

## Prevalence and antibiotic use in hospitalized patients with a history of penicillin allergy

Cheeratikarn Phithakham<sup>1</sup>, Napaporn Pinmanee<sup>2</sup>, Ronnakrit Chotinun<sup>3</sup>, Romanee Chaiwarith<sup>4</sup>

<sup>1</sup>Drug Information Services, Pharmacy Department, Maharaj Nakorn Chiang Mai Hospital

<sup>2</sup>In-patient Pharmacy Unit, Pharmacy Department, Maharaj Nakorn Chiang Mai Hospital

<sup>3</sup>Out-patient Pharmacy Unit, Pharmacy Department, Maharaj Nakorn Chiang Mai Hospital

<sup>4</sup>Department of Medicine, Faculty of Medicine, Chiang Mai University

### Abstract

**Objectives:** To explore the prevalence of hospitalized patients with a history of penicillin allergy and the pattern of prescribed antibiotics in these patients. **Methods:** A cross-sectional study was conducted in the following three departments: surgery, internal medicine and orthopedics at Maharaj Nakorn Chiang Mai Hospital from January 1 to December 31, 2014 using electronic medical records as data source. **Results:** Overall, 339 hospitalized patients with a history of self-reported penicillin allergy were identified, given a prevalence of 1.2% among 28,025 patients (95% CI 1.1, 1.3). One hundred and ninety-four subjects were female (57.2%). Median age of the subjects was 61 years old (range: 52-74). There were 178 patients (52.5%) with age more than 60 years old. The most common reported drug allergy was natural penicillins (241 reports or 69.7%). The most frequently reported drug reaction type was skin reaction (293 reports or 84.7%). The five most common antibiotics prescribed to this group of patients were cephalosporins (20.6%), clindamycin (20.6%), fluoroquinolones (17.2%), carbapenems (10.0%), and vancomycin (6.8%). **Conclusions:** The prevalence of hospitalized patients with a history of penicillin allergy is quite low at Maharaj Nakorn Chiang Mai Hospital. Pattern of antibiotic prescription in this group of patients was similar to that reported in the previous studies. Documenting a detailed allergy history as well as consulting with allergists could increase the safe use of  $\beta$ -lactam antibiotics among this population and improve patient outcomes.

**Keywords:** prevalence of penicillin allergy, antibiotic use, drug allergy, adverse drug reaction

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Correspondence: Cheeratikarn Phithakham, Drug Information Services, Pharmacy Department, Maharaj Nakorn Chiang Mai Hospital  
Mueang Chiang Mai, Chiang Mai 50200. E-mail: cheeratikarn.p@gmail.com

## **Introduction**

$\beta$ -lactam antibiotics are important drugs and the use of these drugs is high compared to other groups of antibiotics (1).  $\beta$ -lactam antibiotics are classified into four subgroups according to their chemical structures, i.e., penicillins, cephalosporins, carbapenems, and monobactams. Currently, monobactams are not available in Thailand (2). Penicillins were discovered in 1928 and since then they have been widely used (3). Penicillins are classified into natural penicillins, aminopenicillins, penicillinase-resistant penicillins, and extended-spectrum penicillins.

The prevalence of patients with a history of penicillin allergy ranges from 4-15.6% (4-7). Due to the concern on cross-reactivity in patients reporting a history of penicillin allergy, most physicians tend to avoid prescribing other  $\beta$ -lactam antibiotics such as cephalosporins and carbapenems and instead use other groups of antibiotics resulting in an increased use of vancomycin and fluoroquinolone in this group of patients (4-5, 8). In addition to a concern on the escalation of healthcare costs (4, 8-9), the increased use of vancomycin and fluoroquinolone may boost the chance of drug resistance. Despite reporting penicillin allergic history, only 10-20% of patients were found to have a true drug allergy when evaluated by a skin test and/or drug challenge (10-13).

