

Clinical and economic burden of hospitalizations with registration of penicillin allergy



Bernardo Sousa-Pinto, MD ^{*,†,‡}; António Cardoso-Fernandes, BSc ^{†,‡}; Luís Araújo, MD ^{*,‡}; João Almeida Fonseca, PhD ^{†,‡}; Alberto Freitas, PhD ^{†,‡}; Luís Delgado, PhD ^{*,‡}

^{*} Basic and Clinical Immunology Unit, Department of Pathology, Faculty of Medicine, University of Porto, Porto, Portugal

[†] MEDCIDS—Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal

[‡] CINTESIS—Center for Health Technology and Services Research, Porto, Portugal

ARTICLE INFO

Article history:

Received for publication October 7, 2017.

Received in revised form November 2, 2017.

Accepted for publication November 29, 2017.

ABSTRACT

Background: Penicillin allergy is commonly reported, but only a minority of claimants has a confirmed diagnosis. Nevertheless, patients labeled as having penicillin allergy are treated with second-line antibiotics, which are more expensive and less effective, possibly increasing the risk of drug-resistant infections.

Objective: To compare hospitalizations with and without registration of penicillin allergy concerning their morbidity and hospital resource use.

Methods: We analyzed a national administrative database containing a registration of all Portuguese hospitalizations from 2000 to 2014. All episodes occurring in adults with a penicillin allergy registration were compared with an equal number of hospitalizations without such registration and matched for inpatients' age, sex, and main diagnosis. We compared those episodes concerning their length of stay, hospital price charges, comorbidities, and frequency of drug-resistant infections. Differences between medical and surgical hospitalizations were explored.

Results: Hospitalizations with registration of penicillin allergy ($n = 102,872$) had a longer average length of stay than the remainder episodes (8 vs 7 days; $P < .001$) and higher hospital charges (3,809.0 vs 3,490.0 USD; $P < .001$). Inpatients with penicillin allergy registration also had a higher mean Charlson Comorbidity Index (0.91 vs 0.76; $P < .001$) and a significantly higher frequency of infections by several agents, including methicillin-resistant *Staphylococcus aureus*, *Enterococcus* species, and *Escherichia coli*. Among surgical episodes, septicemia was 1.2-fold more frequent among penicillin allergy cases.

Conclusion: Hospitalizations with registration of penicillin allergy are associated with increased economic costs and frequency of infections by drug-resistant agents, reinforcing the need to establish a correct diagnosis of penicillin allergy.

© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Drug hypersensitivity reactions represent 15% of all adverse drug reactions.¹ When these reactions are immunologically mediated, they consist of drug allergies, which can present with a wide range of clinical manifestations and with different levels of severity.^{2,3} Drug allergy is commonly reported; although estimates vary among different populations, the frequency of self-reported drug allergy has

been found to be higher than 30% by some investigators.^{4,5} The β -lactam class of antibiotics is one of the drug classes patients most often claim to be allergic to; it is estimated that 8% of Americans are labeled as being allergic to penicillins, but fewer than 5% of them have a confirmed diagnosis.⁶ Therefore, although some true allergic reactions might remain unidentified, overdiagnosis appears to be a much more common phenomenon. Overdiagnosis of penicillin allergy might be explained by several factors, such as the diversity of clinical manifestations, misdiagnosis with other adverse reactions or infectious rashes, and underperformance of confirmation tests.^{7,8} In addition, in patients who are truly allergic to penicillins, loss of sensitization over the years might occur.⁹

Overdiagnosis of penicillin allergy can have several clinical consequences. Inpatients with such a label often receive second-line treatments (such as vancomycin and fluoroquinolones), which are less effective and associated with a higher risk of antibiotic-resistant infections than penicillins.^{10,11} Those second-line antibiotics also are more expensive and, in addition to the increased

Reprints: Bernardo Sousa-Pinto, MD, CINTESIS—Center for Health Technology and Services Research, Rua Dr Plácido da Costa, Porto, Portugal; E-mail: bernardo@med.up.pt.

Disclosures: Authors have nothing to disclose.

Prior Presentations: Preliminary results were presented at a poster session at the 2017 Annual Meeting of the AAAAI (March 3–6, 2017; Atlanta, Georgia) and the respective abstract was published (Sousa-Pinto B, Fernandes A, Araújo L, et al. Clinical and economic burden of hospitalizations with registry of penicillin allergy. *J Allergy Clin Immunol*. 2017;139[suppl]:AB59).

