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Dilemmas, Confusion, and Misconceptions Related to Small Airways Directed Therapy

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During the past decade, there has been increasing evidence that the small airways (ie, airways < 2 mm in internal diameter) contribute substantially to the pathophysiologic and clinical expression of asthma and COPD. The increased interest in small airways is, at least in part, a result of innovation in small-particle aerosol formulations that better target the distal lung and also advanced physiologic methods of assessing small airway responses. Increasing the precision of drug deposition may improve targeting of specific diseases or receptor locations, decrease airway drug exposure and adverse effects, and thereby increase the efficiency and effectiveness of inhaled drug delivery. The availability of small-particle aerosols of corticosteroids, bronchodilators, or their combination enables a higher total lung deposition and better peripheral lung penetration and provides added clinical benefit, compared with large-particle aerosol treatment. However, a number of questions remain unanswered about the pragmatic approach relevant for clinicians to consider the role of small airways directed therapy in the day-to-day management of asthma and COPD. We thus have tried to clarify the dilemmas, confusion, and misconceptions related to small airways directed therapy. To this end, we have reviewed all studies on small-particle aerosol therapy systematically to address the dilemmas, confusion, and misconceptions related to small airways directed therapy.

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Inhaled therapy is the mainstay of the modern treatment of asthma and COPD. However, little consideration has been given to the potential advantage of targeting specific airway regions within the lungs. In theory, by increasing the precision of drug deposition, it may be possible to target specific disease or receptor locations and decrease drug exposure and side effects, thus increasing the efficiency and effectiveness of inhaled drug delivery in daily clinical practice.[1]

The small airways (airways with internal diameter < 2 mm) comprise airway

ABBREVIATIONS: BDP = beclomethasone dipropionate; CFC = chlorofluorocarbon; DPI = dry powder inhaler; GSD = geometric standard deviation; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; LABA = long-acting β2-adrenergic bronchodilator; MMAD = mass median aerodynamic diameter; pMDI = pressurized metered-dose inhaler; VHC = valved holding chamber

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generations eight to 23[2] and are a significant component of obstructive airway disease. Emphysema classically involves the terminal bronchioles,[3] but it is increasingly recognized that asthma also involves small airways,[4,5] not only in patients with severe asthma[6] but also in those with milder disease.[7] Distal airway inflammation and dysfunction also have been demonstrated in distinct clinical asthma phenotypes,[8] such as nocturnal asthma,[9,10] exercise-induced asthma,[11] and allergic asthma.[12] These phenotypes support the targeting of inhaled drug therapy toward the small airways.

Most inhaled therapies do not reach the small airways sufficiently.[13-18] Although the drug particle size pattern may vary markedly among inhalers, conventional pressurized metered-dose inhalers (pMDIs) and most dry powder inhalers (DPIs) emit drug particles too large to target the small airways effectively (Table 1). Overall, these aerosol devices deposit approximately 20% of the drug dose in the lungs,[19] with a high proportion of the drug being deposited in the oropharynx, which can cause local and systemic effects through gastrointestinal absorption.[20] However, technological advances in device engineering and drug formulation have led to a new generation of inhalers emitting small-particle drug aerosol at slower velocities, with enhanced lung deposition (~ 50%) and, most importantly, more effective aerosol penetration into the lung periphery.[13-18] These new inhalers and drug formulations include solution-based hydrofluoroalkane (HFA)-propelled pMDIs delivering aerosols of inhaled corticosteroid (ICS)—namely, beclomethasone dipropionate (BDP), ciclesonide, and flunisolide; long-acting β2-adrenergic bronchodilators (LABAs)—namely, formoterol; and ICS/LABA fixed-dose combinations—namely, BDP/formoterol. Furthermore, a multidose DPI (NEXThaler, Chiesi, Italy) delivering a small-particle ICS/LABA drug combination,[21] as well as a novel device category—namely, a soft mist inhaler (Boehringer Ingelheim), delivering small-particle aerosols of long-acting bronchodilators—also have been developed.[22]

Because of the high drug deposition in the lungs and better targeting of the small airways, these new inhaler devices in theory should be more effective for treating the peripheral lung compartment in patients with asthma and COPD. Studies in patients with asthma[7,13,14,23-25] and COPD[26] show larger improvements in markers of small airway function with small-particle aerosols, compared with large-particle aerosols, and lend support to this theory. However, several questions still need clarification. For instance, the optimal particle size for an inhaled drug to reach and deposit into the small airways effectively has not been defined clearly, as reflected by the different terms and

