Asthma in children

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Epidemiology

300 million people worldwide

(chiffres GINA 2022)

Mortality 250,000 patients/year

Epidemiology

300 million people worldwide

(chiffres GINA 2022)

Mortality 250,000 patients/year

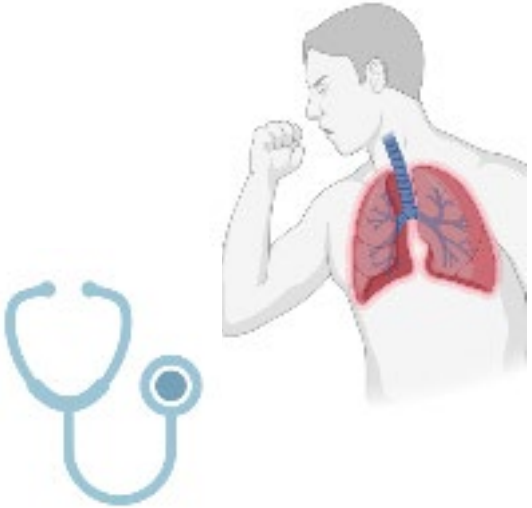
30% of infants have 1 episode of wheezing

↓

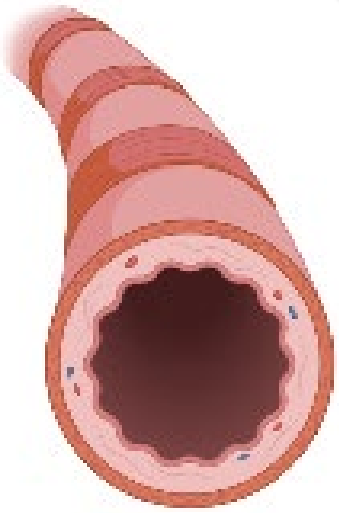
25-40% of infants with wheezing will have asthma later

Most common chronic disease in children of age school (5-12%)

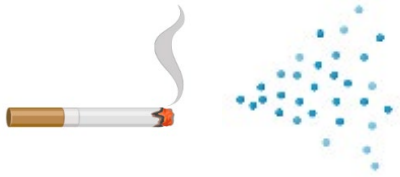
Outdoor pollution



Cold

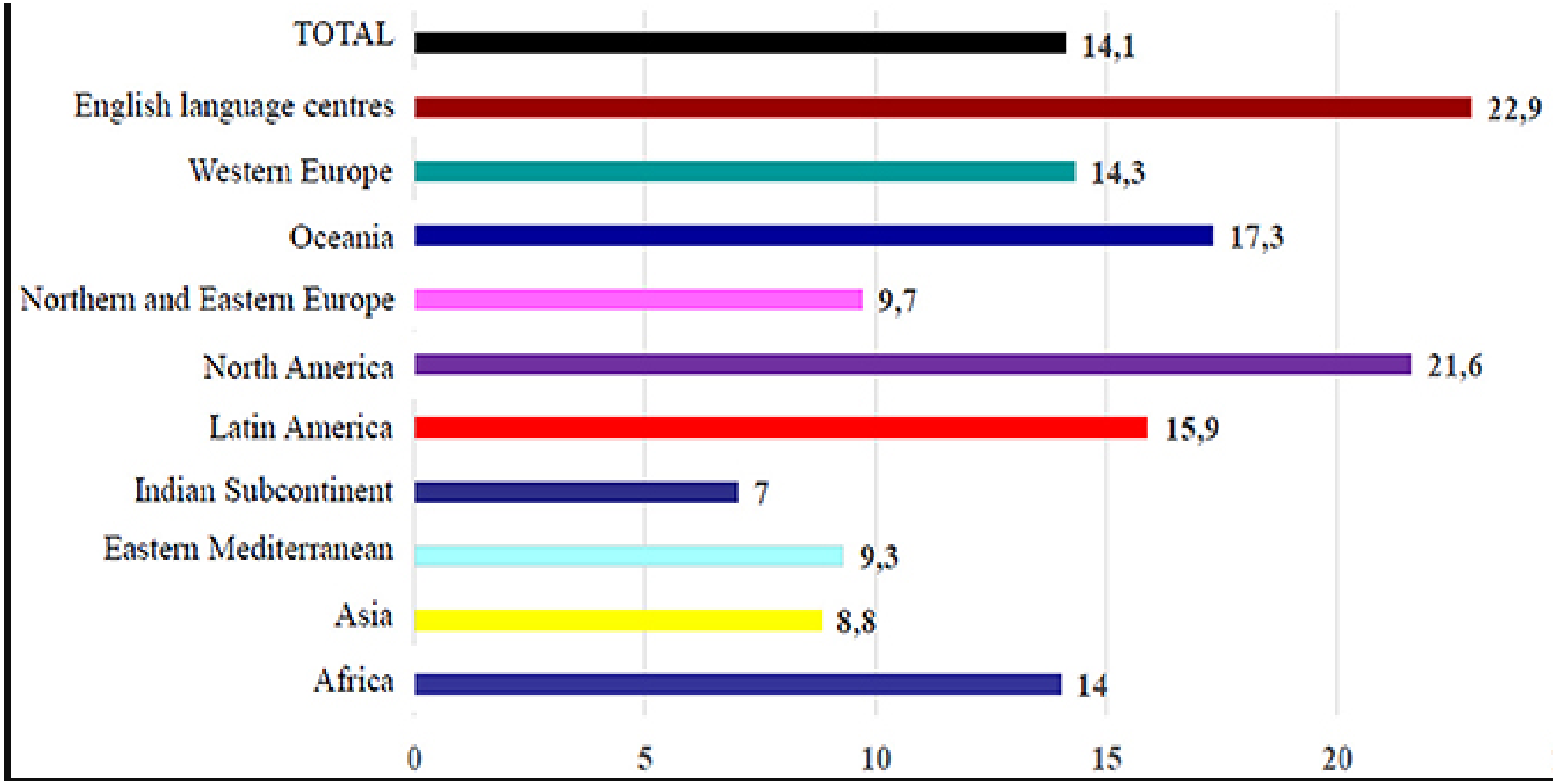


Pollens



Indoor pollution

What is the prevalence of asthma in children worldwide?



Adapted from Ferrante et La Grutta, Frontiers ,2018

What type of asthma phenotype in life ?

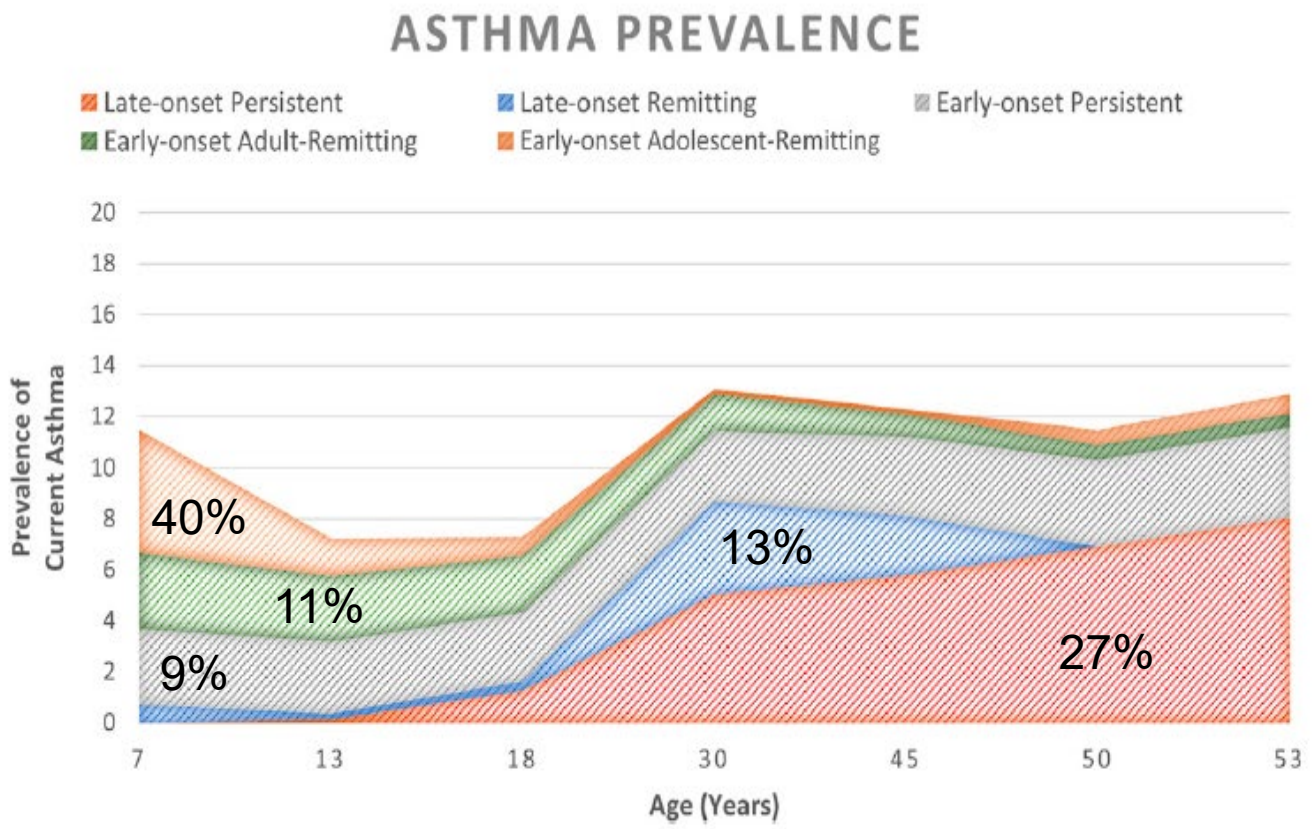
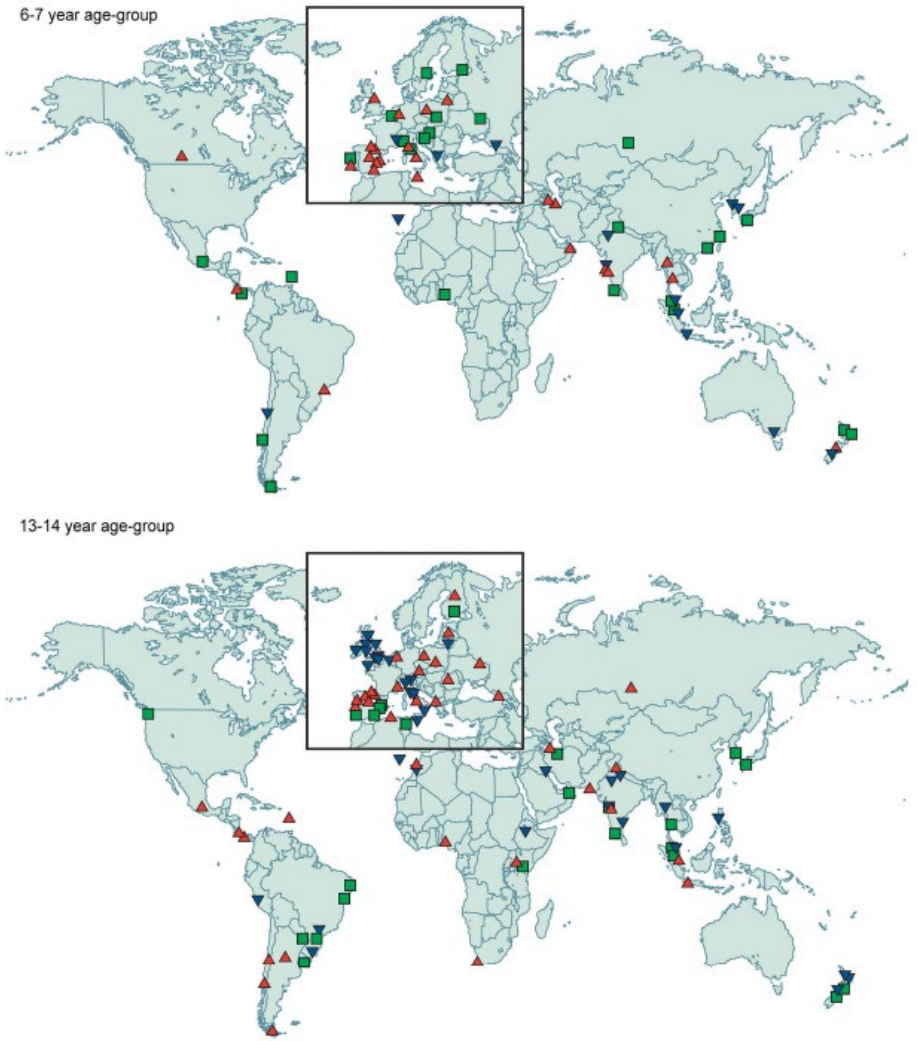


Figure 2. Contribution of each phenotype to asthma prevalence at each time point from ages 7–53years (whole sample).

