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Controversies in Drug Allergy: Drug Allergy Pathways

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Abstract

Drug allergy pathways are standardized approaches for patients reporting prior drug allergies with the aim of quality improvement and promotion of antibiotic stewardship. At the International Drug Allergy Symposium during the 2018 American Academy of Allergy, Asthma and Immunology / World Allergy Organization Joint Congress in Orlando, Florida, drug allergy pathways were discussed from international perspectives with a focus on beta-lactam allergy pathways and pragmatic approaches for acute care hospitals. In this expert consensus document, we review current pathways, and detail important considerations in devising, implementing, and evaluating beta-lactam allergy pathways for hospitalized patients. We describe the key patient and institutional factors that must be considered in risk stratification, the central feature of pathway design. We detail shared obstacles to widespread beta-lactam allergy pathway implementation, and identify potential solutions to address these challenges.

Keywords

policy; guideline; stewardship; adverse drug reaction; hypersensitivity; allergy; beta-lactam; drug; allergy; penicillin; test dose; graded challenge; skin test; quality improvement

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INTRODUCTION

Drug allergy pathways are standardized algorithms used by a group of providers with the aim of quality improvement for patients with previously reported drug allergies. There are four primary methods in which health care improvements are broadly achieved: (1) standardization, (2) coordination, (3) improving treatment decisions, and (4) prevention.¹ Drug allergy pathways target improvements in patient care using more than one of these methods. Users of drug allergy pathways may be allergists who have, for example, standardized their internal approach to drug allergy. However, larger-scale drug allergy pathways target a diverse group of providers in large institutions or health systems. Devising, implementing, and evaluating drug allergy pathways for patients with reported beta-lactam allergies is becoming increasingly common, particularly for multidisciplinary teams tasked with improving antibiotic choices for patients with a beta-lactam allergy label.

Standardization of drug allergy recommendations into pathways requires sufficient clinical data, and in general, drug allergy research has lagged other areas of investigation in the field of Allergy and Immunology. While expert panels have previously been convened to set drug allergy clinical and research advancement agendas,²⁻⁵ none previously addressed drug allergy pathways or the translation of drug allergy assessments into acute care. At the International Drug Allergy Symposium, organized during the 2018 American Academy of Allergy, Asthma and Immunology (AAAAI)/World Allergy Organization (WAO) Joint Congress in Orlando, Florida, drug allergy pathways were discussed from diverse international perspectives, with a focus on beta-lactam allergy pathways and pragmatic approaches for acute care hospitals. This consensus paper summarizes the key messages from the group of international experts.

BETA-LACTAM ALLERGY PATHWAYS

Background

Antibiotic use has increased 65% between 2000 and 2015, fueled by increased use in low to middle income countries.⁶ High income countries, which have processes aimed at curbing antibiotic resistance (e.g., antibiotic stewardship) experienced slower growth.⁶ Beta-lactam antibiotics, the first class of antibiotics discovered, include the commonly prescribed penicillins, cephalosporins, carbapenems, and monobactams. To date, penicillin and its derivatives remain effective and well-tolerated antibiotics indicated to treat common infections, including many of those which affect hospitalized patients, such as urinary tract infection, pneumonia, and bacteremia.

Beta-lactam allergies, recorded in up to 15% of hospitalized populations,^{7,8} lead to increased broad-spectrum antibiotic use unless clear institutional-level policies encourage allergy investigation at the time of antibiotic prescription. Most patients reporting a beta-lactam allergy are not allergic. From 1-30% of outpatients undergoing a comprehensive drug allergy evaluation have their allergy confirmed.^{3,9-11} A recent meta-analysis showed that only 5% of patients with a documented penicillin allergy tested in acute care settings were allergic (i.e., had penicillin-specific Immunoglobulin E (IgE) antibodies).⁹ Therefore, refraining from beta-lactam antibiotics based on the patient-reported clinical history is unnecessarily

restrictive. More importantly, while avoidance of beta-lactams ensures that no potentially iatrogenic allergic reactions recurs, other unfavorable iatrogenic consequences, such as more side effects and reduced efficacy against specific infections, may ensue.^{12,13} Additionally worrisome, alternative antibiotics contribute to drug-resistant organisms and *Clostridium difficile* infections.^{14,15}

