

Cost and Risk Analysis of Lifelong Penicillin Allergy

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Abstract

Patients labeled as being penicillin-allergic require the use of alternative antibiotics. The objective of this study was to estimate the lifetime antibiotic costs of patients labeled as being penicillin allergic prior to age 10 compared with those who were not penicillin allergic and to compare antibiotic utilization between these 2 groups with regard to risks of adverse effects. Using the low end of the antibiotic cost range, penicillin-allergic patients had a mean lifetime antibiotic cost of \$8171 per patient, compared with \$6278 for non-penicillin-allergic patients, a difference of \$1893. Penicillin-allergic patients utilized more moderate-spectrum antibiotics, more fluoroquinolones, and had a higher estimated *Clostridium difficile* risk.

Keywords

antibiotics, penicillin allergy, antibiotics costs

Introduction

Penicillin allergy is the most common drug allergy. However, 90% of children labeled as penicillin allergic are not truly allergic and are able to safely utilize penicillins.^{1,2} A large proportion of penicillin-allergy labeling occurs during the pediatric years, probably due to the greater frequency of viral exanthems, high-dose amoxicillin use, and issues related to environmental and food allergies. Most penicillins are highly efficacious, inexpensive, and have low risk of serious side effects. A penicillin allergy label on a patient obligates practitioners to utilize alternative antibiotics that are often more costly, have a greater risk of side effects, and are potentially less efficacious. The purpose of this study is to compare the lifetime risks and costs of antibiotics for patients who are labeled as penicillin-allergic during childhood compared with those who are not labeled as penicillin-allergic.

Methods

We utilized database information from the electronic medical record (EMR) of a 4-hospital health care system that includes 3 general hospitals, 1 children's/women's specialty hospital, and their associated outpatient facilities. This EMR was operating in this health care system since 2008. In order to estimate the lifetime costs of antibiotic therapy, we chose to examine 5-year periods of patient activity for patients who had a

registered primary care provider within this health care system, presumably meaning that nearly all of their inpatient orders and outpatient prescriptions would all be contained within this EMR's database. We selected a sample of 50 penicillin-allergic patients (ie, those who were labeled as being penicillin allergic in the EMR) and 50 non-penicillin-allergic patients in each of 18 five-year age groups (10 to <15, 15 to <20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, 40 to <45, 45 to <50, 50 to <55, 55 to <60, 60 to <65, 65 to <70, 70 to <75, 75 to <80, 80 to <85, 85 to <90, 90 to <95, and ≥95) for their age as of June 2018. Penicillin-allergic patients must have been labeled as penicillin-allergic for the duration of the 5-year period, which is why we excluded the age group <10 years. Additionally, this model is meant to simulate patients who are labeled as being penicillin-allergic during childhood since this maximizes the lifetime consequence (as opposed to being labeled as penicillin-allergic during adulthood). Since there were more than 50 patients available in each

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age group, we selected the 50 patients with the most recent primary care visit as of June 2018. Patients aged ≥ 95 years constitute a special confidentiality group because of small numbers and the potential to identify patients based on medication utilization. Thus, the 90 to <95 and the ≥ 95 age groups were combined to a single ≥ 90 years age group. Since this age group is a combination of 2 age groups, there were 100 subjects in the penicillin-allergic and the non-penicillin-allergic groups (200 subjects in total).

For each patient in this sample, we examined all antibiotic orders and prescriptions from 2012 to 2017. We excluded antiviral agents, antifungal agents, antimalarial agents, ophthalmic drugs, and topical drugs, because utilization of these agents would be unrelated to penicillin allergy.

