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A Practical Guide for Managing Antibiotic Allergies in the Emergency Department

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Abstract
Up to 30% of patients report at least one antibiotic allergy, but oftentimes these antibiotic allergies are misdiagnosed. In fact, of the 10% of patients reporting penicillin allergies, 90%–98% are not truly allergic. In an era of increasing antibiotic resistance coupled with a limited number of new antibiotics, evaluating antibiotic allergies is critical in providing optimal patient care. Differentiating adverse drug reactions from antibiotic allergies may seem like a daunting task for clinicians and providers, especially in the emergency department, where decisions are made quickly. However, a systemic approach, including medical record review coupled with patient and/or family interview, is vital in managing patients with antibiotic allergies. Inappropriate, alternative antibiotics are frequently chosen due to patient allergies, and data suggest higher rates of broad-spectrum antibiotic use, antibiotic resistance, and poor outcomes as a result. Herein, we review antibiotic selection in patients reporting antibiotic allergies in the emergency department. **Key words:** allergic drug reaction, antibacterial agents, drug hypersensitivity, hypersensitivity

APPROXIMATELY 10%–30% of patients report allergic drug reactions to one or more antibiotics (Romano & Warrington, 2014; Trubiano & Phillips, 2013). However, these "labels" may be misleading to prescribers, as patients often refer to a side effect as an allergy. Prescribers generally make clinical decisions regarding antibiotic therapy based on patient-reported allergies and adverse drug effects, which can oftentimes be incorrect. As a result, less appropriate alternative antibiotics are utilized and can be associated with dire outcomes (MacFadden et al., 2016; Macy & Contreras, 2014). Therefore, it is critical to accurately evaluate antibiotic allergies to avoid unintentional reexposure in addition to unnecessarily withholding an optimal antibiotic when the patient may not truly be allergic to the drug. The purpose

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of this article is to discuss antibiotic selection for patients with antibiotic allergies in the emergency department (ED).

DIFFERENTIATING ALLERGIC DRUG REACTIONS FROM ADVERSE DRUG REACTIONS

Adverse drug reactions can be categorized as either Type A, predictable reactions, or Type B, unpredictable reactions (Demoly et al., 2014). Type A reactions account for 85%–90% of adverse drug reactions, which are most commonly dose-dependent reactions directly related to the known pharmacological actions of the drug (e.g., nephrotoxicity resulting from vancomycin). Alternatively, Type B reactions occur in 10%–15% of cases and represent an unintended response to a given drug and dose typically used in patients. Furthermore, Type B reactions are dose-independent, unrelated to the underlying drug action, and develop due to immunological or other mechanisms in susceptible patients. Type B reactions may be further categorized as drug intolerance or toxicity, idiosyncratic reactions, and immunological reactions. Immunological reactions, also known as hypersensitivity reactions or allergic drug reactions, are mediated by immunoglobulin (Ig)E and non-IgE or T-cell-mediated reactions.

Historically, allergic drug reactions were divided according to the Gell and Coombs system into four categories according to pathophysiological mechanisms (see Table 1; Demoly et al., 2014; Joint Task Force on

Table 1. Classification of drug allergies

Type of reaction	Gell and Coombs classification	Mechanism	Time of onset	Manifestation
IgE-mediated	I	IgE-mediated	Within 30 min to 2 hr	Angioedema, bronchospasm, urticarial rash, anaphylaxis
Non-IgE-mediated	II	Cytotoxic (IgG-, IgM-mediated)	At least 72 hr to weeks	Hemolytic anemia, thrombocytopenia, granulocytopenia
Non-IgE-mediated	III	Immune complex	At least 72 hr to weeks	Fever, rash, lymphadenopathy, arthralgia
Non-IgE-mediated	IV	Cell-mediated (delayed)	At least 72 hr	Delayed maculopapular rash, acute interstitial nephritis, allergic contact dermatitis, severe cutaneous adverse reactions (drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson syndrome [SJS], toxic epidermal necrolysis [TEN])

Note. Ig = immunoglobulin. From Demoly et al. (2014), Joint Task Force on Practice Parameters et al. (2010), and Romano and Caubet (2014).

Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, & Joint Council of Allergy, Asthma and Immunology, 2010; Romano & Caubet, 2014). However, many allergic drug reactions could not be classified into only one category. As a result, the World Allergy Organization suggested allergic drug reactions be classified on the basis of timing to differentiate IgE-mediated reactions, also referred to as immediate reactions, from other non-IgE or T-cell-mediated reactions (see Table 1). Immediate reactions occur within 1 hr of drug administration, accounting for the time frame in which most IgE-mediated reactions occur, although administration via oral route or with food may delay symptom onset. Immediate reactions manifest as an urticarial rash, bronchospasm, angioedema, or anaphylaxis (Demoly et al., 2014). Notably, neither fever nor increased C-reactive protein is observed with immediate reactions. Nonimmediate or delayed reactions occur after at least 1 hr but typically between 6 hr to several days after drug administration (Demoly et al., 2014). Clinical findings of nonimmediate reactions are heterogeneous but commonly involve the skin. Patients with reported Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and other skin reactions categorized by nonimmediate reactions secondary to β-lactam use should avoid β-lactams and not undergo a rechallenge, skin testing, or desensitization (Demoly et al., 2014; Joint Task Force on Practice Parameters et al., 2010; Macy & Contreras, 2014; Pichichero & Zagursky, 2014; Terico & Gallagher, 2014).

PENICILLIN ALLERGIES

Penicillin allergies are reported in approximately 10% of patients in the United States, making them the most common antibiotic and drug class allergy (Macy, 2014). The potentially antigenic components of penicillins include core β-lactam ring, adjacent ring structures, and side chains (Romano, Gaeta, Arribas Poves, & Valluzzi, 2016). However, additional data emphasize side chain similarities as the cause of allergic reactions. Surprisingly, of those patients reporting penicillin allergies, at least 90%, but up to 98%, are not truly allergic (Joint Task Force on Practice Parameters et al., 2010; Macy & Ngor, 2013). These findings could be the result of misinterpretation of reactions, belief that allergies are inherited, and/or inaccurate history, which emphasizes the importance of obtaining a detailed medical history. Penicillin allergies are often diagnosed in childhood, which increases the possibility of misdiagnosing or misinterpreting a viral or non-IgE-mediated rash for a drug reaction. Even in patients with true allergies, IgE antibodies may wane over time, resulting in loss of hypersensitivity (Trubiano et al., 2017). Indeed, up to 80% of patients with IgE-mediated penicillin allergies lose their penicillin-specific antibodies after 10 years (Joint Task Force on Practice Parameters et al., 2010).

Avoiding β-lactams owing to a documented penicillin allergy is commonly seen in clinical practice, especially in the ED (MacFadden et al., 2016; Trubiano et al., 2017). However, use of less optimal antibiotic therapy is linked to an increased use of broad-spectrum antibiotics, which has been associated with adverse drug events and increased rates of resistance, *Clostridioides difficile* (formerly *Clostridium difficile*) infection, treatment failure, and mortality. For the empiric treatment of bloodstream infections due to gram-negative bacilli in patients with β-lactam allergy, the use of β-lactam antibiotics was associated with a lower rate of treatment failure compared with those who received alternative therapy (27.4% and 38.7%, respectively; Jeffres, Narayanan, Shuster, & Schramm, 2016). In addition, another study showed that patients who did not receive preferred β-lactam therapy had a 20% higher rate of readmission compared with those who received the preferred β-lactam therapy for treatment of multiple sites of infection, most commonly bacteremia without primary source, followed by skin and soft tissue infections (MacFadden et al., 2016). No significant difference in

adverse outcomes was reported between patients with a β-lactam allergy who received β-lactam therapy and those who did not report a β-lactam allergy.

Multiple mechanisms are available for diagnosing penicillin allergies. Penicillin skin testing (PST) is an easy and precise tool used to diagnosis penicillin allergies. However, it is only predictive of drug reactions that are mediated by IgE (Type I reactions) (see Table 1). Negative PST suggests that penicillins can be administered with minimal risk (negative predictive value ~97%); however, a test dose and close monitoring are still recommended (Gruchalla & Pirmohamed, 2006; Legendre, Muzny, Marshall, & Swiatlo, 2014). Alternatively, penicillin desensitization can be completed if no alternatives exist but involves administration of increasing incremental doses of penicillin resulting in decreased sensitivity of mast cells. As a result, therapeutic doses of penicillin may be administered. However, use of test doses and penicillin desensitization requires close clinical observation and may delay initiation of appropriate antibiotic therapy in the ED setting. Rechallenging a patient with penicillin after documented penicillin allergy is generally safe, especially when PST is utilized; however, it should be noted to never rechallenge or use PST in patients with documented non-IgE-mediated reactions such as SJS.

