

Penicillin Allergy...Maybe Not? The Military Relevance for Penicillin Testing and De-labeling

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ABSTRACT Introduction: Penicillin allergy is the most common drug allergy reported. About 8–10% of individuals in the USA have a documented penicillin allergy, yet 90% are not truly allergic to penicillin. A penicillin allergy “label” results in increased antibiotic-related adverse reactions and increased health care costs, thus impacting the overall “readiness” of the military. Materials and Methods: A review of the current literature and approaches to penicillin allergy and “de-labeling” a patient who reports penicillin allergy was conducted and future strategies to identify and assess military beneficiaries were outlined. Military allergists had a formal discussion at the Tri-service Military Allergy Immunology Assembly regarding the state of penicillin allergy testing in military allergy clinics. Results: A PubMed search yielded 5,775 results for “penicillin allergy” and 484 results for “penicillin allergy testing.” There were two formalized penicillin testing programs in the military treatment facilities. In 2017, the military trained nearly 165,000 new recruits. If 5–10% reported a penicillin allergy and 90% were de-labeled, that would yield a \$15–30 million cost savings annually. Further, de-labeling of the 9.4 million active duty, beneficiaries and retirees with a 90% success rate could result in even greater savings for the military health care system. Conclusion: A penicillin allergy label is a risk to military readiness secondary to associated increases in the length of hospitalizations and emergency department and medical visits. Penicillin de-labeling is a simple intervention that can improve readiness, significantly decrease health care costs and prevent antibiotic resistance, as well as antibiotic-associated adverse events. The military allergist should be “front and center” providing expertise guidance and leadership for clinic and hospital-based penicillin de-labeling efforts which are nested within the antibiotic stewardship programs.

INTRODUCTORY STATEMENT OF PURPOSE

Individuals labeled with a penicillin allergy are invariably treated with alternative antibiotics, have increased antibiotic-resistant infections, incur higher health care costs and experience more adverse reactions.¹ Drug allergy awareness is critical to prevent iatrogenic adverse events, yet there is significant evidence that more than 90% of patients labeled with a penicillin allergy are not allergic to penicillins (or any beta-lactams).¹ Despite this evidence, providers may be reluctant to prescribe a medication within the penicillin drug class to a penicillin “allergic” patient without a formal assessment. In this article, the epidemiology, health care implications and relevance for military members regarding penicillin allergies are reviewed.

HISTORICAL REVIEW AND THE EPIDEMIOLOGY OF PENICILLIN ALLERGY

Penicillin was the first antibiotic discovered by Alexander Fleming in 1928. The U.S. government recognized penicillin’s critical role in military medicine early on and following extensive collaboration with the Office of Scientific Research and Development, it was FDA approved in 1945 with subsequent mass production for World War II, see Figure 1.² Since that time period, based on clinical guidelines, penicillins have continued to be a commonly prescribed antibiotic class due to their clinical efficacy in many types of infections. Chemically, penicillins share a beta-lactam ring which is found in penicillin G, ampicillin, amoxicillin, piperacillin, and other “cillins.” At present, 8–10% of the U.S. population report a penicillin allergy, which is the most common documented drug allergy.¹ Although not all adverse drug reactions are a true immune-mediated “drug allergy,” for the purpose of this article, any beta-lactam (or penicillin class medication) associated adverse drug reaction that has been recorded in a medical record by a health professional is included as a penicillin allergy. Once a patient is labeled with a penicillin allergy, many clinicians avoid all beta-lactam antibiotics which often includes the cephalosporins due to potential for cross-reactivity. Despite this high prevalence of reported penicillin allergies, studies have shown that less than 1% of the population are actually allergic.¹ A penicillin allergy “label” impacts the health care system in four recognized ways: (1) increased risk for antibiotic

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FIGURE 1. (Left) Source: Advertisement for penicillin production from Life magazine, August 14, 1944. “Thanks to Penicillin...He Will Come Home!” From the National WWII Museum, New Orleans, LA, USA. (Right) Source: Record Group 44, Records of the Office of Government Reports, 1932-44-PA-1505 “Penicillin Saves Soldiers’ Lives! Every Minute Saved in Building This Plant Means a Life Saved on the Fighting Fronts. Give This Job Everything You’ve Got, 1941-54,” National Archives, College Park, MD, USA.

resistance, (2) increased antibiotic-related adverse events, (3) reduced quality of care, and (4) increased health care costs.¹ In the military, this impact can start on the first day of recruit training.