TABLE 1] Drug Particle Size and Inhaler Type of Most Frequently Prescribed ICS, LABA, LAMA, and ICS/LABA Formulations

ICS	Inhaler Type	MMAD,[a] μm
Fluticasone propionate	Diskus DPI	5.4
Fluticasone furoate	Ellipta DPI	3.0-3.9
Fluticasone propionate	Suspension HFA pMDI	2.4
Budesonide	Turbuhaler DPI	4.0
BDP	Suspension HFA pMDI	4.1
BDP	Solution HFA pMDI	1.1
Ciclesonide	Solution HFA pMDI	1.1
Flunisolide	Solution HFA pMDI	1.2
LABA		
Formoterol	Solution HFA pMDI	1.2
Salmeterol	Suspension HFA pMDI	2.8
Indacaterol	Breezhaler DPI	3.2
Vilanterol	Ellipta DPI	1.8-2.5
LAMA		
Tiotropium	Soft mist inhaler	2.0
	HandiHaler DPI	3.9
Aclidinium	Genuair DPI	2.4
Glycopyrronium	Breezhaler DPI	2.8
ICS/LABA		
Formoterol/BDP	Solution HFA pMDI	1.5
Formoterol/BDP	NEXThaler DPI	1.5
Salmeterol/fluticasone propionate	Suspension HFA pMDI	2.7
Salmeterol/fluticasone propionate	Diskus DPI	3.5
Formoterol/budesonide	Turbuhaler DPI	3.0
Formoterol/fluticasone propionate	Suspension HFA pMDI	3.15-3.52

BDP = beclomethasone dipropionate; DPI = dry powder inhaler; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; LABA = long-acting β2-adrenergic agonist; LAMA = long-acting muscarinic antagonist; MMAD = mass median aerodynamic diameter; pMDI = pressurized metered-dose inhaler.

[a]Drug particle size is expressed as MMAD. (MMAD data are adapted from Usmani,[14,15] Chapman et al,[16] Colthorpe et al,[17] Lock et al,[18] and Labiris et al.[20])

sizes (ie, submicron,[27] < 1 μm; ultrafine,[28] 1.1 μm; extrafine,[21] 1.5 μm^2) used to describe the finer small-particle aerosols delivered by these inhalers. In agreement with the literature,[13-15] we define "small particles" as those with a size expressed as mass median aerodynamic diameter (MMAD)—the aerodynamic diameter above and below which 50% of the mass resides[20]—of < 2 μm. We also call particles < 1 μm "submicron" and those > 2 μm "large" or "coarse," as has been used by other authors.[27,29]

The aim of this article is to address six clinical questions related to the use of small-particle aerosols that are relevant to practicing health-care professionals in their day-to-day clinical practice. These questions were selected by means of consensus by the members of the Aerosol Drug Management Improvement Team (www.admit-inhalers.org), a working group of physicians with combined clinical and research expertise on the topic of inhaled therapy for respiratory diseases. The six questions listed are not meant to be hierarchical or all-inclusive, but, in our view, they cover the major concerns practicing clinicians have related to small-particle aerosol therapy. To address the questions, we scanned electronic databases (PubMed, MEDLINE, Embase, Scopus, and Google Scholar) from the date of inception up to December 2015 with cross-search using the following keywords: "aerosols," "inhalation," "small particles," "fine particles," "extrafine particles," "chronic obstructive pulmonary disease," "COPD," "asthma," and "inhaler." All studies considered to be relevant for the six questions were evaluated; no restriction was placed on study design and language of publication.

Questions

1. Is Particle Size Important to Achieve Better Lung Deposition?

The terms and definitions used to describe the principles of aerosol medicine and particle size are important to mention to be able to address the question. Aerosol particles range in size between 0.01 and 100 μm.[30] Because the aerodynamic behavior of an aerosolized particle is influenced critically by its mass, it is important to describe the size distribution of the aerosolized particles. In clinical studies, the MMAD and the geometric standard deviation (GSD) often are used to characterize the dimensions of an aerosol. The MMAD divides the aerosol size distribution in one-half; it represents the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.[30] In general, particles with a MMAD > 5 μm are most likely to deposit by impaction in the oropharynx and be swallowed. Conversely, particles with a MMAD < 5 μm, the so-called respirable particles, are those with the highest probability of penetrating beyond the oropharynx and depositing in the lungs.[30] The proportion of particles within the aerosol that are < 5 μm is often referred to as the "fine particle fraction" or the "fine particle dose," if expressed in absolute mass of drug.[28] Both the particle size and fine particle fraction of an aerosol play a significant role in the deposition of an inhaled drug and its relative distribution within the large and small airways.[31-33] The GSD measures the dispersion of the particle diameter and is defined as the ratio of the median diameter to the diameter at ± 1 SD from the median diameter.[30] If the particle size varies over a wide range (ie, GSD > 1.2), the aerosol is described as having a polydisperse particle distribution; if the particles are of similar size (ie, GSD < 1.2) the aerosol particle distribution is described as monodisperse.[30]

