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A Patient-Centred Approach to Optimizing Inhaled Therapy: Integrating Patient, Device, Drug and Disease Factors

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Abstract

Inhaled medications are crucial for the management of respiratory conditions such as chronic obstructive pulmonary disease and asthma, although their efficacy is contingent upon selecting the most appropriate inhaler and medication for each patient. Consideration should be given to factors such as inhaler technique, patient preference, coordination, inspiratory flow, small airway disease, and medication-related side effects. A patient-centred approach can maximize the benefits of inhaled therapy while minimizing potential risks.

Introduction

Respiratory conditions, such as asthma and chronic obstructive pulmonary disease

(COPD), represent significant causes of morbidity worldwide and frequently require long-term pharmacological management. While inhaled therapies are fundamental to the treatment of many respiratory conditions, their clinical efficacy can be highly dependent on proper administration. Consequently, patient education and evaluation of inhaler device technique are critical components of care. The Global Initiative for Obstructive Lung Disease (GOLD) emphasizes that it is essential to consider both the patient's ability to use the device effectively and their individual preferences when selecting an inhaler device.¹ These considerations set the stage for a more detailed exploration of the underlying factors that influence successful inhaler use.

Patient Characteristics and Device

Inspiratory flow rate, flow acceleration, and inhaled air volume are key patient characteristics that can affect the delivery of particles from inhaler devices to the lower respiratory tract.¹ Different inhaler devices, such as pressurized metered-dose inhalers (pMDIs) and soft mist inhalers (SMIs), require a slow, deep inhalation, whereas dry powder inhalers (DPIs), require a rapid and forceful inhalation.¹ Therefore, the patient's cognitive abilities, dexterity, and physical strength should be considered when selecting and prescribing inhaler therapy.

The Canadian Thoracic Society (CTS) recommends assessing a patient's peak inspiratory flow (PIF) when evaluating the suitability of a DPI.¹ In clinical practice, PIF can be readily measured using an In-Check DIAL.² To achieve effective medication delivery, the patient must generate sufficient force to produce the required PIF to overcome the internal resistance of the DPI and to separate the active drug from its carrier molecules.³ For most DPIs, a PIF of 60 L/min is considered optimal for adequate powder deaggregation.⁴ However, suboptimal PIF is common among hospitalized patients with COPD. A real-world study conducted by Mahler et al.⁵ reported that 44.6% of hospitalized COPD patients who were using a DPI demonstrated suboptimal PIF. Similarly, a real-world study conducted by the Montreal Chest Institute reported suboptimal PIF in 28% of stable outpatients with COPD.⁶ Three factors associated with suboptimal PIF included the degree of severity of airflow obstruction (40.5% in GOLD 4), female sex (suboptimal PIF was observed in 49% females versus 8% of males), and a low body mass index.⁶

Patient Behaviour

The CTS recommends administering triple inhaler therapy through a single inhaler.⁷ Single-inhaler triple therapy (SITT) is preferred over multiple-inhaler triple therapy due to its potential for increased benefits, improved adherence, and reduce inhaler technique errors.^{7,8}

Patient's Level of Consciousness and Coordination

Metered-dose inhalers (MDI) require patients to coordinate device actuation with inhalation,

and to inhale slowly (count of 5) and deeply.¹ For patients who are unable to perform a conscious inhalation manoeuvre, a pressurized metered-dose inhaler (pMDI) with a spacer or a nebulizer is recommended. In conscious patients with poor coordination and insufficient PIF, suitable options include a pMDI with a spacer, a soft mist inhaler, a nebulizer, or a breath-actuated MDI.^{9,10}

Disease and Drug Factors

Both asthma and COPD are airway diseases commonly treated with inhaled medications. To achieve optimal therapeutic benefit, it is essential that these medications are delivered to the sites of disease activity within the respiratory tract. This is particularly pertinent given the recognized role of small airway disease (SAD) in the pathophysiology of both COPD and asthma. Small airways, defined as airways with a diameter of less than 2 mm, serve as an important anatomical bridge between conductive larger airways and gas exchanging peripheral airways of the lung. Thus, optimizing the delivery of inhaled medications to the smaller airways may be an important consideration for the management of COPD and asthma.

