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The Safety, Accuracy, and Cost-Effectiveness of Confirmatory Penicillin Allergy Testing in the Outpatient Setting as a Means of Reducing Patient Morbidity and Mortality

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by

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Abstract

The purpose of this review is to investigate the prevalence of documented penicillin (PCN) allergies in health care and any negative outcomes associated with being labeled as such. Additional topics researched included the safety and accuracy of PCN allergy testing, the cost-effectiveness of PCN allergy testing versus using non-PCN related antibiotics, and barriers to confirmatory PCN allergy testing implementation. A complete review of the aforementioned topics included meta-analysis', systematic reviews, cohorts, clinical trials, and cross-sectional studies from the last five years. Databases utilized for this research included PubMed, Cochrane Review, Embase, Dynamed Plus, and ClinicalKey. Sources that were excluded from this review included opinion-based editorials and those that failed to include analytical review of scientific research. A total of 18 scholarly sources were utilized for this review. The research revealed a significant portion of the population is incorrectly labeled as having a PCN allergy when properly tested. It also showed that having a PCN allergy is associated with increased morbidity and mortality. Research related to PCN allergy testing indicated high levels of safety and accuracy. Also, PCN allergy testing costs were found to be significantly lower than those associated with using alternative antibiotics. Lastly, a majority of the barriers related to performing PCN allergy testing were largely due to a lack of education on behalf of medical providers and incorrect perceptions from both patients and medical providers alike. These findings together indicate that confirmatory PCN allergy testing in the outpatient setting is safe, accurate, and cost-effective in decreasing the morbidity and mortality associated with having an incorrect PCN allergy label. However, further research is needed to adequately address the barriers and incorrect perceptions both providers and patients possess related to PCN allergy testing.

Keywords: *penicillin allergy, β-lactam allergy, allergy testing, penicillin, penicillin testing, penicillin cost, and penicillin allergy risks.*

Introduction

Penicillin (beta-lactam) allergies are the most commonly reported antibiotic allergies in the United States, with 10% of the population being labeled as such. However, when tested for an actual PCN allergy, more than 90% of these patients test negative. Also, 80% of those patients with a true documented PCN allergy will eventually lose their initial allergy to PCN's after ten years (Kufel, Justo, Bookstaver, & Avery, 2019). This is significant as having a PCN allergy label forces clinicians to prescribe alternative and often more broad-spectrum antibiotics that are associated with increased adverse effects, increased medical costs, increased development of antibiotic resistance, and worse clinical outcomes (Kufel et al., 2019). These negative outcomes could be avoided if patients with PCN allergies were safely and accurately tested to confirm or deny the presence of an actual PCN allergy. Unfortunately, of those clinicians that have antibiotic allergy testing (AAT) services available to them, 40% were unaware of the specific types of testing available to them when surveyed (Trubiano et al., 2016). This is one of the barriers that prevents clinicians from referring patients for PCN allergy testing. The purpose of this study is to highlight the cost-effectiveness, safety, and accuracy of confirmatory PCN allergy testing in reducing the increased morbidity and mortality associated with having an unconfirmed documented PCN allergy.

Statement of the Problem

Patients with a history of PCN allergy are at an increased risk for also reacting to beta-lactam antibiotics in the cephalosporin and carbapenem groups. Specifically, there is a 5-10% chance of cross-reactivity to cephalosporins and a relatively low risk of reaction with

carbapenems at 1% (Papadakis, McPhee, & Rabow, 2019). Unfortunately, this removes three significant families of antibiotics that can be prescribed to a patient with an unclear or unconfirmed history of a PCN allergy. Avoiding use of beta-lactams or similar antibacterial agents due to a reported unconfirmed PCN allergy has been shown to increase hospital readmissions and adverse drug outcomes compared to patients without a PCN allergy (DynaMed Plus, 2018). Also, patients with a documented PCN allergy have an increased risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infections and *Clostridioides difficile* infections (CDI). This is unfortunate as the overall safety of PCN allergy testing has been well documented as being safe in many patients, including pregnant women, patients requiring organ transplants, and children (DynaMed Plus, 2018). This means that clinicians could safely and significantly lower the increased morbidity and mortality associated with having an unconfirmed PCN allergy label by recommending and referring patients for confirmatory PCN allergy testing in the outpatient setting.

Research Question

In otherwise healthy patients with an unclear or unconfirmed history of PCN allergy, would confirmatory PCN allergy testing in the outpatient setting versus using more broad-spectrum antibiotics not related to PCN's be more cost-effective and safer in limiting overall patient morbidity and mortality?

Methodology

Studies included in the review of research were limited to the last five years in both the United States and abroad. Editorials and other opinion-based articles were eliminated. Databases searched included: PubMed, Cochrane Review, Embase, Dynamed Plus, and ClinicalKey. MeSH terms used to populate relevant research included: *penicillin allergy, β-*

lactam allergy, allergy testing, penicillin, penicillin testing, penicillin cost, and penicillin allergy risks. The population of patients this research focused on included men, women, and children of varying ages with a documented PCN allergy in their medical records. Research studies reviewed included meta-analysis', systematic reviews, cohorts, clinical trials, and cross-sectional studies. This thorough review of studies ultimately focused on the prevalence of incorrect PCN allergies; the morbidity and mortality associated with having an incorrect PCN allergy; the safety and accuracy of PCN allergy testing; the cost-effectiveness of PCN allergy testing, and any barriers to the implementation of PCN allergy testing.

Review of Literature

An extensive and thorough literature review shows there is a significant amount of research indicating the prevalence of patients having an incorrect PCN allergy label when properly tested (Kufel et al., 2019). In addition to this, current research indicates elevated levels of patient mortality and morbidity associated with having an incorrect PCN allergy label (West et al., 2019). Other research proves the overall safety, accuracy, and cost-effectiveness of PCN allergy testing. Lastly, the current research indicates several barriers as to why PCN allergy testing is not routinely being performed in the outpatient setting. These include physician and patient misconceptions regarding PCN allergy testing and an overall lack of knowledge on medical providers' behalf regarding confirmatory PCN allergy testing (Trubiano et al., 2016).

The Prevalence of an Incorrect Penicillin Allergy

PCN allergies are one of the most common allergies reported to medical providers in the outpatient and inpatient setting. In fact, 10% of the United States population is labeled as having a PCN allergy. However, when properly tested, more than 90% of these patients actually test negative for a PCN allergy (Kufel et al., 2019). Several reasons may account for this including

but not limited to: unverified allergic reactions reported to patients by their parents during childhood, incorrect patient recall of the allergic reaction, and incorrect medical recording of reactions. Another factor that may account for these staggering statistics lies in the fact that 80% of patients who do have a true documented PCN allergy will eventually lose their PCN allergy after a period of ten years (Kufel et al., 2019). So, even those patients who are correctly identified as having a known PCN allergy will likely test negative eventually.

Kleris, Tang, Radojicic, and Lugar instituted a clinical trial in the form of a pilot clinic in May of 2017 to test the feasibility of a dedicated outpatient PCN testing clinic (2018). This was done to address the negative issues related to having an unconfirmed PCN allergy. The pilot clinic was created in May of 2017 using an allergist and an allergy registered nurse trained in penicillin skin testing (PST). Their method of PCN testing consisted of a history and physical reviewing the details of the patient's PCN reaction, skin prick testing, intradermal testing, and a two-step graded challenge with amoxicillin (400 mg). Each of these tests was dependent upon the negative result of the prior test in order to proceed to the next test. The patients were observed for 30 minutes following each graded challenge for any reactions. If no reaction was observed during the graded challenge, then the patient's PCN allergy status was removed from their medical records.

