PG 2 : Asthma and COPD

Monitoring Asthma : state-of-the-art physiological, imaging, and biomarker assessment

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Introduction

- ERS Postgraduate Courses
  ‘Improve knowledge and skill applied in daily practice’

- Monitoring (not Diagnosis) in Asthma
  Daily practice (clinical) vs. State-of-the-art (Research)
  Adults & Children; Primary & Secondary Care

Aims

- **Aim 1** Learn about the state-of-the-art approaches for monitoring asthma in physiology and imaging
- **Aim 2** Understand the position of asthma monitoring tools in current guidelines and strategy documents
- **Aim 3** Review the role of Th-2 mediated biomarkers in asthma management
Key Bibliography


• Asthma diagnosis and monitoring; NICE draft guideline 2016.

https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0640 Undergoing implementation feasibility project. Full Guidelines Due 2017


Why Monitor Asthma?

Tailoring of asthma management to **disease control**

Definition of ‘disease control’ varies: GINA, NHLBI-NAEPP, BTS/SIGN

**ERS TF Statement Children 2015**

**SYMPTOMS**
- **daily practice**

Patients & clinicians both underestimate asthma severity and overestimate asthma control


every breath counts
For many aspects of monitoring asthma in children (and adults) there is lack of evidence. Need for further research.

---

**Monitoring Tools for Asthma**

<table>
<thead>
<tr>
<th>Monitor</th>
<th>0-2</th>
<th>2-4</th>
<th>4-6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical tools</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>C-ACT/ACT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACQ</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>x</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>QoLQ</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>x</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow-volume curves/BDR</td>
<td>[Tidal]</td>
<td>[Tidal]</td>
<td>(x)</td>
<td>x</td>
</tr>
<tr>
<td>PEF</td>
<td>-</td>
<td>-</td>
<td>(x)</td>
<td>x</td>
</tr>
<tr>
<td>$R_{int}$-IOS-FOT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>LCI</td>
<td>x</td>
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<tr>
<td>ILF</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BHR</td>
<td>-</td>
<td>-</td>
<td>(x)</td>
<td>x</td>
</tr>
<tr>
<td>Direct (methacholine/histamine)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Indirect (exercise, mannitol)</td>
<td>x</td>
<td>x</td>
<td>(x)</td>
<td>x</td>
</tr>
<tr>
<td><strong>Inflammatory markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$FeNO$</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Induced sputum (eosinophils, LTE4, EPX)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Exhaled breath condensate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>x</td>
</tr>
</tbody>
</table>

C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; QoLQ: quality of life questionnaire; BDR: bronchodilator response; PEF: peak expiratory flow; $R_{int}$: interrupter resistance; IOS: impulse oscillometry; FOT: forced oscillation technique; LCI: lung clearance index; ILF: infant lung function; BHR: bronchial hyperresponsiveness; $FeNO$: fraction of exhaled nitric oxide; LTE4: leukotriene E4; EPX: eosinophil peroxidase. x: can be used in this age category; (x): might be possible to use in this age group in specialised centres. #: modified exercise challenge possible at preschool age.
<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms and Questionnaires</strong></td>
<td></td>
</tr>
<tr>
<td>12+yrs</td>
<td></td>
</tr>
<tr>
<td>Asthma Control Test (ACT)</td>
<td>Developed by QualityMetric Inc. and GSK</td>
</tr>
<tr>
<td>5-items (activity limitations, shortness of breath, nocturnal symptoms, rescue medication, overall control in past 4 weeks) Each scored from 1 (worst) to 5 (best) Range 5-25 (better indicated by higher values)</td>
<td></td>
</tr>
<tr>
<td>Paediatric ACT (CACT)</td>
<td>Developed by QualityMetric Inc. and GSK</td>
</tr>
<tr>
<td>7-item scale (4 child-reported and 3 caregiver-reported) The child-completed items use a 4-point response scale and the caregiver-completed items use a 6-point response scale Range 0-27 (better indicated by higher values)</td>
<td></td>
</tr>
<tr>
<td>4-11yrs</td>
<td></td>
</tr>
<tr>
<td>7 items (specific symptoms, timing of symptoms, activity limitation, rescue medications, lung function) Each scored from 0 (best) to 6 (worst) Range 0-6 (better indicated by lower values)</td>
<td></td>
</tr>
<tr>
<td>6+yrs</td>
<td></td>
</tr>
<tr>
<td>3 items Each Item scored 0 (no) or 1 (yes) (better indicated by lower values)</td>
<td></td>
</tr>
<tr>
<td><strong>Asthma QoL questionnaires</strong></td>
<td></td>
</tr>
<tr>
<td>32 items 7 point scale, 1-7 (better indicated by higher values)</td>
<td></td>
</tr>
<tr>
<td>15 items 7 point scale, 1-7 (better indicated by higher values)</td>
<td></td>
</tr>
<tr>
<td>23 items 7 point scale, 1-7 (better indicated by higher values)</td>
<td></td>
</tr>
<tr>
<td>13 items 7 point scale, 1-7 (better indicated by higher values)</td>
<td></td>
</tr>
</tbody>
</table>