<https://doi.org/10.1016/j.anai.2017.11.022>

1081-1206/© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

frequency of hospital readmissions, account for the higher costs observed in the treatment of inpatients labeled with penicillin allergy.^{10,12,13} Although the clinical and health care repercussions of penicillin allergy labeling have been studied in the United States, this issue remains poorly studied in Europe and nationwide studies are lacking. In a previous study performed in children (under review), we observed a significant association between having a registration of penicillin allergy and having more comorbidities and longer hospitalizations. Therefore, we aimed to complement this assessment by comparing the frequency of antibiotic-resistant infections, length of stay, comorbidities, and hospitalization charges in adult inpatients with and without registration of penicillin allergy on a nationwide basis and over a period of 15 years. We also aimed to assess whether there were differences between surgical and medical hospitalizations for having a penicillin allergy label.

Methods

We analyzed a database that contains a registration of all hospitalizations occurring in public hospitals in mainland Portugal from 2000 to 2014. Hospitalizations were defined as (1) episodes with hospital stays lasting at least 24 hours and (2) shorter episodes in which the inpatient dies, is transferred, or leaves against medical advice. This database was provided by the Portuguese Central Health System Administration (Administração Central do Sistema de Saúde) and contains, for each episode, information about the main diagnosis (corresponding to the diagnosis that, at discharge, was deemed responsible for the inpatient's admission), up to 19 other accompanying diagnoses, and up to 20 external causes of injury and poisoning (including drug-induced allergic reactions). Diagnoses and external causes were coded using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes.

All hospitalizations of adult patients (≥ 18 years old) with a registration of penicillin allergy were compared with an equal number of randomly chosen episodes without such registration for patients' sex, age, and main diagnosis. Penicillin allergy was identified by the V14.0 code as the main or accompanying diagnosis, or by the E930.0 code as external cause of injury and poisoning (corresponding, respectively, to "personal history of allergy to penicillin" and "penicillins causing adverse effects in therapeutic use"). The main diagnosis was previously classified into 259 clinically homogeneous and mutually exclusive categories, as defined by the Clinical Classification Software.¹⁴

Hospitalizations with registration of penicillin allergy were subsequently compared with an equal number of cases without such registration matched by sex, age, and main diagnosis by propensity score matching. The 2 groups were compared for their length of stay, comorbidities (assessed using the Charlson Comorbidity Index¹⁵), in-hospital mortality, and hospital charges. The latter were calculated indirectly using a classification system based on the Diagnosis Related Groups (DRG) system¹⁶ and mostly reflect associated diagnoses, performed procedures, and inpatients' demographic characteristics. Hospital charges were converted into US dollars (USD) using an exchange rate of 1 € equals 1.236 USD. This rate was the mean of the 2000 to 2014 average yearly exchange rates.

Matched episodes with and without penicillin allergy registration also were compared for the frequency of infections with agents with enhanced surveillance in the most recent epidemiologic report on antimicrobial resistance and healthcare-associated infections published by the European Centre for Disease Prevention and Control.¹⁷ In particular, we assessed the frequency of infections with *Staphylococcus aureus* (038.11, 041.11, 482.41, 038.12, 041.12, 482.42, V12.04; the last 4 ICD-9-CM codes concern methicillin-resistant *S aureus* [MRSA]), *Escherichia coli* (ICD-9-CM codes 008.0, 038.42, 041.4), *Klebsiella pneumoniae* (041.3, 482.0), *Pseudomonas* species (008.42, 038.43, 041.7, 482.1), *Enterococcus* species (041.04), and *Streptococ-*

cus pneumoniae (041.2). We could not assess the frequency of *Acinetobacter* infections, because these do not have a specific ICD-9-CM code. In addition, we compared the frequency of *Clostridium difficile* infections (008.45), drug-resistant infections other than MRSA (V09.x), and septicemia (038.x).

Subgroup analyses were performed by comparing surgical and medical episodes. According to the DRG system, episodes had been classified as "surgical" or "medical" based on whether a surgical procedure was or was not performed. In addition, we performed subgroup analyses aiming to assess differences in length of stay and hospital charges according to inpatients' sex, age, occurrence of drug-resistant and/or enhanced surveillance infections, and episode severity (the latter was based on the patients' DRG, but only data from 2011 to 2015 were available).

Statistical analyses were performed using IBM SPSS Statistics 22 (IBM Corp, Armonk, New York), using .05 as the level of significance. Continuous variables were characterized using medians, means, and percentiles. Absolute frequencies and percentages were used for categorical variables. Continuous variables were compared using the Mann-Whitney *U* test, and the χ^2 test was used for categorical variables. This study was exempted from institutional review board approval, because the analyzed data had been previously anonymized.

