Choosing the Best Inhaled Medication Device

Key Aspects of Aerosol Science for the Clinician and Educator

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MDHHS ASTHMA SHARING DAY

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UNIVERSITY OF MICHIGAN PEDIATRIC PULMONARY

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Objectives

1. Describe the advantages and limitations of common aerosol medication delivery devices
   - Metered dose inhalers (pMDI, baMDI)
   - Dry powder inhalers (DPI)
   - Soft mist inhalers (SMI)
   - Nebulizers (Neb)
2. Identify patient characteristics that fit well with each of the common aerosol medication delivery devices.

Disclosures

I have no financial relationships with any pharmaceutical companies or respiratory equipment manufacturers discussed here

Where possible I have tried to utilize generic drug names and use non-branded visual images.

Some slides include references to brand name drugs or show brand names in images. This is either from the source material or used to help clinicians connect concepts to brands they may know.

I do not endorse or promote any particular drug or product

CASE:

A 15 year old boy has refilled his albuterol inhaler monthly for the last 6 months.

You ask him to show you his medications and how he is taking them.

I take it like this:

Why don’t you use the spacer we gave you last visit?

Its too big to fit in my pocket, and I don’t like my friends to see me use it.

Photo credit: Mehmet Hilmi Barcin; Getty Images/iStockphoto

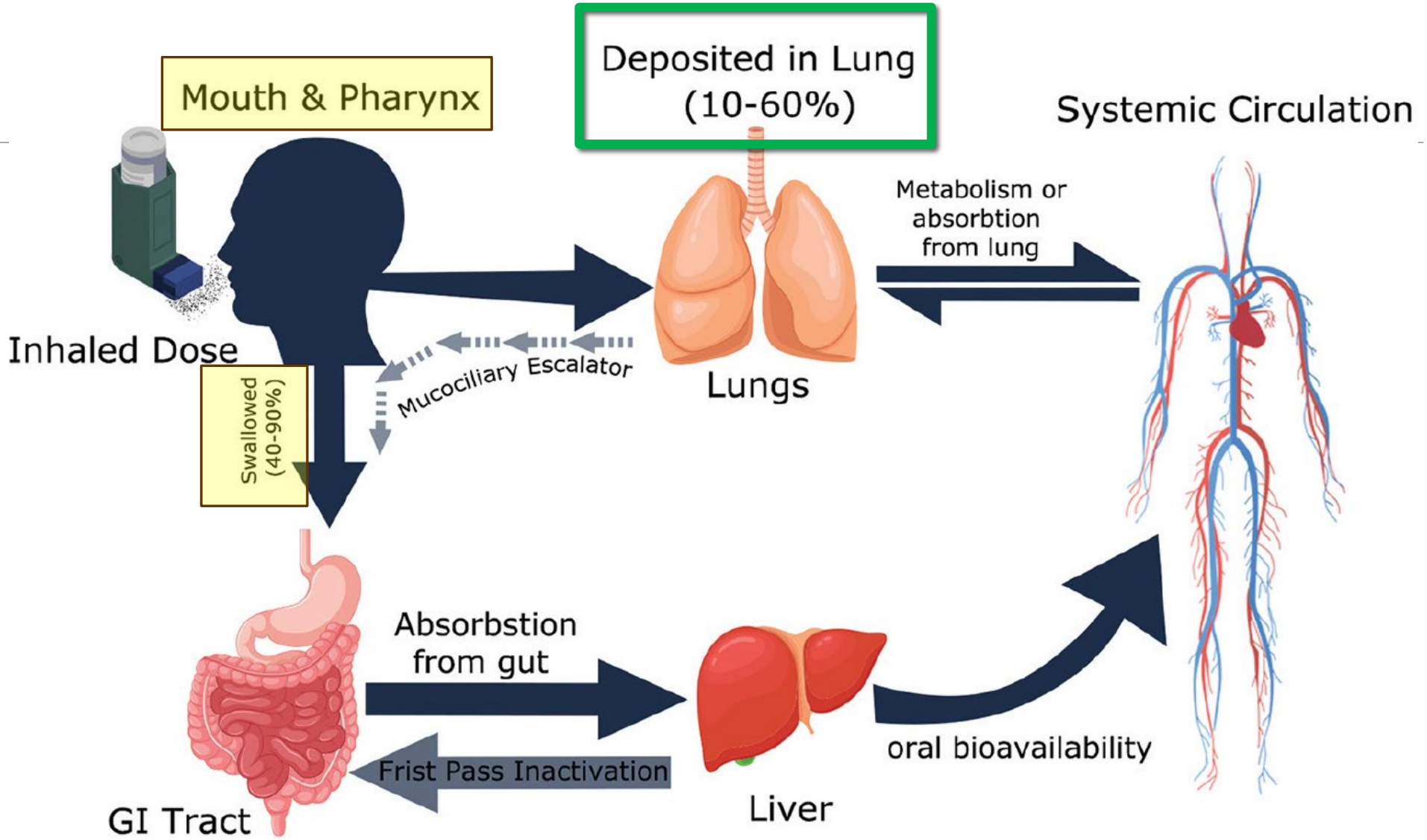
Q1. How would you help improve medication delivery for this patient?

A. Help optimize his technique with the standard inhaler (pMDI) without a spacer because he seems unwilling to use a valved holding chamber (VHC).

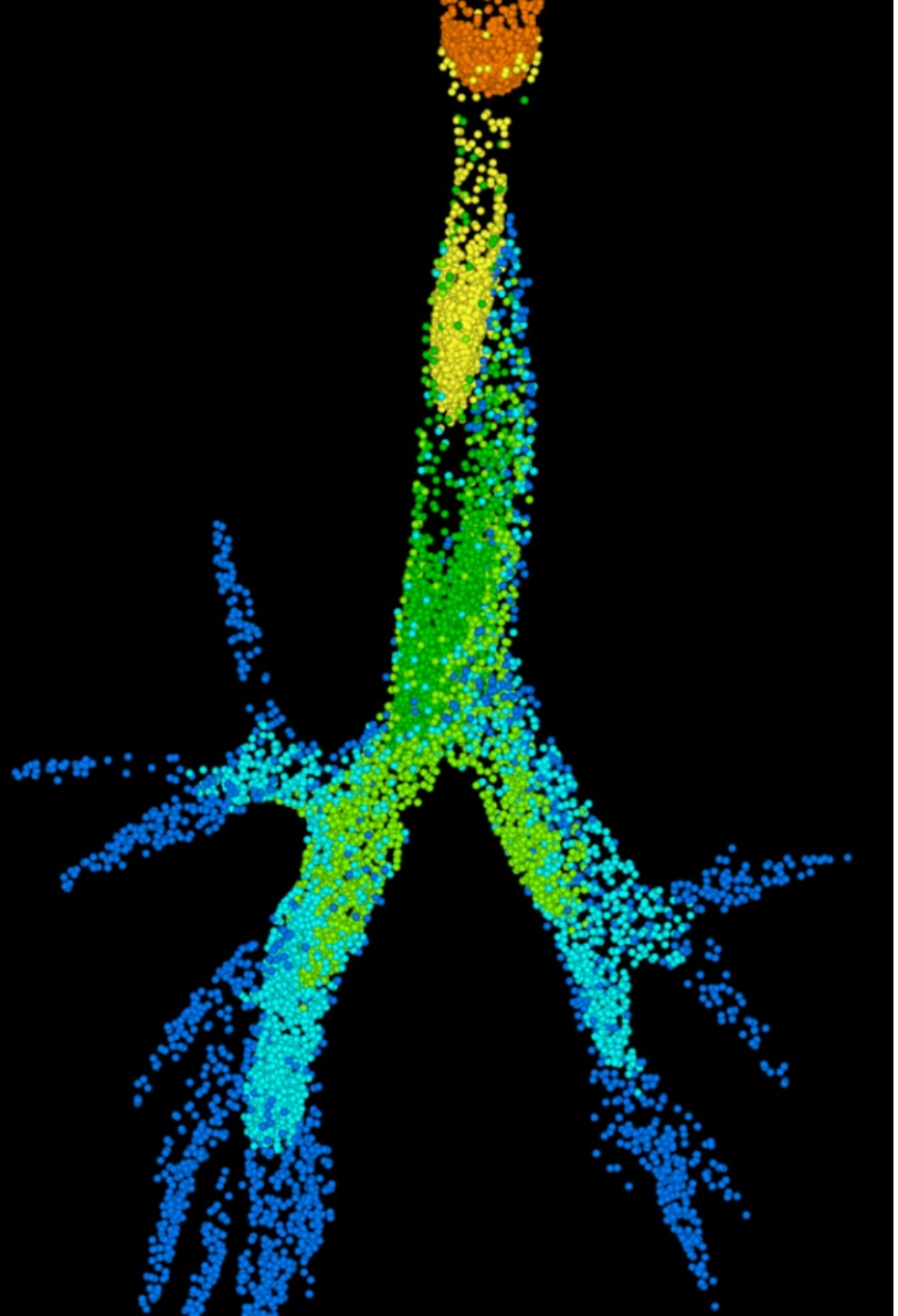
B. Explain the benefits of the chamber and teach the technique for using a pMDI with chamber

C. Select a different delivery device that doesn't require the use of a chamber, like a breath-actuated inhaler (baMDI) or a dry powder inhaler (DPI).

Where do inhaled aerosols go?



Alharbi AS, Yousef AA,et al. Application of aerosol therapy in respiratory diseases in children: A Saudi expert consensus. Ann Thorac Med 2021;16:188-218



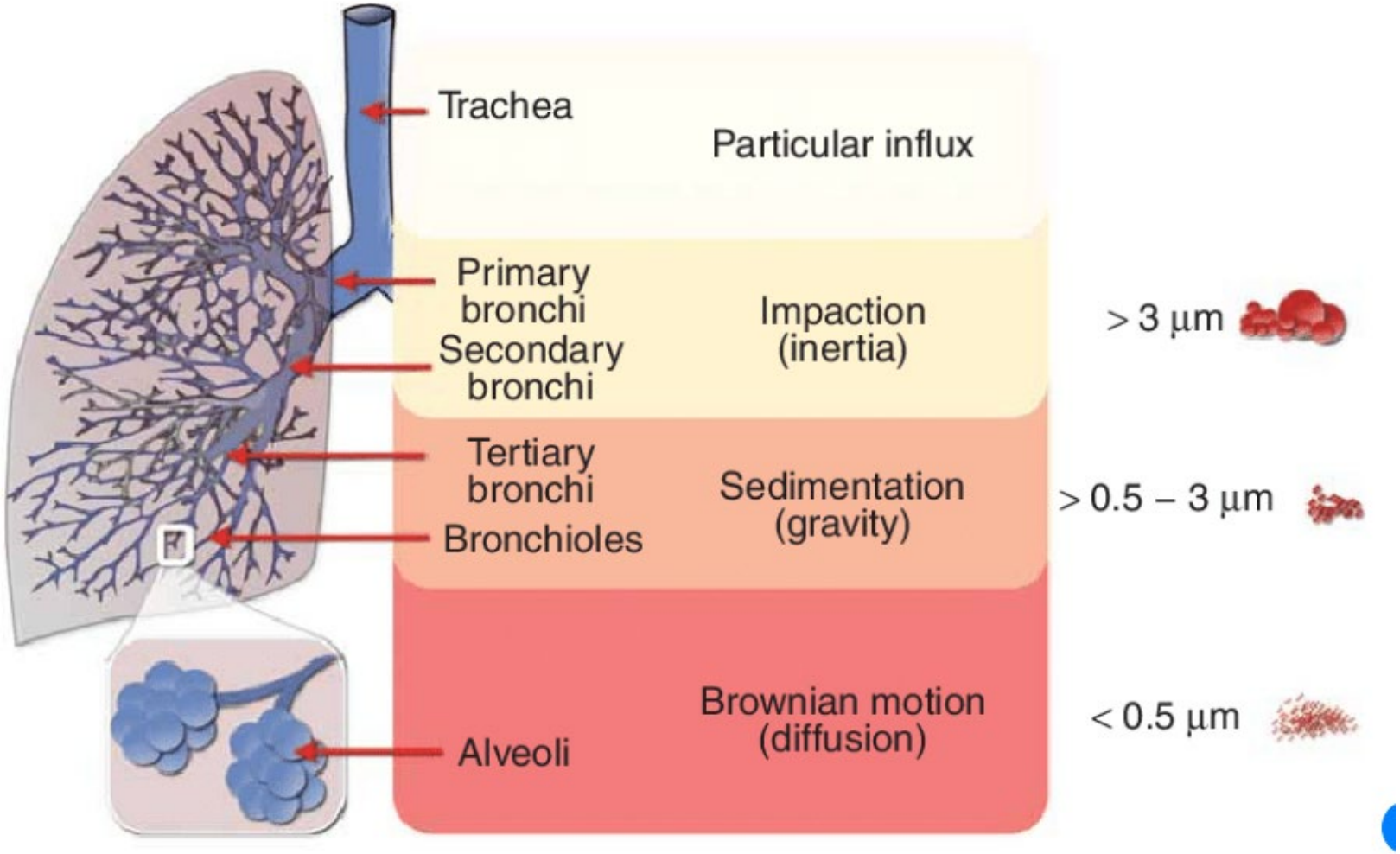
Aerosols deposit unevenly in the respiratory tract

Where an aerosol lands will determine whether it has a therapeutic effect, an undesired side effect, or no effect at all

Why does knowing about aerosol drug delivery matter?

