1] P Herránz,[3,5] I Bobolea,[1] MC López-Serrano,[1] S Quirce,[1] T Bellón[4,5]

Table 2. Results of Lymphocyte Transformation Test (LTT), Intradermal Tests, and Epicutaneous tests with piperacillin/tazobactam in 8 Patients

Patient No.	Patch Test	Intradermal Test	LTT (SI)[c]
1	-	ND	3.3, 7, 14.3, 25.8
2	-	[a](+) (7x9 mm)	19, 36
3	ND	ND	4.06, 17.17, 22.33, 25.25
4	-	[a](+) (10x10 mm)	5.8, 6.3, 7.7
5	ND	[a](+) (8x10 mm)	4.44, 6.46
6	+	[b](-)	3.5, 3.8, 7.03, 13.5
7	ND	ND	10.6, 34.63
8	ND	ND	4.82, 24.9, 46.73, 57.92, 46.89

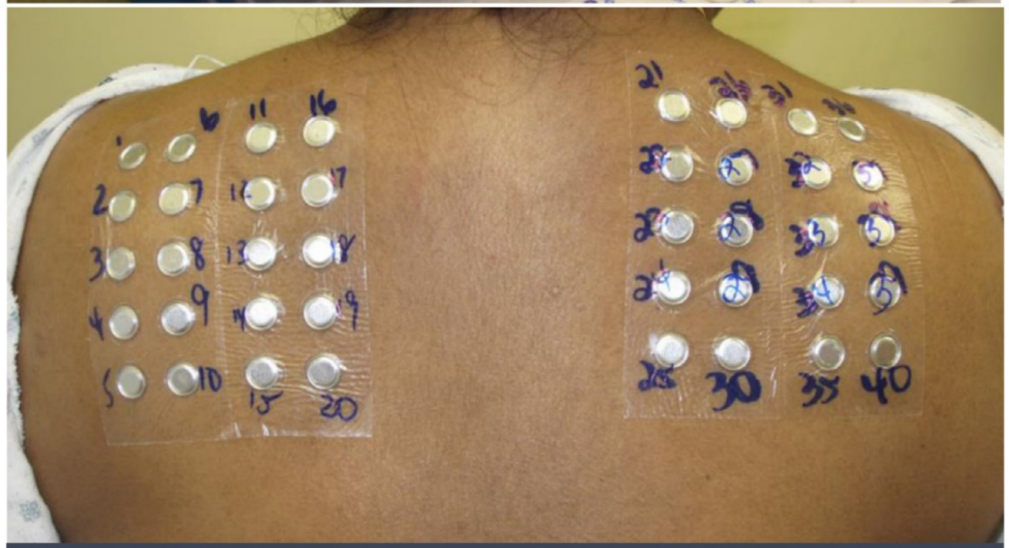
J Allergy Clin Immunol Pract. 2017;5:829-30
J Investig Allergol Clin Immunol. 2014;24:425-30
J Investig Allergol Clin Immunol.2016;26:119-20



