Original Article

The High Impact of Penicillin Allergy Registration in Hospitalized Patients

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What is already known about this topic? Suspected penicillin allergy is often not verified or excluded by diagnostic testing.

What does this article add to our knowledge? Prevalence of penicillin allergy registration in a general population of patients hospitalized in a Dutch University Medical Center is 5.6%, has high impact on antibiotic prescribing, and is associated with a higher risk of readmission within 12 weeks.

How does this study impact current management guidelines? Verification of the penicillin allergy in hospitalized patients might restrict the use of reserve antibiotics and improve patient outcome.

BACKGROUND: Suspected penicillin allergy (Pen-A) is often not verified or excluded by diagnostic testing.
OBJECTIVE: To assess the prevalence and impact of Pen-A registration in a Dutch University Medical Center.
METHODS: In a prospective matched cohort study, all admitted patients (July 2013-July 2014) who underwent a pharmacotherapeutic interview were selected. Patients with a registered Pen-A were matched on age, sex, and department of admission with up to 3 patients without a registered Pen-A. Relative risks (RRs) of receiving a reserve antibiotic, death during hospitalization, and rehospitalization were compared in the 2 cohorts. The number and type of antibiotics prescribed during admission and duration of hospitalization were compared.
RESULTS: Of 17,959 patients, 1010 (5.6%) patients (66.7% women; median age, 55 years) had a Pen-A registration. These patients had a higher risk of receiving reserve antibiotics (RR, 1.38; 95% CI, 1.22-1.56) and of being rehospitalized within 12 weeks (RR, 1.28; 95% CI, 1.10-1.49). A significantly larger proportion of Pen-A registered patients received reserve antibiotics such as tetracyclines (1.8% vs 0.8%), macrolides/lincosamides/streptogramins (12.5% vs 4.9%), and quinolones (7.9% vs 4.3%) or received 2 or more types of antibiotics during hospitalization (21.7% vs 16.9%).
CONCLUSIONS: Prevalence of Pen-A registration in hospitalized patients is high, has high impact on antibiotic prescribing, and is associated with a higher risk of readmission. Verification of the Pen-A in hospitalized patients might restrict the use of reserve antibiotics and improve patient outcome. **(J Allergy Clin Immunol Pract 2016;4:926-31)**

Key words: *Allergy registration; Antimicrobial stewardship; Beta-lactam antibiotic; Drug hypersensitivity; Penicillin*

Antibiotics are one of the most frequently prescribed type of drugs, of which beta-lactam antibiotics account for the most.[1-3] Beta-lactam antibiotics are characterized by their high safety profile, narrow spectrum of activity, and low costs. One of the main factors limiting their use is the suspicion of penicillin allergy (Pen-A).[4] Pen-A is the most commonly registered drug allergy,[5-7] but the true prevalence in the general population is unknown, and remains difficult to determine because of varying study populations and designs. A Danish study reported a prevalence of 5% in hospitalized patients, whereas studies from the United States report higher prevalences of up to 16%.[5,8-12] A recent study performed in a Dutch general practice population in which Pen-A registration in medical files was assessed reported a prevalence of 2%.[13]

Diagnostic workup for evaluation of Pen-A may include detailed patient history, skin testing, *in vitro* testing, and drug

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Abbreviations used
ATC- Anatomical Therapeutic Chemical
Pen-A- penicillin allergy
RR- relative risk
UMCU- University Medical Center Utrecht

challenge. Studies on outpatient adult patients showed that an alleged Pen-A can be confirmed in only a minority (16.5%-29.0%) of patients.[6,9,10,14-20] This percentage of confirmed Pen-A seems lower in children than in adults (7.9%-15.9%) and also lower in hospitalized patients when compared with outpatients. In patients with a history of possible Pen-A who are admitted to hospitals, the prevalence of confirmed allergy varies from 1% to 14 %.[21-25] Altogether, most patients with a suspected Pen-A are not currently allergic and should tolerate penicillin antibiotics.