During the first year of their pilot program, a total of 104 patients were evaluated. Of these patients, the most commonly reported PCN reaction was hives or rash (83 patients [79.8%]) followed by an unknown reaction (11 [10.6%]). A majority of the patients (87 [84.5%]) reported reactions that had occurred 10 or more years prior. The mean of ages tested was 54.4 years of age plus or minus 16.7 years. Of those patients, 35 were male (33.7%), 69 were female (66.3%), 78 were white (75.7%), 23 were black (22.3%), 1 was Hispanic (1%), and

1 was of other race (1%). The number of reactions to different types of PCN's and related antibiotics reported by patients was as follows: 45 (43.3%) to PCN, 19 (18.3%) to Amoxicillin/Augmentin, 34 (32.7%) to an unknown PCN, and 5 (4.8%) to a Cephalosporin. Finally, patients tested with other known comorbidities were as follows: 44 patients with cardiac disease (42.3%), 43 patients with pulmonary disease (41.3%), and 20 patients with oncologic disease (19.2%).

The results of their testing revealed a total of 95 patients (91.3%) with negative PCN skin testing. Four patients had a positive intradermal skin test and therefore were not challenged any further. Of the patients with a positive skin test, none reported/ experienced anaphylaxis. A total of 99 (95.2%) out of 104 patients with a reported PCN related allergy passed the final graded oral challenge and were therefore cleared of their PCN allergy.

Limitations of this study are that it did not include many pediatric patients and its results were limited to one year with no follow up testing to evaluate for any return of PCN sensitivity. This study is noteworthy as it demonstrated that a majority of patients with a reported PCN allergy were actually not allergic to PCN's when properly evaluated. It also shows that graded PCN testing safely, accurately, and efficiently identified patients with a negative PCN allergy in the outpatient setting.

Another study that was performed by Moussa et al. involved a multi-step semi-prospective clinical trial to evaluate the potential value of de-labeling patients with a beta-lactam allergy. Patients included in this study had a PCN allergy noted in their electronic medical record (EMR) and who were scheduled for an upcoming surgery (2018). Surgical patients are often given intraoperative prophylactic antibiotics to improve surgical outcomes. The authors of this study wanted to evaluate if beta-lactam de-labeling optimized the choice of prophylactic

antibiotics and ultimately improved intraoperative time and efficiency. Their method of study began by establishing a service and protocol to provide perioperative evaluation of patients identified via EMR with a possible beta-lactam allergy at Montreal General Hospital. Eligible study participants were adults (eighteen years of age or older) who had a history of an allergic reaction to penicillin and who were scheduled for elective surgery within six months following the date of their preoperative visit. These patients were then evaluated using standardized prescriptions, policies, procedures, and a risk assessment tool. Study participants were given a tiered graded PCN testing approach based on their risk assessment for anaphylaxis. This consisted of skin prick testing, intradermal testing, and an oral challenge provided they were negative for a reaction with the previous test. The testing was performed in an outpatient interventional allergy care unit with an allergist present to evaluate for any reactions following their last dose of PCN challenge. Patients, if cleared of reaction after two hours of observation, were then required to call 24 hours post-testing to report any possible delayed reactions.

A total of 194 study participants were identified using EMR. The cohort portion of the study involved 129 females (66.5%) and 65 males (33.5%). Study participants had a previously reported reaction to PCN or a related PCN antibiotic within the past five years (4.6%), between 5-20 years ago (18.6%), or more than 20 years ago (50%). The remaining patients (26.8%) had an unknown or undocumented date of a PCN allergy reaction. A majority of the reported reactions to PCN's was an unspecified rash (29.9%) and urticaria (20.1%). The types of surgical patients varied from orthopedic, general, thoracic, plastic, and maxilla-facial.

Results of the study were as follows: of the 194 study participants, four had a positive skin test and were not orally challenged and 44 had a negative skin test and were not orally challenged based on their low-risk assessment. This was due to the extremely low likelihood of

them having a PCN reaction. Of the 146 remaining patients who were systematically evaluated using skin testing and oral drug challenge, only seven patients were positive for a reaction. Ultimately, eleven individuals were positively identified as having a confirmed beta-lactam allergy. This meant that 183 out of 194 (94.3%) of the study participants were successfully and safely de-labeled from having a documented beta-lactam allergy. Antibiotic use both preoperatively and prophylactically in the study patients was as follows: of the 139 patients with a negative challenge, 19 did not require preoperative antibiotics and cefazolin was prescribed to 102 of the remaining patients. Cefazolin is a beta-lactam antibiotic of the cephalosporin family, which is related to the PCN family of antibiotics and otherwise would not have been prescribed due to its close relation to PCN's. Of the 44 patients with a negative skin test who were not given an oral challenge, eight did not require prophylactic antibiotics and cefazolin was prescribed in 18 of the remaining 36 patients (50%).

Some of the limitations of this study were that it relied on data that was subject to poor patient recall or incomplete data entry related to penicillin versus amoxicillin reactions. The study also failed to evaluate patients who were not referred for preoperative allergy evaluation or who were given antibiotics outside of the ones noted in the study. Overall, this study exhibited that patients can safely and effectively be de-labeled from having a PCN allergy and that a majority of patients with a documented/ reported PCN allergy were actually not allergic when tested.

Morbidity/ Mortality Associated with a Penicillin Allergy

It is well established that having a documented PCN allergy results in patients being placed on alternative antibiotics that are often more broad-spectrum. These broad-spectrum antibiotics have been associated with increased adverse effects, worse clinical outcomes, and

increased development of antibiotic resistance (Kufel et al., 2019). All of these factors contribute to patients having an increased risk for morbidity and mortality when compared to those patients who are not documented as being PCN allergic.

This is well demonstrated by a series of cross-sectional/ retrospective cohort studies performed by West et al. to determine the prevalence of PCN allergy records in the United Kingdom, any patient characteristics associated with PCN allergy records, and the ultimate impact of PCN allergy records on antibiotic prescribing/ health outcomes in primary care settings (2019). This research was also performed to support a "preemptive" testing strategy for the presence of an actual PCN allergy. The method of study involved three parts: part one was a cross-sectional study of adult patient EMR's identifying any factors associated with a PCN allergy; part two was a retrospective cohort of the patients in part one looking for the potential impacts of a PCN allergy on several health outcomes including asthma, cancer, congestive heart disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, peripheral artery disease, stroke, and transient ischemic attack; and part three was a retrospective cohort that only included those patients prescribed at least one antibiotic during the study year. The study group included all adults aged 18 to 100 years with EMR's on ResearchOne and those patients who had died since April 1st, 2013. Study participants were considered to have a PCN allergy if their EMR included either a sensitivity or an allergy to any PCN class antibiotic agent, including amoxicillin, ampicillin, penicillin V and G, flucloxacillin, and piperacillin. Health care outcomes measured included associated infections such as MRSA, CDI, and vancomycin-resistant enterococci (VRE). If a record of prescription of a subsequent antibiotic of a different class was prescribed within 28 days following the prescription of one the monitored antibiotics, it was considered a lack of treatment response.

A total of 2,350,803 adult patients met the initial inclusion criteria of the study. Of those patients, 139,437 patients had a PCN allergy recorded in their EMR which gave a prevalence for the population of 5.9% (95% CI 5.9-6.0%). It was discovered women were more likely to have a recorded PCN allergy (7.4%) and the prevalence of this increased significantly with increasing age (8.5% of patients aged 75-100 years of age). The monitored comorbidities had a small, but significant increased likelihood of having a PCN allergy record with asthma having the highest (8.9%). In the second part of the study, patients with a PCN allergy record received approximately 5% more antibiotic prescriptions than those without a PCN allergy record during a 12 month follow up. Antibiotics, including macrolides, tetracyclines, cephalosporins, quinolones, clindamycin, nitrofurantoin, and trimethoprim were all prescribed significantly more in patients with a documented PCN allergy. The top three most prescribed antibiotics were clindamycin with a relative rate (RR) of 5.47 ($p<0.001$), macrolides with a RR of 4.03 ($p<0.001$), and quinolones with a RR of 2.10 ($p<0.001$).

