The Effect of Providing Stratification of Low Risk Penicillin Allergies on Penicillin Allergy Label Removal

Cosby Stone, Jr. MD, MPH
Mentor: Elizabeth Phillips, MD
Vanderbilt University Division of Allergy, Pulmonary and Critical Care Medicine
1161 21st Ave so T-1218, MCN
Nashville, TN 37215
cosby.a.stone@vumc.org
elizabeth.j.phillips@vanderbilt.edu

Revision Date: August 17, 2018

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1.0 Background

Up to 20% of the US population carries a label of penicillin allergy, the most commonly reported medication allergy. However, in the presence of appropriate skin and oral challenge testing in current practice only 4% or less of these allergy labels can be verified as accurate. Because most patients reporting allergy to penicillin aren't actually allergic their reported allergy leads to unnecessary avoidance of penicillins, treatment with less effective 2nd and 3rd line antibiotics with more side effects, and worsened outcomes. At Vanderbilt, in current practice, only 13.4% of patients ever get their penicillin allergy label removed, despite up to 96% being potentially able to tolerate a penicillin safely.

When asked about their history of penicillin allergy, most patients report symptoms that are considered low-risk by specialists in allergy. Low-risk penicillin allergies are routinely challenged by allergy doctors with test dose challenges, meaning a small dose of amoxicillin is given and the patient is observed. Patients who tolerate the medication during observation have their allergy label to penicillin removed from the chart. Test dose challenges are known to be safe in low-risk patients and are recommended as a tool in penicillin allergy evaluation by the American Academy of Asthma, Allergy and Immunology. Unfortunately, test dose challenges are not performed as a part of routine practice outside of the field of allergy due to most physicians being unfamiliar with the features of low-risk penicillin allergy and the procedure of performing a test dose challenge.

Therefore, we developed a risk stratification tool validated on the outcomes of penicillin allergy testing in the Vanderbilt Drug Allergy Clinic that can help physicians to identify low-risk penicillin allergy patients who would successfully tolerate a test dose challenge.

Our objective is to increase the familiarity with penicillin allergy history taking among physicians, and the rate at which low-risk penicillin allergies are tested and removed in current practice.

We plan to perform a stepped wedge cluster randomized trial of this best practices intervention to provide risk stratification and test dose amoxicillin challenges in patients who are at low risk of having an ongoing penicillin allergy, using our internally validated risk stratification tool.

We anticipate that this study will provide evidence that our approach is an effective strategy by which to implement current guidelines recommending the use of allergy evaluations and test dose challenges in hospitalized patients with low risk penicillin allergy. We anticipate that the current study will lead to further studies in specialized populations with a more frequent need for antibiotics, such as transplant patients, cancer patients, and immune deficient patients.

Improvements in the management of penicillin allergy will provide significant direct and indirect benefits to patients, society, and the healthcare system.

2.0 Rationale and Specific Aims:

Currently it is estimated that at least 25 million people in the United States are labeled as penicillin allergic although less than 1.5 million of these are truly allergic. Although combined skin testing and oral challenge is an evidence-based de-labeling strategy the high burden of penicillin allergy labels means these services are available only through specialty allergy practices. There is therefore a need to provide evidence for alternative penicillin de-labeling strategies such as direct oral challenge. Previous studies have utilized quasi-experimental designs. Test dose challenges are currently recommended as a strategy for removal of low risk drug allergies, but the current experience is limited to single arm observational studies and evidence-based strategies for identifying low risk patients are lacking. Our objective is to demonstrate the benefit of providing risk stratification in removing penicillin allergy labels for low risk penicillin allergy patients in a randomized controlled trial.

We therefore aim to establish the safety, effectiveness, and impact of single dose oral challenge as a testing strategy to remove the label of low-risk penicillin allergy.

3.0 Inclusion/Exclusion Criteria

- Inclusion Criteria:
    - For Pilot Study: VUMC patients age 18 or older with a penicillin allergy reported in their chart and are medically stable, currently admitted to ICU.
    - For the RCT: VUMC patients age 18 or older with a penicillin allergy reported in their chart, and are medically stable, currently admitted to stepdown unit or regular floor bed.
- Exclusion Criteria: Patients with a penicillin allergy reported in their chart, but who are currently medically unstable. Patients whose primary care is not at Vanderbilt.