In clinical practice, hospitalized patients with a documentation of penicillin antibiotic allergy are more often treated with reserve antibiotics such as fluoroquinolones, macrolides, glycopeptides, vancomycin, and aminoglycosides.[5,11,12] Use of these reserve antibiotics has been associated with a higher risk of treatment failure, adverse drug reactions, complications such as *Clostridium difficile* infection, methicillin-resistant *Staphylococcus aureus* infection, and vancomycin-resistant Enterococcus infections, and higher costs and reinforce the development of antibiotic resistance.[4,5,7-10,26-29]

Recent studies showed that patients with a Pen-A registration have a longer duration of hospitalization than do patients without this registration.[5,12] However, evidence on these various consequences of registered Pen-A was based mostly on very small patient numbers and poorly designed studies.[4,5,7,10,11]

This study aimed to assess the prevalence of registered Pen-A in a large Dutch tertiary university medical hospital center and its impact on health care—related factors such as the number and type of antibiotics prescribed, mortality during hospitalization, duration of hospital stay, and risk of readmission.

METHODS

Setting and study population

This prospective, matched cohort study included patients from the Utrecht Patient Orientated Database, which includes all patients treated at the University Medical Centre in Utrecht (UMCU), a university hospital in the Netherlands with 1042 beds. All patient data are electronically registered and anonymized.[30] This study was approved by the local medical research ethical committee (METC 14-626/C).

The source population included all patients admitted to the UMCU (N = 24,165) from July 1, 2013, until July 1, 2014. A systematic standardized pharmacotherapeutic interview was introduced in 2010 for all patients admitted to the UMCU and is performed by a trained nurse or pharmacist assistant before admissions or at patient bedside within 24 hours of admission of all patients unselectively. The study population included all patients (children and adults) who underwent a standardized pharmacotherapeutic interview for evaluation and registration of drug usage and drug hypersensitivity. If patients report a drug allergy, the following criteria for registration of drug hypersensitivity are used by the trained nurse or pharmacist assistant: (1) evaluation by a specialist or general practitioner and/or (2) symptoms of cutaneous reactions, dyspnea, collapse, or fever after drug exposure up to a few days. Drug hypersensitivity is registered in the patients electronical medical file. This registration can be updated by physicians at any time. There is no standardized recommendation on how to deal with a drug allergy registration.

The study population excluded patients admitted to intensive care wards, patients admitted for day treatments, patients admitted and discharged during the same weekend, and healthy women admitted because of labor and neonates, because the standardized pharmacotherapeutic interview was not implemented reliably for these patients in the study period.

Patient cohort

Patients with a registered Pen-A (Pen-A patients) in their medical journal during their first admission during the study period (index date) were matched with up to 3 patients who had no Pen-A registered in their medical file (non—Pen-A patients) on the index date. *Penicillin* is defined as all class Anatomical Therapeutic Chemical (ATC)-J01C penicillin beta-lactam antibiotics including among others ampicillin and amoxicillin.[31] Registered Pen-A patients were matched to non—Pen-A patients on sex, age up to ± 3 years, and department of admission.

Study outcomes

The primary outcome measure of this study was prevalence of Pen-A registration. The secondary aim was to compare the risk of the first antibiotic prescribed during admission being a reserve antibiotic, the risk of death during hospitalization, and assessing the number, type, and route (intravenous) of antibiotics prescribed during admission and duration of hospitalization (in days) in patients with and without a Pen-A. In addition, the risk of readmission within 4 and 12 weeks from discharge was assessed.

Duration of hospitalization was defined as 1 day plus the date of discharge minus the date of admission. Prescribed antibiotics were grouped into the following 10 ATC classes: tetracyclines (J01A); amphenicols (J01B); beta-lactam antibacterials, penicillins (J01C); other beta-lactam antibacterials (J01D); sulfonamides and trimethoprim (J01E); macrolides, lincosamides, and streptogramins (J01F); aminoglycoside antibacterials (J01G); quinolone antibacterials (J01M); combinations of antibacterials (J01R); and other antibacterials (J01X).[31] *Reserve antibiotics* were defined as all ATC groups excluding penicillins (J01C).

STATISTICAL ANALYSIS

Prevalence was measured by defining the number of patients with a registered Pen-A in the study population. Descriptive statistics for the matched cohort were reported using proportions, medians, and interquartile ranges. The associations between having a Pen-A registration and receiving a reserve antibiotic as a first prescription during hospitalization, mortality during hospitalization, and rehospitalization within 4 weeks and 12 weeks after discharge were estimated as relative risk (RR) with 95% CI using stratified Cox proportional hazards analysis. Differences in proportion were assessed for the type of antibiotics prescribed during hospitalization, receiving 2 or more antibiotics, and receiving antibiotics through intravenous administration using Mantel-Haenszel chi-square test. Medians were compared using Mann Whitney tests. Differences were considered statistically significant when the *P* value was less than .05. All statistical analyses were conducted with SAS9.4.

