A Retrospective Cross-sectional Study Evaluating Beta-lactam Allergy Labeling in Hospitalized Patients

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ABSTRACT

Background
Beta-lactam allergy is one of the most commonly reported drug allergies and often leads to avoidance of beta-lactams. The majority of people with a penicillin allergy can tolerate beta-lactams, since many of the reported reactions do not represent true allergy or their IgE-mediated penicillin allergy has waned over time. Beta-lactams are commonly avoided in these patients, even when they are the preferred therapy leading to the use of second-line antibiotics, which may be less effective and have greater risk of adverse events. Official allergy documentation at our institution does not always reflect data available in the chart of previous beta-lactam tolerance; therefore, we aim to quantify this discordance.

Primary Objective
To assess our institutional performance of updating allergy labels in the electronic health record (EHR) in patients with a documented beta-lactam allergy who have documentation or evidence of previous exposure to beta-lactam(s) in the EHR.

Methods
A retrospective chart review was performed for inpatients with a beta-lactam allergy label in 2016 until a predetermined sample size of 95 was reached. Patients ≥ 18 years of age were included if they had previous exposure to a beta-lactam with no adverse reaction in the EHR or clinical documentation of safe exposure.

Results
Approximately 94% of the patients had a penicillin allergy, and 43% of them tolerated a first generation cephalosporin. For the primary outcome, 81% of medical charts contained beta-lactam allergy related information not reflected in the official allergy history in our EHR. The beta-lactam allergy label was modified in 19% of the medical charts indicating safe exposure.

Conclusion
At our institution, beta-lactam allergy labels were infrequently modified despite the patient having clinical documentation or evidence of prior exposure to a beta-lactam.
INTRODUCTION

Beta-lactam allergy (BLA) is one of the most commonly reported drug allergies and often leads to unnecessary avoidance in patients who could in fact tolerate beta-lactam therapy. Most patients with BLA cannot recall the reaction, and consequently receive alternative antibiotics that may be of broader spectrum which are clinically inferior, have greater adverse effect profiles and higher associated costs [1, 6]. A guide by Gonzale-Estrada et al. (2015) indicates that about 10% of the general population is labeled with a penicillin allergy; however, the prevalence of a life-threatening allergic reaction is only about 0.02% to 0.04% in this population [2].

Penicillins and cephalosporins are two major categories of BL antibiotics; the four minor categories include carbapenems, beta-lactamase inhibitors, monobactams and oxacephem (not currently available in Canada). The difference in side chains between beta-lactams contributes to allergic cross-reactivity. Table 1 in Appendix A depicts subgroups of beta-lactams with a higher possibility of cross-reactivity due to similarity in side chain C-7 or C-3. For instance, ampicillin and cephalexin share an identical C-7 side chain, indicating a possibility of cross-reactivity [3]. Studies have shown cross-reactivity rate between penicillins and cephalosporins to be in a range of 2.6% to 38% [4,5]. However, 38% is not the true rate since the high cross reactivity found in early studies was likely due to contamination of the study drugs with penicillin [14]. The cross-reactivity rate between penicillins or cephalosporins and carbapenems is very low, approximately 1%; therefore, a patient with a true penicillin allergy is very unlikely to have an allergic reaction to meropenem. [5]

Table 2 in Appendix A describes the Gell and Coombs classification of hypersensitivity reactions. Type I and IV reactions are most commonly seen with antibiotics. Type I is IgE-mediated and usually occurs within one hour of drug exposure, whereas type IV has a delayed reaction which may take days to weeks. [3]

Avoidance of a BL due to a reported allergy can potentially lead to detrimental consequences. A prospective cohort study conducted in Toronto, Canada by Macfadden et al. (2016) found that 35% of patients with reported BLA did not receive the preferred BL therapy. The primary outcome of the study was a composite of adverse events, including acute kidney injury, Clostridium difficile infections (CDI), adverse drug reaction
requiring discontinuation or readmission with the same infection. Patients with a reported BLA who did not receive preferred BL were at a 3.1 times greater risk of adverse events compared with those without reported BLA. In contrast, patients with a reported BLA who received preferred BL therapy had a similar risk of adverse events compared with those without reporting BLA (adjusted odds ratio 1.33, 95% CI 0.62-2.87). Their secondary outcomes consisted of individual primary composite outcomes as well as mortality. Patients with a reported BLA who did not receive preferred BL had a greater risk of readmission (24% vs. 6% p<0.05) and drug reaction (8% vs. 0.5%, p<0.05) compared with those who did not have a BLA label [7].