Tan et al.Am.J.Respire Med Care 2023

Is there an increase in the prevalence of asthma symptoms worldwide ?



Adapted from Asher et al. Lancet 2009

What role does outdoor and indoor pollution have on asthma?

Outdoor pollution

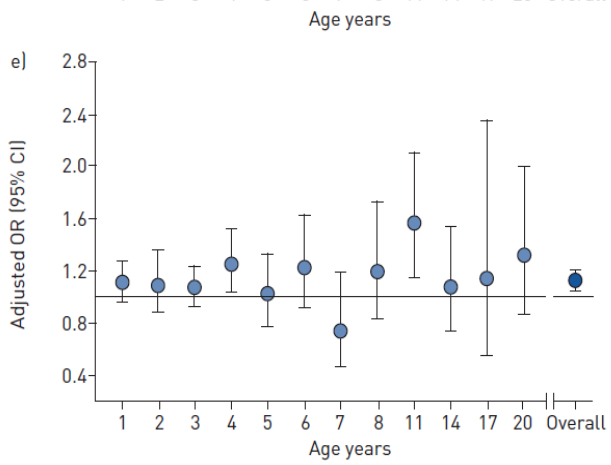
Table 4. Indoor PM concentrations, asthma symptoms, and rescue medication use: multivariate models.

Symptom	$PM_{2.5-10}$ (per 10 μg/m³ increase)[a] IRR (95% CI)	*p*-Value	$PM_{2.5}$ (per 10 μg/m³ increase)[b] IRR (95% CI)	*p*-Value
Cough, wheezing, chest tightness	1.06 (1.01–1.12)	0.02	1.03 (0.99–1.07)	0.18
Slow down	1.08 (1.02–1.14)	0.01	1.04 (1.0–1.09)	0.06
Symptoms with running	1.00 (0.94–1.08)	0.81	1.07 (1.02–1.11)	< 0.01
Nocturnal symptoms	1.08 (1.01–1.14)	0.02	1.06 (1.01–1.10)	0.01
Limited speech	1.11 (1.03–1.19)	< 0.01	1.07 (1.00–1.14)	0.04
Rescue medication use	1.06 (1.01–1.10)	0.02	1.04 (1.01–1.08)	0.04

IRR, incidence rate ratio.
[a]Adjusted for age, sex, race, parent education level, season, indoor fine PM, ambient fine PM, ambient coarse PM.
[b]Adjusted for age, sex, race, parent education level, season, indoor coarse PM, ambient coarse PM, ambient fine PM.

Gehringet al. Eur Respir J 2020

Indoor pollution



McCormack et al. Children's health 2009

Have we changed our practices?

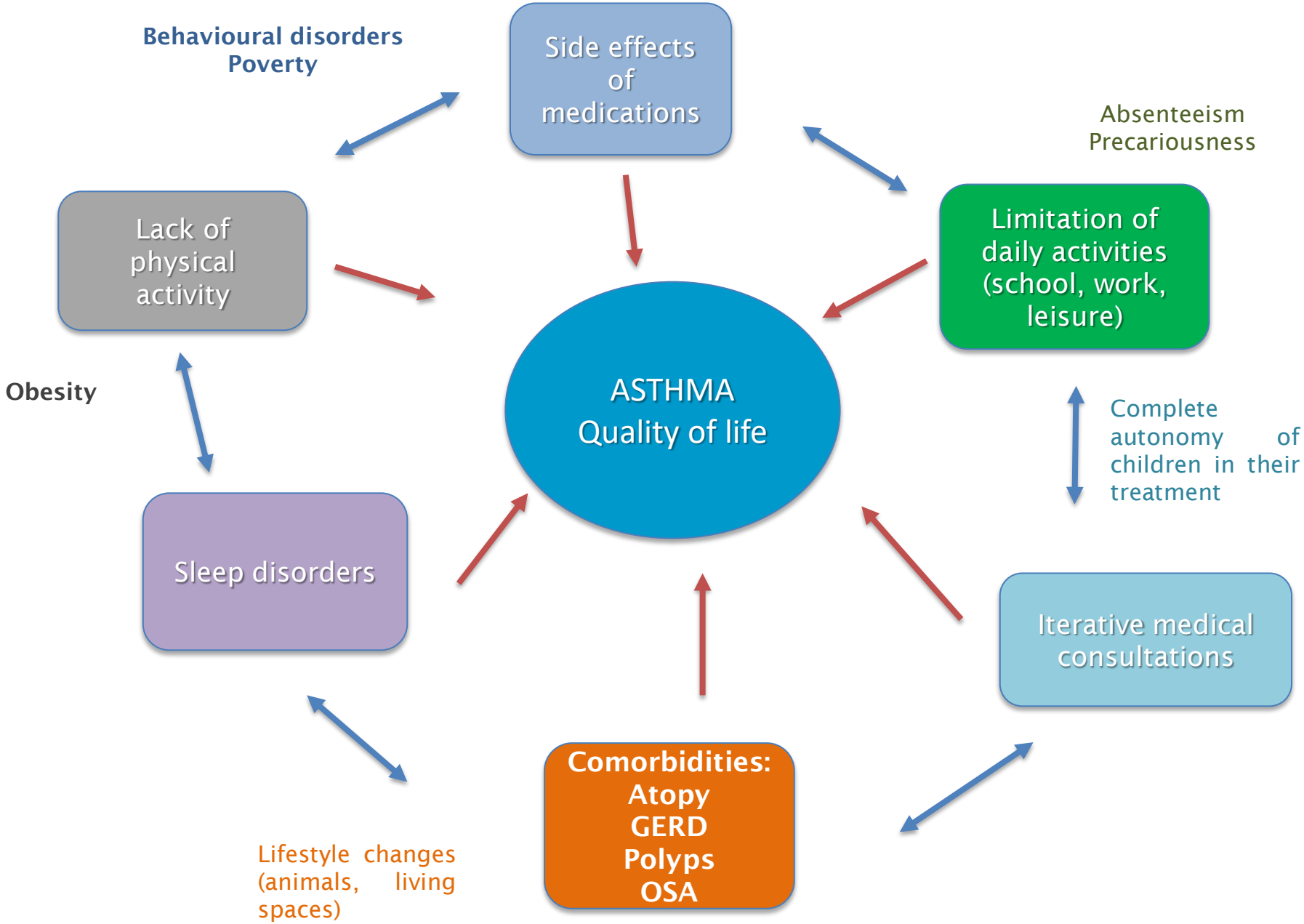
Are we using more Salbutamol in recent years?

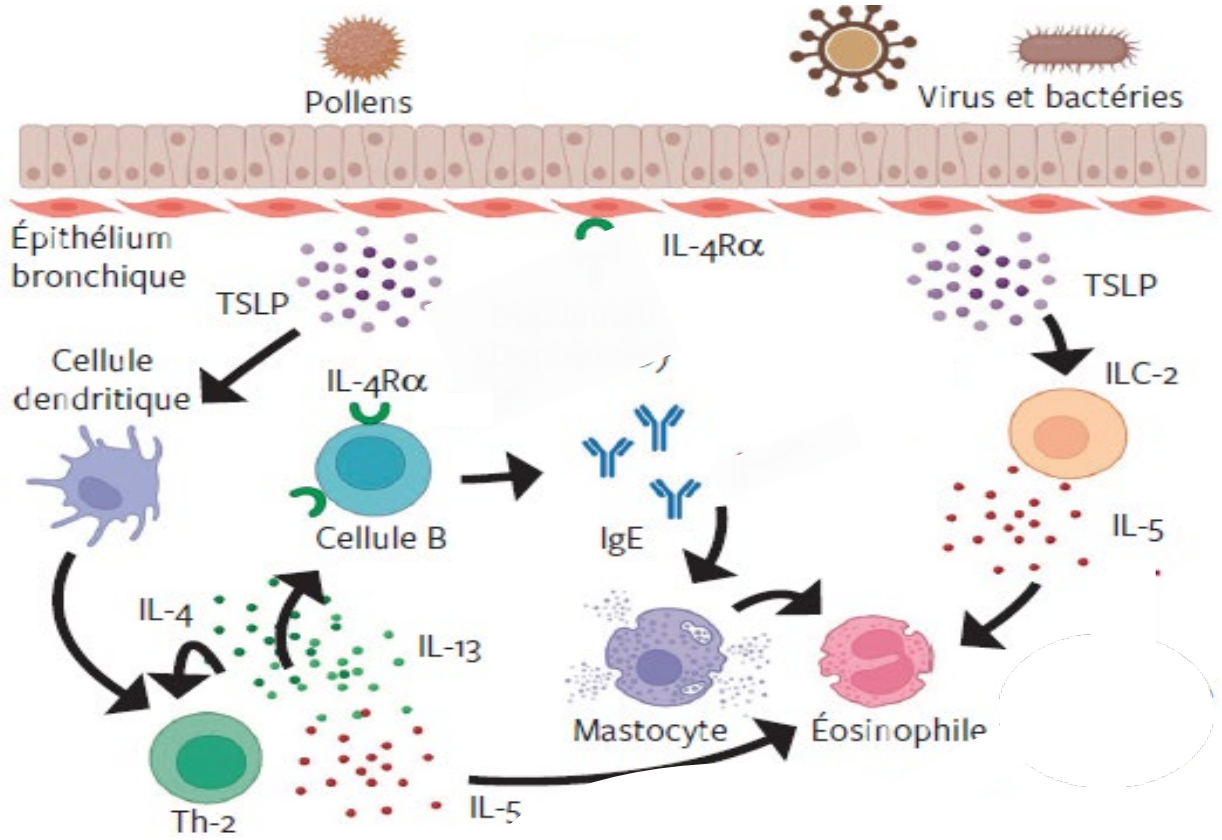
Have we changed our practices?

Better detection of pediatric asthma
External Exposure Factor

Are we using more Salbutamol in recent years?

Dissemination of guidelines for rapid processing...
But this should change


Behavioural disorders
Poverty
Side effects of medications
Absenteeism
Precariousness
Lack of physical activity
Limitation of daily activities (school, work, leisure)
Obesity
ASTHMA
Quality of life
Complete autonomy of children in their treatment
Sleep disorders
Iterative medical consultations
Lifestyle changes (animals, living spaces)
Comorbidities:
Atopy
GERD
Polyps
OSA



Early phase
Bronchospasm
Edema

Late phase
Inflammation
Bronchial hypereactivity

Bronchospasm

Symptomatic treatment

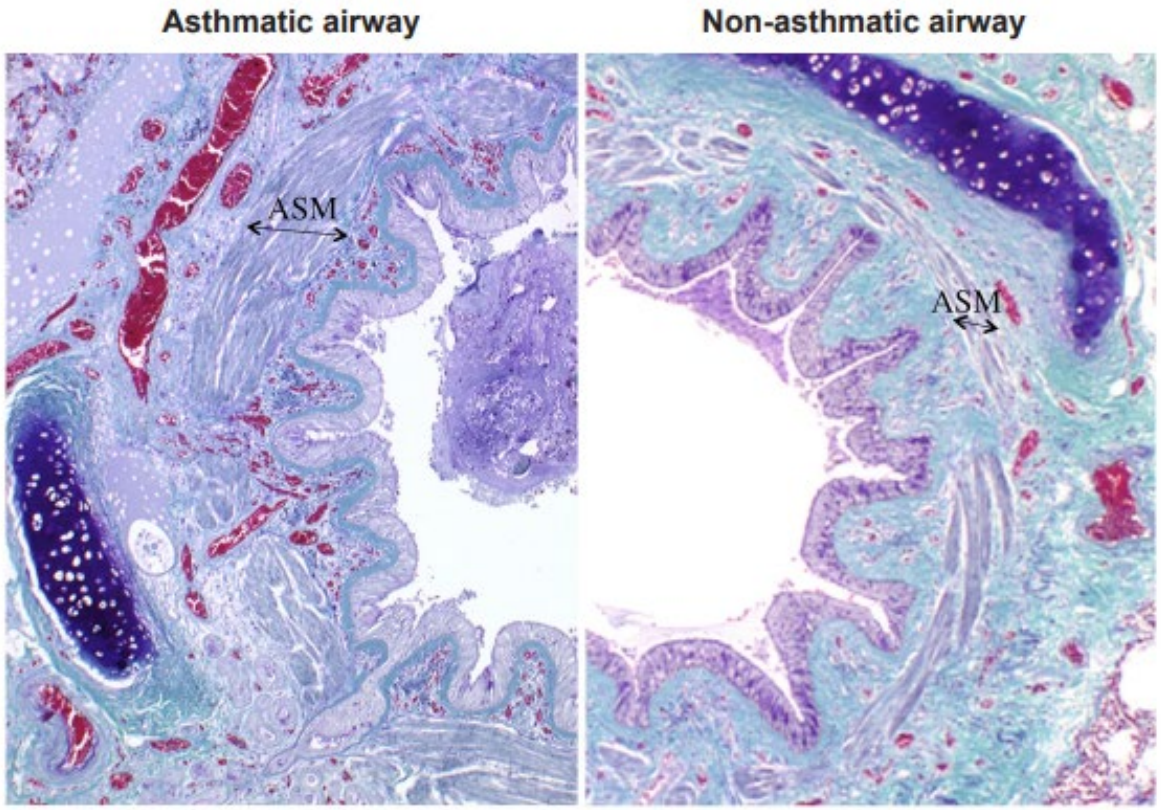
Bronchodilators as needed
β2-receptor agonist
Anticholinergic

