The Incidence of Antimicrobial Allergies in Hospitalized Patients

Implications Regarding Prescribing Patterns and Emerging Bacterial Resistance

Collin E. Lee, RPh; Teresa R. Zembower, MD; Michael A. Fotis, RPh; Michael J. Postelnick, RPh; Paul A. Greenberger, MD; Lance R. Peterson, MD; Gary A. Noskin, MD

Background: The development of antimicrobial guidelines is one way in which institutions attempt to control emerging resistance, but the real challenge falls on promoting and ensuring adherence to these guidelines. Investigating reasons for the prescribing of alternative antimicrobial agents outside of these guidelines is crucial for modifying practices that may adversely impact institutional antimicrobial goals.

Methods: Retrospective cross-referencing of computerized pharmacy printouts and concurrent manual medical record review.

Results: Approximately 25% (470/1893) of the patients requiring antimicrobial therapy reported an allergy to at least 1 antimicrobial agent. The most commonly reported antimicrobial allergy was penicillin (295/1893 [15.6%]). Eighty-five patients (18.1%) reported having an allergy to 2 or more antimicrobial agents. Only 4% (27/601) of the reported antimicrobial allergies contained documentation as to the nature of the specific allergic reactions, while a manual medical record review revealed that 32% (23/73) of the antimicrobial allergies contained documentation of the specific allergic reaction. Ninety-eight (39.7%) of 247 patients reporting an allergy only to penicillin and/or cephalosporin received vancomycin in comparison with 247 (17.4%) of 1423 patients without any antimicrobial allergies ($P<.001$). Similarly, 53 (21.5%) of 247 patients with reported penicillin and/or cephalosporin allergies received levofloxacin compared with 114 (8.0%) of 1423 patients without any antimicrobial allergy ($P<.001$).

Conclusion: The incidence of penicillin allergy at our institution exceeds population averages. This finding, in combination with limited documentation of drug allergies, appears to lead to the prescribing of alternative antimicrobial agents that do not fit into institutional antimicrobial guidelines and, in some instances, may put the patient at risk for infection and/or colonization with resistant organisms. Use of these alternative agents may adversely impact the ability to manage emerging antimicrobial resistance.

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From the Northwestern Prevention Epicenter (Ms Lee, Drs Zembower, Peterson, and Noskin, and Mr Postelnick) and Department of Pharmacy (Ms Lee and Messrs Fotis and Postelnick), Northwestern Memorial Hospital, and Divisions of Infectious Diseases (Drs Zembower, Peterson, and Noskin) and Allergy/Immunology (Dr Greenberger), Department of Medicine, and Division of Clinical Microbiology, Department of Pathology (Dr Peterson), Northwestern University Medical School, Chicago, Ill.

THE REPORTED incidence of allergic reactions to penicillin ranges from 1% to 10%[1,2]; however, the true incidence of anaphylactic (life-threatening) reactions is in the range of 0.004% to 0.015%.[2] Often, patients are labeled as allergic to penicillin in their medical record without an in-depth investigation as to the nature of their reaction. When questioned about their reactions, many patients who report an allergy to penicillin do not meet the criteria for a true drug allergy[3-6] and have in fact received a cephalosporin or a penicillin in the past without adverse effects.[5] Also, some patients reporting an allergic reaction to penicillins (β-lactams), especially those without anaphylaxis, can subsequently receive a related class of antimicrobials, the extended-spectrum cephalosporins.[7,8] Therefore, proper classification and documentation of the allergic reaction is essential before choosing empiric antimicrobial therapy in patients reporting an allergy to penicillin.

Northwestern Memorial Hospital (NMH), located in Chicago, Ill, is a 683-bed (96 intensive care unit beds) tertiary-care academic medical center with approximately 35000 annual discharges. Our institutional antimicrobial guidelines attempt to limit the unneces-

METHODS

The procedure for documentation of a medication allergy at our institution is such that, upon admission, the patient is queried for medication allergies by a nurse and the information is recorded on a nursing intake form, which becomes part of the medical record. The physician then makes a notation as to the presence and type of allergy in a written note. For the purposes of our study, no special alert was given to the nursing or physician staff that this investigation was being conducted.

