Personalized and precision medicine in asthma and COPD

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Lecture Asthma and COPD for Healthcare Workers
10.20-11.00 Thursday 26th July 2019
Miracle Grand Convention
## Conflict of interest disclosure

| **Medical Advisory Board**: Pfizer, Boehringer Inhelheim, Novartis and Astra Zeneca |
| **Speaker bureau**: Glaxo Smith Kline, Astra Zeneca, MSD, Novartis, Pfizer, Takeda, Otsuka and Boehringer Inhelheim |
| **Travel grant**: Astra Zeneca, Boehringer Inhelheim and Novartis |
| **Research grant**: Otsuka, Novartis and MSD |

- I have no conflict of interests regarding this presentation include off labelled discussion of medical products
Topics of my talk & my favorites

- Personalized medicine or precision medicine
- What are biomarkers?
- How to use biomarker in asthma and COPD?
- Personalized asthma COPD management
- Conclusions
หนังสือการรักษาผู้ป่วยสำหรับโรคหืดรุนแรง

Targeted therapies for severe asthma

Booth

ข่ายมือสุดของห้องประชุม
การรักษาระดับประชากร (Population based)

การรักษาแบบจำเพาะจากลักษณะทางคลินิก (Personal based)

การรักษาแบบจำเพาะจากสารชีวภาพ (Biomarkers) Personal based

การประเมินการตอบสนองต่อการรักษา Predictive

การรักษาแบบจำเพาะจากลักษณะทางคลินิก (Clinical phenotype)

แนวทางการรักษาจ้าเฉพาะบางรายใช้การตรวจหาสารชีวภาพลักษณะทางคลินิก

แนวทางการรักษาจ้าเฉพาะบางรายใช้การตรวจหาสารชีวภาพลักษณะทางคลินิก

ไม่มีการเลือกผู้ป่วยทุกรายได้รับการรักษาแบบเดียวกัน

แนวทางการรักษาทั่วไปใช้อาการหรืออาการแสดงของโรคเป็นหลัก

แนวทางการรักษาทั่วไปใช้อาการหรืออาการแสดงของโรคเป็นหลัก
Asthma phenotypes in SARP-T
(Not one size fit all)

**ASTHMA**

- **Allergic asthma** (Mainly eosinophilic)
- **Late onset asthma**
- **Asthma with fixed airflow obstruction** (Airway re-modeling)
- **Non allergic asthma**
- **Asthma in obesity**

Global Strategies for Asthma Management and Prevention GINA report 2018
Severe asthma from endotype to phenotype

Clinical presentation
- Wheeze
- FEV₁
- Dyspnea
- Hyper-responsiveness
- Exacerbation
- Inflammation
- Atopy

Age of onset
- Genetic
- Environmental

Clinical and statistical clustering

Phenotypes
- Early onset Eosinophilic
- Eosinophilic
- Exercise induced
- Obesity
- Paucigranulocytic

Underlying Pathobiology
- Early onset Allergic (IL-4/IL-13)
- Late onset Eosinophilic (IL-5, LTC4, D4)
- Mast cells LTC4, LTD4
- Late onset Obese (ADAM)
- Non Th2 Related biology
  - Non Th2 Related immunity
  - Non Th2 Related biology
  - Non Th2 Related immunity
  - Non Th2 Related biology

Endotypes
The Omalizumab (Xolair) retrospective study and registry in Thai asthmatic patients (OXYGEN)

Long-term effectiveness of Omalizumab in Thai severe asthmatic patients: a real-life experience

Abstract

Background: To evaluate long-term effectiveness of Omalizumab in 'real-life' setting of Thai asthmatic patients.

Methods: We conducted a multi-center, observational study in severe asthma patients who received Omalizumab in Thailand. Outcomes were asthma exacerbation (hospitalization and ER visit), asthma control test (ACT), and daily ICS dose. Data were evaluated at baseline, 16 Week, and 52 Week.

Results: A total of 78 patients received Omalizumab treatment (average duration 16.9 months with range 16 weeks-2 years). The mean annualized rate of exacerbations was reduced from baseline (3.79) at Week 16 (3.54) and Week 52 (1.16), (p<0.05), respectively. The mean hospitalization rate was reduced from 0.49 in previous year to 0.15 at Week 16 and 0.19 at Week 52. A reduction in ER visit rates was observed at Week 16 (0.15) and Week 52 (0.97) respectively from baseline (1.44) (p<0.05). The ACT score increased from 15.4 at baseline to 20.6 at Week 16 (p<0.001) and increased to 21.5 at Week 52 (p<0.001). The number of patients with controlled asthma (ACT<20) increased from 16 of 51 at baseline to 32 of 45 at Week 16 and 25 of 32 at week 52, respectively. The median daily dose of ICS equivalent to Fluticasone was reduced from baseline 680 mcg to 500 mcg at Week 52. In all, 22 patients discontinued Omalizumab after 1 year. Six patients who discontinued Omalizumab were restarted due to relapse of symptoms.

Conclusions: These data confirms the effectiveness of one-year duration of Omalizumab treatment in Thai severe asthmatic patients. Furthermore, 27% of patients who discontinued treatment required restarting due to relapse of symptoms.

