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De-labeling of β-lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis☆

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ABSTRACT

Background: Suspected penicillin allergic individuals receive suboptimal non-β-lactams for intraoperative prophylaxis which may prolong operations and have negative clinical outcomes. We therefore studied if β-lactam de-labeling optimized choice of prophylactic antibiotics and improved intraoperative time efficiency.

Methods: A multistep approach was used. It included a risk assessment tool by an allergist, β-lactam skin testing and oral provocation. To determine the value of de-labeli[illegible]e appraised intraoperative antibiotic choices and correlated them with time to first incision.

Results: A total of 194 patients were evaluated preoperatively. Four patients were diagnosed β-lactam allergic on skin testing. Of the remaining 190 skin test negative patients, 146 were β-lactam challenged. Only 5% reacted and were considered β-lactam allergic. Cefazolin became the perioperative antibiotic of choice for 77% of patients requiring antibiotic prophylaxis. Only 5 confirmed β-lactam allergic patients received intraoperative vancomycin. Patients avoiding use of vancomycin saved an average of 22 minutes in operative time. Of the 44 patients not having a β-lactam challenge, 36 received antibiotics and 18 (50%) of these were prescribed intraoperative cefazolin.

Conclusion: Using this three step process, almost all of those claiming penicillin allergy were de-labeled. In most patients that were drug challenged, β-lactam antibiotics became the perioperative drug of choice. In cases where oral challenge was not used in the assessment only 50% were given a β-lactam. The reduced use of vancomycin minimized delays in initiation of incision time, thus improving operative efficiency. Ultimately, randomized controlled studies are required to objectively determine the effectiveness of this approach.

Introduction

Antimicrobial resistant infections affect more than 2 million people in the United States and result in about 23,000 deaths annually, at an estimated cost of $55 billion USD.[1] The prescription of "antibiotics of last resort" (such as carbapenem) is of major concern, because of an increase in reported cases of resistance to these antibiotics due to over-prescription.[2,3]

Penicillins remain among the most commonly prescribed antibiotics worldwide.[4-7] They provide many advantages; including high effectiveness, low cost, and minimal side effects.[8] Unfortunately, about 10% of the general population carries a label of penicillin allergy.[9-11] Among those who claim to be penicillin allergic, 90% are not truly allergic when properly evaluated.[12,13] Intolerance and non-specific adverse events are often inappropriately attributed to penicillin allergy. This in turn leads to the prescription of inappropriate antibiotics that contribute to the development of antibiotic resistance.

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The American Academy of Allergy, Asthma & Immunology points out that without β-lactam testing, an unverified history of penicillin allergy can contribute to higher costs and greater risk for adverse effects from alternative non-β-lactam antibiotics, along with increased rates of serious antibiotic resistant infections such as *c.difficile* and methicillin-resistant *staphylococcus aureus*.[14]

Surgical site infections are a common cause of healthcare-related infections.[15,16] Perioperative antimicrobial prophylaxis is implemented in order to lessen the chance of microorganisms taking hold at the site of surgery during the procedures.[17] The most commonly used antibiotics in perioperative prophylaxis are cefazolin and vancomycin. Cefazolin, a first generation cephalosporin, is the drug of choice due to its antimicrobial effectiveness, reasonable cost, and a short duration of action.[18] In cases of suspected β-lactam allergy, vancomycin is the most commonly prescribed alternative despite some major drawbacks, such as longer administration time (approximately an hour)[19] and significant side effects—red man syndrome,[20] nephrotoxicity, and ototoxicity.[21] Patients with a reported penicillin allergy have 50% increased odds of surgical site infections, attributable to use of second-line perioperative antibiotics. These infections incur an estimated cost exceeding $25,000 USD per case.[22]

A systematic institutional approach to confirming penicillin allergy is not currently implemented in many large Canadian hospitals and as a result, patients are often permanently labeled allergic to penicillin. Given the obvious need to clarify suspected penicillin allergy status, a service and protocol to provide preoperative evaluation of possible β-lactam allergy was established at the Montreal General Hospital (MGH) (Fig 1) using standardized prescriptions, policies, procedures, and a risk assessment tool (Fig 2). A need to determine the value of this service was identified.

