

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

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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, $>3\ \mu\text{m}$ 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;■■■:■■■-■■■.)

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

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

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 $<3\ \mu\text{m}$) 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.

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

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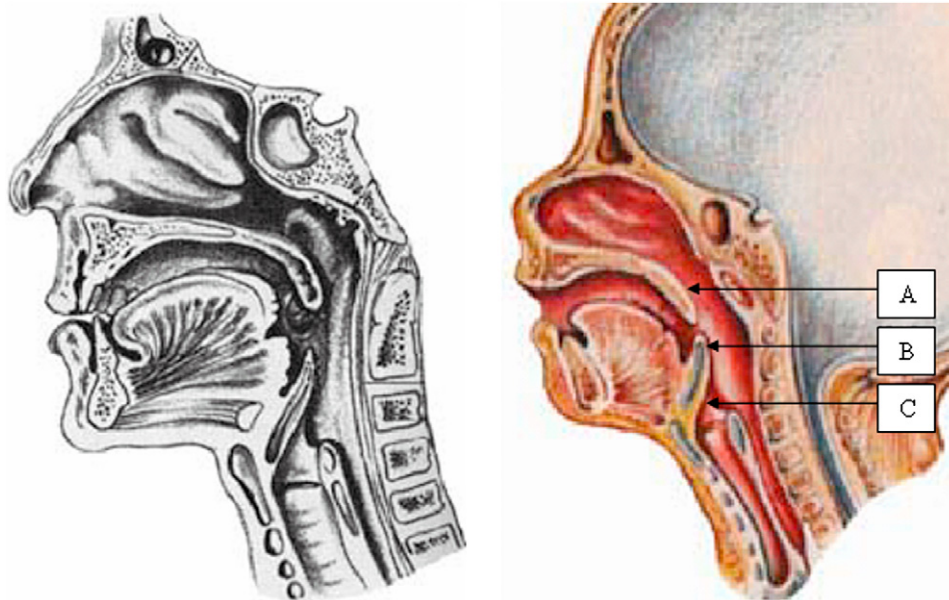


FIG 1. The upper airway of adults (*left*) compared with that of infants (*right*): A, pharynx and supraglottic—less rigid; B, epiglottis—narrow, floppy, and closer to the palate; C, larynx—higher and very close to the base of the tongue.

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 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

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.

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.

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 al⁷ found that lung deposition was $2.0\% \pm 0.7\%$ of the nebulized dose. Chua et al³ 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 al⁸ reported lung deposition of $1.74\% \pm 0.21\%$ (mean $\pm$ 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 trend to increased peripheral deposition starts as early as 2.5 years of age.¹⁰

All of these studies used conventional aerosols, which have relatively large particles (MMAD of $>3\ \mu\text{m}$). The observations indicate that the major patient-related factors that determine, limit, or both LRT aerosol deposition are LRT anatomy and physiopathology rather than specific diseases. Therefore when mucosal edema, secretions, and bronchospasm occur in infants, from whatever cause, their anatomically narrower airways greatly limit airflow. The high rate of respiration associated with respiratory diseases could further reduce aerosol delivery to the lungs. This is particularly relevant to the youngest patients, such as preterm infants and those with chronic lung disease. For this age group, aerosol particles should be small enough to bypass the upper and central LRT airways with minimal inertial impaction. On the other hand, because small extrafine particles ($<1\text{--}2\ \mu\text{m}$) are deposited mainly by means of sedimentation and because this process is time dependent, the respiratory rate is very important. Preterm and very young infants have high rates of respiration, and therefore the residence time of particles in the LRT is reduced. Therefore the aerodynamic particle size should be small enough to bypass the URT but large enough to provide relatively efficient lung deposition during the short residence time in the respiratory tract; this would minimize loss of the therapeutic aerosol on exhalation. Particle size is thus very important from both anatomic and physiological perspectives.

BEHAVIOR AND ADHERENCE

The most important determinants of the total aerosol dose delivered to the lungs of infants and young children are their behavior during administration and caregiver adherence. Appropriate administration of the daily dose prescribed, the fit of the face mask, squirming and crying during aerosol administration, and general acceptance of treatment are crucial, real-life factors for consideration.