Keywords: Omalizumab, Severe Asthma, Effectiveness, Long-term, Real life

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n, F/M)</td>
<td>51/27</td>
</tr>
<tr>
<td>Age, median and IQR (y)</td>
<td>58.5 (50.7-68.0)</td>
</tr>
<tr>
<td>Body weight, median IQR (kg)</td>
<td>62.7 (53.0-68.4)</td>
</tr>
<tr>
<td>Duration of asthma, median &amp; IQR (y)</td>
<td>10 (2.75-23.25)</td>
</tr>
<tr>
<td>Baseline total IgE, median &amp; IQR (IU/mL)</td>
<td>257 (97-544)</td>
</tr>
<tr>
<td>Patients with allergic tests</td>
<td>61 (78.2%)</td>
</tr>
<tr>
<td>Positive allergic tests, n (%)</td>
<td>51 (65.4%)</td>
</tr>
<tr>
<td>(aeroallergen: house dust mite, cockroach, cat dander)</td>
<td></td>
</tr>
<tr>
<td>Baseline FEV&lt;sub&gt;1&lt;/sub&gt;, median IQR (% predicted)</td>
<td>67.5 (54.0-89.3)</td>
</tr>
<tr>
<td>Baseline PEFR, median &amp; IQR (L/min)</td>
<td>310 (211-684)</td>
</tr>
<tr>
<td>Concomitant allergic diseases, n (%)</td>
<td>78 (100%)</td>
</tr>
<tr>
<td>Omalizumab dose median &amp; IQR (mg)</td>
<td>300 (160-1200)</td>
</tr>
<tr>
<td>Baseline ICS dose FP equivalent (µg)</td>
<td>500 (160-2000)</td>
</tr>
</tbody>
</table>

Kawamatawong T et al. Asian Pac J Allergy Immunol 2017
DOI 10.12932/AP0872
Asthma control
Driven by exacerbation rate and GINA step

Asthma control is driven by the rate of exacerbations and the GINA step.

Asthma
300 million

GINA step 4-5
20-28% of total asthma

Asthma exacerbation
1-2/year (13-17%)

Asthma exacerbation
≥ 2/year (3-4%)

Suruki RY et al. BMC Pulm Med 2017;17:74
Asthma which requires Rx for GINA steps 4–5 (high dose ICS-LABA or LTRA /theophylline) for the previous year or systemic CS for > 50% of the previous year to prevent asthma from becoming uncontrolled or remains uncontrolled despite therapy.

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ > 1.5, ACT <20, not well controlled by NAEPP/GINA
2) Frequent severe exacerbations: 2 or more bursts of OCS (>3 days each) in the previous year
3) Serious exacerbations: at least one hospitalization, ICU stay or MV in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV\textsubscript{1} < 80% predicted (in the face of reduced FEV\textsubscript{1}/FVC defined as less than LLN)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Difficulty of controlling asthma
With available treatments

Summary approach

Severe asthma
(requiring high intensity of treatment)

Good control if on high intensity treatment
Poor control despite high intensity treatment

Potentially treatment responsive but with persistent problems
(Poor compliance, inhaler technique, allergen exposure and smoking)

Persistent co-morbidities
• Psychosocial aspect
• Reflux disease
• Allergic rhinitis/sinusitis

Treatment resistance (Refractory) asthma
Biologic agents
Targeted therapies

Phenotypic approach

Difficult to control asthma vs. severe asthma

1. Watch patient using their inhaler
   - Discuss adherence & barriers

2. Confirm the diagnosis of asthma

3. Remove potential risk factors.
   - Assess & manage comorbidities

4. Consider treatment step-up

If PFT normal during symptoms:
- Consider halving ICS dose and repeating PFT after 2–3 weeks

Check risk factors or inducers (smoking, B-blockers, NSAIDs, allergen)
- Check comorbidities (rhinitis, obesity, GERD, depression/anxiety)

Consider step up to next treatment level.
- Share decision-making, and balance potential benefits and risks

Severe asthma

Refer to a specialist or severe asthma clinic

If asthma still uncontrolled after 3–6 months on Step 4 treatment, refer for expert advice
- Refer earlier if symptoms severe or doubts about diagnosis
**Difficult to treat and Severe asthma in adults**

**Assess and treat severe asthma phenotype**

Assess the severe asthma phenotypes during high dose ICS (or lowest possible dose of OCS)

<table>
<thead>
<tr>
<th>Type 2 inflammation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is patients likely to have residual type 2 airway inflammation?</td>
<td>Blood eosinophilia ≥ 150/µl and/or FeNo ≥ 20 ppb and/or Sputum eosinophils ≥ 2 % and/or Asthma is clinically allergen driven (Repeat blood Eo &amp; FeNO up to 2 x on OCS)</td>
<td>Is add-on type 2 biologic therapy available and affordable</td>
</tr>
</tbody>
</table>

**Investigate for comorbidities/differential diagnosis and treat/refer as appropriate**

- Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins, CXR, and or HRCT chest, DLCO
- Skin prick test or specific IgE for relevant allergen if not already done
- Other directed testing (ANCA, CT sinuses, BNP, echo) based on clinical suspicion
- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

**If no evidence of type 2 inflammation**

- Consider adherence tests
- Consider ↑ ICS dose 3-6 m
- Consider AERD, ABPA, CRS, NP, AD (Clinical type 2 phenotypes with specific add-on Rx)

