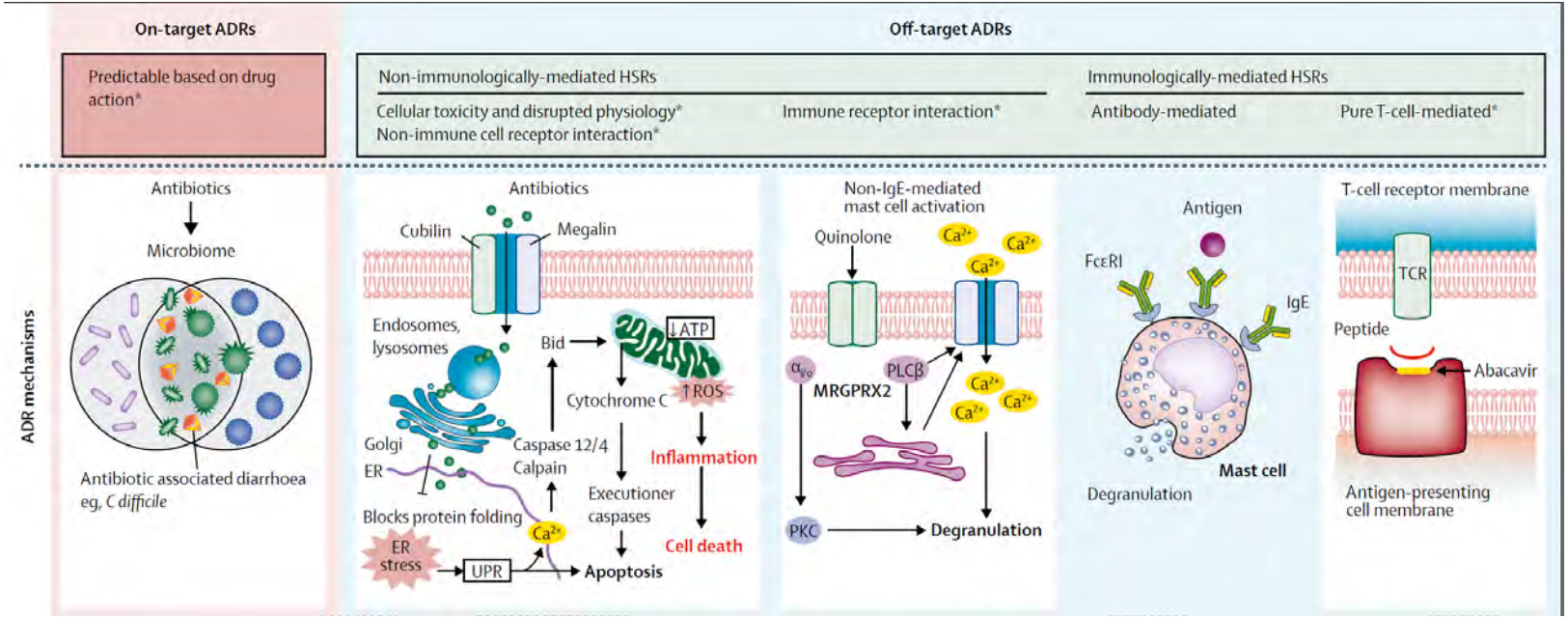
UPMC LIFE CHANGING MEDICINE

APPROACH TO COMMON DRUG ALLERGIES

Andrej Petrov MD
Chief, Section of Allergy,
Division of Pulmonary, Allergy & CCM-UPMC Presbyterian
Chief, Division of Allergy-UPMC Shadyside
University of Pittsburgh Medical Center



Lancet 2019; 393: 183–98

ADVERSE DRUG REACTIONS

Any noxious, unintended and undesired effect of a drug that occurs at doses used in humans for diagnosis, prevention, or treatment.

UPMC LIFE CHANGING MEDICINE

EPIDEMIOLOGY

- ADRs account for 3%-6% of all hospital admissions and occur in 10%-20% of hospitalized patients.
- Drug allergy accounts for up to 20% ADRs.
- Drug allergy, occurs in 1%-2% of all admissions and 3%-5% of hospitalized patients, respectively

https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/drugallergies#:~:text=Drug%20allergy%20is%20relatively%20uncommon,children%20and%20adults%2C%20is%20unknown.

Lancet 2019; 393: 183-98

UPMC LIFE CHANGING MEDICINE

EPIDEMIOLOGY

- The true incidence of drug allergy in the community is unknown; it's been reported in 8% of population
- Many patients are misdiagnosed as being "allergic" to various medications, particularly antibiotics, and end up carrying this label
- These patients are frequently treated with alternate medications that may be more toxic, less effective and more expensive

https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/drugallergies#:~:text=Drug%20allergy%20is%20relatively%20uncommon,children%20and%20adults%2C%20is%20unknown.

Lancet 2019; 393: 183–98

UPMC LIFE CHANGING MEDICINE

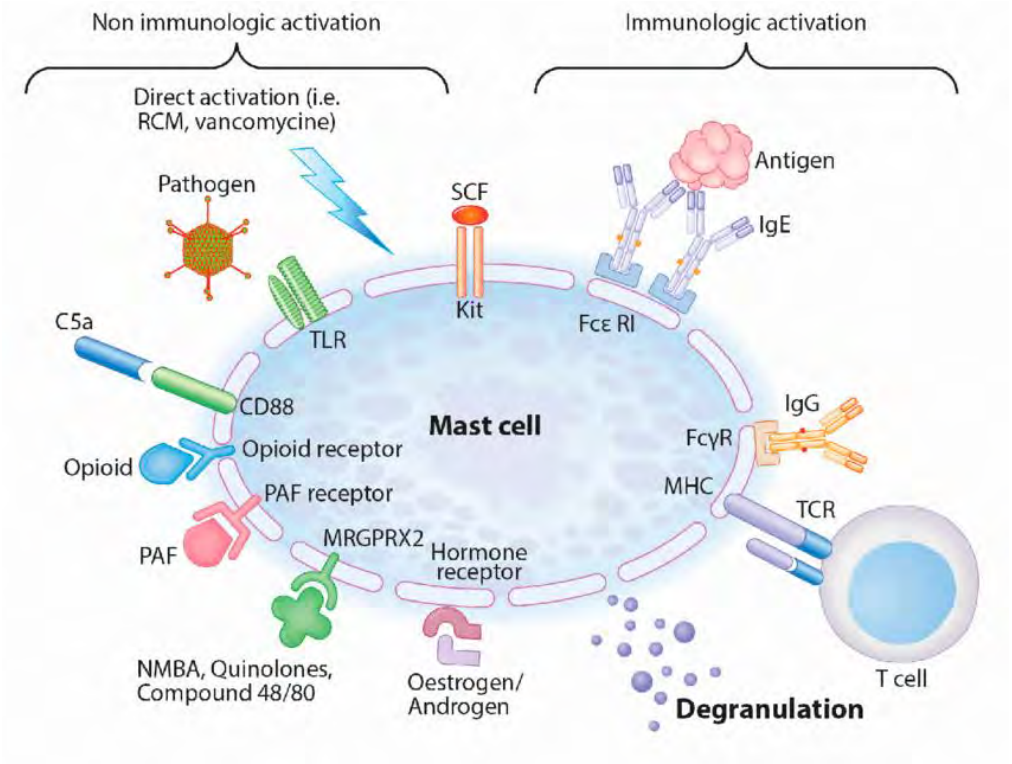
Types of Hypersensitivity Reactions

Type	I	II	III	IV
Description	IgE-mediated	Antibody-mediated	Immune complex-mediated	T-lymphocyte- mediated
Onset	Immediate (minutes – hours)	Delayed (days to weeks)		
Reaction examples	Anaphylaxis **Urticaria (hives)** Angioedema Wheezing Shortness of breath Syncope Cardiac arrest	Hemolytic anemia Thrombocytopenia Neutropenia	Serum sickness Vasculitis	**Maculopapular rash** **Fixed drug eruption** **Contact dermatitis** **SCAR** – DRESS – SJS – TEN – AGEP Acute interstitial nephritis Drug-induced liver injury

SCAR: Severe cutaneous adverse reactions
AGEP: Acute generalized exanthematous pustulosis
DRESS: Drug rash with eosinophilia and systemic symptoms
SJS: Stevens—Johnson syndrome
TEN: Toxic epidermal necrolysis

Blumenthal KG, et al. Lancet 2019;393(10167):183-198 doi: 10.1016/S0140-6736(18)32218-9
Maker JH, et al. Pharmacy (Basel) 2019;7(3) doi: 10.3390/pharmacy7030122

