

High-Cost, High-Need Patients: The Impact of Reported Penicillin Allergy

Kimberly G. Blumenthal, MD, MSc; Nicolas M. Oreskovic, MD, MPH; Xiaoqing Fu, MS; Fatma M. Shebl, MD, PhD; Christian M. Mancini, BS; Jennifer M. Maniates, MA; and Rochelle P. Walensky, MD, MPH

High-cost, high-need (HCHN) patients comprise 5% of patients nationwide and account for 50% of healthcare spending.¹ Although less than 5% of Medicare spending is considered potentially preventable, almost three-quarters of the preventable costs are incurred by this HCHN subset.² Addressing modifiable risk factors present in HCHN patients may improve clinical outcomes while curbing overall US healthcare spending.^{1,3}

Prominent comorbidities in HCHN patients include conditions associated with increased risk of bacterial infection, such as diabetes, chronic obstructive pulmonary disease, and chronic renal failure.⁴ Acute bacterial lung and urinary tract infections are among the most common reasons for preventable hospitalizations in HCHN patients^{2,5,6}; the costs of bacterial pneumonia alone comprised almost one-fourth of preventable hospital costs in HCHN patients in 2006, resulting in excess spending of \$7.2 billion.⁷

Beta-lactam antibiotics are first-line treatments for many of these bacterial infections; however, approximately 10% of Americans report a penicillin allergy, limiting treatment choice.⁸ Patients with infections who report a penicillin allergy are often administered alternatives to beta-lactam antibiotics that can be less effective, resulting in treatment failures^{9,10}; more toxic, resulting in adverse drug reactions^{9,10}; and broader-spectrum, resulting in higher risks of antibiotic resistance.^{11,12} However, more than 90% of patients reporting a penicillin allergy have their allergy disproved when formally evaluated.⁸

Active care management that combines chronic disease management and case management improves care and reduces costs in HCHN patients.¹³⁻¹⁶ Although medication management is a proven feature of successful care management programs for HCHN patients,^{16,17} programs have generally not previously assessed or addressed drug allergies.¹⁸ To assess the potential benefits of proactive drug allergy evaluation in the HCHN population, we described the epidemiology and impact of reported penicillin allergy on antibiotic use and healthcare resource utilization (HRU) in HCHN patients.

ABSTRACT

OBJECTIVES: More than 90% of patients who report a penicillin allergy have the allergy disproved when tested. Unnecessary use of alternative (non-beta-lactam) antibiotics can result in more treatment failures and adverse reactions. We described the prevalence and impact of a reported penicillin allergy in high-cost, high-need (HCHN) patients.

STUDY DESIGN: Retrospective cohort.

METHODS: We identified HCHN patients in a care management program of an urban academic medical center (January 1, 2014, to December 31, 2016). We used multivariable logistic regression models to determine the association between a reported penicillin allergy and antibiotic use. We used multivariable Poisson regression models to determine the association between a reported penicillin allergy, with or without multiple drug intolerance syndrome (MDIS; ≥ 3 reported drug allergies), and healthcare resource utilization (HRU).

RESULTS: Of 1870 HCHN patients, 383 (20%) reported penicillin allergy, 835 (45%) had MDIS, and 290 (16%) had both. HCHN patients reporting penicillin allergy had an increased odds of beta-lactam alternative antibiotic use (adjusted odds ratio, 3.84; 95% CI, 2.17-6.80). HRU was significantly higher for patients reporting a penicillin allergy alone (adjusted relative risk [aRR], 1.13; 95% CI, 1.03-1.25) and with concurrent MDIS (aRR, 1.20; 95% CI, 1.08-1.34).

CONCLUSIONS: HCHN patients had a high burden of reported drug allergy. A reported penicillin allergy conferred a 4-fold increased odds of beta-lactam alternative antibiotic use. Reporting penicillin allergy, with and without MDIS, was associated with significantly more HRU. HCHN care management programs should consider systematic drug allergy evaluations to optimize antibiotic use in these fragile patients.

Am J Manag Care. 2020;26(4):154-161. doi: 10.37765/ajmc.2020.42832

METHODS

Study Design and Population

This study was conducted at a large Boston-based academic medical center with an active care management program for HCHN patients. HCHN patients received their primary care at 1 of 15 affiliated practice sites. We considered a 36-month study period (January 1, 2014, through December 31, 2016) and included only HCHN patients continuously followed by the active care management program for at least 34 of these months. All data were retrieved exclusively from electronic sources. The study was approved by the Partners Human Research Committee (protocol 2017P000456).

Exposure

The primary exposure of interest was a reported penicillin allergy, defined as any reported allergy or intolerance to any penicillin antibiotic. After being electronically retrieved, allergy data were manually verified by chart review to determine the first date of penicillin allergy “active” status, the reaction(s) listed, and any allergy status changes that occurred during the study period. Given that antibiotic prescribing might not be affected for patients reporting only a penicillin intolerance, we considered a sensitivity analysis definition of a reported penicillin allergy that excluded patients who had gastrointestinal penicillin intolerance only. We separately considered multiple drug intolerance syndrome (MDIS) as an exposure, defined as a reported allergy or intolerance to 3 or more drugs (1 of which may have been a penicillin) at the time of study entry.^{19,20}

Outcomes

The primary outcome was antibiotic use, defined as antibiotic exposure, regardless of duration, captured by any inpatient antibiotic administration or outpatient antibiotic prescribed in the study period. We considered narrow-spectrum beta-lactam antibiotics as any penicillins, other than antipseudomonal penicillins or penicillin class antibiotic/beta-lactamase inhibitor combinations, and first- or second-generation cephalosporins.^{11,21,22} Beta-lactam alternative antibiotics included fluoroquinolones, macrolides, vancomycin, clindamycin, sulfonamides, tetracyclines, aminoglycosides, and linezolid.^{11,21,22}

The secondary outcome was HRU, which considered inpatient, emergency, and outpatient visit counts. Inpatient visits excluded residential inpatient stays, and emergency visits excluded those that led to an inpatient visit. Outpatient visits were specified as primary care or specialist visits.

