Asthma Pharmacotherapy

Giving patients room to breath

May, 2000

Pre-Quiz - to get you thinking…	**True or False**
◆A whistling Aerochamber® indicates inspiration is too fast.	T / F
◆MDIs with Spacers are as effective as nebulizers.	T / F
◆Flovent® 125ug/puff is equipotent to Becloforte® 250ug/puff.	T / F
◆Long acting beta agonists (e.g. Serevent®) are steroid sparing.	T / F
◆Administration of inhaled corticosteroids should overlap with the administration of oral steroids given for acute exacerbations	T / F
◆Leukotriene receptor antagonists are effective in preventing exercise induced asthma and asthma in ASA sensitive patients	T / F

Despite a greater understanding of the pathophysiology of asthma, its prevalence and severity have actually increased over the past 2 decades. This edition of the ***RxFiles*** looks at optimizing the therapeutic ***non-emergency*** management of this condition as well as improving drug delivery.

DRUGS …. and DRUG DELIVERY:

Although earlier consensus guidelines advocated a "stepped care" approach to the treatment of asthma, current thinking favors a "continuum" of care with "acceptable" control (vs. "ideal" - i.e. no symptoms) as the goal (Table 1).[1] This is achieved through a combination of environmental controls and patient education (beyond the scope of this paper) as well as individualized pharmacotherapy that is reassessed regularly and adjusted accordingly (Figure 1).

Drugs for treating asthma fall into two broad categories:

- **Controllers** - taken on a **regular basis** to **control** asthma (e.g. anti-inflammatory agents, long acting beta agonists, etc.)
- **Relievers** - short acting bronchodilators **used on demand** to **alleviate acute symptoms** (e.g. short acting beta 2 agonists)

Table 1: Indicators of asthma control

Parameter	Frequency or value
Daytime symptoms	< 4 days/week
Night-time symptoms	< 1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school	None
Need for short-acting β_2-agonist	< 4 doses/week*
FEV_1 or PEF	>85% of personal best**
PEF diurnal variation✞	< 15% of diurnal variation

FEV_1 = forced expiratory volume in 1 second;
PEF = peak expiratory flow obtained with a portable peak flow meter.
*May use 1 dose/day for prevention of exercise-induced symptoms. ** Ideally ≥ 90%
✞Diurnal variation is calculated by subtracting the lowest PEF from the highest and dividing by the highest PEF multiplied by 100.
Tables 1&2-Adapted from the *Canadian Asthma Consensus Report*[2]; Used by permission

CONTROLLERS

Since inflammation is now recognized to have a pivotal role in asthma, **inhaled glucocorticosteroids (ICS)** have become the cornerstone of therapy for all but the most mild asthma cases (e.g. exercise-induced bronchospasm) regardless of age. The **Inhalation route** is preferred as it localizes therapy at the target site and reduces systemic side effects associated with oral therapy. Patients can have a significant amount of the drug impact the back of the throat where it is later swallowed; using a **spacer with their MDI** as well as r**insing and spitting** after use helps reduce oral thrush and systemic absorption.

ICS should be **used regularly** to suppress airway inflammation, improve lung function, reduce bronchial hyper-reactivity, and prevent or reverse airway remodeling. Early initiation in the course of disease is associated with better functional outcomes.[3] While benefits are evident within days, the greatest effects take several months so allow 3-6 months for an adequate trial. Although a dose response curve has been exhibited with inhaled steroids, most of the therapeutic benefit is obtained with an optimal adult daily dose of ≤500ug fluticasone, equivalent to 1000ug beclomethasone dipropionate (BDP).[4] Fluticasone (Flovent®, Flovent Diskus®) is twice as potent as BDP and has the advantage <1% bioavailability with reduced systemic effects.