Addressing inaccurate or poorly documented beta-lactam allergies, while recently encouraged as part of antibiotic stewardship,^{3,16,17} has been classically performed in outpatient settings by allergy specialists, following society recommendations.¹⁸⁻²¹ The typical diagnostic evaluation of drug allergy is often labor-intensive, time-consuming, resource-dependent, and complex. At a minimum, allergy specialist investigation includes a thorough drug allergy history and *in vivo* testing (i.e., skin testing, drug challenge, patch testing, as indicated). In some countries, *in vitro* tests (e.g., specific IgE measurement) are also used.^{3,22} Although outpatient drug allergy evaluations have benefits in terms of diagnostic accuracy and patient safety, the evaluation is difficult to translate into the acute care hospital bedside for an infected patient requiring immediate antibiotic treatment.

While beta-lactam allergy pathways have been developed, their use remains uncommon, especially outside the United States (US).²³⁻²⁶ To address the evolving and unmet needs of inpatients with reported beta-lactam allergies today, drug allergy pathways targeted towards providing proactive, practical guidance in acute therapeutic situations are needed. Such pathways would include focused beta-lactam allergy evaluations that are less resource-intensive, but still ensure the safety of our patients. Most patients report low risk allergy histories²⁷ and thus many beta-lactams are likely safe for use. Furthermore, pathways can be used by trained personnel beyond allergy specialists, including medical doctors from other specialties, advanced practitioners, and pharmacists,^{28,29} to enable more and cost-effective hospital-based allergy evaluations.³⁰

Current Beta-Lactam Allergy Pathways

A commonly used beta-lactam allergy pathway in the US, originally developed by Massachusetts General Hospital, has more recently been adapted for educational materials,^{31,32} and spread in an electronic form with clinical decision support within a large northeastern health system (Figure 1A).³³ A number of other US institutions have adopted a similar approach, including Dartmouth-Hitchcock Medical Center,³⁴ Mayo Clinic Jacksonville,³⁵ University of Nebraska,³⁶ and Rush University Medical Center.³⁷ These collective experiences demonstrate this beta-lactam allergy pathway to be safe and beneficial in terms of optimizing clinical care.^{26,35,37-39}

A team in the United Kingdom (UK) also devised a clinical decision support tool along with a beta-lactam allergy pathway that focuses on identifying the lowest risk penicillin allergy patients who do not require allergy testing for allergy delabeling (Figure 1B).⁴⁰ While national drug allergy pathways are rare, the Australian Therapeutic Guidelines include a universal approach to beta-lactam allergy that provides a framework for institutional prescribing guidelines throughout Australia (Figure 1C).⁴¹ The first risk stratification algorithm proposed by the Drug Allergy Interest Group/European Network of Drug Allergy of the European Academy of Allergy and Clinical Immunology is in development.

Multidisciplinary inpatient penicillin allergy testing programs,^{29,42,43,24,29} and allergy specialist-driven models^{44,45} may also be considered beta-lactam allergy pathways. Inpatient penicillin skin testing programs have used different methods to identify patients that would benefit most from a hospital-based penicillin allergy evaluation. A study at the Brigham and Women's Hospital sought to skin test all hospitalized patients on internal medicine services with a label of penicillin allergy on therapeutic antibiotics. Of 179 skin test eligible patients, 43 were skin tested; reasons for skin testing failures (136 were not skin tested) included coordination issues related to other scheduled tests or proximal patient discharge, patient test refusal, and team test refusal (e.g., primary team did not consider testing appropriate considering their admission reason, goals of care, etc.).²⁶ Patients in other studies have been more targeted, selected from Infectious Diseases referrals,⁴⁶ or identified by a specific antibiotic use (e.g., aztreonam).^{43,47-49} A unique electronic prioritization schema for a penicillin skin testing intervention at the University of Texas Southwestern Medical Center included important patient factors in a hierarchical manner: No current discharge order, active carbapenem or aztreonam order, and patient comorbidities (human immunodeficiency virus (HIV) infection, malignancy, or diabetes mellitus).²⁹ This approach led to the identification of hospitalized patients with penicillin allergy histories who may acutely benefit from evaluation (228 patients were skin tested of 1,203 screened).²⁹