Mast cell activation

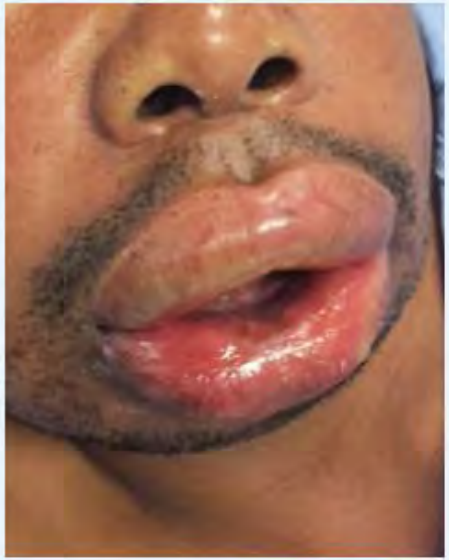


June 2017 International Journal of Molecular Sciences 18(6):1223

UPMC LIFE CHANGING MEDICINE

Mast cell activation

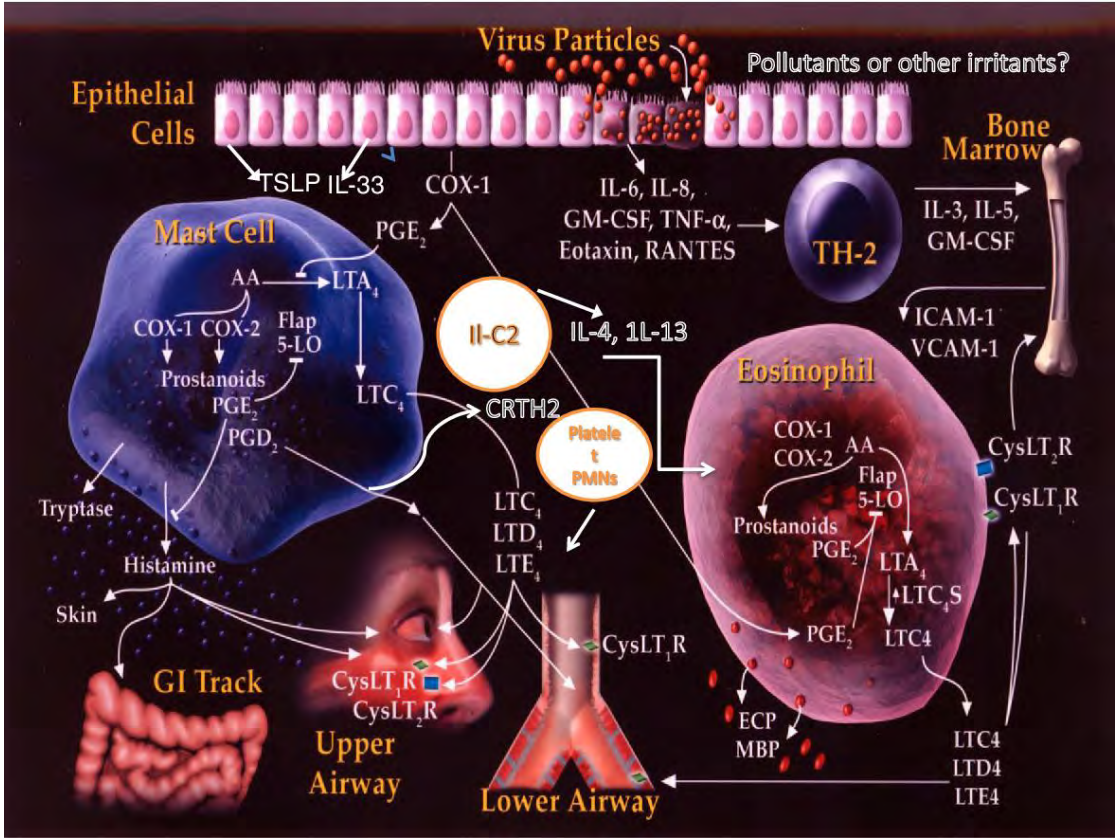
Fluoroquinolone urticaria



Penicillin angioedema

Lancet 2019; 393: 183-98

ASPIRIN ALLERGY



Current Allergy and Asthma Reports **volume 17**,Article number: 2 (2017)

UPMC LIFE CHANGING MEDICINE

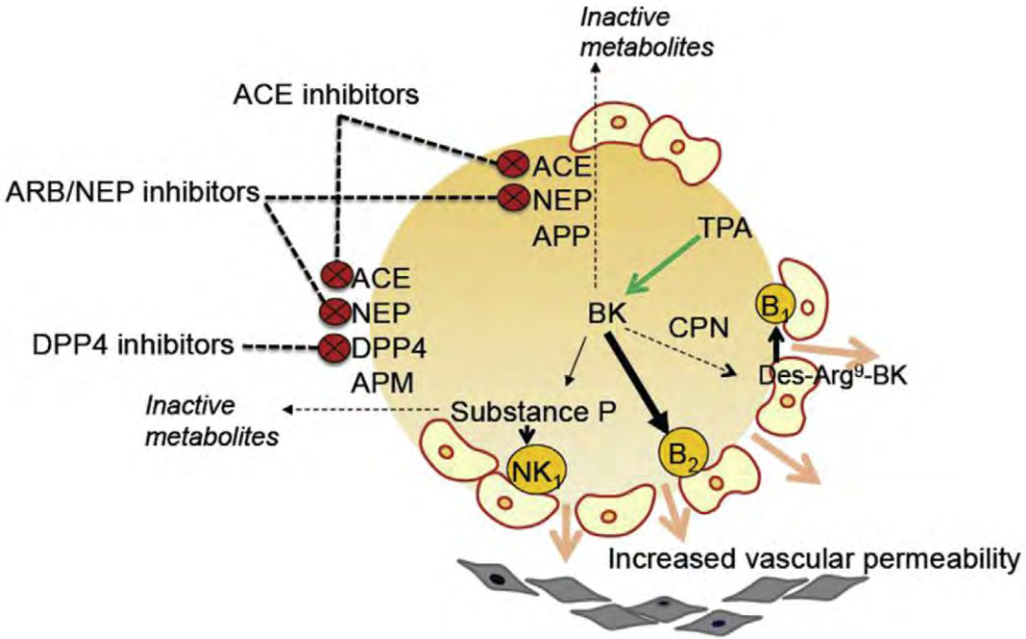
ASPIRIN (NSAID) ALLERGY

TABLE I. Classification of NSAID-induced hypersensitivity reactions

Timing of reaction	Clinical symptoms	Cross-reactivity within NSAID class	Presence of underlying disease	Putative mechanism
AERD				
Acute	Rhinitis, nasal congestion, bronchoconstriction, asthma exacerbation	Cross-reactive	Asthma/rhinosinusitis/nasal polyps	COX-1 inhibition
Multiple NSAID-exacerbated urticaria/angioedema in patients with underlying cutaneous disease				
Acute	Urticaria/angioedema	Cross-reactive	Chronic urticaria	COX-1 inhibition
Multiple NSAID-induced urticaria/angioedema in otherwise asymptomatic patients				
Acute	Urticaria/angioedema	Cross-reactive	None	Likely COX-1 inhibition
Single NSAID-induced anaphylactic reactions				
Acute	Anaphylaxis, urticaria/angioedema	Single drug-induced	Atopy is common	IgE-mediated
Delayed reactions to NSAIDs				
Delayed	Varied: Fixed drug eruptions, severe bullous skin reactions, maculopapular drug eruptions	Can be single drug-induced or cross-reactive	None	Varied: T-cell–mediated, cytotoxic T cells, natural killer cells, other

J ALLERGY CLIN IMMUNOL PRACT
VOLUME 5, NUMBER 3 2017

ACE-induced angioedema



Immunol Allergy Clin N Am 37 (2017) 483–495
http://dx.doi.org/10.1016/j.iac.2017.04.006

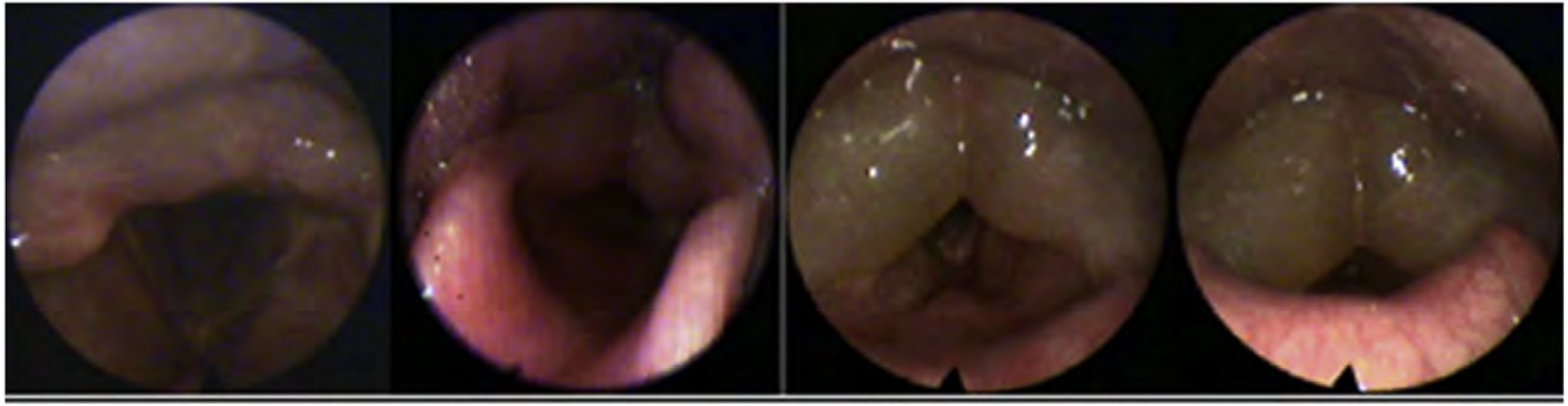
UPMC LIFE CHANGING MEDICINE

Tongue angioedema

Lips borders clearly visible	Palate and uvula partially not visible	Small space between lips and tongue Uvula not visible	Tongue completely fills mouth office
Grade I	Grade II	Grade III	Grade IV
	Hospitalization	Hospitalization	Hospitalization
	Intensive care	Intensive care	Intensive care

Immunol Allergy Clin N Am 37 (2017) 183–200
http://dx.doi.org/10.1016/j.iac.2016.08.011

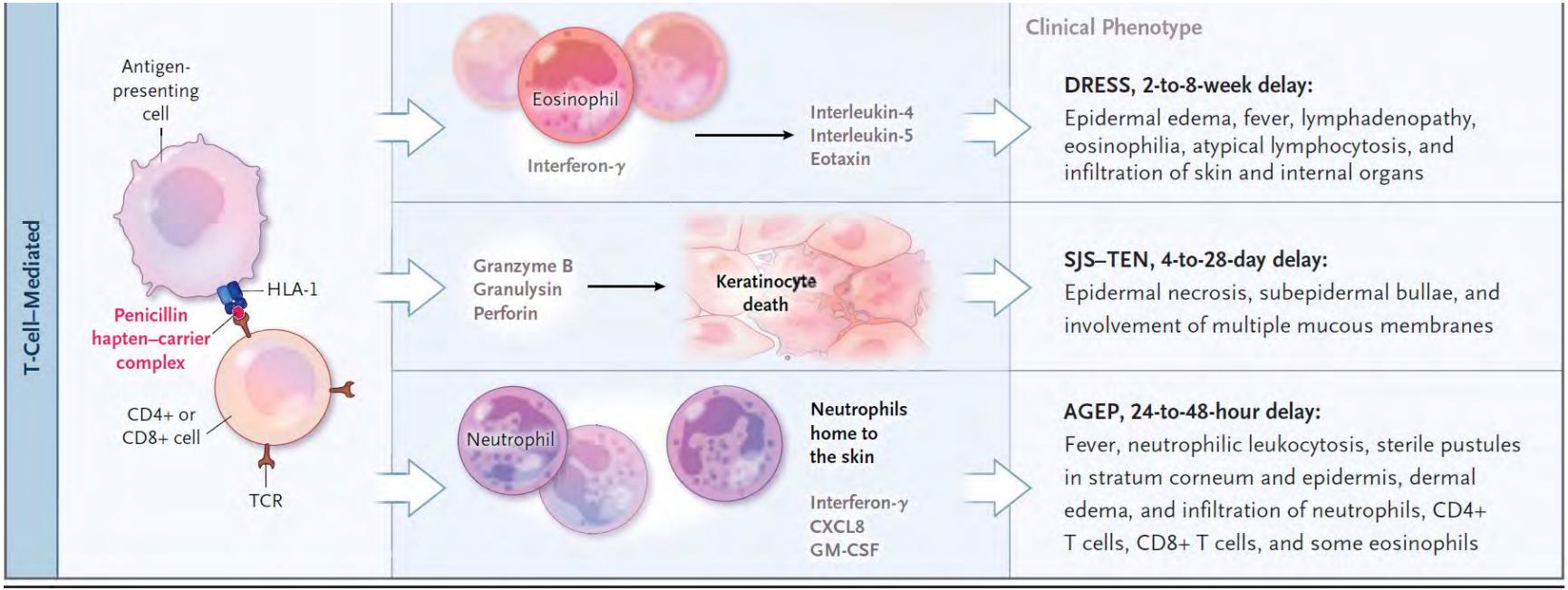
Laryngeal angioedema



25% obstruction of supralarynx	50% obstruction of supralarynx	75% obstruction of supralarynx	90% obstruction of supralarynx
Grade LOC I	Grade LOC II	Grade LOC III	Grade LOC IV

Immunol Allergy Clin N Am 37 (2017) 183–200
http://dx.doi.org/10.1016/j.iac.2016.08.011

LYMPHOCYTE ACTIVATION



J Allergy Clin Immunol Pract 2017;5:547-63

UPMC LIFE CHANGING MEDICINE

VIRAL VS. DRUG RASH

Diagnosis
Measles (rubeola)
Rubella
Roseola infantum (exanthem subitum)
Erythema infectiosum (fifth disease)
Infectious mononucleosis
Acute graft-versus-host disease
Acute human immunodeficiency virus seroconversion
Other viral exanthems

N Engl J Med 2012;366:2492-501.

