

Hospitalizations in Children with a Penicillin Allergy Label: An Assessment of Healthcare Impact

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Keywords

Children · Drug allergy · Epidemiology · Hospital management · Penicillins

Abstract

Background: Beta-lactam allergy is overdiagnosed. Diagnosis of penicillin allergy has been associated with a greater use of hospital resources and an increased risk of antibiotic-resistant infections, although this issue remains poorly studied in children. We aimed to compare patient characteristics and use of hospital resources in hospitalized children with and without a record of penicillin allergy. **Methods:** We identified all hospitalizations in children labelled as being allergic to penicillin in a database containing all hospitalizations in Portuguese public hospitals between 2000 and 2014, and compared these with a similar number of age-, sex-, and main diagnosis-matched hospitalizations without a penicillin allergy label. Comparisons were made for length of hospital stay, comorbidities (Charlson Comorbidity Index), in-hospital mortality, and hospitalization costs. **Results:** We identified 1,718 hospitalizations corresponding to children labelled as penicillin-allergic. Compared with patients without such a label, these children had longer hospital stays (mean 5 vs. 4 days, $p = 0.03$) and a higher comorbidity index (mean

0.11 vs. 0.09, $p < 0.001$). Hospitalization costs were also higher (EUR 2,071 vs. 1,798), but the difference was not significant ($p = 0.12$). **Conclusions:** Hospitalizations of children labelled as allergic to penicillin are associated with longer hospital stays, more comorbidities, and a tendency towards higher hospitalization costs. An accurate diagnosis of penicillin allergy based on clinical history and confirmatory tests is therefore essential in all paediatric patients.

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Introduction

Beta-lactams are the most commonly used antibiotics in children [1, 2]. Allergic reactions are among the most feared adverse effects and can manifest as immediate IgE-mediated or non-immediate T cell-mediated reactions [1, 3–6]. Although approximately 8% of Americans are labelled as being allergic to penicillin [7], a meta-analysis by Harandian et al. [8] found that just 3% of patients with penicillin allergy in their medical records had a confirmed diagnosis of immediate reactions by skin or drug provo-

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cation tests. The difference appears to be even more striking in the paediatric population, in whom penicillin allergy diagnoses based solely on clinical history are more common [1, 9, 10]. According to the above-mentioned meta-analysis, the frequency of confirmed immediate reactions to penicillin is less than 2% in children [8]. Overdiagnosis of penicillin allergy has also been reported for non-immediate reactions, as children with infectious rashes are frequently misdiagnosed with allergic maculopapular exanthemas [1, 9].

Overdiagnosis of penicillin allergy thus appears to be common, and this may have important consequences. Penicillin allergy labelling is associated with a greater use of alternative antibiotics, which are usually less effective, less safe, and more expensive; they also usually have a broader spectrum of activity, which can increase the risk of infections by *Clostridium difficile* and multiresistant agents [11–13]. There may also be economic and management consequences, including higher hospitalization costs, increased readmissions, and longer hospital stays [11, 14, 15]. While several of these studies have analysed the impact of a penicillin allergy label in adults and the general population, this phenomenon has not been studied in children. The aim of this study was to compare length of stay, frequency of comorbidities, in-hospital mortality, and hospitalization costs in hospitalized children with and without a record of penicillin allergy.

Materials and Methods

We analysed a database provided by the Portuguese Central Health System Administration that contains a record of all hospitalizations in mainland Portugal public hospitals (range 50–94 hospitals) between 2000 and 2014. For each hospitalization, information is available on the main diagnosis, up to 19 accompanying diagnoses, and up to 5 external causes of injury and poisoning (including drug allergy). Both diagnoses and external causes are coded with ICD-9-CM codes.

We selected all hospitalizations corresponding to children (1–18 years old) labelled as being allergic to penicillin (identified by ICD-9-CM code V14.0 as the main or accompanying diagnosis or by the code E930.0 as an external cause of injury and poisoning). These hospitalizations were compared with an equal number of randomly selected paediatric hospitalizations without such a label in terms of patient age, sex, and main diagnosis. The main diagnoses had been previously grouped into 259 clinically homogeneous and mutually exclusive categories, as defined by the Clinical Classification Software (an ICD-9-CM categorization scheme developed as part of the Healthcare Cost and Utilization Project) [16].

