MDI/spacer vs Nebulizer for treatment of acute asthma

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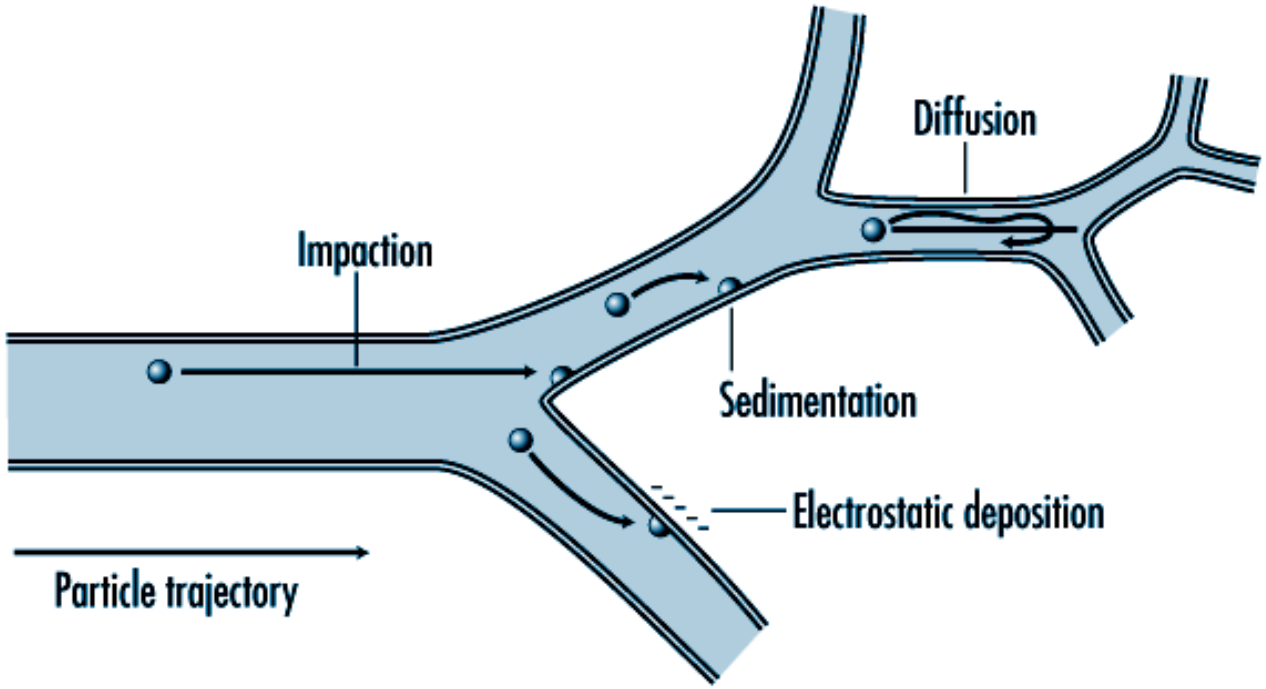
Table 1. Inhalation Devices Available on the Market

Pressurized metered-dose inhaler with valved holding chamber
Soft mist inhaler
Breath-actuated dry powder inhaler
Dry powder inhaler
Jet nebulizer
Continuous-output
Breath-enhanced
Breath-actuated
Ultrasonic nebulizer
Vibrating mesh nebulizer

Berlinski, Respiratory Care, 2017


Diffusion
Impaction
Sedimentation
Electrostatic deposition
Particle trajectory

The Science

Aerosol principles

Aerosols are suspensions of liquid or solid particles in a carrier gas

- 1. **Inertial impaction**
  - Upper airway
  - Turbulent airflow
  - ∝particle size & velocity
- 2**. Sedimentation**
  - Successive generations
  - Laminar airflow
  - Gravitational sedimentation
- 3**. Diffusion**
  - Diffusion rather than bulk flow
  - Deposition by electrostatic

