

Effect of a Drug Allergy Educational Program and Antibiotic Prescribing Guideline on Inpatient Clinical Providers' Antibiotic Prescribing Knowledge

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What is already known about this topic? Patients commonly report allergy to penicillin. General providers lack knowledge of penicillin allergy evaluation. Allergy assessment of inpatients with reported penicillin allergy is important for high quality patient care and appropriate utilization of antibiotics.

What does this article add to our knowledge? Providers lack formal education in drug allergy and express interest in tools to help them care for drug-allergic inpatients. A brief educational initiative, paired with a clinical guideline, was associated with improved drug allergy knowledge.

How does this study impact current management guidelines? Allergists can work effectively with colleagues from infectious diseases and pharmacy to create guidelines that improve the care of inpatients with drug allergy. Inpatient providers will require additional education about drug allergy.

BACKGROUND: Inpatient providers have varying levels of knowledge in managing patients with drug and/or penicillin (PCN) allergy.

OBJECTIVES: Our objectives were (1) to survey inpatient providers to ascertain their baseline drug allergy knowledge and preparedness in caring for patients with PCN allergy, and (2) to assess the impact of an educational program paired with the implementation of a hospital-based clinical guideline.

METHODS: We electronically surveyed 521 inpatient providers at a tertiary care medical center at baseline and again 6 weeks after an educational initiative paired with clinical guideline implementation. The guideline informed providers on drug allergy history taking and antibiotic

prescribing for inpatients with PCN or cephalosporin allergy.

RESULTS: Of 323 unique responders, 42% (95% CI, 37–48%) reported no prior education in drug allergy. When considering those who responded to both surveys ($n = 213$), we observed a significant increase in knowledge about PCN skin testing (35% vs 54%; $P < .001$) and loss of PCN allergy over time (54% vs 80%; $P < .0001$). Among those who reported attending an educational session ($n = 62$), preparedness to determine if an allergy was severe significantly improved (77% vs 92%; $P = .03$). Other areas, including understanding absolute contraindications to receiving a drug again and PCN cross-reactivity with other antimicrobials, did not improve significantly.

CONCLUSIONS: Inpatient providers have drug allergy knowledge deficits but are interested in tools to help them care for inpatients with drug allergies. Our educational initiative and hospital guideline implementation were associated with increased PCN allergy knowledge in several crucial areas. To improve care of inpatients with drug allergy, more research is needed to evaluate hospital policies and sustainable educational tools. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:407-13)

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Approximately half of all patients admitted to the hospital receive antibiotics, and 25% of inpatients who require antibiotics have at least 1 antimicrobial drug allergy.¹ Penicillin (PCN) allergy is reported in up to 10% of the general population and up to 16% of inpatients.¹⁻⁶ Patients with reported PCN allergies receive more costly and broad-spectrum antibiotics than patients without these reported allergies.¹⁻⁶ Furthermore, many patients with reported

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Abbreviations used

HSR- Hypersensitivity reaction

MD- Medical doctor

NP- Nurse practitioner

PCN- Penicillin

PCN allergy are not receiving drugs, such as later-generation cephalosporins and carbapenems, that are safely tolerated despite a PCN allergy.^{1,5,7-13} Reported allergies to PCN, however, do not equate with true IgE-mediated allergy. After formal allergy evaluation, including skin testing, up to 99% of patients with reported PCN allergy are found not to be allergic.^{2-5,14,15}

General providers have limited knowledge about drug allergy, PCN cross reactivity with other antibiotics, and the utility of PCN skin testing.^{13,16,17} Despite these knowledge deficits, it is these providers who are evaluating and prescribing antibiotics to inpatients with drug allergy. Prior efforts to survey providers on this topic have been limited by low or unreported response rates, or by a lack of detail.^{13,16-18} Past surveys have not assessed the impact of interventions targeted at improving provider management of patients with drug and PCN allergy. This study sought to identify gaps in PCN and drug allergy knowledge among inpatient providers at a single tertiary care center and to assess the impact of a targeted educational program paired with the implementation of a hospital-based clinical guideline.

METHODS

In anticipation of an educational initiative and implementation of a hospital-wide clinical guideline, we electronically surveyed inpatient providers at the Massachusetts General Hospital, a 947-bed tertiary care facility in Boston, Massachusetts. Providers included house staff from neurology, pediatrics, internal medicine, orthopedic surgery, and general surgery as well as attending hospitalist physicians and nurse practitioners (NP). Participants received a link to a Web-based survey 1 week before implementation of the clinical guideline and 6 weeks after implementation of the clinical guideline. The research protocol was approved by the Partners Human Research Committee. The survey was conducted and data maintained by using research electronic data capture (REDCap) hosted at Partners Healthcare.¹⁹ The survey was voluntary and anonymous. Through the REDCap interface, survey responses between identical responders can be paired through modules for tracking responders and viewing data are separate, allowing for responder anonymity to be maintained.

The survey questions were created by specialists from allergy/immunology (A.B., K.G.B.), infectious diseases (D.C.H., E.S.S.), and 2 survey research experts. Although no validated survey instrument on PCN allergy existed, 2 questions from a previously published instrument were adapted for use.¹⁶ The survey instrument was tested and revised through detailed interviews with 5 Massachusetts General Hospital clinical fellows. Survey questions covered 3 areas: respondent characteristics, preparedness and/or comfort, and knowledge (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

After the initial survey was conducted, we implemented a hospital-based clinical guideline to help providers in drug allergy history taking and antibiotic prescribing for inpatients with PCN or cephalosporin allergy. The guideline includes a standardized method for primary teams to perform test doses, a limited step

graded challenge, to β -lactam antibiotics and institution-specific information regarding inpatient skin testing and desensitization, antimicrobial resistance patterns, and pharmacy formulary considerations (see this article's Online Repository at www.jaci-inpractice.org). Coincident with guideline implementation, 10-minute educational presentations were offered to 15 different groups of providers throughout the hospital from April 3, 2013, through May 15, 2013. The presentation's goal was to introduce the clinical guideline and show providers how to navigate to the guideline electronically. The educational initiative also relayed antibiotic stewardship goals and key concepts about PCN allergy, including (1) patients with reported PCN allergy may not be truly allergic (IgE-mediated allergy); (2) the evaluation of PCN allergy begins with a drug allergy history; (3) even those who are truly PCN allergic may have lost their allergy over time; (4) skin testing for IgE-mediated PCN allergy is a valid tool that is available; (5) many cephalosporins, especially in the later generations, can be safely tolerated despite true PCN allergy; and (6) severe cutaneous reactions and hypersensitivity reactions (HSR) with organ involvement preclude future use of that drug. After providing brief evidence that supports these concepts, providers were presented with 3 clinical vignettes that highlight the inpatient relevance of the guideline. The educational initiative did not review any answers to the survey instrument questions. After each presentation, cards with figures from the clinical guideline were distributed and posted in hospital workrooms. The full guideline was available electronically to all staff.