RESULTS

Characteristics of the study population

A total of 17,959 patients (50.2% women; median age, 51.0 years) admitted underwent a pharmacotherapeutical interview. Of these, 1010 patients (5.6%) had a Pen-A registration (66.8% women; median age, 55.5 years, interquartile range, 37-68), of which 997 (98.7%) could be matched with at least 1 patient without a Pen-A registration. A total of 962 registered Pen-A patients were matched to 3 non−Pen-A patients, 18 registered Pen-A patients were matched to 2 non−Pen-A patients, and 17 registered Pen-A patients were matched to 1 non−Pen-A patient (Table I).

Antibiotic treatment

A total of 2292 (58.2%) patients (Pen-A and non−Pen-A patients) did not receive antibiotic treatment during admission (54.5% of registered Pen-A patients vs 59.5% of non−Pen-A patients), whereas 1644 patients (41.8%) received 1 or more antibiotic (Table II). Most of the patients who did receive antibiotic treatment got monotherapy (n = 932 [57.6%]).

Pen-A registered patients had a higher risk of receiving a reserve type of antibiotic as a first antibiotic prescription on admission (RR, 1.38; 95% CI; 1.22-1.56). When analyzing the specific types of antibiotics, a statistically significant higher proportion of Pen-A registered patients received tetracycline, nonpenicillin beta-lactam antibacterials, macrolides/lincosamides/streptogramins, quinolones, or other antibacterials when compared with patients without a Pen-A registration (Table II). Also, a significantly higher proportion of patients with a Pen-A registration were prescribed 2 or more antibiotics during hospitalization (21.7% vs 16.9%). There was no significant difference in the proportion of patients receiving sulfonamides or trimethoprim or aminoglycosides. As to be expected, a lower proportion of patients with a Pen-A registration got a penicillin beta-lactam antibiotic prescribed compared with patients without a Pen-A registration. Interestingly, 14.5% (n = 66) of all registered Pen-A patients, treated with antibiotics, were exposed to penicillin beta-lactam antibiotics despite their Pen-A registration. The ranking and percentages of frequency of specific antibiotic prescription differed in patients with and without a Pen-A registration (Table III).

Other outcomes

Duration of hospitalization did not differ statistically between patients with and without a Pen-A registration and ranged from 1 day to 195 days, with a median duration of 4.00 days (interquartile range, 2.00-8.00). Mortality during hospitalization was not significantly different between patients with (1.2%) and without (1.0%) Pen-A registration (RR, 1.49; 95% CI, 0.58-3.85). There was no significant difference in the risk of readmission within 4 weeks after discharge between patients with (18.3%) and without (15.1%) Pen-A registration (RR, 1.19; 95% CI, 0.98-1.44). The RR of readmission within 12 weeks after discharge was significantly higher in patients with (27.0%) a Pen-A registration (RR, 1.28; 95% CI, 1.10-1.49) than in patients without a Pen-A registration (21.9%).

TABLE I. Baseline characteristics of patients with and without Pen-A registration

Characteristic	No. of patients (%)	
	Registered Pen-A patients (n = 997)	Non−Pen-A patients (n = 2939)
Age (y), median (IQR)	55.5 (37-68)	55.0 (37-68)
Sex: female, n (%)	666 (66.8)	1957 (66.6)
Specialism of admission, n (%)		
Surgery	262 (26.3)	772 (26.3)
Internal medicine	144 (14.4)	380 (12.9)
Small surgical specialisms*	127 (12.7)	406 (13.8)
Cardiovascular	87 (8.7)	258 (8.8)
Gynaecology & obstetrics	82 (8.2)	242 (8.2)
Urology	66 (6.6)	127 (4.3)
Neurology/psychiatry	60 (6.0)	194 (6.6)
Oncology	38 (3.8)	139 (4.7)
Pediatrics	36 (3.6)	124 (4.2)
Gastroenterology	31 (3.1)	102 (3.5)
Nephrology	27 (2.7)	81 (2.8)
Geriatrics	14 (1.4)	43 (1.5)
Dermatology	12 (1.2)	49 (1.7)
Supportive departments†	11 (1.1)	22 (0.7)

*Oral surgery, dental medicine, otolaryngology, and ophthalmology.
†Anesthesia, pain team, nuclear radiology, radiology, radiotherapy, and pathology.