When compared with those patients without a recorded PCN allergy, those with a recorded PCN allergy had a significantly increased risk of death in the following year at 2056 patients (1.5% [$p<0.001$]), re-prescription of a new antibiotic class within 28 days at 10,111 patients (7.3% [$p<0.001$), and MRSA infection/ colonization at 95 patients (0.1% [$p<0.001$]). This meant a PCN allergy record was associated with 6 in 1000 more deaths and 1 in 1000 more patients with documented MRSA infections/ colonization. There was a non-statistically significant increase risk of CDI at 26 patients (p-value 0.027). Overall, a documented PCN allergy affected 1 in 17 general practice patients. A PCN allergy was associated with increasing age, comorbidity, and being female. Also, a PCN record was associated with more antibiotic prescriptions, different antibiotic prescribing profiles, a higher rate of re-prescription of

antibiotics within 28 days, a greater risk/ burden of MRSA infections/ colonization, and an increased risk of death.

The limitations of the study relate mainly to its method of data collection. The use of routinely collected clinical data such as allergic reactions carries a risk of bias. The authors may have missed other conditions that were affected by having a PCN allergy but were not recorded. It is also important to note that the use of electronic data is at risk of bias due to issues with data migration, patient recall, documentation differences, and the variability of reported drug reactions. However, this study does provide compelling evidence that documented PCN allergies are associated with an increased amount of antibiotic prescriptions, different antibiotic prescribing profiles, increased rates of repeat antibiotic prescriptions within 28 days of initial treatment, a greater risk of MRSA infection, and an increased risk of mortality.

A similar study was a population-based matched cohort study performed by Blumenthal et al. (2018). The authors sought to evaluate the relationship between having a PCN allergy and the development of MRSA and CDI. This study performed in the United Kingdom utilized EMR's to identify patients older than 18 years of age who had a PCN allergy documented with no known exposures or incidences of CDI or MRSA within the last year. This group was then compared to other patients of similar characteristics without a known PCN allergy for the development of CDI and MRSA.

A total of 64,141 patients with a PCN allergy and 237,258 patients without a PCN allergy were studied over a period of 6 years. Of the PCN allergy patients, 442 developed MRSA and 442 developed CDI. Of those patients without a PCN allergy, 923 developed MRSA and 1,246 developed CDI. The adjusted hazard ratio for MRSA was 1.69 (95% CI, 1.51 to 1.90) and 1.26 for CDI (1.12 to 1.40). Overall, having a PCN allergy label accounted for a 68% increased risk

of MRSA and a 26% increased risk for CDI. The use of non-PCN related antibiotics accounted for 55% of the increased risk for MRSA and 35% for the increased risk of CDI. It was also discovered that a PCN allergy label results in a four-fold increased incidence in macrolide and clindamycin use and a two-fold increase in fluoroquinolone use. Lastly, half of the increased risk of MRSA and more than one-third of the increased risk of CDI among patients with a PCN allergy was attributable to the use of antibiotics other than beta-lactams.

Some of the limitations of this study are that it relies on EMR data, which can be subject to data entry errors and patient recall bias. It also failed to test the PCN allergy patients to ensure they had a true PCN allergy. That being stated, the study did exhibit an increased incidence and risk of MRSA and CDI in patients with a documented PCN allergy largely due to the use of alternative antibiotics not related to PCN's. It also showed that a PCN allergy label increases a patient's risk of being prescribed more broad alternative antibiotics.

Macy and Shu (2017) completed a study that was a matched cohort study of PCN allergic patients who had not been tested to confirm a PCN allergy (308) and PCN allergic patients who had been tested and were found to be negative for a documented PCN allergy (1251). This was done to evaluate the effect of PCN allergy testing on future health care utilization. Health care utilization was measured by outpatient department visits (OPD), emergency department (ED) visits, and days spent in the hospital. The authors method of study included utilizing EMR data in the Kaiser Permanente Southern California area. The average time of follow up was 3.6 and 4 years. Results of the study showed that during the time period of study, PCN allergy-tested patients averaged 0.09 fewer OPD visits ($p<0.001$), 0.55 fewer hospital days ($p<0.001$), and 0.13 fewer ED visits. The PCN tested patients were also found to be prescribed more PCN's and second-generation cephalosporins with fewer prescriptions for clindamycin and macrolides.

Both clindamycin and macrolides being more broad-spectrum antibiotics with increased risks for adverse effects.

The limitations of this study are similar to other studies in that it relied on data that is subject to possible documentation errors and patient recall bias. Overall, this study reveals both the cost-saving benefits and decreased health care utilization associated with successfully being PCN allergy de-labeled.

Another study completed in 2017 sought to identify whether PCN allergy testing affected patient clinical outcomes during hospitalization. This systematic review was performed by Sacco, Bates, Brigham, Imam, and Burton using an electronic search of literature from the past 20 years including Ovid MEDLINE/ PubMed, Embase, Web of Science, Scopus, and Cochrane Library (2017). Inpatients with a documented PCN allergy who underwent PCN allergy testing while hospitalized were included in the study. Overall, 24 studies met their criteria with sample sizes ranging between 24 and 252 inpatients. PCN skin testing with/ without oral amoxicillin challenge was the main intervention.

The population weight mean for a negative penicillin skin testing (PST) was 95.1% with a CI of 93.8 to 96.1. It was found during their review of studies that a significant change in prescribing more narrow antibiotics was noted following PST. This was greatest in the inpatient ICU setting (77.97%; CI 72.0-83.1) versus the general inpatient population (54.73%; CI 51.2-58.2). It was mentioned that this could be due to providers in the ICU setting having to treat more complex patients with organ failure giving them an incentive to rule out an incorrect PCN allergy to aid in treatment. Greater mortality, morbidity, and health care costs in the ICU associated with antibiotic resistance were also cited as possible reasons for increased PST in the ICU. It was also noted that there was a rise in PCN (range 9.9% to 49%) and cephalosporin

(range 10.7% to 48%) prescriptions following PCN testing. A decrease in vancomycin and fluoroquinolone use was found to be present in all studies with an increase in PCN and cephalosporin prescriptions following PST noted.

Some of the limitations of this review are that it largely relied on observational cohort studies and not higher levels of evidence such as randomized control trials. This study was also limited to only inpatients and did not include patients outside of the hospital. Overall, this study shows that PCN allergy testing leads to positive changes in antibiotic prescribing habits, such as prescribing more narrow-spectrum antibiotics. It also shows a statistically significant number of inpatients with a documented PCN allergy who underwent PST were actually negative at 95.1%.

The Safety and Accuracy of Penicillin Allergy Testing

The safety and accuracy of PCN allergy testing in the outpatient setting is of the utmost importance when attempting to convince patients and providers alike of its benefits. If a patient were to be incorrectly de-labeled from having a PCN allergy he or she may experience a life-threatening anaphylactic reaction if then given PCN. Bourke, Pavlos, James, & Phillips performed a clinical trial in Australia from 2008 to 2013 to evaluate the effectiveness of PCN allergy de-labeling in clinical practice (2015). This was done to develop further risk stratification models to guide future testing strategies. Patients aged 15 years or older were referred to a Western Australia public hospital drug allergy service for beta-lactam allergies. A total of 405 patients were referred to tertiary care public hospitals to undergo skin prick testing (SPT), intradermal testing (IDT), and/ or amoxicillin oral challenge (OC) testing to evaluate their reported beta-lactam allergy. Information was collected prior to testing which included: the reported antibiotic allergy, the timing and nature of the reaction, comorbidities, and any co-medications. Results and reactions were later reviewed following testing to classify reactions as

being immediate (likely IgE mediated, ≤ 1 hour), accelerated (possible IgE reaction, ≤ 72 hours), delayed (non-IgE mediated, any reaction >72 hours), or other. IgE mediated reactions are acute anaphylactic reactions which can be dangerous to a patient's health. Any patients with a past history relating to a delayed reaction with severe systemic, cutaneous, mucosal, or organ involvement were not included in the study. Testing for beta-lactam allergies was conducted per recommended guidelines using a graded challenge consisting of SPT, IDT, and/ or OC testing based on the patient's history of results from subsequent tests.