UPMC LIFE CHANGING MEDICINE

Acute Contact Dermatitis and Photoallergic Dermatitis

Immunol Allergy Clin N Am 37 (2017) 165–181
http://dx.doi.org/10.1016/j.iac.2016.08.006

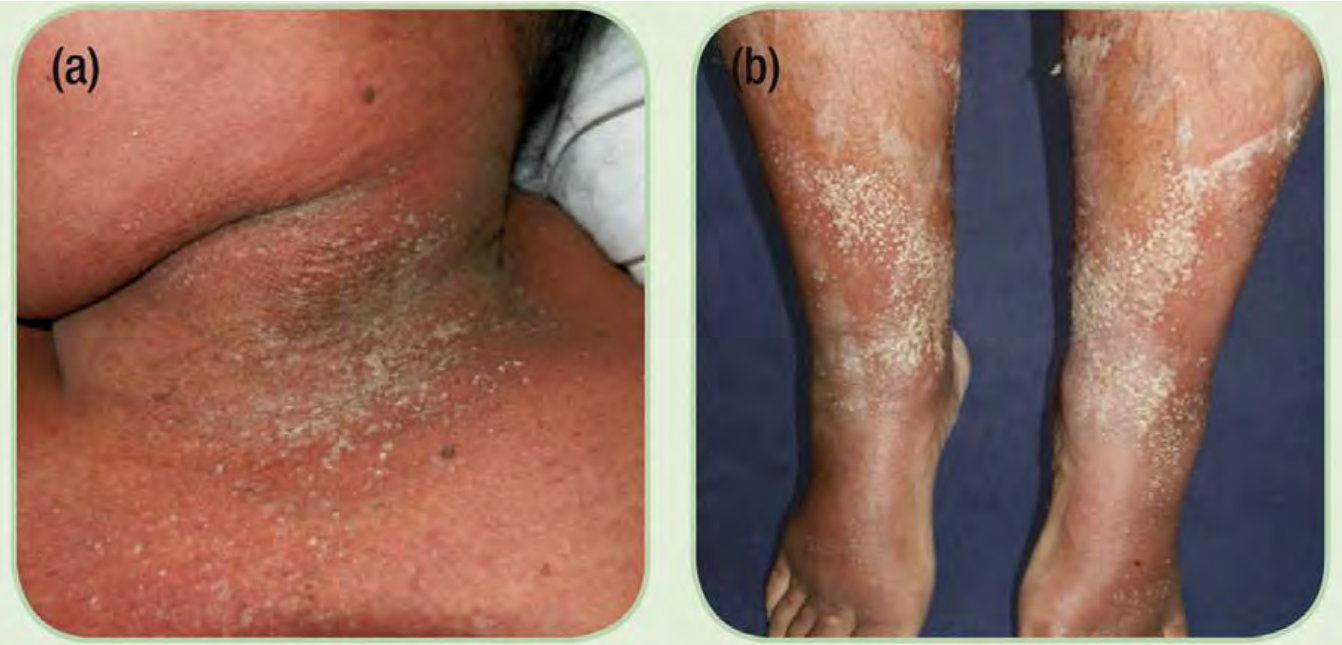
Fixed Drug Eruption

Fixed drug eruption *(a) Extensive disease showing pigmented macules, some with blistering (b) bullous variant resembling SJS and (c) acute fixed drug eruption showing indurated oedematous plaques.*

UPMC LIFE CHANGING MEDICINE

J Allergy Clin Immunol Pract 2017;5:547-63.

Acute Generalized Exanthematous Pustulosis



Acute generalized exanthematous pustulosis (AGEP) *(a) classic flexural pustules (b) small pustules on a background of indurated erythema.*

J Allergy Clin Immunol Pract 2017;5:547-63.

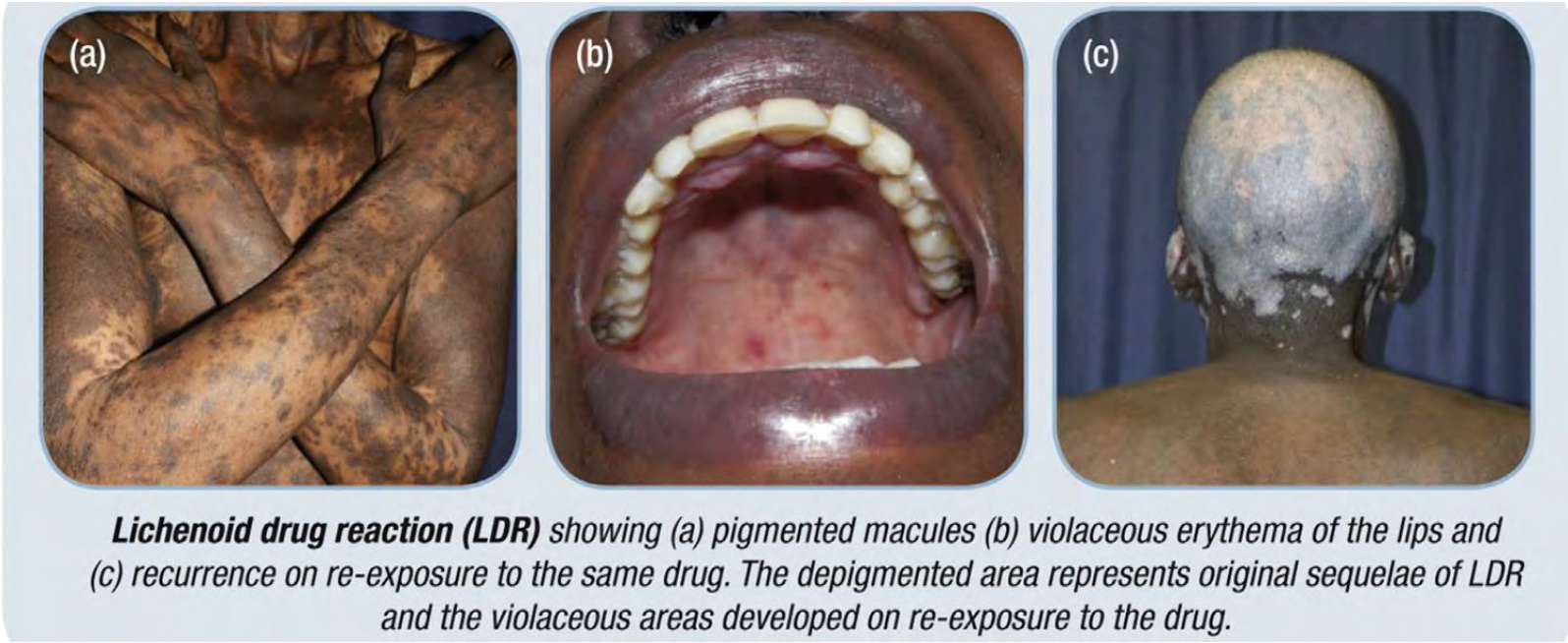
Drug-Induced Vasculitis

Vasculitis *showing (a) palpable purpura on the lower legs and (b) a more severe variant showing blisters and ulceration.*

J Allergy Clin Immunol Pract 2017;5:547-63.

UPMC LIFE CHANGING MEDICINE

Lichenoid Drug Reaction



Lichenoid drug reaction (LDR) *showing (a) pigmented macules (b) violaceous erythema of the lips and (c) recurrence on re-exposure to the same drug. The depigmented area represents original sequelae of LDR and the violaceous areas developed on re-exposure to the drug.*

J Allergy Clin Immunol Pract 2017;5:547-63.

UPMC LIFE CHANGING MEDICINE

Symmetrical drug-related intertriginous and flexural exanthem

- Within the first 2 days of exposure
- Symmetrical erythematous lesions involving the flexural intertriginous and gluteal areas

https://doi.org/10.1016/j.clindermatol.2020.06.013

UPMC LIFE CHANGING MEDICINE

Drug Reaction, Eosinophilia, and Systemic Syndrome(DRESS)

Japanese Consensus Group[7]
1) Maculopapular eruption developing >3 weeks after starting a limited number of drugs 2) Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug 3) Fever (>38ºC) 4) Liver abnormalities (alanine aminotransferase [ALT] >100 U/L)* 5) Leucocyte abnormalities (at least one present) - Leukocytosis (>11 x 109/L), - Atypical lymphocytosis (>5%) - Eosinophilia (>1.5 x 109/L) 6) Lymphadenopathy 7) HHV-6 reactivation

A.R. Cardones MD, Drug reaction, eosinophilia, and systemic symptoms (DRESS) syndrome, Clinics in Dermatology (2020)

UPMC LIFE CHANGING MEDICINE

Polymorphous maculopapular eruption (85%) and facial edema (76%); pustules, purpura, infiltrated plaques, blisters, target-like lesions, urticarial lesions, an exfoliative dermatitis, eczema-like lesions, and lichenoid lesions

A.R. Cardones MD, Drug reaction, eosinophilia, and systemic symptoms (DRESS) syndrome, Clinics in Dermatology (2020)

DRESS COMPLICATIONS

- Symptoms may worsen after the drug therapy is discontinued and may persist for weeks or even months
- Reported DRESS syndrome mortality rates worldwide are approximately 10%
- Some patients develop late-onset sequelae such as myocarditis or autoimmune conditions even years after the initial cutaneous eruption

A.R. Cardones MD, Drug reaction, eosinophilia, and systemic symptoms (DRESS) syndrome, Clinics in Dermatology (2020)

Table 2. Short and long-term sequelae of DRESS/DIHS

Arthritis
Arthralgia, reactive arthritis, rheumatoid arthritis
Autoimmune thyroiditis
Colitis / enteropathy
Cutaneous autoimmune disease
Vitiligo, alopecia areata
Diabetes mellitus
Encephalitis
Fulminant hepatic failure
Hemolytic anemia
Myocarditis
Pneumonitis
Renal failure
Systemic lupus erythematosus
Venous thrombosis