We subsequently performed a propensity score matching [17] to identify a comparable number of hospitalizations with and without a penicillin allergy label matched in terms of age, sex, and main diagnosis. We then compared the length of hospital stay, fre-

quency of comorbidities, in-hospital mortality, and hospitalization costs for the children in both groups. Comorbidities were assessed using the Charlson Comorbidity Index (CCI), a scoring system based on ICD diagnosis codes in which higher scores are associated with an increased risk of death or resource use [18]. Hospitalization costs were assessed indirectly using a classification system based on Diagnosis-Related Groups [19].

The data are presented as absolute frequencies and percentages for categorical variables, and as means and standard deviations or medians and interpercentile ranges for continuous variables. Categorical variables were compared using the χ^2 or Fisher exact test, while continuous variables were assessed using the Mann-Whitney U test. p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Ethical approval was not necessary for this study as it was based on previously anonymised administrative data. Informed consent was also not obtained, as the study did not involve direct contact with patients.

Results

Between 2000 and 2014, we identified a total of 1,718 paediatric hospitalizations with a diagnosis record of penicillin allergy. Most of the patients in this group and in the group without a penicillin allergy label were male (52 and 57%, respectively, $p = 0.006$). The median age was significantly higher in the group with a label of penicillin allergy (11 vs. 5 years, $p < 0.001$). Acute or chronic tonsillitis was the most common main diagnosis in both groups. It accounted for 17.6% of diagnoses in patients with a penicillin allergy label and 7.6% in those without ($p < 0.001$; Table 1). Acute bronchitis, intestinal infections, and urinary tract infections, by contrast, were significantly less common in the penicillin allergy group of children ($p < 0.001$; Table 1).

After adjusting for age, sex, and main diagnosis by propensity score matching, we found that hospitalizations with a penicillin allergy label were significantly longer than those without such a label (mean 4.5 vs. 4.0 days, $p = 0.03$; Table 2), despite similarities in median lengths of stay (2 days for both groups). No significant differences were observed for in-hospital mortality as the percentage of hospitalizations with a fatal outcome was 0.2% in the penicillin allergy group and 0.1% in the matched non-allergic group ($p = 0.63$; Table 2). Children labelled as being allergic to penicillin also had significantly more comorbidities (mean CCI 0.11 vs. 0.09, $p < 0.001$; Table 2). Finally, mean hospitalization costs were higher for penicillin allergy hospitalizations (EUR 2,071 vs. 1,798), although the difference was not statistically significant ($p = 0.12$; Table 2).

Table 1. Frequencies of infection as the main diagnosis in all paediatric hospitalizations with a penicillin allergy label ($n = 1,718$) compared with an equal number of randomly selected paediatric hospitalizations without this label for the period 2000–2014

	Hospitalizations with a penicillin allergy label ($n = 1,718$)	Hospitalizations without a penicillin allergy label ($n = 1,718$)	p value
All infections	578 (33.6)	612 (35.6)	0.22
Acute and chronic tonsillitis	303 (17.6)	131 (7.6)	<0.001
Pneumonia	64 (3.7)	90 (5.2)	0.03
Otitis media	44 (2.6)	51 (3.0)	0.47
Skin and subcutaneous infections	37 (2.2)	21 (1.2)	0.03
Urinary tract infections	22 (1.3)	50 (2.9)	<0.001
Acute bronchitis	12 (0.7)	90 (5.2)	<0.001
Intestinal infections	11 (0.6)	66 (3.8)	<0.001
Other infections	85 (14.7)	113 (18.5)	0.04

Data are presented as n (%).

Table 2. Comparison of patient sex, age, length of stay, in-hospital mortality, comorbidities, and hospitalization costs in all paediatric hospitalizations with a penicillin allergy label ($n = 1,718$) versus age-, sex-, and main diagnosis-matched children without this label ($n = 1,683$) for the period 2000–2014

	Hospitalizations with a penicillin allergy label ($n = 1,718$)	Hospitalizations without a penicillin allergy label ($n = 1,683$)	p value
Males, n (%)	893 (52.0)	875 (52.0)	0.99 ^a
Mean age, years (median; min.–max.)	10.0 (11; 0–17)	10.0 (11; 0–17)	0.84 ^b
Mean length of stay, days (median; p5–95)	4.5 (2; 1–13)	4.0 (2; 1–12)	0.03 ^b
In-hospital deaths, n (%)	3 (0.2)	1 (0.1)	0.63 ^c
Mean CCI (median; p5–95)	0.11 (0; 0–1.0)	0.09 (0; 0–0.8)	<0.001 ^b
Mean indirect hospitalization costs, EUR (median; p5–95)	2,071.0 (1,250.6; 530.5–5,711.5)	1,798.7 (1,250.6; 530.5–4,107.7)	0.12 ^b

p5–95, 5th to 95th percentile; CCI, Charlson Comorbidity Index. ^a χ^2 test. ^b Mann-Whitney U test. ^c Fisher exact test.