Drug “costs” were determined using pricing information published in UpToDate (UpToDate, Inc, Waltham, MA) in July 2018. Most drugs have oral liquid, pill, capsule, and parenteral formulations. Within each of these, UpToDate provided a price range. We utilized the low end of the range as a cost per milligram of drug for the appropriate formulation. The “cost” of the drug was calculated as the milligram of drug ordered or prescribed for the duration, multiplied by the cost per milligram. This underestimates the actual cost because it cites the low end of the cost range and it does not account for unit dosing. A 1-g vial of ceftriaxone has a cost of \$13.92 (\$0.01392 per mg). If the patient’s dose is 800 mg, the entire 1-g vial would normally be used. However, this makes the cost calculation more complex. The vial size that was utilized was not available in the EMR, and in many instances, unit dose intravenous premixed bags were utilized instead. Thus, a more simplified cost calculation was used in which the cost was calculated as 800 mg multiplied by \$0.01392 per mg, equaling \$11.14 per dose, rather than the true cost of \$13.92. Since this method was used for both the penicillin-allergic and the non-penicillin-allergic groups, there was no bias favoring one group over the other. Using less than one vial is more common in pediatrics but fairly uncommon in adult medicine, and since this would occur similarly in both groups, it is not likely to affect the comparison between the 2 groups.

If the cost/pricing information was not available on UpToDate, we utilized the cost/pricing information in IBM Micromedex (IBM Corp, Armonk, NY) and/or Red Book Online (Truven Health Analytics, Ann Arbor, MI), and similarly utilized the low end of the price range. Just as a clarification, this “Red Book” is the pharmacy *Red Book* and not the American Academy of Pediatrics *Red Book Report of the Committee on Infectious Disease*.

Single doses of antibiotics were included in the totals (eg, single-dose ceftriaxone in the emergency

Table 1. Median 5-Year Antibiotic Costs per Patient^a.

Age Group	Penicillin- Allergic, Median	Non-Penicillin- Allergic, Median	P ^b
10 to <15	\$178.32	\$41.00	.015
15 to <20	\$58.32	\$79.20	.62
20 to <25	\$75.04	\$37.48	.88
25 to <30	\$112.00	\$77.48	.11
30 to <35	\$107.76	\$37.29	.016
35 to <40	\$122.15	\$76.46	.076*
40 to <45	\$95.00	\$98.83	.48
45 to <50	\$97.28	\$99.13	.37
50 to <55	\$98.33	\$61.83	.089*
55 to <60	\$157.68	\$39.39	.003
60 to <65	\$205.39	\$49.38	.016
65 to <70	\$169.73	\$62.81	.004
70 to <75	\$93.76	\$52.40	.30
75 to <80	\$273.28	\$154.27	.18
80 to <85	\$168.45	\$128.51	.61
85 to <90	\$125.02	\$141.02	.72
≥ 90	\$118.62	\$120.18	.58
All	\$129.72	\$78.90	$<.0001$

^aOne hundred patients per age group (50 penicillin-allergic, 50 non-penicillin-allergic), except for the ≥ 90 age group (200 patients, 100 penicillin-allergic, 100 non-penicillin-allergic).

^bP values are 2-tailed probabilities.

*One-tailed probability is $<.05$.

department). Inpatient order durations were determined by the start and stop dates/times. Outpatient prescriptions costs for pills, capsules, and similar units were calculated per pill. Liquid antibiotics costs were calculated per milligram of the drug ordered by the prescription. This results in an underestimate of the true cost since most liquid antibiotics are dispensed or removed from the shelf by whole bottle sizes.

Results

Antibiotic costs were summed for each patient (aggregate cost of antibiotics) in his/her 5-year data time span. Medians and means were determined for each age group. A test of normality confirmed nonnormality due to outlier values; thus, a nonparametric statistical test was used to compare the medians between the penicillin-allergic and non-penicillin-allergic groups in Table 1.

P values were calculated using the Wilcoxon rank sum test. The costs were significantly higher in the penicillin-allergic group for the 10 to <15 , 30 to <35 , 55 to <60 , 60 to <65 , and 65 to <70 years age groups (2-tailed probabilities), and the 35 to <40 and 50 to <55 years age groups (1-tailed probability).

