Effective Bronchodilator Resuscitation of Children in the Emergency Room: Device or Interface?

Aerosol therapy is a vital component in the treatment of children with asthma, and inhaled β -agonists are the first-line therapy for bronchospasm in acute asthma. In the emergency department, bronchodilators are commonly administered to children via small-volume jet nebulizer (SVN) or large-volume jet nebulizer (LVN). SVNs have been widely used in hospitals and emergency departments for more than 50 years. An SVN delivers 1–5 mL over 8–15 min. In the United States the drug label for inhalation solution of albuterol is a 0.083% solution (2.5 mg in 3 mL), administered 3 or 4 times per day, but that dosage is often not sufficient to relieve a severe asthma exacerbation, even though such dosing may be sufficient for mild to moderate reactive airway disease in an ambulatory setting.

Albuterol, like most drugs approved for inhalation, was approved based on trials with ambulatory patients with mild to moderate asthma. Patients presenting to the emergency department with severe bronchospasm may not respond to the standard label dose of albuterol and require higher doses at shorter intervals than the stable patient at home. This has led clinicians to devise effective “off-label” strategies for administration of bronchodilators and other drugs to treat severely ill patients, including higher doses, higher drug concentration, shorter intervals between doses, and continuous nebulization. Continuous nebulization with an LVN or an SVN with a continuous feed and a delivery rate of 10–20 mg/h is as effective as, or superior to, intermittent doses via SVN.^{1–6} Comparison of 4 LVNs found relatively consistent emitted aerosol output, with similar performance during the first 5 hours of use.⁷

Breath-actuated nebulizers generate aerosol only during inhalation, which reduces aerosol waste but extends the treatment time.^{8,9} Since the introduction of the breath-actuated nebulizer in 2000, *in vitro* and *in vivo* studies have shown the breath-actuated nebulizer’s potential for better lung deposition and possibly greater efficacy. For example, Sangwan et al compared MistyNeb and AeroEclipse for particle-size distribution *in vitro*, with no breathing (standing cloud), and with simulated ventilation, and reported that the mass median aerodynamic diameter (MMAD) for both nebulizers was affected by ventilation: MistyNeb 5.2 μm versus AeroEclipse 4.6 μm for standing cloud, and MistyNeb 3.1 μm versus AeroEclipse 2.2 μm

during ventilation. With inhaled radio-labeled interferon-gamma, lung deposition averaged $68.1 \pm 0.1\%$ with AeroEclipse, and $30.9 \pm 0.0\%$ with MistyNeb, with fill volumes of 2 mL and 4 mL, respectively.¹⁰ Those studies stimulated speculation that breath-actuated nebulizer might generate smaller aerosol particles and thus have greater lung dose with other drugs, such as bronchodilators.

Despite the widespread interest in breath-actuated nebulizers for hospital practice, precious few studies have compared breath-actuated nebulizers to other bronchodilator delivery strategies in the emergency department. In this issue of *RESPIRATORY CARE*, Sabato et al present findings from their randomized study of the efficacy of albuterol administered via the AeroEclipse breath-actuated nebulizer versus their institution’s standard therapy (either SVN or LVN) in the treatment of pediatric patients presenting with asthma to the emergency department.¹¹ They are the first to report significant differences in admission rate and symptom-score improvement between the 2 treatment groups. Sabato and colleagues made a multidimensional assessment, including clinical asthma score, heart rate, respiratory rate, peak expiratory flow, patient tolerance of the treatment, nausea, tremor, vomiting, and hyperactivity. Those variables are the best way to capture all domains of patients’ response to therapy, and they were measured at baseline and at follow-up to determine changes in health status. From the statistical point of view, the study was appropriately powered and had a very small sample loss, which are strengths of the study.

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Sabato’s team at Children’s Hospital and Research Center Oakland has over 2 decades of experience in innovating “off-label” strategies for treating severe asthma in the emergency department. In addition to use of undiluted bronchodilator delivered via SVN, since 1985, Benton et al described effective bronchodilator response with titration to effect with 4–14 puffs from a pressurized metered-dose inhaler with valved holding chamber.¹² The quest to develop effective bronchodilator techniques in their busy urban emergency department resulted in development of aggressive, innovative strategies that evolved into their standard asthma algorithm, in which patients with less

severe symptoms receive SVN, and sicker patients receive continuous nebulization via LVN. The nominal and emitted doses depend on patient weight: SVN dose 2.5 mg in 0.5 mL for patients < 20 kg, and 5 mg in 1 mL for larger patients; LVN dose 10 mg in 20 mL, administered over one hour.

This background of aggressive therapy makes it even more remarkable that Sabato et al found that the AeroEclipse breath-actuated nebulizer was associated with fewer hospital admissions than their standard therapy. The study poses some challenges to the reader in interpreting the data to determine how to apply the lessons learned into practice.

Is Breath-Actuated Nebulizer Superior to SVN?

No randomized trials have demonstrated greater bronchodilator efficacy with breath-actuated nebulizer than with SVN in the emergency department. This trend continues in the study by Sabato et al, who report that the admission rate with breath-actuated nebulizer and SVN were both 40%.¹¹ The mean clinical asthma score was lower in the SVN group (3.0) than in the AeroEclipse group (5.1). The results suggest that in patients with less severe asthma the SVN was as effective as AeroEclipse, but the comparison is complicated by the relatively small number of patients who received SVN (10 patients) versus AeroEclipse (86 patients). While AeroEclipse may be more effective than SVN in patients with more severe asthma, this was not evaluated by Sabato et al.