Analysis and statistical methods

For preparedness questions, Likert responses were dichotomized into "prepared" (providers who responded very prepared or somewhat prepared) or "unprepared" (providers who responded very unprepared or somewhat unprepared). For knowledge questions, answers were scored as incorrect or correct for single-item questions. For the multi-item questions, frequencies and scores were calculated by using the number each provider got correct of the 13 possible correct for the question on cross-reactivity and of 5 possible correct for the question on absolute contraindications to receiving a drug again. For those ordinal scores, medians and quartiles were reported.

Statistical methods to assess the education and guideline impact included nonparametric tests, such as the Wilcoxon signed rank test for paired continuous and rank data, and the McNemar test for paired binary data. An analysis of providers whose answers changed from the pre- to postsurvey was conducted and assessed by a 1-sample test of proportions. The providers who reported that they had attended one of the educational sessions or used the clinical guideline were compared with those who did not attend by using a nonparametric test for trend. Responses of NPs were compared with those of medical doctors (MD) by using the Fisher exact test or the Wilcoxon rank sum test. Postsurvey responses of 38 people who did not take the first test were compared with those of 285 people who did take the first test by using Wilcoxon rank sum test. All statistical analyses were conducted in SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Sixty-two percent of providers (323 of 521) responded to at least 1 of the 2 surveys. Two hundred and eighty-five providers (55%) responded to the presurvey, and 250 (48%) responded to the postsurvey. Two hundred and thirteen inpatient providers (41%)

TABLE I. Characteristics of survey respondents and prior drug allergy education (n = 323)

Respondent role	No. (%)	No. (%) who reported no prior drug allergy education
Physician trainees	265 (82)	106 (40)
House staff	263 (81)	106 (40.3)
PGY- 1	78 (29.6)	37 (47.4)
PGY- 2	75 (28.5)	27 (36)
PGY-3	73 (27.8)	28 (38.3)
PGY-4	25 (9.5)	10 (40)
PGY-5	11 (4.1)	4 (36.4)
PGY-6	1 (0.4)	0 (0)
Fellow	2 (0.6)	0 (0)
Attending physician	27 (8.4)	15 (55.5)
Nurse practitioner	26 (8.1)	14 (53.8)
Other or no response	5 (1.8)	1 (20)
Total	323	136 (42)

PGY, Postgraduate year.

completed both surveys. Of MD respondents to both surveys, more were from nonsurgical specialties than from surgical specialties (43% vs 29%; $P < .01$) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Of all respondents, 82% (n = 265) were physician trainees (residents or fellows), 8% (n = 27) were attending hospitalist physicians, and 8% (n = 26) were NPs (Table I). One hundred and thirty-six of the respondents (42%) reported no prior drug allergy education. Fewer NPs reported receiving drug allergy education than MDs (36% vs 53%; $P = .18$).

In the preintervention survey (n = 285), 193 (68%), providers reported that they were very prepared or somewhat prepared to prescribe antibiotics to patients with PCN allergy (Table II). More providers felt prepared to determine if a hypersensitivity reaction was severe or life-threatening, with 236 (83%) reporting that they were very or somewhat prepared. Baseline knowledge about PCN skin testing was poor, with only 103 of providers (36%) knowing that skin testing is a valid tool for assessing PCN allergy. More than half of respondents (163 [57%]) reported that a PCN allergy was permanent. Respondents had a median score of 85% (interquartile range, 77%-92%) when asked to identify antibiotics that could be safely prescribed in patients with PCN allergy. When considering β -lactam antibiotics, 95 respondents (33%) would not prescribe meropenem, 153 respondents (54%) would not prescribe cefepime, and 179 respondents (63%) would not prescribe ceftriaxone to a patient with PCN allergy. Conversely, 42 respondents (15%) would give piperacillin-tazobactam (an antipseudomonal penicillin), 39 respondents (14%) would give cephalexin (a second-generation cephalosporin), and 7 respondents (2.5%) would give amoxicillin (an aminopenicillin) to a patient with PCN allergy. Respondents had a median score of 60% (interquartile range 60%-80%) when asked to identify conditions that are absolute contraindications to receiving the culprit drug again. Symptoms consistent with Stevens-Johnson syndrome—toxic epidermal necrolysis and drug rash eosinophilia and systemic symptoms syndrome were not recognized as absolute contraindications to receiving that drug again by 85 (30%) and 96 (34%), respectively.

A subgroup analysis of NPs in the preintervention survey (n = 22) found they had a significantly lower score for knowing which antibiotics can be safely prescribed for patients with a history of PCN allergy than MDs (73% vs 83%; $P < .001$).

TABLE II. Responses to presurvey (n = 285)

Text of survey question	Result	
Please describe the extent to which:	Very prepared or somewhat prepared, No. (%)	
You feel prepared to prescribe antibiotics for the patients with PCN allergy	193 (68)	
You feel prepared to determine if a patient has a history of an allergic reaction that was severe or life-threatening	236 (82.8)	
True/false:	No. (%) correct	Correct answer
Skin testing is a valid tool for assessing whether a patient is PCN allergic	103 (36.1)	True
Once a patient develops an allergy to PCN, the patient will always have this allergy	163 (57.2)	False
Check all that apply:	No. (%) yes	Correct answer
Which of the following may be safely prescribed in the patient with PCN allergy:		
Meropenem	190 (66.7)	×
Amoxicillin	7 (2.5)	
Levofloxacin	275 (96.5)	×
Aztreonam	239 (83.9)	×
Cephalexin	39 (13.7)	
Sulfamethoxazole-trimethoprim	274 (96.1)	×
Doxycycline	260 (91.2)	×
Cefepime	132 (46.3)	×
Ceftriaxone	106 (37.2)	×
Vancomycin	273 (95.8)	×
Piperacillin-tazobactam	42 (14.7)	
Metronidazole	279 (97.9)	×
Azithromycin	265 (93)	×
Which of the following reactions to PCN are considered absolute contraindications to receiving the medication again, even by a process of desensitization:		
Hives	14 (4.9)	
Swelling of mouth and tongue (angioedema)	122 (42.8)	
Fever with rash that involves ulceration of the buccal mucosa (Stevens-Johnson syndrome—toxic epidermal necrolysis)	200 (70.2)	×
Kidney failure characterized by eosinophiliuria (acute interstitial nephritis)	170 (59.7)	×
Rash, lymphadenopathy, fever, and increased liver function tests (drug rash eosinophilia and systemic symptoms syndrome)	189 (66.3)	×

Knowledge about PCN skin testing and allergy being permanent was only slightly lower for NPs than MDs (27.3% vs 37.2%, $P = .49$; and 45.5% vs 58.2%, $P = .27$, respectively).