Physicians are required to document the presence of a drug allergy on a patient's admission orders and/or institutional antibiotic order form. Physicians are also required to fill out an antibiotic order form when prescribing any antimicrobial agent. The orders are then sent to pharmacy personnel for processing. It is the policy of the pharmacy department not to dispense medications without knowledge of the patient's allergy status except in emergency situations when the patient is unable to relay his or her allergy status to the medical team. Each patient's medication allergy profile is then entered into the pharmacy's computer system.

Computerized pharmacy reports of all patients hospitalized at NMH were collected over a 2-month period in August and September 1998. The first report contained a list of all patients who required antimicrobial therapy during this period and the antimicrobial agents they received. The second report listed all patients admitted to the hospital during this period plus their allergy profiles as entered by the pharmacy department from the patient's admission orders or antibiotic order forms. The reports were cross-referenced to generate a list of all patients receiving an antimicrobial agent who reported an antimicrobial allergy.

Once the incidence of a specific antimicrobial allergy was determined, the antimicrobial agents prescribed to patients with this specific antimicrobial allergy were evaluated and considered in the context of our institutional guidelines. In addition, the incidence of multiple antimicrobial allergies (2 or more) was obtained. From the pharmacy database, we tabulated the number of patients for whom a specific description of the allergic reaction was documented on the admission orders or antibiotic order forms. In order to assess the likelihood of the documentation of a specific reaction at a place in the chart other than the admission orders or antibiotic order forms, a concurrent manual medical record review of all identified patients was conducted over a 2-week period (n=122).

Adverse drug reaction reports were also obtained for the study period in order to assess the incidence of adverse reactions in the patients with a reported penicillin allergy who had received either vancomycin, a fluoroquinolone, or a β-lactam antimicrobial agent.

sary use of both vancomycin and fluoroquinolones in an effort to control the emergence of vancomycin-resistant enterococci and fluoroquinolone-resistant *Pseudomonas*, requiring the substantial use of β-lactam antibiotics.[9] After reviewing antimicrobial usage patterns at our institution, we postulated that the higher-than-expected use of antimicrobial agents outside of our established guidelines could, in part, be attributed to their use as alternative therapy for patients with a purported allergy to penicillin. Therefore, we examined the prevalence of reported antimicrobial allergies in patients requiring antimicrobial therapy at NMH over a 2-month period. We also evaluated how often health care professionals documented the specific allergic reaction in the medical record. Last, we focused on the empiric antimicrobial regimens prescribed to patients reporting a penicillin and/or cephalosporin allergy and compared them with our institutional guidelines for initial therapy.

Table 1. Incidence of Patient-Reported Antimicrobial Allergies in Patients Requiring Antimicrobial Therapy in August and September 1998 at Northwestern Memorial Hospital (N = 1893)

Reported Allergy	No. (%)
Penicillin	295 (15.6)
Sulfonamide	138 (7.3)
Erythromycin	37 (2.0)
Cephalosporin	32 (1.7)
Quinolone	22 (1.2)
Tetracycline	19 (1.0)
Vancomycin	13 (0.7)
Clindamycin	8 (0.4)
Gentamicin	6 (0.3)
Clarithromycin	5 (0.3)
Nitrofurantoin	4 (0.2)
Neomycin	4 (0.2)
Streptomycin	3 (0.2)
Metronidazole	3 (0.2)
Fluconazole	2 (0.1)
Azithromycin	2 (0.1)

RESULTS

A total of 2013 patients who received an antimicrobial agent were identified. Of these, 120 patients were excluded from the study either because their profiles did not specify the presence or absence of a medication allergy or because their allergy status was entered as "unknown." Of the remaining 1893 study patients, 470 (24.8%) reported 601 antimicrobial allergies; 295 (15.6%) reported a penicillin allergy. Of the 295 patients allergic to penicillin, 69 gave a history of at least 1 additional antimicrobial allergy (**Table 1**).

Eighty-five patients (18.1%) reporting an allergy claimed they were allergic to 2 or more agents. The most common antimicrobial allergy combined with penicillin was sulfonamide (26% [22/85]), followed by erythromycin (12% [10/85]) and cephalosporin (8% [7/85]).