Inflammation **Bronchial hyperactivity**

Background treatment

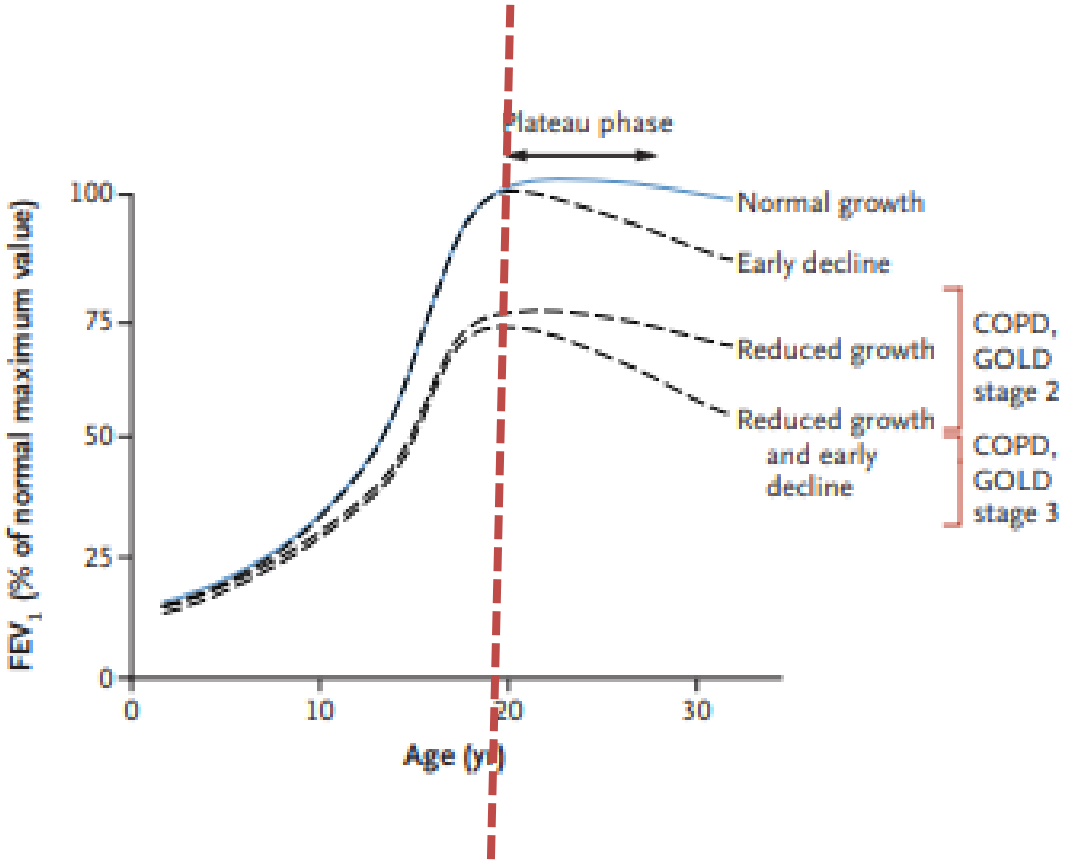
Inhaled cortictosteroids
Long bronchodilators
Duration of action
Leukotriene antagonist

Why optimally treat asthma in childhood?



Qui et al J Allergy Clin Immunol 2018

Why is the respiratory status during the pediatric period so important ?

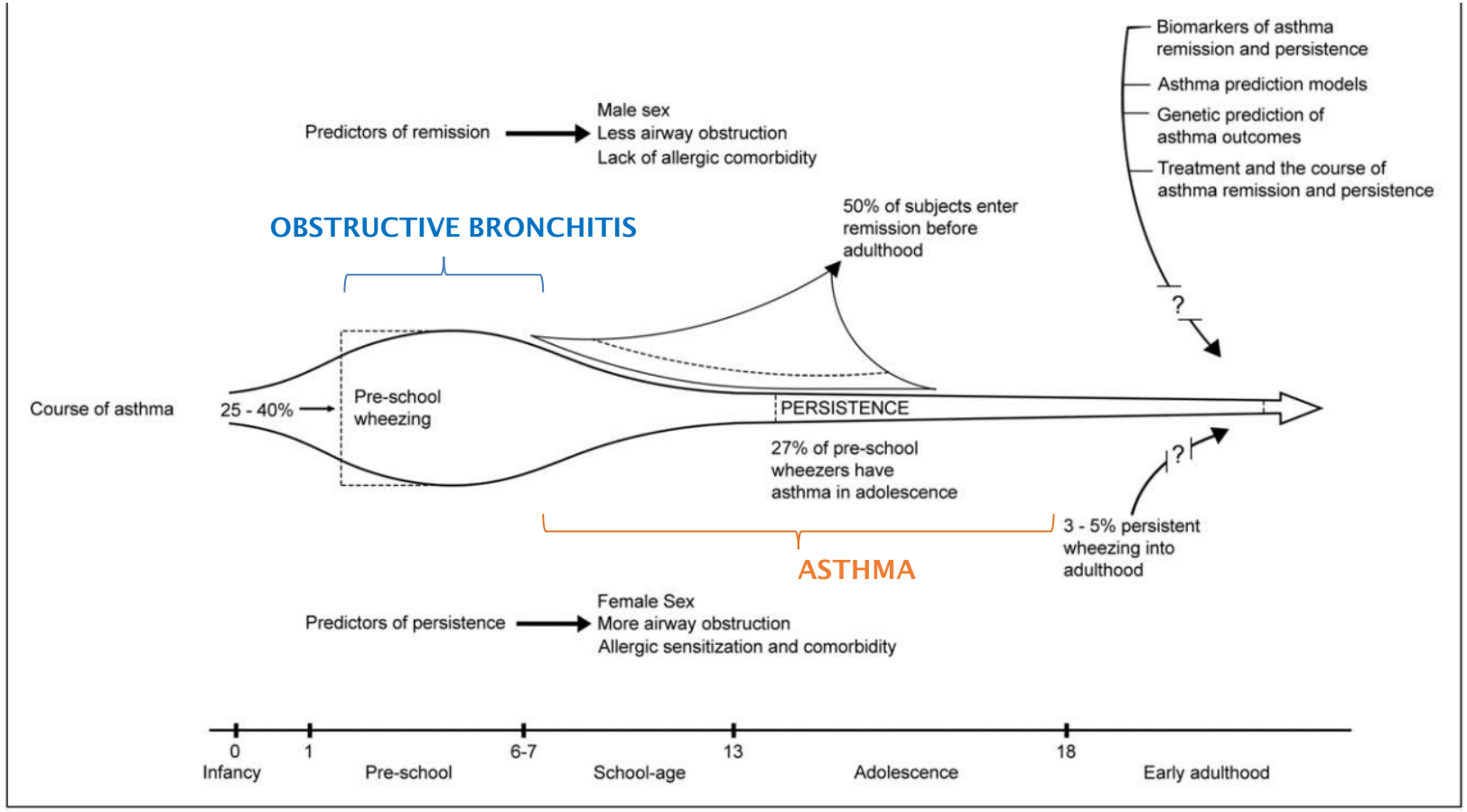


Plateau of respiratory function after 20 years

Importance of getting a correct pulmonary function before
respiratory decline in the paediatric population
And even more so in children at risk

McGeache et al. NEJM 2016

Obstructive bronchitis and asthma in children: what is the evolution?



Adapted from Koefoed et al. Current opinion 2022

Pre-schoolers wheezing: the obstructive bronchitis

Lower respiratory tract infection

No risk factors

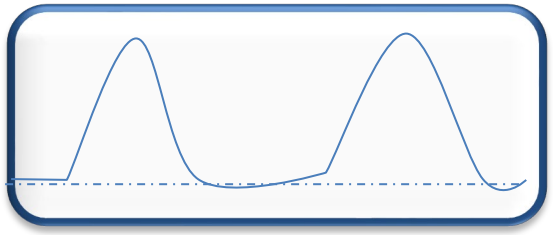
Repeated episodes
(wheezing, cough and dyspnea)

Exclusively viral triggering

Max duration 2 weeks

No intercritical symptoms

Usual disappearance at school age

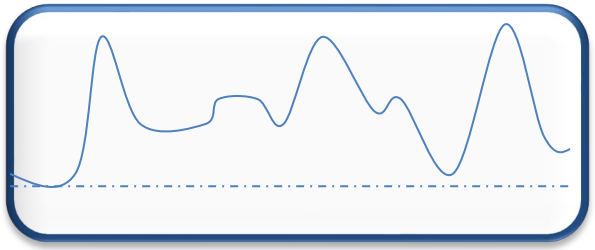


With risk factors

Repeated episodes
(wheezing, cough and dyspnea)

Triggering multiple causes (URTIs, crying, laughing, cold air, smoke, pollutants, allergies)

Persistence of interctritic symptoms



Risk factors for a bad course to look for on the patient's medical history

Asthma-related factors
Instability with increased intake of bronchodilators for >1 month
History of ICU hospitalization
Recent withdrawal from systemic corticosteroids
Decreased sensitivity to treatment as usual
Inhalation technique and lack of an action plan

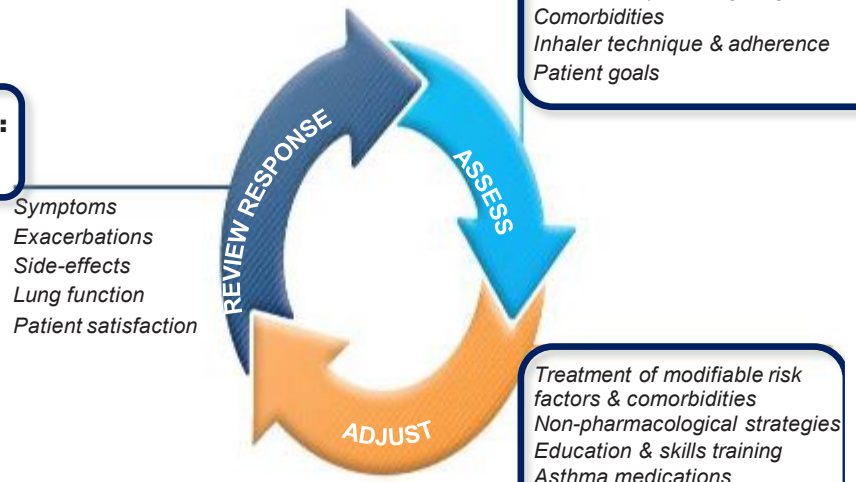
Factors related to the terrain Child <4 years old or teenagers
Polysensitization, food allergies
Poor perception of symptoms
Poor compliance

Specific triggers
Food
Anesthesia
Viruses in atopic
Aletrnaria, mites

Marguet and GRAPP, Rev Mal Respir 2007

GINA guidelines

Personalized asthma management:
Assess, Adjust, Review response



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

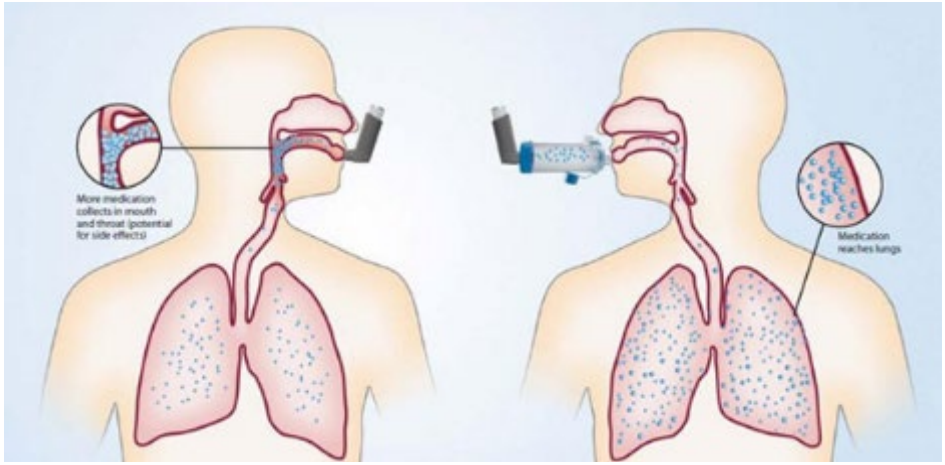
Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