In asthma, SAD contributes to overall airway resistance.¹¹ Histopathology studies have confirmed the presence of small airway abnormalities in asthma, irrespective of the severity of the disease.^{12,13} In COPD, the small airways are considered to be the primary site of disease progression. The prevalence of SAD increases with disease severity, affecting an estimated 51% of patients with GOLD stage 2 COPD and 95% of those with GOLD stage 4 disease.¹⁴ SAD has also been observed in pre-COPD patients, smokers, and patients with normal spirometry. Evidence of ventilation inhomogeneity and peripheral acinar inhomogeneity has been observed in patients with SAD,¹⁵ while histopathologic sampling of micro computed tomography (CT) imaging studies have demonstrated SAD in pre-COPD patients who exhibit symptoms or structural/physiological abnormalities despite non-obstructive spirometry.^{16,17}

Over the past several decades, growing attention has focused on the early origins of lung diseases. Research into these origins has identified that small airway inflammation may be a potential driver of disease progression.¹⁸ A variety of methods are available to assess SAD, with oscillometry increasingly recognized as a

non-invasive, reproducible physiologic tool for its assessment.^{19,20} Oscillometry enables the measurement of opposition to oscillatory airflow using the formula: **Impedance = Resistance + Reactance**

Resistance reflects the peripheral airway diameter and reactance reflects the stiffness (elastance) of the lung (**Figure 1**). More negative reactance values are indicative of small airway dysfunction, as airway narrowing or closure reduces the number of communicating lung units and increases the elastic stiffness of the lungs (**Figure 1**). Thus, reactance measured at 5 Hz (X5) may indicate SAD.²¹ Resistance measured at 5 Hz (R5) represents total airway resistance, while resistance at 20 Hz (R20) reflects resistance within the central airways. The difference (R5-R20) is a useful index of small airway resistance.²²

A growing understanding of SAD and advances in its assessment have increasingly

influenced inhaler selection by gauging the device's ability to deliver medication to the small airways.²³ The presence of SAD can influence COPD patient outcomes. Measures of quality of life and dyspnea have been shown to correlate more strongly with SAD as assessed by oscillometry than with forced expiry volume in 1 second (FEV1).²⁴ In addition, functional SAD identified by CT analysis has been recognized as an independent risk factor for future exacerbations.²⁵ Patients who experience frequent exacerbations also demonstrate significantly greater acinar zone inhomogeneity compared to those with infrequent exacerbations.²⁶ Small airway dysfunction has been associated with an increased risk of all cause, cardiovascular, respiratory, and neoplasm-related mortality, supporting a role for SAD as a prognostic marker of mortality.²⁷ In addition, functional SAD identified by CT in the early stages of COPD independently predicted accelerated loss