Improved reporting and assessment of BLA can have impact on costs to the health care system. A retrospective analysis was conducted on adult patients with BLA who underwent penicillin skin testing and oral challenge. 54 out of the 55 patients who underwent the procedure tested negative, and 37 were successfully switched to a BL. The overall estimated cost savings were $11,005, $297 per patient switched to a BL [8].

In 2015, the Association of Medical Microbiology and Infectious Diseases Canada released the following statement: “Don’t prescribe alternate second-line antibiotics to patients reporting non-severe reactions to penicillin when beta-lactams are the recommended first-line therapy” [10]. Despite the recommendation, some physicians still intentionally avoid preferred BL when the patient has a reported history of BLA. All drugs have the potential to cause adverse drug reactions, without all of them being allergic in nature, and some are more appropriate to be classified as intolerance. Computerized record systems often cannot distinguish between intolerance and a true drug allergy which often leads to inaccurate allergy labeling, especially if the person’s reaction took place many years ago. In addition, majority of people do not keep a record of their own drug allergies, and this can result in confusion regarding the validity of the allergy label [15].

At THP, our allergy process entails the documentation of patient allergy status on admission. The allergy status is taken by a health care practitioner (HCP) such as nursing staff, entered by a registration clerk or Unit Coordinating Assistant and verified by another HCP. However, the nature of allergy is often not apparent from our official EHR documentation; thus, it cannot always be established whether a drug reaction is allergic or non-allergic without investigation. Furthermore, the lack of accuracy in this official documentation is believed to negatively impact treatment choices. For example, a matched cohort study found that cases with a penicillin allergy used more vancomycin,
fluoroquinolone and clindamycin. As a result, cases had 23.4% (15.6%-31.7%) more *Clostridium difficile*, 14.1% (7.1%-21.6%) more MRSA, and 30.1% (12.5%-50.4%) more VRE infections compared to control subjects without penicillin allergy. They also averaged 0.59 (95% CI, 0.47-0.71) more total hospital days during 20.1± 10.5 months of follow-up compared with control subjects [1]. Therefore, an unverified label of BLA may lead to the inappropriate use of alternative antibiotics that may be clinically inferior or have broader spectrum.

Furthermore, when a clinician discovers the allergy to not be true and indicates this finding in clinical or consultation notes, this documentation is often ineffective or even ignored leading to re-use of alternative antibiotics over time. In order to assess the impact of allergy label on clinical decision making, our study will assess the discordance of BLA labeling in Meditech compared to clinical documentation in the medical chart or consult notes at THP - Mississauga Hospital.

**AIM OF THE PROJECT**

The aim of this project is to assess our institutional performance of updating allergy labels in the EHR in patients with a BLA who have documentation of previous tolerance to a BL. Specifically, we want to determine the prevalence of discordance between: 1) beta lactam allergy labels in our EHR and 2) clinical documentation or evidence of previous exposure to BL within the past 4 years. If discordance is identified, then subsequent steps to address this performance gap can be implemented in the future.

**METHODS**

**Study Design**
This is a cross-sectional, retrospective study, conducted by reviewing medical charts of patients admitted to Mississauga Hospital in 2016 until the predetermined sample size was reached.

**Study Population**
*Inclusion Criteria:*

- Adult inpatients 18 years of age or older with a reported beta-lactam allergy
- Previous exposure to a BL with no adverse reaction documented in or clinical documentation of safe exposure

**Exclusion Criteria:**
- Documentation of previous exposure to a BL resulting in adverse reactions
- Patients with a BL allergy with no previous exposure to BL or clinical documentation of safe exposure

**Study Outcomes**

**Primary Outcome**
- Percentage of patients with a beta lactam allergy label that inaccurately reflects previous safe drug exposure to beta-lactam or clinical documentation of safe exposure

**Secondary Outcomes**
1. Percentage of BLA labeled patients with evidence of prior exposure to a beta-lactam in the EHR
2. Percentage of BLA labeled patients with documentation of safely receiving beta-lactam in clinical notes
3. Percentage of patients with BLA label in the 2016 cohort who did not receive the preferred beta-lactam when beta-lactam was the preferred therapy based on infectious disease physician and pharmacist review
Statistical Analysis

Sample Size
With the assumption of at least 45% of medical charts containing BL allergy-related information not reflected in the official allergy history in Meditech, a Z-value of 1.96 based on 95% level of confidence, and a precision of 0.1, the calculated sample size is 95.

Data Analysis
Results are expressed as proportions (%).

