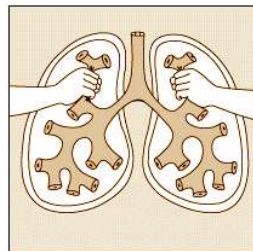


New Trends in the Treatment of bronchial asthma and COPD

<http://pharmacology.jfmed.uniba.sk>

<http://portal.jfmed.uniba.sk>



Definition of bronchial asthma

Chronic **inflammatory disease of airways**, with participation of various **cells** and cell elements, particularly mastocytes, eosinophiles, T-lymfocytes, macrophages, neutrophiles and epithelial cells. This inflammation cause in susceptible individuals recurrent episodes or **attacks** of wheezing, cough, dyspnea and chest oppressions, mainly during night and in the morning. Concommitantly there is diffuse, but variable **obstruction of airways**, which is **often reversible** either spontaneously or after treatment. The inflammation is responsible also for enhancing of bronchial **hyperreactivity** to various stimuli.

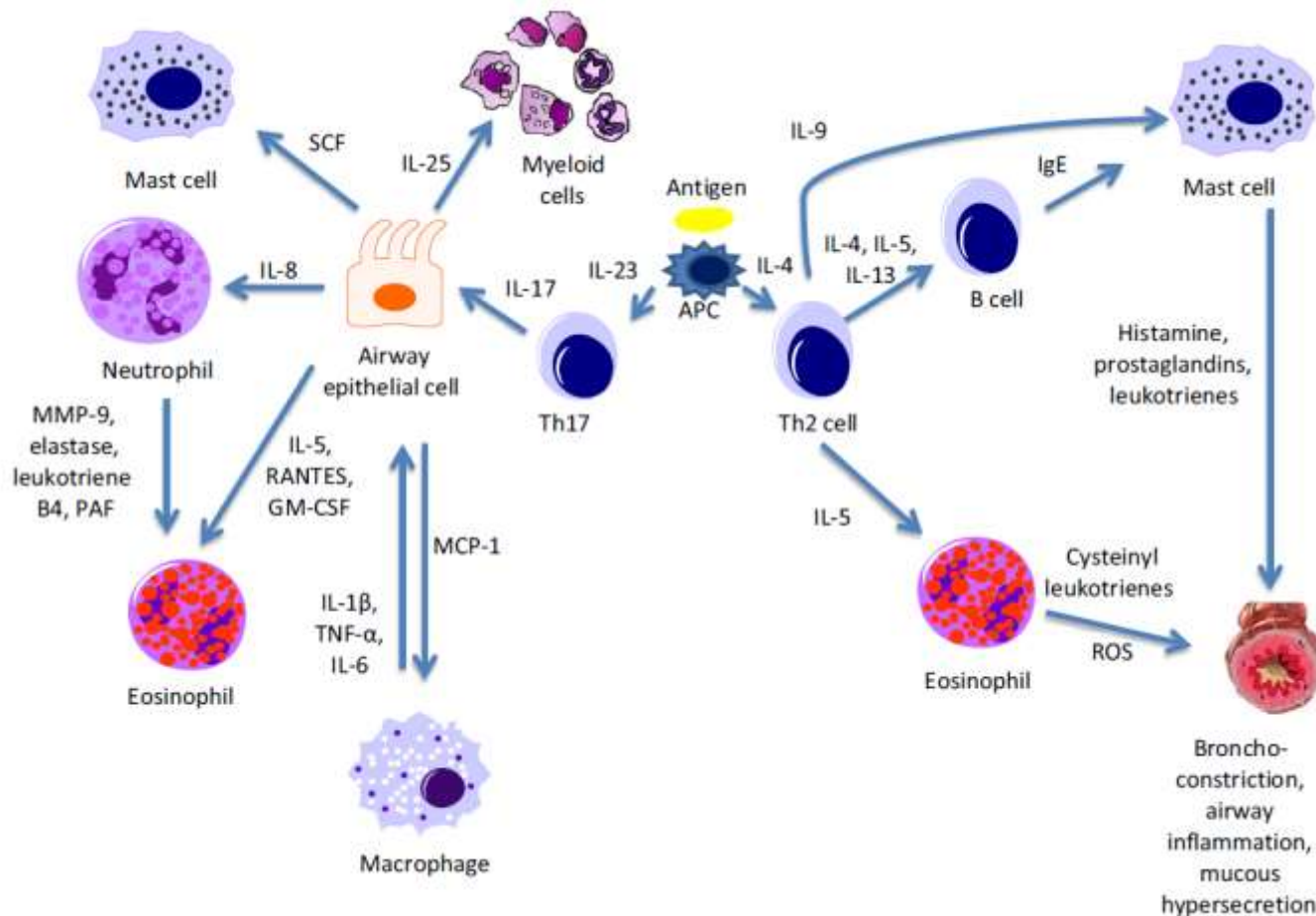
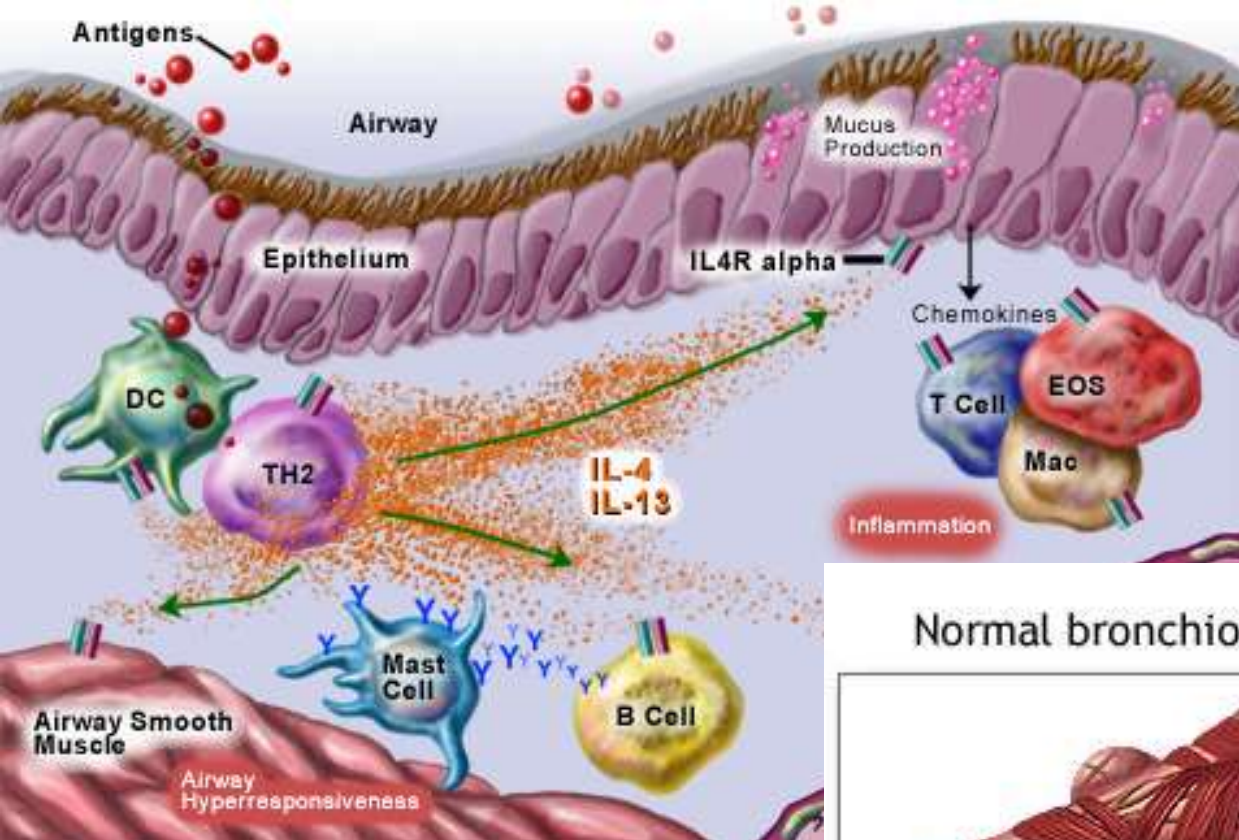
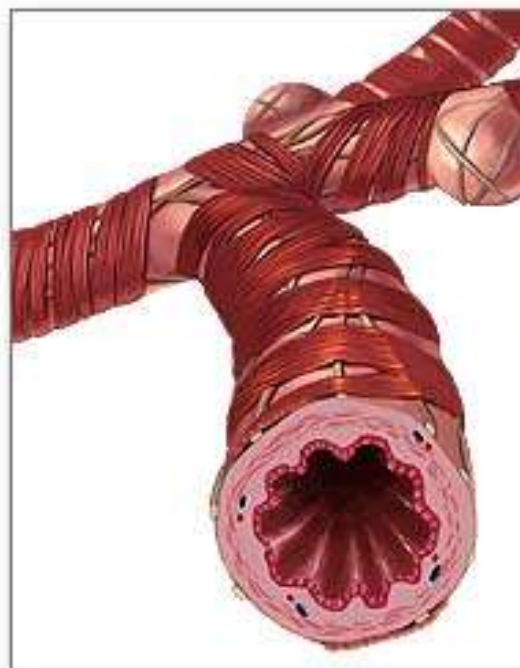


Figure 1 Th2 and Th17 allergen responses in the asthmatic airway. Upon allergen presentation to Th0 cells by antigen-presenting cells (APC), Th cells differentiate into Th2 cells in the presence of IL-4, and Th17 cells in the presence of IL-23. Th2 cells then go on to produce IL-4, IL-5, and IL-13-activating B cells to release IgE which attaches to the surface of mast cells. When stimulated by antigen, mast cells release histamine, prostaglandins, and leukotrienes resulting in smooth muscle bronchoconstriction, airway inflammation, and mucous hypersecretion. Eosinophils activated by IL-5 produce cysteinyl leukotrienes and reactive oxygen species (ROS), which act in a similar manner on the airways, and additionally contribute to oxidative stress. Th17 cells producing IL-17 act on airway epithelial cells to stimulate the release of multiple factors.

These factors include macrophage chemoattractant protein-1 (MCP-1) which recruits macrophages, IL-5, regulated on activation, normal T cell expressed and secreted (RANTES), and GM-CSF (granulocyte-macrophage colony-stimulating factor) which activate eosinophils, IL-8 which mobilizes neutrophils, stem cell factor (SCF) which works to promote mast cell survival, and IL-25 which induces myeloid cells to release Th2-type cytokines. Neutrophils release matrix metalloproteinase 9 (MMP9), elastase, leukotriene B4, and platelet-activating factor (PAF), which work to enhance the activity of eosinophils. Activated macrophages release IL-1, tumor necrosis factor alpha (TNF- α), and IL-6 which interact with other inflammatory cells and result in a positive feedback loop with airway epithelial cells.



Normal bronchiole

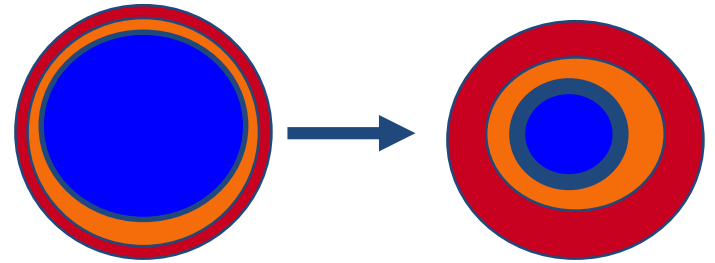


Asthmatic bronchiole



Pathogenesis of BA

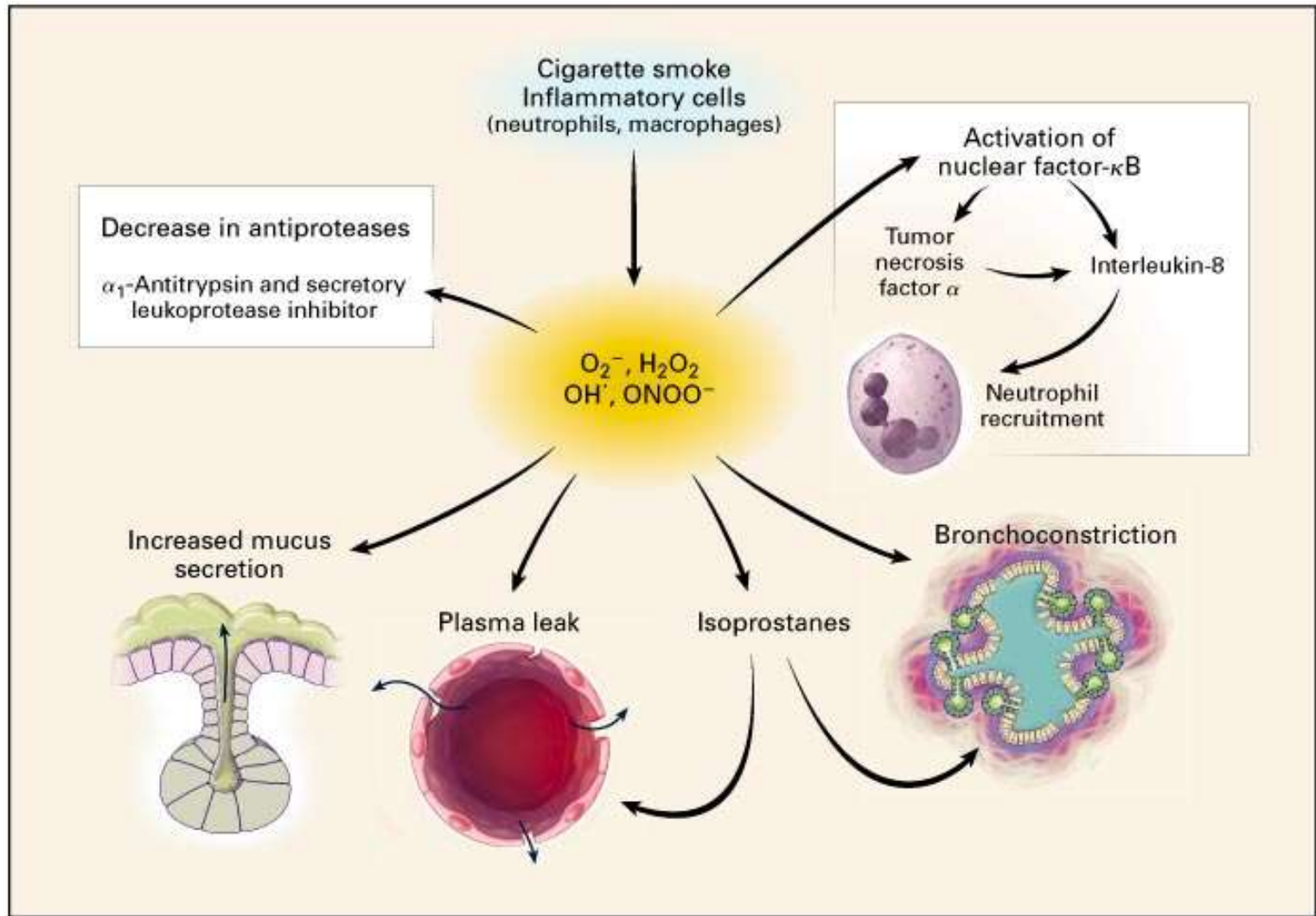
- Eozinophil inflammation
- Bronchoconstriction
- Edema of mucous membranes (plasma leakage, vasodilation)
- Hypersecretion of mucus
- Activation of senzoric nerve endings (cough, cholinergic reflexes)
- **Remodeling** of lung parenchyma (fibrosis, smooth muscle hypertrophy, more vessels and cells)
- Symptomatology – based on pathogenesis



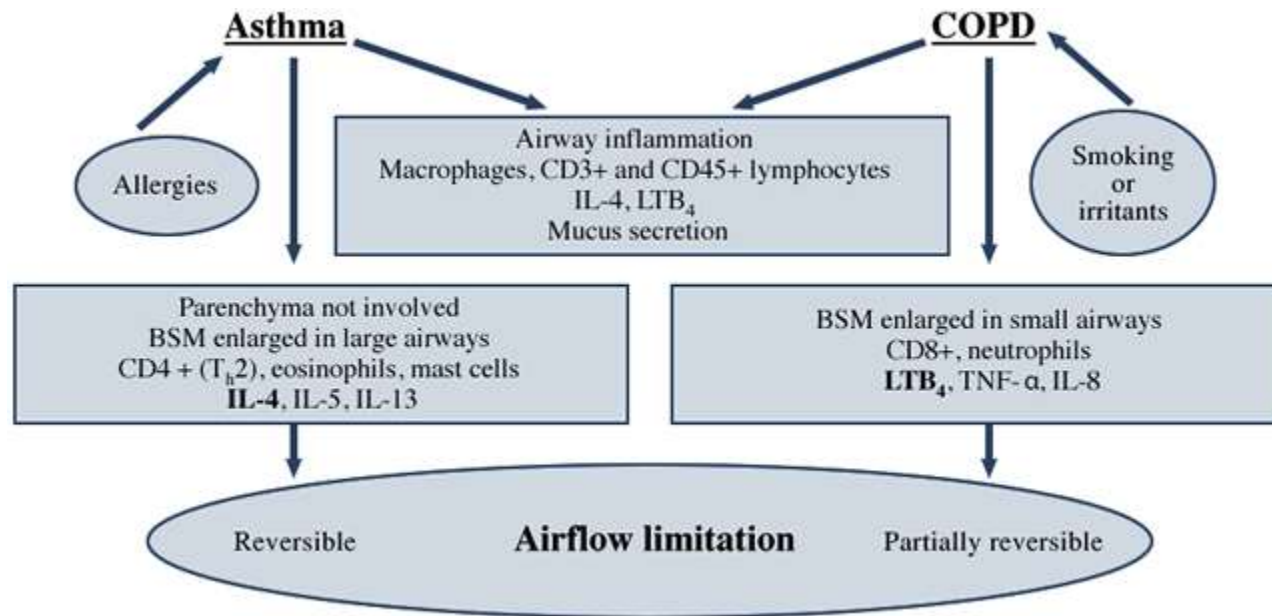
Definition of COPD

COPD is disease characterised by **limitation of air flow through airways**, which is **not completely reversible**. The limitation of air flow has usually **progressive character** and is associated with **inflammatory reaction** of lungs to various particules or gases.