Study Design

Standardized drug allergy testing was initiated in January 2015 when policies, standard operating procedures, and consent forms were created. The preoperative staff was engaged to facilitate the referral process; patients were evaluated on the same day as their regular scheduled preoperative visit. A mandatory risk assessment tool defined the level of challenge required for each patient. Experienced clinical staff performed the clinical evaluations and drug testing. Higher risk patients required a graded challenge, whereas those at low risk underwent a skin challenge and a single full dose challenge. The tests were performed in an interventional allergy care unit. An allergist was present to supervise the procedure for up to 2 hours following the administration of the last dose. Patients were required to call 24 hours post testing to report any delayed reactions. Results were entered in the patient electronic medical record (EMR).

To determine the impact of this algorithm, a semiprospective study of patients with possible penicillin allergy was undertaken in May 2016. The aim of the study was to evaluate β-lactam allergy de-labeling with respect to perioperative antibiotic. Data were obtained from April 1, 2015 to March 31, 2017. The Research Ethics Board of the McGill University Health Center Research Institute approved the study. Eligible study participants were adults, 18 years of age and older, who had a history of an allergic reaction to penicillin and were scheduled for elective surgery within six months following the date of their preoperative visit.

All patients that were referred for preoperative evaluation by the Allergy Division were prospectively registered in the study as of May 2016 and the data captured in real time. Because the algorithm was established in January 2015 using methods, policies, procedures, and consent forms that did not change over time, we retroactively collected testing data from April 2015 to May 2017. For that period of time, patient charts were reviewed to identify those that met the study inclusion and exclusion criteria. The staff, methods, and procedures remained identical between the prospective and retrospective time frames. We verified all data with source documents in the patient electronic medical records. The allergist opinion, skin and drug challenge tests (for patients who were β-lactam skin test negative) were used to formally ascribe β-lactam allergic status. The results of each step were routinely sent to the pre op clinic and entered in the EMR allergy module. Information on the antibiotics used during surgery was obtained from the anesthesia and surgical records. The intraoperative antibiotics were chosen entirely by the operative team based on recommendations adopted from surgical practice guidelines.[23-25]

Clinical assessment

The initial consultation with the allergist included: a history of previous drug allergies, a personal and family history of allergy, current medication use, and presence of asthma and other acute medical problems. A risk assessment tool was used to preclude those where drug challenge testing was contraindicated.

Prick skin testing

Skin testing was performed with a PRE-PEN solution (benzylpenicilloyl polylysine injection USP). Controls included histamine 1mg/mL (positive control), saline (negative control) alongside diluted penicillin G (10,000U/mL). Fifteen minutes after administration the skin was evaluated for appearance of a wheal, erythema, and occurrence of itching at the test site. A positive reaction was defined by the development of a pale wheal within 15 minutes, surrounding the puncture site and varying in diameter from 3 mm or larger.

Intradermal testing

PRE-PEN in duplicate spots, penicillin G (10,000 units/ml) and saline (negative control) was injected in 3 different skin sites of the forearm to form an intradermal bleb. Skin reactions were diagnosed as negative if there was no increase in size of original bleb and no reaction greater than the negative control. The test was deemed positive if itching and an increase in size of original blebs of at least 3 mm occurred.

Oral challenge

Oral challenges were carried out in cases where the skin test was negative, the history was suggestive of true allergy, and there was no absolute contraindication related to both a history of severe allergic reactions and poor medical health status. The drug allergy risk assessment tool was used to determine risks of anaphylaxis or serious adverse reaction upon provocation testing. Based on the result of the risk assessment, a decision was made to proceed with the test and decide on the level of monitoring and intervention required during the procedure. If provocation testing was not contraindicated, those at low risk were given a single oral dose and observed with basic monitoring. Those at high risk had graded oral provocation under intensive supervision in a treatment recliner chair, with intravenous access and frequent evaluation of vital signs and pulmonary function.