Table 2. Mean and Standard Deviation (SD) 5-Year Antibiotic Costs per Patient^a.

Age Group	Penicillin-Allergic, Mean Cost (SD)	Non-Penicillin-Allergic, Mean Cost (SD)
10 to <15	\$357.23 (401.96)	\$358.12 (1098.49)
15 to <20	\$167.8 (311.86)	\$438.82 (2212.56)
20 to <25	\$197.13 (277.43)	\$295.25 (565.82)
25 to <30	\$200.70 (303.56)	\$146.13 (207.05)
30 to <35	\$298.29 (900.99)	\$131.34 (308.55)
35 to <40	\$537.01 (1349.623)	\$230.44 (450.48)
40 to <45	\$510.68 (1219.89)	\$287.28 (515.32)
45 to <50	\$272.48 (470.93)	\$218.52 (528.64)
50 to <55	\$1353.85 (6446.43)	\$686.62 (2158.36)
55 to <60	\$378.30 (806.31)	\$105.79 (165.76)
60 to <65	\$323.96 (483.76)	\$317.18 (932.93)
65 to <70	\$391.89 (708.17)	\$598.21 (2872.49)
70 to <75	\$468.23 (1585.80)	\$231.35 (567.81)
75 to <80	\$510.88 (700.02)	\$589.35 (1852.15)
80 to <85	\$522.65 (1227.86)	\$463.35 (1057.75)
85 to <90	\$858.15 (2819.09)	\$394.69 (819.86)
≥90	\$410.89 (824.21)	\$392.69 (1121.739)
All	\$453.95 (1851.17)	\$348.77 (1271.74)

^aOne hundred patients per age group (50 penicillin-allergic, 50 non-penicillin-allergic), except for the ≥90 age group (200 patients, 100 penicillin-allergic, 100 non-penicillin-allergic).

For information, the means and standard deviation are listed in Table 2. Note that the means in Table 2 are much higher than the medians in Table 1, which indicate that there are many patients with low 5-year antibiotic costs (lowering the median), and there are a few patients with very high 5-year antibiotic costs (increasing the means).

Over the aggregate lifetime, the mean antibiotic costs were \$8171 per patient for penicillin-allergic patients, and \$6278 per patient for non-penicillin-allergic patients. The difference is \$1893.

Table 3 describes the frequency of orders and prescriptions for each of the antibiotic groups in the penicillin-allergic and the non-penicillin-allergic groups. Each of these groups were classified as narrow spectrum, moderate spectrum, and broad spectrum. Table 4 tabulates the total number of orders and prescriptions for each of the antibiotic spectrum groups. While the number of orders and prescriptions for the broad-spectrum antibiotics was similar in the penicillin-allergic and non-penicillin-allergic age groups, there were more moderate-spectrum antibiotic orders/prescriptions and fewer narrow-spectrum antibiotic orders/prescriptions in the penicillin-allergic group ($P < .0001$).

Brown et al reviewed the literature on *Clostridium difficile* risk among the different antibiotic treatment

groups.³ The right columns in Table 3 lists the *C difficile* odds ratio (which closely approximates the relative risk) for the major antibiotic categories. The odds ratio values that are non-italicized are taken from this Brown's publication. The italicized odds ratio values are extrapolated estimates of the odds ratios obtained as follows. Since in Brown's publication the odds ratio is at 5.7 for cephalosporins, monobactams, and carbapenems, we also used this 5.7 value for the other "broad-spectrum" classes in Table 3 that did not have a specific odds ratio cited by Brown's publication. Brown et al determined odds ratios of 2.7, 1.8, and 2.7 for macrolides, sulfonamides, and penicillins, respectively. Thus, we used the value of 2.0 for the other "moderate spectrum" classes in Table 3 that did not have a specific odds ratio cited by Brown's publication.

