

Letters

ASTHMA IN IMMUNE-COMPETENT CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS

Elevations of serum IgE and drug hypersensitivities have been commonly reported in patients with human immunodeficiency virus (HIV).¹⁻⁶ Asthma, however, was rarely reported to occur in HIV-infected persons in the pre-antiretroviral therapy (ART) era.⁷ In the era of ART and immune reconstitution in HIV-infected individuals, there have been reports of increased incidence of asthma in patients with HIV.⁸ We report an overall increase in the incidence of asthma in our children infected with HIV and a correlation of asthma diagnosis with reconstitution of CD4⁺ T cells after ART therapy in HIV-infected children. These findings are of interest to HIV practitioners who will be treating patients with increased asthma symptoms and who will be concerned about the competence of newly reconstituted T cells. The findings are of interest to allergists because of the implication that CD4⁺ T cells are necessary for the localized inflammatory response in asthma.

Patients were recruited from the Pediatric HIV Clinic at Children's Hospital of Michigan, Detroit. The study was approved by the Human Investigation Committee of Wayne State University, Detroit, and written consent was obtained from all families. Patients were recruited, and their medical records were reviewed for any evidence of asthma by symptom and/or treatment history. Those with asthma had detailed medical record reviews starting at the time of HIV diagnosis. Data were collected on asthma exacerbations based on emergency department visits, hospitalizations, and steroid bursts. Pulmonary function data were reviewed to confirm diagnosis. CD4⁺ T-cell percentages and absolute counts were recorded. The asthma severity was evaluated by the recommendations of the National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program guidelines. Differences in T-cell numbers and percentages were analyzed by the Mann-Whitney *U* test.

A total of 85 HIV-infected children (aged 3–16 years) were recruited for the study; 24 (28%) had persistent asthma (12 girls and 12 boys). Six of the asthmatic patients had a history of intermittent wheeze without need for inhaled corticosteroid in infancy. At the time of persistent asthma diagnosis, the CD4⁺ T cells of all asthmatic patients were within acceptable limits for age. Twenty patients had never had a significant decrease in T cells, and 4 had decreases in T-cell percentage and/or absolute count below *Pneumocystis carinii* or *Pneumocystis jiroveci* prophylaxis level before starting HIV therapy (nadirs of absolute CD4⁺ T-cell counts: 204, 32, 23, and 24 cells/ μ L). The T cells of these 4 patients were subsequently reconstituted. A previous review of our pediatric HIV medical records from the pre-ART era revealed no persistent asthmatic patients (0 of 148 patients receiving treatment for persistent asthma) compared with the 28% at the time of the study. The 4 children with reconstituted T cells showed significant differences in T-cell percentage (nadir/diagnosis values, 12%/23%, 2%/24%, 1%/29%, and 4%/20%; *P* = .02) and absolute values (nadir/diagnosis values, 204/736, 32/816, 23/812, and 24/440 cells/ μ L; *P* = .02) between nadir of T-cell count (preasthma) and values at the time of diagnosis with persistent asthma.

Interestingly, the CD4⁺ T-cell levels decreased transiently below the level recommended for *P. carinii*/*jiroveci* prophylaxis in 2 patients whose T cells had never been reconstituted (previously per-

sistent adequacy of CD4⁺ T-cell counts), and the decrease in each case coincided with improvement in asthma (persistent to intermittent).

This study highlights the ability of reconstituted CD4⁺ cells (in HIV-infected children receiving ART) to assist in asthmatic inflammation. It also introduces a new population of asthmatic children (whose T cells were reconstituted or never immune depleted): immune-competent HIV-infected children.