The mean age of patients in the study was 47.4 years (range 15-85 years) with 272 female patients (67.1%) out of 401 total patients. Patients were classified based upon their most recent known reaction. Of the 401 patients, 151 (37.7%) were classified as immediate reaction (IMM, ≤ 1 hour from dosing) and 250 patients as being non-immediate reactions (NIM >1 hour). Out of a total of 341 patients, 42 (12.3%) were SPT/IDT positive to ≥1 PCN reagents per their medical history. This included 35/114 (30.4%) in the IMM group and 7/227 (3.1%) in the NIM group ($p<0.0001$). The most common beta-lactam related antibiotic reactions reported were as follows: PCN (n=181), amoxicillin (n=94), amoxicillin-clavulanate (n=49), and cephalexin (n=56). It was also noted that 60 (15%) of patients reported having a previous reaction to ≥ 2 different beta-lactam related antibiotics.

Skin testing was performed within six months of reaction in 108/401 (26.9%) of patients, six to twelve months in 52/401 of patients (13%), one to five years in 54/401 of patients (13.5%), 5 to 10 years in 24/401 of patients (6%), and after more than ten years in 163/401 of patients (40.6%). In patients with a history of multiple reactions, their most recent date of reaction was used. Patients who were skin tested ≤ 6 months since their reaction (27/73 [37%], $p<0.0001$))

and in the IMM group (35/112 [31.3%], p< 0.0001) had the highest proportion of positive skin results when compared with the other patients.

Results of the study showed that out of the patients that were tested with SPT/ IDT, three (0.8%) in the IMM group had non-serious positive OC reactions to a single dose of PCN VK (SPT/IDT negative predictive value (NPV) 99.2%). Overall, selective or unrestricted beta-lactam use was recommended in almost 90% of study participants. This included 238/250 (95.2%) in the NIM group and 126/151 (83.4%) in the IMM group (p=0.0001). Patients were contacted following the clinical trial (median 15 months) and assessed whether or not they were following their new recommended guidelines for or against beta-lactam use. Of 182 patients contacted, 137 (75.3%) were following their allergy label modifications (ALM) at the time of follow-up. And of those patients, 101 had subsequently received antibiotics following the study with only 17 (16.8%) reporting a subjective adverse drug reaction (ADR). None of these reactions were IMM reactions and it was not always possible to confirm these reports or the antibiotics responsible.

Limitations of this study are mostly due to bias in reporting from patients. Often, a patient's recollection of past events can be skewed and even the follow-up evaluation for drug reactions since being de-labeled largely relied on subjective reports which could not be verified. That being said, this study does add more evidence supporting the prevalence of incorrect PCN allergy labels in the medical field and the accuracy of tiered/ graded PCN allergy protocol testing. Selective or unrestricted beta-lactam use was recommended in almost 90% of the study's subjects after testing. It was also noted that the NPV of beta-lactam allergy using SPT/IDT was 99.2%. Lastly, 75.3% of study participants were following their new allergy label

modifications at the time of follow up. This shows patients can be trusting of the testing protocols and procedures in relation to PCN allergy testing.

A retrospective review was recently completed by Dorman, Seth, and Khan between the years of 2010 and 2016 of adult patients at the University of Texas Southwestern Medical Center hospitals and clinics (2017). The patients studied had previously tested negative with PCN allergy testing. They specifically sought to evaluate the risk of allergic reactions to repeated doses of intravenous (IV) PCN's in patients who had previously tested negative to PCN SPT and amoxicillin OC testing. Medical records were reviewed in those patients who had been given two or more courses of IV PCN's since having tested negative for PCN allergies. A "course" of IV PCN administration was defined as being as little as a single dose or as long as needed to treat the illness as long as there was not a break-in dosing longer than seven days in duration. After each PCN type antibiotic administration, the subject's EMR was reviewed for any evidence of immediate allergic reactions or any delayed adverse drug reactions (ADR's).

The study included 32 subjects with four having undergone PCN allergy testing in an ambulatory setting and 28 in a hospitalized setting. Seventeen subjects (53%) were women and the average age at PCN skin testing was 46.9 years (range 24-79 years). Differences in race were as follows: 13 identifying as black, 10 white, 3 Hispanic, and 6 of unknown race. A majority of the subjects (75%) had historical reactions to PCN's greater than ten years prior and 16% reported a reaction to PCN within a year of PCN allergy testing taking place. A majority of the reported reactions to PCN's were some type of cutaneous reaction.

The total number of parenteral PCN courses reviewed was 111. This broke down further to a mean of 3.5 courses per patient (range 2-12 courses). A total of more than 50% of patients received three or more courses of IV PCN's. The types of IV PCN's patients were exposed to

included: ticarcillin, nafcillin, ampicillin, penicillin G, and piperacillin. The most common antibiotic given was piperacillin (30/32 subjects) and the least common was penicillin G with only one patient being exposed once. The median time between the negative PCN skin testing and the first IV course of PCN's was 19 days (range 1-933 days). And the time from negative PCN skin testing to the second course of IV PCN's was a median of 129 days (range 14-1055 days).

The results of the study showed that there were no documented IMM reactions identified in those who had tested negative for PCN allergies and then treated with repeated doses of IV PCN's. Three subjects reported delayed adverse reactions, including subjective throat pruritis (one), acute interstitial nephritis (one), and benign exanthema (one). Overall, the estimated reaction rate was 0% with a 95% CI of 0% to 3.3% to 11%. The varying range of the upper limit of the CI is directly related to how one chooses to perceive the sample size. This being if each PCN course (N=111, CI 3.3%) is treated separately or each patient involved in the study is counted (n=32, CI 11%).

Some of the limitations of this study are related to its somewhat small sample size, but more than 50% of the study's participants did receive three or more courses of IV PCN's. It also relies solely on a retrospective review of EMR documentation. This is subject to significant bias in reporting and documentation. Also, a majority of patients were observed in the inpatient setting and any possible delayed allergic reactions may have been missed or under-reported. This study is significant in that it reveals both the overall accuracy of PCN allergy testing/ de-labeling and the safety of such testing. It goes further to show that re sensitization following PCN allergy testing is less likely. Finally, it shows that repeated PCN allergy testing following negative skin testing and IV PCN administration is not necessarily warranted, provided both

were tolerated by the patient without any allergic reaction. Larger studies will need to be performed to confirm further this study's results, which were largely based on a small population of patients.

Another study seeking to evaluate the safety and accuracy of PCN allergy testing was a five-year institutional retrospective study that was performed using adult patients (age ≥18 years-of-age) who were evaluated by allergists-immunologists at a local affiliate hospital and outpatient practice (Mawhirt, Fonacier, Calixte, Davis-Lorton, & Aquino, 2016). These patients were initially evaluated between the years of 2009 and 2014. The main objective of this study was to evaluate any relationship between a patient self-reported antibiotic hypersensitivity history and subsequent skin testing results during an allergy evaluation of those patients. Specifically, the authors were seeking to "(1) identify putative risk factors for antibiotic drug challenge reactions, (2) analyze the relation between the reported index reaction severity and the observed challenge reaction severity, and (3) examine the safety and outcomes of single-step and multistep challenge methods" (Mawhirt et al., 2016). The primary study method involved the authors gathering the patient population using inpatient and outpatient billing records and a search of an allergy-immunology consultation log book. Only patients with a clinical history positive for prior immediate-type hypersensitivity reactions were included in the study. Further data including patient age, sex, atopic disease, type of antibiotic reaction, reaction severity, route of administration, and treatments received was collected and reviewed from the patients' electronic medical records.