- Review the basics: DDX, inhaler device technique, adherence, comorbid, side effects
- Consider investigation (if available and not done)
  - Sputum induction
  - HRCT of chest
  - Bronchoscopy for alternative diagnosis
- Consider add-on treatments
  - Trial tiotropium or macrolide
  - Consider add-on low dose OCS
  - Stop ineffective add-on therapy
  - Consider bronchial thermoplasty
Phenotypes of severe asthma

Umbellar of severe asthma

- Early onset
  - Th2 cytokine Pathway Approach
  - ICS
  - Anti-IgE
  - Anti-IL-5
  - Anti-IL-13/IL-4
- Late onset
  - FeV1
- Symptom exacerbation
- No or less Th2 Inflammation

Phenotype 1
Phenotype 2
Phenotype 3
Phenotype 4

Small Airway RX
Extra fine ICS/LABA
Large Airway RX
Tiotropium Bronchial thermoplasty

Wenzel S. Nature Medicine 2012
Biomarkers to identify T2 phenotypes
For personalized treatment of asthma

What is the impact of monoclonal Ab for Th2/eosinophilic phenotype asthma?

- Sputum eosinophils (>2% or 3%)
- Exhaled nitric oxide (>30 ppb)
- Circulating eosinophils (150-400/μl)
- Serum periostin (> 50 ng/ml)
- Serum IgE
- Allergen skin testing

- Eosinophilic/Th2 phenotypes (IL-4, IL-5 and IL-13)
- Non eosinophilic (sputum eosinophils< 2% or blood Eo <200/μl)

Green et al, Lancet 2002; 360: 1715-21
PG Gibson et al Lancet 2011; 378: 983-991
Severe asthma
Inflammatory phenotypes and current therapies

Blood eosinophilia > 150/µl and/or FeNO > 20 ppb and/or Sputum eosinophils > 2 % and/or Asthma is clinically allergen driven

“T2 high”
Eosinophilic
↑ Steroids
Anti-eosinophilic
Anti-IgE
Anti IL-5/IL5Rα
Anti IL4Rα/IL-13
Anti TSLP
Anti IL-33
CRTH2 antagonist

“T2 low”
Neutrophilic
Steroid resistance
Anti-neutrophilic
Macrolides
CXCR2 antagonist
Anti TNF
Anti IL-1
Anti IL-17/IL-23
P38 MAPK inhibitor
PDE4 inhibitors

Paucigranulocytic
Steroid resistance
LAMA
LAMA+LABA
LABA/LAMA/ICS
Bronchial thermoplasty

Barnes PJ. J Allergy Clin Immunol 2015; 136:631-645
Targets for biologics
(Current and pipeline treatments for T2 predominant asthma)

Dendritic Cells
(Antigen presenting cell)

Allergen

T cell receptor

Th0 cell

Th2 cell

B cell

Eosinophil

Plasma cell

Mast cell

IL-4

IL-13

IL-4Rα

IL-5

IL-4Rα

IL-5Rα

Mepolizumab

Reslizumab

Benralizumab

Dupilumab

Tralokinumab

Lebrikizumab

Dupilumab

Omalizumab

FcεRI

IL-4

IL-13

Eosinophilic vs. Allergic asthma

Eosinophilic vs. Allergic asthma
<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Blood EO Requirement</th>
<th>Usual Dosing &amp; Schedule</th>
<th>Approval Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Omalizumab</td>
<td>Blood EO &gt;150/mm³</td>
<td>Q 2-4 weeks</td>
<td>US FDA, EMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(75-375 mg SC)</td>
<td></td>
<td>≥ 6 years</td>
</tr>
<tr>
<td>2015</td>
<td>Mepolizumab</td>
<td>Blood EO &gt;400/mm³</td>
<td>Q 4 weeks</td>
<td>US FDA</td>
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<tr>
<td></td>
<td></td>
<td>(3 mg/Kg IV)</td>
<td></td>
<td>≥ 12 years</td>
</tr>
<tr>
<td>2016</td>
<td>Reslizumab</td>
<td>Blood EO &gt;300/mm³</td>
<td>Q 4 weeks</td>
<td>US FDA, EMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(30 mg SC)</td>
<td></td>
<td>≥ 18 years</td>
</tr>
<tr>
<td>2017</td>
<td>Benralizumab</td>
<td>Blood EO ≥300/mm³</td>
<td>Q 8 weeks</td>
<td>US FDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(200 mg SC)</td>
<td></td>
<td>&gt; 12 years</td>
</tr>
<tr>
<td>2018</td>
<td>Dupilumab</td>
<td>Blood EO &gt;300/mm³</td>
<td>Q 2-4 weeks</td>
<td>Not approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(150-300 SC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lebrikizumab</td>
<td>Blood EO &gt;300/mm³</td>
<td>Q 4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**Blood EO** refers to blood eosinophil count.
Diagnosis criteria of severe eosinophilic asthma

**Major criteria**

- Severe asthma
- Blood eosinophil ↑ (> 2 occasions)
- Frequent exacerbation (> 2 per year)
- Need for (chronic intermittent) oral steroid

**Minor criteria**

- Late onset
- Involvement of upper airway (chronic sinusitis, nasal polyps)
- Other biomarker (FeNO)
- Fixed airflow obstruction
- **Hyperinflation** or mucus plug

