# Asthma in children – what's new?

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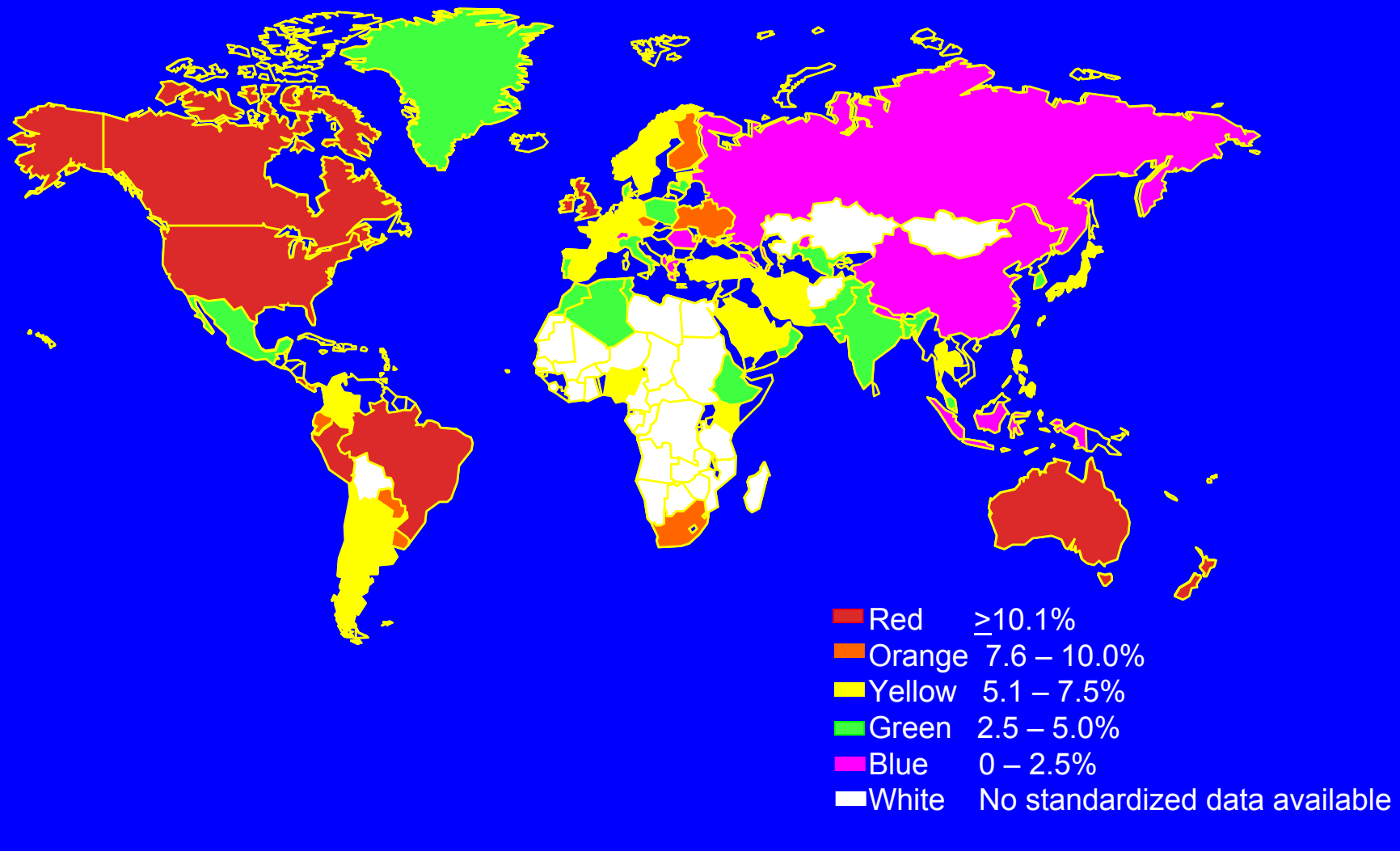
# Childhood asthma – new developments

- epidemiology
- diagnosis
- new classification
- chronic treatment
- treatment of acute asthma

# Prevalence of Clinical Asthma



# BHR – African children

| Study | Population | Outcome | Prevalence |
|---|---|---|---|
| Keeley 1991 | 7-9yr Zimbabwe | 15% PF exercise | 0.1 rural<br>5.8 urban rich/ 3.1 poor |
| Nganga 1992 | 9-12 yr Kenya | 15% FEV1 exercise | 10.5 urban |
| Addo Yobo 1997 | 9-16 yr Ghana | 12.5% PF, exercise | 2.7 rural<br>4.7 urban rich/ 2.2 poor |
| Nganga 1998 | 8-12 yr Kenya | 15% FEV1 exercise | 3.2 rural peasant/12.9 plant<br>10.3 urban rich/ 9.1 poor |
| Perzanowski 2001 | 8-12 yr Kenya | 15% FEV1 exercise | 9.8 rural plantation<br>12.4 urban |

58

2.1

1.6

1.2

# BHR – South African children

| Study | Population | Outcome | Prevalence |
|---|---|---|---|
| Van Niekerk 1979 | 6-9yr Transkei, CT | 15% FEV1/ PF exercise | 0.14 rural 3.17 urban |
| Vermeulen 1990 | 8-16 yr Transkei | 20% FEV1 histamine | 14.2 |
| Terblanche 1990 | 6-19 yr, CT | 10% FEV1, exerc | 5.1 |
| Calvert 2000 | 8-13yr Transkei, CT | 15% FEV1 *or* 26% FEF exercise | 8.7 rural 14.9 urban |
| Steinman 2002 | 10-14yr, Transkei, CT | 20% FEV1 histamine | 17 rural 34.4 urban |

22

1.2

2

# Asthma 12 month prevalence 1995-2002 in South Africa – video questionnaire

| **Symptom** | **ISAAC 3 2002** | **ISAAC 1 1995** | **p** |
|---|---|---|---|
| Wheeze | **8.2%** | 6.4% | <0.001 |
| Exercise induced wheeze | **12.8%** | 11.5% | 0.048 |
| Severe wheeze | **6.0%** | **5.1%** | **0.032** |

*Zar et al, 2005*

# Prevalence childhood asthma in Africa

- Increasing in urban and rural populations
  - – Decline in urban-rural gradient
- Changes in prevalence – lifestyle
  - Hygiene hypothesis - less infectious diseases – Th2 response, increased allergic disease
  - Diet - reduced anti-oxidants, increase in obesity
  - Environment – house dust mite exposure, smoke exposure, passive smoke, pollution

# Diagnosing asthma in children

- Clinical definition
  - recurrent cough / wheeze
  - responsive to bronchodilator
- Other features
  - family history
  - atopy
  - night, exercise-induced symptoms

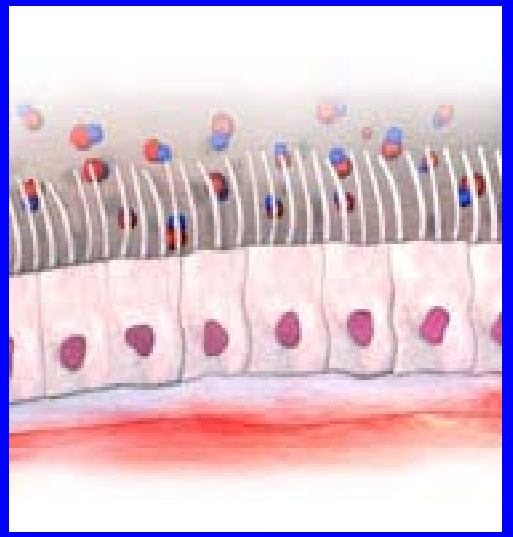
# Predictive index for asthma in children

| **Major criteria** | **Minor criteria** |
| --- | --- |
| Parent asthma | Allergic rhinitis |
| Eczema | Wheezing apart from colds |
| | Eosinophilis >4% |