TABLE II. Antibiotic prescribing and health care use during hospitalization

Treatment	No. of patients (%)		
	Registered Pen-A patients (n = 997)	Non−Pen-A patients (n = 2939)	*P* value*
Duration of hospitalization (d), median (IQR)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	.80
Antibiotic prescribing during hospitalization, n (%)			
No antibiotic use	543 (54.5)	1749 (59.5)	<.01
Tetracycline (J01A)	18 (1.8)	24 (0.8)	<.01
Beta-lactam antibacterials (J01C)	66 (6.6)	391 (13.3)	<.01
Nonpenicillin beta-lactam antibacterial (J01D)	283 (28.4)	741 (25.2)	.03
Sulfonamides and trimethoprim (J01E)	55 (5.5)	139 (4.7)	.29
Macrolides, lincosamides, & streptogramines (J01F)	125 (12.5)	144 (4.9)	<.01
Aminoglycosides (J01G)	23 (2.3)	57 (1.5)	.44
Quinolones (J01M)	79 (7.9)	127 (4.3)	<.01
Other antibacterials (J01X)	101 (10.1)	228 (7.8)	<.01
≥2 antibiotics	216 (21.7)	496 (16.9)	<.01
Intravenous administration	350 (35.1)	946 (32.2)	.06

*Mantel-Haenszel χ^2 test for differences between registered Pen-A patients and non−Pen-A patients.

DISCUSSION

This is the first study in Europe investigating the prevalence and impact of Pen-A registration in hospitalized patients and shows a prevalence of 5.6% in this Dutch tertiary medical center. These patients have a significantly higher risk of receiving a reserve antibiotic of a broad-spectrum type than do patients without a Pen-A registration. They received more often antibiotics during hospitalization and when treated with antibiotics, a

TABLE III. Top 10 antibiotics (chemical substance) used by registered Pen-A and non–Pen-A patients

S. no.	Registered Pen-A patients (N = 997)	Non–Pen-A patients (N = 2939)
1	Cefazolin: n = 156 (21.4%)	Cefazolin: n = 481 (26.8%)
2	Ceftriaxone: n = 75 (10.3%)	Amoxicillin and enzyme inhibitor: n = 252 (14.0%)
3	Clindamycin: n = 67 (9.2%)	Ceftriaxone: n = 162 (9.0%)
4	Metronidazole: n = 57 (7.8%)	Metronidazole: n = 147 (8.2%)
5	Ciprofloxacin: n = 47 (6.4%)	Ciprofloxacin: n = 97 (5.4%)
6	Sulfamethoxazole and trimethoprim: n = 36 (4.9%)	Sulfamethoxazole and trimethoprim: n = 96 (5.3%)
7	Amoxicillin and enzyme inhibitor: n = 32 (4.4%)	Clindamycin: n = 72 (4.0%)
8	Azithromycin: n = 25 (3.4%)	Flucloxacillin: n = 60 (3.3%)
9	Erythromycin: n = 22 (3.0%)	Cefuroxime: n = 43 (2.4%)
10	Cefuroxime: n = 21 (2.9%)	Tobramycin: n = 37 (2.1%)

Multiple prescriptions of the same antibiotic during hospitalization were counted only once.

significantly larger proportion receives 2 or more types of antibiotics, especially reserve antibiotics such as macrolides, clindamycin, quinolones, and tetracyclines when compared with patients without Pen-A registration. Furthermore, patients with Pen-A registration have a higher risk of readmission within 12 weeks.

In this study, the prevalence of Pen-A registration is based on systematically performed standardized pharmacotherapeutic interviews, which strongly reduces potential recall bias and increases reliability, by fewer registration of adverse effects of antibiotics as an allergic reaction to antibiotics. We observed a lower prevalence of registered Pen-A than reported in earlier studies from the United States[5,10-12] and the United Kingdom,[8] which range from 11.2% to 15.6%. These differences might partly be explained by the effect of a reliable pharmacotherapeutic interview in our study. Difference in prevalence might also be influenced by the study design and type of populations because higher prevalences (up to 15.6%) were shown in studies investigating populations with antibiotic need only.[10-12] Another explanation of differences in the prevalence of documented Pen-A between these countries might be the difference in antibiotic use in the specific population. Dutch guidelines for the use of antibiotics advise prudent antimicrobial prescribing,[32] resulting in a low defined daily dosage of 8.9 per 1000 people per day of antibiotics in the Netherlands compared with the United States (defined daily dosage of 25 per 1000 people per day).[2,33,34] A recent small Danish study on 3642 patients supports this hypothesis with a low prevalence of suspected Pen-A of 5% in a university hospital population and a low defined daily dosage in Denmark (11.3 per 1000 people per day).[2,9]