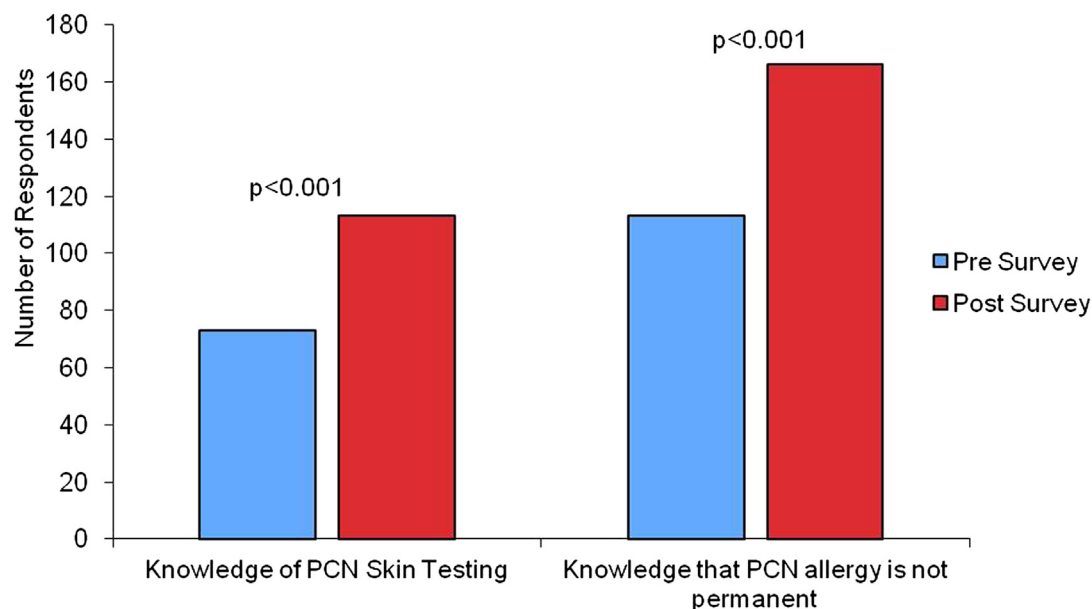


FIGURE 1. Impact assessment of the educational initiative and implementation of a hospital-based clinical guideline on knowledge of PCN skin testing and loss of PCN allergy over time ($n = 213$).

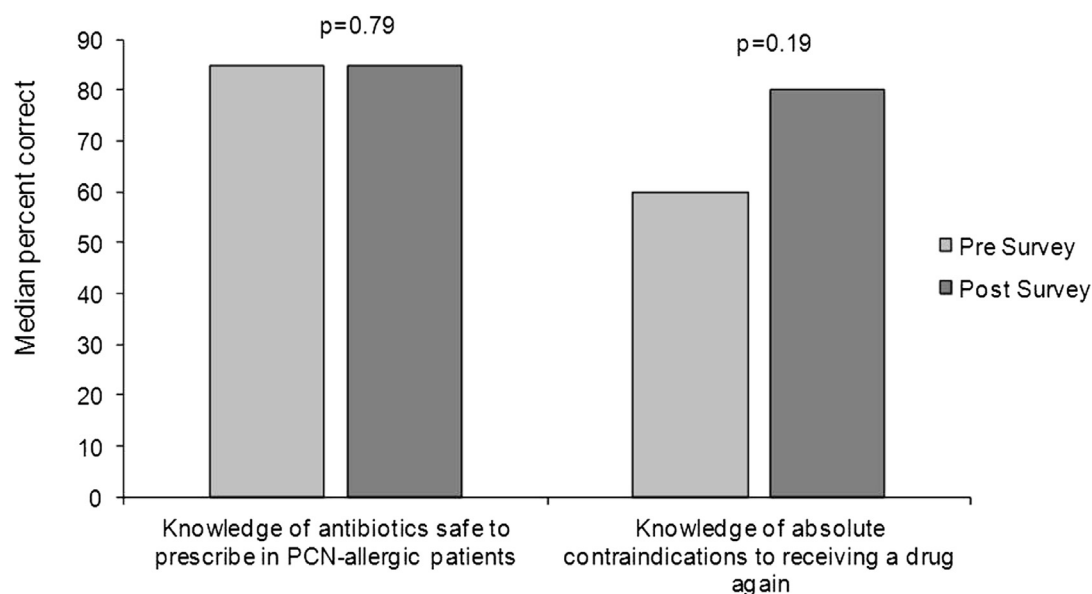


FIGURE 2. Impact assessment of the educational initiative and implementation of a hospital-based clinical guideline on knowledge of PCN cross reactivity with other drugs and contraindications to receiving a drug again ($n = 213$).

In the postintervention survey, an overwhelming majority of respondents (244/250 [98%]) indicated that they were interested in using a clinical guideline to help with drug allergy history taking and antibiotic prescribing in patients with PCN or cephalosporin allergies. Of the 247 responders, 175 (71%) reported being aware of the clinical guideline, 75 (30%) reported being present at an educational session, and 43 (17%) reported that they had used the clinical guideline in their inpatient care.

Postintervention survey responses showed no significant knowledge difference between those providers who took the first survey and those who did not.

When considering responders to both surveys ($n = 213$), changes from the preintervention to postintervention showed a significant increase in knowledge of PCN skin testing from 35% to 54% ($P < .001$) (Figure 1). Likewise, knowledge about allergy not being permanent improved from 54% to 80% ($P < .001$).

Knowledge of cross reactivity and absolute contraindications to giving a drug did not change significantly between the 2 surveys (Figure 2). Changes from the preintervention to postintervention survey showed a small, nonsignificant increase in preparedness to prescribe antibiotics to patients with PCN allergy, from 82% ($n = 172$) to 85% ($n = 179$) of respondents, which indicates that they were more prepared ($P > 0.5$). The number of respondents who felt prepared to determine if an allergy was severe showed a small change that was not statistically significant.