F,Martinez, USA

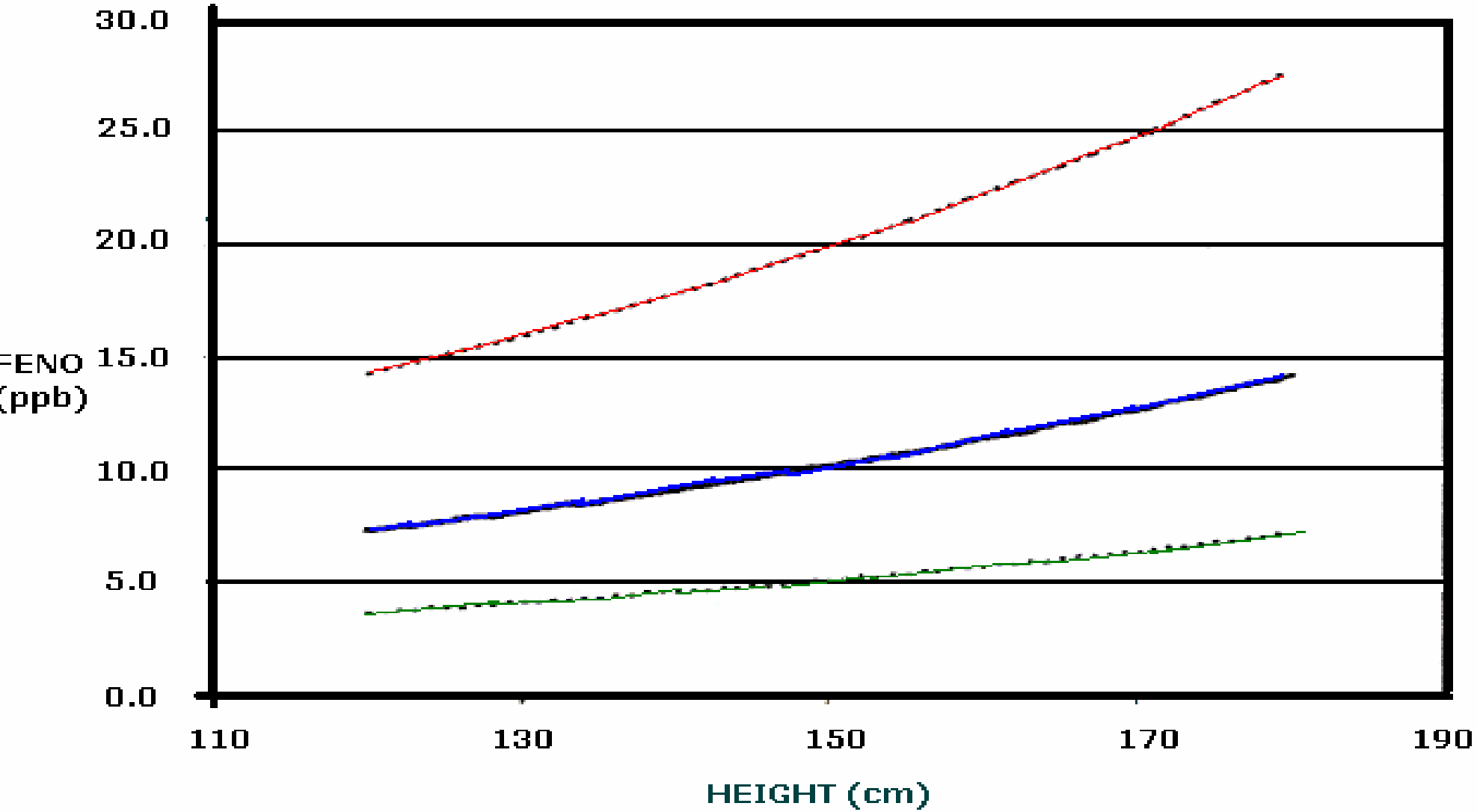
# Exhaled nitric oxide (FeNO)

- NO is produced in epithelial cells of the bronchial wall part of the inflammatory process
- NO production increases with eosinophilic airway inflammation



# Exhaled nitric oxide (FeNO)

- measure of airway inflammation
- derived from airway epithelial cells
- relatively easily measured (hand held device) – 4 years and older
- reproducible, measurement takes secs
  - normal 5-15ppb in children
  - asthmatics – 2-4x increase




Predicted FENO (solid blue line) as function of height and 95% prediction intervals (dashed green and red lines). Adapted from Malmberg et al, Exhaled Nitric Oxide in Healthy Nonatopic School-Age Children:Determinants and Height-Adjusted Reference Values; Pediatric Pulmonology 41:635-642 (2006)

# Asthma diagnosis

- Exhaled air of asthmatic subjects shows between double and four times the normal NO level
- with symptoms and other techniques such as spirometry, FeNO can be used to help diagnose eosinophilic inflammation in asthma

# Factors increasing FeNO

- Airway viral infection (100%)
- Allergic rhinitis (50%)
- Nitrate rich diet (50%)
- Bronchiectasis
- Pneumonia
- Chronic bronchitis
- Chronic lung disease

# Factors decreasing FeNO

- Cystic fibrosis (60%)
- Ciliary dyskinesia (45%)
- Exercise (5-25%)
- Bronchoconstriction (25%)
- Pulmonary hypertension
- Heart failure
- HIV

# Former classification of asthma

- Intermittent
- Persistent
  - mild
  - moderate
  - severe

# CLASSIFY SEVERITY AT PRESENTATION

| | Intermittent | Persistent | | |
|---|---|---|---|---|
| | | Mild | Moderate | Severe |
| **Category** | 1 | 2 | 3 | 4 |
| Daytime symptoms | ≤ 2 / week | 2 - 4 / week | > 4 / week | **Continuous** |
| Night-time symptoms | ≤ 1 / month | 2 - 4 / month | > 4 / month | **Frequent** |
| PEF (predicted) | ≥ 80% | ≥ 80% | 60 - 80% | < 60% |

Start treatment at any step depending on the level of severity.

**ALL CATEGORIES**

- Short-acting $\beta_2$ agonist as needed (reliever)
- Environmental control
- Education / self management

**STEP 1: Intermittent**

- No daily preventer or controller medication needed.

