Original Article

Outcomes from an inpatient beta-lactam allergy guideline across a large US health system

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Abstract

Objective: To assess the safety of, and subsequent allergy documentation associated with, an antimicrobial stewardship intervention consisting of test-dose challenge procedures prompted by an electronic guideline for hospitalized patients with reported β-lactam allergies.

Design: Retrospective cohort study.

Setting: Large healthcare system consisting of 2 academic and 3 community acute-care hospitals between April 2016 and December 2017.

Methods: We evaluated β-lactam antibiotic test-dose outcomes, including adverse drug reactions (ADRs), hypersensitivity reactions (HSRs), and electronic health record (EHR) allergy record updates. HSR predictors were examined using a multivariable logistic regression model. Modification of the EHR allergy record after test doses considered relevant allergy entries added, deleted, and/or specified.

Results: We identified 1,046 test-doses: 809 (77%) to cephalosporins, 148 (14%) to penicillins, and 89 (9%) to carbapenems. Overall, 78 patients (7.5%; 95% confidence interval [CI], 5.9%–9.2%) had signs or symptoms of an ADR, and 40 (3.8%; 95% CI, 2.8%–5.2%) had confirmed HSRs. Most HSRs occurred at the second (ie, full-dose) step (68%) and required no treatment beyond drug discontinuation (58%); 3 HSR patients were treated with intramuscular epinephrine. Reported cephalosporin allergy history was associated with an increased odds of HSR (odds ratio [OR], 2.96; 95% CI, 1.34–6.58). Allergies were updated for 474 patients (45%), with records specified (82%), deleted (16%), and added (8%).

Conclusion: This antimicrobial stewardship intervention using β-lactam test-dose procedures was safe. Overall, 3.8% of patients with β-lactam allergy histories had an HSR; cephalosporin allergy histories conferred a 3-fold increased risk. Encouraging EHR documentation might improve this safe, effective, and practical acute-care antibiotic stewardship tool.

(Received 2 January 2019; accepted 15 February 2019)

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penicillin skin testing (PST) is operationally challenging in acute-care settings.\textsuperscript{11,12} Furthermore, many of the antibiotics generally used in hospitalized patients after a negative PST can be administered safely without preceding PST with a full-dose or test-dose challenge.\textsuperscript{13–15}

The Partners HealthCare System (PHS) guideline for inpatients with \(\beta\)-lactam allergy histories is an antibiotic stewardship tool that includes penicillin and cephalosporin hypersensitivity pathways that direct PST when institutionally available and needed (ie, patients reporting IgE-mediated allergy symptoms to a penicillin who require a penicillin or cross-reactive cephalosporin), but it encourages direct full-dose and test-dose (ie, standardized 2-step graded) drug challenges. Prior to this study, our results demonstrated that the guideline safely increased \(\beta\)-lactam antibiotic use at 2 academic medical centers.\textsuperscript{12,14–16} In this study, we sought to further assess the safety of guideline-directed \(\beta\)-lactam antibiotic test doses after implementation of the computerized guideline throughout 5 acute-care PHS hospitals with varied resources.

Methods

Computerized guideline with optional clinical decision support

We developed \(\beta\)-lactam hypersensitivity pathways in 2013 at the Massachusetts General Hospital (MGH), which were modified and studied prospectively at the Brigham and Women’s Hospital (BWH).\textsuperscript{12,14,16} All pathways were implemented as hospital guidelines with electronic health record (EHR) support throughout PHS acute-care sites in 2016 (Supplemental Table 1 online).\textsuperscript{15}

Study design overview

We identified all PHS \(\beta\)-lactam antibiotic test doses performed from April 2016 through December 2017. Although \(\beta\)-lactam test doses were not performed at community hospital sites prior to April 2016, test doses at academic sites prior to guideline adoption occurred exclusively at the direction of an allergist. The \(\beta\)-lactam antibiotic test doses reviewed included those performed with and without preceding PST; PST was available at 3 sites by an allergy/immunology consultation. All patients receiving 1 or more test-dose challenge had their EHR reviewed by PHS house staff, with data entry and maintenance supported by research electronic data capture (RedCap) hosted by PHS.\textsuperscript{17}

Data definitions and outcomes

The EHR-abstracted data included characteristics of the test dose (ie, drug, hospital, ordering clinician, patient care service, allergy/immunology consultation use, PST use, test-dose timing, and length of stay) and patient characteristics (ie, demographics and allergy history). Historical penicillin and cephalosporin reactions were recorded. Itching, flushing, rash, and hives were considered nonsevere cutaneous reactions; bronchospasm, shortness of breath, wheezing, anaphylaxis, angioedema, swelling, syncope, arrhythmia, hypotension, dizziness, and positive skin testing were considered severe IgE histories. Other EHR drug allergies were recorded.