Key Variables

Key variables assessed included patient demographics, insurance, comorbidities, corticosteroid use, other drug allergies, and resistant

TAKEAWAY POINTS

- ▶ More than 20% of high-cost, high-need (HCHN) patients reported a penicillin allergy, and 45% had multiple drug intolerance syndrome (MDIS; ≥ 3 drug allergies).
- ▶ HCHN patients had high prevalence of risk factors for bacterial infections: diabetes (51%), cancer (46%), and systemic corticosteroid exposure (34%).
- ▶ A reported penicillin allergy was associated with an almost 4-fold increased odds of alternative antibiotic exposure, with odds of clindamycin exposure increased more than 8-fold.
- ▶ Reporting a penicillin allergy, with or without MDIS, conferred a 10% to 20% increase in healthcare utilization.
- ▶ HCHN patients may be ideal candidates for systematic drug allergy evaluations, including penicillin allergy testing, to optimize first-line antibiotic treatments.

organisms. Comorbidities considered were cardiovascular disease, diabetes, renal disease, and cancer, defined from established diagnostic codes, when available (eAppendix Table 1 [eAppendix available at ajmc.com]).²³⁻²⁵ Charlson Comorbidity Index (CCI) score was electronically calculated based on diagnostics codes.^{26,27} Systemic corticosteroid use, a binary variable, was considered *yes* for any patients with a documented inpatient administration and/or an outpatient prescription for an oral or parenteral steroid. Other reported drug allergies were defined similarly to a reported penicillin allergy (ie, any reported allergy or intolerance). We captured the total number of reported allergies, reported cephalosporin allergies, and reported sulfonamide antibiotic allergies. Colonization or infection with methicillin-resistant *Staphylococcus aureus* (MRSA) was determined by the presence of a MRSA microbiology culture. Colonization or infection with vancomycin-resistant *Enterococcus* (VRE) was determined by the presence of a VRE microbiology culture.

Statistical Analysis

Numbers with frequencies and means with SDs were used to describe categorical and continuous variables, respectively. We used simple regression models (ie, models with a single independent variable) to assess bivariate relationships. Multivariable regression models were used to assess the relationship between the exposure(s) and outcomes. Because a patient's penicillin allergy status can change during the study period (from no reported penicillin allergy to reported penicillin allergy, or vice versa), we used generalized estimating equations to construct regression models to account for the within-patient correlation. Multivariable logistic regression models were used to determine the association of penicillin allergy status with antibiotic use, and multivariable Poisson regression models were used to determine the association between penicillin allergy status and number of healthcare visits per follow-up year.

We considered patient demographics and CCI score as potentially confounding variables warranting inclusion in the final models a priori. All other key variables were individually assessed for confounding. Although we identified other drug allergies as a confounder, this variable was determined to be collinear with the exposure and was not included in the final models. We report odds ratios (ORs) with 95% CIs for antibiotic use outcomes and relative risks (RRs)

with 95% CIs for healthcare visits. All *P* values were 2-sided, with *P* < .05 considered statistically significant. Statistical analyses were performed in SAS version 9.4 (SAS Institute; Cary, North Carolina).

RESULTS

Cohort Description

Of 1870 patients enrolled in the study, 383 (20%) had a reported penicillin allergy at any time during the study period. There were 835 (45%) patients with MDIS, including 290 patients (16%) with both a reported penicillin allergy and MDIS. The 383 patients reporting penicillin allergy had a total of 513 reactions, commonly rash or dermatitis (*n* = 179; 35%), unknown (*n* = 83; 16%), urticaria or hives (*n* = 75; 15%), gastrointestinal upset (*n* = 74; 14%), angioedema or swelling (*n* = 42; 8%), and anaphylaxis (*n* = 31; 6%) (eAppendix Table 2). There were 40 patients whose only penicillin reaction was gastrointestinal upset. There were 25 patients whose penicillin allergy status changed during the study period: 19 patients had a new penicillin allergy label applied and 6 patients had their penicillin allergy label resolved (4 [67%] of which were resolved by allergy testing). Therefore, the final cohort consisted of 1895 penicillin allergy observations in 1870 unique patients, with a total of 5599 person-years of follow-up time for analysis.

Age, race, and body mass index did not differ by penicillin allergy status (Table 1). Patients reporting a penicillin allergy were more often female (73% vs 56%; *P* < .001). The most common insurance was an accountable care organization external risk (89%), with fewer patients part of a commercial external risk-based contract (11%). Active smoking was uncommon (8%), and former smokers comprised 38% of patients.

CCI scores were high, on average (mean [SD] = 4.74 [3.30]), but also not differential by penicillin allergy status. Patients had cardiovascular disease (61%), diabetes (51%), renal disease (45%), and cancer (46%), not differential by reported penicillin allergy status. Systemic corticosteroid use was present in 34% overall, with no difference by penicillin allergy status.

Only 14% of patients had no reported drug allergies overall. One or 2 drug allergies were present in 42% of patients overall, 3 or 4 drug allergies were present in 21% of patients, and 5 or more drug allergies were present in 24% of patients. Compared with patients not reporting penicillin allergy, patients with a reported penicillin allergy more frequently had more total reported drug allergies (*P* < .001). Reported cephalosporin and sulfonamide antibiotic allergies were present in 3% and 16% of patients overall, more frequently in patients reporting penicillin allergy (cephalosporin: 6% vs 2%; *P* < .001; sulfonamide antibiotic: 26% vs 13%; *P* < .001). MRSA and VRE colonization and/or infection were overall low at baseline (4%), without a difference by penicillin allergy status.

Primary Outcome: Antibiotic Use

Antibiotics in HCHN patients included fluoroquinolones (*n* = 912), first-generation cephalosporins (*n* = 576), macrolides (*n* = 529),

vancomycin (*n* = 431), third-generation cephalosporins (*n* = 380), sulfonamides (*n* = 360), tetracyclines (*n* = 334), and clindamycin (*n* = 184) (Table 2). HCHN patients used beta-lactam alternative antibiotics more frequently than narrow-spectrum beta-lactam antibiotics overall.