Pathogenesis of COPD



Pathologic Changes and Inflammatory Mediators in Asthma and COPD



BSM, bronchial smooth muscle; CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; IL, interleukin; LTB₄, leukotriene B₄; Th, T helper; TNF-α, tumor necrosis factor-α.



Differences between COPD and BA

	ASTHMA	COPD
Prevalence	5-10%	>10%
Inflammation	eozinophiles	neutrophiles
Causal Th	hyposenzibilization	??? stop smoking
Smoking	No?	Yes
Symptomatic Th	bronchodilators	bronchodilators
Prognosis	stabilization, healing	progression
Disease onset	rapid	progressive
Reversibility of obstruc.	over 15%	No or small
Hyperreactivity	always	sometimes

Classification of BA

- 1. level - Mild **intermittent** asthma
- 2. level - Mild **persistent** asthma
- 3. level - Moderate **persistent** asthma
- 4. level - Severe **persistent** asthma

Clinical classification of BA

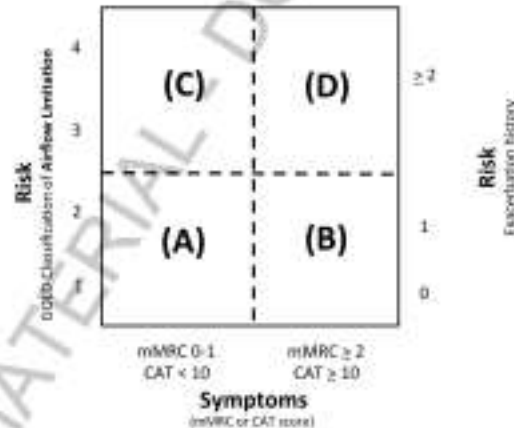
Clinical classification (≥ 12 years old)					
Severity	Symptom frequency	Night time symptoms	%FEV ₁ of predicted	FEV ₁ Variability	SABA use
Intermittent	$\leq 2/\text{week}$	$\leq 2/\text{month}$	$\geq 80\%$	$< 20\%$	≤ 2 days/week
Mild persistent	$> 2/\text{week}$	3–4/month	$\geq 80\%$	20–30%	> 2 days/week
Moderate persistent	Daily	$> 1/\text{week}$	60–80%	$> 30\%$	daily
Severe persistent	Continuousl y	Frequent (7 \times /week)	$< 60\%$	$> 30\%$	\geq twice/day

Figure 2. Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV₁

Stage I: Mild	FEV ₁ /FVC < 0.70 FEV ₁ ≥ 80% predicted
Stage II: Moderate	FEV ₁ /FVC < 0.70 50% ≤ FEV ₁ < 80% predicted
Stage III: Severe	FEV ₁ /FVC < 0.70 30% ≤ FEV ₁ < 50% predicted
Stage IV: Very Severe	FEV ₁ /FVC < 0.70 FEV ₁ < 30% predicted <i>or</i> FEV ₁ < 50% predicted plus chronic respiratory failure

Table 4. Combined Assessment of COPD

(When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.)



Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

mMRC – modified Medical Research Council dyspnoea scale; **CAT** – COPD Assessment Test

Vaše meno:

Dnešný dátum:



Ako by ste popísali vašu chronickú obštrukčnú chorobu pľúc (CHOCHP)? Vyplňte test vyhodnotenia CHOCHP (COPD Assessment Test™) (CAT)

Tento dotazník pomôže vám a profesionálnemu zdravotníkovi posúdiť vplyv CHOCHP (chronická obštrukčná choroba pľúc) na vaše zdravie a každodenný život. Vaše odpovede a hodnotenie testu môžete vy a profesionálny zdravotník použiť na zlepšenie manažmentu choroby CHOCHP a získanie čo možno najväčšieho prínosu z liečby CHOCHP.

Príklad: Som veľmi šťastný/á

☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Som veľmi smutný/á

Nikdy nekašlem

☐ 0 ☐ 1 ☒ 2 ☐ 3 ☐ 4 ☐ 5

Stále kašlem

V hrudníku nemám vôbec hlien

☐ 0 ☐ 1 ☒ 2 ☐ 3 ☐ 4 ☐ 5

hlien Hrudník mám celkom plný hlienu

Vôbec nepociťujem tlak na hrudníku

☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Pociťujem výrazný tlak na hrudníku

Po zdolaní kopca alebo jedného poschodia nie som zadychčaný/á

☒ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Po zdolaní kopca alebo jedného poschodia som veľmi zadychčaný/á

Moja činnosť v domácnosti nie je vôbec obmedzená

☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Moja činnosť v domácnosti je veľmi obmedzená

Aj napriek stavu pľúc s istotou vychádzam von z domova

☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

V dôsledku stavu pľúc nemám vôbec istotu vyjsť z domova

Spím hlbokým spánkom

☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Nespím hlbokým spánkom v dôsledku stavu mojich pľúc

Mám veľa energie

☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Nemám vôbec žiadnu energiu

VÝSLEDOK

2

2

1

0

1

1

1

1

9

COPD Assessment Test a logo CAT je ochranná známka skupiny spoločností GlaxoSmithKline.
©2009 skupina spoločností GlaxoSmithKline. Všetky práva vyhradené.

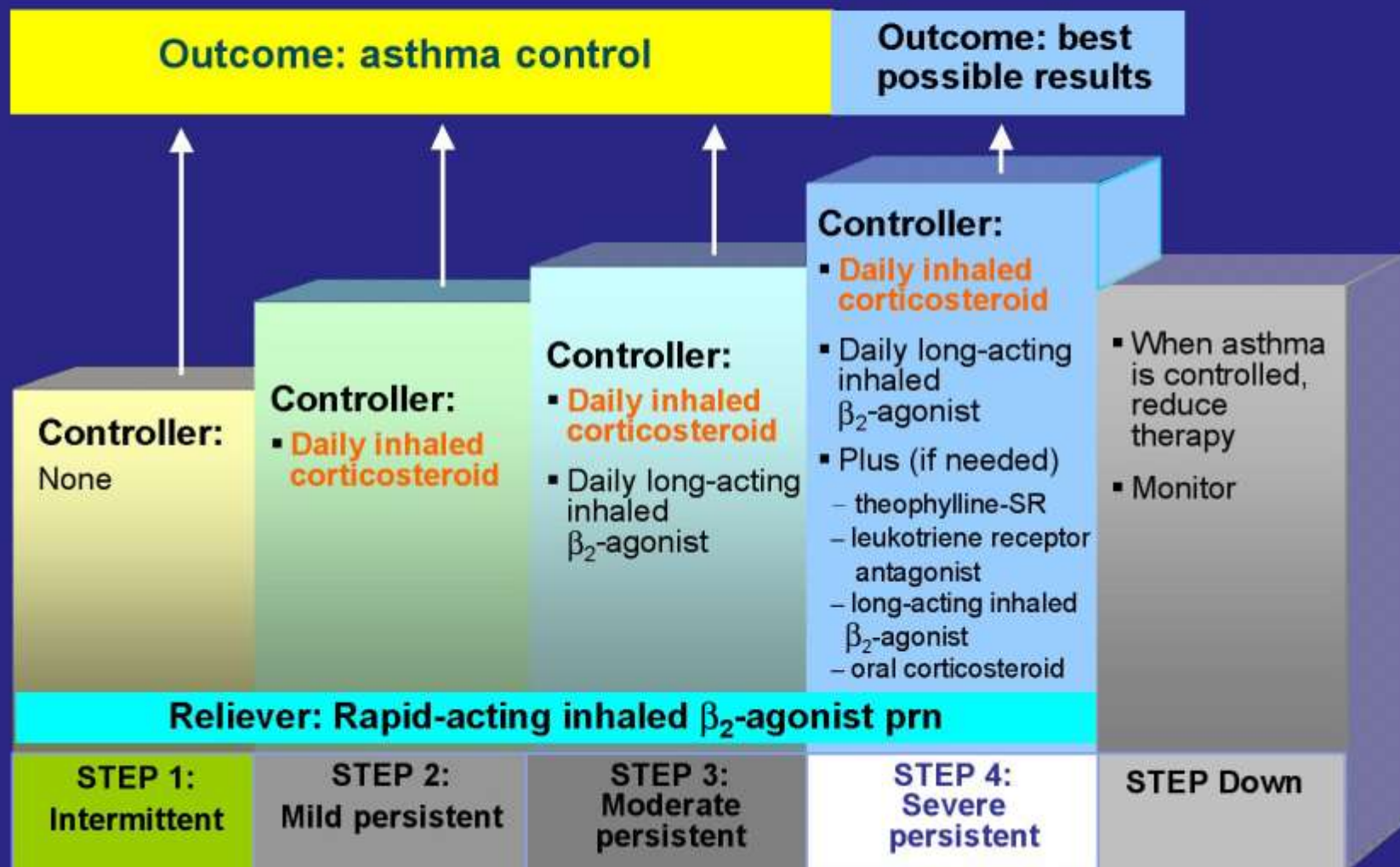
Kliknutím zobrazíte celkové skóre

Therapy of BA



- **Diagnostics**
- Regular examinations and **monitoring**
- Depistage and control of **worsening factors**
- **Long-term pharmacological treatment**
- **Management of asthma exacerbations**
- **Education** and leading of asthamtic patients to partnership in treatment

GINA stepwise approach to asthma therapy in adults



LEVEL OF CONTROL

TREATMENT OF ACTION

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

REDUCE

INCREASE

TREATMENT STEPS

STEP

1

STEP

2

STEP

3

STEP

4

STEP

5

REDUCE		TREATMENT STEPS				INCREASE		
		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5		
		asthma education						
		environmental control						
		as needed rapid-acting β_2 -agonist	as needed rapid-acting β_2 -agonist					
CONTROLLER OPTIONS		SELECT ONE	SELECT ONE	TO STEP 3 TREATMENT, SELECT ONE OR MORE		TO STEP 4 TREATMENT, ADD EITHER		
		low-dose ICS*	low-dose ICS <i>plus</i> long-acting β_2 -agonist	medium- <i>or</i> high-dose ICS <i>plus</i> long-acting β_2 -agonist		oral glucocorticosteroid (lowest dose)		
		leukotriene modifier**	medium- <i>or</i> high-dose ICS	leukotriene modifier		anti-IgE treatment		
			low-dose ICS <i>plus</i> leukotriene modifier	sustained-release theophylline				
			low-dose ICS <i>plus</i> sustained-release theophylline					

*inhaled glucocorticosteroids

** receptor antagonist or synthesis inhibitors

© Global Initiative for Asthma

Shaded green - preferred controller options

Therapy of acute symptoms in AB

„Relievers“ (rescuing drugs)

- Short-acting β_2 -sympatomimetics (β_2 -agonists) - SABA

Muscarinic antagonists (anticholinergics, antimuscarinics) - SAMA

- Systemic corticoisteroids in a rescue dose
- Theophylline???

Long-term pharmacological treatment

Controllers (preventive drugs)

- Inhalative and systemic corticoids
- Cromones
- Long-acting β_2 -sympatomimetics (β_2 -agonists) - LABA
- Theophyllines with sustained release
- Antileukotriens (LT modifiers)
- Omalizumab (antibodies against IgE)

Initial controller treatment for adults, adolescents and children 6–11 years

- Start controller treatment early
 - For best outcomes, initiate controller treatment as early as possible after making the diagnosis of asthma
- Indications for regular low-dose ICS - any of:
 - Asthma symptoms more than twice a month
 - Waking due to asthma more than once a month
 - Any asthma symptoms plus any risk factors for exacerbations
- Consider starting at a higher step if:
 - Troublesome asthma symptoms on most days
 - Waking from asthma once or more a week, especially if any risk factors for exacerbations
- If initial asthma presentation is with an exacerbation:
 - Give a short course of oral steroids and start regular controller treatment (e.g. high dose ICS or medium dose ICS/LABA, then step down)



NEW!

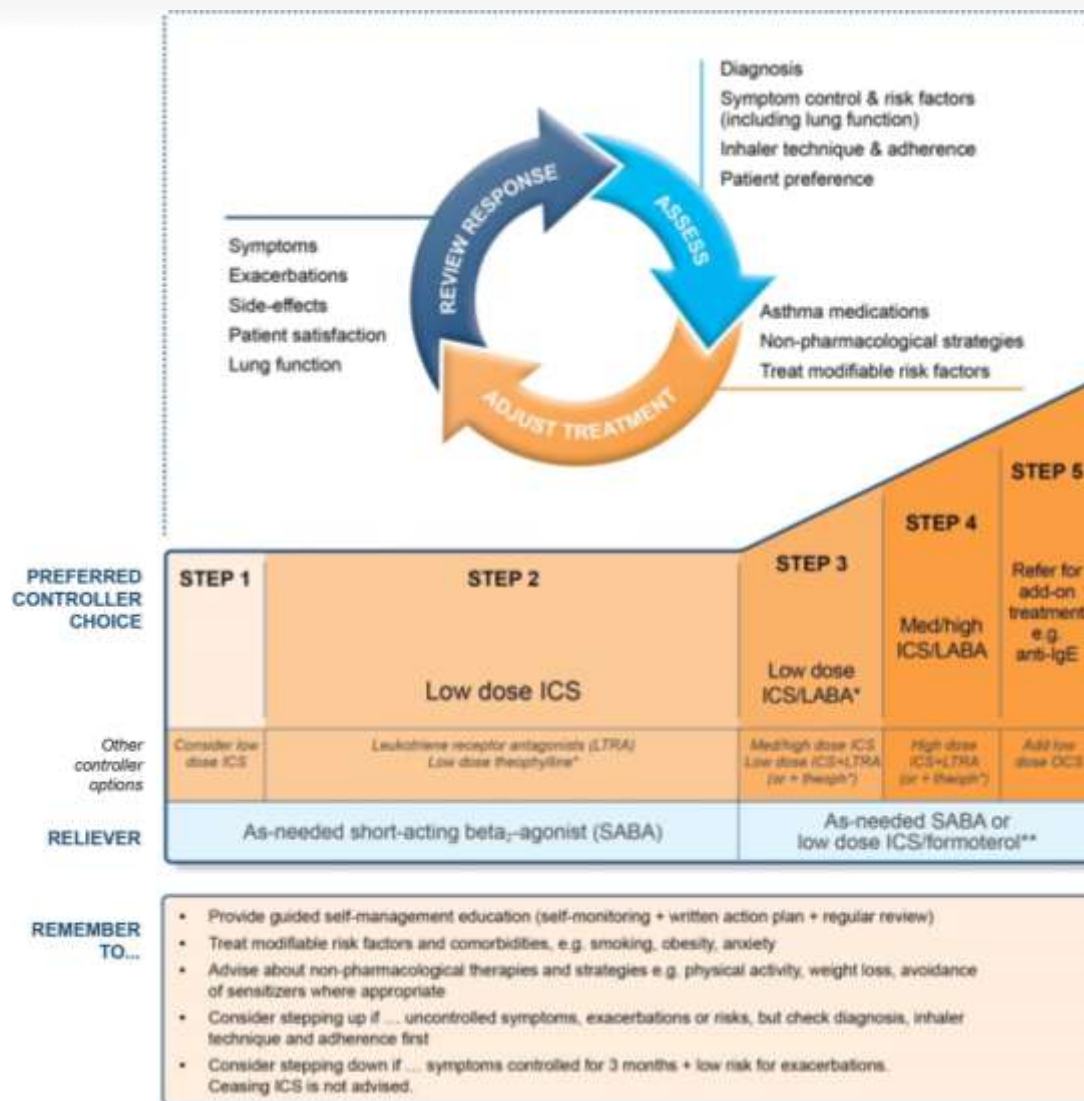
Initial controller treatment

- Before starting initial controller treatment
 - Record evidence for diagnosis of asthma, if possible
 - Record symptom control and risk factors, including lung function
 - Consider factors affecting choice of treatment for this patient
 - Ensure that the patient can use the inhaler correctly
 - Schedule an appointment for a follow-up visit
- After starting initial controller treatment
 - Review response after 2-3 months, or according to clinical urgency
 - Adjust treatment (including non-pharmacological treatments)
 - Consider stepping down when asthma has been well-controlled for 3 months



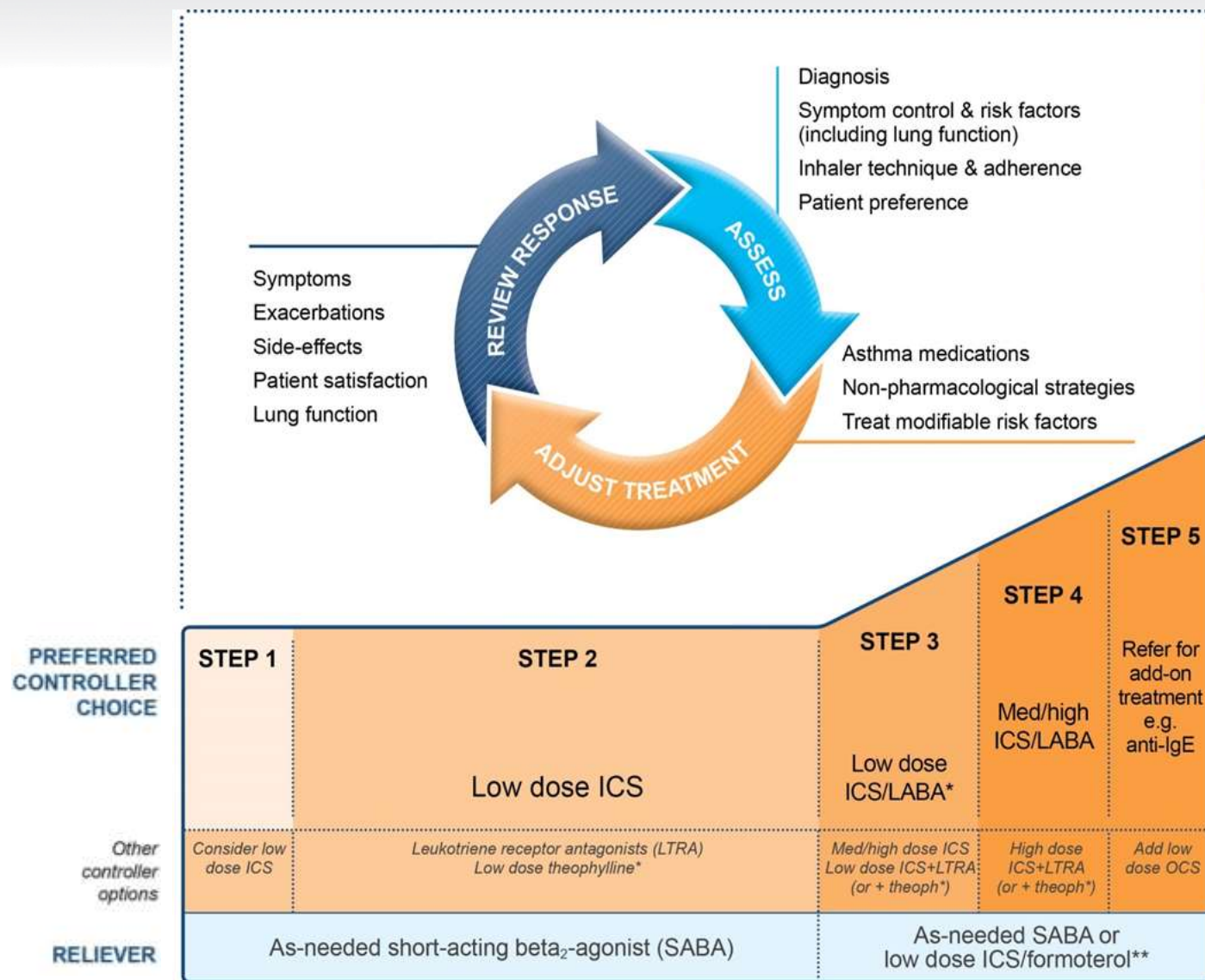
NEW!

