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Clinical and economic burden of hospitalizations with registration of penicillin allergy

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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.

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

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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 Index[15]), in-hospital mortality, and hospital charges. The latter were calculated indirectly using a classification system based on the Diagnosis Related Groups (DRG) system[16] 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 *Streptococcus 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).