Only anecdotal information is available about the relationship between infant behavior and lung deposition during aerosol administration (Table II).¹⁰⁻¹⁴ Tal et al¹¹ reported that lung deposition of metered-dose inhaler (MDI)-generated aerosol from an AeroChamber with Mask (TMI International, Inc, London, Ontario, Canada), as measured scintigraphically, was reduced 6-fold in 2 crying infants compared with that seen when they breathed quietly (0.3% vs 2.0%). Murakami et al¹² reported that in crying infants receiving therapy through a nebulizer and a face mask, lung deposition was negligible compared with that seen when they breathed quietly. Furthermore, Iles et al¹³ reported a 4-fold reduction in lung deposition in crying infants. Wildhaber et al¹⁰ described one crying child whose lung aerosol deposition was markedly reduced compared with that of 16 non-crying children. In addition, there was a 7-fold increase in the ratio of gastrointestinal to lung deposition in the crying infants. We showed a relationship between infants' agitation in response to application of the mask and deposition of inhaled radiolabeled aerosol in the mouth and oropharynx; the aerosol was subsequently swallowed and detected in the gastrointestinal tract. The greater the level of infant distress, the greater the amount

TABLE II. Relationship between behavior and lung deposition in infants

Reference	Mean age (mo)	Deposition during crying (%)	Deposition without crying (%)
Tal et al, ¹¹ 1996	15	0.3	2.0
Murakami et al, ¹² 1990	0-24	Negligible	?
Wildhaber et al, ¹⁰ 1999	24	1.3	5.4
Iles et al, ¹³ 1999	13	0.1*	0.4*
Amirav et al, ¹⁴ 2003	8	High URT:GIT	Low URT:GIT

GIT, Gastrointestinal tract.

*By means of urinalysis.

of extrathoracic deposition.^{14,15} Therefore infant behavior can not only reduce LRT but also increase URT and gastrointestinal deposition.

FACE-MASK SEAL AND DESIGN

MDIs are commonly used with valved holding chambers (VHCs) to overcome coordination difficulties in young children. VHCs extend the distance between the actuator and the mouth and allow the larger aerosol particles that have little or no therapeutic benefit to decelerate and deposit in the spacer; this reduces ballistic and inertial impaction of particles in the URT. The VHC provides a reservoir of the aerosol for inhalation and removes the need to coordinate the actuation of the inhaler with inspiration. VHCs are not generic devices, and there are differences in performance among different VHCs.¹⁶ In infants and young children who cannot reliably breathe through a mouthpiece, the face mask serves as the interface between the patient and the VHC. The seal between the mask and the face is a critical factor in ICS delivery in that age group.¹⁷ A good seal of the mask around the nose and mouth will ensure that inspiration takes place from the VHC and not from the environment. The seal between the mask and the infant's face also depends on face-mask design.¹⁸ More than 10 years ago, Everard et al¹⁹ showed that with a small-volume jet nebulizer, even a 1-cm gap between the mask and the face reduced the dose delivered to the respiratory tract by 50%. A good seal has been repeatedly shown to be required for efficient aerosol delivery to the LRT.^{17,18}

Drug delivery can be improved by use of a round face mask with a flexible rim.¹⁸ Sangwan et al²⁰ correctly called attention to different effects of design on nebulizers compared with VHCs. When therapy is delivered through a VHC, the seal is critical for adequate dose inhalation, whereas with a nebulizer mask, the seal is less critical because the nebulizer flow usually exceeds the minute ventilation. However, leakage can result in unwanted deposition of the drug on the face and in the eyes. Sangwan et al showed that all face masks leaked nebulized aerosol, resulting in significant facial and eye deposition. However, when aerosols of large (MMADs of $3\text{--}4\ \mu\text{m}$) and small (MMADs of $1\text{--}2\ \mu\text{m}$) particles were compared, the smaller MMAD caused less facial deposition. It is important to remember that children younger than 4 years can only inhale aerosol medications by means of tidal breathing and require a face mask, whereas older children can use a mouthpiece reliably. Therefore the only way to deliver therapeutic aerosols to the younger children is to apply a mask with an adequately tight seal using the least possible force. The tidal volume of infants is small, and therefore the dead space of masks is also a major factor in aerosol delivery; mask design should ensure a minimal amount of dead space.

TABLE III. Lung deposition in infants and young children by using small particles

Reference	Disease	Mean age (mo)	No.	Findings
Janssens et al, ²⁴ 2003	<i>In vitro</i>	NA	NA	MDI: Small particles lung dose > large particles independently of Vt
Janssens et al, ¹⁶ 2004	<i>In vitro</i>	NA	NA	MDI: Small particles lung dose > large particles, independently of Vt
Schüeppe et al, ²⁵ 2005	<i>In vitro</i>	NA	NA	Optimal particle size <2.4 μ m
Mallol et al, ⁷ 1996	CF	12	5	Deposition of nebulized small particles > large particles
Schüeppe et al, ²⁶ 2004	Wheezy infants	34	6	Deposition of nebulized small particles > large particles
Köhler et al, ²⁷ 2008	Preterm infants	Preterm	17	Highest lung deposition with nebulized small particles
Schüeppe et al, ¹⁵ 2009	Asthma	20	10	Nebulized: Small particles increased lung deposition and reduced oropharyngeal deposition

CF, Cystic fibrosis; NA, not applicable; Vt, tidal volume.