J Allergy Clin Immunol Pract. 2018;6:2108-2109

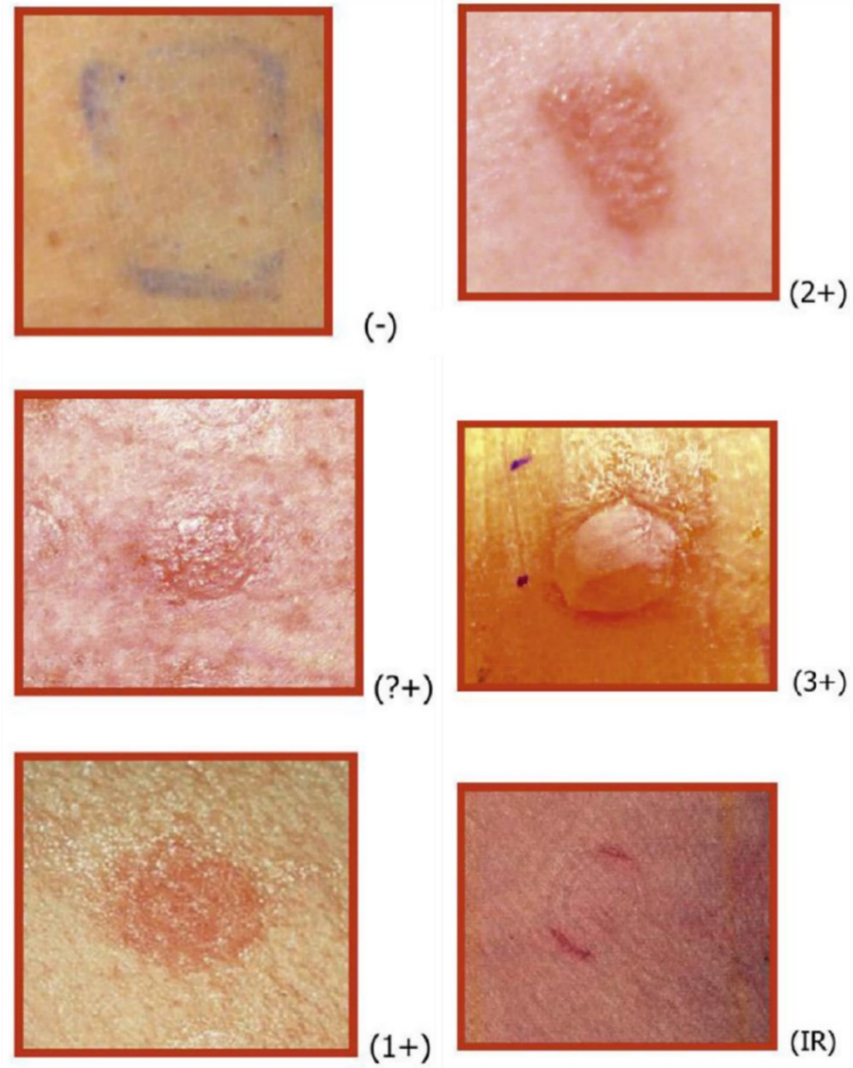
• Patch test

Loading the patch test chambers



Application of the patch test

Grading system for patch test interpretation



J Allergy Clin Immunol Pract. 2020;8:1883-1893

• Patch test for SCAR

Positive Allergy Study (Intradermal, Patch, and Lymphocyte Transformation Tests) in a Case of Isoniazid-Induced DRESS

Arruti N[1], Villarreal O[1], Bernedo N[1], Audicana MT[1], Velasco M[1], Uriel O[1], Martinez A[1], Bellón T[2]

[1]*Servicio de Alergia e Inmunología Clínica, Hospital Universitario Araba, Vitoria-Gasteiz, Spain*

[2]*Hospital La Paz Health Research Institute (IdiPAZ), Madrid, Spain*

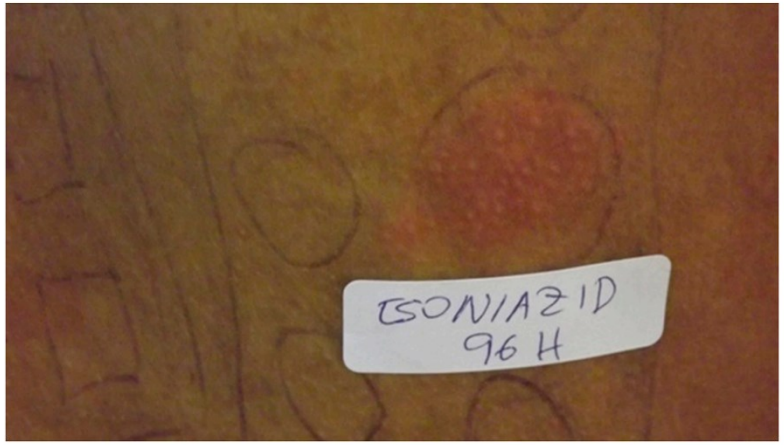


Figure. Positive patch test with isoniazid at 96 hours.

TABLE 4 Sensitivity of patch testing in DRESS

Drugs	Nr. tested[a]	Positive patch tests n (%)	Comments	Ref.
Groups of patients				
Drugs not specified	68	39 (57)	Eight had mild flare of DRESS	241
	28	14 (50)		242
	16	9 (56)	Eight of nine reactions were caused by carbamazepine	243
	15	9 (60)		244
Drugs specified	72	46 (64)	Fourteen reactions to beta-lactams and 11 to carbamazepine	50
	56	18 (32)	The group consisted of 33 antiepileptic drugs, 19 allopurinol, and sulfasalazine, cotrimoxazole, tenoxicam, and amoxicillin, one each. 17/18 positive reactions were to antiepileptics (13 to carbamazepine) and 0 to allopurinol	52
	14	5 (36)	Children: drugs used were mostly antibiotics and anticonvulsants	67
Classes of drugs				
Antiepileptics	33	17 (52)	Thirteen caused by carbamazepine	52
	18	11 (61)	Unclear data in this article	81
	10	9 (90)	Six reactions to carbamazepine, 2 to phenytoin, one to topiramate; many co-sensitizations to antibiotics	58
Antibiotics	19	6 (32)	4/6 caused by amoxicillin	60
	17	9 (53)	Six reactions to amoxicillin and three to cephalosporins, 0/7 to fluoroquinolones (ciprofloxacin, levofloxacin); six of the nine reactors had primary DRESS to antiepileptics and three to allopurinol	58
Iodinated contrast media	12	10 (83)	The patients had been selected on the basis of a positive skin or challenge test, which may (partly) explain the high percentage of positive patch tests	61
Antibiotics, beta-lactam	10	9 (90)	Six positive reactions to amoxicillin	59
Fluoroquinolones	7	0 (0)	Five ciprofloxacin, two levofloxacin	58

