“Asthma Management: From Current to New Era Airways Treatment”

Prof. Orapan Poachanukoon

Center of Excellence for Allergy, Asthma and Pulmonary Diseases
Housekeeping

Please switch your Mobile phone, Tablet and Computer to silent mode
Write down your Questions on question card and send to support staff for real-time Q&A
Your feedback is important to us and will Help us to improve future meetings
Agenda

- Snapshot asthma management recommendation
- Similarities & Differences
- Tips & Tricks of ICS/LABA usage in real life practice
Agenda

- Snapshot asthma management recommendation
- Similarities & Differences
- Tips & Tricks of ICS/LABA usage in real life practice
Asthma control is poor across disease severity

Asthma control according to treatment step (n = 624)\(^1\)

<table>
<thead>
<tr>
<th>Step</th>
<th>Controlled asthma</th>
<th>Partially controlled asthma</th>
<th>Uncontrolled asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.5%</td>
<td>28.0%</td>
<td>52.4%</td>
</tr>
<tr>
<td>2</td>
<td>19.2%</td>
<td>37.4%</td>
<td>43.4%</td>
</tr>
<tr>
<td>3&amp;4</td>
<td>12.7%</td>
<td>36.2%</td>
<td>51.1%</td>
</tr>
<tr>
<td>5</td>
<td>4.0%</td>
<td>12.0%</td>
<td>84.0%</td>
</tr>
</tbody>
</table>

*Based on 2006 GINA guidelines\(^2\).

GINA, Global Initiative for Asthma; GCS, glucocorticoids; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β\(_2\)-agonist; SABA, short-acting β\(_2\)-agonist.

There is an unmet need for improved understanding and attainment of asthma control

REALISE study (N=8,000)

45.1% of patients had GINA-defined uncontrolled asthma (n=3,611)

83.7% of these patients perceived their asthma as controlled (n=3,023)

69.9% of these patients perceived their asthma as not serious (n=2,523)

The REALISE survey was conducted in patients aged 18–50 years who were active on social media.
Price D. et al. NPJ Prim Care Respir Med. 2014;24:14009 (REALISE)
The patients’ perception of asthma control

Evidence of excessive prescribing of reliever medication

- **39%** of patients who were on short-acting relievers at the time of death had been prescribed more than
- **12** SABA inhalers in the year before they died
- **4%** had been prescribed more than

**50 reliever inhalers approximately 1 inhaler per week**

Evidence of under-prescribing of preventer medication

- **38%** of patients on preventer inhalers* received fewer than
- **4** inhalers in the year leading up to their death…

**80% received fewer than 12 preventer inhalers**

*Of those patients for which the number of prescriptions was known. Among 189 patients who were on short-acting relievers at the time of death, the number of prescriptions was known for 165. Among 168 patients on preventer inhalers at the time of death, either as stand-alone or in combination, the number of prescriptions was known for 128.

NRAD, National Review of Asthma Deaths; SABA, short-acting β₂-agonist
STOP ASTHMA!
START SMART

STOP for Asthma
WORLD ASTHMA DAY
MAY 7, 2019 | GINASTHMA.ORG/WAD | @GINASTHMA

Symptom Evaluation
Test Response
Proceed to Adjust Treatment
Observe and Assess

Asthma Talks by Dr. Ann
ICS introduced 1972

- Large use of short-acting β2-agonists
- Fear to use SABA
- Adding LABA to ICS therapy

Evolution of treatment options:
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000
- 2005
- 2010
- 2020

- Single inhaler therapy: ICS+LABA (BUD/FOR)
- Biologics therapy
- Treatment by phenotype with associated biomarker (high TH2)
- (BUD/FOR) AIR (Anti-inflammatory reliever) 2020
- (BUD/FOR) SMART 2006
Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was 'preferred'.

GINA 2018 – main treatment figure

Step 1 treatment is for patients with symptoms <twice/month and no risk factors for exacerbations.

Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was 'preferred'.
Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Asthma medication options:
Adjust treatment up and down for individual patient needs

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

PREFERRED RELIEVER
Other reliever option

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>Low dose ICS-LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-needed low dose ICS-formoterol *</td>
<td>Low dose ICS taken whenever SABA is taken</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 2</th>
<th>Medium dose ICS-LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-needed low dose ICS-formoterol *</td>
<td>Medium dose ICS, or low dose ICS+LTRA #</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 3</th>
<th>High dose ICS-LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-needed low dose ICS-formoterol ‡</td>
<td>High dose ICS, add-on tiotropium, or add-on LTRA #</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 4</th>
<th>STEP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium dose ICS, or low dose ICS+LTRA #</td>
<td>High dose ICS-LABA</td>
</tr>
<tr>
<td>Add low dose OCS, but consider side-effects</td>
<td></td>
</tr>
</tbody>
</table>