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

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

GINA 2022

Method of administration

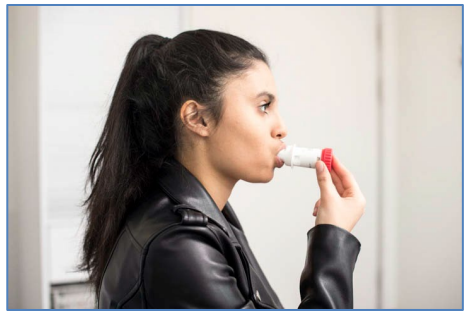


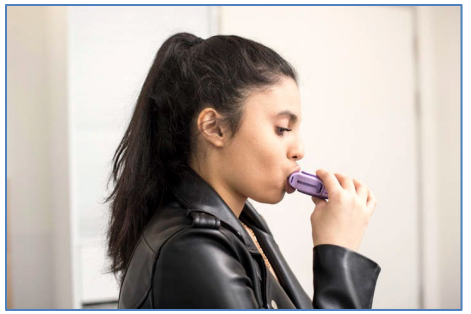
Non-waterproof mask: 0.1%

Cris: 1%

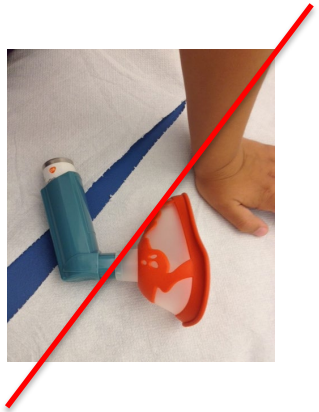
Correct Method:
6% Pulmonary Deposition
with face mask

Straubet Wildhaber, Paediatrica 2002



Technique d'inhalation en fonction de l'âge		
Inhalateur	**Age**	**Technique d'inhalation**
Nébuliseur dès 3 ans avec embout buccal	Tous	Inspirations calmes
Aérosol doseur avec chambre à inhaler et masque	0–2	10 inspirations calmes
Aérosol doseur avec chambre à inhaler sans masque	≥3 ans	10 inspirations calmes
	>5 ans	Inhalation maximale lente et 10 secondes de pause en inspiration
Inhalateurs à poudre sèche (après vérification préalable du flux inspiratoire maximal)	Diskus >6 ans Turbuhaler >8 ans	Inhalation énergique et profonde avec 10 secondes de rétention de la respiration



http://www.sgpp-sspp.ch/fr/Thérapie-par-inhalation.html

- Inspiratory flow> 30 L/min to use powder treatment
- Not possible in small children (coordination as well), nor in case of asthma attack

Adapted de Oswald Ligue Pulmonaire Suisse 2016

What are the side effects of regular/frequent use of SABA?

β-receptors down-regulation, decreases bronchoprotection and bronchodilators response

Hancox, Respir Med 2000

Use of high doses of SABA = bad outcome

Use of ≥3 sprays/year (average 1.7 push/day) associated with a higher risk of going to the emergency room

Stanford, AAAI 2012

Use of ≥12 sprays/year is associated with a higher risk of mortality

Suissa, AJRCCM 1994

Can the response to treatment vary?

Salbutamol

Single nucleotide polymorphism (SNP) du gène ADRB2

Amino acid Arg16gly : Influence density of beta2 adrenergic receptors

Secondary tachyphylaxis

Corticosteroids

Influence the ADRB2 gene and increase its expression + action

FCER2 gene SNPs, poorer response to corticosteroids and increased blood IgE

Nwokoro and Grigg 2018

What are the different stages of asthma ?

Selection of treatment step		Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Correspondent severity[a]		Mild intermittent	Mild persistent	Moderate persistent	Severe persistent
Features of asthma symptoms	Frequency	Less than once a week	Once or more a week, not every day	Every day	Every day
	Intensity	Mild and brief	Disturbs daily life or sleep at least once a month	Disturbs daily life or sleep at least once a week	Restricts daily life
				Need for SABA use almost every day	Worsens frequently even under treatment
	Symptoms at night	Less than twice a month	Twice or more a month	Once or more a week	Frequently

Hichikawa and Sugiura, Advance in Asthma 2019

< 5 years old

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

< 5 years old

Asthma medication options:
Adjust treatment up and down for individual child's needs

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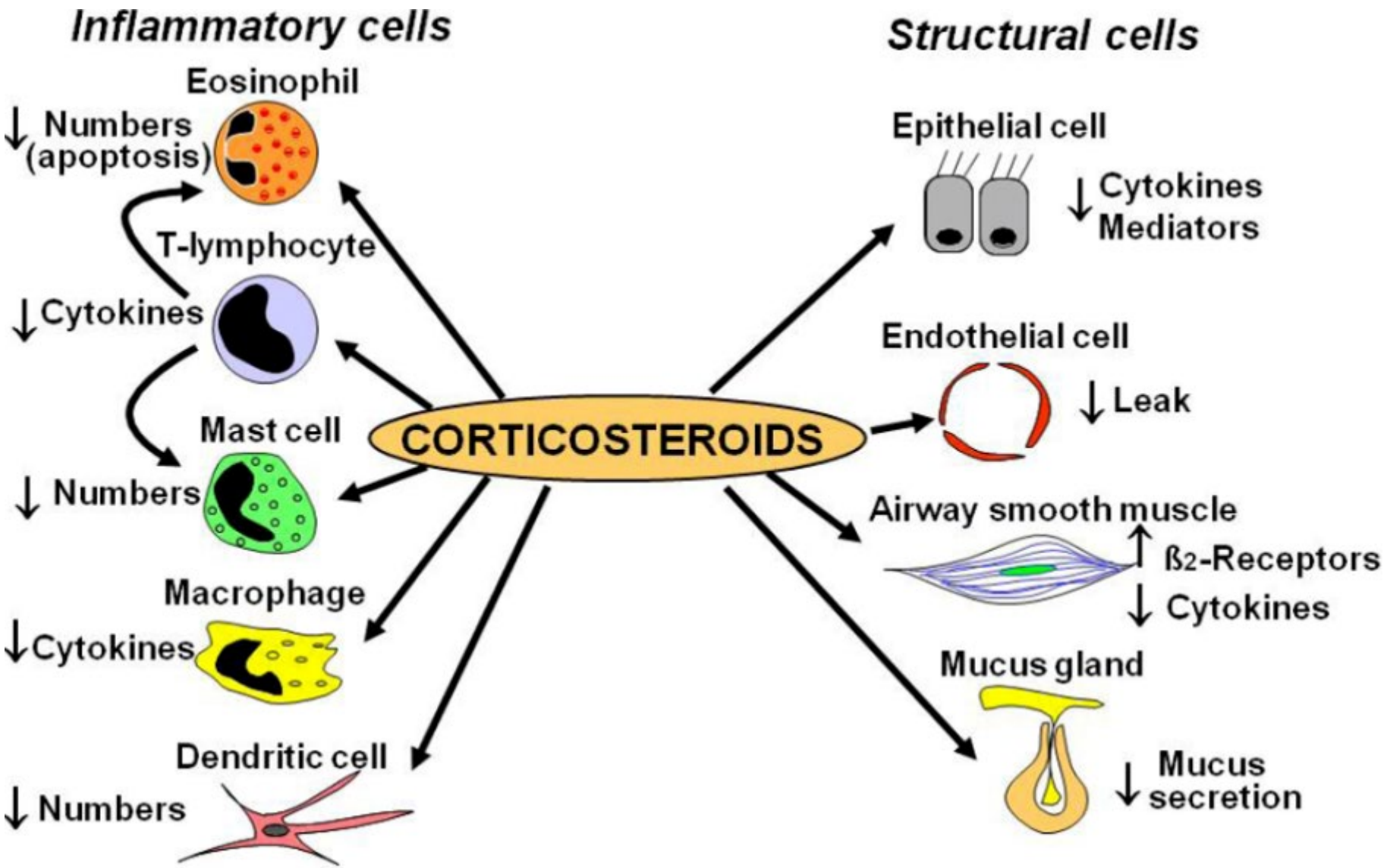
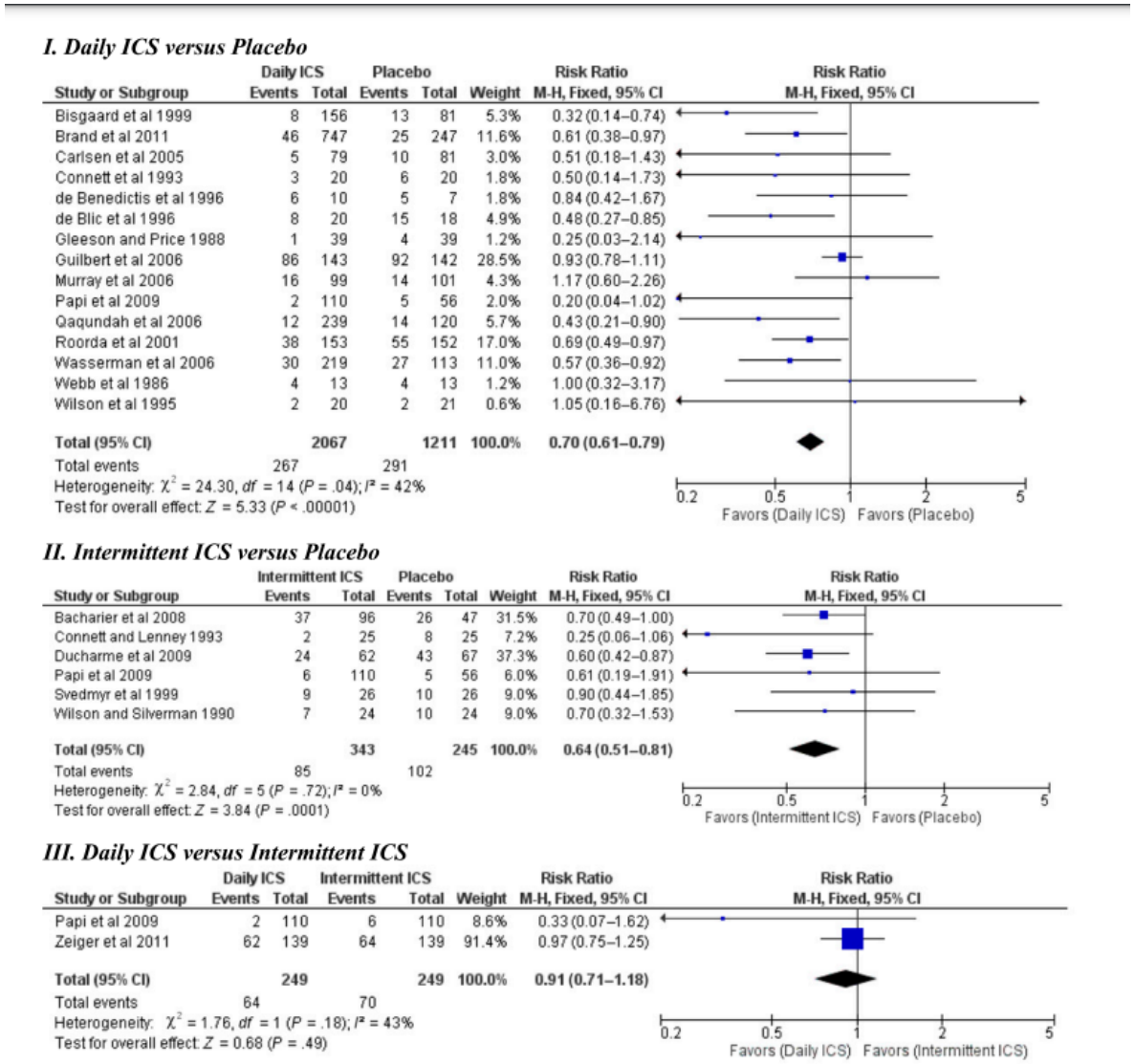
Corticosteroid: a multiple role ?



Barnes, Pharmaceuticals Journal 2010

Prevention of severe exacerbation in recurrent wheezer: what treatment for inhaled cortisteroids?