Among those who reported attending an educational session ($n = 62$), preparedness to determine if allergy was severe significantly improved from 77% to 92% ($P = .03$) and preparedness to prescribe antibiotics to patients with PCN allergy showed a small improvement, from 66% to 76%, that was not statistically significant ($P = .13$). Among those who reported attending an educational session or using the clinical guideline ($n = 84$) and whose answers changed between surveys, preparedness to prescribe antibiotics in patients with PCN allergy, and, to determine if allergy was severe, both showed a significant change in providers becoming prepared ($P = .03$ and $P = .018$, respectively).

DISCUSSION

To our knowledge, this is the first report of a successful drug allergy educational initiative for general inpatient providers. The survey results highlight that, although inpatient providers have limited prior education about drug allergy and have deficits in knowledge and comfort regarding drug and PCN allergy, they are interested in tools to help them care for patients with drug allergy, and significant improvements can be seen with brief education sessions and adoption of clinical guidelines. In areas crucial to the judicious and appropriate use of antibiotics among patients with reported PCN allergy, our educational initiative and integration of a clinical guideline was associated with significant knowledge improvements. However, in areas critical to safe antibiotic prescribing for patients with drug allergy, such as β -lactam cross reactivity and determining absolute contraindication to drug use, we were unable to demonstrate an overall impact of our educational initiative and guideline.

Baseline knowledge was most deficient in understanding the usefulness of PCN skin testing and was worse than previously described. In 1 previous survey, 65% of internists knew about the validity of PCN skin testing.¹⁶ Although it is unclear why more of our surveyed providers did not know about the validity of PCN skin testing, this difference may be due to the recent variability in the availability of reagents for PCN skin testing. Although skin testing to PCN has been used since the 1960s, from September 2000 through November 2001 and from September 2004 through September 2009, the essential reagent (penicilloyl-poly-lysine) for PCN skin testing was commercially unavailable. The surveyed providers were mostly house staff, which suggests that they received their initial medical training during or immediately after this period when skin testing was not available. Furthermore, despite the current availability of this reagent, only approximately 600 hospitals have penicilloyl-poly-lysine (Pre-Pen, ALK Pharmaceuticals, Horsholm, Denmark) on formulary (L. Davis, written communication, September 2013). Our educational initiative and clinical guideline resulted in a 1.5-fold increase in providers' knowledge of the validity of PCN skin testing. This change is important because inpatient use of PCN skin testing has been shown to be associated with decreased costs and broad-spectrum antibiotics use in some settings.^{2,3,15,20}

Understanding that a drug allergy is not a permanent, lifelong condition was lacking and similar to prior data.¹⁶ Although approximately half of our responders understood that PCN allergy was not permanent at baseline, after our intervention, the majority (80%) answered correctly. PCNs and early-generation cephalosporins remain first-line antimicrobial management for many inpatient infections, including common infections with methicillin-sensitive staphylococcus, streptococcus, and enterococcus, and with rare infections, such as *Peptostreptococcus*, actinomyces, propionibacterium, and listeria.²¹⁻²⁶ With the knowledge that PCN allergy wanes over time, providers may increasingly consider further PCN allergy evaluation for optimal treatment of these and other infections.

These survey results raise significant concerns regarding patient safety. Approximately 30% of providers did not recognize symptoms of HSRs that are absolute contraindications to receiving a drug again, and this deficit in knowledge was unchanged by our intervention. This finding was important because more than 90% of respondents were MDs. Learning the classification and pathophysiology of HSRs is part of preclinical medical education and has been recommended as clinical medical education for medical students by the American College of Allergy, Asthma, and Immunology.²⁷ This study indicates that inpatient providers need more education on the different types of HSRs, including those that should be considered absolute contraindications such as Stevens-Johnson syndrome—toxic epidermal necrolysis and drug rash eosinophilia and systemic symptoms syndrome.

Understanding cross reactivity between PCN and other β -lactam antibiotics is challenging, even for allergists.^{4,13,28} Although the allergic determinants of cephalosporins in later (third and/or fourth) generation are most commonly derived from the side chain (R-group) rather than the β -lactam ring,^{7-9,11} providers did not know if they could prescribe later-generation cephalosporins to patients with PCN allergy. Improved education for inpatient providers about how to give patients with PCN allergy cephalosporins must be clearly communicated for improved stewardship and patient safety.

Our intervention did not significantly improve providers' reported preparedness to prescribe antibiotics or to determine if an allergy was severe. One explanation for not seeing a significant improvement is survey timing. We distributed our post-intervention survey only 6 weeks after the educational initiative and guideline implementation, so providers may not have yet encountered a patient for whom this guideline would be relevant. Indeed, only 17% of providers had used the clinical guideline at the time of this second survey. This hypothesis is further supported by the significant improvement in preparedness seen by the subgroup of providers who were directly present at an educational initiative or used the guideline in practice.

NPs trended toward having less drug allergy education and knowledge than MDs. This is a crucial area of future study because NPs, as well as physician assistants, are increasingly providing front-line inpatient care, a trend that is likely to continue due to shortages of physicians, efforts to reduce health care costs, decreasing funding for graduate medical education, and limitations in house staff work hours. If NPs have little knowledge of PCN or drug allergy, we should not only investigate their current education and training modules but also create appropriate in-service education to ensure that their education is commensurate with their inpatient expectations for taking a drug

allergy history and safely, and appropriately ordering antibiotics for patients with drug allergies.

Strengths of this study include the pairing of individual provider data, anonymous survey design, strong response rate, and rigorous guideline implementation. We were able to use survey responders as their own controls, which, therefore, increased internal validity. By keeping the survey anonymous, we likely had lower reporter bias. Our overall survey response rate was consistent with previously published data that surveyed physicians and was as high or higher than previous surveys on drug allergy.^{16,17,29,30} Based on prior data that showed that successful guideline implementation is dependent on multiple implementation strategies,³¹⁻³⁴ we paired our guideline implementation with educational outreach.

Potential limitations to our study include a paired provider response rate of just over 40%, a lack of long-term follow-up, and assessment of only a single institution. Because of limited collected demographic information, we were only able to assess whether responders to our survey differed from nonresponders in limited ways, which raises the possibility of selection bias. However, because we surveyed only inpatient providers at a single institution and response rates by role and specialty were in proportion to those invited to complete the survey, it is likely that responders and nonresponders had similar demographic characteristics. Because of house staff turnover in July 2013, we could not administer additional surveys to assess whether the gains from our intervention were sustainable. Lastly, the educational program and the clinical guideline were implemented at a single institution, albeit an institution that is similar to many other tertiary care referral centers.