- All clinicians monitor asthma control by symptom enquiry
- Monitor at every review
  *NICE draft guideline 2016*
- Use ‘closed’ not ‘open’ questions to monitor asthma monitoring children & adults - BTS/SIGN 2014
- No evidence to support diaries to monitor asthma symptoms
  *Arga, J Asthma 2014; ERS TF Statement Children 2015*
- Using composite asthma control scores not shown improve symptoms
  *ERS TF Statement Children 2015*
- Consider ACQ, ACT to monitor in 16+ as benefit for QoL (low quality studies)
  *NICE draft guideline 2016*
- QoLQ time-consuming, no evidence better clinical outcomes. Research tool.
  *ERS TF Statement Children 2015*
Incorrect use of peak flow meters: are you observing your patients?

Self et al, J Asthma 2014

- Routine PEFR **not useful** to monitor asthma in children

- **Useful**: monitor asthma control >5yrs age with PEFR variability

ERS TF Statement Children 2015

RCT’s in children, Tantisira JACI 2006; Wensley, AJRCCM 2004

- No benefit of PEFR guided treatment compared with management based on symptoms alone
- Addition of PEF did not enhance self-management, even during exacerbations
<table>
<thead>
<tr>
<th>Maximal Expiratory Flow–Volume Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>‘Gold standard’ for the assessment of lung function</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flow (L/s)</th>
<th>Volume (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>-4</td>
<td>-4</td>
</tr>
</tbody>
</table>

**Asthma**

- Decreased flow at the beginning of downslope
- Straight line
- Curve during residual breaths

**FeV₁**

- Defines asthma severity
- Independent predictor of risk of asthma attack: adults (Kitch, Chest 2004; Fuhlbrigge, JACI 2001) children
- Correlates poorly with patient symptoms

**Annual spirometry adults and children >5yrs of age**
Other Lung Function Tools

● Bronchodilator reversibility (FEV$_1$ ≥12% and/or ≥200ml)
  Used in asthma diagnosis, but not helpful in daily-practice monitoring

● Body plethysmography
  Not useful in monitoring

● Bronchial hyper-responsiveness / Challenge tests
  Do not use to monitor asthma control

Routine assessment not useful in children; may be a place in exercise limitation, atypical symptoms, poor symptom perception, not responding to current treatment

NICE draft guideline 2016

ERS TF Statement Children 2015

European Respiratory Society every breath counts
Forced Oscillation Technique (FOT)

Oscillating pressure/flow signals of moving air within lungs used to determine airway mechanics

Impedance \((Z) = \text{Resistance (R)} + \text{Reactance (X)}\)

Courtesy Paolo Paredi, Imperial College London
Low oscillation frequencies (5Hz).

High oscillation frequencies (20Hz).

Resistance (R).

Reactance (X) (out of phase).