J Investig Allergol Clin Immunol. 2016;26:119-20
Contact dermatitis. 2022;86:443-479

BJD
British Journal of Dermatology

A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions

A. Barbaud,[1] E. Collet,[2] B. Milpied,[3] H. Assier,[4] D. Staumont,[5] M. Avenel-Audran,[6] A. Grange,[7] S. Amarger,[8] P. Girardin,[9] M.-T. Guinnepain,[10] F. Truchetet,[11] A. Lasek[12] and J. Waton[1] on behalf of the Toxidermies group of the French Society of Dermatology

Background Drug patch tests (PTs) can reproduce delayed hypersensitivity to drugs and entail a moderate re-exposure of patients to offending drugs.

Objectives To determine the value of PTs for identifying the responsible drug in severe cutaneous adverse drug reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

Methods In a multicentre study, PTs were conducted on patients referred for DRESS, AGEP or SJS/TEN within 1 year of their SCAR. All drugs administered in the 2 months prior to and the week following the onset of the SCAR were tested.

Results Among the 134 patients included (48 male, 86 female; mean age 51·7 years), positive drug PTs were obtained for 24 different drugs. These included positive tests for 64% (46/72) of patients with DRESS, 58% (26/45) of those with AGEP and 24% (4/17) of those with SJS/TEN, with only one relapse of AGEP. The value of PTs depended on the type of drug and the type of SCAR (e.g. carbamazepine was positive in 11/13 DRESS cases but none of the five SJS/TEN cases). PTs were frequently positive for beta lactams (22 cases), pristinamycin (11 cases) and in DRESS with pump proton inhibitors (five cases), but were usually negative for allopurinol and salazopyrin. Of 18 patients with DRESS, eight had virus reactivation and positive PTs. In DRESS, multiple drug reactivity was frequent (18% of cases), with patients remaining sensitized many years later.

Conclusions PTs are useful and safe for identifying agents inducing SCAR.

Br J Dermatol. 2013;168:555-62

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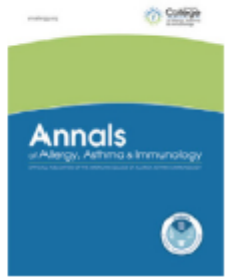

Editorial

Drug patch testing for severe cutaneous adverse reactions: Not in the United States?