Stepwise approach to control asthma symptoms and reduce risk



NEW!

Stepwise management - pharmacotherapy



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

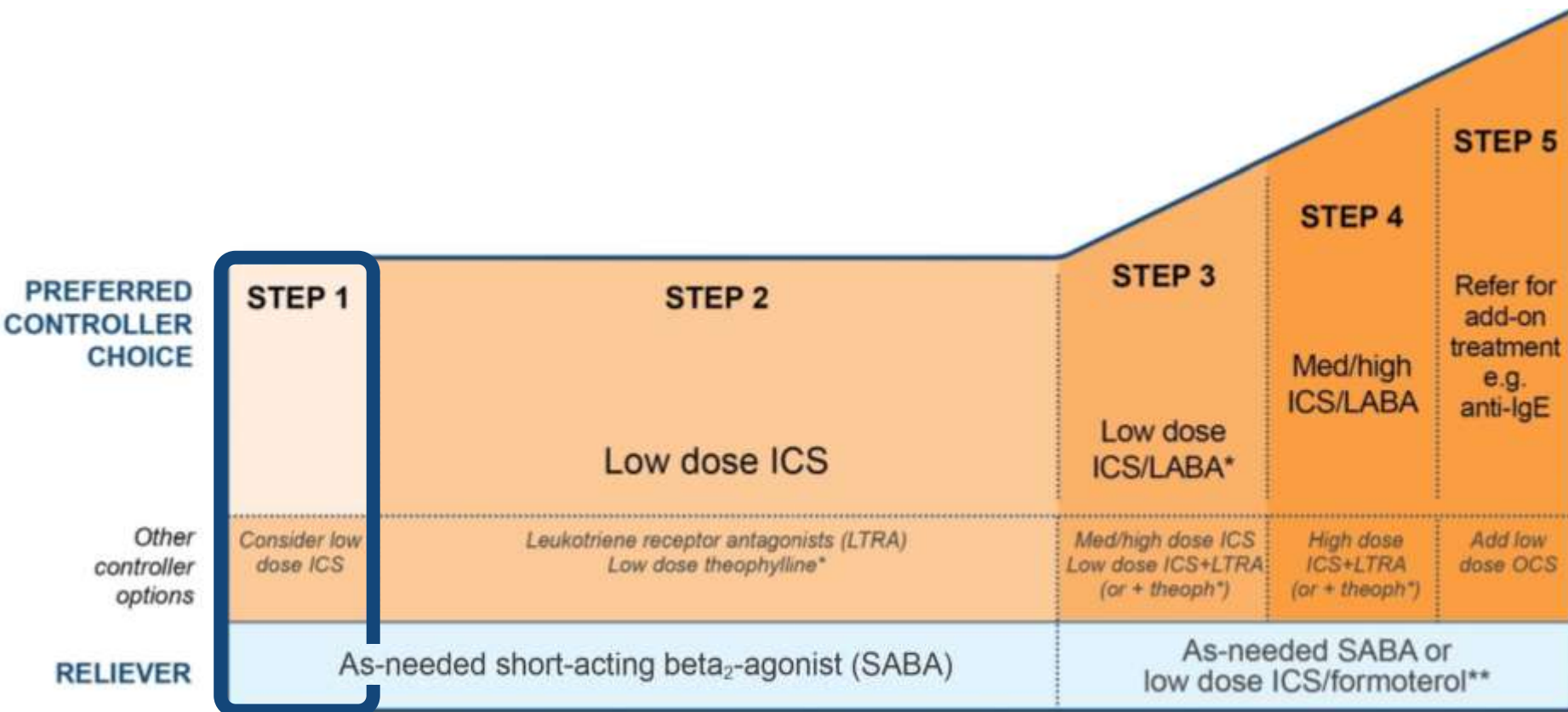
Stepwise management – additional components



REMEMBER TO...

- Provide guided self-management education
- Treat modifiable risk factors and comorbidities
- Advise about non-pharmacological therapies and strategies
- Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider stepping down if ... symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

Step 1 – as-needed inhaled short-acting beta₂-agonist (SABA)



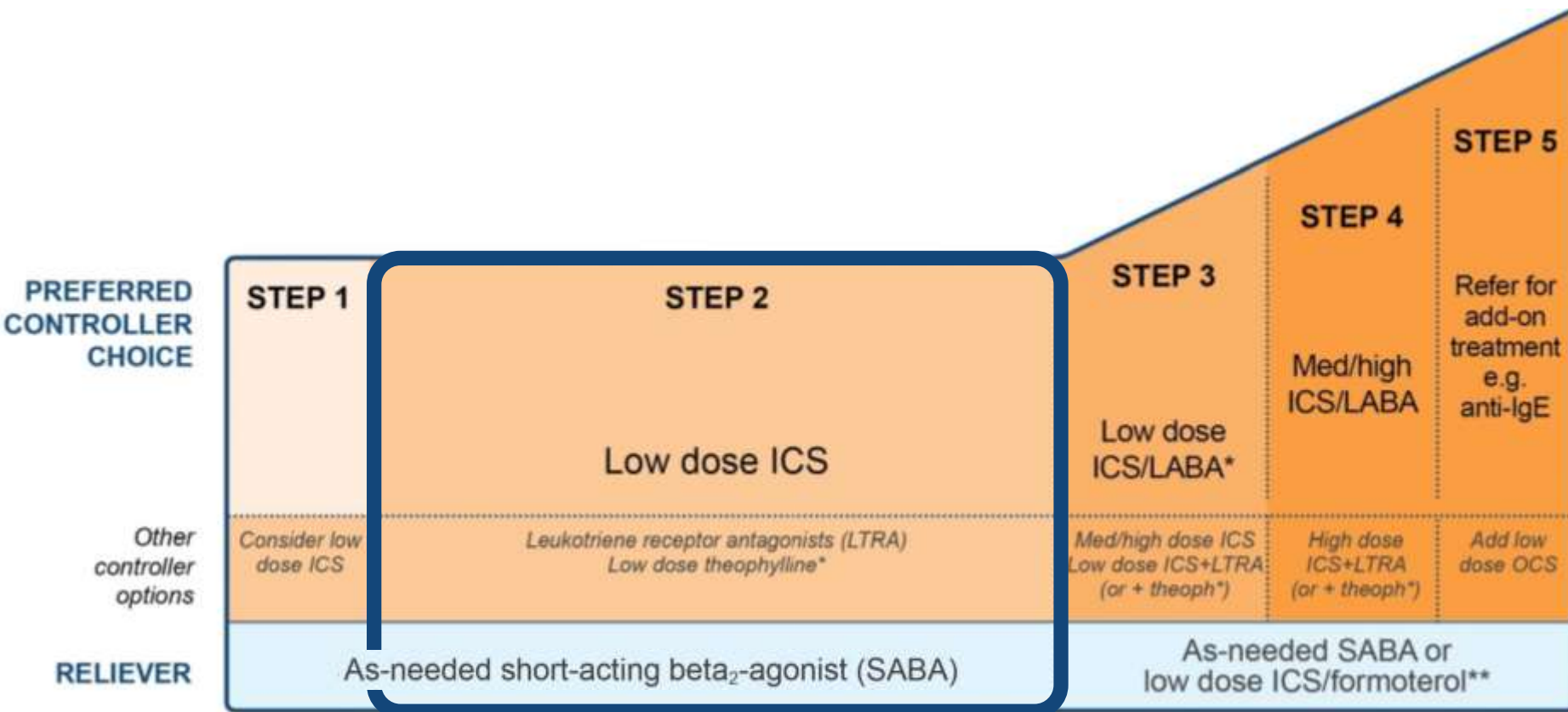
*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Step 1 – as-needed reliever inhaler

- Preferred option: as-needed inhaled short-acting beta₂-agonist (SABA)
 - SABAs are highly effective for relief of asthma symptoms
 - However there is insufficient evidence about the safety of treating asthma with SABA alone
 - This option should be reserved for patients with infrequent symptoms (less than twice a month) of short duration, and with no risk factors for exacerbations
- Other options
 - Consider adding regular low dose inhaled corticosteroid (ICS) for patients at risk of exacerbations

Step 2 – low-dose controller + as-needed inhaled SABA



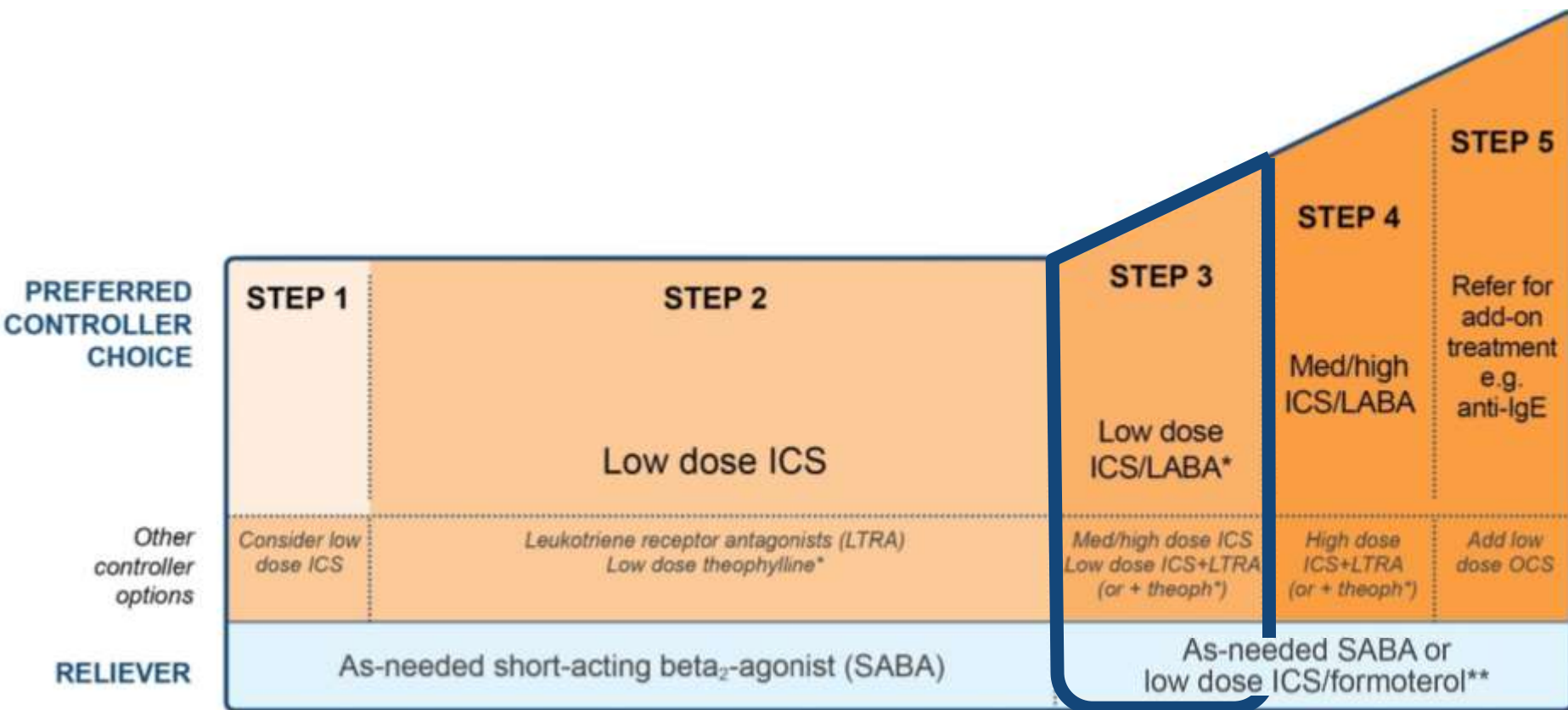
*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Step 2 – Low dose controller + as-needed SABA

- Preferred option: regular low dose ICS with as-needed inhaled SABA
 - Low dose ICS reduces symptoms and reduces risk of exacerbations and asthma-related hospitalization and death
- Other options
 - Leukotriene receptor antagonists (LTRA) with as-needed SABA
 - Less effective than low dose ICS
 - May be used for some patients with both asthma and allergic rhinitis, or if patient will not use ICS
 - Combination low dose ICS/long-acting beta2-agonist (LABA) with as-needed SABA
 - Reduces symptoms and increases lung function compared with ICS
 - More expensive, and does not further reduce exacerbations
 - Intermittent ICS with as-needed SABA for purely seasonal allergic asthma with no interval symptoms
 - Start ICS immediately symptoms commence, and continue for 4 weeks after pollen season ends

Step 3 – one or two controllers + as-needed inhaled reliever



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

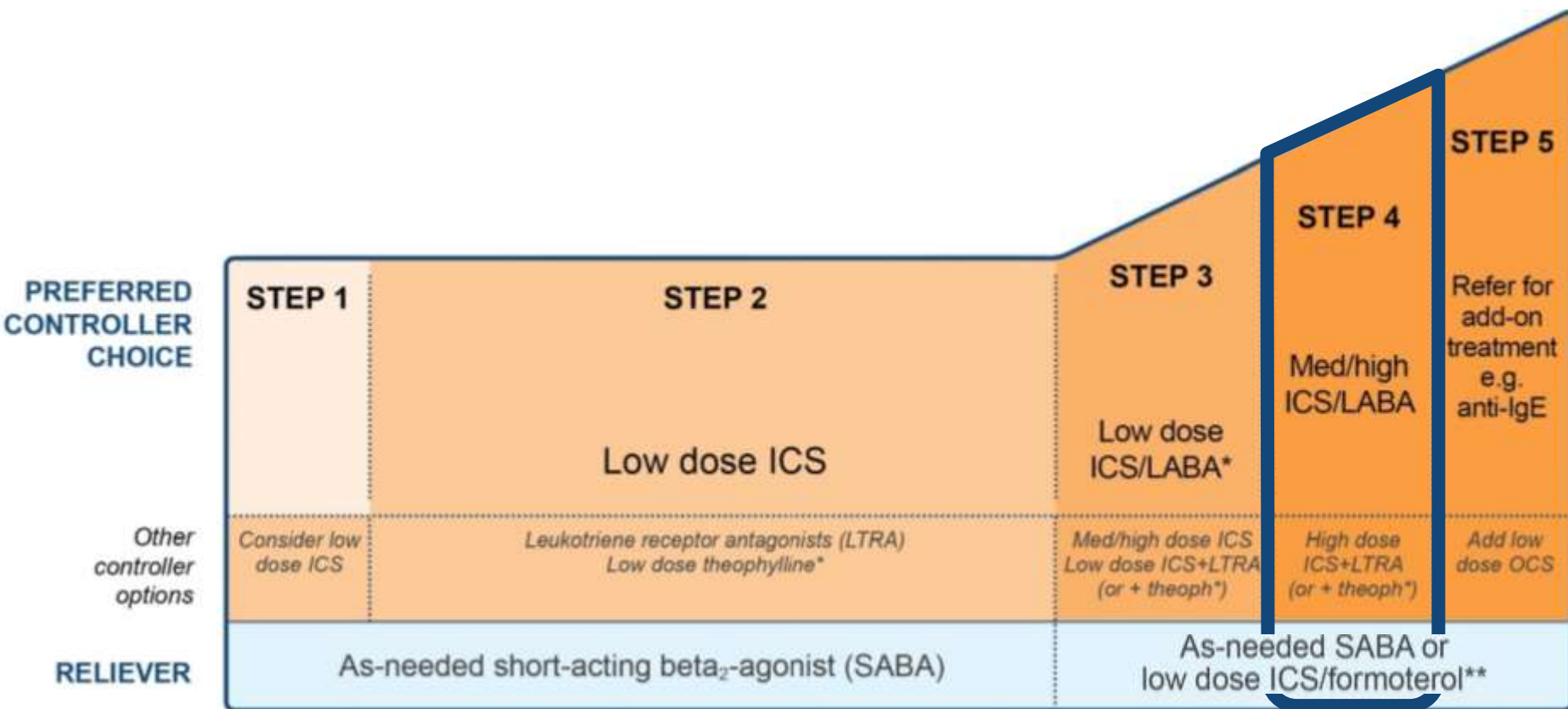
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Step 3 – one or two controllers + as-needed inhaled reliever