The use of narrow-spectrum beta-lactam antibiotics was lower in patients reporting a penicillin allergy (17% vs 47%; *P* < .001) (Table 2). In the multivariable adjusted regression model, patients reporting penicillin allergy had lower odds of narrow-spectrum beta-lactam antibiotic use (adjusted OR, 0.20; 95% CI, 0.15-0.26) compared with those reporting no penicillin allergy (Figure [A]). This association strengthened in the sensitivity analysis that excluded patients with gastrointestinal penicillin intolerance only (adjusted OR, 0.11; 95% CI, 0.08-0.16) (data not shown).

Alternative antibiotic use was higher in patients reporting a penicillin allergy (80% vs 71%; *P* < .001) (Table 2). Specific alternative antibiotics used more in patients reporting a penicillin allergy were fluoroquinolones (53% vs 47%; *P* = .026), clindamycin (28% vs 5%; *P* < .001), and tetracyclines (25% vs 16%; *P* < .001). In the multivariable regression model, patients reporting penicillin allergy had an increased odds of beta-lactam alternative antibiotic use (adjusted OR, 3.84; 95% CI, 2.17-6.80) (Figure [B]), with clindamycin use having the greatest OR (adjusted OR, 8.40; 95% CI, 5.99-11.79) compared with those reporting no penicillin allergy. This association between reported penicillin allergy and beta-lactam alternative antibiotic use strengthened in the sensitivity analysis that excluded patients with gastrointestinal penicillin intolerance only (adjusted OR, 5.64; 95% CI, 2.78-11.44).

Secondary Outcome: HRU

Total number of visits per follow-up year were higher for patients reporting a penicillin allergy (3.03 vs 0.70; *P* < .001) and for those who also had MDIS (2.05 vs 0.44; *P* < .001) (Table 3). Inpatient visits per follow-up year were comparable between patients with and without a reported penicillin allergy, but emergency, primary care, and specialist outpatient visits were more frequent for patients reporting a penicillin allergy (Table 3). All visit types were more frequent in patients reporting MDIS (Table 3).

In the multivariable adjusted analysis, numbers of healthcare visits were significantly greater for patients with a reported penicillin allergy compared with those not reporting a penicillin allergy (RR, 1.13; 95% CI, 1.03-1.25) (Table 4). The RR demonstrating increased visits was nearly identical when excluding patients with gastrointestinal penicillin intolerance only. Patients with reported penicillin allergy and concurrent MDIS had a higher incidence of HRU (RR, 1.20; 95% CI, 1.08-1.34) (Table 4) compared with those without penicillin allergy and MDIS.

DISCUSSION

We performed a retrospective cohort study of HCHN patients and identified that more than 1 in 5 of these patients had a reported

TABLE 1. High-Cost, High-Need Patient Characteristics by Reported Penicillin Allergy Status

	All Patients (N = 1895)			Reported Penicillin Allergy (n = 383)			No Reported Penicillin Allergy (n = 1512)			P ^a
Age in years, mean (SD) ^b	77 (12.3)			78 (12.2)			77 (12.3)			.13
	n	PY	% PY ^c	n	PY	% PY ^c	n	PY	% PY ^c	
Female sex	1132	3338	60	279	806	73	853	2532	56	<.001
Race/ethnicity										.65
White	1617	4779	85	321	926	84	1296	3853	86	
Black	122	356	6	26	75	7	96	282	6	
Hispanic	50	150	3	12	36	3	38	114	3	
Asian	35	105	2	6	18	2	29	87	2	
Other	40	117	2	13	38	3	27	79	2	
Unknown	31	93	2	5	15	1	26	78	2	
Body mass index										.27
<18.5	34	102	2	6	18	2	28	84	2	
18.5-<25.0	438	1284	23	82	232	21	356	1053	23	
25.0-<30.0	622	1848	33	120	352	32	502	1495	33	
≥30.0	801	2366	42	175	505	46	626	1861	41	
Insurance										.69
ACO external risk	1681	4967	89	344	995	90	1337	3972	88	
Commercial external risk	206	611	11	38	110	10	168	501	11	
Other ^d	8	21	<1	1	2	<1	7	19	<1	
Smoking status										.18
None	876	2572	46	191	543	49	685	2029	45	
Former	714	2117	38	140	410	37	574	1707	38	
Current	151	449	8	22	64	6	129	385	9	
Unknown	154	461	8	30	90	8	124	371	8	
Charlson Comorbidity Index score ^b	1895	5599	4.74 (3.30)	383	1107	4.80 (3.22)	1512	4493	4.72 (3.31)	.76
Comorbidities										
Cardiovascular disease	1154	3401	61	233	667	60	921	2734	61	.71
Diabetes	967	2856	51	195	566	51	772	2290	51	.76
Renal disease	865	2544	45	178	509	46	687	2035	45	.87
Cancer	862	2557	46	181	531	48	681	2026	45	.79
Systemic corticosteroid use	651	1919	34	137	394	36	514	1525	34	.98
Total reported drug allergies										<.001
0	258	764	14	4	9	<1	254	755	17	
1-2	789	2336	42	89	253	23	700	2083	46	
3-4	403	1185	21	104	299	27	299	886	20	
≥5	445	1315	24	186	545	49	259	769	17	
Other reported drug allergies										<.001
Cephalosporin antibiotics	53	153	3	24	69	6	29	84	2	
Sulfonamide antibiotics	298	868	16	99	284	26	199	585	13	
Prior resistant organisms										
MRSA colonization or infection	134	398	7	30	88	8	104	310	7	.82
VRE colonization or infection	57	168	4	10	28	3	47	140	3	.53

ACO indicates accountable care organization; MRSA, methicillin-resistant *Staphylococcus aureus*; PY, person-years; VRE, vancomycin-resistant *Enterococcus*.