Drug challenges were carried out at 10%, 30%, and full strength of a single dose of penicillin V (300 mg) or amoxicillin (500 mg). Patients were observed for an hour for any adverse reactions. If no immediate reactions were observed, patients were discharged and were instructed to call back 24 hours later to report any delayed reactions.

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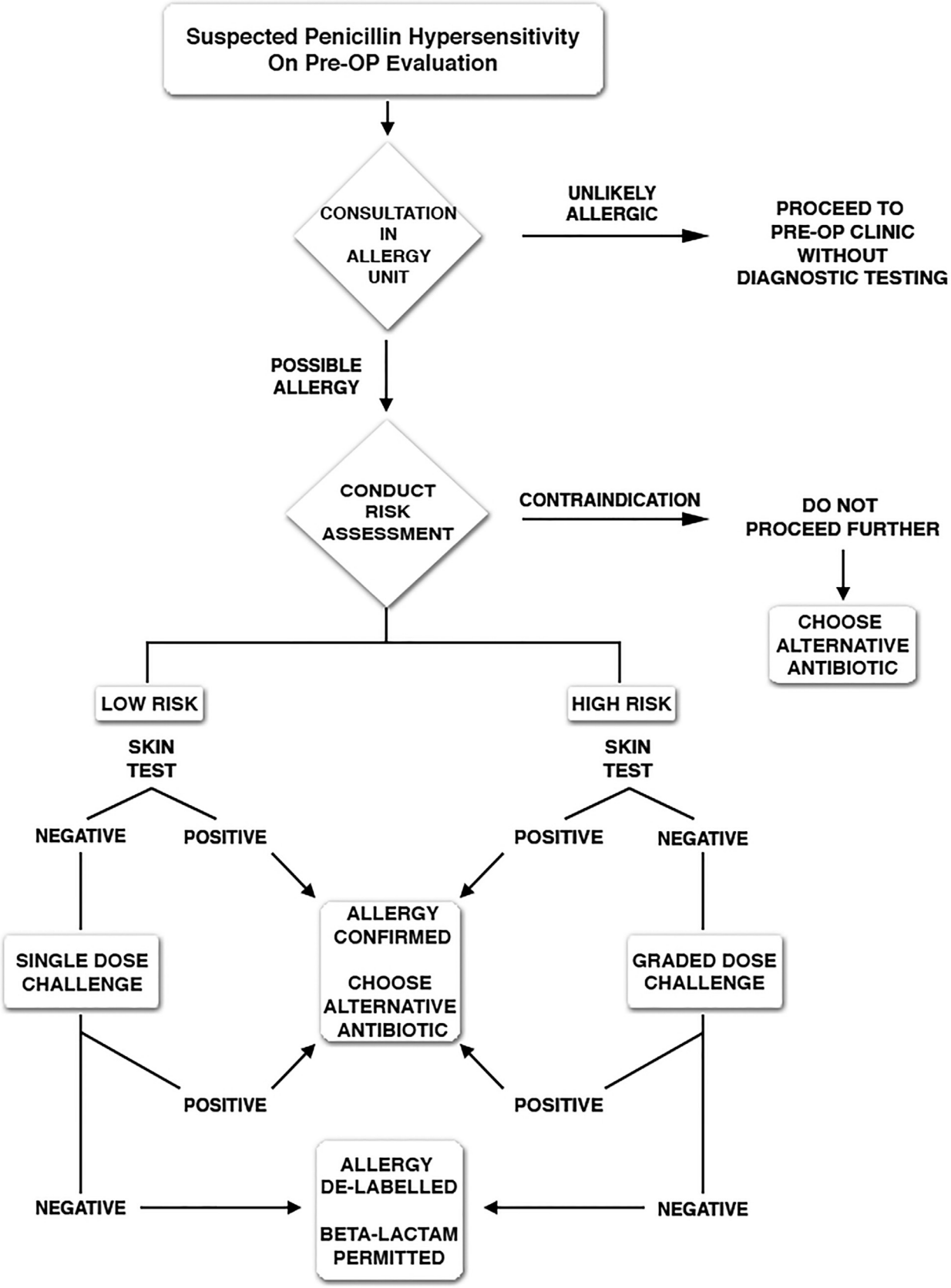

Fig. 1. Algorithm of Pre-op Evaluation of Suspected Penicillin Allergy.