The risk of allergy cross-reactivity in patients who report penicillin allergies and are subsequently challenged with cephalosporins is approximately 2% (Joint Task Force on Practice Parameters et al., 2010) but is dependent upon side chain similarity between the drugs (see Table 2). Lower rates of allergy cross-reactivity are observed when using intravenous first-generation cephalosporins (e.g., cefazolin), third-generation cephalosporins (e.g., ceftazidime, ceftriaxone), or fourth-generation cephalosporins (e.g., cefepime) (DePestel et al., 2008; Macy & Contreras, 2014; Terico & Gallagher, 2014). The rate of allergy cross-reactivity is even lower with the use of carbapenems (e.g., ertapenem, meropenem, doripenem, imipenem/cilastatin) or monobactams (e.g., aztreonam) in patients reporting penicillin allergies (Kula, Djordjevic, & Robinson, 2014). Based on a recent systematic review of the 27 published medical malpractice or negligence cases that involved administration of β-lactams to patients with penicillin allergies who experienced an adverse outcome, the likelihood of prescribers being found liable was low when administering a cephalosporin or carbapenem (Jeffres, Hall-Lipsy, King, & Cleary, 2018). Of the 15 cases with published legal outcomes, the plaintiff prevailed in three of 10 cases involving penicillins, one of four cases involving cephalosporins, and zero of one case involving carbapenems. Although most lawsuits are not reported or published, availability of these data coupled with the fact that most patients with penicillin allergies can safely receive cephalosporins with dissimilar side chains, carbapenems, or monobactams, is reassuring.

Table 2. β-Lactam antibiotics with similar side chains

• Ampicillin • Amoxicillin • Cephalexin	• Penicillin • Cefoxitin	• Cefotaxime • Ceftriaxone • Cefuroxime • Ceftazidime • Cefepime	• Ceftazidime • Aztreonam

Note. Each column lists β-lactam antibiotics with similar side chains. From DePestel et al. (2008), Joint Task Force on Practice Parameters et al. (2010), Macy and Contreras (2014), Pichichero and Zagursky (2014), Romano, Gaeta, Arribas Poves, et al. (2016), and Terico and Gallagher (2014).

CEPHALOSPORIN ALLERGIES AND CROSS-REACTIVITY

Cephalosporin allergies are much less prevalent than penicillin allergies. Approximately 0.1%–2% of the population have true cephalosporin allergies, of which anaphylaxis occurs in 0.1% (Joint Task Force on Practice Parameters et al., 2010; Pichichero & Zagursky, 2014). Recent data report that 0.17%–0.7% of patients with a penicillin allergy have allergy cross-reactivity with cephalosporins. Diagnosis of cephalosporin allergies is more ambiguous than penicillin allergies. Penicillin skin testing does not accurately predict cephalosporin allergy. Thus, a detailed medical history is a vital part of accurately diagnosing cephalosporin allergies.

Cephalosporins, similar to penicillins in chemical structure, consist of a β-lactam ring and a variety of side chains (Joint Task Force on Practice Parameters et al., 2010; Pichichero & Zagursky, 2014). Different side chains create variation in the spectrum of activity against bacterial species and are usually the cause for allergy cross-reactivity between penicillins and cephalosporins. In the clinical setting, recent evidence suggests that the allergy cross-reactivity of β-lactam antibiotics with dissimilar side chains is less than 1% (Romano, Gaeta, Arribas Poves, et al., 2016). Allergy cross-reactivity to cephalosporins or penicillins with similar side chains should be avoided (see Table 2; Joint Task Force on Practice Parameters et al., 2010; Pichichero & Zagursky, 2014).

CARBAPENEM ALLERGIES AND CROSS-REACTIVITY

Carbapenems (e.g., ertapenem, meropenem, doripenem, imipenem/cilastatin) also contain a β-lactam ring, similar to penicillins and cephalosporins, but a different adjacent ring structure (Terico & Gallagher, 2014). On the basis of previous studies, adverse drug events, including rash and pruritus, occurred in less than 4% of patients whereas no patients experienced anaphylaxis. Historically, rates of allergy cross-reactivity were approximately 50% between carbapenems and penicillins whereas those of carbapenems and cephalosporins were almost 25% (Saxon, Adelman, Patel, Hajdu, & Calandra, 1988; Terico & Gallagher, 2014). However, additional data emerged, suggesting that the true incidence of allergy cross-reactivity was much lower than previously thought, approaching 10% (Prescott, DePestel, Ellis, & Regal, 2004; Sodhi, Axtell, Callahan, & Shekar, 2004). More recently, results from a systematic review in children and adults with a history of IgE-mediated hypersensitivity to penicillins and/or cephalosporins revealed drastically lower rates of allergy cross-reactivity with carbapenems, approximately 1% (Kula et al., 2014). In addition, the risk of hypersensitivity reactions with carbapenems is comparable between patients with and without penicillin allergies (Wall, Nayima, & Neumeister, 2014). On the basis of available data, carbapenems can be safely administered to almost all patients with IgE-mediated hypersensitivity reactions to penicillins or cephalosporins.