CONSENSUS APPROACH TO BETA-LACTAM ALLERGY PATHWAYS

The key considerations in designing, implementing, and evaluating beta-lactam allergy pathways are summarized in Table 1. The central feature of pathway design should be risk stratification, based on both patient-level and institutional-level risks.

Patient Risk Stratification

Patient-level risk stratification includes historical reaction details and current clinical information, including clinical condition (e.g., cardiopulmonary status, pregnancy, etc.), and active medications (e.g., beta-blockers). The allergy history is useful for identification of high risk severe phenotypes. Prior data demonstrate that patients who report an anaphylactic history have a 2-4-fold increased risk of true allergy.⁵⁰ Anaphylactic history additionally confers an increased risk of anaphylaxis during allergy testing,⁵¹ and cross-reactivity with other beta-lactams.⁵² Further, a recent study of 182 patients with positive challenge tests to beta-lactams identified that the only clinical risk factor for developing anaphylaxis during drug challenge was an index reaction of anaphylaxis, with more than a 10-fold risk increase observed.⁵³

History can also identify patients who may have had other severe phenotypes, including the severe cutaneous adverse reactions (SCARs) and organ-specific reactions, where re-challenge is unsafe. While some patients may not recall enough detail for the interviewer to make a judgment about the nature of skin lesions (urticaria vs maculopapular rash vs other), patients can generally confirm that their rash did not blister, peel extensively, or involve mucosal surfaces. Additionally, patients often know the general severity of their reaction, such as if hospitalization was needed. Further, patients with no recall of their index reaction, who ultimately have a positive challenge, most commonly have only a benign cutaneous

eruption.⁵³ However, exceptions exist and it is unknown if it is best for pathways to assume that an unknown reaction is severe/high risk or benign/low risk.⁵⁴

Allergy evaluations are ideally performed when patients are clinically stable in their usual state of health. While patients with chronic diseases and end-organ impairments are often evaluated, acute symptoms or findings are often considered contraindications to drug allergy testing. While not predictive of the risk of provoking an allergic reaction, clinical stability and comorbidities must be considered in the risk stratification process, since they may enhance the severity of an allergic reaction should one occur. Pathways may choose to indicate this differently. For example, one pathway indicates that clinical instability is an exclusion for pathway eligibility,^{26,33} and another considers patients with clinical instability high risk, regardless of the allergy history.⁴⁰

Allergy outpatients are asked to abstain from drugs that could alter test interpretation, such as antihistamines, or treatment of an allergic reaction, such as beta-blockers.²¹ However, therapeutic situations inherently differ; there may not be time to withhold antihistamines for skin testing or a beta-blocker may need to be continued.⁵⁵ Modifications to the choice of the procedure (e.g., drug challenge instead of skin testing) and risk level may need to be made based on the patients' therapeutic medication needs.

Institutional Risk Stratification

Institutional-level modifications related to risk include consideration of the provider type that will collect the history and/or perform risk stratification, the underlying prevalence of true penicillin/cephalosporin allergy, antibiotic formulary, local experience and interpretations of beta-lactam cross-reactivity, and resources available. The performance of the drug allergy history and risk stratification likely varies by operator. For example, the drug allergy history may be more accurate when performed by allergy specialists (i.e., it may have a lower false negative rate compared to the same history taken by a generalist). Therefore, pathways must consider the primary user and personnel that will implement the pathway when developing the history tool and pathway structure. While we would anticipate less variability if a standard data collection instrument were used (Figure 2, Figure 3), or an electronic/clinical decision support tool, this has not been specifically assessed.