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DURATION OF BRONCHOPROTECTION OF INHALED IPRATROPIUM AGAINST INHALED METHACHOLINE

Anticholinergic bronchodilators are infrequently used in the management of asthma; however, we occasionally see subjects who are using ipratropium bromide referred for methacholine challenge. Ipratropium is a potent antagonist of muscarinic agonists such as methacholine,¹⁻³ which is commonly used to measure airway responsiveness. Inhaled ipratropium significantly inhibits methacholine³; the duration of inhibition is unknown. Current guidelines from the American Thoracic Society recommend withholding inhaled ipratropium for 24 hours before a methacholine challenge test (MCT).¹ We evaluated the inhibitory effect of ipratropium, 40 μ g, on the methacholine provocation concentration causing a 20%

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forced expiratory volume in 1 second (FEV₁) decrease (PC₂₀) at 6 and 12 hours.

Twelve adults (8 women and 4 men; mean [SEM] age, 33.0 [3.4] years; mean [SEM] height, 170 [2] cm) with asthma and airway hyperresponsiveness to methacholine (methacholine PC₂₀ <16 mg/mL) were recruited. The baseline mean [SEM] FEV₁ was 86.0% [3.8%] predicted, and subjects were stable (with no change in medications or symptoms for 2 months before testing). Subjects were using infrequent rescue salbutamol, which was withheld for 48 hours before any testing. None of the subjects were using long-acting β -agonist or anticholinergic therapy. This study was approved by the University of Saskatchewan, Saskatoon, ethics committee. Written informed consent was obtained.

In this random-order, double-blind, placebo-controlled, crossover study, subjects were allocated to receive ipratropium, 20 μ g, inhaler and placebo (propellant only) inhaler on 2 days within a 1-week period. The subjects were blinded to the ipratropium and placebo inhalers by having a third party affix an opaque label over the commercial label. On each test day, the subjects were instructed to take 2 puffs from the inhaler at the appropriate time. An MCT was then performed at both 6 and 12 hours; tests were performed at the same time of day in each subject. The MCT was performed by the tidal breathing method,^{1,2} using a Bennett Twin jet nebulizer (Puritan Bennett, Carlsbad, California) calibrated to deliver 0.13 mL/min; the same nebulizer was used in each individual for all 4 tests. Spirometry was performed in triplicate. Saline was then inhaled for 2 minutes, and the FEV₁ was repeated at 30 and 90 seconds. Doubling concentrations of methacholine up to 32 mg/mL were then inhaled for 2 minutes at 5-minute intervals, with starting concentrations based on the subjects' known response. The FEV₁ was repeated 30 and 90 seconds after each inhalation, and inhalations were discontinued when the FEV₁ had decreased by more than 20%. The percentage decrease in FEV₁ was calculated from the lowest post-saline FEV₁ to the lowest postmethacholine FEV₁, and the PC₂₀ was calculated by an algebraic equation.⁴

Logarithmic transformation was used for the PC₂₀ values. Geometric mean PC₂₀ values were compared using the paired *t* test (STATISTIX for Windows, version 7.0; Analytical Software, Tallahassee, Florida).

The results are summarized in Figure 1. The geometric mean PC₂₀ 6 hours after 2 puffs of ipratropium was 4.2 vs 2.0 mg/mL with placebo (*P* = .006). At 12 hours, these values were 2.7 and 2.4 mg/mL, respectively (*P* > .20) (Fig 1). On the active treatment, 6 of the 12 subjects had more than 1 doubling concentration increase in PC₂₀ compared with 0 of the 12 subjects at 12 hours.

Patients in whom asthma is suspected clinically may already be using short-acting bronchodilators, occasionally including ipratropium. It is important to withhold medications for an appropriate time. Our study indicates that there is bronchoprotection at 6 hours but none at 12 hours. Hence, we recommend that it is acceptable to perform an MCT 12 hours after the last dose of ipratropium, rather than the 24 hours after, as recommended in the American Thoracic Society guidelines.