Daily or increasing use of short acting beta-2 agonists (**SABAs**) is a signal to increase the steroid dose or consider add-on therapy. **Rather than escalating the steroid dose, current guidelines favor earlier initiation of adjunct agents** such as Leukotriene Receptor Antagonists or Long-Acting Beta Agonists.[5] **It is absolutely critical that patients remain on ICS along with adjunctive therapy**! When asthma is adequately controlled, steroid doses should be reduced to the minimum effective dose.

Table 2: Proposed dose equivalencies for ICS[2]

	Dose ug/d		
Product	***Low***	***Med***	***High***
BDP MDI & spacer	≤500	501-1000	>1000
BUD Turbuhaler	≤400	401-800	>800
FP MDI & spacer	≤250	251-500	>500
FP Diskus	≤250	251-500	>500
BDP MDI (HFA)	≤250	251-500	>500
BUD wet nebulizer	≤1000	1001-2000	>2000

Note: for children, low dose defined as <400ug of BDP via a MDI + spacer.
BDP=beclomethasone dipropionate; FP=Fluticasone propionate;
BUD=budesonide; HFA= hydrofluroalkane propellant

Oral steroids are associated with significant systemic side effects so should be reserved for the most refractory cases or acute exacerbations. They are best used along with ICS in "**short burst**" therapy of 7-10 days to regain control. Except for patients who cannot take oral medication, IV administration does not offer any advantage over oral as response rates are similar.[6] Unless patients have had numerous courses of oral steroids, tapering the dose before discontinuation is usually not necessary as it does not appear to affect outcome.[7] If chronic oral steroids must be used for severe asthma, an alternate day regimen may reduce systemic side effects (e.g. glucose tolerance, ↑weight, ↑BP, ↓growth in children, cataracts, immunosupression).

Leukotriene Receptor Antagonists (LTRAs) including zafirlukast (Accolate®), and montelukast (Singulair®), inhibit leukotriene mediated inflammation. Though promising, their potential for modifying the natural course of the disease and long-term toxicity has yet to be confirmed. Their current role is as an adjunct along with moderate to high doses of ICS to control more persistent symptoms. When taken regularly, they reduce exercise-induced bronchospasm (**EIB**) and are also useful in patients with ASA intolerant asthma. Although generally not recommended as first line therapy, LTRAs are considered drug of choice in patients unable/unwilling to take or tolerate ICS. Montelukast may be used in children >6 yrs old while zafirlukast should not be used in patients <12 yrs old.

LTRAs are well tolerated with headache being the most common side effect although its incidence is only slightly higher than placebo. Rare cases of eosinophilic vasculitis (Churg-Strauss syndrome) have been reported, although this may be related to the withdrawal of oral corticosteroids.[8]

Long-acting beta agonists (LABAs) such as formoterol (Foradil®/Oxeze®) and salmeterol (Serevent®) have a sustained bronchodilator effect over a 12hr period and are intended for **regular** BID dosing. They are **not suitable for acute relief** of symptoms or exacerbations but can be useful for nocturnal asthma. Adding a LABA to an ICS regimen is a preferred alternative to increasing the steroid dose. [9,10,11] **Advair Diskus®** contains a combination of salmeterol with fluticasone. This product may improve compliance with the inhaled steroid, but reduces the flexibility in making steroid dosage adjustments. A separate steroid inhaler would be required for periods when two to fourfold increases in the steroid dose are needed for control.

Anti-Allergens such as sodium cromoglycate (Intal®) or nedocromil (Tilade®) inhibit mast cell degranulation. They can prevent both early and late phase allergen induced asthmatic responses but must be used regularly to provide sufficient protection. They are not useful for relief of acute exacerbations as they have no bronchodilator effect. They are less effective alternatives to SABAs in preventing EIB. They can be **used in place of** rather than added to **ICS in mild asthma when low dose ICS are not tolerated**. A 4 week trial is required for assessing efficacy. Nedocromil is not recommended for patients < 12 yrs old.