Table 3. Common causes of DRESS/DIHS

Anti-gout medications
Allopurinol
Anti-microbials
Abacavir
Dapsone
Minocycline
Nevirapine
Trimethoprim-sulfamethoxazole
Vancomycin
Anti-epileptics
Carbamazepine
Lamotrigine
Phenytoin
Phenobarbital
Anti-inflammatory medications
Sulfasalazine

A.R. Cardones MD, Drug reaction, eosinophilia, and systemic symptoms (DRESS) syndrome, Clinics in Dermatology (2020)

SERUM SICKNESS & SERUM SICKNESS-LIKE REACTION

- Urticaria, polycyclic plaques, or a morbilliform exanthem.
- Skin eruptions (90%), arthritis (52%), fever (41%), arthralgia (38%), abdominal pain (21%), and lymphadenopathy (10%).
- Low complement levels in true serum sickness

https://doi.org/10.1016/j.clindermatol.2020.06.013

Quirt J, Rogala B, Cichocka-Jarosz E. Serum Sickness. McMaster Textbook of Internal Medicine. Kraków: Medycyna Praktyczna. https://empendium.com/mcmtextbook/chapter/B31.II.17.2. Accessed September 09, 2020

Drug Reactions with Bullae

- Fixed drug eruption
- Bullous pemphigoid
- Pemphigus vulgaris
- Linear IgA bullous dermatosis
- SJS/TEN

S. Cheraghlou and L.L. Levy, Fixed Drug Eruptions, Bullous Drug Eruptions, and Lichenoid Drug Eruptions, *Clinics in Dermatology* (2020)

UPMC LIFE CHANGING MEDICINE

SJS & TEN

- Onset 4 to 21 days after first dose of drug
- Mucous membranes nearly always involved with blisters and erosions
- Temperature >38.5°C, systemic signs initially
- Severe, acute blistering; initially, rash may be macular erythema or exanthem on the trunk
- Extent of epidermal necrosis according to body-surface area:
  - 10 -30% in SJS–TEN overlap
  - < 10% in SJS
  - >30% in TEN

Pediatrics Vol. 146, Issue 31 Sep 2020
N Engl J Med 2012;366:2492-501.

UPMC LIFE CHANGING MEDICINE

ERYTHEMA MULTIFORME

The Lancet; VOLUME 392, ISSUE 10147, P592, AUGUST 18, 2018

https://www.nidirect.gov.uk/conditions/erythema-multiforme

UPMC LIFE CHANGING MEDICINE

EM & SJS

Multiforme E. Journal Of Advances In Allergy & Immunologic Diseases, Volume 1, Issue 1, 2015

UPMC LIFE CHANGING MEDICINE

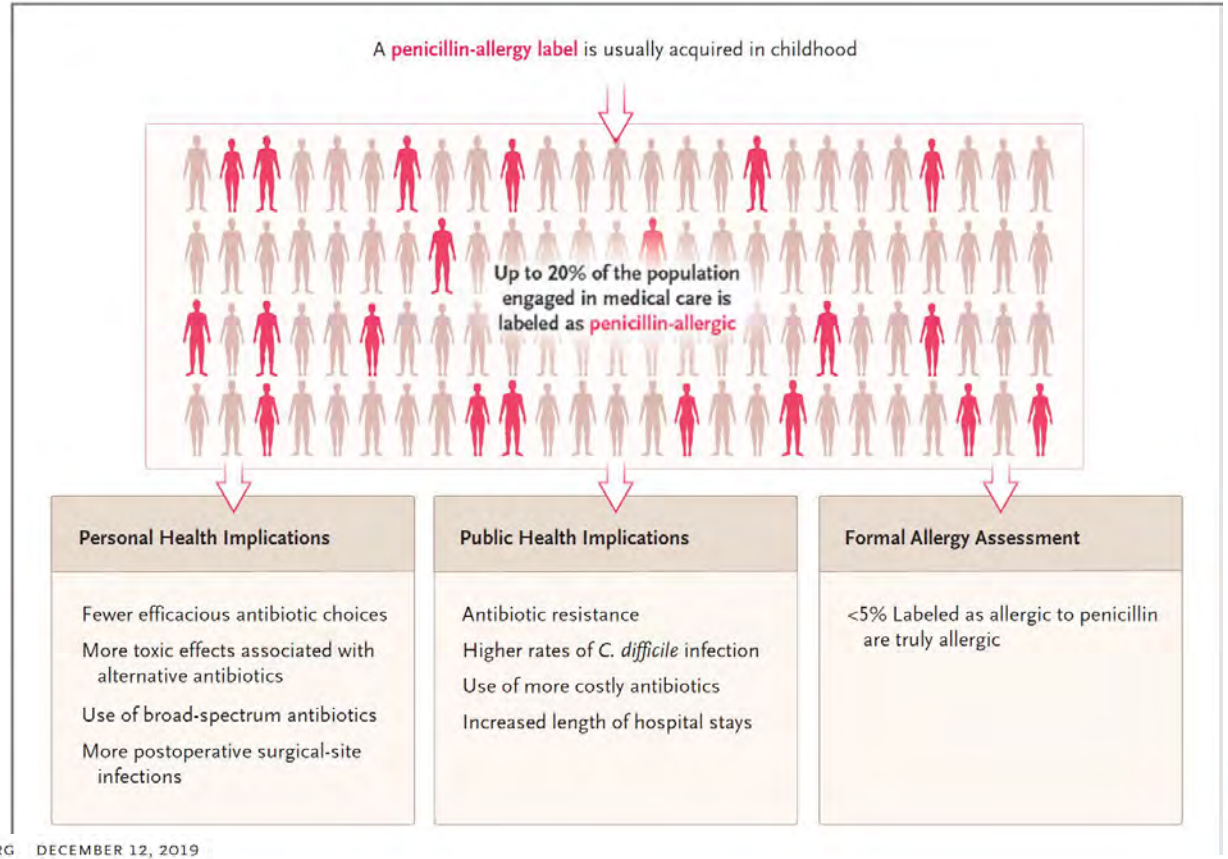
BETA-LACTAM ALLERGY

URTICARIA VS. MACULOPAPULAR RASH

N Engl J Med 2012;366:2492-501.

UPMC LIFE CHANGING MEDICINE

PENICILLIN ALLERGY LABEL



Harms associated with use of non-β-lactam antibiotics

Increased use of 2nd-line antibiotics

- Vancomycin
- Aztreonam
- Fluoroquinolones
- Clindamycin

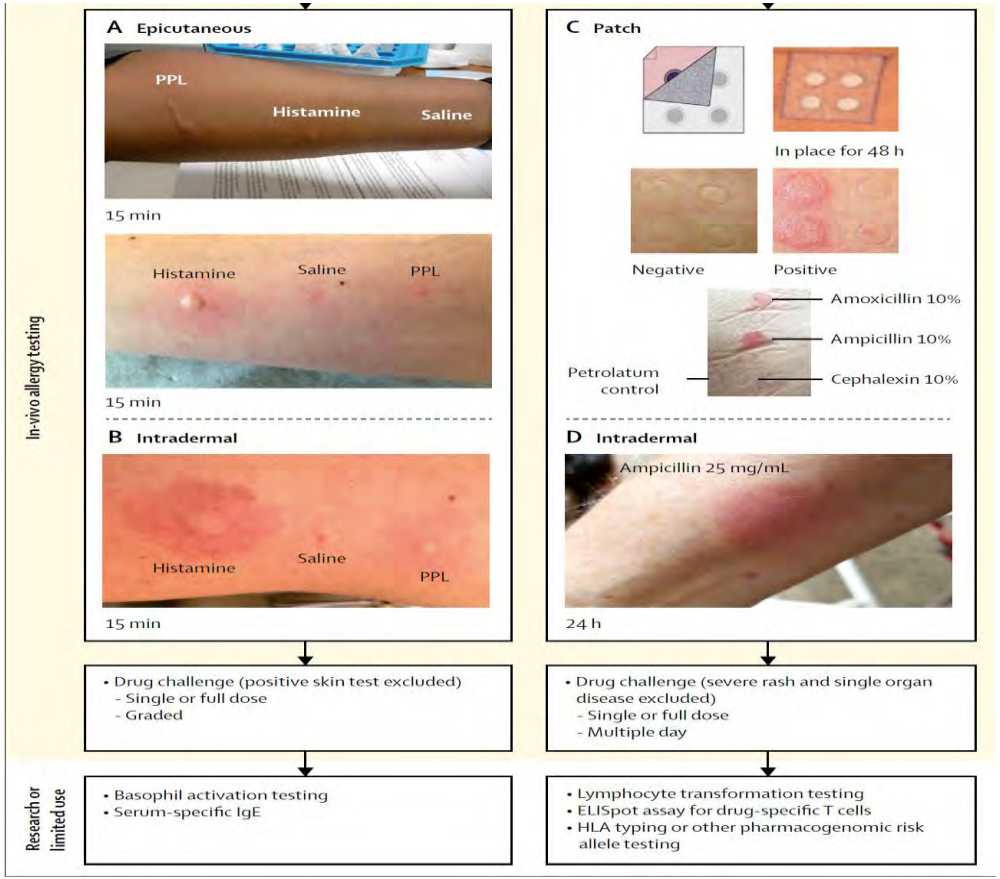
Increased use of unnecessarily broad-spectrum antibiotics

- Meropenem

- ❑ **↑ mortality**
- ❑ **↑ treatment failures**
- ❑ **↑ adverse effects** (e.g. nephrotoxicity, QTc prolongation)
- ❑ **↑ colonization and/or infection with resistant pathogens**
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Vancomycin-resistant enterococci (VRE)
  - *Clostridium difficile*
- ❑ **↑ surgical site infections**