Results

From 2000 to 2014, we identified 102,872 hospitalizations with registration of penicillin allergy in adults, corresponding to 0.9% of all hospitalizations in adults ($n = 11,482,091$) that occurred within the same period in mainland Portugal public hospitals. Those episodes were initially compared with an equal number of episodes without such registration. The proportion of women was significantly larger in the penicillin allergy group compared with cases without reported penicillin allergy (71.4% vs 57.3%; $P < .001$). The participants' median age was similar in the 2 compared groups (60 years). The frequency of hospitalizations with infections as the main diagnosis was similar in the 2 compared groups (10.6%) as was the frequency of episodes with a diagnosis of septicemia (1.1%). Nevertheless, among hospitalizations with registration of penicillin allergy, we observed a significantly higher frequency of urinary tract infections, skin and subcutaneous tissue infections, and acute and chronic tonsillitis and a significantly lower frequency of pneumonia (eTable 1).

Then, we compared hospitalizations with and without registration of penicillin allergy matched by age, sex, and main diagnosis. The mean length of stay was significantly longer for episodes with registration of penicillin allergy vs those without such label (8 vs 7 days; $P < .001$), despite similarities in the median value (4 days; Table 1). Thus, the total number of hospitalization days was 8.7% larger for penicillin allergy episodes (805,429 days) compared with the remainder (741,045 days; Fig 1). A significantly higher mean Charlson Comorbidity Index also was found for hospitalizations of patients with penicillin allergy (0.91 vs 0.76; $P < .001$; Table 1).

Mean hospitalizations charges were significantly higher for penicillin allergy episodes compared with episodes without such record (3,809.0 vs 3,490.0 USD; $P < .001$). The sum of hospitalization charges for penicillin allergy episodes was more than 391.8 million USD, which was 9.1% higher than the 359.0 million USD for the remaining cases (corresponding to a difference > 32.8 million USD over the 15-year period; Fig 1). eTable 2 lists the results of subgroup analyses performed comparing differences in length of stay and hospital charges. We observed a greater effect of having a penicillin allergy label in some subgroups; for example, in inpatients with more severe conditions, having a label of penicillin allergy was associated with an increase of 23.5% in length of stay and of 10.2% in hospital charges. These values increased to 49.1% and 27.1%, respectively, in the subgroup of patients no older than 30 years (eTable 2).

Table 1
Demographic, Clinical, and Economic Characteristics of Hospitalizations Occurring in Adults With and Without Registration of Penicillin Allergy (Matched According to Patients' Age, Sex, and Main Diagnosis; 2000–2014)

	Hospitalizations with penicillin allergy label (n = 102,872)	Hospitalizations without penicillin allergy label (n = 102,872)	P value
Sex, n (%)			
Men	29,399 (28.6)	30,307 (29.5)	<.001 ^a
Women	73,473 (71.4)	72,565 (70.5)	
Age (y), mean (SD)	57.4 (19.2)	57.4 (19.5)	.423 ^b
Length of stay (days)			<.001 ^b
Mean (SD) [95% CI]	7.8 (10.9) [7.8–7.9]	7.2 (12.0) [7.1–7.3]	
Median (IQR)	4.0 (7)	4.0 (6)	
Total	805,429	741,045	
Charlson Comorbidity Index			<.001 ^b
Mean (SD) [95% CI]	0.91 (1.6) [0.90–0.92]	0.76 (1.6) [0.75–0.76]	
Median (IQR)	0 (1)	0 (1)	
Hospitalization charges (USD)			<.001 ^b
Mean (SD) [95% CI]	3,809.0 (4,432.2) [3781.9–3836.0]	3,490.0 (4,079.5) [3465.0–3514.9]	
Median (IQR)	2418.3 (2055.5)	2285.3 (2035.3)	
Total	391,835,492.5	359,020,533.1	
Frequency of in-hospital deaths, n (%)	3,065 (3.0)	4,691 (4.6)	<.001 ^a

Abbreviations: CI, confidence interval; IQR, interquartile range.

^aBy χ^2 test.

^bBy Mann-Whitney *U* test.