# Asthma control

- Increasing recognition of importance of asthma control in management
- Increasing recognition that control achievable in majority of patients
- Major revision of Global Initiative for Asthma (GINA) guidelines 2006

# New Asthma classification

- **CONTROL key**
- Classification by level of control
  - Controlled
  - Partly Controlled
  - Uncontrolled

# What is CONTROLLED ASTHMA?

- No (*twice or less/ week*) daytime symptoms
- No limitations of activity
- No nocturnal symptoms
- No (*twice or less/ week*) use rescue medication
- Normal or near normal lung function
- No exacerbations

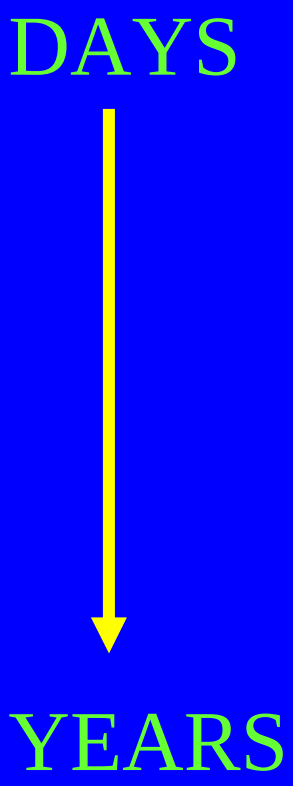
***2006 www.ginasthma.org***

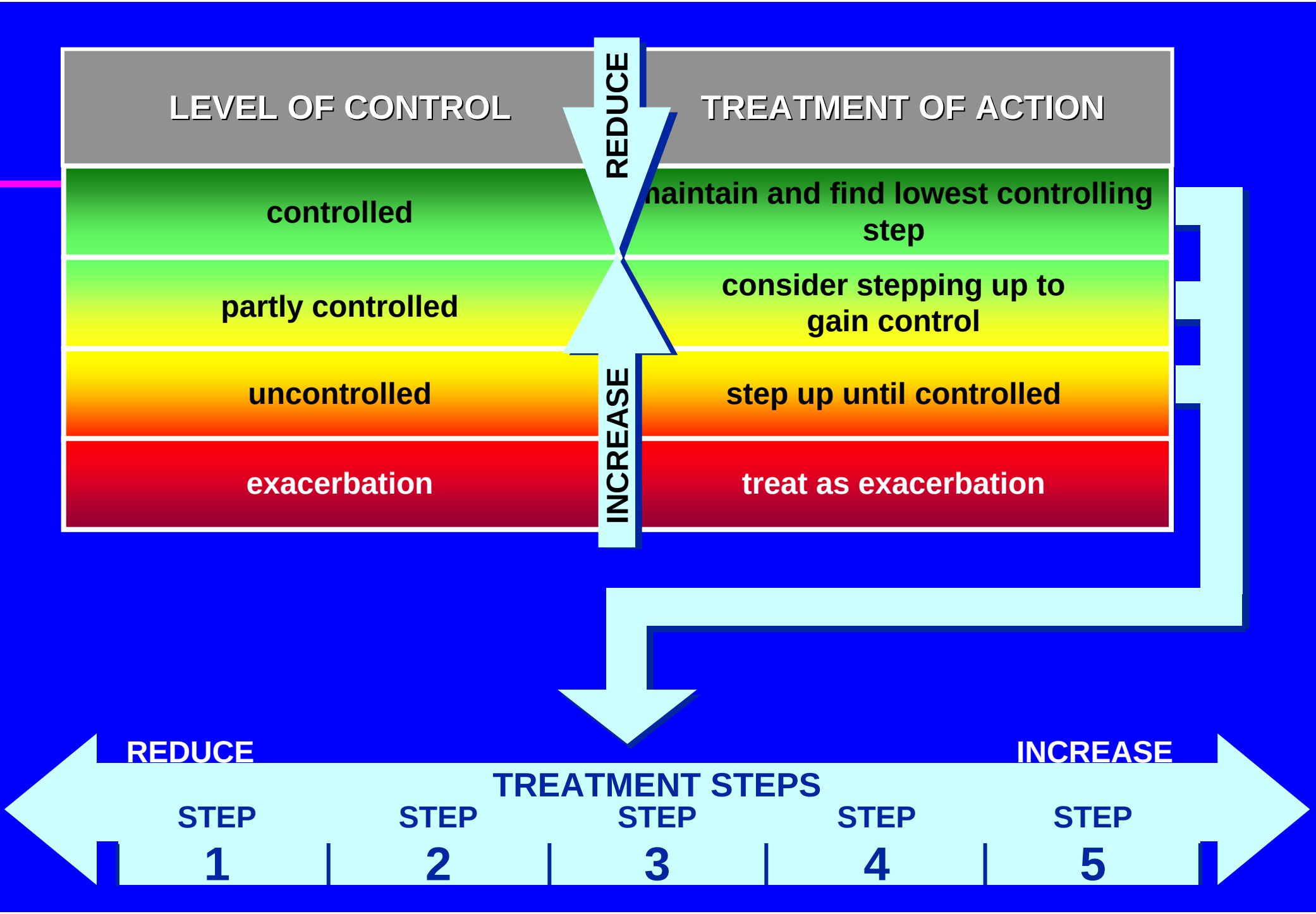
# Levels of Asthma Control

| Characteristic | Controlled | Partly controlled (Any present in any week) | Uncontrolled |
|---|---|---|---|
| Daytime symptoms | None (2 or less / week) | More than twice / week | 3 or more features of partly controlled asthma present in any week |
| Limitations of activities | None | Any | |
| Nocturnal symptoms / awakening | None | Any | |
| Need for rescue / "reliever" treatment | None (2 or less / week) | More than twice / week | |
| Lung function (PEF or $FEV_1$) | Normal | < 80% predicted or personal best (if known) on any day | |
| Exacerbation | None | One or more / year | 1 in any week |

# Control graded

- Night symptoms
- Exercise symptoms
- FEV1/ PEF
- Reduction in rescue medication
- Bronchial hyperesponsiveness




LEVEL OF CONTROL
TREATMENT OF ACTION
REDUCE
INCREASE
controlled
maintain and find lowest controlling step
partly controlled
consider stepping up to gain control
uncontrolled
step up until controlled
exacerbation
treat as exacerbation
REDUCE
INCREASE
TREATMENT STEPS
STEP 1
STEP 2
STEP 3
STEP 4
STEP 5

# How to Assess control?

***Composite measures:***

- Symptoms - constellation
- PFT, BHR
- Measures of airway inflammation
  - Sputum – eosinophils, cytokines
  - BAL, bronchial biopsy
  - Blood – eosinophils, ECP
  - Exhaled breath condensate
  - FeNO

# Paediatric Asthma control test

- validated questionnaire on asthma control in children
- 7 questions
  - 4 completed by child, 3 by parent
- numerical score of  27
  - higher, better control
  - < 19 poor control
- available in SA
  - Eng, Afr, Xhosa, Zulu, Sesotho

## Have your child answer these questions.

SCORE

**1.** How is your asthma today?

| | | | |
|---|---|---|---|
|  0 Very bad |  1 Bad |  2 Good |  3 Very good |

**2.** How much does your asthma bother you when you run, exercise or play sports?

| | | | |
|---|---|---|---|
|  0 It bothers me a lot. I can't do what I want to do. |  1 It bothers me and I don't like it. |  2 It bothers me a little but it's okay. |  3 It doesn't bother me. |

**3.** Do you cough because of your asthma?

| | | | |
|---|---|---|---|
|  0 Yes, always. |  1 Yes, most of the time. |  2 Yes, sometimes. |  3 No, never. |

**4.** Do you wake up during the night because of your asthma?

| | | | |
|---|---|---|---|
|  0 Yes, always. |  1 Yes, most of the time. |  2 Yes, sometimes. |  3 No, never. |

## Please answer the following questions on your own.

**5.** During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

| | | | | | |
|---|---|---|---|---|---|
| 5 None | 4 1-3 days | 3 4-10 days | 2 11-18 days | 1 19-24 days | 0 Every day |

**6.** During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

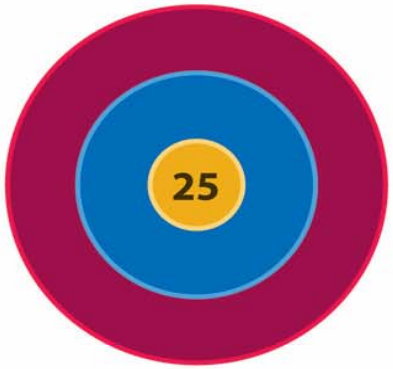
| | | | | | |
|---|---|---|---|---|---|
| 5 None | 4 1-3 days | 3 4-10 days | 2 11-18 days | 1 19-24 days | 0 Every day |

**7.** During the last 4 weeks, how many days did your child wake up during the night because of asthma?

| | | | | | |
|---|---|---|---|---|---|
| 5 None | 4 1-3 days | 3 4-10 days | 2 11-18 days | 1 19-24 days | 0 Every day |

TOTAL

## Know your asthma score – ACT now




**Score: 25 – Congratulations!**

You have **TOTAL CONTROL** of your asthma. You have no symptoms and no asthma-related limitations. See your doctor or nurse if this changes.