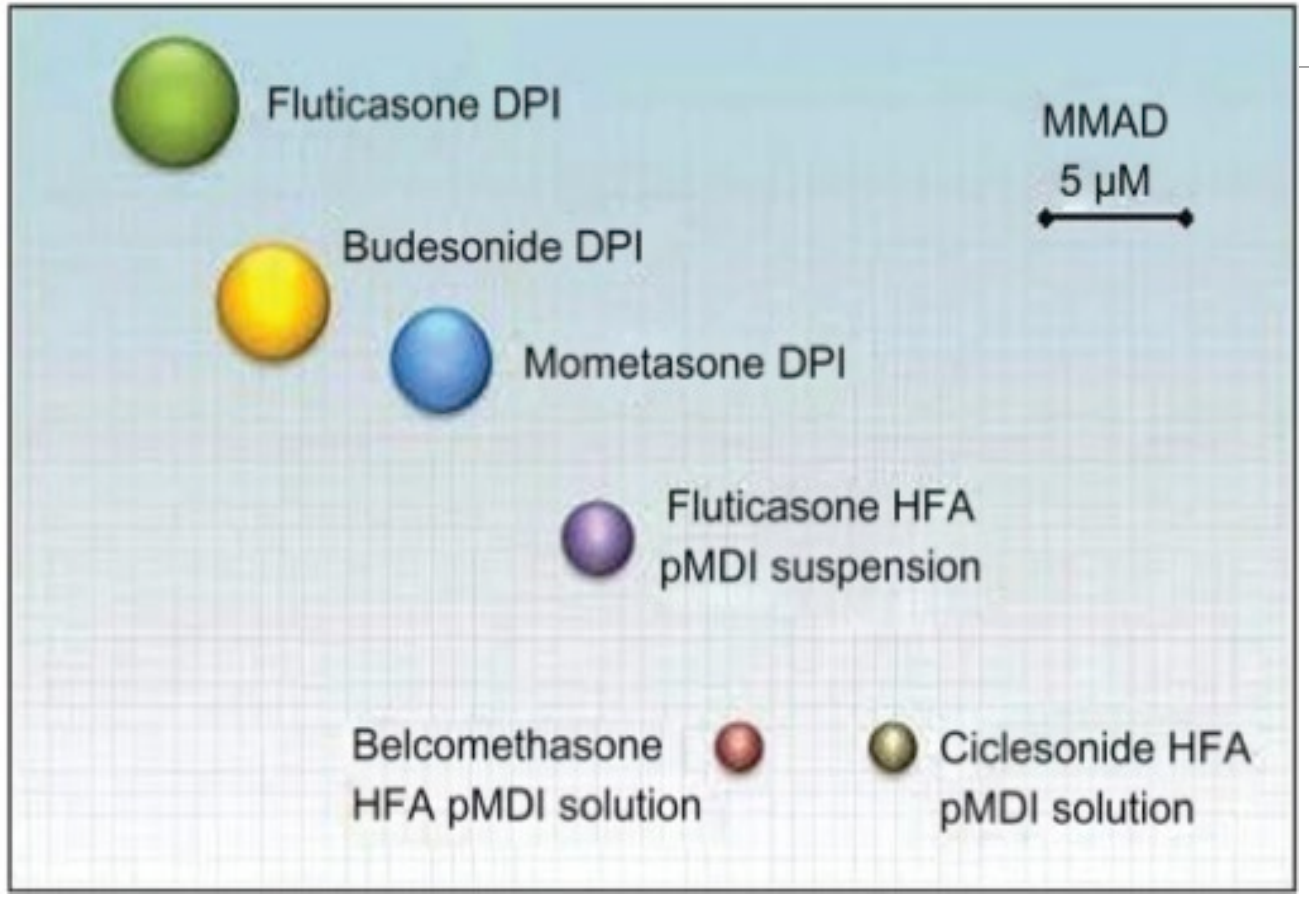
1. Efficacy of aerosolized meds depend on good delivery to airways
2. Delivering medications to the lung topically, can dramatically reduce side effects associated with systemic administration
3. Knowing factors that improve drug delivery to the target tissue helps prescribers select the most effective delivery device for their patient

Particle size is a key influence of mechanism and location of deposition



M, Klinger-Strobel & Lautenschläger, C et al., (2015). Aspects of pulmonary drug delivery strategies for infections in cystic fibrosis - where do we stand?. Expert Opinion on Drug Delivery. Feb (2):1-24.

Different meds and devices generate different particle sizes



Guide to common brand names:

Fluticasone DPI= Flovent discus

Budesonide DPI = Pulmicort Turbuhaler

Mometasone DPI = Asmanex Twisthaler

Fluticasone HFA = Flovent HFA MDI

Beclomethasone HFA = Qvar Redihaler

Ciclesonide HFA = Alvesco HFA MDI

NR Mueller, “From inhaler to lung: clinical implications of the formulations of ciclesonide and other inhaled corticosteroids”, Int J Gen Med, 2013

Where aerosols land depends on many factors

Device properties

- Actuator
- Mouthpiece
- Cleanliness
- With/without spacer
- Propellants

User properties

- Age (younger = more NP and tracheal deposition)
- Training/complexity of use
- Body position
- Inspiratory technique/flow
- Coordination
- Disease state and severity

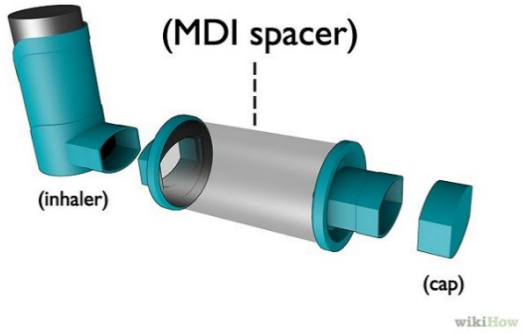
- **Aerosol properties**
  - Particle size: Mass median aerodynamic diameter (MMAD)
  - Fraction of fine particles
  - Air/particle velocity
- **Particle properties**
  - Density
  - Shape
  - Charge
  - Agglomeration (“stickiness”)
- **Physical-chemical properties**
  - Solubility

M Ibrahim, R Verma, L Garcia-Contreras, “Inhalational drug delivery devices: technology update”, Med Devices, 2015; 8:131-139

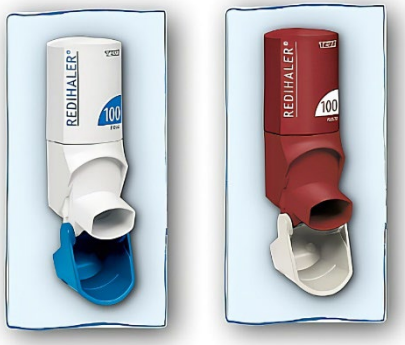
Many Choices of Devices

Metered Dose Inhaler

- **Pressurized (pMDI)**
  - Can be used with a valved holding chamber (VHC)



- **Breath Actuated (bMDI)**



Dry Powder Inhaler (DPI)

Soft mist inhaler (SMI)

Jet Nebulizer

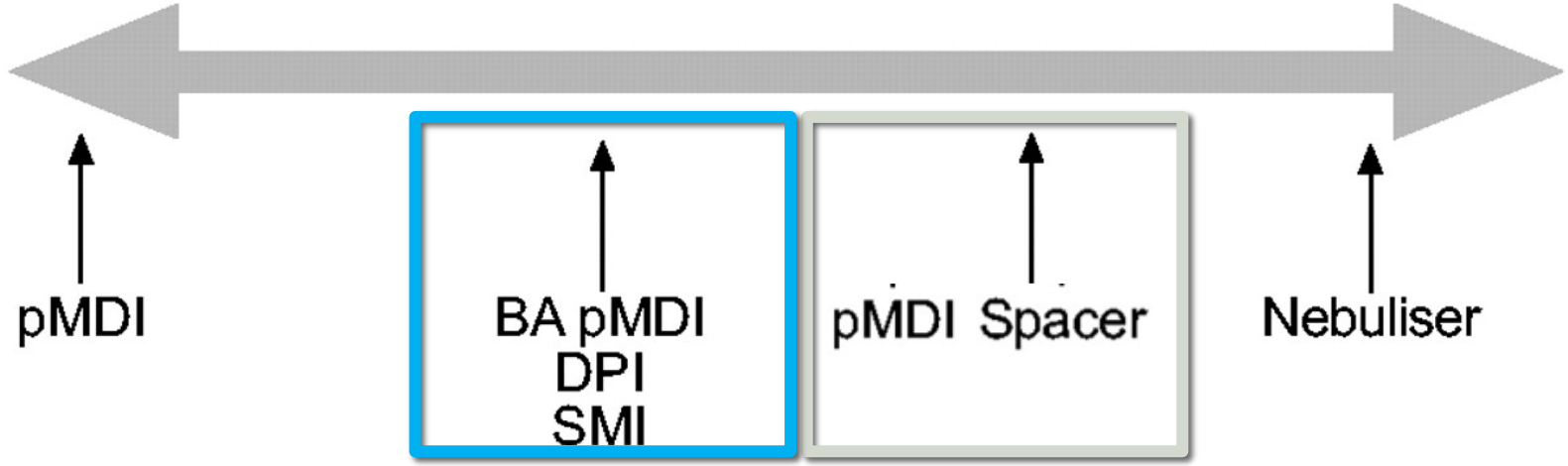
Balance between convenience, ease of use, and efficient drug delivery

Small, portable

Require lip seal, inspiratory flow, follow instructions on inhalation technique

Bulkier, requires more equipment

Better for those who need passive technique



pMDI = pressurized metered-dose inhaler

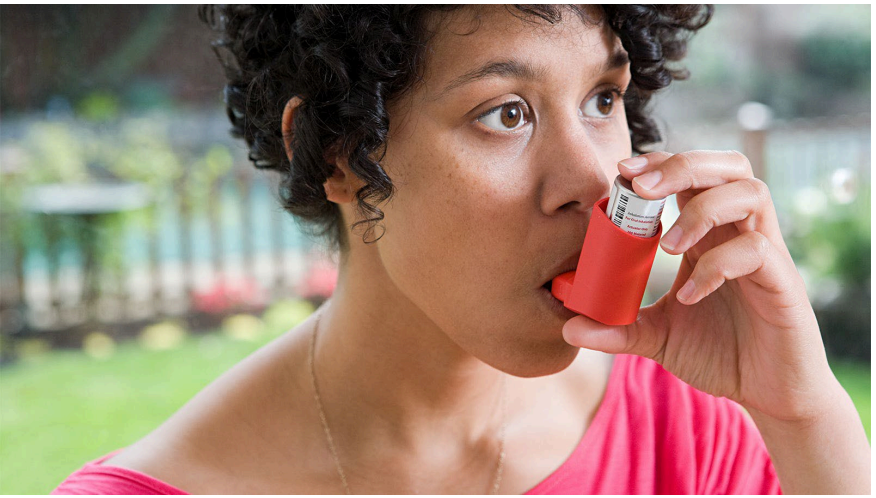
BA pMDI = breath-actuated pressurized metered-dose inhaler