Although there were several studies on the prevalence of penicillin allergy and the use of antibiotics for allergic patients in other countries (4-6), there is a lack of similar studies in Thailand. Maharaj Nakorn Chiang Mai Hospital is a 1,400-bed, tertiary care hospital and referral center in northern Thailand which serves a large number of patients. Antibiotic consumption is high and there is an increasing number of antibiotic resistant pathogens including vancomycin-resistant Enterococci (VRE), and carbapenem-resistant Enterobacteriaceae (CRE). In

2014, there were 45,621 patients hospitalized at Maharaj Nakorn Chiang Mai hospital. With the large numbers of patients and probably a large numbers of patients with a self-reported history of penicillin allergy, the concern over cross-sensitivity would influence the pattern of antibiotic prescribing and having a significant impact on healthcare cost of the hospital. Therefore, this study was conducted to determine the prevalence of hospitalized patients with a history of penicillin allergy and the pattern of prescribed antibiotics for these patients.

## **Methods**

This cross-sectional study was conducted at Maharaj Nakorn Chiang Mai Hospital from January 1 to December 31, 2014. This study was approved by the 4<sup>th</sup> Research Ethic Committee of Faculty of Medicine at Chiang Mai University. In the studied hospital, there were 2 sources of information on patient's drug allergy. The first was the verification of drug allergy by physicians with the assessment of the relationship between suspected drug(s) and reactions using the Naranjo's algorithm. This information was documented in medical record under the section "drug allergy" detailing name of the suspected drug(s), identified reactions and relationship between drug(s) and reactions. The second source of information on drug allergy was self-report by patients but without possible verification from health professionals such as self-report of developing rashes from penicillin in some 20 years ago. The reported information was deemed as an insufficient evidence to assess the causality between drug(s) and reactions. Pharmacist documented this kind of information in medical record using the term "self-reported history of drug allergy". This study focused on the second source of information on drug allergy.

Electronic medical records of all patients admitted to the departments of surgery, internal

medicine and orthopedics were reviewed to identify patients with a self-reported history of penicillin allergy. Data on those with such history were collected, including their age, gender, type of allergic penicillins, allergic reactions, and antibiotics prescribed to them during hospital stay.

Data were presented in mean±SD, median and IQR (interquartile range), percent as appropriate. Association between patient characteristics and the receiving of  $\beta$ -lactam antibiotics during hospitalization was tested using Chi-square test and Fisher's exact test. Statistical testing was 2-tailed with p-value 0.05 regarded as significant levels. All statistical analyses were performed using the SPSS software version 22.

## Results

There were 339 patients with a history of self-reported penicillin allergy identified, given a prevalence of 1.2% among 28,025 patients (95% CI 1.1, 1.3) admitted to the departments of surgery, internal medicine and orthopedics. Out of 339 patients, 194 patients were female (57.2%) and the median age was 61 years old (52-74). There were 178 patients older than 60 years old (52.5%).

There were 346 penicillin allergy reports among 339 patients with five allergic to two different penicillin classes and one allergic to three different penicillin classes. The most commonly reported class of allergic penicillins was natural penicillins (penicillin G and penicillin V) (241 reports or 69.7%), followed by amino-penicillins (ampicillin and amoxicillin) (60 reports or 17.3%) as shown in Table 1. The most frequent type of drug reaction was skin reaction (293 reports or 84.7%). These reports can be broken down further to 240 reports of skin rash (69.4%), 38 reports of angioedema (11.0%), and 15 reports of urticaria (4.3%). The second most commonly reported drug reaction was respiratory reaction (21 reports or 6.1%), as shown in table 1