The bronchodilator response to antimuscarinic drugs shows interindividual variability.⁵ This was evident in our study on the active treatment day: at 6 hours, when there was still bronchoprotection; the PC₂₀ increased by more than 1 doubling concentration in half the subjects. Similarly, the cholinergic component of bronchoconstriction varies in magnitude in different asthmatic patients.⁶ The placebo arm also demonstrated a statistically and clinically insignificant increase in the PC₂₀, which might be

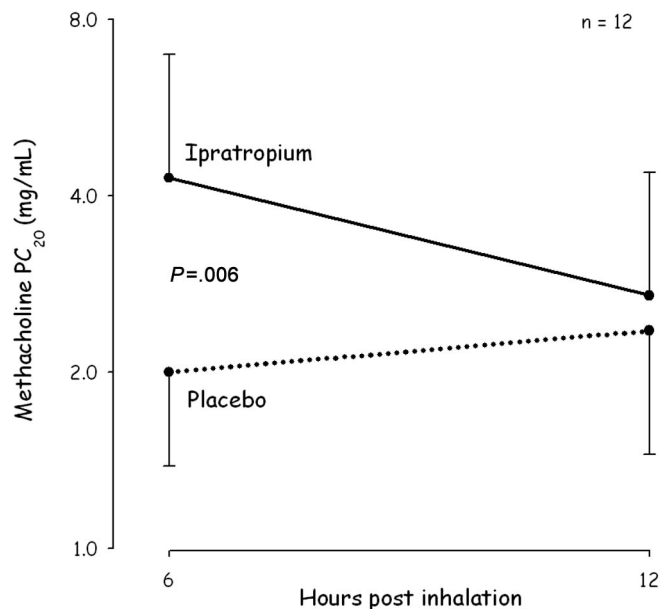


Figure 1. Geometric mean (SEM) provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC₂₀) after ipratropium and placebo administration.

explained by the diurnal variation in the bronchial tone and/or tolerance to methacholine.^{7,8}

In conclusion, these data show that a 12-hour withhold time for ipratropium metered-dose inhaler is adequate before performing a methacholine challenge.

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OCCUPATIONAL ASTHMA CAUSED BY ARTIFICIAL CYANOACRYLATE FINGERNAILS

Cyanoacrylates have been previously described as a causative agent of allergic contact dermatitis and occupational asthma (OA).^{1,2} However, cyanoacrylates contained in sculptured nails, which are becoming widely used in beauty saloons, have not been reported as a causative agent of OA to date.

We describe a 25-year-old nonsmoking woman who had worked for 7 years as a manicurist and cosmetologist. She had a history of allergic rhinoconjunctivitis and asthma due to pollen sensitization. She had applied artificial fingernails on the nail plate during the past 6 months. Shortly after applying the sculptured fingernails, she developed rhinoconjunctivitis and asthma symptoms, with worsening several hours later. According to the Material Safety Data Sheets, the only sensitizer contained in the products was cyanoacrylate in a fingernail adhesive gel (Diamond Rock Nails, Valencia, Spain). The patient did not use any respiratory personal protective equipment.

Results of skin prick tests to common environmental allergens (ALK-Abelló, Madrid, Spain) were positive to animal dander (dog and cat) and pollens (grass, *Olea europaea*, *Platanus acerifolia*, *Cupressus arizonica*, and *Plantago lanceolata*). Patch testing with European standard (T.R.U.E. Test; Mekos Laboratories AS, Hillerød, Denmark) and with metals and acrylates series (Chemotechnique Diagnostics, Vellinge, Sweden) produced positive results to nickel sulfate hexahydrate 1.0% aqueous, cadmium chloride 1.0% aqueous, and silver nitrate 1.0% aqueous. Findings from chest radiography were normal.

The total serum IgE concentration (Immulite, Los Angeles, California) was 271 kU/L. Specific IgE (ImmunoCAP; Phadia, Uppsala, Sweden) was positive to *Lolium perenne* pollen (61.80 kU/L), dog dander (0.90 kU/L), and cat dander (4.86 kU/L). Measurements of fractional exhaled nitric oxide (FeNO) were performed using a handheld analyzer (NIOX Mino; Aerocrine AB, Solna, Sweden).