DPI= dry powder inhaler

SMI = soft mist inhaler

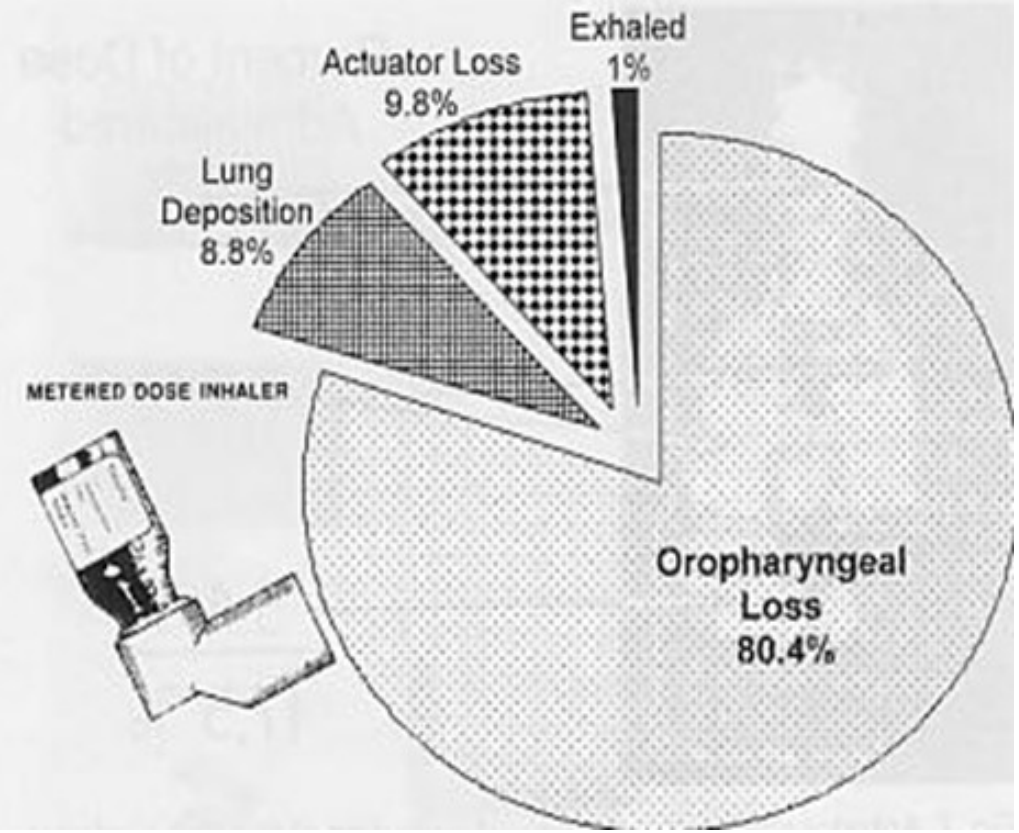
Adapted from Newman SP, Eur Resp Rev, 2005

“Traditional” Pressurized Metered Dose Inhalers (pMDI)

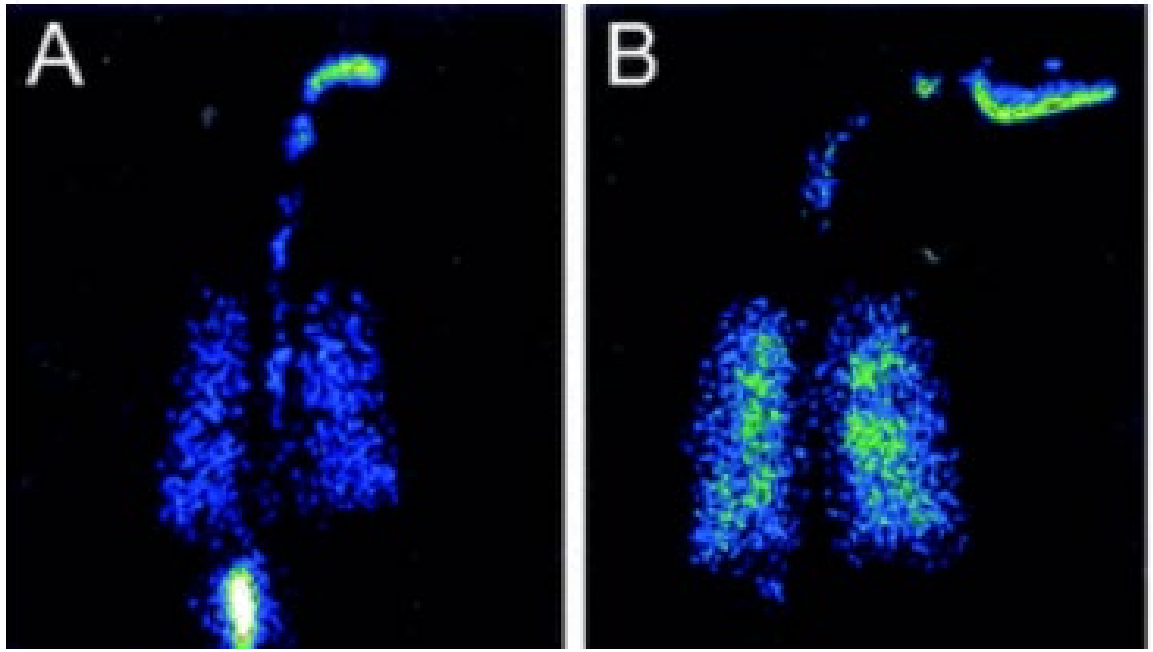


pMDIs are inefficient – but can be made better with a VHC

- Lung deposition with a traditional MDIs, without a valved holding chamber, has been shown to be only 10% to 20% of the dose.



- Using a valved holding chamber, increases delivery of medication to lungs.

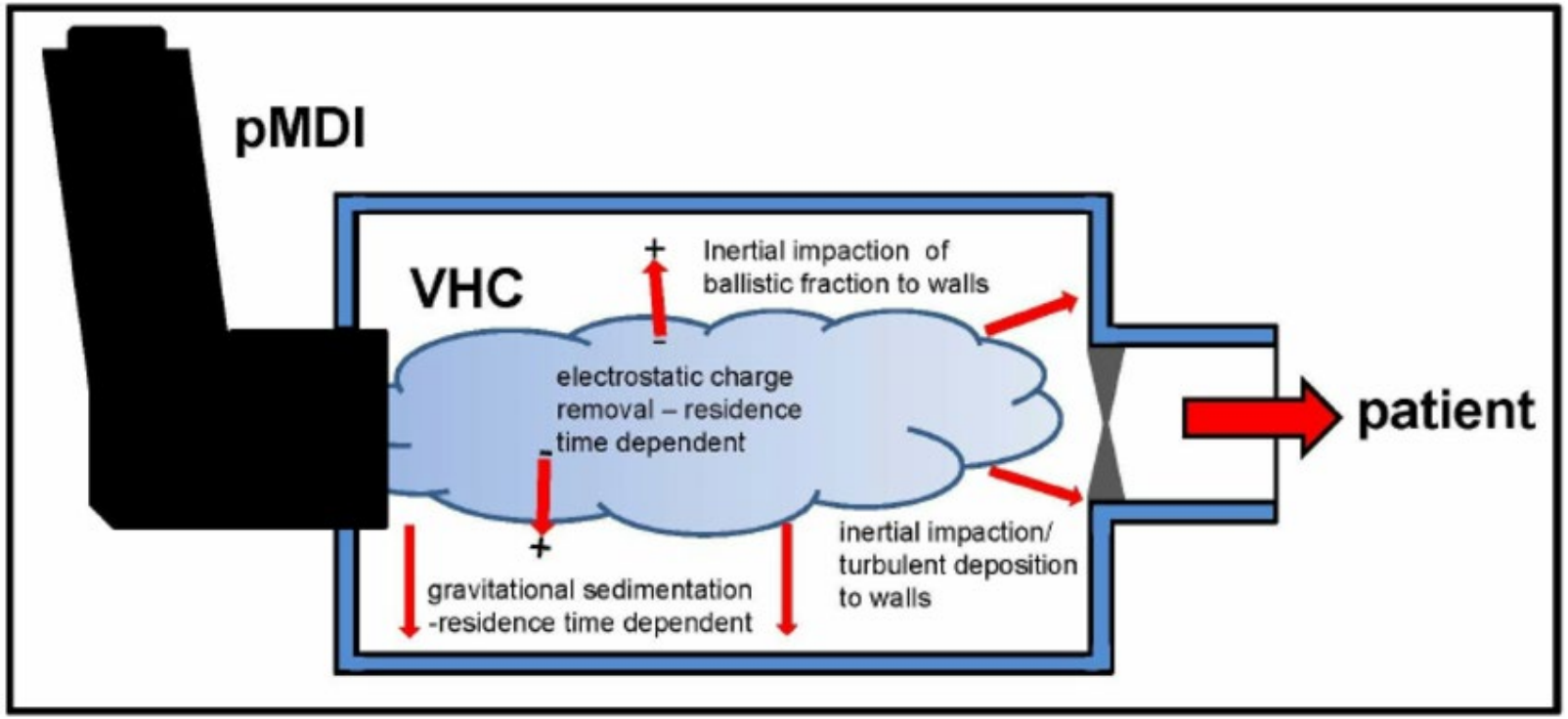


Newman SP et al, J Pharm Sci 1996;**85**(9):960–964

Valved holding chambers (VHCs)

Reduces the velocity and size of the aerosol particles

Size selective function and retains non breathable particles (>10 µm)



Terzano C. Pulm Pharmacol Ther 2001;14:351-66

Valved Holding Chambers

Reduces the need to coordinate actuation of the MDI with inhalation.

Reduces the oropharyngeal deposition of drug

Reduces the likelihood of local side effects

For drugs with significant GI absorption, a VHC reduces systemic absorption

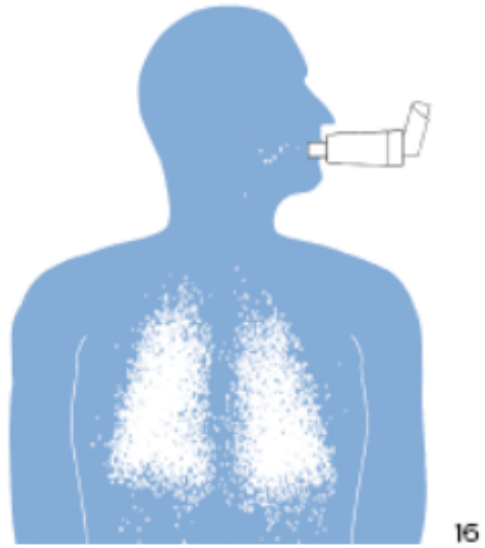
Valved Holding Chambers (VHC)

Without them, a high degree of coordination with inhalation, actuation and breath holding in a precise sequence is necessary

The benefits of a spacer or valved holding chamber

Inhaler only

Medicine end up in the mouth, throat and stomach which may cause side effects.



Inhaler with spacer

More medicine is delivered to the lungs where it can be most effective.

[16] https://www.usa.philips.com/c-e/hs/respiratory-care/what-is-asthma-spacer.html Adapted from: Hirst, PH., et al. Deposition and pharmacokinetics of an HFA formulation of Triamcinolone Acetonide delivered by pressurized metered dose inhaler. Journal of Aerosol Medicine. 2001; Volume 14 (2):155-166.