Our study expands on the previous limited data that demonstrate knowledge deficiencies among inpatient providers in PCN and drug allergy, and expands on what is known to offer a potential solution. Despite the observed deficits, the educational needs of inpatient providers are not being routinely met. Few institutions have implemented guides for when to order PCN skin testing or have used allergists or pharmacists to help inpatient providers appropriately prescribe antibiotics in patients with PCN allergy.^{2,3,5,20} Standardized guidelines for hospitals created with multidisciplinary support from allergy/immunology, infectious disease, and pharmacy are needed. Inpatient providers will need additional education about PCN and drug allergy in this setting for safe and appropriate antibiotic use. Further research is needed to elucidate the most effective strategies for management of inpatients with drug allergy and the optimal way to educate their inpatient providers.

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Table E1: Survey Instrument. The post-intervention survey was identical to pre-intervention survey with an added first section (*Section 0*).

Section A: Demographic Information

A1: I am a...

- ☐ Houseofficer
- ☐ Physician Assistant
- ☐ Nurse Practioner
- ☐ Attending Physician
- ☐ Fellow
- ☐ Other_____

A1b: If you are a houseofficer, what PGY level are you?:

- ☐ PGY 1
- ☐ PGY2
- ☐ PGY3
- ☐ PGY4
- ☐ PGY5
- ☐ PGY6
- ☐ PGY7
- ☐ PGY8
- ☐ PGY9+

A2: At the MGH, which of the following types of instruction have you received on antibiotic allergy and/or taking a drug allergy history? (Please check all that apply)

- ☐ A single lecture
- ☐ A lecture series or dedicated learning block
- ☐ Printed materials
- ☐ Online education
- ☐ None

Section B: Comfort and attitudes

B1: Please describe the extent to which you feel prepared to prescribe antibiotics for the penicillin-allergic patient:

- ☐ Very prepared
- ☐ Somewhat prepared
- ☐ Somewhat unprepared
- ☐ Very unprepared

B2: Please describe the extent to which you feel prepared to determine if a patient has a history of an allergic reaction that was severe or life –threatening

- ☐ Very prepared
- ☐ Somewhat prepared
- ☐ Somewhat unprepared
- ☐ Very unprepared

Section C: Diagnosis and Management of Penicillin Allergy.

C1. Skin testing is a valid tool for assessing whether a patient is penicillin- allergic.

- ☐ True
- ☐ False
- ☐ Don't know

C2. Which of the following may be safely prescribed in the penicillin-allergic patient (Check all that apply)

- | | |
|--|---|
| ☐ Meropenem (a carbapenem) | ☐ Cefepime (4th generation cephalosporin) |
| ☐ Amoxicillin | ☐ Ceftriaxone (3rd generation cephalosporin) |
| ☐ Levofloxacin | ☐ Vancomycin |
| ☐ Aztreonam | ☐ Piperacillin-tazobactam (Zosyn) |
| ☐ Cephalexin (1st generation cephalosporin) | ☐ Metronidazole |
| ☐ Sulfamethoxazole-trimethoprim (Bactrim) | ☐ Azithromycin |
| ☐ Doxycycline | |

C3. Which of the following reactions to penicillin would be **absolute** contraindications to receiving the medication again, even during a process of desensitization (Check all that apply)

- ☐ Hives
- ☐ Swelling of the mouth and tongue
- ☐ Fever with rash that involves ulcerations on the buccal mucosa
- ☐ Kidney failure characterized by eosinophiluria
- ☐ Eosinophilia, rash, lymphadenopathy, fever, and increased liver function tests

C4: Once a patient develops an allergy to penicillin, they will always have this allergy

- ☐ True
- ☐ False
- ☐ Don't Know

Section D: Infectious Disease Knowledge

D1: Aztreonam provides similar anti-pseudomonal coverage as anti-pseudomonal penicillins

- ☐ True
- ☐ False
- ☐ Don't Know

D2: For susceptible organisms, penicillins are less likely to be rapidly effective compared to vancomycin.

- ☐ True
- ☐ False
- ☐ Don't Know

Section 0 (Post Survey Only): Pathway exposure and interest

01: Were you present at an educational initiative about the new MGH Penicillin/Cephalosporin Hypersensitivity Pathway during the period 04/03/2013 through 04/24/2013?

- ☐ Yes
- ☐ No

02: Are you aware of the new MGH Penicillin/Cephalosporin Hypersensitivity Pathway?

- ☐ Yes
- ☐ No

03: Have you used the new MGH Penicillin/Cephalosporin Hypersensitivity Pathway

- ☐ Yes
- ☐ No

04: How interested are you in using the new MGH Penicillin/Cephalosporin Hypersensitivity Pathway?

- ☐ Very Interested
- ☐ Somewhat interested
- ☐ Somewhat disinterested
- ☐ Very disinterested

Abbreviations: MGH, Massachusetts General Hospital

Table E2: Survey response rate of medical doctors by specialty. More medical doctors from non-surgical specialties completed both surveys compared from surgical specialties (43% vs. 29%, $p < 0.01$).

	Invited to complete surveys (N, %)	Completed both surveys (N, %)
Non-surgical Specialties		
Neurology	56 (11.3)	21(10.7)
Pediatrics	71 (14.3)	34(17.3)
Internal medicine	236 (47.5)	102(52)
Surgical Specialties		
General surgery	73 (14.7)	23(11.7)
Orthopedics	61(12.3)	16(8.2)
Total Medical Doctors	497	196

Online Repository text: The Massachusetts General Hospital's Penicillin and Cephalosporin Hypersensitivity Pathway. The following is the complete internal guideline available electronically to all inpatient providers at MGH and used in all inpatient areas at MGH. All blue underlines represent hyperlinks. This version is the adult version, which differs only from the pediatric version in the final page the test dose procedure.

Title: Penicillin and Cephalosporin Hypersensitivity Pathway

Applies to: All Adult Inpatient Care Areas

3-Step Guideline for Clinicians:

Step 1. Obtain and document an accurate history of the adverse reaction from the patient.

