

subjects with high IL-10 producer haplotype GCC (OR, 0.39; 95% CI, 0.19-0.82; $P = .012$; Fig 1). The strongest cat exposure-related protective effect against cat sensitization was found in the combined group of asthmatic and control subjects with a history of parental asthma or allergy. In this group ($n = 128$) the prevalence of a positive reaction to cat allergen was 14.5% in exposed and 40.4% in nonexposed subjects (OR, 0.25; 95% CI, 0.11-0.58; $P = .001$). When the *IL1A* and *IL10* polymorphisms were taken into the analyses, yet stronger associations were found in *IL1A* (+4845) allele G homozygotes (OR, 0.09; 95% CI, 0.02-0.31; $P < .001$; Fig 1) and *IL10* haplotype GCC carriers (OR, 0.17; 95% CI, 0.060-0.49; $P = .001$; Fig 1).

In our study we show for the first time that the *IL1A* and *IL10* genes are substantially related to the development of cat exposure-induced tolerance. Because *IL1A* (+4845) G homozygosity and *IL10* GCC carrier states are very common, these observations have a substantial effect on the risk of sensitization at the population level. Exposure-related tolerance is strongest in subjects reporting a family history of atopy.^{1,8} *IL1A* (+4845) G homozygosity is more common in subjects with atopy,⁵ and it could be one of the factors that mediate the effect of family background.

It can be further concluded from our results that avoiding pets cannot be recommended as a preventive measure to avoid atopy. The associations of *IL1A* and *IL10* illustrated in the present study indicate that exposure-related tolerance is a biologic phenomenon with demonstrable genetic background. It further remains to be elucidated whether the *IL1A* and *IL10* genotypes mediate the responses in induced tolerance (ie, in immunotherapy).

Jussi Karjalainen, MD, PhD^a

Miia Virta, MD^b

Tanja Pessi, PhD^b

Janne Hulkkonen, MD, PhD^b

Markku M. Nieminen, MD, PhD^a

Mikko Hurme, MD, PhD^{b,c}

^aTampere University Hospital

Department of Respiratory Medicine

^bDepartment of Microbiology and Immunology

University of Tampere Medical School

^cTampere University Hospital

Centre for Laboratory Medicine

FIN-33014 Tampere

Finland

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Rapid intravenous cephalosporin desensitization

To the Editor:

On review of the literature, 2 protocols for intravenous cephalosporin desensitization were found requiring either a 2-day¹ or 14-day² period of time. Although cephalosporins are commonly prescribed in numerous nonemergency clinical settings, situations arise in which urgent cephalosporin therapy is the best or only treatment option available. One such setting is in the patient with cystic fibrosis who requires either an intravenous third- or fourth-generation cephalosporin for the treatment of *Pseudomonas aeruginosa*-induced pneumonia. It would thus be desirable to have a rapid protocol for cephalosporin desensitization, as is currently available for penicillin. Here we report rapid intravenous cephalosporin desensitization protocols that have been used successfully at the University of Iowa Hospitals and Clinics (UIHC) and Barnes-Jewish Hospital (BJH) over the past several years.

After institutional review board approval at both institutions, a retrospective chart review was performed. There were 49 patients who were seen between July 1997 and June 2002 at UIHC and 44 patients who were seen between January 1999 and January 2004 at BJH in whom penicillin and cephalosporin skin testing was performed. The 8 individuals, 2 from UIHC and 6 from BJH, included in this retrospective study were those who had positive skin test results and eventually underwent rapid intravenous desensitization to a cephalosporin (Table I). At both UIHC and BJH, it is our practice not to give cephalosporins to patients with penicillin allergy without prior penicillin and cephalosporin skin testing. Patients who had uniquely positive skin test results to penicillin determinants (negative skin test results to cephalosporins) were not desensitized to cephalosporin before receiving cephalosporin therapy. The remainder of the 93 subjects had negative skin test results and received a β -lactam antibiotic without adverse events. Given that this is a retrospective study, we