Delivery efficiency varies significantly by device type

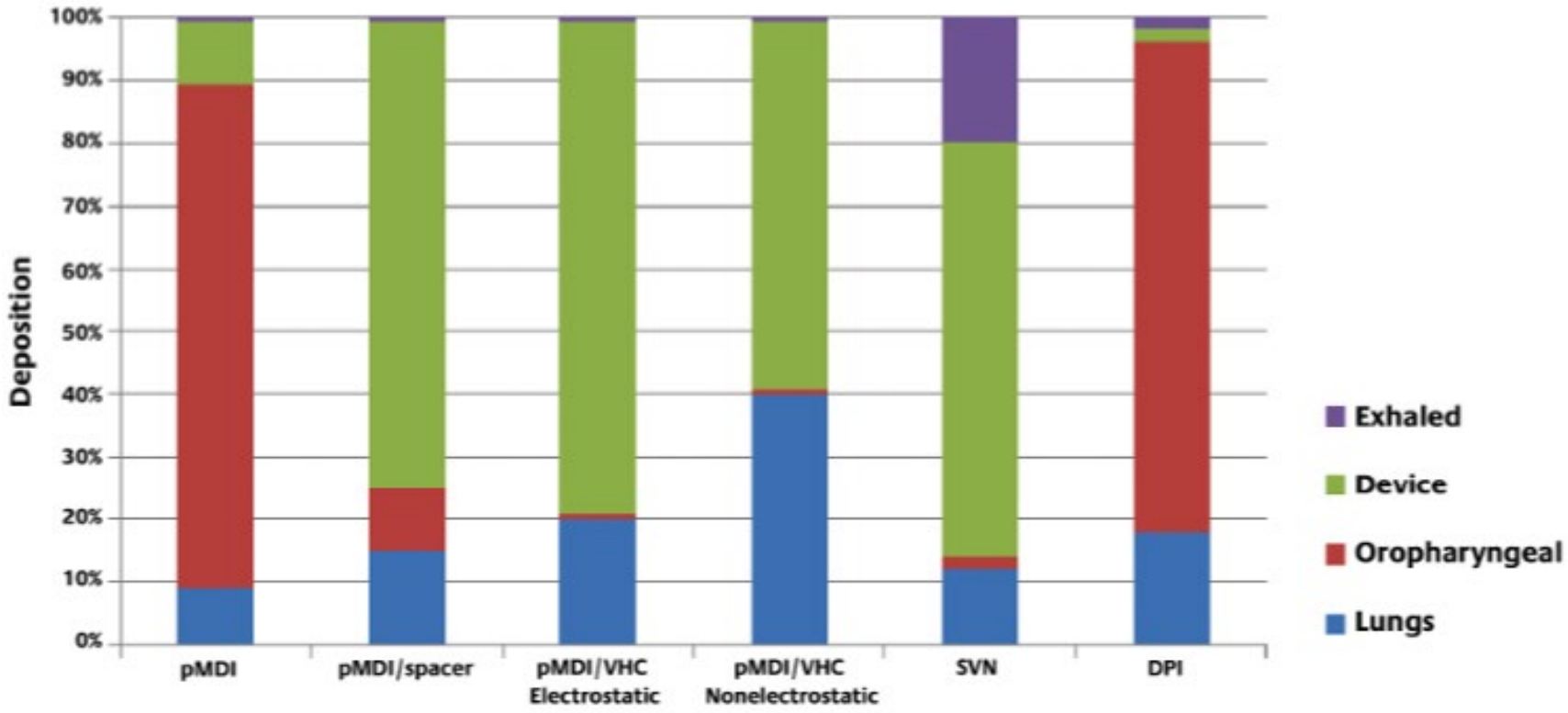


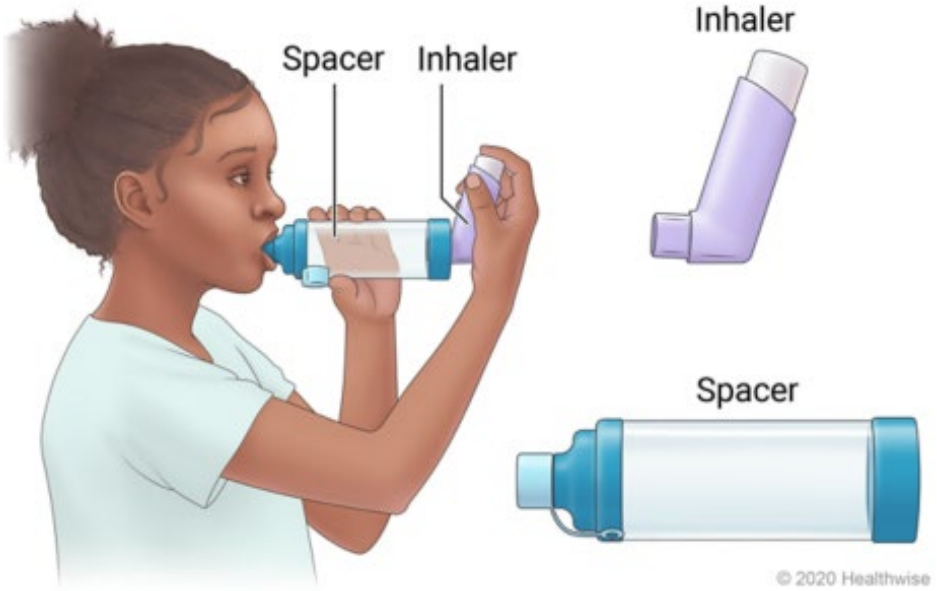
Figure 2. Drug deposition with common aerosol inhaler devices. Shown by color are the varying percentages of drug lung deposition and drug loss in the oropharynx, device, and exhaled breath.

pMDI = pressurized metered-dose inhaler; VHC = valved holding chamber; SVN = small-volume nebulizer; DPI = dry-powder inhaler

(Modified, with permission, from Reference 1 and Reference 7)

American Association for Respiratory Care, "A Guide to Aerosol Delivery Devices for Respiratory Therapists, 4th edition, 2017

VHCs – They're not just for kids!



* Be careful that you're ordering a valved holding chamber (VHC) and not an un-valved spacer – though the terms are often used interchangeably

A tight seal with lips or mask is important

The benefits of using a mask with a spacer or valved holding chamber for children with asthma

17

Mask with a poor seal

Inhaling with a poorly fitted facemask means that most of the medicine will be lost and not delivered to the lungs[17].

17

Mask with an effective seal

Inhaling through a mask that provides a soft but effective seal can help to maximize delivery of medication to the lungs[17].

https://www.usa.philips.com/c-e/hs/respiratory-care/what-is-asthma-spacer.html; [17] Adapted from Erzinger, S. et al. Facemaks and aerosol delivery in vivo. Journal Aerosol Medicine 2007; 20 (Suppl 1):S78-S84

Q2. Valved holding chambers

In practice, a pressurized meter dose inhaler (MDI) ***without*** a valved holding chamber (VHC), delivers about _____ of the emitted drug to the lower airways

a) 10%
b) 25%
c) 45%
d) 60%

Breath-Actuated Metered Dose Inhalers (bMDI)

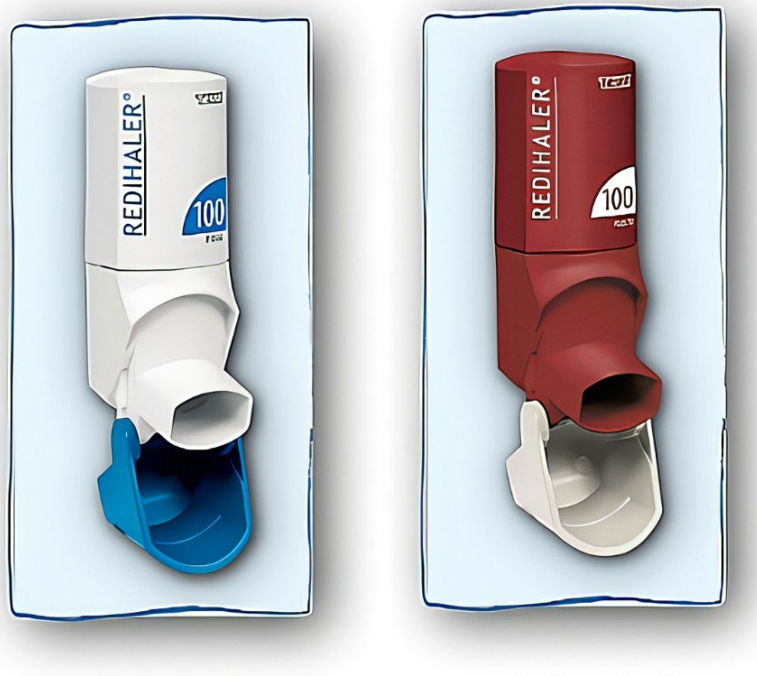
University of Maryland College of Pharmacy:
Using a Breath Actuated Inhaler - YouTube

- Opening the cap prepares the dose for release
- Patient puts their lips directly on the mouthpiece
- The patient's inspiratory effort triggers the dose to be released from the MDI.
- There is still a propellant pushing the dose out at high velocity
- **For patients using a pMDIs without a chamber who have poor coordination, bMDIs can increase lung deposition from 7% to 21% (3x)**

Breath-Actuated Metered Dose Inhalers (bMDI)

Box 1. The advantages of breath-actuated inhalers.

- Portable and durable
- Less inspiratory effort required
- Delivered dose is independent of inspiratory flow
- Release the drug at a low velocity – decreased oropharyngeal deposition and increased lung deposition
- Spacer not required
- No coordination required
- Simple to learn and use
- Can be used in children and elderly
- Cost effective in the long-run



Example: QVar RediHaler

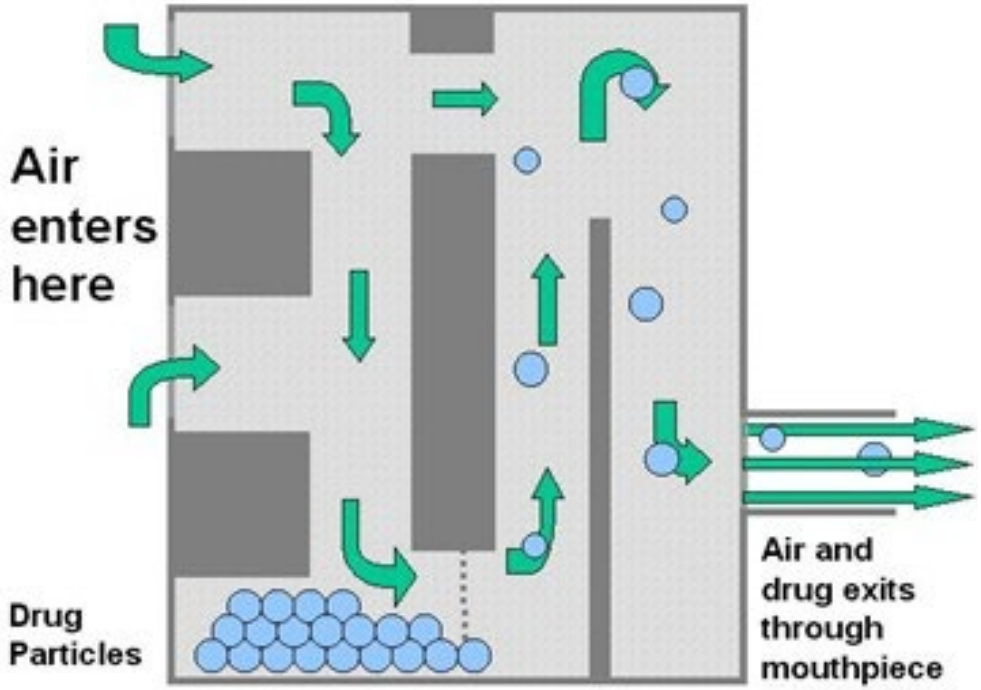
Newman SP, et al. Thorax 46, 712–716 (1991).