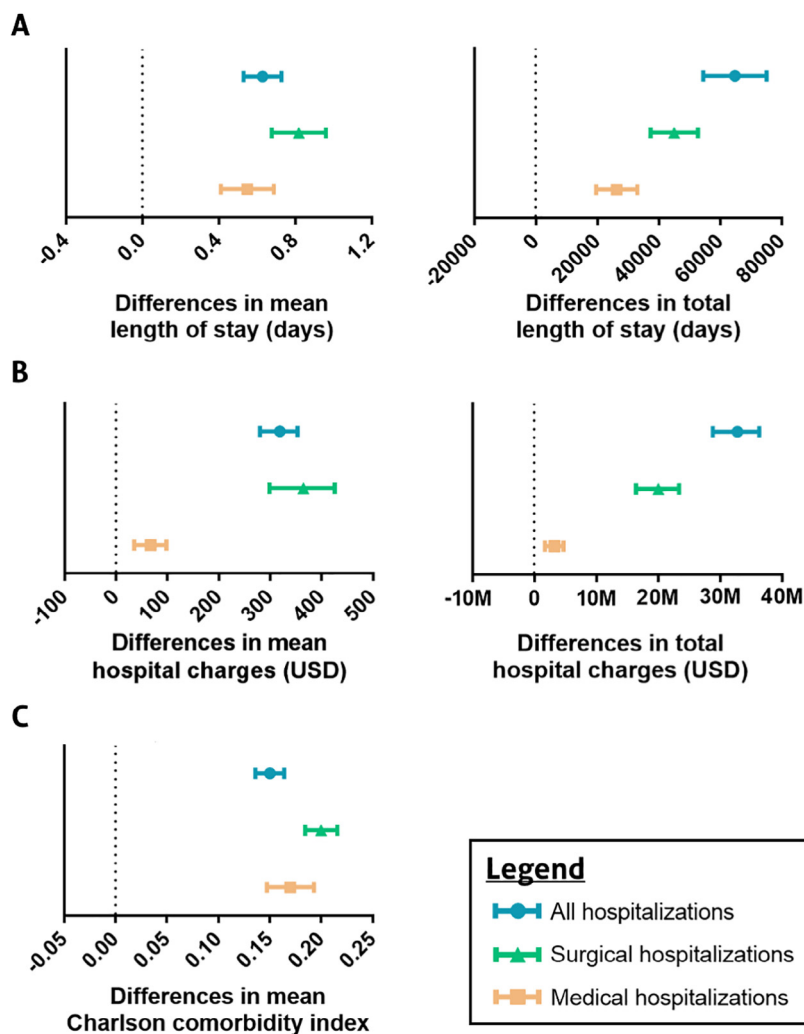


Figure 1. Differences in (A) mean and total length of stay, (B) mean and total hospital charges, and (C) mean Charlson Comorbidity Index when comparing hospitalizations with vs hospitalizations without a label of penicillin allergy.

Table 2
Frequency of Infections by Drug-resistant and Enhanced Surveillance Agents Occurring in Hospitalizations With and Without Registration of Penicillin Allergy (Matched According to Patients' Age, Sex, and Main Diagnosis; 2000–2014)

Frequency of infections, n (%)	Hospitalizations with penicillin allergy label (n = 102,872)	Hospitalizations without penicillin allergy label, (n = 102,872)	P value
<i>Staphylococcus aureus</i>	923 (0.9)	689 (0.7)	<.001 ^a
Methicillin-resistant <i>Staphylococcus aureus</i>	323 (0.3)	211 (0.2)	<.001 ^a
<i>Escherichia coli</i>	2,056 (2.0)	1,552 (1.5)	<.001 ^a
<i>Klebsiella pneumoniae</i>	637 (0.6)	506 (0.5)	<.001 ^a
<i>Pseudomonas</i> sp	571 (0.6)	509 (0.5)	.059 ^a
<i>Enterococcus</i> sp	460 (0.4)	274 (0.3)	<.001 ^a
<i>Streptococcus pneumoniae</i>	376 (0.4)	309 (0.3)	.010 ^a
<i>Clostridium difficile</i>	121 (0.1)	111 (0.1)	.511 ^a
Other drug-resistant infections	117 (0.11)	84 (0.08)	.020 ^a
Septicemia	1,160 (1.1)	1,147 (1.1)	0.785 ^a

^aBy χ^2 test.

Significantly more *S aureus*, MRSA, *E coli*, *K pneumoniae*, *Enterococcus*, *S pneumoniae*, and drug-resistant infections other than MRSA were found among hospitalizations of patients with penicillin allergy (Table 2). *Enterococcus* and MRSA infections were 1.7 and 1.5 times, respectively, more frequent among penicillin allergy episodes, whereas overall *S aureus* infections, *E coli*, and *K pneumoniae* were each 1.3-fold more common. Conversely, significantly lower in-hospital mortality was observed for episodes with registration of penicillin allergy (3.0% vs 4.6% in remainder cases; $P < .001$). No significant differences were found concerning the frequency of septicemia and infections with *Pseudomonas* species or *C difficile*.

