TABLE I. Characteristics of the patients

	Total	Mites	Pollens
N	86	41	45
Male/female	38/48	16/25	22/23
Age, y (range)	35.4 (14-66)	36.3 (15-65)	34.8 (14-66)
Rhinitis alone	42	19	23
Rhinitis plus asthma	43	22	21
Asthma alone	1	0	1
Adherence assessed at		13 ± 1 month	18 ± 2 weeks

were graded as mild (no medical advice/treatment required, no dose adjustment), moderate (interference with everyday activities or need for drug treatment or SLIT discontinuation), or severe (life-threatening events needing hospitalization and/or emergency care).

In November 2003, 86 patients (mean age, 35.4 years; 44% male) were included (Table I): 41 received SLIT to mite and 45 to pollens (24 grasses, 18 *Parietaria*, 3 ragweed). The mean duration of the pollen SLIT was 18 ± 2 weeks. The count of the tablets (taken/expected) was 5080/5248 in the mite group and 3952/4050 in the pollen group; therefore, the adherence was 96.8% and 97.6%, respectively (cumulative adherence, 97.3%). Omitted doses were documented in 11 patients. Seven patients postponed the administration of 1 to 2 doses because of concurrent nonallergic illness, 3 patients reported occasional forgetting, and 1 patient skipped multiple doses because of working habits. Eleven mild side effects were reported in 6 (7%) patients: 6 oral itching, 2 rhinitis, 2 nausea, and 1 generalized itching. Because of the high adherence rate, no socioeconomic determinant affecting the adherence could be ruled out.

Currently, adherence is one of the major concerns about SLIT managed by the patient at home. The problem is the same with other drugs (inhaled corticosteroids, antihistamines), and it is well known that the low adherence is a major cause of failure or poor efficacy of treatments.[6] In the case of immunotherapy, it could be expected that SLIT is inferior to SCIT in terms of adherence, although the experimental data show that the adherence to SCIT is far from being satisfactory, mainly because of inconvenience or side effects.[7,8] Thus, in the case of immunotherapy, the safety and tolerability of the treatment should play a relevant role. Measuring the adherence is not easy to do: reliable data could be obtained with electronic recorder devices,[9] but this approach is expensive and not applicable to all drugs. With SLIT in solution, one possible approach is to measure the volume of the extract in the returned vials, but this does not exclude that patients have discharged part of the vaccine. Simply counting the returned tablets is not sufficient, because it gives no information about the doses taken. On the contrary, calling the patients randomly and asking to count the tablets immediately avoids that bias: it is unlikely that patients can calculate in seconds the correct number of remaining tablets and the expected consumption. Thus, we are confident that our results reflect the real adherence of patients. The rate of adherence was independent of economical aspects, because all of our patients had the treatment fully reimbursed by the National Healthcare System, whereas the good safety profile was probably an important determinant. In conclusion, despite the fact that SLIT is self-managed at home, the adherence seems to be satisfactory.

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Safety of cephalosporin administration to patients with histories of penicillin allergy

To the Editor:

Physicians have prescribed penicillins and cephalosporins for more than 50 years. Both families have similar chemical structures and share a β-lactam ring and thus have a potential for allergic cross-reactivity. Ten

percent of all inpatients and outpatients claim to have a penicillin allergy.[1] As a result, physicians are often forced to choose alternative, non–β-lactam antibiotics.[2]

The safety of administering a cephalosporin to patients who report a penicillin allergy continues to remain an area of controversy. Early *in vitro* and skin testing studies in the 1960s and 1970s showed cross-reactivity rates between these 2 classes of antibiotics to be 50% or higher.[3–5] These findings may have been confounded by the presence of trace amounts of penicillin in cephalosporins as well as the fact that benzyl penicillin shares a similar side chain with early first-generation cephalosporins.[1] More recent studies have questioned these high degrees of cross-reactivity.[6,7]

A recent review article presented the available data on administration of cephalosporins to patients with a history of penicillin allergy.[6] Patients who had a positive skin test to penicillin or who were not tested to penicillin had much higher reaction rates (4.4% and 11.8%, respectively) when treated with cephalosporins compared to patients with a negative skin test (0.6%). According to current guidelines,[1] all patients with a positive penicillin history should undergo penicillin skin testing before cephalosporin administration.

In our hospital (Parkland Memorial Hospital), a large, county-based facility, hospitalized patients with a history of penicillin allergy are frequently treated with cephalosporins without previous penicillin skin testing. We sought to determine in this retrospective study the degree to which these patients tolerated the prescribed cephalosporins. Institutional Review Board (IRB) approval was obtained through the Office of the IRB at the University of Texas Southwestern Medical Center (IRB #0903-582).

With the assistance of hospital pharmacy records, all patients admitted to Parkland Memorial Hospital between August 1999 and June 2001 who reported a history of penicillin allergy and who were treated with a cephalosporin were recorded in a database on a weekly basis.