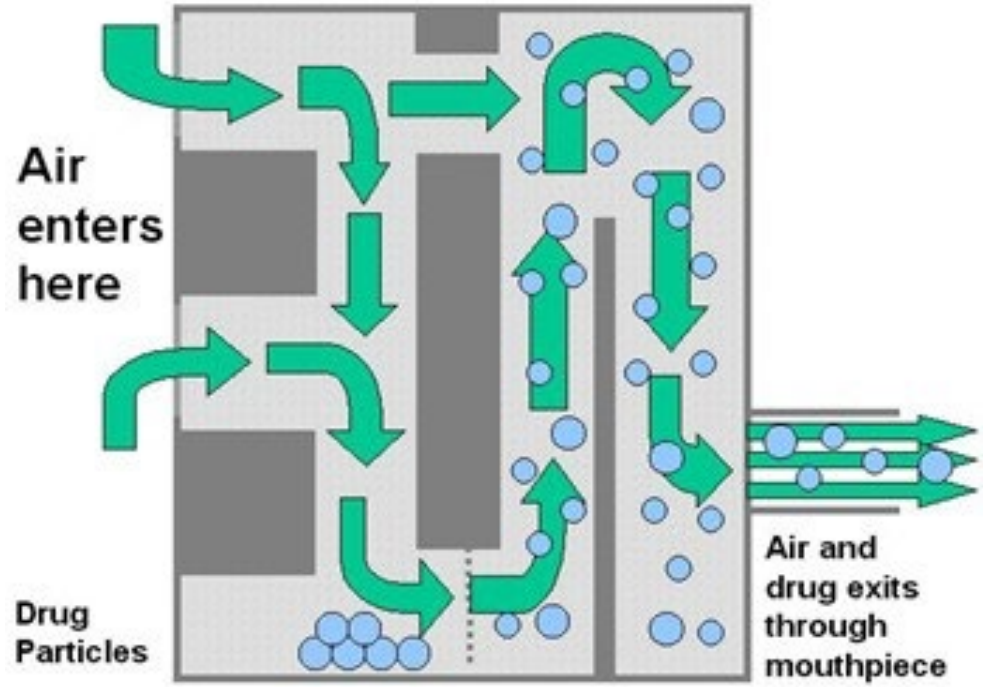
Dry Powder Inhalers

A sample of some of the many dry powder inhalers available in the United States

Image courtesy of Asthma and Allergy Network

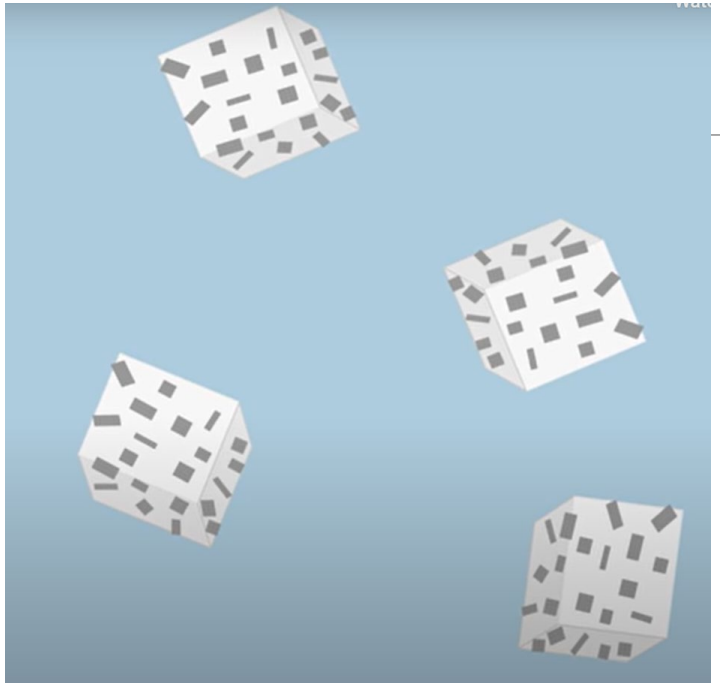
DPI – Role of flow rate and resistance



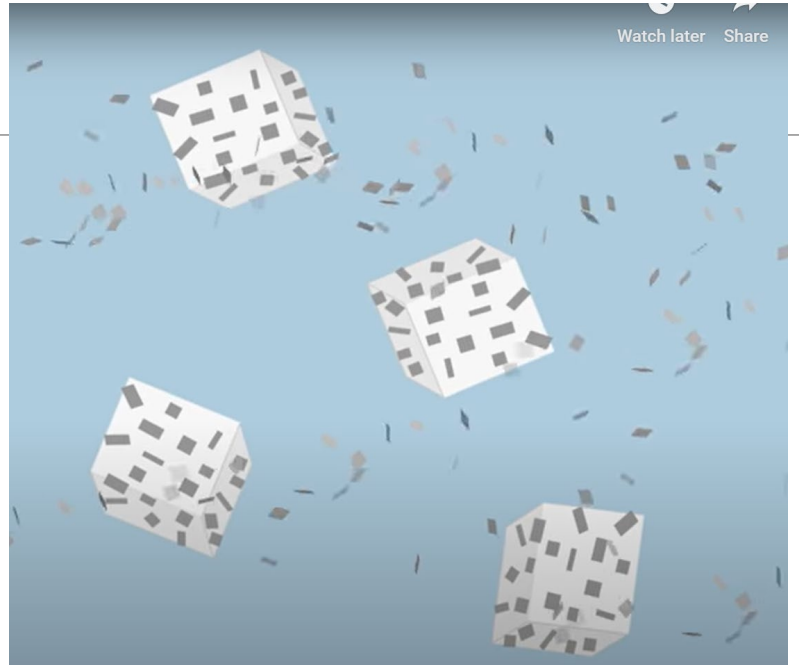


- Higher flow rate helps dispense drug but increases likelihood of impaction on oropharynx
- Resistance of device to airflow is another key characteristic influencing drug delivery

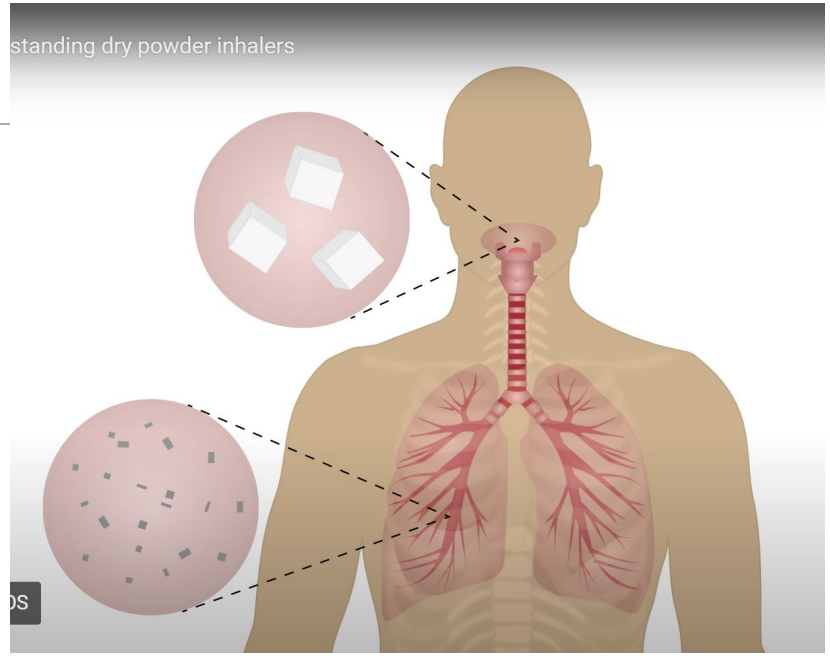
Dry Powder Inhalers



Dry powders consist of micro-particles of active medication adhered to carrier molecules, like lactose



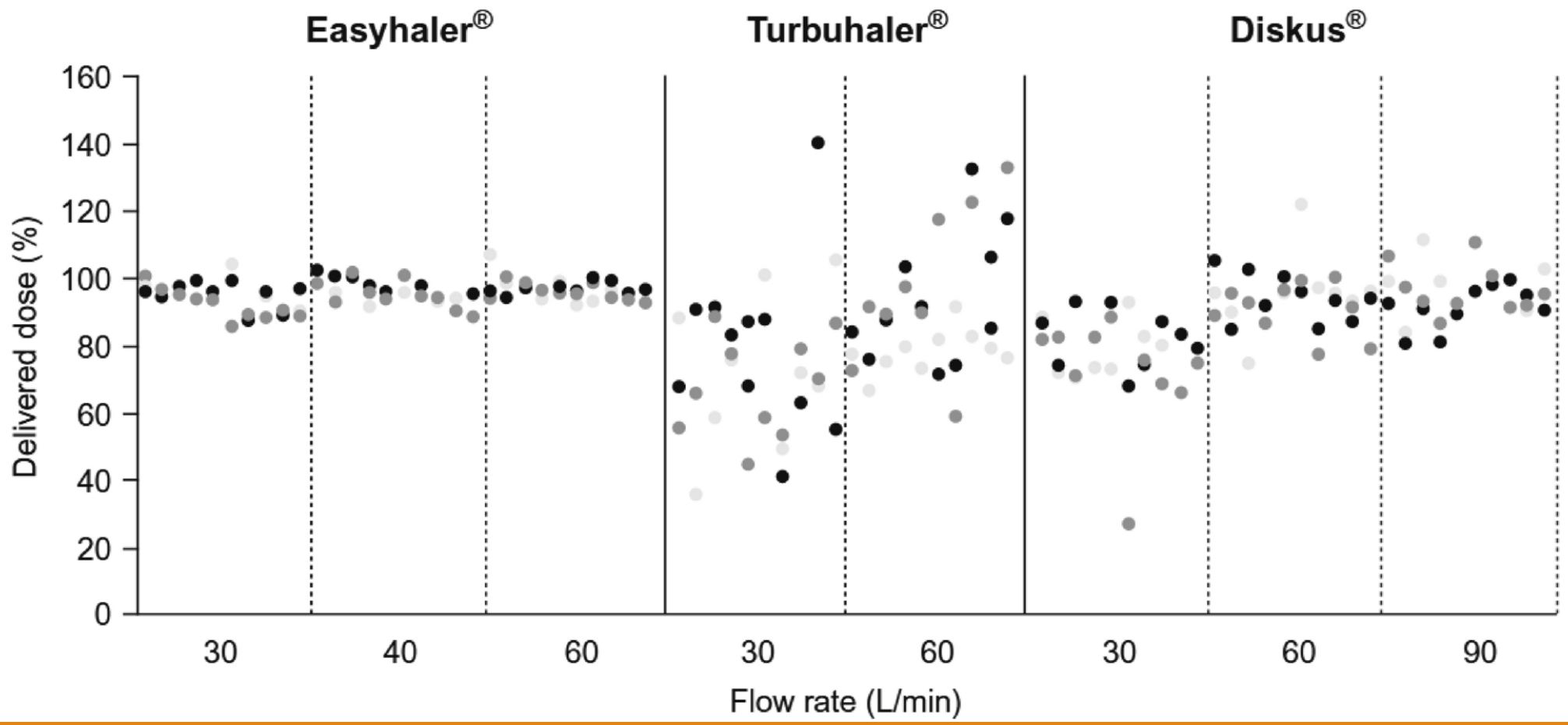
The inspiratory flow separates the active drug from the carrier.



The active drug is delivered deep into the lungs, while the larger carrier gets deposited in the mouth/throat

Levy ML et al, “Understanding Dry Powder Inhalers.” Adv Ther 2019; 36:2547-2557
https://www.youtube.com/watch?v=F43vX19FUW8

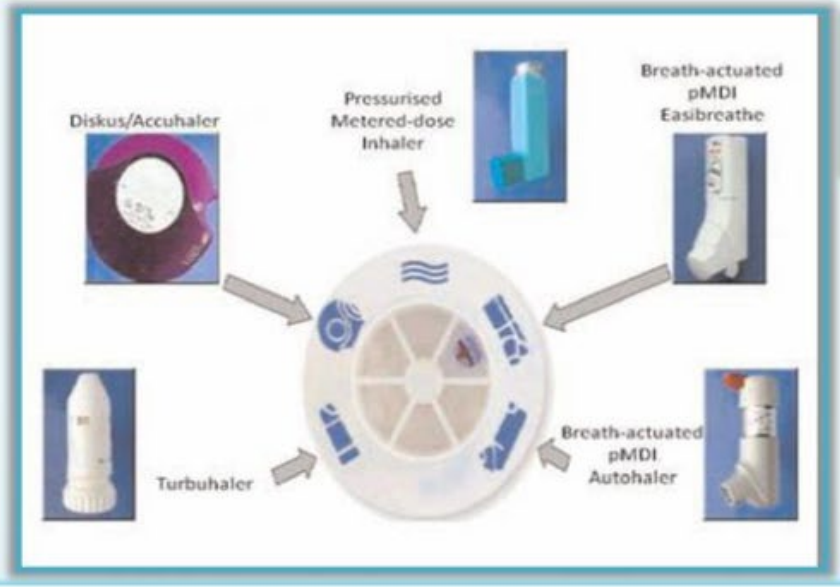
Variability in dose delivery by device and inspiratory flow



Lavorini, F., *et al. Pulm Ther* **7**, 409–427 (2021).