Study Definitions
Previous safe exposure to beta-lactam determined by identifying beta-lactams entered in the Meditech system for 24 hours or more, without any documentation of adverse reaction to the medication.
Clinical documentation to safe exposure defined as the documentation by a physician indicating patient’s safe tolerance to the beta-lactam in the electronic dictated note.
Allergy label change includes any modifications done to the BLA label by a health care professional (i.e. the addition of a label comment).

RESULTS

Figure 1: Data Collection
A total of 2584 patient charts from 2016 were reviewed until a sample size of 95 was reached. (Figure 1)

Table 1: Type of BLA Label and Evidence of Nature of Allergy

<table>
<thead>
<tr>
<th>Group</th>
<th>Penicillin Label</th>
<th>Other BLA Label</th>
<th>Nature of Allergy Attached to Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group with label change (18)</td>
<td>17 (94%)</td>
<td>1 (6%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Group without label change (77)</td>
<td>72 (94%)</td>
<td>5 (6%)</td>
<td>32 (42%)</td>
</tr>
<tr>
<td>All (95)</td>
<td>89 (94%)</td>
<td>6 (6%)</td>
<td>42 (44%)</td>
</tr>
</tbody>
</table>

Majority (94%) of the BLA labels were penicillin. The rest of the 6% BLA labels included a cephalosporin, amoxicillin or cephalexin. Out of all of the labels, only 44% had the nature of the allergy attached. 32 out of 42 of the allergy reactions were hives or rash. 2 of the reactions were gastrointestinal intolerance and 1 reaction was indicated as anaphylaxis.

Figure 2: Type of BL Safely Tolerated by Patients with a Penicillin Allergy (n=108)

Out of all of the patients labeled with a penicillin allergy, majority (43%) of them received a 1st generation without any documented allergic reaction. 26% and 19% of them safely received a 3rd generation cephalosporin and beta-lactamase inhibitor, respectively.
Primary Outcome

Figure 3: Allergy Label Changed in Patients with Previous BL Exposure or Clinical Documentation of Tolerance

Our study found that 81% of the BLA labels was modified despite the patient having a history of safe exposure to a beta-lactam. The remaining 19% of the BLA labels had some type of modification done.

Table 2: Type of Health Care Professional Associated with Label Modification

<table>
<thead>
<tr>
<th>Health Care Professional</th>
<th>Pharmacist</th>
<th>Nurse</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 18</td>
<td>15/18 (83%)</td>
<td>2/18 (11%)</td>
<td>1/18 (6%)</td>
</tr>
</tbody>
</table>

Most of the label modifications (83%) were done by a pharmacist, and 11% was done by a nurse.

Secondary Outcomes

Figure 4: In Each Group: Percentage of Previous Exposure, Clinical Documentation of Tolerance and Both
In the group where the BLA label was changed, 78% of the patients had an actual exposure to a BL, 6% had documentation of safe exposure by a physician, and 17% had both actual exposure and documentation of exposure.

In the group where the BLA label was not changed, 62% of the patients had an actual exposure to a BL, 19% had documentation of safe exposure by a physician, and 18% had both actual exposure and documentation of exposure.

Table 3: Analysis of Patients with Antibiotic Therapy in 2016 Cohort (n=24)

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients that did not receive 1st line therapy with a beta-lactam when indicated</td>
<td>4.2% (1/24)</td>
</tr>
<tr>
<td>Patients received a beta-lactam in 2016</td>
<td>91.7% (22/24)</td>
</tr>
<tr>
<td>Documentation of safe exposure to beta-lactam by a physician in the clinical note</td>
<td>54.5% (12/22)</td>
</tr>
</tbody>
</table>

In the cohort of patients who received antibiotic therapy in 2016, only 1 out of 24 did not receive the first line therapy with a beta-lactam when it was indicated. Out of the 22 patients who received a beta-lactam in 2016, about half of their physicians acknowledged the event of safe exposure to a beta-lactam in their documentation.

**DISCUSSION**

In this retrospective, cross-sectional study, we found that majority (94%) of the BLA labels was penicillin, but only about half (44%) of the labels indicated nature of allergy. The most common reaction was hives or rash, which is not specific to penicillin because the reaction could potentially be due to the illness itself or a concomitant medication. Two reactions indicated gastrointestinal intolerance, which is in fact classified as drug intolerance, not allergy. Lastly, the one patient with documented anaphylactic reaction to penicillin did receive ceftriaxone without any documented reactions. This finding aligns with the literature indicating that about 10% of general population label themselves as being allergic to penicillin, being one of the most commonly reported drug allergies [2]. Unfortunately, when a patient is labeled as being allergic penicillin with an unknown reaction, clinicians are still hesitant in prescribing a beta-lactam since there is still a risk of cross-reactivity, although it is as low as 2.6% [4]. As a result, alternative antibiotics may be used instead of the first line beta-lactam.
Out of all the patients with a penicillin allergy, about half of them (43%) received a first generation cephalosporin without any documented reaction. Cefazolin was the most common first generation cephalosporin since it was used preoperatively, and the medication administration record was checked to ensure the medication was given. According to Table 1 in Appendix A, cefazolin and penicillin do not share a similar side chain and thus have a lower possibility of cross-reactivity [3]. Furthermore, about 26% of penicillin allergic patients received a 3rd generation cephalosporin without any documented reaction, with ceftriaxone being the most common. Once again, ceftriaxone and penicillin do not share a similar side chain, and hence lower possibility of cross-reactivity.

