PROPOSAL: PENICILLIN ALLERGY DE-LABELLING IN A RURUAL HOSPITAL COMPLETED BY NON-ALLERGIST PHYSICIANS: A COST-SAVING ANALYSIS

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Abstract:

Many patients who are labeled as being penicillin allergic are not truly allergic.[1-11] The label is often applied due to a past mild reaction, such as a benign rash and no longer accurately reflects the patient's status.[1,2] These patients are often prescribed inappropriate and ineffective antibiotics, many of which have a broader spectrum and are more expensive than is necessary.[1-3,5-10] Direct oral challenge (OC) via oral challenge can identify low-risk patients who are incorrectly labeled and lead to the removal of the false allergy label.[1-5,7,11,12] This proposed project is a retrospective chart review of patients attending the Brandon Penicillin Allergy Testing Clinic, which is run by non-allergist physicians, demonstrating a safe protocol for amoxicillin DPT that does not require specialized personnel. The demographics of participants, as well as the outcomes of testing, both immediate and delayed would be consolidated. The project would also review patient antibiotic prescriptions after being de-labeled to determine if the de-labeling led to subsequent penicillin use and if so, how the use of penicillin has impacted costs for the healthcare system. This would be done by comparing penicillin costs to the cost of the most likely alternative antibiotic. This research could demonstrate how smaller centres with non-allergist personnel can still achieve better anti-microbial stewardship and reduce healthcare costs with penicillin allergy de-labeling initiatives.

Introduction:

Approximately 10% of children in North America are labeled as penicillin allergic[1,2] and various sources put the number of labeled patients in the USA at 7%[3], 10%[4], or 8-15%[5]. They are often labelled as penicillin/amoxicillin allergic after a minor reaction such as a benign rash that occurs in early childhood following a course of penicillin or amoxicillin during a viral illness.[1,2] This label can stay with the patient throughout their life. However, recent studies suggest that most of these patients are not actually allergic to penicillin.[1-11] The initial reaction that prompts the labeling can be due to numerous other factors, such as coincidence, normal side effects, adverse reactions, or a concurrent viral infection[1,3-6] and some mild allergic reactions to penicillin can resolve later on in life, meaning that many of these patients will not have any reaction several years after the initial reaction.[1,4,5]

Penicillin and other β-lactams are used to treat a wide range of conditions caused by many different organisms.[1,3,6,7] For this reason, the labeling of patients as allergic to penicillin can disrupt patient treatment significantly, with many patients being prescribed broad-spectrum antibiotics when penicillin would suffice to treat their infection.[1,4,5,7,8] The use of broad-spectrum antibiotics may contribute to increased antibiotic resistance and increased adverse effects such as medication side effects, and *Clostridium difficile*, Methicillin Resistant *Staphylococcus Aureus* (MRSA), or Vancomycin Resistant *Enterococcus* (VRE) infections.[1,3,5-9] Penicillin allergy labels can lead to longer hospital stays[1,5,7,10] and increased risk of surgical site infections[5,9]. These factors lead to higher costs for the medical system[1,6,7,9-11] including prescription costs up to twice as much.[1]

Several studies have shown that allergy testing can identify patients who can be safely de-labeled.[1-12] Once the label of penicillin allergy is removed, future prescribing practices can be altered to make use of penicillin and related β-lactam antibiotics. One study of children and adults who had been de-labeled found that 70% of patients had since been prescribed penicillin at least once.[8] Of those patients, only 5.5% had any adverse reactions, with the majority suffering from a mild rash.[8] Another study surveyed the caregivers of de-labeled children and found that 73% of the respondents felt "comfortable" or "very comfortable" with using penicillin for their child after being de-labeled.[11] In that population, the extrapolated cost saving was $192,223 based on the potential population to be de-labeled.[11] When examining inpatient populations, Li *et al* found that de-labeling and subsequent use of β-lactams lead to a reduced length of hospital stays compared to controls and projected savings of $1,743,077 per year based on both hospital and prescription costs.[10] Yet another study indicated that the cost savings per de-labeled patient was $314.75, based on prescription cost.[6]