**Score: 20 to 24 – On Target**

Your asthma may be **WELL CONTROLLED** but not **TOTALLY CONTROLLED**. Your doctor or nurse may be able to help you aim for **TOTAL CONTROL**.

**Score: less than 20 – Off Target**

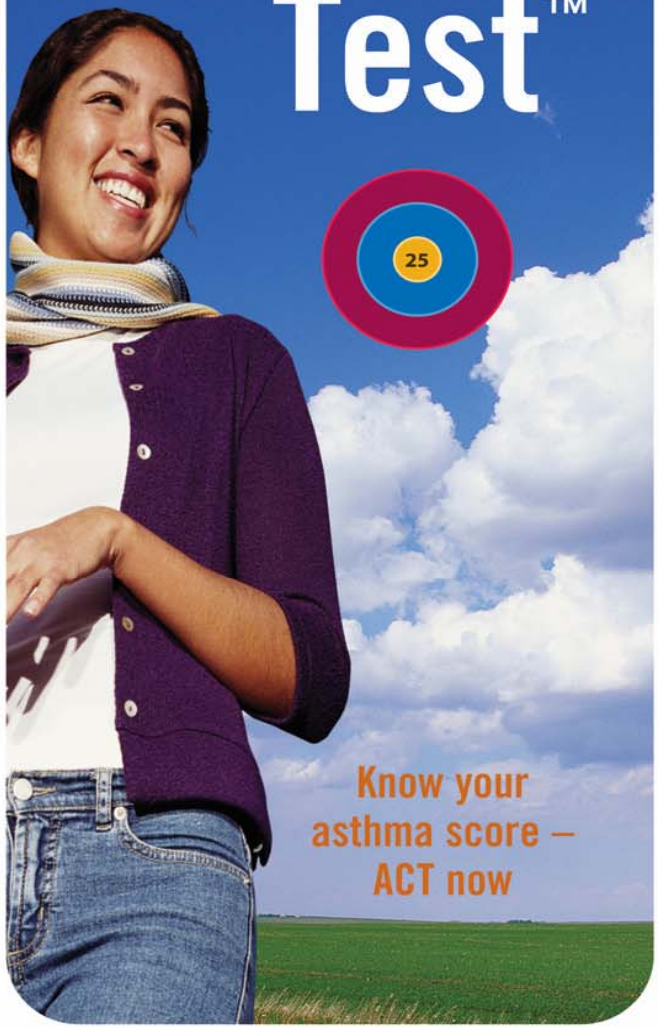
Your asthma may **NOT BE CONTROLLED**. Your doctor or nurse can recommend an asthma action plan to help improve your asthma control.

Note:

ACT0042


[Insert link to local website]

# Asthma Control Test™



# Alternatives

- Bronchial alveolar lavage (BAL) eosinophils, inflammatory cytokines
- Induced sputum
- Urine
- Blood: eosinophils, ECP
- Breath condensate
- Exhaled air - FeNO

# Clinical applications of FeNO

- confirmation of diagnosis of asthma
- response to inhaled steroids
- titrating steroids
- diagnosing relapse or loss of control
- assessing adherence

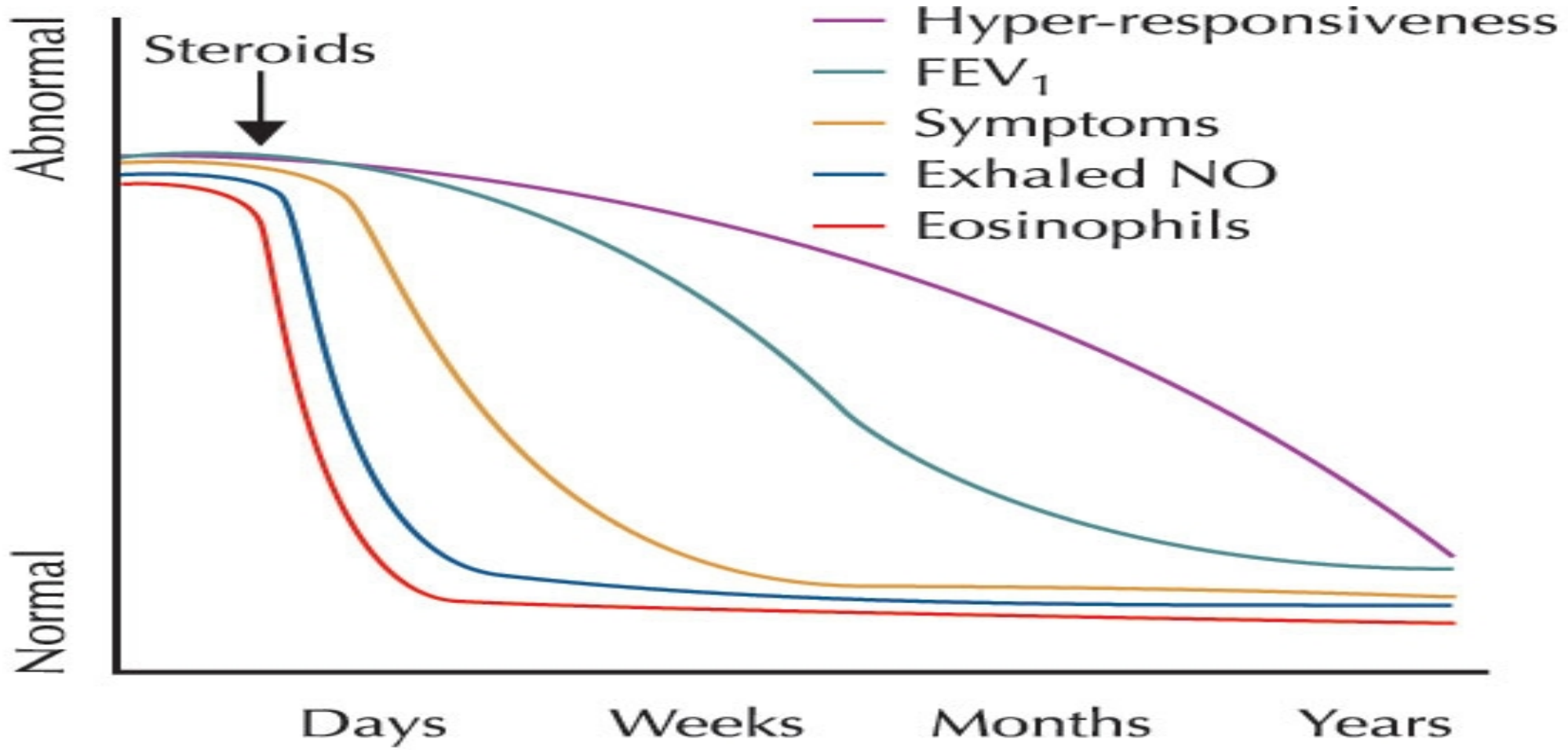



*Figure 5. Different markers of airway inflammation and asthma respond at different rates. $FEV_1$ = forced expiratory volume in 1 second. Courtesy of Professor de Jongste.*