The primary outcome was a hypersensitivity reaction (HSR) resulting from a \(\beta\)-lactam antibiotic test dose. PHS house staff reviewers recorded reaction details including timing or onset, test-dose step, symptoms and presentation, treatment, and clinical context for all possible reactions. Allergy specialist coinvestigators (K.G.B., P.G.W., J.T.H., and A.R.W.) determined whether the signs and/or symptoms were consistent with an HSR. All reactions not consistent with HSRs were considered adverse drug reactions (ADRs). For all HSRs, allergy specialists determined whether objective findings were present and whether the pathways were followed correctly. Confirmed HSRs were grouped as follows. Nonsevere cutaneous reactions included itching, flushing, rash, tingling, and urticaria; severe IgE reactions included angioedema, swelling, bronchospasm, wheezing, hypotension, and anaphylaxis; and severe delayed immunologic reactions included organ-specific reactions and severe cutaneous adverse reactions. We assessed HSRs overall by drug class, and we separately considered direct challenges (ie, challenges performed without prior PST).

Modification of the EHR allergy record after a test dose was determined by assessing whether the allergy module had a relevant allergy entry added, deleted, and/or specified (ie, additional detail was included).

Statistical analysis

We used descriptive statistics such as numbers with frequencies and medians with interquartile ranges. Univariable comparisons were made using \(\chi^2\) and Kruskal-Wallis tests. Confidence intervals (CIs) were calculated using exact (ie, Clopper Pearson) methods. The HSR and ADR predictors were identified using multivariable logistic regression models, and we reported adjusted odds ratios (aORs) with 95% confidence intervals (CIs). The selection of variables to include in multivariable models involved a priori knowledge of variable association with outcome. Statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Test-dose characteristics

From April 2016 through December 2017, 1,046 test doses to \(\beta\)-lactams were administered to 942 patients across 5 PHS hospitals (Table 1). Test-dose procedures were performed to penicillins (n = 148), cephalosporins (n = 809), and carbapenems (n = 89). Test doses were performed largely at academic sites (83%) by house staff (59%). The most common service performing test-dose procedures was internal medicine (45%).

Allergy/Immunology staff were consulted for 96 (9%) test-dose challenges administered, more often for penicillin test doses (19%) than for carbapenem test doses (16%) or cephalosporins (7%; \(P < .001\)). A PST prior to the test dose was performed for 38 patients (4%), most commonly prior to penicillin test doses (13%), compared to cephalosporins test doses (2%) and carbapenem test doses (0%; \(P < .001\)).

Patients were in the hospital a median of 2 days prior to their test dose (interquartile range [IQR], 1–4 days); patients received penicillin test doses later in the hospitalization (3 days; IQR, 1–7 days) than patients who received cephalosporin (2 days; IQR, 1–4 days) or carbapenem test doses (2 days; IQR, 1–6 days; \(P = .003\)). The overall median length of stay was 10 days (IQR, 5–19 days) for patients receiving test doses.

Patient characteristics

Patients receiving test doses were mostly female (65%) with a median age of 64 years (IQR, 51–75). Patients receiving test doses had penicillin allergy histories (96%); 29% had cephalosporin allergy histories. Penicillin allergy histories included nonsevere
Table 1. Test Dose and Patient Characteristics