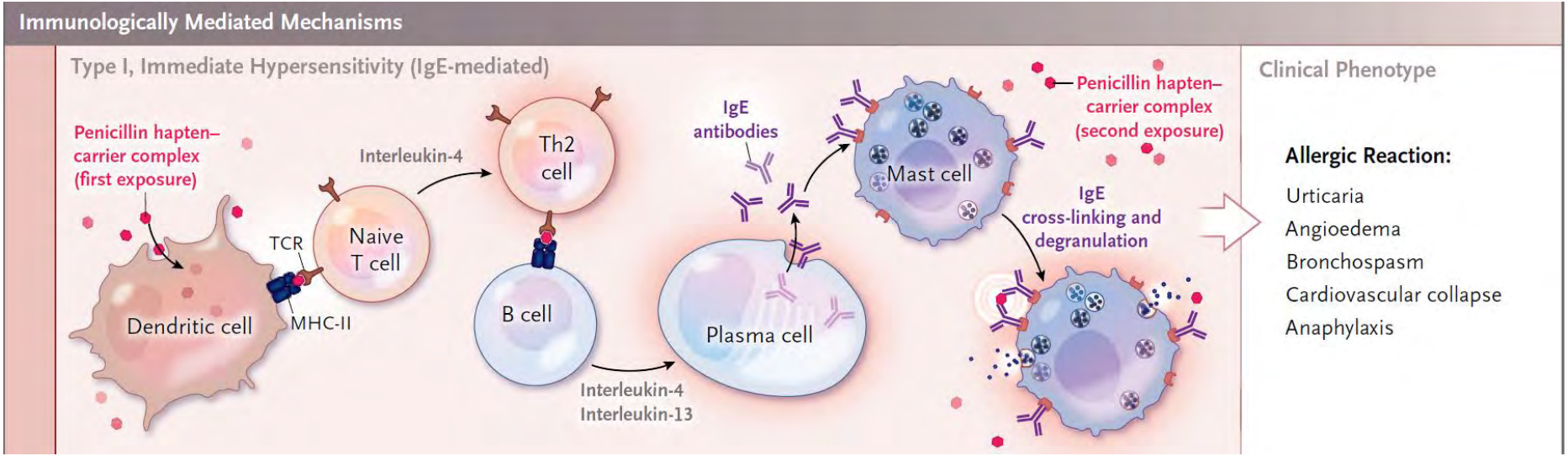
Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol 2014; 133:790–6.
https://www.idsociety.org/globalassets/idsa/topics-of-interest/antimicrobial-resistance/foar-report-1-up-final-1.pdf Infectious Disease Society
https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf Center for Disease Control

DIAGNOSIS



Lancet 2019; 393: 183–98

UPMC LIFE CHANGING MEDICINE



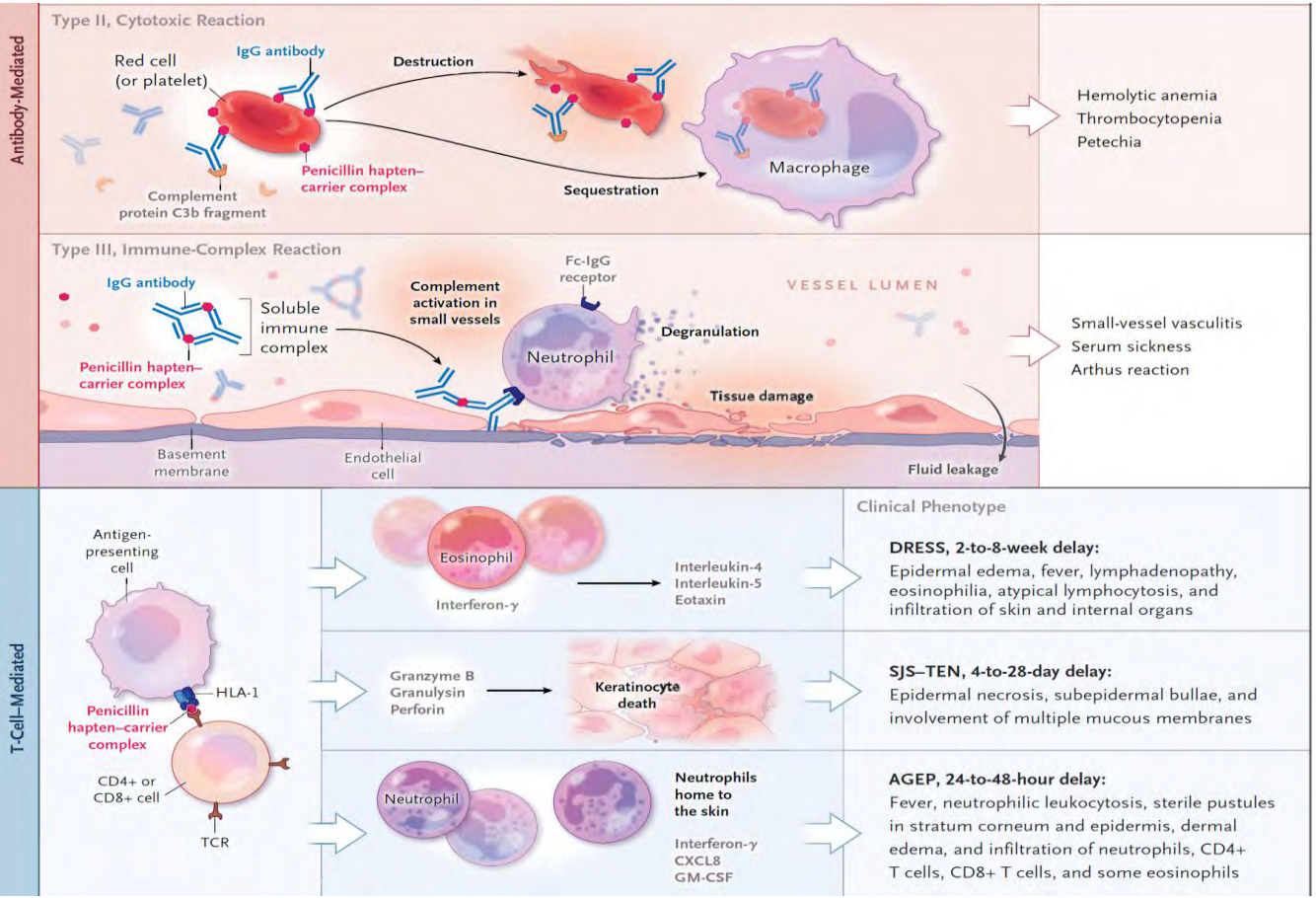
N ENGL J MED 381;24 NEJM.ORG DECEMBER 12, 2019

PENICILLIN TESTING-YES

- Skin testing evaluates only for IgE-mediated reactions
- IgE-mediated reactions wane over time: 80% no longer allergic after 10+ years
- Low cross-reactivity with cephalosporins (2%)

UPMC LIFE CHANGING MEDICINE

N ENGL J MED 381;24 NEJM.ORG DECEMBER 12, 2019



PENICILLIN TESTING-NO

UPMC LIFE CHANGING MEDICINE

Don’t overuse non-beta-lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.

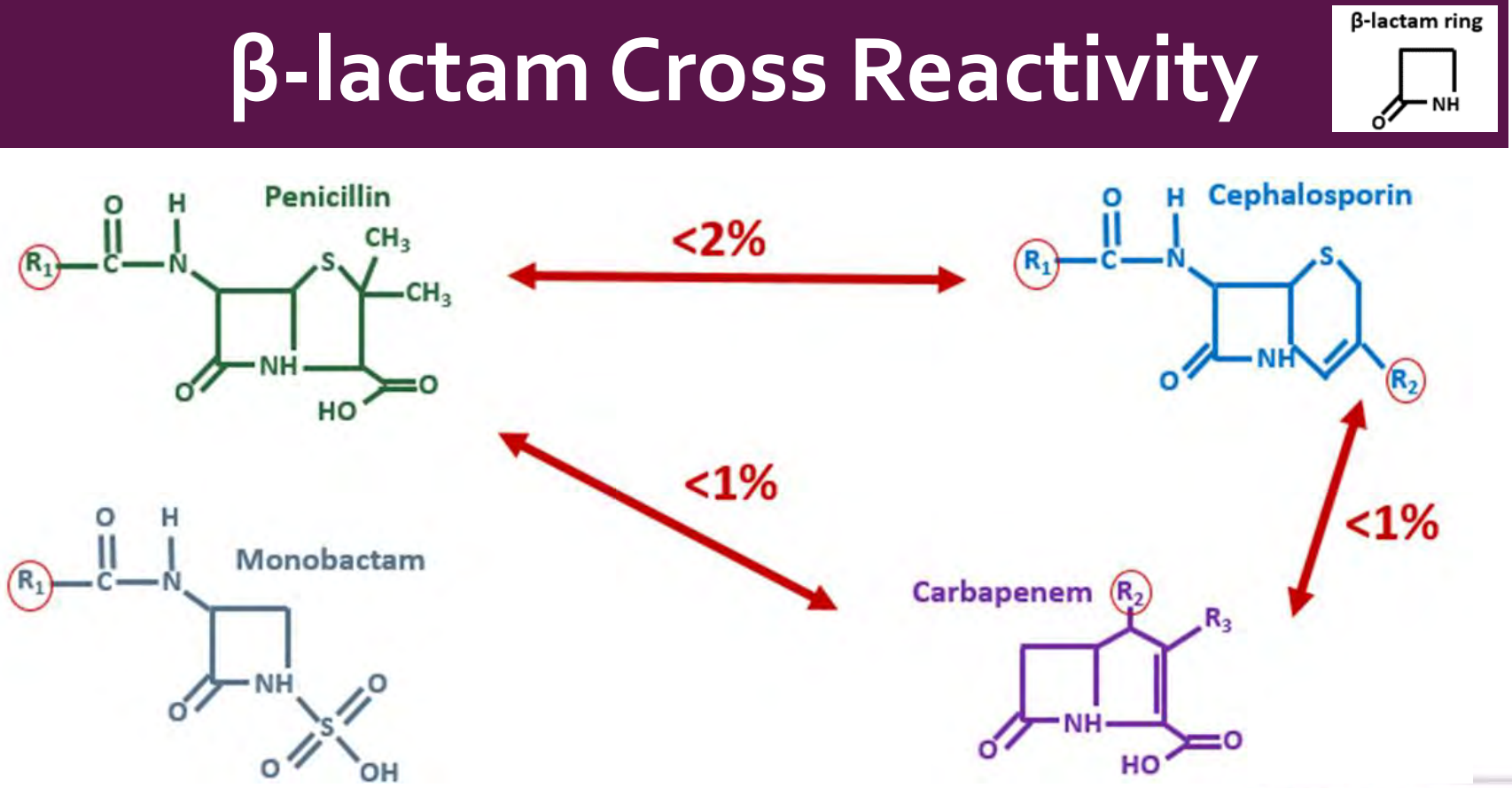
Choosing Wisely®

CELEBRATING OUR 7TH YEAR

An initiative of the ABIM Foundation

UPMC LIFE CHANGING MEDICINE

β-lactam Cross Reactivity



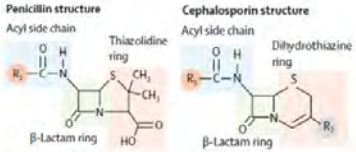
Blumenthal KG, et al. Lancet 2019;393(10167):183-198 doi: 10.1016/S0140-6736(18)32218-9

Heatmap of similarities between R1 side chains.

