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Piperacillin-Tazobactam Hypersensitivity: A Large, Multicenter Analysis

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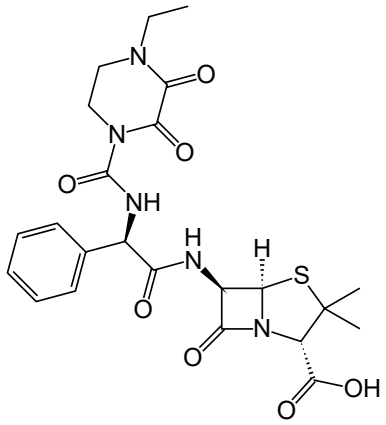
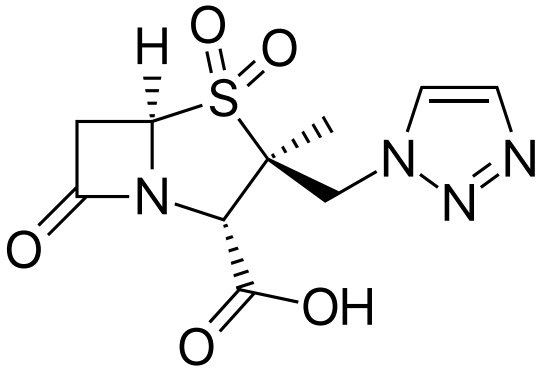
Disclosures

- No disclosures

Introduction:

- Piperacillin-tazobactam (PPZ-TZB) consist of 2 components:
  - semi-synthetic ureidopenicillin piperacillin
  - Beta-lactamase inhibitor tazobactam
- Both immediate hypersensitivity reactions (IHRs) and nonimmediate hypersensitivity reactions (NIHR) have been described (ex drug eruptions DRESS, AGEP, DRESS/AGEP overlap, SJS, TENS)
- In patients with cystic fibrosis (CF), PPZ-TZB has been cited as most frequent cause of drug hypersensitivity reactions
- In significant number of patients with confirmed beta-lactam allergy immune response is directed against unique side chain
- However in some patients cross-reactivity is demonstrated and specific “phenotypes” of cross reactivity have been described





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Methods:

- Four UK allergy centers and one Greek allergy center collected data from patients referred to their services between 2012 and 2019 with history of suspected PPZ-TZB allergy
  - Guy's and St Thomas', London; Addenbrooke's, Cambridge; Royal Hallamshire Hospital, Sheffield; and Royal Liverpool University Hospital, Liverpool
  - Attikon University Hospital, Athens
- All data obtained solely for clinical reasons: age, sex, time from presentation to diagnosis, index reaction, med hx, skin test (ST), skin prick test (SPT), intradermal test (IDT), drug provocation test (DPT), baseline and acute tryptase measurement, specific IgE to penicillins
- Severity of IHR was graded according to Brown's classification of systemic reactions
- Diagnosis of DRESS was made using the RegiSCAR criteria

Results:

- Provisional diagnosis of IHR and NIHRs to PPZ-TZB was based on timing of index reaction according to the European Network for Drug Allergy classification of drug hypersensitivity reaction (updated by Drug Allergy Interest Group)
- 87 patients referred with suspected PPZ-TZB hypersensitivity
  - 41 (47%) presented for IHR's
  - 46 (53%) presented for NIHR's
  - 23 (26%) had comorbid CF
    - 8 patients with IHR
    - 15 for NIHR

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Immediate Hypersensitivity Results

IHR Results

- ST positive in 25 patients (61%)
  - 20/25 females (p=0.045)
- 24/25 of ST positive patients underwent STs to other penicillins
  - 16/24 were sensitized to PPZ-TZB only
  - 8/24 were cross-sensitized to other penicillins (on SPT, immediate IDT, or sIgE)
- ST negative in16 patients
  - 5/16 underwent reintroduction
  - Most did not undergo reintroduction