We also performed a subgroup analysis comparing results of medical vs surgical episodes (eTable 3). A significantly lower in-hospital mortality among penicillin allergy cases was found among medical episodes (5.0% vs 7.6%; $P < .001$), but not among surgical cases (1.2% vs 1.2%; $P = .464$). Moreover, we observed a significantly higher frequency of septicemia among surgical hospitalizations with registration of penicillin allergy compared with hospitalizations without such record; this significant difference was not found in the medical episodes group. Conversely, in the medical but not in the surgical subgroup, *S pneumoniae* and drug-resistant infections other than MRSA were found with significantly higher frequency among hospitalizations of patients with penicillin allergy. No other differences were found in this subgroup analysis.

Discussion

In this study, we analyzed a database containing a registration of all hospitalizations occurring in Portuguese public hospitals. From 2000 to 2014, we observed that 102,872 hospitalizations had a registration of penicillin allergy. These episodes were found to be longer, costlier, and associated with a higher frequency of drug-resistant infections (and septicemia among surgical episodes) than those without label of penicillin allergy, even after adjusting for patients' age, sex, and main diagnosis. These differences might result from the increased use of less effective and costlier second-line antibiotics in patients reporting to be allergic to penicillins.^{10,12} In fact, we found that hospitalizations with registration of penicillin allergy were, on average, 8.7% longer and with 9.1% more hospital charges than the remainder. The reported significant associations between having a penicillin allergy label and worse outcomes were observed even after adjustment for the Charlson Comorbidity Index by multivariable analyses (data not shown).

This suggests that penicillin allergy is associated with higher health care costs because of longer stays and because of inpatients having costlier diagnoses and procedures performed. We could not assess the proportion of hospitalizations in which penicillin allergy was confirmed. However, if we assume that 10% of labeled episodes had "true penicillin allergy" (a conservative estimate^{6,18}),

we can estimate that de-labeling of patients without allergy could prompt annual decreases of up to 3,863 admission days and up to 1.9 million USD in hospital charges. In some subsets of episodes, the relative impact of having a penicillin allergy label appeared to be higher (eg, inpatients <30 years old and with more severe conditions), reaching increases of up to almost 50% in length of stay and up to 27% higher hospital charges. Thus, these results of subgroup analyses might identify subsets of patients in whom performing confirmation tests might be particularly cost-effective.

Surprisingly, we observed lower in-hospital mortality among medical episodes with registration of penicillin allergy. Although this finding is intriguing, it might result from lack of assessment of allergy history in patients with more severe and acute conditions. In fact, among medical hospitalizations, the in-hospital mortality of episodes lasting no longer than 1 day surpassed 30%. However, although in non-allergic medical cases almost 20% of in-hospital deaths occurred in episodes within that duration, this percentage reached only 12% among the allergic cases. In contrast, a history of drug allergy is frequently assessed before surgical procedures, which might explain why in-hospital mortality was not significantly different between episodes with and without registration of penicillin allergy. In accordance, we found that the frequency of penicillin allergy registration was twice as high for surgical as for medical episodes (1.0% vs 0.5%, respectively).

Nevertheless, in what appears to be the main limitation of our study, the overall frequency of episodes with registration of penicillin allergy (<1% of all hospitalizations) was well below those of previous studies, which estimated the frequency of self-reported drug allergy among inpatients to range from 7.5% to 23.5%.¹⁹ This discrepancy is consistent with previous studies performed using administrative databases and is probably more the result of incompleteness of the clinical registries and of the analyzed database than of a selective registration of cases with confirmed diagnosis of penicillin allergy.²⁰ Another important limitation concerns the impossibility to assess the frequency of inpatients who had an allergic reaction to penicillins during their hospital stays vs those with a history (or claimed history) of penicillin allergy before admission. In addition, we could not assess the percentage of cases in which the diagnosis of penicillin allergy had been confirmed. The frequency of hospitalizations with occurrence of drug-resistant infections also appears to be underestimated; in fact, only one-third of all hospitalizations with an associated diagnosis of *S aureus* infection had a registration indicating methicillin resistance, although Portuguese surveillance data indicate that more than 50% of invasive *S aureus* isolates are resistant to methicillin.¹⁷ In addition, Portugal has one of the highest frequencies in Europe of *K pneumoniae* with combined resistance, fluoroquinolone-, aminoglycoside-, or carbapenem-resistant *Acinetobacter* species, and aminoglycoside- or vancomycin-resistant *Enterococci* species,¹⁷

suggesting that the frequency of drug-resistant infections other than MRSA is underreported in the database. In the identification of episodes with registration of penicillin allergy, we used a combination of external cause and personal history diagnosis ICD-9-CM codes. Although this approach aimed to increase the sensitivity of the case identification process,²¹ the validity of the V14.0 code has not been assessed. For the E930 code, we performed a validation study by chart review of the same administrative database and found that the positive predictive value of the E930 code was 80.8% (unpublished data).

