IN THE NAME OF GOD

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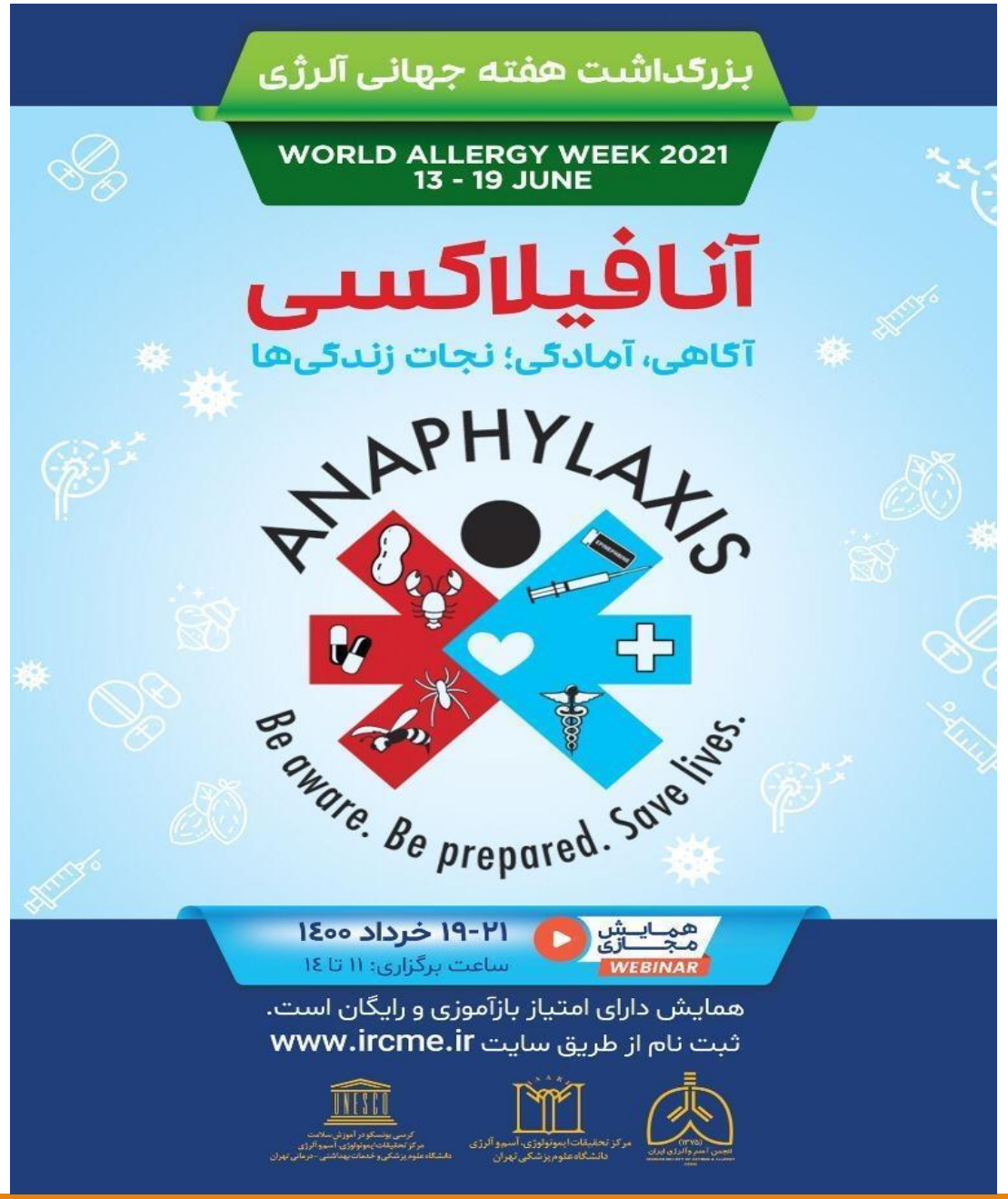
Arak.UMS



PENICILLIN AND BETA-LACTAM HYPERSENSITIVITY

EPIDEMIOLOGY

Penicillin allergy is the most commonly reported medication allergy

Penicillin allergy is self-reported by approximately 10% of patients.

However, following thorough evaluation, 90% or more of individuals with a history of penicillin allergy tolerate penicillin

Approximately 50% of penicillin-allergic patients lose their sensitivity over 5 years, and approximately 80% over 10 years

Penicillin induced anaphylaxis is relatively rare, with several studies suggesting a rate of approximately 0.01% to 0.04% of treated patients

Physicians frequently choose alternative antibiotics for those labeled with “penicillin allergy.”

Unfortunately, this is associated with increased antimicrobial resistance, increased Clostridium difficile infections, prolonged length of hospital stays, increased intensive care admissions, increased hospital readmissions, and increased mortality.

Beyond compromising one’s health, there are significantly higher costs associated with the “penicillin allergy” label.

CLASSIFICATION

Type I (hypersensitivity) is an IgE-mediated reaction, with onset occurring minutes to hours after exposure, and is one of the most severe drug reactions.

Type II (cytotoxic) immune reactions are IgG and IgM antibodyemediated cytotoxic reactions that involve activation of the complement system.