Cephalosporins		Penicillins						
		Penicillin G	Penicillin V	Ampicillin	Amoxicillin	Cloxacillin	Piperacillin	Ticarcillin
1st	Cefadroxil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephalexin	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefazolin	0,176	0,110	0,099	0,088	0,078	0,032	0,088
	Cefradine	0,344	0,200	0,517	0,371	0,155	0,082	0,263
	Cephalothin	0,563	0,321	0,337	0,295	0,154	0,035	0,268
	Cefatrizine	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephaloridine	0,563	0,321	0,337	0,295	0,154	0,035	0,268
2nd	Cefaclor	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefoxitin	0,330	0,245	0,211	0,180	0,148	0,043	0,180
	Cefprozil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cefuroxime	0,304	0,220	0,274	0,248	0,320	0,044	0,228
	Cefamandole	0,592	0,333	0,714	0,485	0,208	0,043	0,412
3rd	Cefixime	0,110	0,110	0,098	0,157	0,219	0,084	0,138
	Cefotaxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Ceftazidime	0,092	0,087	0,092	0,142	0,198	0,064	0,127
	Ceftriaxone	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefpodoxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefdinir	0,147	0,083	0,143	0,156	0,207	0,047	0,238
	Ceftibuten	0,167	0,127	0,148	0,165	0,237	0,079	0,165
4th	Cefepime	0,141	0,090	0,138	0,142	0,249	0,049	0,182

J ALLERGY CLIN IMMUNOL PRACT
VOLUME 7, NUMBER 8

APPENDIX B3. Table of β-Lactam Cross-Reactivity



β-lactam cross-reactivity is *primarily* thought to be predicted based on shared R1 and R2 side chains between antibiotics.

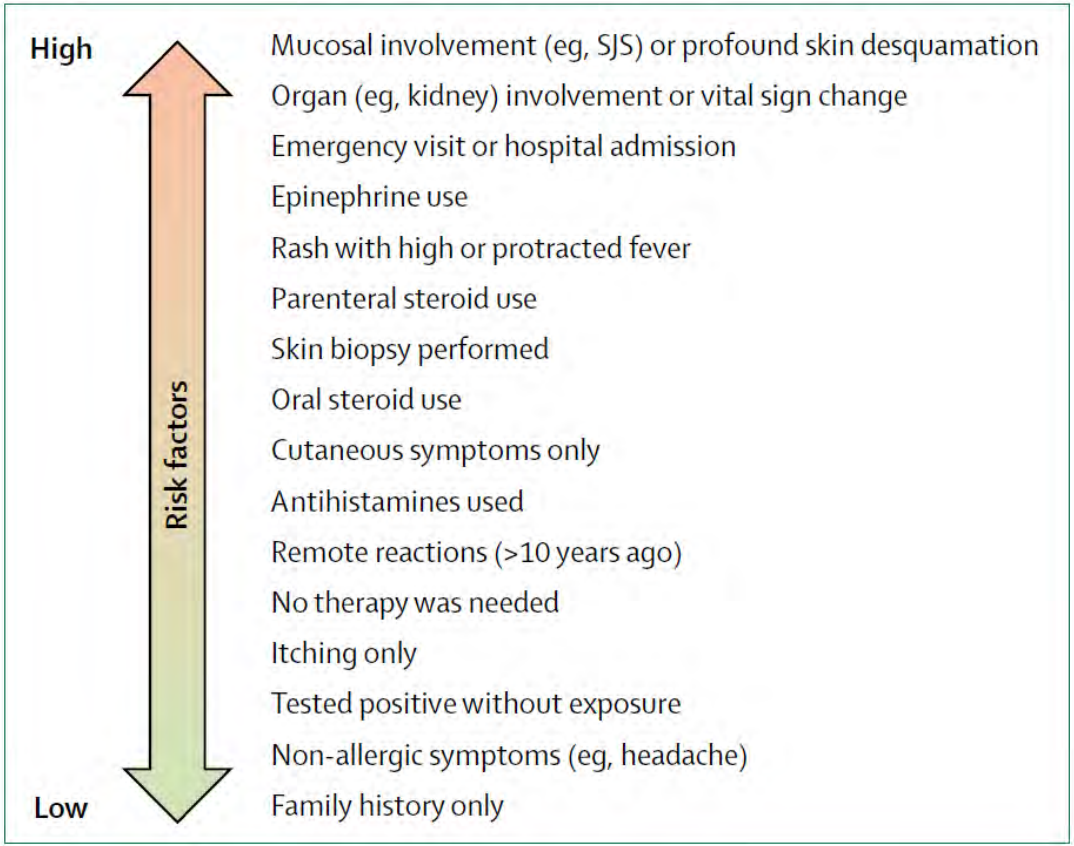
Patient can exhibit hypersensitivity reactions to non-cross reacting antibiotics based on other mechanisms.

		Penicillin	Amoxicillin	Ampicillin	Nafcillin	Oxacillin	Dicloxacillin	Piperacillin/tazobactam	Cefadroxil	Cephalexin	Cefazolin	Cefaclor	Cefprozil	Cefuroxime	Cefotetan	Cefoxitin	Cefdinir	Cefixime	Ceftibuten	Cefditoren	Cefpodoxime	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Ceftaroline	Cefiderocol	Ceftazidime/avibactam	Ceftolozane/tazobactam	Ertapenem	Imipenem/cilastatin	Imipenem/cilastatin/relebactam	Meropenem	Meropenem/vaborbactam	Aztreonam
Penicillins	Penicillin		•	•	•	•	•	•	•	•	•	•	•			•																			
	Amoxicillin	•		•	•	•	•	•	•	•	•	•	•																						
	Ampicillin	•	•		•	•	•	•	•	•	•	•	•																						
	Nafcillin	•	•	•		•	•	•	•	•	•	•	•																						
	Oxacillin	•	•	•	•		•	•	•	•	•	•	•																						
	Dicloxacillin	•	•	•	•	•		•	•	•	•	•	•																						
	Piperacillin/tazobactam	•	•	•	•	•	•		•	•	•	•	•																						
1st Generation Cephalosporin	Cefadroxil	•	•	•	•	•	•	•		•	•	•	•																						
	Cephalexin	•	•	•	•	•	•	•	•		•	•	•																						
	Cefazolin																																		
2nd Generation Cephalosporin	Cefaclor	•	•	•	•	•	•	•	•	•			•																						
	Cefprozil	•	•	•	•	•	•	•	•	•		•																							
	Cefuroxime															•		•		•	•	•	•	•	•			•							
	Cefotetan																																		
	Cefoxitin	•												•																					
3rd Generation Cephalosporin	Cefdinir																	•	•	•	•	•	•	•	•	•	•	•	•						
	Cefixime													•			•		•	•	•	•	•	•	•	•	•	•	•						
	Ceftibuten																•	•		•	•	•	•	•	•	•	•	•	•						
	Cefditoren													•			•	•	•		•	•	•	•	•	•	•	•	•						
	Cefpodoxime													•			•	•	•	•		•	•	•	•	•	•	•	•						
	Cefotaxime													•			•	•	•	•	•		•	•	•	•	•	•	•						
	Ceftriaxone													•			•	•	•	•	•	•		•	•	•	•	•	•						
	Ceftazidime													•			•	•	•	•	•	•	•		•	•	•	•	•						•
4th Generation Cephalosporin	Cefepime													•			•	•	•	•	•	•	•	•		•	•	•	•						
Advanced Generation Cephalosporin	Ceftaroline																•	•	•	•	•	•	•	•	•		•	•	•						
	Cefiderocol																•	•	•	•	•	•	•	•	•	•		•	•						•
	Ceftazidime/avibactam													•			•	•	•	•	•	•	•	•	•	•	•		•						•
	Ceftolozane/tazobactam																•	•	•	•	•	•	•	•	•	•	•	•							•
Carbapenems	Ertapenem																														•	•	•	•	
	Imipenem/cilastatin																													•		•	•	•	
	Imipenem/cilastatin/relebactam																													•	•		•	•	
	Meropenem																													•	•	•		•	
	Meropenem/vaborbactam																													•	•	•	•		
Monobactam	Aztreonam																							•			•	•	•						

• *Increased potential for cross-reactivity*

UPMC LIFE CHANGING MEDICINE

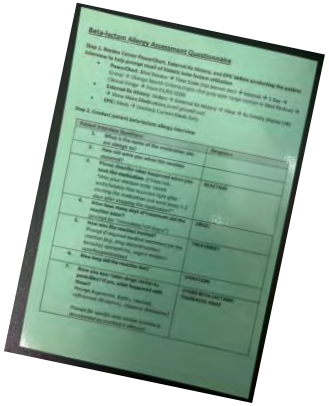
STRATIFY RISK



Lancet 2019; 393: 183–98

UPMC LIFE CHANGING MEDICINE

Conduct THOROUGH History / Patient Interview



Interview patient

- ✓ Medication – name of medication
- ✓ Age – how old when reaction occurred
- ✓ **REACTION** – describe reaction
  - If hives, prompt itchy, raised welts/wheels
- ✓ **ONSET** – how many days into therapy did reaction occur
- ✓ **TREATMENT** – drug discontinuation, antihistamine, ED visit, hospitalization
- ✓ **DURATION** – how long reaction lasted
- ✓ Other medications tolerated
  - Prompt “Augmentin, Keflex, Omnicef, ceftriaxone (Rocephin), cefepime (Maxipime) and/or specific β-lactams identified upon chart review

UPMC LIFE CHANGING MEDICINE

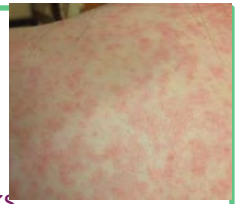
Differentiating Cutaneous Drug Reactions

Urticaria (hives)

- Fast onset (minutes to hours)
- Raised off skin
- Pruritic
- Duration < 24 hours
- No scarring

Benign rash

- Delayed onset (days)
- Less pruritic than urticaria
- Duration >24hours
- Fine desquamation with resolution over days to weeks



SCAR

- Delayed onset (days to weeks)
- Blistering / desquamation
- Mucosal and/or organ involvement
- Hospitalization

UPMC LIFE CHANGING MEDICINE

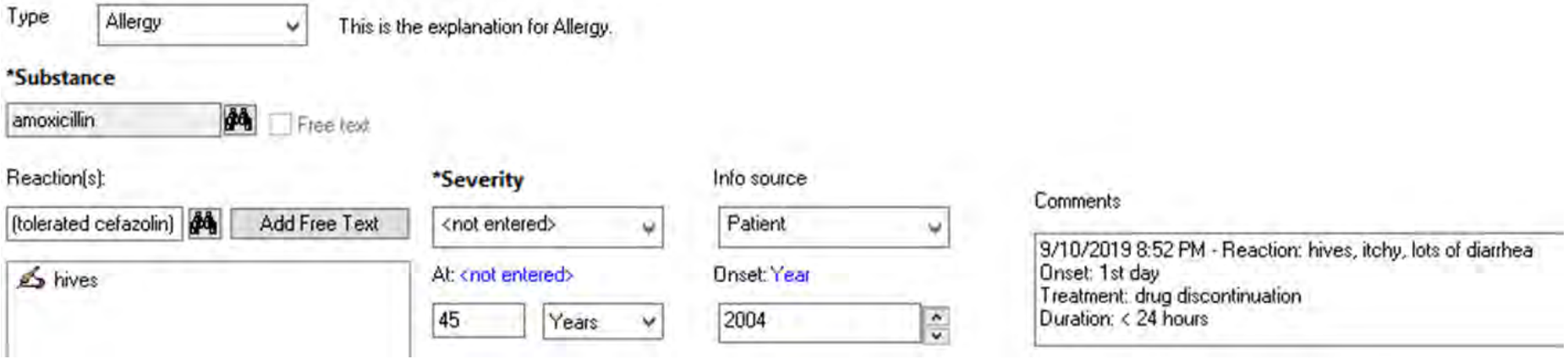
Shenoy et al. JAMA. 2019;321(2):188-199. doi: 10.1001/jama.2018.19283.

