This ratio is negatively associated with adverse asthma outcomes. A cutoff of 50% each patient-year was selected as a satisfactory ratio.

RESULTS. A total of 343 520 individuals met the case definition of asthma. In 7.6% of patient-years, SABAs were prescribed inappropriately. When patient-years with no prescriptions filled were removed, this number increased to 11.9%. In 0.9% of patient years, SABAs were prescribed excessively. In 29.6% of patient-years, the ratio of ICS to total prescriptions was >50%.

CONCLUSIONS. Inappropriate prescriptions of SABAs are still prevalent but halved from 2002 to 2013, and excessive SABA prescriptions declined by more than 60%. Excessive SABA use declined over the study period but increased over the time course of asthma. Excessive SABA use was most notable in older patients and might explain higher mortality in this group.

REVIEWER COMMENTS. Asthma guidelines have been around for over 2 decades and emphasize the use of ICS as first-line treatment to control chronic inflammation in persistent asthma. This study shows that inappropriate and excessive prescriptions of SABAs are still prevalent but appear to be decreasing in this population. The major limitation in this study is use of pharmacy data to reflect actual medication usage. Patients frequently want prescriptions for multiple SABAs to have in various locations or to replace lost medications. In addition, filling a prescription does not equate to medication use. So, the number of prescriptions for SABAs is likely higher than actual usage. Devices that measure the actual number of puffs accentuated from a device are available and may more acutely reflect patient medication usage. Preparation, distribution, and implementation of guidelines is no small task. It is refreshing to see data showing the benefits of guideline usage.

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Spacers Versus Nebulizers in Treatment of Acute Asthma - A Prospective Randomized Study in Preschool Children

Mitselou N, Hedlin G, Hederos CA. *J Asthma*. 2016; 53(10):1059–1062

PURPOSE OF THE STUDY. To compare administration of bronchodilators by nebulizers with delivery by metered dose inhalers (MDIs) with spacers and to evaluate the clinical effect of the treatment of acute asthma in preschool children.

STUDY POPULATION. Children 0–6 years of age who presented to the emergency department with viral infection–associated wheezing or acute asthma flares.

METHODS. A prospective randomized clinical trial in a pediatric emergency department (PED). Preschool children who were admitted for virus-induced wheezing or acute asthma exacerbation were randomly allocated to receive bronchodilator treatment by nebulizer or by MDI. Parents completed a questionnaire during the PED visit.

RESULTS. Baseline data were similar for both groups, except for family history of asthma and atopic disease being more frequently reported in the nebulizer group. The length of stay in the PED and rate of hospitalization were similar. No significant differences were seen in heart rate, respiratory rate, and oxygen saturation at baseline and after the treatment. No difference was seen in the parents' view of ease of use and device acceptance. According to the parents, 40% of the participants had asthma diagnosis, but up to 66% were previously prescribed some kind of asthma medication.

CONCLUSIONS. The results suggest that MDIs with spacers are at least as effective as nebulizers in the delivery of β agonists to treat preschool children with virus-induced wheezing or acute exacerbations of asthma in the PED. It is important to provide adequate information to the staff and parents to treat pediatric acute asthma successfully.

COMMENTS. There are numerous studies that have addressed the efficacy of MDIs versus nebulized medication delivery in children. Despite evidence that either method is suitable for medication delivery, there remains the perception that nebulization is superior to MDI/spacer use, particularly in younger children. The authors highlight parents' perceptions in an acute setting that both methods achieve acceptance if presented correctly. This information should encourage clinicians to distribute appropriate MDIs/spacer devices to preschool-aged children without hesitation.

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The Effect of a Holding Chamber on Albuterol Metered-Dose Inhaler Product Differences

Johnson JL, Guthrie D, Hyde J, Hanson T, Karlage K, Myrdal PB. *Ann Allergy Asthma Immunol*. 2016; 117(3):246–250

PURPOSE OF THE STUDY. To investigate the differences in 3 albuterol sulfate metered-dose inhaler (MDI) products and their particle size. The study also evaluated if use of a valved holding chamber (VHC) would impact drug delivery and/or diminish systemic adverse effects.

STUDY POPULATION. The study did not use human subjects, but rather examined Ventolin hydrofluoroalkane (HFA), Proventil HFA, and ProAir HFA, the 3 racemic albuterol sulfate pressurized MDI products available in the United States.

METHODS. The experimental design involved a nonviable 8-stage Anderson Cascade Impactor (ACI) with a US Pharmacopeia (USP) throat model with a mean (SD) airflow rate of 28.3 (0.5) mL/min. Each of the 3 albuterol MDI products had their particle size assessed 6 times with and 6 times without spacer or holding chamber. With the use of high-performance liquid chromatography (HPLC) albuterol sulfate deposition was analyzed at each stage of the ACI.

