

Are Cephalosporins Safe for Use in Penicillin Allergy without Prior Allergy Evaluation?



Eric Macy, MD, MS, FAAAAI^a, and Kimberly G. Blumenthal, MD, MSc^{b,c,d} San Diego, Calif; and Boston, Mass

INTRODUCTION

At the American Academy of Allergy, Asthma, and Immunology 2017 Annual Meeting in Atlanta, Georgia, the following issue was debated: "Cephalosporins are safe for use in penicillin allergy (without prior allergy evaluation)." The pro position was presented by Eric Macy, and the con position was presented by Kimberly Blumenthal. Each position considered the existing data on the safety of using cephalosporins in patients with a history of penicillin allergy, without prior allergy evaluation to confirm acute tolerance to that cephalosporin. The present article is an account of the pro/con debate and does not constitute a systematic review of the literature.

THE PRO POSITION—DR MACY

The basic argument for the pro position relies on the underappreciation of the risks of avoiding a needed therapeutic cephalosporin when it is the drug of choice for a documented bacterial infection, versus the dramatically exaggerated risk of serious immunologically mediated reactions to cephalosporins in the very common setting of an unconfirmed penicillin allergy (ie, what is noted in a medical record pertaining to an adverse reaction or intolerance associated with the previous use of a specific medication or medication class without verification of an IgE-mediated mechanism responsible), or even the relatively rare setting of a confirmed immunologically mediated hypersensitivity to penicillin.

I strongly believe that the literature supports that all individuals, particularly hospitalized individuals, with an unconfirmed penicillin allergy should have the penicillin allergy confirmed or removed for patient safety.¹⁻⁴ This does not mean

one could not treat a patient with a cephalosporin before removing the penicillin allergy or confirming a penicillin allergy (ie, a clinically significant IgE-mediated reaction). Penicillin allergy testing supports effective antibiotic stewardship and helps reduce health care expenditure, specifically excess hospital days.⁵ Additional testing to document acute tolerance to a cephalosporin in the setting of a penicillin allergy, before therapeutic use of the cephalosporin, is not clinically useful because it has such a high number needed to treat for even a minimal hypothetical benefit.⁶ Recommending that cephalosporin tolerance testing must occur does not improve overall patient safety or clinical outcomes because of the high number needed to treat, time, expense, and the low likelihood of such testing occurring, and will potentially result in ever greater use of less effective non-beta-lactam antibiotics.

Epidemiology

About 9.0% of the US population that uses health care carries a history of a penicillin allergy and about 1.3% carries a history of any cephalosporin allergy.⁷ The adverse reaction rate reported in the electronic health record (EHR) is higher for females than for males for all antibiotic exposures.⁸ The prevalence rates of both rise with age and are typically much higher in hospitalized populations. There is a predictable rate of adverse reactions reported in the EHR after all penicillin, cephalosporin, or any other antibiotic exposures.⁷ There is no such thing as a risk-free antibiotic exposure, even after negative allergy testing. An individual may tolerate several courses of a specific antibiotic, then have an antibiotic-associated reaction, and then tolerate several more courses without any new reactions. For penicillins, the 95% CIs for reactions reported in the EHR within 1 year of the exposure are 1.34% to 1.57% for females and 1.01% to 1.24% for males. For cephalosporins, the 95% CIs are 0.96% to 1.21% for females and 0.49% to 0.72% for males.⁷ The rates are lower if the time interval for reporting is shortened from 1 year to 30 days.⁶ What is reported in the drug allergy or intolerance field of the EHR is the current reference standard for a clinically significant adverse drug reaction.⁹ If an adverse reaction is not reported, it cannot influence future antibiotic prescribing.

Most reported cephalosporin allergies are benign rashes. Only an extremely small minority of cephalosporin-associated reactions are life-threatening anaphylaxis or a severe cutaneous adverse reaction (SCAR).⁶ In a study of 3,999,290 individuals with at least 1 health care visit between January 1, 2010, and December 31, 2012, including 622,456 individuals exposed to 901,908 courses of oral cephalosporins, and 326,867 individuals exposed to 487,630 parenteral cephalosporins, anaphylaxis occurred after only 5 (0.00002%) oral exposures (95% CI, 1/1,428,571-1/96,154) and only 8 (0.00016%) parenteral exposures, (95% CI, 1/200,000-1/35,971) ($P = .08$). There were only 3 documented cephalosporin-associated SCARs (95% CI, 0-1 in 217,291),

^aDepartment of Allergy, Southern California Permanente Medical Group, San Diego Medical Center, San Diego, Calif

^bDivision of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Mass

^cHarvard Medical School, Boston, Mass

^dEdward P. Lawrence Center for Quality and Safety, Massachusetts General Hospital and Massachusetts General Professional Organization, Boston, Mass

Conflicts of interest: E. Macy has received research support from ALK Abello, Inc, to study adverse drug reactions; has served on clinical trial safety and monitoring committees for BioMarin, Audentes, and Ultragenyx; and is a partner in the Southern California Permanente Medical Group. K. G. Blumenthal has received research support from the National Institutes of Health (grant no. K01AI125631) and the American Academy of Allergy, Asthma & Immunology Foundation.

Received for publication July 7, 2017; revised July 27, 2017; accepted for publication July 28, 2017.

Available online September 22, 2017.

Corresponding author: Eric Macy, MD, MS, FAAAAI, Department of Allergy, Kaiser Permanente, 7060 Clairemont Mesa Blvd, San Diego, CA 92111. E-mail: eric.m.macy@kp.org.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.07.033>

Abbreviations used

C difficile- *Clostridium difficile*

EHR- Electronic health record

FDA- Food and Drug Administration

PPV- Positive predictive value

SCAR- Severe cutaneous adverse reaction

none of them was uniquely associated with a cephalosporin, and all had other associated antibiotic or other drug exposures that may have been more likely to have induced the SCAR.

