STUDY TITLE: Oral Penicillin Challenge in the Pediatric Emergency Department

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Children's Hospital and Health System™

INSTITUTIONAL REVIEW BOARD SUMMARY

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STUDY TITLE: Oral Penicillin Challenge in the Pediatric Emergency Department

A. PURPOSE OF THE STUDY

The purpose of this study is to utilize a parent-reported penicillin allergy questionnaire in a pediatric emergency department (PED) and demonstrate that providers will administer, and families will be willing to receive an oral penicillin challenge in those children deemed to have non-allergic and low-risk symptoms of true penicillin allergy.

B. HYPOTHESES / SPECIFIC AIMS

Aim 1: Demonstrate that a low-risk group of children with reported penicillin allergy will complete an oral penicillin challenge during a pediatric emergency department visit.

Hypothesis 1a: Providers will administer an oral penicillin challenge in the PED to children identified as having non-allergic and low-risk allergy symptoms.

Hypothesis 1b: Children with non-allergic and low-risk allergy symptoms will complete an oral penicillin challenge in the PED.

Aim 2: Conduct follow-up one day after oral challenge for all children and seven days after oral challenge for patients discharged with a prescription antibiotic to determine if a delayed or T-Cell mediated reaction occurs after exposure to multiple doses of penicillin or any other antibiotic prescribed at discharge.

Hypothesis 2a: Next day contact will be possible for over 95% of children who complete an oral challenge to demonstrate the ability to evaluate symptoms after PED discharge.

Hypothesis 2b: Seven-day follow-up will be completed in at least 90% of children who are discharged on a penicillin or other antibiotic to demonstrate the ability to monitor for delayed or T-Cell mediated reaction following the administration of multiple doses of penicillin.

Aim 3: Examine health care outcomes and prescription-related costs associated with illness treatment plans in children who are de-labeled as penicillin allergic after an oral challenge.

Hypothesis 3a: Health care outcomes (allergic reactions, number of illnesses, antibiotics prescribed, and ER/Urgent Care/Primary care visits) will be similar between children de-labeled as penicillin allergic compared to the general population.

Hypothesis 3b: Prescription-related costs associated with illness treatment plans will be significantly less in children de-labeled as penicillin allergic.

C. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Children often present to the pediatric emergency department with a parent reported allergy to medications. Allergy to an antibiotic in the penicillin family (hereafter termed penicillin) is the most commonly reported medication allergy, reported in 5-20% of patients.[1-6] Since physicians and advanced practice providers (hereafter termed providers) rely on these patient/parent reported allergies when making treatment decisions, a large group of patients are denied first-line antibiotic therapy due to misunderstood or misdiagnosed penicillin allergy. [7] As a consequence, patients are prescribed second or third line medications that are more expensive and not the antibiotic of choice for their bacterial infection.[8,9] An example of the health risks associated with

reported penicillin allergy was highlighted by Macy et al who found that, "A penicillin "allergy" history, although often inaccurate, is not a benign finding at hospital admission. Subjects with a penicillin "allergy" history spend significantly more time in the hospital, are exposed to significantly more antibiotics associated with Clostridium difficile (C. diff) and Vancomycin-Resistant Enterococci (VRE) and are associated with increased hospital use."[9] Additionally it has been shown that de-labelling patients reported to have penicillin allergy can lead to decreased prescription costs with very low rates of subsequent adverse reactions.[10] Specific to penicillin allergy, greater than 95% of patients may actually tolerate a penicillin, either because they were never allergic or because they had an earlier allergy that subsequently resolved.[11]

Our prior work utilized a novel structured penicillin allergy questionnaire in the PED and found that 76% of the children with penicillin allergy reported by families had exclusively low-risk allergy symptoms for true allergy (Table 1).[12] These symptoms were often adverse reactions, inconsistent with true allergy.[13-15]