This study also has several strong points, because it analyzed all public hospital admissions occurring in a nationwide scope and over a 15-year period. Such an assessment would be very expensive and time consuming to perform using other methodologic approaches, such as chart review or prospective studies, supporting administrative databases as potentially valuable instruments in the epidemiologic assessment of allergy reactions.^{22,23} Another strong point of our study concerns the strategy to match hospitalizations with and without registration of penicillin allergy, ensuring that these 2 groups were similar for inpatients' sex, age, and main diagnosis.

In conclusion, in this study, we analyzed a national database containing a registration of all public hospital admissions in a 15-year period. We confirmed that hospitalizations with registration of penicillin allergy are associated with increased length of stay, economic costs, and frequency of infections by drug-resistant agents. Intriguingly, we also found lower in-hospital mortality among medical allergy episodes (but not among surgical ones), a finding that merits further investigation in future studies. To mitigate the negative impact of having a penicillin allergy registration, it is paramount to ensure that only patients with true allergy are labeled as such and that a penicillin allergy diagnosis is based on a detailed clinical history and confirmation tests.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.janai.2017.11.022>.

References

- [1] Torres MJ, Romano A, Celik G, et al. Approach to the diagnosis of drug hypersensitivity reactions: similarities and differences between Europe and North America. *Clin Transl Allergy*. 2017;7:7.
- [2] Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014;69:420–437.
- [3] Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:259–273.
- [4] Velickovic J, Palibrk I, Miljkovic B, et al. Self-reported drug allergies in surgical population in Serbia. *Acta Clin Croat*. 2015;54:492–499.
- [5] MacPherson RD, Willcox C, Chow C, et al. Anaesthetist's responses to patients' self-reported drug allergies. *Br J Anaesth*. 2006;97:634–639.
- [6] Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep*. 2014;14:476.
- [7] Lang DM. The malady of penicillin allergy. *Ann Allergy Asthma Immunol*. 2016;116:269–270.
- [8] Zambonino MA, Corzo JL, Munoz C, et al. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol*. 2014;25:80–87.
- [9] Blanca M, Torres MJ, Garcia JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol*. 1999;103:918–924.
- [10] 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.
- [11] Jeffres MN, Narayanan PP, Shuster JE, et al. Consequences of avoiding beta-lactams in patients with beta-lactam allergies. *J Allergy Clin Immunol*. 2016;137:1148–1153.
- [12] van Dijk SM, Gardarsdottir H, Wassenberg MW, et al. The high impact of penicillin allergy registration in hospitalized patients. *J Allergy Clin Immunol Pract*. 2016;4:926–931.
- [13] King EA, Challa S, Curtin P, et al. Penicillin skin testing in hospitalized patients with beta-lactam allergies: effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol*. 2016;117:67–71.
- [14] Healthcare Cost and Utilization Project (HCUP). Clinical Classifications Software (CCS) for ICD-9-CM. Agency for Healthcare Research and Quality; 2017. www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed July 10, 2017.
- [15] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
- [16] Ministério da Saúde. Portaria no 567/2006 12 de Junho de 2006. *Diário da República*. 2009;1.
- [17] European Centre for Disease Prevention and Control. Annual Epidemiological Report 2014. Antimicrobial Resistance and Healthcare-Associated Infections. Stockholm: European Centre for Disease Prevention and Control; 2015.
- [18] Harandian F, Pham D, Ben-Shoshan M. Positive penicillin allergy testing results: a systematic review and meta-analysis of papers published from 2010 through 2015. *Postgrad Med*. 2016;128:557–562.
- [19] Sousa-Pinto B, Fonseca JA, Gomes ER. Frequency of self-reported drug allergy: a systematic review and meta-analysis with meta-regression. *Ann Allergy Asthma Immunol*. 2017;119:362–373.
- [20] Miguel A, Bernardo M, Freitas A, et al. Detection of adverse drug reactions using hospital databases—a nationwide study in Portugal. *Pharmacoepidemiol Drug Saf*. 2013;22:907–913.
- [21] Saff RR, Camargo CA Jr, Clark S, et al. Utility of ICD-9-CM codes for identification of allergic drug reactions. *J Allergy Clin Immunol Pract*. 2016;4:114–119, e1.
- [22] Miguel A, Azevedo LF, Lopes F, et al. Methodologies for the detection of adverse drug reactions: comparison of hospital databases, chart review and spontaneous reporting. *Pharmacoepidemiol Drug Saf*. 2013;22:98–102.
- [23] Iezzoni LI. Assessing quality using administrative data. *Ann Intern Med*. 1997;127:666–674.