A total of 211 patients with a documented antibiotic immediate-type hypersensitivity reaction history who underwent allergy consultation were identified. The median age was 67 years (range 50-76 years) with 58% being women. Multiple families of antibiotic reactions were

included, but for the purposes of this study, the beta-lactam antibiotics and related families were focused on. Of those patients, 165 (78%) reported reactions to PCN's (penicillin, amoxicillin or piperacillin-tazobactam), 16 (7.6%) to cephalosporins including first-generation through fifth-generation cephalosporins, and 8 (3.8%) to carbapenems (meropenem, ertapenem, and imipenem). A majority of patients reported a reaction having resulted from an oral route of administration (44%) and a non-anaphylactic (71%) type reaction (grade 1 or 2). A total of 141 patients received SPT/IDT for their respective antibiotic allergy. Of those patients receiving skin testing (positive versus negative reactions) were 4 vs. 49 for PCN's, 1 vs. 52 for cephalosporins, and 0 vs. 31 for carbapenems. A majority (125 of 134) of patients with a negative skin test went on to receive a further antibiotic challenge.

Results of the study were as follows: patients with a reported PCN allergy who completed the challenges showed a high tolerance to other PCN's (88%), cephalosporins (96%), and carbapenems (90%). Overall, 179 patients in total completed the allergy challenges with a median age of 67 years, a range of 50-76 years, and 58% of those patients were women. Of those patients, 16 (8.9%) experienced challenge reactions with 5/28 patients for a single-step challenge and 11 of 151 for a multistep challenge. Eleven of these patients had negative skin allergy testing prior to the challenge. It was also noted that challenge reactive patients were "significantly" younger ($p=0.007$), more likely to be female ($p=0.036$), and more likely to have additional reported antibiotic allergies ($p=0.005$). The route of administration of antibiotics and the severity of their reaction failed to yield any correlation ($k=-0.05$, 95% CI of -0.34 to 0.24). Also, the rates of anaphylaxis observed with single step and multistep challenges were similar with 3.6% vs. 3.3%, respectively.

Limitations of this study are that it centered on a retrospective design that relies on EMR and often subjective patient histories. The risk of patient recall bias is significant, and the smaller sample size limited the data available for further comparing two-step and three-step challenge results. This study is unique in that it specifically sought to evaluate the outcomes related to skin testing and oral challenges only in those patients with a history of an antibiotic immediate-type reaction. It also reviewed the safety and outcomes of skin and oral challenge testing in those patients. This study helps support the necessity of graded allergy testing as negative skin testing in this study did not exclude the possibility of oral challenge reactions. It also shows that a patient's reported severity of an initial allergic reaction was not predictive of an oral challenge outcome. Finally, the risks of anaphylaxis during multistep and full dose methods of allergy testing showed similar risks of reaction, which supports both methods being suitable testing methods based on history and physical exam.

Another study performed in 2012 by Mill et al. sought to assess the accuracy of a graded provocation challenge (PC) of amoxicillin in diagnosing immediate and nonimmediate allergic reactions in children with a suspected amoxicillin allergy (2016). The study design included both a retrospective and a prospective portion. Children that were referred to the allergy clinic of the Montreal Children's Hospital with a suspected allergy to amoxicillin were included in the study, including those with a past reaction history consistent with anaphylaxis. Any children with suspected reactions relating to Stevens-Johnson syndrome or toxic epidermal necrolysis were not included. Consent was obtained from children's parents and a standardized questionnaire was completed by the parents. The questionnaire included questions related to comorbidities, suspected antibiotic exposures, and management of the reaction they experienced. All pediatric patients consenting were then given a graded PC (10% of the therapeutic dose of amoxicillin,

then 90% of the therapeutic dose was given 20 minutes later). The children were then observed for at least one hour following their last dose. The authors of the study also followed the patients following the PC to assess for any further amoxicillin use or amoxicillin reactions. An allergic reaction within one hour of the PC was labeled as having an immediate antibiotic allergy. These symptoms included urticaria, wheezing, rhinitis, vomiting, diarrhea, abdominal pain, or shock. Non-immediate reactions were described as any symptoms including arthritis and arthralgia more than one hour after PC and up to one week later.

From March 2012 and April 2015, 818 study participants underwent amoxicillin PC. The median age was 1.7 years (interquartile range, 1.0-3.9 years) and 441 (53.9%) were males. Three groups of study were separated following testing to include: those tolerant of PC, those with an immediate reaction to PC (< 1 hour), and those with a nonimmediate reaction to PC (>1 hour). The results of the study showed that 770 (94.1%) of the children tolerated PC. There were 16 patients with an immediate reaction consisting of hives, but all resolved within a few hours of treatment with second-generation antihistamines. The third group of children consisted of 31 total patients (3.8%) with nonimmediate type reactions to PC. Those reactions were mild and varied from a maculopapular rash with angioedema to serum-like sickness reactions. The median of time from PC and a delayed reaction was 12 hours (29%; 95% CI, 14.9%-48.2%).

A total of 250 patients (72.3%; 95% CI, 67.2%-76.8%) were successfully followed up with after the completion of PC testing via a telephone call. Of those patients, 55 had received subsequent full treatment with amoxicillin with 49 of them (89.1%) tolerating full treatment and 6 (10.9%) experiencing a delayed skin reaction. Ultimately, it was discovered that graded PC had a specificity of 100.0% (95% CI, 90.9-100.0%), a NPV of 89.1%, and a positive predictive value (PPV) of 100.0% (95% CI, 86.3%-100.0%).

The limitations of this study are that it was limited to pediatric patients and it did not include adults. This means that amoxicillin was mostly evaluated and no other forms of beta-lactam containing antibiotics commonly prescribed to adults. Other studies reviewed so far have indicated increased incidences of reactions with allergy testing in pediatric patients vs. adult patients, which may skew this study's findings. Lastly, in addition to other studies reviewed, this study relied on the parents recall of allergic reaction variables via questionnaire and are therefore subject to information and recall bias. This study is significant as it shows the high levels of specificity, NPV, and PPV of graded PC with amoxicillin in children. This study also showed that a majority of children suspected of having an amoxicillin allergy are actually negative when tested using a graded PC with amoxicillin, which supports the prevalence of an incorrect PCN allergy in children.

A clinical trial to evaluate the feasibility of offering PCN allergy testing to outpatients regardless of their chief complaint was completed by two allergy/ immunology physicians at an outpatient practice between April 2017 and June 2017 (Ramsey & Mustafa, 2018). During their trial, they collected a PCN allergy history from patients and skin testing and/ or challenge testing was offered based on the patient's allergy history obtained. PST and IDT were performed and then if negative, an oral amoxicillin challenge was given with patients being monitored in the clinic for any reactions for 30 minutes after. A total of 978 patients were screened for PCN allergies with 150 (15.7%) patients reporting a PCN allergy. The average age range of patients was 32.4 ± 23.6 years. Ninety-six (61.9%) of patients positive for PCN allergy were female. The leading reasons for patients presenting to the allergy/ immunology clinic were PCN or multiple drug allergy (n=38; 24.5%), asthma (n=35; 22.6%), chronic rhinitis (n=32; 20.6%), and food allergy (n=21; 16.8%). Forty-six patients (49%) reported that more than ten years had

passed since their last known reaction, five to ten years in 19 patients (12.3%), more than one to five years in 33 patients (21.3%), and one year or less in 16 patients (10.3%). Eleven patients did not recall when their reactions occurred. The top reaction histories included rash in 82 patients (52.9%), hives in 45 patients (29%), dyspnea in 3 patients (1.9%), angioedema in 3 patients (1.9%), anaphylaxis in 2 patients (1.3%), and itching in 2 patients (1.3%).

A total of 66 out of 155 patients (42.6%) were administered PST. Of those patients, 58/66 (87.9%) were PST negative and all of those 58 patients then underwent an oral challenge. All skin prick tests were negative in the PST positive patients. Three patients had a positive IDT. The average time for the entire PST and oral challenge was 71.1 minutes ± 12 minutes. Two patients (1.3%) received a same-day oral challenge without PST and six patients (3.9%) were de-labeled solely on the basis of history. Only one patient experienced nausea and vomiting starting two hours after PST and oral challenge. In total, 66 of 155 (42.6%) of patients with a reported PCN allergy were successfully and safely de-labeled.

