

time.<sup>10</sup> Long-standing asthma thus might be associated with less inflammation and mucus secretion. This remains speculative, however, because the relationship between the duration of asthma and the pathological features of airways remains unknown.

In conclusion, patients with asthma who have long-standing disease and lack a smoking history are less likely to produce induced sputum successfully. The characteristics of patients should be considered when analyzing the results of induced sputum studies, because potential selection bias may preclude the extrapolation of such results to patients with asthma in general.

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## The economic effect of the hydrofluoroalkane albuterol transition on children with asthma

To the Editor:

More than 6.5 million children in the United States have asthma, making it the most common chronic respiratory disease in children. Asthma is responsible for potentially life-threatening

acute episodes and is associated with significant morbidity and costs totaling approximately \$18 billion dollars in 2006.<sup>1</sup> For nearly 30 years, albuterol inhalation by metered dose inhaler (MDI) has been widely used for the management of acute asthmatic symptoms, allowing portable and immediate relief. Albuterol MDIs continue to be used frequently, with more than 52 million prescriptions for chlorofluorocarbon albuterol MDIs written in the United States annually.<sup>2,3</sup>

Within the next year, the medical community must comply with the federally mandated transition from use of chlorofluorocarbon propellant MDIs to newer, more environmentally friendly hydrofluoroalkane propellant-based MDIs.<sup>4</sup> The mandate affects the mainstay of immediate relief short acting  $\beta$ -agonists (SABAs) as well as long-term controller medications for asthma, including inhaled corticosteroids. The pharmacologic subtleties of the newer hydrofluoroalkane propellant medications have been considered by Hendeles et al.<sup>5</sup> In the near term, this transition will mark the end of availability of a true generic SABA in the US marketplace because of patent issues. Although there has been significant study by the US Food and Drug Administration regarding the initial cost effect for patients of the chlorofluorocarbon transition to hydrofluoroalkane,<sup>3</sup> there may be unforeseen results for children, especially those in low-income families, not fully considered.

Currently there are 2.3 million children diagnosed with asthma enrolled in federal programs such as Medicaid, State Children's Health Insurance Program, and other Title V programs.<sup>1</sup> The costs of asthma medications to the individuals enrolled is limited (or relatively low). Nevertheless, because of the lack of a generic SABAs, the cost of hydrofluoroalkane SABA medicines to federal programs is expected to increase significantly. Several states including Pennsylvania and Florida have appealed the Food and Drug Administration's decision to move forward with hydrofluoroalkane transition because of their calculated cost increases. In 2005, Florida Medicaid and Pennsylvania Medicaid were expected to have a projected increase of \$14 million (a 350% increase) and \$2 million (a 100% increase), respectively, to these already strained systems for the costs of hydrofluoroalkane albuterol alone.<sup>6</sup>

The Center for Medical Services has capped the maximum price that pharmaceutical companies can charge individual federal programs for hydrofluoroalkane MDIs at approximately 5% to 15% less than average wholesale price (AWP) for each participating state program.<sup>7</sup> Currently, generic medications have a limited cost plus a standard dispensation fee and administration fee budgeted for each program. For example, as of 2005 in the state of Michigan, AWP albuterol MDI (90  $\mu$ g/puff) was \$11 per inhaler, and Proventil hydrofluoroalkane (90  $\mu$ g/puff; Schering-Plough, Kenilworth, NJ), a typical cost of branded hydrofluoroalkane, AWP was \$39 per inhaler.<sup>8,9</sup> In 2007, the state of Michigan paid approximately 15% below AWP on all brand name medications under Center for Medical Services authority, resulting in an approximately \$20 difference in the cost of each MDI.<sup>8</sup> Nationally, assuming each child receiving federal support requires 3 albuterol MDIs annually, this represents a potential cost increase of \$150 to \$200 million annually for federal programs covering children and \$1.2 billion nationally for eligible patients with asthma of all ages.<sup>2,5</sup>

Although federal programs offer an insurance safety net for the most financially vulnerable, more than 650,000 children with asthma are uninsured. Many others participate in health plans with high deductible levels.<sup>1</sup> Costs will increase for anyone paying cash

and affect copayment for an MDI. Even modest increases in out-of-pocket costs can be a tremendous burden for some families. Some insurance companies and health care providers are addressing the problem by reducing copayments for these medications or providing free sample medications. However, these remedies are not universally practiced and may not be beneficial for a given family. Many families may not know the effect of changing health care plans and the subtleties of pharmaceutical drug coverage at the time of enrollment or even have a choice if employed by a small business. Pharmaceutical drug samples may not be fully available to all practitioners and ultimately rely on the industry to subsidize.