Table 1: Categorization of Allergy Symptoms

Low Risk Group		**High Risk Group**	
Non-Allergic Symptoms	**Low-Risk Symptoms**	**High-Risk Symptoms**	
Runny nose	Rash	Facial swelling	Seizures
Diarrhea	Itching	Difficulty breathing	Rash*
Headache	Dizziness	Lip swelling	Itching*
Vomiting with med administration	Vomiting	Wheezing	Vomiting**
	Nausea	Throat swelling	Abdominal pain*
	Cough	Skin peeling	Serum Sickness
	Family History	Mouth blisters	Fever
		Drop in BP	
		Syncope	

*Within 1 hours of Antibiotic Administration
**Multiple episodes of vomiting within 1 hour

Traditional penicillin allergy testing utilizes a standard 3-tier testing process, which involves first performing a percutaneous skin test, followed by more sensitive intracutaneous testing and finally an oral drug challenge which ultimately determines whether or not the drug hypersensitivity exists.[16] This process tests only for IgE mediated allergy, however studies have shown that less than 2% of patients tested in this fashion will show signs of an allergic reaction upon re-exposure to the medication.[10,17] This process is the gold standard for diagnosing penicillin allergy, yet it is time consuming, expensive and painful. In our prior study we assessed the ability of our questionnaire to identify a low-risk population capable of taking penicillin without an allergic reaction, we performed the standard 3-tier test on 100 children presenting to the PED with low-risk symptoms on a parent-reported penicillin allergy questionnaire; all 100 (100%; 95% CI 96.4% - 100%) children were negative for penicillin allergy after oral challenge.[18] These preliminary studies lay the groundwork for providing a penicillin oral challenge in the PED and highlight the questionnaire's ability to identify a very low risk group for penicillin allergy, and to provide a safe alternative to time consuming, costly and painful skin testing for select patients.

Since the time our study was completed, several additional studies have shown the safety and utility of both single dose and extended dose (5 day) penicillin oral challenges. A study completed by Mill et al published in JAMA Pediatrics gave graduated oral penicillin challenges to 818 children as the initial test to evaluate for penicillin allergy.[19] They found that 48 children (5.8%) had reactions, all of which were not serious nor life threating. A second study completed by Confino-Cohen et al gave 5-day oral penicillin challenges to 417 patients, and partial oral penicillin challenges (2-4 days) to an additional 44 patients.[20] Out of these 461 patients, 30 had mild, non-life-threatening reactions that consisted or mild rash or pruritis. These studies highlight that single dose and extended dose (5 day) penicillin oral challenges are safe and effective in de-labeling penicillin

allergy. We believe that by utilizing our questionnaire to segregate patients into a low-risk group for a PED oral challenge we are adding additional safety to a practice that has been shown to be safe and effective in the literature.

An estimated 65,000 children per year are seen in our PED and approximately 10% (6,500) report penicillin allergy. The majority are not allergic and are unable to go to the allergy clinic for testing due to the time required and other variables (insurance/cost). We have considered completing this study in the allergy clinic and CHW TRU, however with that model we are missing a substantial number of children who are reportedly allergic to penicillin but could not otherwise be de-labeled as penicillin allergic. The long-term goal of this project is to complete a multi-center PED study utilizing the questionnaire to identify low-risk children who can tolerate an oral challenge in the PED. We believe that our results and other studies have shown that giving an oral challenge with penicillin to a selected low-risk population is safe, effective and worthy of further research.

The study team for this project includes experts in Pediatric Emergency Medicine, Allergy and Immunology and Infectious Disease. Dr. Brousseau is a Professor of Pediatrics, Section Chief and Research Director of Pediatric Emergency Medicine at the Medical College of Wisconsin and an R01-funded investigator. Dr. John Routes is the Section Chief of Allergy and Immunology at the Medical College of Wisconsin. Dr. Asriani Chiu is an allergist and the director of the Asthma and Allergy Clinic since 2011, her areas of interest include drug allergy and anaphylaxis. Dr. Marianna Castells is the director of the Adverse Drug Reaction and Desensitization Program for inpatients and outpatients at Brigham and Women's Hospital. Dr. Castells is an independent basic science investigator with a primary research interest in mast cell inhibitory mechanisms. She is viewed as one of the national experts on IgE mediated drug reactions. Dr. Elizabeth Phillips is an Infectious Disease specialist and is a Professor of Medicine and the Director of Personalized Immunology, Oates Institute for Experimental Therapeutics at Vanderbilt University. Dr. Phillips is an expert on variation in drug responses, in particular interactions between drugs and the immune system. The study team has been involved in the creation of this protocol and have rigorously reviewed and approved it with patient safety being viewed as the highest priority.

