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# Optimizing preoperative prophylaxis in patients with reported β-lactam allergy: a novel extension of antimicrobial stewardship

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**Background:** Use of alternative second-line antibiotics is associated with adverse events in patients reporting β-lactam allergy. In the perioperative setting, we hypothesized that structured allergy histories, without the use of skin testing, can reduce alternative prophylactic antibiotic use.

**Objectives:** Assess the impact of structured allergy histories on patients with self-reported β-lactam allergy (SRBA) undergoing elective surgical procedures.

**Methods:** Structured allergy histories were performed by a pharmacist and reviewed with an infectious diseases physician. Patients were deemed safe to proceed with cefazolin prophylaxis if they did not describe a history of type I-mediated or severe reaction. Antibiotic prophylaxis orders (with approval by the surgical team) were scheduled into the computerized order entry system to be given prior to first incision of the operation.

**Results:** Of the 485 patients with SRBA that underwent structured allergy histories, 117 (24.1%) reported a type I-mediated allergy history; 267 (55.1%) patients received cefazolin prophylaxis and none subsequently experienced an adverse reaction. After intervention implementation, the overall use of alternative antibiotic prophylaxis at Michael Garron Hospital (Toronto, Canada) among those with SRBA decreased from 81.9% to 55.9%. This drop was associated with the number of monthly assessments ($P < 0.001$) in a regression analysis.

**Conclusions:** Using a simple structured history and the principles of prospective audit and feedback, we were able to increase the use of cefazolin perioperative prophylaxis without any serious adverse events and in the absence of skin testing or diagnostic challenges.

## Introduction

Use of second-line antibiotic therapy among patients with self-reported β-lactam allergy (SRBA) is associated with adverse events as these therapies are often broader, more toxic and less effective.[1] In patients with SRBA, only 1%–3% are found to have a true penicillin allergy after confirmation with positive skin testing.[2] There is also good evidence that cephalosporins, including cefazolin, may be safely used without further screening among individuals with SRBA.[3] In the perioperative setting, cefazolin is the most commonly recommended surgical site infection (SSI) prophylaxis.[4] In patients with SRBA, alternative prophylaxis agents include vancomycin and clindamycin, both associated with an increased risk of toxicity and antibiotic-resistant organisms.[5,6]

Routine preoperative penicillin skin testing as a means of allergy verification[7–11] has previously been used to increase cefazolin use; however, timely access to allergy testing is not an option for most centres. There is therefore a need for a more widely accessible strategy to optimize perioperative antimicrobials among those with SRBA. Our aim was to establish whether a structured allergy history, without skin testing, could be safely applied in the perioperative setting and increase cefazolin use as preoperative antibiotic prophylaxis.

## Methods

### *Setting*

We conducted our study at an urban community teaching hospital (Michael Garron Hospital, Toronto, Canada), which performs over 14 000 elective surgeries annually. Among patients undergoing elective surgery, 50% are assessed at a preoperative assessment clinic (PAC) in-person or have their chart screened preoperatively by PAC staff. During this assessment, the patient's health status including

medications and allergy history are collected and perioperative orders are finalized.

### Intervention implementation

Beginning in August 2013, we implemented our detailed assessment, named RASH (Reassessing Antibiotic Side effect Histories), for patients assessed by the PAC with SRBA. The PAC pharmacist performed a structured allergy history on each patient to determine the nature, timing and consequence of their SRBA. Each case was then reviewed with one of two infectious diseases physicians in person or by phone to provide direction on perioperative antimicrobials.

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 β-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. Patients describing the above history were recommended to otherwise receive therapy that included vancomycin, an aminoglycoside, metronidazole, ciprofloxacin or clindamycin (alone or in combination, as recommended by guidelines[4]) as SSI prophylaxis and referred for formal allergy testing.

All other patients, including those whose allergies were not recalled, were deemed safe to receive perioperative cefazolin. After discussion with the patient, orders were entered into the computerized order entry system for administration prior to the first incision. No allergist or immunologist consultation was sought at the time of RASH assessment.

The PAC pharmacists were trained in allergy assessment through education sessions and one-on-one case-based training with an infectious diseases physician over a 4 month period. The operative care staff, anaesthetists and surgeons were educated about the intervention by an infectious diseases physician.

### Balancing measures

Balancing measures included medication-associated adverse reactions during the operation and postoperative admission until discharge, delays in the initiation of the operation due to antibiotic administration and appropriate timing for perioperative antibiotic administration (defined as within at least 1 h before incision).