The number of orders/prescriptions for each antibiotic class was multiplied by these odds ratios to obtain "*C difficile* points." Greater numbers of antibiotic orders/prescriptions place patients at higher *C difficile* risk, and higher *C difficile* odds ratios place patients at higher *C difficile* risk. Multiplying these 2 numbers together combines these 2 known risk factors to estimate an overall risk by calculating "*C difficile* points" for the penicillin-allergic and non-penicillin-allergic groups in the 2 columns on the right of Table 3. This method calculated 30 674 "*C difficile* points" for the penicillin-allergic group, which was 31% higher than the 23 454 "*C difficile* points" in the non-penicillin-allergic group.

Table 5 tabulates the range of "costs" for the top 29 antibiotic forms (includes dosing form, size, concentration). This study utilized the "low" value in the left column. The cost sources that we used almost always provided a cost range. The "high" values are the high end of this cost range. The "Schein" column is the lowest purchase price cited on www.HenrySchein.com (Henry Schein, Inc, Melville, NY) on January 1, 2019. The Schein price provides a current real-world cost for the antibiotic acquisition cost. This sampling of the cost variability of the most commonly ordered/prescribed antibiotics shows modest variation in many instances, but large variation in other instances.

Discussion

Across the lifetime, patients labeled as being penicillin-allergic have antibiotic costs that are significantly greater than those of nonallergic patients. Over the aggregate lifetime, a penicillin-allergic patient's antibiotic orders and prescription costs were estimated to be \$1893 greater than that of a non-penicillin-allergic patient using the low end of the cost range. The increased cost of antibiotics in penicillin-allergic patients could be

Table 3. Antibiotic Class Utilization^a.

Antibiotic Class	PCN-Allergic	Non-PCN-Allergic	Broad-Spectrum Class	<i>C diff</i> Odds Ratio ^b	<i>C diff</i> Risk Points ^b	
					PCN-Allergic	Non-PCN-Allergic
Penicillin	13	52	Narrow	1.0	13.0	52.0
Amoxicillin/ampicillin	47	443	Moderate	2.0	267.9	2525.1
Dicloxacillin	0	10	Narrow	1.0	0	10.0
Broad-spectrum penicillin + penicillinase inhibitor	107	567	Broad	5.7	609.9	3231.9
Cephalosporin/cephamycin	800	1298	Broad	5.7	4560.0	7398.6
Meropenem (carbapenem)	62	153	Broad	5.7	353.4	872.1
Aztreonam (monobactam)	2	43	Broad	5.7	11.4	245.1
Macrolide	1877	1156	Moderate	2.7	5067.9	3121.2
Fluoroquinolone	1287	808	Broad	5.5	7078.5	4444
Sulfonamide + trimethoprim	502	367	Moderate	1.8	903.6	660.6
Clindamycin	618	143	Broad	16.8	10 382.4	2402.4
Tetracyclines	627	344	Moderate	0.9	564.3	309.6
Vancomycin	245	185	Moderate	2.0	49.0	370.0
Linezolid	13	11	Broad	5.7	74.1	62.7
Metronidazole	208	104	Moderate	2.0	416.0	208.0
Pentamidine	0	4	Narrow	1.0	0	4.0
Dapsone	2	3	Narrow	1.0	34.2	0
Aminoglycosides	45	36	Moderate	2.0	90.0	72.0
Rifamycin/isoniazid	15	20	Moderate	2.0	30.0	40.0
Rifaximin	6	9	Narrow	1.0	6.0	9.0
Daptomycin	6	0	Broad	5.7	2.0	3.0
Sum	6482	5756			30 674	23 454

Abbreviations: PCN, penicillin; *C diff*, *Clostridium difficile*.

^aNumber of orders/prescriptions for each antibiotic class in penicillin-allergic and non-penicillin-allergic patients.

^bItalicized *C diff* numbers are extrapolated estimates (see text), while non-italicized *C diff* odds ratios are from directly taken Brown et al.³

Table 4. Frequencies of Orders/Prescriptions for Antibiotic Spectrum Class Groups, $P < .0001$.