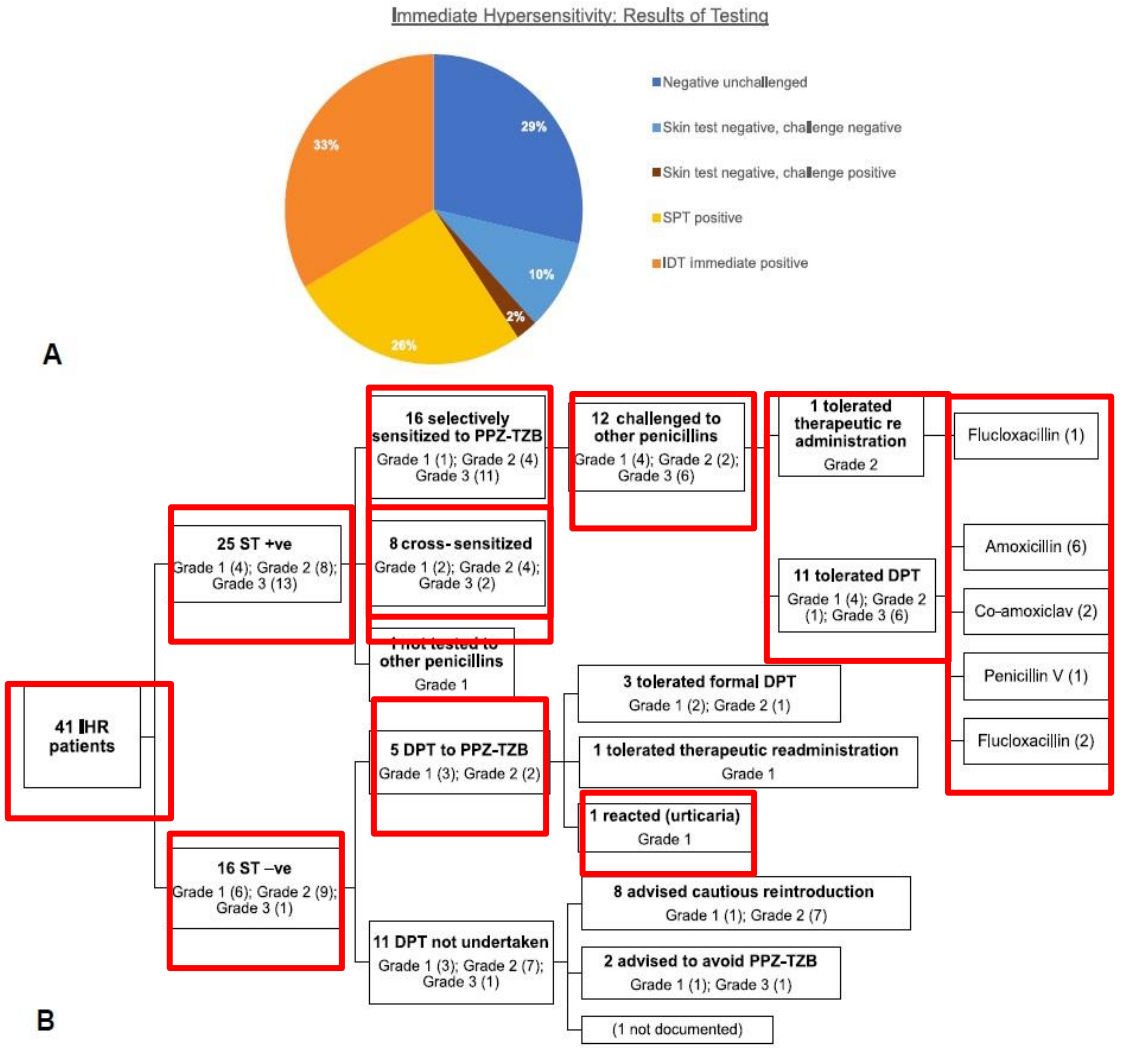

FIGURE 1. (A) Results of all tests in patients with a history of immediate reaction. (B) Overview of all patients referred with suspected IH to PPZ-TZB.

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IHR Results

TABLE III. Results of all testing to beta-lactam antibiotics in patients with positive immediate ST results to PPZ-TZB

Cross-reactors	Amoxicillin	Ampicillin	BenPen	MD	PPL	Pen V	Pen G	Co-amoxiclav	Clavulanic acid
Patient 1	SPT*		SPT*						
Patient 2	IDT	IDT	IDT	IDT					
Patient 3			IDT						
Patient 4				IDT	IDT				
Patient 5	IDT + sIgE	IDT							
Patient 6						sIgE	sIgE	IDT	IDT
Patient 7	IDT + sIgE			IDT	IDT	sIgE	sIgE		
Patient 8	sIgE*					sIgE*			

BenPen, Benzylpenicillin; *Pen V*, penicilloyl V; *Pen G*, penicilloyl G.