^aUnadjusted P values for reported penicillin allergy were calculated using generalized estimating equations logistic model.

^bAge and Charlson Comorbidity Index score numbers shown are mean (SD).

^cPercentage of PY was calculated as PY/total PY.

^dOther includes nonrisk other, nonrisk preferred provider organization/other, UnitedHealthcare, and none.

TABLE 2. Unadjusted Association of Reported Penicillin Allergy Status and Antibiotic Use

	All Patients (N = 1895)			Reported Penicillin Allergy (n = 383)			No Reported Penicillin Allergy (n = 1512)			P ^b
	n	PY	% PY ^a	n	PY	% PY ^a	n	PY	% PY ^a	
Narrow-spectrum beta-lactams ^c	767	2275	41	66	188	17	701	2087	47	<.001
Penicillins ^d	317	940	17	13	36	3	304	905	20	<.001
Cephalosporins, first generation	576	1707	31	51	143	13	525	1563	35	<.001
Cephalosporins, second generation	50	150	3	9	27	2	41	123	3	.64
Beta-lactam alternatives ^e	1367	4041	73	306	889	80	1061	3152	71	<.001
Fluoroquinolones	912	2695	48	204	587	53	708	2108	47	.026
Macrolides	529	1561	28	122	354	32	407	1206	27	.075
Vancomycin	431	1269	23	90	258	23	341	1011	23	.81
Clindamycin	184	536	10	108	312	28	76	224	5	<.001
Sulfonamides	360	1068	19	84	245	22	276	823	18	.14
Tetracyclines	334	984	18	96	282	25	238	702	16	<.001
Aminoglycosides	64	188	3	14	39	4	50	149	3	.78
Linezolid	35	101	2	10	27	2	25	75	2	.23
Other beta-lactams										
Beta-lactamase penicillins ^f	395	1167	21	18	46	4	377	1121	25	<.001
Cephalosporins, third generation	380	1128	20	68	196	18	312	932	21	.14
Carbapenems	40	115	2	8	21	2	32	95	2	.94

PY indicates person-years.

^aPercentage of PY was calculated as PY/total PY.

^bUnadjusted *P* values for penicillin allergy were calculated using generalized estimating equations logistic regression model.

^cIncludes penicillins and cephalosporins in the first and second generations.

^dOther than beta-lactamase penicillins.

^eBeta-lactam alternatives included fluoroquinolones, macrolides, parenteral vancomycin, clindamycin, sulfonamides, tetracyclines, aminoglycosides, and linezolid. Patients may use beta-lactam alternatives multiple times.

^fBeta-lactamase penicillins included piperacillin-tazobactam, amoxicillin-clavulanate/clavulanic acid, and ampicillin-sulbactam.

penicillin allergy and almost half had MDIS. Patients had risk factors for bacterial infections, but MRSA and VRE were infrequent, suggesting that narrow-spectrum beta-lactams would be potentially useful treatments in this population. HCHN patients had high antibiotic use overall; HCHN patients with a reported penicillin allergy were about 7-fold less likely to be exposed to narrow-spectrum beta-lactams and more than 3-fold more likely to be exposed to beta-lactam alternative antibiotics. HCHN patients with penicillin allergy alone had 13% more healthcare visits; there were 20% more healthcare visits if there was concurrent MDIS.

The HCHN patients had a markedly high prevalence of reported penicillin allergy (20%). Although the prevalence of reported penicillin allergy varies among adult populations, it is often reported to range from 6% to 10%.^{19,28,29} Penicillin allergy reporting increases with increasing age, and our HCHN cohort was composed of older adults (mean age, 77 years).³⁰ Hospitalized patients and patients with cancer have even higher reported penicillin allergy prevalence rates (up to 15%).³¹⁻³⁴ MDIS was identified in almost half (45%) of HCHN patients, but previous studies indicated that general patient populations rarely have MDIS (from 2% to 6%).^{19,20}

Penicillin allergy testing removes false penicillin allergy labels in more than 90% of patients who carry a historical penicillin allergy diagnosis.⁸ Testing includes a detailed allergy history

and often procedures such as penicillin skin testing and/or drug administration under medical observation (ie, a drug challenge). Although penicillin allergy evaluation is broadly encouraged by organizations such as the CDC and the National Quality Forum, currently less than 1% of Americans with a documented penicillin allergy report having been tested.³⁵⁻³⁷ Drug allergy testing for other antibiotics is available in some US allergy practices and can be used to disprove prior drug allergies and clarify true drug reactions in patients with MDIS. Antibiotic allergy evaluations in one Australian center disproved 85% of all reported antibiotic allergies.²¹ Although fewer antibiotic allergies may be disproved in an HCHN population, it is quite likely that many antibiotic allergies will be found untrue, which would improve antibiotic prescribing and minimize risks of treatment failure and adverse effects.

The HCHN patients had high prevalence of risk factors for bacterial infections that included diabetes (51%), cancer (46%), and systemic corticosteroid exposure (34%). Additionally, almost half of the patients (46%) were current or former smokers, a strong risk factor for bacterial pneumonia that was the single most common reason for preventable hospitalization in HCHN patients.^{2,5,6} Increasing the use of narrow-spectrum beta-lactam antibiotics in HCHN patients may not only serve to improve their clinical outcomes but may also reduce HRU and decrease healthcare costs. Although this has

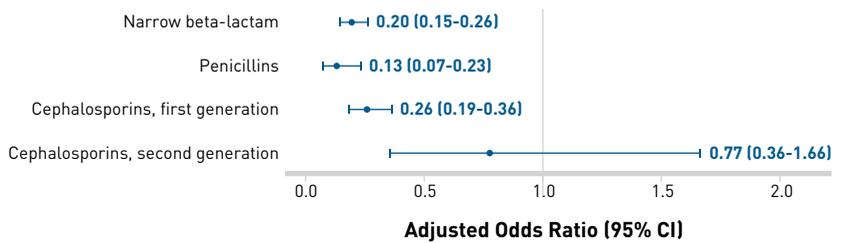
not been assessed specifically to date, one study demonstrated that patients reporting a penicillin allergy who received penicillin allergy evaluations had lower antibiotic costs in the year after their allergy testing compared with the year before their allergy testing.³⁸