  Forces <1micrometer

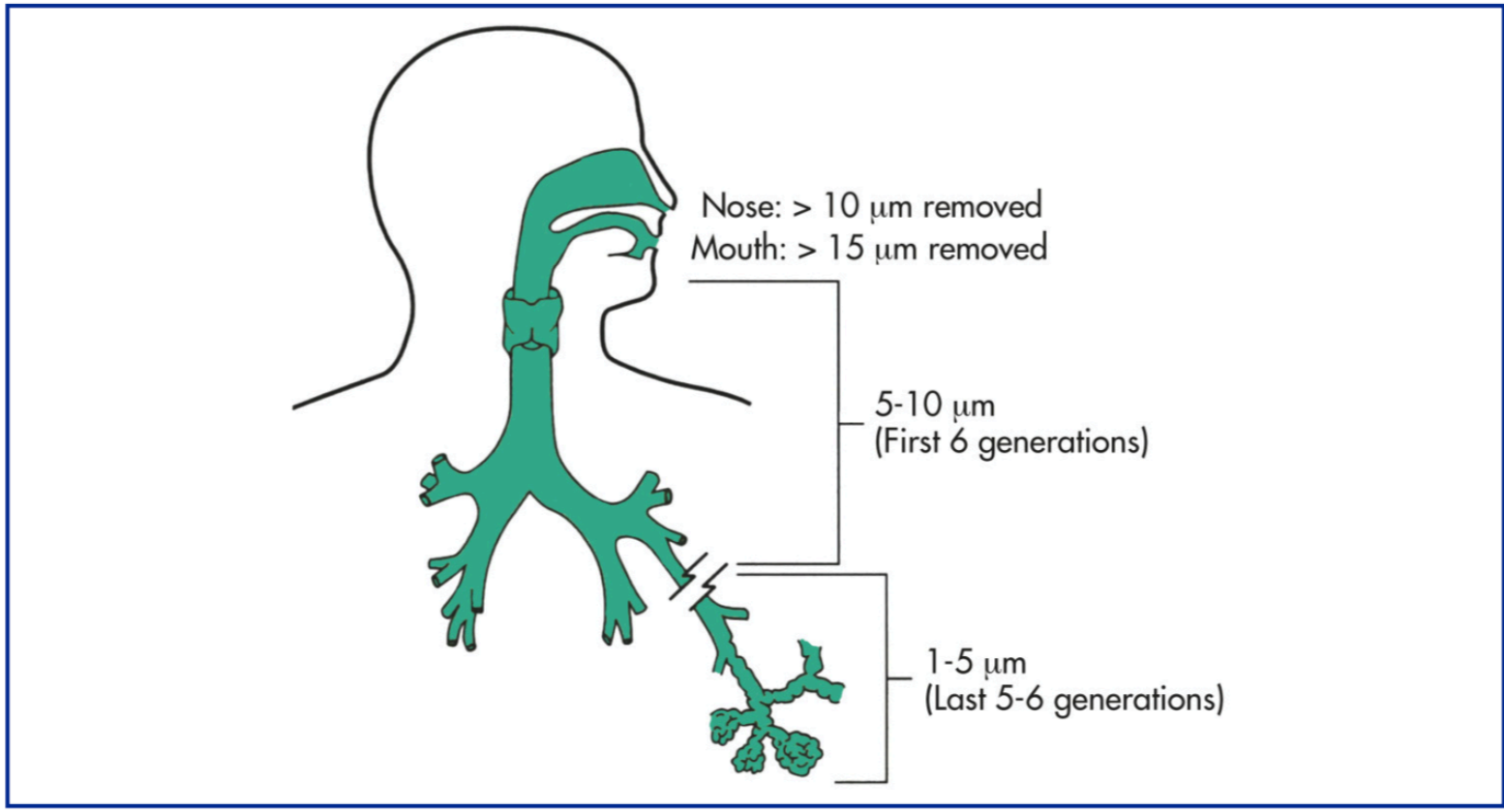


Figure 1. A simplified view of the effect of aerosol particle size on the site of preferential deposition in the airways

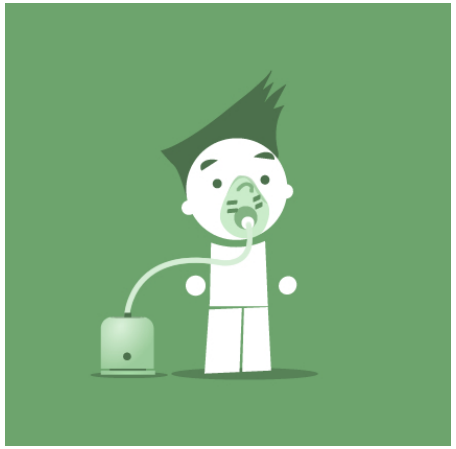
Pediatric Respiratory Medicine, ERS handbook, 2013

A guide to aerosol delivery devices for respiratory therapists; American Ass for Resp Care. 2009.