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

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**Box 3-5A**

**Adults & adolescents 12+ years**

### Personalized asthma management:
Assess, Adjust, Review response

- **Symptoms**
- **Exacerbations**
- **Side-effects**
- **Lung function**
- **Patient satisfaction**

### Asthma medication options:
Adjust treatment up and down for individual patient needs

#### PREFERRED CONTROLLER
To prevent exacerbations and control symptoms

- As-needed low dose ICS-formoterol *
- Low dose ICS taken whenever SABA is taken†

#### Other controller options

#### PREFERRED RELIEVER
Other reliever option

- As-needed low dose ICS-formoterol *

### Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training

### Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence

### Patient goals

---

**STEP 1**
As-needed low dose ICS-formoterol *

**STEP 2**
- Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *
- Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA is taken†

**STEP 3**
Low dose ICS-LABA
- Low dose ICS-LABA

**STEP 4**
Medium dose ICS-LABA
- Medium dose ICS, or low dose ICS+LTRA #
- High dose ICS, add-on tiotropium, or add-on LTRA #

**STEP 5**
High dose ICS-LABA
- Add low dose OCS, but consider side-effects

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* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers

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Box 3-5A
Adults & adolescents 12+ years

**Personalized asthma management:**
Assess, Adjust, Review response

‘Controller’ treatment means the treatment taken to prevent exacerbations

**Asthma medication options:**
Adjust treatment up and down for individual patient needs

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

**PREFERRED RELIEVER**
Other reliever option

**STEP 1**
As-needed low dose ICS-formoterol *

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Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *

Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA is taken†

**STEP 3**
Low dose ICS-LABA

Medium dose ICS, or low dose ICS+LTRA #

**STEP 4**
Medium dose ICS-LABA

High dose ICS, add-on tiotropium, or add-on LTRA #

**STEP 5**
High dose ICS-LABA

Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

Add low dose OCS, but consider side-effects

**As-needed short-acting β₂-agonist (SABA)**

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers

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STEP 1
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Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Add low dose OCS, but consider side-effects

*SMART: Single Maintenance And Reliever Therapy

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Agenda

- Snapshot asthma management recommendation
- Similarities & Differences
- Tips & Tricks of ICS/LABA usage in real life practice
Dry powder inhaler (DPI)

- Single dose DPI
- Multiple dose DPI

Metered dose inhaler (MDI)

- Breath actuated MDI
- Soft mist inhaler
Budesonide/Formoterol characteristics for Asthma and COPD

Budesonide

- Optimize particle size
- High water solubility
- Short dissolution time
- Esterification to long retention
- Rapid systemic elimination

Formoterol

- Selective long-lasting β2-agonist
- Fast-onset of bronchodilation
- Short time in peak bronchodilation
- Effective bronchodilator & safety

Budesonide & Formoterol combination

- High level of disease control
- Good safety profile
- Rapid onset of bronchodilation

Budesonide is high water solubility, short dissolution time and esterification that provide fast onset and long action anti-inflammation.

<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Half-life (hr)</th>
<th>Volume of distribution (L)</th>
<th>Plasma protein binding (%)</th>
<th>Water solubility (µg/ml)</th>
<th>Dissolution time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>0.5</td>
<td>20</td>
<td>ND</td>
<td>0.13</td>
<td>&gt;5 hr</td>
</tr>
<tr>
<td>Budesonide</td>
<td><strong>2.3</strong></td>
<td><strong>180</strong></td>
<td>88</td>
<td><strong>16</strong></td>
<td><strong>6 min.</strong></td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>0.9</td>
<td>203</td>
<td>99</td>
<td>&lt;0.1</td>
<td>ND</td>
</tr>
<tr>
<td>Ciclesonide-active metabolite</td>
<td>2.8</td>
<td>844</td>
<td>99</td>
<td>7</td>
<td>ND</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td><strong>14.4</strong></td>
<td><strong>859</strong></td>
<td>91</td>
<td><strong>0.14</strong></td>
<td><strong>&gt;8 hr</strong></td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>5.8</td>
<td>332</td>
<td>99</td>
<td>0.1</td>
<td>ND</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>1.5</td>
<td>150</td>
<td>71</td>
<td>21</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviation: ND: not determined.
Budesonide Esterification

Increased lipophilicity
Prolonged retention & efficacy
Rapid systemic elimination

Budesonide esterification provide long acting asthma control.

At 96 hours, %Lung > 70%

Sustainable efficacy

OD usage approval
Budesonide esterification was low drug accumulation in blood and tissue.

