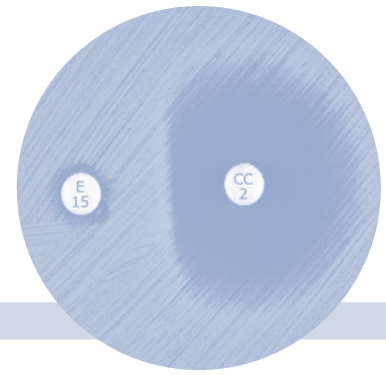


# the d-zone

VOL. 36 SUPP. 4 ISSN 1939-6910 SEPTEMBER 2007



## Study of the Month

In a four-year study conducted in ICUs in Thailand, the implementation of an educational module for healthcare workers resulted in sustained reductions in the incidence of ventilator-associated pneumonia (VAP), duration of hospital stay, and cost of antibiotics, and hospitalization.

**Apisarntharak A, Pinitchai U, Thongphubeth K, et al.** Effectiveness of an educational program to reduce ventilator-associated pneumonia in a tertiary care center in Thailand: a 4-year study. *Clin Infect Dis* 2007; 45(6): 704-711.

## Review of the Month

Yang and Guglielmo provide a concise, easy-to-read summary of the identification and treatment issues concerning two very important mechanisms of bacterial resistance.

**Yang K, Guglielmo BJ.** Pharmacokinetic Diagnosis and treatment of extended-spectrum and AmpC beta-lactamase-producing organisms. *Ann Pharmacother* 2007; 41(9): 1427-1435.

## Quote of the Month

“Even on the most exalted throne in the world we are only sitting on our own bottom.”

—Michel de Montaigne

## the d-zone

a monthly supplement to *Drug Therapy Topics* published by the UW Drug Information Center

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also published online at <http://uw.pnrx.org/therapyTopics.asp>

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Black D. Antibiotic Cross-Reactivity: A Quartet of Scenarios *The D-Zone* 2007; 36(Suppl 4): S13-S16.

## Antibiotic Cross-Reactivity: A Quartet of Scenarios

### Introduction

Immune-mediated or allergic reactions account for approximately 15% of all adverse drug reactions.<sup>1</sup> Immediate reactions (type I), such as anaphylaxis, urticaria, and angioedema, are mediated predominantly by drug-specific IgE antibody. Cytotoxic reactions (type II) and immune complex reactions (type III) are mediated by drug-specific IgG or IgM antibody. Delayed hypersensitivity reactions, such as the tuberculin skin test, are T-cell mediated and were labeled as type IV in the original Coombs and Gell classification. Since the creation of that classification system 40 years ago, data has emerged supporting subdivision of type IV reactions into four categories (see Table 1).<sup>1</sup>

A patient who has experienced an allergic reaction to an antibiotic may experience a similar reaction to a structurally related antibiotic. This phenomenon is known as cross-reactivity. A common, but often erroneous, assumption is that structurally related antibiotics within a class (e.g., fluoroquinolones), or between classes (e.g., penicillins and cephalosporins), will cross-react. A further complication is that many reactions deemed allergic are, in reality, nonimmunologic in nature. As a result, a patient may be treated with an alternative antibiotic that is less effective, more toxic, or more expensive than the antibiotic of first choice.

This issue of *The D-Zone* examines four commonly encountered situations in which an accurate assessment of allergic cross-reactivity between antibiotics is required.

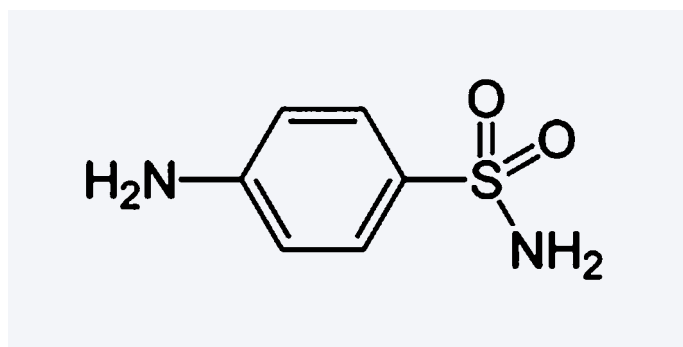
### Is it safe to use a cephalosporin in my penicillin-allergic patient?