PENICILLIN ALLERGY AND OPERATIONAL RELEVANCE

Penicillin’s role in the military starts during basic training with an initial intramuscular injection of benzathine penicillin for group A *Streptococcus* prophylaxis.^{3,4} At present there are eight basic training sites for the Army, Air Force, Navy, and Marine Corps, which train approximately 165,500 new recruits each year, Table I. However, if a recruit reports a penicillin allergy, they are treated with an alternative and less effective broader spectrum antibiotic, (typically azithromycin). Recruits are then required to carry a red medical warning tag, often referred to as a “dog tag,” which lists any allergies. Given the evolving penicillin allergy literature, less than 1% of service members have an immediate-type hypersensitivity to beta-lactam agents.¹ As these penicillins are often first-line for a wide variety of common infections, have less adverse side effects, and are readily available, even in remote or austere operating conditions, access to this class of antibiotics is of paramount importance in the medical readiness of the U.S. military.

INFECTIOUS DISEASES AND ANTIBIOTIC RESISTANCE

Infectious diseases have always accompanied military activity, including common infections and tropical diseases.⁵ Despite comprehensive vaccine and preventative medicine programs, military members are at high risk for a variety of infections (respiratory, gastrointestinal, etc.) in both peace

time and combat activities, inevitably making antimicrobial resistance a serious health and readiness threat.^{3,6} Though there are no military specific studies, in the United States, over 2 million people acquire antibiotic-resistant infections annually and 23,000 people subsequently die from these infections.⁷ Over 250,000 illnesses and 14,000 deaths annually are due to *Clostridium difficile* alone.⁷ There are many factors contributing to the increase in antibiotic resistance, however, one significant cause is the use of broad spectrum antibiotics. Further, broad spectrum antibiotics are often used when first-line agents, such as penicillins, cannot be used due to a reported “allergy.”

BROAD SPECTRUM ANTIBIOTIC USE AND ADVERSE EVENTS

Antibiotics are frequently used in both the inpatient and outpatient settings. In one CDC study, 49.9% of hospitalized patients received at least one antibiotic.⁸ According to other studies, 20% of hospitalized patients will have an adverse event related to their antibiotic and 19.3% of emergency room visits for adverse drug reactions are from antibiotics.^{9,10} In the latter study, sulfonamides, clindamycin, and quinolones were the antibiotics most commonly associated with adverse reactions.¹⁰

In a large Kaiser study, 462,225 hospitalizations were analyzed and compared for clinical outcomes and health care use in patients with and without a penicillin allergy.¹¹ When matched by age and sex to a similar cohort hospitalized for the same medical condition, patients who had a penicillin allergy were noted to have significantly longer hospitalizations, as well as increased rates of *C. difficile*, Methicillin Resistant *Staphylococcus Aureus* (MRSA), and Vancomycin Resistant *Enterococcus* (VRE); all subsequently were treated

TABLE I. 2017 Estimated Recruits and Projected Health care Savings Annually With Penicillin De-labeling

Service Branch	Location	Recruits	Report Penicillin Allergy ^a	Projected Cost Savings Annually (\$) ^b
Army	Fort Jackson, SC	62,500	3,125–6,250	\$6,250,000–12,500,000
	Fort Leonard Wood, MO			
	Fort Sill, OK			
	Fort Benning, GA			
	Total Army Sites			
Air Force	Lackland Air Force Base, TX	35,000	1,750–3,500	\$3,500,000–7,000,000
Navy	Great Lakes, IL	35,000	1,750–3,500	\$3,500,000–7,000,000
Marine Corps	Parris Island, SC	17,000	850–1,700	\$1,700,000–3,400,000
	San Diego, CA	16,000	800–1,600	\$1,600,000–3,200,000
TOTAL Estimate		165,500	8,275–16,550	14,895,000–29,790,000 ^c

^aBased on estimated 5–10% reported penicillin allergy.

^bBased on \$2000 per penicillin de-labeled individual.