**US FDA approval: Preg. Cat. B**

**US FDA approval: Preg. Cat. C**

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# ICS/LABA Pharmacology

<table>
<thead>
<tr>
<th>Pharmacological differences between formoterol and salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of action</strong></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td><strong>Peak bronchodilation</strong></td>
</tr>
<tr>
<td><strong>Drop in serum potassium</strong></td>
</tr>
<tr>
<td><strong>Finger tremor</strong></td>
</tr>
<tr>
<td><strong>Heart rate and Q-Tc intervals</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 second; pMDI, pressurised metered dose inhaler
Efficacy: BUD/FOR produces as rapid bronchodilation as Salbutamol

Improvement in FEV$_1$ is as rapid and effective with formoterol 4.5 or 9 µg as with salbutamol 100 or 200 µg.

The formoterol in BUD/FOR works as fast as salbutamol.

Figure source: Seberová E and Andersson A. 2000

FEV$_1$: forced expiratory volume in 1 second; pMDI, pressurised metered dose inhaler
Budesonide/formoterol* is the only ICS/LABA demonstrated to be as effective as salbutamol for acute asthma in the emergency room setting.1**

The formoterol in BUD/FOR works as salbutamol in acute asthma patients in emergency room.

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*Adapted from reference 1

**Patients should not be initiated on Budesonide/Formoterol during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.2

Randomized, double-blind parallel group study of 104 patients (mean age 45 years) seeking medical attention for acute asthma (mean FEV1 43% predicted) received two doses repeated of either Budesonide/formoterol 320/9 μg x 2 inhalations, or salbutamol 100 μg x 8 inhalations and FEV1 assessed over 3 hours. FEV1 90 min after dosing (primary variable) increased compared with pre-dose FEV1 by an average of 30% and 32% for Budesonide/formoterol and salbutamol, respectively (p=0.66), with similar increases at all timepoints from 3 to 180 min for both groups.1

FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; prn, as needed.

Doubling doses of methacholine to 20% fall in FEV$_1$ (PD$_{20}$)

Formoterol has dose-response curve: more doses mean more efficacy

Increase dose, increase efficacy

Flexible for step up & step down

Safety & convenience

Formoterol has dose-response curve: more doses mean more efficacy

Formoterol

Salmeterol

P=0.0021

P=0.0001

Palmqvist M, et al., *Am J Respir Care Med* 1999; 160: 244-249

SMART: a new asthma management approach
Severe exacerbation was defined as deterioration in asthma resulting in emergency treatment or hospitalisation or the need for oral steroids for 3 days or more (as judged by the investigator). 

COMPASS : SMART reduce rate of severe exacerbation though using lower daily steroids dose

Study type: 6 month, Randomised, double-blind, double-dummy, parallel-group study (n=3335)

**Fewer severe exacerbations**

(95% CI, 0.49-0.76, p<0.001)

39% reduction

p<0.001

28% reduction

p<0.01

**Lower mean ICS dose**

Lower ICS dose compared with SAL/FLU 50/250 µg bd + SABA as needed

163 (as-needed)

320 (actual dose*)

755 (BDP equivalents)

500 (actual dose*)

640 (actual dose*)

1000 (BDP equivalents)

1000 (BDP equivalents)

SAL/FLU 250/50 µg bid + SABA

BUD/FOR 160/4.5 µg bid + BUD/FOR as needed

BUD/FOR 320/9 µg bid + SABA

BUD/FOR 160/4.5 µg bid + BUD/FOR as needed

Asthma control days defined as:

- no day-time symptoms
- no night-time symptoms
- no night awakenings caused by asthma
- no as-needed medication use

BUD/FOR*: Baseline 5.8% vs Treatment 41.3%

*BUD/FOR maintenance and reliever therapy
Randomized, double-blind 6-month study of 3335 symptomatic adult and adolescent asthma patients (mean FEV1 73% predicted, mean inhaled corticosteroid dose 745 µg/day). BUD/FOR Maintenance and Reliever 160/4.5 µg one inhalation bd + additional inhalations as needed. BUD/FOR prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs fixed-dose salmeterol/fluticasone (p=0.0034). Study results also showed salmeterol/fluticasone 25/125 µg two inhalations bd + terbutaline as needed has similar asthma control days results: Baseline 5.7% vs Treatment 43.7%.


COMPASS : BUD/FOR provides standard of care 24-hour symptom control
COSMOS: SMART reduce severe exacerbations vs salmeterol/fluticasone in 12 months

*SAL/FLU 50/250 µg bid + SABA as needed† (n = 1076)  BUD/FOR 2 x 160/4.5 µg bid + BUD/FOR as needed† (n = 1067)

Exacerbation subtypes

Total number of all severe exacerbations (a) and exacerbations by subtype (b–d). Subtypes are presented here as mutually exclusive categories and were defined in order of increasing severity as follows: unscheduled visits; oral steroid courses; hospitalisation/ER visits. Exacerbations fulfilling ≥1 subtype were categorised by the most severe criterion.