The incidence of self-reported penicillin allergy in the population is 1-10%.<sup>2</sup> Penicillin is the most common cause of drug-induced anaphylaxis, occurring once every 5,000 to 10,000 courses of therapy; this translates into at least 300 penicillin-related deaths each year.<sup>3,4</sup> Skin testing is a simple and effective way to identify patients who are truly allergic. Only 10–20% of patients who claim to be penicillin-allergic will be positive by skin testing.<sup>5</sup> In patients with a history of penicillin allergy who are skin-test negative and then administered penicillin, IgE-mediated reactions occur in 4% or less, which is probably no greater than the incidence in patients who receive a penicillin with a negative allergy history.<sup>6</sup> Unfortunately, the management of penicillin-allergic patients has been complicated by the voluntary removal of benzylpenicilloyl-polylysine (Pre-Pen<sup>®</sup>), the commercial major determinant product, from the market in 2004.<sup>7</sup>

**Table 1.** Type IV hypersensitivity reactions

TYPE	T-CELL TYPE	EFFECTOR MECHANISM	EXAMPLE
IVa	Th1	Monocyte activation	Tuberculin skin test
IVb	Th2	Eosinophilic activation	Maculopapular rash
IVc	Cytotoxic T-cells	CD4+/CD8+ mediated killing	Maculopapular rash
IVd	T cells	Neutrophil recruitment and activation	Pustular exanthema

## Antibiotic Cross-Reactivity: A Quartet of Scenarios (continued)



**Figure 1.** Sulfanilamide

It is increasingly recognized that the commonly quoted rate of allergic reactions to cephalosporins among penicillin-allergic patients (8–18%) is probably an overestimate. Why, after a half century of cephalosporin use, should the precise rate of cross-reactivity not be firmly established? Factors complicating interpretation of the available studies include the following:

1. Because penicillin-related compounds are produced by the *Cephalosporium* mold, early (prior to 1980) cephalosporin preparations contained trace amounts of penicillin. Therefore, assessments of cross-reactivity in studies conducted before 1980 are likely exaggerated.
2. The antigenic determinants of cephalosporins have not been fully characterized, so it is not possible to prospectively assess reactivity with cephalosporin skin testing.
3. A large amount of published literature uses historical data that probably include non-allergic reactions. The only “true” allergic reactions are IgE-mediated.
4. Patients with true drug allergies have at least a 3-fold increased risk of adverse reactions to unrelated, non-cross-reacting drugs.
5. When an allergic reaction to a cephalosporin occurs in a penicillin-allergic patient, it may simply be a coincidence. Estimates of cross-reactivity should take into account the possibility of a primary cephalosporin allergy (approximately 1–3%).

Penicillins and cephalosporins are relatively low molecular weight compounds consisting of a  $\beta$ -lactam ring fused with a sulfur-containing thiazolidine or dihydrothiazine ring, respectively. The  $\beta$ -lactam ring of a penicillin degrades to form a stable derivative, with an intact thiazolidine ring, that binds to proteins (i.e., functions as a hapten). In contrast, cephalosporins undergo rapid fragmentation of both ring structures, which may render the cephalosporin ring structure clinically irrelevant.<sup>8</sup> The important differences in chemistry of penicillins and cephalosporins thus suggest that cross-reactivity should be minimal.<sup>9</sup>

Taking into account the complicating factors listed above, Pichichero analyzed 23 studies evaluating allergic reactions to cephalosporins.<sup>9</sup> About 2,200 patients in these studies had the existence of penicillin allergy evaluated by skin test. His analysis suggests that the incidence of cross-reactivity to cephalosporins in penicillin-allergic patients depends on the chemical similarity of the cephalosporin side chain on C-7 to the side chain of penicillin or amoxicillin. Specifically, the attributable risk of an allergic reaction to a cephalosporin in a penicillin-allergic patient was increased by about 0.5% with some (not all) first-generation cephalosporins. Second- and third-generation cephalosporins were not associated with increased risk. Cefazolin is unique among commercially available first-generation cephalosporins in that its side chain is unrelated to penicillins or other cephalosporins, and it also was not associated with increased risk.<sup>8</sup>

In summary, the use of certain first-generation cephalosporins with a similar side chain to penicillin (cefactor, cefadroxil, cephalexin, cephadrine) should probably be avoided in patients with a documented IgE-mediated penicillin allergy because of a small (0.5%) increase in attributable risk of reaction. However, all other cephalosporins have dissimilar side chains and may be safely administered, especially if the allergic reaction to penicillin was not severe.