Inhalation Therapy- training tools- In-check Dial

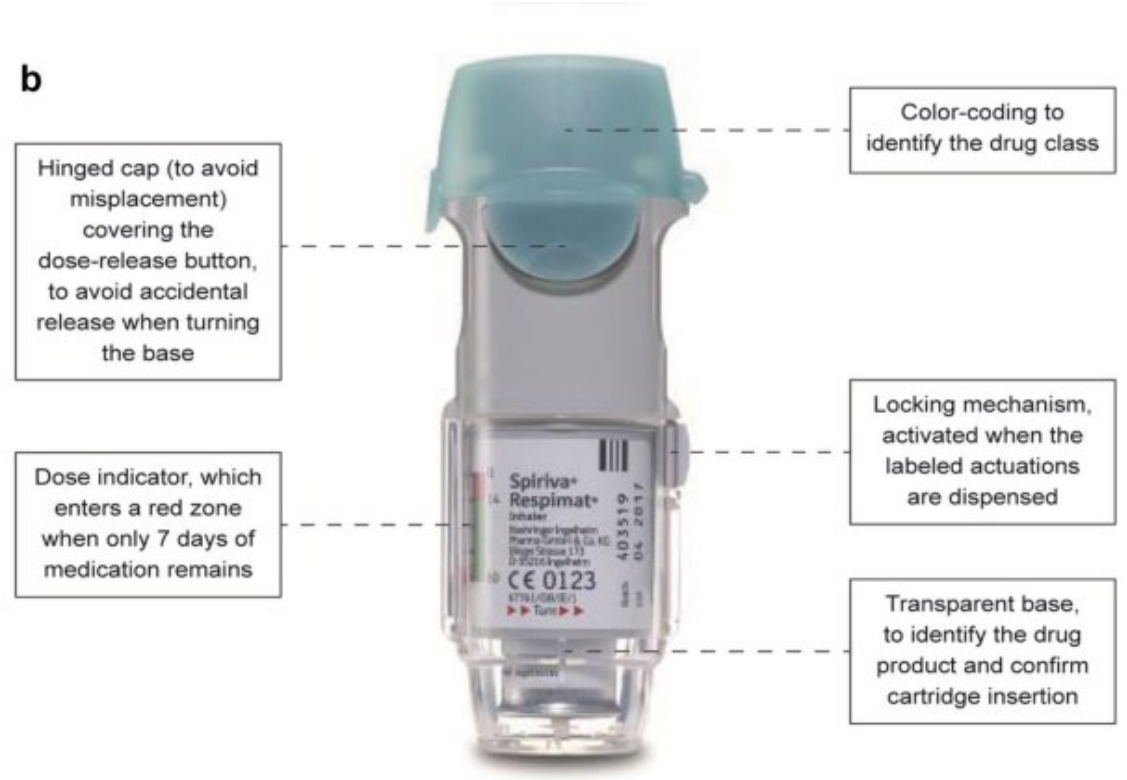
Inhalation Therapy: training tools: In-Check Dial



Rotating dial to select inhaler resistance

In-Check Dial is a hand-held inspiratory airflow meter designed to identify the most appropriate inhaler device for patients, based on their ability to learn and achieve an optimal flow rate. It accurately simulates the resistance encountered when using a number of different inhalers currently on the market, and measures the inspiratory flow rate achieved by the patient.

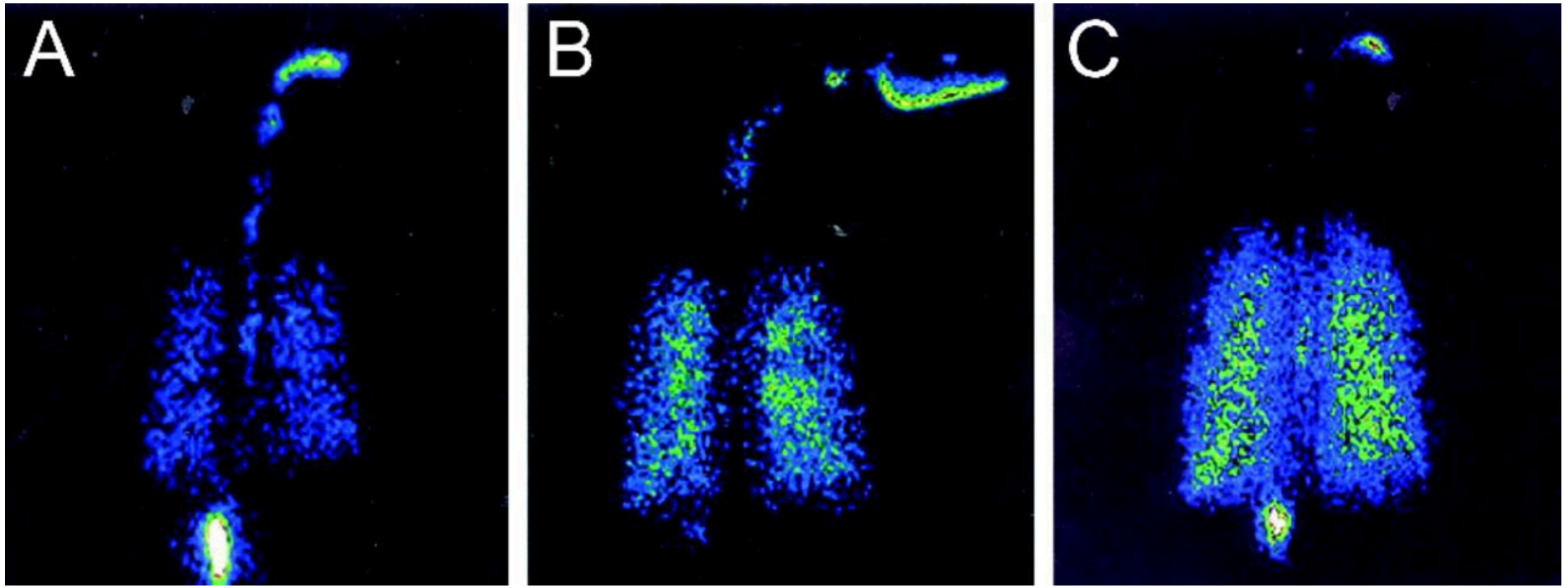
Soft Mist Inhaler (SMI)



Example: Respimat – Combivent (albuterol/ipratroprium) or Spiriva (tiotroprium)

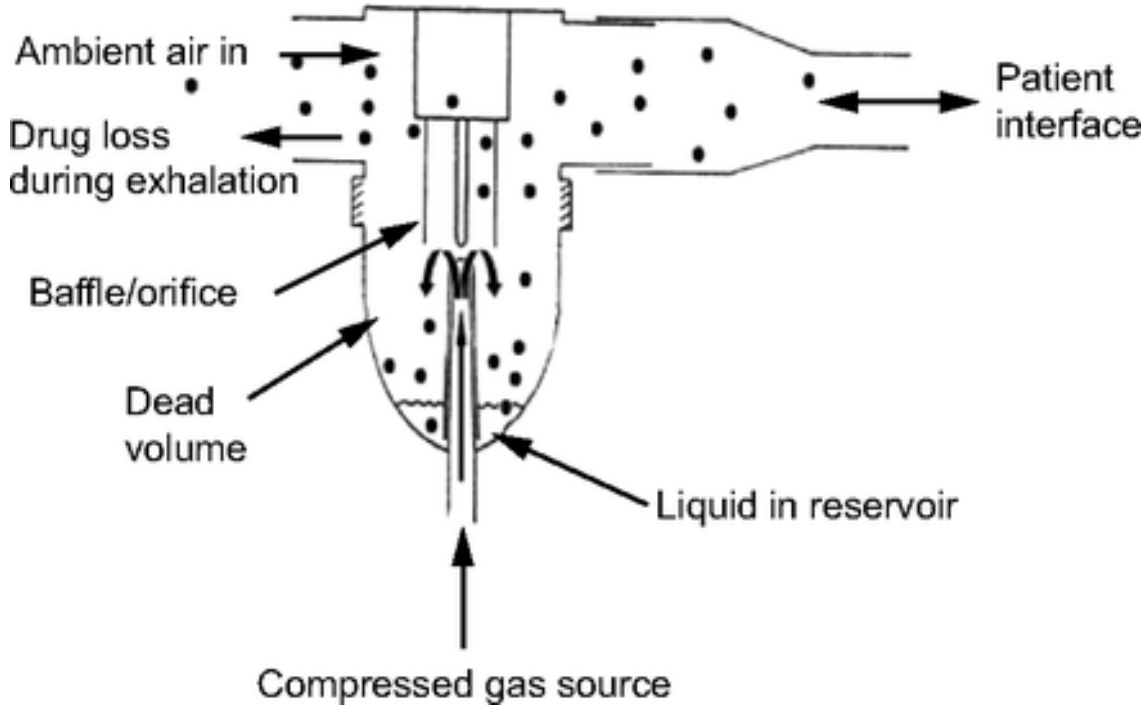
Aerosol Deposition

Aerosol deposition with a pressurized metered-dose inhaler without a spacer (A), and with a spacer (B), compared to the soft mist inhaler (C) using radio scintigraphy.



Roy A Pleasants, and Dean R Hess Respir Care 2018;63:708-733

Jet Nebulizers



Pros/Cons of Nebulizer

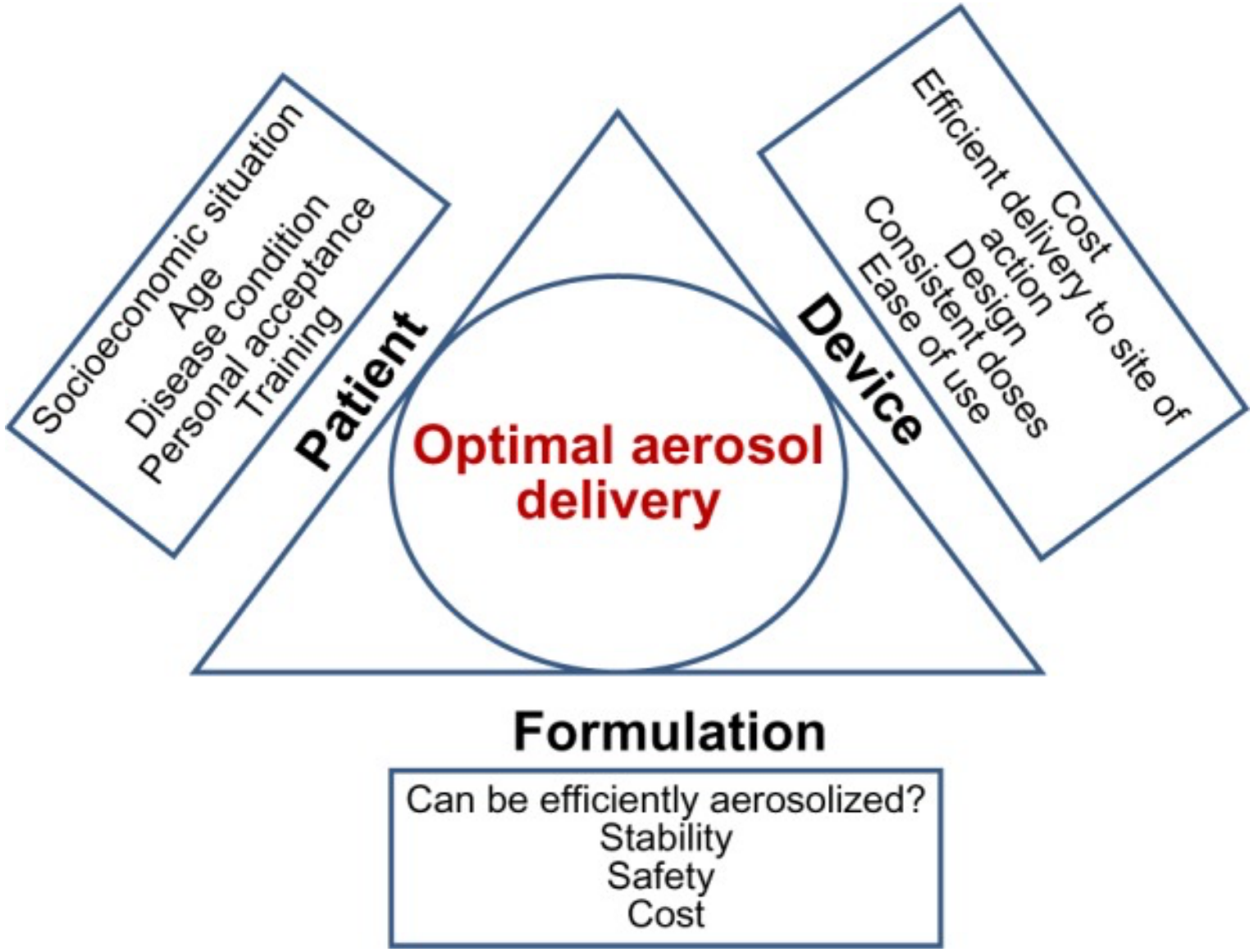
Table 4. Advantages and disadvantages of SVNS (Modified, with permission, from Reference 1)

Advantages	Disadvantages
Ability to aerosolize many drug solutions	Treatment times may range from 5–25 minutes.
Ability to aerosolize drug mixtures (>1 drug), if drugs are compatible	Equipment required may be large and cumbersome.
Minimal patient cooperation or coordination is needed.	Need for power source (electricity, battery, or compressed gas)
Useful in very young, very old, debilitated, or distressed patients	Potential for drug delivery into the eyes with face mask delivery
Drug concentrations and dose can be modified.	Potential for drug delivery exposure to clinicians and caregivers
Variability in performance characteristics among different types, brands, and models	Assembly and cleaning are required.
Normal breathing pattern can be used, and an inspiratory pause (breath-hold) is not required for efficacy.	Contamination is possible with improper handling of drug and inadequate cleaning.