MONOBACTAM ALLERGIES AND CROSS-REACTIVITY

Aztreonam, the only available monobactam in the United States, contains a monocyclic β-lactam core, which is a dissimilar β-lactam core found in penicillins, cephalosporins, or carbapenems (Terico & Gallagher, 2014). Notably, allergy cross-reactivity may exist between aztreonam and ceftazidime, a third-generation cephalosporin, due to the presence of an identical side chain (Perez Pimiento et al., 1998). However, not all patients with an allergy to ceftazidime will develop a hypersensitivity reaction to aztreonam, as the risk is less than 5% (Romano et al., 2010). Among multiple studies that evaluated the risk of aztreonam cross-reactivity in patients with IgE-mediated hypersensitivity to penicillins, only three participants out of a combined 297 had positive

allergy tests to aztreonam (Gaeta et al., 2015; Moss, 1991; Patriarca et al., 2008; Vega et al., 1991). Cross-reactivity to aztreonam was not observed in 214 patients with T-cell-mediated hypersensitivity to penicillins (Romano, Gaeta, Valluzzi, et al., 2016). Overall, the risk of allergy cross-reactivity with aztreonam in patients with penicillin allergies is negligible (Lagace-Wiens & Rubinstein, 2012).

"SULFA" ALLERGIES

Reporting a "sulfa" allergy can be somewhat vague as the hypersensitivity reaction occurs due to the presence of a sulfonamide, which is present in many drugs (Schnyder & Pichler, 2013; Wulf & Matuszewski, 2013). Sulfonamide allergies are estimated to occur in 3%–6% of patients but are most likely the result of T-cell-mediated reactions (e.g., delayed-type reactions) rather than IgE-mediated (e.g., immediate-type reactions). Sulfonamide medications contain a sulfonamide group (SO_2NH_2) but may be further classified as antibiotic sulfonamides and nonantibiotic sulfonamides (see Table 3). Antibiotic sulfonamides have two functional groups, an arylamine and a five- to six-member ring attached to the sulfonamide group. The presence of both groups is crucial for their antibiotic activity and development of hypersensitivity reactions. Most commonly, manifestations of hypersensitivity reactions to sulfonamide antibiotic include fever, maculopapular exanthems, and organ involvement, usually developing within 1–2 weeks after initiating therapy. In addition, sulfonamide antibiotics have been associated with development of SJS, TEN, and drug rash with eosinophilia and systemic symptoms (DRESS).

Since nonantibiotic sulfonamides do not contain one or both of the aforementioned functional groups, the risk of IgE- or T-cell-mediated cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides is minimal (Joint Task Force on Practice Parameters et al., 2010). In patients with delayed-type reactions, such as mild rashes without mucosal or extracutaneous involvement, the sulfonamide antibiotic may be continued safely (Schnyder & Pichler, 2013). Alternatively, in the setting of severe delayed-type reactions, sulfonamide antibiotics should be avoided.

Table 3. Commonly used antibiotic sulfonamides and nonantibiotic sulfonamides

Antibiotic sulfonamides	Nonantibiotic sulfonamides
• Sulfadiazine • Sulfamethoxazole • Sulfasalazine	Loop diuretics • Furosemide • Torsemide • Bumetanide Thiazide diuretics • Hydrochlorothiazide • Chlorothiazide • Chlorthalidone • Metolazone Sulfonylureas • Glipizide • Glimepiride • Glyburide Miscellaneous • Acetazolamide • Celecoxib • Sumatriptan • Tamsulosin • Topiramate

Note. From Schnyder and Pichler (2013) and Wulf and Matuszewski (2013).

EVALUATING PATIENTS WITH ANTIBIOTIC ALLERGIES IN THE EMERGENCY DEPARTMENT

In the ED, clinicians and providers frequently encounter patients reporting one or more antibiotic allergies. Often, these health care providers will be the first to assess the accuracy of these reports. Gathering accurate information to verify antibiotic allergies early in a patient's care is important and can have a positive impact going forward, not only for the current visit but also for encounters in the future. However, it should be noted that patients may present to the ED with an acute illness, such as sepsis. In these situations,

emergent antibiotic therapy should not be delayed or withheld in an attempt to collect accurate allergy history due to the risk of increasing mortality associated with delayed antibiotic therapy in sepsis (Levy, Evans, & Rhodes, 2018; Rhodes et al., 2017). Rather, once antibiotics have been initiated, additional data regarding antibiotic allergy history may then be gathered.

