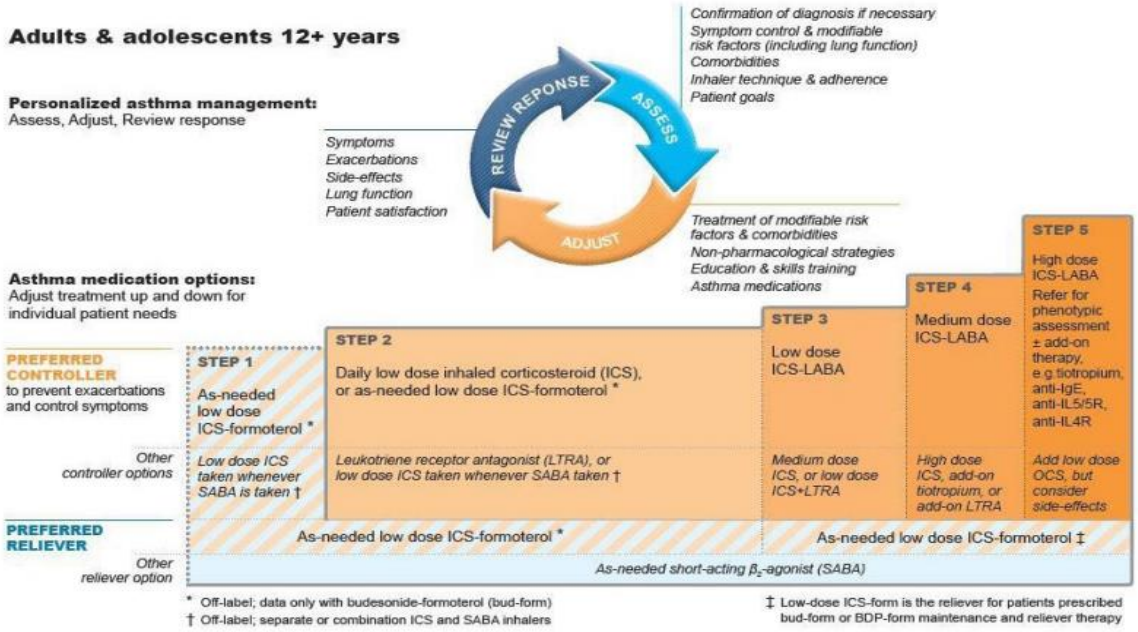
Thames Valley
Family Health Team

THE DOSE

Significant Changes in the Management of Asthma in Adolescent and Adults



LTRA = leukotriene receptor antagonist; Anti-IgE = Anti-immunoglobulin E; Anti-IL5/5R = anti-interleukin 5/anti-interleukin 5 receptor; Anti-IL4R = Anti-interleukin 4 receptor; OCS = Oral corticosteroid; HDM SLIT = House dust mite sublingual immunotherapy; FEV = forced expiratory volume

Rationale for changing reliever to either: low dose ICS+ salbutamol OR low dose ICS/formoterol

- Patients with mild asthma are still at risk for serious events. Mild asthma is responsible for:
  - **Acute asthma symptoms:** 30-37%
  - **Near fatal asthma events:** 16%
  - **Adults dying of asthma:** 15-20%
- Avoid establishing a pattern of patient reliance on SABA monotherapy early in the disease
- Frequent or regular use of SABAs increase the risk of asthma related complications
  - **≥3 SABA** inhalers per year increases the **risk of severe exacerbation increases by 2 times**
  - **≥12 SABA** inhalers per year increases the risk for **asthma related death**
    - Regular SABA use is associated with: Beta receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness
  - Inappropriate SABA use was associated with **45% increased risk of hospitalization** and **25% increased risk of an ER visit**
- ICS treats the underlying cause of asthma while SABA provides short term relief of symptoms
- Low dose ICS has been shown to reduce hospitalizations, prevent exacerbations, and improve lung function
- Budesonide/formoterol has a lower severe exacerbation rate compared to Salbutamol or Budesonide maintenance therapy

	Exacerbation rate reduction	Severe Exacerbation reduction
Budesonide/Formoterol prn vs salbutamol 100mcg x2 prn	51% (0.195 vs 0.4 annualized events per pt)	60% (9 vs 23 events per yr)
Budnesonide/Formoterol prn vs Budnesonide 200mcg bid	Not significant	56% (9 vs 21 events per yr)

Budesonide/Formoterol n=222, Salbutamol n=223, budesonide bid n=227

Bottom line:

The use of Budesonide/Formoterol in mild asthma as a rescue inhaler may reduce the rate of asthma exacerbations and severe exacerbations by 51% and 60% compared to salbutamol alone. Frequent use (3 or more inhalers per year) of salbutamol/terbutaline alone has been associated with a 2-fold increase in severe asthma exacerbations and ≥12 SABA inhalers per year increases the risk for asthma related death.