CRYING

Thirty-eight percent to 50% of infants and young children cry when a face mask is applied.²¹ In the past, crying was believed to have no detrimental effect or even to improve aerosol delivery to the lungs of children because of their deep inspiratory breaths at the end of the cry. In fact, crying is a very long exhalation followed by several rapid, brief, relatively high flow velocity inhalations. During these rapid inhalations, inertial impaction makes it more likely that aerosol will be deposited mainly in the URT, with little medicine reaching the LRT. This effect was demonstrated in adults and was especially marked when patients received aerosols with large particles (MMAD of 6 μ m) but was progressively less pronounced as the particle size decreased to MMADs of 3 μ m or 1.5 μ m. In delivering large-particle aerosols of MMAD 6- μ m, the effect of inspiratory flow velocity was shown to be extremely important. Clark et al²² achieved high (40%) deposition of 200-mL aerosol boluses in the peripheral lung zones of patients who started to inhale slowly from functional residual capacity (resting end expiration) to total lung capacity at 8 L/min for the initial 3 seconds. This low flow helped to bypass the URT and normally high flow velocity central airways (anatomic and physiological dead space) and was then followed by inhaling at about 30 L/min to total lung capacity.

Crying affects not only the breathing patterns of infants but also the adequacy of the seal between the mask and face. The main reasons for crying likely include fear and the increasing pressure applied by frustrated caregivers who try to achieve a tight mask fit while preventing infants from squirming. Infants predictably become angry and frightened; the most common causes of poor mask seal are crying and distress associated with the force required for administration of aerosol therapy.²³ Therefore in contrast to previous assumptions, crying is detrimental to effective aerosol therapy; all possible measures should be undertaken to minimize or eliminate crying during aerosol administration. Low levels of lung deposition are expected in upset crying children or when the mask seal is poor because of design or inadequately trained caregivers. All of these behavioral challenges are amplified in infants and young children receiving conventional suspension aerosols (particle MMADs of 3–4 μ m).

ARE SMALLER PARTICLES BETTER?

Assuming adequate aerosol administration to a noncrying baby with a well-fitting mask and an efficient aerosol generator, the dose of ICS that reaches the bronchiolar region of infants is probably limited by their small airway caliber and the short residence time of therapeutic aerosols in the airways. This is particularly so when pediatric patients receive the aerodynamically large aerosol

particles that are generated by most small-volume jet nebulizers and some MDIs. Aerodynamic size is proportional to the cubed value of the droplet diameter. Therefore a typical jet nebulizer-generated aerosol with particles of 3 to 4 μ m in MMAD behaves, aerodynamically, like one with particles that are 27 to 64 times larger than those of an identically formulated aerosol with particles of MMAD 1 μ m. As a result, small particles (MMADs of 1–2 μ m) are likely to be deposited more uniformly throughout the LRT than larger particles. Small particles are less likely than large particles to be influenced by impaction in the URT and the first few bronchial divisions, and because of their long residence time in the airways, they deposit mainly by means of sedimentation. The sedimentation rate of small particle aerosols is slow; in normal adults small particles are exhaled at a rate that is approximately 6-fold greater than that of larger particles, even after a 10-second breath hold. The differences might be similar or even larger during tidal breathing in infants, but there do not appear to be any studies of this in infants or young children. Aerosols with small particles appear to result not only in less URT and more lung deposition but more peripheral deposition in the lungs than larger particles. In young children with small airways narrowed by edema and the hypersecretion associated with inflammatory airway diseases, small particle size is necessary for efficient aerosol. Aerosol particle size is even more important when considering the obligate nasal breathing and relatively high inspiratory airflow of infants.

Several *in vitro* and *in vivo* studies indicated that small particles might be more beneficial than larger particles for infants and young children. Administration of small-particle aerosols could allow the dose to be reduced and adverse effects may thus be minimized (Table III).^{7,15,16,24–27} Using an anatomically correct model of the infant upper airway, Janssens et al^{16,24} showed that a 4-fold greater lung deposition of hydrofluoroalkane 134a (HFA)–pressurized MDI solution aerosols (MMAD of 1.1 μ m) was delivered compared with that seen after use of larger particles of chlorofluorocarbon (CFC) MDIs (MMADs of 3–4 μ m). The same studies also demonstrated that tidal volume did not affect small-particle deposition, whereas it does affect large particle deposition. In another *in vitro* study, Schüeppe et al²⁵ demonstrated that the optimal MMAD of nebulized aerosols is less than 2.4 μ m, a smaller particle size than that generated by most available, small-volume jet nebulizers and suspension HFA MDIs. These findings are particularly important for the design of aerosol therapies for infants and young children because the normal respiratory rate in this age group is relatively high and can be higher in children with respiratory disease.