Broad-Spectrum Class	Penicillin-Allergic	Non-Penicillin-Allergic
Narrow	21	78
Moderate	3566	2655
Broad	2895	3023

explained by alternative antibiotics being more expensive. Because patients are labeled as being penicillin-allergic, patients who would have received a penicillin prescription are being prescribed higher cost alternative antibiotics in its place, such as second- or third-line medications even though it may not be the antibiotic of choice for the patient's bacterial infection.⁴

A penicillin allergy label was also associated with the patient utilizing more moderate-spectrum antibiotic orders and prescriptions. This increase in moderate-spectrum antibiotic utilization and decrease in narrow-spectrum antibiotic utilization could be explained by the penicillin

allergy label limiting therapeutic options for patients, leading to the use of broader-spectrum antibiotics.⁵

Patients with a penicillin allergy label were more likely to receive fluoroquinolones than patients without a penicillin allergy label, probably as a substitute first-line penicillin-class antibiotics.⁶ Our findings are consistent with previous studies that have found significantly higher fluoroquinolone use among penicillin-allergic patients.⁷ Fluoroquinolones are associated with more adverse reactions and complications (such as tendon rupture) and higher costs.⁸

We found an increased calculated risk of *C difficile* in patients with a penicillin allergy label. There was a 31% higher risk of *C difficile* for the penicillin-allergic group compared with the non-penicillin-allergic group because penicillin-allergic patients receive alternative antibiotics, such as fluoroquinolones, clindamycin, and third-generation cephalosporins.⁹

In this study, the cost spread is roughly 50-fold (Table 5). For each drug, we used the lowest value of the price range, which had a modest to large variation for most drugs. This cost variability could mean that we

Table 5. Low to High Price Ranges for the Top 29 Antibiotic Orders/Prescriptions.

Drug	Low	High	Schein	Unit	No. of Orders
Azithromycin 250 mg tabs	\$7.77	\$7.78	\$0.73	Tab	2252
Ciprofloxacin HCl 500 mg tabs	\$0.22	\$5.59	\$0.15	Tab	844
Doxycycline hyclate 100 mg tabs	\$2.62	\$6.15	\$0.13	Tab	815
Sulfamethoxazole-TMP 800-160 mg tabs	\$0.37	\$1.40	\$0.10	Tab	665
Cephalexin 500 mg caps	\$0.34	\$1.97	\$0.17	Cap	448
Clindamycin HCl 300 mg caps	\$3.72	\$3.76	\$0.27	Cap	422
Levofloxacin 500 mg tabs	\$0.21	\$20.09	\$0.16	Tab	401
Amoxicillin-clavulanate 875-125 mg tabs	\$5.05	—	\$0.44	Tab	374
Ciprofloxacin HCl 250 mg tabs	\$0.24	\$4.59	\$0.12	Tab	267
Metronidazole 500 mg tabs	\$0.23	\$0.69	\$0.15	Tab	231
Azithromycin 500 mg tabs	\$15.54	\$15.57	\$1.30	Tab	230
Vancomycin HCl in 1-5 g/200 mL	\$0.18	—	\$0.06	mL	195
Azithromycin 200 mg/5 mL	\$1.16	—	\$2.06	mL	192
Ceftriaxone 2-2.22 g	\$22.25	—	\$6.60	2 g	189
Cefazolin 2-3 g	\$11.02	—	\$15.58	2 g	184
Ceftriaxone 1-3.74 g	\$13.92	—	\$3.30	1 g	178
Amoxicillin 500 mg caps	\$0.19	\$5.88	\$0.11	Cap	163
Moxifloxacin HCL 400 mg tabs	\$27.19	\$27.23	—	Tab	161
Clarithromycin 500 mg tabs	\$4.52	\$6.02	\$0.95	Tab	158
Cefazolin 1-4 g	\$5.04	—	\$7.79	1 g	158
Ertapenem Sodium 1 g IV soln	\$162.10	—	\$146.28	1 g	136
Clindamycin 600 mg/50mL IV soln	\$0.17	\$0.30	\$0.16	mL	136
Amoxicillin 875 mg PO tabs	\$0.87	—	\$0.20	Tab	131
Ceftriaxone 1 g	\$1.80	\$47.05	\$3.30	1 g	126
Clindamycin 900 mg/50 mL IV	\$0.19	\$0.36	\$0.24	mL	122
Cefdinir 300 mg PO caps	\$5.11	—	\$1.15	Cap	104
Levofloxacin 750 mg PO tabs	\$0.33	\$36.12	\$0.27	Tab	101
Amoxicillin-clavulanate 500-125 mg tabs	\$3.78	—	\$0.45	Tab	94
Sulfamethoxazole-TMP DS 800-160 mg	\$3.12	—	\$0.10	Tab	93