The underlying true penicillin (or cephalosporin) allergy prevalence locally must also be considered, including the type and route of implicated penicillin. A pathway designed for a US system with a <5% true penicillin allergy would likely be different than one designed for a European population where a higher true positive penicillin allergy frequency (especially to aminopenicillin) is anticipated. Specifically, applying the Partners HealthCare System algorithm for beta-lactam utilization on the outpatients with proven penicillin allergy patients in France would result in one of five allergic patients receiving a drug to which they react.⁵⁶ Further, approximately 1 in 4 patients suffering perioperative anaphylaxis to antibiotics in France have only a vague drug allergy history.⁵⁷ Thus, geographical differences may preclude the development of a single risk stratification approach.

A comprehensive understanding of local beta-lactam prescribing practices and antibiotic availability (e.g., formulary) for patients with reported penicillin allergy is necessary prior to

pathway development. Prior data demonstrate wide prescribing variability,^{58,59} potentially related to varied interpretations of beta-lactam cross-reactivity (Figure 4), clinical experiences, and institutional restrictions. For example, some hospitals do not permit any cephalosporin prescription in patients with severe penicillin allergy histories.⁶⁰ Hospitals using electronic health records (EHRs) in the US may have automatic allergy alerts when a cephalosporin is prescribed to a patient with a recorded penicillin allergy, regardless of the reaction type or severity.⁶¹ Although cross-reactivity between penicillins and cephalosporins appears in clinical studies to be between 2% and 5%,⁶² populations selected for higher risk allergic reactions (e.g., penicillin anaphylaxis) have recently been shown to have almost 40% cross-reactivity.⁵² Thus, in addition to cross-reactivity from the shared beta-lactam ring, it is also important to consider side chain homology.⁵²

Finally, institutional resources impact pathway development and implementation, since many hospitals lack devoted funding for drug allergy pathway builds, rollouts, and assessments. Additionally, most hospitals have little or no access to allergy specialists.^{40,63,64} A WAO survey reported that only 23 of 33 countries have allergy specialists; Even when allergy specialists exist, the current workforce could not meet population demands.⁶⁵ Given this, a pathway that is heavily reliant on the allergist is unlikely to spread to other institutions, regions, or countries. Although allergy testing can be adopted by non-allergists,^{28,29,42,46} it requires education, training, and a unique resource commitment. Thus, allergy specialist guidance in some form is advisable. Other required resources include pharmacy and nursing training, and computer programming resources to support the pathway implementation and reporting of outcomes. Quality and safety assessments must also be in place to assure process improvement and successful electronic health record (EHR) utilization and systemization.

SHARED OBSTACLES TO BETA-LACTAM ALLERGY PATHWAY IMPLEMENTATION

After beta-lactam allergy pathways have been designed and approved, challenges remain with respect to implementation. First, providers tasked with implementation may not have sufficient drug allergy education and knowledge.⁶⁶⁻⁶⁹ Even Allergy and Immunology trainees have variable exposure to drug allergy.⁷⁰ Providers may feel ill-equipped to explain drug allergy and cross-reactivity to patients, and may also be concerned that they may induce an allergic reaction that could be severe. Professional liability concerns also exist with administering any beta-lactam to patients with a penicillin allergy history, especially where alternative antibiotics may be available.^{27,71}

Guidance on allergy documentation must accompany any beta-lactam allergy pathway. Some pathways will facilitate the removal of a penicillin allergy label, but others may allow only clarifying comments that indicate tolerance of a drug that is potentially cross-reactive (e.g., “tolerates cephalexin” may be added to comments of an EHR allergy to penicillin). Patients and their care providers need adequate communication and education at the time of any change in allergy status, including clear documentation guidance.⁷² Even with clear penicillin allergy delabelling practices, up to one third of patients (or their prescribing

doctor) continue to erroneously report a penicillin allergy.⁷³ Further, while some inpatient allergy evaluations may achieve a short term objective (e.g., first-line antibiotic surgical prophylaxis or immediate therapy), additional allergy evaluation may be warranted. Establishing appropriate criteria for Allergy and Immunology outpatient referral upon discharge is crucial; the outpatient setting remains the ideal location for comprehensive drug allergy investigations.