### Do carbapenems cross-react with penicillins?

For many years, the best data concerning the cross-reactivity of penicillins and carbapenems were the work of Saxon, et al. Thirty-nine patients with a history of allergic reactions to penicillin were studied. Twenty patients were skin-test-negative to a battery of penicillin determinants (major and minor), and none of the 20 reacted to skin testing with the analogous imipenem major and minor determinants. Of the 19 patients with a history of penicillin allergy who reacted to one or more penicillin determinants, nine also reacted to one or more of the imipenem determinants. Of importance, it was the penicillin minor determinants that demonstrated the highest degree of cross-reactivity with imipenem; none of the five patients who reacted to the penicillin major determinant reacted to the imipenem major determinant. Overall, this study suggested that up to 50% of penicillin-allergic (by history) skin-test-positive patients would react to one or more imipenem determinants; however, the data were skewed toward patients with penicillin minor determinant reactivity, and the true degree of clinically relevant cross-reactivity cannot be ascertained without *in vivo* challenge.

## Antibiotic Cross-Reactivity: A Quartet of Scenarios (continued)

Three retrospective studies designed to assess the clinical risk of cross-reactivity between penicillin and carbapenems have been published since 2000. McConnell et al. reviewed the medical records of 63 bone marrow transplant patients with self-reported or clinically documented penicillin allergy (none by skin testing) treated with imipenem/cilastatin. Only six patients (9.5%) experienced an allergic reaction (rash) to imipenem/cilastatin. Interestingly, 33% of the patients with clinically documented penicillin allergy experienced an allergic reaction to imipenem/cilastatin compared to only 7% of the patients with self-reported allergy.<sup>11</sup> Prescott et al. retrospectively analyzed 211 patients treated with imipenem/cilastatin or meropenem; 100 patients had reported or clinically documented penicillin allergy (none by skin testing), 111 were not penicillin-allergic. An equal number of patients in the two groups each received both carbapenems. The incidence of penicillin-allergic patients experiencing an allergic reaction to a carbapenem was 11%, compared to 2.7% of patients not allergic to penicillin ( $p=0.024$ ). No difference between imipenem/cilastatin and meropenem was discernible.<sup>12</sup> Sodhi et al. retrospectively reviewed 266 patients who received imipenem/cilastatin or meropenem; 163 had self-reported penicillin allergy whereas 103 were not penicillin-allergic. Fifteen (9.2%) of the penicillin-allergic patients experienced a carbapenem hypersensitivity reaction, compared to four (3.9%) of the patients who were not penicillin-allergic ( $p=NS$ ). No attempt was made to exclude patients treated with aminopenicillins which are often responsible for nonimmunologic reactions such as rash; therefore, a substantial number of patients in the penicillin-allergic group may not have been truly allergic, which could explain the nonsignificant difference between the groups.<sup>13</sup>

In a prospective trial evaluating the use of meropenem in patients with documented penicillin allergy, 104 consecutive patients with a history of immediate allergic reaction to penicillin and a positive skin test to at least one penicillin determinant (major or minor) were skin tested with meropenem; skin-test-negative patients were then challenged with escalating doses of intravenous meropenem (up to a full therapeutic dose). Only one patient (0.9%, 95% CI 0.02-5.2%) reacted to the meropenem skin test; the remaining 103 patients tolerated meropenem challenge without incident.<sup>14</sup>

Taken together, the data suggest that the true incidence of cross-reactivity between penicillins and carbapenems is considerably lower than suggested by Saxon et al. Carbapenems should still be used cautiously in patients with a history of life-threatening allergy to penicillin.

### If my patient has an allergic reaction to one fluoroquinolone, should I try a different one?

The safety profile of fluoroquinolones is generally excellent. However, adverse reactions of an immunologic nature have been described at a frequency of about one per 50,000 treatments or less.<sup>15</sup> Almost 400 case reports of probable allergic reactions to fluoroquinolones have appeared in the literature in the last 40 years. Ciprofloxacin is most frequently implicated although, among the currently available fluoroquinolones, it has also been in use the longest. The most commonly reported allergic reactions to fluoroquinolones are immediate in nature, such as urticaria, angioedema, and anaphylaxis. A wide range of less common reactions with a probable immune mechanism have also been described, such as photosensitivity, maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, hemolytic-uremic syndrome, various cytopenias, acute interstitial nephritis, and acute hepatitis. Some of these reactions are associated with specific features of the fluoroquinolone chemical structure.