Ann Allergy Asthma Immunol. 2023;130:538-539

Drug patch testing in Stevens-Johnson syndrome and toxic epidermal necrolysis

A systematic review

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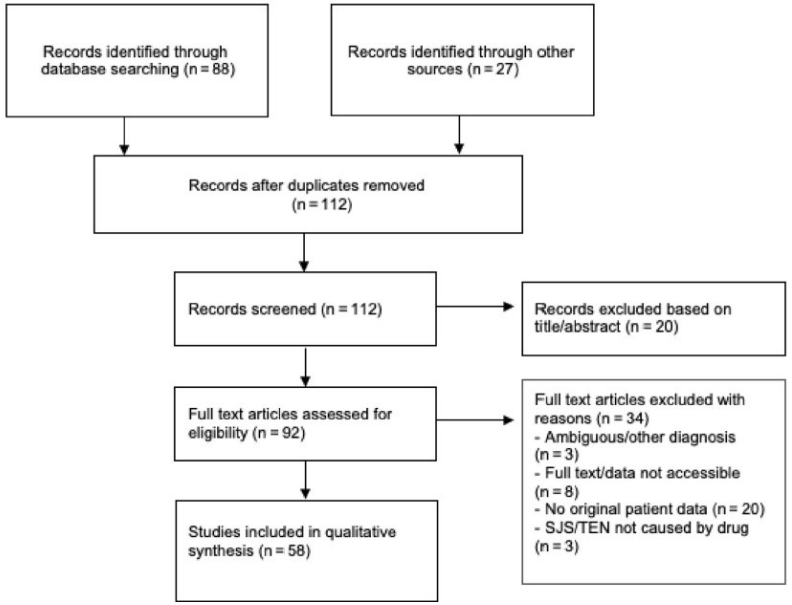
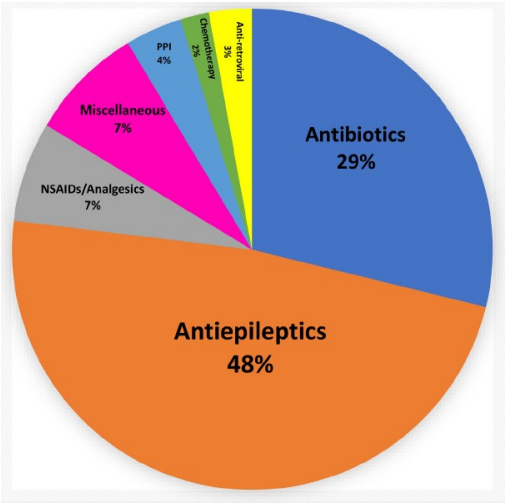


Positivity Rates of Drugs With Positive Patch Test Results

Drug	Positivity (all tests)	Positivity (suspected causative)
Antibiotics		
Amoxicillin	60.0% (6/10)	60% (6/10)
Ampicillin	50.0% (5/10)	100% (4/4)
Bucillamine	100.0% (1/1)	100% (1/1)
Clindamycin	16.7% (1/6)	100% (1/1)
Erythromycin	16.7% (1/6)	100% (1/1)
Isoniazid	100.0% (4/4)	100% (4/4)
Meropenem	20.0% (1/5)	100% (1/1)
Metronidazole	16.7% (1/6)	100% (1/1)
Penicillin	100.0% (1/1)	100% (1/1)
Penicillin G	100.0% (1/1)	100% (1/1)
Pristinamycin	75.0% (3/4)	75.0% (3/4)
Procaine benzylpenicillin	100.0% (1/1)	100.0% (1/1)
Pyrazinamide	50.0% (1/2)	50.0% (1/2)
Sulfamethoxazole	100.0% (1/1)	100.0% (1/1)
Sulfonamide	100.0% (1/1)	100.0% (1/1)
Vancomycin	12.5% (1/8)	33.3% (1/3)
Antiepileptic drugs		
Carbamazepine	48.7% (19/39)	50% (18/36)
Carbamazepine-10,11-epoxide	12.5% (1/8)	12.5% (1/8)
Diphenylhydantoin	33.3% (1/3)	50% (1/2)
Ethosuximide	100.0% (1/1)	100.0% (1/1)
Ethylbutylmalonylureum	100.0% (1/1)	100.0% (1/1)
Lamotrigine	19.0% (4/21)	50% (2/4)
Oxcarbazepine	17.6% (3/17)	Never suspected
Phenobarbital	25.0% (1/4)	50% (1/2)
Phenytoin	35.3% (6/17)	Never suspected
Tetrazepam	100.0% (9/9)	100% (9/9)
Valproate	50.0% (4/8)	57.1% (4/7)
Antiretrovirals		
Kivexa (Abacavir-Lamivudine)	100.0% (1/1)	100.0% (1/1)
Truvada (Emtricitabine-Tenofovir)	100.0% (1/1)	100.0% (1/1)
Lamivudine	100.0% (1/1)	100.0% (1/1)
Chemotherapies		
Bortezomib	100.0% (1/1)	100.0% (1/1)
Chlorambucil	100.0% (1/1)	100.0% (1/1)
NSAIDs/analgesics		
Diclofenac	50.0% (1/2)	100% (1/1)
Ibuprofen	20.0% (1/5)	0% (0/4)
Metamizole	100.0% (1/1)	100% (1/1)
Phenazone	100.0% (1/1)	100% (1/1)
Phenylbutazone	66.7% (2/3)	66.7% (2/3)
Voltaren (Diclofenac)	100.0% (1/1)	100% (1/1)
Proton pump inhibitors		
Esomeprazole	50.0% (1/2)	50.0% (1/2)
Lansoprazole	33.3% (1/3)	33.3% (1/3)
Omeprazole	50.0% (1/2)	50.0% (1/2)
Miscellaneous		
(RS)-2,3-Bis(sulfonyl) propane-1-sulfonic acid	100.0% (1/1)	100.0% (1/1)
Bromisovalum	100.0% (1/1)	100.0% (1/1)
Fexofenadine	100.0% (1/1)	100.0% (1/1)
Iohexol	100.0% (1/1)	100.0% (1/1)
Lamisil (Terbinafine)	100.0% (1/1)	100.0% (1/1)
Propranolol	100.0% (1/1)	100.0% (1/1)
Pseudoephedrine	100.0% (1/1)	100.0% (1/1)
Ramipril	100.0% (1/1)	100.0% (1/1)