Deeper Airways

Proximal Airways

Goldman, Pulm Pharmacol Ther 2001

Courtesy Paolo Paredi, Imperial College London
Monitoring Asthma: state-of-the-art physiological, imaging, and biomarker assessment
Lung Imaging Modalities

- Chest radiograph
- Gamma-scintigraphy
  - Parameswaran, Can Resp J 2007
- High-resolution computed tomography (HRCT)
  - Niimi, AJRCCM 2000; Kim AJR 2012
- HRCT and Computational Fluid Dynamics
  - De Backer, J Biomech 2008
- Single-photon emission CT (SPECT)
  - King, Semin Nuc Med 2010
- Positron emission tomography (PET)
  - Harris, AJRCCM 2006
- Hyperpolarised (He, Xe) magnetic resonance imaging (MRI)
  - van Beek, AJR 2004
- Oxygen-enhanced MRI
  - Zhang, Eur J Radiol 2015

Daily practice vs. State-of-the-art
Imaging ‘Biomarkers’ – HRCT

- Cross-sectional studies – characterise/phenotype asthma
  Niimi, AJRCCM 2000; Laurent, Eur Radiol 2000; Fujimoto, Respirol 2006; Akira, AJR 2009

- Markers of airway remodelling?
  Saglani, Respir Res 2006; Donohue, JACI 2013


- Using low-dose CT Dijkstra, Respir Res 2013
3D reconstruction (Modelling) of airway geometry (HRCT) and airflow simulation (CFD) with colour coded density

- Assess changes in regional airways (large vs. small):
  - Airway volume
  - Airway resistance
  - Ventilation heterogeneity
  - Gas trapping

- Assess effects of drug targeting to different lung regions

DeBacker et al, J Biomech 2008
• He\textsuperscript{3+} remains in airways does not transfer to blood
• Assess degree to which diffusion-driven displacement of inhaled He\textsuperscript{3+} atoms are restricted by the airway walls
Regional ventilation changes in severe asthma after bronchial thermoplasty with (3)He MR imaging and CT. Thomen, Radiology 2015
Effect of Different Drug Particle Sizes on Lung Deposition in Mild Asthma

Usmani, AJRCCM 2005; Biddiscombe, JAMPDD 2011
Monitoring Asthma: state-of-the-art physiological, imaging, and biomarker assessment

Biomarkers
Why Do We Want/Need Biomarkers?
Assess / Predict / Monitor

- Asthma Phenotypes & Optimise Diagnosis
- Response to Therapy (ICS, Biologics)
- In daily practice identify responders vs. non responders
  Asthma Phenotypes, Sally Wenzel
- Patient Adherence to Therapy
- Disease Control
- Adverse-effects
Biomarkers in Asthma

- $F_{ENO}$
- Sputum eosinophils
- Blood eosinophils
- Blood - periostin (Corren, NEJM 2011 / IgE / YKL-40 Konradsen, JACI 2013)
- Exhaled breath
  - volatile organic compounds (e.g. ethane) (van Mastright, CEA 2015)
  - breath temperature, (Garcia, Int J Tuberc Lung Dis 2013)
  - inflammatory mediators (e.g. 8-isoprostane, LTB$_4$ / pH) (Konstandini, ScientificWorldJournal 2015)
- Sputum
  - non-eosinophilic (Berry, Thorax 2007)
  - neutrophils (Farah, Respirology 2015)
- Nasal mediators / Electronic nose (Fens, AJRCCM 2015)
- Skin - allergen testing
- Urine - bromotyrosine (Cowan, JACI 2015 / LTE$_4$ Cai, Lung 2007)
- Future: genomics, proteomics and metabolomics
## Biomarkers – Confusion?