QUIZ ?

N Engl J Med 2012;366:2492-501.

UPMC LIFE CHANGING MEDICINE

Update the Electronic Health Record



UPMC LIFE CHANGING MEDICINE

Desensitization versus Graded Challenge

Desensitization

- Administering the offending agent at a concentration and rate that will cause drug-specific IgE-armed mast cells to degranulate at low rates without causing an allergic reaction, and ultimately allow for the drug to be administered at a full therapeutic dose
  - **“Temporary drug tolerance”**

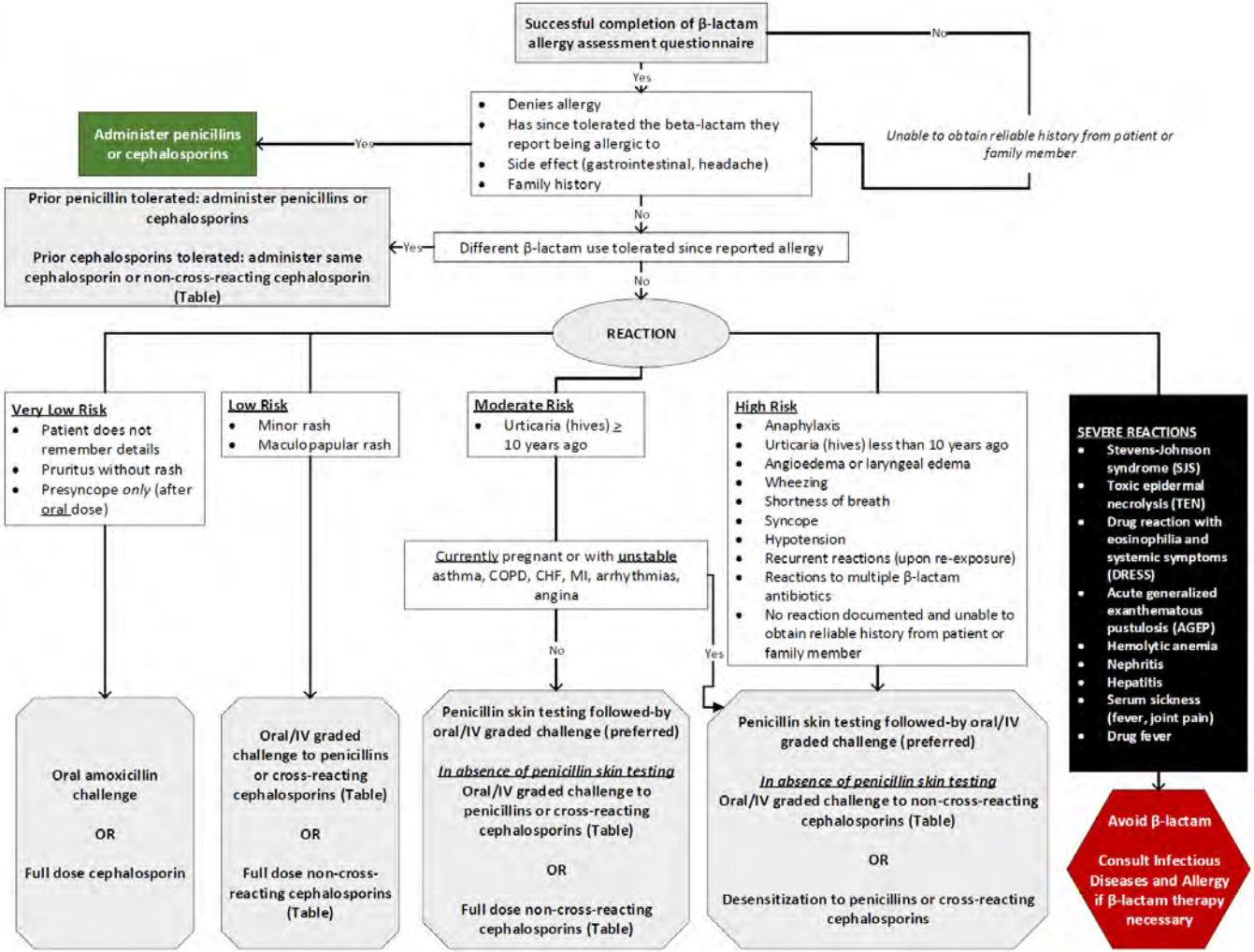
Graded Challenge

- Administering 1-2 TEST doses to **rule-out** the presence of IgE-mediated reaction
  - **“Test dose procedure: 10%, wait 1 hour, then administer 100%”**

Desensitization versus Graded Challenge

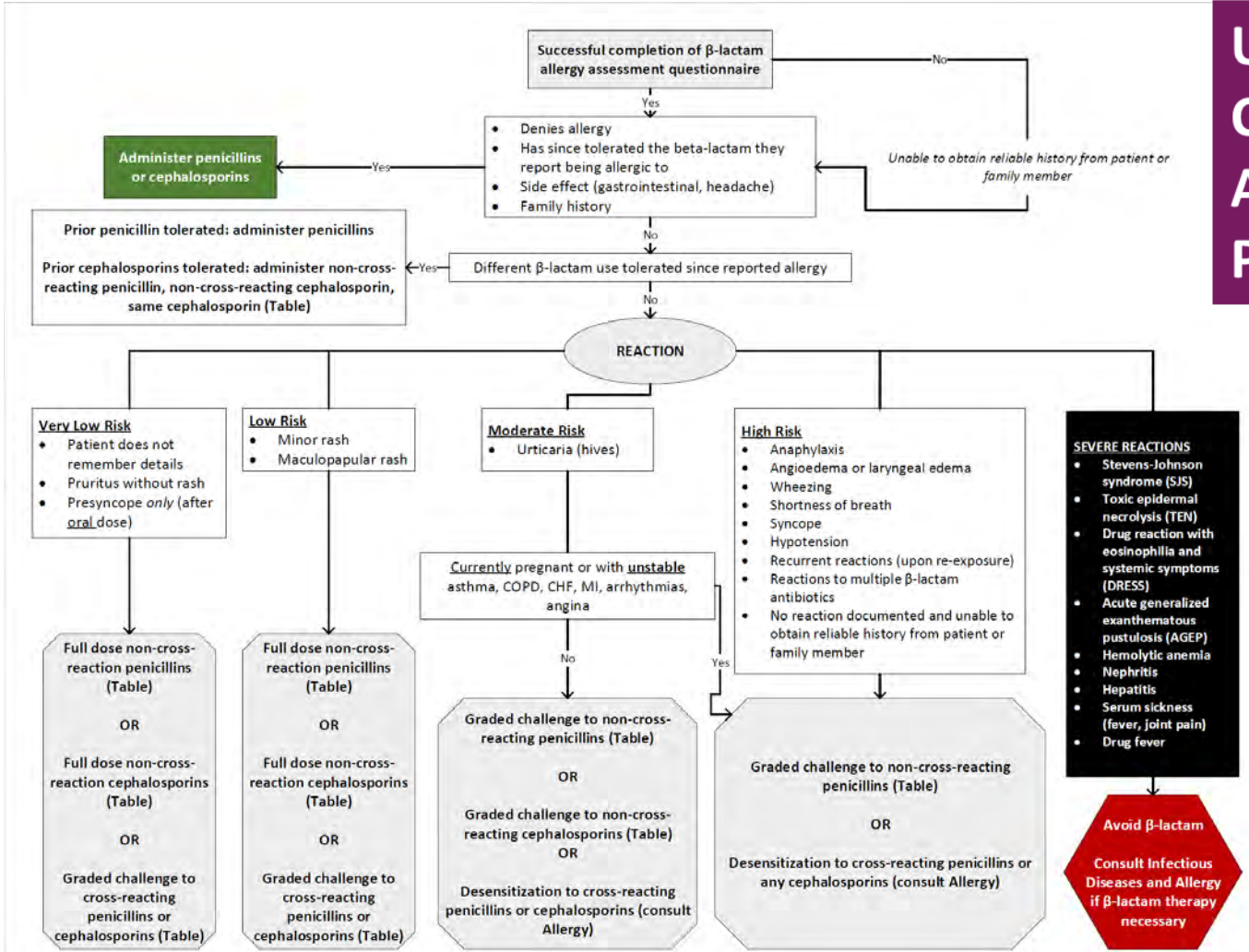
Characteristic	Desensitization	Graded Challenge
Description	Temporary drug tolerance	**TEST dose procedure**
Risk of IgE-mediated hypersensitivity reaction (i.e. anaphylaxis)	High (e.g. history of anaphylaxis)	**Low-Moderate**
Location	ICU	**Any unit**
Ordered by	Allergy/ID	**Any prescriber** **(Allergy/ID consult recommended)**
Duration of procedure	4-6 hours	**2 hours**
Vitals	Q15min	**Q30min**
Rescue medications	The following medications will be available to RN: Albuterol Famotidine Diphenhydramine Methylprednisolone Epinephrine	