This study demonstrates PCN allergy testing can safely and efficiently be performed in the outpatient setting even using less than the recommended staff and observation times. The authors of this study cited similar studies with increased attrition rates due to prolonged allergy testing protocols. This study's authors avoided increased rates of attrition by having a shorter window of testing and observation. The limitations of this study are related to its setting and expertise. While it is true that only two providers were able to successfully test and de-label PCN allergic patients, it does not mean all providers outside of allergy/ immunology would be comfortable or financially able to do so also. This study also suffers as other studies do to recall and information bias from patients regarding their prior allergic reactions. It also fails to consider other types of antibiotic allergies in the beta-lactam family. Overall, this study shows

that with ideal conditions and training, medical providers can safely and efficiently de-label PCN allergy patients in the outpatient setting. That being said, further research regarding the accelerated testing schedule would need to be performed to ensure safety and accuracy for any resensitization of patients.

The Cost-effectiveness of PCN Allergy Testing

Concerns related to the cost-effectiveness of PCN allergy testing remain at the forefront of health care analysts and health care systems. Variables related to resources, staff, and training are all factors to consider when factoring the costs to benefits ratio of PCN allergy testing. To understand the potential cost savings of PCN allergy testing one must first understand the basic cost of the actual testing process.

Blumenthal et al. performed a study seeking to investigate the basic costs of PCN allergy testing (2017). Specifically, they sought to evaluate the cost of PCN allergy evaluation using time-drive-activity-based costing (TDABC). The TDABC is a method created by health care economists to estimate costs using both the time spent using a specific resource and the per-unit cost of that resource. This method has successfully been used to estimate costs in other health care specialties. This evaluation was then compared with other cost estimating models, such as the ratio of costs to charges method (RCC) and the relative value unit method (RVU). They began the clinical trial using TDABC during the care of 30 outpatients being evaluated for PCN allergies.

Results of the study using the TDABC method showed the following: estimated personnel cost of $98, consumables cost of $119, and space cost of $3 for a PCN allergy evaluation. This amounted to a total of $220 USD for a PCN allergy evaluation. The lowest and highest TDABC estimates based on the type of provider, materials, time, and demand were $40

and $537, respectively. Results of the RCC model revealed the estimated costs of PCN allergy testing being $829. This included the cost of a new visit evaluation and management ($306) and the procedure ($523). The range of estimated costs using the RCC model was $225 (no evaluation and management and a two-step allergy test only) and $1,247 (two visits with a PCN skin test using ampicillin and a two-step challenge after initial skin testing). Results of the RVU model estimated PCN allergy testing being a total of $328 ($218 for evaluation and management and $118 for the procedure). Overall, estimated costs using the RVU model ranged from $110 (no evaluation and management charge with a skin test and one step challenge) to $555 (two visits with an ampicillin skin test and a two-step challenge after initial skin testing).

This study is helpful as it demonstrates the costs of PCN allergy testing using multiple cost estimating models commonly used in health care. This study also is beneficial as it took into consideration other variables outside of PCN allergy testing such as personnel, space for testing, and consumables. Limitations of this study are that it does not include all of the costs related to health care evaluation such as billing and other clinic staffing costs. Its study group was also limited to only 30 patients. Lastly, it failed to address the varying costs of supplies depending on the location and the amount of supplies being ordered.

Another study investigating the basic costs of PCN allergy testing was performed by Kufel et al. (2019). They performed a systematic review of the different variables related to PCN allergy testing in the outpatient setting. First, they performed a thorough review of the available literature related specifically to PCN allergy testing in the outpatient setting as performed by pharmacists. They searched PubMed using search terms such as *skin tests, penicillin,* and *outpatient.*

Their findings related to costs revealed that the median time necessary to perform a detailed allergy history is 13.8 minutes and the median time to perform skin prick and intradermal testing is 20 minutes. A one-step oral challenge with monitoring was 60 minutes or more and a two-step oral challenge required a 30 minute plus 60-minute testing/ observation time frame. Overall, the total time required for testing and observation was 45-120 minutes. They also found the total cost of PST supplies to be between $140 to $160 per patient.

They also noted that outpatient PST is a reimbursable process with a CPT code of 95018 for each prick/ intradermal test, and 95076 for the oral ingestion challenge with a 61 to 120-minute observation period. The CPT code of 95018 is reimbursed $18.95 on average by Medicare and Medicaid services.

Limitations of this review are that it does not specifically investigate the costs of not performing PCN allergy testing. It also focuses solely on pharmacists performing PCN allergy testing as a means to reduce patient morbidity/ mortality and increase antibiotic stewardship. Another weakness of this study is that the authors only utilized PubMed for their search of available literature.

Next, it is important to evaluate the potential cost savings of performing confirmatory PCN allergy testing when investigating the total cost-effectiveness of such testing. Mattingly et al. performed a systematic review of studies evaluating the clinical and economic outcomes associated with having a PCN allergy (2018). This was done in an attempt to provide recommendations for future analyses regarding the cost-effectiveness of PCN allergy testing. Their research included data from the databases SCOPUS, EMBASE, and PubMed. The results of their research were limited to peer-reviewed publications in English that were published up to the year 2017.

Their review found that the total potential cost savings of de-labeling a patient in the inpatient setting driven by the length of stay reductions was $1,145 to $4,254 per patient. They also discovered a study demonstrating that PCN allergic patients were estimated to experience a 38% higher cost due to having more expensive medications at discharge from the hospital. The average outpatient prescription costs of those patients with a PCN allergy were estimated to be $14 to $193 per patient.

Limitations of this review are that it included studies outside of the United States, which makes it hard to compare costs and health care protocols. Also, a majority of the studies it included were of shorter observation lengths and failed to evaluate the costs related to missed work and productivity losses in those patients with a documented PCN allergy. This review is important as it shows the costs associated with longer hospital stays and more expensive outpatient prescriptions in those with a PCN allergy.

Another cost savings investigation of PCN allergy testing was performed using follow up with pediatric patients who were previously successfully de-labeled from having a PCN allergy in a prior study. Vyles et al. performed a follow-up phone survey of the parents of the pediatric patients and their primary care provider (PCP) (2018). A total of 100 pediatric patients' parents and PCP's were interviewed. They then performed a three-tier economic analysis from prescription information gathered by the survey to estimate actual cost savings, cost avoidance, and potential cost savings of those pediatric patients having been successfully de-labeled.

Eighty-one percent of the 100 families contacted completed the follow-up survey. Of those parents: 73 (90%) were aware of their child's negative PCN allergy results and 65 (80%) notified their child's provider of their child's negative PCN allergy results. Ninety-eight percent of the PCPs completed the follow-up survey. Of those providers, 82 (84%) stated they were

notified by the parents of their patients regarding their child's negative PCN allergy results. Fifty-one (52%) children still had a reported PCN allergy on their PCP medical record despite being testing negative. The race of the pediatric patients was as follows: 24 (69%) white, 5 (14%) African American, and 4 (11%) Hispanic.

Thirty-six patients had filled at least one prescription since being de-labeled, and ten patients had filled two prescriptions for a total of 46 prescriptions. The most commonly prescribed antibiotic was amoxicillin and/ or PCN (n=24, 52%). Others prescribed by PCP's included azithromycin (n=13; 28%), cefdinir (n=6; 13%), amoxicillin with clavulanic acid (n=2; 4%), and cefadroxil (n=1; 2%). Of those prescriptions given by PCP's, only one (4%) formerly de-labeled child experienced a reaction (rash) approximately 24 hours after receiving amoxicillin.

Results of the study revealed the cost savings of those 24 children receiving PCN and/ or amoxicillin ($10 median price per prescription), as opposed to a nonpenicillin (average cost $70 per prescription), was $1,368.13. The cost avoidance was $1,812 (calculated on the basis that the 24 PCN prescriptions would have likely been cefdinir instead). Lastly, the total potential cost savings extrapolated to include 6700 pediatric patients with a PCN allergy being treated at their pediatric emergency department per year was $192,223.

