Drug Hypersensitivity Reactions

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Adverse drug reactions

Reactions	Example
Predictable	
Overdosage	Acetaminophen – hepatic necrosis
Side-effect	Albuterol – tremor
Secondary effect	Clindamycin – *Clostridium difficile* pseudomembranous colitis
Drug-drug interaction	Terfenadine/erythromycin – torsade de pointes arrhythmia
Unpredictable	
Intolerance	Aspirin – tinnitus (at usual dose)
Idiosyncratic	Chloroquine – hemolytic anemia in G6PD-deficient patient
Allergic	Penicillin – anaphylaxis
Pseudoallergic	Radiocontrast material – anaphylactoid reaction

- In otherwise normal patients
- Dose-dependent
- Related to the known pharmacologic actions of the drug
- Predictable

- In genetic susceptible individuals
- Dose-independent
- Not related Related to the pharmacologic actions of the drug
- Not predictable

Adverse drug reactions

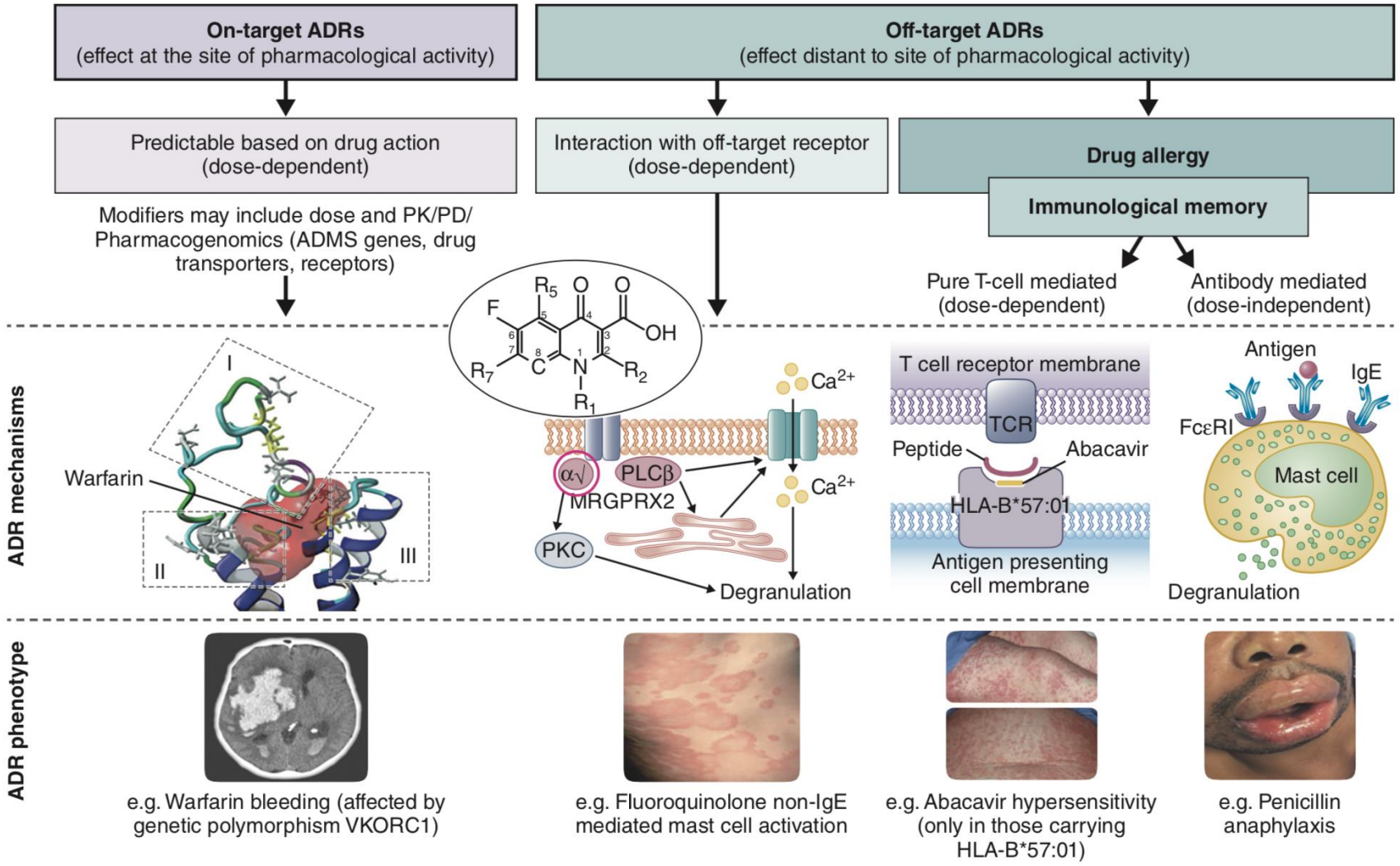
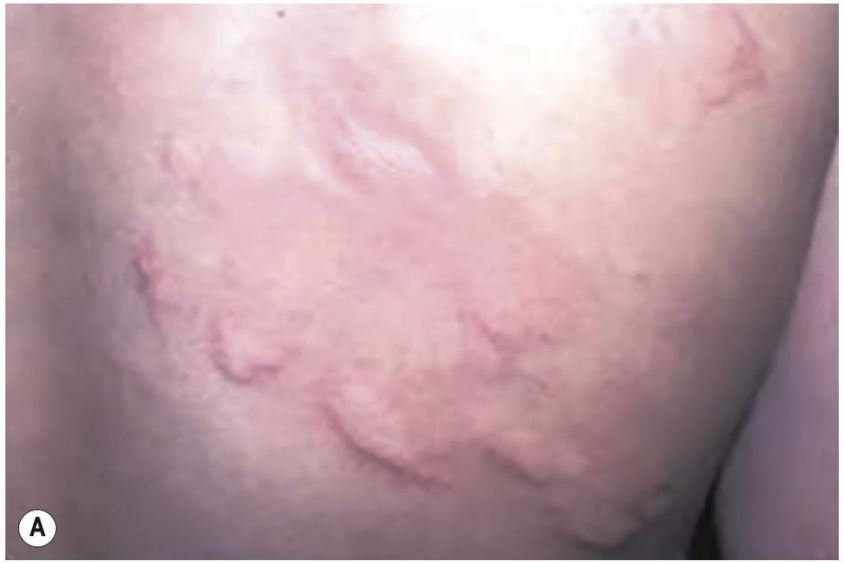