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Pre Drug Provocation Testing Risk Assessment Tool

Drug to be tested:

1) Answer all questions to confirm no contraindication to testing

Contraindications

	YES	NO
Patient is pregnant		
Stevens-Johnson Syndrome		
Acute Generalized Exanthematous Pustulosis (AGEP)		
High fever		
Drug Induced Hypersensitivity Reactions with Eosinophilia and Systemic Symptoms (DIHS/DRESS)		
Toxic Epidermal Necrolysis (TEN)		
Exfoliative dermatitis		
Agranulocytosis		
Serum sickness		
Severe blood cytopenia		
Drug inducted vasculitis, autoimmunity to test drug		
Drug induced internal organ involvement		
Documented severe anaphylaxis to the suspect drug		
Poor respiratory, cardiac or other health issues (If yes, drug desensitization recommended)		

2) Determine level of risk

Manifestations of the historical adverse drug event:
☐angioedema ☐urticaria ☐asthma ☐anaphylaxis
☐other
Onset of symptoms post-drug ingestion:
☐ after first dose ☐ <1hr after drug
☐ 1-3 hrs after drug ☐ >3hrs-24 hrs after drug ☐ after 24hrs.

Asthmatic: Yes ☐ No ☐ If yes, controlled: Yes ☐ No ☐

Other known drug allergies:

Results of prior skin tests to drugs: ☐ Not done ☐ Positive ☐ Negative

The patient is on a beta-blocker☐ ACE-inhibitor☐ receptor antagonist☐:

Can this medication be stopped? Yes ☐ No ☐

Does the patient have a medical condition that could be important during provocation? Describe:_____

Based on the above the risk of provocation testing is: LOW ☐ HIGH ☐

Fig. 2. Pre Drug Provocation Testing Risk Assessment Tool.

Data collected

Date of birth, gender, and drug allergy history including: date of reaction, clinical presentation, results of drug allergy skin testing, and oral challenges. The number of doses taken and presenting symptoms following challenge were documented. The types of surgery, time of patient arrival in the operating room, the incision start time and the antibiotics used in surgery were documented.

Results

There were 255 patients referred for allergy testing prior to scheduled surgery from April 1, 2015 to March 31, 2017. Of these, 61 were excluded because they did not meet the study criteria as they did not undergo surgery within 6 months of their testing, underwent surgery at another institution, were deceased, or had incomplete files. The EMRs of the 194 patients meeting the eligibility criteria were reviewed for completeness and accuracy

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Table 1
Skin test and penicillin challenge results.

Penicillin Skin Test	N = 194 (%)
Negative*	190 (98%)
Positive**	4 (2.0)
Penicillin Challenge	N = 146 (%)
Negative	139 (95%)
Positive	7 (5%)

* 44 patients did not require drug challenge based on allergist evaluation.
** Oral penicillin challenge was not carried out in the penicillin skin test positive patients.

Table 2
Choice of perioperative prophylactic antibiotics based on penicillin allergy testing.

Patients with positive testing		
Antibiotic	Skin Test Positive (N = 4)	Challenge Positive (N = 7)
Cefazolin	0	2
Vancomycin	3	2
Ciprofloxacin	0	0
Clindamycin	1	2
No Antibiotic	0	1

Patients with negative testing		
Antibiotic	Skin Test Negative (N = 44)	Challenge Negative (N = 139)
Cefazolin	18	102
Vancomycin	8	7
Clindamycin	10	8
Ciprofloxacin	0	1
Amoxicillin	0	2
No Antibiotic	8	19

Table 3
Mean delay in surgery initiation per antibiotic used.