D. DESIGN AND METHODS

Objective

Our primary objective is to demonstrate the feasibility of utilizing a novel penicillin allergy questionnaire in the PED to identify a low-risk group of patients who will complete an oral challenge in the PED to test for an IgE-mediated allergic reaction. This project will begin as a single site feasibility study, however including up to 2 other collaborative sites for enrollment has been favorably discussed. We do not anticipate this to be a single IRB scenario and will submit a timely comprehensive amendment if plans become concrete and the initial data here proves reliable.

Our secondary objective is to examine whether health care outcomes and prescription-related costs are comparable between children who are de-labeled as penicillin allergic after an oral challenge compared to a standard of care group who are not challenged in the PED.

Aim 1: Demonstrate that a low-risk group of children with reported penicillin allergy will complete an oral penicillin challenge during a pediatric emergency department visit.

Design/setting:

This will be a prospective study of children (2-16) presenting to the PED at the Children's Hospital of Wisconsin with a child or parent reported allergy to penicillin.

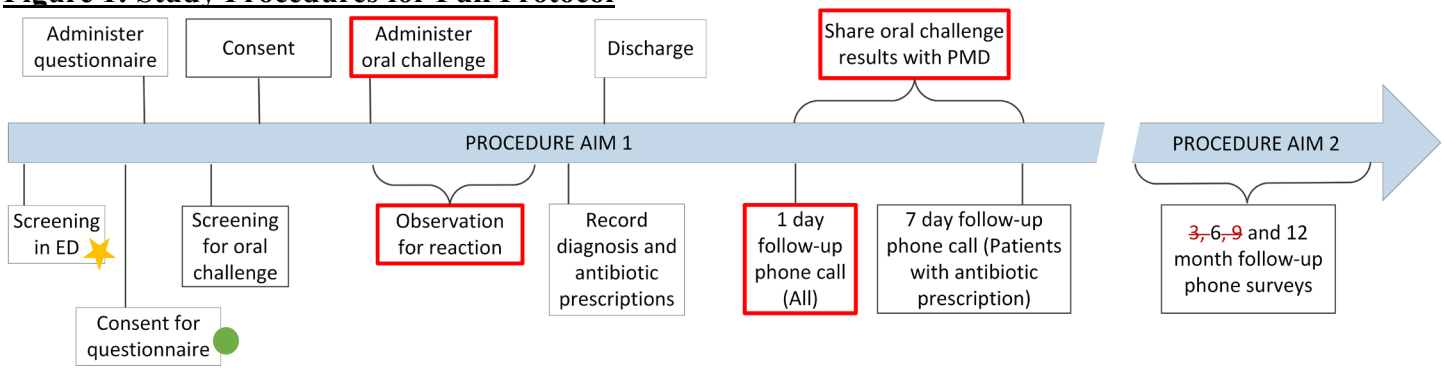
Population:

Inclusion Criteria: Children aged 2-16 with a parent/guardian (hereafter termed parent) reported history of allergy to a penicillin antibiotic in which the reported allergic reaction occurred at least twelve months prior to the current PED visit.
Exclusion Criteria: Children will be excluded:

- If they have a history of severe developmental delay or inability to communicate the effects of an allergic reaction (non-verbal). ED care team discretion can be utilized to determine ability to proceed with study with regards to developmental delay.
- History of a severe allergic reaction to skin tests
- Anaphylaxis in the past six weeks
- Current pregnancy
- Child is currently on a beta blocker medication
- Children who present to the PED with a rash
- Children who present with multiple episodes of vomiting on day of presentation
- Children presenting to the ED for asthma exacerbation
- Patients deemed too acutely ill for participation as deemed by the ED patient care team
- Non-English speaking families
- Wards of the state, in foster care or police custody or detention will be excluded.