CONCLUSIONS

Beta-lactam allergy pathways are needed to address an unmet need in the acute care of patients with reported beta-lactam allergies. Prior studies demonstrated that without a pathway, even when there are allergy specialists and penicillin skin testing available, allergy evaluations are vastly underutilized.^{26,74} Pathway development includes comprehensive risk stratification, with both an assessment of the patient's risk for allergy using their reaction details and their current clinical condition. Risk categories and pathways must then be adapted to the local environment, considering reliability of the interviewer and interview instrument, beta-lactam allergy epidemiology and cross-reactivity, antibiotic utilization, and resources. Erring on being conservative to maintain patient safety while improving beta-lactam use is advised.

Although there are not enough allergy specialists to address this problem alone,^{75,76} most known successful beta-lactam allergy pathways have had allergist guidance, or support.^{29,39,40,77} To enable more broad implementation, allergy specialists might train a hospital-based workforce, or work to identify novel methods to support hospital-based multidisciplinary programs, such as electronic consults/telehealth,^{78,79} electronic guidelines or clinical decision support,^{26,33,40} and/or computer-based prediction models.^{50,80,81}

In the context of global antibiotic stewardship initiatives, professional societies can encourage the development and use of beta-lactam allergy pathways. Future drug allergy research agendas should encourage large-scale beta-lactam allergy pathway comparisons that evaluate hospital clinical outcomes, long-term patient outcomes, and overall resource impact, including analyses of cost-effectiveness. Following initial models for beta-lactams, other drug allergy pathways could be envisioned for highly-used and acutely necessary drugs/products, such as aspirin (i.e., used as an antiplatelet drug, especially following percutaneous coronary intervention) and radiocontrast media.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AAAAI	American Academy of Allergy, Asthma and Immunology
WAO	World Allergy Organization
IgE	Immunoglobulin E
US	United States
UK	United Kingdom
HIV	Human Immunodeficiency virus
SCARs	severe cutaneous adverse reactions
EHR	Electronic Health Record

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A1**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

Drug Fever

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)

Record lists allergy, but patient denies

Avoid using PCN, cephalosporin, or carbapenem

Use alternative agents by microbial coverage‡

If clinical indication for a beta-lactam, please involve the Infectious Disease service and Allergy/Immunology, if available.

OK to:

Use 3rd/4th/5th generation cephalosporins or carbapenems* by **Test Dose Procedure**

OR

Use alternative agent by microbial coverage‡

OR

Aztreonam*

OR

If a PCN or a 1st/2nd generation cephalosporin is preferred, PCN skin testing is indicated. Call/consult Allergy/Immunology, if available. If not available, desensitization may be considered.

OK to:

Use full dose 3rd/4th/5th generation cephalosporin

OR

Use penicillin or 1st/2nd generation cephalosporin by **Test Dose Procedure**

OR

Use carbapenem*

A2

A3

PARTNERS HEALTHCARE

Penicillin and Cephalosporin Hypersensitivity Pathway

Was there a rash?

Yes

Was there organ involvement (e.g. liver enzyme elevation, creatinine elevation or acute kidney injury)?

No

Were there mucosal lesions or skin desquamation?

PARTNERS HEALTHCARE

Penicillin and Cephalosporin Hypersensitivity Pathway

Was there a rash?

Yes

Was there organ involvement (e.g. liver enzyme elevation, creatinine elevation or acute kidney injury)?

No

Were there mucosal lesions or skin desquamation?

No

Were there joint pains, fever, or myalgias?

No

Was the rash hives (Typically immediate onset and lesions are raised, erythematous, and pruritic with each lesion typically lasting less than 24hrs)?

No

Was the rash relieved in onset with a

Assessment

Likely mild delayed maculopapular rash

Mild Reaction

Recommendation

1. Use full dose 3rd/4th/5th generation cephalosporin

Cephalosporin generation information: 3rd ceftriaxone/cefixime / cefotaxime / cefpodoxime / ceftazidime* • 4th ceftipime • 5th ceftaroline*

OR

2. Use penicillin or 1st/2nd generation cephalosporin by [Test Dose Procedure](#)

OR

3. Carbapenem*

Suggested management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is definitely required

DRESS = drug rash with eosinophilia and systemic symptoms; SJS/TEN = Stevens–Johnson syndrome / toxic epidermal necrolysis

NB1: An IgE-mediated (allergic) immediate reaction is characterised by the development of urticaria, angioedema, bronchospasm or anaphylaxis within 1 to 2 hours of drug administration.