The risk of penicillin-associated anaphylaxis is also very low.¹⁰ In a study of 5,201,036 individuals, mean age 35.6 ± 20.7 years and 52.5% females, who had at least 1 health care visit between January 1, 2009, and December 31, 2015, there were 1,840,830 individuals exposed to 3,837,003 courses of oral penicillins and 172,840 individuals exposed to 237,404 courses of parenteral penicillins. There were a total of 26,195,595 patient-years of follow-up. There were only 17 cases, or 1 in 225,706 (0.00044%), 95% CI 1 in 430,218 (0.00023%) to 1 in 152,983 (0.00065%), 11 females, with anaphylaxis associated with oral penicillin exposures, and 3 cases, or 1 in 79,134 (0.00126%), 95% CI 0 (0%) to 1 in 37,125 (0.0027%), 2 males, with anaphylaxis associated with parenteral penicillin exposures ($P < .001$).

The rate of confirmed penicillin allergy has been falling over the past 50 years.¹¹ Only about 2% to 3% of individuals with a history of penicillin allergy will be confirmed to have clinically significant IgE-mediated allergy or delayed-onset T-cell-mediated hypersensitivity by the current reference standard test, an oral amoxicillin challenge.¹² The most common severe cephalosporin-associated adverse reaction is *Clostridium difficile* (*C difficile*), which occurs within 90 days after about 3% of all third- to fifth-generation cephalosporin exposures, and about 1% of all cephalosporin exposures.⁶

Risk of not using a cephalosporin, when it is the drug of choice

Many previous studies have confirmed that avoidance of cephalosporins in patients with penicillin allergy results in negative outcomes, which include an increased risk of adverse events,¹³ suboptimal treatment of infections,^{14,15} and treatment failures^{16,17} (Table I). Avoidance of cephalosporins, when indicated for perioperative prophylaxis, can also lead to more surgical-site infections.¹⁸

Risk of using a cephalosporin in individuals with an unconfirmed penicillin allergy

In the study of 3,999,290 individuals with at least 1 health care visit between January 1, 2010, and December 31, 2012, noted previously,⁶ the 95% CIs for the rate of cephalosporin-associated anaphylaxis in penicillin-allergic males were 0% to 0.0073%, and this was not significantly different than the rate for males with any other drug allergy, 0% to 0%, or no drug allergy, 0% to 0.0013%.⁶ The 95% CIs for penicillin-allergic females, 0.0023% to 0.0055%, were also not clinically significantly different than the rate for females with any other drug allergy, 0% to 0.002%, or no drug allergy, 0.0001% to 0.0002%.

In that study, cephalosporins were the most commonly used antibiotic family used in penicillin-allergic individuals.⁶ There were 65,915 penicillin-allergic individuals exposed to 127,125 cephalosporin courses without any cephalosporin tolerance

testing performed. There were also 3,313 cephalosporin-allergic individuals exposed to 6,404 courses of another cephalosporin. The 95% CIs for new cephalosporin-associated adverse reaction reported in the EHR within 30 days of a cephalosporin course for males with a penicillin allergy were 0.95% to 1.15%, for cephalosporin allergy 0% to 0.43%, for any other drug allergy 0.37% to 0.44%, and for no drug allergy 0.34% to 0.37%. The 95% CIs for new cephalosporin-associated adverse reaction reported in the EHR within 30 days of a cephalosporin course for females with a penicillin allergy were 1.10% to 1.24%, for cephalosporin allergy 0.60% to 1.11%, for any other drug allergy 0.52% to 0.57%, and for no drug allergy 0.40% to 0.44%. Most of these reported adverse events were benign rashes or gastrointestinal reactions and not life-threatening events.

Risk of using a cephalosporin in individuals with a confirmed penicillin allergy

Cephalosporins are safely used in individuals with penicillin allergy confirmed by positive penicillin skin test results, without any testing for cephalosporin tolerance. In a cohort of 118 penicillin skin test positive individuals and 1,566 penicillin skin test negative individuals, 70.7% females, with a mean follow-up of 4.5 ± 2.9 years, and exposed to a mean of 8.2 ± 10.5 total courses of antibiotics, there were 118 courses of cephalosporins administered to penicillin skin test positive individuals and 1,038 courses of cephalosporin administered to penicillin skin test negative individuals.¹⁹ The 95% CIs for a newly reported cephalosporin-associated adverse reaction for penicillin skin test negative females were 0.93% to 2.07% versus 0% to 1.01% for males. The 95% CIs for a newly reported cephalosporin-associated adverse reaction for penicillin skin test positive females were 0% to 0% versus 0% to 7.92% for males.

In a group of 513 penicillin-allergic surgical patients receiving antibiotic prophylaxis during 624 surgeries, there was 1 benign urticarial rash (0.7%) out of 153 total cephalosporin courses, 127 courses of cefazolin, and 26 courses of cefoxitin in 140 patients.²⁰ No testing for cephalosporin tolerance was performed. This compared with 8 (2.0%) rashes or other reported side effects associated with 387 courses of clindamycin and 3 (15.8%) rashes or other side effects associated with 19 courses of ciprofloxacin.