Specific inhalation challenge (SIC) with cyanoacrylate was performed in a 7-m³ challenge chamber by handling the cyanoacrylate adhesive gel as previously described.^{1,2} As a control challenge test, a physiologic saline solution was used. The patient measured her lung function (forced expiratory volume in 1 second [FEV₁] and peak expiratory flow) for 24 hours after SIC using a portable, pocket-sized spirometer (Jaeger Asthma Monitor Software; Viasys Healthcare GmbH, Hoechberg, Germany).

At the first visit, the provocation concentration of methacholine that caused a decrease in FEV₁ of 20% (PC₂₀), measured after the tidal breathing method,³ was negative (PC₂₀ >16 mg/mL), and the FeNO value was increased (65 ppb). At that time, the patient was still at work, but she avoided direct exposure to sculpture nails. On visit 2, SIC with cyanoacrylate for 30 minutes elicited an isolated late asthmatic response. After 11 hours, she had a 23.7% decline in FEV₁ and experienced rhinorrhea and asthma symptoms that worsened progressively until she received short-acting β_2 -agonists (Fig 1). Twenty-four hours after cyanoacrylate SIC, an increase in FeNO concentration (100 ppb) was observed, and results of the methacholine inhalation test became positive (PC₂₀, 0.85 mg/mL).

The first cases of OA due to acrylates were reported by Lozewicz et al,⁴ who described that adequate ventilation and a relative humidity higher than 55% reduce the concentration of environmental acrylates. The widest series of OA due to acrylates were reported by

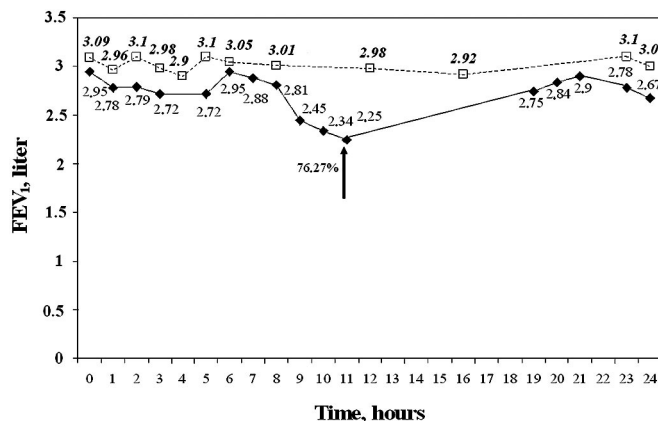


Figure 1. Forced expiratory volume in 1 second (FEV₁) after placebo (control) (□- -) and specific inhalation challenge to cyanoacrylate adhesive gel (◆- -). An isolated late asthmatic reaction was observed. Arrow indicates salbutamol inhalation (200 μ g).

Savonius et al⁵ and Piirilä et al.⁶ Jaakkola et al⁷ reported that the risk of adult-onset asthma, nasal symptoms, and other respiratory symptoms significantly increases with daily use of methacrylates in dental assistants' work. Sauni et al⁸ recently described the first 2 cases of OA caused by sculptured nails containing methacrylates. Both patients had a dual type of asthmatic reaction after a work simulation test, and 1 also had allergic contact dermatitis from exposure to methacrylates.⁸ In contrast, the present patient developed an isolated late asthmatic reaction, and results of patch testing with acrylates were negative. To our knowledge, this is the first case report of OA due to cyanoacrylates contained in sculptured fingernails, confirmed by means of SIC, significant changes in airway hyperresponsiveness to methacholine, and an increase in FeNO concentration.

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TOXIC EPIDERMAL NECROLYSIS INDUCED BY LEVOFLOXACIN

Toxic epidermal necrolysis (TEN) is a severe bullous dermatitis with a mortality rate of 30% to 35%.¹ Fluoroquinolones, especially ciprofloxacin, have been implicated in cases of TEN.^{2–7} However, there is little published information on levofloxacin-induced TEN.^{4,6,7} We report a fatal case of TEN induced by levofloxacin.