TABLE 77.1 Gell and Coombs Classification of Hypersensitivity Disorders

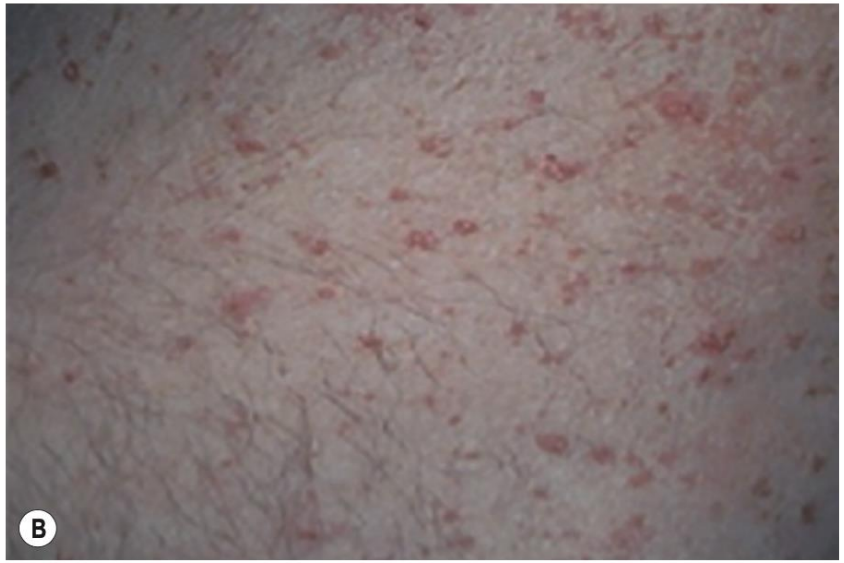
TYPE	INTERVAL BETWEEN EXPOSURE AND REACTION	EFFECTOR MOLECULE	TARGET OR ANTIGEN	EXAMPLES OF MEDIATORS	EXAMPLES
I Immediate Late phase	<30 min 2-12 hr	IgE	Pollens, food, venom, drugs	Histamine, tryptase, leukotrienes, prostaglandins, platelet-activating factor	Anaphylaxis, urticaria, allergic rhinitis, allergic asthma
II Cytotoxic antibody	Variable (minutes to hours)	IgM, IgG, IgA	Red blood cells, platelets	Complement	Hemolytic anemia, thrombocytopenia, Goodpasture syndrome
III Immune complex	1-3 wk after drug exposure	Antigen-antibody complexes	Blood vessels, liver, spleen, kidney, lung	Complement, anaphylatoxin	Serum sickness, hypersensitivity pneumonitis
IV Delayed type	2-7 days after drug exposure	Lymphocytes	*Mycobacterium tuberculosis*, chemicals	Cytokines (IFN-γ, TNFα, GM-CSF)	TB skin test reactions, contact dermatitis, graft-versus-host disease