Buhl R et al Eur Resp J 2017
Asthma T2 phenotypes and treatment response

- **Non atopic asthma**
  - Anti-IL-5 (A)
  - Other Th2 mAb (A)
  - Omalizumab (C)

- **Atopic asthma with eosinophilia**
  - Omalizumab (A)
  - Anti-IL-5 (A)
  - Other Th2 mAb (A)

- **Th2 low asthma**
  - Bronchial thermoplasty (B)
  - Macrolides (C)
  - Weight loss (B)

- **Atopic asthma**
  - Omalizumab (A)

**Blood eosinophils (cell/mm³)**
- Low
- High

**Serum total IgE (IU/ml)**
- Low
- High

**Sputum eosinophils (%)**
- Low
- High

A Froideure, Eur Respir J 2016; 47: 304-319
SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes  

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

**Anti-IgE**

Is the patient eligible for anti-IgE for severe allergic asthma?

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

no

no

**Anti-IL5 / Anti-IL5R**

Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?

- Exacerbations in last year
- Blood eosinophils ≥300μl

no

no

**Anti-IL4R**

Is the patient eligible for anti-IL4R... for severe eosinophilic asthma?

- Exacerbations in last year
- Blood eosinophils ≥150μl or FeNO ≥25 ppb

no

no

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥290μl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

Extend trial to 6-12 months

Good asthma response?

yes

no

Choose one if eligible; trial for at least 4 months and assess response

Good response to T2-targeted therapy

STOP add-on

Consider switching to a different Type 2-targeted therapy, if eligible

Little/no response to T2-targeted therapy

Eligible for none?
Return to section 6a

© Global Initiative for Asthma, www.ginasthma.org
### Potential phenotypes

**Targeted therapies for severe asthma in clinical practice (Thailand)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Associations</th>
<th>Specific target treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe allergic asthma</td>
<td>Blood and sputum eosinophils Highs serum IgE High FeNo</td>
<td>Anti-IgE (Adult and children) Anti-IL-4/IL-13 Anti-IL-4 receptor</td>
</tr>
<tr>
<td>Eosinophilic asthma</td>
<td>Blood and sputum eosinophils Recurrent exacerbation High FeNo</td>
<td>Anti-IL-5 and anti-IL-5R Anti-IL-4/IL-13 Anti-IL-4 receptor</td>
</tr>
<tr>
<td>Neutrophilic asthma</td>
<td>Corticosteroid insensitivity Bacterial infection</td>
<td>Anti-IL-8 CXCR2 antagonists Anti-LTB4 (Adult and children) Macrolide (Adult and children)</td>
</tr>
<tr>
<td>Chronic airflow obstruction</td>
<td>Airway wall remodeling as increased airway wall thickness</td>
<td>Anti-IL-13 Tiotropium bromide Bronchial thermoplasty</td>
</tr>
<tr>
<td>Recurrent exacerbation</td>
<td>Sputum eosinophilia Reduced response to ICS/OCS</td>
<td>Anti-IL-5 Anti-IgE (Adult and children)</td>
</tr>
<tr>
<td>Corticosteroid insensitivity</td>
<td>Increased sputum neutrophilia</td>
<td>P38 MAPK inhibitor Theophylline (adult &amp; children) Macrolides (adult and children)</td>
</tr>
</tbody>
</table>

KF Chung et al, Eur Respir J 2014; 43: 343-373
**Adults & adolescents 12+ years**

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

### STEP 1
**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**

### STEP 2

- Daily low dose ICS) OR As-needed low dose ICS-formoterol *
- Leukotriene receptor antagonist (LTRA) OR low dose ICS taken whenever SABA 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

### Other reliever option

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

* Off-label; data only with Budesonide-formoterol
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed BUD-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted
### Step 1
Not recommended
- Consider low dose ICS
- As needed short-acting β2 agonist (SABA)

### Step 2
Low dose ICS
- Intermittent ICS LTRA
- Low dose theophylline

### Step 3
Low dose ICS-LABA
- Mod/high dose ICS
- Low dose ICS + LTRA
- Low dose ICS + Theophylline

### Step 4
Med/high dose ICS /LABA (with or without other controllers)
- Add tiotropium
- Med/High dose ICS + LTRA
- Med/high dose ICS + Theophylline

### Step 5
Refer to add-on treatment*
- Tiotropium
- Anti-IgE**
- Anti-IL-5***
- Anti-IL-5R***

---

**STEP 5**
Add low dose OCS

**Preferred controller choice**

- **STEP 1**
- **STEP 2**
- **STEP 3**
- **STEP 4**

**Other controllers**

- **STEP 1**
- **STEP 2**
- **STEP 3**

**Reliever**

- **STEP 1**
- **STEP 2**
- **STEP 3**

**For all patients**

- Asthma education, inhaler device training, allergen avoidance, environmental control including smoking cessation
- Influenza vaccine and pulmonary rehabilitation
- Identification and management of comorbidities

**For selected patients**

- For ICS intolerant patients or asthma with allergic rhinitis#
- For ICS intolerant and LTRA intolerant patients ##
- Consider SLIT for asthma with HDM allergy
- For severe allergic asthma**
- For severe eosinophilic asthma***
- Consider bronchial thermoplasty for severe asthma*
Muscarinic and β2 Adrenergic receptor distribution in human airways