Ask about:

1. Timing of adverse reaction after taking antibiotic: minutes to hours or days later? Was this a first dose reaction?
2. How many years ago was the reaction?
3. How was the reaction treated: was there a need for urgent care or epinephrine administered?
4. Has the patient tolerated similar medications, such as ampicillin, amoxicillin or cephalexin with a history of penicillin allergy?
5. Symptoms of adverse reaction:
 - 1.5.1 Raised, erythematous, pruritic rash with each lesion typically lasting less than 24hrs? (hives/urticaria)
 - 1.5.2 Swelling of the tongue, mouth, lips, or eyes (angioedema)
 - 1.5.3 Respiratory or hemodynamic changes (anaphylaxis)
 - 1.5.4 Lesions or ulcers involving the mouth, lips, or eyes; skin desquamation (Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and other severe type IV reactions)
 - 1.5.5 Organ involvement such as kidneys or liver (Acute Interstitial Nephritis (AIN). Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome, and other severe type IV reactions)
 - 1.5.6 Joint pains (serum-sickness like reaction)
 - 1.5.7 Rashes that were not hives, were mild, or delayed in onset (mild type IV reaction or maculopapular rash)
 - 1.5.8 Nausea, vomiting, diarrhea, minor laboratory abnormalities or local injection reactions are **minor adverse effects**, and should not preclude consideration of penicillin/cephalosporin use with appropriate monitoring.
 - 1.5.9 Severe cytopenias or other significant laboratory abnormalities (i.e., nephrotoxicity) are **major adverse effects that may preclude use**.
 - 1.5.10 This pathway does not address antibiotic prescription for patients who have experienced adverse reactions.

Step 2. Document details of the reaction in the electronic medical record allergy section.

Step 3. Follow the pathway for patient with PCN Allergy (Figure 1) or Cephalosporin Allergy (Figure 2). If the pathway suggests a Test Dose Procedure, follow directions on [Test Dose Procedure](#) sheet. Page Allergy Fellow on Call with patient's name/Medical Record Number if you have questions related to pathway.

Purpose

1. To guide clinicians in classifying and assessing risk in patients with known or suspected allergic reactions to penicillin / cephalosporins
2. To guide clinicians in prescribing antibiotics in a patient with history of allergy to penicillins or cephalosporins

Background

As many as 80-90% of patients who report a penicillin (PCN) allergy do not have a true Type 1 allergy (urticaria, angioedema, anaphylaxis). ¹Identification of such patients can improve patient care through use of effective, less toxic or less costly antibiotics. The following protocol developed by representatives from Allergy and Immunology and Infectious Diseases provides information to guide clinicians in their antibiotic choices and provides advice on when involvement of Infectious Disease and/or Allergy/Immunology services is indicated.

Rationale for Penicillin Hypersensitivity Pathway

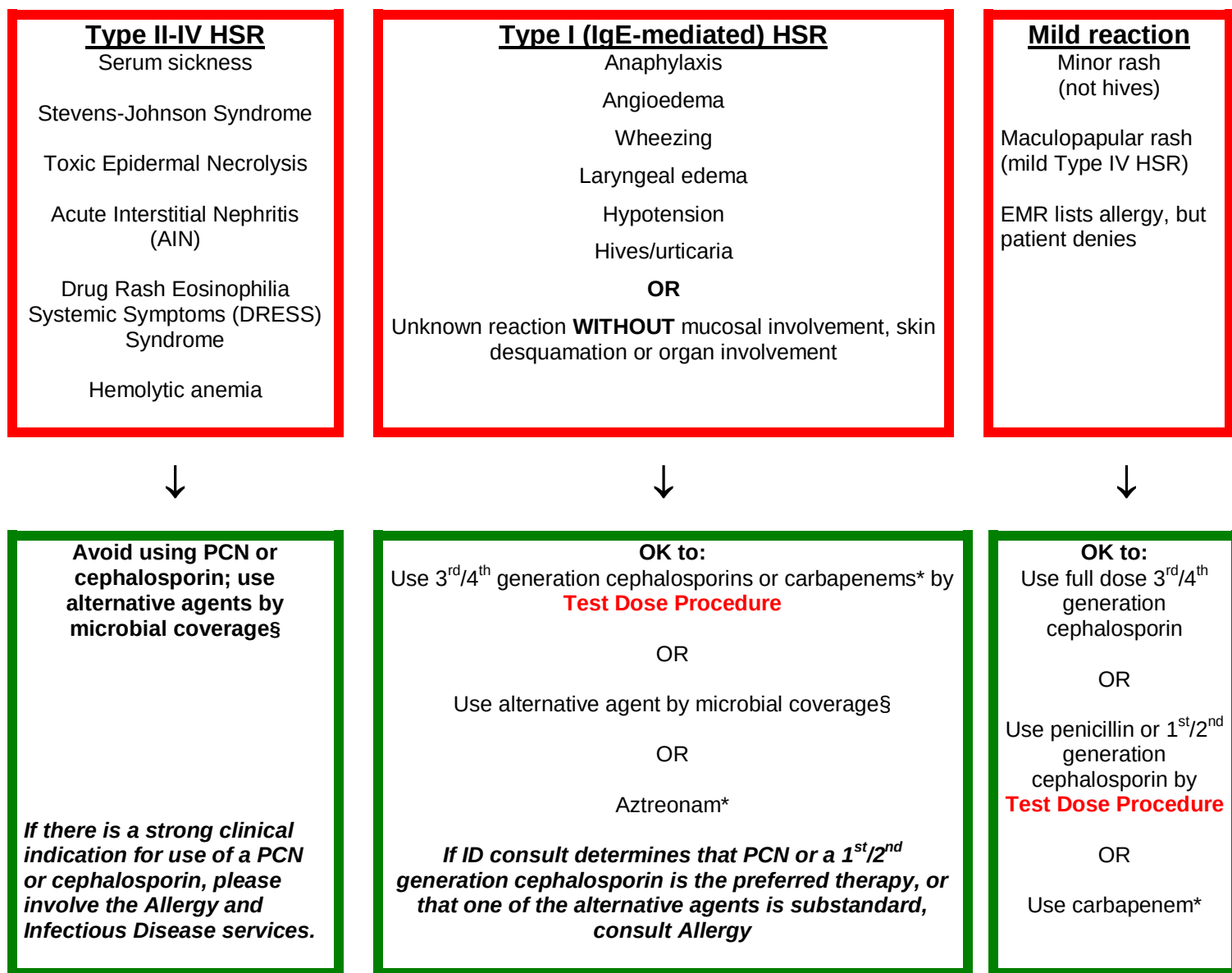
1. Even with a history of suggestive of an IgE-mediated penicillin allergy, most patients will likely tolerate this class of drug over time. Among patients with IgE-mediated allergy to penicillin, 70-80% lose their penicillin allergy over a period of 10 years².
 - 1.1 Penicillin skin testing is a validated tool for evaluating penicillin allergy with a negative predictive value (NPV) of 95%³⁻⁸. Penicillin is broken down into both major and minor determinants. Currently, we do not have minor determinant for skin testing. It is for this reason that we follow a negative skin test to penicillin with a test dose procedure. Inpatients will only receive penicillin skin testing after Infectious Disease service documents the need for a penicillin or 1st/2nd generation cephalosporin in a patient with a history of allergy to penicillin.
 - 1.2 Desensitization is a procedure performed by Allergy specialists by which a drug can be given despite true IgE-mediated allergy to that medication. The desensitized state is temporary and generally can be achieved only against Type I hypersensitivity reactions. Inpatients will only be evaluated for possible desensitization after the Infectious Disease service documents the need for an antibiotic to which the patient has a history of IgE-mediated reactions.
2. Patients with PCN allergy can still safely receive many cephalosporins, particularly those in the 3rd and 4th generation (Table 1)⁹⁻¹¹.
3. PCN-allergic patients can safely receive carbapenems. In patients with a history of IgE mediated penicillin allergy, there is a <1% risk of cross-reactivity to carbapenems¹². Because of their broad spectrum, carbapenems require approval by Infectious Disease for their use. This is noted by asterisk *.
4. Patients confirmed to be selectively allergic to amoxicillin or ampicillin (i.e. who tolerate penicillin) should avoid cephalosporins with identical R group side chains or receive them via desensitization (Table 2).