**Table 1.** Allergic penicillins, reaction and antibiotic use in 339 patients (N = 346 reports)

allergic penicillins and reaction	number (%)
allergic penicillins	
natural penicillins (penicillin g, penicillin v )	241 (69.7)
aminopenicillins (ampicillin, amoxicillin)	60 (17.3)
penicillinase-resistant penicillins (cloxacillin, dicloxacillin)	34 (9.8)
extended-spectrum penicillins (ampicillin-sulbactam, piperacillin-tazobactam, amoxicillin-clavulanate)	11 (3.2)
allergic reaction	
dermatology	293 (84.7)
respiratory	21 (6.1)
anaphylactic shock	15 (4.3)
gastrointestinal	5 (1.4)
central nervous system	4 (1.2)
cannot recall/no record	8 (2.3)
antibiotics received during hospital stay	
$\beta$ -lactam antibiotic	
cephalosporins	109 (20.6)
carbapenems	53 (10.0)
penicillins	26 (4.9)
non $\beta$ -lactam antibiotic	
clindamycin	109 (20.6)
fluroquinolones	91 (17.2)
vancomycin	36 (6.8)
co-trimoxazole	27 (5.1)
macrolides	23 (4.4)
metronidazole	20 (3.8)
colistin	12 (2.3)
fosfomycin	10 (1.9)
doxycycline	8 (1.5)
aminoglycosides	4 (0.8)

There were 433 hospitalizations among 339 patients with a self-reported history of penicillin allergy. One hundred and four of these patients didn't receive any antibiotics during hospitalization. There were 276 hospitalizations among 235 patients who received antibiotics during their stay in the hospital.

There were 528 antibiotic prescriptions among 235 patients. The five most common antibiotics prescribed were cephalosporins (20.6%), clindamycin (20.6%), fluoroquinolones (17.2%), carbapenems (10.0%), and vancomycin (6.8%) as shown in table 1.

One hundred and thirty three patients with a history of penicillin allergy were prescribed  $\beta$ -lactam antibiotics for 188 prescriptions. Only one patient was found to have  $\beta$ -lactam antibiotic induced adverse

reaction. This patient had a history of anaphylaxis with natural penicillin. During the hospital admission, this patient was given ceftriaxone and developed redness without any rashes. The probability of the suspected adverse drug reaction was assigned as possible. Ceftriaxone was discontinued and replaced with meropenem. There was no meropenem-induced adverse drug reactions reported for this patient.

Age, gender and type of allergic reaction among those with a self-reported allergic history of penicillins showed no correlation with the receiving of  $\beta$ -lactam antibiotics (table 2).

### Discussion and conclusion

Our study found that the prevalence of patients with a self-reported history of penicillin allergy

**Table 2.** Association between characteristics of patients with a self-reported history of penicillins allergy and the receiving of  $\beta$ -lactam antibiotics during hospital stay.

	number (%) of patients who received $\beta$ -lactam antibiotics (n=133)	number (%) of patients who received non- $\beta$ -lactam antibiotics (n=102)	P <sup>1</sup>
gender			
male	51 (38.3%)	42 (41.2%)	0.76
age group			0.11
0-20 years old	2 (1.5%)	2 (2.0%)	
<20-40 years old	14 (10.5%)	22 (21.6%)	
<40-60 years old	45 (33.8%)	27 (26.5%)	
>60 years old	72 (54.1%)	51 (50.0%)	
allergic reaction			0.83
Dermatology	110 (82.7%)	90 (88.2%)	
gastrointestinal	2 (1.5%)	2 (2.0%)	
Respiratory	7 (5.3%)	4 (3.9%)	
anaphylactic shock	8 (6.0%)	4 (3.9%)	
central nervous system	2 (1.5%)	0 (0%)	
cannot recall /no record	4 (3.0)	2 (2.0)	

1: chi-square test

was 1.2%, which is lower than in that reported in the previous studies which ranged from 4% to 15.6% (4-7). The low prevalence might be due to a difference in study cohort, as our study focused on admitted patients from three different departments: orthopedics, surgery and internal medicine. Borch et al. found that prevalence was influenced by study cohort composition, with some departments having a higher prevalence rate (6). Hospital size or inclusion of departments known to have higher prevalence rate may affect the findings. Therefore, our findings may not accurately reflect the prevalence in other departments at this hospital.

Most patients who reported penicillin allergy were women, which is similar to that reported in other studies (4,6). Median age was 61 years and most patients were elderly (more than 60 years old) which was also similar to the results in other studies (6-7). More exposure to medicines during adulthood in comparison to children is one of the possible explanations for a higher rate of documented drug allergy in elderly patients. The most frequently reported causative agent of allergy was natural penicillins (penicillin G and penicillin V), which accounted for 69.7%. The most frequently reported drug reaction was dermatologic reaction which was also the most common adverse drug reaction found in other studies (6,8).