Adapted from J Haughney Respiratory Medicine. 2010; 3 125-131
Clinical trials of bronchial thermoplasty in asthma

<table>
<thead>
<tr>
<th>Feasibility trial</th>
<th>AIR (RCT) n=108</th>
<th>RISA (RCT) n=32</th>
<th>AIR 2 (RCT) n=297</th>
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</thead>
<tbody>
<tr>
<td>A.M. PEFR</td>
<td>AQLQ</td>
<td>AQLQ</td>
<td>AQLQ</td>
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<tr>
<td>P.M. PEFR</td>
<td>Rescue Medications</td>
<td>Rescue Medication</td>
<td>Severe exacerbations</td>
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<tr>
<td>Symptom free days</td>
<td>Symptom free day</td>
<td>FEV₁</td>
<td>ER visit</td>
</tr>
<tr>
<td></td>
<td>Exacerbation</td>
<td>Oral steroid (NS)</td>
<td>Day lost from work and school or activities</td>
</tr>
<tr>
<td>AJRCCM 2006</td>
<td>NEJM 2007</td>
<td>AJRCCM 2007</td>
<td>AJRCCM 2010</td>
</tr>
</tbody>
</table>

Ex 5 year AIR 2
89% rate
No AE
No RS AE
No EXA
FEV₁ NS
BDR+

JACI 2013

X 3 procedure vs. sham control
Roadmap & milestone for anti-eosinophilic in asthma
From corticosteroid to biologic agents

- **IgE (Reagin)**: 1968
- **ICS**: 1973
- **Omalizumab**: 2003
- **Mepolizumab**: 2015
- **Reslizumab**: 2016
- **Benralizumab**: 2017
- **Dupilumab**: 
- **Trakolinumab**: 
- **Lebrikizumab**: 
- **Bertilimumab**: 
- **Fevipiprant**: 

**Corticosteroid**

**mAb**

- **IL-4Rα**
- **IL-5Rα**
- **IL-5**
- **IL-13**
COPD phenotypes

(Medical Research Council definition of chronic bronchitis)

Blue boater

(HRCT diagnosis pulmonary emphysema)

Pink Puffer
Should eosinophil be a biomarkers for ICS treatment in COPD?

**Eosinophil**

**Corticosteroid**

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>High-dose range (µg)</th>
<th>Medium-dose range (µg)</th>
<th>Low-dose range (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>&gt;500–1000</td>
<td>&gt;250–500</td>
<td>100–250</td>
</tr>
<tr>
<td>Budesonide</td>
<td>&gt;800–1600</td>
<td>&gt;400–800</td>
<td>200–400</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>&gt;500–1000</td>
<td>&gt;250–500</td>
<td>100–250</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>&gt;320–1280</td>
<td>&gt;160–320</td>
<td>80–160</td>
</tr>
<tr>
<td>Mometasone</td>
<td>&gt;800–1600</td>
<td>&gt;400–800</td>
<td>200–400</td>
</tr>
</tbody>
</table>
Asthma

GINA Step 1  Step 2  Step 3  Step 4  Step 5

Mild asthma  ICS

Severe asthma

ICS  ICS  ICS  ICS/LABA  Biologic
Low dose  High dose  + LABA  + LAMA

COPD

GOLD A  B  C  D

Eosinophilic COPD

SABA  LAMA  LAMA/LABA  LABA/LAMIA
or SAMA  or LABA  + ICS

Exacerbation risks

Steroid resistance

ACO

Prior asthma

Eosinophil
Risk assessment in COPD
A potential role for biomarkers

Exacerbation

Biomarker
Symptoms

Time

Eosinophil should be a biomarker for ICS treatment in COPD?

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018

Blood eosinophil should be a biomarker for ICS containing treatment regimens in COPD with frequent exacerbations

Agree  Disagree

Agree  Agree
<table>
<thead>
<tr>
<th>Tests</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; low &lt;80% predicted</strong></td>
<td>Risk factor for asthma exacerbation</td>
<td>Indicator of spirometry severity</td>
</tr>
<tr>
<td><strong>Improvement FEV&lt;sub&gt;1&lt;/sub&gt; &gt;12% and 200 ml post BD</strong></td>
<td>Usual at some time in course of disease, but not when controlled or when on controllers</td>
<td>Often present but an asthmatic component should be considered</td>
</tr>
<tr>
<td><strong>Improvement FEV&lt;sub&gt;1&lt;/sub&gt; &gt;12% and 400 ml post BD</strong></td>
<td>High probability of asthma or asthma component</td>
<td>Unusual</td>
</tr>
<tr>
<td><strong>DL&lt;sub&gt;CO&lt;/sub&gt;</strong></td>
<td>Normal or high</td>
<td>Often reduced</td>
</tr>
<tr>
<td><strong>FENO, blood and sputum eosinophil</strong></td>
<td>High level supports a diagnosis of eosinophilic asthma</td>
<td>Usually normal-eosinophil COPD phenotype</td>
</tr>
<tr>
<td>High resolution CT</td>
<td>Normal or some bronchial wall thickening</td>
<td>Emphysema can be quantified</td>
</tr>
<tr>
<td>Atopy (specific IgE or skin prick test)</td>
<td>Increases in probability of asthma <strong>but not essential for diagnosis</strong></td>
<td>Confirm to background prevalence <strong>Dose not rule out COPD</strong></td>
</tr>
</tbody>
</table>
### Pharmacotherapy for stable COPD