Our study shows that the treatment of hospitalized patients is highly influenced by the "Pen-A" registration. When receiving antibiotics, significantly larger proportions of patients with Pen-A registration are treated with macrolides and clindamycin, quinolones, and tetracyclines, suggesting that these antibiotics are used as reserve antibiotics. These reserve antibiotics are known for higher costs and more adverse reactions and are more likely to induce resistance compared with beta-lactam penicillins.[35,36] Increased usage of macrolides and clindamycin, quinolones, and tetracyclines in patients with Pen-A registration was also shown in studies from Israel, the United States, and the United Kingdom.[4,5,7,11] However, these studies also demonstrated vancomycin as a reserve antibiotic, which is significantly more often used in patients with suspected allergy for penicillin antibiotics.[4,5,7,11] In the Netherlands, the prevalence of methicillin-resistant *Staphylococcus aureus* infection is low, explaining the very low (n = 39 [1.5%]) frequency of vancomycine usage in our study population, without significant difference between cases and control subjects.[37]

Studies from the United States found a significantly increased duration of hospitalization for patients with a Pen-A registration compared with control subjects.[5,12] This finding was not confirmed in our study. However, the other studies differed from ours in design because the cumulative duration of hospitalization days included the index admission and all readmissions during the study period.

We did not find a significant difference in the risk of readmission within 4 weeks in those with and without Pen-A. This is in line with results of the study by Charneski et al[12] who investigated the relation between Pen-A registration and readmission within 4 weeks of hospital discharge and found no association between Pen-A registration and frequency of readmission. When we assessed the risk of readmission within 12 weeks after discharge, we found this to be significantly higher in patients with Pen-A registration. So far, this study is the first study that reports a significantly higher risk of readmissions for patients with a Pen-A registration. This higher risk of readmission might be a secondary result of treatment with second-choice antibiotics, but more research is needed to explain this observation.[38]

We observed no difference in mortality between patients with registered Pen-A and those without. However, a 1.6-fold increased risk of mortality during admission in patients with this allergy registration compared with controls was reported in a study from the United States by Charneski et al.[12] Further research is needed to investigate whether mortality is influenced by Pen-A registration.

The main strengths of this study are the systematically performed standardized pharmacotherapeutic interviews, reliable statistical analysis, and the high number of patients evaluated. However, the study also has several limitations. Patients without pharmacotherapeutic interviews were excluded, including patients from the intensive care unit, a population that is of high interest. Furthermore, although patients with and without Pen-A registration were matched on the department of admission, other factors such as medical diagnosis, disease severity, or the number of drug allergies that also might influence the antibiotic treatment and risk of readmission could not be considered. However, because we presume that only approximately 20% or less of the patients with Pen-A registration are truly allergic, we expect the

possible bias due to these conditions to be small. However, this should be confirmed in an additional study. Lack of details of the registered patients' reactions is another limitation of the study.

Our study shows that Pen-A registration has a high impact on treatment and the risk of readmission in hospitalized patients. Several studies have demonstrated that in patients with suspected Pen-A this diagnosis is excluded by allergological workup in the vast majority of patients.[9,15-20] We therefore can assume that in most hospitalized patients with Pen-A registration the prescribing of beta-lactam antibiotics is wrongfully avoided and patients are unnecessarily strained by the subsequent disadvantages.

Antimicrobial resistance is widely considered as one of the major risks to the global society and is among others caused by inappropriate use of available antibiotics such as unnecessary use of second-choice antibiotics.[39] Integration of antibiotic allergy management into the decision support systems of antimicrobial stewardship programs might represent an opportunity to restrict the use of reserve antibiotics and the subsequent risk of antimicrobial resistance for the individual patient and the society.

Several studies have shown that active antibiotic allergy verification by skin testing and drug challenge results in reduction in the use of reserve antibiotics.[25,40,41] However, further studies are needed to investigate whether exclusion of Pen-A more consistently can bring antibiotic use and risk of readmission in patients with Pen-A registration back in line with those seen in patients without Pen-A registration.

In conclusion, this study shows a 5.6% prevalence of Pen-A registration in hospitalized patients in a Dutch tertiary medical center. Pen-A registration in hospitalized patients has a high impact on antibiotic treatment strategies, including higher risk for prescribing broad-spectrum antibiotics and increased risk of readmission within 12 weeks of discharge. Further studies are needed to investigate whether better verification of Pen-A does improve policy in antibiotic treatment in these patients.

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