Cross-sensitization was seen in 8 patients; each had a unique pattern of cross-reactivity. *//SPT/ IDT/ sIgE*: test type of the positive result to other beta-lactam antibiotic.

*Patients 1 and 8 were positive to PPZ-TZB on SPT. All others tested positive to PPZ-TZB on immediate IDT.

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IHR Results

- Four patients were nurses and reacted only with occupational exposure when preparing PPZ-TZB for administration.
- Statistically significant difference in the severity of presentation (P=0.003, *t test)* between those with positive and negative ST

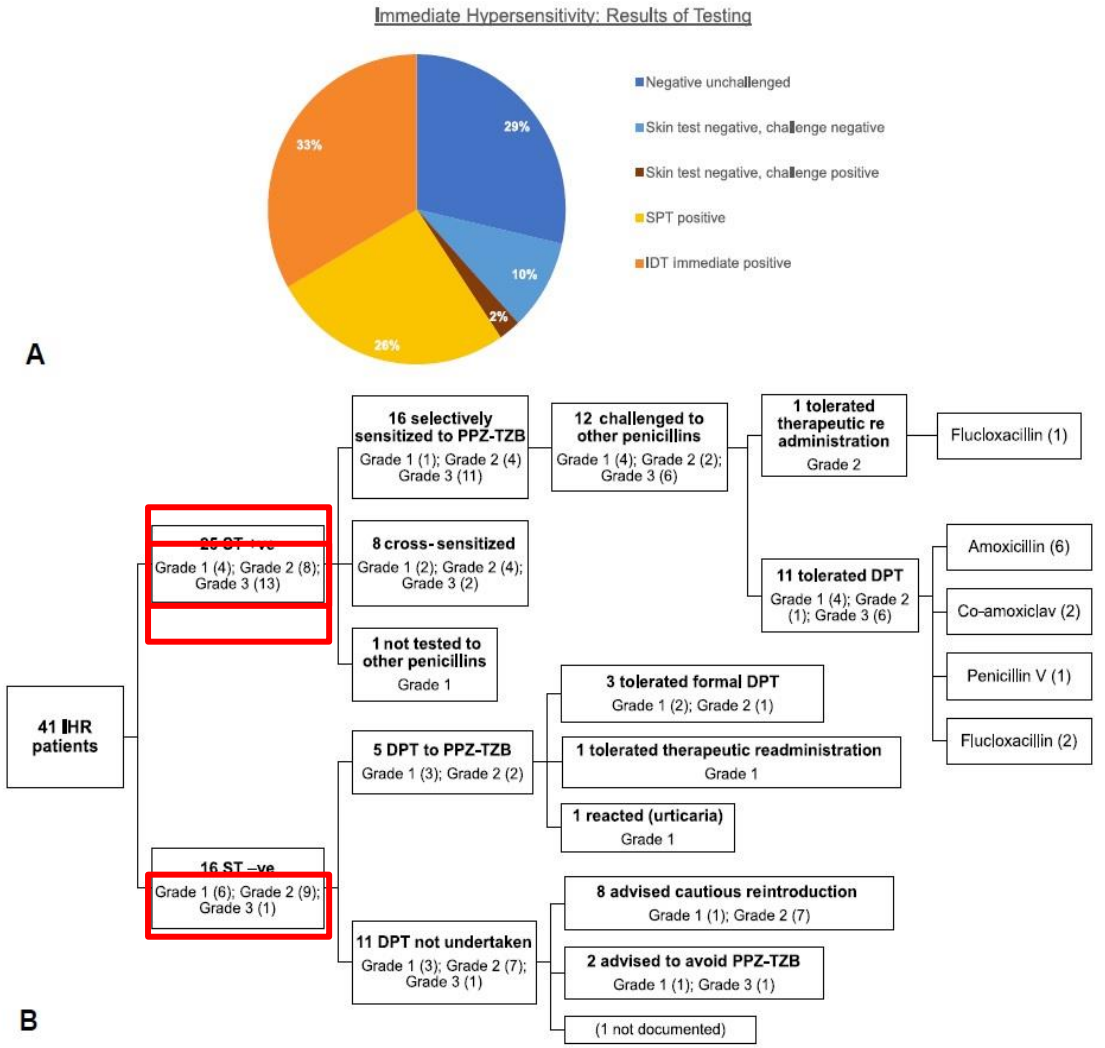

FIGURE 1. (A) Results of all tests in patients with a history of immediate reaction. (B) Overview of all patients referred with suspected IH to PPZ-TZB.