**: p<0.01, statistically significant between-group difference derived from Poisson regression analysis of the rate of exacerbations.

22%

Total number of all severe exacerbations (a) and exacerbations by subtype (b–d). Subtypes are presented here as mutually exclusive categories and were defined in order of increasing severity as follows: unscheduled visits; oral steroid courses; hospitalisation/ER visits. Exacerbations fulfilling ≥1 subtype were categorised by the most severe criterion.

**: p<0.01, statistically significant between-group difference derived from Poisson regression analysis of the rate of exacerbations.

*BUD/FOR maintenance and reliever therapy.
†After 4 weeks, physicians could titrate maintenance doses in accordance with normal clinical practice
Severe exacerbation was defined as a deterioration in asthma, resulting in hospitalisation/emergency room (ER) treatment, oral steroids for ≥3 days or an unscheduled visit (i.e. patient initiated) leading to treatment change
ER, emergency room; SABA, short-acting β2-agonist; SAL/FLU, salmeterol/fluticasone.
Early intervention with Budesonide/formoterol* as part of a maintenance and reliever regimen can prevent exacerbations\(^1,2\)

Potential outcomes with different asthma treatment regimens in response to worsening symptoms\(^1\)

- Budesonide/formoterol (SMART)
- Budesonide/formoterol+SABA
- ICS+SABA

*This is a historical regimen which no longer features on the SmPC

There were no notable differences between BUD/FOR®* and alternative fixed dose-treatment in terms of the incidence of β₂-agonist or ICS class-related AEs.

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Patients reporting ≥1 AE, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BUD/FOR®* (n = 5,584)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>61 (1.1)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>58 (1.0)</td>
</tr>
<tr>
<td>Tremor</td>
<td>33 (0.6)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>34 (0.6)</td>
</tr>
<tr>
<td>Pneumonia†</td>
<td>33 (0.6)</td>
</tr>
<tr>
<td>Cataract</td>
<td>3 (0.05)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>4 (0.07)</td>
</tr>
</tbody>
</table>

* BUD/FOR maintenance and reliever therapy
† Pneumonia was included for completeness, due to the current debate on the relationship between ICS use and pneumonia risk in COPD; †as there were multiple arms in some of the clinical trials, the number of patients in the comparator groups exceed those in the BUD/FOR® maintenance and reliever therapy groups.

Agenda

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- Tips & Tricks of ICS/LABA usage in real life practice
GINA Guidelines symposium, where Professor Guy Brusselle, GINA board member, presented his vision for how the guidelines should change, with anti-inflammatory reliever therapy replacing SABA at all stages of severity.

Expected guideline recommendation from Q1 2020


1 SYGMA data on file (confidential)
2 Kuna et al 2007, International Journal of Clinical Practice
3 Paul O’Byrne
Convenient: SMART is convenient for HCPs and Patients

- No need for SABA
  - Patient bring only 1 device – Easy to carry
  - Patient learn only 1 device – Reduce confusion & improve compliance
  - HCP teach only 1 device – Reduce workload

Controller

- 1 puff in the morning

Reliever

- 1 puff in the evening
- Average 5.5 puffs as needed/months

Providing options for your patient: DPI and pMDI

COPD  
Recommended dose  
BUD/FOR 160/4.5 2 puffs BID  
BUD/FOR 320/9 1 puff BID  

Asthma  
Regular maintenance: BUD/FOR 160/4.5 1-2 puffs BID  
SMART: BUD/FOR 160/4.5 1-2 puffs BID + as needed or 2 puffs OD + as needed

Maximum dose

COPD
Recommended dose  
(age ≥ 18 yrs) 2 Puffs BID  

Asthma
Recommended dose  
(age ≥ 18 yrs) 2 Puffs BID  

Package Insert of BUD/FOR pMDI
160/4.5 micrograms/actuation, pressurised inhalation, suspension
Turbuhaler: Fully effective at flow rate as low as 30 L/min

Turbuhaler is fully effective at flow rate $\geq 30 \text{ L/min}$ at patients aged $\geq 6$ years


Higher Lung deposition
More inhaled drug reaches to the lung with Turbuhaler
Particle size range matters for optimal lung deposition

- Particles 1–5 µm are optimal for lung deposition
- Turbuhaler delivered the highest fine particle fraction (FPF) 1–3 µm of the 4 DPIs tested* as percent of label claim in vitro¹

* Budesonide/Formoterol Turbuhaler, SAL/FLU Diskus, Rolenium Elpenhaler and Foster NEXThaler

STOP ASTHMA! START SMART

วันนี้คุณ
STOP
ASTHMA!
และ
START
SMART
หรือยังคะ?