Supplementary Data

eTable 1

Frequency of Infections as Main Diagnosis in All Hospitalizations Occurring in Adults With a Penicillin Allergy Label (n = 102,872) Compared With an Equal Number of Randomly Selected Hospitalizations Without This Label (Mainland Portugal; 2000–2014)

	Hospitalizations with penicillin allergy label (n = 102,872)	Hospitalizations without penicillin allergy label (n = 102,872)	P value
All infections, n (%)	10,924 (10.6)	10,895 (10.6)	.836
Pneumonia, n (%)	3,937 (3.8)	4,352 (4.2)	<.001
Urinary tract infections, n (%)	1,820 (1.8)	1,675 (1.6)	.013
Skin and subcutaneous tissue infections, n (%)	1,449 (1.4)	899 (0.87)	<.001
Acute bronchitis, n (%)	891 (0.87)	817 (0.79)	.072
Otitis media and related conditions, n (%)	336 (0.33)	291 (0.28)	.072
Acute and chronic tonsillitis, n (%)	285 (0.28)	235 (0.23)	.028
Other infections, n (%)	2206 (2.1)	2626 (2.6)	<.001

eTable 2

Relative Differences in Length of Stay and Hospital Charges for Hospitalizations With Registration of Penicillin Allergy vs Hospitalizations Without Such Label Among Different Subgroups of Episodes

	Sex		Age group			Type of episode		Severity ^a			Infection ^b	
	Women	Men	18–30 y	31–60 y	≥61 y	Medical	Surgical	Low	Intermediate	High	No	Yes
Sex												
Women	—	—	+6.7% ^c	+8.4% ^c	+11.1% ^c	+6.8% ^c	+14.0% ^c	+4.2% ^c	+7.7% ^c	+28.9% ^c	+6.3% ^c	+13.1% ^c
Men	—	—	+5.3% ^d	+9.3% ^d	+8.6% ^d	+2.2% ^d	+8.4% ^d	+2.0% ^d	+7.1% ^d	+16.0% ^d	+7.5% ^d	+13.4% ^d
Age group												
18–30 y	+6.7% ^c	+2.4% ^c	—	—	—	+4.7% ^c	+5.9% ^c	+13.9% ^c	−17.4% ^c	+49.1% ^c	+3.2% ^c	−5.9% ^c
31–60 y	+5.3% ^d	+10.0% ^d	—	—	—	+3.6% ^d	+5.7% ^d	+6.6% ^d	−5.8% ^d	+27.1% ^d	+4.4% ^d	+9.6% ^d
≥ 61 y	+8.4% ^c	+7.5% ^c	—	—	—	+7.8% ^c	+11.2% ^c	+5.0% ^c	+6.1% ^c	+1.9% ^c	+5.4% ^c	+11.2% ^c
Type of episode												
Medical	+6.8% ^c	+8.9% ^c	+4.7% ^c	+7.8% ^c	+8.7% ^c	—	—	+6.4% ^c	+5.4% ^c	+27.6% ^c	+4.4% ^c	+5.9% ^c
Surgical	+2.2% ^d	+4.6% ^d	+3.6% ^d	+2.6% ^d	+3.4% ^d	—	—	+0.7% ^d	+1.3% ^d	−3.0% ^d	+1.1% ^d	+5.5% ^d
Severity												
Low	+14.0% ^c	+8.7% ^c	+5.9% ^c	+11.2% ^c	+14.4% ^c	—	—	+4.6% ^c	+2.8% ^c	+5.2% ^c	+9.0% ^c	−1.3% ^c
Intermediate	+8.4% ^d	+7.7% ^d	+5.7% ^d	+8.1% ^d	+6.7% ^d	—	—	+1.6% ^d	−1.7% ^d	+10.0% ^d	+7.4% ^d	−9.1% ^d
High	+6.3% ^c	+5.4% ^c	+3.2% ^c	+5.4% ^c	+7.5% ^c	+4.4% ^c	+9.0% ^c	+4.3% ^c	+4.0% ^c	+22.4% ^c	—	—
Infection												
No	+7.5% ^d	+10.5% ^d	+4.4% ^d	+9.5% ^d	+8.1% ^d	+1.1% ^d	+7.4% ^d	+2.6% ^d	+5.7% ^d	+10.2% ^d	—	—
Yes	+13.1% ^c	+8.3% ^c	−5.9% ^c	+11.2% ^c	+12.8% ^c	+5.9% ^c	−1.3% ^c	+0.2% ^c	+8.6% ^c	+13.3% ^c	—	—
Total	+13.4% ^d	+6.0% ^d	+9.6% ^d	−0.5% ^d	+17.8% ^d	+5.5% ^d	−9.1% ^d	+11.2% ^d	+6.3% ^d	+6.2% ^d	—	—
	+9.3% ^c	+8.0% ^c	+5.2% ^c	+7.8% ^c	+10.9% ^c	+7.0% ^c	+12.5% ^c	+5.1% ^c	+7.1% ^c	+23.5% ^c	+5.7% ^c	+10.7% ^c
	+8.6% ^d	+11.0% ^d	+6.0% ^d	+9.7% ^d	+9.4% ^d	+2.5% ^d	+8.3% ^d	+2.8% ^d	+6.2% ^d	+10.2% ^d	+8.2% ^d	+9.6% ^d