Ann Allergy Asthma Immunol. 2023;130:628-636

REVIEW

CONTACT DERMATITIS WILEY

Results of patch testing in acute generalized exanthematous pustulosis (AGEP): A literature review

Diagnostic criteria of AGEP

Features of AGEP	Absent	Present/yes	Typical
Exanthema			
Pustules	0	1	2
Erythema	0	1	2
Distribution pattern	0	1	2
Collaret-shaped postpustular desquamation	0	1	
Course			
Mucosal involvement	0	−2	
Acute onset ≤10 days	−2	0	
Resolution ≤15 days	−4	0	
Fever, temperature ≥38°C	0	1	
Neutrophilia ≥7000/mm^3	0	1	
Histology			
Other diagnosis	0	−10	
Histology not typical or not performed	0	0	
Exocytosis of peripheral neutrophils	0	1	
Subcorneal and/or intraepidermal non-spongiform pustules or pustules not further specified with papillary edema or subcorneal and/or intraepidermal spongiform pustules or pustules not further specified without papillary edema	0	2	
Spongiform subcorneal and/or intraepidermal pustules	0	3	

Positive patch tests in AGEP

Drug	No. positive patch tests	%
Amoxicillin	36	13.9
Pristinamycin	25	9.7
Diltiazem	14	5.4
Amoxicillin-clavulanic acid	13	5.0
Clindamycin	11	4.2
Iomeprol	8	3.1
Iodixanol	6	2.3
Nystatin	6	2.3
Pseudoephedrine	6	2.3
Spiramycin	6	2.3
Ceftriaxone	5	1.9
Hydroxyzine	5	1.9
Prednisolone	5	1.9
Acetaminophen (paracetamol)	4	1.5
Celecoxib	4	1.5
Ciprofloxacin	4	1.5

Exacerbations after patch testing

Drug	Patch test concentration and vehicle	Symptoms and comments	Ref.
Acetaminophen	1% and 10% pet.	On D7 of a first and D6 of a second patch test session, a symmetric versicular eruption appeared on the trunk, arms and legs; the patch tests themselves were negative	52
Carbamazepine	Data unknown	Patch tests reproduced the skin eruption	88
Ceftriaxone	10, 1 and 0.1% pet.	Mild flare reaction consisting of papules and vesicles with erythema on the gluteal region during patch testing	93
Ciprofloxacin	Data unknown	Patch tests reproduced the original lesional pattern both clinically and histologically; there were also positive patch tests to other quinolones	102
Diltiazem	1% water and pure	Patch testing resulted in an erythematous and very pruriginous reaction on the patch tested area, neck, and abdomen that resolved in a few days	118
Diltiazem	1% pet.	Eczematous eruption on both forearms during patch testing; atypical AGEP case	49
Diltiazem	CP 30% pet. (3% a.i.) and pure drug 10% pet.	Patch testing induced an angry back reaction associated with maculopapular exanthema involving the face, neck, and armpits, but there were no systemic reactions; the authors suggested to start patch testing with 1% pet. instead of 10%	114
Hydroxyzine	Pure drug 2.5%	Flare-up of previously involved areas during patch testing	140