TABLE I. Subjects undergoing rapid intravenous cephalosporin desensitization

Subject	Institution	Age (y)	Diagnosis	Reported allergy / reaction	PCN ST+	CS ST+	Desensitization	Time	Complications
1	UIHC	35	CF, PNA	Cefepime/U	MaD	Cefepime	Cefepime	8 h, 30 min	None
2	UIHC	79	Endocarditis	Ceftriaxone/U	MaD, MiD	Ceftriaxone	Ceftriaxone	7 h	None
3	BJH	51	AML, NF	Ampicillin/U	MaD	Cefepime	Cefepime	2 h, 15 min	None
4	BJH	19	CF, PNA	Cefepime/U	None	Cefazolin, ceftazidime	Cefepime*	2 h, 15 min	None
5	BJH	23	CF, PNA	PCN and ceftazidime/Ana	MaD	Cefazolin, ceftazidime	Cefepime*	2 h, 15 min	None
6	BJH	37	PNA	Ceftazidime/Ana	None	Ceftazidime	Cefepime*	2 h, 15 min	None
7	BJH	32	Meningitis	Amoxicillin/U	MaD	Ceftriaxone	Ceftriaxone	2 h, 15 min	None
8	BJH	59	Osteomyelitis	PCN and CS/U	MaD	Cefazolin	Cefazolin	2 h, 15 min	None

PCN, Penicillin; ST+, positive skin test result (intradermal); CS, cephalosporin; UIHC, University of Iowa Hospitals and Clinics; CF, cystic fibrosis; PNA, pneumonia; U, urticarial rash; MaD, major determinant; MiD, minor determinant; BJH, Barnes-Jewish Hospital; AML, acute myelogenous leukemia; NF, neutropenic fever; Ana, anaphylaxis.

*Patients were desensitized to the clinically indicated cephalosporin on the basis of potential cross-reactivity among cephalosporin generations (subjects 4-6).

were unable to reliably determine the time between index adverse antibiotic reaction and skin testing. Skin testing and desensitization were always accomplished on the same day. In every case, the risks and benefits of skin testing and rapid intravenous cephalosporin desensitization were discussed with the patient in detail, and written consent was obtained. At UIHC, desensitizations were performed in either a medical or surgical intensive care unit, and at BJH, they were performed on either standard inpatient floors or intensive care units, depending on the patients' location. Rapid intravenous desensitizations at both locations were supervised by a clinical fellow of allergy and immunology, an attending physician in allergy and immunology, or both.

At both institutions, skin testing was performed according to standard percutaneous and intradermal skin testing methods.³ Patients were tested either on the volar aspect of the forearm or the posterior aspect of the upper arm, with normal saline as the negative control, histamine as the positive control, penicillin major (benzylpenicilloyl polylysine-Pre-pen; Hollister-Stier, Spokane, Wash), and minor determinants (benzylpenilloate, benzylpenicilloate, Pen A,⁴ and Pen G) and cephalosporins. Cephalosporins were diluted to 6.0 mg/mL at UIHC and 3.33 mg/mL at BJH.⁵ Prior negative skin test results to these penicillin and cephalosporin preparations in patients at UIHC and BJH showed that these concentrations have no irritant effect on normal human skin. There was a 15-minute period between the time that skin tests were placed and when they were read. A skin prick test result was considered positive if the wheal was greater than or equal to 5 mm in diameter. Negative epicutaneous skin prick test results were followed by intradermal testing with diluent-negative, histamine-positive controls and 0.02 mL of the drug (6.0 mg/mL at UIHC = 0.12 mg and 3.33 mg/mL at BJH = 0.07 mg). An intradermal test result was considered positive if the wheal was at least 3 mm greater than that elicited by the negative control.