Type III (serum sickness) immune reactions are mediated by IgG and IgM, with the onset of symptoms occurring 10 to 21 days after exposure.

Type IV (delayed hypersensitivity) immune reactions are mediated by IgG and cellular responses. They occur approximately 72 hours after drug exposure. The most common type of type IV reactions is maculopapular exanthema.

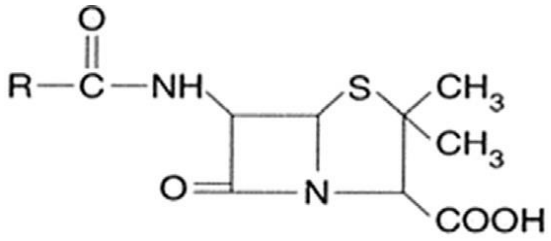
Many drug reactions do not fit into the Coombs and Gell classification and were proposed later as a “catch-bag” for reactions not meeting the criteria of types I to IV. These reactions have their onset typically after 72 hours and are nonspecific

IMMUNOCHEMISTRY

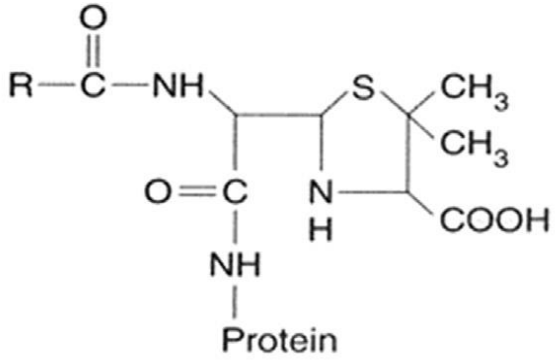
- Penicillin, like most drugs, is generally too small to be immunogenic; therefore, the immune response is directed against complexes of penicillin degradation products covalently bound to self-proteins.
- The allergic components of penicillin are derived from either the beta-lactam core ring structure or from a specific side chain R group (Fig. 1).
- The core beta-lactam ring structure is shared among all penicillin antibiotics,

  whereas the R-group side chains differentiate penicillin antibiotics from each other

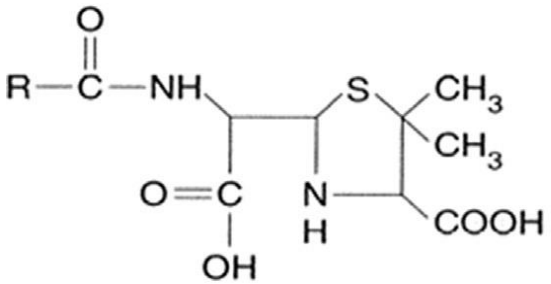
Penicillin metabolite:



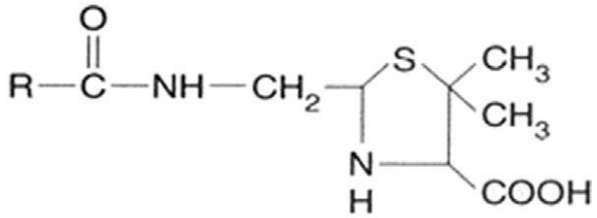
Penicillins



Penicilloyl



Penicilloate



Penilloate

Penicillin metabolite:

- After penicillin administration, the beta-lactam ring opens spontaneously to form several breakdown products.
- The most prevalent of these is penicilloyl polylysine, or major allergenic determinant, which comprises 95% of the breakdown products.
- Of the remaining minor allergenic determinants, penicilloate and penilloate are the most important.

- Some patients do not react to the core ring, but instead to the R-group side chain.