I. Daily ICS versus Placebo

Study or Subgroup	Daily ICS Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bisgaard et al 1999	8	156	13	81	5.3%	0.32 (0.14–0.74)
Brand et al 2011	46	747	25	247	11.6%	0.61 (0.38–0.97)
Carlsen et al 2005	5	79	10	81	3.0%	0.51 (0.18–1.43)
Connett et al 1993	3	20	6	20	1.8%	0.50 (0.14–1.73)
de Benedictis et al 1996	6	10	5	7	1.8%	0.84 (0.42–1.67)
de Blic et al 1996	8	20	15	18	4.9%	0.48 (0.27–0.85)
Gleeson and Price 1988	1	39	4	39	1.2%	0.25 (0.03–2.14)
Guilbert et al 2006	86	143	92	142	28.5%	0.93 (0.78–1.11)
Murray et al 2006	16	99	14	101	4.3%	1.17 (0.60–2.26)
Papi et al 2009	2	110	5	56	2.0%	0.20 (0.04–1.02)
Qaqundah et al 2006	12	239	14	120	5.7%	0.43 (0.21–0.90)
Roorda et al 2001	38	153	55	152	17.0%	0.69 (0.49–0.97)
Wasserman et al 2006	30	219	27	113	11.0%	0.57 (0.36–0.92)
Webb et al 1986	4	13	4	13	1.2%	1.00 (0.32–3.17)
Wilson et al 1995	2	20	2	21	0.6%	1.05 (0.16–6.76)
Total (95% CI)		**2067**		**1211**	**100.0%**	**0.70 (0.61–0.79)**
Total events	267		291			

Heterogeneity: $\chi^2 = 24.30$, $df = 14$ ($P = .04$); $I^2 = 42\%$
Test for overall effect: $Z = 5.33$ ($P < .00001$)

Risk Ratio M-H, Fixed, 95% CI
0.2 0.5 1 2 5
Favors (Daily ICS) Favors (Placebo)

II. Intermittent ICS versus Placebo

Study or Subgroup	Intermittent ICS Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bacharier et al 2008	37	96	26	47	31.5%	0.70 (0.49–1.00)
Connett and Lenney 1993	2	25	8	25	7.2%	0.25 (0.06–1.06)
Ducharme et al 2009	24	62	43	67	37.3%	0.60 (0.42–0.87)
Papi et al 2009	6	110	5	56	6.0%	0.61 (0.19–1.91)
Svedmyr et al 1999	9	26	10	26	9.0%	0.90 (0.44–1.85)
Wilson and Silverman 1990	7	24	10	24	9.0%	0.70 (0.32–1.53)
Total (95% CI)		**343**		**245**	**100.0%**	**0.64 (0.51–0.81)**
Total events	85		102			

Heterogeneity: $\chi^2 = 2.84$, $df = 5$ ($P = .72$); $I^2 = 0\%$
Test for overall effect: $Z = 3.84$ ($P = .0001$)

Risk Ratio M-H, Fixed, 95% CI
0.2 0.5 1 2 5
Favors (Intermittent ICS) Favors (Placebo)

III. Daily ICS versus Intermittent ICS

Study or Subgroup	Daily ICS Events	Total	Intermittent ICS Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Papi et al 2009	2	110	6	110	8.6%	0.33 (0.07–1.62)
Zeiger et al 2011	62	139	64	139	91.4%	0.97 (0.75–1.25)
Total (95% CI)		**249**		**249**	**100.0%**	**0.91 (0.71–1.18)**
Total events	64		70			

Heterogeneity: $\chi^2 = 1.76$, $df = 1$ ($P = .18$); $I^2 = 43\%$
Test for overall effect: $Z = 0.68$ ($P = .49$)

Risk Ratio M-H, Fixed, 95% CI
0.2 0.5 1 2 5
Favors (Daily ICS) Favors (Intermittent ICS)

ICS: Yes

Daily better than intermittent

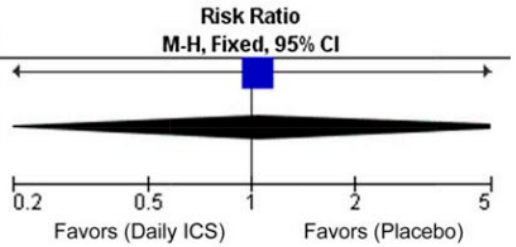
Kaiser et al. Peaditrics 2018

Intermittent wheezing virus-induced wheezer: what treatment for inhaled cortisteroids?

I. Daily ICS versus Placebo

Study or Subgroup	Daily ICS Events	Daily ICS Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wilson et al 1995	2	20	2	21	100.0%	1.05 (0.16–6.76)
Total (95% CI)		**20**		**21**	**100.0%**	**1.05 (0.16–6.76)**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: $Z = .05$ ($P = .96$)



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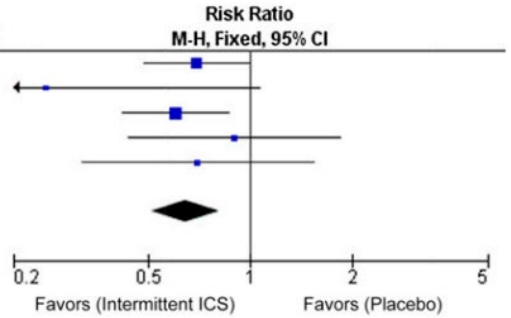
Wilson and Silverman 1990	7	24	10	24	9.6%	0.70 (0.32–1.53)
Total (95% CI)		**233**		**189**	**100.0%**	**0.65 (0.51–0.81)**
Total events	79		97			

Heterogeneity: $\chi^2 = 2.83$, $df = 4$ ($P = .59$); $I^2 = 0\%$
Test for overall effect: $Z = 3.75$ ($P = .0002$)



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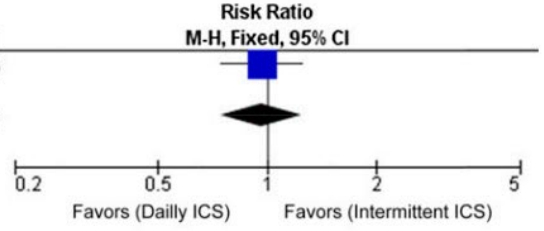
Zeiger et al 2011	62	139	64	139	100.0%	0.97 (0.75–1.25)
Total (95% CI)		**139**		**139**	**100.0%**	**0.97 (0.75–1.25)**
Total events	62		64			

Heterogeneity: Not applicable
Test for overall effect: $Z = .24$ ($P = .81$)



➡ ICS: Yes

➡ Daily better than intermittent??

Kaiser et al. Peaditrics 2018

Inhaled corticosteroids: which dose?

Adults and adolescents (> 12 years old)

Inhaled Corticoistéroids (ICS)	Total dose ICS/d (mcg) Mild	Moderate	Severe
Budenoside PULMICORT® / VANNAIR®/ SYMBICORT®	1/ / ,3/ /	3/ / ,7/ /	=7/ /
Fluticasone propionate RELVAR®/ SERETIDE®/ FLUTIFORM®	0/ / ,14/	14/ ,4/ /	=4/ /
Beclometasone dipropionate QVAR®	0/ / ,1/ /	1/ / ,3/ /	=3/ /

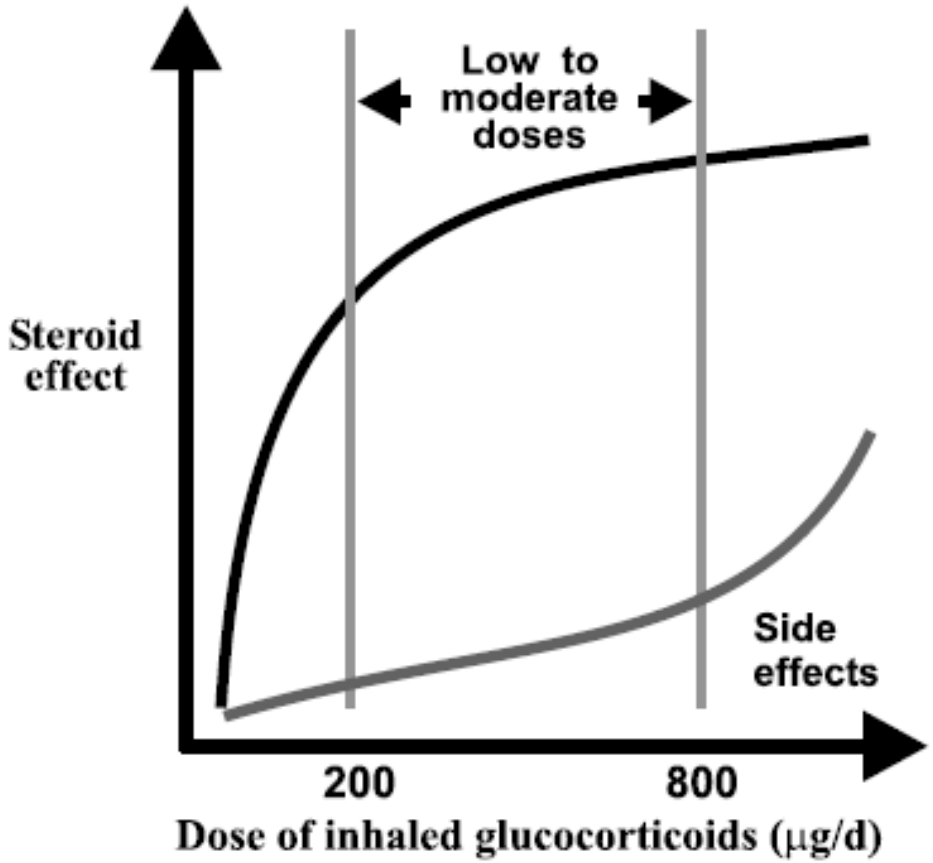
Children 6-11 years old

Inhaled Corticoistéroids (ICS)	Total dose ICS/d (mcg) Mild	Moderate	Severe
Budenoside PULMICORT® / VANNAIR®/ SYMBICORT®	0/ / ,1/ /	1/ / ,3/ /	=3/ /
Budenoside (respules)PULMICORT®	14/ ,4/ /	=4/ / ,0/ / /	=0/ / /
Fluticasone propionate SERETIDE® AXOTIDE®	4/ ,0/ /	0/ / ,1/ /	=1/ /
Beclometasone dipropionate QVAR®	4/ ,0/ /	0/ / ,1/ /	=1/ /

Children < 6 years old

Inhaled Corticoistéroids (ICS)	Total dose ICS/d (mcg)
Budenoside PULMICORT®	400 '= 0 year old(
Budenoside (respules) PULMICORT®	1000 '= 1 year old(
Fluticasone propionate AXOTIDE®	20/ '= 1 year old(

The dose-response curve of inhaled glucocorticoids



Kankaanrantaet al, Respir. Research Journal 2004

[Intervention Review]

Inhaled corticosteroids in children with persistent asthma: effects on growth

- 25 studies analyzed with 8,471 children
- Persistent mild asthma
- <18 years with at least 3 months of treatment with ICS
- Small to medium daily ICS

- Loss of 0.48 cm/year in growth rate and 0.61 cm over one year of growth
- Maximum effect in the first year with the possibility of catching up in the
- majority of cases
- A study with 400 mcg of Budesonide daily for 4.3 years shows a loss in adulthood of 1.2 cm

(Kelly et al, NEJM 2012)

Cochrane review 2014

Side effects of ICS ?

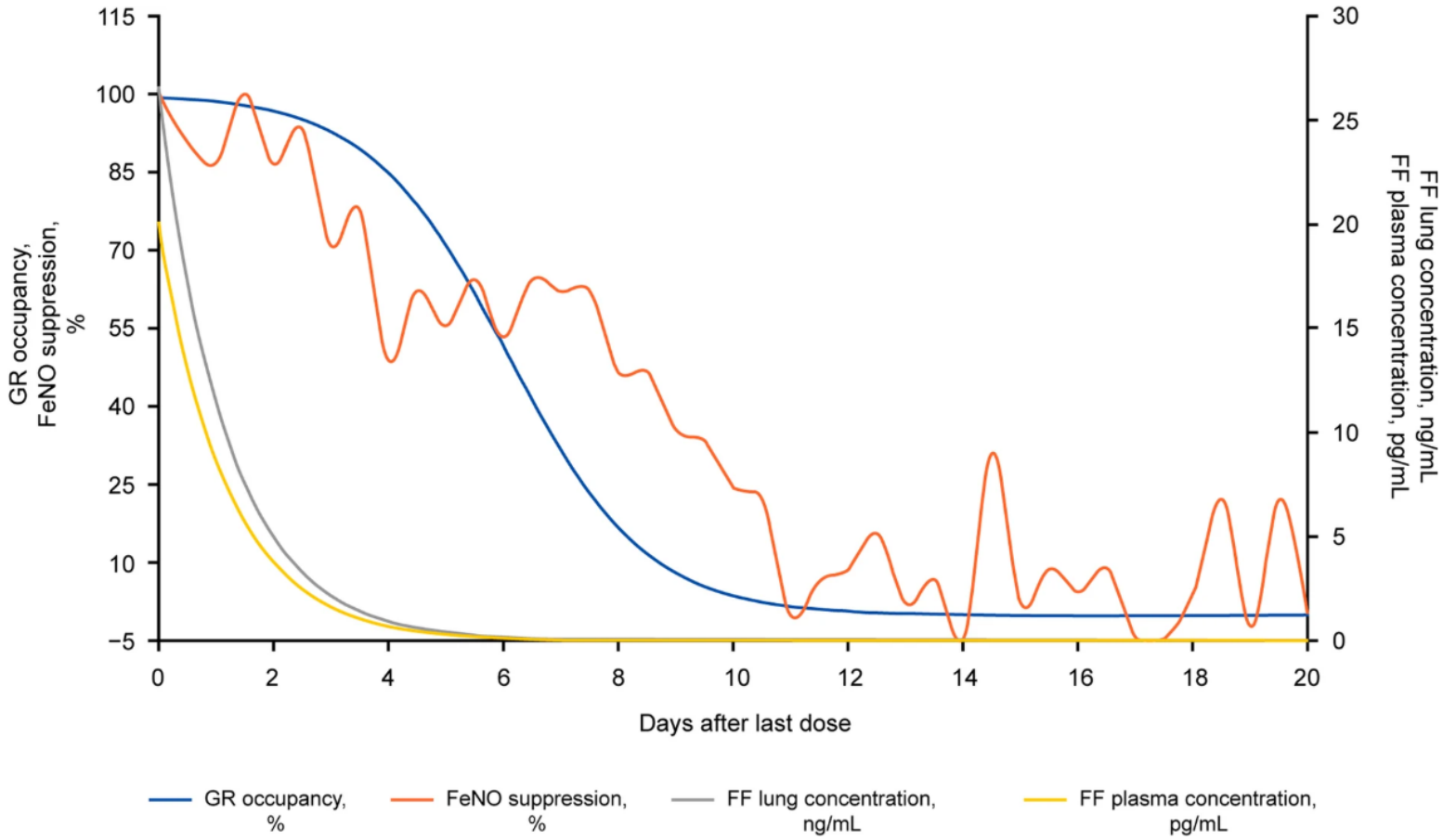
Low to moderate ICS doses on children 3 to 8 years of age with
of the measurements every 6 months does not show any difference in growth