| Variable                        | No. (%) (n = 1,046) |
|--------------------------------|---------------------|
| **Test-dose characteristics**   |                     |
| β-lactam drug class             |                     |
| Penicillin                      | 148 (14)            |
| Cephalosporin                   | 809 (77)            |
| Carbapenem                      | 89 (9)              |
| **Hospital type**               |                     |
| Academic                        | 867 (83)            |
| Community                       | 179 (17)            |
| **Ordering provider**           |                     |
| House staff                     | 621 (59)            |
| Physician assistant             | 144 (14)            |
| Attending physician             | 142 (14)            |
| Nurse practitioner              | 120 (12)            |
| Unknown                         | 19 (2)              |
| **Service**                     |                     |
| Internal medicine               | 469 (45)            |
| Emergency department            | 131 (13)            |
| Surgery                         | 126 (12)            |
| Oncology                        | 111 (11)            |
| Intensive care                  | 110 (11)            |
| **Intensive care**              |                     |
| Cardiology                      | 24 (2)              |
| Neurology                       | 16 (2)              |
| Obstetrics/Gynecology           | 13 (1)              |
| Pediatrics                      | 11 (1)              |
| Unknown                         | 35 (3)              |
| Allergy/Immunology consultation | 96 (9)              |
| Penicillin skin test performed  | 38 (4)              |
| Days in hospital prior to test dose, median (IQR) | 2 [1, 4] |
| Length of stay, median (IQR)    | 10 [5, 19]          |
| **Patient Characteristics**     | n = 942             |
| Female                          | 612 (65)            |
| Age at admission, median y (IQR)| 64 [51, 75]         |
| Allergy to penicillin           | 900 (96)            |
| Penicillin reaction             |                     |
| Nonsevere cutaneous             | 453 (48)            |
| Severe IgE                      | 185 (20)            |
| Allergy to cephalosporin        | 273 (29)            |
| Cephalosporin reaction          |                     |
| Nonsevere cutaneous             | 164 (17)            |
| Severe IgE                      | 42 (5)              |
| Other drug allergy              |                     |
| Sulfonamide antibiotics         | 254 (27)            |
| Opioids                         | 170 (18)            |

**Note.** IQR, interquartile range; Ig, immunoglobulin; MGH, Massachusetts General Hospital; BWH, Brigham and Women’s Hospital; NWH, Newton Wellesley Hospital; NSMC, North Shore Medical Center; BWF, Brigham and Women’s Faulkner Hospital.

Table 1. (Continued)

| Variable                        | No. (%) (n = 1,046) |
|--------------------------------|---------------------|
| Fluoroquinolones               | 128 (14)            |
| Macrolides                     | 106 (11)            |

Adverse and hypersensitivity reactions

We identified 78 ADRs (7.5%; 95% CI, 5.9%–9.2%), of which 40 (3.8%; 95% CI, 2.8%–5.2%) were HSRs and 38 (3.6%; 95% CI, 2.6%–5.0%) were non-ADRs (eg, somatic symptoms, intolerances, or toxicities).

Most HSRs occurred after 24 hours from the initial test dose (n = 16, 40%), but 14 (35%) occurred during the 1-hour test-dose observation period (Table 2). HSRs were nonsevere cutaneous reactions (n = 25, 63%). Symptoms suggestive of severe IgE-mediated reactions (n = 10, 25%) and severe delayed HSRs (n = 3, 8%) were also observed. Most HSRs required no treatment (n = 23, 58%). Treatments included antihistamines (n = 16, 40%), parenteral corticosteroids (n = 3, 8%), and epinephrine (n = 3, 8%). Objective findings had been recorded for most HSRs (n = 34, 85%). The pathway was interpreted correctly in most cases (n = 34, 85%); however, the pathway was not followed correctly for 1 of the 3 patients treated with epinephrine.

An allergy to cephalosporin antibiotics (adjusted odds ratio [aOR], 2.96; 95% CI, 1.34–6.58) was associated with increased odds of an HSR (Supplemental Table 2 online). Female sex (aOR, 1.86; 95% CI, 1.11–3.13), allergy to cephalosporin antibiotics (aOR, 2.49; 95% CI, 1.37–3.13), and allergy consultation (aOR, 2.42; 95% CI, 1.30–4.51) were associated with significantly increased odds of an ADR.