The resistant organisms MRSA and VRE were surprisingly uncommon in HCHN patients (4%). This low level of colonization with resistant organisms suggests that, when infected, HCHN patients may have infections treatable with narrow-spectrum beta-lactams. As such, reclaiming the use of narrow-spectrum beta-lactams in HCHN patients previously labeled as penicillin-allergic would be helpful. Findings of prior studies identified that patients reporting penicillin allergy had an increased prevalence of MRSA and VRE³⁹ and an increased incidence of new MRSA, with more than half of the increased MRSA risk attributable to beta-lactam alternative antibiotic prescribing.¹¹ Addressing reported penicillin allergies, therefore, is also a useful antibiotic stewardship tool for fighting antimicrobial resistance.⁸

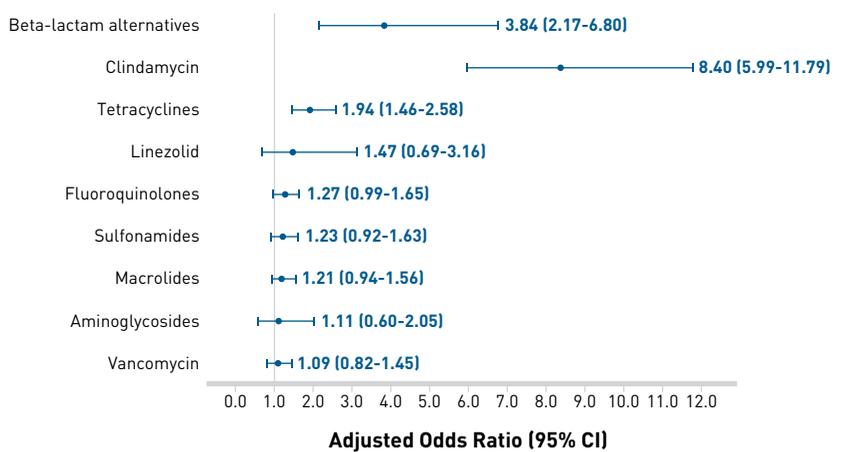
A reported penicillin allergy in HCHN patients was associated with a 7-fold lower use of narrow-spectrum beta-lactams and a more than 3-fold increased use of alternative antibiotics. These associations magnified to 9-fold less likely to receive a narrow-spectrum beta-lactam and 6-fold more likely to receive beta-lactam alternatives when excluding patients with gastrointestinal penicillin intolerance in a sensitivity analysis. A prior population-based outpatient cohort study found that patients reporting penicillin allergy had approximately 4-fold increased risks of macrolide and clindamycin exposure and 2-fold increased fluoroquinolone exposure.¹¹ Although we found that all beta-lactam alternative antibiotics were used more frequently in HCHN patients in this study, the largest difference by reported penicillin allergy status was clindamycin use, where a more than 8-fold increased odds of use was identified in patients reporting a penicillin allergy. Clindamycin is considered one of the most common causative antibiotics for *Clostridioides difficile* infection (CDI).⁴⁰ Findings of prior studies support that CDI incidence is greater for patients with a reported penicillin allergy and that some of the observed increased

FIGURE. The Association of Reported Penicillin Allergy With Antibiotic Use in High-Cost, High-Need Patients^a

A. The Association of Reported Penicillin Allergy With Narrow-Spectrum Antibiotic Use^b



B. The Association of Reported Penicillin Allergy With Beta-Lactam Alternative Use



^aOdds ratios are adjusted for age, sex, race, and Charlson Comorbidity Index score.

^bPenicillins exclude anti-*Pseudomonas* penicillins and penicillins that are combined with beta-lactamase inhibitors (eg, tazobactam). See Methods for details.

TABLE 3. Unadjusted Association of Penicillin Allergy and Other Drug Allergy Status on Healthcare Resource Utilization

Incident Rate ^a	All Patients (N = 1895)	Reported Penicillin Allergy		P ^b	Multiple Drug Intolerance Syndrome		P ^b
		Yes (n = 383)	No (n = 1512)		Yes ^c (n = 848)	No (n = 1047)	
Total number of visits	1.16	3.03	0.70	<.001	2.05	0.44	<.001
Inpatient visits	0.06	0.09	0.05	.24	0.11	0.03	<.001
Emergency visits	0.07	0.19	0.04	.003	0.12	0.03	<.001
Outpatient visits	1.03	2.70	0.62	<.001	1.80	0.41	<.001
Primary care	0.27	0.74	0.16	<.001	0.43	0.15	<.001
Specialist	0.51	1.95	0.46	<.001	1.29	0.32	<.001

^aPatient visits that occurred between January 1, 2014, and December 31, 2016, displayed per follow-up year.

^bUnadjusted P values determined using Poisson regression.

^cPatients with 3 or more drug allergies or intolerances.

TABLE 4. Association Between Reported Penicillin Allergy and Other Drug Allergy Status on Healthcare Visits

Healthcare Visits	Unadjusted		Adjusted Model ^a		Adjusted Model ^b	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Reported penicillin allergy ^c	1.12 (1.01-1.24)	.034	1.14 (1.04-1.27)	.008	1.13 (1.03-1.25) ^d	.014
Reported penicillin allergy with concurrent MDIS ^e	1.19 (1.06-1.33)	.002	1.22 (1.09-1.36)	<.001	1.20 (1.08-1.34)	<.001

MDIS indicates multiple drug intolerance syndrome; RR, risk ratio.

^aAdjusted for age, sex, and race.

^bAdjusted for age, sex, race, and Charlson Comorbidity Index score.

^cThe reference group is patients without a reported penicillin allergy.