Manfredi et al. assayed the serum of 55 patients who had experienced an immediate allergic reaction to a fluoroquinolone for the presence of fluoroquinolone-specific IgE. Most had successfully received prior fluoroquinolone treatment. Fluoroquinolone-specific IgE was identified in 30 patients (54.5%), 24 of whom had IgE directed toward multiple fluoroquinolones. In a small unpublished study of patients who developed a delayed maculopapular rash to ciprofloxacin or norfloxacin, specific T-cells were detected and cloned; 50% of the clones cross-reacted to multiple chemically-related compounds.<sup>15</sup> These data suggest that a patient who has experienced an allergic reaction to one fluoroquinolone should avoid treatment with a different fluoroquinolone. However, based on limited evidence, it may be reasonable to consider the use of a different fluoroquinolone if the original reaction was mild.

### Does a "sulfa" allergy mean antibiotics only, or all sulfonamide compounds?

A sulfonamide antibiotic is a derivative of sulfanilamide (Figure 1). About 3% of sulfonamide antibiotic treatment courses result in a hypersensitivity reaction. The typical presentation includes fever and maculopapular rash, typically developing 7–14 days after initiation of therapy. Other manifestations of hypersensitivity include anaphylactic or anaphylactoid reactions, fixed drug eruptions, Stevens-Johnson syndrome, and toxic epidermal necrolysis.<sup>16</sup> Up to 60% or more of HIV-infected patients experience trimethoprim/sulfamethoxazole hypersensitivity reactions; proposed explanations include slow rates of acetylation and decreased glutathione concentrations.<sup>17</sup>

## Antibiotic Cross-Reactivity: A Quartet of Scenarios (continued)

Sulfonamide hypersensitivity reactions are not fully understood. Non-IgE-mediated reactions are thought to occur most commonly. A key part of the structure of all sulfonamide antibiotics is an N4-arylamine (also found in fosamprenavir, a protease inhibitor). A proposed mechanism involves drug oxidation by liver microsomal enzymes to a hydroxylamine and eventually a nitroso metabolite. These metabolites are known to bind to endogenous proteins (haptenation). Potentially severe reactions may also occur independent of sensitization, suggesting the existence of other pathophysiologic mechanisms.

Non-antibiotic sulfonamides (see Table 2) do not possess the N4-arylamine feature. In a recent retrospective cohort study, Strom et al. found that the adjusted odds ratio for the association between hypersensitivity after receipt of a nonantibiotic sulfonamide and a history of allergy to sulfonamide antibiotics, compared to no such history, was 2.8. However, the adjusted odds ratio for the association between penicillin hypersensitivity and a history of allergy to sulfonamide antibiotics, compared to no such history, was 3.9 (even greater). Among those with an allergic reaction after receipt of a sulfonamide antibiotic, the adjusted odds ratio for an allergic reaction to a subsequent sulfonamide nonantibiotic,

as compared to a subsequent penicillin, was 0.7. The risk of an allergic reaction following receipt of a sulfonamide nonantibiotic was lower among patients with a history of sulfonamide antibiotic hypersensitivity than among patients with a history of penicillin hypersensitivity (adjusted odds ratio, 0.6). These data suggest that the risk of cross-reactivity between sulfonamide antibiotics and non-antibiotic sulfonamides reflects a general heightened risk of allergic reactions in the former group, rather than a specific cross-reactivity with drugs containing a sulfa moiety. Therefore, patients with a history of sulfonamide antibiotic allergy need not necessarily avoid all sulfonamide compounds.<sup>18</sup>

**Table 2.** Some non-antibiotic sulfonamides

Acetazolamide	Dapsone	Metolazone
Acetohexamide	Diazoxide	Probenecid
Bumetanide	Furosemide	Sulfasalazine
Celecoxib	Glipizide	Tolazamide
Chlorpropamide	Glyburide	Tolbutamide
Chlorthalidone	Hydrochlorothiazide	Torseamide
	Indapamide	

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