#### Bronchodilator
- $\beta_2$ agonists
- Antimuscarinic drugs
- Mehylixanthine
- Combination BDs

#### Anti-inflammatory
- ICS
- OCS
- PDE-4 inhibitors
- Antibiotics
- Mucoregulator and antioxidant agents
- Other anti-inflammatory

#### Other treatment
- $\alpha$-1 AAT augment
- Antitussives
- Vasodilator
Effect of ICS in COPD Exacerbation
Only for eosinophil causing exacerbation

Without ICS

Eosinophilic exacerbation

Non eosinophilic exacerbation

Pollution, viruses and bacteria

Annual exacerbation rate

Eosinophil count cells/mm³

With ICS

Eosinophilic exacerbation

Non eosinophilic exacerbation

Pollution, viruses and bacteria

T Greulich & P Vogelmeier Lancet Respir Med 2018
Benefit and risk of ICS regarding blood eosinophilia

Risk of pneumonia
Risk of COPD exacerbation

Constant risk of ICS across spectrum of COPD treated with ICS

Overall COPD
COPD cohort with blood eosinophilia ≥ 2%
65 % of all cohort

COPD cohort with blood eosinophilia ≥ 4%
20 % of all cohort

Samy Suissa  Chest 2017; 152:227-231
A pragmatic approach
Simplify inhaler therapy for COPD

Diagnosis of COPD
Classification according risk of exacerbation

< 2 exacerbations/year
No hospital admission
COPD GOLD group B

LABA/LAMA

COPD GOLD group C, D

≥ 2 exacerbations/year
OR hospital admission
Assess eosinophil count

Low eosinophil count
(<300 cells/mL)
LABA/LAMA

High eosinophil count
(≥300 cells/mL)
LABA/LAMA/ICS

B Lipworth & S Jabbal Lancet. 2017. DOI:https://doi.org/10.1016/S2213-2600(17)30264-3
Blood eosinophil levels as a biomarker in COPD

Brusselle G et al Respir Med. 2018; 138, 21-31
### NNT and NNH for ICS

(Comparison between NNT to prevent exacerbation and NNT to induce pneumonia
Cumulative incidence of events SFC compared to LABD)

<table>
<thead>
<tr>
<th>ICS/LABA Studies</th>
<th>Time to span NNT</th>
<th>COPD exacerbation</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CI at end of study</td>
<td>CI at end of study</td>
</tr>
<tr>
<td></td>
<td>ICS</td>
<td>No ICS</td>
<td>NNT</td>
</tr>
<tr>
<td>TORCH</td>
<td>3 year</td>
<td>0.922</td>
<td>0.945</td>
</tr>
<tr>
<td>INSPIRE</td>
<td>2 years</td>
<td>0.578</td>
<td>0.59</td>
</tr>
<tr>
<td>Kardos</td>
<td>44 wks</td>
<td>0.47</td>
<td>0.55</td>
</tr>
<tr>
<td>Ferguson</td>
<td>1 year</td>
<td>0.58</td>
<td>0.66</td>
</tr>
<tr>
<td>Anzueto</td>
<td>1 year</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Pneumonia risk of ICS
According exposure duration and dose

Serious pneumonia event during the 5.4 years of follow-up

GOLD 2019 Therapeutic Recommendations

Initial pharmacologic treatment

- **Group C**: LAMA
- **Group D**: LAMA + LABA* or ICS+ LABA**
  * Consider if highly symptomatic (CAT >20)
  ** Consider if EOS > 300

- **Group A**: A bronchodilator
- **Group B**: A Long Acting bronchodilator (LABA or LAMA)

- > 2 moderate exacerbations or > 1 leading to hospitalization
- 0 or 1 moderate exacerbations (not leading to hospitalization)

mMRC 0-1 CAT < 10

mMRC >2 CAT > 10
COPD maintenance therapies
Mono-bronchodilator vs. dual bronchodilator

Monotherapy of LABD
(LAMA or LABA)
- Newly diagnosed COPD and therapy naïve
- Moderate symptomatic
- Exacerbation history ±

Dual LABDs
(LABA plus LAMA)
- Still symptomatic despite LABA or LAMA therapy
- Highly symptomatic
- Exacerbation ++

- CAT or MMRC
- Patient preference
- Side effect
- Cost

- CAT or MMRC and Exacerbation
- Patient preference
- Side effect
- Cost
Symptom algorithm according to CAT™ using bronchodilator (s) for COPD

Cardiac diseases
Comorbidities
Inhaler technique
Treatment adherence
Inhaler devices

SABA or SAMA
LABA
OR
LABA
SABA or SAMA
LABA plus LAMA

CAT < 10
10 < CAT < 20
CAT > 20

CAT™ Score
0
0
0
0
0
0
0
5
5
5
5
5
5
5

Best
Worst

Cough
Phlegm
Chest tightness
Breathlessness
Activity limitation
Confidence
Sleep
Energy
Use of ICS for COPD and adverse effects in COPD

Overused ICS in GOLD A and B

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Randomized trials</th>
<th>Observational studies</th>
<th>Systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Bone fracture</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cataract</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal candidiasis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>