Aerosol Therapy

- The 5 D's:

1. Disease
2. Drug
3. Device
4. Disability of the patient
5. Deposition



Pediatric Respiratory Medicine, ERS handbook, 2013

Determinants of aerosol deposition

TABLE 18-1 DETERMINANTS OF AEROSOL DEPOSITION

AEROSOL FACTORS	PATIENT FACTORS
Particle size	Age
Particle velocity	Inspiratory flow rate
Hygroscopic properties	Breathing pattern (inspiratory volume, rate)
Drug viscosity and surface tension	Nasal versus mouth breathing
Suspension versus solution	Anatomy (upper and lower airways) Disease severity Physical and cognitive ability Adherence, contrivance

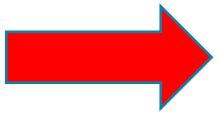
Optimal aerosol delivery to the lungs:

1. Good facemask seal
   - even a leak of 0.2cm will dramatically reduce the output of a pMDI/spacer-mask combination. [Amirav 1999 Am J Resp Crit Care Med]
   - suitable for nasal & oral breathing
2. Good co-operation of the child
3. Quiet tidal breathing
4. Aerosol with small particles

Janssens et al, Paeds Resp Reviews, 2006

Acute severe asthma

- Severe obstructive lung disease
- Higher respiratory rates
- Lower inspiratory volumes
- ±decreased co-operation
- Younger patients
  - Lower inspiratory flows
  - Nasal breathing



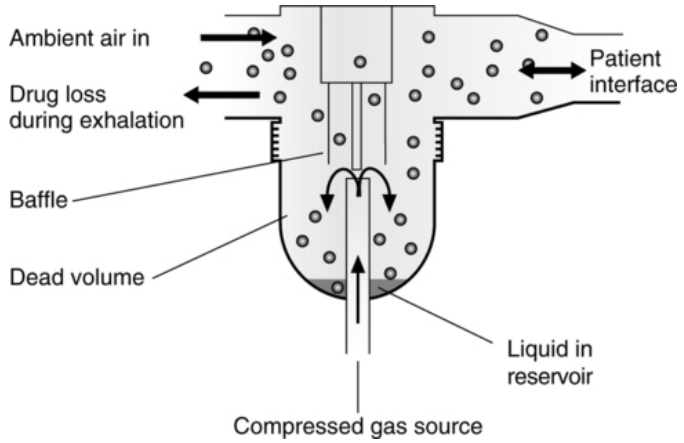
- Upper airway deposition
- Deposition at sites of obstruction & central airways
- Shorter dwell time in the lungs
- Flows patchy lung distribution
- Need for larger doses of drug

Pediatric Respiratory Medicine, ERS handbook, 2013
Jessens et al, Paediatric Resp Reviews, 2006

TABLE 18-3 ADVANTAGES AND DISADVANTAGES OF COMMON AEROSOL DEVICES

DEVICE	ADVANTAGES	DISADVANTAGES
Jet nebulizer with compressor	• Easy technique (quiet tidal breathing) • May be used at any age • Can deliver large doses (e.g., antimicrobials) • Can use with any disease severity • Can deliver wide range of medication types • Some models are small and portable with DC or battery power • Can use with artificial airways, mechanical ventilation	• Some technique is required (need to inhale by mouth if using mouthpiece) • More expensive • Noisy (if compressor driven) • Longer treatment times • Requires power supply • Requires regular servicing, cleaning, and disinfection • Some drugs contain preservatives; osmolality and pH may vary • Large variability in drug output and aerosol characteristics between different brands (portable models generally are slower and have larger particle size)

Jet nebulizers: driving gas of compressed air or oxygen through jet, creating a negative pressure which entrains large aerosolized liquid droplets into gas stream.
Particles then reduced in size by their impaction upon internal baffles, resulting in smaller 1 to 5microm particles.



