Factors that affect the efficacy of inhaled corticosteroids for infants and young children

Israel Amirav, MD,[a] Michael T. Newhouse, MD, MSc, FRCP(C),[b] Stefan Minocchieri, MD,[c] Jose A. Castro-Rodriguez, MD, PhD,[d] and Karen G. Schüepp, MD[e] *Haifa, Israel, Hamilton, Ontario, Canada, Subiaco, Australia, Santiago, Chile, and Bern, Switzerland*

Infants (0–1 years of age) and young children (1–3 years of age) are a unique subpopulation with regard to inhaled therapies. There are various anatomic, physiological, and emotional factors peculiar to this age group that present significant difficulties and challenges for aerosol delivery. Most studies of therapeutic aerosols that have been performed with patients of this age group, particularly recent studies with inhaled corticosteroids (ICSs), administered aerosols with relatively large particles (ie, >3 μm in mass median aerodynamic diameter). These drugs were designed for use in adults and older children and were administered with masks, which are frequently rejected by patients. Based on these studies, it was recently suggested that ICSs might not be as therapeutically effective in infants and young children as in adults. We review the reasons that large-particle corticosteroid aerosols are not likely to be effective in infants and young children. This patient population differs from adults in airway anatomy and physiology, as well as in behavior and adherence to therapy. We suggest that the benefit of ICSs in this age group requires further evaluation to determine whether better therapeutic outcomes might be achieved with smaller particles. (J Allergy Clin Immunol 2010;125:1206-11.)

Key words: *Small-particle aerosols, asthma, infants, nebulizers, inhalers, corticosteroids, aerosol delivery devices, adherence*

Inhaled corticosteroids (ICSs) are the cornerstone of asthma therapy. However, there are concerns that ICSs are not as effective in infants and young children as they are in adults.[1] There are crucial differences between infants and young children compared with older children and adults, particularly with respect to the optimal device-drug combination during ICS therapy. These differences might require significant changes in current recommendations for ICS therapy for the youngest age groups. Optimal inhaled therapy should not only be made infant friendly to overcome behavioral problems, but also particle size should be optimized for delivery to the central or peripheral airways, depending on the site of the disease. Infants are not small adults; they have unique behavioral aspects that require a different therapeutic approach than adults, particularly with respect to airway-targeted inhaled therapy. This review discusses aerosol particle-size recommendations for infants and young children and the potential effects of administering aerosols that contain smaller particles (mass median aerodynamic diameter [MMAD] of <3 μm) to infants based on their airway anatomy and physiology. We review the *in vitro* and *in vivo* evidence that smaller aerosol particles might be more appropriate for treating infants and young children regardless of their disease. Based on current information and given the potential for improved therapy of very young children with asthma, we suggest that the current recommendations for ICS therapy be reconsidered for the youngest age groups.

Abbreviations used
BDP: Beclomethasone dipropionate
CFC: Chlorofluorocarbon
HFA: Hydrofluoroalkane 134a
ICS: Inhaled corticosteroid
LRT: Lower respiratory tract
MDI: Metered-dose inhaler
MMAD: Mass median aerodynamic diameter
URT: Upper respiratory tract
VHC: Valved holding chamber

ANATOMY AND PHYSIOLOGY

The upper airways of infants are quite different from those of adults (Fig 1). The infant larynx is situated much higher in the upper respiratory tract (URT), close to the base of the tongue, and the epiglottis, which is relatively narrow and floppy, is located closer to the palate. The infant pharynx and supraglottic tissues are less rigid than those of adults and thus more susceptible to collapse and obstruction of the URT, particularly during inspiration. These anatomic differences could partially explain the infant preference for nose breathing and the difficulty of delivery of therapeutic aerosols to the lower respiratory tract (LRT).[2]

Delivery of aerosol to the lungs through the nose has been shown to be less effective than delivery through the mouth.[3] This is probably because of the resistance, high flow velocity, and the resulting increased turbulence in the nose and nasopharynx.[4] Mathematic models indicate that under conditions of tidal breathing, the infant nose might be more efficient at excluding foreign particulates from the airways than that of the adult.[2] Thus the infant nose is an effective aerodynamic filter, not only of potentially

From [a]the Pediatric Department, Ziv Medical Center, Safed, Faculty of Medicine, Technion, Haifa; [b]the Firestone Institute of Respiratory Health, St Joseph's Hospital, McMaster University, Hamilton; [c]the School of Paediatrics and Child Health, University of Western Australia, Princess Margaret Hospital for Children, Subiaco; [d]the School of Medicine, Pontificia Universidad Catolica de Chile, Santiago; and [e]the Swiss Paediatric Respiratory Research Group, Department of Respiratory Medicine, University Children's Hospital, Bern.

S. Minocchieri has been supported by a personal grant (PBZHP3-123293) from Swiss National Science Research Foundation.

Disclosure of potential conflict of interest: M. T. Newhouse is a shareholder of Pfizer. S. Minocchieri and K. G. Schüepp have received research support from the Swiss National Science Foundation. The rest of the authors have declared that they have no conflict of interest.

Received for publication October 8, 2009; revised January 13, 2010; accepted for publication January 14, 2010.

Available online March 25, 2010.

Reprint requests: Israel Amirav, MD, Pediatric Department, Ziv Medical Center, Safed, Faculty of Medicine, Technion, Haifa 12000, Israel. E-mail: amirav@012.net.il.