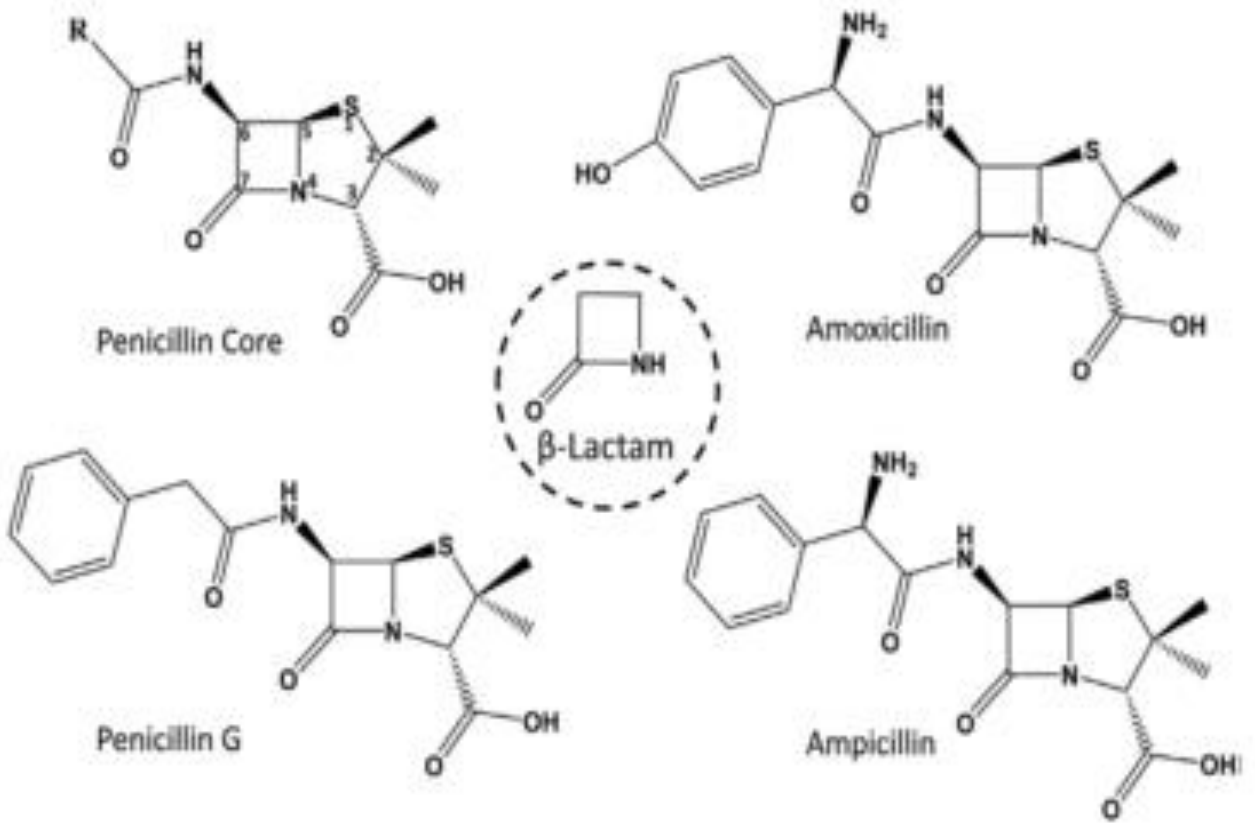
For example, an individual may tolerate penicillin, but develop an allergic response to amoxicillin or ampicillin (eg, the aminopenicillins).

- The prevalence of aminopenicillin-specific allergy is much lower in the United States (fewer than 5% of skin test–positive patients), compared with Southern Europe (25%–50% of skin test–positive patients).

- Additionally, some patients react only to clavulanic acid, and not to other penicillin determinants. In other words, they tolerate amoxicillin but react to amoxicillin-clavulanate

Allergic component of **penicillin G**	Beta lactam ring
Allergic component of **amino- penicillin**	Beta lactam ring and R- chain
Allergic component of **cephalosporin**	R- chain

Penicillin structure:

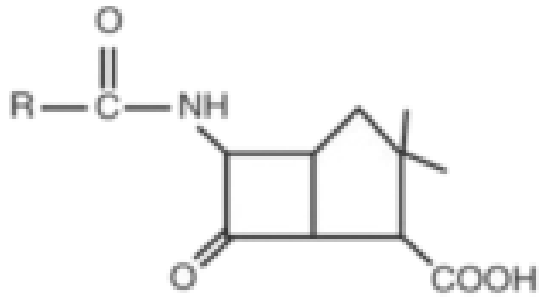


Some patients who had an immediate reaction to amoxicillin had tolerance to penicillin G or other penicillins.

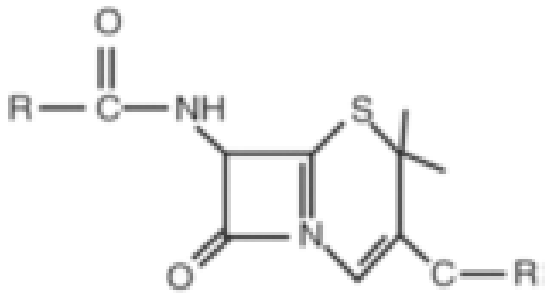
These authors conclude that the allergy reactions are directed toward the side chain of amoxicillin

However, this does not rule out the involvement of the penicillin b-lactam-thiazolidine backbone in either the native penicillin or minor determinant product as being a component of the antigenic determinant.

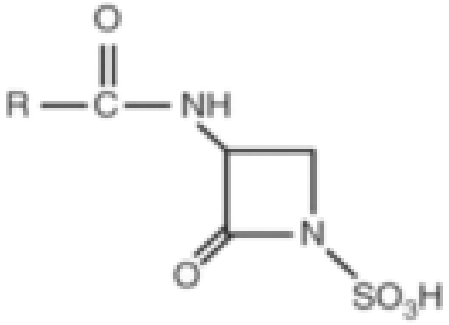
Beta-lactam structure:



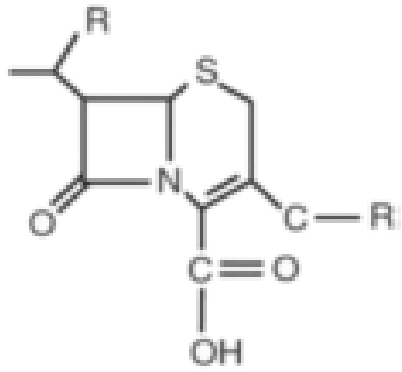
Penicillins



Cephalosporins



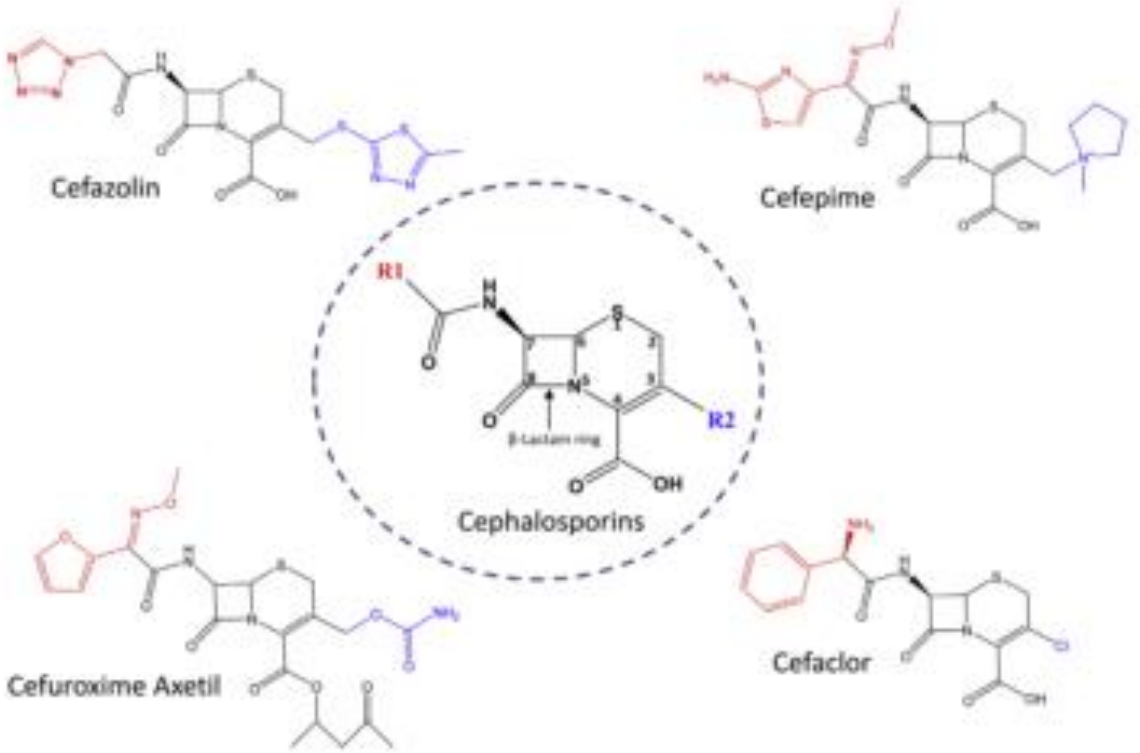
Monobactams



Carbapenems

- Penicillin is chemically inert in its natural state and spontaneously converts to form reactive intermediates under physiological conditions.
- These reactive intermediates may then bind to tissue and serum proteins, forming complexes capable of eliciting an immune response
- The major product of cephalosporin metabolism, cephalosporoyl, is unstable and undergoes rapid fragmentation.
- These fragments have no chemical resemblance to penicilloyl but may act as haptens and cause hypersensitivity reactions.
- However, the major determinants of cephalosporin-allergic reactions are their side chains

Cephalosporin structure:



- Carbapenem metabolism results in a stable carbapenoyl that is chemically similar to penicilloyl.
- Both native carbapenems and carbapenoyl can cause IgE-mediated reactions.
- The frequency of hypersensitivity reactions to imipenem was estimated to be <3%.
- Side chains seem to be the major determinant of monobactam allergy

The cross-reactivity between cephalosporins and penicillins is generally mediated by similarities in side-chain structures rather than the structure of their β-lactam core.