NB2: A cephalosporin or carbapenem may be considered in some circumstances—see ‘Cross-reactivity between beta lactams’.

NB3: Immunology and some clinical data suggest that there is an increased risk of immediate hypersensitivity reactions to aztreonam in patients hypersensitive to ceftazidime, due to the similarity of their side chains.

Figure 1.

Drug allergy pathways that include both history tools and guidance on beta-lactam prescriptions.

A. Partners HealthCare System (Boston, MA, USA)

Penicillin (A1) and cephalosporin (A2) hypersensitivity pathways with optional computerized clinical decision support (A3) (Boston, MA, USA). These pathways were originally used with a history tool at Massachusetts General Hospital (Figure 2A), with subsequent modification into an electronic App that is provider-facing and uses the patient-reported history and available patient records. This pathway is active throughout hospitals affiliated with Partners HealthCare System (PHS),³³ and has been adopted by other hospitals in the US. The App uses patient-reported clinical history to group patients into one of the three reaction groups and is currently only available for use at PHS hospitals. Research studies on this pathway demonstrate its safety, and its association with an increase in beta-lactam antibiotic use and increase first-line therapies for some inpatient infections.^{26,38,39} PHS hospitals performed over 1,000 drug challenges (test doses) per year with this infrastructure. * Antibiotic-stewardship program restricted antibiotics *Abbreviations:* PCN, penicillin

B. Computerized clinical decision support system (Birmingham, UK)

This computerized clinical decision support system (CDSS, Birmingham, UK) begins with an electronic questionnaire that is available as an App to assist providers in taking the allergy history. The computer uses entered information to stratify patients into high and low risk allergy groups (**B1**) with subsequent suggested actions (**B2**). High risk included patient acuity, high risk delayed reactions such as Stevens Johnson syndrome and organ involvement), and (1) rash <1 hour after first dose; 2) isolated hypotension, (3) upper or lower airway involvement, or (4) clinical features of anaphylaxis. Low risk patients are given direct amoxicillin challenge, with 1 hour observation.⁴⁰

C. Australian Therapeutic Guidelines (Melbourne, Australia)

Suggested management of patients reporting penicillin hypersensitivity in whom a beta-lactam antibiotic is definitely required (Therapeutic Guidelines, Melbourne, Australia).²¹

This is a national antibiotic prescribing document, available online for all physicians to reference in Australia. Most hospitals in Australia base their institutional guidelines on this national guideline.

A

Title: Penicillin and Cephalosporin Hypersensitivity Pathway

Applies to: All 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 penicillin allergy or cephalosporin allergy (see figures). If the pathway suggests a Test Dose Procedure, follow directions on Test Dose Procedure sheet. *While this guideline is helpful for all patients reporting a prior penicillin or cephalosporin allergy, test dose challenge procedures should not be performed on clinically unstable patients.* Page Allergy fellow on call with patient's name/medical record number if you have questions related to pathway.

C

**MICHAEL
GARRON
HOSPITAL**
TORONTO EAST HEALTH NETWORK

BETA-LACTAM QUESTIONNAIRE

Affix Patient Label Here

OR DATE: _____ **PAC APPT DATE:** _____
PROCEDURE: _____ **SURGEON:** _____
RECORDER: _____ **Rx / RN** _____
 Name of suspected drug: penicillin _____ other: _____
 Weight: _____ Height: _____ EBW: _____
 Date of reaction: _____ Current Age: _____
 Description of the reaction and severity: _____