# What's new? - pharmacotherapy

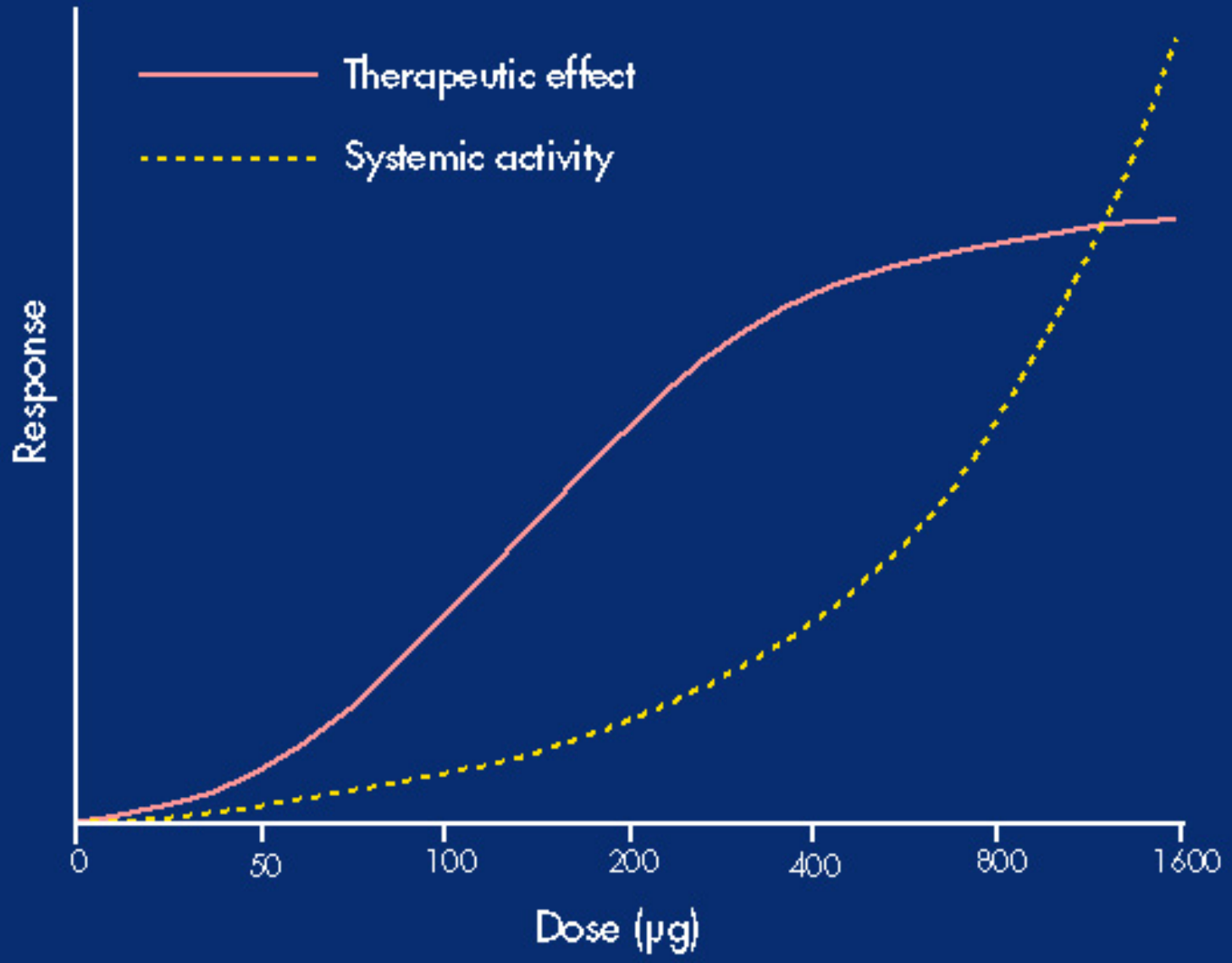
- ICS
- LTRA
- LA $\beta_2$ bronchodilators
- Combination therapy

# Inhaled corticosteroids in children

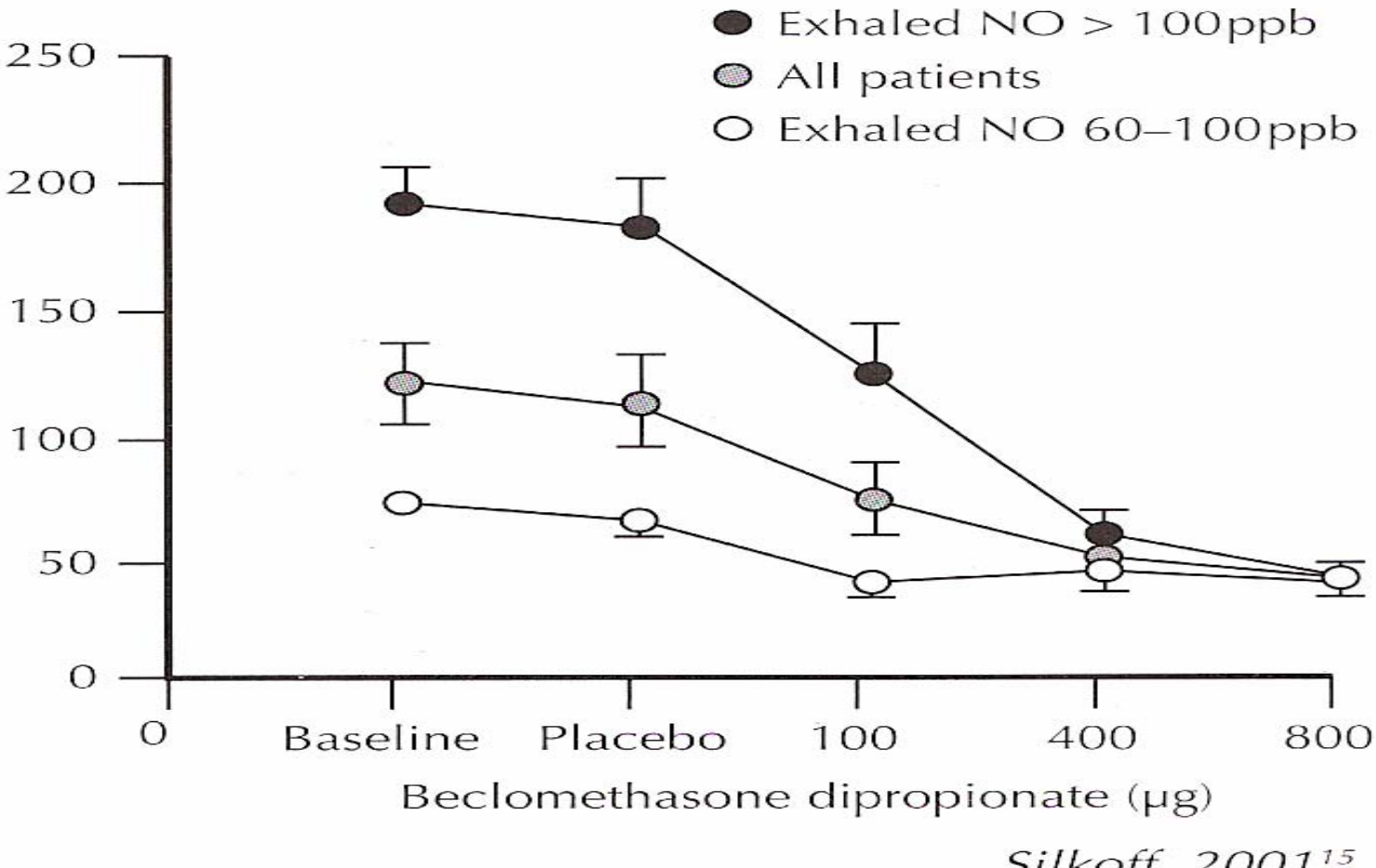
- most effective preventative therapy for asthma
- dose-response trials
  - *marked, rapid clinical improvement in symptoms at low daily doses*
  - *similar response except for EIA*
- most children well controlled on doses