Hypersensitivity reactions to direct test-dose challenges

Overall, 570 penicillin allergy patients who had IgE histories or unknown histories directly challenged with cephalosporins (third, fourth, or fifth generation) or carbapenems [Fig. 1(A)]. Of the 514 patients directly challenged with third-, fourth-, or fifth-generation cephalosporins, 14 (2.7%) had HSRs (95% CI, 20% cutaneous reactions (48%) and severe IgE-mediated reactions (20%). Cephalosporin allergy histories included nonsevere cutaneous reactions (17%) and severe IgE-mediated reactions (5%).

https://doi.org/10.1017/ice.2019.50 Published online by Cambridge University Press
Overall, EHR allergy sections of 474 of 1,046 patients (45%) were updated after the β-lactam antibiotic test-dose challenge. Among the updated cases, 37 (8%) had an allergy added, 75 (16%) had an allergy deleted, and 390 (82%) had an allergy specified (records could have >1 action). The PHS community hospitals updated the EHR more frequently after test doses than did PHS academic hospitals (54% vs 43%; P = .009). Of patients who had had an allergy/immunology consultation (n = 96), the EHR was updated for 59 (61%).

**Discussion**

We implemented a healthcare system-wide guideline to standardize the approach to inpatients with β-lactam allergy histories as an antibiotic stewardship tool. We report the outcomes of 1,046 β-lactam antibiotic test-dose challenges performed by 5 diverse acute-care hospitals within a single healthcare system, largely without preceding PST (96%). Test doses were predominantly to cephalosporin antibiotics. The ADR rate was 7.5% and the HSR rate was 3.8%. Most HSRs occurred after the full-dose step and required no treatment beyond drug discontinuation. Among 10 HSRs consistent with severe IgE-mediated HSRs, 3 were treated with intramuscular epinephrine. Although a cephalosporin allergy history conferred a 3-fold increased HSR risk, HSRs to cephalosporins were infrequent in patients with specific penicillin allergy histories. Allergy records after test doses were not routinely updated.

Hospitalized patients with documented β-lactam allergies experience inferior outcomes, including treatment failures, adverse events, resistant organisms, and healthcare-associated infections. To address this problem, hospitals implemented structured allergy histories, PST, and/or comprehensive guidelines. Because PST can pose operational challenges, effective skin testing interventions often select inpatients for PST evaluation based on “need,” such as patients on broad-spectrum or nonpreferred antibiotics, or patients referred through an infectious diseases consultation. When more inclusive inpatient PST studies were attempted, only 20%–33% of eligible inpatients underwent testing. Our guideline uses PST only when indicated, given both the allergy history and the desired therapeutic antibiotic, and when institutionally available. This guideline applies to all adults, children, and pregnant women in all care units (eg, emergency departments, medical wards, and intensive care units). Previously, this guideline increased β-lactam allergy histories as an anti-inflammatory agent. Overall, 15%–45%) The highest HSR rate was to cefepime (4.4%; 95% CI, 2.1%–8.0%). Of 56 patients direct challenged to carbapenems, none had HSRs.

We identified 179 patients with mild penicillin reaction histories who received direct test-dose challenges. Of 76 patients direct challenged to penicillin, 3 had HSRs (4.0%; 95% CI, 0.8%–11.1%). Of 103 patients directly challenged with cephalosporins (first or second generation), 2 patients exhibited HSRs (1.9%; 95% CI, 0.2%–6.8%) [Fig. 1(B)].

There were 135 patients with cephalosporin allergy histories directly challenged with β-lactams: 34 with penicillins (2 HSRs, 5.9%; 95% CI, 0.7%–19.7%), 86 with cephalosporins (6 HSRs, 7.0%; 95% CI, 2.6%–14.6%), and 15 with carbapenems (1 HSR, 6.7%; 95% CI 0.2%–32.0%) [Fig. 1(C)].

### Table 2. Hypersensitivity Reactions Resulting From β-Lactam Test-Dose Challenge Procedures

| Variable                      | Hypersensitivity Reactions (n = 40) |
|-------------------------------|------------------------------------|
| **Reaction timing, h**        |                                    |
| ≤1 h                          | 14 (35)                            |
| > 1 h to <4 h                 | 4 (10)                             |
| ≥ 4 h to <24 h                | 2 (5)                              |
| > 24 h                        | 16 (40)                            |
| Unknown                       | 4 (10)                             |
| **Symptoms or presentation**  |                                    |
| Nonsevere cutaneous reactions | 25 (63)                            |
| Severe IgE reactions          | 10 (25)                            |
| Severe delayed reaction       | 3 (8)                              |
| **Reaction treatment**        |                                    |
| None                          | 23 (58)                            |
| Antihistamines                | 16 (40)                            |
| Parenteral corticosteroids    | 3 (8)                              |
| IM epinephrine                | 3 (8)                              |
| Albuterol                     | 1 (3)                              |
| Unknown                       | 13 (33)                            |
| Objective findings            | 34 (85)                            |
| Pathway followed and correctly implemented | 34 (85) |