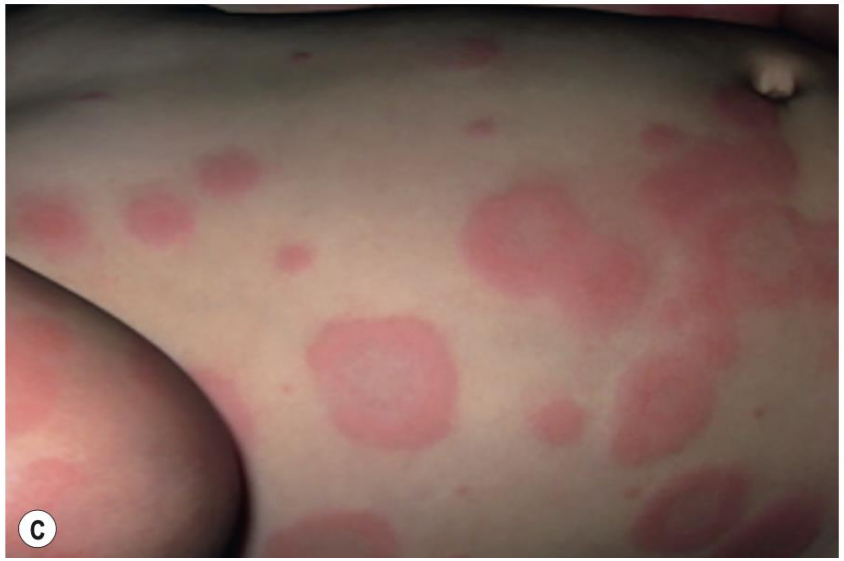
CSF, Cerebrospinal fluid; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IFN-γ*, interferon-γ; *TB*, tuberculosis; *TNFα*, tumor necrosis factor-α.

Urticaria

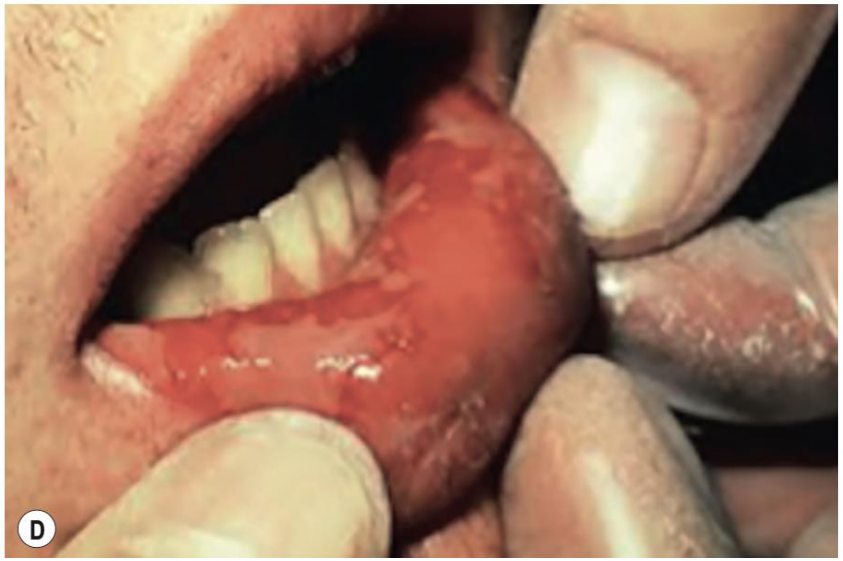


Morbilliform rash





Erythema multiforme



TEN

- **Evaluation of the clinical history:**
  - The timing of the reaction
  - The nature of the drugs involved
  - The dosage and rout of administration
  - The Hx of a previous exposure
  - Medical/genetic background
  - The severity of reaction
  - Differential Dxs

- **Drug allergy labeling**
  - Approximately 90% of patients with a clinical history of penicillin allergy do not have evidence of penicillin-specific IgE antibodies