^aData only available for 2011 through 2015.

^bCorresponding to drug-resistant infections and infections by enhanced-surveillance agents (*Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus* species, *Streptococcus pneumoniae*, and *Clostridium difficile*).

^cDifferences in length of stay in days.

^dDifferences in hospital charges in US dollars.

eTable 3

Comparison of Demographic, Clinical, and Economic Characteristics of Medical vs Surgical Hospitalizations Occurring in Adults With and Without Registration of Penicillin Allergy (Mainland Portugal; 2000–2014)

	Surgical hospitalizations (n = 104,393)			Medical hospitalizations (n = 101,351)		
	Hospitalizations with penicillin allergy label (n = 54,958)	Hospitalizations without penicillin allergy label (n = 49,435)	P value	Hospitalizations with penicillin allergy label (n = 47,914)	Hospitalizations without penicillin allergy label (n = 53,437)	P value
Sex, n (%)			.082 ^a			<.001 ^a
Men	15,341 (27.9)	13,561 (27.4)		14,058 (29.3)	16,746 (31.3)	
Women	39,617 (72.1)	35,874 (72.6)		33,856 (70.7)	36,691 (68.7)	
Age (y), mean (SD)	55.9 (17.4)	55.2 (17.7)	<.001 ^b	59.1 (21.0)	59.3 (20.8)	<.001 ^b
Length of stay (d), median (IQR)	4.0 (6)	4.0 (5)	<.001 ^b	5.0 (7)	5.0 (8)	<.001 ^b
Charlson Comorbidity Index, median (IQR)	0 (1)	0 (0)	<.001 ^b	0 (2)	0 (1)	<.001 ^b
Hospitalization charges (USD), mean (SD)	4,751.5 (5,357.2)	4,386.8 (5,149.3)	<.001 ^b	2,727.8 (2,659.1)	2,660.4 (2,465.0)	<.001 ^b
Frequency of in-hospital deaths, n (%)	652 (1.2)	611 (1.2)	.464 ^a	2,413 (5.0)	4,080 (7.6)	<.001 ^a
Frequency of infections, n (%)						
<i>Staphylococcus aureus</i>	351 (0.6)	195 (0.4)	<.001 ^a	572 (1.2)	494 (0.9)	<.001 ^a
Methicillin-resistant <i>Staphylococcus aureus</i>	114 (0.2)	46 (0.09)	<.001 ^a	209 (0.4)	165 (0.3)	.001 ^a
<i>Escherichia coli</i>	384 (0.7)	186 (0.4)	<.001 ^a	1,672 (3.5)	1,366 (2.6)	<.001 ^a
<i>Klebsiella pneumoniae</i>	149 (0.3)	90 (0.2)	.003 ^a	488 (1.0)	416 (0.8)	<.001 ^a
<i>Pseudomonas</i> sp	155 (0.3)	106 (0.2)	.029 ^a	416 (0.9)	403 (0.8)	.043 ^a
<i>Enterococcus</i> sp	147 (0.3)	77 (0.2)	<.001 ^a	313 (0.7)	197 (0.4)	<.001 ^a
<i>Streptococcus pneumoniae</i>	16 (0.03)	15 (0.03)	.908 ^a	360 (0.8)	294 (0.6)	<.001 ^a
<i>Clostridium difficile</i>	31 (0.06)	17 (0.03)	.098 ^a	90 (0.2)	94 (0.2)	.656 ^a
Other drug-resistant infections	15 (0.03)	11 (0.02)	.606 ^a	102 (0.2)	73 (0.1)	.004 ^a
Septicemia	307 (0.6)	229 (0.5)	.031 ^a	853 (1.8)	918 (1.7)	.449 ^a

Abbreviation: IQR, interquartile range.

^aBy χ^2 test.

^bBy Mann-Whitney U test.