JAMA Clinical Guidelines Synopsis

Evaluation of Suspected Antibiotic Allergies

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GUIDELINE TITLE Drug Allergy: A 2022 Practice Parameter Update

DEVELOPER AND FUNDING SOURCE American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma & Immunology (ACAAI)

PRIOR VERSION 2010

TARGET POPULATION Adults and children with antibiotic-associated adverse drug reactions

SELECTED RECOMMENDATIONS

- Drug challenges, when indicated, should be performed to remove incorrect drug allergies from a patient's medical record, especially for penicillin or sulfonamide allergies (strong recommendation; moderate certainty of evidence [COE]).
- For individuals at low risk of an antibiotic drug allergy, a supervised drug challenge may rule out a true allergy (conditional recommendation; low COE).
- Children with prior benign cutaneous symptoms (eg, morbilliform drug eruption, urticaria) from use of aminopenicillins do not require skin testing before monitored direct amoxicillin challenge (strong recommendation; moderate COE).
- For adults with remote history (>5 years) of mild nonanaphylactic reactions, such as benign cutaneous symptoms, monitored drug challenges without prior skin testing may be considered to rule out allergies to β-lactam, sulfonamide, fluoroquinolone, and macrolide antibiotics (conditional recommendation; low COE).
- For individuals with prior nonanaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions. In patients with prior anaphylaxis to penicillin, a structurally dissimilar cephalosporin (eg, cefazolin, cefpodoxime, ceftriaxone, ceftazidime, cefepime) can be administered without prior testing (conditional recommendation; moderate COE).
- For individuals with a history compatible with penicillin or cephalosporin allergy, a carbapenem, such as ertapenem, may be given without special precautions (conditional recommendation; moderate COE); aztreonam may also be considered but should not be used among individuals with ceftazidime allergy due to ceftazidime-aztreonam cross-reactivity (conditional recommendation; moderate COE).

Summary of the Clinical Problem

Antibiotic-associated adverse drug reactions are often mild (eg, nausea or diarrhea) and typically occur 1 to 6 hours after drug exposure. IgE-mediated reactions cause urticaria, angioedema, bronchospasm, or, in severe cases, anaphylaxis. Cell-mediated delayed hypersensitivity can occur over days to weeks, most commonly as benign cutaneous morbilliform eruptions, although more severe manifestations, such as Stevens-Johnson syndrome, may occur.

Supplemental content

CME at jamacmelookup.com

The guideline provides evidence-based recommendations for evaluating possible drug allergy in nonsteroidal anti-inflammatory drugs, chemotherapies, immune checkpoint inhibitors, biologic agents, and excipients (inactive substances formulated with pharmaceuticals). This JAMA Clinical Guidelines Synopsis focuses on practice recommendations for antibiotic allergy evaluation.

Characteristics of the Guideline Source

This guideline was commissioned by the Joint Task Force on Practice Parameters, supported by the AAAAI and the ACAAI. All members of the work group disclosed conflicts of interest. Consensus-based statements were developed after literature review and reflect expert opinion for topics with limited evidence (eTable in the Supplement). The guideline was reviewed by the AAAAI and ACAAI and posted for public comment.

Evidence Base

This guideline emphasizes the role of risk-stratifying individuals according to their prior drug reaction (anaphylactic vs nonanaphylactic) and deemphasizes the need for skin testing. Patients with a remote history (>5 years) of an antibiotic-associated adverse drug reaction, including benign cutaneous reactions (eg, morbilliform drug eruption, urticaria) and subjective symptoms without physical findings, are at low risk of having a drug allergy.

A drug challenge can be performed to rule out drug allergy in patients who are unlikely to be allergic. Testing is generally not required if the history is inconsistent with allergy (eg, headache, diarrhea) or if there is a family history of penicillin allergy, although a drug challenge can be considered for patient reassurance. Drug challenges are generally contraindicated in patients with a history of anaphylaxis or severe cutaneous adverse reactions (eg, Stevens-Johnson syndrome). For penicillin allergy, a decision tool, PEN-FAST, uses patient-reported history to identify patients at low risk who might be amenable to direct oral challenge. In a study of 622 patients, a PEN-FAST score of 0 had a negative predictive value of 99.4% (95% CI, 96.6%-100%) and a score of less than 3 had a negative predictive value of 96.3% (95% CI, 94.1%-97.8%).[1]

For patients at low risk of drug allergy, drug challenges have low rates of adverse drug reactions (0.8%-4%).[2] Most commonly, the challenge medication is administered in 2 steps, starting with a test dose (eg, one-tenth of the therapeutic dose or one-fourth tablet), followed after 30 minutes by a full dose or the remainder of a therapeutic dose

in patients who do not react to the initial dose. Patients are then monitored for 60 minutes. Single-dose challenges may also be considered when the suspected risk of reaction is low.