- Before considering step-up
 - Check inhaler technique and adherence, confirm diagnosis
- Adults/adolescents: preferred options are either combination low dose ICS/LABA maintenance with as-needed SABA, OR combination low dose ICS/formoterol maintenance and reliever regimen*
 - Adding LABA reduces symptoms and exacerbations and increases FEV₁, while allowing lower dose of ICS
 - In at-risk patients, maintenance and reliever regimen significantly reduces exacerbations with similar level of symptom control and lower ICS doses compared with other regimens
- Children 6-11 years: preferred option is medium dose ICS with as-needed SABA
- Other options
 - Adults/adolescents: Increase ICS dose or add LTRA or theophylline (less effective than ICS/LABA)
 - Children 6-11 years – add LABA (similar effect as increasing ICS)

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Step 4 – two or more controllers + as-needed inhaled reliever



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

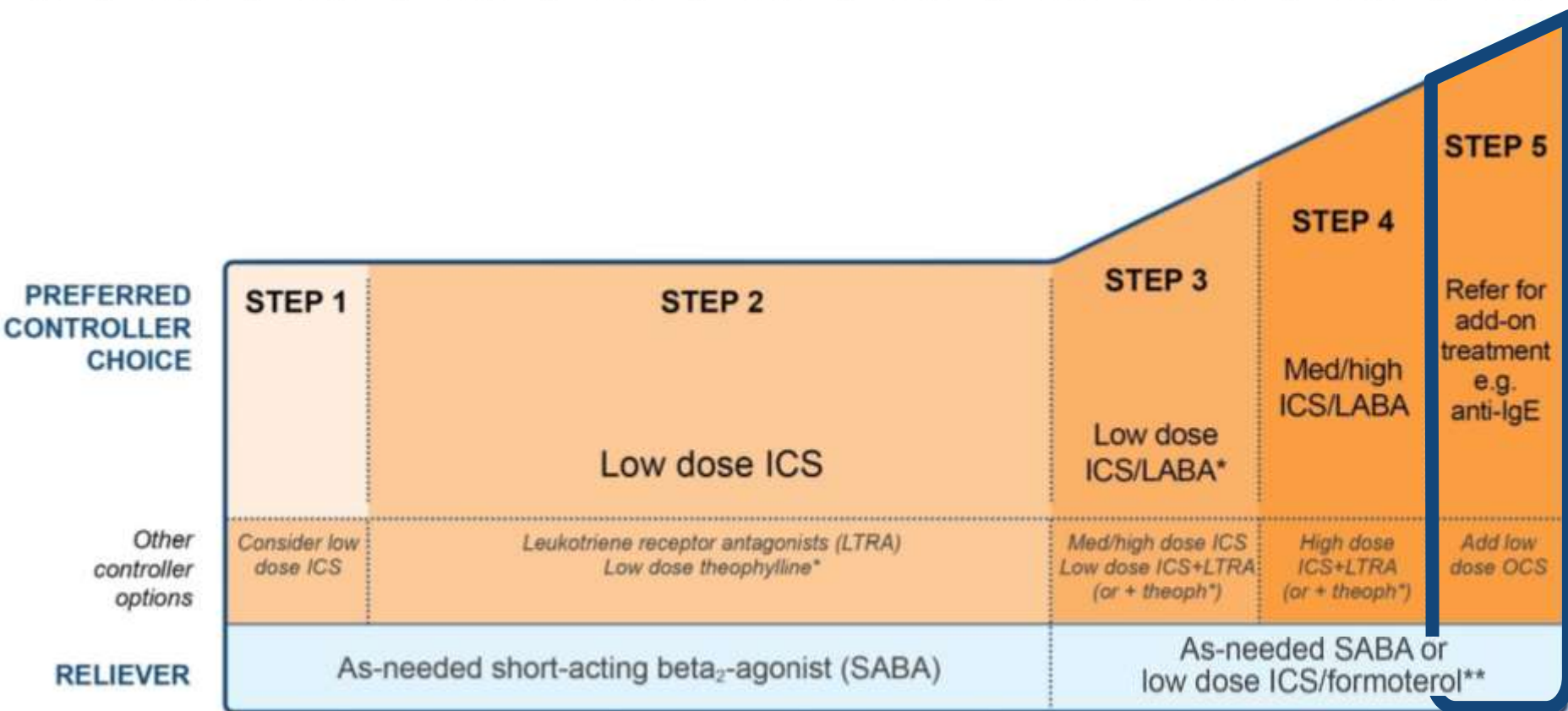
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Step 4 – two or more controllers + as-needed inhaled reliever

- Before considering step-up
 - Check inhaler technique and adherence
- Adults or adolescents: preferred option is combination low dose ICS/formoterol as maintenance and reliever regimen*, OR combination medium dose ICS/LABA with as-needed SABA
- Children 6–11 years: preferred option is to refer for expert advice
- Other options (adults or adolescents)
 - Trial of high dose combination ICS/LABA, but little extra benefit and increased risk of side-effects
 - Increase dosing frequency (for budesonide-containing inhalers)
 - Add-on LTRA or low dose theophylline

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Step 5 – higher level care and/or add-on treatment



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS

**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Step 5 – higher level care and/or add-on treatment

- Preferred option is referral for specialist investigation and consideration of add-on treatment
 - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
 - Add-on omalizumab (anti-IgE) is suggested for patients with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment
- Other add-on treatment options at Step 5 include:
 - Sputum-guided treatment: this is available in specialized centers; reduces exacerbations and/or corticosteroid dose
 - Add-on low dose oral corticosteroids (≤ 7.5 mg/day prednisone equivalent): this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis
 - See Severe Asthma Guidelines (Chung et al, ERJ 2014) for more detail

Low, medium and high dose inhaled corticosteroids

Adults and adolescents (≥ 12 years)

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

Low, medium and high dose inhaled corticosteroids

Children 6–11 years

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebulas)	250–500	>500–1000	>1000
Ciclesonide (HFA)	80	>80–160	>160
Fluticasone propionate (DPI)	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–200	>200–500	>500
Mometasone furoate	110	≥220–<440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

Reviewing response and adjusting treatment



- How often should asthma be reviewed?
 - 1-3 months after treatment started, then every 3-12 months
 - During pregnancy, every 4-6 weeks
 - After an exacerbation, within 1 week
- Stepping up asthma treatment
 - *Sustained step-up*, for at least 2-3 months if asthma poorly controlled
 - Important: first check for common causes (symptoms not due to asthma, incorrect inhaler technique, poor adherence)
 - *Short-term step-up*, for 1-2 weeks, e.g. with viral infection or allergen
 - May be initiated by patient with written asthma action plan
 - *Day-to-day adjustment*
 - For patients prescribed low-dose ICS/formoterol maintenance and reliever regimen*
- Stepping down asthma treatment
 - Consider step-down after good control maintained for 3 months
 - Find each patient's minimum effective dose, that controls both symptoms and exacerbations

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

General principles for stepping down controller treatment

- Aim
 - To find the lowest dose that controls symptoms and exacerbations, and minimizes the risk of side-effects
- When to consider stepping down
 - When symptoms have been well controlled and lung function stable for ≥ 3 months
 - No respiratory infection, patient not travelling, not pregnant
- Prepare for step-down
 - Record the level of symptom control and consider risk factors
 - Make sure the patient has a written asthma action plan
 - Book a follow-up visit in 1-3 months
- Step down through available formulations
 - Stepping down ICS doses by 25–50% at 3 month intervals is feasible and safe for most patients
 - See GINA 2014 report Box 3-7 for specific step-down options
- Stopping ICS is not recommended in adults with asthma

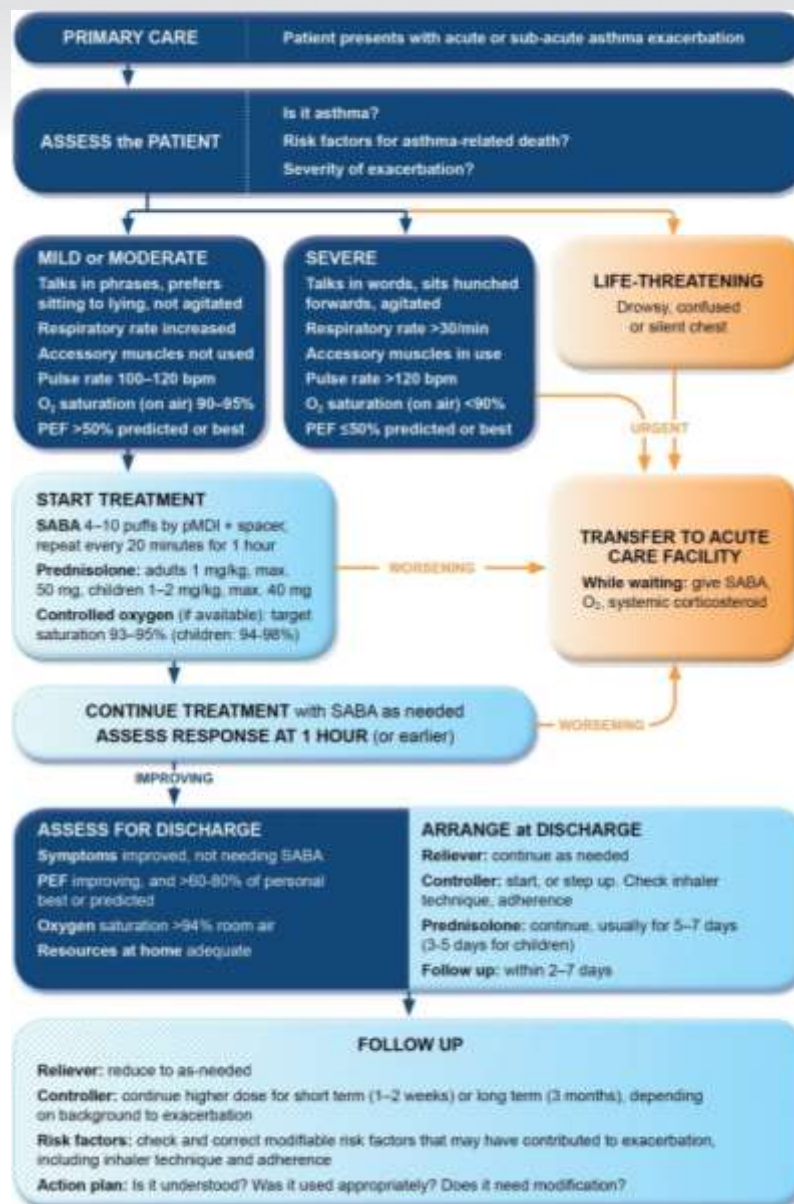


Treating modifiable risk factors

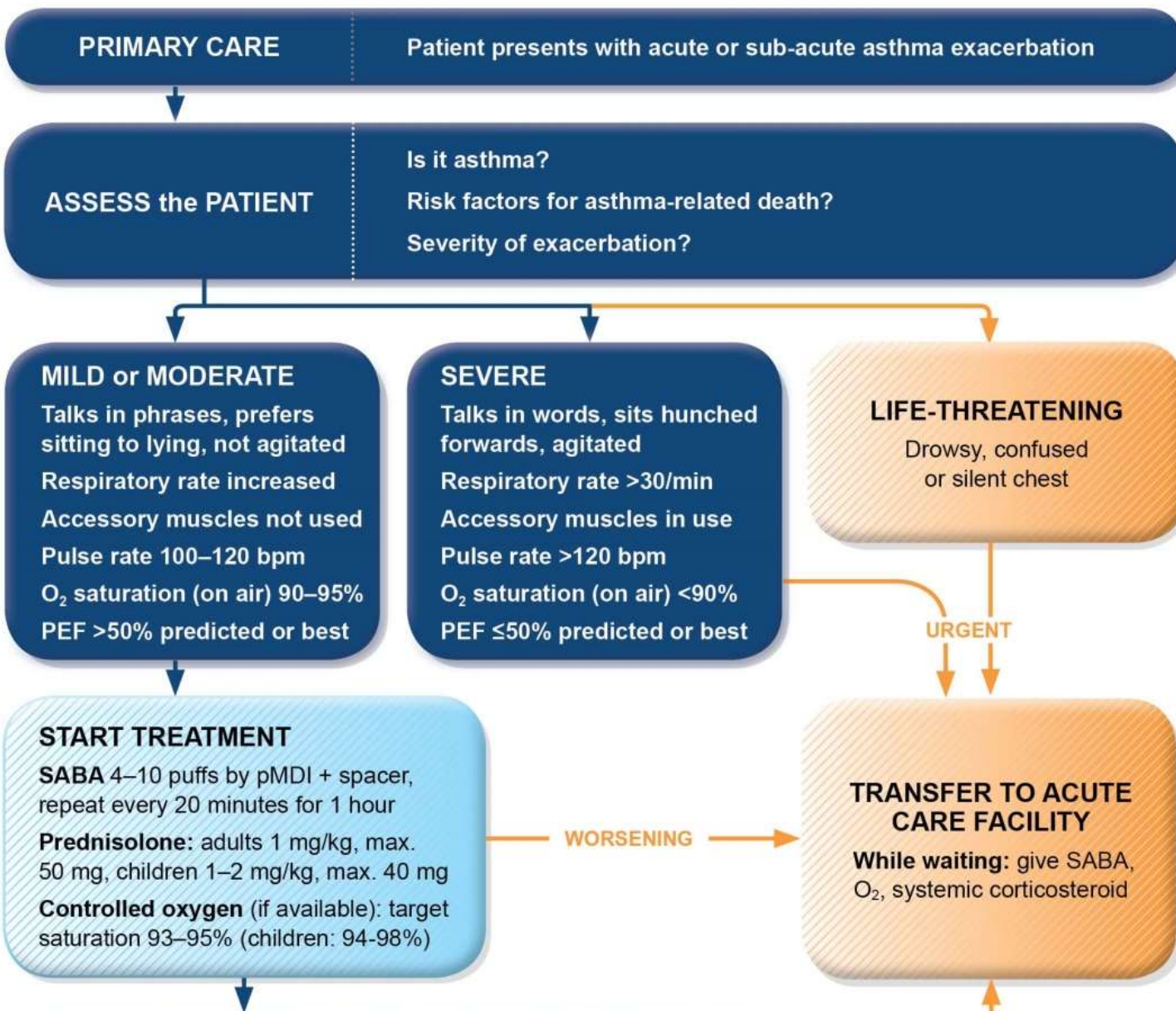
- Provide skills and support for guided asthma self-management
 - This comprises self-monitoring of symptoms and/or PEF, a written asthma action plan and regular medical review
- Prescribe medications or regimen that minimize exacerbations
 - ICS-containing controller medications reduce risk of exacerbations
 - For patients with ≥ 1 exacerbations in previous year, consider low-dose ICS/formoterol maintenance and reliever regimen*
- Encourage avoidance of tobacco smoke (active or ETS)
 - Provide smoking cessation advice and resources at every visit
- For patients with severe asthma
 - Refer to a specialist center, if available, for consideration of add-on medications and/or sputum-guided treatment
- For patients with confirmed food allergy:
 - Appropriate food avoidance
 - Ensure availability of injectable epinephrine for anaphylaxis

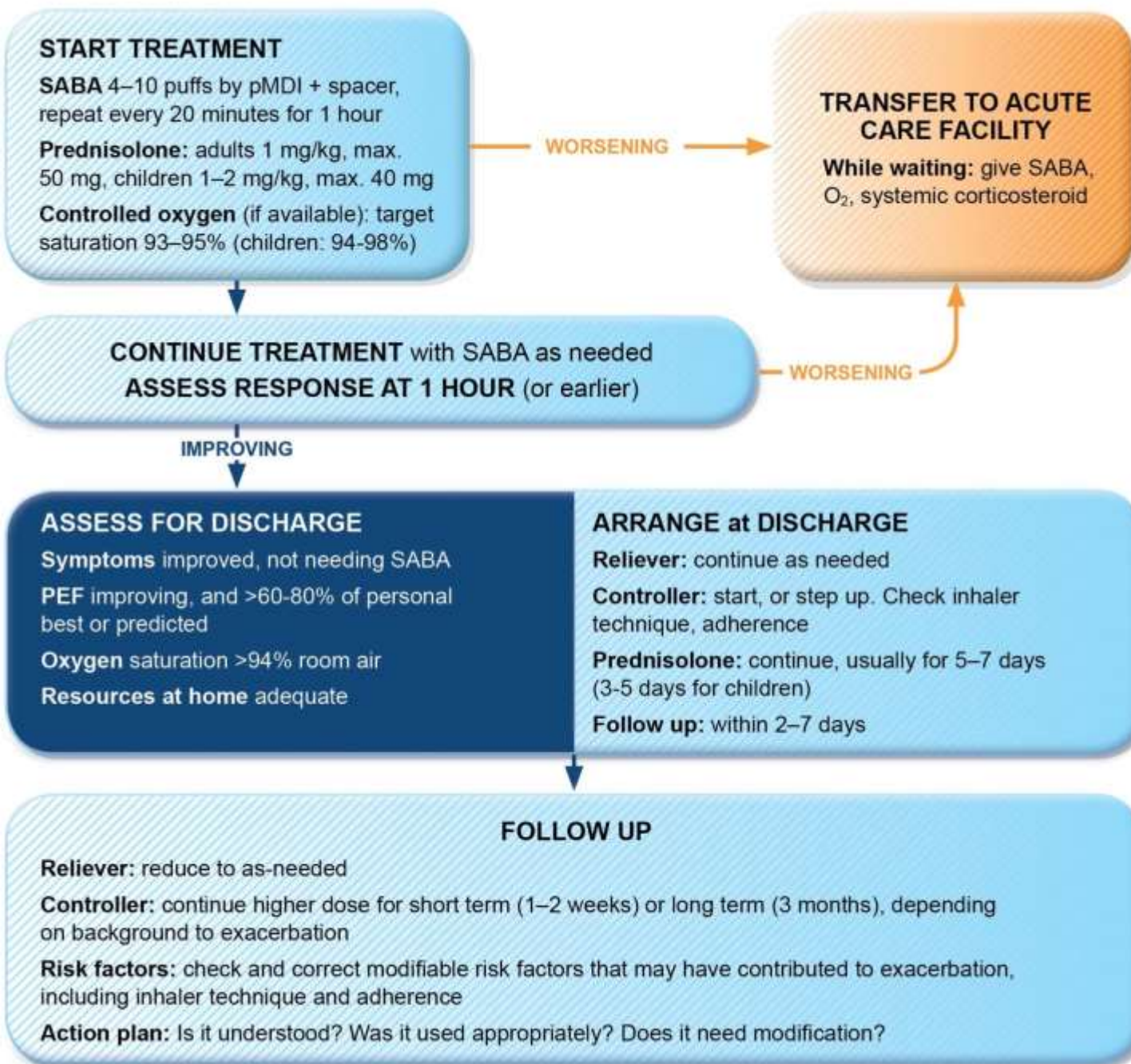
*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Managing exacerbations in primary care