Contact dermatitis. 2022;87:119-141

Drug	HLA risk allele*	Reaction	Ethnic population	PPV (NPV)*
Antibiotics				
Benznidazole	A*11:01	DRESS	Bolivian	100 (70)
	A*29:02			100 (70)
	A*68			48 (84)
Dapsone	B*13:01	DRESS	Chinese	7.8 (99.8)
		DRESS, SJS/TEN	Thai	
		DRESS	Taiwanese	
			Malaysian	
Sulfamethoxazole	A*29	SJS/TEN	European ancestry	
	A*11:01	SJS/DRESS	Japanese	
	B*13:01	SCAR	Asian	4.05 (99.92)
		DRESS		3.64 (99.92)
	B*44 (B12 serotype)	SJS/TEN	European ancestry	
	B*38		European ancestry	
	DR*07		European ancestry	
Vancomycin	A*32:01	DRESS	European ancestry	
Anticonvulsants				
Carbamazepine	A*24:02	SJS/TEN	Han Chinese	
	A*31	DRESS, SJS/TEN	Japanese	
	A*31:01	DRESS	European ancestry	0.77 (99.98)
			Han Chinese	0.67 (99.97)
		SJS/TEN	European ancestry	
			Han Chinese	
		DRESS, SJS/TEN	Korean	
		SCAR	European ancestry	
	B*15:02	SJS/TEN	Han Chinese	2.24 (99.94)
			Indian	
			Korean	
			Malaysian	
			Thai	
			Taiwanese	93.6 (100)
	B*15:11	SJS/TEN	Han Chinese	
			Asian	43.8 (95.1)
		DRESS, SJS/TEN	Chinese	
	B*15:21	SJS/TEN	Thai	
		SJS/TEN	Filipino	1.03 (87.5)
	B*51:01	DRESS	Han Chinese	
	B*57:01	SJS/TEN	European ancestry	
	B*58:01	DRESS	Asian	90.4 (37)
Lamotrigine	A*02:07	MPE,DRESS, SJS/TEN	Thai	
	A*31:01	DRESS, SJS/TEN	Korean	
	A*68:01	DRESS, SJS/TEN	European ancestry	
	B*15:02	SJS/TEN	Han Chinese	
		DRESS, SJS/TEN	Thai	
		SJS/TEN	Iranian	78.57 (56.41)
	B*38	SJS/TEN	European ancestry	
	B*58:01	DRESS, SJS/TEN	European ancestry	
	C*07:18			
	DQB1*06			
	DRB1*13			
	DRB1*16:02			
Zonisamide	A*02:07	SJS/TEN	Japanese	
Antiretrovirals				
Abacavir	B*57:01	HSS	African	50 (100)
			European ancestry	50 (100)
			Hispanic	96 (60)
Nevirapine	Cw4	DRESS	Han Chinese	
	C*04:01	SJS/TEN	Malawian	2.6 (99.2)
	C*08	DRESS	Japanese	
	C*08:02, B*14:02	DRESS	European ancestry (Sardinian)	
	B*35:05	Skin rash	Thai	
	DRB1*01:01	DRESS	European ancestry	
Raltegravir	B*53:01	DRESS	African	
Other drugs				
Acetazolamide	B*59	SJS/TEN	Korean	
Allopurinol	B*58:01	DRESS, SJS/TEN	European ancestry	
		DRESS	European ancestry (Portuguese)	
		DRESS, SJS/TEN	Han Chinese	3 (100)
		DRESS, SJS/TEN	Korean	2.06 (99.98)
		DRESS	Thai	8.26 (100)
		SJS/TEN	Vietnamese	
		SJS/TEN	Japanese	
		SJS/TEN	European ancestry	
			Thai	10.48 (100)
	C*03:02	DRESS, SJS/TEN	Korean	1.77 (99.98)
		DRESS	Vietnamese	
	A*33:02	DRESS, SJS/TEN	Korean	0.8 (99.96)
Isoxicam	A*02	SJS/TEN	European ancestry	
	B*12			
Methazolamide	B*59:01	SJS/TEN	Japanese	
			Korean	
			Han Chinese	100 (96.8)
	B*55:02		Han Chinese	
Oxicams	B*73	SJS/TEN	European ancestry	
Strontium renalate	A*33:03	SJS/TEN	Han Chinese	
Sulfasalazine	B*13:01	DRESS	Han Chinese	
IL-6 and IL-1 inhibitors	DRB1*15	DRESS	European ancestry	