Is Breath-Actuated Nebulizer Superior to Continuous Nebulization?

To answer this question, the first step is to analyze the devices' output. The high-flow MiniHeart nebulizer has a listed output of 20 mL/h and an MMAD of 2–3 μm , which corresponds to a respirable fraction of > 70%. In contrast, the AeroEclipse has a claimed MMAD of 2.8 μm and a 78% respirable fraction. Those characteristics are used in the following example.

With an inspiratory-expiratory ratio of 1:4 in a child with moderate to severe bronchospasm, 20% of the emitted dose of 10 mg ($10 \text{ mg} \times 0.2 = 2 \text{ mg}$) is inhaled, and 70% of the respirable particles, or 1.4 mg ($2 \text{ mg} \times 0.7 = 1.4 \text{ mg}$) of albuterol could reach the lung. If 35% of the breath-actuated nebulizer dose is inhaled, and the respirable fraction is 78%, a respirable dose of approximately 1.4 mg ($5.0 \text{ mg} \times 0.35 \times 0.78 = 1.4 \text{ mg}$) could be achieved with the 5-mg dose, and approximately 0.7 mg ($2.5 \text{ mg} \times 0.35 \times 0.78 = 0.68 \text{ mg}$) with the 2.5-mg dose. Although this example does not account for the residual drug remaining in the MiniHeart nebulizer at the end of nebulization (possibly 0.5–1.0 mg of albuterol),

it does indicate a similar lung dose with the 5 mg breath-actuated nebulizer dose and the 10 mg/h LVN dose.

If the Inhaled Dose Is Similar Between Breath-Actuated Nebulizer and LVN, What Other Factors Apply?

Although Sabato et al identified a relationship between the admission rate and the first bronchodilator treatment administered in the emergency department, it is unclear how many aerosol treatments were required for any one patient. As a group, 69% of the AeroEclipse group required additional bronchodilator treatments, compared to 57% of the standard-therapy group. To understand the causal relationship between treatment and admission, we need to understand how many total doses were administered.

The AeroEclipse and SVN treatments were administered by respiratory therapists who remained at the bedside during the treatments, which assures that the aerosol was in fact administered and tolerated through the treatment. In contrast, after initial setup, the continuous nebulization via LVN was largely overseen by the parent, and was not supervised by the respiratory therapist, so we are not sure how much of each LVN treatment was actually administered during the LVN treatment hour. One might infer that aerosol therapy directly observed by a clinician is more reliable and effective than unobserved therapy.

Is Interface the Key?

The LVN patients were sicker than the AeroEclipse patients (clinical asthma score 5.5 vs 5.1, respectively). However, the key to the difference in hospital admission may be associated more with the interface than with the aerosol generators. Treatment tolerance was greater in the AeroEclipse group than the standard-therapy group. Blow-by was used in 23% of the standard-therapy group, and in less than 4% of the AeroEclipse group. If the therapeutic benefit of blow-by is negligible, then this difference in interface may account for much of the difference in therapeutic response.

Sabato et al report that more of the AeroEclipse patients tolerated mask, which might indicate that breath-actuation is better tolerated than continuous nebulization, which involves cold aerosol blowing onto the face between breaths.¹¹ This aspect of aerosol therapy has not been well studied and merits further investigation. Loose-fitting mask and blow-by dramatically reduce aerosol deposition.^{13–21} Lung dose is less than 1% with a face mask leak of $\geq 0.2 \text{ cm}^2$,¹³ so optimal mask/face seal is important in maximizing aerosol delivery. Blow-by decreases aerosol delivery with the distance between the face and mask,²⁰ so variability in mask/face

distance during the LVN treatment hour with an untrained parent administering blow-by may have been a large factor in inhaled dose. Therefore, the trend toward better clinical asthma score and difference in admission rate may be associated with patient tolerance of the patient/device interface with AeroEclipse.

A key issue in aerosol therapy in children is intolerance of the interface. We must use an interface the patient will tolerate, so improvements that make the interface more tolerable may be more important than the type of aerosol generator. It is well known that screaming, struggling, and crying decrease aerosol delivery to children,^{17,22,23} whereas tolerance is associated with greater lung deposition and better adherence to therapy. For instance, Janssens et al²⁴ compared aerosol delivery in awake and asleep children and found that lung dose was significantly higher in the sleeping children. When the interface is better tolerated, it causes less agitation and leads to better deposition and outcomes. Up to 49% of infants and children do not tolerate aerosol via mask without agitation, which decreases deposition, and with blow-by the lung delivery is negligible. This is a problem in the emergency department and at home, and is associated with low adherence to therapy.

A better-tolerated interface may be the key to more effective therapy. Recent research on aerosol delivery via high-flow nasal cannula to pediatric patients was promising.^{25,26} Infants and children have preferential nasal breathing and tolerate nasal cannula better than mask, and in vitro studies suggested that delivery via nasal cannula provided a high inhaled dose and may be worthy of further evaluation.^{25,26}

Sabato et al address a very important research question: comparing breath-actuated nebulizer to LVN and SVN.¹¹ If breath-actuated nebulizer and LVN have similar particle-size distributions and respirable dose, then any differences in clinical response are more about the interface than about the aerosol generator. The observation that AeroEclipse with mask was better tolerated by children with severe asthma may provide an important insight into the observed difference in hospital admission. Through additional research we can determine the best aerosol delivery method for children in the emergency department and determine the effect of each device/interface in children with asthma. Therefore, future studies should concentrate not only on aerosol devices but also on patient-related factors that affect aerosol delivery in children of all ages, races, and ethnicities.

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