In this study it was found that patients with a history of penicillin allergy were more likely to receive non  $\beta$ -lactams antibiotics which is also consistent with the results in previous studies (4-5,8). The prescribing of non-  $\beta$ -lactam antibiotics for these patients raises concern about the increased risk of drug-resistant bacteria and has a direct association with increased medical expenses (2,6-7).

Interestingly, 133 patients out of 235 patients who received antibiotics during hospitalization received  $\beta$ -lactam antibiotics (188 prescriptions). All

but one had no adverse drug reaction. Previous studies have documented low rates of cross-reactivity of penicillins with cephalosporin (14) and even lower rates with carbapenems (15-16). Withholding  $\beta$ -lactam antibiotics from patients who could benefit from them might influence treatment outcomes (17). In fact, several studies found that 80 to 90% of patients who reported penicillin allergy were not truly allergic to the drug, when evaluated by a skin test (10-13). Therefore, accurate diagnosis and a detailed history of allergy reactions are very important, as they could help physicians decide whether  $\beta$ -lactam antibiotics use is appropriate in these patients. A detailed history of the patient's allergic reaction on suspected drug names, nature of reactions, date and time of occurrence, severity of the reactions and reactions following subsequent penicillin re-exposure can help exclude the true allergy. Doctors should allow the use of  $\beta$ -lactam antibiotics if indicated (18).

Although several studies have shown the beneficial effect of penicillin skin testing among patients with a history of penicillin allergy (11, 19), use of penicillin skin testing is limited in Thailand because the test reagent is not available and there are a limited number of allergists in Thailand (20-21). One study demonstrated that collaboration between pharmacists and allergists can increase  $\beta$ -lactam antibiotic prescriptions and decrease non-  $\beta$ -lactam antibiotic prescriptions in patients with a history of penicillin allergy (22). Pharmacists should have a better coordination with physicians to optimize antibiotic use for patients. In addition, pharmacists should provide updated information on cross-reactivity of the  $\beta$ -lactam antibiotics to physicians and other pharmacists. National standard practice guidelines for managing patients with a history of penicillin allergy should be developed and used in Thailand.

This study has a few limitations. Firstly, patients' allergy information was taken from their

electronic medical records and patients were not directly interviewed to get a detailed history on the nature of their allergic reactions. Therefore, the allergy information might not be fully accurate. Secondly, the hospital adverse drug reaction monitoring center which supplied adverse drug reaction data for the study, relies on spontaneous or voluntary reporting, therefore the actual number of adverse reactions may be underreported. Lastly, in some cases where non  $\beta$ -lactam antibiotics are administered towards managing particular infections which  $\beta$ -lactam antibiotics are not drugs of first choice, concerns of cross-reactivity may be secondary to their use. Therefore, the pattern of non  $\beta$ -lactam antibiotics used in this study may not reflect the avoidance of penicillin allergy. Further studies on the use of non  $\beta$ -lactam antibiotics should consider this point.

In conclusion, the prevalence of hospitalized patients with a history of penicillin allergy is quite low at Maharaj Nakorn Chiang Mai hospital. Pattern of antibiotic prescription in this group of patients in this study was similar to those in previous studies. The detailed allergy histories and consultation with allergists could increase the safe use of  $\beta$ -lactam antibiotics among this population and improve patient outcomes. This also has an implication to the health care costs since non  $\beta$ -lactam antibiotics are significantly cheaper than other non  $\beta$ -lactam antibiotics.