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Non-Immediate Hypersensitivity Results

NIHR Results

- Delayed IDT positive in 20/44 patients tested (45%)
  - 14/20 were selectively sensitized to PPZ-TZB
  - 6/20 cross-sensitized
- 9 underwent further challenges
  - 2 underwent DPT to other beta-lactams
  - 7 underwent therapeutic readministration
- 7/15 patients with CF were ST-positive

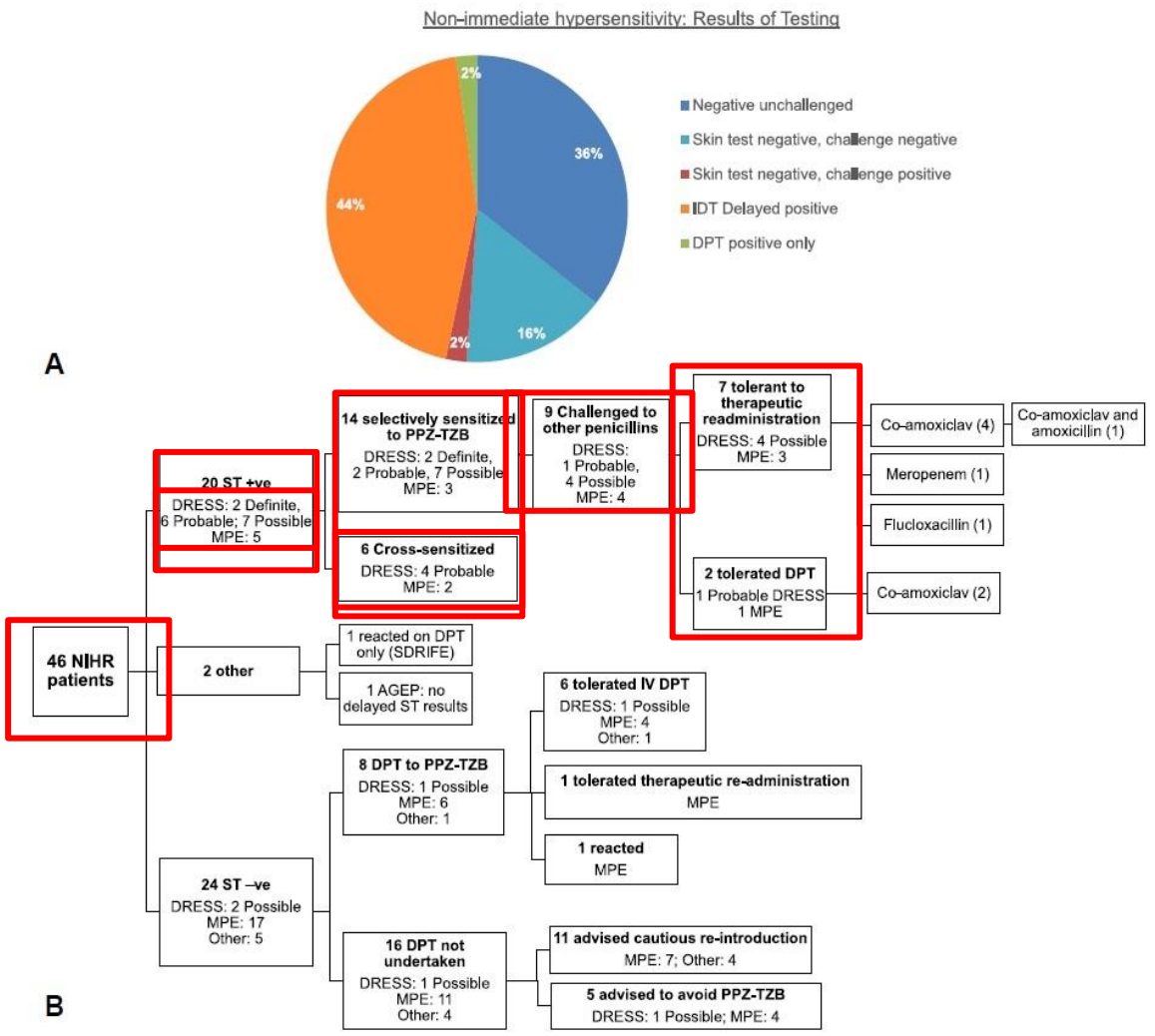

FIGURE 2. (A) Results of all tests in patients with a history of nonimmediate reaction. (B) Overview of all patients referred with suspected to PPZ-TZB.