David Price et al Prim Care Respir J 2013
ICS containing regimens in COPD treatment
Friend or foe

<table>
<thead>
<tr>
<th>Strong support</th>
<th>Consider use</th>
<th>Avoidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized exacerbation</td>
<td>1 moderate exacerbation /year</td>
<td>Repeat pneumonia episode</td>
</tr>
<tr>
<td>Frequent (≥ 2) moderate exacerbations /years</td>
<td>Blood eosinophils 100-300 cell/mm³</td>
<td>Blood eosinophils &lt; 100 cell/mm³</td>
</tr>
<tr>
<td>Blood eosinophils ≥ 300 cell/mm³</td>
<td></td>
<td>History of mycobacterial lung infection</td>
</tr>
<tr>
<td>History of asthma or concomitant asthma (ACO)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Relationship of blood eosinophils and efficacy for preventing exacerbation of ICS

COPD with history of frequent exacerbations with high blood eosinophilia

- Low response
- Moderate response
- High response

- Frequent exacerbations (>2/years)
- Non-frequent exacerbation (<2/years)

D Singh Am J Respir Crit Care Med 2017; 196: 100-116
Obstructive airway diseases in practice
Phenotypic approach: No one size fit all

Frequent exacerbation

C
Low symptoms

D
More symptoms

Non-Frequent exacerbation

A

B

Bronchodilator (S)
± Anti-inflammation

Escalation treatment-Evaluate effect
Deescalate treatment when ineffective or adverse effect

D Singh Am J Respir Crit Care Med 2018; 194: 511-516
Management cycle of COPD

**REVIEW**
Symptoms
Dyspnea
Exacerbation

**ADJUST**
- Escalate
- Switch inhaler device or molecular
- De-escalate

**ASSESS**
- Inhaler technique and adherence
- Non-pharmacologic approaches
  - (Including pulm rehab and self-management education)

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019
**GOLD 2019 Therapeutic Recommendations**

**Follow-up pharmacologic treatment**

**Dyspnea**

- LABA or LAMA
  - LABA + LAMA
    - Consider Switching inhaler device or molecules
    - Investigate (and treat) other cause of dyspnea

**Exacerbation**

- LABA or LAMA
  - LABA + LAMA
    - LABA/ICS
      - LAMA + LABA + ICS
      - Consider if EOS > 300 or > 100 and > 2 moderate exacerbation/1 hospitalization
      - **Consider de-escalation of ICS or switch if pneumonia or inappropriate original indication or lack of response to ICS**

- LABA + LAMA
  - LABA + ICS
    - Consider Roflumilast if FEV₁ < 50% & chronic bronchitis
    - Consider Azithromycin in former smokers

- LABA + LAMA + ICS
  - LABA + ICS

---

* Consider if EOS > 300 or > 100 and > 2 moderate exacerbation/1 hospitalization
** Consider de-escalation of ICS or switch if pneumonia or inappropriate original indication or lack of response to ICS
In patients with severe and very severe COPD (GOLD 3 & 4) and a history of exacerbations and chronic bronchitis, the phosphodiesterase-4 inhibitor (roflumilast) reduces exacerbations treated with oral glucocorticosteroids (GOLD 2015).

# Anti-inflammatory therapy in stable COPD

<table>
<thead>
<tr>
<th>Drugs classes and example</th>
<th>Description and recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroidal drugs</strong></td>
<td><strong>Steroidal drugs</strong></td>
</tr>
<tr>
<td>• Inhaled corticosteroid</td>
<td>• Reduce exacerbation in moderate-severe COPD with exacerbations</td>
</tr>
<tr>
<td>• Oral corticosteroid</td>
<td>• Predictive role of blood eosinophil</td>
</tr>
<tr>
<td><strong>Nonsteroidal drugs</strong></td>
<td>• Risk of pneumonia</td>
</tr>
<tr>
<td>• PDE4 Inhibitor (roflumilast)</td>
<td>• Numerous side effects</td>
</tr>
<tr>
<td>• Antibiotics (long term)</td>
<td><strong>Nonsteroidal drugs</strong></td>
</tr>
<tr>
<td>• Mucoregulator &amp; antioxidant</td>
<td>• FEV$_1 \leq$ 50% with chronic bronchitis</td>
</tr>
<tr>
<td></td>
<td>• Azithromycin 250 OD (hearing loss)</td>
</tr>
<tr>
<td></td>
<td>• NAC in patients without ICS</td>
</tr>
<tr>
<td></td>
<td>• Statin and LTRA are not effective</td>
</tr>
</tbody>
</table>
HRCT in COPD phenotypes
pulmonary emphysema and chronic bronchitis

Male 59 years old BMI 18 kg/m²
FEV₁ 35% predicted
CAT score 30 m MRC 3
Infrequent COPD exacerbation

Male 59 years old BMI 21 kg/m²
FEV₁ 32% predicted
CAT score 26 m MRC 2
Frequent COPD exacerbation

Low attenuation area (LAA < -950 HU) without perceivable wall of centrilobular emphysema of upper and lower lungs

Mild bronchial wall thickening and bronchial luminal dilatation and centrilobular emphysema of both lungs (right)
Percentage COPD phenotypic patients
Based on HRCT detected emphysema