^dIn the sensitivity analysis excluding the 40 patients with gastrointestinal penicillin intolerance only: adjusted RR, 1.13; 95% CI, 1.02-1.25.

^eThe reference group is patients without penicillin allergy and without MDIS.

CDI risk is directly attributable to macrolide, clindamycin, and fluoroquinolone prescribing.¹¹ As such, if routine penicillin allergy evaluations could improve antibiotic prescribing, CDI cases might be averted. Recently, patients with penicillin allergy histories who were penicillin tested were subsequently exposed to less clindamycin and macrolides than matched patients who were not penicillin tested.⁴¹

Although all patients were high utilizers, reporting a penicillin allergy, both alone and with concurrent MDIS, conferred a 10% to 20% significant increase in HRU. The observed utilization differences were driven by increased emergency and outpatient visits. Given that narrow-spectrum beta-lactams are first-line therapies for many infections,⁸ utilization might be reduced after removal of the penicillin allergy label. Indeed, one prior matched cohort study determined that patients with penicillin allergy histories who received penicillin allergy evaluations had fewer outpatient visits ($P < .001$), emergency visits ($P = .29$), and hospital days ($P < .001$) per coverage year during follow-up compared with matched controls with penicillin allergy histories who did not receive the penicillin allergy evaluation.⁴¹

Limitations

This study used a retrospective design. Although we reduced misclassification through manual review of the primary exposure (penicillin allergy) and studied outcomes derived from electronically captured antibiotic and HRU data, misclassification could still exist. Because drug dosage and duration details were not consistently available, we studied antibiotic and corticosteroid use, regardless of dose and duration. However, drug use did include both inpatient and outpatient use through administration and prescription data. We assessed total healthcare system visits as our measure of HRU and did not consider inpatient length of stay nor procedures and tests performed. We assessed many potential confounders in our analysis but could not consider all possible confounders; other illnesses and/or social factors (eg, living situation) might affect antibiotic choice or healthcare visits. However, because these

factors would not be related to the exposure of penicillin allergy, their inclusion into our models would be unlikely to yield different results. Our findings come from 1 sample of HCHN patients enrolled in the care management program of a single large academic medical center in the Boston area; such patients may not be representative of other HCHN patients in the United States.

CONCLUSIONS

This large, retrospective cohort analysis demonstrates that there is a high burden of drug allergy in HCHN patients and substantial room for improvement in the antibiotic choices made for HCHN patients reporting a penicillin allergy. Systematic efforts focused on penicillin and drug allergy management in HCHN patients may benefit both the patients and the healthcare systems tasked with supporting the care of these complex patients in a cost-conscious manner. ■

Acknowledgments

The authors thank Tyler Harkness, BS, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, for his research assistance.

Author Affiliations: Division of Rheumatology, Allergy, and Immunology (KGB, XF, CMM) and Division of Infectious Diseases (RPW), Department of Medicine, Massachusetts General Hospital, Boston, MA; The Medical Practice Evaluation Center, The Mongan Institute, Massachusetts General Hospital (KGB, FMS, CMM, RPW), Boston, MA; Harvard Medical School (KGB, NMO, FMS, RPW), Boston, MA; Division of General Academic Pediatrics, Massachusetts General Hospital for Children (NMO), Boston, MA; Integrated Care Management Program, Massachusetts General Hospital (NMO, JMM), Boston, MA.

Source of Funding: Dr Blumenthal receives career development support from NIH K01AI125631; the American Academy of Allergy, Asthma & Immunology (AAAAI) Foundation; and the Massachusetts General Hospital (MGH) Claflin Distinguished Scholar Award. Dr Walensky was supported by the Steven and Deborah Gorlin MGH Research Scholars Award. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health, the AAAAI Foundation, or MGH.

Author Disclosures: Dr Blumenthal reports a clinical decision support tool used institutionally for beta-lactam allergy at Partners HealthCare System. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (KGB, RPW); acquisition of data (KGB, NMO, JMM); analysis and interpretation of data (KGB, NMO, XF, FMS, CMM, RPW); drafting of the manuscript (KGB); critical revision of the manuscript for important intellectual content (KGB, NMO, FMS, RPW); statistical analysis (XF, FMS, CMM); provision of patients or study materials (KGB, NMO, JMM); obtaining funding (KGB); administrative, technical, or logistic support (XF, CMM, JMM); and supervision (KGB, RPW).

Address Correspondence to: Kimberly G. Blumenthal, MD, MSc, Division of Rheumatology, Allergy, and Immunology, The Medical Practice Evaluation Center, The Mongan Institute, Massachusetts General Hospital, 100 Cambridge St, 16th Floor, Boston, MA 02114. Email: kblumenthal@mg.harvard.edu

REFERENCES

- Blumenthal D, Abrams MK. Tailoring complex care management for high-need, high-cost patients. *JAMA*. 2016;316(16):1657-1658. doi: 10.1001/jama.2016.12388.
- Figueroa JF, Joynt Maddox KE, Beaulieu N, Wild RC, Jha AK. Concentration of potentially preventable spending among high-cost Medicare subpopulations: an observational study. *Ann Intern Med*. 2017;167(10):706-713. doi: 10.7326/M17-0767.