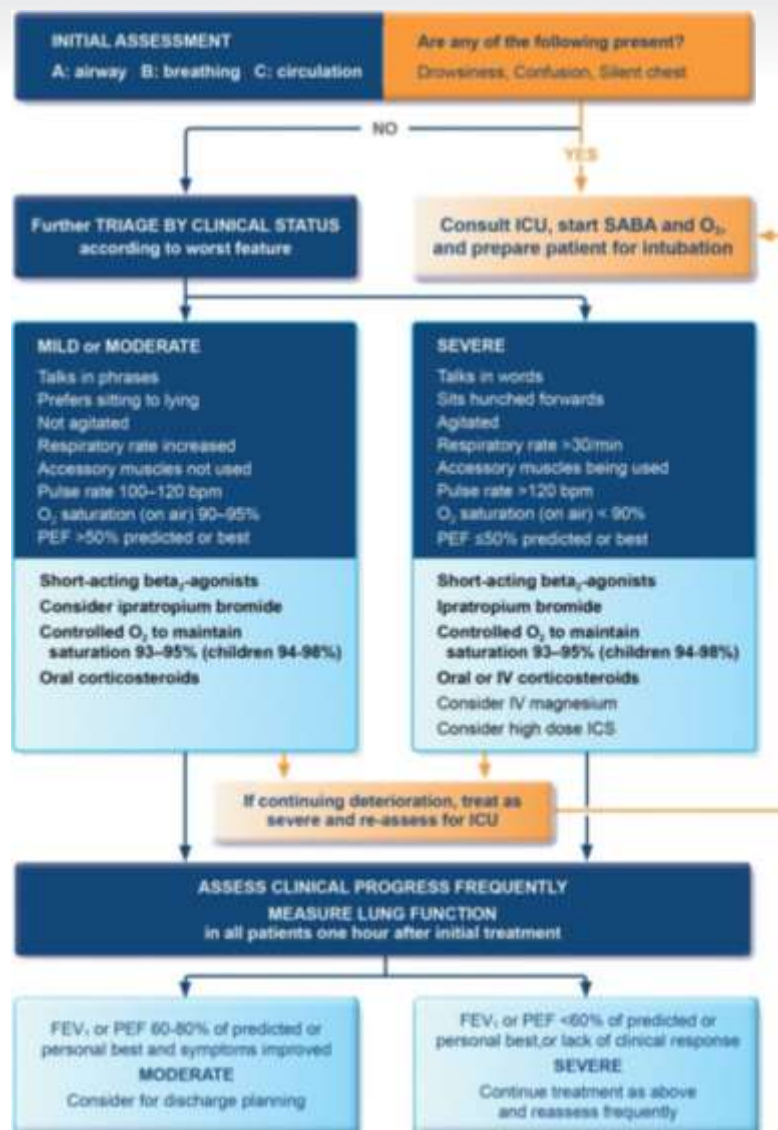


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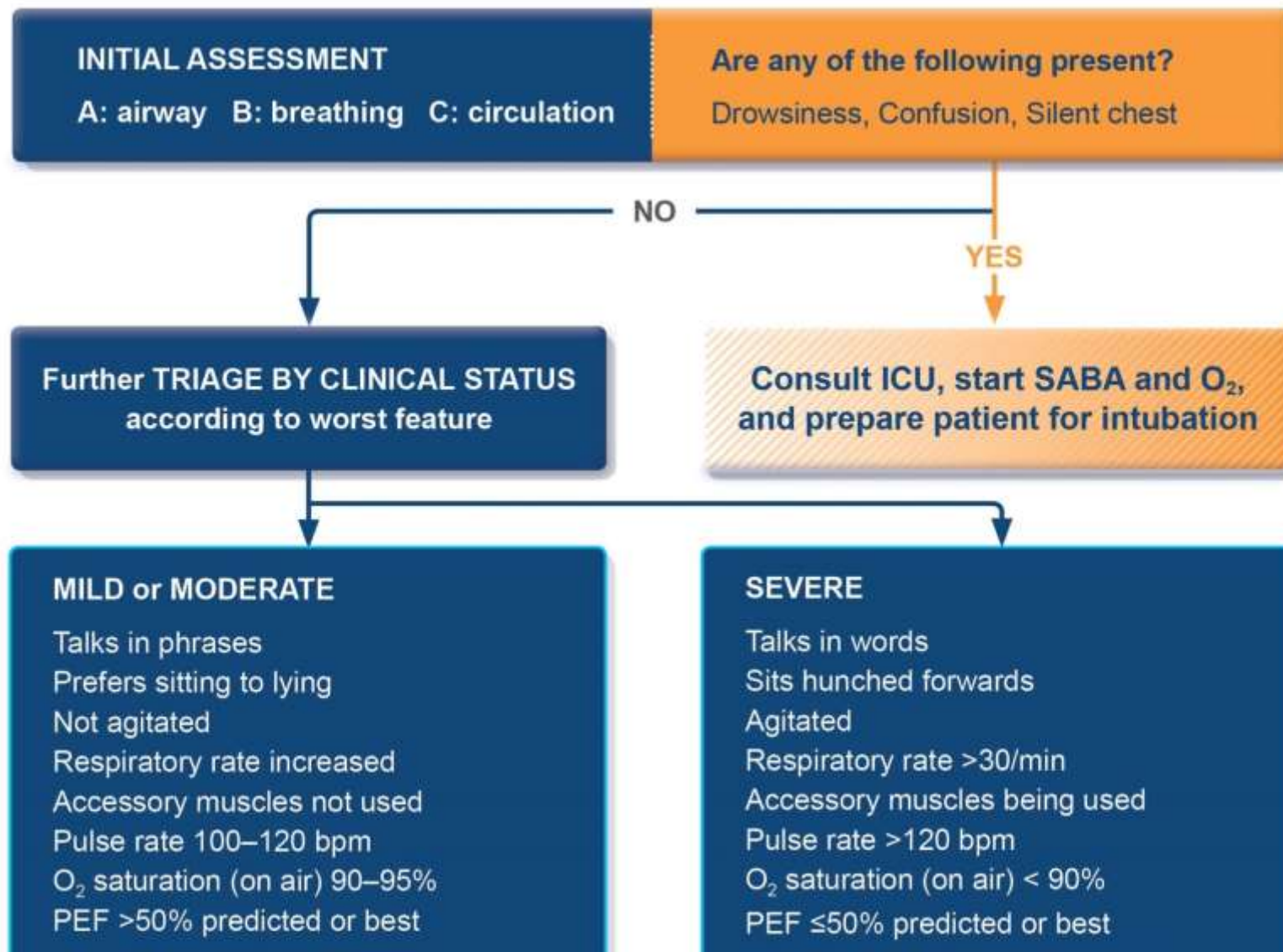




Managing exacerbations in acute care settings



NEW!



MILD or MODERATE

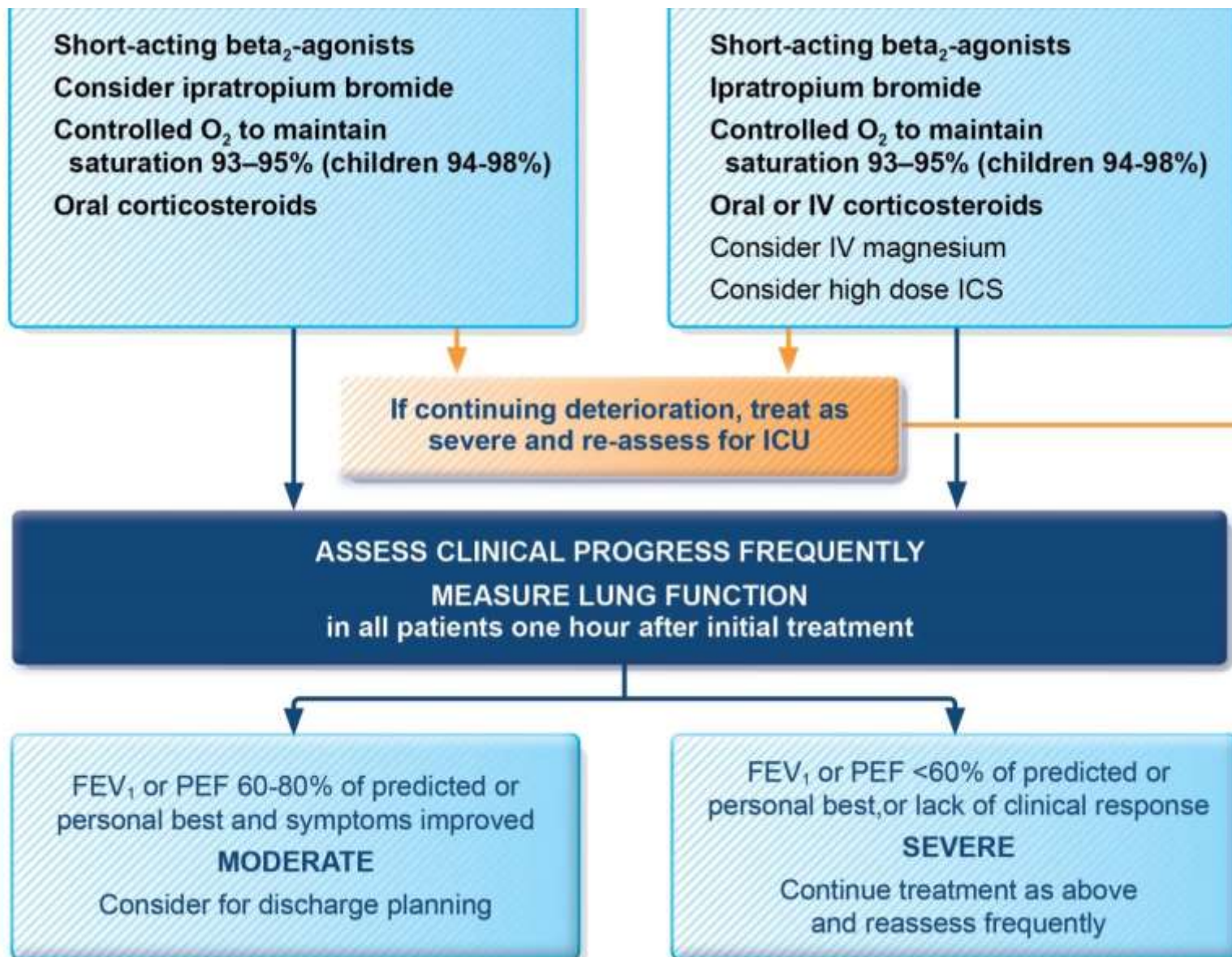
Talks in phrases
Prefers sitting to lying
Not agitated
Respiratory rate increased
Accessory muscles not used
Pulse rate 100–120 bpm
O₂ saturation (on air) 90–95%
PEF >50% predicted or best

Short-acting beta₂-agonists
Consider ipratropium bromide
Controlled O₂ to maintain
saturation 93–95% (children 94–98%)
Oral corticosteroids

SEVERE

Talks in words
Sits hunched forwards
Agitated
Respiratory rate >30/min
Accessory muscles being used
Pulse rate >120 bpm
O₂ saturation (on air) < 90%
PEF ≤50% predicted or best

Short-acting beta₂-agonists
Ipratropium bromide
Controlled O₂ to maintain
saturation 93–95% (children 94–98%)
Oral or IV corticosteroids
Consider IV magnesium
Consider high dose ICS

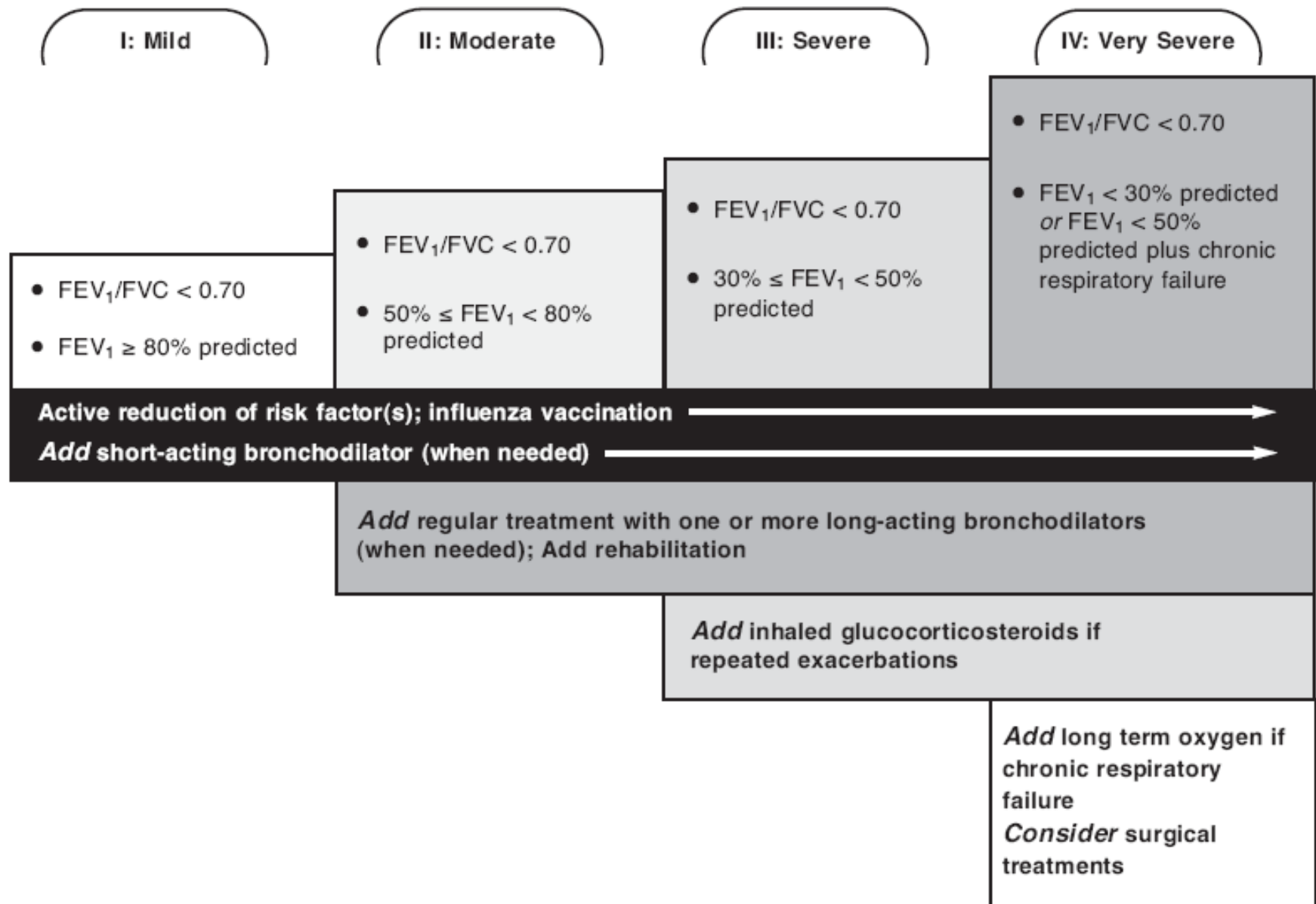


Management of COPD

- **Diagnostics** and disease monitoring
- **Reduction of risk factors**
- **Treatment of stable COPD**
- **Treatment of exacerbations**

Figure 7. Therapy at Each Stage of COPD

Postbronchodilator FEV₁ is recommended for the diagnosis and assessment of severity of COPD.





Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: All COPD Patients

■ Avoidance of risk factors

- smoking cessation
- reduction of indoor pollution
- reduction of occupational exposure

■ Influenza vaccination



Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

Patient	Recommended First choice	Alternative choice		Other Possible Treatments
A	SAMA prn or SABA prn	LAMA or LABA or SABA and SAMA		Theophylline
B	LAMA or LABA	LAMA and LABA		SABA and/or SAMA Theophylline
C	ICS + LABA or LAMA	LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.		SABA and/or SAMA Theophylline
D	ICS + LABA and/or LAMA	ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.		Carbocysteine SABA and/or SAMA Theophylline



Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE

http://www.catestonline.org/english/index_Slovakia.htm

GOLD 4	C	ICS + LABA or LAMA	D	ICS + LABA and/or LAMA	2 or more or ≥ 1 leading to hospital admission	Exacerbations per year
GOLD 2	A	SAMA <i>prn</i> or SABA <i>prn</i>	B	LABA or LAMA	1 (not leading to hospital admission)	
CAT < 10 mMRC 0-1		CAT ≥ 10 mMRC > 2		0		



Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

ALTERNATIVE CHOICE

GOLD 4

GOLD 3

GOLD 2

GOLD 1

C

LAMA and LABA
or
LAMA and PDE4-inh
or
LABA and PDE4-inh

D

ICS + LABA and LAMA
or
ICS + LABA and PDE4-inh
or
LAMA and LABA
or
LAMA and PDE4-inh.