The results of the primary outcome showed that 81% of the BLA labels was not modified despite the patient having a history of safe exposure to a beta-lactam. The remaining 19% of the BLA labels had some type of modification done (figure 3). An example of label modification included adding a comment to the penicillin allergy label indicating the patient is able to receive ceftriaxone safely. It is important to note that our data does not include the population that had their BLA label deleted in 2016. Furthermore, we were interested in the type of health care professional that was most involved in BLA label modification, and we found that pharmacists made 83% of the modifications (table 2). When the BLA label is not modified despite tolerance to a beta-lactam, it could result in the patient receiving an alternative antibiotic that may be inferior and/or have more adverse effects than the preferred beta-lactam [7].

From the secondary analysis, we found that having an actual exposure to a beta-lactam was more influential in prompting the health care provider to modify the allergy label, whereas the documentation by a physician was often not acknowledged (figure 4). The Meditech system used at THP allows easy access to past medications, whereas reading through the physician’s clinical notes require more time, and thus having an actual exposure to a beta-lactam is more influential. The other part of secondary analysis focused on the cohort of patients who received an antibiotic in 2016 (table 3). We found that only 1/24 patient did not receive the first line therapy with a beta-lactam when it was indicated. This result may falsely make us believe the BLA label does not affect the clinician’s choice of antibiotic; however, it is important to remember that our study only included patients who did receive a beta-lactam in 2016 without any documented reactions, and hence we cannot conclude the magnitude of effect. Lastly, in this cohort, we also found that only about half (54.5%) of the physicians acknowledged that their patient safely received a beta-lactam despite the proclaimed allergy.
There are several limitations to our study. First of all, our extracted data was not able to capture BLA labels that were removed in 2016, which theoretically is more effective than label modifications. Secondly, we made the assumption of actual exposure to the beta-lactam if the medication was entered in the Meditech system for greater than 24 hours. However, whenever there was doubt, we double-checked with the medication administration record. Lastly, we assumed safe exposure if there was no documented adverse reaction to a beta-lactam.

**Future Directions**

There are several immediate actions that can be taken based on the results of this study. Firstly, re-educating health care professionals on the difference between intolerance and true drug allergy. For example, if a patient indicates that they have had nausea and vomiting to a beta-lactam, then the reaction should be labeled as a drug intolerance. Secondly, as pharmacists, we are constantly reviewing patient’s medication profile, and thus we should take the time and effort to update their allergy profile if a discrepancy is noted. In the long run, a more robust system is needed for both assessment and documentation to reflect true beta-lactam allergies at our institution. Appendix B displays a sample questionnaire that could be used to obtain a more comprehensive allergy history. Lastly, beta-lactam allergy skin testing can be explored as a method to remove inaccurate BLA labels.

**Conclusions**

In conclusion, we found that beta-lactam allergy labels were infrequently modified at our institution despite the patient having clinical documentation or evidence of previous exposure to a beta-lactam. We also found that many patients were able to safely receive a beta-lactam despite being labeled with penicillin allergy. A more robust system is needed for both assessment and documentation of allergies.
References


10. Choosing Wisely Canada: AMMI Canada Recommendations. Association of Medical Microbiology and Infectious Disease Canada. Available at: https://choosingwiselycanada.org/infectious-disease/


Appendix A: Background

Table 1. Groups of Cephalosporins and beta-lactams with similar C3 and C7 side chains [3]