Absence of emphysema (A Phenotype 28.3%)
Bronchial wall thickening (-)
N = 13

Emphysema with bronchial wall thickening (+)
N = 30

Emphysema without bronchial wall thickening (E Phenotype 36.5%)
N = 31

Yoshiaki Kitaguchi, Keisaku Fujimoto Res Med 2006
Relationship between COPD exacerbation and HRCT detected BWT vs. emphysema score

Largely independent effects of emphysema or BWT

↑AECOPD at ↑emphysema
Effect of BWT at ↓emphysema

↑BWT and ↑AECOPD at low levels of emphysema

LVRS and survival benefit in COPD

- Low lung reserve with low exercise capacity
- Predominate upper lobe disease

Benefit on survival, lung function and symptoms

Predicting Outcome in LVRS
(Baseline CT scan of LAA-950 HU)

Relationship of the change in FEV\textsubscript{1} (value at 6-month baseline value) and preoperative % emphysema (%LAA-950; measured from baseline CT scan)

\[ R = 0.20, \ P < 0.0001 \]

### Patient characterization for LVRS

(Who should be treated with LVRS?)

<table>
<thead>
<tr>
<th>Indication (non-high-risk, better outcome chance)</th>
<th>Contraindication (high-risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;75 years</td>
<td>Severe parenchymal loss with DLCO &lt;20% of predicted</td>
</tr>
<tr>
<td>Marked dyspnea; MRC score &gt;3</td>
<td>FEV₁ &lt;20%</td>
</tr>
<tr>
<td>Severe emphysema: Hyperinflation: TLC &gt;125% of predicted, RV/TLC &gt;0.65, and FEV₁ &lt;35% of predicted</td>
<td>Pulmonary hypertension; mean pulmonary artery pressure &gt;35 mmHg</td>
</tr>
<tr>
<td>Upper-lobe predominant emphysema (ULP) with low exercise capacity</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Homogenously distributed emphysema</td>
</tr>
</tbody>
</table>

M Meena et al. Pulmonary Medicine 2014
Techniques available for lung volume reduction

Different approach to LVR/Surgical Management of emphysema

Surgical (LVRS)
- Open procedure
- VATS

Bronchoscopic LVR
- Valve
- Plug
- Coils
- Bio LVR
- Airway Bypass
- Thermal Ablation

Other procedure for LVRS/emphysema
- Costochondrectomy
- Phrenic nerve interruption
- Thoracoplasty
- Glometomy
- Radical hilar denervation
- Pleural stripping
<table>
<thead>
<tr>
<th>Phenotypes in COPD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical phenotype</td>
<td>Chronic bronchitis or emphysema</td>
</tr>
</tbody>
</table>
| Overlap phenotype  | Overlap phenotype with asthma (ACOS)  
|                    | Overlap phenotype with OSAHS  |
| Imaging phenotype  | Airway diseases or emphysema or bronchiectasis |
| Exacerbation phenotype | Frequent or infrequent exacerbation |
| Airway inflammatory phenotype | Airway eosinophilia or neutrophilia |
| Systemic inflammatory phenotype | Fibrinogen, hsCRP, WBC |
| Rapid decline lung function | Rapid decline or slow decline FEV₁ |
| Bronchodilator reversibility phenotype | Bronchodilator reversibility phenotype |
Obstructive airway diseases in practice
Phenotypic approach: No one size fit all

Treatment of COPD by Clinical and Imaging Phenotypes

Exacerbation frequency
- 0-1/year
- >2/year

Emphysematous phenotype
Chronic bronchitic phenotype
Asthma/COPD (ACOS) Phenotype

M. Miravitlles et al. Eur Respir J. 2013; 41(6)1252-6
# Inhaler devices and inspiratory maneuver

## Dry powder inhaler (Lactose carrier)
- **Multiple dose DPI-blister**
  - Accuhaler
  - Ellipta
- **Single dose DPI capsule**
  - Breezhaler
  - Handihaler
- **Reservoir multi-dose DPI**
  - Turbhaler
  - Easyhaler
- **Metered dose inhaler**
  - Pressurized MDI
  - ACE spacer
  - Optichamber
  - NEXThaler
  - Twisthaler
  - Spinhaler

## Aerosol generator (w or w/o propellant)
- **Breath actuate MDI**
  - Propellant (HFA) High speed aerosol
- **Soft mist inhaler**
  - Propellant free Low speed aerosol

## Inhalation Maneuver
- Inhale **FAST and DEEP**
- Inhale **SLOW and STEADY**

## Lactose and Drug
- Lactose
- Drug

## Propellant
- HFA
Inhaler Device Phenotype Considerations
Choosing the right inhaler device

**Conscious inhalation possible**
- Patients with severe hyperinflation and during exacerbations
- Coordination +
  - Sufficient inspiratory flow
  - pMDI ± spacer
  - DPI
  - Breath-actuated aerosol
  - Soft mist inhaler
- Coordination –
  - Insufficient inspiratory flow
  - Poor hand-lung coordination
  - pMDI + spacer
  - Breath-actuated aerosol
  - Soft mist inhaler

**Conscious inhalation not possible**
- Elderly patients with cognitive limitations
- Coordination +
  - pMDI ± spacer
  - Breath-actuated aerosol
  - Soft mist inhaler
- Coordination –
  - Poor hand-lung coordination
  - pMDI + spacer
  - Nebuliser

Thank you for your attention