Abbreviations: Tab, tablets; Cap, capsules; IV, intravenous; Soln, solution.

underestimated the difference in cost between the allergic and nonallergic groups. Despite the cost difference being underestimated, we still found the difference between the 2 groups to be significant. The true cost difference between the penicillin-allergic and non-penicillin-allergic groups could be as high as 50 times the values found in this study.

Contrary to what would be ideal, orders/prescriptions consisting of penicillins were prescribed to patients labeled as penicillin-allergic. In these cases, the practitioner prescribed a penicillin in error or noted awareness of the patient's penicillin allergy label, but still prescribed the antibiotic, in error or for a clinically valid reason.

Limitations to this study include unclear order/prescription information. Because this was a retrospective chart review, the durations or doses of the orders/prescriptions were not always clear. As a result, the

calculations for the costs of the orders/prescriptions are only estimates.

Inappropriate penicillin allergy labels force clinicians to select alternatives that often lead to increased health care costs, potentially less efficacy, and a higher risk for adverse effects. The misuse and overuse of antibiotics can also lead to greater antibiotic resistance. Previous studies have found that patients who require alternative antibiotics have 24% more *C difficile*, 14% more methicillin-resistant *Staphylococcus aureus*, and 30% more vancomycin-resistant enterococci infections.⁷

Since it is well known that patients with a penicillin allergy label are usually not truly penicillin allergic, one approach to removing an inappropriate penicillin allergy label would be to test for penicillin allergy with a combination of RAST (radioallergosorbent test) and skin testing. For those who test negative, a drug challenge under medical supervision can be done to more definitively

rule out true penicillin allergy. This appears to be cost-effective since the cost of testing and clinical evaluation is lower than the cost differences between the 2 groups estimated in this study. In a 1994 study of RAST testing on patients thought to be penicillin-allergic, only 8 out of 92 patients had a positive test. Physicians assessing the likelihood of true penicillin allergy were only able to predict this 10% of the time, suggesting that testing should be used before confirming or disproving a patient's penicillin allergy label.¹⁰

In conclusion, a penicillin allergy label on patients leads to increased health care costs, a higher frequency of moderately broad-spectrum antibiotics and fluoroquinolones use, and a theoretical increase in *C difficile* risk. More accurate labeling of penicillin allergies could lead to improved antibiotic use, increased patient safety, and improved quality of patient care.

Authors' Note

The master data file contains patient information. The authors could de-identify the data or provide other means to corroborate the data if requested.

Author Contributions

LYCA: Performed original spreadsheet reorganizations, carried out data analysis, summarized statistics, presentation of abstract at Pediatric Academic Societies meeting, composed manuscript.

AMS: Obtained IRB exemption, obtained original data query, assisted with spreadsheet reorganizations, performed statistical analysis, oversaw research project progress.

LGY: Original research idea, developed research protocol, oversaw research project progress, corrected data reorganizations, oversaw and corrected manuscript development for submission to journal.

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