Inhaled Corticosteroids for Young Children with Wheezing
Diane R. Gold, M.D., M.P.H., and Anne L. Fuhlbrigge, M.D.

In the Childhood Asthma Management Program study of school-aged children with established mild-to-moderate persistent asthma, twice-daily therapy with inhaled corticosteroids controlled symptoms of asthma but slightly reduced height growth and did not improve lung growth or affect the natural course of the disease. In this issue of the Journal, two studies involving young children test the hypothesis that the natural history of wheezing in early life may be altered by the administration of continuous or intermittent doses of inhaled corticosteroids when symptoms first occur but when the diagnosis of asthma is still uncertain. Both groups of authors conclude that inhaled corticosteroids do not alter the natural history of the disease and that the risk of wheezing will persist beyond the first years of life.

As described by Guilbert et al., among children who were two or three years of age at study entry, twice-daily administration of inhaled corticosteroids for two years, as compared with placebo, controlled symptoms but had an effect only during the treatment period, with no carryover effect after the drug was stopped (during the third study year). In contrast, as reported by Bisgaard et al., the use of short courses of inhaled corticosteroids only after the onset of symptoms did not reduce the development of further symptoms in infants and toddlers.

The study by Guilbert et al. strengthens the evidence that treatment with inhaled corticosteroids in early life does not alter the natural history of asthma. However, the study provides an imperfect link to the Childhood Asthma Management Program study of older children with asthma, in that it lacks information on the effects of corticosteroids on the growth of lung function and airway responsiveness, which are important phenotypic characteristics related to asthma. Nevertheless, although many of the young children studied by Guilbert et al. had difficulty performing spirometric tests, the investigators documented that airway resistance measured by oscillometry was improved during treatment but not during the subsequent observation period.

Thus, the study by Guilbert et al. offers strong evidence supporting the use of twice-daily inhaled corticosteroids for symptomatic control in a select subgroup of children who are at high risk for asthma with an established history of four or more wheezing episodes in the first two to three years of life, as well as additional risk factors for the persistence of wheezing. These factors include a family history of asthma, atopic dermatitis or allergy (particularly allergy to inhalants), and eosinophilia. The selectivity of the study by Guilbert et al. contrasts with the inclusiveness of that by Bisgaard et al., which enrolled infants with a maternal history of asthma after only one episode of wheezing. A weakness of the study by Bisgaard et al. is heterogeneity in the level of symptoms in the population, as well as variability in the quality of documentation of symptoms and episodes of wheezing. This variability, combined with the limited population size, may have resulted in insufficient power to distinguish a subgroup of children who had a response to treatment, defined either according to age or according to the frequency of previous episodes. The potential for symptomatic relief may also have been reduced by the initiation of treatment with inhaled corticosteroids three days after the onset of symptoms.

The study by Bisgaard et al. does not provide adequate evidence to justify disregarding the cur-
rent guidelines of the National Asthma Education and Prevention Program for the use of corticosteroid therapy in young children. In recognition of the fact that the diagnosis of asthma is difficult in very young children, the guidelines suggest that among high-risk children who are five years of age or younger, a diagnostic trial of inhaled bronchodilators and antiinflammatory medications may be helpful, with careful monitoring of the response to therapy. Since risk is partly defined by recurrence or the persistence of symptoms over time, the level of risk is usually uncertain before the age of two years.

The use of inhaled corticosteroids for infants with a first episode of wheezing is still controversial, given the heterogeneity of both the causes of wheezing and the response to therapy in this age group (Fig. 1). After the neonatal period, clinicians tend to use intermittent therapy with inhaled corticosteroids for wheezing in children with established bronchopulmonary dysplasia, though studies evaluating the efficacy of treatment are few. Normally, the lungs of young children have relatively thick airway walls and are relatively compliant. Infants with wheezing who have small or collapsible airways are more likely to outgrow their symptoms and may be less likely to respond to corticosteroids than are those who have incipient chronic airway inflammation. Some virally induced inflammation in infants may also be resistant to therapy with inhaled corticosteroids. Whereas rhinovirus is probably the dominant virus inciting mild wheezing in susceptible infants, respiratory syncytial virus has been documented as the predominant virus among patients who visit emergency rooms because of wheezing. Wheezing that is induced by respiratory syncytial virus — which involves the obstruction of airways with desquamated airway epithelial cells, polymorphonuclear cells, and lymphocytes — is generally unresponsive to corticosteroid treatment, even for infants in whom asthma will ultimately develop. "Respiratory support, oxygen, and time" are the mainstays of treatment for severe bronchiolitis.

Persistent environmental exposures (e.g., smoking in the household and exposure to cockroach allergens) and genetic factors may also reduce the responsiveness to corticosteroids in infancy. A substantial proportion of children in the study by Bisgaard et al. were exposed to maternal smoking during pregnancy and environmental tobacco smoke in the home. Exposure to tobacco smoke in utero is known to alter the growth of fetal air-
ways and lungs, which increases both airway resistance in infants and the risk of wheezing in early life.12,13 Much of this effect may occur early in gestation, when the number and structure of airways are determined.6 The effects of in utero tobacco exposure on lung architecture and the effects of postnatal exposure to environmental tobacco smoke on long-term inflammation may make children relatively resistant to intermittent treatment with corticosteroids for wheezing.

It is difficult to identify a subgroup of toddlers under the age of two years whose symptoms will respond to inhaled corticosteroids; it is also difficult to measure physiological responses, such as lung function, and effects on somatic growth (other than on height) in very young children. The long-term use of inhaled corticosteroids in early life may have adverse effects not only on height growth but also on alveolar growth, which, in contrast to airway development, occurs in the last months of gestation and the first few years of life.6,14

These two clinical studies add to the evidence that although inhaled corticosteroids may control persistent or severe wheezing, such drugs should not be used in the hope of altering the course of asthma in childhood. Given the potential risks of therapy in early life, prolonged treatment for toddlers under the age of two years should be highly selective. While we await better criteria for the selection of young children who are likely to respond to therapy, there is no substitute for clinical judgment in deciding whether and for how long to use corticosteroids in very young children.

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Influence of Graft Characteristics on the Outcome of Kidney Transplantation

Jean-Paul Soulillou, M.D., and Magali Giral, M.D.

The characteristics of renal allografts before transplantation present a multifaceted puzzle that in large part predetermines the outcome of kidney transplantation. Compatibility at the major-histocompatibility-complex (MHC) loci, the age of the donor, cold-ischemia times, and nephron mass1-2 all contribute to long-term results through interacting effects involving initial damage to parenchymal or vascular cells and possible hyperfiltration. Many factors are involved in chronic allograft dysfunction, in which immune-mediated lesions caused by chronic rejection are only one component.3

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