Antibiotic	Mean time delay to surgery initiation (mins)	N (SD)
Vancomycin	59	20 (35)
Cefazolin	37	122 (18)
Clindamycin	32	21 (13)
No Antibiotic	21	28 (10)

Surgery start time was defined as time of first incision. The mean time from entry to the operating theater and first incision defined surgical delay.
SD, standard deviation.

of data. Data collection forms were used to transcribe information on predetermined variables and then entered in a relational database. All suspected β-lactam allergic patients were evaluated using the allergy-testing algorithm (Fig 1). The cohort included 129 females (66.5%) and 65 males (33.5%). All eligible patients had reported a previous reaction to penicillin or its derivatives within the past 5 years (4.6%), between 5–20 years ago (18.6%), or more than 20 years (50%). The remaining cohort (26.8%) had unknown or undocumented dates of reaction. The reported allergy defining symptoms among all cases were predominantly unspecified rash (29.9%), unknown (patients could not recall type/time of reaction) (29.4%), and urticaria (20.1%). The types of surgery were: orthopedic (34.0%), general (33.5%), maxillo-facial (9.8%), thoracic (11.3%), plastic (6.7%), and other (4.6%).

Out of the 194 eligible patients, 4 had a positive skin test and thus were not orally challenged. In addition, 44 patients were clinically evaluated, had skin tests but no drug challenges were ordered because, in the opinion of the allergists, a negative skin test and very weak history was sufficient to rule out penicillin allergy. Of the remaining 146 that were subjected to skin testing and oral drug challenge, only 7 were positive (Table 1). In total we identified 11 individuals out of 194 with a confirmed β-lactam allergy. We thus de-labeled 183 of 194 (94.3%) individuals referred to us. Among 139 patients with a negative challenge, 19 did not require preoperative antibiotics. Cefazolin was prescribed in 102 of the remaining 120 surgeries (85%). However, of the 44 individuals who had a negative skin test and did not have a challenge, 8 did not require prophylactic antibiotics and cefazolin was prescribed in only 18 out of the remaining 36 (50%). In those who had a positive challenge to β-lactams, vancomycin was used in two patients, cefazolin in two, clindamycin in two individuals and one did not receive any antibiotics. In patients with a positive skin test, vancomycin was used in three cases and clindamycin in one case (Table 2).

The mean delay in operations due to the administration of antibiotics was calculated by measuring the difference between the time the patients arrived in the operating room and the actual start of surgery at first incision. It is recommended that vancomycin be infused 1 hour prior to start of surgery, whereas cefazolin must be administered approximately 30 minutes prior to incision. We recorded a mean time to first incision of 59 minutes with vancomycin administration, 37 minutes with cefazolin, and 21 minutes when no antibiotics were used. The use of cefazolin reduced the incision time delay by an average of 22 minutes in comparison to the time required for vancomycin (Table 3).

Discussion

Comprehensive penicillin allergy evaluation successfully de-labeled 94.3% of patients referred for preoperative β-lactam allergy evaluation. By identifying patients who were truly penicillin allergic, vancomycin was used only in five surgeries (3%) and cefazolin was subsequently prescribed for 120/155 (77.4%) of the de-labeled patients that received prophylactic antibiotics. Despite the preoperative evaluation and the allergist recommendation, for unknown reasons, two out of seven patients that had a positive oral challenge were given cefazolin during surgery. The high use of alternative non-β-lactam antibiotics in 50% of the skin test negative patients that did not have drug challenge testing was surprising. It is unclear if this occurred because of poor communication or delays in conveying the negative skin test findings.