The study of monodisperse aerosols has increased our knowledge of the effects of particle size on regional drug deposition in the human lung.[34] Usmani et al[35,36] undertook gamma scintigraphy to investigate the radio-aerosol lung distribution of monodisperse salbutamol particles with MMADs of 1.5-, 3.0-, and 6.0-μm sizes in patients with mild asthma (Fig 1). The authors showed 1.5-μm particles achieved higher total lung deposition (56% of the emitted dose) than did 3.0- and 6.0-μm particles (51% and 46% of the emitted dose, respectively) (Table 2).[36] They also observed significantly greater penetration into the peripheral airways with the smaller particles. Additionally, although slow inhalation (30 L/min) was better than fast inhalation (> 60 L/min) for effective lung deposition with 3.0- and 6.0-μm particles, lung deposition was less affected by the differences in inhalation flow with 1.5-μm particles.[36] Despite the higher deposition with 1.5-μm particles, large-particle (3.0 and 6.0 μm) salbutamol aerosols improved FEV_1 more effectively than did 1.5-μm aerosols.[36] Zanen et al[37] also observed that inhalation of monodisperse salbutamol aerosols with a MMAD of 2.8 μm caused more marked FEV_1 increases than that obtained with monodisperse salbutamol aerosols with a MMAD of 1.5 μm.

Although these studies[36,37] have improved our insights into the effects of particle size on lung deposition and airway function, they have assessed the effects of treatment by using FEV_1, which mainly reflects large-airway patency. It would have been interesting to know the results if the main outcome had been effects on small-airway physiologic parameters, such as peripheral airway