Kendig's, Eighth edition; UpToDate

Inhalation therapy in asthma: Nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children

Johannes H. Wildhaber, MD, Nigel D. Dore, Joyce M. Wilson, Sunalene G. Devadason, PhD, and Peter N. LeSouëf, MD

THE JOURNAL OF PEDIATRICS
VOLUME 135, NUMBER 1

- P Children with stable asthma (n=17) aged 2 to 9 years in random order
- I Radiolabeled salbutamol from a neb and a pMDI/spacer (non-static)
- C Nebulizer vs pMDI/spacer
- O Efficiency in aerosol delivery as measured by body and lung deposition of radiolabeled salbutamol using a gammma camera

Table I. Comparison of lung deposition expressed as a percentage of the total actuated or nebulized dose and in µg salbutamol from the nebulizer and the pMDI/holding chamber in younger children (2 to 4 years, group 1) and older children (5 to 8 years, group 2)

Patient No. (age)	Lung deposition/ nebulizer (%)	Lung deposition/pMDI-holding chamber (%)
Group 1 Younger children		
1 (4 y)	3.6	9.7
2 (2 y 2 mo)	4.9	5.7
3 (3 y 10 mo)	5.2	5.3
4 (2 y 1 mo)	6.1	5.7
5 (2 y 9 mo)	8.2	5.2
6 (2 y)	6.0	3.3
7 (2 y 8 mo)	4.5	2.5
8 (2 y 8 mo)	4.6	6.1
Mean (SD)	5.4% (SD 1.4)	5.4% (SD 2.1)
	=108 µg salbutamol	=21.6 µg salbutamol
	=21.6 µg/min	=14.4 µg/min
9 (2 y)	1.3	1.1
Group 2 Older children		
10 (8 y 4 mo)	10.2	14.5
11 (6 y 8 mo)	10.1	13.5
12 (6 y 9 mo)	9.6	9.4
13 (5 y 2 mo)	10.3	4.9
14 (6 y 10 mo)	14.5	6.3
15 (7 y)	11.1	14.0
16 (7 y)	12.9	8.7
17 (5 y 8 mo)	10.2	5.6
Mean (SD)	11.1 (SD 1.7)	9.6 (SD 3.9)
	=222 µg salbutamol	=38.4 µg salbutamol
	=44.4 µg/min	=25.6 µg/min

Group 1, inhaling quietly through a mask (1 to 8) and screaming during inhalation (9) and group 2, older children (5 to 9 years) inhaling through a mouthpiece (10 to 17).

Study conclusions:

- Nebulizer & pMDI/spacer can be equally efficient in delivery of beta2 agonists to the lungs of asthmatic children.
- Much **higher absolute dose** can be delivered from the nebulizer compared with the pMDI/spacer (higher starting dose)
- A nebulizer also delivers a higher dose when its longer inhalation time is taken into account and the total deposited dose is expressed as the dose deposited per minute of inhalation.
- Older generation nebulizers (e.g. unvented nebulizers) much less efficient lung deposition:
  - 5.4% vs 0.7% (younger kids)
  - 11.1% vs. 3.1% (older kids)
- Much more efficient non-electrostatic (detergent coated) aerochambers also
  - 5.4% and 9.5% vs 2% in previous studies [Tal et al, Journal of Peds, 1996)

Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction

Asher Tal, MD, Haim Golan, MD, Nissan Grauer, MSc, Micha Aviram, MD, David Albin, PhD, and Michael R. Quastel, MD, PhD

The Journal of Pediatrics
April 1996

Mean aerosol deposition via pMDI with spacer:

- 2% in the lungs,
- 1.28% in the oropharynx and
- 1.11% in the stomach.
- The remainder stayed in the spacer.
- Crying subjects had lung deposition of 0.35%
- → higher doses may be needed in young children.
- 2 adult patients were used as controls and lung deposition was 19%

Clinical evidence & guidelines

Judgements to be made

Cochrane Library

Cochrane Database of Systematic Reviews

Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma (Review)

Cates CJ, Welsh EJ, Rowe BH

Multiple treatment of beta$_2$-agonist via spacer (chamber) compared to nebuliser for children with acute asthma