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NIHR Results

TABLE V. Results of all testing to beta-lactam antibiotics in patients with positive delayed STs to PPZ-TZB

Cross-reactors	Amoxicillin	Ampicillin	BenPen	MD	PPL	Co-amoxiclav	Meropenem
Patient 1	IDT					IDT	
Patient 2	IDT					IDT	
Patient 3						IDT	
Patient 4						IDT	
Patient 5							IDT
Patient 6							IDT

BenPen, Benzylpenicillin.

Cross-sensitization was seen in 6 patients using delayed IDT. There were 3 phenotypic patterns of cross-reactivity: co-amoxiclav and amoxicillin (2), co-amoxiclav only (2), and meropenem only (2). All patients were positive on delayed IDT to PPZ-TZB and the beta-lactam antibiotics indicated.

NIHR Results

- Negative ST to PPZ-TZB and all other penicillins recorded in 24/44 (55%)
- 8/24 underwent further testing
  - 6 tolerated IV DPT
  - 1tolerated therapuetic readministration
  - 1 reacted to IV DPT within 24 hours of single dose

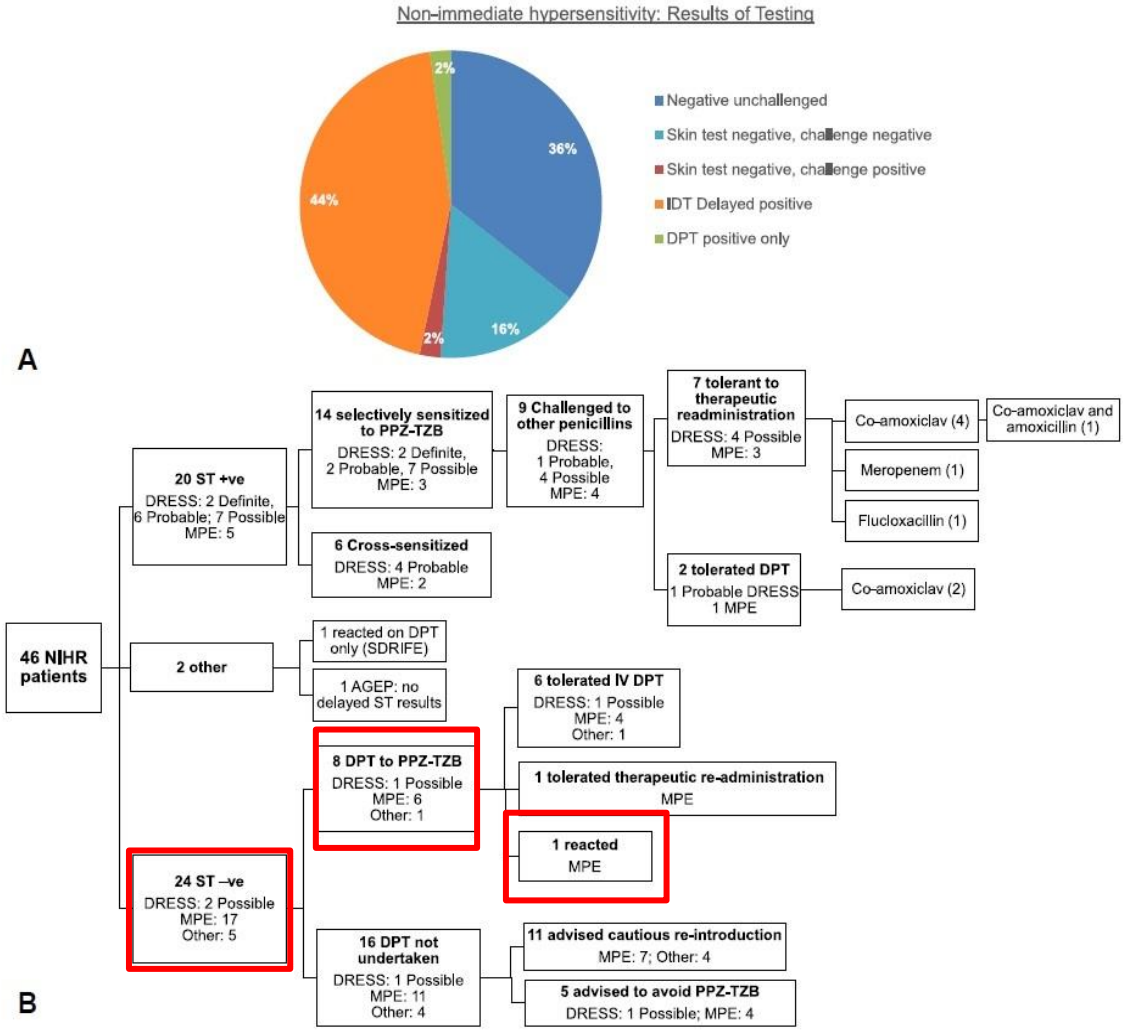

FIGURE 2. (A) Results of all tests in patients with a history of nonimmediate reaction. (B) Overview of all patients referred with suspected to PPZ-TZB.

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Conclusion/Discussion:

- Largest clinical review of patients with suspected PPZ-TZB hypersensitivity
- NIHR comprised larger portion (44%) of PPZ-TZB HR compared to other beta-lactams (ex flucloxacllin, IHR is significantly more common, 82.5% Kennard et al 25)
- Selectively sensitized patients with both IHR and NIHR tolerated other penicillins
- Reintroduction of Zosyn in a small group of skin-test negative patients was tolerated by most patients
- Although skin testing in DRESS has historically been avoided, selecting patients with negative ST and a history of mild reaction for IV DPT appears to be safe
- ST results were more likely to be positive in patients presenting for severe reactions
- Special populations: IHR more common in women(4-1), in patients with CF NIH was more common, PPZ-TZB is a cause of occupational hypersensitivity, minority of patients may be allergic to TZB component only
- Limitations

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European Network for Drug Allergy: Immediate v Nonimmediate

Box 2: Classification of drug hypersensitivity reactions

1. Drug hypersensitivity reactions (DHRs) are heterogeneous.
2. Clinically, DHRs can be classified as:
   - **a** Immediate DHRs (urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms [nausea, vomiting, diarrhea, abdominal pain], anaphylaxis, anaphylactic shock); they typically occur within 1–6 h after the last drug administration.
   - **b** Nonimmediate DHRs (delayed urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, and Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis and symmetrical drug-related intertriginous and flexural exanthemas; internal organs can be affected either alone or with cutaneous symptoms (DRESS, vasculitis) and include hepatitis, renal failure, pneumonitis, anemia, neutropenia, thrombocytopenia); they may occur at any time as from 1 h after from the initial drug administration.
3. Mechanistically, DHRs can be defined as allergic (Table 2) and nonallergic.

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Brown grading system for anaphylaxis

TABLE V. Grading system for generalized hypersensitivity reactions

Grade	Defined by
1—Mild (skin and subcutaneous tissues only)*	Generalized erythema, urticaria, periorbital edema, or angioedema
2—Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3—Severe (hypoxia, hypotension, or neurologic compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, LOC, or incontinence

SBP, Systolic blood pressure; *LOC*, loss of consciousness.
*Mild reactions can be further subclassified into those with and without angioedema (see text).

RegiSCAR score for DRESS

Scoring system for the diagnosis of DRESS

Clinical parameters	Score			Comments
	–1	0	1	
Fever ≥101.3°F (38.5°C)	No/unknown	Yes		
Lymphadenopathy		No/unknown	Yes	>1 cm, at least 2 sites
Eosinophilia $\geq 0.7 \times 10^9$ or ≥10% if leucopenia		No/unknown	Yes	Score 2 points of $\geq 1.5 \times 10^9$
Atypical lymphocytes		No/unknown	Yes	
Skin rash				
▪ Rash suggestive of DRESS	No	Unknown	Yes	Suggestive features: ≥2 facial edemas, purpura, infiltration, desquamation
▪ Extent ≥50% of BSA		No/unknown	Yes	
Skin biopsy suggestive of DRESS	No	Yes/unknown		
Organ involvement		No	Yes	1 point for each organ involvement, maximum score: 2
Disease duration ≥15 days	No/unknown	Yes		
Exclusion of other causes		No/unknown	Yes	1 point if 3 of the following tests are performed and are negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture

Total score:

- <2: Excluded
- 2 to 3: Possible
- 4 to 5: Probable
- ≥6: Definite

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