Study Procedure (Figure 1):

Figure 1: Study Procedures for Full Protocol



[1]*Red boxes indicate oral-challenge-only study procedures*

Nursing and research staff will screen for questionnaire eligible patients
If nursing questionnaire is not done, research staff to obtain consent for the questionnaire

1) Trained research staff will review the medical records of children in the PED for reported penicillin allergy and other inclusion/exclusion criteria and discuss any patient with the treating attending physician/nurse practitioner/physician assistant. If nursing has administered an allergy questionnaire (on secure CHW computers in the EDTC directly into EPIC), the study team will approach eligible patients (as determined by the nursing questionnaire results in EPIC) to obtain consent/assent for the oral challenge only.

2) If the nursing staff did not implement the questionnaire, research staff will approach for consent/assent including both the questionnaire and the oral challenge per the full protocol. They will also express that their PED physician/nurse practitioner/physician assistant is available to answer any clinical questions the family may have and will facilitate that contact if requested. The Oral Challenge consent will also ask permission to contact families for later follow-up as outlined in Aim 3.

3) Research staff is present in the PED 16 hours per day on weekdays and 10 hours per day on weekends allowing for more than sufficient coverage to meet enrollment goals. We will limit administration of the oral challenge to 3 patients per day in an attempt to limit PED flow disruption. Administration of the questionnaire alone should not be disruptive to flow.

4) The questionnaire includes a "yes/no" option about interest in an oral challenge with penicillin if the patient is deemed eligible. Patients who indicate an interest will have their chart and the questionnaire results reviewed by the PED physician/nurse practitioner/physician assistant . If the parent reports the child had symptoms of allergy that place them into a low-risk group for true allergy, they will be eligible to be offered an oral challenge in the PED. If any high-risk symptom of allergy is identified, no oral challenge will be offered (Table 1). For patients with complex past medical histories or symptoms listed as "other", their chart will be reviewed by the PED physician/nurse practitioner/physician assistant, and their eligibility to be tested will be determined before proceeding at their discretion.
5) If the parent/child agree to an oral challenge and are deemed to be in the low-risk group, then a separate consent and assent will be signed at that time. The consent will also give permission to contact families for later follow-up as outlined in Aim 3.
6) Patients who are consented and determined eligible for the oral challenge will receive a 500-mg oral challenge with amoxicillin in either tablet, chew tablet or liquid form depending on patient preference. All the ED faculty and fellows will be trained on the study protocol and documentation of that training will occur. Only trained providers will order study medications. The Research Assistants will be in attendance of the enrollment and will be fully trained in the protocol to assist with compliance. Nursing meetings will be attended in all 3 shifts to give in-person trainings of our ED nursing staff as well. Just-in-time training/reminders will be provided by the research assistants at the time of any enrollment. Only study PED physician/nurse practitioner/physician assistant will order study medications in the ED. Nursing staff will be trained on the study and will administer the medication under the supervision of the study trained attending.
7) Following the challenge patients will be observed for 60 minutes for signs of allergic reaction, consistent with the duration of observation time in the department of Allergy and Immunology. They will be sent home with a special set of discharge instructions relevant to tracking for late reactions and resources to call for support if they have questions.
8) Patients who complete the oral challenge will be provided with a $50 gift card.
9) If there is a serious or anaphylactic reaction, emergency medicine will be given right away. The medicine is called epinephrine and comes in an Epi-Pen. Additional medications that could also be given include steroids, Benadryl, Zantac, and IV fluids. If a reaction occurs that requires emergency medicine the patient or the patient's insurance are liable for the cost of this continued treatment. Their liability also includes any copay that may associated with the use of their insurance or if insurance does not cover the inpatient hospitalization. The potential costs for treating a reaction in which a patient is hospitalized may be thousands of dollars. However, we believe the risk of this occurrence to be very low as the incidence of true IgE mediated penicillin allergy is estimated to be in the range of 0.004% to 0.015%.[21,22] Additionally, those children deemed low-risk on our questionnaire, likely never had an IgE mediated allergic reaction to begin with and are most likely falsely labeled as penicillin allergic. Families are also notified in the Oral Challenge consent and assent to call 9-1-1 and seek immediate medical attention if any serious reaction occurs after their child leaves the ED.
10) At the end of the visit the diagnosis will be recorded, and treatment/discharge will continue at the discretion of the PED physician/nurse practitioner/physician assistant . All patients who receive an oral challenge will be given an Allergy Oral Challenge Information sheet.
11) If a child is negative after oral challenge and has no need for an antibiotic at the time of discharge, the child will be discharged home.
12) If a child is negative after oral challenge and treatment would indicate a penicillin antibiotic, the child will be discharged home with a penicillin antibiotic.
13) Family contact information will be obtained in the questionnaire and utilized to complete follow-up phone calls after PED oral challenge.
14) The patient's PMD (primary medical doctor) and pharmacy of record will be notified of the testing and results via fax within 7 days. Fax confirmations will be kept by the study team in the patient's research file.