  $\leq$ 400ug/day ICS (BDP)
- safe at these doses

Dose-response curves for the therapeutic effect and systemic activity of increasing doses of inhaled corticosteroid.



# FeNO and response to ICS




*Silkoff, 2001*[15]

# Giving inhaled steroids

- MDI-spacer optimal delivery system – ease, cost, efficacy, safety
- Use MDI with spacer
  - Reduced oropharyngeal deposition
  - Reduced side effects
  - Increased delivery medication to lungs

# Commercially available spacers

# 500ml Plastic bottle spacer

# Choice of spacer devices:

- < 3 years MDI + spacer with mask
- > 3 years MDI + spacer with mouthpiece or DPI

# What's new? - ICS
# CFC free inhaled corticosteroids

- Switch to HFA preparations
- HFA-BDP vs CFC-BDP
  - smaller particles
  - slower velocity
  - increased lung deposition
  - increased penetration small airways
- same effect at half dose

# Add-on therapy

- Long acting $\beta_2$ agonists
- Leukotriene antagonists

# Long acting $\beta_2$ agonists, single-dose

- salmeterol, formoterol
- formoterol rapid onset action
- bronchodilation for up to 12 hrs
- protection against EIA up to 12 hrs
- heterogeneity in response - drug delivery, disease, $\beta_2$ receptors

# Safety - LA $\beta_2$

- increased asthma deaths in salmeterol multicentre (SMART) study, ***Chest 2006***
- 28 week study – salmeterol vs placebo

| | salmet | placebo | RR |
|---|---|---|---|
| | n=13176 | n=13179 | |
| All | 13 (0.1%) | 3 (0.02%) | 4.37 (1.2-15.3) |
| Afr/Amer | 7 (0.3%) | 1 (0.04%) | 7.26 (8-46) |

*But – pts poorly controlled at baseline, under-use ICS*

# LA $\beta_2$ versus increasing dose ICS

- Adult studies – reduced exacerbations, better control, improved PFTs when add-on LA $\beta_2$ rather than increasing dose steroid
- Paediatric studies - DIFFERENT
  - significant small improvement FEV1, PF
  - impact on asthma control, exacerbation rate variable and inconsistent – ***Greenstone et al, Cochrane review 2006***
- ? clinical importance
- individual benefit

# Combination therapy

| Combination Device | Dose (ug) |
|---|---|
| salmeterol/ fluticasone (Seretide) | 50/100 |
| DPI (Accuhaler) | 50/250 |
| | 50/500 |
| MDI CFC free | 25/50, 25/125, 25/250 |
| | |
| formoterol/ budesonide (Symbicort) | 4.5/80 |
| DPI (Turbuhaler) | 4.5/160 |
| | 9/320 |

# Combination therapy

- Little data in children, especially preschool
- Approved for use in children older than 4 years
- Preferable rather than 2 separate inhalers
- LA $\beta_2$ should NOT be used as monotherapy

# Current recommendation: LA $\beta_2$ in childhood asthma

- Add -on therapy if poorly controlled on 400ug/ day inhaled budesonide
- EIB as needed
- Fixed combination products promising for maintenance and relief – only formoterol

# Use of leukotriene antagonists

- add-on therapy in mild / moderate asthma with ICS
- children with mild persistent (monotherapy)
- children with viral induced exacerbations
- inability / refusal to take inhaled therapy
- individual variability in response to LTRA

***Meyer JACI 2003***

# Montelukast add-on - 6-14 year olds

| Trial | Number patients | Duration of study | Study design | Outcome |
|---|---|---|---|---|
| **Simon** *J Pediatr, 2001* | 279 persistent asthma | 12 weeks | montelukast 5mg + budesonide 200 ug per day | FEV1 improved (p=0.06) less B2 use fewer exacerbations |
| **Knorr** *JAMA, 1998* | 336 with asthma 35% on ICS | 8 weeks | montelukast 5mg with/out ICS | improved morning FEV1 less B2 use |

# LTRA - add-on therapy in children

- improvement in lung function
- decrease in bronchodilator use
- decrease exacerbations

***Simons, Allergy, 2000,***
***Knorr et al  JAMA 1998***

# Montelukast monotherapy 2-5 year olds

| Trial | No. of patients | Duration | Study design | Outcome |
|---|---|---|---|---|
| **Knorr**<br>*Pediatr 2001* | 689 children<br>2-5 yrs with asthma | 12 weeks | Montelukast 4mg vs placebo<br>Primary endpoint - safety | well tolerated, safe<br>improvement in asthma control |
| Bisgaard H<br>*AJRCCM 2003* | 130 infants<br>3-36 mnths post RSV bronchiolitis | 28 days | Montelukast 5mg vs placebo within 7 days of symptoms | Reduced symptoms |
| **PREVIA**<br>Bisgaard H<br>*AJRCCM 2005* | 768 children with intermittent asthma | 12 month | montelukast 4/5 mg vs placebo | asthma exacerbations decreased 32%<br>prolonged time to exacerbations |

# Montelukast monotherapy 6-14 years

| Trial | Number patients | Duration study | Study design | Outcome |
|---|---|---|---|---|
| ***Knorr***<br><br>*JAMA 1998* | 336 asthmatics (FEV1 50-85%) | 8 weeks | montelukast 5mg vs placebo | improved morning FEV1<br>less B2 use |
| *Szefler SJ*<br>*JACI 2005* | 45 mild persistent asthma | 18 week | Fluticasone 100 bd vs montelukast | improved FEV1<br>89% fluticasone vs 49% montelukast |
| ***MOSAIC***<br>*Garcia*<br>*ERS 2004* | 996 mild persistent | 12 months | montelukast 5mg vs fluticasone 100 bd for rescue free days | comparable rescue free days and no.attacks |

# LTRA vs ICS as monotherapy

- CLIC study – montelukast vs fluticasone (100 bd) in 144 children 6-17yr with mild/ moderate
- crossover design 8 weeks each therapy
- more responded to fluticasone, but some responded to montelukast only