From 2010 through 2017 in my practice at Kaiser Permanente, we have used an oral amoxicillin challenge in all penicillin skin test negative individuals to confirm acute tolerance. We have tested more than 2,500 individuals during this period. We identified 24 penicilloyl-poly-lysine and native penicillin skin test negative individuals with acute-onset (within 1 hour) oral amoxicillin-associated reactions and additional 10 individuals with delayed-onset (more than 1 hour) oral amoxicillin-associated reactions. We reviewed these patients' exposures to cephalaxin and cefaclor, the 2 cephalosporins that share an exact side chain with amoxicillin, both before and after their index penicillin class antibiotic-associated adverse reactions, which was also to amoxicillin in almost all of them. There were 4 (16.6%) subjects with confirmed acute amoxicillin hypersensitivity who had tolerated 11 courses of cephalaxin before their index penicillin-associated reaction. There were 8 (33.3%) subjects with confirmed acute amoxicillin hypersensitivity who tolerated 48 courses of cephalaxin after their index penicillin-associated reaction. One of these 8 individuals also tolerated a course of cefaclor. There was 1 (10%) individual with confirmed

TABLE I. Studies assessing the risk of withholding cephalosporins/beta-lactams in patients with penicillin/beta-lactam allergy

Study	Population	Findings	Comments
MacFadden et al ¹³	Prospective study of 507 hospitalized patients requiring infectious diseases consultation across 3 academic medical centers in Canada; 95 (19%) with reported beta-lactam allergy	Increased odds of adverse events (composite outcome of readmission for the same infection, acute kidney injury, <i>C difficile</i> infection, or drug-related adverse reactions requiring discontinuation) in those not treated with a beta-lactam (aOR, 3.18; 95% CI, 1.28-7.89). Patients who received preferred beta-lactam therapy had a similar risk of adverse events compared with patients not reporting allergy (aOR, 1.33; 95% CI, 0.62-2.87)	Most beta-lactam allergy was penicillin; most patients had indications for cephalosporin use
Koliscak et al ¹⁴	Retrospective study of 116 inpatients in a single US medical center with reported beta-lactam allergy and gram-negative pneumonias, urinary tract infections, or bacteremias assessing the adequacy of beta-lactam and alternative therapies	Single beta-lactam alternative agents were adequate less frequently than beta-lactams and combination regimens (beta-lactam plus a beta-lactam alternative)	Although allergy histories were considered severe, patients included those with unknown reactions and urticaria
Jeffres et al ¹⁶	US multicenter, retrospective cohort study of 552 patients with gram-negative bloodstream infections	Patients with a reported beta-lactam allergy treated with a beta-lactam (n = 433) had lower rate of clinical failure (27.4%) compared with those given alternatives (n = 119 [38.7%]; <i>P</i> = .03)	
Blumenthal et al ¹⁷	Decision analytic model with literature-based input parameters assessing clinical outcomes for patients with MSSA bacteremia and reported penicillin allergy	Giving the most common beta-lactam alternative antibiotic (ie, vancomycin) resulted in the fewest patients achieving MSSA cure and the highest rate of recurrence (67.3%/14.8%), compared with allergy-history-guided therapy (83.4%/9.3%) and penicillin skin testing-guided therapy (84.5%/8.9%)	
Blumenthal et al ¹⁵	US single-center retrospective cohort of 456 inpatients with MSSA bacteremia; 59 (13%) with a reported penicillin allergy	Patients reporting penicillin allergy were less likely to receive optimal therapy (ie, nafcillin, oxacillin, cefazolin) than those without a penicillin allergy history (47% vs 80%, <i>P</i> < .001). Adjusting for other factors, penicillin allergy was the largest negative predictor of optimal therapy trial (RR, 0.64 [0.49-0.83])	

aOR, Adjusted odds ratio; MSSA, methicillin-sensitive *Staphylococcus aureus*; RR, relative risk.

delayed-onset amoxicillin hypersensitivity who had tolerated 5 courses of cephalexin before her index penicillin-associated reaction. There were 5 (50%) individuals who tolerated cephalexin after their index penicillin-associated reactions. There was 1 individual out of the entire group of 34 with a history of a cephalalexin allergy and 1 individual with a cefaclor allergy, but there was no documentation of the date of these index reactions. In summary, there were no cephalalexin- or cefaclor-associated adverse reactions occurring in 13 (38.2%) individuals, exposed to 54 total courses of cephalexin or cefaclor, with confirmed IgE-mediated or T-cell-mediated amoxicillin hypersensitivity.

Thus, if there is clinically significant immunologic cross-reactivity between amoxicillin and cephalosporins that share the same side chain, it is rare.

Number needed to treat for any benefit when cephalosporin tolerance testing

There is about 1 more new cephalosporin allergy noted for every 135 penicillin-allergic individuals given a cephalosporin, without any tolerance testing, compared with individuals given a cephalosporin with no drug allergies.⁶ Most of these reactions are benign rashes. Given this high number to treat for benefit, the

benefit of identifying these rare individuals would have to be large, given the compelling evidence for using cephalosporins when they are clinically indicated. There is no evidence, given the very low cephalosporin-associated anaphylaxis and SCAR rates, that these additional reactions reported in the EHR cause significant clinical morbidity that would outweigh their therapeutic benefit. This number needed to treat would rise to 159 for when comparing penicillin-*allergic* individuals to individuals with any other drug *allergy*.⁶

Summary for the pro position

There is a small increased risk of having a new cephalosporin *allergy* reported in the EHR in penicillin-*allergic* individuals treated with cephalosporins, without any cephalosporin tolerance testing, compared with individuals with any other drug *allergy* or no drug *allergy*, but these risks are very low and there is no study showing that any practical cephalosporin tolerance testing protocol leads to better clinical outcomes than direct reexposure.