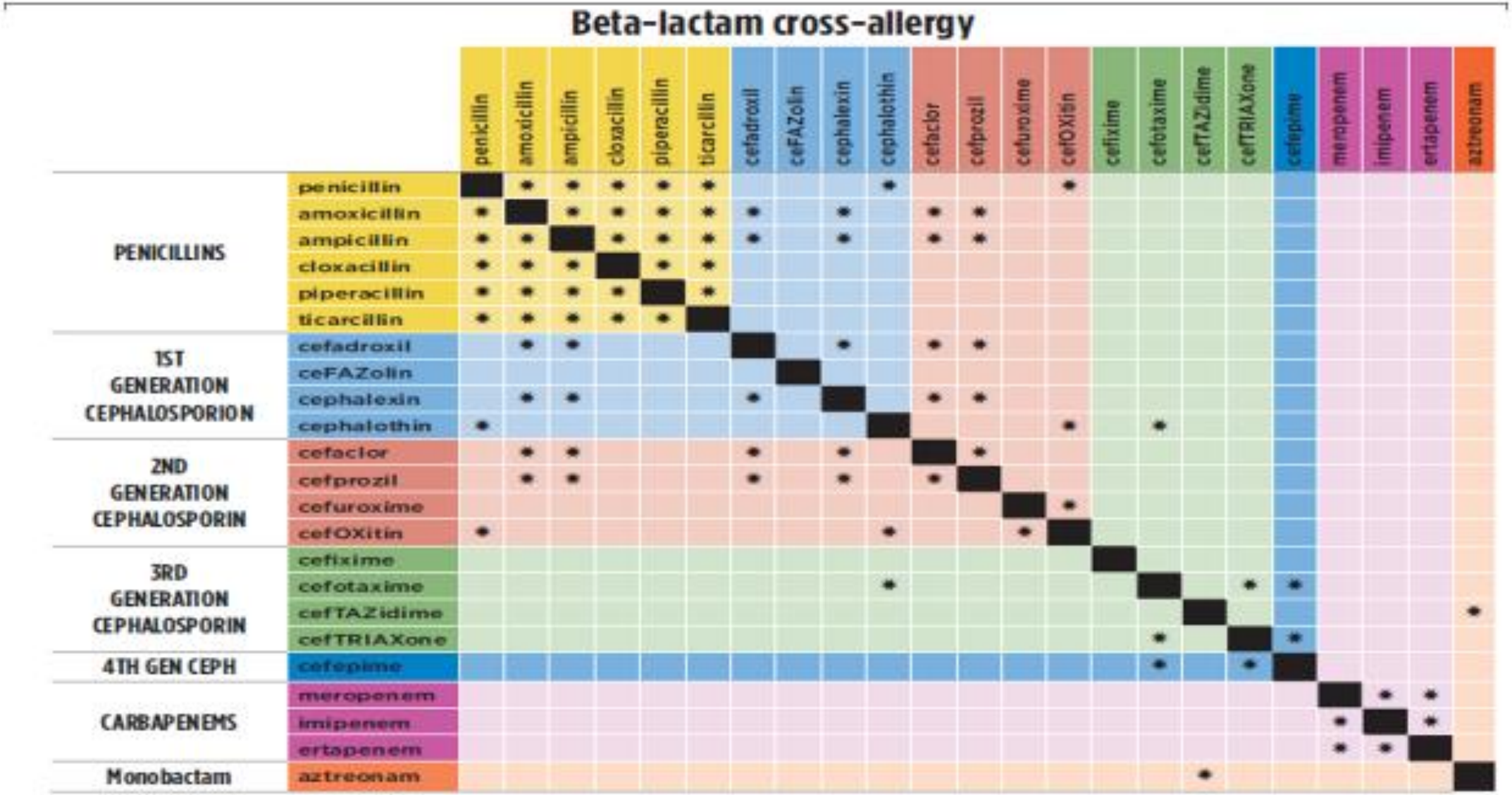
In contrast, cephalosporins with side chains dissimilar to penicillin or amoxicillin are not associated with an increased risk of allergic reactions in penicillin or amoxicillin-allergic individuals.

Regarding cross-reactivity between cephalosporins, the risk is quite low due to the heterogeneity in the side chains of different cephalosporins .

However, cross-reactions may occur when cephalosporins with similar side chains are used.

Cross-reactivity between penicillins and carbapenems is very low (<1%), especially in patients with proven penicillin allergy.

Few data are available for reactions between cephalosporins and carbapenems, between individual carbapenems, and between aztreonam and other β-lactams, but in general cross-reactivity seems to be very low


Beta-lactam cross-allergy
penicillin
amoxicillin
ampicillin
cloxacillin
piperacillin
ticarcillin
cefadroxil
ceFAZolin
cephalexin
cephalothin
cefaclor
cefprozil
cefuroxime
cefOXitin
cefixime
cefotaxime
ceftAZidime
ceftRIAXone
cefepime
meropenem
imipenem
ertapenem
aztreonam
PENICILLINS
penicillin
amoxicillin
ampicillin
cloxacillin
piperacillin
ticarcillin
1ST GENERATION CEPHALOSPORION
cefadroxil
ceFAZolin
cephalexin
cephalothin
2ND GENERATION CEPHALOSPORIN
cefaclor
cefprozil
cefuroxime
cefOXitin
3RD GENERATION CEPHALOSPORIN
cefixime
cefotaxime
ceftAZidime
ceftRIAXone
4TH GEN CEPH
cefepime
CARBAPENEMS
meropenem
imipenem
ertapenem
Monobactam
aztreonam

- penicillin G and the first-generation cephalosporin, cephalothin, exhibit cross-reactivity, despite different side chains, due to their identical three-dimensional structure

Cross-reactions are expected between ceftazidime and aztreonam due to their identical side chain; proven history of allergy in either antibiotic should preclude treatment with the other.

between cephalexin and amoxicillin that share similar side chains, cross-reactivity occurs but not cephazolin.

Penicillin Skin Test Reagents

- Penicillin skin test reagents are based on the immunogenicity and include major and minor determinants.
- Penicilloyl polylysine (PPL) is the synthetically made major determinant,

whereas penilloate, penicilloate, penicillin G, amoxicillin and ampicillin are

grouped as minor determinants (Table 1)

Table 1
Penicillin skin test reagents

Reagent	Concentration Used for Skin Testing
Penicilloyl-polylysine (Pre-Pen)	6×10^{-5} M
Penicillin G	10,000 units/mL
Penicilloate	0.01 M
Penilloate	0.01 M
Ampicillin/amoxicillin	3–25 mg/mL

Skin Testing Predictive Value

- PPL is necessary for skin testing, as up to 84% of penicillin skin test–positive patients are positive to PPL.
- The positive predictive value (PPV) of PPL is unclear. However, limited retrospective data demonstrate that the PPV of penicillin skin testing is approximately 50% (with a range of (33%–100%).
- The negative predictive value (NPV) of PPL ranges from 84% (in European studies) to 99%, with the theory that the variability is due to a higher prevalence of selectively allergic amoxicillin/ampicillin patients in Europe

- With respect to minor determinants, approximately 10% of penicillin skin test–positive patients are positive to only penicilloate and/or penilloate.
- As it is rare to skin test without PPL, the overall NPV of PPL and MDM (with all 3 reagents) is greater than 95%, which parallels that of PPL and penicillin G.