<table>
<thead>
<tr>
<th>Similar C7 side chain. Cross reactions between agents within one group is possible</th>
<th>Similar C3 side chain. Cross reactions between agents within one group is possible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong> Penicillin Cephalothin Cefoxitin</td>
<td><strong>Group 2</strong> Amoxicillin Ampicillin Cefaclor Cephalexin Cefadroxil</td>
</tr>
<tr>
<td><strong>Group 3</strong> Cefepime Cefotaxime Ceftriaxone</td>
<td><strong>Group 1</strong> Cefadroxil Cephalexin</td>
</tr>
<tr>
<td><strong>Group 2</strong> Cefotaxime Cephalothin</td>
<td><strong>Group 3</strong> Cefotaxime Cephalothin</td>
</tr>
<tr>
<td><strong>Group 5</strong> Cefuroxime</td>
<td><strong>Group 6</strong> Cefixime</td>
</tr>
<tr>
<td><strong>Group 7</strong> Ceftazidime</td>
<td></td>
</tr>
</tbody>
</table>

*Group 4 is not included because ceftibuten and ceftizoxime are not available in Canada

Table 2. Gell and Coombs Classification of hypersensitivity reactions [2, 3]

<table>
<thead>
<tr>
<th>Type</th>
<th>Mediator</th>
<th>Clinical Reaction</th>
<th>Utility of skin test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Immediate (&lt;1 hour)</td>
<td>IgE antibodies</td>
<td>Anaphylaxis, hypotension, laryngeal edema, bronchospasm, angioedema, urticaria</td>
<td>Yes</td>
</tr>
<tr>
<td>II Delayed cytotoxic antibody-mediated (&gt;72 hours)</td>
<td>IgG and IgM antibodies</td>
<td>Haemolytic anemia, hemolysis of platelets, neutropenia</td>
<td>No</td>
</tr>
<tr>
<td>III Antibody complex-mediated (&gt;72 hours)</td>
<td>IgG, IgM antibodies, immune complex</td>
<td>Serum sickness (fever, cutaneous eruptions, lymphadenopathy, arthralgias, myalgias,), glomerulonephritis</td>
<td>No</td>
</tr>
<tr>
<td>IV Delayed (&gt;72 hours)</td>
<td>T-cells</td>
<td>Contact dermatitis</td>
<td>No</td>
</tr>
</tbody>
</table>
### Appendix B: Sample Questionnaire

**Questionnaire for determination of beta-lactam tolerance [2, 16]**

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>What medication caused the reaction?</td>
<td></td>
</tr>
<tr>
<td>What was the route of administration?</td>
<td>Oral ___ IV ____ Other _____________</td>
</tr>
<tr>
<td>What was the indication for the medication?</td>
<td></td>
</tr>
<tr>
<td>How long ago did the reaction occur?</td>
<td>___ Childhood ____ ≤3 months ____ ≤1 year _ __ 1-4 years ____ 5-9 years ____ &gt;10 years __ Unknown</td>
</tr>
<tr>
<td>What symptoms were present during the reaction?</td>
<td>___ Pruritus ____ Urticaria or angioedema ____ Respiratory ____ Gastrointestinal ____ Cardiovascular ____ Other ____ Unknown</td>
</tr>
<tr>
<td>Details of the symptoms:</td>
<td></td>
</tr>
<tr>
<td>How soon did the symptoms appear after taking the medication?</td>
<td>___ &lt;5 min ____ 5-60 min ____ 1-24 hours ___ 1-7 days ____ 1-3 weeks ____ Unknown</td>
</tr>
<tr>
<td>How was the reaction managed? What was the outcome?</td>
<td>Management: ___ Antihistamine ____ Epinephrine ____ Steroids ____ None ____ Unknown</td>
</tr>
<tr>
<td></td>
<td>Outcome:</td>
</tr>
<tr>
<td><em>have similar symptoms occurred without taking the medication?</em></td>
<td>___ Yes ____ No ____ Unsure</td>
</tr>
<tr>
<td>Details:</td>
<td></td>
</tr>
<tr>
<td>Have you tolerated other penicillins since the reaction? If yes, which one?</td>
<td></td>
</tr>
</tbody>
</table>
Appendix C: Recommendations on Allergy Documentation [15]

Recording drug allergy status

8. Document people’s drug allergy status in their medical records using 1 of the following:
   • ‘drug allergy’
   • ‘none known’
   • ‘unable to ascertain’ (document it as soon as the information is available).

9. If drug allergy status has been documented, record all of the following at a minimum:
   • the drug name
   • the signs, symptoms and severity of the reaction
   • the date when the reaction occurred.

Documenting new suspected drug allergic reactions

10. When a person presents with suspected drug allergy, document their reaction in a structured approach that includes:
   • the generic and proprietary name of the drug or drugs suspected to have caused the reaction, including the strength and formulation
   • a description of the reaction
   • the indication for the drug being taken (if there is no clinical diagnosis, describe the illness)
   • the date and time of the reaction
   • the number of doses taken or number of days on the drug before onset of the reaction
   • the route of administration
   • which drugs or drug classes to avoid in future.