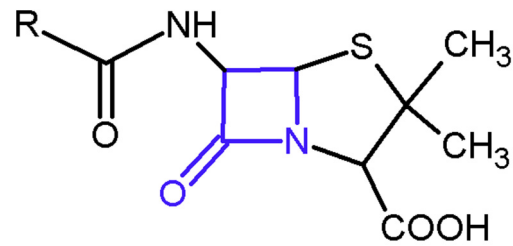
THE CON POSITION—DR BLUMENTHAL

I agree that cephalosporin antibiotics should not be unnecessarily withheld in patients who report a previous penicillin allergy. Doing so has been shown to lead to negative patient outcomes, including more adverse events, treatment failures, and death (Table I).¹³⁻¹⁷ Withholding cephalosporin antibiotics in patients labeled with a penicillin allergy also has negative consequences in terms of antibiotic resistance and health care-associated infections: One previous study identified that patients with a penicillin allergy history had a 23% increased odds of *C difficile* infection, a 14% increased odds of methicillin-resistant *Staphylococcus aureus* infection, and a 30% increased odds of vancomycin-resistant *Enterococcus* infection.²¹ Ultimately, withholding cephalosporin antibiotics also leads to higher health care costs. Not only are beta-lactam antibiotics generally less expensive than beta-lactam alternative antibiotics,²² but the negative clinical consequences of withholding beta-lactams when they are indicated have an additional economic impact: Hospital readmissions can cost \$15,000 per event,²³ adverse drug reactions can cost \$7,000 per event,^{24,25} and health care-associated infections can cost up to \$25,000 per event.²⁶

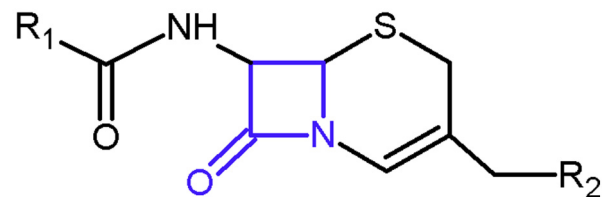
Beta-lactam cross-reactivity: What is known and still unknown

However, the harms associated with beta-lactam antibiotic avoidance in patients with penicillin allergy histories must be balanced with the risk of administering cross-reactive drugs. All beta-lactam antibiotics share a common chemical structure (ie, the beta-lactam ring, Figure 1). Beta-lactams also have side chains, or R groups, and cross-reactivity is possible through either the beta-lactam ring or an R group.²⁷ Penicillins and cephalosporins can have identical, or similar, side chains. For example, the penicillin *amoxicillin* has an identical side chain to the cephalosporins *cefadroxil*, *cefprozil*, and *ceftrizine*.²⁷⁻²⁹ Cross-reactivity from identical side chains has been demonstrated in previous clinical studies, with observed reaction rates exceeding 10%.³⁰⁻³²

To understand the true risk of an allergic reaction to a cephalosporin in patients with a penicillin allergy, we first need to fully understand the data on penicillin and cephalosporin cross-reactivity. However, much of what we know about cross-reactivity comes from data that suffer from systematic error



Penicillins



Cephalosporins

FIGURE 1. The chemical structure of penicillin and cephalosporin antibiotics. Penicillin and cephalosporin antibiotics share a common beta-lactam ring, shown in blue. The penicillin side chain, designated with “R,” can also be a source of cross-reactivity, especially when the side chains between 2 beta-lactam antibiotics are identical (eg, cephalexin and ampicillin, cefadroxil and amoxicillin). Cephalosporins have 2 different side chains: The R₁ (3-position) side chain is thought to be more important to clinical cross-reactivity than the R₂ (7-position) side chain.

and/or selection bias.^{6,20,33-37} First, in the earliest studies of cross-reactivity, penicillins physically contaminated cephalosporins, which led to falsely high cross-reactivity estimates.^{38,39} Many previous observational studies assessed cross-reactivity risk (Table II). However, these data are largely composed of patients who were unlikely to be truly allergic to penicillin at the time of the study because of misdiagnosis (ie, sometimes patients were never allergic to penicillin), mechanism (ie, often patients’ immunologic reaction was a delayed morbilliform eruption that is unlikely to recur), and/or time (ie, IgE-mediated penicillin allergy predictably wanes over time). The lack of true penicillin allergy among similar hospitalized and preoperative patients was previously documented in prospective testing studies.⁴⁰⁻⁴³ Patients included in the observational studies were also subject to clinician selection for cephalosporin administration. Specifically, because clinicians were unlikely to have given cephalosporins to patients with recent, severe, and/or recurrent penicillin allergy histories, a selection, or inclusion, bias exists (Table II, rightmost column). To interpret whether these data can be applied to all patients with penicillin allergy, including those with higher risk allergy histories, we would need to know the allergy histories of

TABLE II. Observational studies of reactions rates to cephalosporins in patients reporting penicillin allergy