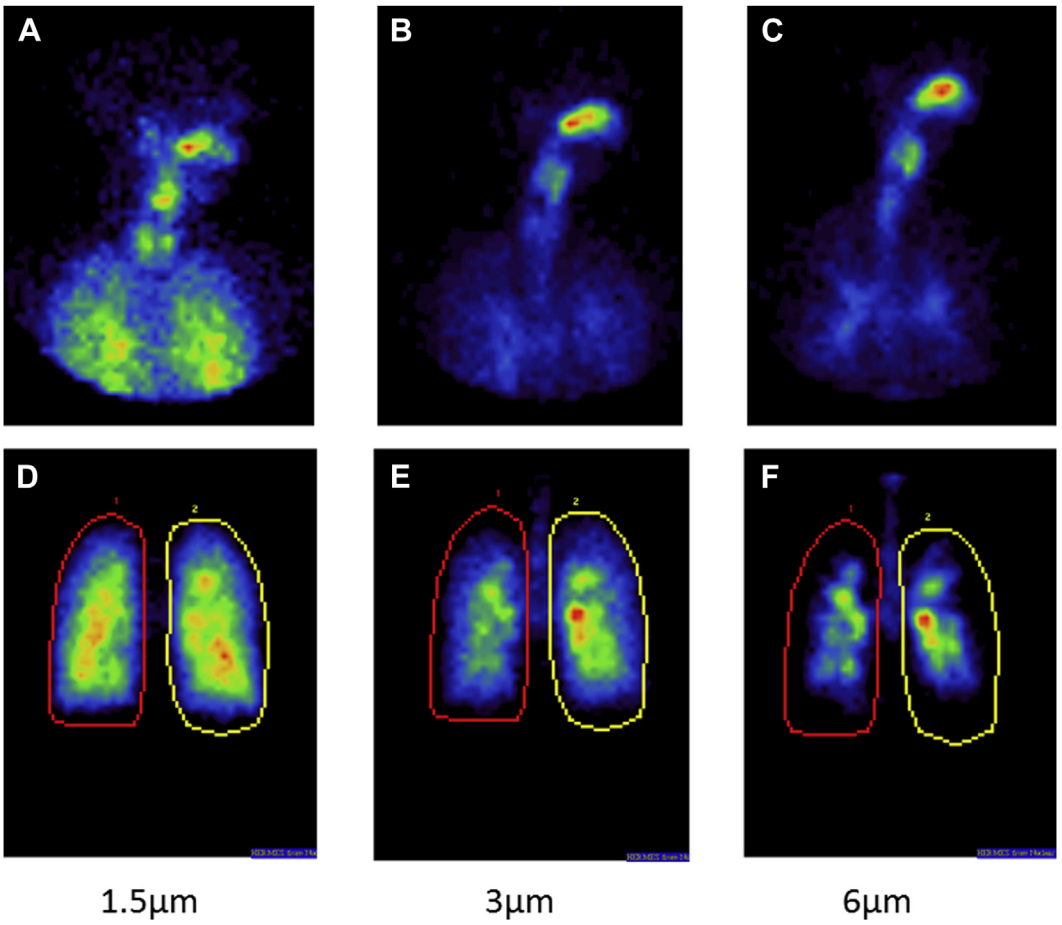

Figure 1 – *A-C, Oropharyngeal and posterior thorax (D-F) gamma camera images of aerosol deposition obtained by using technetium-99m-labeled salbutamol particles of 1.5-, 3-, and 6-µm mass median aerodynamic diameter. Red areas indicate regions of highest radioactivity, and black areas indicate regions of least radioactivity. Total lung deposition was greater with the 1.5-µm aerosols than with the 6- and 3-µm aerosols, whereas oropharyngeal deposition increased with increasing particle size. (Adapted with permission from Usmani et al[36].)*

resistance measured with forced oscillometry,[38] air trapping measured with body plethysmography,[38] or ventilation heterogeneity measured with the single- or multiple-breath nitrogen washout test.[39,40] In addition, both studies,[36,37] investigated the effects of monodisperse (GSD < 1.2) salbutamol, whereas commercially available aerosols are polydisperse (GSD > 1.2), consisting of a mix of different sizes of particles. In this case, not only is MMAD important but so is the particle size distribution in the overall clinical effectiveness of the aerosol. Patients should benefit the most if both the large and the small airways are treated properly, especially in asthma, which is

TABLE 2] Mean (SD) Values[a] of TLD, OD, Ex, and PI Observed Following Inhalation of Technetium-99m-labeled Monodisperse Salbutamol Aerosols of 1.5-, 3-, and 6-µm MMAD in 12 Patients With Mild to Moderate Asthma

MMAD, µm	TLD[b]	OD[b]	Ex[b]	PI[c]
1.5	56.3 (9.2)	14.6 (4.5)	21.9 (5.7)	0.79
3.0	51.0 (8.9)	30.6 (7.2)	8.3 (1.5)	0.60
6.0	46.0 (13.6)	42.6 (14.6)	2.3 (0.1)	0.36

Ex = exhaled fraction data; OD = oropharyngeal deposition; PI = penetration index; TLD = total lung deposition. See Table 1 legend for expansion of other abbreviations.

[a]Mean (SD) FEV_1 was 76.8 (11.4%) predicted value.

[b]Values of TLD, OD, and Ex are expressed as percentages of the delivered drug dose.

[c]PI is the ratio of drug deposition in the central and peripheral areas of the lung. (Modified with permission from Usmani et al.[35,36])

a disease of the whole airway tree.[33] Lung deposition images show whole airway tree targeting can be achieved by small-particle polydisperse aerosols, but not with large-particle polydisperse aerosols.[36]

Several studies have investigated the lung deposition of the small-particle aerosols of ICS monotherapy. The traditional chlorofluorocarbon (CFC)-propelled pMDI BDP suspension formulation delivers particles with a MMAD of 3 to 4 μm, leading to approximately 15% of the dose reaching the lung, whereas the remainder is deposited in the oropharynx.[31,32] In contrast, the newer solution-based HFA pMDI BDP formulation delivers particles with a MMAD of approximately 1 μm.[27] Scintigraphic studies reveal that HFA BDP deposits more than 50% of the delivered drug dose in the airways, with effective penetration to the peripheral airways.[31,32,41,42] Furthermore, although HFA BDP delivers particles with a MMAD of 1 μm, it includes a range of particles allowing some of the larger particles to deposit in both the intermediate and large airways.[31,32,41] Similarly, in patients with mild asthma, small-particle HFA pMDI ciclesonide solution has been shown to achieve a uniform drug deposition in both central (44%) and peripheral (56%) airways.[43] An in vitro study[44] found that different HFA pMDIs of ICS may differ in the size of emitted particles: budesonide, 3.5 μm; fluticasone propionate, 2.8 μm; BDP, 1.9 μm; and ciclesonide, 1.9 μm. Solution-based aerosols of BDP and ciclesonide had a greater proportion of fine particles (defined as particles < 3.1 μm) than did the HFA pMDI suspension aerosols of budesonide and fluticasone propionate.[44]