This research project would involve conducting a retrospective chart review of patients who were tested for a penicillin or amoxicillin allergy using direct provocation oral challenge (OC) with amoxicillin at the Brandon Penicillin Allergy Testing Clinic. Direct OC has been shown to be safe to use in patient populations where the initial allergic reaction was mild.[1-5,7,10,12]. As part of the testing, patients will be followed up with via phone at 1 week and again at 3 months to ask about any delayed reactions. The project will also involve a cost analysis, which will be conducted by reviewing the patient's hospital and provincial electronic medical records for any subsequent penicillin prescriptions and estimating cost savings. This research is novel as the Brandon Penicillin Allergy Testing Clinic is operated by non-allergists, allowing them to share a protocol that could be carried out in other institutions without requiring specialized personnel while also demonstrating the safety of the protocols used. The goal is to determine how safe and effective the clinic's de-labeling process has been by determining how many patients have had adverse reactions and how the results have impacted patient prescription habits. The major outcome to be examined is cost savings due to proper prescribing of β-lactams when appropriate.

Methods:

The proposed research would involve a retrospective chart review of outpatients who underwent penicillin allergy testing at the Brandon Penicillin Allergy Testing Clinic with an OC. All patients tested were considered to be low or moderate risk based on the clinic's protocol. The OC consists of administering 10% of the therapeutic dose of amoxicillin, observing the patient for 1 hour, then administering the full therapeutic dose and observing for 2 hours. The dose is age adjusted up to a maximum dose of 500 mg. This method of testing for penicillin allergies is in line with previous research, which demonstrated the safety and efficiency of DPT for penicillin allergies.[1-4,6,10,11] As part of the clinic's testing protocol, patients will be followed up with at 1 week and again at 3 months to evaluate for any adverse reactions such as a delayed rash. The participant population would be anyone who had been tested at the Brandon Penicillin Allergy Testing Clinic, including both adults and children over the age of 2.

In order to examine cost-savings, the hospital and provincial electronic medical records of patients who had been de-labeled following testing would be reviewed to see if they have since been prescribed any β-lactam antibiotics that may have been avoided in the past. The cost difference between the prescribed β-lactam and the most likely alternative antibiotic based on the Prairie Mountain Health drug formulary would be calculated for each patient who subsequently received a β-lactam. The sum of these differences would provide an estimate as to how much money had been saved by accurate prescribing over the time that the clinic has been open.

The risk to the participants is low, as the information comes from a retrospective chart review and not clinical trials, therefore the only real risk is of a breach of confidentiality. The testing, follow up, and any further prescriptions are part of the patient's own healthcare and the study does not require anything above and beyond that. Furthermore, the information that will be gathered is itself low risk as it is not likely to be stigmatizing. The data collected such as demographic information and outcome of the OC is not necessarily stigmatizing, although it will include information about the patient's current conditions and medications. The major risk of stigma comes from the subsequent penicillin use, as penicillin can be used to treat sensitive infections such as syphilis[6,7], however the data collected does not include what the prescription is for, only that it was prescribed instead of an alternative antibiotic. The results will only examine the cost difference without reporting on the infection that the penicillin was prescribed for. This should reduce the risk of stigma to the participants.

The participants will not receive any direct benefits or compensation as the research is all conducted on their charts. However, there is an indirect benefit in that if the research should prove that the penicillin allergy testing protocol is cost saving and safe for patients there could be increased support for future testing and further de-labeling of patients. Broadly, this would help reduce the prevalence of antibiotic resistant organisms and lead to reduced costs to the healthcare system, which benefits everyone using the system.

The patient data will be anonymized in the research paper, with only demographics (age, sex, comorbidities, other medications, and initial penicillin reaction), test results, and penicillin prescriptions and costs being recorded. The clinic's paper charts will be accessed only at the clinic and will be otherwise stored in the Brandon Regional Health Center's medical records department. The electronic charts are protected via the Prairie Mountain Health (PMH) system, and will require a password to access. The consolidated data will be de-identified, with patients being coded by their initials and date of testing and kept on a PMH computer or on a password-protected USB. The master list will be accessible only to Dr. Taft Micks and Dr. Norm Silver. At the time of publication, the patient data sheets will be destroyed by deleting them. There is no anticipated need to retain data beyond the publication of the study. All participating researchers will have PHIA training.