Patient or population: children with acute asthma
Settings: Community or Emergency Department
Intervention: Multiple treatments with beta$_2$-agonist via spacer (chamber)
Comparison: Multiple treatments with beta$_2$-agonist via nebuliser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Nebuliser	Multiple treatment of beta$_2$-agonist via spacer (chamber)				
Hospital admission	**110 per 1000**	**78 per 1000** (52 to 119)	**RR 0.71** (0.47 to 1.08)	757 (9 studies)	⊕⊕◯◯ **low**[1,2]	Large increases in the proportion of children admitted to hospital on spacer in comparison to nebuliser are ruled out by this 95% confidence interval
Duration in emergency department (minutes)	The mean duration in emergency department (minutes) in the control groups was **103 minutes**	The mean duration in emergency department (minutes) in the intervention groups was **33 minutes shorter** (43 minutes shorter to 24 minutes shorter)		396 (3 studies)	⊕⊕⊕◯ **moderate**[1]	There was a consistent direction of shortening of time in ED in all 3 studies, and although the size of this effect varied between studies (I^2 = 66%), we

Authors' conclusions

Nebuliser delivery produced outcomes that were not significantly better than metered-dose inhalers delivered by spacer in adults or children, in trials where treatments were repeated and titrated to the response of the participant. Spacers may have some advantages compared to nebulisers for children with acute asthma. The studies excluded people with life-threatening asthma; therefore, the results of this meta-analysis should not be extrapolated to this patient population.

ERS/ISAM TASK FORCE REPORT

What the pulmonary specialist should know about the new inhalation therapies

B.L. Laube, H.M. Janssens, F.H.C. de Jongh, S.G. Devadason, R. Dhand, P. Diot, M.L. Everard, I. Horvath, P. Navalesi, T. Voshaar and H. Chrystyn

Eur Respir J 2011; 37: 1308–1331

- Life-threatening asthma esp if consciousness alteration
- Ability to aerosolize high doses of drugs and give drug “cocktails”
- Patient coordination not required – use nebulizer if patient cannot use pMDI/spacer effectively
- No propellant needed
- May be used to dispense drugs that are not available for delivery by pMDI
- Hypoxemic patients -Oxygen rate of 6 - 8L/min

What the pulmonary specialist should know about the new inhalation therapies

B.L. Laube, H.M. Janssens, F.H.C. de Jongh, S.G. Devadason, R. Dhand, P. Diot, M.L. Everard, I. Horvath, P. Navalesi, T. Voshaar and H. Chrystyn

Eur Respir J 2011; 37: 1308–1331

The choice of device for children is affected by the child's cognitive ability. Children up to ~3 yrs of age are generally unable to adopt specific inhalation techniques and are therefore treated with nebulisers with a facemask [89], or with pMDIs with a VHC and facemask [114]. Refer to the inhalation instructions for nebulisers and pMDIs with spacers and facemasks provided in table 4. If the VHC+facemask combination does not achieve a tight fit over the child's nose and mouth, drug delivery to the lungs will be significantly reduced [88]. In a struggling child, it is difficult to achieve a good seal with the facemask and the inhaled dose is substantially reduced. If the child is screaming or crying, most of the inhaled drug deposits in the upper airway, not in the lungs [90].

DynaMed Plus

- treatment for severe or life-threatening asthma exacerbation
  - first-line treatments[1, 2, 3]
    - oxygen recommended for patients with hypoxia
    - give nebulized SABA 2.5-5 mg mixed with ipratropium bromide 250 mcg/dose every 20-30 minutes for 3 doses (NHLBI Evidence A; BTS.SIGN Grade A; GINA Evidence A), then nebulized SABA frequently or continuously
    - give IV corticosteroids and single dose of IV magnesium sulfate (NHLBI Evidence B; BTS/SIGN Grade B)
    - per British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines, consider adding 3 doses of nebulized magnesium sulfate (150 mg/dose) to SABA and ipratropium nebulizer treatments in the first hour of treatment for children ≥ 2 years old

- 1. Global Initiative for Asthma (GINA) global strategy for asthma management and prevention. GINA 2017)
- 2. British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) national clinical guideline on management of asthma. BTS/SIGN 2016 Sept PDF
- 3. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007 Nov;120(5 Suppl):S94-138 or at National Heart, Lung, and Blood Institute (NHLBI) PDF, correction can be found in J Allergy Clin Immunol 2008 Jun;121(6):1330