The Respimat (Boehringer Ingelheim) device is the only soft mist inhaler currently available on the market. This device does not require propellants because it is powered by the energy of a compressed spring inside the inhaler. Individual doses are delivered via a precisely engineered nozzle system as a slow-moving aerosol cloud (hence the term "soft mist").[22] In vitro[45] and scintigraphic[46] studies have shown that Respimat (Boehringer Ingelheim International GmbH, Germany) emits a small-particle ($\sim$ 2 μm) aerosol with higher (51.6%) levels of lung deposition, lower (19.3%) oropharyngeal deposition, and greater peripheral lung penetration (peripheral-to-central ratio, 1.34) than do large-particle aerosols optimally administered from a DPI (lung deposition, 28.5%; oropharyngeal deposition, 49.3%; peripheral-to-central ratio, 0.95).

Deposition studies using a small-particle (1.5 μm) HFA pMDI solution BDP/formoterol fixed-dose combination in patients with asthma have shown approximately one-third of drug is deposited in the peripheral lung region and two-thirds is deposited in the central lung region.[47] A multidose DPI device delivering small particles (1.5 μm) of BDP/formoterol also has shown a similar peripheral to central lung distribution.[21] In contrast, several studies show that large-particle aerosols of fluticasone/salmeterol fixed-dose combination have poor peripheral airway penetration.[48] Taken together, lung deposition studies conclusively demonstrate that small-particle aerosols achieve not only better pulmonary deposition but also effective penetration into the peripheral areas of the lung.

2. Oropharyngeal Deposition With Small-Particle Aerosols: Does It Matter Clinically?

The oropharyngeal 90° bend is the main determinant of loss of inhaled drug before it reaches the lungs.[34] It is well documented[31-33] that the majority of the inhaled drug dose delivered by conventional pMDIs deposits in the oropharynx, thus contributing to local side effects, such as candidiasis and dysphonia for ICSs.[49] In addition, the drug deposited in the oropharynx can be swallowed into the gastrointestinal tract and may increase the risk of systemic adverse effects.[50] In contrast, solution-based small-particle, HFA, pMDI aerosols deposit less drug in the oropharynx than do large-particle aerosols.[41-43] Usmani et al[35] found that 1.5-μm salbutamol particles achieved lower (15%) (Table 2) throat deposition than did 3- and 6-μm particles (31% and 43%, respectively) (Table 2). The lower oropharyngeal deposition of an inhaled drug observed with a small-particle aerosol is likely to result from the lower plume velocity observed with these aerosols.

The reduction in oropharyngeal deposition with small-particle ICS aerosols has clinical implications for local and systemic side effects. In patients with moderate to severe asthma, Bateman et al[51] observed a significantly lower rate of oral adverse events (candidiasis and dysphonia) with small-particle ciclesonide aerosol than with large-particle fluticasone propionate aerosol. In patients with mild asthma, Newman et al[43] observed a low (approximately 33%) oropharyngeal deposition and high (approximately 52%) lung deposition with small-particle pMDI ciclesonide aerosol. Even when one-half of the drug dose targeted the distal lung region, this did not translate into greater pulmonary bioavailable adverse effects.[41] In this regard, Derom et al[52,53] found that small-particle ciclesonide aerosols (320 or 640 μg

daily) did not cause significant suppression of 24-hour urinary cortisol levels in contrast to findings with large-particle fluticasone propionate aerosols (500 or 1,000 μg daily). Both ICS treatments decreased airway hyperresponsiveness to adenosine monophosphate,[52] and methacholine.[53] Thus, in this scenario, the therapeutic ratio (ie, the clinical benefit vs the adverse effects) actually may be improved with small-particle aerosols of ciclesonide.

With respect to ICS/LABA treatment, Huchon et al[24] showed that morning urinary cortisol was significantly higher after inhalation of the small particles of an HFA pMDI BDP/formoterol fixed-dose combination (400 μg/24 μg daily, respectively) than after inhalation of the large particles of CFC pMDI BDP at the dose of 1,000 μg daily together with CFC pMDI formoterol at 24 μg daily. Furthermore, treatment with small-particle aerosols achieved significantly better levels of asthma control,[24] thus supporting the concept of an improved therapeutic ratio. In summary, compared with large-particle aerosols, small-particle aerosols result in lower oropharyngeal deposition, fewer local side effects, and less systemic absorption from the swallowed dose.