Desensitization to cefepime (fourth generation) and ceftriaxone (third generation) at UIHC was performed by using a protocol requiring 8.5 hours and 7 hours, respectively. Protocols were initiated at 0.5- to 1-mg doses (similar dose exposure to the intradermal skin test dose of 0.12 mg) and increased at a rate that approximately doubled the dose every 30 minutes. Once higher doses and volumes were reached, time between doses was increased accordingly.

Desensitization to cefepime (fourth generation), ceftriaxone (third generation), and cefazolin (first generation) at BJH was performed in 2.25 hours, as shown in Table II. Protocols were initiated according to the goal therapeutic intravenous dose, either 1 or 2 g. In both examples, the initiating dose is 0.1 mg (similar dose exposure to the intradermal skin test dose of 0.7 mg). Dosing was calculated in a retrospective fashion so that the cumulative dose administered over the course of rapid desensitization equaled the goal therapeutic dose (1-2 g intravenously depending on the circumstance). Doses were rounded to make accurate preparations and administration feasible. Dose escalation was done by half-log₁₀ (approximately 3.162278) increments, and dosing intervals were set at 15 minutes.

The patients who underwent rapid intravenous cephalosporin desensitization are detailed in Table I. All patients included in this analysis had positive skin test results to cephalosporins, and 6 of these 8 subjects also had positive skin test results to penicillin determinants. In 3 subjects (subjects 4-6) the patient underwent skin testing to cefazolin, ceftazidime (third generation), or both but later underwent intravenous desensitization to cefepime. Outside of the β -lactam ring, there are no shared side chains (R1 or R2) between the cefazolin and ceftazidime.⁶ Cefepime and ceftazidime have similar R1 chains; however, it is not clear whether the structural similarity is solely responsible for this potential cross-reactivity. Romano et al⁷ showed that 5 of 14 patients had positive

TABLE II. Rapid intravenous cephalosporin desensitization protocol: Goal dose, 1 g and 2 g intravenously

Dose	Goal dose, 1 g IV		Goal dose, 2 g IV		Time
	mg	mg, rounded	mg, rounded		
1	0.1	0.1	0.1		15 min
2	0.2	0.2	0.4		15 min
3	0.7	1.0	1.0		15 min
4	2.2	2.0	4.0		15 min
5	6.9	10.0	10.0		15 min
6	21.8	20.0	40.0		15 min
7	69.0	70.0	140.0		15 min
8	218.1	200.0	400.0		15 min
9	689.7	700.0	1400.0		15 min
Cumulative	1008.6	1003.3	1995.5		2 h, 15 min

Protocol for intravenous desensitization to all cephalosporins with a goal dose of 1 g and 2 g (Barnes-Jewish Hospital).

IV, Intravenous.

skin test results to at least 1 cephalosporin, which have side-chain structures different from those of penicillins. These results demonstrate that the increased risk for cross-reactivity is not solely a result of structural similarities. The specific haptens involved in hypersensitivity to cephalosporins have not been identified. Given this, we presumed the potential for cross-reactivity and desensitized. The time for desensitization varied from 2.25 hours (BJH) to 8.5 hours (UIHC), depending on the protocol used. All 8 subjects underwent rapid intravenous cephalosporin desensitization without adverse events.

Intravenous cephalosporin desensitization procedures requiring 2-day¹ or 14-day² periods have been documented in the literature. In these studies no problems or major systemic reactions were observed.^{1,2} Our examples demonstrate intravenous desensitization protocols that were well tolerated in a much shorter time frame. The 8 aforementioned patients illustrate the feasibility and safety of acute intravenous desensitization to selected cephalosporins over a 2.25- to 8.5-hour period. Although the time frames among the protocols presented vary, we believe that with the proper precautions, including close patient observation and very small initial dosing, intravenous cephalosporin desensitization can be successfully accomplished in 1 day. Because all 8 rapid desensitizations were without adverse event, we suggest using the shorter BJH protocol encompassing a 2.25-hour time span, as outlined in Table II.