^c90% of those with reported penicillin allergy de-labeled.

with broader spectrum antibiotics. During that three year period, the cost of having a penicillin allergy equated to 30,433 extra hospital days and \$64,626,630 more than those who did not have the penicillin allergy label.¹¹

RISKS ASSOCIATED WITH OTHER BROAD SPECTRUM ANTIBIOTICS

Although penicillins continue to be the first-line treatment for many common infections (including sinus/ear/soft tissue infections, strep throat, dental prophylaxis, Group B strep in pregnancy, *H. pylori* regimens, syphilis, etc.), when a patient has an “allergy” to penicillin, they may be treated with an alternative broader spectrum antibiotic. These second and third-line antibiotics are less effective, hence considered second or third-line, and associated with both adverse events and increased resistant organisms. Common alternatives include macrolides, fluoroquinolones, and vancomycin.

Macrolides are a common class of antibiotics used as an alternative for penicillins, particularly azithromycin and clarithromycin, but have known adverse reactions including gastrointestinal side effects (nausea, vomiting, diarrhea, and abdominal pain), liver toxicity (abnormal liver function tests, hepatitis, and liver failure), and cardiac risks (QT prolongation and sudden death). In several large pharmacoepidemiologic studies there was an increased risk for cardiovascular mortality in those patients receiving azithromycin, when compared to amoxicillin.^{12–14} Similar increased risk ratios with clarithromycin, compared with amoxicillin have been shown in other studies as well.^{15,16}

Another frequently prescribed antibiotic class is fluoroquinolones, which includes levofloxacin, ciprofloxacin, and moxifloxacin. Fluoroquinolones come with a black box warning on the package insert for their known serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, exacerbations of myasthenia gravis, and central nervous system effects. This medication class has also been associated with cardiac effects, such as QT prolongation and life-threatening arrhythmias. In a population-based study of over 10 million people, the use of fluoroquinolones (moxifloxacin), compared with

amoxicillin, was associated with significantly increased risk of ventricular arrhythmias and cardiovascular death.¹⁴ In addition to various adverse reactions, fluoroquinolone use has also been associated with a risk of developing *C. diff*, as demonstrated in one large prospective study.^{17,18} When adjusted for age, sex, medical history, medications, and other factors, prior fluoroquinolone use was associated with the highest risk for developing *C. diff*, with 82% of tested strains being resistant to fluoroquinolones.^{17,18} Another study examining the risk factors for MRSA among all antibiotics showed that fluoroquinolones were the only antibiotic class associated with an increased risk.¹⁹

Vancomycin emerged into use after *Staphylococcus aureus* developed resistance to methicillin. Methicillin-susceptible *S. aureus* (MSSA), as the name implies can be treated with methicillin and other beta-lactams. Patients are often treated with vancomycin due to concerns of MRSA, however, studies have shown that vancomycin is less effective than methicillin in clearing MSSA bacteremia and is also associated with increased morbidity and mortality.^{20,21} Unfortunately, patients labeled with a penicillin allergy will often be treated with vancomycin, which is a suboptimal treatment with more complications.²² For example, vancomycin is used as an intrapartum antibiotics for group B streptococcal disease when the patient reports an allergy to penicillin.²³ One study has linked pregnant women with an unverified penicillin allergy to significantly increased hospital utilization, morbidity and use of second-line antibiotics leading to more adverse reactions.²⁴

Lastly, patients with a reported penicillin allergy have a 50% increased risk for surgical site infections related to second-line antibiotic use during the perioperative period.²⁵ These patients will often receive clindamycin, vancomycin, and gentamicin, which are all less effective and associated with more adverse reactions.²⁵

QUALITY CARE

Executive Order 13676 was issued in 2014 to combat antibiotic-resistant bacteria, followed by the publication of a National Action Plan in 2015. This in turn led to the Joint

Commission requirement for antibiotic stewardship standards in 2016. Antibiotic Stewardship Programs (ASPs) were developed by the Society for Healthcare Epidemiology of America and the Infectious Diseases Societies, supported by the Centers for Disease Control and Prevention. All acute care hospitals participating in Medicaid and Medicare are now required to implement ASPs, including all military treatment facilities (MTFs). MTFs are currently in the process of developing ASP programs depending on the size of their facilities, services provided and resources available. Penicillin allergy testing and verification will be an important part of this program to avoid unnecessary use of broader spectrum antibiotics and suboptimal treatment regimens, as well as to decrease the rising number of drug-resistant organisms.