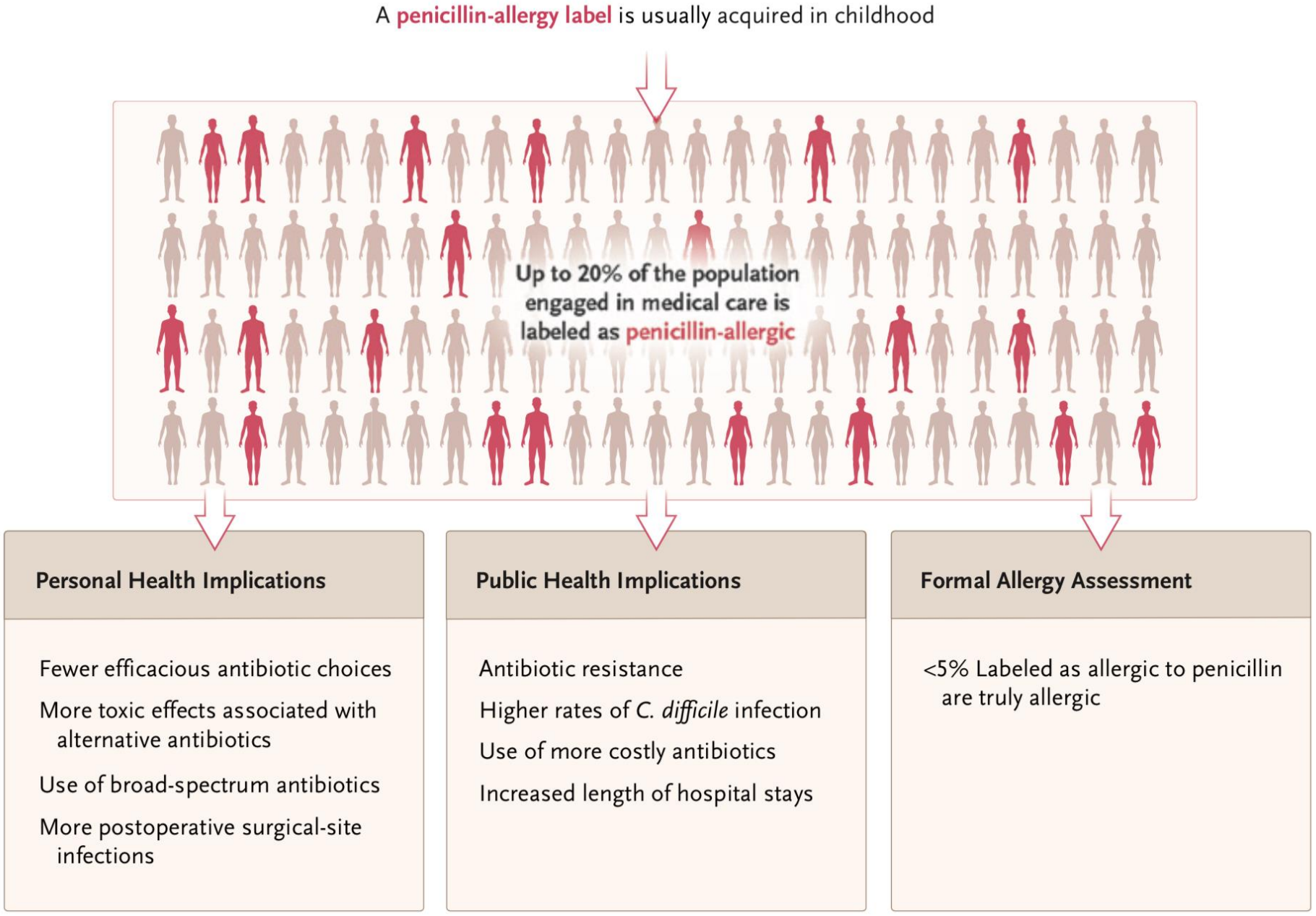
Risk Factors for Hypersensitivity Reactions to Drugs

- Prior exposure
- Previous reactions
- Age (20-49 yr)
- Route of administration (parenteral or topical)
- Dose (high)
- Dosing schedule (intermittent)
- Genetic predisposition (slow acetylators, HLA associations)
- BUT NOT ATOPY