In Vitro Testing:

In vitro tests using enzyme-linked immunosorbent assays to PPL, penicillin G, penicillin V, amoxicillin, and ampicillin are commercially available but are of limited value.

Sensitivity of in vitro IgE antibodies is as low as 45% and studies with positive in vitro tests report a high number of false-positive results.

Skin Testing:

- Penicillin skin testing is the most optimal method to evaluate for IgE-mediated penicillin allergy.
- When skin testing is executed properly, it is very safe; it has been studied in young children, pregnant women, emergency department patients, preoperative patients, and hospitalized critically ill patients.
- However, there is a rare risk of systemic reactions
- Mill and colleagues demonstrated that in 818 children with histories of cutaneous reactions to amoxicillin, a graded amoxicillin challenge was tolerated in 94%, with the remaining developing mild hives or a maculopapular rash.
- Of note, none of their patients had a history of anaphylaxis and most patients reported reactions during their first course of amoxicillin.

Another approach involves skin testing with only the major determinant and penicillin G followed by oral challenge to amoxicillin in those with negative skin testing results.

With this methodology, individuals with negative skin testing results had an oral challenge reaction rate of 1%.

These reactions typically involved urticaria only, although epinephrine was required to treat the reaction in rare instances.

Recent studies have explored the utility and safety of direct oral challenges in low-risk individuals, with a limited role of penicillin skin testing.

These studies suggest a possible role for direct oral challenges without preceding penicillin skin testing in certain patient populations.

However, each of these studies were single center experiences with limited numbers of patients, and thus these practices are not yet considered standard of care

- In general, drug challenges should be performed when there is a low likelihood of a drug allergy, as the purpose is to confirm that a patient is not allergic and can tolerate the drug.

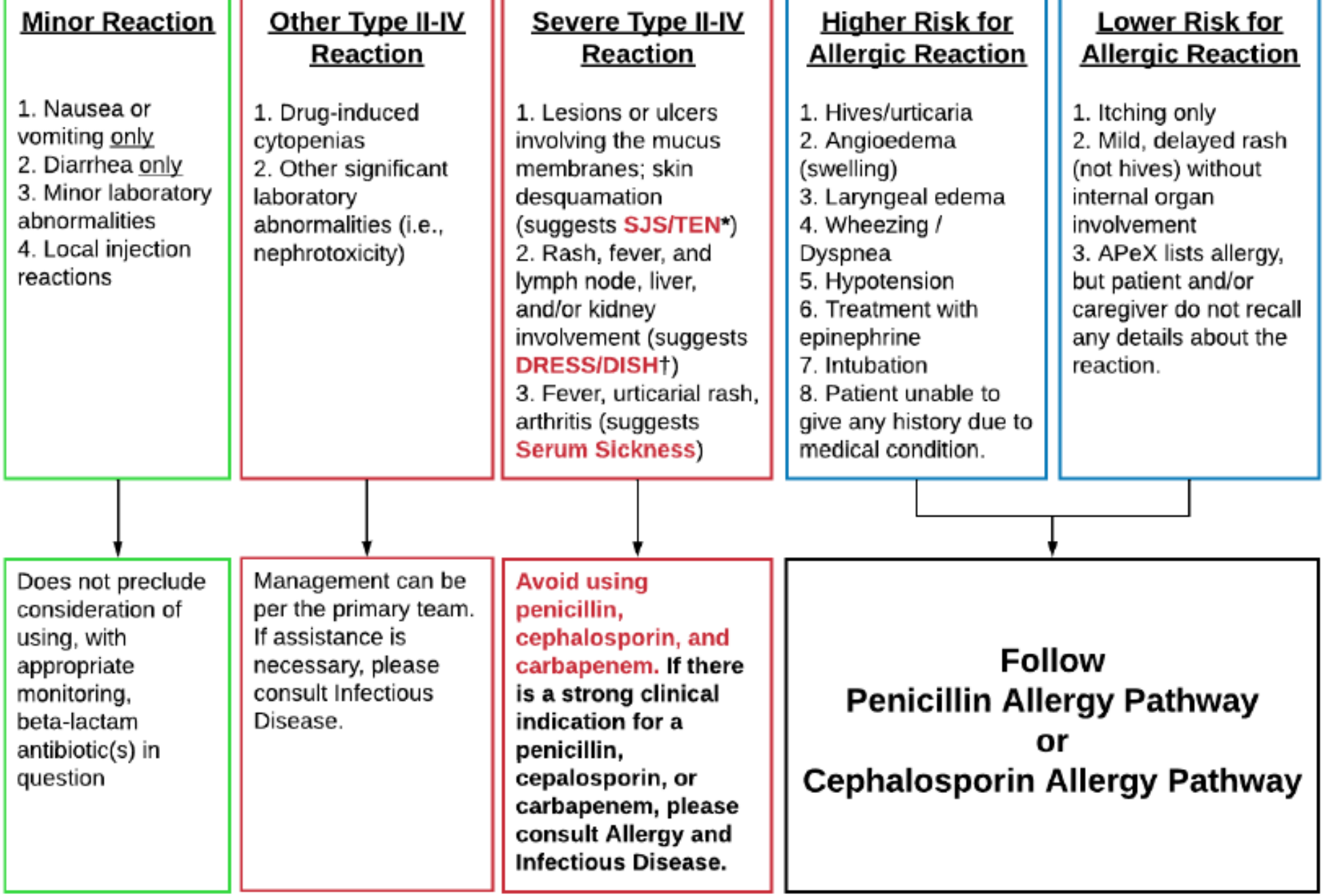
it has become standard of care to routinely perform a challenge immediately after a negative skin test.(but not in IRAN)