The literature remains controversial as to the necessity of penicillin skin testing for a history of penicillin allergy when a cephalosporin is the drug of choice. Per practice parameters, the recommendation remains that these patients be skin tested to penicillin major and minor determinants to determine whether the patient has specific IgE antibodies. If skin test results are negative, the patient can receive a cephalosporin at no greater risk than that of the general population.⁸ Anne and Reisman⁹ reported that if patients with a history of allergy to penicillin are not skin tested but given a second- or third-generation cephalosporin directly, the overall incidence of adverse reactions

from cephalosporins ranges from 1% to 10%, with rare anaphylaxis (<0.02%). From this, Anne and Reisman proposed that penicillin skin tests do not predict the likelihood of allergic reactions to cephalosporins in patients with histories of penicillin allergy because 1 (1%) reaction occurred in 98 patients with positive penicillin skin test results, and 6 (2%) reactions occurred in 310 patients with negative test results. They concluded that it is safe to administer cephalosporin antibiotics to patients with penicillin allergy. However, Pumphrey and Davis¹⁰ reported from their data analysis of fatal anaphylaxis in the United Kingdom between 1992 and 1997 that 6 of the 12 anaphylactic reactions to antibiotics occurred with the first dose of cephalosporin. Three patients had a history of allergy to amoxicillin and one to penicillin, but none had been skin tested. Furthermore, a recent study by Romano et al⁷ showed that 10 (71.4%) of 14 subjects with positive skin test results to cephalosporins also reacted to the penicillin minor determinant mixture. Our study is in agreement with the latter because 6 (75%) of our 8 subjects who had positive skin test results to cephalosporins also had positive skin test results to penicillin determinants.

According to current practice guidelines,⁵ there is a continued need for cephalosporin desensitization in patients who have had severe IgE-mediated allergic reactions to penicillin. This retrospective study documents rapid intravenous desensitization to a first-, a third-, and a fourth-generation cephalosporin in less than 1 day. Furthermore, the BJH protocol can be accomplished safely and effectively in 2.25 hours.

Patrick H. Win, MD^a

Holly Brown, MD^b

Ahmad Zankar, MD^b

Zuhair K. Ballas, MD^b

Iftikhar Hussain, MD^a

^aWashington University in St Louis/School of Medicine

Division of Allergy and Immunology

660 South Euclid Ave

Campus Box: 8122

Saint Louis, MO 63110

ihussain@wustl.edu

^bUniversity of Iowa Hospitals and Clinics Program

Department of Internal Medicine

Iowa City, Iowa

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Expression of FcεRI on dendritic cell subsets in peripheral blood of patients with atopic dermatitis and allergic asthma

To the Editor:

Allergic disorders are characterized by elevated serum IgE levels. Cross-linking of IgE bound to FcεRI on mast cells and basophils results in release of proinflammatory mediators that mediate an allergic response. Besides mast cells and basophils, which play a role in the effector phase of an allergic response, antigen-presenting cells in humans have also been shown to express FcεRI. Expression of IgE on FcεRI on antigen-presenting cells has been shown to increase the efficiency of antigen presentation and thereby lowers the threshold for allergen uptake. Therefore, FcεRI-expressing dendritic cells might be important in the initiation of allergic responses. In contrast with mast cells and basophils, which express FcεRI consisting of 4 subunits (αβγγ), FcεRI on dendritic cells lacks the signal amplifying β-chain and consists of only 3 subunits.¹ Previous studies have shown FcεRI expression on Langerhans cells in skin of patients with atopic dermatitis (AD)² and on dendritic cells (DCs) in the lung of patients with allergic asthma (AA).³ In a study published in this journal,⁴ an increased FcεRI expression was observed on basophils, myeloid DCs (mDCs), and plasmacytoid DCs (pDCs) in the blood of patients with AA compared with healthy controls (HCs). Recently it was demonstrated that in patients with AD, pDCs can release IL-10 on aggregation of FcεRI.⁵

In the current study, we investigated the expression of FcεRI on basophils, mDCs, and pDCs in the blood of patients with AD and AA and HCs to examine whether these FcεRI-expressing blood DCs are a general finding in allergy or whether it might be disease-specific.