There was lower intraoperative vancomycin use in those that had challenge testing than in those with skin testing alone. Furthermore our rate of vancomycin use was lower than in reported studies. In patients with suspected penicillin allergy, Park et al showed that following testing 75% of patients were prescribed cefazolin and 16% vancomycin[26]; Frigas et al similarly reported a cephalosporin use of 70% and vancomycin at 10%[9]; and McDanel et al found that 84% of cases utilized cefazolin and 8% vancomycin.[27]

The direct costs related to the use of nonpenicillin based antibiotics are higher than for use of β-lactam antibiotics.[28] The estimated acquisition costs of antibiotics in penicillin allergic individuals compared to nonallergic patients are estimated to be 2.3 times higher than in those who are nonallergic.[29] The direct costs of pharmacologic treatment result not only from the cost of the drugs but also include ancillary expenses such as drug administration and the monitoring and treating of side effects requiring additional nursing and medical care. These additional expenses are estimated to be 8 times the drug acquisition cost or approximately $300 CAD per patient for each full treatment.[30] For antibiotic prophylaxis with vancomycin, these direct costs are less and are estimated at $35 CAD per infusion. However, delays in operating time amplify the total cost because of delays caused by the need for intraoperative intravenous administration.

Our findings suggest that β-lactam de-labeling is associated with overall cost savings. The use of cefazolin rather than vancomycin reduced delays in initiating surgery by 22 minutes. This operative time improvement resulting from penicillin allergy de-

labeling has never been previously reported. In a surgical cost analysis previously performed at our institution, Lee et al demonstrated that the cost per operating room hour was $866 CAD.[31] Based on the direct cost of vancomycin of $35 CAD and $317 CAD cost of time in the operating room (22/60 minutes × $866 CAD), we estimated the direct per patient intraoperative cost of vancomycin to be $352 CAD. Since 120 patients received cefazolin, we calculated a possible institutional saving of $42,240 CAD.

Our institution has an annual volume of 30,000 patients that undergo surgery.[32] Assuming an 11.5% institutional prevalence of suspected penicillin allergy[33] and an estimated 75% requirement for prophylactic antibiotics, we calculate a yearly need for 2587 preoperative allergy assessments. Given 77% use of cefazolin in penicillin allergy de-labeled individuals, 1992 patients would require alternative antibiotics, half of whom would use vancomycin. Thus 996 could avoid using vancomycin every year. Using these estimates, the 22-minute delay reduction in operating room time would save 365 hours of operating theater time and $350,867 CAD in direct costs on an annual basis. The additional indirect costs are difficult to calculate yet are substantial, given the considerable subsequent costs from potential adverse events, prolonged hospitalization, and antibiotic resistance. One study demonstrated that the indirect costs result from increased use of fluoroquinolones (RR 1.5 [95% CI 1.5−1.6]), clindamycin (RR 3.8 [95% CI 3.6−4.0]) and vancomycin (RR 5.0 [95% CI 4.3−5.8]) in those with suspected β-lactam allergy.[34] Use of these drugs results in greater lengths of hospitalization, increased costs of care from surgical site infections[22], and increased rates of *Clostridium difficile*,[35] vancomycin-resistant *Enterococcus*,[36] and methicillin-resistant *Staphylococcus aureus*.[34] The estimated cost per case of clostridium difficile infection is as high as $24,064 USD.[37]

Our study underestimated potential benefits of preoperative β-lactam allergy de-labeling, since it only captured a proportion of those patients claiming to be penicillin allergic. Preoperative allergy referrals were not mandatory. The use of non-β-lactam antibiotics in preoperative patients not referred for allergy evaluation was not captured, underestimating the actual utilization of these antibiotics during surgery. Despite the cost benefits, of great importance in β-lactam de-labeling is the improvement in quality of care. Improving and optimizing prophylactic antibiotic choice have direct patient health benefits in both therapeutic safety and potential for improved outcomes.