**Pavord & Hilvering, JACI 2015**

<table>
<thead>
<tr>
<th>F\textsubscript{E}NO</th>
<th>Sp-Eos</th>
<th>BI-Eos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1, GINA 2015</strong></td>
<td>not recommended</td>
<td>not recommended; in severe asthma help adjust therapy</td>
</tr>
<tr>
<td><strong>2, ERS/ATS Severe Asthma 2014</strong></td>
<td>not recommended</td>
<td>specialist centres; help adjust therapy; avoid overtreatment</td>
</tr>
<tr>
<td><strong>3, ERS Task Force Children 2015</strong></td>
<td>not recommended; monitor disease in difficult asthmatics</td>
<td>not recommended</td>
</tr>
<tr>
<td><strong>4, UK NICE draft Asthma 2016</strong></td>
<td>not routinely; but symptomatic asthmatics on ICS</td>
<td>-</td>
</tr>
<tr>
<td><strong>5, ATS Clin Pract Guidline FeNO</strong></td>
<td>recommended ; identify eosinophilic inflammation &amp; CS-responsiveness</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>6, UK NICE FeNO</strong></td>
<td>recommended; help diagnose asthma; support management in symptomatic asthmatics on ICS</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>7, Cochrane 2007</strong></td>
<td>n/a</td>
<td>use to tailor therapy in frequent exacerbators and in severe asthma</td>
</tr>
<tr>
<td><strong>8, Cochrane 2009</strong></td>
<td>not routinely recommended at this stage in adults or children</td>
<td>n/a</td>
</tr>
</tbody>
</table>

6. Measuring fractional exhaled nitric oxide concentration in asthma. NICE diagnostic guideline 2014. [https://www.nice.org.uk/guidance/dg12](https://www.nice.org.uk/guidance/dg12)
Harry Brown 1958 - first ‘biomarker’ study to show presence of eosinophils indicates steroid responsiveness

_Treatment of chronic asthma with prednisolone; significance of eosinophils in the sputum._ Brown HM. Lancet 1958 Dec 13;2(7059):1245-7

- 1956 UK MRC multi-central trial of oral corticosteroids in chronic asthma concluded OCS were no better than bronchodilators
- Brown, studied 90 patients treated with OCS and after 3 months observed 60 were clinically better but 30 were unchanged
- Developing a rapid wet smear method of looking for eosinophils in the clinic, he discovered the 60 who responded to OCS had many eosinophils, while the 30 non-responders had none

Elevated levels of sputum eosinophils (≥ 2% of all inflammatory cells) are a _biomarker_ of late-onset eosinophilic asthma

Sputum Eosinophil Directed Asthma Management

Reduction in exacerbations & admissions without need for more anti-inflammatory Rx

N=74 Refractory Asthma
Treatment based on Symptoms & Sputum Eos >3%
Strategy directed at normalising Sputum Eos count

Cumulative asthma exacerbations

**63%**
*48%

No correlation between EOS and PFT, Asthma symptoms or QoL
Sputum Eosinophils: Systematic review and Meta-analysis

Meta-analysis showed adults whose treatment adjusted to sputum eosinophils had significantly fewer exacerbations than controls

Petsky et al, Thorax 2012

Number of patients who had >1 asthma exacerbation over the study period*

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Sputum</th>
<th>Control</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Chlumsky 2006</td>
<td>8</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Green 2002</td>
<td>18</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>Jayaram 2006</td>
<td>26</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>Subtotal</td>
<td>52</td>
<td>109</td>
<td>51</td>
</tr>
<tr>
<td>Total events</td>
<td>52</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.92$, df = 2 ($p = 0.38$); $I^2 = 0$
Test for overall effect: $Z = 3.49$ ($p = 0.0005$)

Odds ratio
M–H, fixed, 95% CI

- Sputum: 0.18 (0.05, 0.61)
- Control: 0.35 (0.12, 0.98)
- Control: 0.52 (0.22, 1.22)
- Control: 0.36 (0.20, 0.64)

N = 215 (number of patients with one or more exacerbations over the study period)
*Variable duration from 12 to 24 months
CI, confidence interval; M–H, Mantel–Haenszel
Evaluate the diagnostic accuracy of $F_{eNO}$, blood eosinophils & total IgE for detecting sputum eosinophilia ($\geq 3\%$) in a large heterogeneous group of adult asthma patients, as well as in patients with different asthma phenotypes

- $F_{eNO}$ and Bl-eos had similar diagnostic accuracy for detecting Sp-eos, whereas total IgE AUC significantly lower

- Combining $F_{eNO}$ & Bl-eos significantly improved diagnostic accuracy compared to either alone