Typically, the challenge is either a single dose or a 2-step graded challenge (one-tenth of full dose, followed 30–60 minutes later by the full dose).

Amoxicillin is the preferable penicillin, because it has both the immunologically significant core beta-lactam ring and the potentially immunologically significant R-group side chain.

If patients report reactions to amoxicillin-clavulanate, they should be challenged with that antibiotic, rather than amoxicillin.

INPATIENT BETA-LACTAM ALLERGY GUIDELINE


Minor Reaction
1. Nausea or vomiting only
2. Diarrhea only
3. Minor laboratory abnormalities
4. Local injection reactions
Other Type II-IV Reaction
1. Drug-induced cytopenias
2. Other significant laboratory abnormalities (i.e., nephrotoxicity)
Severe Type II-IV Reaction
1. Lesions or ulcers involving the mucus membranes; skin desquamation (suggests SJS/TEN*)
2. Rash, fever, and lymph node, liver, and/or kidney involvement (suggests DRESS/DISH†)
3. Fever, urticarial rash, arthritis (suggests Serum Sickness)
Higher Risk for Allergic Reaction
1. Hives/urticaria
2. Angioedema (swelling)
3. Laryngeal edema
4. Wheezing / Dyspnea
5. Hypotension
6. Treatment with epinephrine
7. Intubation
8. Patient unable to give any history due to medical condition.
Lower Risk for Allergic Reaction
1. Itching only
2. Mild, delayed rash (not hives) without internal organ involvement
3. APeX lists allergy, but patient and/or caregiver do not recall any details about the reaction.
Does not preclude consideration of using, with appropriate monitoring, beta-lactam antibiotic(s) in question
Management can be per the primary team. If assistance is necessary, please consult Infectious Disease.
Avoid using penicillin, cephalosporin, and carbapenem. If there is a strong clinical indication for a penicillin, cepalosporin, or carbapenem, please consult Allergy and Infectious Disease.
Follow
Penicillin Allergy Pathway
or
Cephalosporin Allergy Pathway

Severe Type II-IV Reaction

1. Lesions or ulcers involving the mucus membranes; skin desquamation (suggests **SJS/TEN***)
2. Rash, fever, and lymph node, liver, and/or kidney involvement (suggests **DRESS/DISH**†)
3. Fever, urticarial rash, arthritis (suggests **Serum Sickness**)

Avoid using penicillin, cephalosporin, or carbapenem. If there is a strong clinical indication for a penicillin, cephalosporin, or carbapenem, please consult Allergy and Infectious Disease.

Higher Risk for Allergic Reaction

1. Hives/urticaria
2. Angioedema (swelling)
3. Laryngeal edema
4. Wheezing / Dyspnea
5. Hypotension
6. Treatment with epinephrine
7. Intubation
8. Patient unable to give any history due to medical condition.

OK to administer full dose:
-- Aztreonam

OK to administer using **Test Dose procedure**:
-- Cefazolin
-- 3rd/4th/5th generation cephalosporin
-- Carbapenem

If ID consult determines that a penicillin or 1st/2nd generation cephalosporin (other than cefazolin) is the preferred therapy, consult Allergy for possible inpatient penicillin skin testing.