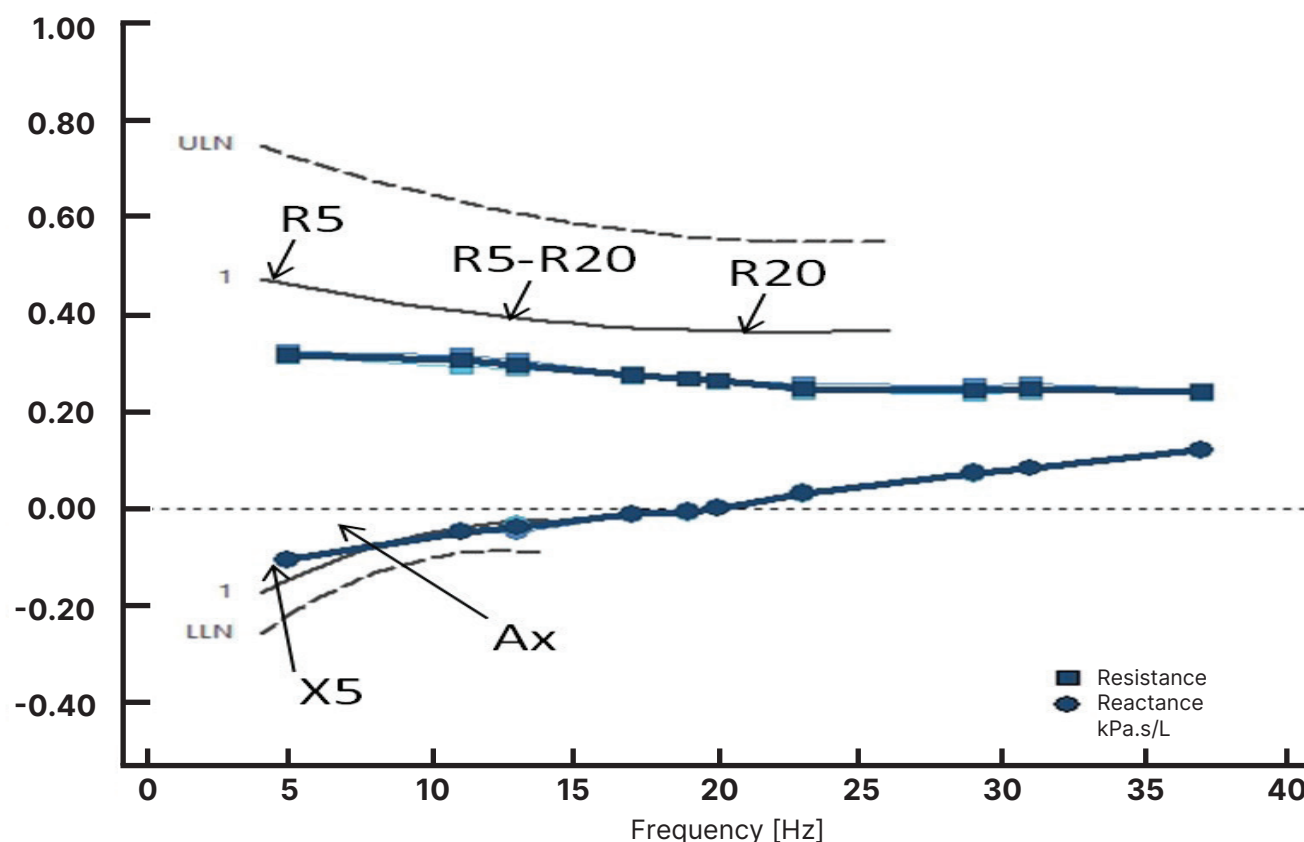


Figure 1. The representative resistance and reactance spectrum obtained during forced oscillation in a healthy adult's lungs. R5: Resistance at 5 Hz, reflecting airflow obstruction; R20: Resistance at 20 Hz, indicating an obstruction at the level of the central airways; R5-R20: Differences in resistance between R5 and R20 indicating an obstruction at the small airway level; X5: Reactance at 5 Hz, with a lower X reflecting a decrease in compliance; and Ax: Reactance area under the curve, with larger Ax values indicating an increase ventilation heterogeneity and greater lung stiffness, often resulting from an airway obstruction or collapse that reduces the volume of the aerated area of the lung; *courtesy of George Philteos, MBBCh, MSc, FRCPC, D. ABSM*

of lung function.²⁸ CT-detected functional SAD was also independently associated with an accelerated decline in FEV1 over a median follow-up period of 32 months among younger smokers with normal spirometry.²⁹

Potential Impact of SAD Evaluation on the Selection of Inhaled Therapies

To assess the impact of SAD on the selection of inhaled medication, Verbanck et al.³⁰ compared peripheral acinar ventilation inhomogeneity, as measured by forced oscillometry, between a DPI and an SMI. The SMI demonstrated significantly greater improvements in ventilation compared to the DPI. These improvements in ventilation was attributed to enhanced small airway function secondary to improvements in peripheral deposition, which is facilitated by the smaller particle size delivered by the SMI.³¹ Particle size is considered to be the critical factor of pulmonary deposition, with extra-fine particles, defined by a mass median aerodynamic diameter (MMAD) of <2.1 µm, achieving more effective delivery to the peripheral airways.³²