Unfortunately, there are fewer and fewer novel antibiotics being developed and approved by the FDA and even as new antibiotics come into clinical use, bacteria develop resistance rapidly.⁷ Overall, not only has there been an increase in antibiotic resistance globally, fewer new antibiotics are available to treat these resistant and evolving organisms.⁷

HEALTH CARE COSTS ASSOCIATED WITH PENICILLIN ALLERGY

Based on the National Health Expenditure Accounts data, health care spending reached 17.9% of the gross domestic product in 2016.²⁶ Unfortunately, penicillin allergies play an important role in these higher costs. As reviewed earlier, Macy et al demonstrated the significantly higher costs associated with having a reported (and unverified) penicillin allergy, including longer hospitalizations, increased complications, and rising rates of nosocomial infections.¹¹ A subsequent analysis of both inpatient and

outpatient settings showed a potential savings of \$2,000/patient/year in health care expenses with the de-labeling of reported penicillin allergies.²⁷ Simply extrapolated to the recruit population, if 5–10% reported a penicillin allergy, \$15–30 million could be saved annually and compounded over the length of their career (Table I). If a de-labeling program was utilized for the 9.4 million Tricare-enrolled beneficiaries (active duty, dependents, retirees, etc) de-labeling of 90% (846,000) beneficiaries would result in an annual savings of \$1.7 billion.²⁸ Current literature provides compelling evidence that all health care plans should implement penicillin allergy testing and de-labeling programs.²⁷ In addition to the inadvertent costs associated with penicillin allergies (whether proven or not), when comparing direct costs between penicillins and alternative broad spectrum antibiotics, the latter are often more expensive and contribute to overall increases in health care costs.²⁹ As most patients with a history of penicillin allergy do not have verified allergy, de-labeling those who do not have a true allergy will have the most individual, public health and cost benefits.^{1,27}

APPROACHES TO PENICILLIN ALLERGIES, TESTING AND DE-LABELING PROGRAMS AS PART OF THE ANTIMICROBIAL STEWARDSHIP PROGRAM

As 90% of individuals who claim a penicillin allergy have lost their sensitivity over time or were never truly allergic to the antibiotic class, testing and de-labeling are critical.¹ With the increase in resistance and shortage of new antibiotics on the horizon, there is an imperative need to focus on first-line therapies, such as penicillins and beta-lactams.⁷ In essence, verifying whether penicillin allergies are real is a

Penicillin De-labeling Procedures		
Personnel – - Physician (or trained licensed independent provider) - Nurse (or equivalent) Resources – - Amoxicillin 250mg capsule or liquid (pediatric weight based, up to 250mg) - Anaphylaxis kit (injectable epinephrine, antihistamine) Procedure – - Ensure patient is not on a beta-blocker or antihistamine, pregnant, or has any medical condition that would not tolerate anaphylaxis. - Clinical history (see questionnaire on right), vital signs, focused exam. - If patient has tolerated any penicillins following their prior reaction, they are CLEARED. No testing indicated. - Informed consent form for medication testing. - If all questions to 1–5 are NO, patient is LOW RISK, proceed to oral challenge. Monitor for 1 hour. - If any answer to 1–3 are YES, patient is at HIGHER RISK, and if testing is available, recommend skin testing first (or allergy referral). - If any answers to 4–5 are YES, STOP and continue to avoid. - If there is no reaction to the test, remove from drug allergies. - If the patient has a systemic reaction concerning for anaphylaxis, treat with epinephrine and antihistamine per local protocols.	Penicillin Allergy Questionnaire	
	YES	NO
	1. Did your reaction occur within the past year?	
	2. If a rash was present, did it last less than 24 hour? If unknown, mark NO.	
	3. Was your reaction life-threatening (i.e. severe anaphylaxis requiring epinephrine, ER visit, ICU admission, intubation)?	
	4. Did your reaction involve blistering, ulceration, sloughing of your skin or lining of your mouth, eyes, genitals – OR – were you diagnosed with Stevens Johnson Syndrome or Toxic Epidermal Necrolysis?	
	5. Did your reaction involve any organ dysfunction/failure – OR – were you diagnosed with serum sickness, drug reaction with eosinophilia, acute interstitial nephritis?	

FIGURE 2. Penicillin de-labeling procedures.

crucial step to ensure the use of optimal and effective first-line treatments, decrease antibiotic resistance, avoid adverse events, and lower health care costs.