4.0 Enrollment/Randomization

Patients with penicillin allergy listed in their chart and admitted to a medical unit qualifying for intervention or control group during the study period will be enrolled in the study to the respective group that their unit is assigned to, with waiver of consent/authorization.

An initial pilot study will be performed in the medical ICU to demonstrate safety in a setting with the highest level of acute nursing and skilled support.

During the trial, randomization will occur using a stepped wedge cluster randomized controlled trial design. Medical units at VUMC will assigned to clusters. A single cluster will be selected for intervention at the outset of the trial. Subsequent additional clusters will first contribute to the control group, and be selected to randomly cross over to the intervention group at regular intervals of 2 months.

Randomization by medical unit with a stepped inclusion of additional medical units over time is the most equitable way of providing the study intervention, which we expect will provide a significant benefit compared to standard of care.

As penicillin allergy is a diagnosis that can affect people across differing age, sex, race/ethnicity backgrounds, we fully expect that patients will receive equitable inclusion due to the randomized nature of our study.

5.0 Study Procedures

Pilot Study: The teams caring for eligible penicillin allergic patients admitted to the ICU will be provided with the study intervention, as described below.

Control Arm: The current standard of care in hospitalized patients with reported penicillin allergy is to do nothing, versus direct challenge with amoxicillin when an allergy history is perceived to be sufficiently low risk, versus obtaining an allergy consultation for help with management, at the discretion of the primary team. Hence, no intervention will be provided.

Intervention Arm: The intervention will provide access to a best-practices alert containing a penicillin allergy risk stratification tool and an oral amoxicillin test dose challenge orderset for patients who stratify as low risk. The risk stratification tool has been demonstrated retrospectively to have a >99% (95% CI 96.4,99.9) negative predictive value for the presence of penicillin allergy in those who stratify as low risk. Test dose challenges are a recommended part of routine practice in patients who report allergy but have symptoms that are low risk for true or ongoing allergy.

Scenario: For patients who qualify for intervention in a unit randomized to intervention, the following best practice alert or a similar alert will be provided to the rounding physician.

"Did you know that 96-99% of patients of patients labeled as allergic to penicillin can safely tolerate these drugs? Use our tool to determine if your patient is low risk (<1% likely to have a positive allergy skin test) and can be considered for a potential challenge with amoxicillin to remove this allergy label. (Link to tool)."

The embedded link will provide an online risk stratification tool that will allow treating physicians to assess if their patient is low risk. For patients who stratify as low risk, information on oral challenges with amoxicillin and the name of an order set that contains the necessary elements for an oral challenge with amoxicillin will be provided (250mg amoxicillin PO x 1 dose, epinephrine at bedside, vital signs at baseline and q 30 minutes x 2.) For patients whose penicillin allergies stratify as higher or highest risk, information will be provided on the management of these penicillin allergies, with or without consultation from the allergy service. **Treatment decisions on whether to act on the provided information will be made by the treating physician and the patient.**

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Data and Safety Monitoring: Given there are minor potential risks to participants in the proposed trial with waiver of consent, it will be performed with monitoring and review by Vanderbilt University Medical Center IRB and under the guidance of the Vanderbilt Institute for Clinical and Translational Research. We propose to implement an overseeing data and safety monitoring plan that includes the appointment of Dr. Todd Rice, MD as an independent data safety monitor.

Investigator Training and Involvement:
1) All investigators, research coordinators, and other staff will complete and maintain training in the protection of human research subjects.
2) All persons accessing trial data, will in addition to the above, complete appropriate institutional training.
3) The physician leader at Vanderbilt (Dr. Stone), will be available to treating physicians who might implement the best practice alert in order to provide additional information about the study, including risks, benefits and alternatives, and to answer questions as needed.
4) All investigators and staff involved with patient care will remain updated on issues related to patient rights and safety through educational programs and updates provided by the institutions.

Data Handling/Confidentiality
1) Training outlined above addresses issues of confidentiality in research.
2) All patients will be assigned a study number and de-identified upon entering the study. A master list linking the patient identifying information such as the electronic health record and de-identified study identification will be kept under double-lock and key at each site with an access log required for when the list is accessed. A computer that is password-protected and behind a restricted, locked office door will also be acceptable.
3) All patient records for the research study will be maintained on the HIPAA-compliant server where the completed case report forms are kept or similarly on the HIPAA-compliant cloud server for photographs. To ensure accuracy, data will be checked and reviewed by research staff. Audits of the data will be done by the Vanderbilt Coordinating Center to ensure quality and completion of the forms.
4) Only de-identified data will be electronically transmitted and this will be done using institutional encryption procedures.