Usmani et al.³³ have shown that extra-fine SITT formulations achieved superior peripheral distribution and airway penetration compared with non-extra-fine formulations in patients with moderate to severe COPD. Similarly, co-suspension delivery using Aerosphere® technology, which employs porous particles made of phospholipids of 1 to 2 µm in size was shown to increase peripheral drug deposition.³⁴ Consistent with these findings, Tzani et al.³⁵ showed that extra fine particle formulations were more effective than conventional formulations in reducing gas trapping and improving dyspnea in patients with COPD and hyperinflation.

Lipworth et al.³⁶ evaluated the potential of inhaled products used in asthma and COPD to penetrate the small airways, highlighting the clinical implications of small airway dysfunction, including poor disease control and worse health status. They used impactor analysis to assess inhaled particle size based on MMAD (**Figure 2**). Extra-fine particle fraction, defined as particles with a diameter <2 µm, was calculated as a percentage of the delivered dose. Smaller particles are more likely to penetrate the small airways

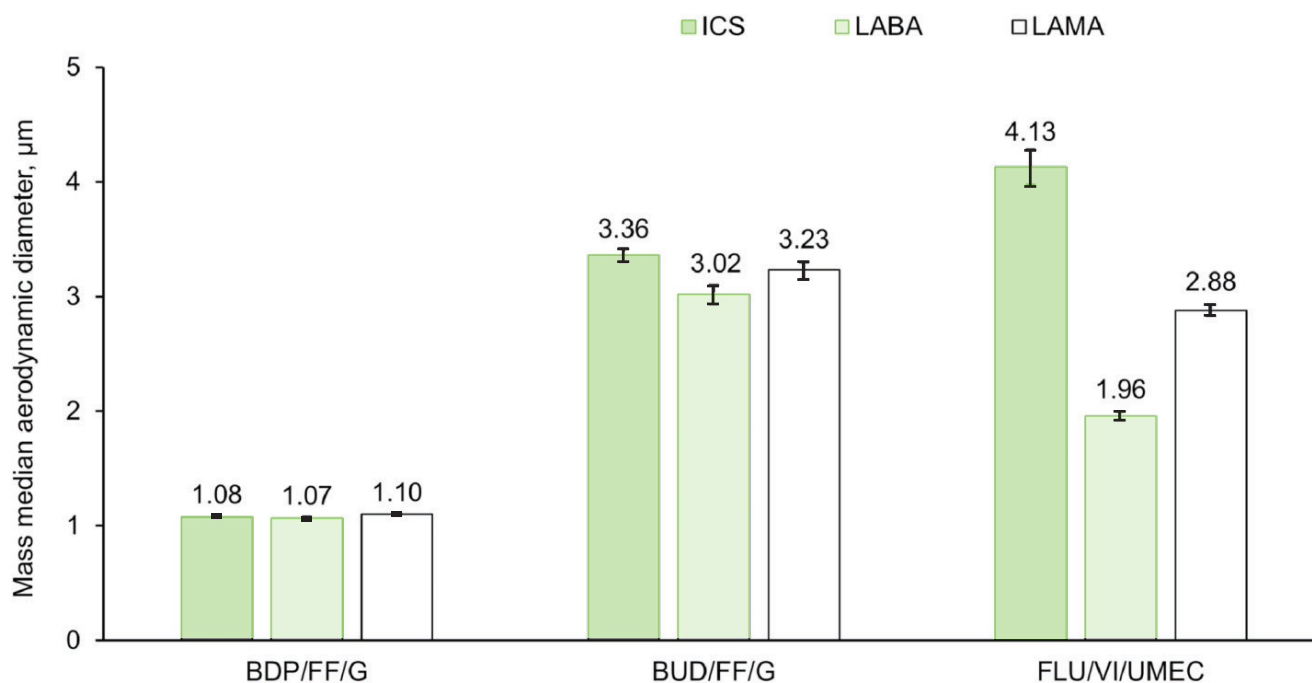


Figure 2. The mass median aerodynamic diameter (MMAD) of the three inhaled triple-therapy formulations. Mean values are presented with 95% CI. BDP/FF/G, n=54; BUD/FF/G, n=6; and FLU/VI/UMEC, n=6; courtesy of George Philteos, MBBCh, MSc, FRCPC, D. ABSM