Study	Population	Cephalosporin(s) administered	Findings	Patient inclusion (selection bias)
Goodman et al ³³	2,933 perioperative patients; 413 (14%) with penicillin allergy history	Cefazolin	1 in 300 (0.3%) with penicillin allergy history had a reaction compared with 1 in 2,431 (0.04%) who reacted without a penicillin allergy history	Only 73% of patients who reported penicillin allergy received cephalosporins (14% were treated with an alternative)
Daulat et al ³⁴	23,270 inpatients; 606 (3.6%) with a history of penicillin allergy	All; 42% first generation, 21% second generation, 37% third or fourth generation	1 in 606 (0.17%) with penicillin allergy history had a reaction compared with 15 of 22,664 (0.07%) who reacted without a penicillin allergy history	Pharmacy policy did not allow for cephalosporins to be administered to patients whose penicillin allergy histories were severe
Fonacier et al ³⁵	186 discharged inpatients who reported penicillin allergy and received cephalosporin were sent surveys; 83 (45%) patients completed the survey and their charts were reviewed	All; mostly first generation (51.0%) and third generation (25.3%)	7 of 83 (8.4%) with penicillin allergy history had a reaction	Study included 186 patients of 2,026 (only 9%) reporting a penicillin allergy history
MacPherson et al ³⁶	1,260 perioperative patients; 420 (33%) ultimately included; 147 (35%) with penicillin allergy history	Cefazolin, cefotetan, ceftriaxone	No reactions among 147 patients with a penicillin allergy history	Only 84 of 147 (57%) patients with a penicillin allergy history received a cephalosporin (43% received an alternative antibiotic)
Crotty et al ³⁷	175 inpatients	Cephalexin, cefoxitin, ceftriaxone, cefepime	7 of 119 (5.9%) with penicillin allergy history had a reaction	Proportion of patients with penicillin allergy history treated with cephalosporins not included in study results
Beltran et al ²⁰	513 perioperative pediatric patients with penicillin allergy histories	Cefazolin, cefoxitin	1 in 153 (0.7%) with penicillin allergy history had a reaction	Cephalosporins were administered to 153 (24.5%) patients with penicillin allergy histories (most penicillin allergy patients, 75.5%, were treated with a beta-lactam alternative)
Macy and Contreras ⁶	3,999,290 patients with history of penicillin allergy	All; 64.9% oral cephalosporins and 35.1% parenteral cephalosporins	Patients with penicillin allergy had new cephalosporin allergy more frequently (1.13%; 95% CI, 1.07%-1.19%) than those without drug allergy (0.39%; 95% CI, 0.37%-0.40%) and those with a drug allergy to another non-beta-lactam (0.50%; 95% CI, 0.48%-0.52%); RR = 2.9	Study design was that of a cohort prescribed cephalosporins, so the proportion of patients with penicillin allergy prescribed alternatives not included
Jeffres et al ¹⁶	552 patients with gram-negative bloodstream infections; 433 patients given a beta-lactam	All beta-lactams (penicillins, cephalosporins, carbapenems)	13 (3%) patients with penicillin allergy histories administered a beta-lactam experienced hypersensitivity reactions; 7 of these patients specifically had a penicillin allergy history and reacted to a cephalosporin	119 (22.8%) patients were not given a beta-lactam; 15.1% of the group not given a beta-lactam had an anaphylactic allergy history, greater than the 7.4% with an anaphylactic penicillin allergy history administered a beta-lactam

RR, Relative risk.

those included and excluded. Yet, many of these studies fail to detail the allergy history of included patients. We would thus expect to observe falsely low reaction rates in the observational studies, but the frequency of reactions reported ranged from none (0.0%) to as high as 8.4%.

The most robust studies assessing penicillin and cephalosporin cross-reactivity are those that prospectively identified patients who are allergic to penicillin (defined as a positive penicillin skin test result) and administered cephalosporin challenges. Because many of these studies were small, it is useful to use a weighted average across all these studies to yield the most accurate reaction frequency. Combining the 12 post-1980 clinical studies with penicillin skin test positive patients^{30,44-54} identified 417 patients with a penicillin allergy who received a cephalosporin, and 8 (2%) with a subsequent reaction. Although this low 2% reaction rate is remarkably encouraging, penicillin skin testing is an imperfect measure of IgE-mediated penicillin allergy with a positive predictive value (PPV) that ranges from 40% to 100%.^{28,55} Therefore, if the PPV were 100%, then the reaction rate would be the 2% identified. However, if the PPV were 40%, then the reaction rate could be as high as 4.8% (8 in 167 patients). Although we cannot attribute the full 2% to 5% reaction risk entirely to cross-reactivity, this frequency notably exceeds the underlying general risk of a *de novo* reaction to a cephalosporin mentioned previously by Dr Macy (0.49%-1.21%).⁷

Although data support that penicillin/cephalosporin cross-reactivity is likely between 2% and 5%, the US Food and Drug Administration (FDA) labels for cephalosporin antibiotics cite up to 10% cross-reactivity. Although the source of the cited 10% is the earlier studies, which were less accurate because of trace penicillin contamination of cephalosporins, we must acknowledge that the FDA warnings suggest that precautions should be taken for patients with penicillin allergy and recommend allergy evaluations accordingly. For example, the FDA cefazolin label warns that "careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefazolin, cephalosporins, penicillins or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross-sensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy label."⁵⁶ Similar warnings exist for all cephalosporins, regardless of generation or side chain structure.⁵⁷⁻⁶¹

Allergy evaluation methods help manage risk

As allergists/immunologists, it is our duty to help all providers, especially nonallergist providers who are less knowledgeable about drug allergy,⁶²⁻⁶⁴ appropriately manage the risk of prescribing potentially cross-reactive drugs by using allergy evaluation tools when prescribing cephalosporins to patients with previous penicillin allergies.

Allergy evaluation tools include the allergy history, which has been used for years by allergists and other prescribers to risk stratify patients.⁶⁵⁻⁶⁹ Previous data support that allergy history-guided therapy can improve prescribing in patients with a penicillin allergy history.^{17,65,70} By encouraging the use of standard drug allergy histories, we can enable the safe use of beta-lactam antibiotics. For example, patients with an EHR reaction of "rash" to penicillin may have had urticaria, a maculopapular rash, or more ominous reaction, such as exfoliative dermatitis or serum-sickness. Taking an improved allergy history with

prescribing decisions based on the allergy history helps distinguish situations in which rechallenge is safe from those in which rechallenge would be unwise.