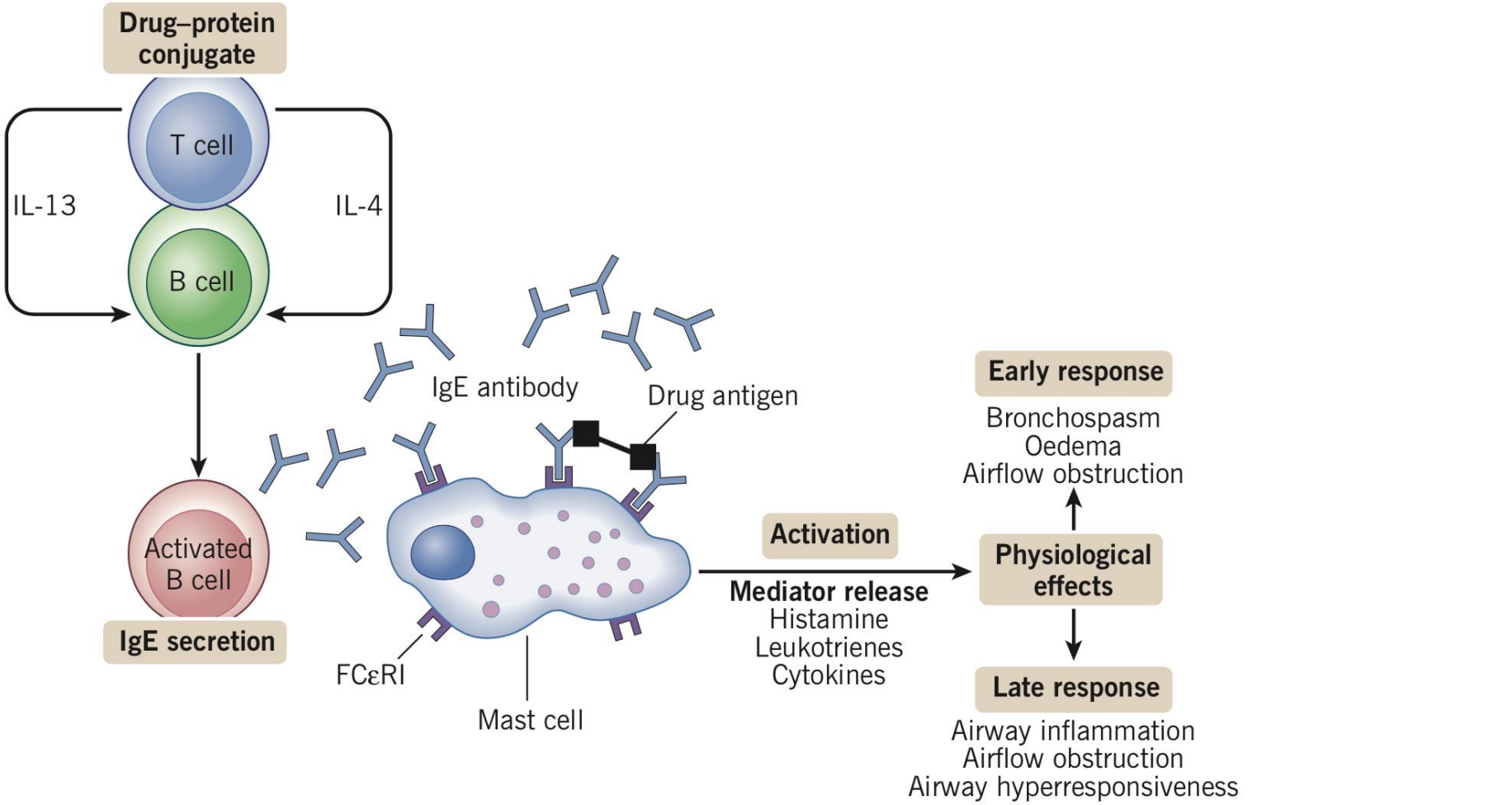
Immediate allergic reactions to Penicillin:

A model to show clinical complexity of drug allergy

Drug allergy labeling



Mechanism of immediate DHRs

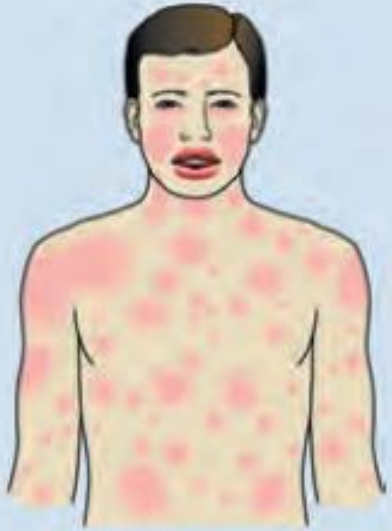


Sensitization phase

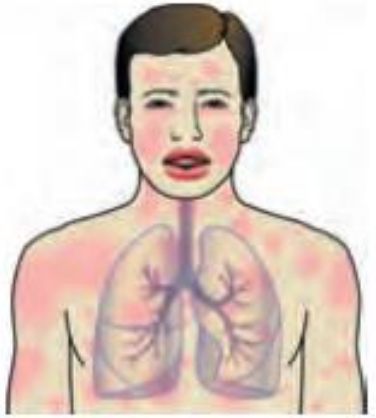
Re-exposure

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

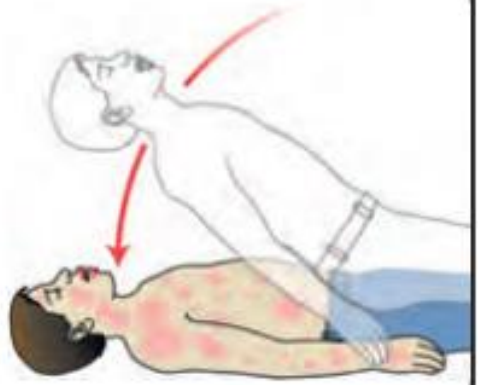
1 **Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)**



And at least one of the following:



Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)



Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

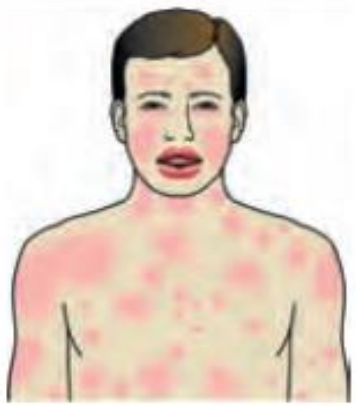
Signs and symptoms of anaphylaxis

TABLE 75.4 Signs and Symptoms of Anaphylaxis: Frequency of Occurrence

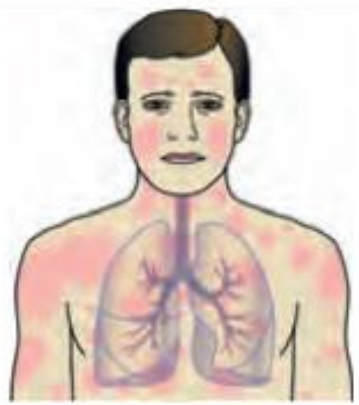
Signs/Symptoms	Approximate Percentage of Cases
Cutaneous	80-90
Urticaria	
Angioedema	
Flushing	
Pruritis	
Other rash	
Respiratory	70
Rhinorrhea, congestion	
Stridor	
Dysphonia	
Shortness of breath	
Chest tightness	
Wheezing	
Cyanosis	
Cardiovascular	45
Chest pain	
Tachycardia	
Bradycardia	
Hypotension	
Dysrhythmias	
Cardiac arrest	
Gastrointestinal	45
Abdominal pain	
Nausea, vomiting	
Diarrhea	
Central Nervous System	15
Sense of impending doom	
Altered mental status	
Dizziness	
Confusion	
Headache	

Modified from Zilberstein et al.[2]

Or **2** **Two or more of the following that occur suddenly after exposure to a *likely allergen or other trigger** *for that patient* (minutes to several hours):**



Sudden skin or mucosal symptoms and signs
(e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)



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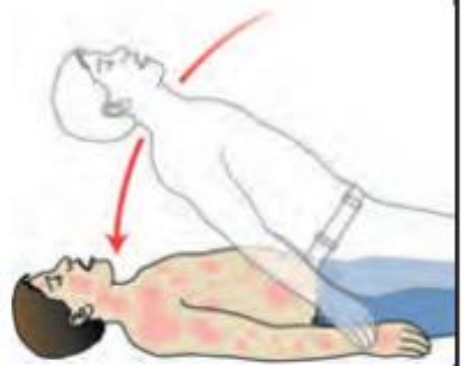
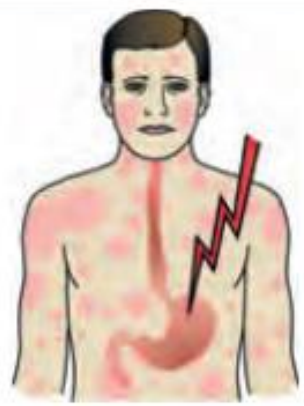


Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)



Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

Or **3** **Reduced blood pressure (BP) after exposure to a *known allergen*** *for that patient* (minutes to several hours):**

Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP***

Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

Severity grading system of immediate type 1 hypersensitivity reactions

Epinephrine

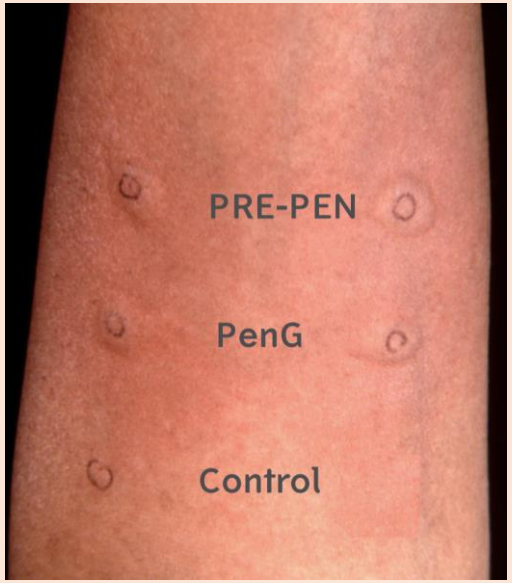
Elevated Tryptase

Grade	Severity	Description
1	Mild	Symptoms are limited to the skin (*e.g.*, flushing) or involve a single organ/system and are mild (*e.g.*, mild back pain).
2	Moderate	Symptoms involve at least two organs/systems (*e.g.*, flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation.
3	Severe	Symptoms typically involve at least two organs/systems, and there is a significant decrease in blood pressure (systolic ≤90 mm Hg and/or syncope) and/or oxygen saturation (≤92%).