REACTION	SEVERITY			COMMENTS
	MILD	MOD	SEVERE	
Rash – generalized? localized?				
Hives				
Urticaria				
Pruritis				
Shortness of breath				
Facial swelling				
Tongue swelling				
Throat swelling				
Swelling – other				
Nausea/vomiting/diarrhea				
Abdominal pain				
Anaphylactic shock				
Other				
Do not remember				

When did the reaction begin? _____ How long did the reaction last? _____
 Any treatment from a physician? _____ Hospitalized? _____
 Have you used similar antibiotics since? (names) _____
 Were you tested for a penicillin allergy? _____
 REFERRAL to allergist for testing? YES _____ NO _____ If yes, date faxed: _____
 Powernote Entered ☐ Email Sent to ID ☐ ID Confirmation ☐
 ID DOCTOR CONTACTED: McCready ☐ Powis ☐ Date: _____
 CONCLUSION: Allergy _____ Side Effect _____ Non-related _____
 Antibiotic Entered ☐ Allergy Comment Entered ☐ Added to RASH List ☐
 Antibiotic Order _____

J. McCready, J. Powis, S. Hicks
Version 2.0, June 2018

Figure 2.

Drug allergy history tools for non-allergists

A. Massachusetts General Hospital history tool (US, inpatients)

In the original (non-electronic app) guideline at the Massachusetts General Hospital, general inpatient providers were asked to follow these 3 steps,³⁹ with allergy history questions.

Future pathway iterations included the option electronic decision support tool (Figure 1A3).

B. Rochester Health Penicillin allergy screening algorithm (US, inpatients)

This penicillin allergy history screening algorithm was used to identify hospitalized patients who would benefit from penicillin skin testing.⁴³ This algorithm assessed and categorized allergic reactions based on the Gell and Coombs classification scheme, time elapsed since the reported penicillin reaction, and whether a penicillin antibiotic had been subsequently

tolerated. The algorithm did not apply to patients hospitalized in the cardiac, medical, or surgical intensive care unit, inability to provide informed consent, and pregnancy.

C. Reassessing Antibiotic Side-effect Histories (RASH, Michael Garron Hospital, Toronto, Canada).

RASH was performed by pharmacists in preoperative patients with subsequent allergy verification with an infectious diseases physician. Guideline-recommended prophylactic antibiotics often include cefazolin or cefoxitin, and patients with a reported penicillin allergy have a 50% increased odds of surgical site infection because their perioperative prophylaxis is inadequate.^{59, 82} Patients were deemed unsafe to receive a perioperative cephalosporin if they had a self-reported or documented history of any of the following reactions to any beta-lactams: (i) type I-mediated reaction, compatible with anaphylaxis as demonstrated by symptoms of bronchospasm, hypotension or angioedema; and (ii) severe non-IgE-mediated reactions [including Stevens–Johnson syndrome/toxic epidermal necrolysis, drug-induced hypersensitivity syndrome (DHIS), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), renal failure, cytopenias, serum sickness or any other life-threatening reaction]. Additionally, any patients describing any symptoms specifically due to cefazolin exposure were also deemed inappropriate to receive cephalosporin prophylaxis. With this tool, a majority (55%) of patients received cefazolin prophylaxis.⁸³

Figure 3.

Beta-lactam structure and cross-reactivity examples

Beta-lactam antibiotics include the penicillins, cephalosporins, carbapenems, and monobactams. This figure demonstrates the overall cross reactivity between classes sharing the core beta-lactam ring. Current data support that cross reactivity between penicillins and cephalosporins is higher for those that share common R1 side chains and in patients with severe reactions histories. This figure demonstrates a few examples of side chains where there has been clinical cross-reactivity observed. More comprehensive side chains cross-reactivity has been discussed elsewhere.^{33, 85, 86}

* Except for shared side chains.^{33,85,86}

[†] Monobactams have no shared cross-reactivity, except for aztreonam and ceftazidime.