For those who reported allergies, only 4% of the antimicrobial allergies (27/601) had documentation on the admission orders or antibiotic order forms describing the specific allergic reaction. The majority of the allergic reactions documented (8/27 [30%]) were listed

as urticaria or hives. To determine if this low incidence of descriptors of antimicrobial allergy was accurate, a manual medical record review was conducted for 122 patients. The manual medical record review revealed that 32% (23/72) of the medical records that documented antimicrobial allergies contained a description of the specific allergic reaction in the physicians' notes section. Because adverse gastrointestinal-related events are common as an allergic reaction to erythromycin, and because true anaphylactic reactions are rare, we analyzed the 42 patients who reported an allergy to erythromycin (37 patients from the computerized reports and 5 patients from the manual medical record review). Only 1 (2%) of the 42 patients had documentation regarding the nature of the reaction; this documented reaction was anaphylaxis.

The antimicrobial agents prescribed for the 226 patients allergic only to penicillin are listed in **Table 2**. Of the 247 patients allergic to penicillin and/or cephalosporin, 98 (39.7%) received vancomycin in comparison with 247 (17.4%) of 1423 who did not report any antimicrobial allergies ($P<.001$). Similarly, 53 (21.5%) of 247 patients with a reported penicillin and/or cephalosporin allergy received levofloxacin in comparison with 114 (8.0%) of 1423 patients without an antimicrobial allergy ($P<.001$).

Two (4%) of the 49 patients who reported an allergy to penicillin and received a fluoroquinolone during the study period reported an adverse reaction (rash, 1; feeling jittery/clammy, 1). Of the 30 patients with a reported penicillin allergy who received a β-lactam antimicrobial, only 1 (3%) reported having an adverse reaction (rash/pruritis) to ceftazidime. There were no adverse events noted for the 87 patients with a reported penicillin allergy who received vancomycin.

Table 2. Antimicrobial Therapy Prescribed to Patients Reporting an Allergy Only to Penicillin (N = 226)

Antimicrobial Agent	No. (%)
Vancomycin	87 (38.5)
Clindamycin	72 (31.9)
Gentamicin	60 (26.5)
Levofloxacin	49 (21.7)
Amikacin	27 (11.9)
Aztreonam	25 (11.1)
Azithromycin	13 (5.8)
Trimethoprim-sulfamethoxazole	13 (5.8)
Cefazolin	13 (5.8)
Metronidazole	13 (5.8)
Fluconazole	12 (5.3)
Erythromycin	10 (4.4)
Piperacillin	4 (1.8)
Tobramycin	4 (1.8)
Ampicillin/sulbactam	4 (1.8)
Ceftazidime	3 (1.3)
Piperacillin/tazobactam	3 (1.3)
Ceftizoxime	3 (1.3)

COMMENT

The prevalence of reported penicillin allergy among hospitalized patients requiring antimicrobial therapy at NMH exceeds overall population estimates.[1] In addition, the majority of the antimicrobial allergies listed (68%) lacked documentation as to the nature and severity of the allergic reaction, which is consistent with the findings of previous investigations.[6,10] Our study extends these observations by evaluating the potential effects of poor penicillin allergy evaluation on our institutional antimicrobial guidelines and goals.

The Centers for Disease Control and Prevention address vancomycin use in instances of penicillin allergy by suggesting its appropriateness only when patients have a serious or life-threatening allergy to β-lactam antibiotics.[11] Many studies have established prior vancomycin use as a risk factor for colonization and infection with vancomycin-resistant enterococci,[12-17] yet it continues to be our hospital's most commonly prescribed antimicrobial agent. Not only does the high level of reported penicillin allergy often lead to the prescribing of agents we are trying to control in order to manage increasing resistance at our medical center, but, in some instances, the prescribing of alternate antimicrobial agents puts patients at risk for colonization/infection with resistant organisms and/or treatment failure due to suboptimal therapy.