### Institutional alternative antibiotic use

Using an interrupted time series to determine the overall effect of RASH assessment, we examined antibiotic selection among all adult patients with SRBA undergoing elective surgery where cefazolin would be considered first-line therapy. Using logistic regression [adjusted for a linear term of month, ranging from April 2011 to July 2013 (baseline) and August 2013 to June 2016 (intervention period)], we estimated the association between the number of monthly RASH assessments and monthly percentage of patients receiving alternative antimicrobials, defined as any combination of antimicrobial agents that did not include cefazolin. We evaluated for residual autocorrelation of our final model by determining the Box–Pierce *P* value against the null hypothesis of no residual autocorrelation.

### Ethics

As this project was part of routine quality improvement work at Michael Garron Hospital (Toronto, Canada), formal application was deferred by the IRB.

## Results

### RASH assessments

During the period between 1 August 2013 and 30 June 2016, 485 patients with SRBA underwent RASH assessment. Patient characteristics and the nature of their reported allergies, along with the recommended/ordered perioperative antibiotics are displayed in Table 1. Approximately one-quarter of patients reported a history of anaphylaxis. Overall, 306 (63%) patients were recommended to receive cefazolin prophylaxis after RASH assessment.

### Balancing measures

Of the 485 patients who underwent RASH assessment, 2 (0.4%) patients did not complete their perioperative antibiotic within the appropriate timeframe prior to the operation—one due to incomplete vancomycin infusion and the other due to sampling of

**Table 1.** Characteristics and recommendations for patients undergoing RASH assessment ($N = 485$) and operative details

| | |
|---|---|
| Age (years), mean ± SD | 59.3 ± 16.3 |
| Male | 137 (28.2%) |
| Reported allergy drug | |
| penicillin | 371 (76.5%) |
| other penicillins[a] | 52 (10.7%) |
| first-generation cephalosporin | 24 (4.9%) |
| other cephalosporin | 24 (4.9%) |
| not recalled | 14 (2.9%) |
| Reported allergy | |
| anaphylaxis | 117 (24.1%) |
| severe non-anaphylactic reaction | 86 (17.7%) |
| rash | 195 (40.2%) |
| non-allergic reaction | 64 (13.2%) |
| not recalled | 23 (4.7%) |
| Formal allergy testing referral made | 91 (18.8%) |
| Operative type | |
| orthopaedic | 165 (34.0%) |
| gastrointestinal | 109 (22.5%) |
| urological | 70 (14.4%) |
| thoracic | 50 (10.3%) |
| plastic | 39 (8.0%) |
| gynaecological | 31 (6.4%) |
| head and neck | 20 (4.1%) |
| cardiac | 1 (0.2%) |
| RASH recommendation and prophylaxis administered | |
| cefazolin recommended ($n = 306$, 63%) | |
| β-lactam administered | 267 (87.3%) |
| non-β-lactam administered | 29 (9.5%) |
| unknown | 10 (3.3%) |
| non-cefazolin recommended ($n = 179$, 37%) | |
| β-lactam administered | 0 (0%) |
| non-β-lactam administered | 167 (93.3%) |
| unknown | 12 (6.7%) |

[a]Other penicillins include anti-staphylococcal penicillin, aminopenicillins or anti-pseudomonal penicillin.

infected tissue prior to cefazolin administration. Two patients had a delay in the start time of their operation (neither of which received cefazolin-based therapy), one due to infusion pump failure and the other inadequate intravenous access. During the operation and for the remainder of their hospital stay, 3 (0.6%) patients experienced antibiotic-associated adverse reactions related to vancomycin administration (red-person syndrome). No patients experienced cefazolin-associated adverse reactions.

### *Institutional alternative antibiotic use*

From April 2011 to June 2016, a total of 21097 elective surgical procedures for which cefazolin was the preferred perioperative agent were performed. Of these patients, 2225 (10.5%) reported a β-lactam allergy; 1275 (57.4%) underwent surgery after 1 August 2013, the start of the RASH intervention. From this time until the end of the study period, 485 of 1275 patients underwent RASH assessment (37.4%). Figure 1 illustrates the monthly percentage of alternative antibiotic use among patients with SRBA for the periods before (81.9%) and after (55.9%) RASH implementation.

Monthly RASH assessments and time in months were associated with a significant decrease in the monthly percentage of alternative antibiotic use (both $P < 0.001$). Our model had no evidence of residual autocorrelation (Box–Pierce $P = 0.414$) and demonstrated that an increase of 10 RASH assessments was associated with a 7.0% decrease in monthly alternative antibiotic use.