SIGN 153 • British guideline on the management of asthma

A national clinical guideline *September 2016*

Moderate asthma	Able to talk in sentences SpO_2 ≥92% PEF ≥50% best or predicted Heart rate ≤140/min in children aged 1–5 years ≤125/min in children >5 years Respiratory rate ≤40/min in children aged 1–5 years ≤30/min in children >5 years
Acute severe asthma	Can't complete sentences in one breath or too breathless to talk or feed SpO_2 <92% PEF 33–50% best or predicted Heart rate >140/min in children aged 1–5 years >125/min in children >5 years Respiratory rate >40/min in children aged 1–5 years >30/min in children >5 years
Life-threatening asthma	Any one of the following in a child with severe asthma:

Clinical signs	Measurements
Silent chest	SpO_2 <92%
Cyanosis	PEF <33% best or predicted
Poor respiratory effort	
Hypotension	
Exhaustion	
Confusion	

Mild/Moderate	Severe	Life-threatening
Give salbutamol† 4-12 puffs (100 mcg/actuation) via pMDI and spacer **Repeat every 20-30 minutes for the first hour if required (sooner, if needed to relieve breathlessness)**	**Give salbutamol† 12 puffs (100 mcg/actuation) via pMDI and spacer** **If patient unable to breathe through a spacer, give 5 mg nebule via nebuliser‡** **Start oxygen therapy if oxygen saturation <95% and titrate to target:** **Adults: 92–95%** **Children: 95% or higher** **Repeat salbutamol as needed. Give at least every 20 minutes for first hour (3 doses)**	**Give salbutamol 2 x 5 mg nebules via continuous nebulisation driven by oxygen‡** **Maintain oxygen saturations:** **Adults: 92% or higher** **Children: 95% or higher** **Arrange immediate transfer to higher-level care** **When dyspnoea improves, consider changing to salbutamol via pMDI plus spacer or intermittent nebuliser‡ (doses as for severe acute asthma)**

pMDI/VHC device issues

- More expensive and less portable than pMDI alone
- Prone to reduced or inconsistent dosing because of electrostatic charge associate with plastic spacers
- Facemask in pre-school children – filtering of drug from upper airway. ?when to switch to mouthpiece
- Steps in administering drug with a spacer are crucial. Mistakes can lead to reduced, or no drug being inhaled (i.e. multiple actuations into spacer before inhalation, and delay of inhalation after actuation)
- Failing to shake between actuations can reduce "respirable" dose by 25-35%
- Some children like to make noise and if they do they will be inhaling too fast.

Laube et al, ERS/ISAm Task Force Report 2011
Kendig's, 8th Edition
Everard et al, Thorax, 1995

Clinical experience

Recent SickKids M&M

- 6 year old - known asthmatics admitted under respiratory with acute severe asthma exacerbation
- “Slow responder” – 7 day admission – still Q1H ventolin MDI/spacer
- Mum administering ventolin on ward and still wheezy and tight after 8 puffs of ventolin →back to back nebs ordered
- experienced nurse came on shift →empty salbutamol MDI → new ventolin MDI → patient stretched to Q4H and discharged by the end of the day

Dose counting and the use of pressurized metered-dose inhalers: running on empty

Nancy Sander*; Sandra J. Fusco-Walker†; Julia M. Harder, BA‡; and Bradley E. Chipps, MD§

Ann Allergy Asthma Immunol. 2006;97:34–38.

500 US survey respondents (78% paediatric cases, mean age 9 years)

Only 36% of BD users had been told to keep track of MDI doses
25% found their MDI empty during an asthma exacerbation

- 82% considered MDI empty when absolutely nothing comes out
- 7 cases of calling EMS

Cost

- cost of treatment comprises several variables:
  - 1) Cost of the device
  - 2) cost of the drug
  - 3) cost of the add-on device e.g. VHC
  - 4) cost of the respiratory therapist therapist time.
- Many centers are going back to using jet nebulizers in the ED after many years spent transitioning from nebulizer to pMDI/VHC therapy due to the high cost of the pMDIs that use hydrofluoralkane as a propellant.

Berlinski, Respiratory Care, 2017

Summary

- Nebulizers still have their uses…
  - Severe/life-threatening asthma exacerbations
  - Delivery of high dose bronchodilators
  - Hypoxemic patients
  - Drug “cocktails” can be administered e.g. ipratropium bromide, magnesium sulphate
  - Uncooperative young children