A

LAMA
or
LABA
or
SABA and SAMA

B

LAMA and LABA

2 or more
or
≥ 1 leading
to hospital
admission

1 (not leading
to hospital
admission)

0

Exacerbations per year

CAT < 10
mMRC 0-1

CAT ≥ 10
mMRC ≥ 2



Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

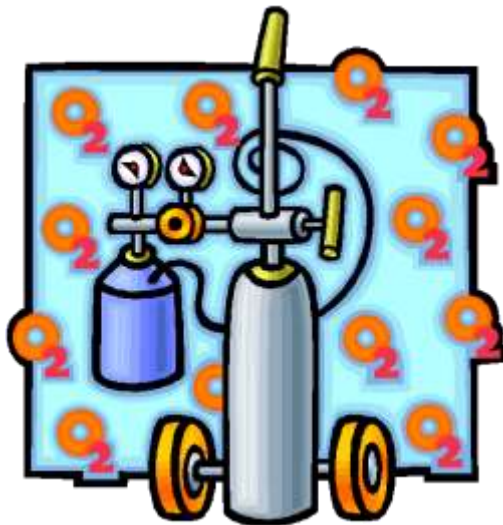
OTHER POSSIBLE TREATMENTS

	C	D		
GOLD 4	<i>SABA and/or SAMA</i> <i>Theophylline</i>	<i>Carbocysteine</i> <i>SABA and/or SAMA</i> <i>Theophylline</i>	2 or more or ≥ 1 leading to hospital admission	Exacerbations per year
GOLD 3				
GOLD 2	<i>Theophylline</i>	<i>SABA and/or SAMA</i> <i>Theophylline</i>	1 (not leading to hospital admission)	
GOLD 1			0	
	CAT < 10 mMRC 0-1	CAT ≥ 10 mMRC ≥ 2		

Treatment of stable COPD

Pharmacological:

- Bronchodilators
- Glucorticoids
- Other forms



Non-pharmacological:

- Smoking cessation
- Rehabilitation
- Oxygen therapy
- Mechanical assistance of ventilation
- Surgical treatment

Bronchodilators

- **parasympatholytics**
- **β_2 -sympathomimetics**
- **methylxanthines**
- **combinations**

Figure 9. Bronchodilators in Stable COPD

- Bronchodilator medications are central to symptom management in COPD.
- Inhaled therapy is preferred.
- The choice between β_2 -agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects.
- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- Long-acting inhaled bronchodilators are more effective and convenient.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Other forms of pharmacotherapy

- **Vaccination (influenza, pneumococcus)**
- **Substitutive therapy α_1 -antitrypsine**
- **Antimicrobial therapy (exacerbations)**
- **Mucolytics**
- **Antioxidants**
- **Immunoregulators**
- **Antitussives**

Drugs used in the therapy of BA and COPD

Role of β_2 -agonists in the therapy of obstructive airways diseases = the base of symptomatic treatment

Bronchial asthma

- drug of choice in acute exacerbation of asthma - as „reliever“
- preventive drug in asthma induced by effort
- in monotherapy indicated only in intermittent asthma
 - i.e. dyspnea attacks less than 1x per week
 - Night dyspnea less than 2x per month
 - PEF, FEV1 better than 80% and their variability is under 20%
- - all other levels of asthma – basic symptomatic drug - „rescue treatment“

COPD

- basic symptomatic drug - if the disorder is min. partially reversible

Other

- in patients with airways diseases with presence of obstruction – as basic symptomatic drug (bronchiectasis, obliterating bronchiolitis etc.)

β_2 -agonists

A. SABA

- **Salbutamol** **VENTOLIN, VENTILASTIN**
- **Fenoterol** **BEROTEC (with ipratropium – BERODUAL)**
- **Terbutalin** **Bricanyl**
- **Albuterol** **Proventil**
- **Levalbuterol** **Xopenex**

B. LABA - peroral

- **Salbutamol** **SALBUTAMOL, VENTOLIN tbl**
- **Clenbuterol** **SPIROPENT sir.**
- **Procaterol** **Lontermin**

C. LABA - inhalatory

- **Salmeterol** **SEREVENT (with fluticasone SERETIDE)**
- **Formoterol** **FORADIL , OXIS, FORMANO, FORMOVENT (with budesonide SYMBICORT, with fluticasone FLUTIFORM, with beclomethasone FOSTER)**
- **Indacaterol** **ONBREZ, HIROBRIZ, ULTIBRO, ULUNAR (with glycopyrronium)**
- **Vilanterol** **RELVAR ELLIPTA (with fluticasone furoate)**
- **Olodanterol** **STRIVERDI**

Parasympatholytics

- **Ipratropium bromide** **ATROVENT**
- **Oxitropium bromide** **OXIVENT**
- **Tiotropium bromide** **SPIRIVA**
- **Aclidinium bromide** **BRETARIS GENUAIR**
- **Glycopyrronium bromide** **SEEBRI BREEZHALER**

Parasympatolytics in combination

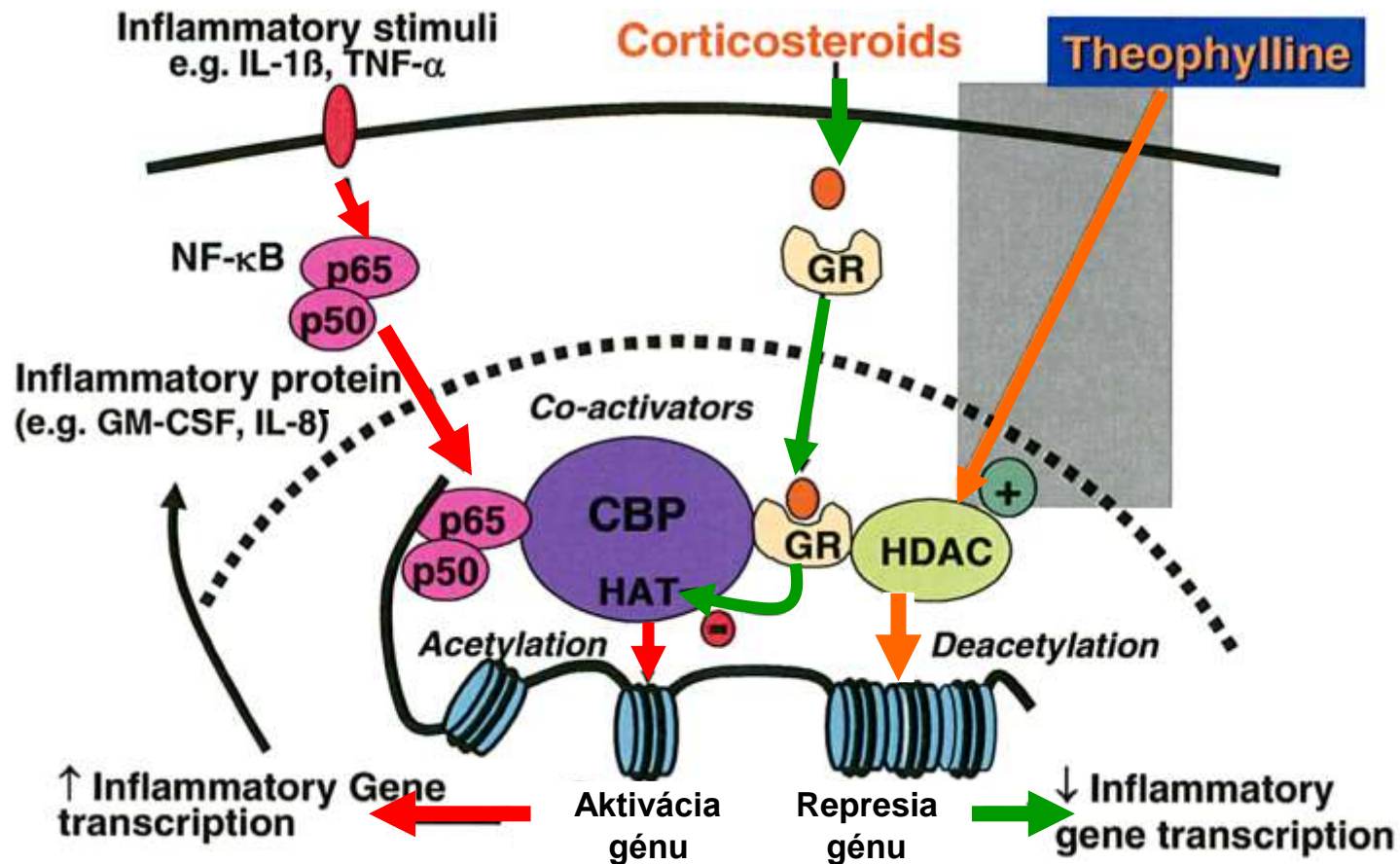
- **Ipratropium bromide + fenoterol** - **BERODUAL**
- **Ipratropium bromide + salbutamol** - **COMBIVENT**
- **Glycopyrronium + indacaterol**

Tiotropium bromid

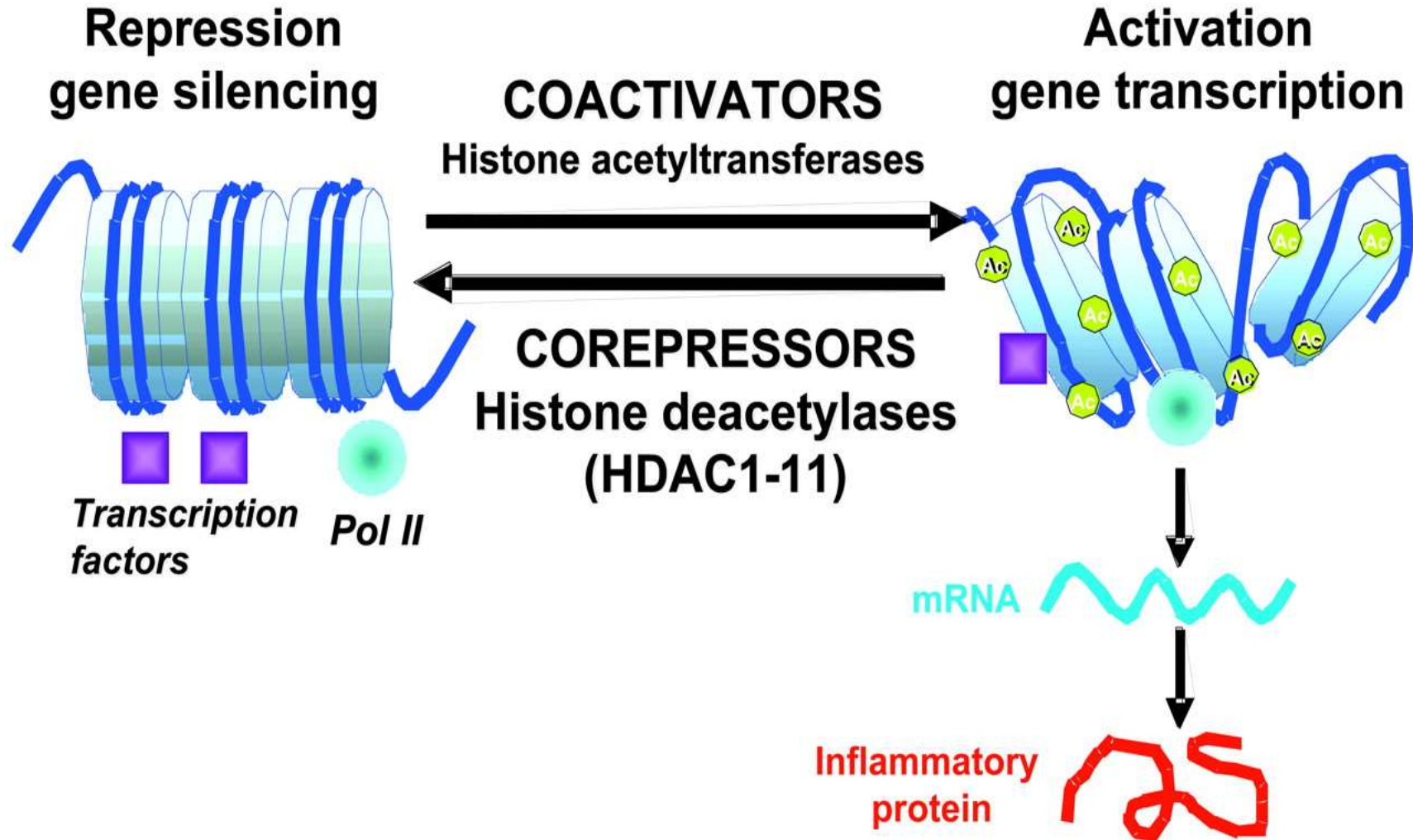
- Slower onset than ipratropium, longer time of persistance at M receptors
 - M_1 – 14,6 h
 - M_2 – 3,6 h
 - M_3 – 34,7 h (ipratropium 16 min)

Pharmacodynamic type of selectivity

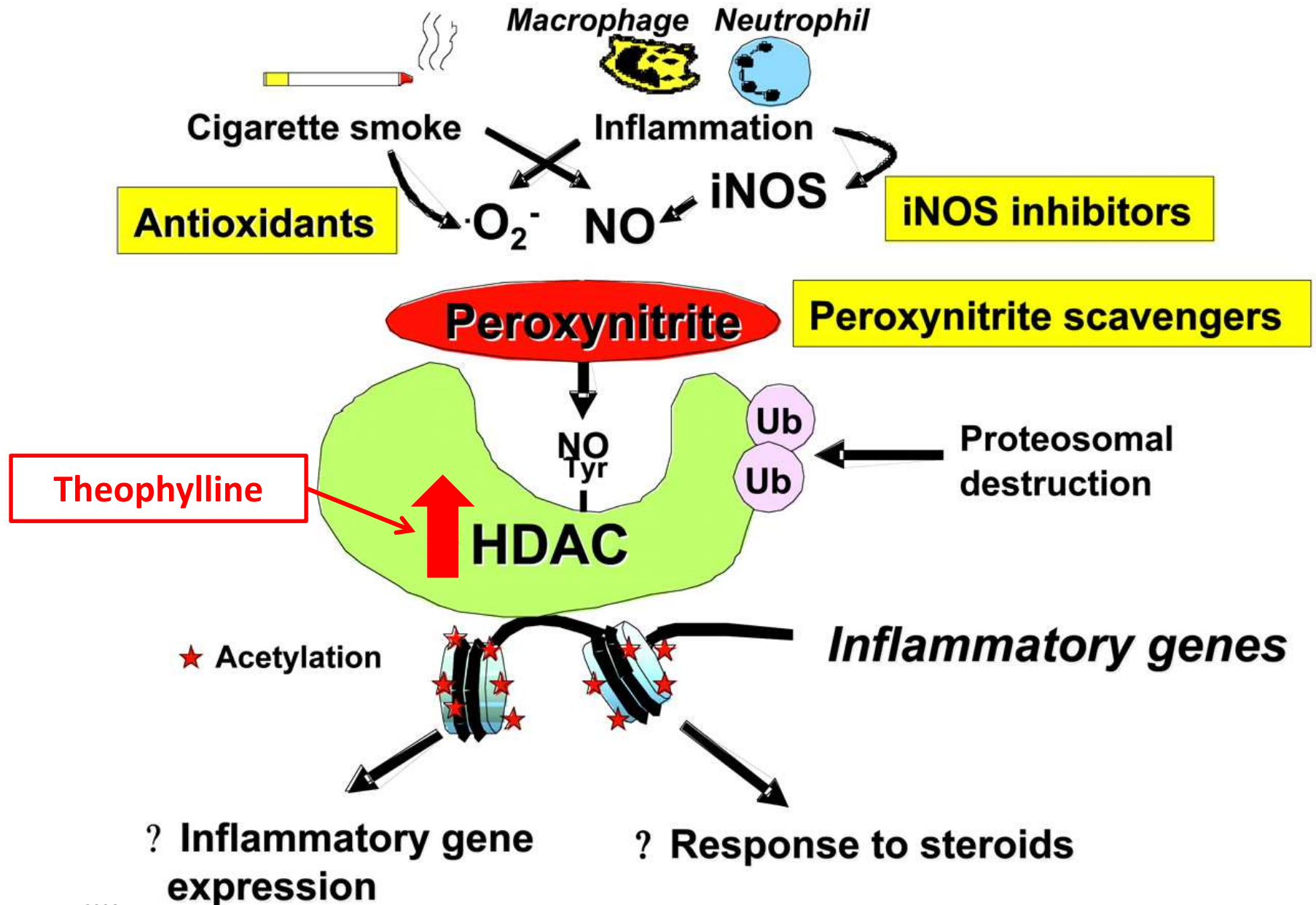
Mechanism of action – influencing HDAC by methyxanthines



Chromatin remodeling and gene expression



Reasons for decreased activity of HDAC in COPD



Xanthines nowadays

- Preference of **SR forms** (slow, sustained release)
- Use **as bronchodilators** after β_2 -agonists and anticholinergics
- Use particularly **in COPD**, less in asthma
- **Monitoring** of activity by determination of serum or saliva concentration of theophylline and its relation to effect
- **New classes of PDE** and their inhibitors

Indications of xanthines in COPD

Peroral SR forms

- ✓ moderate and severe obstruction (especially 3rd and 4th stage)
- ✓ prevention of night obstructions and O₂ desaturation
- ✓ disease of small bronchioles
- ✓ no response to previous antiphlogistic and bronchodilatory therapy

Indications of xanthines in COPD

Peroral forms with short effect

- ✓ only in cases with better individual toleration

Intravenous form

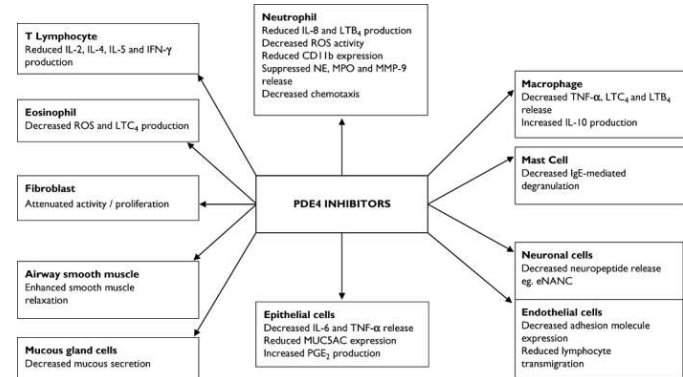
- ✓ acute exacerbations of COPD, event. with decompensation of cor pulmonale, where did not help usual therapy (essential monitoring)