The de-labeling of PCN allergy in pediatric patients led to their PCP's using more PCN's for follow up treatment. PCN's are cheaper than most other more broad-spectrum antibiotics. Ultimately, this led to a cost savings with using PCN's versus if these children had been treated with more expensive non-PCN antibiotics. Limitations of this study are that it involves data within only one hospital system and a smaller study group as not all of the families could be contacted for follow up. This means the study's authors cannot guarantee one of those children

not followed up with did not experience a severe allergic reaction. This study also fails to consider the associated costs of PCN allergy testing or the longer-term savings associated with being PCN allergy de-labeled.

This study shows both the safety of confirmatory PCN allergy testing and the potential for cost savings with not having to prescribe other broader spectrum, expensive antibiotics. This study is also beneficial in that it breaks down the actual cost savings, cost avoidance, and potential cost savings on a large scale using PCN's instead of other antibiotics.

Moussa et al.'s study referenced earlier in this review also evaluated the potential cost savings of de-labeling surgical patients with a beta-lactam allergy (2018). Their study results related to costs showed of those patients who tested positive for a beta-lactam reaction, vancomycin was given to two patients instead of a beta-lactam, cefazolin in two patients, clindamycin to two patients, and one patient did not receive any antibiotics. The use of vancomycin instead of a beta-lactam resulted in a 59-minute mean time to first incision, 37 minutes with cefazolin, and 21 minutes with no antibiotics. Cefazolin use instead of vancomycin reduced incision time delay by an average of 22 minutes. Study authors concluded this time savings resulted in an overall cost savings of $42,240 in the 120 patients that were successfully de-labeled and able to receive cefazolin. They then extrapolated this data and applied it to the 30,000 patients who receive surgery annually at their facility. They assumed an 11.5% prevalence of suspected PCN allergy and of those patients 75% would likely require prophylactic antibiotics. This equated to an estimated 2,587 preoperative allergy assessments, of which 996 could successfully be de-labeled and avoid having to use vancomycin. That time savings ultimately equaled a saving of 365 hours of operating theater time and $350,867 Canadian dollars (CAD) in direct costs annually.

Macy and Shu's study also referenced earlier in this review calculated the cost-benefit ratio via the reduction of health care utilization in those patients who had performed PCN allergy testing (2017). Their results showed -0.089 OPD visits per year at a per-visit cost of $145, -0.132 ED visits per year at a per-visit cost of $1,233, and -0.553 days spent in the hospital at $3,146 per hospital day. This amounted to $1,915.40 less in health care expenses per patient per year. They compared this to a one-time cost of PCN allergy testing at $145 which revealed a possible health plan savings of over two million dollars over a period of 3.6 years. The minimal cost and time needed to safely perform PCN allergy testing is a modest investment that can have significant savings for patients and health systems alike.

Barriers to PCN Allergy Testing in the Outpatient Setting

As the research referenced so far has shown, incorrect PCN allergies are prevalent throughout the world. It has also been shown that the risks of having an incorrect PCN allergy label are significant when it comes to morbidity and mortality. Lastly, PCN allergy testing has been well documented as being safe and cost-effective. The question remains then, why aren't more providers and patients having their vague or unclear PCN allergies confirmed with outpatient PCN allergy testing? This next section will evaluate the barriers as to why confirmatory PCN allergy testing is not being utilized more.

Recently, Jones and Kim performed a study to evaluate the current perceptions regarding PCN allergies, perceived barriers to allergy clinic referrals, and formulate logical interventions aimed at more outpatient referrals for PCN allergy testing (2019). Their study was done via email (Survey Monkey Platform) sent to primary care physicians to evaluate their knowledge related to PCN allergies and any perceived barriers to PCN allergy clinic referrals. Providers from the University of California San Diego Department of Internal Medicine and Department of

Family medicine were the target study group. A total of 204 providers were invited to complete the email survey. Of those, 85 providers (42%) participated in the survey. This included 26 attending physicians and 59 resident physicians. The most commonly cited barriers by providers to allergy clinic referrals for PCN allergy evaluation included the following: “Patients have multiple other medical problems which take priority in time-limited encounters” (41%), “I did not realize that this service was available for my patients” (26%), “I am concerned that the allergy history is inaccurate or unclear” (12%), “I don’t think my patients will follow through with the referral” (5%), and “Other” (16%)” (Jones & Kim, 2019). Educational intervention training was offered with 19 primary care providers participating. Following the training, 12 (63%) residents stated that an alert visible to patients on an EMR portal prompting patients to discuss their PCN allergy with their provider would help increase allergy referrals and that it would not be a burden on their overall practice. Eleven residents (58%) responded that they would be interested in a smartphone application that detailed the best practice for patients with PCN allergies and appropriate questions for a referral to help increase PCN allergy referrals. After the educational intervention, the total of referrals for PCN allergy testing remained relatively unchanged with 24 referrals before the intervention and 25 after the intervention.

This study highlights the barriers, both real and perceived, that deter providers from referring patients for confirmatory PCN allergy testing. The study also hints at the possible benefits of educating primary care providers regarding the benefits of PCN allergy testing and the possible realistic interventions that could help providers, patients, and allergists come together for the benefit of the patients and the medical community abroad. Limitations of this study were its limited pool of participants from a single medical community. It also only targeted providers from one specialty.

Another study investigating barriers and perceptions regarding PCN allergy testing was performed by Trubiano et al. (2016). The authors surveyed members of the Emerging Infections Network (EIN) of The Infectious Diseases Society of America (IDSA) to evaluate the current availability of antibiotic allergy evaluation services and the overall receptiveness for initiating antibiotic allergy testing (AAT) strategies into programs to encourage proper antibiotic stewardship. A ten-item survey was created and distributed to EIN members between September 15th and October 13th of 2015. A total of 736 of 1545 (48%) of respondents were active EIN members with 558/736 (75%) being adult physicians, 154/ 736 (20%) being pediatricians, and 24/736 (3.2%) being both. A majority of respondents (500/736; 68%) estimated the prevalence of PCN allergy to be between 5 to 20% of their patient populations. Forty-three percent (317/736) of physicians had SPT or IDT available to them and only 27% (204/736) had SPT and IDT combined with an oral challenge available. It is noted in the study that SPT/IDT with a combined oral challenge is currently considered the gold standard for PCN allergy testing. Twenty-three percent (171/736) of respondents did not have access to any form of allergy testing in their practice areas. Lastly, it was found that of those who did have antibiotic allergy testing (AAT) services, 40% (182/460) were unaware of the specific types of testing actually available to them.

Respondents noted that AAT was most frequently performed in outpatient facilities in their practice areas with 274/432 (63%) stating as such. There was also a large number of respondents who offered testing in either an inpatient setting (202/432; 47%) and/ or an intensive care setting (218/432; 50%). It was revealed that a majority of providers believed it was of value to refer patients for allergy testing (410/442; 93%) and that they believed confirmatory allergy testing would be successful in removing patients' antibiotic allergy label (336/432; 78%). It was

also interesting to find that respondents with less than 15 years' experience were more likely than respondents with ≥ 15 years' experience to believe in the overall effectiveness of antibiotic testing in removing an antibiotic allergy label from patients (82%; 198/241 vs. 63%; 138/219 with p=0.0001).

Interestingly, in the instance that a patient had a "remote" history of PCN allergy and where treatment with PCN would be the preferred therapy, respondents of the study stated they would provide treatment as follows: "(1) point-of-care testing (40%, 177 of 442); (2) use of an alternative non-β-lactam antibiotic, even if inferior (13%, 57 of 442); (3) desensitization with maintenance of penicillin allergy label (8%, 37 of 442); or (4) desensitization then allergy clinic referral for penicillin allergy testing (7%, 30 of 442)" (Trubiano et al., 2016). Lastly, most physicians (277/446; 62%) included in the study replied that they believed antibiotic allergy testing in an effort to de-label patients would improve general practice behavior by using more appropriate antibiotics, causing safer administration of antibiotics, and ultimately causing improved antibiotic stewardship practices.