$F_{eNO}$ and blood eosinophils (but not total IgE) can be used to confirm or exclude sputum eosinophilia with high certainty in up to half of adult asthma patients, irrespective of asthma phenotype
Elevated peripheral blood eosinophils associated with greater risk of severe asthma attack than increased FeNO levels

**Blood Eosinophils – Future Risk**

Current asthma

Current wheeze

Asthma attack

Asthma related ED visits

Malinoschi, JACI 2013
**Blood Eosinophils – Biomarker guided therapy**

*Mepolizumab for severe eosinophilic asthma (DREAM).*

Pavord, Lancet 2012;380:651-59

Evaluated IV Mepolizumab (75, 250 and 750 mg) vs. placebo; 13 infusions at 4 weekly intervals

- Large study – 621 patients (81 centres)
- Adults, Severe Asthma on OCS
- 2 or more exacerbations in previous year
- Sputum eosinophils $\geq$ 3%
- FeNO $\geq$ 50 ppb
- Blood eosinophils $\geq$ 300/cc
Mepolizumab for severe eosinophilic asthma (DREAM).

Exacerbations

Highly significant reduction

Pavord, Lancet 2012;380:651-59
MEPO in a highly selected asthma population;
- reduced risk of asthma exacerbations vs. placebo
- lowered blood & sputum eosinophil counts
  • No better lung function
  • No better ACQ
  • No better AQLQ

“measures of asthma control do not indicate improvements elicited by reduced eosinophils in the airways”
“traditional markers of asthma such as FEV₁ were not related to the efficacy of MEPO”
Complements spirometry in disease management
- **Adds a needed dimension to help in phenotyping**

- Identifies steroid-responsive patient (Th-2 inflammation)
  - **And those that do not need ICS**

- Guides changes in dosing of anti-inflammatory medication (step-down/step-up/discontinue)
  - **Avoids overtreatment with corticosteroids**

- Evaluates/unmasks unsuspected poor adherence to ICS
  - **Stratifies patient being considered for expensive biologics**
FeNO Identifies Steroid Responsiveness

FeNO predicts steroid responsiveness more consistently than spirometry, bronchodilator response, PEF variation, or AHR

- FEV\textsubscript{1} > 12%
- PEF > 15%
- Symptoms reduce > 1 point
- AHR > 2 dd

- N=52 patients with \textit{undiagnosed} persistent respiratory symptoms > 6/52
- Steroid responsiveness to FP 500µg/d for 4/52 was assessed by 4 OUTCOME measures
FeNO identifies steroid responsiveness more consistently than spirometry, bronchodilator response, PEF variation, or AHR.

Smith, AJRCCM 2005

- N=52 patients with undiagnosed persistent respiratory symptoms >6/52
- Steroid responsiveness to FP 500µg/d for 4/52 was assessed by 4 OUTCOME measures:
  - FEV\(_1\) >12%
  - PEF >15%
  - Symptoms reduce >1 point
  - AHR >2 dd

Regardless of diagnosis, subjects with high FeNO has significantly greater steroid responses for all 4 OUTCOME measures by 4 OUTCOME measures.

High FeNO levels can be used as a tool to predict ICS response.
FeNO predicts steroid responsiveness more consistently than spirometry, bronchodilator response, PEF variation, or AHR

**Accuracy** of FeNO was assessed by comparison with conventional PREDICTORS of ICS response

For all 4 OUTCOME measures, baseline FeNO provided greater sensitivity and NPV than each of the other PREDICTORS for identifying responders

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Cut-point</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeNO</td>
<td>&gt;47 ppb</td>
<td>67</td>
<td>78</td>
<td>47</td>
<td>89</td>
</tr>
<tr>
<td>PD&lt;sub&gt;20&lt;/sub&gt;</td>
<td>&lt;8 umol</td>
<td>58</td>
<td>69</td>
<td>37</td>
<td>84</td>
</tr>
<tr>
<td>PEFR var</td>
<td>&gt;20%</td>
<td>0</td>
<td>97</td>
<td>NA</td>
<td>76</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;%</td>
<td>&lt;80%</td>
<td>17</td>
<td>88</td>
<td>29</td>
<td>78</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, BD response</td>
<td>&gt;12%</td>
<td>8</td>
<td>95</td>
<td>33</td>
<td>78</td>
</tr>
</tbody>
</table>