Theophylline: With the introduction of LTRAs and LABAs, theophylline is now considered 3rd line therapy due to its narrow therapeutic window and potential for toxicity. It may have some immunomodulary effects but is used mainly for its modest bronchodilation. Rather than increasing inhaled steroids, oral theophylline can be added to moderate to high doses of ICS to improve symptom control. It can decrease the frequency and severity of symptoms in nocturnal asthma. Side effects may be significantly reduced without compromising clinical benefit by aiming for serum concentrations of **28-55 umol/L** rather than the previously recommended 55-110 umol/L.[12] Careful dose titration, periodic serum level monitoring, and many drug interactions make its use cumbersome.

RELIEVERS

Inhaled Short-acting beta agonists (SABAs) such as salbutamol (Ventolin®) are the drugs of choice for prophylaxis of EIB and relief of acute symptoms. They produce maximal bronchodilation within 10-15 minutes and last 2-6hrs.[13] Although they are potent bronchodilators, they have no anti-inflammatory activity and little effect on the late phase of asthmatic response. They should be prescribed on a prn basis for all patients along with suitable controlling agents. Regular use of SABAs provides no benefit over "prn" use.[14] Chronic administration is thought to down- regulate B2 receptors and reduce their binding affinity; steroid treatment can both prevent and partially reverse this phenomena.[15] Regular use may also increase the cellular inflammatory response[16] thereby enhancing early and late responses to allergens and the degree of bronchoconstriction resulting from exercise.[17,18] **If rescue with SABAs is required >3 times per week in mild asthma or daily in moderate/persistent asthma, anti-inflammatory treatment should be added or increased**.[2]

When administered in equipotent doses, salbutamol, fenoterol and terbutaline produce the same intensity of response, duration of action and degree of bronchoselectivity. Oral SABA products are not generally recommended due to delayed onset, reduced bronchodilator effect, and systemic side effects such as tremor and tachycardia. Inhalation not only enhances bronchoselectivity but also offers better bronchoprotection.[9]

The anticholinergic agent **Ipratroprium** (Atrovent®) is not recommended first line but is a suitable alternate for patients unable to take or tolerate SABAs. It has a slower onset but its bronchodilator effect lasts longer so it is useful as an adjunct with SABAs in some patients. It may also be more beneficial in those with COPD and elderly patients as adrenergic sensitivity declines with age while cholinergic response appears relatively unchanged.[19] Caution must be used however in patients with glaucoma, prostate hypertrophy, or bladder neck obstruction due to the anticholinergic effect.

What about the beta 2 agonist controversy?

- Overuse of SABAs has been associated with an increase in mortality but re-analysis of earlier studies, as well as more recent ones, suggest increased beta-2 agonist use is an **indicator of asthma deterioration rather than a causative factor**.[20] Currently there is no convincing evidence that regular use of long-acting beta agonists worsens asthma or increases risk of death.[7, 13]

What about alternative asthma therapies?

- This will be covered in an upcoming *RxFiles* Q&A Summary

Answers to Page 1 Quiz: T, T, T, T?, T, T

INHALATION DRUG DELIVERY SYSTEMS

Efficacy and side effects of inhaled medication are highly dependent on both the device and the user. Many systems are available to improve drug delivery and patient compliance.

Metered Dose Inhalers (MDIs)

These are the most common devices. To be effective the inhaler must produce an aerosol of medication with a high percentage of particles in the "respirable" range of 1-5 microns that can be drawn into the lower airways. Even when used correctly, most MDIs deliver only 10-20% of the dose to the target site.[21] Unfortunately, many studies have shown at least 50% of patients do not use their MDI properly with lack of hand/breath coordination being the biggest problem.[22] Inhaler technique should be checked and reinforced regularly.

MDI with Spacer

A spacer device can help optimize the delivery of drug from a MDI and is highly recommended with inhaled steroid therapy. It should be used if a patient is unable to properly use an MDI alone or if oropharyngeal or systemic effects are a problem.