UPMC PENICILLIN ALLERGY PATHWAY



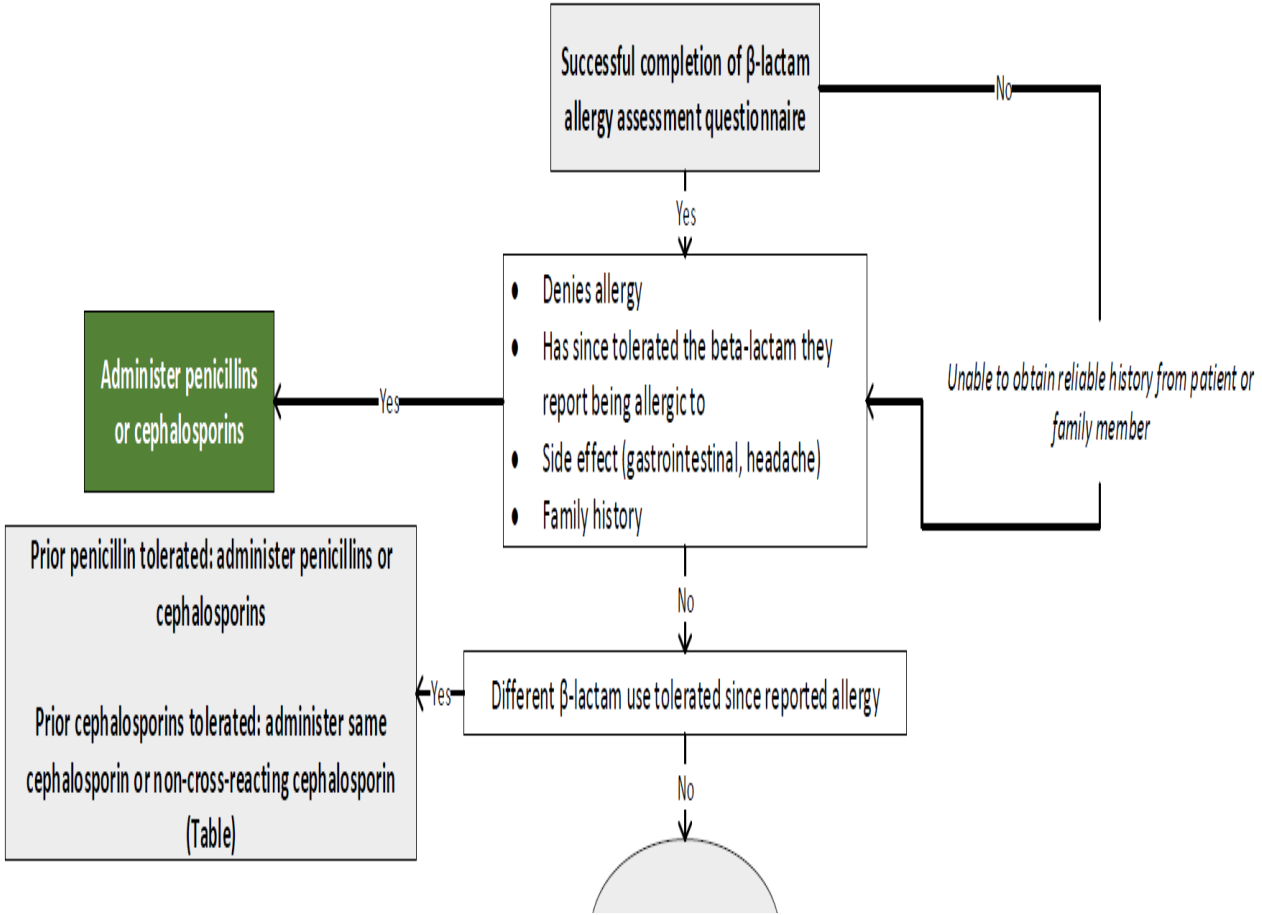
UPMC LIFE CHANGING MEDICINE

UPMC CEPHALOSPORIN ALLERGY PATHWAY



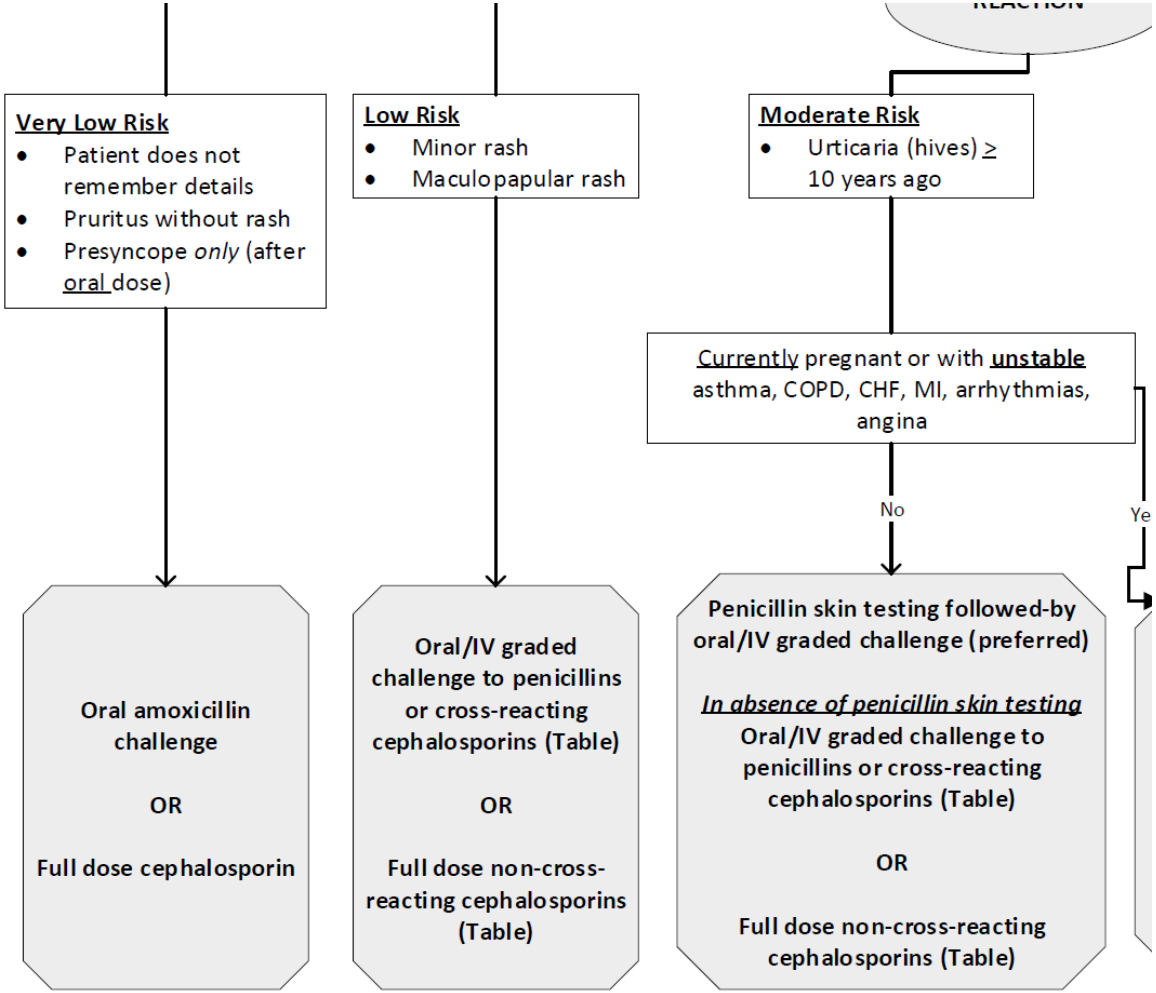
UPMC LIFE CHANGING MEDICINE

UPMC PENICILLIN ALLERGY PATHWAY



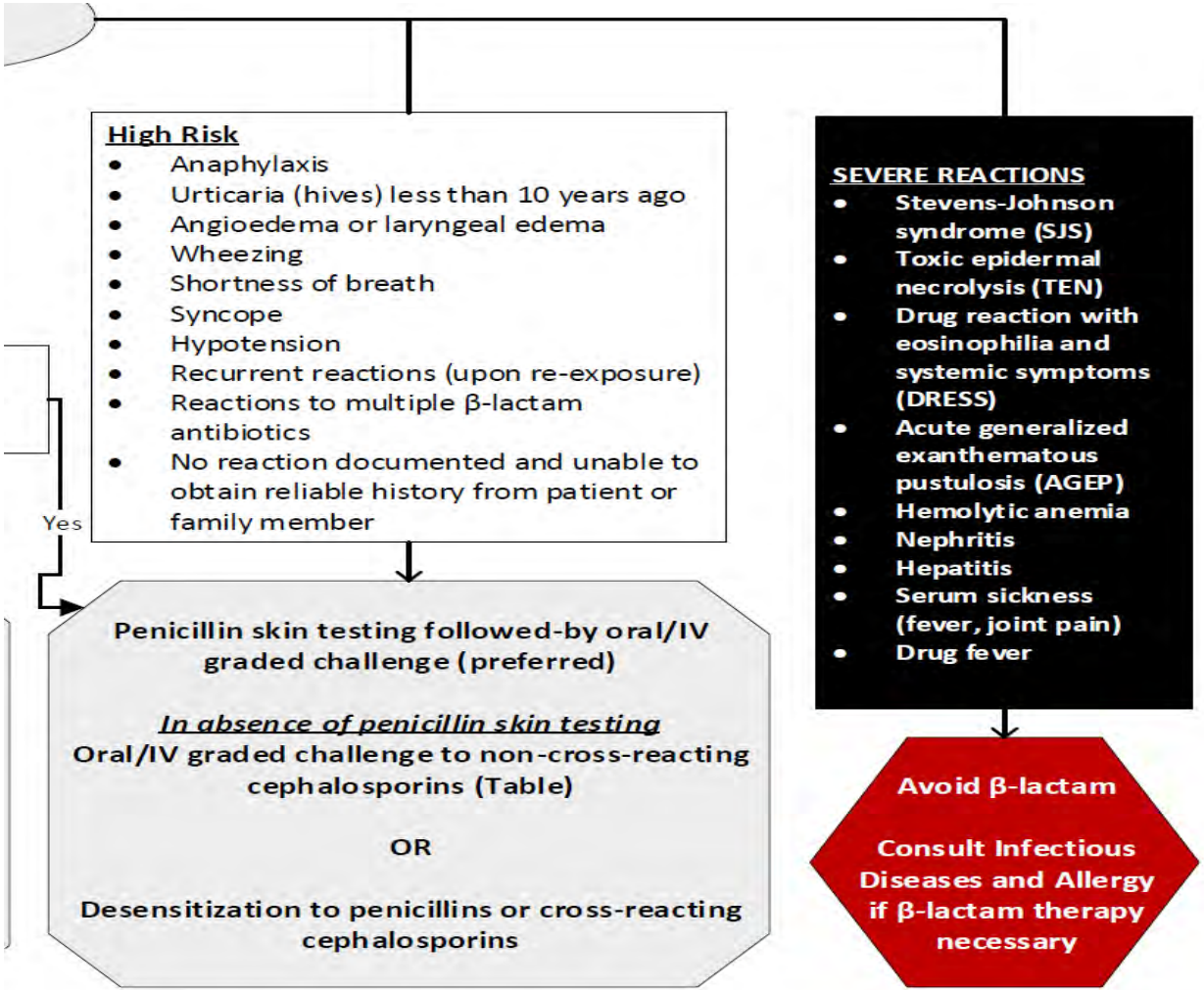
UPMC LIFE CHANGING MEDICINE

UPMC PENICILLIN ALLERGY PATHWAY



UPMC LIFE CHANGING MEDICINE

UPMC PENICILLIN ALLERGY PATHWAY



UPMC LIFE CHANGING MEDICINE

Photograph taken by A. Petrov

THANK YOU !