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## ความชุกและการใช้ยาต้านจุลชีพของผู้ป่วยในที่มีประวัติแพ้ยาในกลุ่มเพนนิซิลิน

จิรติการณ พิทาคำ<sup>1</sup>, นภาพร ปิ่นมณี<sup>2</sup>, รณกฤต โชตินันท์<sup>3</sup> และรมณีย์ ชัยวาฤทธิ์<sup>4</sup>

<sup>1</sup>หน่วยเภสัชสนเทศ ฝ่ายเภสัชกรรมโรงพยาบาลมหาราชนครเชียงใหม่

<sup>2</sup>หน่วยบริการจ่ายยาผู้ป่วยใน ฝ่ายเภสัชกรรม โรงพยาบาลมหาราชนครเชียงใหม่

<sup>3</sup>หน่วยบริการจ่ายยาผู้ป่วยนอก ฝ่ายเภสัชกรรม โรงพยาบาลมหาราชนครเชียงใหม่

<sup>4</sup>ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาความชุกของผู้ป่วยในที่มีประวัติแพ้ยาในกลุ่มเพนนิซิลินและลักษณะการสั่งใช้ยาต้านจุลชีพในผู้ป่วยกลุ่มนี้ **วิธีการ:** งานวิจัยแบบภาคตัดขวางทำใน 3 หอผู้ป่วยได้แก่ ศัลยกรรม อายุรกรรม และ ออร์โทปิดิกส์ โดยใช้ข้อมูลจากฐานข้อมูลอิเล็กทรอนิกส์ของโรงพยาบาล ตั้งแต่เดือนมกราคมถึงธันวาคม พ.ศ. 2557 ณ โรงพยาบาลมหาราชนครเชียงใหม่ **ผลการวิจัย:** โดยรวม ผู้ป่วยใน 339 รายจากผู้ป่วยที่เข้ารับการรักษาทั้งหมด 28,025 ราย แจ้งว่า ตนเองมีประวัติแพ้ยาในกลุ่มเพนนิซิลิน คิดเป็นความชุกร้อยละ 1.2 (95%CI 1.1,1.3) ผู้ที่แจ้งประวัติการแพ้ยา 194 ราย (ร้อยละ 57.2) เป็นเพศหญิง ผู้แพ้ยามีมีพื้นฐานของอายุ คือ 61 ปี (พิสัย 52-74) ผู้ป่วยที่แพ้ยามีอายุมากกว่า 60 ปีขึ้นไป 178 ราย (ร้อยละ 52.5) ยาที่มีการแจ้งประวัติแพ้มากที่สุดคือยา natural penicillins คือ 241 ครั้ง (ร้อยละ 69.7) อาการแพ้ยาที่พบบมากที่สุด คือ การแสดงอาการแพ้ทางผิวหนัง (293 เหตุการณ์หรือร้อยละ 84.7) ยาต้านจุลชีพที่มีการใช้มากที่สุด 5 อันดับแรกในผู้ป่วยกลุ่มนี้ คือ cephalosporins (ร้อยละ 20.6) clindamycin (ร้อยละ 20.6) fluoroquinolones (ร้อยละ 17.2) carbapenems (ร้อยละ 10.0) และ vancomycin (ร้อยละ 6.8) **สรุปผล:** ความชุกของผู้ป่วยในที่มีประวัติแพ้ยาในกลุ่มเพนนิซิลินอยู่ในระดับที่ค่อนข้างต่ำในโรงพยาบาลมหาราชนครเชียงใหม่ ลักษณะการใช้ยาต้านจุลชีพในผู้ป่วยกลุ่มนี้คล้ายกับที่รายงานในงานวิจัยอื่นที่ผ่านมา การบันทึกประวัติและอาการแพ้ยาอย่างละเอียดร่วมกับการปรึกษาผู้เชี่ยวชาญด้านภูมิแพ้และภูมิคุ้มกันจะช่วยเพิ่มความปลอดภัยในการใช้ยาต้านจุลชีพกลุ่ม  $\beta$ -lactam ในผู้ป่วยกลุ่มนี้และทำให้ผลลัพธ์ในการรักษาผู้ป่วยให้ดีขึ้น

**คำสำคัญ:** ความชุกของการแพ้ยาในกลุ่มเพนนิซิลิน การใช้ยาต้านจุลชีพ การแพ้ยา อาการไม่พึงประสงค์จากยา