Brown SGA, et al. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004; 114: 371–376.

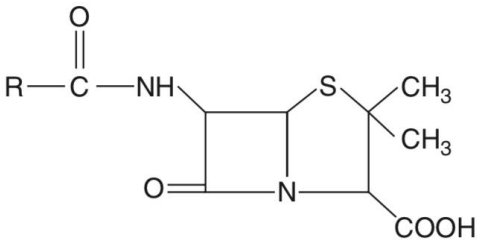
Diagnostic measures:

- Search for drug specific specific IgE :
  - Skin tests
  - In vitro tests
- Drug Provocation tests
- Diagnosis of Anaphylaxis: elevated tryptase level

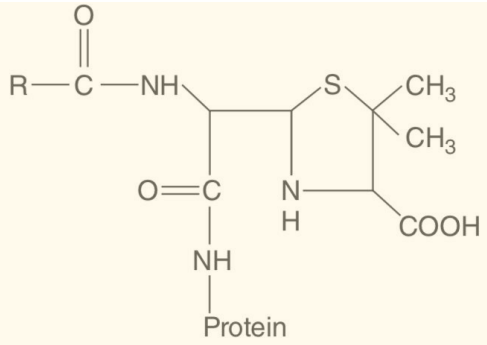


Penicillin allergenic determinants

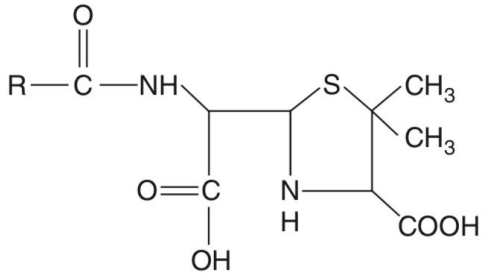
- Minor determinants
  - MDM
  - Penicillin G