Advantages include:[23]

- **equal or superior delivery to MDI alone or nebules**
- reduces need for hand/lung coordination ∴can be used in elderly, disabled, infants & children (may also require mask)
- improves drug delivery to lower airways as favors production and inhalation of particles in respirable range
- reduces local effects such as taste, reflex cough, "cold Freon effect", steroid-induced dysphonia and thrush
- may reduce systemic effects given more efficient delivery of drug to the lung (less drug swallowed; lower doses over long term)

Of the ten spacers available in Canada, the **Aerochamber**® combines the greatest number of desired features; the Opti-Chamber®, Medi-Spacer®, and Space Chamber® are also good options. Manufacturers suggest replacing spacers about every 2 years. Spacers cost approximately $20-30 with masks costing an additional $15-20.

Dry Powder Inhalers (DPIs)

Advantages include:

- breath actuated so reduces need for hand/breath coordination
- CFC propellant free

Disadvantages include:

- not suitable for children <5 yrs old (& some elderly)
- humidity can cause drug clumping and reduce delivery
- tipping or exhaling into device before inhalation can expel dose
- requires more rapid inhalation to drive the system and obtain optimal airway deposition (**Diskus**® efficiency appears to be relatively flow independent over a wide range & delivers 10-15% of a dose while the **Turbuhaler**® requires a greater inspiratory flow rate but delivers 20-30% of a dose[24])

Home **Nebulizers** are rarely indicated at any age or level of severity unless an MDI with spacer is not effective.[1] Nebulized therapy is costly, time-consuming, higher maintenance, and not easily portable. It is also no more effective than an MDI + Spacer, which most studies show to be equal or superior to the nebulizer.[25]

Device	% dose delivered	Comment	Cost
MDI	<5 - 20%	proper use - difficult	$$
MDI + Spacer	~20%	↑s MDI efficiency ✓	$$*
Turbuhaler	20 - 30%	requires higher inspiratory flow rate	$$
Diskus	10 - 15%	flow independent ✓	$$
Nebulizer	1 - 10%	consider MDI+ Spacer	$$$$

*Spacer optimizes MDI drug delivery & will ↓ drug cost over time

References available on request

We wish to acknowledge those who have assisted in the development and review of this newsletter supplement: Dr. D. Cockcroft (Resp. Med) , Barb Evans (RUH Pharmacy), Dr. T. Laubscher, Dr. M. Jutras and Dr. Z. Tymchak (Family Medicine), & the rest of the CDUP Advisory Committee.

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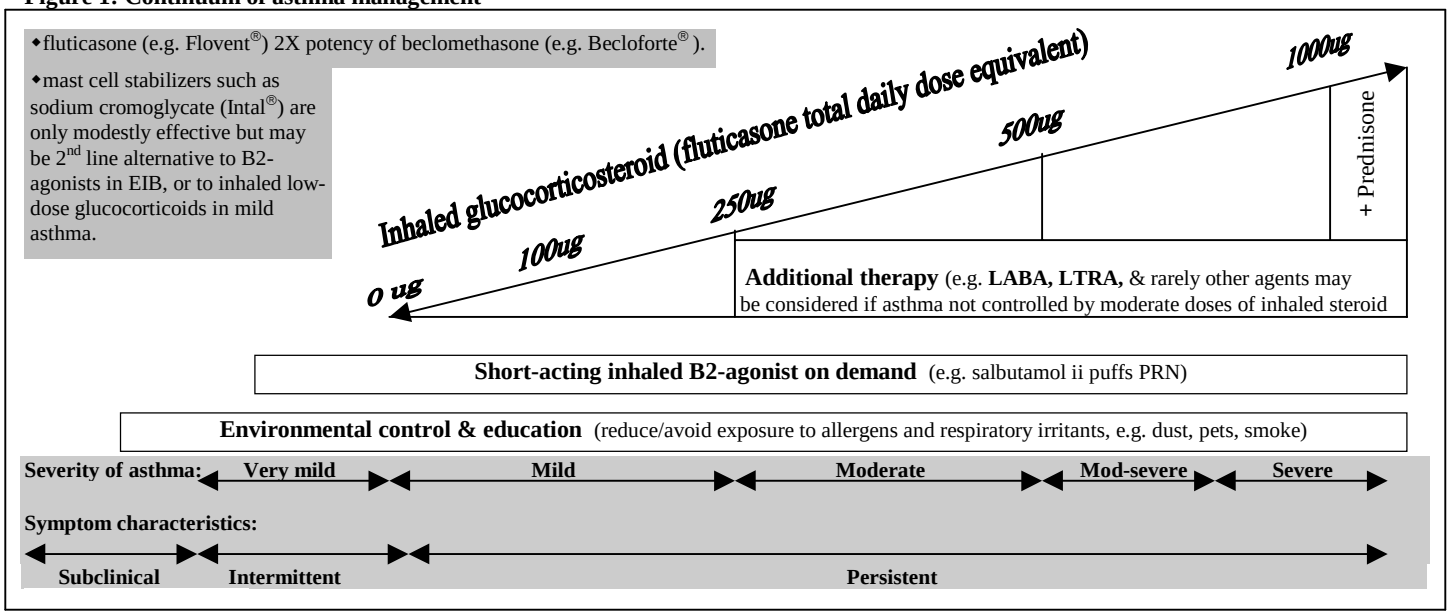
Figure 1: Continuum of asthma management [2]