American Association for Respiratory Care, "A Guide to Aerosol Delivery Devices for Respiratory Therapists, 4th edition, 2017

So how do I choose?

Optimal Aerosol Delivery is Complex



Choosing an Inhaler Device

INHALE

Uncontrolled Asthma or COPD?

- ✓ Adherence
- ✓ Affordability
- ✓ Address triggers, smoking, poor technique
- ✓ Discuss device preferences and treatment goals
- ✓ Allow patient input on the device
- ✓ (Re)educate on the device
- ✓ Schedule follow-up

#1 Check Cognitive Function

IMPAIRED
pMDI or SMI + VHC with Mask*
NMT*

OK
Go to #2

#2 Check Manual Dexterity

POOR
pMDI or SMI + VHC with Mask*
NMT*

OK
Go to #3

#3 Check Peak Inspiratory Flow (PIF)

SUBOPTIMAL
pMDI + VHC
SMI
NMT

OPTIMAL
pMDI + VHC
SMI
DPI

Patients at Risk for Suboptimal PIF

- <5 or >65 years in age
- Female
- ↑ Airflow obstruction severity

➡ **Choose device, check cognitive function & manual dexterity, correct technique, use teach-back to confirm**

NMT: nebulized mist treatment
SMI: soft mist inhaler
pMDI: pressurized metered dose inhaler
DPI: dry-powder inhaler
VHC: valved holding chamber (spacer)
* With assistance

Peak inspiratory flow testing enables clinicians to tailor the selection of the inhaler device to the patient. It can also be used to train proper inspiratory technique to improve use of an inhaler and medication deposition to the lungs.

https://alliancetechmedical.com/check-dial-training-device/

Adapted from: Mahler, DA. The role of inspiratory flow in selection and use of inhaled therapy for patients with chronic obstructive pulmonary disease. *Resp Med* 2019;161.
Kaplan, A., Van Boven, J.F.M. Switching inhalers: a practical approach to keep UR RADAR. *Pulm Ther.* 2020;6(2):381-392.

TABLE

SELECT INHALED CORTICOSTEROIDS USED IN THE PEDIATRIC POPULATION

PROPRIETARY NAME	GENERIC NAME	DELIVERY DEVICE	INSPIRATORY FLOW RATE	AVAILABLE DOSAGES	DOSING FREQUENCY	FDA AGE APPROVAL
Alvesco	Ciclesonide	MDI	N/A	80 mcg, 160 mcg	Twice daily	≥12 y
Arnuity	Fluticasone furoate	Ellipta (DPI)	60 L/min	50 mcg, 100 mcg, 200 mcg	Once daily	≥5 y
Asmanex	Mometasone furoate	Twisthaler (DPI)	30-60 L/min	110 mcg, 220 mcg	Once or twice daily	4-11 y
		MDI	N/A	100 mcg, 200 mcg	Twice daily	≥12 y
Flovent	Fluticasone propionate	Diskus (DPI)	60 L/min	50 mcg, 100 mcg, 250 mcg	Twice daily	≥4 y
		MDI	N/A	44 mcg, 110 mcg, 220 mcg	Twice daily	≥4 y
Pulmicort	Budesonide	Flexhaler (DPI)	30-60 L/min	90 mcg, 180 mcg	Twice daily	≥6 y
		Respule (solution)	N/A	0.25 mg, 0.5 mg, 1 mg	Once or twice daily	1-8 y
QVAR	Beclomethasone dipropionate	RediHaler (BAI)	20 L/min	40 mcg, 80 mcg	Twice daily	≥4 y

Medications are shown with corresponding delivery mechanism, inspiratory flow rate requirement according to the FDA label, available dosages, and FDA-approved age groups.

Abbreviations: BAI, breath-actuated inhaler; DPI, dry powder inhaler; FDA, US Food and Drug Administration; MDI, metered dose inhaler.

Jabre NA et al., Contemporary PEDS J, 2018:35(9)

CASE:

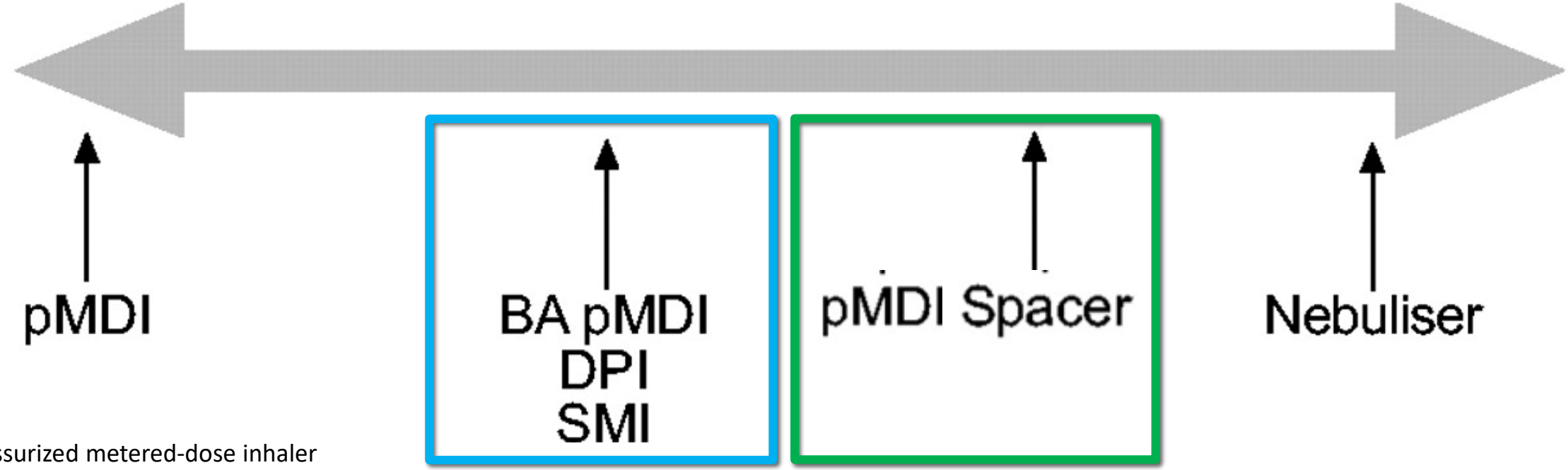
A 15 year old boy with poorly controlled asthma.

He is using a pMDI without a chamber, putting it directly in his mouth.

You are concerned he is not getting good drug delivery with this technique.

He’s convinced you that he won’t use a chamber.

You think he might be a good candidate for either a BA pMDI or a DPI



pMDI = pressurized metered-dose inhaler
BA pMDI = breath-actuated pressurized metered-dose inhaler
DPI= dry powder inhaler
SMI = soft mist inhaler

Adapted from Newman SP, Eur Resp Rev, 2005

You run through a few quick questions:

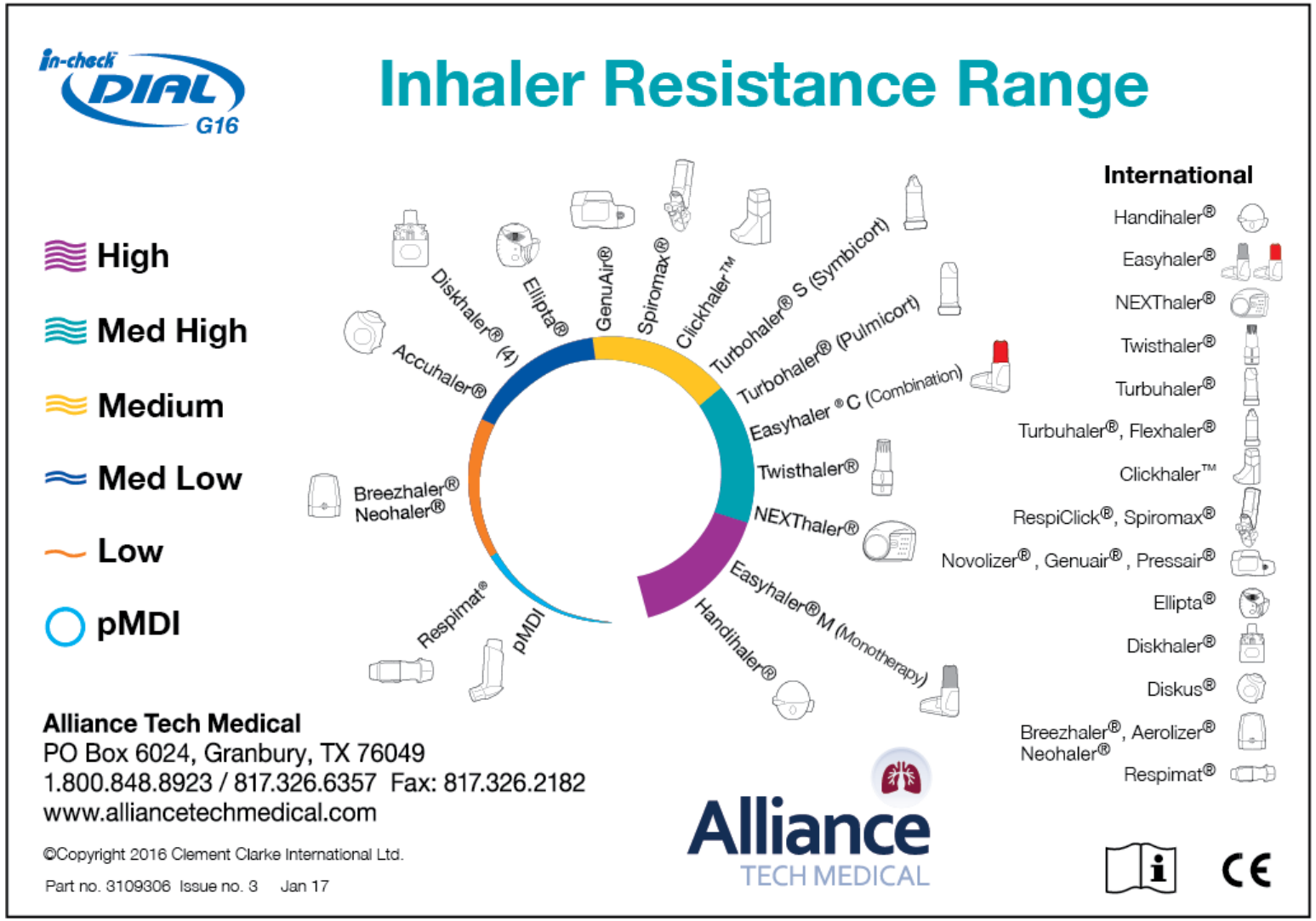
Is he cognitively able to follow instructions? YES

Does he have the dexterity to hold/activate these devices? YES

How much inspiratory flow can he generate?