An interesting finding from this study was the vagueness of the presenting symptoms for most of the patients who were referred for allergy testing. Similar vague symptoms were also observed in Sagar et al, Chang et al, and Solensky et al studies.[38-40] A total of 59.3% of patients reported presenting symptoms as either an unspecified rash or simply unknown. These findings highlight the need for better patient and health care worker education on how penicillin allergy is diagnosed. In contrast, only 1% of our patients reported anaphylaxis, which is comparable with other studies; Wong et al reported 2% and Bhattacharya reported <1%.[41,42] Furthermore, half of our patients gave a remote history of reaction occurring more than 20 years prior to their evaluation.

As this was a semiprospective study, certain limitations were unavoidable. Poor patient recall and the incomplete data related to a history of penicillin versus amoxicillin reactions influenced the use of penicillin challenges as opposed to use of amoxicillin. These inaccuracies likely affected the quality of data collected. In the retrospective study component, the patients were identified only if they had been skin tested. We could not identify patients referred for evaluation but not skin tested or challenged due to the severity of their initial presentation. Furthermore, it did not assess those individuals who were not referred for preoperative allergy evaluation and given alternative antibiotics by the surgical team. Of note, preoperative patients were not specifically screened for cefazolin allergy. They were challenged for either amoxicillin or penicillin, whereas they were given cefazolin during surgery.

Building on our findings, prospective studies are required to establish the role of de-labeling using our protocol in promoting high value care, cost savings, and antibiotic stewardship.

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References

1. Daniel GW, Schneider M, McClellan MB. Addressing antimicrobial resistance and stewardship: the Priority Antimicrobial Value and Entry (PAVE) Award. *JAMA*. 2017 Aug 03 PubMed PMID: 28772301.
2. Kohler PP, Volling C, Green K, Uleryk EM, Shah PS, McGeer A. Carbapenem Resistance, initial antibiotic therapy, and mortality in Klebsiella pneumoniae bacteremia: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2017;27:1–10.
3. Lee GC, Lawson KA, Burgess DS. Clinical epidemiology of carbapenem-resistant enterobacteriaceae in community hospitals: a case-case-control study. *Ann Pharmacother*. 2013;47:1115–1121.
4. Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med*. 2000;160:2819–2822.
5. Brauer R, Ruigomez A, Downey G, Bate A, Garcia Rodriguez LA, Huerta C, et al. Prevalence of antibiotic use: a comparison across various European health care data sources. *Pharmacoepidemiol Drug Saf*. 2016;25(Suppl 1):11–20.
6. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Taylor TH. Trends and seasonal variation in outpatient antibiotic prescription rates in the United States, 2006 to 2010. *Antimicrob Agents Chemother*. 2014;58:2763–2766.
7. Ferech M, Coenen S, Dvorakova K, Hendrickx E, Suetens C, Goossens H, et al. European surveillance of antimicrobial consumption (ESAC): outpatient penicillin use in Europe. *J Antimicrob Chemother*. 2006;58:408–412.
8. Wilke MS, Lovering AL, Strynadka NC. Beta-lactam antibiotic resistance: a current structural perspective. *Curr Opin Microbiol*. 2005;8:525–533.
9. Frigas E, Park MA, Narr BJ, Volcheck GW, Danielson DR, Markus PJ, et al. Preoperative evaluation of patients with history of allergy to penicillin: comparison of 2 models of practice. *Mayo Clin Proc*. 2008;83:651–662.
10. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy*. 2004;34:1597–1601.
11. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol*. 2014;133:790–796.
12. Salden OA, Rockmann H, Verheij TJ, Broekhuizen BD. Diagnosis of allergy against beta-lactams in primary care: prevalence and diagnostic criteria. *Fam Pract*. 2015;32:257–262.
13. Har D, Solensky R. Penicillin and beta-lactam hypersensitivity. *Immunol Allergy Clin North Am*. 2017;37:643–662.
14. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. *J Allergy Clin Immunol Pract*. 2017;5:333–334.
15. Solomkin JS, Mazuski J, Blanchard JC, Itani KMF, Ricks P, Dellinger EP, et al. Introduction to the Centers for Disease Control and Prevention and the Healthcare Infection Control Practices Advisory Committee guideline for the prevention of surgical site infections. *Surg Infect (Larchmt)*. 2017;18:385–393.
16. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017;152:784–791.
17. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis*. 2006;43:322–330.
18. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)*. 2013;14:73–156.
19. Catanzano A, Phillips M, Dubrovskaya Y, Hutzler L, Bosco J. The standard one gram dose of vancomycin is not adequate prophylaxis for MRSA. *Iowa Orthop J*. 2014;34:111–117.
20. Polk RE, Israel D, Wang J, Venitz J, Miller J, Stotka J. Vancomycin skin tests and prediction of "red man syndrome" in healthy volunteers. *Antimicrob Agents Chemother*. 1993;37:2139–2143.
21. Bailie GR, Neal D. Vancomycin ototoxicity and nephrotoxicity. A review. *Med Toxicol Adverse Drug Exp*. 1988;3:376–386.

22. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The Impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis*. 2018;66:329–336.
23. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)*. 2013;14:73–156.
24. Friedman ND, Styles K, Gray AM, Low J, Athan E. Compliance with surgical antibiotic prophylaxis at an Australian teaching hospital. *Am J Infect Control*. 2013;41:71–74.
25. Kao LS, Lew DF, Doyle PD, Carrick MM, Jordan VS, Thomas EJ, et al. A tale of 2 hospitals: a staggered cohort study of targeted interventions to improve compliance with antibiotic prophylaxis guidelines. *Surgery*. 2010;148:255–262.
26. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol*. 2006;97:681–687.
27. McDanel DL, Azar AE, Dowden AM, Murray-Bainer S, Noiseux NO, Willenborg M, et al. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty*. 2017 Jan 17 PubMed PMID: 28236547.
28. Satta G, Hill V, Lanzman M, Balakrishnan I. Beta-lactam allergy: clinical implications and costs. *Clin Mol Allergy*. 2013;11:2.
29. Picard M, Begin P, Bouchard H, Cloutier J, Lacombe-Barrios J, Paradis J, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. *J Allergy Clin Immunol Pract*. 2013;1:252–257.
30. Plumridge RJ. Cost comparison of intravenous antibiotic administration. *Med J Aust*. 1990;153:516–518 5.
31. Lee L, Sudarshan M, Li C, Latimer E, Fried GM, Mulder DS, et al. Cost-effectiveness of minimally invasive versus open esophagectomy for esophageal cancer. *Ann Surg Oncol*. 2013;20:3732–3739.
32. The MUHC Annual Report. McGill University Health Center, 2015-2016.
33. Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc*. 2014;35:489–494.
34. Shah NS, Ridgway JP, Pettit N, Fahrenbach J, Robicsek A. Documenting penicillin allergy: the impact of inconsistency. *PloS one*. 2016;11.
35. Pepin J, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41:1254–1260.
36. Martinez JA, Ruthazer R, Hansjosten K, Barefoot L, Snydman DR. Role of environmental contamination as a risk factor for acquisition of vancomycin-resistant enterococci in patients treated in a medical intensive care unit. *Arch Intern Med*. 2003;163:1905–1912.
37. Ghantoji SS, Sail K, Lairson DR, DuPont HL, Garey KW. Economic healthcare costs of Clostridium difficile infection: a systematic review. *J Hosp Infect*. 2010;74:309–318.
38. Sagar PS, Katelaris CH. Utility of penicillin allergy testing in patients presenting with a history of penicillin allergy. *Asia Pac Allergy*. 2013;3:115–119.
39. Chang C, Mahmood MM, Teuber SS, Gershwin ME. Overview of penicillin allergy. *Clin Rev Allergy Immunol*. 2012;43:84–97.
40. Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol*. 2000;85:195–199.
41. Wong BBL, Keith PK, Waserman S. Clinical history as a predictor of penicillin skin test outcome. *Ann Allergy Asthma Immunol*. 2006;97:169–174.
42. Bhattacharya S. The facts about penicillin allergy: a review. *J Adv Pharm Technol Res*. 2010;1:11–17.

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