Note: IM, intramuscular; PST, penicillin skin test.
aIncludes rash (n = 19), itching (n = 6), hives (n = 2), tingling (n = 1). Numbers do not sum because patients can have >1 reaction.
bIncludes bronchospasm/wheezing (n = 5), angioedema/swelling (n = 4), hypotension/dizziness (n = 3), anaphylaxis (n = 1). Numbers do not sum because patients can have >1 reaction.
cIncludes acute interstitial nephritis (n = 1), severe cutaneous adverse reaction (n = 1), and acute generalized exanathematous pustulosis (n = 1)
dAll 3 patients whose HSR required IM epinephrine treatment had cephalosporin test-dose challenges. The first patient had a history of urticaria and angioedema to penicillin and developed throat tightness, diffuse pruritus, abdominal pain, and wheezing during the cefepime full dose; IM epinephrine, hydroxyzine, and albuterol led to resolution. The second patient had a history of ampicillin anaphylaxis and received ceftriaxone by test dose and full dose uneventfully, but developed throat tightness when broadened to cefepime for *Pseudomonas* spp coverage. Symptoms resolved with IM epinephrine, parenteral steroids, and antihistamines. The third patient had a history of penicillin anaphylaxis and was administered cefoxitin by test dose without prior PST. The patient experienced blurry vision, throat closing, and diffuse pruritus; symptoms resolved with IM epinephrine and diphenhydramine.

Pathway was not followed because: patient was too sick/deemed inappropriate candidate for test dose (n = 3), patient had active allergy symptoms (n = 2), or the algorithm was not correctly interpreted (n = 1).

https://doi.org/10.1017/ice.2019.50 Published online by Cambridge University Press
In this study, 7.5% of test-dose challenges resulted in an ADR. Notably, a nocebo effect (i.e., noxious symptoms from a placebo drug) can occur in patients with prior drug reactions. A recent US study reported that 10% of patients who thought they were challenged to amoxicillin in an outpatient allergy practice "reacted" to the placebo. ADR risk factors included female sex, patients with cephalosporin allergy histories (also a significant HSR risk factor), and allergy/immunology consultation. Female sex was previously associated with higher rates of reported drug allergies/intolerances. Allergy/Immunology consultation was
associated with a higher ADR risk by design: consultations were indicated after positive challenges in locations with allergy/immunology access. The overall ADR frequency is important to consider; all patient-reported symptoms require assessment, and although reassurance may be possible for patients with only subjective symptoms, ADRs after test-dose procedures often result in drug discontinuation.

The HSR rate observed in this study was 3.8%, which is similar to our prior study at MGH (3.9%) and comparable to the penicillin HSR rate observed previously by allergy specialists (1.5%–2.6%). Furthermore, all drug administration carries a comparable risk; hospitalized patients with infections have a baseline incidence of antibiotic allergy between 0.5% and 5.0%. The HSRs in this study were determined by allergist review and were largely supported by objective data. Although ∼25% of HSRs had signs or symptoms suggestive of a severe IgE-mediated HSR, most HSRs required no antiallergy treatment, and only 3 HSR patients were treated with epinephrine. More than one-third (35%) of HSRs were triggered by the test dose, which may have led to those 14 patients having less severe HSRs.

This study provides insight into “real world” β-lactam cross reactivity in patients with specified IgE penicillin allergy histories, including patients with severe IgE histories. Prior observational studies of cephalosporins administered to penicillin allergy patients largely excluded patients with higher-risk penicillin allergy histories because they were selected out. Patients with severe IgE histories have an increased risk of true allergy and β-lactam cross reactivity. Although the later (third-, fourth-, or fifth-) generation cephalosporins overall had a low 2.6% HSR rate in patients with IgE penicillin allergy histories, the cefepime HSR rate was 4.4% with a 95% CI of up to 8.0%. It remains unclear whether later-generation cephalosporins need to be initiated with a test-dose challenge (many clinicians initiate these cephalosporins in penicillin allergy histories with a full dose). Of 56 carbapenem test-doses administered to patients with IgE penicillin allergy histories (including almost half with severe IgE histories), there were no HSRs, which prompts us to consider modification of the penicillin hypersensitivity pathway to indicate that carbapenems be administered by a full dose. For mild penicillin allergy histories, full-dose challenges for first- or second-generation cephalosporins are a safe modification that would facilitate the use of any cephalosporin for any patient with mild penicillin allergy histories.