Rational for Cephalosporin Hypersensitivity Pathway

1. The allergic determinants of cephalosporins can be derived from the beta-lactam structure, but in later (3rd/4th generation) cephalosporins, they are most commonly derived from the R-group¹⁰⁻¹¹.
2. Cephalosporin skin testing has a poor negative predictive value because the actual allergic epitopes derived from the R-groups are unknown. Inpatients will not receive skin testing to cephalosporins.
3. Examination of similarity or dissimilarity of side chains is useful for Type 1 allergy to cephalosporins (Table 2).

Figure 1. Penicillin Hypersensitivity Pathway.²⁻⁵

For a printable version of Figure 1 click [here](#).



§ ALTERNATIVE AGENTS BY MICROBIAL COVERAGE (see Table 1 for additional details):

Gram positive coverage: Vancomycin, linezolid*, daptomycin*, clindamycin, doxycycline, TMP/SMX

Gram negative coverage: Quinolones, sulfamethoxazole / trimethoprim, aminoglycosides, carbapenems*, aztreonam*

Cephalosporins by class available on the MGH Formulary:

1stcephalexin/cefazolin • 2ndcefoxitin/cefuroxime

3rdceftriaxone/cefixime/cefotaxime/cefpodoxime/ceftazidime* • 4thcefepime • 5thceftaroline*

HSR: Hypersensitivity Reaction

* ID approval required either by the Antibiotic Approval Pager or by ID Consult Service

Table 1. Antibiotic options, allergy cross reactivity, activity and considerations for selected pathogens. ¹⁰⁻¹¹

	MGH formulary examples	% Cross reactivity with patients reporting penicillin allergy (range)	Activity	No activity	Notes
1st generation cephalosporin	cefazolin cephalexin†	0.5-2	- Selected Enterobacteriaceae - MSSA - Strep spp - Some anaerobes	- MRSA - Enterococcus - Pseudomonas	
2nd generation cephalosporins	cefuroxime, cefoxitin	Unlikely (-0.8 to 0.2)	- Selected Enterobacteriaceae - MSSA - Strep spp - Some anaerobes	- MRSA - Enterococcus - Pseudomonas	
3rd generation cephalosporins	ceftriaxone, ceftazidime‡	Unlikely (-0.8 to 0.2)	- Enterobacteriaceae - MSSA - Strep spp - Some anaerobes - Pseudomonas (see “Notes”)	- MRSA - Enterococcus	- Ceftazidime has activity against Pseudomonas - Ceftriaxone has no activity against Pseudomonas
4th generation cephalosporins	cefepime	Unlikely (-0.8 to 0.2)	- Enterobacteriaceae - MSSA - Strep spp - Pseudomonas	- MRSA - Enterococcus - Anaerobes	
Monobactam	aztreonam‡§	0	- Enterobacteriaceae - Pseudomonas	- MRSA - Strep spp - Enterococcus - Anaerobes	Some Pseudomonas isolates have reduced susceptibility to aztreonam compared to cefepime, ceftazidime, piperacillin/tazobactam or carbapenems
Carbapenems	imipenem, meropenem, ertapenem	0.9	- Enterobacteriaceae - Pseudomonas (see “Notes”) - MSSA - Strep spp - Some anaerobes	MRSA	- Reserved primarily for ESBL organisms or when no other reasonable options exist. - Ertapenem Is not clinically indicated for treatment of Pseudomonas

† Note that cephalexin and ampicillin have similar side chains so a reaction with one precludes use of the other.

‡ Note that ceftazidime and aztreonam have similar side chains so a reaction with one precludes use of the other.

§ Aztreonam should be reserved for the patient with a type 1(IgE-mediated) allergy

MSSA: Methicillin-sensitive *Staphylococcus aureus*; Strep: streptococcus; MRSA: methicillin-resistant *Staphylococcus aureus*

Figure 2. Cephalosporin Hypersensitivity Pathway

For a printable version of Figure 2 click [here](#).

Type II-IV HSR

Serum sickness
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis
Acute interstitial nephritis (AIN)
Drug Rash Eosinophilia
Systemic Symptoms (DRESS)
syndrome
Hemolytic anemia

Type I (IgE-mediated) HSR:

Anaphylaxis
Angioedema
Wheezing
Laryngeal edema
Hypotension
Hives/urticaria
OR
Unknown reaction
WITHOUT mucosal involvement, skin desquamation, or organ involvement.

Mild reaction

Minor rash (not hives)
Maculopapular rash
(mild Type IV HSR)
EMR lists allergy, but patient denies

Reaction to:

1st/2nd Generation

3rd/4th Generation

Avoid using cephalosporins

Use alternative agents by microbial coverage§

If there is a strong clinical indication for use of a cephalosporin, please involve the Allergy and Infectious Disease services.