J Allergy Clin Immunol. 2023;151:289-300

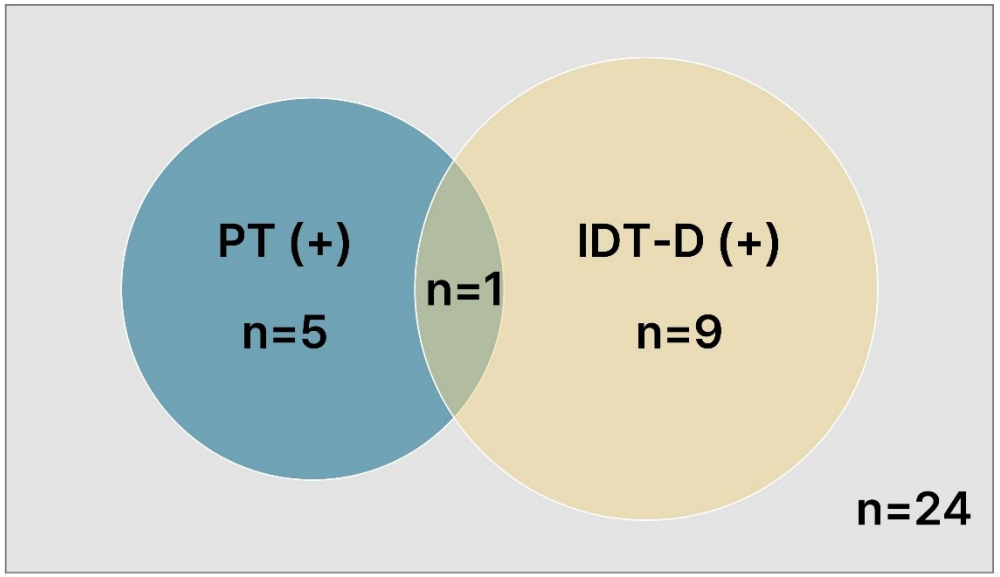


Figure 1. Frequency of positive patch test and delayed-reading intradermal test in all patients (n=39). IDT-D, delayed-reading intradermal test; PT, patch test.

Table 1. Clinical characteristics of 10 cases of positive delayed-reading intradermal test.

No.	Age (yr)	Sex	Diagnosis	Drug	PT	IDT-D
1	48	F	MPE	Gentamicin	-	+
2	71	M	DRESS syndrome	Carbamazepine	-	+
3	63	M	DRESS syndrome	Carbamazepine	-	+
4	54	M	DRESS syndrome	Carbamazepine	-	+
5	76	F	DRESS syndrome	Teicoplanin	-	+
6	63	F	DRESS syndrome	Teicoplanin	-	+
7	74	F	DRESS syndrome	Cefepime	-	+
8	18	M	DRESS syndrome	Minocycline	-	+
9	21	M	DRESS syndrome	Vancomycin	+	+
10	38	M	TEN	Ofloxacin	-	+

Unpublished data

Drug challenges

- Drug provocation test (DPT)

- Aim
  - Identification of the drug eliciting a DHR / Exclusion of DHR

- Method
  - Graded challenge
  - Single dose challenge
    - Low risk history
  - Placebo-controlled drug challenges
    - Subjective symptoms
    - Multiple reported drug allergies

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TABLE 2 Contraindications and relative contraindications to drug provocation test (DPT).[1]

Contraindications for provocation test with suspected drug
In cases with a clear history of drug hypersensitivity when allergy was proven by other means such as skin tests or in vitro tests
With the suspected drug, in severe anaphylaxis (≥Grade 3) except in settings equipped for and experienced in performing high-risk provocations such as perioperative anaphylaxis
With the suspected drug, in generalized bullous fixed drug eruption
With the suspected drug, in toxic epidermal necrolysis (TEN) and Stevens–Johnson Syndrome (SJS)
With the suspected drug, in leucocytoclastic vasculitis
With the suspected drug, in Drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)
Drug-induced specific organ dysfunction: cytopenia, hepatitis, nephritis, pneumonitis
Drug-induced autoimmune disease: systemic lupus erythematosus, linear IgA bullous dermatosis
Relative contraindications for provocation test with suspected drug
Severe comorbidity, for example, uncontrolled asthma, severe chronic obstructive airways disease, severe ischemic heart disease
Pregnancy—DPT can be performed when benefit of suspected drug outweighs the risk, such as severe infections (e.g., syphilis) and suspected penicillin allergy, or suspected local anesthetic allergy when spinal anesthesia may be needed for caesarean section

TABLE IV. Contraindications to drug challenges

Severe cutaneous adverse drug reactions
SJS/TEN
DRESS
AGEP
Drug-induced neutrophilic dermatosis
Sweet's syndrome
Drug-induced autoimmune diseases
Bullous pemphigoid
Pemphigus vulgaris
Linear IgA bullous disease
Drug induced lupus
Other cutaneous drug reactions
Generalized bullous FDE
Exfoliative dermatitis
Severe drug anaphylaxis*
Organ-specific drug reactions
Cytopenias (anemia, neutropenia, leukopenia, thrombocytopenia)
Drug induced liver injury
Nephritis
Pneumonitis
Meningitis
Pancreatitis
Drug-induced vasculitis
Leukocytoclastic vasculitis
Eosinophilic granulomatosis with polyangiitis
Angiotensin-converting enzyme inhibitor angioedema