While we do not want to minimize the potential importance of the presence of a medication allergy, data show that immediate hypersensitivity reactions to penicillin and β-lactam antibiotics decrease with time. Among a group of 825 patients allergic to penicillin, only 146 (18%) had current evidence for immediate cutaneous reactivity to major and minor determinants.[18] Use of penicillin skin testing to detect antipenicillin IgE antibodies, which cause anaphylaxis, urticaria, and other acute reactions, would permit accurate immunologic determination of current penicillin hypersensitivity and potentially reduce the overall number of patients requiring alternative therapy to a very small percentage.

Our data suggest that health care professionals should carefully assess subjective claims of penicillin allergy before choosing alternative antimicrobial therapy. Use of these alternative antimicrobial agents, which are not truly required in the absence of an IgE-mediated allergic reaction or other serious reaction, such as Stevens-Johnson syndrome, will adversely impact the ability to manage emerging antimicrobial resistance.

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Corresponding author: Collin E. Lee, RPh, Northwestern Memorial Hospital, Galter Carriage House, Room 701B, 215 E Chicago Ave, Chicago, IL 60611 (e-mail: clee@nmh.org).

REFERENCES

1. Kerr JR. Penicillin allergy: a study of incidence as reported by patients. *Br J Clin Pract*. 1994;48:5-7.
2. Ahlstedt S. Penicillin allergy: can the incidence be reduced [review]? *Allergy*. 1984; 39:151-164.
3. Boguniewicz M. Adverse reactions to antibiotics: is the patient really allergic [review]? *Drug Saf*. 1995;13:273-280.
4. Tripp DM, Brown GR. Pharmacist assessment of drug allergies. *Am J Hosp Pharm*. 1993;50:95-98.
5. Kapila SP, Mitrzyk B, Patel P. Assessment of the accuracy of documented penicillin allergy and impact on antibiotic selection. Presented as an abstract at: Great Lakes Pharmacy Residence Conference; April 22-24, 1999; Lexington, Ky.
6. Absy M, Glatt AE. Antibiotic allergy: inaccurate history taking in a teaching hospital. *South Med J*. 1994;87:805-807.
7. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy [review]. *Ann Allergy Asthma Immunol*. 1995;74:167-170.
8. Audicana M, Bernaola G, Urrutia I, et al. Allergic reactions to beta-lactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy*. 1994;49:108-113.
9. Postelnick MJ, Peterson LR, Noskin GA. Effect of changes in antimicrobial agent use on bacterial pathogens recovered from hospitalized patients: a 6-year assessment. *J Clin Outcomes Manage*. 1998;5:21-32.
10. Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. *Am. J Hosp Pharm*. 1994;51:79-84.
11. Hospital Infection Control Practices Advisory Committee. Recommendations for preventing the spread of vancomycin resistance [review] [published correction appears in *Infect Control Hosp Epidemiol*. 1995;16:498]. *Infect Control Hosp Epidemiol*. 1995;16:105-113.
12. Rubin LG, Tucci V, Cercenado E, Eliopoulos G, Isenberg HD. Vancomycin-resistant *Enterococcus faecium* in hospitalized children. *Infect Control Hosp Epidemiol*. 1992;13:700-705.
13. Handwerger S, Raucher B, Altarac D, et al. Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin and gentamicin. *Clin Infect Dis*. 1993;16:750-755.
14. Linden PK. Clinical implications of nosocomial gram-positive bacteremia and superimposed antimicrobial resistance [review]. *Am J Med*. 1998;104:24S-33S.
15. Boyce JM, Mermel LA, Zervos MJ, et al. Controlling vancomycin-resistant enterococci. *Infect Control Hosp Epidemiol*. 1995;16:634-637.
16. Dahms RA, Johnson EM, Statz CL, Lee JT, Dunn DL, Beilman GJ. Third-generation cephalosporins and vancomycin as risk factors for postoperative vancomycin-resistant enterococcus infection. *Arch Surg*.1998;133:1343-1346.
17. Gin A, Zhanel G. Vancomycin-resistant enterococci [review]. *Ann Pharmacother*. 1996;30:615-624.
18. Sogn DD, Evans R III, Shepherd G, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med*.1992;152:1025-1032.