Adverse Events
1) Exclusion criteria include patients who are currently medically unstable and unable to receive study procedures, or patients whose primary care is received outside of Vanderbilt University Medical Center. We know that by restricting inclusion to patients who receive the majority of their care at Vanderbilt that this will enable better long term monitoring of adverse events via the EHR.
2) All adverse events will be discussed with and evaluated by a physician investigator as soon as the subject or study personnel report them.

3) Adverse events including SAEs upon initial amoxicillin challenge or upon subsequent administration of penicillin class drugs in patients whose penicillin allergy label has been removed, or any unanticipated problems will be appropriately reported to the IRB, safety monitor, and NIAID. In addition to the IRB review of adverse events outlined above, the PIs will meet at least quarterly with staff to discuss any problems that arise that could compromise patient safety. Meetings will be held more frequently to quickly rectify problems if they arise. When necessary, the IRB will be consulted for further guidance. This is particularly true for reactions, which, in their most severe forms, threaten life or function. A serious AE (SAE) or serious adverse drug experience (SADE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening. 'Life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E6).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity (as per reporter's opinion)
- Is a congenital anomaly/birth defect
- Is another medically important condition. Important medical conditions that may not result in death, be life-threatening or require hospitalization may be considered as SAEs or SADEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events relevant to this trial are urticaria, angioedema, respiratory distress, prolonged nausea or vomiting after direct provocation testing with amoxicillin that might be the prelude to anaphylactic shock. [Code of Federal Regulations Title 21, Volume 5, 21CFR312.32, revised April 1, 2006].

4) The PI, staff, and the research coordinators (or qualified persons providing coverage) will be available 24 hours each day to participants and other investigators, should an emergency arise.

5) The Vanderbilt Coordinating Center will submit an annual safety and adverse event report to the NIAID program official and the Vanderbilt IRB.

7.0 Study Withdrawal/Discontinuation

Participants will contribute data to the study under conditions of waiver of consent/assent, as our intervention is an improvement upon best practices that poses minimal to low additional risk to participants compared to standard of care. **Treatment decisions on whether to act on the provided information will be made by the treating physician and the patient.**

Patients who seek to have their data removed from the study can do so at any time by contacting the study team.

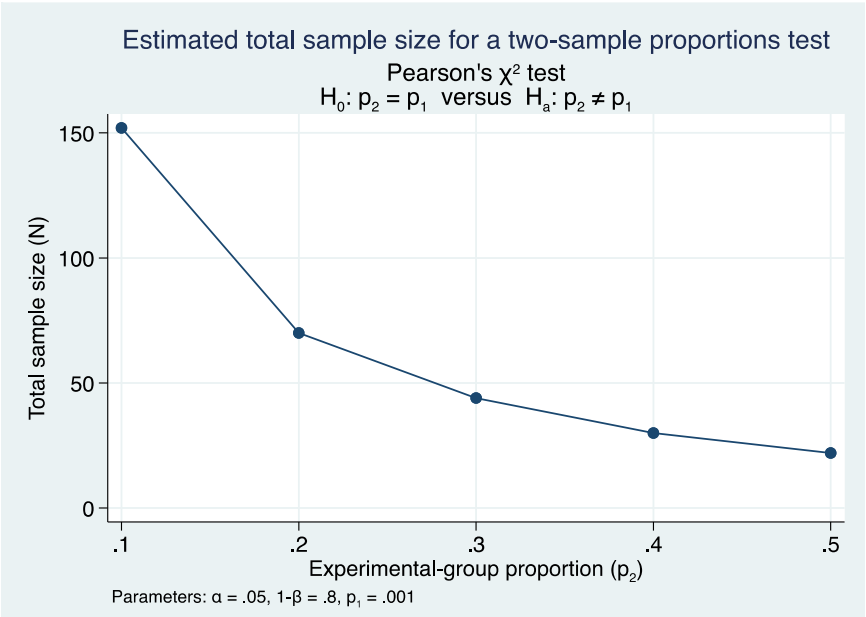
8.0 Statistical Considerations

Statistical Analysis Plan: Our primary endpoint will be the percentage of patients who had their penicillin allergy label removed prior to discharge, comparing those who received intervention versus controls. We will also assess the number of patients who

underwent oral challenge with amoxicillin in both arms. We will assess these outcomes using intention-to-treat analysis, with a Chi-squared test comparing two independent proportions.