Testing for a penicillin allergy is safe and cost effective. Skin tests and oral challenges are the two main components of testing and if skin testing is negative, the oral challenge effectively clears the patient for penicillin administration in the future (Fig. 2). Clinical evaluation pathways and de-labeling programs can occur in both inpatient and outpatient settings. These evaluations can also occur in pre-op, surgical, dental clinics, or virtually any location where antibiotics are prescribed or medication reconciliation is conducted. There are several hospitals and clinics that have implemented allergy evaluations alongside pre-operative clinics where patients undergoing elective surgeries are de-labeled of their penicillin allergy prior to surgery. This process has been successful in significantly decreasing the rates of vancomycin use and lessening the morbidity associated with the use of this second-line antibiotic.^{23,26,30}

Military allergists have identified this clinical need for penicillin allergy verification and have implemented initial penicillin de-labeling programs at multiple sites. At the 2018 Tri-Service Military Allergy Immunology Assembly meeting, military allergists participated in a discussion about penicillin testing and de-labeling in the military. At the Marine Corp Recruiting Depot (MCRD), located in San Diego, CA, USA, 16,000 recruits are trained annually. In a recent study, 5% of marines entering basic training reported a penicillin allergy. Over a 20-month study period, 397 of 402 (98.7%) recruits were cleared of their reported penicillin allergy while five had a reaction.³¹ Since then, an additional 300 recruits have been tested and over 99% have been de-labeled thus allowing them to receive penicillin prophylaxis and future beta-lactams (personal communication, Dr Mark Tucker).

At the Walter Reed National Military Medical Center (WRNMMC), a standardized penicillin de-labeling program was established in 2015. This effort includes both inpatient and outpatient referral and assessment workflow processes.³² The inpatient strategy is directly linked with the hospital's antibiotic stewardship program and features proactive assessments of patients with a documented beta-lactam allergy. The outpatient referral system was structured with medical readiness as a prominent aspect. Active duty service members are proactively identified by regional medical readiness clinics and referred as part of their annual health assessments. This referral network has expanded to include other beneficiaries to such as geriatric and pediatric patient populations. Over 400 patients have been evaluated with a more than 99% successful de-labeling rate. Furthermore, since August 2016, the WRNMMC Allergy/Immunology has used a history-based risk stratification method. Using this screening technique, over 83% of patients were determined as "low risk" and proceeded straight to a single step 250 mg amoxicillin challenge; no reported reactions have occurred (author, Dr Taylor Banks' unpublished data).^{33,34} Extrapolated to the data from these two military

settings (MCRD and WRNMMC) over a 1.5- to 2-year period where approximately 800 individuals were de-labeled (at \$2,000/year), there could be \$1.6 million saved annually, in addition to the clinical and public health benefits.²⁷ These innovative approaches in the inpatient and outpatient settings have dramatically increased provider/patient awareness and access to de-labeling assessments, and have also developed a robust infrastructure for continued expansion.

Penicillin allergies are an important barrier to effective antibiotic treatments with associated with worse outcomes and higher costs. In addition to immunizations, infection control and education to reduce spread of infections, penicillin allergy verification and de-labeling programs should be an integral part of any ASP. In the military, along with ASPs, de-labeling programs early in a service member's career (i.e., recruit training sites) would be most beneficial to allow treatment with first-line antibiotics, decrease risk for adverse reactions, and antibiotic resistance, as well as prevent complications from use of broad spectrum second or third-line antibiotics. This process also has important implications on operational readiness of the individual and unit as well. In reference to the DoD 2015 Agency Strategic Plan, penicillin testing and de-labeling would align with Goal #3, which is to "strengthen and enhance the health and effectiveness of the total workforce."³⁵ In the current climate of modernizing and standardizing the DoD, implementing this type of program across all services would have significant benefits for all involved.

CONCLUSION

Accurate accounting for the presence or absence of a penicillin allergy has military relevance and is a significant readiness, safety, and public health issue. Rigorous assessment of reported penicillin allergies would allow providers to have increased confidence to strictly avoid these agents in the small portion of the population who demonstrate a persistent penicillin (or all beta-lactam) allergy following appropriate allergy evaluation. The military would also benefit substantially in terms of improved medical readiness, safer delivery and enhanced quality of care in all environments, and decreased health care costs by allowing access to beta-lactam agents in the vast majority of those patients who can be cleared through allergy testing. Though further studies are needed in military populations, based on the current research and national guidelines, proactive penicillin allergy evaluation and de-labeling of military members should be implemented.

PREVIOUS PRESENTATION

Part of the information was presented at a Grand Round's lecture at the Naval Medical Center San Diego on January 19, 2018.

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