ASTHMA PHARMACOTHERAPY IN ADULTS: Comparison Chart Prepared by: Loren Regier, Sharon Downey - ***The RxFiles*** **- AUG, 2000**

Generic Name	Dosage Form & Strength	*BRAND*	Daily Dosage Range (Adult)	Sample Adult Dose (in asthma unless otherwise designated)	Cost# per Month	Comments
Inhaled Corticosteroids ◆first line to prevent asthma (not for acute asthma); use regularly at the lowest effective dose to prevent asthma						
Beclomethasone diprop. (BDP)	MDI 50ug	*VANCERIL, ALTI-Beclomethasone*	100-1000 ug	vi puffs BID (~600ug/d)	$ 25	◆SE: oral thrush, dysphonia; to ↓SE's, use spacer & rinse mouth ◆QVAR = ↑potency due to ↑lung deposition; ↓oral & systemic SEs ◆Fluticasone ✓: 2X as potent as BDP & less systemic absorption ◆if ↑dose required, consider adding on a LABA or LTRA
	BDP products from Glaxo Wellcome (e.g. *Becloforte, Beclodisk, Beclovent Rotacaps*) have been **discontinued**.					
	MDI 50ug, 100ug	*QVAR*	100-600 ug	i-ii puffs BID (~200ug/d)		
Budesonide	Turbuhaler 100,200,400ug	*PULMICORT*	400-2400 ug	400ug puffs BID	$ 40	
	*Nebs 0.25, 0.5, 1 mg/2ml	*PULMICORT NEBUAMP*	0.5 - 4mg	1mg per neb BID	$120	
Fluticasone propionate	MDI 25, 50, 125, 250ug	*FLOVENT*	100-1000 ug	ii 125ug puffs BID	$ 49	
	Diskus 50, 100, 250, 500ug	*FLOVENT DISKUS*		250ug inhaled BID	$ 49	
Inhaled short-acting B2 agonists (SABA) ◆effective for treating acute asthma; if using >3X/week add inhaled corticosteroid; frequent use suggests poor control; ✓prevention EIB						
Salbutamol	MDI 100ug	*VENTOLIN, APO-, ALTI-, NOVO-*	prn - 1200ug	i-ii puffs PRN	$ 15	◆EIB: ii puffs 15min pre-exercise ◆SE: tremor, nervousness, ↑HR, headache, ↓K^+, ↑insulin effect ◆oral agents available but have slower onset and cause more SE's ◆PF = "preservative free" nebs ◆Airomir®: "CFC free" but is a difficult fit for Aerochamber®
	MDI 120ug	*AIROMIR* {see comments column}		Cost calculated based on QID use		
	Rotahaler 200,400ug	*VENTOLIN ROTACAPS*	prn - 1600ug	200ug inhaled PRN	$ 31	
	Diskhaler 200,400ug	*VENTODISK*	prn - 1600ug	200ug inhaled PRN	$ 31	
	Inhal'n sol'n 5mg/ml	*VENTOLIN INHAL'N SOLN*	prn - 15mg	2.5mg per neb PRN	$ 49	
	*Nebs 1.25, 2.5, 5mg/2.5ml	*VENTOLIN NEBULES P.F.*	prn - 15mg	2.5mg per neb PRN	$ 50	
Terbutaline	Turbuhaler 500ug	*BRICANYL*	prn - 4000ug	500ug inhaled PRN	$ 17	
Fenoterol	MDI 100ug (*nebs available)	*BEROTEC*	prn - 1600ug	i-ii puffs PRN	$ 22	
Inhaled long-acting B2 agonists (LABA) ◆ add-on agents in pts requiring higher-dose corticosteroids (steroid sparing effect?); ✓nocturnal asthma & EIB; not for acute asthma						
Formoterol	Capsules for inhal'n 12ug	*FORADIL CAPS for inhal'n*	24-48mg	12ug inhaled BID	$ 57	◆full B2 agonist (∴ caution regarding SEs in elderly)
	Turbuhaler 6ug, 12ug	*OXEZE*		12ug puff BID	$ 57	
Salmeterol xinafoate	MDI 25ug	*SEREVENT*	100-200ug	ii puffs BID	$ 66	◆partial B2 agonist ◆slower onset