RESULTS. Testing of MDI products without a VHC showed that Ventolin HFA had an inhalable dose of 21 μg and a noninhalable mean dose of 66 μg of albuterol sulfate, an inhalable fraction of 24%. In contrast, Proventil HFA had a mean inhalable dose of 40 μg and a noninhalable dose of 35 μg (58% inhalable fraction). ProAir HFA had a mean inhalable dose of 64 μg and a noninhalable dose of 42 μg, yielding a 61% inhalable fraction. All 3 of the products had inhalable doses significantly lower than their total doses. Nonetheless, there was only a significant difference ($P < .01$) between the mean total doses of Proventil HFA (75 μg) and ProAir HFA (107 μg). When a VHC was used, the inhalable fraction for Ventolin HFA was 94%, Proventil HFA 98%, and ProAir HFA 97%. However, the total dose for Ventolin HFA, Proventil HFA, and ProAir HFA were 25 μg, 54 μg, and 63 μg, respectively. These values were less in all 3 albuterol sulfate MDIs compared with when a VHC was not used. This indicates that larger, noninhalable particles were more likely to stick to the spacer device and are not deposited on the mouth or tongue, while the smaller inhalable particles were still delivered.

CONCLUSIONS. These results show a difference between the 3 products and their total dose delivered with or without spacer use. Ventolin HFA was found to deliver 2 to 3 times lower dose than Proventil HFA and ProAir HFA. The results in this study support that spacers increase the inhalable percentages of all 3 products while preventing deposition of larger, noninhalable particles on the mouth and tongue. This would likely decrease the side effect profiles on these medications.

REVIEWER COMMENTS. The ability to make well-informed decisions regarding safety and efficacy of the medications we prescribe for our patients is essential. All devices do not deliver the same amounts of medication. This study delivers more justification for recommending spacer use in our patients, as they may prevent the deposition of larger particles of the inhaled medications in the mouth and decrease the potential adverse side effect profile of these medications. Although these in vitro studies add evidence to previously published findings on differences between the various albuterol sulfate MDI products, in vivo studies are needed.

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Randomized Trial of Once-Daily Fluticasone Furoate in Children With Inadequately Controlled Asthma

Oliver AJ, Covar RA, Goldfrad CH, et al. *J Pediatr*. 2016;178:246–253.e2

PURPOSE OF THIS STUDY. To assess the efficacy, dose response, and safety of inhaled corticosteroid, fluticasone furoate (FF), in children with inadequately controlled asthma.

STUDY POPULATION. This was a multicenter, multicountry study with the following inclusion criteria: children between ages 5 to 11 years who had asthma symptoms at least 6 months before the study screening and who at the intake were on short-acting β-agonist (SABA) alone, SABA with leukotriene modifying agent, or SABA with low-dose inhaled corticosteroid for >4 weeks before the screening.

METHODS. The design is a phase IIb, multiple center, randomized, double-blind, placebo- and active-controlled study. The study assessed a 4-week pretreatment period, 12-week treatment period, and a 1-week follow-up period. The children were randomly placed in 1 of 5 groups including placebo, fluticasone propionate (FP) 100 mcg, FF at 25 mcg, 50 mcg, and 100 mcg. The primary endpoint was assessed by the mean change from baseline in daily morning peak expiratory flow (PEF) over the 12 weeks. Secondary endpoints such as rescue-free days were assessed to further expand on the clinical impact of the treatment. Pharmacokinetic and safety endpoints were also measured.

RESULTS. One thousand five-hundred forty children were initially assessed for eligibility for which 881 children were placed in the 4-week pretreatment period. Of those patients, 593 children entered the study and were randomly assigned to 1 of the 5 treatment groups. There was a statistically significant change from baseline daily morning PEF average over the 12 weeks in each FF dose group by an increase of 18.6 L/min (FF 25mcg), 19.5 L/min (FF 50 mcg), and 12.5 L/min (FF mcg 100); the P value was $< .001$ on all dose groups. The only significant PEF average increase above baseline in the FP group was for the 100 mcg (14.0 L/min with $P < .001$) dose. Importantly, there were statistically significant percent increases of rescue-free days in the FF 50 mcg and FF 100 mcg (9.8%, $P = .023$ and 12.2%, $P = .004$, respectively) which meant 0.7 and 0.9 rescue-free days per week. Adverse events (AEs) in FF treatment groups (32%–36%) were greater than in the placebo group (29%); the most frequent AE being cough.

CONCLUSIONS. The study suggested that both FP and FF had significant improvements compared with placebo in terms of asthma control. Although AEs were slightly increased over placebo, FP and FF were generally well-tolerated; therefore, both formulations are reasonable options for patients with uncontrolled asthma.

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