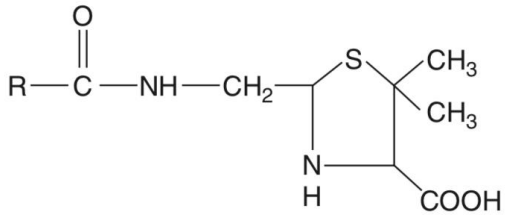
Penicillins



Penicilloyl



Penicilloate



Penilloate

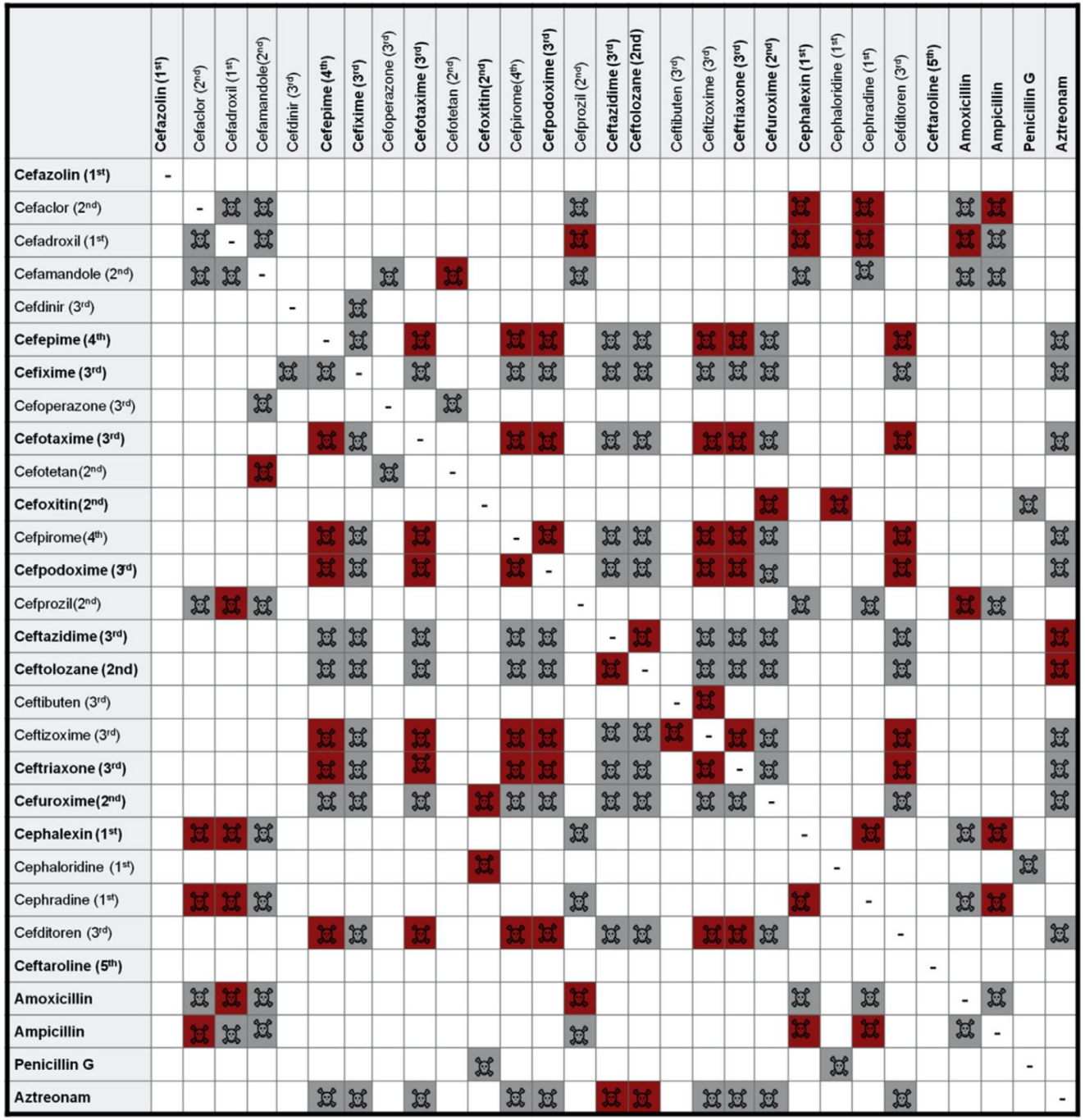
- Major determinant
  - Pre-Pen

Positive Penicillin Skin-Test Patterns Among Patients Reporting a History of Penicillin Allergy: Results in Three Studies Using PPL, Benzylpenicillin, Benzylpenicilloate, Benzylpenilloate, and Amoxicillin Reagents

Reagent	Macy et al, 1997[43] N = 60[a] n (%)	Lin et al, 2010[45] N = 243[b] n (%)	Geng et al, 2017[47] N = 107[b] n (%)
Positive to specified reagent, alone or in combination			
Penicilloyl-polylysine (PPL)[c]	41 (68.3%)	157 (64.6%)	39 (36.4%)
Benzylpenicillin	9 (15.0%)	111 (45.7%)	24 (22.4%)
Benzylpenicilloate	5 (8.3%)	90 (37.0%)	58 (54.2%)
Benzylpenilloate	8 (13.3%)	84 (34.6%)	23 (21.5%)
Amoxicillin	4 (6.7%)	75 (30.9%)	41 (38.3%)
Positive to specified reagent only			
PPL only	24 (40.0%)	45 (18.5%)	13 (12.1%)
Benzylpenicillin only	2 (3.3%)	16 (6.6%)	2 (1.9%)
Benzylpenicilloate only	4 (6.7%)	7 (2.9%)	25 (23.4%)
Benzylpenilloate only	7 (11.7%)	16 (6.6%)	3 (2.8%)
Amoxicillin only	1 (1.7%)	14 (5.8%)	8 (7.5%)
Positive to one or more specified reagents only			
Benzylpenicilloate or benzylpenilloate only	12 (20.0%)	39 (16.0%)	28 (26.2%)
PPL or benzylpenicillin only	32 (53.3%)	Not reported	Not reported
Benzylpenicilloate, benzylpenilloate, or amoxicillin only	16 (26.7%)	Not reported	Not reported
Benzylpenicillin, benzylpenicilloate, or benzylpenilloate only	15 (25.0%)	55 (22.6%)	30 (28.0%)

[a]Outpatients.
[b]Inpatients.
[c]Macy et al used commercially available PPL, whereas, because PRE-PEN was not commercially available in 2004, Lin et al synthesized the PPL for their trial. The site whose retrospective data Geng et al reported used PRE-PEN or PPL synthesized by the site according to published methods.

Beta-lactam Cross-reactivity



Current Penicillin hypersensitivity testing recommendations

Direct oral amoxicillin challenge can be performed in any patients with a history of the following symptoms associated with penicillin occurring more than 12 months ago:

- Any benign rash
- GI symptoms
- Headaches
- Other benign somatic symptoms
- Unknown history

Request allergy to penicillin skin test first if

- The reaction to penicillin has occurred within the past 12 months
- The patient has any history of shortness of breath or anaphylaxis associated with penicillin

and proceed to amoxicillin challenge only if skin test negative

Do not perform any penicillin allergy testing if there is a history of penicillin-associated

- Blistering rash involving $\geq 10\%$ of body surface area with skin loss
- Hemolytic anemia
- Nephritis
- Hepatitis