Why can't you use the other ICS/LABA combinations?

- The other LABAs have a longer onset of action compared to formoterol. The onset of action for:
  - Formoterol (Symbicort™ and Zenhale™) ~1 to 3mins
  - Salmeterol (Advair™) 30mins
  - Vilanterol (Breo™) 15mins

What is a low dose ICS?

Drug	Equivalent to Low Dose
Arnuity™ (fluticasone Furoate)	100mcg/day
Alvesco™ (ciclesonide)	≤200mcg day
Asmanex™ (mometasone furoate)	≤ 200mcg day
Flovent™ (fluticasone propionate)	≤250mcg day
Pulmicort™ (Budesonide)	≤400mcg/day
QVAR™ (beclomethasone)	≤200mcg/day

Potential Barriers to implementation

- Cost
  - Budesonide+formeterol 200/6mcg 120 dose inhaler: $90 + pharmacy fees
    - Coverage criteria for ODB and some private plans require patients to be on "optimum anti-inflammatory treatment and still experiencing breakthrough symptoms"
  - Budesonide 200mcg inhaler 200 dose inhaler- $66 + pharmacy fee
  - Salbutamol HFA 100mcg 200 dose inhaler- $5 + pharmacy fee
- Potential issues with compliance if using individual inhalers for ICS and SABA.

More details of trials

- Comparison of salbutamol 100mcg x2 puffs prn vs budesonide 200mcg 1 bid+ salbutamol prn vs budesonide/formoterol 200/6mcg 1 puff prn in mild asthma (open label trial)[3]

Primary outcome was the annualized rate of asthma exacerbations per patient			
	High-use Episode 16 doses of salbutamol/24hrs 8 dose of Budesonide/formoterol/24hrs	Urgent Medical care	Course of Systemic Steroids
Salbutamol group	45	36	23
Budesonide Maintenance	10	24	21
Budesonide-Formoterol	25	13	9

- The mean overall exposure to Budesonide was lower in budesonide/formoterol prn compared to Budesonide alone

- Comparison of terbutaline 0.5mg as needed vs budesonide 200mcg bid plus terbutaline prn vs budesonide/formoterol 200/6mcg prn in mild asthma (RCT)[4]
  - 14% increase in odds of having a well-controlled week with bud/formoterol compared to terbutaline (Bricanyl™) alone with a 64% reduction in the rate of severe exacerbations
  - Comparable rate of exacerbations between Budesonide/formoterol and budesonide 200mcg bid but with a lower mean inhaled steroid dose (57mcg compared to 340mcg)
- The trials were funded by AstaZeneca (Symbicort™)

References

1. Global Initiative for Asthma (GINA). Asthma management and prevention for adults and children older than 5 years. A pocket guide for health professionals. Updated 2019. www.ginasthma. org/reports
2. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, Devillier P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy 2007;62:591-604
3. Beasley R, Holliday M, Reddel H, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med. 2019;380:2020-30
4. O'Byrne P, Fitzgerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol in mild asthma. N Engl J Med. 2018;378:1865-76
5. Bateman ED, Reddel HD, O'Byrne P, et al. As needed budesonide formoterol vs. maintenance budesonide in mild asthma. N Engl J Med. 2018; 3781877-87
6. Hardy J, Baggott, C et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terutaline reliever therapy in adults with mild to moderate asthma (Practical): a 52 week, open-label, multicentre, superiority, randomized controlled trial. Lancet 2019:394:919-28
7. CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2016 [updated 2019 JAN 07; cited 2020 JAN 17]. Breo Ellipta [product monograph]. Available from: http://www.e-cps.ca or http://www.myrxtx.ca. Also available in paper copy from the publisher.
8. CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2016 [updated 2018 OCT 15; cited 2019 JAN 17]. Advair [product monograph]. Available from: http://www.e-cps.ca or http://www.myrxtx.ca. Also available in paper copy from the publisher.
9. CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2016 [updated 2019 SEP 26; cited 2020 JAN 17]. Symbicort [product monograph]. Available from: http://www.e-cps.ca or http://www.myrxtx.ca. Also available in paper copy from the publisher.