The economic effect of changes caused by the transition is not restricted to low-income families. For the 3.6 million children with asthma who are insured, most participate in pharmaceutical plans that have copay rates of \$5 to \$10 per generic drug prescription to encourage generic medication use. In the near future, there will be no generic option, and patients will be forced to carry branded product copayments reaching anywhere from \$20 to \$50 per prescription for tier 1 to 3 products. This can amount to a 200% to 400% increase in out-of-pocket costs for an insured individual per prescription. In addition, because of classification issues of the MDIs, a patient's copayment may in some cases approach the total cash cost for the MDI product alone. This situation offers little savings for a family either purchasing medications through an insurance company plan or paying out of pocket. With increased use of high deductible medical plans, families are often forced to pay for many medications out of pocket until the deductible is met, creating further financial burden. Although some insurance companies are beginning to modify copay policies, families must assume the cost burden in the meantime. Frequently, children need multiple MDI inhalers to have them available at school, on the athletic field, and at home. MDIs generally must be replaced yearly. These factors point to potential increases in family expenses in copays alone for a child by \$100 to \$200 per year, assuming no refills of hydrofluoroalkane MDIs are needed. Unintended outcomes of the transition could include less availability of valuable medicines and/or use of less effective or convenient alternatives—for example, nebulized SABA delivery. Use of less than optimum therapies has been shown to affect urgent health care use and morbidity.<sup>10</sup>

Of course, the positive results of the hydrofluoroalkane transition for the environment are thought to be important. Further, the possibility of an increase in out-of-pocket costs of SABAs for families may encourage their more consistent use controller medications. However, patients may choose to use their limited financial resources to purchase immediate rescue medications at the expense of controller medications. Health care providers may have an additional argument when counseling patients that long-term controller use is a cost-effective approach to disease control. However, the lack of affordable rescue medicine potentially leading to the need for more urgent and costly care may detract from such an argument.

The transition from chlorofluorocarbon-based medication to hydrofluoroalkane propellant technology has been protracted and not entirely easy to accomplish. The leaders of the change are to be commended. However at this junction, it appears that gaps in practices of both the health care system and pharmaceutical industry may leave children with asthma stranded in ways not anticipated. Federal and private insurance systems should take steps to reduce the costs of hydrofluoroalkane medications for

vulnerable families to prevent the negative consequences of forced noncompliance or use of less effective therapies.

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## Recall antigen reactions in patients with atopic dermatitis treated with tacrolimus ointment for 1 year

### To the Editor:

Tacrolimus is an immunosuppressive drug that acts by inhibiting early T-cell activation. Topical treatment, indicated for atopic dermatitis (AD), is associated with systemic tacrolimus levels of only 3% to 4% of those seen in patients with systemic immunosuppression after organ transplantation.

Skin tests with recall antigens are an indirect measure of delayed-type hypersensitivity. Patients with active AD have impaired reactions compared with the normal population.<sup>1</sup> Apparently normal patients with multiple skin cancers also have impaired cell-mediated immunity.<sup>2</sup>

We studied the effect of 1-year topical tacrolimus treatment on T-cell reactions of the skin in patients with AD. Further impaired recall antigen test reactions could indicate an increased skin cancer or lymphoma risk.

A total of 48 adult patients (aged  $\geq 16$  years) with moderate-to-severe AD according to the Rajka and Langeland criteria were treated with 0.1% tacrolimus ointment in a 1-year, open-label, prospective clinical trial. Patients applied tacrolimus ointment twice daily to all areas affected by AD. Patients were instructed to apply ointment for 1 week after cessation of itch and to select new areas for treatment on the basis of the presence of itch. Other treatments for AD, except nonmedicated emollients, were not permitted during the study. The washout period for topical