3. Blumenthal D, Chernof B, Fulmer T, Lumpkin J, Selberg J. Caring for high-need, high-cost patients: an urgent priority. *N Engl J Med*. 2016;375(10):909-911. doi: 10.1056/NEJMp1608511.
4. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol*. 2003;42(7):1226-1233. doi: 10.1016/s0735-1097(03)00947-1.
5. Joynt KE, Gawande AA, Orav EJ, Jha AK. Contribution of preventable acute care spending to total spending for high-cost Medicare patients. *JAMA*. 2013;309(24):2572-2578. doi: 10.1001/jama.2013.7103.
6. Niefeld MR, Braunstein JB, Wu AW, Saudek CD, Weller WE, Anderson GF. Preventable hospitalization among elderly Medicare beneficiaries with type 2 diabetes. *Diabetes Care*. 2003;26(5):1344-1349. doi: 10.2337/diacare.26.5.1344.
7. Jiang HJ, Russo CA, Barrett ML. Nationwide frequency and costs of potentially preventable hospitalizations, 2006. Healthcare Cost and Utilization Project website. hcup-us.ahrq.gov/reports/statbriefs/sb72.pdf. Published April 2009. Accessed May 9, 2019.
8. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321(2):188-199. doi: 10.1001/jama.2018.19283.
9. MacFadden DR, LaDelfa A, Leen J, et al. Impact of reported beta-lactam allergy in inpatient outcomes: a multicenter prospective cohort study. *Clin Infect Dis*. 2016;63(7):904-910. doi: 10.1093/cid/ciw462.
10. Blumenthal KG, Parker RA, Shenoy ES, Walensky RP. Improving clinical outcomes in patients with methicillin-sensitive *Staphylococcus aureus* bacteremia and reported penicillin allergy. *Clin Infect Dis*. 2015;61(5):741-749. doi: 10.1093/cid/civ394.
11. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ*. 2018;361:k2400. doi: 10.1136/bmj.k2400.
12. 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(3):329-336. doi: 10.1093/cid/cix794.
13. Bodenheimer T. Coordinating care—a perilous journey through the health care system. *N Engl J Med*. 2008;358(10):1064-1071. doi: 10.1056/NEJMp0706165.
14. Bodenheimer T, Berry-Millett R. Follow the money—controlling expenditures by improving care for patients needing costly services. *N Engl J Med*. 2009;361(16):1521-1523. doi: 10.1056/NEJMp0907185.
15. Bernstein RH. New arrows in the quiver for targeting care management: high-risk versus high-opportunity case identification. *J Ambul Care Manage*. 2007;30(1):39-51. doi: 10.1097/00004479-200701000-00007.
16. Anderson GF, Ballreich J, Bleich S, et al. Attributes common to programs that successfully treat high-need, high-cost individuals. *Am J Manag Care*. 2015;21(11):e597-e600.
17. Brown RS, Peikes D, Peterson G, Schore J, Razafindrakoto CM. Six features of Medicare coordinated care demonstration programs that cut hospital admissions of high-risk patients. *Health Aff (Millwood)*. 2012;31(6):1156-1166. doi: 10.1377/hlthaff.2012.0393.
18. Charlson M, Charlson RE, Briggs W, Hollenberg J. Can disease management target patients most likely to generate high costs? the impact of comorbidity. *J Gen Intern Med*. 2007;22(4):464-469. doi: 10.1007/s11606-007-0130-7.
19. Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol*. 2012;108(2):88-93. doi: 10.1016/j.anai.2011.11.006.
20. Blumenthal KG, Li Y, Acker WW, et al. Multiple drug intolerance syndrome and multiple drug allergy syndrome: epidemiology and associations with anxiety and depression. *Allergy*. 2018;73(10):2012-2023. doi: 10.1111/all.13440.
21. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis*. 2017;65(1):166-174. doi: 10.1093/cid/cix244.
22. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: assessing tools for antimicrobial stewardship. *J Allergy Clin Immunol*. 2017;140(1):154-161.e6. doi: 10.1016/j.jaci.2017.02.005.
23. Wilke RA, Berg RL, Peissig P, et al. Use of an electronic medical record for the identification of research subjects with diabetes mellitus. *Clin Med Res*. 2007;5(1):1-7. doi: 10.3121/cmr.2007.726.
24. Bash LD, Coresh J, Köttgen A, et al. Defining incident chronic kidney disease in the research setting: the ARIC Study. *Am J Epidemiol*. 2009;170(4):414-424. doi: 10.1093/aje/kwp151.
25. Weiner MG, Livshits A, Carozzini C, et al. Derivation of malignancy status from ICD-9 codes. *AMIA Annu Symp Proc*. 2003;2003:1050.
26. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251. doi: 10.1016/0895-4356(94)90129-5.
27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619. doi: 10.1016/0895-4356(92)90133-8.
28. Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy*. 2004;34(10):1597-1601. doi: 10.1111/j.1365-2222.2004.02070.x.
29. Zhou L, Dhopeswarkar N, Blumenthal KG, et al. Drug allergies documented in electronic health records of a large healthcare system. *Allergy*. 2016;71(9):1305-1313. doi: 10.1111/all.12881.
30. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009;122(8):778.e1-e7. doi: 10.1016/j.amjmed.2009.01.034.
31. Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med*. 2000;160(18):2819-2822. doi: 10.1001/archinte.160.18.2819.
32. van Dijk SM, Gardarsdóttir H, Wassenberg MW, Oosterheert JJ, de Groot MC, Rockmann H. The high impact of penicillin allergy registration in hospitalized patients. *J Allergy Clin Immunol Pract*. 2016;4(5):926-931. doi: 10.1016/j.jaip.2016.03.009.
33. Trubiano JA, Leung VK, Chu MY, Worth LJ, Slavin MA, Thursky KA. The impact of antimicrobial allergy labels on antimicrobial usage in cancer patients. *Antimicrob Resist Infect Control*. 2015;4:23. doi: 10.1186/s13756-015-0063-6.
34. Huang KG, Cluzet V, Hamilton K, Fadugba O. The impact of reported beta-lactam allergy in hospitalized patients with hematologic malignancies requiring antibiotics [erratum in *Clin Infect Dis*. 2018;67(7):1151. doi: 10.1093/cid/ciy431]. *Clin Infect Dis*. 2018;67(1):27-33. doi: 10.1093/cid/ciy037.
35. Find an allergist/immunologist. American Academy of Allergy, Asthma & Immunology website. allergist.aaaai.org/find. Accessed May 9, 2019.
36. NQF launches antibiotic stewardship initiative [news release]. Washington, DC: National Quality Forum; October 16, 2015. qualityforum.org/News_And_Resources/Press_Releases/2015/NQF_Launches_Antibiotic_Stewardship_Initiative.aspx. Accessed May 9, 2019.
37. Evaluation and diagnosis of penicillin allergy for healthcare professionals: is it really a penicillin allergy? CDC website. cdc.gov/antibiotic-use/community/for-hcp/Penicillin-Allergy.html. Updated October 31, 2017. Accessed May 9, 2019.
38. Macy E. Elective penicillin skin testing and amoxicillin challenge: effect on outpatient antibiotic use, cost, and clinical outcomes. *J Allergy Clin Immunol*. 1998;102(2):281-285. doi: 10.1016/s0091-6749(98)70097-1.
39. 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(3):790-796. doi: 10.1016/j.jaci.2013.09.021.
40. Palmore TN, Sohn S, Malak SF, Eagan J, Sepkowitz KA. Risk factors for acquisition of *Clostridium difficile*-associated diarrhea among outpatients at a cancer hospital. *Infect Control Hosp Epidemiol*. 2005;26(8):680-684. doi: 10.1086/502602.
41. Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract*. 2017;5(3):705-710. doi: 10.1016/j.jaip.2017.02.012.