In a randomized trial, 159 individuals with prior reactions to penicillin that involved cutaneous findings only (which could include urticaria) were randomized either to penicillin skin testing followed by oral amoxicillin challenge to rule out aminopenicillin allergy (if skin testing was negative) or to amoxicillin challenge without initial skin testing. Among those randomized to skin testing, 70 of 80 (87.5%) had a negative skin test, and all 70 then tolerated amoxicillin challenge without any adverse effects.[3] Among individuals randomized to direct oral amoxicillin challenge, 76 of 79 (96.2%) had no reactions; the 3 who reacted to the challenge had mild skin symptoms.[3]

Cross-reactivity between penicillins and cephalosporins is lower than prior studies have reported[2,4] because previous estimates of 10% cross-reactivity were falsely elevated by contamination of cephalosporins with penicillins prior to 1980.[2] Among 12 observational studies performed after 1980 (n = 417), the cross-reactivity between penicillin and cephalosporin hypersensitivities ranged from 2.0% to 4.8%.[2] A meta-analysis of 11 observational studies (n = 1127) found 0.87% cross-reactivity between carbapenems and penicillins,[4] while a systematic review of 10 observational studies (n = 838) reported cross-reactivity of 4.3%,[5] supporting safe use of carbapenems in patients with penicillin allergies.

Most patients who report sulfonamide allergy will tolerate reexposure without reaction. In an observational study of 204 patients with history of remote, mild, or unknown reactions to sulfonamides, 94% tolerated a monitored direct trimethoprim-sulfamethoxazole challenge.[6] In this study, most patients received a single-dose challenge. However, 2-dose challenges were performed in patients with higher-risk histories, including those suggestive of anaphylaxis; 20 of 25 (80%) of these patients tolerated challenges; in 13 patients who reacted to oral challenges, reactions were nonsevere. In patients with HIV, for whom trimethoprim-sulfamethoxazole is used for prophylaxis, 70% with past reactions tolerated oral rechallenge.[6] Notably, sulfonamide antimicrobials are structurally different from nonantimicrobial sulfonamides (eg, thiazide and loop diuretics, nonsteroidal anti-inflammatory drugs), and cross-reactivity is unlikely.

Benefits and Harms

Clarifying the type of antibiotic-associated adverse drug reaction facilitates appropriate antibiotic choices to decrease surgical site infection risk and to reduce antimicrobial resistance and health care costs. The benefit of drug allergy testing is the opportunity to "delabel" and remove inaccurate allergy information from patient medical records. Patients with mislabeled allergy information are at risk of receiving less effective medications that may cost more and have more adverse effects.[7-9] In 2 large-scale case-control studies, patients with reported penicillin allergy were more likely to develop vancomycin-resistant *Enterococcus*, *Clostridium difficile*, or methicillin-resistant *Staphylococcus aureus* and had longer hospital stays and higher medical costs vs controls without allergy.[7,8] In a large retrospective study, patients with reported penicillin allergy were more likely to develop postoperative surgical site infections due to suboptimal perioperative prophylaxis.[9] Potential harms of a drug challenge include allergic reactions or adverse effects, including a small risk of triggering anaphylaxis, and patient anxiety.

Discussion

Accurate history and decision tools can identify many patients at low risk of true antibiotic allergy, and outpatient drug challenges can provide information on poorly supported allergy lists. Collaboration of antimicrobial stewardship teams, primary care clinicians, and allergists within health care systems improves use of drug allergy assessment pathways to support and guide delabeling efforts.

Areas in Need of Future Study

Important clinical decisions are based on the allergy section of an electronic health record, which is often inaccurate and commonly includes nonallergic reactions. Guidance on improving documentation of antibiotic-associated adverse drug reactions is detailed in a AAAAI work group report and calls on electronic health record vendors to collaborate with allergists to modernize the allergy section to improve its clinical utility.[10] Use of artificial intelligence, such as natural language processing algorithms that can review free-text entries and clinic notes to identify antibiotic-associated adverse drug reactions, is an evolving area of study.

ARTICLE INFORMATION

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