Four studies used *in vivo* techniques to evaluate small-particle delivery to infants and young children. Mallol et al⁷ demonstrated

that particles of MMAD 3.6 μm had greater deposition in the LRT than those with 7.7- μm particles. Schüepp et al²⁶ showed that lung deposition improved by 36% to 38% when patients were given aerosols of MMAD 2.5 μm compared with 5% to 8% improvement when they received nebulized particles of MMAD 4.2 μm . Higher levels of lung deposition were achieved in pre-term infants receiving nebulized particles that were less than 2 μm in MMAD.²⁷ Recently, Schüepp et al¹⁵ demonstrated that even in children who are crying, smaller ICS particles were able to reach the peripheral airways; they observed up to 20% total lung deposition and greatly reduced oropharyngeal deposition. These data indicate that small particles have 10-fold greater therapeutic potential than large particles.

Some studies of small-particle aerosols have included older children. A study by Geller et al²⁸ compared the effects of nebulized small (MMAD of 2.1 μm) and large (MMAD of 4.9 μm) particles in adolescents and reported a trend toward greater improvements in pulmonary function among the patients receiving the small particles. Agertoft et al²⁹ showed that lung deposition was 3-fold greater and systemic bioavailability increased in children with asthma receiving an HFA-beclomethasone dipropionate (BDP) solution aerosol of 1.1 μm in MMAD (using an HFA-pressurized QVAR Autohaler, 3M, UK) compared with those receiving CFC-BDP of approximately 2 to 3 μm in MMAD through a Volumatic (GSK, UK) large-volume VHC. Devadason et al³⁰ scintigraphically measured lung deposition and showed a greater (36.9%) deposition in children receiving HFA-BDP with small particles (MMADs of 1.1 μm) compared with larger particles; they also observed increased oropharyngeal deposition with decreasing age. Roller et al³¹ demonstrated high levels of lung deposition in children receiving HFA-BDP with small particles (MMADs of 1.1 μm) through a VHC. Their data demonstrated that the VHC decreased oropharyngeal and gastrointestinal deposition compared with the results of a previous pediatric study that used the same formulation delivered through breath-actuated MDI without a VHC.³⁰

Large-particle aerosols may be associated with systemic side effects, such as reduced gains in height and weight among preschool children.³² Because of their increased lung deposition, aerosols with smaller particles might have even more systemic side effects. These safety concerns were addressed in 2 major studies, which found that HFA-BDP with small particles had no effect on growth compared with CFC-BDP with conventional particles or ciclesonide compared with placebo.^{33,34} The reason that aerosols with smaller particle sizes did not have the same side effects as those with larger particles might be that small-particle aerosols can control asthma with half the dose of the much larger MMAD 3-4 μm suspension aerosols. Whereas delivery of smaller particles results in greater lung deposition, it might also reduce systemic absorption from the URT and gastrointestinal tract and decrease adverse effects. Further studies, including those that include larger numbers of patients, are required to evaluate these possibilities, particularly among infants and young children.

SUMMARY

Data obtained from studies of adults should not be extrapolated to children without careful consideration, particularly to infants and children less than 3 to 4 years of age. Infants and young children have narrower URT and LRT airways and a greater inspiratory flow velocity, resulting in greater upper and central

LRT aerosol deposition compared with adults. This is especially true for children younger than 18 months, who are obligate nose breathers.

Rejection of masks used for aerosol administration is a major obstacle to delivery of aerosol medications to the LRTs of infants and young children. Challenges such as these make it inappropriate to apply results of ICS studies in adults and older children to infants and young children in whom relatively few adequate studies have been carried out. There is relatively little but growing evidence that ICS aerosols with small particles could achieve better clinical outcomes in children (and adults with airflow obstruction) and be given at lower doses than conventional aerosols.³⁵ Administration of aerosols with small particles might not address all the obstacles encountered during ICS delivery to infants, particularly those related to behavioral factors. However, given these complexities, small-particle therapeutics could improve clinical outcomes in infants and young children. Additional studies of the therapeutic efficacy of ICSs with small particles are needed; these might demonstrate improved delivery of aerosols to the peripheral airways and lung parenchyma, particularly among infants and young children. Recent studies reporting a lack of benefit of ICSs in wheezy infants given large-particle aerosols¹ should be reconsidered; recent studies that used ICSs with smaller particles have shown promising preliminary results.^{15,35}

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