Visit ajmc.com/link/4551 to download PDF and eAppendix

eAppendix Table 1. Diagnostic Codes Used in Covariate Assessment

Diagnosis	Codes
Cardiovascular disease	410.9x, 414.0x, 428.xx
Diabetes(1)	250.00-250.92, 357.2, 362.01-362.02, 583.81
Renal disease(3)	581–583 or 585–589, 403, 404, 593.9, 250.4, 39.95, 54.98, 591, 593.7, 753
Cancer(2)	140-149.9, 150-159.9, 160-164.9, 170-172.9, 174-175.9, 180.x, 182-186.9, 187.3, 187.4, 187.9, 188-189.9, 190-197.8, 199.x, 235.x, 236.1, 236.2, 236.4, 236.5, 236.6, 236.7, 236.91, 237.xx, 238.1, 238.2, 238.8, 238.9, 239.xx
Charlson comorbidity index(4, 5)	<p><i>1 point each:</i> Myocardial Infarction: 410 to 410.9, 412 Congestive heart failure: 428 to 428.9 Peripheral vascular disease: 443.9, 441, 441.9, 785.4, v43.4', 38.48 Cerebrovascular disease: 430 to 438 Dementia: 290 to 290.9 Chronic pulmonary disease: 490 to 496, 500 to 505, 506.4 Connective tissue disease: 710.0, 710.1, 710.4,714.4,714.8,725,714.0, 714.2 Ulcer disease: 531 to 534.9 Mild liver disease: 571.2, 571.4 to 571.49, 571.5, 571.6 Diabetes: 250 to 250.3, 250.3</p> <p><i>2 points each:</i> Hemiplegia: 344.1, 342 to 342.9 Moderate or severe renal disease: 582 to 582.9, 583 to 583.7, 585, 586, 588 to 588.9 Diabetes with end organ failure: 250.4 to 250.6 Any tumor, leukemia, or lymphoma: 140 to 172.9, 174 to 195.8, 200 to 208.9</p> <p><i>3 points each:</i> Moderate or severe liver disease: 572.2 TO 572.</p> <p><i>6 point each:</i> Metastatic solid tumor: 196 to 199.1 AIDS: 042 to 044.98</p>

^a 40 patients had only gastrointestinal upset and were excluded from the reported penicillin allergy group in the sensitivity analysis (see methods).

^b Includes hypotension, shock, arrest and/or arrhythmia.

^c Includes bronchospasm, wheezing, and/or asthma.

^d Includes one patient with acute interstitial nephritis

^e Other includes: Headache (n = 2), hepatotoxicity (1), mental status change (n = 2), eye floater (n = 1), musculoskeletal pain (n = 1), fainting (n = 1), muscle spasms (n = 1), redness (n = 1), tinnitus (n = 1), difficult swallowing (n = 1), hepatitis (n = 1), tachycardia (n = 1), flushing (n = 1), other (n = 1).

eAppendix Table 2. High-Cost High-Need Patients Reporting a Penicillin Allergy Had a Total of 513 Penicillin Adverse and Allergic Reactions

Reactions	n (%)
Rash or dermatitis	179 (35)
Urticaria/hives	75 (15)
Gastrointestinal upset	74 (14) ^a
Angioedema/swelling	42 (8)
Anaphylaxis ^b	31 (6)
Shortness of breath ^c	9 (2)
Renal injury ^d	4 (1)
Other ^e	16 (3)
Unknown	83 (16)
<i>Total</i>	<i>513 (100)</i>

^a 40 patients had only gastrointestinal upset and were excluded from the reported penicillin allergy group in the sensitivity analysis (see methods).

^b Includes hypotension, shock, arrest and/or arrhythmia.

^c Includes bronchospasm, wheezing, and/or asthma.

^d Includes one patient with acute interstitial nephritis

^e Other includes: Headache (n = 2), hepatotoxicity (1), mental status change (n = 2), eye floater (n = 1), musculoskeletal pain (n = 1), fainting (n = 1), muscle spasms (n = 1), redness (n = 1), tinnitus (n = 1), difficult swallowing (n = 1), hepatitis (n = 1), tachycardia (n = 1), flushing (n = 1), other (n = 1).

eAppendix References

1. Wilke RA, Berg RL, Peissig P, Kitchner T, Sijercic B, McCarty CA, et al. Use of an electronic medical record for the identification of research subjects with diabetes mellitus. *Clin Med Res.* 2007;5(1):1-7.
2. Weiner MG, Livshits A, Carozzoni C, McMenamin E, Gibson G, Loren AW, et al. Derivation of malignancy status from ICD-9 codes. *AMIA Annu Symp Proc.* 2003:1050.
3. Bash LD, Coresh J, Kottgen A, Parekh RS, Fulop T, Wang Y, et al. Defining incident chronic kidney disease in the research setting: The ARIC Study. *Am J Epidemiol.* 2009;170(4):414-24.
4. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47(11):1245-51.
5. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613-9.