<u>Aim 2:</u> Conduct follow-up one day after oral challenge for all children and seven days after oral challenge for patients discharged with a prescription antibiotic to determine if a delayed or T-Cell mediated reaction occurs after exposure to multiple doses of penicillin or any other antibiotic prescribed at discharge.

Design/setting and study population:
This study will include all children from Aim 1 who underwent an oral challenge in the PED after being determined to have low-risk symptoms on the allergy questionnaire.

Study Procedure (Figure 1, Aim 2)
1) A follow-up phone call will be made to all families whose child received an oral challenge.
2) If a family receives a one-time dose of antibiotic but does not receive a prescription for a penicillin antibiotic then they will be called on day 1 by a research team member who will administer a 5-minute allergy questionnaire that will review any possible symptoms of allergic reaction following the ED visit.
3) If a family receives a penicillin antibiotic prescription following the oral challenge, then they will be called on days 1 and 7 by a research team member for a 5-minute allergy questionnaire that will review any possible symptoms of allergic reaction following the ED visit.
4) The patient's primary medical provider will also be notified of the oral challenge results for both groups of patients via fax within 7 days of the oral challenge date.

<u>Aim 3:</u> Examine health care outcomes and prescription-related costs associated with illness treatment plans in children who are de-labeled as penicillin allergic after an oral challenge.

Design/setting and study population:
This study will include children identified as having low-risk symptoms of allergy from Aim 1 who underwent an oral challenge (Group 1), and those who did not undergo an oral challenge in the PED (Group 2).

Study Procedure (Figure 1, Aim 3)
1) A follow-up 5-minute phone survey will be completed by research staff to the family. This follow-up will occur after their initial PED visit at 6 and 12 months.
2) The follow-up survey will include questions on health care outcomes since the PED visit that include but are not limited to: the number and type of diagnosed infections, number and type of antibiotics given, and allergic reaction history.

E. TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR THIS STUDY AT THIS SITE AND GLOBALLY. WHAT ARE THESE NUMBERS BASED ON?

We have determined that we need 100 low-risk patients to complete the oral challenge at each of the three sites participating including here at Children's Hospital of Wisconsin. We will consent for questionnaire-screening approximately 500 children to achieve that number. This number is based off of our previous study; during that study 50 patients were approached per month for survey participation, 80% (40) agreed to participation, and 25% (10) of patients were found to have high-risk symptoms of allergy and thus were found to be ineligible. If 50% of patients with low-risk symptoms will have either provider/family refusal to oral challenge this will leave approximately 15 patients per month to complete an oral challenge and complete this portion of the study in approximately 7 months.