Allergy evaluation tools also include allergy procedures, such as skin testing and test dosing. If penicillin skin tests were performed before cephalosporin administration, the true penicillin allergy status of patients would be known, and there would be improved clarity with respect to subsequent cephalosporin treatment. If the skin test results were negative, the patient would be at no higher risk of reacting to a cephalosporin than a patient without a penicillin allergy history. If the skin test result were positive, the patient would have about 2% to 5% chance of reaction and could weigh the risks of allergic reaction with benefits of cephalosporin therapy appropriately. The penicillin skin test, a relatively low-cost intervention,⁷¹ has been performed on outpatients,⁷² inpatients,^{43,70,73} perioperative patients,⁴² and emergency room⁷⁴ patients. Testing can be done by allergy physicians, registered nurses, nurse practitioners, or trainees as well as medical doctors from other specialties^{43,75} and pharmacists.⁷⁰

Observed graded challenges, or test doses, to cephalosporins can be performed directly (ie, without previous penicillin skin testing) in patients with penicillin allergy histories that are consistent with a possible IgE-mediated reaction.^{29,65} Test doses have been safely used in both outpatient^{67,76} and inpatient^{65,73} settings. At Partners HealthCare System, a not-for-profit health care system in the northeastern US which includes the Massachusetts General Hospital and the Brigham and Women's Hospital, nonallergists perform test doses of beta-lactam antibiotics, predominantly without allergy/immunology consultation.^{29,65,73} Across 5 Partners HealthCare System hospitals, more than 1000 inpatient beta-lactam test doses have been performed to date by various clinicians including internists, pediatricians, surgeons, anesthesiologists, and others.^{29,65,73} Initiating cephalosporins with a test dose in patients with convincing IgE-mediated penicillin allergy histories allows for patients and providers to engage in a shared discussion about the risk of an allergic reaction (low but present), and the benefits of cephalosporin use compared with alternative antibiotics. Open, shared communication with patients will ultimately result in improved understanding and documentation of the allergy history. Furthermore, if and when a cephalosporin reaction occurred, the patient would be less likely to be angry or litigious.⁷⁷⁻⁸⁰

Hospitalwide guidelines and/or algorithms can be useful for clinicians by providing a standard framework for approaching penicillin allergy patients. Standardization is a main pathway toward improvements in health care.⁸¹ At Partners HealthCare System, we implemented a guideline that uses the allergy history to advise how cephalosporins should be used in patients with different penicillin allergy histories (full dose, test dose, or allergy consultation for penicillin skin testing).²⁹ A uniform process may ensure simultaneous quality improvement—appropriately using cephalosporins when beneficial to the patients—and patient safety, minimizing iatrogenesis.

Allergy evaluations are not an impediment to cephalosporin use in patients reporting penicillin allergy. To the contrary, we observed that our guideline, when implemented at the Brigham and Women's Hospital, was associated with an almost 2-fold increased use of favorable beta-lactams (mostly cephalosporins) compared with a baseline period without the guideline.⁷³

Summary of the con position

Although cephalosporins should be considered for treatment in patients with a reported penicillin allergy, they are a common cause of hypersensitivity reactions and the risk of a reaction to cephalosporins in patients with penicillin allergy is higher than the underlying rate of cephalosporin allergy. The observed reaction rate from observational data in penicillin allergy reporters was 0% to 8%; these data should not be applied to patients with recent or severe reactions. The reaction rate for patients with a confirmed penicillin allergy was 2%, but varying the PPV, the rate reaches almost 5%. All cephalosporin FDA labels advise caution when prescribing cephalosporins to patients with penicillin allergy histories, and cite 10% cross-reactivity. Allergy evaluation tools help balance the risks of an allergic reaction with the benefits of cephalosporin administration in an open dialogue with patients. Through implementation of allergy evaluation tools, the interests of the patients are clearly communicated, and the interests of the providers are strongly protected.

CONCLUSIONS

We agree that the vast majority of patients with an unconfirmed penicillin allergy will tolerate cephalosporins without clinically significant severe adverse reactions such as anaphylaxis or SCARs. From 2% to 5% of patients with a true penicillin allergy will react to cephalosporins. The most likely risk is of a benign cutaneous reaction. The increased risk must be weighed against the risks of giving suboptimal antibiotic therapy, as well as the practicality, costs, and benefits of systematically using allergy evaluation tools (history, skin testing, test dosing) to reduce cephalosporin-associated adverse reactions.