Discussion

In this study, we found that hospitalizations in children labelled as allergic to penicillin were associated with a significant increase in comorbidities, longer hospital stays, and a tendency towards higher hospitalization costs. Between 2000 and 2014, we identified just 1,718 paediatric hospitalizations with a penicillin allergy label. This corresponds to less than 1% of all hospitalizations of children during this period. Although this rate is consistent with previous reports based on administrative databases [20], it is considerably lower than rates found by studies that have used other methodological approaches. In one chart review study, for example, approximately 16% of inpatients had a penicillin allergy label in their

medical records [21]. The difference is probably due more to underreporting than to large-scale rigorous diagnosis of penicillin allergy (which would mitigate the phenomenon of overdiagnosis, leading to a lower percentage of false positives). While not incompatible with overdiagnosis, underreporting of drug hypersensitivity reactions is common and might be a limitation in itself, particularly if penicillin allergy is not consistently recorded for all admissions [22]. Underreporting also limits the possibility of studying other variables, such as the frequency of infections by *C. difficile* or multiresistant agents. Low rates of paediatric hospitalizations with a penicillin allergy label might also be partly due to the assignment of incorrect or less specific ICD-9-CM codes, such as codes indicating a history of drug allergy without identifying the culprit

drug class. In fact, incorrect coding is common in the context of drug and food allergy [23].

Another methodological limitation of our study is related to the lack of information on how penicillin allergy was diagnosed in each case. While this limitation can be overcome by chart review, such an approach is time-consuming, expensive, and difficult to implement in a multi-centre study conducted over such a wide a period of time [20, 24]. In our case, we tried to overcome this limitation by using ICD-9-CM codes E930.0 and V14.0 to identify hospitalizations with a penicillin allergy label. While E930.0 is more likely to be used to identify cases of penicillin allergy during admission, V14.0 is particularly indicated for identifying patients with a history of allergy. Despite possible underreporting, our results appear to be consistent with reports from studies conducted using other methodological approaches. The median length of stay, for example, was similar to that reported by a recent Dutch study performed in the general population [12].

Children labelled as penicillin-allergic were significantly older than those without this label. This might be a reflection not only of the cumulative effect of age, but also of the fact that patients requiring more hospitalizations are more often exposed to penicillin, increasing the risk of allergy to these antibiotics [25]. With the exception of tonsillitis and skin and subcutaneous infections, the frequency of infections as a main diagnosis was not significantly higher among children with penicillin allergy. On the contrary, certain infections, such as acute bronchitis and intestinal infections (possibly with a predominant viral aetiology for which antibiotics are not indicated), were significantly less common in the penicillin-allergic group of children.

Even after matching for age, sex, and main diagnosis, penicillin allergy hospitalizations had a significantly higher CCI, indicating a greater use of hospital resources in this group. However, while previous studies have used the CCI in the paediatric population, it has not been validated in this setting and does not take into account comorbidities that are exclusive to children [26].

We observed that penicillin allergy labelling was associated with longer hospitalizations and a tendency towards higher hospitalization costs. These 2 phenomena may be related, as higher costs could be partly due to longer hospital stays. Additionally, several studies have suggested that patients with penicillin allergy frequently receive more expensive antibiotics [14, 27]. Empirical use of alternative antibiotics, such as fluoroquinolones, clindamycin, and vancomycin, is also associated with higher treatment failure and adverse event rates, and an

increased risk of infections by *C. difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* [11, 15, 21]. A detailed clinical history should thus always be taken in patients reporting penicillin allergy. Li et al. [28], for example, showed that a structured clinical history (focusing on clinical presentation, time of onset of the reaction, and prescription history) reduced the number of inpatients with suspected penicillin allergy by 40%. Additionally, when a patient's clinical history is not sufficient, penicillin allergy should be confirmed by skin and/or drug provocation tests (unless these are contraindicated or unlikely to be helpful), as this might allow for more effective penicillin allergy delabelling [29, 30].

In conclusion, our study suggests that penicillin allergy labelling in children is associated with negative hospitalization outcomes, including longer stays, greater use of hospital resources, and possibly higher costs. These negative impacts could be minimized by a proper diagnosis of penicillin allergy based on a detailed clinical history, but also on skin and/or drug provocation tests.

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