Table 3. Potential side effects of short courses of oral steroids, and the longer-term potential effects of recurrent use[1,30,49]

Potential side effects of short courses of oral steroids	Effects of long-term dosing with steroids
• Sleep disturbance • Behavioural disturbance • Vomiting • Gastritis • Gastrointestinal disturbance • Facial flushing • Nocturia • Dry skin	• Weight gain • Cushingoid facies • Mood changes (irritability, hyperactivity) • Reduction in final height or growth velocity • Osteoporosis • Cataracts • Hypertrichosis • Cutaneous atrophy • Hypertension • Hypothalamic–pituitary–adrenal axis suppression

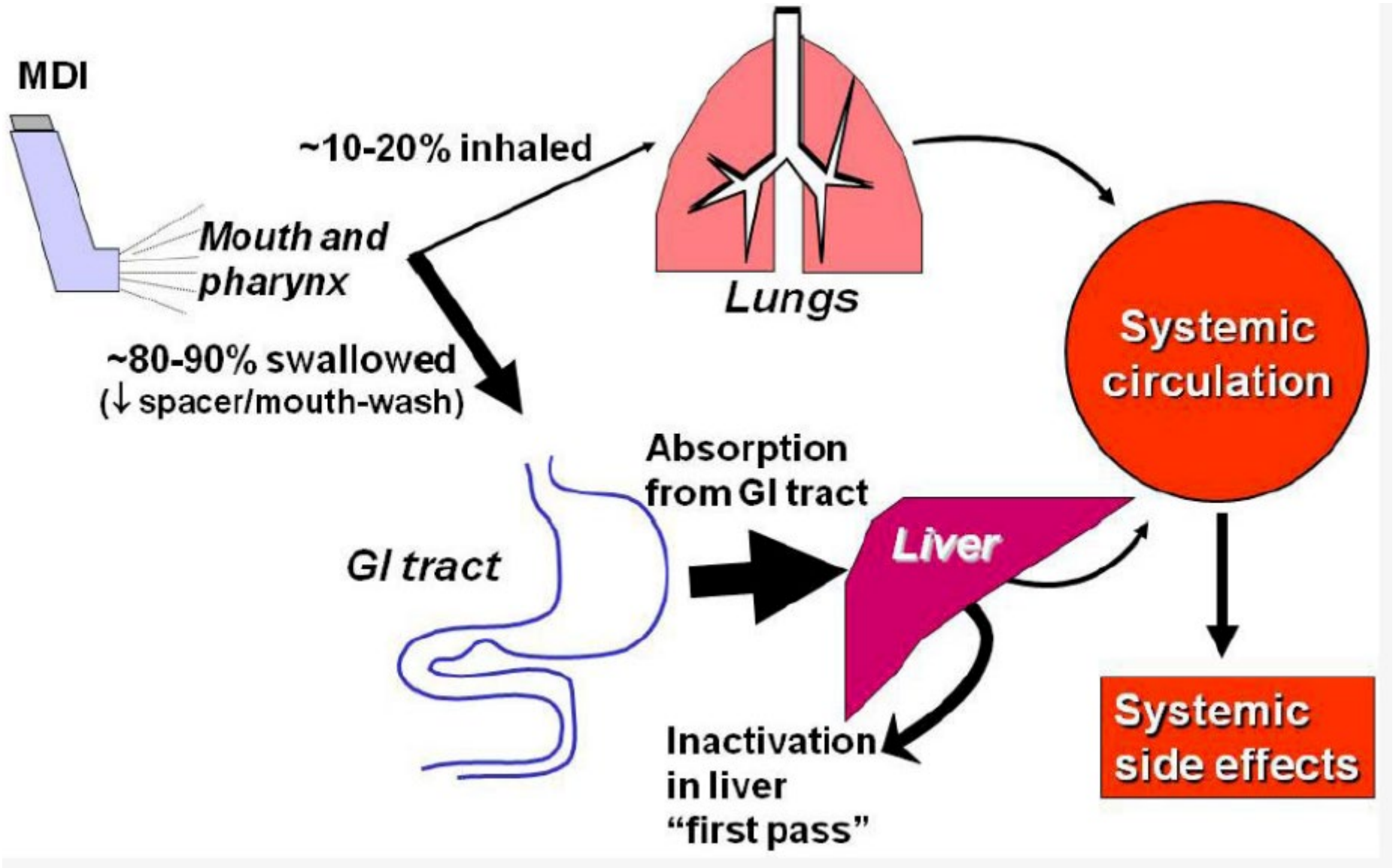
Hatziagorou et l. J.Asthma 2018

Days after corticosteroids treatment and lenght of effect ?



Daley-Yates et al, Adv Ther Journal 2024

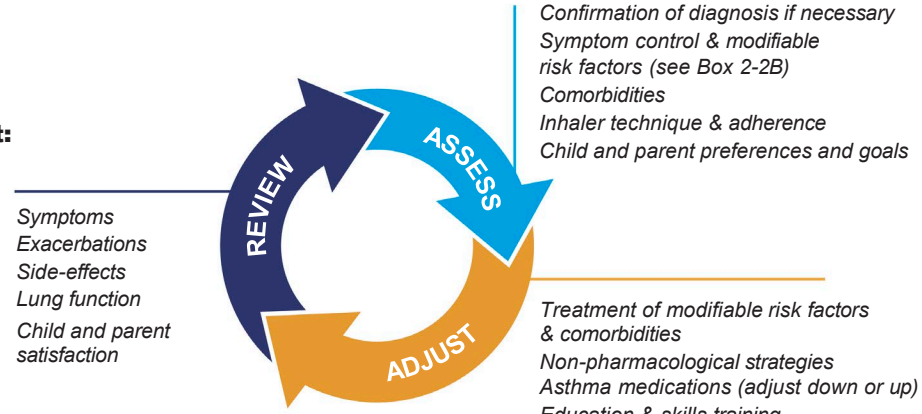
Pharmacokinetics of inhaled glucocorticoids



Barnes, Pharmaceuticals Journal 2010

>6- 11 years old

Personalized asthma management:
Assess, Adjust, Review



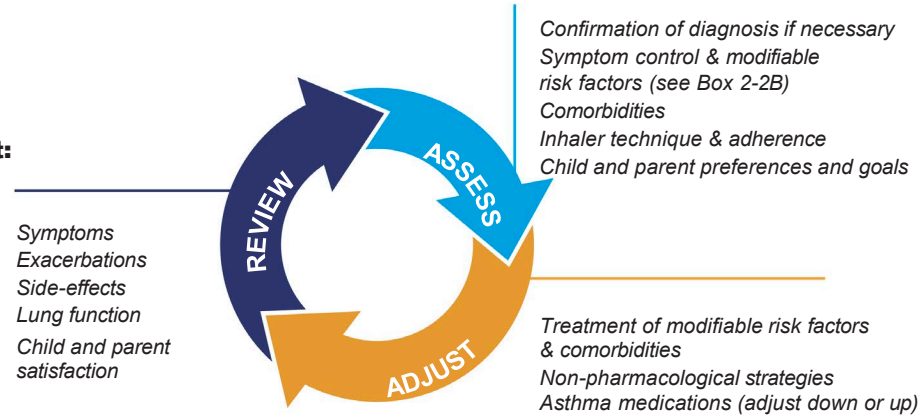
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4R
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*Add-on anti-IL5 or, as last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

*Very low dose: BUD-FORM 100/6 mcg
†Low dose: BUD-FORM 200/6 mcg (metered doses).

>6- 11 years old

Personalized asthma management:
Assess, Adjust, Review



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4R
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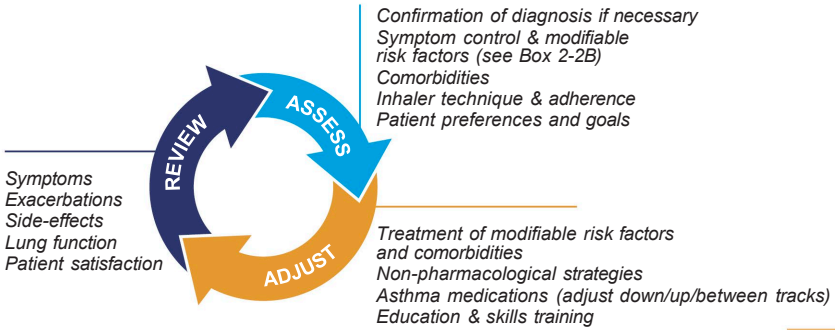
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

> 12 years old



CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

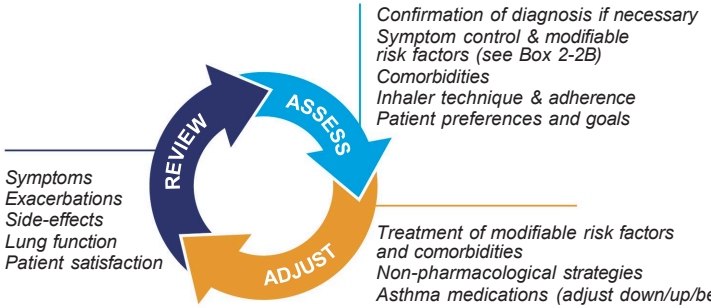
CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed short-acting beta$_2$-agonist				

Other controller options for either track (limited indications, or less evidence for efficacy or safety)	*Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

GINA 2022, Box 3-5A

> 12 years old



CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2
As-needed low dose ICS-formoterol

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol

See GINA severe asthma guide

CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1
Take ICS whenever SABA taken

STEP 2
Low dose maintenance ICS

STEP 3
Low dose maintenance ICS-LABA

STEP 4
Medium/high dose maintenance ICS-LABA

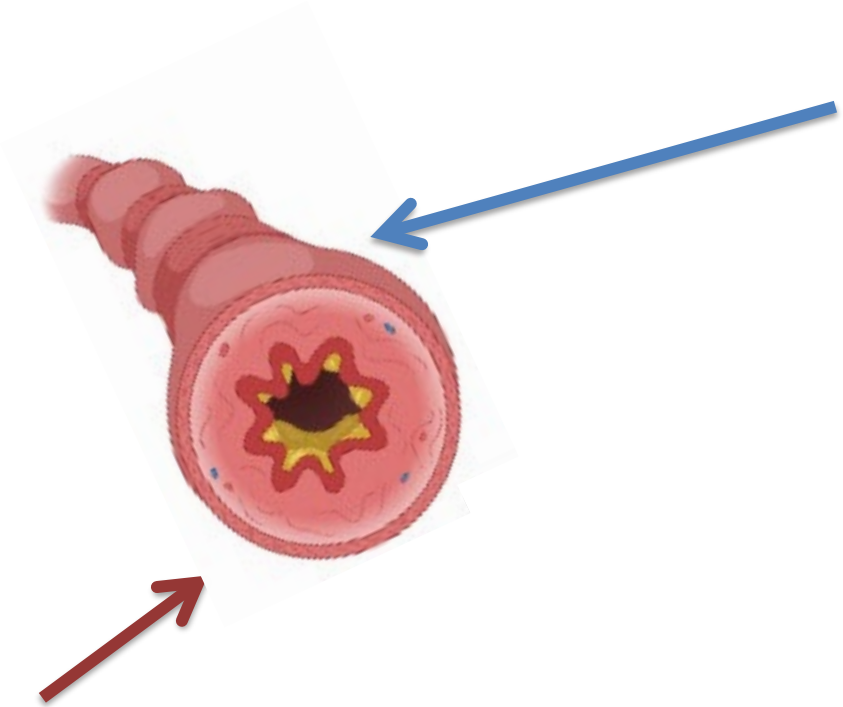
STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed short-acting beta$_2$-agonist