A 59-year-old woman with a history of endometrial carcinoma (stage III), type 2 diabetes mellitus, and allergy to streptomycin and penicillins was admitted to the oncology department with pyelonephritis. Treatment with levofloxacin, 500 mg/d, was started. On the ninth day of treatment, the patient developed generalized purpuric exanthema. Levofloxacin use was discontinued, and the exanthema improved spontaneously. Four days later, the patient was discharged from the hospital, in good health. Forty-eight hours after discharge, the patient visited the emergency department with urinary syndrome and fever (temperature, 39°C). During the interview with the patient, a possible allergy to quinolones was not acknowledged and treatment with levofloxacin was restarted. Six hours after the administration of the first dose, the purpuric exanthema reappeared; after 24 hours, it had extended to 40% of the total body surface and became painful. Progression to desquamation and formation of conjunctival and epidermal erosions were observed in the next 24 hours. A characteristically lateral displacement of the necrotic epidermis in response to slight pressure was confirmed (Nikolsky sign) (Fig 1). The skin and mucous lesions involved the chest, back, face, neck, hands, legs, mouth, eyes, ears, and vagina. The laboratory results revealed normal red and white blood cell counts with a slightly increased erythrocyte sedimentation rate of 18 mm/h. The level of total serum proteins was 5.5 g/L; glucose, 221 mg/dL; creatinine, 1.5 mg/dL; and urea, 69 mg/dL. Levels of total bilirubin, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase, potassium, and sodium were within normal limits.

The patient was transferred to the intensive care unit and treated as a severe burnt patient. Protection of the skin and denuded areas and replacement of fluids and electrolytes were begun immediately. The patient also received methylprednisolone, 1 mg/kg intravenously, for 2 days, with no improvement. Laboratory test results showed abnormal liver and kidney function, hyperglycemia, hypoalbuminuria, and hypopotassemia. Her fever continued, and *Pseudomonas aeruginosa* was isolated from the blood and urine cultures. Five days later, the patient died.

TEN and Stevens-Johnson syndrome are 2 forms of the same life-threatening process.¹ Characteristically, severe mucosal erosions with widespread erythematous cutaneous maculae are the main features of the disease. The cutaneous lesions often become confluent, with a positive Nikolsky sign and epidermal detachment. TEN is defined as an epidermal detachment of more than



Figure 1. Evidence of the Nikolsky sign in a 59-year-old woman with toxic epidermal necrolysis.

30% of the skin, and it has the highest mortality rate (range, 30%–35%). Stevens-Johnson syndrome–TEN is essentially a drug-induced disease. A few cases are related to infections, such as herpes simplex and mycoplasma; also, genetic susceptibility has been suggested.

Fluoroquinolones have seldom been implicated in TEN.^{2–7} Levofloxacin is effective against a number of gram-positive and gram-negative bacteria. Because of its broad spectrum of action, levofloxacin is empirically prescribed for a wide range of infections but there is little published information on levofloxacin-induced TEN.^{4,6} To our knowledge, there is only 1 report of a fatal outcome.⁷

The risk of death in patients with TEN can be accurately predicted by the TEN-specific severity-of-illness score.⁸ According to this scale, our patient had a final score of 6 and a mortality risk higher than 90%. Patients with TEN must be quickly referred to burn or intensive care units for supportive management and nutritional support (correction of electrolyte disturbances, administration of high-caloric enteral nutrition, and prevention of sepsis).

There are no randomized controlled trials of pharmacologic agents in the treatment of this disorder. Consequently, although case reports of a variety of therapeutic approaches have emerged, more research is needed to determine the real efficacy of any new treatment. These new agents include intravenous immunoglobulin, systemic corticosteroids, tumor necrosis factor α inhibitors, cyclosporine, cyclophosphamide, plasmapheresis, and hemodialysis.⁹

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