F. DRUGS OR PROCEDURES

Patient's family or guardian will be asked to answer an allergy symptom questionnaire that will be administered via an iPad. Patient's charts who are between the ages of 2-16 whose family has indicated an interest in allergy oral challenge will be reviewed.

If a child is eligible as defined in the questionnaire for allergy oral challenge and the family completes the challenge, then a gift card in the amount of $50 will be provided for their time.

If a family completes all the telephone follow-up questionnaires at 6 and 12 months they will be mailed a $25 gift card at the conclusion of each of the follow-up calls. (total of $50 in follow-up stipends for full participation over one year.)

The allergy challenge consists of an oral amoxicillin challenge in the PED. A nurse will administer the oral challenge and will also be present during the process all of which will occur in the PED.

A follow up telephone survey monitoring for any adverse side effects/allergic reactions will be completed within 24 hours of the allergy oral challenge. If a patient receives a prescription for a penicillin or any other antibiotic then a follow up call will be made to monitor for any adverse side effects/allergic reactions at 7 days as well. Patients will also receive discharge instructions relevant to the study with phone numbers to call with questions.

A follow-up 5-minute phone survey will be completed by research staff to families of groups after their initial PED visit at 6 and 12 months. PI will review these results monthly or as relevant (notified by the study team) to monitor the long-term outcomes and safety of the protocol.

G. RISK CATEGORY:

(2) 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

H. RISKS AND THE PRECAUTIONS WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE

All parents/children who complete the survey are at risk for the loss of privacy and confidentiality of personal and health information. To protect the patient's confidentiality, a study ID number will be assigned to each patient and they will only be identified using this number. A master key will be kept password protected on a secure server. The files will be kept in a secure password protected file

For children who undergo allergy oral challenge, the risks and side effects related to this challenge include:

- These do not happen often but can lead to death if they are not treated. Patients and Families are instructed to tell the nurse or doctor right **away** if the child has any of the following allergy symptoms:
    - **Hives**
    - **Swelling-** Any part of the body, inside or out. This includes the mouth, tongue, and throat. It can be one or many parts of the body.
    - **Breathing problems-** Shortness of breath, coughing, wheezing, or chest tightness.
    - **Other-** Sneezing that does not stop, feeling dizzy, sick to the stomach, or just not feeling right.
    - **Anaphylactic shock possibly leading to Death-** This is rare but is the most serious allergic reaction.

If there is a serious or anaphylactic reaction in the ED, epinephrine (i.e. an Epi-Pen) will be given immediately, as well as histamine blockers and intravenous fluids as needed. Patients who require medical intervention will be stabilized in the emergency department. If a reaction occurs that requires ED treatment or inpatient hospitalization, the patient or the patient's insurance are liable for the cost of this continued treatment. Their liability also includes any copay that may associated with the use of their insurance or if insurance does not cover the inpatient hospitalization. The potential costs for treating a reaction in which a patient is hospitalized may be thousands of dollars. However, we believe the risk of this occurrence to be very low as the incidence of true IgE mediated penicillin allergy is estimated to be in the range of 0.004% to 0.015%. Additionally, those children deemed low-risk on our questionnaire, likely never had an IgE mediated allergic reaction to begin with and are most likely falsely labeled as

penicillin allergic. All of this will be made clear by the study team at consent. Families will receive study specific discharge instructions with phone numbers for contact/support at home. Additionally, patient's PMD's will be notified of the testing and results via fax within 7 days.

I. PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS *(confidentiality, health and financial risks)* AND TO MAINTAIN THE CONFIDENTIALITY OF DATA

To protect the patient's confidentiality, a study ID number will be assigned to each patient and they will only be identified using this number. A master key will be kept password protected on a secure server. The files will be kept in a secure password protected file. Paper copies of study materials are kept in secure, access limited, locked drawer space in the ED at the Research station until the RA's are done with them and then they are moved up to C550 also to locked cabinets in our secure suite. The data that is entered into the electronic tablet will not be stored on the tablet but be transmitted via the encrypted CHW server directly to the RedCap data website. Data kept electronically here such as our screening and enrollment logs will be kept on the secure MCW server with limited access by our research team only.

J. PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE

All adverse events associated with allergy oral challenge will be monitored in the study protocol and reported to the study principal investigators in real time. The patient will be observed immediately after the administration of the oral challenge for signs of allergic reaction such as rash, airway compromise, increased irritability or any other change in status. Prior to discharge from the Pediatric ED patients will again be assessed for any adverse effects of the allergy challenge. True IgE mediated allergic reactions of penicillin are reported to occur less than 0.0014% of the time. However, there is a possibility that an allergic reaction may occur. Dr. Vyles, Dr. Brousseau, Dr. Chiu and Dr. Routes will review the data after any reaction requiring ED care. If a patient requires treatment in the PED or inpatient hospitalization following allergy oral challenge this will be reported to the IRB as a serious adverse event. The study investigators will also review the data after every reaction to determine if there is a pattern of questionnaire responses that could predict a reaction. If we determine/suspect any specific low risk patient symptoms are predisposing the population to a systemic reaction, it will be removed from the questionnaire as "low risk" and transferred to the "high risk" symptoms where patients are not deemed testable.

K. ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL *(value or desired outcome / advantage)* TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY *(medical, psychosocial, altruistic)*

Benefits to Participants: If patients agree to take part in this study, there is a potential direct medical benefit to the patient in knowing whether or not they are truly allergic to penicillin. From the survey: we will have a better understanding of the symptoms that lead to a report of antibiotic allergy. This won't lead to direct benefit to the child. From the challenge: if they are found not to be allergic it increases the ability to prescribe a class of antibiotics that is often the first line for common pediatric bacterial illnesses. Benefits to Society: We anticipate the information learned from this study will identify a low risk population of patient's who report an allergy to penicillin and are actually not allergic. This would lead to a direct benefit to the medical community by increasing the ability to prescribe penicillin in the setting of common bacterial infection when someone has a reported allergy to penicillin. This not only provides the appropriate treatment of common bacterial infections but also is likely a more cost-effective approach as second- and third-line antibiotics are often more expensive with a wider range of antimicrobial activity leading to the development of resistance.

L. STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

The study will be stopped once our sample size has been accrued.

M. IS THERE A DATA SAFETY MONITORING BOARD IN PLACE? WHO ARE IT'S MEMBERS? HOW OFTEN DO THEY MEET?

Dr. Vyles will monitor for overall safety throughout the study duration and will review safety data each time 10 subjects are enrolled in the oral challenge group. The patient will be observed immediately after the administration of the oral challenge for signs of allergic reaction such as rash, airway compromise, increased irritability or any other change in status. Prior to discharge from the Pediatric ED patients will again be assessed for any adverse effects of the allergy challenge. Dr. Vyles, Dr. Brousseau, Dr. Chiu and Dr. Routes will review the data after any reaction requiring ED care. If a patient requires treatment in the ED or inpatient hospitalization following allergy oral challenge this will be reported to the IRB as a serious adverse event. The study investigators will also review the data after every reaction to determine if there is a pattern of questionnaire responses that could predict a reaction. If we determine/suspect any specific low risk patient symptoms are predisposing the population to a systemic reaction, it will be removed from the questionnaire as "low risk" and transferred to the "high risk" symptoms where patients are not deemed testable.

N. DESCRIBE HOW THE CONSENT AND ASSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED.

Trained research staff will review the medical records of children in the PED for reported penicillin allergy and other inclusion/exclusion criteria and discuss any patient with the treating attending physician. If nursing has administered an allergy questionnaire (on secure CHW computers in the EDTC directly into EPIC), the study team will approach eligible patients (as determined by the nursing questionnaire results in EPIC) to obtain written informed consent/assent for the oral challenge only.