***Szefler et al JACI 2005***

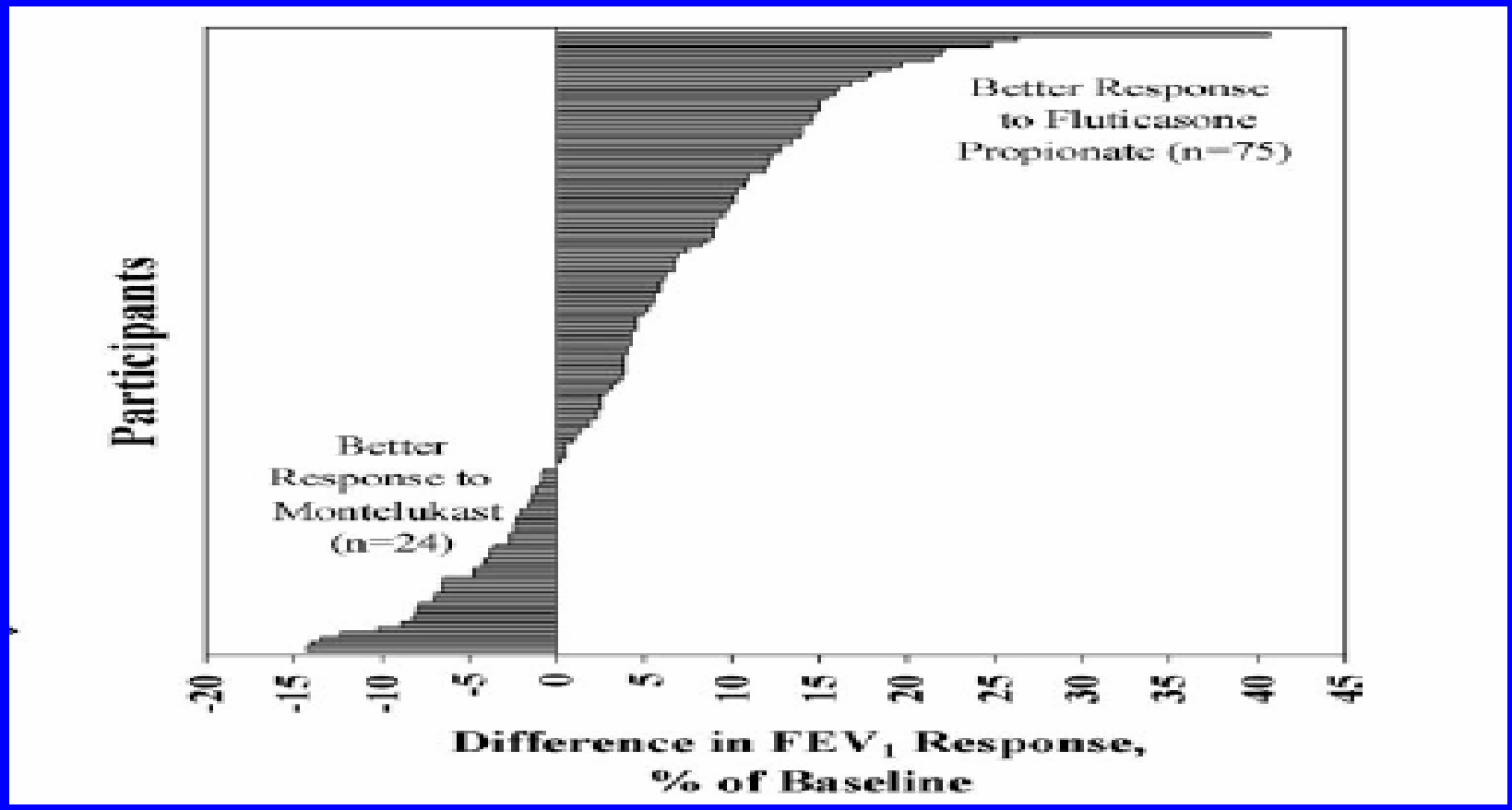
# LTRA vs ICS as monotherapy

- 17% responded to both, 23% to fluticasone alone, 5% to montelukast alone, 55% no response as defined by change in FEV1
- Clinical vs PFT response

| | **FEV1** | **asthma free days** |
|---|---|---|
| Both | 17% | 52% |
| FP alone | 23% | 17% |
| Monteluk alone | 5% | 4% |
| Neither | 55% | 36% |

***Szefler et al JACI 2005***

# Difference in FEV1 response between fluticasone and montelukast




*Szefler et al JACI 2005*

# LTRA vs ICS as monotherapy

- response to fluticasone assoc with more airway inflammation – higher FeNO, IgE, BHR, lower FEV1
- response to montelukast associated with young age, short duration symptoms

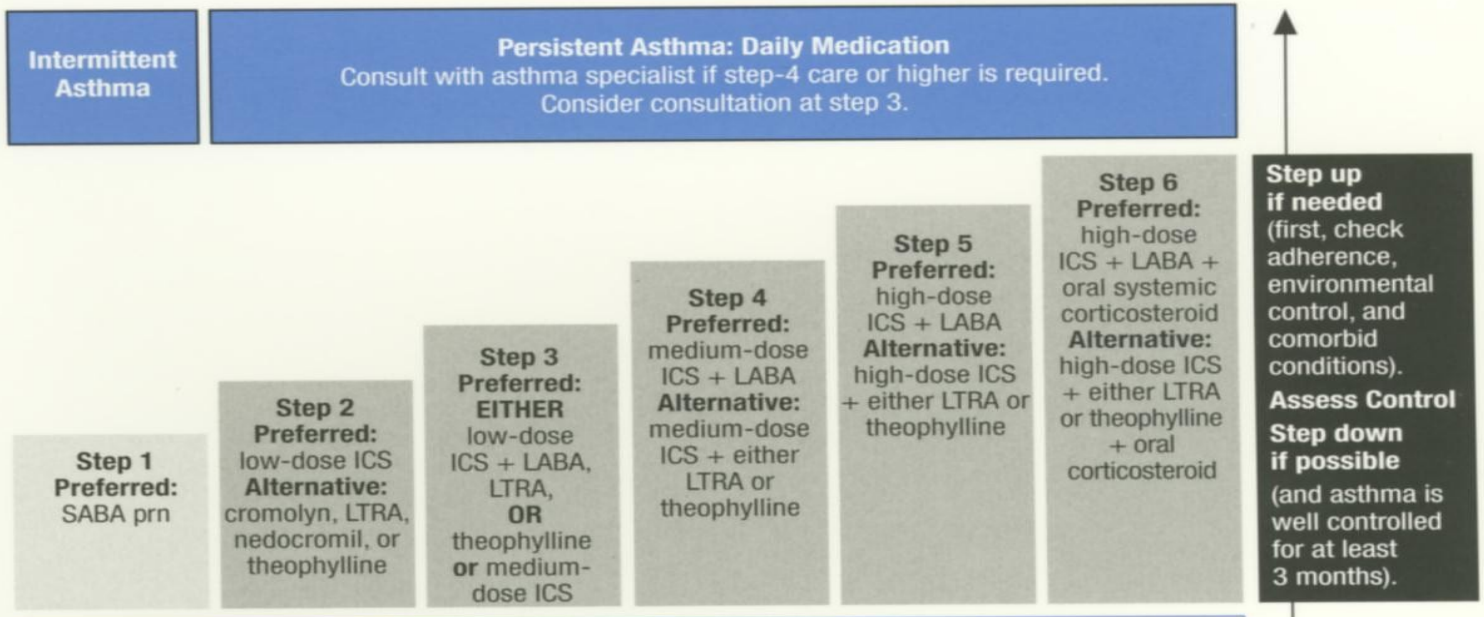
***Szefler et al JACI 2005***

# New paediatric asthma guidelines

- Previous asthma management guidelines for children deficient
- 2007: Expert Panel Report-NHLBI
- 2007: The Practall Guidelines