Study participants will all be asked for consent to use their charts for this study at the time of their testing or retrospectively after testing by Dr. Taft Micks and Dr. Silver. The consent process will include all necessary information, such as an explanation of the purpose of the

study, what data is collected and why, and how their privacy is protected as well as assurances that they can refuse or withdraw their consent without impacting their treatment. It shall be made clear that employees at the clinic are carrying out the research to address any concerns of conflict of interest. The participants will sign a standardized consent form at the time of their testing or will be contacted retrospectively to sign the forms. Children will be provided with an assent form and an explanation of the study process appropriate for their age. Consent will also be obtained from their parent/guardian. If a child does not agree to participate, their data will not be used for the study, regardless of parental/guardian consent.

The timeline for this research is to start the chart review as soon as possible. The Brandon Penicillin Allergy Testing Clinic continues to be active and will therefore continue to grow the participant population. The retrospective chart review will be completed over the next year as patients are continually enrolled at the clinic. Following data collection, a few months will be required to draft a manuscript for potential publication.

Results:

The data examined would yield results exploring several outcomes. Firstly, the demographics of patients tested at the clinic, including age, sex, co-morbidities, other medications, and details of the initial reaction that led to the allergy label. Secondly, the number participants who have an adverse reaction to penicillin due to the challenge protocol, either immediate or delayed, to illustrate the safety of the penicillin de-labelling protocol. Thirdly, the practical impact of de-labeling, as measured by the number of patients who were de-labeled and subsequently were prescribed a β-lactam. Fourthly, the estimated cost savings to the healthcare system as a result of more accurate antibiotic prescribing practices following de-labeling. The cost of the various prescriptions will be estimated using the PMH drug formulary. The first, second, and third outcomes can be described as a percentage of participants from each demographic who were tested, the percentage that experienced any adverse events due to the testing, and the percentage of de-labeled participants whose charts indicate a subsequent penicillin prescription. The fourth outcome would be best represented as the dollar difference of the cost of each β-lactam antibiotic prescription following de-labeling compared to the theoretical cost of the alternative antibiotic most likely to have been prescribed had the participant still carried the penicillin allergy label.

Discussion:

This project provides an opportunity to evaluate the necessity for allergy testing in cases where patients are labeled as having a penicillin allergy following a remote and mild reaction. By removing erroneous or outdated labels, the patient can be provided with better, more accurate care and the healthcare system can benefit from reduced costs. The results could also suggest that there is a safe way to implement effective penicillin allergy testing without the need for direct supervision by allergists, allowing for a framework that can be safely used by smaller healthcare centres that do not have a specialist on hand at all times. These cost-saving and improved patient outcomes could be realized in smaller communities all across Canada.

The major limit to this study is the fact that the allergy clinic in Brandon has only been active since September 2019, so long term outcomes are currently unclear, although patient follow up for delayed reactions is part of the testing process. The population is small due to both the relatively short time the clinic has been active and the fact that the clinic only serves the surrounding community. There is no national or international patient data available for this study. Finally, several studies have shown that even once a patient is de-labeled, the penicillin allergy label can remain on their charts.[7,8,11] This means that the practical effect of de-labeling can be hindered by a lack of follow up on the patient's records. At the Brandon Penicillin Allergy Testing clinic, multiple letters are provided to the patient's family doctor, pharmacy of choice, or hospital pharmacy to attempt to update their medical record that an OC was performed and they are not at risk for anaphylaxis from β-lactam antibiotics. In the near future, wallet-sized cards will be provided for individuals who were successfully de-labelled to carry on them at all times. These methods should help to counteract this limitation.

The cost-savings potential of de-labeling false penicillin allergies is clear based on previous studies that indicate that de-labeling leads to reduced direct costs by use of less-expensive antibiotics as well as indirect costs via shorter hospitalizations and reduced infections after surgery.[1,6,7,9-11] The benefits of de-labeling also extend to better care for the patients as it reduces the risk of cultivating antibiotic resistant infections that arises from the use of broad-spectrum alternative antibiotics.[1,3,5-9] This chart review could illustrate the effectiveness of the Brandon Penicillin Allergy Testing Clinic and demonstrate a safe protocol for other centres to use where there is no easy access to a board certified allergist. The results could therefore allow for further cost savings and antibiotic stewardship regardless of the presence of an allergy specialist.

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