3. Does Exhalation of Drug Matter With Small-Particle Aerosols?

The inspiratory maneuver is a key determinant for the penetration and deposition of drug particles into the airways and, thus, the dose delivered to the target site.[32] Particles that are not deposited may be exhaled.[32] Previous in vitro modeling studies[27,54,55] showed a large (approximately 80%) proportion of inhaled small particles could be exhaled because they were able to remain airborne for a considerable time, even with a breath-hold pause maximizing the effect of gravitational sedimentation.[35] Particles that remain airborne in the larger airways are likely to be exhaled because of a greater settling distance before coming into contact with the airway walls. However, these in vitro modeling studies[27,54,55] did not account for features of inhaled drug delivery in vivo that can affect aerosol deposition in the lungs, such as the breath-hold pause that retains most particles within the airways or the effect of different inhalation maneuvers when using pMDIs or DPIs. In their in vivo study, Usmani et al[36] found that, although the exhaled fraction of a monodisperse salbutamol aerosol increased with the decreasing particle size (Table 2), the small particles were exhaled far less than previously predicted by in vitro models. Studies performed in both healthy subjects[31,33,56] and patients with asthma,[21,43,44] using commercial polydisperse aerosols, showed that the exhaled fraction of small-particle ICS aerosols was similar to that observed with large-particle aerosols, ranging between 2% and 14% (Table 3). In conclusion, small-particle aerosols are not exhaled to any significantly greater level than are large-particle aerosols when assessed using in vivo lung deposition studies.

4. Are Small-Particle Aerosols More Effective Than Large-Particle Aerosols?

Several studies have shown that small-particle aerosols improve markers of small-airway dysfunction and inflammation in both asthma and COPD.[13-15,57,58] However, the question remains[59] as to whether treatment with small-particle aerosols leads to added benefit in patients with asthma or COPD when compared directly with large-particle aerosols. Few studies have compared the effect of the same drug delivered as a small- or a large-particle aerosol. Such head-to-head comparisons are limited to CFC-driven vs HFA-driven BDP, but with the CFC propellants no longer available, additional comparisons cannot be made. Findings from studies comparing different drugs delivered by different inhaler devices are difficult to interpret. In addition, the lack of direct comparison of small- vs large-particle aerosol therapies using the same ICS also may influence the validity of equivalent dosages reported by current guidelines.[60]

TABLE 3] Percentage of Ex Observed With ICSs of Different Sizes

ICS	MMAD, μm	Ex	Reference
Ciclesonide HFA pMDI	1.1	3.70	Newman et al[43]
BDP HFA pMDI	1.1	6.0, 14.0	Leach et al[31,33]
BDP/formoterol DPI	1.5	3.30	Corradi et al[21]
BDP CFC pMDI	3.5	3.0	Leach et al[31,33]
Fluticasone CFC pMDI	2.4	2.0	de Vries et al[44]
Budesonide DPI	3.7	1.0	Warren et al[56]

CFC = chlorofluorocarbon. See Table 1 and 2 legends for expansion of other abbreviations.

A recent review of the literature[14] revealed that, in controlled clinical trials involving highly selected adult patients with asthma who fulfilled precise inclusion and exclusion criteria, treatments with small-particle aerosols achieved efficacy similar to that of large-particle aerosols. However, patients enrolled in controlled clinical trials may not represent the heterogeneity of patients with asthma seen in real-life daily clinical practice.[61] As little as 6% of real-life patients with asthma fit the criteria of controlled clinical trials, which calls into question the application of clinical trial results to patients seen in daily clinical practice.[62] The same review found that, in real-life asthma studies, treatment with small-particle aerosols resulted in greater daily asthma control; better quality-of-life indexes; and, importantly, lower daily ICS dose, when compared with large-particle aerosol treatment.[14] Recently, the effectiveness of small-particle ICS pMDI therapy was compared with that of large-particle ICS treatment in children with asthma who were either initiating or stepping up ICS therapy.[63] Over 1 year, small-particle ICS was more effective than large-particle ICS for asthma control and as effective as adding a LABA in a fixed-dose combination inhaler.[63] Noticeably, the differential effects of small- vs large-particle ICS were more pronounced in younger than in older children.[63] The key studies comparing the effects of small-particle aerosols vs large-particle aerosols in adult patients with asthma or COPD are reported in e-Tables 1-3.