0091-6749/$36.00

doi:10.1016/j.jaci.2010.01.034

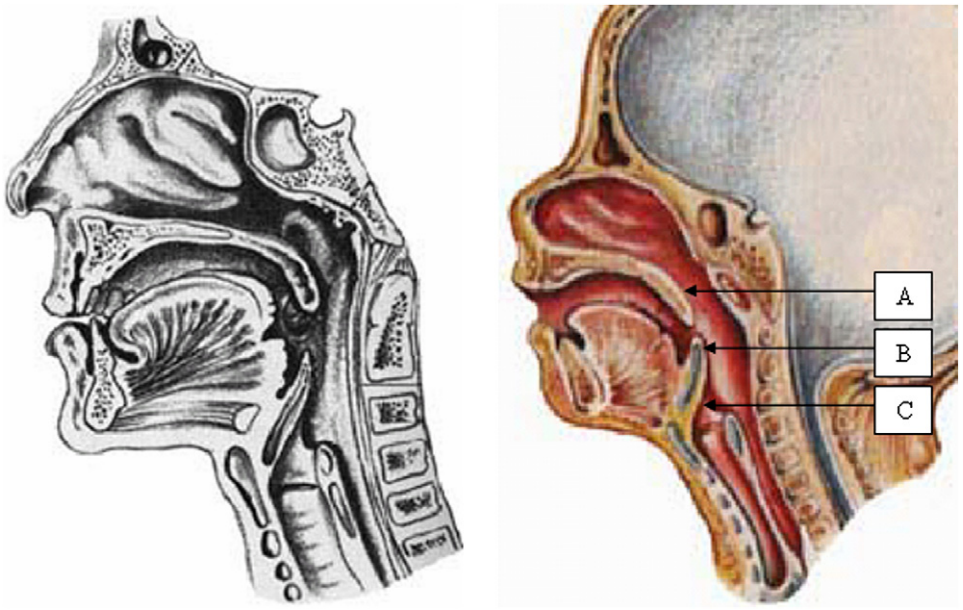

FIG 1. The upper airway of adults *(left)* compared with that of infants *(right)*: *A*, pharynx and supraglottic—less rigid; *B*, epiglottis—narrow, floppy, and closer to the palate; *C*, larynx—higher and very close to the base of the tongue.

noxious particles but also of therapeutic aerosols. Therefore it is not surprising that if the URT aerodynamic filter is bypassed by aerosol inhalation through the mouth, delivery of medication to the lungs is 2- to 3-fold greater.[3] Until approximately 18 months of age, infants are virtually obligatory nose breathers, decreasing aerosol delivery to their LRT. Furthermore, aerosol deposition and distribution in the LRT are also influenced by age-dependant characteristics of airway anatomy because the airway caliber is considerably smaller in infants and young children than in older children and adults.[5] This factor is particularly important in diseases characterized by airflow obstruction because airway resistance is inversely proportional to the fourth power of the radius: according to Poiseuille's law, $R = 8l\eta r^4$, where l is defined as the length of the tube, η is defined as gas viscosity, and r is defined as the radius of the tube. Thus if the radius of an airway is reduced by 50% (eg, by edema or secretions), resistance will increase by a factor of 16. As a consequence, factors that limit ventilation and thereby delivery of peripheral airway aerosols may be magnified in infants compared with older children and adults.

LUNG DEPOSITION

Drug deposition within the respiratory system is determined by impaction and sedimentation. High inspiratory airflow promotes impaction of particles in the URT, particularly for larger particles (ie, MMADs of 3–5 μm).[6] The smaller the particle mass and the lower the inspiratory flow velocity, the greater the probability that impaction will not occur; rather, particles bypass the URT and deposit throughout the LRT (mainly by means of impaction in the first 6–10 bronchial divisions and sedimentation distal to these). Smaller particles deposit by sedimentation within the LRT airways more slowly than large particles. This process is greatly facilitated by breath holding to prolong particle residence in the airways. Infants are unable to hold their breath, and therefore a greater proportion of the inhaled medication is likely to be exhaled.

TABLE I. Lung deposition of aerosol therapeutics with large particles (MMADs of 3-4 μm) given to infants and young children with different disorders

Reference	Disease	Mean age (mo)	No.	Lung deposition (%)
Chua et al,[3] 1994	CF	9	12	1.3
Mallol et al,[7] 1996	CF	12	5	2.0
Fok et al,[8] 1996	BPD	3	13	1.7
Wildhaber et al,[10] 1999	Asthma	33	8	5.4
Amirav et al,[9] 2002	Bronchiolitis	8	12	1.5

BPD, Bronchopulmonary dysplasia; *CF*, cystic fibrosis.

Aerosol deposition is commonly quantified by using particles that have been labeled with radioactive agents (eg, 99m technetium). Although the risk of this procedure is extremely small, obvious ethical concerns have limited its use in studies of pediatric patients. However, there have been few studies of pulmonary aerosol deposition in infants and young children; all have produced similar results, regardless of the drug used or the disease of the patients (Table I).[3,7-10] In a study of 5 infants with cystic fibrosis, Mallol et al[7] found that lung deposition was 2.0% ± 0.7% of the nebulized dose. Chua et al[3] found lung deposition to be a median of 1.3% (range, 0.3% to 1.6%) in 12 infants with cystic fibrosis, and Fok et al[8] reported lung deposition of 1.74% ± 0.21% (mean ± SEM) in 13 infants with bronchopulmonary dysplasia.

A deposition study in infants with acute bronchiolitis produced results that were similar to those reported in infants with other obstructive airway diseases, even though the latter were in clinically stable condition.[9] Not only was total lung deposition similar between studies, so was regional distribution of radiolabeled aerosol within the lung, with a marked predominance of central airway deposition. By contrast, in healthy adults the distribution of aerosol is more uniform because of greater aerosol penetration into the peripheral airways. In healthy infants the