Methylxanthines

- Theophyllin 12 h – AFONILLUM SR, EUPHYLLIN CRN (RESPICUR), Euphylong, Spophyllin retard, Teotard, Theo-Dur, Theodyl, THEOPLUS, Theophyllard
- Theophyllin 24 hours – Uni-Dur SR, Unilair
- Aminophyllin short – SYNTOPHYLLIN, Aminophyllin
- Aminophyllin 12 h – Aminophyllinum retard Lek
- Etofyllin – short – Oxyphyllin
- Etofyllin + theophyllin – Oxantil
- Doxofylline (ANSIMAR)

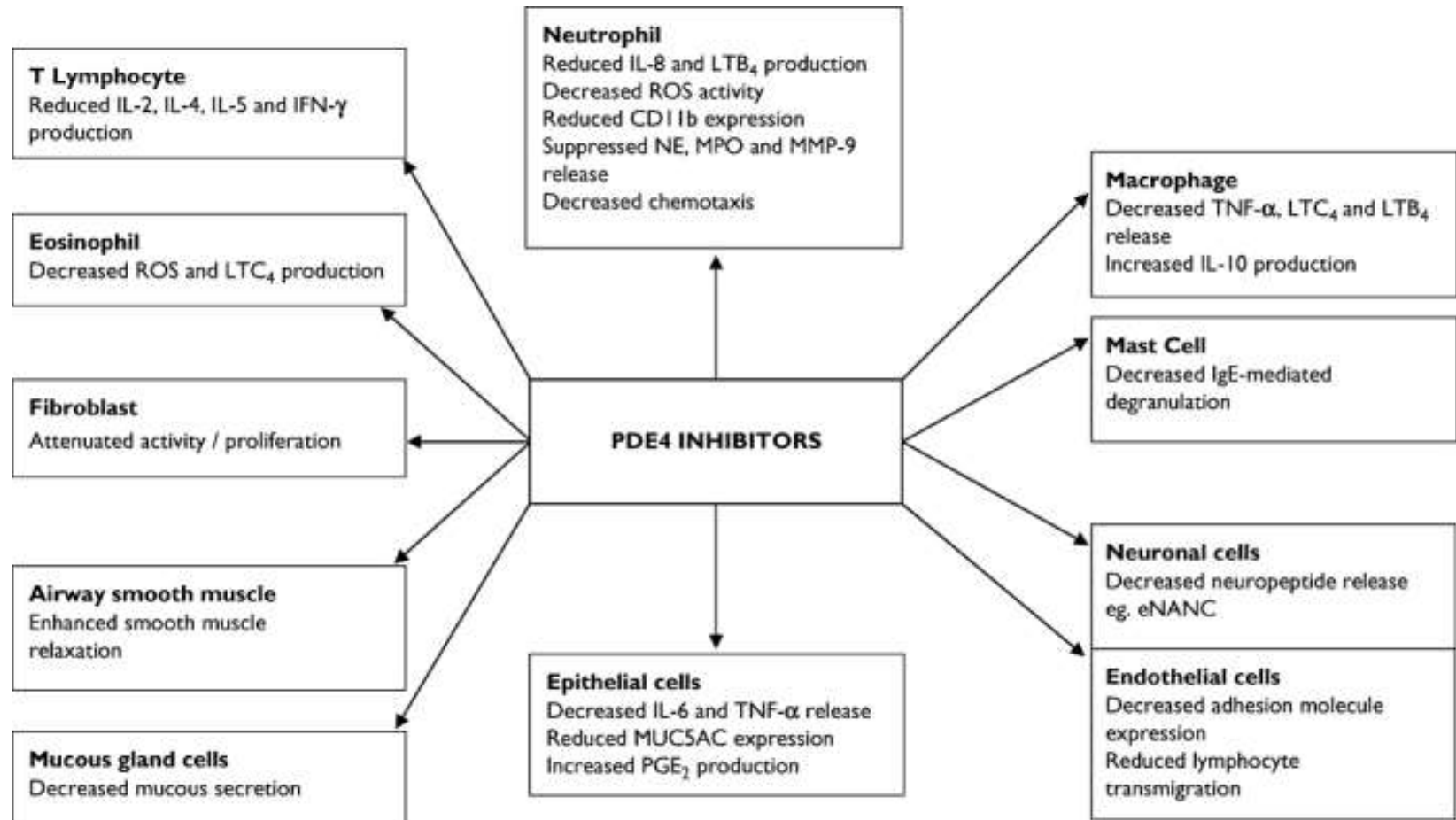
Selective PDE4 inhibitors

- increase **cAMP**
- ↓ activation of T-cells
- ↓ WBC functions
- ↓ activation of macrophages
- relax ASM (dual inhibition of PDE3/4)
- ↓ cytokine release (TNF- α)

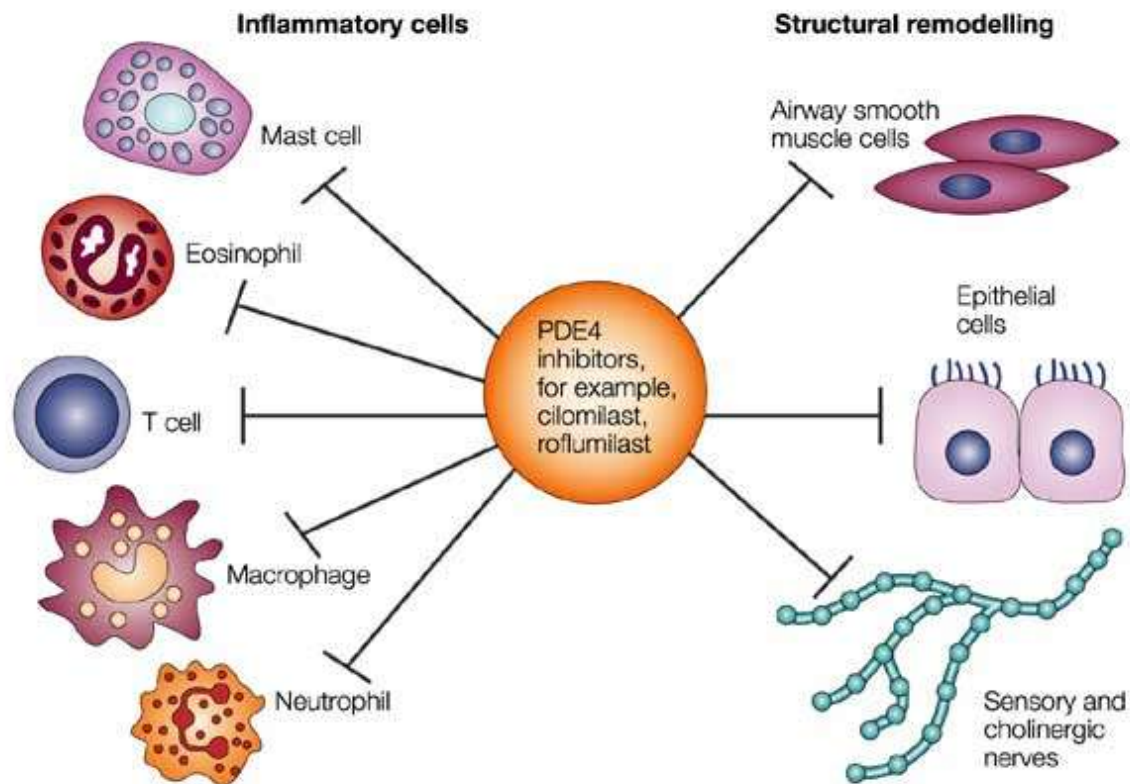


- **rolipram, citalopram** – 1st generation → AE (nausea, vomiting)
- **cilomilast, roflumilast, piclamilast** – 2nd generation → same antiinflammatory and immunomodulatory effects, less bronchodilation, **less adverse effects**

PDE4 inhibitors and inflammation



PDE4 inhibitors and inflammation

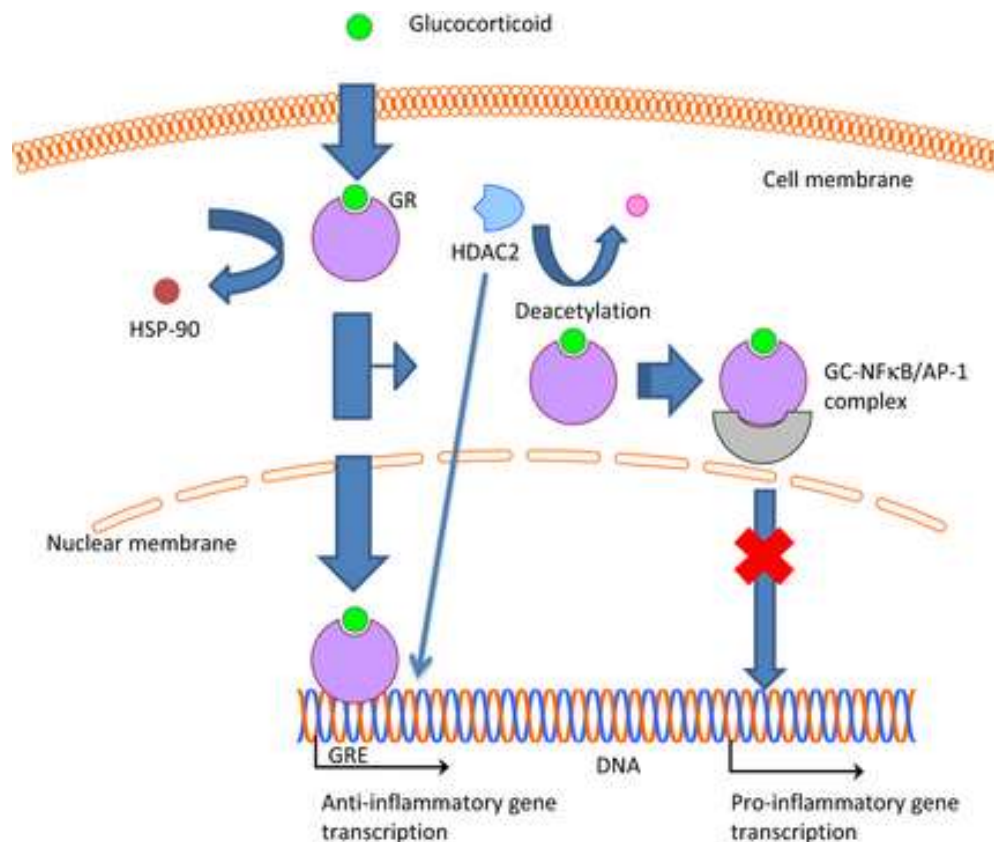


New recently approved PDE4 inhibitor

- **roflumilast (DAXAS)** – July 2010 – approved by **EMA** for use in **EU**
- Once daily, **p.o. tablets**, 500 µg
- ***Indication:*** maintenance treatment of severe COPD (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in patients with a history of frequent exacerbations as add on to bronchodilator treatment
- AE – diarrhea (5,9 %), weight loss (3,4 %), nausea (2,9 %), abdominal pain (1,9 %) and headache (1,7 %).

Corticosteroids

- not as direct muscle relaxants (however, indirect bronchodilators)
- strong **suppression of inflammatory response** e.g. by inhibition of arachidonic acid release from cell membranes, decreased production of PG and LT (inflammation mediators)
- stopping the migration and **decrease of bronchial hyperreactivity, edema suppression**
- **prevention of chronic irreversible changes** (hypertrophy and hyperplasia of airways smooth muscle, subendothelial fibrosis and thickening of mucous basal membranes)
- **increase sensitivity and expression of β -adrenergic receptors of smooth muscles** to β_2 -agonists



Mechanisms of action of glucocorticoids (GC). GC diffuse across the cell membrane where they bind with GC receptors (GR) in the cytoplasm. Upon binding of the GC, this causes release of inhibitory proteins such as heat shock protein 90 (hsp-90), allowing the GC-bound GR to diffuse across the nuclear membrane where it binds to the glucocorticoid response element (GRE). The GRE is responsible for transcribing anti-inflammatory proteins. Additionally, binding of GC to GR results in recruitment of histone deacetylase 2 (HDAC2), which is responsible for deacetylating GR, permitting its binding to nuclear factor-kappa B (NF-κB) and activating protein-1 (AP-1). Upon binding, these transcription factors are deactivated, thereby inhibiting the transcription of pro-inflammatory proteins. Additionally, HDAC2 deacetylates the histone permitting transcription of anti-inflammatory genes by GR.

Trevor JL, Deshane JS. Refractory asthma: mechanisms, targets, and therapy. *Allergy* 2014; 69: 817–827.

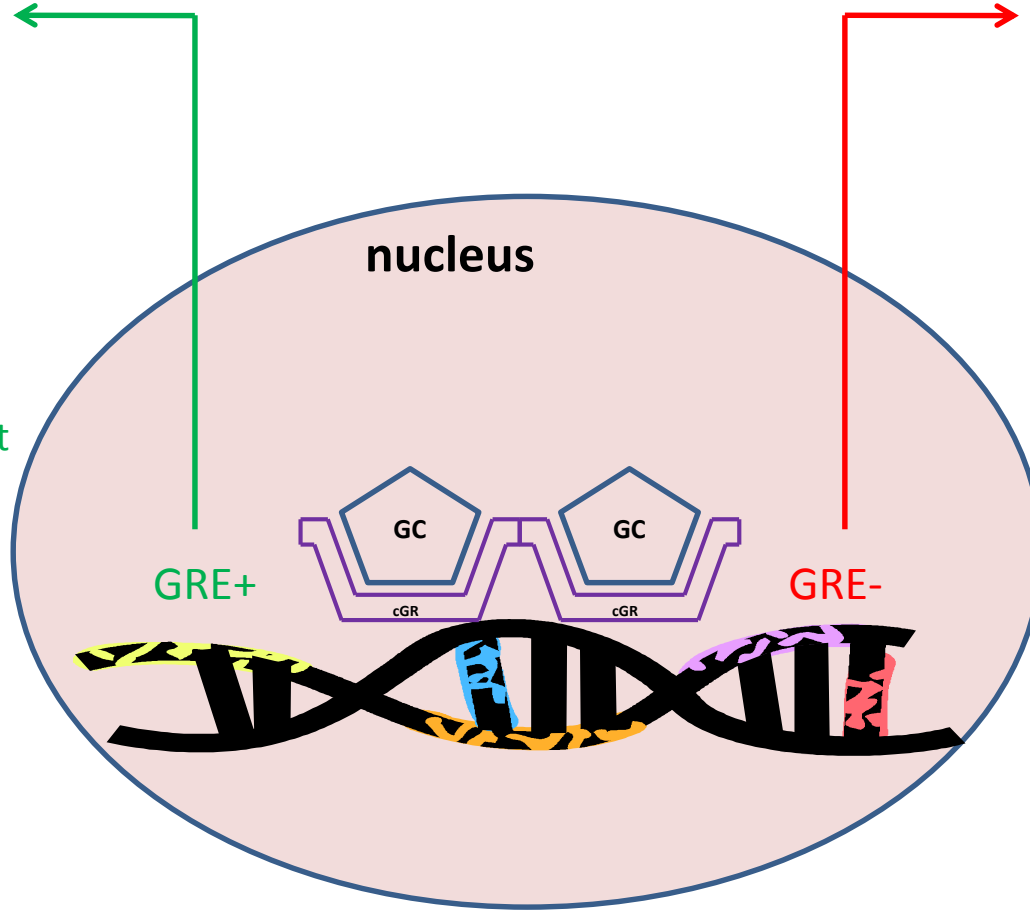
Allergy

Volume 69, Issue 7, pages 817-827, 29 APR 2014 DOI: 10.1111/all.12412

<http://onlinelibrary.wiley.com/doi/10.1111/all.12412/full#all12412-fig-0002>

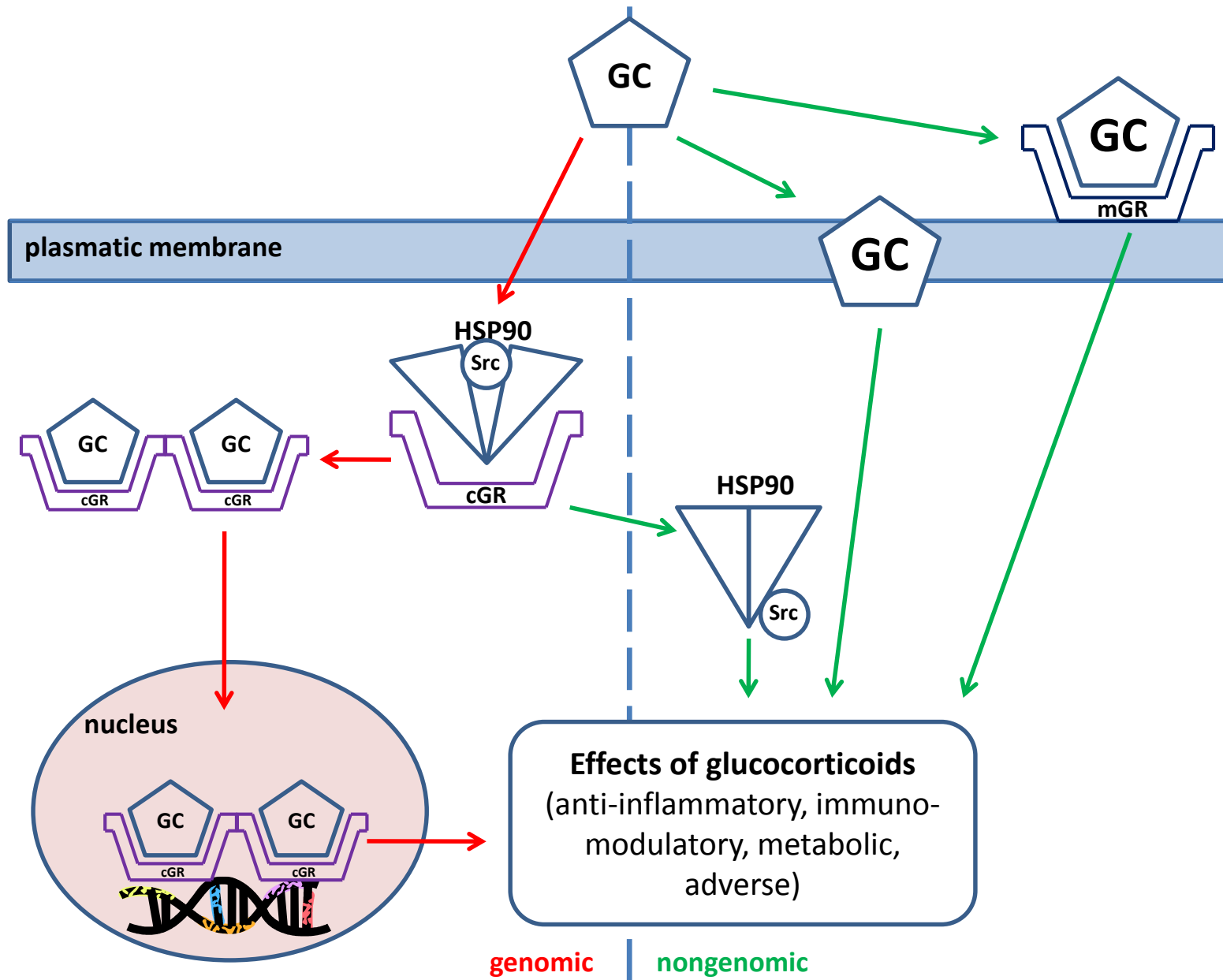
Trans-activation

↑ transcription of
genes coding
antiinflammatory
proteins
↑ lipocortin-1
↑ interleukin-10
↑ interleukin-1-
receptor antagonist