Through the medical record department, all adverse reactions to cephalosporins were recorded during the same period (August 1999 to June 2001). These adverse reactions were reported as E-codes on the basis of the ICD-9 international classification system. Reactions were initially recorded in the patient's chart by an in-house physician and were later coded and recorded by certified medical coders in our hospital as E-codes. The pharmacy record database was compared with the E-code database to determine whether any patient who reported a history of penicillin allergy and who had received a cephalosporin developed an adverse reaction.

By using hospital pharmacy records, during the study period, the researchers identified a total of 23,270 inpatients who had received a cephalosporin, and 606 of these patients reported a history of penicillin allergy. In this subset of patients, a total of 685 cephalosporin courses were administered, the majority of which were given parenterally. Of these courses, 42% were first-generation, 21% were second-generation, and 37% were third-generation or fourth-generation cephalosporins.

During this same period, the medical records department recorded a total of 16 E-codes for adverse reactions to cephalosporins among all inpatients. Hence, the overall cephalosporin reaction rate in all inpatients was 0.07%. We next sought to determine the reaction rate in patients who reported a history of penicillin allergy. We cross-matched the 16 patients who had E-codes to cephalosporins with the 606 patients who reported a penicillin allergy and who had received at least 1 cephalosporin course. Only 1 patient was found to be in both groups. Thus, in these 606 patients with a positive history for penicillin allergy, the cephalosporin cross-reactivity rate was 1 of 606, or 0.17%. In reviewing this patient's chart, she was noted to have a mild worsening of her underlying eczema several days after being placed on cefazolin.

Random chart reviews were performed to confirm that the information we had received through pharmacy and medical records was correct. In reviewing 50 of the 606 charts, no cephalosporin adverse drug reactions were identified. Charts from 10 of the 16 patients who had had a documented cephalosporin reaction (E-code) were available for review, and all were found to have been coded correctly.

In further discussions with pharmacy personnel, we were informed that hospitalized patients who reported a severe penicillin allergy history (such as anaphylaxis) and who were prescribed a cephalosporin were either denied the cephalosporin and treated with a non–β-lactam antibiotic or were referred to allergy and immunology for evaluation.

There are approximately 25 inpatient pharmacists at our hospital. Before administering any antibiotic, an inpatient pharmacist reviews the antibiotic order written by the prescribing physician and any drug allergy history noted in that patient's chart. If the drug allergy history is unclear, the pharmacist interviews the patient to clarify the history. We issued an anonymous questionnaire to each inpatient pharmacist to determine the frequency of cephalosporin denial. On average, each pharmacist reported evaluating 4 inpatients per month who gave a penicillin allergy history and for whom a cephalosporin was ordered. Each pharmacist typically identified a severe penicillin allergy history in 1 of these 4 patients and consequently denied the prescribed cephalosporin for these individuals. As a result, potentially 25 inpatients per month (1 per pharmacist) may have been excluded from our database because of pharmacy intervention.

In our hospital, patients who report a history of penicillin allergy are frequently treated with cephalosporins without previous penicillin skin testing. Recent surveys have shown that the practice of empirically administering cephalosporins to patients with a history of penicillin allergy is not uncommon.[2] We found that 605 of 606 patients who had penicillin allergy histories and who were administered a cephalosporin tolerated the medication without an adverse drug reaction. As a result, our cross-reactivity rate was 0.17%, significantly lower than the published cross-reactivity rates of 8% to 12% in patients not skin tested.[6]

A limitation of our study is the fact that pharmacy intervention likely excluded some patients with more serious penicillin allergy histories, and this may have lowered our cross-reactivity rate. However, we suspect that the pharmacists overestimated the number of situations in which they intervened. If, as was reported in the survey, each of 25 pharmacists approved a cephalosporin prescription in 3 of 4 patients allergy to penicillin monthly (denied 1), there should have been at least 1725 ($25 \times 3 \times 23$) patients allergic to penicillin treated with cephalosporins during the 23-month study period. Instead, there were only 606 such patients documented as receiving a cephalosporin. Despite this overestimation, the fact remains that at least some patients who gave a history of penicillin allergy were denied a cephalosporin.

It is impossible to know what proportion of the treated patients had penicillin-specific IgE antibodies at time of cephalosporin administration. Previous studies have shown penicillin skin test positive rates of 10% to 20% in history-positive patients.[8,9] Furthermore, it is known that a third of patients with a positive penicillin skin test have vague histories of penicillin allergy.[10] Hence, even if patients with more convincing allergic histories were excluded from our study group, some individuals almost certainly did have penicillin-specific IgE antibodies.

In summary, cephalosporins appear to be well-tolerated drugs with a low reaction rate (0.07%) among all patients who received them. Like others, we demonstrated that most patients who report a history of penicillin allergy were able to tolerate cephalosporins safely. However, because it is likely that some patients who had a severe penicillin allergy history were excluded from the analysis, broad administration of cephalosporins to patients with a history of penicillin allergy cannot be recommended at this time.

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