## Discussion

The implementation of a structured allergy history for preoperative patients with SRBA resulted in a dramatic reduction in alternative antibiotic prophylaxis without any serious adverse events, substantial delays in antibiotic administration or delays in operating times related to the intervention. This interdisciplinary intervention applied the stewardship principles of prospective audit and feedback to optimize antimicrobial use and would be broadly transferable to institutions with antimicrobial stewardship expertise. Our approach builds on prior studies suggesting that non-physician members of the healthcare team can be empowered to perform β-lactam allergy assessments.[12,13]

Traditionally, history has been considered an unreliable method of excluding β-lactam allergy with many experts advocating for more rigorous means of evaluation.[14–16] Prior studies have evaluated the use of penicillin skin testing and allergist consultation in the preoperative setting[7,9,11] to increase β-lactam use even though these measures may not be feasible in the majority of institutions. Our study is the first, to our knowledge, to utilize effectively the patient history without allergy testing in the preoperative setting to increase β-lactam utilization.

No clinically significant adverse reactions were seen in patients given cefazolin prophylaxis following RASH because our strategy safely selected a population of patients with a low risk of adverse reactions. The safety of our strategy is supported by prior observational studies in the perioperative setting showing that cephalosporin use in those reporting non-IgE-mediated reactions to penicillin (and in the absence of skin testing) resulted in no adverse reactions.[17,18] Our intervention should not be regarded as a replacement for penicillin skin testing but rather used as a tool to optimize allergist referral by identifying those with convincing histories for type I reactions.

There are several limitations to our intervention. First, it was conducted at a single centre with expertise in antimicrobial stewardship, which may limit its external validity. Second, some RASH recommendations were not followed by the surgery team at the time of surgery. This supports the notion that improving culture around appropriate allergy histories is universally required to prevent over-diagnosis of β-lactam allergies. Lastly, although initial assessment of allergies was carried out by pharmacists, it did require the availability of a physician to review these cases within a reasonable timeframe.

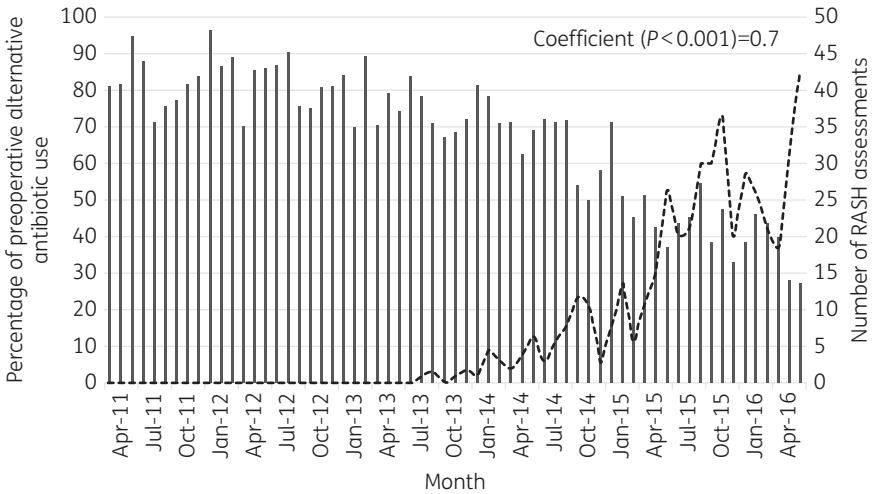


**Figure 1.** Number of RASH assessments and percentage of preoperative alternative antibiotic use by month among patients with SRBAs, before and after RASH intervention initiation. Primary *y*-axis, with data demonstrated by the bars, represents the monthly percentage of preoperative alternative antibiotic use (defined as any antibiotic therapy other than cefazolin or cefazolin and metronidazole) among patients with an SRBA. Secondary *y*-axis, with data demonstrated by the broken line, represents the monthly number of RASH assessments. RASH intervention was initiated in August 2013 on patients undergoing orthopaedic procedures and was then generalized to all patients by October 2013.

### *Conclusions*

A structured allergy history used to clarify SRBA in the preoperative setting resulted in a significant reduction in the use of alternative second-line prophylaxis without the use of upfront allergy testing. This extension of antimicrobial stewardship into the perioperative setting was successfully implemented using existing hospital resources and can be transferable to other institutions that lack routine availability of allergy testing. Future research should include cross-validation in other institutions with a larger sample size powered to detect safety and impact on operative outcomes including SSI rates.

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## Transparency declarations

None to declare.

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