Abbreviations: BDP: beclomethasone dipropionate; BUD: budesonide; CI: confidence interval; FF: formoterol fumarate; FLU: fluticasone furoate; G: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist; LAMA: long-acting muscarinic antagonist; UMEC: umeclidinium; VI: vilanterol (Lipworth et al., 2026).²⁰

(Figure 2). However, the authors emphasized the need for prospective randomized clinical trials to confirm whether treatment with extra-fine particle formulations can better target the small airways and subsequently improve disease control in patients with asthma and COPD.

Impact of Health Status and Comorbidities on the Selection of Inhaled Corticosteroids

Inhaled corticosteroids (ICSs) play an important role in the management of asthma and are recommended for use in selected patients with COPD. However, the clinical benefits of ICS should be weighed against the risk of local and systemic adverse effects, particularly in patients with relevant comorbidities. Evidence suggests that ICS use may be associated with an increased risk of respiratory infections, cataracts, and reductions in bone mineral density.³⁷ Systemic exposure to ICS can occur through both gastrointestinal absorption of the swallowed fraction and direct absorption from the lungs, which may increase the risk of systemic adverse effects. The likelihood of systemic side effects varies among ICS agents.³⁸ As noted by Baptist and Reddy,³⁹ lower bioavailability is generally associated with reduced systemic side effects. They noted that among ICSs, ciclesonide has a particularly low bioavailability, while ciclesonide and mometasone exhibit high serum protein binding, further reducing systemic effects. Moreover, fluticasone has low oral bioavailability due to fast metabolism in the liver.

Other adverse effects of ICSs are localized to the oropharynx, and include dysphonia, pharyngitis, and oropharyngeal candidiasis. Dysphonia affects up to 58% of patients using ICSs.⁴⁰ Williams et al.⁴¹ postulated that dysphonia may result from bilateral vocal cord adductor myopathy, identified as bowing in the vocal folds, secondary to local deposition of ICS. Notably, ciclesonide and beclomethasone are administered as prodrugs that undergo activation in the lungs. Ciclesonide requires hydrolyzation by esterases in the lung tissue to form the active metabolite, while exhibiting a low rate of transformation to the active metabolite in the mouth.⁴² Similarly, beclomethasone is activated by hydrolysis in the lung tissue.⁴³ Due to these properties, both ciclesonide and beclomethasone are postulated to exhibit a lower occurrence rate of oropharyngeal side effects. In summary, when selecting ICS

prescribers should consider the pharmacokinetic properties and potential adverse effects alongside patient-specific tolerance to inform the selection of appropriate inhaled therapies.

Conclusion

Inhaled therapies retain a central role in the management of respiratory conditions such as asthma and COPD, providing targeted delivery of medication directly to the lungs. However, the effectiveness of these therapies depends on factors beyond the pharmacological properties of the medication alone. Appropriate inhaler technique, adherence to treatment, particle size, and consideration of the pharmacokinetic properties and potential adverse effects of inhaled medications are important factors in optimizing treatment outcomes. When selecting inhaled therapy, prescribers should consider individual patient characteristics, preferences, and treatment tolerability. Ensuring that patients receive adequate education and ongoing assessment of their inhaler technique may further improve medication delivery and therapeutic effectiveness. Ultimately, optimal inhaled therapy selection for each patient requires an individualized approach that integrates patient, device, drug, and disease factors to achieve the best possible clinical outcomes.

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