In summary, randomized controlled trials show small-particle aerosols are as effective as large-particle aerosols. However, real-life studies reveal small-particle aerosols are more efficacious in patients' reported outcomes than are large-particle aerosols at much lower daily ICS doses.

5. Do Small-Particle Aerosols Cause More Adverse Effects Than Do Large-Particle Aerosols?

Data obtained from large-scale asthma studies showed that the overall incidence of at least one adverse event was significantly lower in patients treated with small-particle HFA, pMDI, BDP aerosols (46%) than in patients receiving the same drug as large-particle aerosols (59%) and was equal to that of HFA placebo (51%).[64,65] Most adverse events were reported as mild to moderate. Administration of high doses (up to 1,000 μg/60 μg) of small-particle BDP/formoterol aerosol combination delivered by means of HFA pMDI was well tolerated, with a safety profile generally similar to that of formoterol alone.[66]

Increased distal lung deposition of ICS might be expected to be associated with increased systemic effects, particularly the suppression of cortisol production. However, reassuringly, data from clinical trials have not documented any increased risk of systemic effects with an inhaled small-particle ICS formulation[64,65,67-69] or a small-particle ICS/LABA combination formulation.[66,70,71] Treatment with small-particle HFA pMDI, ICS/LABA, solution-based aerosols has resulted in less suppression of the hypothalamic-pituitary-adrenal axis, as assessed by means of cortisol levels, than has treatment with an equipotent dose of large-particle CFC, pMDI ICS plus LABA.[72] However, because ICSs may differ substantially in their gastrointestinal bioavailability, findings from one drug should be generalized with caution to other drugs. The available data suggest that the more distal deposition of small-particle formulations of ICS are safe in patients with asthma, and, for some drugs, may even result in a reduced effect on the hypothalamic-pituitary-adrenal axis, probably through less oropharyngeal deposition and, hence, decreased gastrointestinal bioavailability.

6. Do You Need to Add a Spacer to Small-Particle Aerosol Devices or Use a Different Inhaler Technique Than With Large-Particle Aerosol Devices?

A spacer is an extension device placed at the interface between the patient and the pMDI.[73,74] Valved holding chambers (VHCs) have a one-way valve at the mouthpiece to prevent exhalation into the chamber and to allow the patient to breathe from a "standing aerosol cloud," thus reducing the need of breath-hand coordination.[73,74] Both spacers and VHCs are used with pMDIs to increase the efficiency of aerosol delivery.[73,74] They reduce the aerosol speed and allow for the evaporation of propellant from larger droplets thereby reducing oropharyngeal deposition and increasing deep lung deposition.[73,74] Some VHCs, such as the AeroChamber Plus Flow-Vu (Monaghan Medical Corporation), can indicate whether the patient is inhaling correctly by means of a whistle when the patient is inhaling too quickly.[74]

In theory, the use of small-particle aerosol therapy should reduce the need for a spacer device or a VHC because they have (1) a lower impact force on the back of the patient's throat, (2) a slower plume, (3) a longer time for particle evaporation, and (4) reduced throat deposition.[19] Because of their less forceful spray and softer plume, small-particle aerosols may deposit a smaller amount of drug into the spacer walls, with a

TABLE 4] Key Aspects and Contrasting Points Related to Small-Particle Aerosols

Question	Key Point, Contrast, or Observation
Is particle size important to achieve better lung deposition?	• Particle size markedly influences the deposition of an inhaled drug and its relative distribution within the large and small airways. • Small-particle aerosols improve drug deposition and regional airway distribution within the lungs.
Oropharyngeal deposition with small-particle aerosols: does it matter clinically?	• Drug deposition at the oropharyngeal level is lower with small-particle aerosols than with large-particle aerosols.
Does exhalation of drug matter with small-particle aerosols?	• In in vivo lung deposition studies, small-particle aerosols are not exhaled to any greater significant level than are large-particle aerosols. • In vitro studies previously suggested exhalation of small particles did not model therapeutic aerosol inhalation with a breath-hold pause.
Are small-particle aerosols more effective than large-particle aerosols?	• In randomized controlled clinical trials, small-particle aerosols are as effective as large-particle aerosols. • In real-life studies, small-particle aerosols are more efficacious in patients' reported outcomes than are large-particle aerosols. • Studies comparing the same drug inhaled as small-or large-particle aerosol are limited essentially to BDP delivered as a CFC or HFA formulation.
Do small-particle aerosols cause more adverse effects than do large-particle aerosols?	• The use of small-particle aerosols is safe in patients with asthma and might result in a reduced effect on the hypothalamic-pituitary-adrenal axis, probably through less oropharyngeal deposition and hence decreased gastrointestinal bioavailability. • Local oropharyngeal adverse effects are fewer with small-particle aerosols. • Comparisons of the systemic effects of ICSs have been performed mainly with ICSs that have a high gastrointestinal bioavailability. More studies are needed with ICSs with low gastrointestinal bioavailability.
Do you need to add a spacer to small-particle aerosol devices or use a different inhaler technique than with large-particle aerosol devices?	• The use of spacers or holding chambers with pMDIs delivering small-particles aerosols reduces throat deposition and improves drug delivery to the lungs. • This can be a valuable option for patients with difficulties achieving an adequate inhalation technique. • Studies are needed to assess whether the beneficial effects are due to a better inhalation technique when a spacer is used.