If the nursing staff did not implement the questionnaire, research staff will approach for written informed consent/assent including both the questionnaire and the oral challenge per the full protocol. They will also express that their PED physician is available to answer any clinical questions the family may have and will facilitate that contact if requested. The Oral Challenge consent will also ask permission to contact families for later follow-up as outlined in Aim 3.

3) Research staff is present in the PED 16 hours per day on weekdays and 10 hours per day on weekends allowing for more than sufficient coverage to meet enrollment goals. We will limit administration of the oral challenge to 3 patients per day in an attempt to limit PED flow disruption. Administration of the questionnaire alone should not be disruptive to flow.

The appropriately trained research personnel will be identified in the registration page of this submission.

O. Statistical Analysis plan

Data collection and Management:

All children will be assigned a unique study ID number. Responses to the allergy questionnaire and oral challenge will be captured on a tablet computer. Data will be entered into RedCap (http://www.project-redcap.org/). Additional data points include child's age in years, child's sex, race/ethnicity (determined by parent and consistent with NIH guidelines) and visit number.

For children who receive an oral challenge, additional data will include the time of medication administration and time of discharge from the PED. The details of any reaction that occurred and corresponding treatment will also be captured. Final ED disposition will be recorded, and home contact information confirmed for follow-up.

Data Analysis:

Descriptive statistics will be used to summarize baseline patient characteristics, allergy questionnaire, and oral challenge data. The percentage of patients who are eligible for oral challenge will be determined. The percent

of patients/families that refuse an oral challenge or that have providers who are unwilling to conduct an oral challenge in the PED will be documented. The frequency of positive oral challenges will be analyzed and reported using a 95% confidence interval. Descriptive statistics will be used to summarize day 1 and 7 patient characteristics and follow-up questionnaire data. The percentage of patients that are lost to follow-up after an oral challenge will be determined. The frequency of delayed allergic reactions after oral challenge will be analyzed and reported using a 95% confidence interval. SPSS version 22 will be used to perform all analyses. SPSS version 22 will be used to perform all analyses.

Descriptive characteristics will also be used to summarize the baseline patient characteristics and follow-up questionnaire responses for months 6 and 12 of the children who underwent the oral challenge in Aim 1. We will then conduct a three-level economic cost savings analysis. First, in order to calculate the potential cost savings if amoxicillin is filled for all penicillin allergic de-labelled patients, the median retail price of each non-penicillin antibiotic filled will be compared to the median retail price of amoxicillin. Second, we will calculate the cost avoidance savings assuming that patients who fill any amoxicillin/penicillin prescriptions would have filled cefdinir in its place. Lastly, we will extrapolate the total cost savings potentially generated by the approximately 6,700 patients per year treated in our PED who report penicillin allergy.

Sample Size Justification/Power Analysis:
We have determined that we need 50 patients to complete the oral challenge for the feasibility study to be complete. We will consent for questionnaire-screening approximately 250 children to achieve that number. This number is based off of our previous study; during that study 50 patients were approached per month for survey participation, 80% (40) agreed to participation, and 25% (10) of patients were found have high-risk symptoms of allergy and thus were found to be ineligible. Assuming that 50% of patients with low-risk symptoms will have either provider/family refusal to oral challenge this will leave approximately 15 patients per month to complete an oral challenge. Of the 50 children who complete the oral challenge, we estimate that 40 patients will receive a one-time oral challenge and 10 patients will receive an oral challenge and be sent home with a prescription. This estimation is based off of our previous study where approximately 20% of children who were eligible and willing to be tested were discharged home with a prescription antibiotic. If we are able to reach our enrollment goal prior to approaching 500 patients, we will end the feasibility study.

P. FINANCIAL RELATIONSHIPS

The study is funded with internal funds from the section of Pediatric Emergency Medicine and a grant from the Children's Research Institute which support the costs of accomplishing the oral challenges and other associated project costs.

Q. ADVERTISEMENTS / FLIERS

N/A

R. BIBLIOGRAPHY *(list pertinent literature references)*

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