REFERENCES

- Macy E, Khan DA, Castells MC, Lang DM. Penicillin allergy testing: a key component of antibiotic stewardship. *Clin Infect Dis* 2017;64:531-2.
- Lang DM, Castells MC, Khan DA, Macy EM, Murphy AW. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. *J Allergy Clin Immunol Pract* 2017;5:333-4.
- Choosing Wisely. AAAAI releases second list of tests and procedures that are overused to diagnose and treat allergies, asthma and immunologic diseases. 2014. Available from: <http://www.choosingwisely.org/aaaai-releases-second-list-of-tests-and-procedures-that-are-overused-to-diagnose-and-treat-allergies-asthma-and-immunologic-diseases/>. Accessed June 29, 2017.
- Centers for Disease Control and Prevention. Is it really a penicillin allergy? Available from: <https://www.cdc.gov/getsmart/week/downloads/getsmart-penicillin-factsheet.pdf>. Accessed June 29, 2017.
- Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract* 2017;5:705-10.
- Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. *J Allergy Clin Immunol* 2015;135:745-752.e745.
- Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med* 2009;122:778.e1-778.e17.
- Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol* 2012;108:88-93.
- Blumenthal KG, Park MA, Macy EM. Redesigning the allergy module of the electronic health record. *Ann Allergy Asthma Immunol* 2016;117:126-31.
- Macy E, Chen LH. The incidence of anaphylaxis associated with oral and parenteral penicillin-class antibiotic exposures. *J Allergy Clin Immunol* 2017;139:AB33.
- Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J* 2009;13:12-8.
- Solensky R, Macy E. Minor determinants are essential for optimal penicillin allergy testing: a pro/con debate. *J Allergy Clin Immunol Pract* 2015;3:883-7.
- MacFadden DR, LaDelfa A, Leen J, Gold WL, Daneman N, Weber E, et al. Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. *Clin Infect Dis* 2016;63:904-10.
- Koliscak LP, Johnson JW, Beardsley JR, Miller DP, Williamson JC, Luther VP, et al. Optimizing empiric antibiotic therapy in patients with severe beta-lactam allergy. *Antimicrob Agents Chemother* 2013;57:5918-23.
- Blumenthal KG, Shenoy ES, Huang M, Kuhlen JL, Ware WA, Parker RA, et al. The impact of reporting a prior penicillin allergy on the treatment of methicillin-sensitive *Staphylococcus aureus* bacteremia. *PLoS One* 2016;11:e0159406.
- Jeffres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding beta-lactams in patients with beta-lactam allergies. *J Allergy Clin Immunol* 2016;137:1148-53.
- Blumenthal KG, Parker RA, Shenoy ES, Walensky RP. Improving clinical outcomes in patients with methicillin-sensitive *Staphylococcus aureus* bacteremia and reported penicillin allergy. *Clin Infect Dis* 2015;61:741-9.
- Murphy J, Isaiiah A, Dyalram D, Lubek JE. Surgical site infections in patients receiving osteomyocutaneous free flaps to the head and neck: Does choice of antibiotic prophylaxis matter? *J Oral Maxillofac Surg* 2017;75:2223-9.
- Macy E, Ho NJ. Adverse reactions associated with therapeutic antibiotic use after penicillin skin testing. *Perm J* 2011;15:31-7.
- Beltran RJ, Kako H, Chovanec T, Ramesh A, Bissonnette B, Tobias JD. Penicillin allergy and surgical prophylaxis: cephalosporin cross-reactivity risk in a pediatric tertiary care center. *J Pediatr Surg* 2015;50:856-9.
- Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014;133:790-6.
- Micromedex. Truven Health Analytics. 2016. Available from: <http://truvenhealth.com/products/micromedex>. Accessed June 29, 2017.
- Barrett ML, Wier LM, Jiang HJ, Steiner CA. Statistical brief #199. All-cause readmissions by payer and age, 2009-2013. Healthcare Cost and Utilization Project. 2015. Available from: <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb199-Readmissions-Payer-Age.jsp>. Accessed June 29, 2017.
- Clancy DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1997;277:301-6.
- Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. *JAMA* 1997;277:307-11.
- Scott RD II. The direct medical cost of healthcare associated infection in U.S. hospitals and the benefits of prevention. 2009. Available from: https://www.cdc.gov/hai/pdfs/hai/scott_costpaper.pdf. Accessed June 29, 2017.
- Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol* 2015;136:685-691.e683.
- Solensky R, Khan D. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259-73.
- Blumenthal KG, Shenoy ES, Wolfson AR, Berkowitz DN, Carballo VA, Balekian DS, et al. Addressing inpatient beta-lactam allergies: a multihospital implementation. *J Allergy Clin Immunol Pract* 2017;5:616-625.e7.
- Audicana M, Bernaola G, Urrutia I, Echechipia S, Gastaminza G, Munoz D, et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy* 1994;49:108-13.
- Sastre J, Quijano LD, Novalbos A, Hernandez G, Cuesta J, Heras MD, et al. Clinical cross-reactivity between amoxicillin and cephadroxil in patients allergic to amoxicillin and with good tolerance of penicillin. *Allergy* 1996;51:383-6.
- Miranda A, Blanca M, Vega JM, Moreno F, Carmona MJ, García JJ, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. *J Allergy Clin Immunol* 1996;98:671-7.
- Goodman EJ, Morgan MJ, Johnson PA, Nichols BA, Denk N, Gold BB. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth* 2001;13:561-4.
- Daulat S, Solensky R, Earl HS, Casey W, Gruchalla RS. Safety of cephalosporin administration to patients with histories of penicillin allergy. *J Allergy Clin Immunol* 2004;113:1220-2.
- Fonacier L, Hirschberg R, Gerson S. Adverse drug reactions to a cephalosporin in hospitalized patients with a history of penicillin allergy. *Allergy Asthma Proc* 2005;26:135-41.
- MacPherson RD, Willcox C, Chow C, Wang A. Anaesthetist's responses to patients' self-reported drug allergies. *Br J Anaesth* 2006;97:634-9.
- Crotty DJ, Chen XJ, Scipione MR, Dubrovskaya Y, Louie E, Ladapo JA, et al. Allergic reactions in hospitalized patients with a self-reported penicillin allergy who receive a cephalosporin or meropenem. *J Pharm Pract* 2017;30:42-8.