See Table 1 and 3 legends for expansion of abbreviations.

consequent increase in lung deposition. Roller et al[75] found that inhalation of small-particle BDP aerosol delivered via an HFA pMDI with the AeroChamber Plus VHC resulted in high lung deposition and marked decrease in oropharyngeal deposition, compared with the same formulation inhaled via the pMDI alone. Recently, a small-particle flunisolide aerosol delivered by an HFA pMDI with a built-in spacer has been introduced in the market for asthma treatment. This formulation enhances the pulmonary/oropharyngeal deposition ratio further compared with that of the traditional formulation without a spacer.[76]

The increased drug deposition in the lungs with spacers or VHCs added to pMDIs delivering small-particle aerosols may raise concerns about the possibility of increased systemic exposure to drugs, especially ICS (see also question 5). However, studies performed in both healthy subjects and patients with asthma show that this does not seem to be the case. Singh et al[77] found in healthy volunteers that adding the AeroChamber Plus VHC to an HFA pMDI delivering small-particle BDP/formoterol aerosol did not affect the systemic exposure of these drugs compared with pMDI alone. Similar results were obtained in adolescents with asthma.[78] The results of these studies are particularly relevant because

they suggest that the use of pMDIs delivering small-particle aerosols in conjunction with the AeroChamber Plus VHC does not affect the safety profile of the product. More studies with other drugs are needed.

In summary, addition of spacers or VHCs to pMDIs delivering small-particle aerosols further reduces throat deposition and improves drug delivery to the lungs. Adding VHCs to small-particle-based pMDIs can be a valuable option for certain patient groups, such as those with difficulties in achieving an adequate inhalation technique.

Summary and Conclusion

A summary of key points and contrasts related to the various questions is reported in Table 4. Pathophysiologic evidence for small-airway dysfunction and the clinical emergence of a small-airway phenotype suggest that we should consider treating the small-airway region when reviewing patients with asthma or COPD clinically. In view of the increasing recognition of the role of small airways in asthma and COPD,[3,4] it is not unexpected that small-particle aerosols are beginning to show a greater impact than traditional large-particle aerosols on asthma and COPD outcomes. A recent review[14] of the available literature suggests that, in randomized controlled trials, small-particle aerosol therapy is as good as large-particle aerosol therapy. However, none of these randomized trials selected patients with documented baseline distal airway dysfunction, in whom the effects of a targeted small-particle aerosol treatment potentially could be larger. The findings of recent studies[13-15] focusing on small airways should be confirmed in large trials in patients with different patterns of severity and control. More importantly, through real-life studies, it is becoming evident that small-particle aerosol therapy has advantages over large-particle therapy that are relevant to our daily practice, as opposed to findings in selective populations entered into randomized clinical trials.[61,62]

Definitive answers to the questions posed in this article are yet to be established fully and will require collaboration and participation among academics and the pharmaceutical industry specifically to undertake head-to-head trials of small- vs large-particle aerosol therapy truly to inform us whether small-particle therapy will be useful to practicing clinicians. In addition, performing trials exploring potential phenotypic differences in response to small- or large-particle aerosols would be important. There have been multiple strong calls to action to undertake definitive clinical trials in this area,[15,79-81] and now is the time to conduct these definitive studies. The respiratory care community needs to make a concerted effort to convince funding agencies to provide support for these much needed studies and to convince the pharmaceutical industry to supply the same corticosteroids in large- and small-particle formulations to make these studies feasible.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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