Power and Sample Size Considerations: With no intervention, we assume 0.5% of patients have their penicillin allergy label intentionally removed or receive a test dose challenge during current practice in a six month period based upon preliminary data at Vanderbilt. We can power our study to detect a clinically meaningful difference of 20 additional penicillin-allergic patients per 100 having their penicillin allergy label removed using our intervention. Preliminary data suggest that around 100 patients per month are admitted and discharged from the 8N medical unit, and that 15-20% of all patients admitted at Vanderbilt have a penicillin allergy listed in their chart. Hence, approximately 15-20 penicillin allergic patients would be eligible for inclusion in the intervention group per month.

Assuming pessimistically that a minimum of 10% of patients randomized to intervention will have their physician engage with the tool, leading to an allergy label removed, and that 0.1% of patients in the control group will have a penicillin allergy label removed during current practice, 1:1 allocation of participants, an alpha of 0.05, power of 0.8 and a two-sided test of proportions, we will need a minimum of 35 patients per group (70 total) to detect a minimally clinically meaningful 20% increase in penicillin allergy label removals or amoxicillin challenges. Much smaller sample sizes will be needed to see effects if higher engagement and utilization is observed.



alpha	power	N	N1	N2	delta	p1	p2
.05	.8	152	76	76	.099	.001	.1
.05	.8	70	35	35	.199	.001	.2
.05	.8	44	22	22	.299	.001	.3
.05	.8	30	15	15	.399	.001	.4
.05	.8	22	11	11	.499	.001	.5

Our study will be intentionally overpowered for the primary outcome of penicillin allergy label removal, in order to try and capture the effect of this intervention upon secondary outcomes of 1) Frequency of risk stratification tool usage by physicians, 2) Any reported adverse events associated with oral challenge, 3) Communication about penicillin allergy label removal in the discharge summary. 4) longer term assessment of durability of label removal (3, 6 and 12 months following label removal) 5) antibiotic utilization and use and tolerance of penicillins following label removal at 3, 6 and 12 months.

9.0 Privacy/Confidentiality Issues

All data collected from patient medical records or through the risk stratification tool will be kept in a REDCap database which can only be accessed by key study personnel who have been given access and have a login and password. Identifiable information will not be linked or shared to data collected. All identifiable information will be stored in a study binder in a locked cabinet or within RedCAP. Only the PI and KSP on the study will have access to this information. Upon discontinuation of the study, the database will be purged of identifiers and kept within the HIPAA compliant RedCAP system. Therefore, we perceive the risks to privacy to be minimal.

We have developed our penicillin allergy risk stratification tool into a secure online questionnaire with data collecting ability within the RedCAP system, such that it can now serve as both an interactive educational tool for physicians and also collect data. This tool and others to be developed will be utilized by KSP during retrospective chart review, as a means for collecting relevant data related to risk stratification and validating the instruments.

The only identifier collected by the current RedCAP risk stratification tool itself is the medical record number, to allow linkage with other data that will be collected in a separate, secure RedCAP database. A copy of the RedCAP risk stratification questionnaire is attached separately in file PenicillinAllergyRiskStratific.pdf.

The anticipated benefits to patients are much larger. Access to the information will allow us to determine the effectiveness of our proposed intervention compared to current practice in a pragmatic, patient-oriented, real world setting. Removal of unnecessary penicillin allergy labels, in turn, has impacts on major patient impacts as described on previous pages of this application.

10.0 Follow-up and Record Retention

Study Duration will be 18 months total, with 12 months in which intervention will be provided.

All data will be de-identified prior to any analyses and data sharing. Data from the study will eventually be published but no identifiers will be mentioned as they will be kept separate once the collection of data is complete. Only authorized study personnel will have access to this information. PHI will no longer be accessed upon closure of the study, at which point any patient identifiers in the database will be deidentified.

Paper versions of any data will be destroyed upon completion of the study.

Electronic data will be stored indefinitely in a secured server using the RedCAP system.