# Expert Panel Report-NHLBI 2007

## Table 2c. Stepwise Approach for Managing Asthma in Children Aged 5–11 Years



# Expert Panel Report-NHLBI 2007

## Table 1c. Stepwise Approach for Managing Asthma in Children Aged ≤4 Years

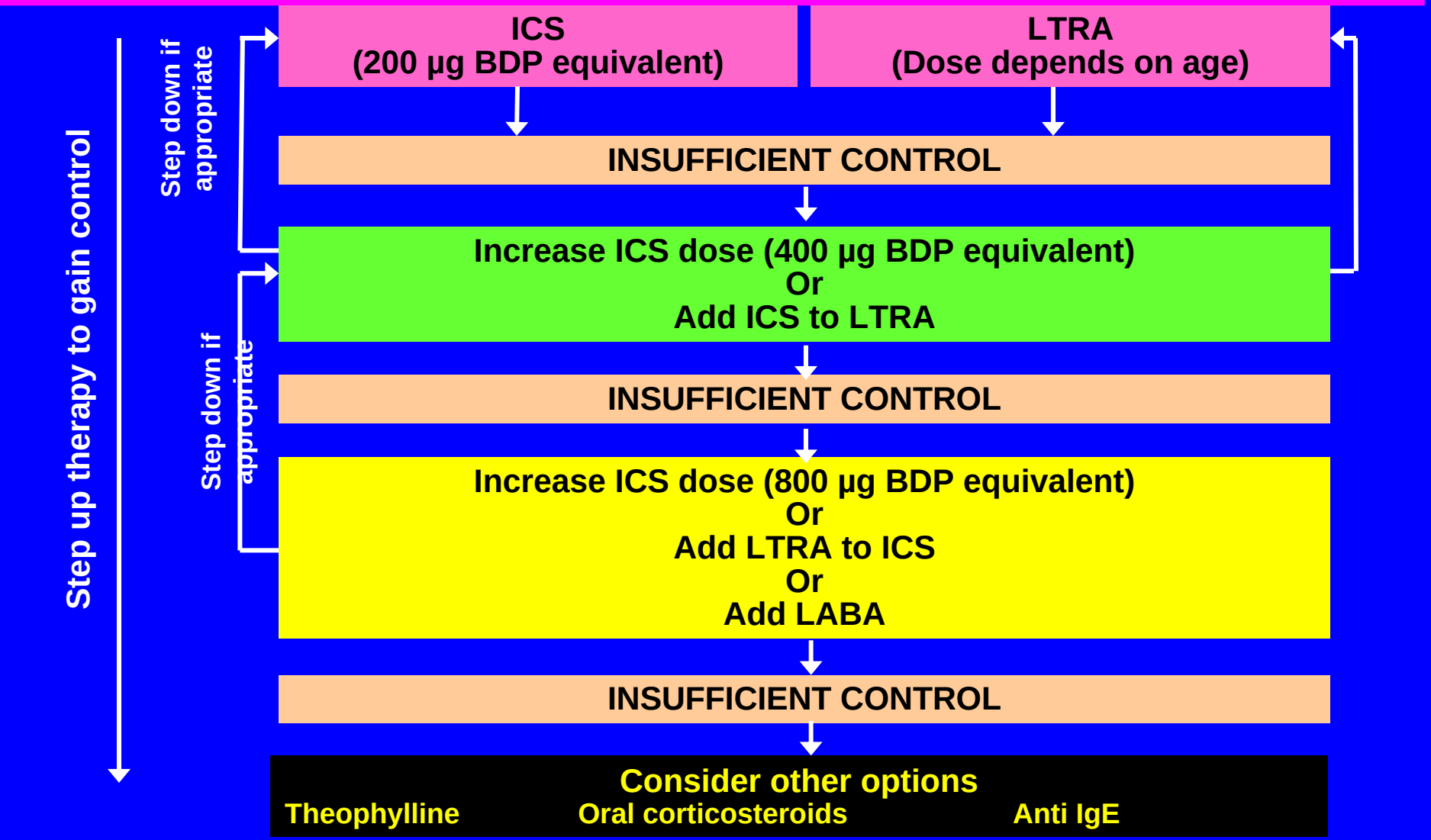
| Intermittent Asthma | Persistent Asthma: Daily Medication<br>Consult with asthma specialist if step-3 care or higher is required.<br>Consider consultation at step 2. | | | | | |
|---|---|---|---|---|---|---|
| **Step 1**<br>**Preferred:**<br>SABA prn | **Step 2**<br>**Preferred:**<br>low-dose ICS<br>**Alternative:**<br>cromolyn or SINGULAIR* | **Step 3**<br>**Preferred:**<br>medium-dose ICS | **Step 4**<br>**Preferred:**<br>medium-dose ICS + either LABA or SINGULAIR* | **Step 5**<br>**Preferred:**<br>high-dose ICS + either LABA or SINGULAIR* | **Step 6**<br>**Preferred:**<br>High-dose ICS + either LABA or SINGULAIR*<br>Oral systemic corticosteroids | **Step up if needed** (first, check adherence, inhaler technique, and environmental control).<br>**Assess Control**<br>**Step down if possible** (and asthma is well controlled for at least 3 months). |

**Patient Education and Environmental Control at Each Step**

Quick-Relief Medications for All Patients:

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
- With viral respiratory infection: SABA every 4 to 6 hours for up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.
- Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendations on initiating daily long-term control therapy.

# Algorithm of preventive pharmacologic treatment for asthma in children >2 yrs of age (The Practall Guidelines-2007)



# Asthma treatment in children aged 0-2yrs (The Practall Guidelines-2007)

- Consider a diagnosis of asthma if >3 episodes of bronchial obstruction within 6 months
- Intermittent β2 agonists are first choice
- LTRA daily controller therapy for viral wheezing
- Nebulized or inhaled corticosteroids as daily controller therapy for persistent asthma
- Evidence of atopy/allergy lowers the threshold for use of ICS
- Use oral corticosteroids (e.g. 1-2 mg/kg prednisone)

# What's new? - acute asthma

- Inhaled $\beta_2$ mainstay
  - MDI-spacer vs nebulised
  - Higher doses MDI-spacer
- Oral corticosteroids
- Inhaled anti-cholinergic – reduction in hospitalisation
- Increased dose ICS – 4x
- $MgSO_4$ – inhaled, iv

Treatment of Asthma Exacerbations

# Magnesium Sulfate

**Controversial:**

- Inconsistent data
- Used in very severe asthma in emergency settings:
  - FEV1 < 25% predicted
  - Other signs of severe disease
- Dosage: 1.2 - 2 gm IV over 10 - 20 min in 50 ml saline
- Minor side effects

# IV Magnesium in acute asthma

- Not to be used routinely
- Selected cases:
  - adults with $FEV_1$ 25-30%
  - adults and children who fail to respond to initial treatment
  - children: $FEV_1$ fails to improve above 60% after 1 hr of care [1,2] (Evidence B)
- Single 2g infusion/20 mins
- No side-effects reported

***Refs: 1. Rowe et al Cochrane database syst rev 2000***

***2. Fitzgerald West J Med 2000***

# Conclusions

- diagnosis – clinical, but FeNO promising
- inhaled therapy optimal – MDI/spacer
- ICS most effective, safe controller therapy
- add-on therapy– LTRA, LABA (combination products preferable)
- $MgSO_4$ for treatment of acute severe asthma?

# THANK YOU