Predictive accuracy of FeNO to identify steroid response significantly greater than conventional predictors
FeNO Levels Indicate Poor Response to ICS in Patients with Noneosinophilic Asthma

Berry, Thorax 2007

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Mometasone 400 µg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>8</td>
<td>1.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

\( P = 0.72 \)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Mometasone 400 µg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

\( P = 0.14 \)

Low FeNO levels can be used to identify those that do not need ICS.
Investigated effectiveness of FeNO testing vs. conventional GINA guidelines (control group) to change ICS dose

- **Phase 1**: (3-12 months)
  ICS dose titrated down until optimal dose reached

- **Phase 2**: (12 months)
  ICS optimal dose continued, with step-up after 2/12 and step down after 4/12
Investigated effectiveness of FeNO testing vs. conventional GINA guidelines (control group) to change ICS dose

**Phase 1**: (3-12 months)
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ICS optimal dose continued, with step-up after 2/12 and step down after 4/12
FENO to Guide Treatment in Chronic Asthma

*FENO group had reduced exacerbations*

46% reduction — 0.5 and 0.9 exacerbations per patient per year in FeNO and control groups, respectively

*Did not meet superiority statistical threshold of 60% reduction
Regular testing of FENO (a signal of active inflammation) in asthmatics reduces ICS dose without compromising asthma control.
## FeNO Interpretation: Role in Monitoring & Managing Patients With Asthma

**Symptomatic**

<table>
<thead>
<tr>
<th>LOW &lt;25 ppb, adults</th>
<th>INTERMEDIATE/INCREASING †</th>
<th>HIGH &gt;50 ppb, adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 ppb, children</td>
<td>25-50 ppb, adults</td>
<td>&gt;35 ppb, children</td>
</tr>
</tbody>
</table>

### YES

- Less responsive to increased ICS dose
- Alternative/comorbid diagnosis†

### NO

- Adequate ICS dose
- Good adherence
- Could reduce ICS

- Potentially uncontrolled airway inflammation
  - Monitor change in FeNO levels and symptoms
  - Do not reduce ICS unless patient remains asymptomatic with stable FeNO levels over time
- Controlled inflammation

- Poor adherence / inhaler use
- Inadequate ICS dose
- Untreated small airways
- Persistent allergen exposure

- Address uncontrolled airway inflammation that precedes symptoms and risk of exacerbation
- Don’t reduce/withdraw ICS or relapse – assess FeNO trend
- Persistent allergen exposure

† Increasing defined as >10ppb increase from previous stable FeNO level
‡ Anxiety-hyperventilation, Bronchiectasis, Cardiac Disease, GERD, Rhinosinusitis, VCD
Assessing biomarkers in a real-world severe asthma study (ARIETTA)

Buhl et al, Respir Med 2016

Aim
• Assess prognostic value of asthma biomarkers in routine clinical practice - relationship between asthma biomarkers and disease-related health outcomes

Study plan
• N=1200 Severe asthmatics, daily ICS (≥500 μg of FP or equivalent) and at least 1 second controller medication, 52 weeks follow-up
• Patients treated according to the investigator's routine clinical practices

Outcomes
• FEV1, FeNO, serum periostin, blood eosinophil count and serum IgE
• Asthma-related symptom and QoL questionnaires
• Medication use, asthma exacerbation data, asthma-related healthcare utilization and events raising safety concerns
Introduction

- **ERS Postgraduate Courses**
  ‘Improve knowledge and skill applied in *daily practice*’

- **Monitoring (not Diagnosis) in Asthma**
  *Daily practice* (clinical) vs. State-of-the-art (Research)
  Adults & Children; Primary & Secondary Care

**Aims**

- **Aim 1**
  Learn about the state-of-the-art approaches for monitoring asthma in physiology and imaging

- **Aim 2**
  Understand the position of asthma monitoring tools in current guidelines and strategy documents

- **Aim 3**
  Review the role of Th-2 mediated biomarkers in asthma management