OK to:

Administer 3rd/4th generation cephalosporin if dissimilar side chains by **Test Dose Procedure (Table 2)**

OR

Use alternative agents by microbial coverage§

OR

If ID consult determines that PCN or a 1st/2nd generation cephalosporin is the preferred therapy, or that one of the alternative agents is substandard, consult Allergy

OK to:

Administer PCN or cephalosporin by if dissimilar side chains **Test Dose Procedure (Table 2)**

OR

Use alternative agents by microbial coverage§

OK to:

Use a different generation cephalosporin or cephalosporin with dissimilar side chains **(Table 2)**

OR

Administer PCN or by **Test Dose Procedure**

OR

Use a carbapenem*

OR

Use alternative agents by microbial coverage§

§ ALTERNATIVE AGENTS BY MICROBIAL COVERAGE (see Table 1 for additional details):

Gram positive coverage: Vancomycin, linezolid*, daptomycin*, clindamycin, doxycycline, TMP/SMX

Gram negative coverage: Quinolones, sulfamethoxazole/ trimethoprim, aminoglycosides, carbapenems*, aztreonam*

Cephalosporins by Class available on the MGH Formulary:

1stcephalexin/cefazolin • 2ndcefoxitin/cefuroxime

3rdceftriaxone/cefixime/cefotaxime/cefpodoxime/ceftazidime* • 4thcefepime • 5thceftaroline*

HSR: Hypersensitivity Reaction

* ID approval required either by the Antibiotic Approval Pager or by ID Consult Service

Table 2 Cross-Reactivity Among Cephalosporins

The matrix (refer to [Cross Reactivity Among Cephalosporins](#)) that describes risk of cross-reactivity between two drugs form the columns and rows. Boxes with a ☠ symbol indicate a similar side-chain, and therefore higher risk for allergic reaction. Empty boxes indicate a lack of side chain similarity and decreased risk of allergic reaction. For example, patients with an allergy to cefepime should avoid cefotaxime, but can receive ceftazidime. Note that cefazolin has a dissimilar side-chain to all other cephalosporins, thus there is very low cross-reactivity with 3rd or 4th generation cephalosporins. **Bolded agents** are on-formulary at MGH.

	Cefaclor (2 nd)	Cefadroxil (1 st)	Cefamandole(2 nd)	Cefdinir (3 rd)	Cefepime (4th)	Cefixime (3rd)	Cefoperazone (3 rd)	Cefotaxime (3rd)	Cefotetan (2 nd)	Cefoxitin(2nd)	Cefpirome(4 th)	Cefpodoxime (3rd)	Cefprozil (2 nd)	Ceftazidime (3th)	Ceftibuten (3 rd)	Ceftizoxime (3 rd)	Ceftriaxone (3rd)	Cefuroxime (2nd)	Cephalexin (1st)	Cephloridine (1 st)	Cephadrine (1 st)
Cefaclor (2 nd)	-	☠											☠						☠		☠
Cefadroxil (1 st)	☠	-											☠						☠		☠
Cefamandole(2 nd)			-				☠		☠												
Cefdinir (3 rd)				-		☠															
Cefepime (4th)					-			☠			☠	☠				☠	☠				
Cefixime (3rd)				☠		-															
Cefoperazone (3 rd)				☠			-		☠												
Cefotaxime (3rd)					☠			-			☠	☠				☠	☠				
Cefotetan(2 nd)		☠					☠		-												
Cefoxitin(2nd)										-								☠		☠	
Cefpirome(4 th)					☠			☠			-	☠				☠	☠				
Cefpodoxime (3rd)					☠			☠			☠	-				☠	☠				
Cefprozil(2 nd)	☠	☠											-						☠		
Ceftazidime (3th)														-							
Ceftibuten (3 rd)															-	☠					
Ceftizoxime (3 rd)					☠			☠			☠	☠			☠	-	☠				
Ceftriaxone (3rd)					☠			☠			☠	☠				☠	-				
Cefuroxime(2nd)								☠		☠								-			
Cephalexin (1st)	☠	☠											☠						-		☠
Cephloridine (1 st)									☠											-	
Cephadrine (1 st)	☠	☠											☠						☠		-

Test Dose Procedure

Please print the [Test Dose Procedure](#) and place in chart for Nursing staff.

The **Test Dose**, as recommended by the **MGH Penicillin and Cephalosporin Hypersensitivity Pathways** is a safe procedure that can be performed by primary teams on a general hospital ward. We currently recommend test doses when patients have a low risk of reaction. If the patient tolerates both the test dose and full dose, then this would confirm that the patient can tolerate the drug without developing a Type I (IgE-mediated) hypersensitivity or other allergic reactions that have been determined to be minor.

Place the following orders in POE prior to Test Dose Procedure:

1. If possible, hold the following medications the day of the Test Dose Procedure:
 - a. Beta blockers: inhibit the action of epinephrine.
 - b. ACE inhibitors: increase the risk of an allergic reaction.
2. RN to record vital signs (blood pressure, heart rate, and respiratory rate) prior to administering the drug (time 0) and every 30 minutes from the start of the procedure to the end of the procedure (time 120 minutes).
3. Write for the following PRN medications to be at the patient's bedside:
 - a. Epinephrine 1:1000 for intramuscular administration (0.3 mg)
 - b. Benadryl 50 mg for IV/PO administration
4. Order: Medication Order:
 - a. Calculate and order 1/10 of the intended treatment dose for an IV medication or ¼ of a pill for an oral medication. Indicated in the instructions for this order that this dose is for step 1 of the Test Dose Procedure per the **MGH Penicillin and Cephalosporin Hypersensitivity Pathway**.
 - b. One dose of the full treatment dose. Indicate in the instructions for this order that this dose is for step 2 of the Test Dose Procedure per the **MGH Penicillin and Cephalosporin Hypersensitivity Pathway**.

Note: orders will only be processed by pharmacy if this is included in the order.

Test Dose Procedure:

- Step #1: The RN administers test dose as per orders above. RN records vital signs just prior to administration of test dose. At 30 minutes later, the RN checks vital signs and makes sure that the patient has not developed any rash or other symptoms. RN repeats vital signs and evaluation at 60 minutes (from initial test dose). If the patient remains asymptomatic and vital signs remain normal the RN may proceed to step #2.
 - Step #2: The RN administers the full intended treatment dose of the medication. At 30 minutes later, the RN checks vital signs and makes sure that the patient has not developed any rash or other symptoms. RN repeats vital signs and evaluation at 60 minutes (from full treatment dose). If the patient remains asymptomatic and vital signs remain normal, then the patient will have successfully completed the test dose procedure without any reaction and can subsequently receive the medication as scheduled by the team.
- If a reaction occurs as a consequence of this procedure, please page the allergy fellow on call (p13042) and complete an Incident Report.
- Please document any appropriate changes in allergy status once Test Dose Procedure is completed.

Signature _____

Date _____

Pager # _____

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Revision Detail

SUBJECT :	DISEASE STATE MANAGEMENT GUIDELINES / PATHWAYS
TITLE:	PENICILLIN AND CEPHALOSPORIN HYPERSENSITIVITY PATHWAY
APPROVED BY:	MESAC 3/2013, 9/2013
REVIEWED BY:	
REVIEWED DATE:	