Table 1. Key considerations in designing, implementing, and evaluating beta-lactam allergy pathways

Domain	Consideration	Detail
Pathway design	Sufficient clinical data	High quality clinical data are needed to standardize drug allergy recommendations.
	Eligible patients	Beta-lactam allergy pathways will apply to patients that are less stable than those typically seen in allergy outpatient practices. Pathways may consider clinically unstable patients ineligible for a drug allergy pathway or may include them as high risk. Guidance for stopping drugs that interfere with testing/treatment (e.g., beta-blockers) is also required. Beta-lactam allergy pathways in the acute care setting may apply to patients of all types, or may specify only inpatients, patients in the emergency room, perioperative patients, etc. Type of patient must also be considered, including obstetric patients, pediatric patients, and geriatric patients. Increased caution is advised for pregnant patients. Children reporting a penicillin allergy are less likely to have substantial time since their reaction occurred but are more likely to have low risk reactions or reactions that were never drug hypersensitivity. Intradermal testing may not be feasible in the very young. In the elderly, there may be a poor histamine response or cognitive impairment that precludes obtaining informed consent.
	Risk stratification by allergy history	Risk satisfaction using patient and provider-reported clinical allergy history detail remains the most important tool in pathway design. However, there is no standardized history tool and no tool that perfectly discriminates between patients who are and are not truly allergic, and risk categories will misclassify some patients. Pathways may exclude all patients with higher risk histories (e.g., anaphylaxis, severe cutaneous adverse reactions), or include different recommendation by reaction type. It is unclear whether <i>unknown</i> reactions should be considered high or low risk.
	Responsible provider	The design of the intervention may be the responsibility of the primary team, an allergy consultation service, or a specialized program run by other healthcare providers (e.g., antibiotic stewardship team). Given varied education and comfort in drug hypersensitivity, the pathway should be more conservative if non-allergists assess the allergy history, especially if there is no structured history tool or clinical decision support tool.
	Penicillin allergy epidemiology	The underlying epidemiology of true beta-lactam allergy differs geographically.
	Cross-reactivity between beta-lactams	There are local variations in beta-lactam cross-reactivity, and considerable research biases to much of the clinical data. Patients with anaphylactic histories are more commonly cross-reactive to similar side chain cephalosporins. Most cephalosporin prescriptions in patients with documented penicillin allergy requires an allergy alert override in the United States. Prior data demonstrate a wide degree of variability in baseline practices of prescribing cephalosporins and carbapenems to patients with a reported penicillin allergy.
	Allergy specialist access	The intervention will vary based on access to allergy specialist expertise, with limited access at most locations.
	Allergy procedures available	The intervention will vary by which allergy evaluation procedures (i.e., skin testing, drug challenges, desensitization) can be performed.
Pathway implementation	Responsible provider	The implementation of the intervention may be the responsibility of the primary team, an allergy consultation service, or a specialized program run by other healthcare providers (e.g., antibiotic stewardship team). Depending on who is responsible for allergy investigation/implementation, different types/levels of education and training will be needed.
	Allergy procedures available	Allergy testing can be conducted by non-specialists, but requires education, training, and access to resources. Allergy specialists have the most comfort with evaluating drug allergy and performing skin tests and drug challenges.
	Education of patients	Addressing beta-lactam allergies during acute inpatient care is associated with a risk of reaction during skin testing or challenges. Patients must be aware of such risk and providers must be trained in discussing the risk and benefits with patients. Informed consent should be obtained.
	Professional liability	Medical providers are taught to abstain from giving patients drugs reported in their allergy list. Concerns about professional liability exist and may impact the effectiveness of the interventions.

Domain	Consideration	Detail
	Communication	The effectiveness of beta-lactam allergy pathways in acute care is reliant on communication. Communication about any change in allergy status should be: (1) documented in the patient's medical chart, (2) communicated to the patient, and (3) communicated to the primary care providers.
Pathway evaluation	Outcome reporting	Important outcomes to consider include safety, impact on antibiotic use, and impact on cost/resources. General usability of the pathway, patient capture, and record updating are also important outcome measures.
	Intervention improvement	Drug allergy pathways are best studied with the methods of quality improvement, such as plan-do-study-act cycles and run charts.
	Follow up	Many patients receiving acute care beta-lactam evaluations may benefit from outpatient Allergy and Immunology drug allergy evaluations.