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

β2 agoniste



Corticosteroids (ICS)

Budesonide
Fluticasone propionate
Ciclesonide
Beclomethasone

Long-Acting- Beta-Agonist (LABA)

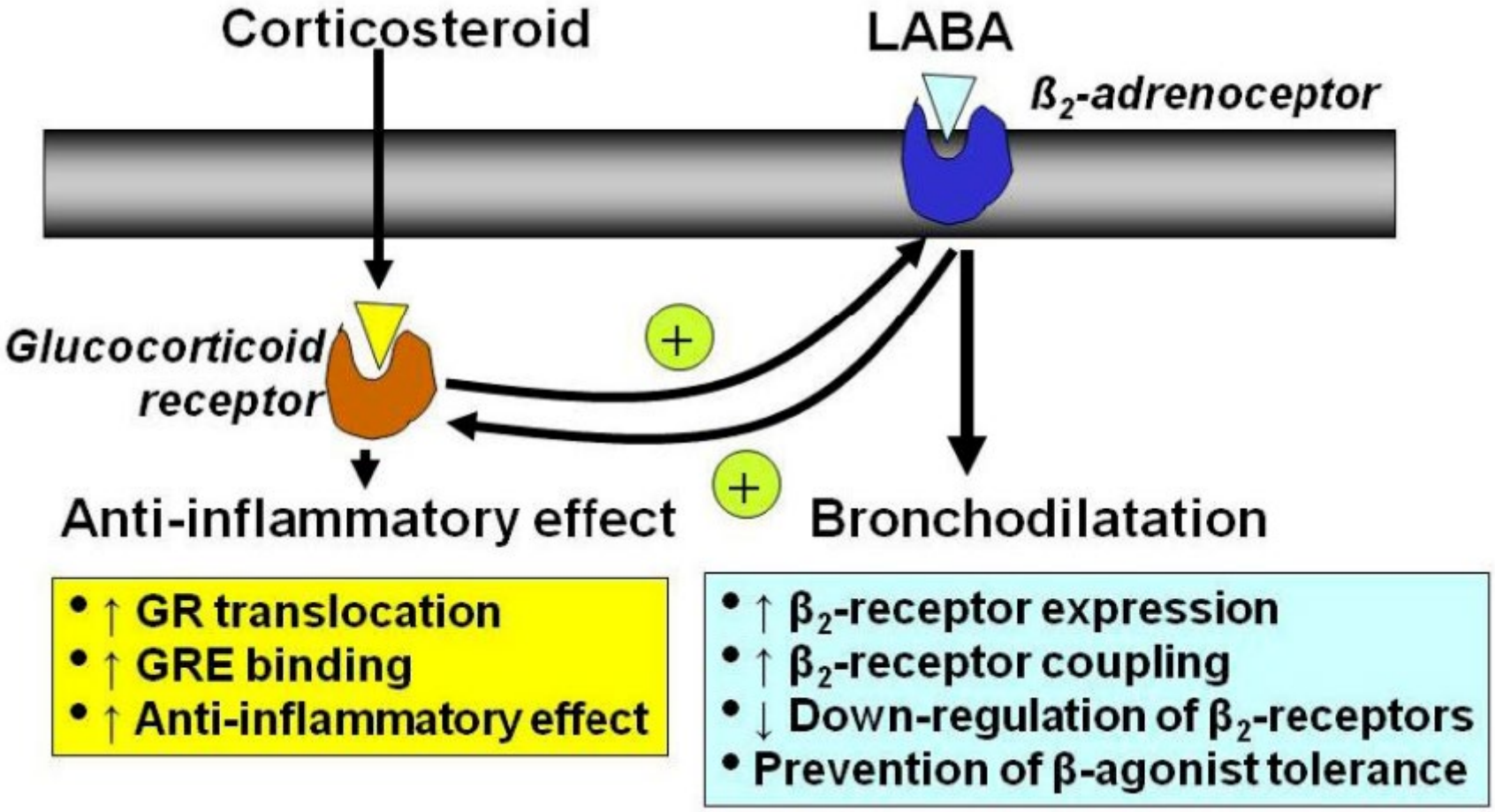
Formoterol
Start of the action: 1-2 min
Duration of the action: 12 h
½ Life 17 h

Salmeterol
Start of the action: 10-20 min
Duration of the action: 12 h
½ Life 12j

Vilanterol
Start of the action: 7 min
Duration of the action: 24 h
½ Life 24h

Which side effects?

Interaction between corticosteroids and long-acting β2-agonists (LABA)



Barnes, Pharmaceuticals Journal 2010



Log acting drug	Drug	Pulmonary dose	Effect Max	1/2 life	Secondary effect
Vilantérol (12 ans)	Relvar	15-27%	7min	16h	Headache, arthalgias,cough, hyperglycemia, hypokaliemia
Formotérol (6 ans)	Symbicort/Vannair	25-30%	10min	17h	Headache, tachycardia, cramps,tremor
Salmétérol (4 ans)	Seretide	20-30%	30 min	12h	Headache, tachycardia, cramps, tremor

ICS	Médicament	Dose Bas	Moyen	Elevé
Budenoside	Symbicort/Vannair	200-400	>400-800	>800
Fluticasone Fuorate	Relvar	100	n.a	200
Fluticasone Propionate	Axotide/Seretide	100-250	>250-500	>500

Some patients require higher ICS doses even if adherence and correct technique

Symptoms versus treatment efficacy ?

Prospective Randomized Multicenter Superiority Study double-blind over

52 weeks

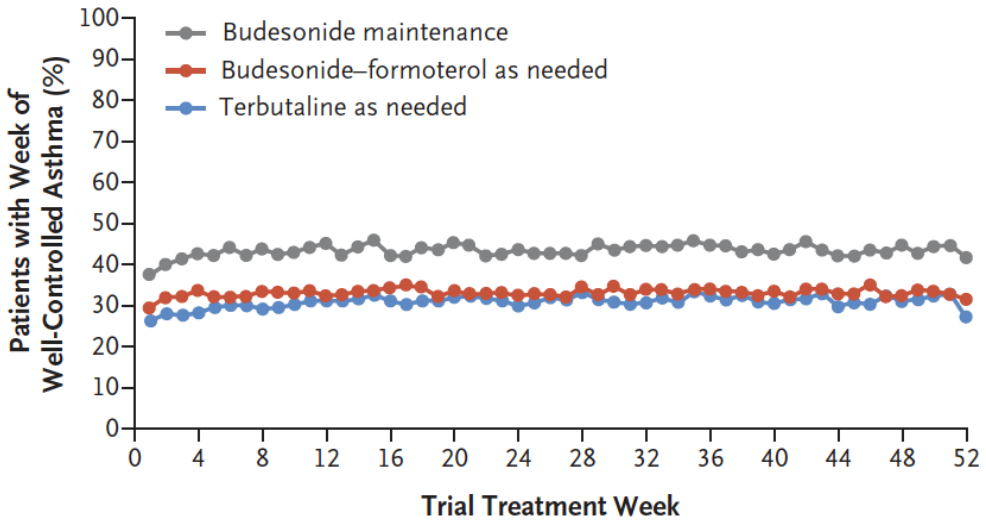
3849 Patients > 12 years of age (Average 41 years)

Persistent mild asthma

Sponsor and support for the analysis carried out by AstraZeneca

CSI= Budenoside
SABA = salbutamol
LABA= Formotérol

A. Placebo –SABA as needed
B. Placebo - Budenoside-Formoterol as needed CSI 200mcg and LABA 6mcg
C. Budenoside- SABA as needed CSI 400mcg



O'Byrne et al. NEJM 2020

What is the difference between a background treatment of Budenoside and Budenoside-Formoterol as needed?

Prospective Randomized Multi-Center Non-Inferiority Study in double-blind over 52 weeks

4176 Patients > 12 years of age (mean 41 years)

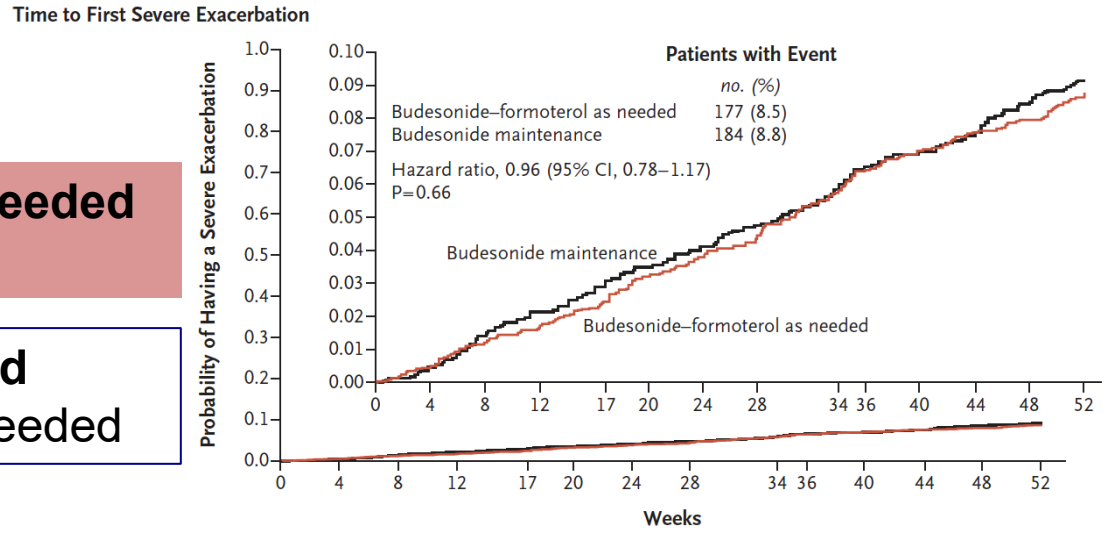
Persistent mild asthma

Sponsor and support for the analysis carried out by AstraZeneca

CSI= Budenoside
SABA = salbutamol
LABA= Formotérol

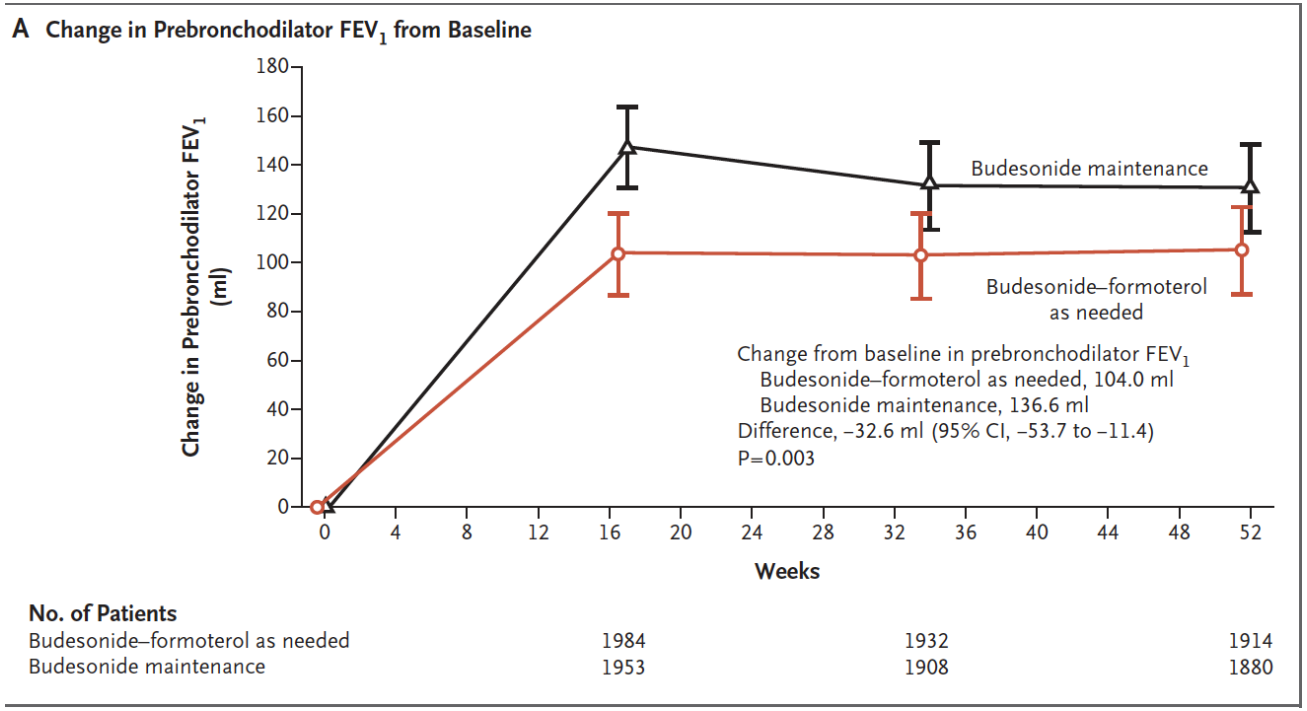
A. Budenoside-Formoterol as needed
CSI 400mcg et LABA 12mcg 2x/d

B. Budenoside- SABA as needed
CSI 200mcg et SABA 0,5 mg as needed



Batemanet al. NEJM 2018

What is the difference between a background treatment of Budenoside and Budenoside-Formoterol as needed?