From each patient group and controls, 6 persons were selected. Patients with AD, age 25 to 55 years, were diagnosed according to the criteria of Hanifin and Rajka⁶ and had moderate to severe AD (mean Leicester Sign Score of 44; range, 28-68). Mean serum IgE levels were determined through use of the CAP system (Pharmacia Diagnostics, Uppsala, Sweden), and the mean value was 7387 kU/L (range, 268-27,765 kU/L). As an objective disease parameter for AD,⁷ serum thymus and activation-regulated chemokine (TARC) levels were measured by ELISA. Mean serum TARC levels in the patients with AD

were 5672 pg/mL (range, 954-13,997 pg/mL). Patients with AA, age 28 to 51 years, were diagnosed according to American Thoracic Society criteria⁸ and had mild to severe disease with a mean PC₂₀ (shortened challenge) of 4.84 (range, 0.5-14). The mean serum IgE level was 172 kU/L (range, 50-431 kU/L), and mean serum TARC level was 136 pg/mL (range, 50-265 pg/mL). Patients with AA had no history of AD, and vice versa. Patients did not use systemic immunosuppressive drugs or antihistamines, but the use of topical or inhaled steroids was allowed. As HCs, persons without a history of allergic disorders were included (mean serum IgE, 31 kU/L; mean serum TARC, 164 pg/mL).

PBMCs were isolated from heparinized blood by density gradient centrifugation using Percoll 1.078 (Amersham Biosciences AB, Uppsala, Sweden). Cell-specific markers and FcεRI expression were determined by flow cytometry (FACSCalibur, Becton Dickinson, San Jose, Calif). Data were analyzed using FCSexpress 2 software (DeNovo Software, Thornhill, Ontario, Canada).

Basophils were characterized by high CD123 expression. mDCs were defined as Lineage cocktail 1 (CD3, CD14, CD16, CD19, CD20, CD56; BD Bioscience, San Jose, Calif)-negative and blood dendritic cell antigen 1-positive (CD1c; Miltenyi Biotec, Bergisch Gladbach, Germany). pDCs were defined as lineage-negative and blood dendritic cell antigen 4-positive (Miltenyi Biotec). Between patients and controls, there was no difference in the percentage of pDCs (0.21% ± 0.07% vs 0.31% ± 0.11%) or mDCs (0.51% ± 0.03% vs 0.52% ± 0.13%). Expression of FcεRI was determined using a CRA-1 antibody (clone AER-37, IgG2b), which was a kind gift of Prof Dr C. Ra (Nihon University School of Medicine, Tokyo, Japan). This antibody shows no competition with IgE in binding to FcεRI. As a control, cells were stained with isotype matched control antibodies. Values of their mean fluorescence intensity were subtracted from each value of the appropriate fluorochrome-conjugated antibody.

On basophils, no significant difference in FcεRI expression was seen between the groups (Fig 1, A). Both mDCs and pDCs showed an increased expression of FcεRI in the patients with AD (Fig 1, B and C). On mDCs of patients with AA, a slight increase in FcεRI expression was seen; however, this was not significant. The FcεRI expression on mDCs was correlated with the FcεRI expression on pDCs ($r = 0.775$; $P < .001$; data not shown).

Subsequently, the correlation between serum IgE levels and FcεRI expression was determined. On basophils, no correlation was observed for the FcεRI expression. For lower serum IgE levels, however, a trend to a positive correlation was noted. For both mDCs and pDCs, a correlation was found between FcεRI expression and serum IgE levels ($r = 0.715$ and $r = 0.684$, respectively).

In the current study, we demonstrated that in contrast with patients with AA, mDCs and pDCs of patients with AD express increased levels of FcεRI. These results are in contrast with an earlier published article in which FcεRI expression was increased on mDCs and pDCs in patients