This study includes an impressive number of physician respondents and their beliefs regarding AAT. A large number of providers believed in the ability of AAT to enhance antibiotic stewardship practices. Unfortunately, only 43% had actual testing available to them and their patients. It was also surprising to find that ID providers with increased experience were less likely to believe in AAT. This information further helps define the barriers and beliefs related to PCN allergy. Some of the limitations of this study involve its target study group. It was mainly directed toward physicians associated with the EIN, rather than primary care providers outside of an infectious disease subspecialty. This causes population bias as it skips

other members of the health care team, including immunologists and allergists. There is also likely selection bias due to the targeted EIN population being more likely to answer the survey.

In summary, this study provides a large amount of data related to the barriers regarding the implementation of PCN allergy testing in the outpatient setting. The study also provided a sizeable test group that showed a great amount of support for confirmatory allergy testing. However, there are gaps when it comes to the availability of skilled testing facilities and deficiencies in providers' knowledge about the availability of testing resources in their areas. Overall, providers are willing to refer patients for allergy testing because they believe it is a necessary step for appropriate antibiotic stewardship.

Discussion

The most recent research shows significant numbers of patients having an incorrect PCN allergy label. This may be due to poor patient recall, poor electronic documentation, or vague reactions that were not actually allergic reactions to a PCN related antibiotic. It is also noteworthy to mention again that even those patients who have been correctly identified as having a PCN allergy will eventually lose their initial allergy to PCN's after a period of ten years (Kufel et al., 2019). This may also contribute significantly to the prevalence of incorrect PCN allergy labels. Several studies in this review demonstrated a majority of patients testing negative for a documented PCN allergy when properly tested. This included Kleris et al.'s study during which 91.3% of the 104 study participants with a documented PCN allergy actually tested negative when properly tested (2018). Moussa et al. had similar results with their study in which 94.3% of the 194 study participants were de-labeled as having a PCN allergy when tested (2018). These two studies echo the statistics presented by Kufel et al. in that 90% of the 10% of

Americans with a documented PCN allergy when properly tested are negative for a PCN allergy (2019).

The presence of an incorrect PCN allergy label forces health care providers to use antibiotics not related to PCN's. These alternative antibiotics are often unnecessarily more broad-spectrum antibiotics that can lead to increased incidences of CDI and MRSA. These infections result in patients having to be hospitalized more frequently and can even lead to death. West et al. showed this with their study results in that a PCN allergy record was associated with six in 1000 more deaths and one in 1000 more patients with documented MRSA infections (2019). Blumenthal et al.'s study results also showed a significant increase in the incidence of MRSA in patients with a documented PCN allergy (2018). Specifically, having a PCN allergy label caused a 68% increased risk of MRSA and also a 26% increased risk for CDI. It was also noted that the use of non-PCN related antibiotics accounted for 55% of the increased risk for MRSA and 35% for the increased risk of CDI. Other studies such as Macy and Shu's showed that those patients who had been successfully de-labeled as having a PCN allergy averaged 0.09 fewer OPD visits, 0.55 fewer hospital days, and 0.13 fewer ED visits (2017). This supports other data describing PCN labeled patients having more health care visits and longer hospital stays.

IgE mediated allergic reactions to PCN are the swiftest and most dangerous type of reactions patients can possibly experience. Patients are extremely hesitant to undergo confirmatory PCN allergy testing in the outpatient setting for this reason. The work performed by Bourke et al. (2015) demonstrated the safety and accuracy of PCN allergy testing. In their study, skin prick testing and intradermal testing for PCN allergies had a negative predictive value of 99.2%. Also, of the 137 patients they were able to follow up with, only 17 experienced a subjective adverse reaction. Another study demonstrated 770 of the 880 children who received

confirmatory PCN allergy testing were safely delabeled from having a PCN allergy (Mill et al., 2016). It was also discovered that the graded PC had a specificity of 100.0% (95% CI, 90.9-100.0%), a NPV of 89.1%, and a positive predictive value (PPV) of 100.0% (95% CI, 86.3%-100.0%). This shows the high levels of accuracy and safety when considering PCN allergy testing.

The process of testing patients to confirm a PCN allergy can avoid increased health care costs for patients and health systems by avoiding increased levels of morbidity and mortality associated with using antibiotics not related to PCN's. Estimated costs for a confirmatory PCN allergy testing range from $40 to $537 (Blumenthal et al., 2017). This is a minimal investment when one considers the potential cost savings of having testing performed. Multiple studies referenced in this review showed a cost saving for patients with a documented PCN allergy who had PCN allergy testing performed compared to those who did not. These included inpatient length of stay reduction savings of $1,145 to $4,254 (Mattingly et al., 2018), a prescription savings of $1,368 (Vyles et al., 2018), and an overall surgical savings of $42,240 for those surgical patients who had PCN allergy testing performed prior to surgery (Moussa et al., 2018). The most significant cost savings was described in the study performed by Macy and Shu (2017). Their study showed patients who had PCN allergy testing performed resulted in $1,915.40 less in health care expenses per patient per year. Which when compared to the one-time cost of PCN allergy testing at $145 and extrapolated across their health system revealed a possible health savings of over two million dollars over a period of just 3.6 years.

If PCN allergy testing is safe, accurate, and cost-effective, then why are not more patients and providers in favor of it? The studies reviewed showed this is largely due to the incorrect patient and provider perceptions regarding the availability, safety, and costs related to

confirmatory PCN allergy testing. It was discovered in one study that 40% of the medical providers were unaware of the specific types of PCN allergy testing available to them (Trubiano et al., 2016). Another study performed by Jones and Kim revealed the different perceptions medical providers had regarding PCN allergy testing (2019). Of those medical providers surveyed in the study: 41% felt they did not have the time to address PCN allergy testing during their patient encounters, 26% were not aware PCN allergy testing was available to them, and 12% felt concerned that their patient's PCN allergy history was vague or unclear. Both of these studies highlight some misunderstandings and need for further education about PCN allergy testing for medical providers. If medical providers are properly educated regarding the availability and benefits of PCN allergy testing in their health systems they can then begin to educate their patients and bring about significant positive change.

In conclusion, would confirmatory PCN allergy testing in the outpatient setting versus using more broad-spectrum antibiotics not related to PCN's be more cost-effective and safer in limiting overall patient morbidity and mortality? The research shows that PCN allergy testing in the outpatient setting is a safe and accurate method of confirming a patient's PCN allergy status. The costs associated with testing are minimal compared to the increased costs of having to use more expensive broad-spectrum antibiotics that can cause infections and increased hospital stays. The data shows a significant portion of the population is incorrectly labeled as having a PCN allergy. If medical providers can begin to educate their patients regarding the benefits of confirmatory PCN allergy testing we can significantly reduce the increased costs, morbidity, and mortality with having an incorrect PCN allergy label.

Applicability to Clinical Practice

With the information provided by this literature review, both clinicians and patients will be able to make a safe and informed decision regarding performing confirmatory allergen testing in the presence of an unclear or unconfirmed PCN allergy. The decision to perform confirmatory PCN allergy testing based on unbiased, evidence-based medicine could lead to reduced health care costs, improved patient outcomes, and decreased adverse effects related to prescribing alternative, more broad-spectrum antibiotics instead of PCN's. It is also important to mention that proper antibiotic stewardship demands the precise prescribing of the narrowest spectrum antibiotic that will effectively treat the patient's infection. Having patients undergo confirmatory PCN allergy testing in an effort to avoid having to use more broad-spectrum antibiotics is a necessary step health care providers need to perform in order to improve patient care, reduce costs, and reduce overall antibiotic resistance.

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