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Allergy. 2024;79:565-579

Grading scale for immediate drug reactions

Grading severity: reaction criteria*	Grade NR: no symptoms or signs	Grade 0: reactions with primarily subjective symptoms only that improve/ resolve without treatment to include *any* of the following:	Grade 1: reactions with 1 or 2 of the following:	Grade 2: reactions with ≥2 of the following:	Grade 3: reactions with ≥1 of the following:	Grade 4: reactions resulting in *any* of the following conditions or interventions:
Mucocutaneous features		Pruritus without rash, tingling, subjective lip/tongue swelling	Flushing/erythema; <5 hives; angioedema of lip, face, or eyelid	≥5 hives, documented tongue or soft palate/ uvula edema	Tongue or uvula edema with dysphonia (surrogate for laryngeal edema) or documented laryngeal edema by laryngoscopy	NA
Respiratory features		Dyspnea, cough, tongue or throat sensation without objective changes, chest tightness	Dyspnea, cough, throat tightness, or chest tightness/ discomfort with an Spo_2 value of 93%-94%† or wheezing with an Spo_2 value of ≥93%	Dyspnea, cough, throat tightness, chest tightness/ discomfort, or wheezing with oxygen desaturation (an Spo_2 value of 90%-92%)	Oxygen desaturation (Spo_2 value < 90%)	Intubation performed for respiratory failure
Cardiovascular features		Dizziness, lightheadedness, heart racing, palpitations, tachycardia, hypertension	NA	Mild hypotension (SBP > 90 mm Hg and a 20%-29% decrease from baseline)	Moderate-to-severe hypotension (SBP < 90 mm Hg and a >30% decrease from baseline)‡	Pulseless Cardiopulmonary resuscitation performed Death

J Allergy Clin Immunol. 2023;152:1581-1586

Drug challenges

- Factors related to the patient and the setting of DPT
  1. DPT should be performed under medical supervision in a setting equipped for treating anaphylaxis including resuscitation equipment
  2. DPT in intermediate and high-risk patients and patients with immediate-type symptoms should be performed in a hospital setting
  3. Patients with mild MPE may be investigated with DPT in, or outside, a hospital setting in collaboration with allergy specialists
  4. The patient should be well on the day of DPT and baseline measurements before drug administration
  5. Intravenous access should be secured in high-risk patients with immediate reactions
  6. Verbal and written informed consent must be obtained before DPT

Allergy. 2024;79:565-579

Drug challenges

- Consensus-based Statement
  1. We suggest that when the clinical probability of a drug allergy is low, in patients without contraindications for a drug challenge, that it be performed with a 1- or 2-step drug challenge (conditional, low)

  2. We suggest that placebo controlled drug challenges be considered in patients with a history of primarily subjective symptoms and/or multiple reported drug allergies (conditional, low)

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TABLE V. Open drug challenge protocols for immediate reactions

	Dose*	Observation
1-step	1 tab or full PO/IV/IM/SC dose†	30-60 min
2-step	Step 1: ¼ tab PO or 1/10 IV/IM/SC dose	30-60 min
	Step 2: 1 tab or full PO/IV/IM/SC dose†	30-60 min
Criteria for positive reaction	Urticaria, angioedema, exanthem, wheezing, hypoxia, hypotension, anaphylaxis	
Criteria for possible reaction‡	Flushing, vomiting, cough, abdominal cramping, persistent pruritus without rash, fever, mouth or eye soreness	
Doubtful reactions‡	Dizziness, tachycardia, subjective lip/tongue swelling, subjective throat tightness, lump in throat, dyspnea, transient pruritus without rash, headache	

TABLE VI. Open drug challenge* protocols for nonsevere delayed reactions†‡

	Dose§	Observation
1-step**	1 tab or full PO‖	60 min to 2 h
2-step	Step 1: 1/10 IV/IM/SC dose	30 min
	Step 2: full PO/IV/IM/SC dose‖	60 min to 2 h
Other*	Multiple-day challenge or graded reintroduction	Outpatient procedure
Criteria for positive reaction	Fever, urticaria, facial swelling, exanthem, hypoxia, hypotension, mouth, urogenital or eye soreness, fixed or blistering eruption, target or atypical target lesions	
Criteria for possible reaction¶	Isolated joint pain, appetite change, persistent pruritus without rash	
Doubtful reactions¶	Dizziness, tachycardia, subjective lip/tongue swelling, subjective throat tightness, lump in throat, dyspnea, transient pruritus without rash, headache, transient pruritus without rash	

Thank you
for your attention ☺