	Diskus 50ug	*SEREVENT DISKUS*		50ug inhaled BID	$ 66	
Salmeterol+fluticasone	Diskus 50ug/100ug, 50ug/250ug, 50ug/500ug	*ADVAIR 100 DISKUS; (Also ADVAIR 250 & 500 DISKUS)*	1-4 inhalations	ADVAIR 100: 1 inhalation BID ADVAIR 250: 1 inhalation BID	$ 46 $ 55	◆convenient; may be less $; but ↓ flexibility in dosage adjustments
Mast cell stabilizers ◆efficacy highly variable from pt to pt; not for acute attacks; may taper to BID over several weeks after effect achieved; role in pediatric, cold air induced asthma & EIB						
Sodium Cromoglycate	MDI 1mg/puff	*INTAL Inhaler* (or *Intal Syncroner*)	2-8mg ?	ii puff QID ?dose too low for effect	$ 63	◆~4week trial needed to evaluate effect; safe in children
	20mg Spincap for inhal'n	INTAL Spincaps	40-160mg	1 cap for inhal'n QID	$ 73	
Nedocromil	MDI 2mg/puff	*TILADE*	4-16mg	ii puffs QID	$ 68	◆taste may limit compliance
Anticholinergics ◆possible alternative/"add on" to SABAs in asthma (delayed onset; longer duration); role in COPD?; ◆SE: dry mouth, taste disturbance; (Avoid eye: mydriasis/glaucoma)						
Ipratroprium bromide	MDI 20 ug;	*ATROVENT (inhalation sol'n also available; dilute as directed)*	80-320ug	ii puffs TID-QID	$ 25	◆ > effect in elderly than SAB2's ◆caution: glaucoma, urine retent.
	*Nebs 250ug/2ml;500ug/2ml		375-2000ug	250ug per neb TID	$ 88	
Ipratroprium bromide + Salbutamol (Combo)	MDI 20ug/100ug	*COMBIVENT*	6-12 puffs	ii puffs TID	$ 27	◆use only if combo indicated ◆PRN use in asthma
	*Nebs **500ug**+2.5mg / 2ml			1 neb TID	$ 165	
Leukotriene Receptor Antagonists (LTRA) ◆not 1st line; not for acute asthma; steroid sparing effect?; ↑ effect of SABAs; oral tx advantage?; ✓EIB & ASA sensitive pts						
Montelukast	5mg chew-tab; 10mg tab	*SINGULAIR*	10mg	10mg po HS (or AM if for EIB)	$ 80	◆rare eosinophilic vasculitis rx's? ◆DI's-Zafirlukast & warf / theoph
Zafirlukast	20mg tab	*ACCOLATE*	40mg	20mg po BID on empty stomach	$ 57	
Theophylline Preparations (Oral) ◆3rd line therapy due to systemic toxicity and mild bronchodilator activity; useful as 'add on' agent in some pts requiring high dose corticosteroids						
Aminophylline	225, 350 mg SR tab	*PHYLLOCONTIN*	450-1250mg	350mg po BID	$ 25	◆Aminophylline = 80% theophyl. ◆Oxtriphylline = 66% theophyl. ◆SE: N&V, abdom. cramps, HA, nervousness, tremor, insomnia, ↑HR; numerous drug interactions
Oxtriphylline	100,200,300mg tab	*CHOLEDYL* (also 100mg/5ml elixir)	600-1600mg	200mg po QID	$ 13	
	400, 600mg SR tab	*CHOLEDYL-SA*		400mg po BID	$ 24	
Theophylline (many products avail)	5.33mg/ml elixir /or solution	*THEOPHYLLINE Elix./THEOLAIR Liq.*	300-1000mg	150mg po QID	$ 22	
	100, 200, 300mg SR tab (BID)	*APO-THEO-LA; NOVO-THEOPHYL SR*		300mg po BID	$ 18	
	400, 600mg SR tab (q24h)	*UNIPHYL (SR products can be halved)*		600mg po **HS**	$ 27	