Allergy to cephalosporin antibiotics was associated with a significant 3-fold increased odds of HSR. Documented cephalosporin allergies may more often be true hypersensitivities that occurred more recently compared to documented penicillin allergies (often “unknown” and/or remote). The cephalosporin hypersensitivity pathway may not be as accurate as the penicillin hypersensitivity pathway in this US acute-care population. Although a notable signal, because only 135 patients with cephalosporin allergy histories received direct cephalosporin test doses to date, more data gathering on this approach is needed prior to considering pathway modifications.

Drug allergy documentation is important for quality and safety. However, EHR allergy documentation is often incomplete and inaccurate. Inpatient β-lactam allergy interventions require taking an allergy history that should then be recorded in the EHR. Furthermore, results of skin tests and drug challenges should be specified in the EHR to ensure communication between providers and settings. We identified that allergy documentation was changed less than half of the time after test doses were performed. Incomplete documentation compromises the effectiveness of any allergy intervention as an antibiotic stewardship tool; β-lactams may be unnecessarily avoided or an allergy procedure might be repeated unnecessarily. Targeted alerting to the test dose prescriber may improve allergy documentation after test doses.
Although the guideline can recommend β-lactam avoidance or administration of a full-dose β-lactam, we only reviewed β-lactams initiated by a test dose in this study. All data were abstracted and analyzed retrospectively, which can result in misclassification; however, HSR determination was rigorously determined by allergist coinvestigators. While evaluating HSRs occurring from direct challenges in patients with different allergy histories provides insight into β-lactam cross-reactivity, patients in this study had an unknown true allergy status. Although we evaluated HSRs occurring from direct challenges in patients with different allergy histories provides insight into β-lactam cross-reactivity, we were unable to obtain the true allergy statuses of patients included in this study. Finally, we report on a multisite intervention in which all hospitals are part of a single geographically localized large US healthcare system. However, non-PHS hospitals have also adopted this guideline.

An electronic guideline with penicillin and cephalosporin hypersensitivity pathways encouraging β-lactam test-dose challenges was implemented in 5 hospitals with different resources using 1 EHR as an antibiotic stewardship tool. The ADR and HSR rates were low, and not higher than expected given a morbid inpatient population with prior reported drug allergies. Certain test-dose challenges may be omitted given their observed safety, and caution is prudent with cephalosporin-allergy challenged inpatients. Additional efforts to improve allergy documentation are important to the success of β-lactam allergy interventions.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/icc.2019.50.

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Acknowledgments. The authors thank Partners Penicillin Hypersensitivity Pathway team members: David W. Kubiak, PharmD, BCPS, Praveen Meka, MD, Diana Balekan, MD, MPH, and Roger P. Clark, DO. The authors thank Partners Quality, Safety, and Value and Clinical Process Improvement Leadership Program sponsors: Brian Cummings, MD and Thomas Sequist, MD, MPH. The authors thank Christian Mancini for his research assistance and Xioqing Fu, MS for her data analysis support. Finally, the authors thank Youyang Yang, MD, Jonathan D. Paolino, MD, Arianne Baker, MD, Yasmin Islam, MD, and Robert P. McLinnis, MD for serving as chart reviewers.

Financial support. This work was supported by Partners Quality, Safety, and Value and the Partners Clinical Process Improvement Leadership Program. Dr. Blumenthal receives career development support from the National Institutes of Health (grant no. K01AI125631), the American Academy of Allergy Asthma and Immunology Foundation, and the MGH Claffin Distinguished Scholar Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of interest. Dr Blumenthal reports royalties from UpToDate and honoraria from New England Society of Allergy, Dartmouth Medical School, and Vanderbilt Medical School, outside the submitted work. Drs Blumenthal and Shenoy report a licensed clinical decision support tool for β-lactam allergy evaluation that is used institutionally at Partners HealthCare System.

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