Peak inspiratory flow = 40 L/min

Medium to Medium-High



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Alvesco	**Ciclesonide**	MDI	N/A	80 mcg, 160 mcg	Twice daily	≥12 y
Arnuity	**Fluticasone furoate**	Ellipta (DPI)	60 L/min	50 mcg, 100 mcg, 200 mcg	Once daily	≥5 y
Asmanex	**Mometasone furoate**	Twisthaler (DPI)	30-60 L/min	110 mcg, 220 mcg	Once or twice daily	4-11 y
		MDI	N/A	100 mcg, 200 mcg	Twice daily	≥12 y
Flovent	**Fluticasone propionate**	Diskus (DPI)	60 L/min	50 mcg, 100 mcg, 250 mcg	Twice daily	≥4 y
		MDI	N/A	44 mcg, 110 mcg, 220 mcg	Twice daily	≥4 y
Pulmicort	**Budesonide**	Flexhaler (DPI)	30-60 L/min	90 mcg, 180 mcg	Twice daily	≥6 y
		Respule (solution)	N/A	0.25 mg, 0.5 mg, 1 mg	Once or twice daily	1-8 y
QVAR	**Beclomethasone dipropionate**	RediHaler (BAI)	20 L/min	40 mcg, 80 mcg	Twice daily	≥4 y

Medications are shown with corresponding delivery mechanism, inspiratory flow rate requirement according to the FDA label, available dosages, and FDA-approved age groups.

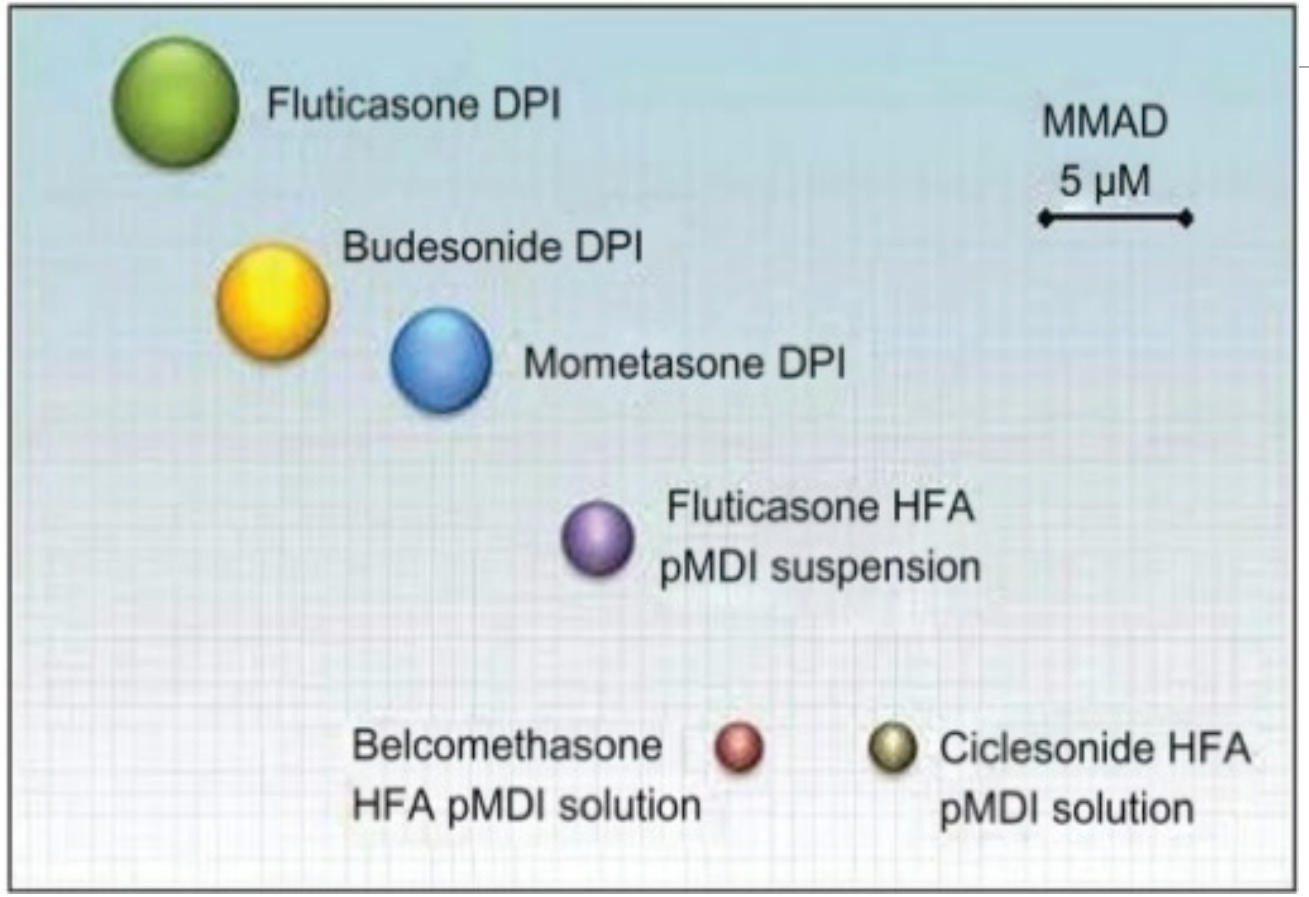
Abbreviations: BAI, breath-actuated inhaler; DPI, dry powder inhaler; FDA, US Food and Drug Administration; MDI, metered dose inhaler.

Jabre NA et al., Contemporary PEDS J, 2018:35(9)

For “tie-breakers”

- Which brand is covered by the patient’s insurance?
  - Helpful mobile app: “Coverage Search”
- Does patient have a preference?
- Any lifestyle issues that would interfere with DPI use (e.g., humid environments)?
- Look for the one with smaller particle size
- DPIs don’t have greenhouse gases (pMDIs do)

Different meds and devices generate different particle sizes



Guide to common brand names:

Fluticasone DPI= Flovent discus

Budesonide DPI = Pulmicort Turbuhaler

Mometasone DPI = Asmanex Twisthaler

Fluticasone HFA = Flovent HFA MDI

Beclomethasone HFA = Qvar Redihaler

Ciclesonide HFA = Alvesco HFA MDI

NR Mueller, “From inhaler to lung: clinical implications of the formulations of ciclesonide and other inhaled corticosteroids”, Int J Gen Med, 2013

Training is critical for all inhalers

TABLE 3 Crucial errors in inhaler use

Error	Devices affected				
	pMDI	BA pMDI	pMDI + spacer	DPI	Respimat® Soft Mist™ Inhaler[§]
Failure to remove mouthpiece cap or device cover	✓	✓	✓	✓	✓
Incorrect preparation/priming of device or loading of dose*		✓		✓	✓
Failure to pierce capsule				✓[#]	
Inhaler upside down	✓	✓	✓		
Breathing out into device*				✓	
Firing device at or after end of inhalation*	✓				✓
Open-mouth inhalation technique		✓		✓	
Weak or very slow inhalation*		✓[¶]	✓[+]	✓[ƒ]	
Inhaling through nose	✓	✓	✓	✓	✓
Stopping inhalation as device is fired*	✓	✓	✓		✓

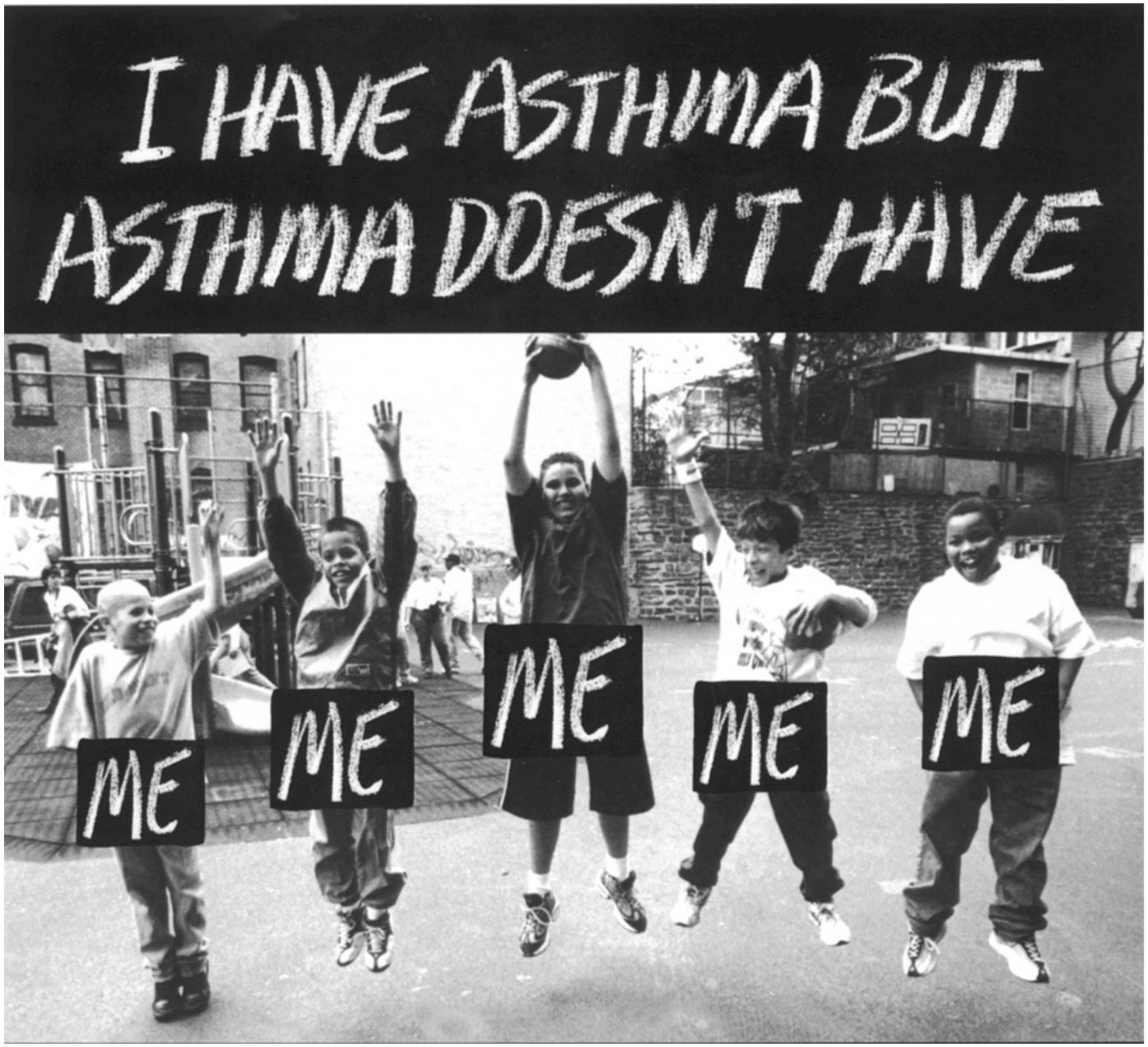
pMDI: pressurised metered-dose inhaler; BA pMDI: breath-actuated pMDI; DPI: dry powder inhaler. *: common errors; [#]: single-dose devices; [¶]: failure to trigger device; [+]: failure to open spacer valve; [ƒ]: too slow to aerosolise the dose; [§]: manufactured by Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany.

Bibliography

Salvi S, Gogtay J, Aggarwal B. Use of breath-actuated inhalers in patients with asthma and COPD - an advance in inhalational therapy: a systematic review. Expert Rev Respir Med. 2014 Feb;8(1):89-99.

Newman SP, Inhaler treatment options in COPD. European Respiratory Review 2005 14: 102-108;

Rogliani P, Calzetta L, Coppola A, Cavalli F, Ora J, Puxeddu E, Matera MG, Cazzola M. Optimizing drug delivery in COPD: The role of inhaler devices. Respir Med. 2017 Mar;124:6-14. doi: 10.1016/j.rmed.2017.01.006. Epub 2017 Jan 24. PMID: 28284323



Picture from the Asthma Information Outreach Project, www.asthma-nyc.org

American Academy of Pediatrics; UNC Children’s Hospital