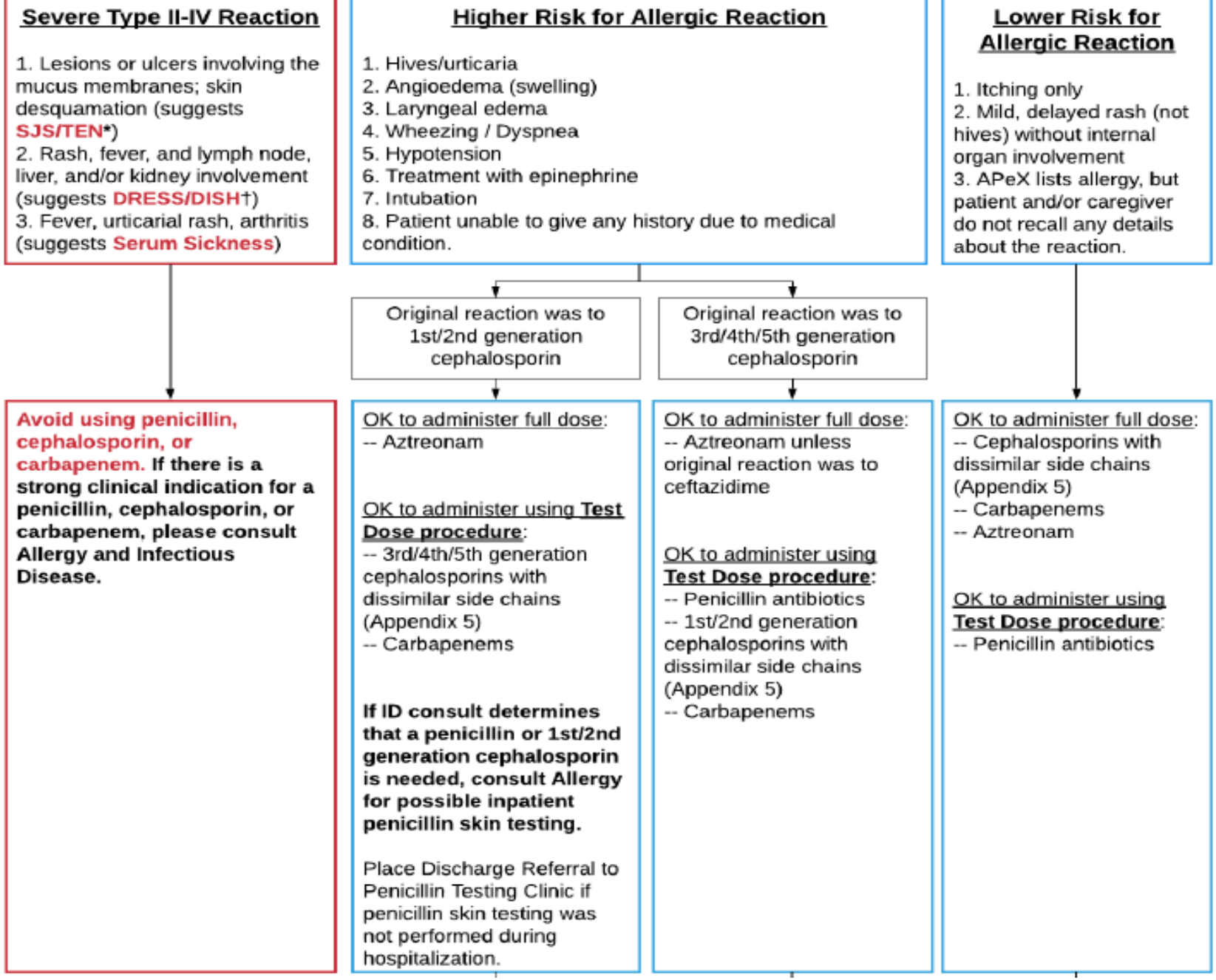
Place Discharge Referral to Penicillin Testing Clinic for penicillin skin testing if penicillin testing was not performed during hospitalization.

Lower Risk for Allergic Reaction

1. Itching only
2. Mild, delayed rash (not hives) without internal organ involvement
3. APeX lists allergy, but patient and/or caregiver do not recall any details about the reaction.

OK to administer full dose:
-- Cefazolin
-- 3rd/4th/5th generation cephalosporin
-- Carbapenem
-- Aztreonam

OK to administer using **Test Dose procedure**:
-- Penicillin antibiotics
-- 1st/2nd generation cephalosporin


Severe Type II-IV Reaction
1. Lesions or ulcers involving the mucus membranes; skin desquamation (suggests SJS/TEN*)
2. Rash, fever, and lymph node, liver, and/or kidney involvement (suggests DRESS/DISH†)
3. Fever, urticarial rash, arthritis (suggests Serum Sickness)
Higher Risk for Allergic Reaction
1. Hives/urticaria
2. Angioedema (swelling)
3. Laryngeal edema
4. Wheezing / Dyspnea
5. Hypotension
6. Treatment with epinephrine
7. Intubation
8. Patient unable to give any history due to medical condition.
Lower Risk for Allergic Reaction
1. Itching only
2. Mild, delayed rash (not hives) without internal organ involvement
3. APeX lists allergy, but patient and/or caregiver do not recall any details about the reaction.
Original reaction was to 1st/2nd generation cephalosporin
Original reaction was to 3rd/4th/5th generation cephalosporin
Avoid using penicillin, cephalosporin, or carbapenem. If there is a strong clinical indication for a penicillin, cephalosporin, or carbapenem, please consult Allergy and Infectious Disease.
OK to administer full dose:
-- Aztreonam
OK to administer using Test Dose procedure:
-- 3rd/4th/5th generation cephalosporins with dissimilar side chains (Appendix 5)
-- Carbapenems
If ID consult determines that a penicillin or 1st/2nd generation cephalosporin is needed, consult Allergy for possible inpatient penicillin skin testing.
Place Discharge Referral to Penicillin Testing Clinic if penicillin skin testing was not performed during hospitalization.
OK to administer full dose:
-- Aztreonam unless original reaction was to ceftazidime
OK to administer using Test Dose procedure:
-- Penicillin antibiotics
-- 1st/2nd generation cephalosporins with dissimilar side chains (Appendix 5)
-- Carbapenems
OK to administer full dose:
-- Cephalosporins with dissimilar side chains (Appendix 5)
-- Carbapenems
-- Aztreonam
OK to administer using Test Dose procedure:
-- Penicillin antibiotics

Thanks For Your Attention