Addressing self-reported antibiotic allergies may seem like a daunting task, but a systematic approach can limit unnecessary use of suboptimal antibiotics and resultant poor outcomes, as previously mentioned (MacFadden et al., 2016; Trubiano et al., 2017). Most importantly, the clinical history should be evaluated to identify the specific antibiotic and determine the likelihood of a true antibiotic allergy. Patients and/or family members should be interviewed with specific questions (see Table 4) to obtain additional details following a critical review of the medical record and outpatient medication records. It is critical to identify the specific antibiotic rather than antibiotic class. Information needed includes the antibiotic indication, when the reaction occurred, the time between antibiotic administration and onset of the reaction, and the associated signs and symptoms with an emphasis on the presence or absence of cutaneous findings. Often times, patients with reported antibiotic allergies do not have a history compatible with a true antibiotic allergy (Gomes & Demoly, 2005). As an example, infusion-related reactions, specifically red man syndrome, can also occur with rapid infusion

Table 4. Helpful questions when discussing antibiotic allergies with a patient in the emergency department

- Does the patient have a history of other allergies and/or reactions?
- What was the specific antibiotic involved?
  - Try to get as specific as possible (e.g., amoxicillin not "penicillins").
- Why was the antibiotic prescribed?
  - It is possible that administration of an antibiotic during another illness, particularly viral, may yield a cutaneous reaction, which could have been blamed on the antibiotic.
- Had this antibiotic previously been prescribed to the patient?
- When did the reaction occur?
  - Many patients report that the reaction occurred decades before.
  - Patients or parents are often instructed to avoid a certain antibiotic going forward, oftentimes an entire class of antibiotics.
- How quickly did the reaction occur after beginning the antibiotic?
  - How many doses were prescribed, and how many taken?
- What type of reaction occurred? What were the symptoms?
  - Pay specific attention to signs and symptoms of anaphylaxis, including tongue swelling, stridor, feeling as if "throat was closing."
  - Were there any cutaneous symptoms? If so, when did they occur? What did they look like? When did they begin and end? Was there any mucosal or organ involvement?
- Did the reaction require any specific treatment modification?
  - Stopping the antibiotic?
  - Additional medications (e.g., antihistamines)?
  - Medical care required?
- What are similar antibiotics previously tolerated?
  - Try to get as specific as possible (e.g., cephalexin not "cephalosporins")

Note. From Blumenthal et al. (2017) and Trubiano et al. (2017).

(less than 1 hr) of vancomycin that commonly is mistaken as an allergy (Sivagnanam & Deleu, 2003). In addition, patients may report an antibiotic allergy but may have received and tolerated that antibiotic or a similar antibiotic based on documentation and review of the medical record.

In the event a patient is transferred from the ED for further care, the information obtained relating to the antibiotic allergy, or lack thereof, should be reported in the handoff to the accepting provider. This not only ensures continuity of care but also allows other providers to know whether additional information is needed to clarify the allergy. These details can be useful only if appropriately documented. If it is determined the patient is not allergic to the suspected antibiotic, it is critical to update the current allergy in the medical record upon patient triage, with details discovered through patient and/or family interview or medical record review, rather than "de-labeling" the patient or deleting the allergy (Trubiano et al., 2017). Upon presentation for future care, patients may again report the same allergy and having a notation to support or refute the allergy may facilitate improved antibiotic selection and treatment.

Hypersensitivity reactions to antibiotics may manifest as mild, moderate, or severe cutaneous, organ-specific, or systemic reactions (Legendre et al., 2014). Treatment is dependent upon symptoms but may include airway management, intravenous or intramuscular epinephrine, intravenous fluids, vasopressors, bronchodilators, H_1 and/or H_2 antihistamines, with or without systemic corticosteroids. However, management of antibiotic allergies commonly involves discontinuation of the suspected antibiotic. Although in select situations, the suspected antibiotic may represent the only available option (e.g., multidrug-resistant organisms), which necessitates drug desensitization.

CONCLUSION

Use of appropriate antibiotics is often avoided in patients reporting antibiotic allergies, possibly leading to treatment failure and suboptimal patient outcomes. It is critical that clinicians and providers thoroughly investigate and evaluate the validity of each reported antibiotic allergy to differentiate a true drug allergy from an adverse drug reaction. Knowledge of data suggesting low rates of cross-reactivity reactions between penicillins, cephalosporins, and carbapenems, as well as understanding the presentation and timing of sulfonamide reactions, may help clinicians avoid utilization of suboptimal antibiotic management with resultant potential consequences. As a result, clinicians and providers can provide the safest and most appropriate therapy, while achieving best possible outcomes.

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