38. Dash CH. Penicillin allergy and the cephalosporins. *J Antimicrob Chemother* 1975;1:107-18.
39. Petz LD. Immunologic cross-reactivity between penicillins and cephalosporins: a review. *J Infect Dis* 1978;137:S74-9.
40. Arroliga ME, Vazquez-Sandoval A, Dvoracek J, Arroliga AC. Penicillin skin testing is a safe method to guide beta-lactam administration in the intensive care unit. *Ann Allergy Asthma Immunol* 2016;116:86-7.
41. Arroliga ME, Wagner W, Bobek MB, Hoffman-Hogg L, Gordon SM, Arroliga AC. A pilot study of penicillin skin testing in patients with a history of penicillin allergy admitted to a medical ICU. *Chest* 2000;118:1106-8.
42. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol* 2006;97:681-7.
43. Rimawi RH, Cook PP, Gooch M, Kabchi B, Ashraf MS, Rimawi BH, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. *J Hosp Med* 2013;8:341-5.
44. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. *J Allergy Clin Immunol* 1982;69:238-44.
45. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204-15.
46. Blanca M, Fernandez J, Miranda A, Terrados S, Torres MJ, Vega JM, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. *J Allergy Clin Immunol* 1989;83:381-5.
47. Shepherd GM, Burton DA. Administration of cephalosporin antibiotics to patients with a history of penicillin allergy. *J Allergy Clin Immunol* 1993;91:262.
48. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr* 1998;132:137-43.
49. Novalbos A, Sastre J, Cuesta J, De Las Heras M, Lluch-Bernal M, Bombin C, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy* 2001;31:438-43.
50. Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up. *Allergy* 2002;57:1151-8.
51. Romano A, Gueant-Rodriguez RM, Viola M, Pettinato R, Gueant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16-22.
52. Greenberger PA, Klemens JC. Utility of penicillin major and minor determinants for identification of allergic reactions to cephalosporins. *J Allergy Clin Immunol Pract* 2005;115:S182.
53. Park MA, Koch CA, Klemawesch P, Joshi A, Li JT. Increased adverse drug reactions to cephalosporins in penicillin allergy patients with positive penicillin skin test. *Int Arch Allergy Immunol* 2010;153:268-73.
54. Ahmed KA, Fox SJ, Frigas E, Park MA. Clinical outcome in the use of cephalosporins in pediatric patients with a history of penicillin allergy. *Int Arch Allergy Immunol* 2012;158:405-10.
55. Fox S, Park MA. Penicillin skin testing in the evaluation and management of penicillin allergy. *Ann Allergy Asthma Immunol* 2011;106:1-7.
56. U.S. Food and Drug Administration. Cefazolin. 2007. Available from: <https://www.fda.gov/ohrms/DOCKETS/DOCKETS/07p0214/07p-0214-cp00001-03-Attachment-02-vol1.pdf>. Accessed June 29, 2017.
57. U.S. Food and Drug Administration. Cefaclor. 1997. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/anda/97/064166_cefaclor_toc.cfm. Accessed June 29, 2017.
58. U.S. Food and Drug Administration. Mefoxin (sterile cefoxitin & cefoxitin sodium) injection. 1997. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/50-517s031_50-581s020_Mefoxin.cfm. Accessed June 29, 2017.
59. U.S. Food and Drug Administration. ROCEPHIN® (ceftriaxone sodium) for injection. 2004. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50585s057_50624s0271bl.pdf. Accessed June 29, 2017.
60. U.S. Food and Drug Administration. MAXIPIMETM (cefepime hydrochloride, USP) for injection. 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050679s0361bl.pdf. Accessed June 29, 2017.
61. U.S. Food and Drug Administration. TEFLARO® (ceftaroline fosamil) for injection, for intravenous use. 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/200327s016s0171bl.pdf. Accessed June 29, 2017.
62. Stukus DR, Green T, Montandon SV, Wada KJ. Deficits in allergy knowledge among physicians at academic medical centers. *Ann Allergy Asthma Immunol* 2015;115:51-55.e51.
63. Blumenthal KG, Shenoy ES, Hurwitz S, Varughese CA, Hooper DC, Banerji A. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. *J Allergy Clin Immunol Pract* 2014;2:407-13.
64. Picard M, Begin P, Bouchard H, Cloutier J, Lacombe-Barrios J, Paradis J, et al. Treatment of patients with a history of penicillin allergy in a large tertiary care academic hospital. *J Allergy Clin Immunol Pract* 2013;1:252-7.
65. Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol* 2015;115:294-300.e292.
66. Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. *J Allergy Clin Immunol Pract* 2015;3:365-34.e1.
67. Iammatteo M, Blumenthal KG, Saff R, Long AA, Banerji A. Safety and outcomes of test doses for the evaluation of adverse drug reactions: a 5-year retrospective review. *J Allergy Clin Immunol Pract* 2014;2:768-74.
68. Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2016;137:1154-64.e12.
69. Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2012;129:443-7.
70. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy testing in hospitalized patients. *J Allergy Clin Immunol Pract* 2017;5:686-93.
71. Blumenthal KG, Li Y, Banerji A, Yun B, Long AA, Walensky RP. The cost of penicillin allergy evaluation [published online ahead of print September 22, 2017]. *J Allergy Clin Immunol Pract* 2017. <https://doi.org/10.1016/j.jaip.2017.08.006>.
72. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract* 2013;1:258-63.
73. Blumenthal KG, Wickner PG, Hurwitz S, Pricco N, Nee AE, Laskowski K, et al. Tackling inpatient penicillin allergies: assessing tools for antimicrobial stewardship. *J Allergy Clin Immunol* 2017;140:154-61.e6.
74. Raja AS, Lindsell CJ, Bernstein JA, Codispoti CD, Moellman JJ. The use of penicillin skin testing to assess the prevalence of penicillin allergy in an emergency department setting. *Ann Emerg Med* 2009;54:72-7.
75. Heil EL, Bork JT, Schmaizie SA, Kleinberg M, Kewalramani A, Gilliam BL, et al. Implementation of an infectious disease fellow managed penicillin allergy skin testing service. *Open Forum Infect Dis* 2016;3:ofw155. <https://doi.org/10.1093/ofid/ofw155>.
76. Kao L, Rajan J, Roy L, Kavosh E, Khan DA. Adverse reactions during drug challenges: a single US institution's experience. *Ann Allergy Asthma Immunol* 2013;110:86-91.e81.
77. Hickson GB, Clayton EW, Githens PB, Sloan FA. Factors that prompted families to file medical malpractice claims following perinatal injuries. *JAMA* 1992;267:1359-63.
78. Vincent C, Young M, Phillips A. Why do people sue doctors? A study of patients and relatives taking legal action. *Lancet* 1994;343:1609-13.
79. Beckman HB, Markakis KM, Suchman AL, Frankel RM. The doctor-patient relationship and malpractice: lessons from plaintiff depositions. *Arch Intern Med* 1994;154:1365-70.
80. Byington M, Bender A. Commentary: communicating with patients. *Harvard Risk Management Foundation Forum* 2000;20:1-5. Available from: <file:///C:/Users/y1799/Downloads/ForumDec2000.pdf>. Accessed June 29, 2017.
81. Timble C. How physicians can fix health care: one innovation at a time. Tampa, FL: American Association for Physician Leadership; 2015.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.