◆**NOTES: Cost** # per ~30days Rx in SK including markup and dispensing fee; = **EDS**; **MDI**=metered dose inhaler; **SE**=side effects; **EIB**=exercise-induced bronchospasm; **B2**=beta-2; **HR**=heart rate; **HA**=headache ◆**Spacer devices (e.g *AEROCHAMBER*®)** will optimize drug delivery of MDIs, increasing efficiency, decreasing pharyngeal & systemic SE; ***MDI+Spacer" or "dry powder inhalation systems" generally preferable to nebs ◆Systemic glucocorticoids-indicated in & following acute asthma exacerbations e.g. **Prednisone**: Adult 30-60mg/d x7-10d; Children 1-2mg/kg OD x3-5d (max 50mg/d); Prednisolone *PEDIAPRED*® 1mg/ml oral liquid avail. ◆Due to environmental concerns, CFC propellants in these formulations are being changed primarily to hydrofluoroalkanes (HFA); these have a smaller particle size & may deliver more drug to the lower airways.[26]

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Characteristics of an ideal spacer include: (from reference 23)

- appropriate chamber volume (ideally 120-200ml) that is neither too small to be effective nor too big to be portable or useful in patients with smaller tidal volumes (eg children, elderly)
- low resistance inhalation/expiration valves that prevent outside air from being drawn and allow expired air to exit; preferably visible to caregivers to ensure proper function
- masks should be flexible and well-fitting with exhalation port to allow humid exhaled air to escape
- minimal dead space between patient's face and mask valves so inspiratory volume easily draws aerosol out of chamber
- flexible universal inlet compatible with all MDIs
- built-in flow rate monitor that warns if breathing is too fast
- charge-neutral….plastic spacers are prone to build up of static electricity which causes drug particles to adhere to the sides of the chamber; this can be reduced by regular washingwith soapy water and **air-drying without rinsing**
- durable, easily cleaned and inexpensive

Produced by the Community Drug Utilization Program, a St. Paul's Hospital/Saskatoon District Health program funded by Saskatchewan Health.
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