- Budenoside-Formoterol as needed has the same efficacy as daily Budenoside treatment for the risk of exacerbation
- The ICS dose, on the other hand, is reduced by 1/4 of the dose.
- FEV1 best under daily background therapy

Batemanet al. NEJM 2018

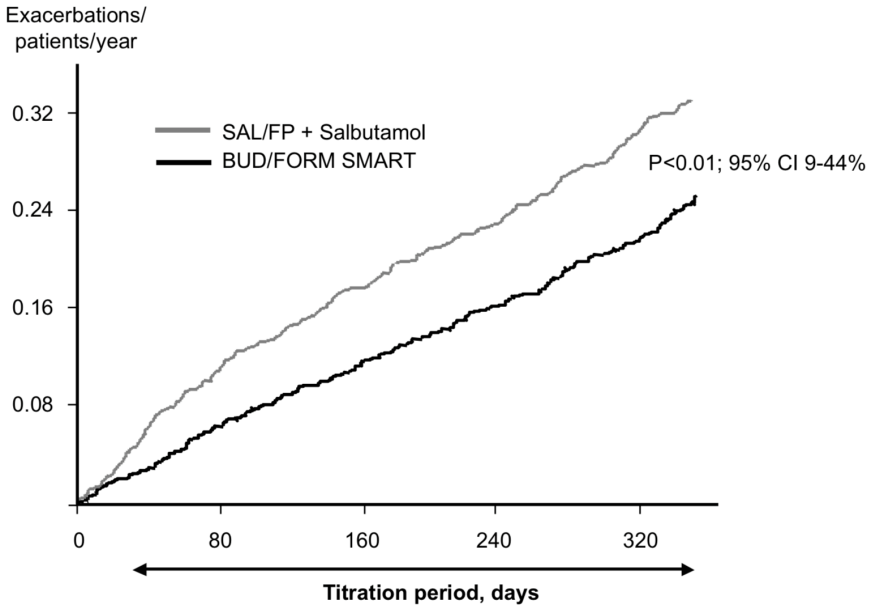
What is the difference with the SMART study ?

Symbicort Maintenance And Reliever Therapy

Prospective 12-month randomized multicenter study
2509 patients > 12 years old (average 45 years old)
Mild persistent asthma previously treated

A. **Salmeterol/Fluticasone (50/250mcg) –SABA au besoin**

B. **Budenoside-Formoterol (160/4,6mcg) - Budenoside-Formoterol au besoin (max 12/j)**



Vogelmeier et al. ERJ 2005
Selroos et al. Therapeutics and clinical Risk managment 2007

What is the difference with the SMART study ?

Symbicort Maintenance And Reliever Therapy

- Mean ICS doses in the 2 identical groups (653mcg budenoside/day vs 583mcg fluticasone/day)
- Simplified strategy is feasible and safe

Vogelmeier et al. ERJ 2005
Selroos Therapeutics and clinical Risk managment 2007

Changes in asthma care ?

Why maximum doses?

Total dose limit/days	Europe	Canada
Salmeterol SERETIDE®	no data	100mcg
Fomoterol VANNAIR®/ SYMBICORT®/ FLUTIFORM®	<12ans 48mcg >12ans 72mcg	<12ans 48mcg >12ans 72mcg
Vilanterol RELVAR®	25mcg	25mcg

- **Formoterol:**

1/2 life = 17 hours, i.e. more than 2.5 days for complete elimination

Cumulative adverse reactions (hypokalemia, tachycardia, tremor, hyperglycemia, headache)

- **Budenoside:**

High doses of corticosteroids if taken regularly of 200 mcg of Budenoside

12 doses of Budenoside 100mcg is equivalent to more than 16mg of prednisone!

Beware of adrenal insufficiency

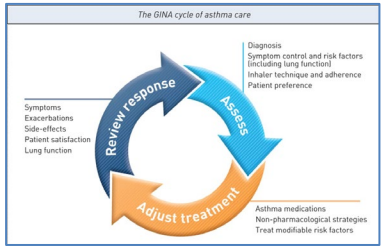
In your daily practice

- Using ICS + SABA on demand can be confusing among parents of children aged 6-11 years.
- Attention to ICS amounts: risk of adrenal insufficiency existing

Using Budenoside + Formoterol on demand can create
Confusion in patients (> 12 years of age) with side effects due to the high dosage of LABA and CSI.

Proposal
- Do not give more than 3-6 inhalations/day as needed
- Maximum 3 days in a row before consulting.
- To be reserved for specific cases only.
- Differentiation of long-term and crisis treatment important!

- Importance of a clear and regularly review the method of administration



Is Montelukast risky to use?

FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis

Risks may include suicidal thoughts or actions

2017 study with 208 children (median age 5 years) treated with Montelukast
Increased risk of suicide in adolescents (x12)

Nightmares and behavioural problems in children (20%)

Benard et al. ERJ 2017

FDA has been drawing attention since March 2020 to the association of disorders possible neuropsychiatric treatment in children on Montelukast

Differential diagnosis

Acquired pathologies

Recurrent viral infections

Foreign body suction

Gastroesophageal reflux disease

Tuberculosis

GDP

Narrowing of the airways

Congenital pathologies

Muccovisidosis

Cilliary dyskinesia

Vascular Rings

Tracheobronchomalacia

Lung malformations

Heart Disease

Immunodeficiency

Congenital tumors

Which patient for the consultation of pediatric pneumology ?

Nasal Polyposis (Ciliary diskinesia)

Family history severe lung disease

Growth disorders (cystic fibrosis)

Respiratory problems present since birth (BPD..)

Which patient for the consultation of pediatric pneumology ?

Nasal Polyposis (Ciliary diskinesia)

Unclear symptoms(heart disease, vascular ring..)

Family history severe lung disease

Growth disorders (cystic fibrosis)

Cough without secretion (Tracheomalacia...)

Respiratory problems present since birth (BPD..)

Which patient for the consultation of pediatric pneumology ?

Steroids dose (>400 µg/day)

Nasal Polyposis (Ciliary diskinesia)

Unclear symptoms(heart disease, vascular ring..)

Family history severe lung disease

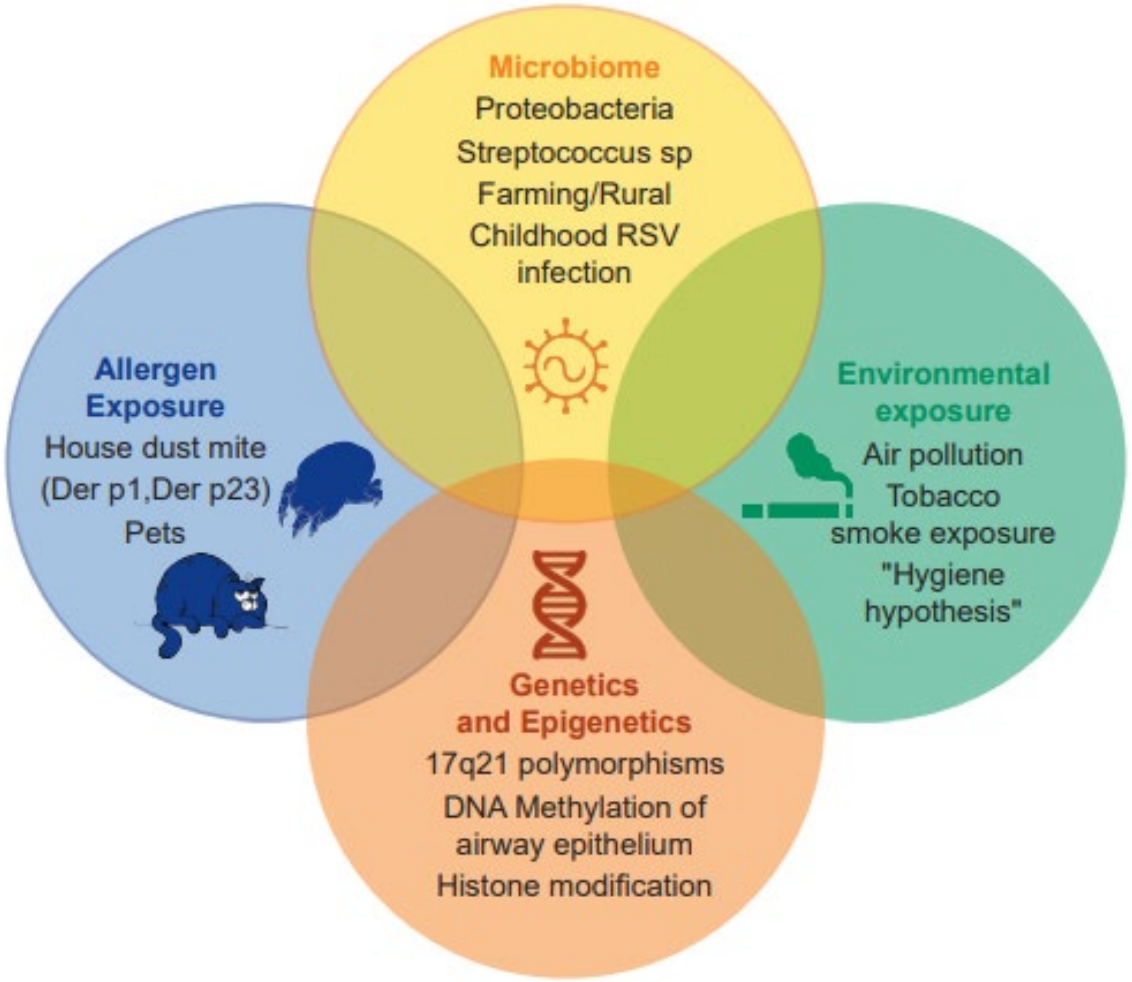
Absence of response to treatment

Growth disorders (cystic fibrosis)

Cough without secretion (Tracheomalacia...)

Respiratory problems present since birth (BPD..)

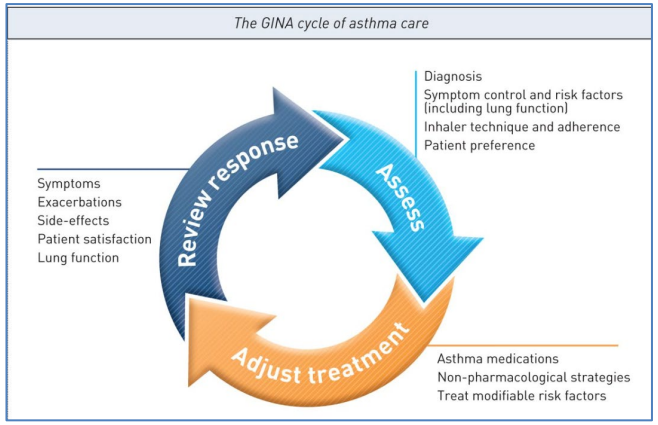
Many factors influencing asthma remain to be explored...



Adapted from EAACI report 2021

Take home message

- Chronic disease more common (10%) in children
- Adequate management is essential to reduce the morbidity and mortality
- Adequate treatment = excellent quality of life
- Good therapeutic teaching essential to reduce side effects or complications



QUESTIONS ?

Administration of small doses as needed of Budenoside-Formoterol?

6-11 years: background and rescue treatment (stages 3-5) or with a plan action

6 inhalations of Budenoside – Formoterol/day max of 100/6!

6–11 years: background and rescue treatment (stages 3–5) or with a plan action

6 inhalations of Budenoside – Formoterol/day max of 100/6!

>12 years: Background and rescue therapy (stages 3-5) or as needed only (stages 1-2)
Importance of an action plan
12 inhalations of Budenoside – Formoterol/day max of 200/6!