Trans-repression

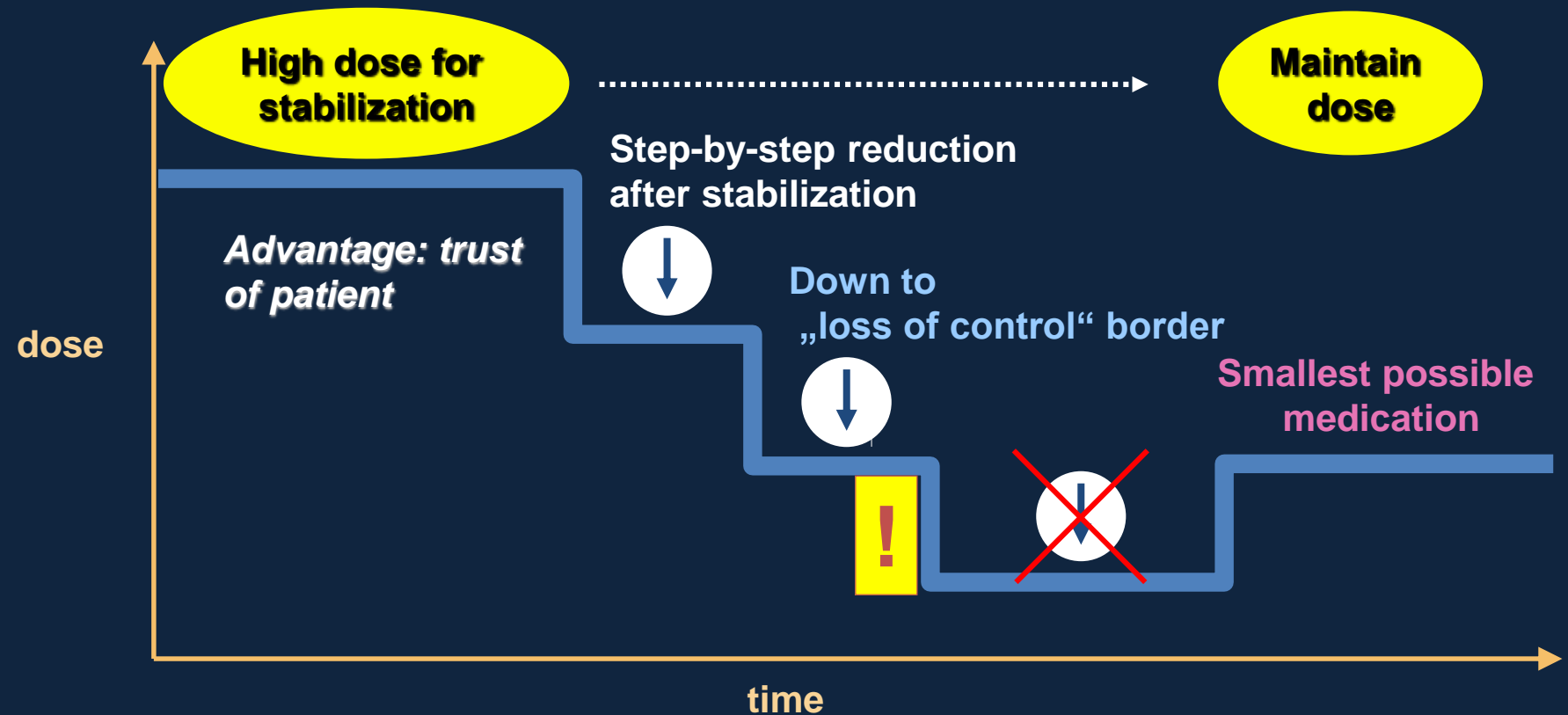
↓ AP-1
↓ NF- κ B
↓ IRF3
↓ expression of
inflammatory genes
(cytokines, enzymes,
receptors, adhesion
molecules)



Inhalatory corticosteroids

- **Local effect**
- Corticoids **soluble in fat**: beclomethasone, budesonid, fluticasone (longest deposition time in lungs, best affinity to corticoid receptor).
- In dose up to **800 μm -1 mg/day** low incidence of systemic adverse effects.
- Decreasing of doses after stabilization of clinical status.
- **Adverse effects**: oropharyngeal candidosis, dysphonia, cough (prevention – washing out of mouth, use of spacers)

Strategy of treatment with ICS

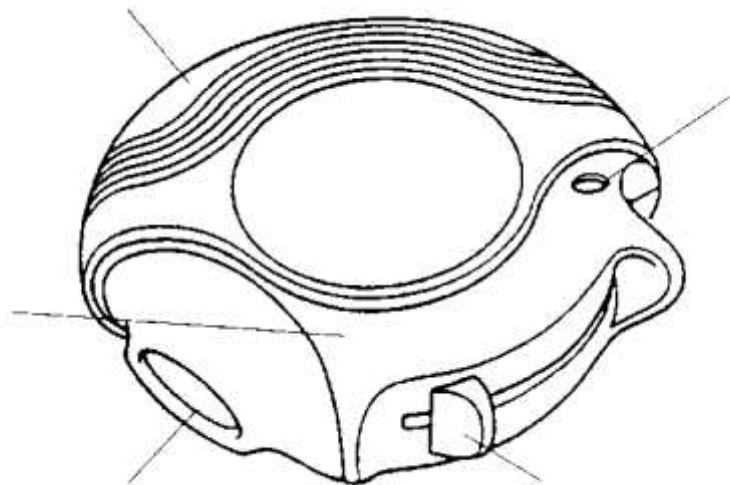
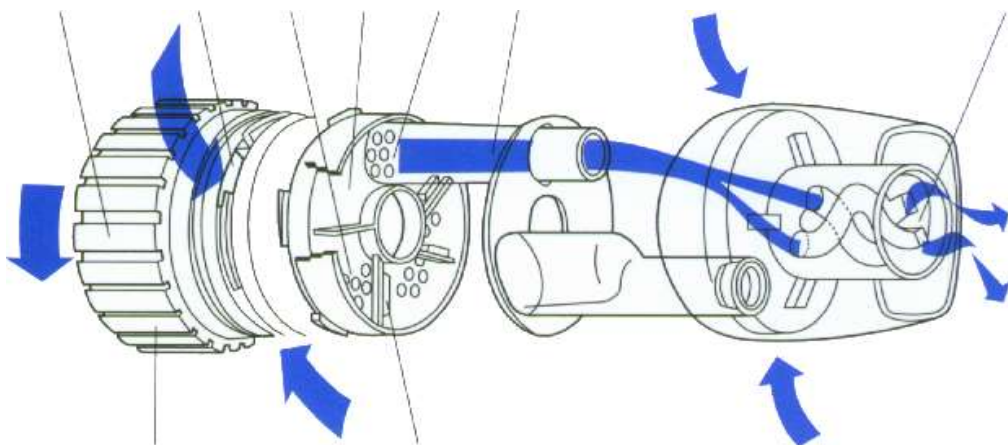
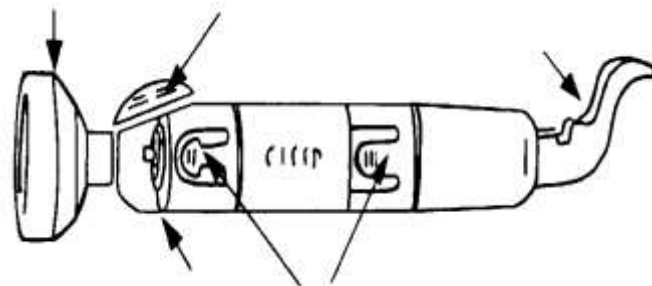
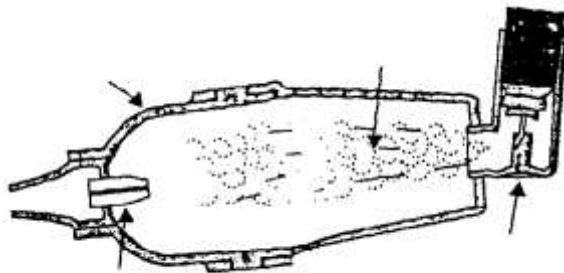
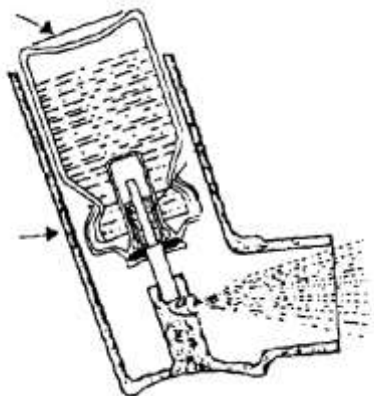


Advantages of inhalational administration

- ✓ Direct drug effect
- ✓ Low total dose
- ✓ Minimalisation of adverse effects

Inhalers

- **MDI** Metered dose inhaler
- **MDI + spacer**
- **DPMDI** + Dry powder metered dose inhaler (DPI)
- **Nebuliser**
- **Discus**



Systemic corticosteroids

- short-term booster cycle (3-10 days) – „maximal therapy" for treating of severe persistent asthma (treatment failure). Usually as an introduction of long-term therapy of patients with unstable asthma or in case of sudden worsening of clinical state.
- long-term peroral corticosteroid therapy (daily or alternative – i.e. one dose every other day) in patients with severe persistent asthma
- peroral administration is preferred to parenteral .
- during attack should be administered within 45 minutes.
- Hydrocortison, prednison, metylprednison, triamcinolon

Corticosteroids in COPD

- Inhalatory
- Only in symptomatic patients with positive response or in patients with FEV₁ < 50% (3rd and 4th stage)
- In exacerbation with ATB
- No influence on FEV₁
- Long-term peroral treatment is not recommended



Estimate Comparative Daily Dosages for Inhaled Glucocorticosteroids by Age

Drug	Low Daily Dose (μg)		Medium Daily Dose (μg)		High Daily Dose (μg)	
	> 5 y	Age < 5 y	> 5 y	Age < 5 y	> 5 y	Age < 5 y
Beclomethasone	200-500	100-200	>500-1000	>200-400	>1000	>400
Budesonide	200-600	100-200	600-1000	>200-400	>1000	>400
Budesonide-Neb Inhalation Suspension		250-500		500-1000		>1000
Ciclesonide	80 – 160	80-160	>160-320	>160-320	>320-1280	>320
Flunisolide	500-1000	500-750	>1000-2000	>750-1250	>2000	>1250
Fluticasone	100-250	100-200	>250-500	>200-500	>500	>500
Mometasone furoate	200-400	100-200	> 400-800	>200-400	>800-1200	>400
Triamcinolone acetonide	400-1000	400-800	>1000-2000	>800-1200	>2000	>1200

Inhalatory corticosteroids

- **Beclometasone** **BECLOMET, ECOBEC**
 - **Budesonide** **PULMICORT, GIONA, BUDELIN, MIFLONID**
 - **Fluticasone** **FLIXOTIDE**
 - **Mometasone** **ASMANEX**
 - **Ciclesonide** **ALVESCO**
- + combined with β_2 -agonists (e.g. SYMBICORT, FLUTIFORM, FOSTER, SERETIDE)**

New bronchodilators

- **Ultra LABAs** – indacaterol, vilanterol, olodanterol – duration of action over 24 hours
- **Tiotropium** – LAMA – only in add-on therapy in severe asthma, more in COPD
- **VIP analogues, K⁺ openers** – side effects due to vasodilation
- **Agonists of bitter taste receptors** (TAS2R) – quinin, chloroquine, saccharine – needs testing
- **Triple inhalers** – LABA+LAMA+ICS – severe asthma

Recently developed combination inhalers for COPD

- LABA and ICS

- Fluticasone propionate/salmeterol, budesonide/formoterol) – several years experience
- Mometasone/formoterol – comparable effectiveness, more rapid onset
- Beclomethasone/formoterol – aerosol
- **Vilanterol trifenate/fluticasone furoate**
 - ultra LABA (24h), highly selective for beta2, more rapid onset and longer duration than salmeterol
 - Fluticasone furoate – 24h, effect comparable to fluticasone propionate twice daily
- **Indacaterol/mometasone**
 - 24h duration, once daily, clinical efficacy of indacaterol comparable with tiotropium
- **Ciclesonid/formoterol**
 - On-site activation, lower systemic bioavailability, more effective in asthma

Recently developed combination inhalers for COPD

- LABA and LAMA

- Formoterol/tiotropium

- not available in combination, however, often combined in the therapy

- Indacaterol/glycopyrronium

- Better than single indacaterol, safe regarding CVS risk

- Olodaterol/tiotropium

- More effective than tiotropium alone

- Carmoterol/tiotropium

- no more tested, failed in effectiveness

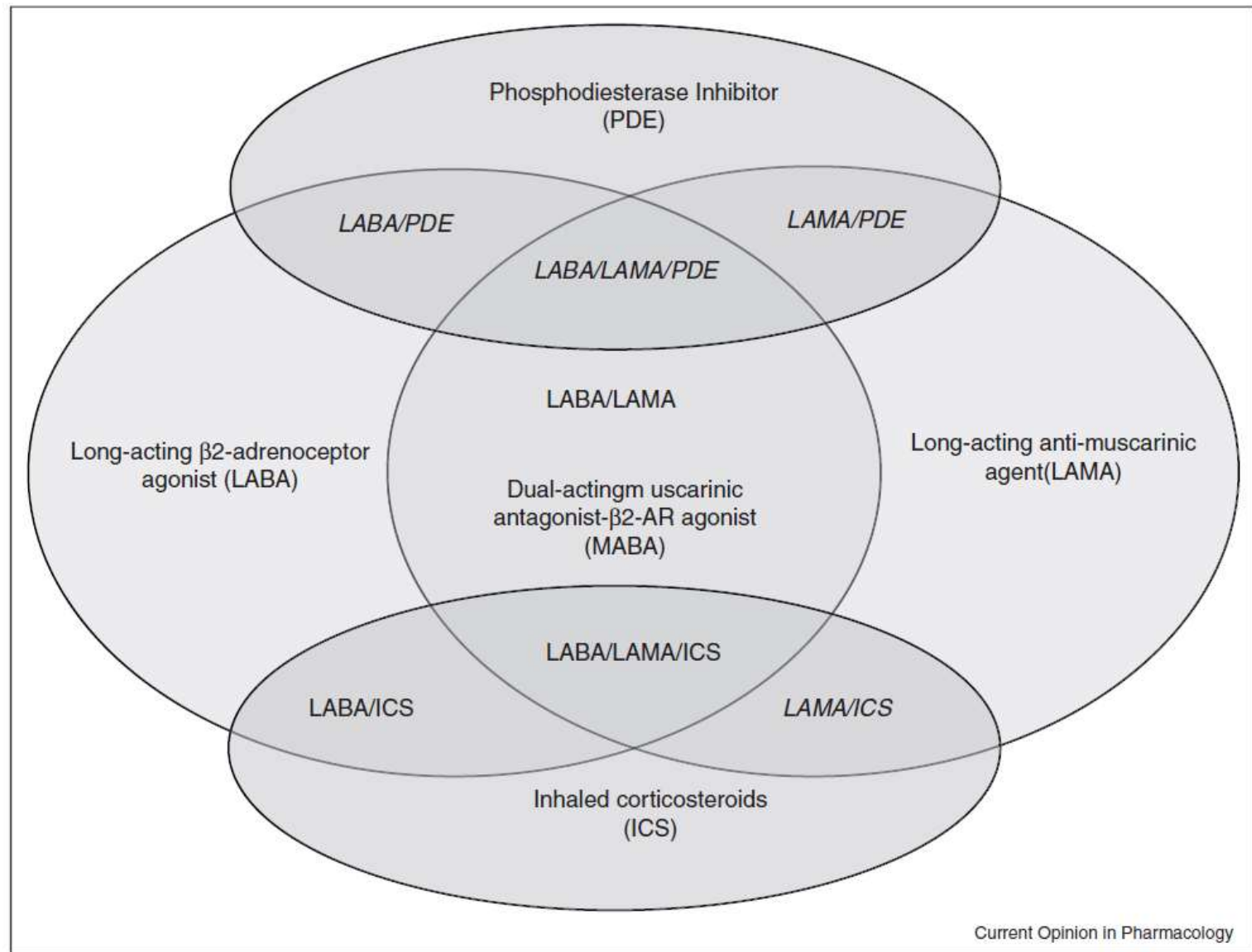
Recently developed combination inhalers for COPD

- **MABA**

- Single molecule with both antimuscarinic and β_2 -agonistic modes of action
- GSK961081 – 400 or 1200 mcg once daily
- PF-3429281

- **Triple therapy**

- LABA+LAMA+ICS
- Single inhaler – better compliance
- Salmeterol/fluticasone propionate/tiotropium



Combination bronchodilator therapy under investigation for clinical use. Italicized combinations indicate limited available clinical data.

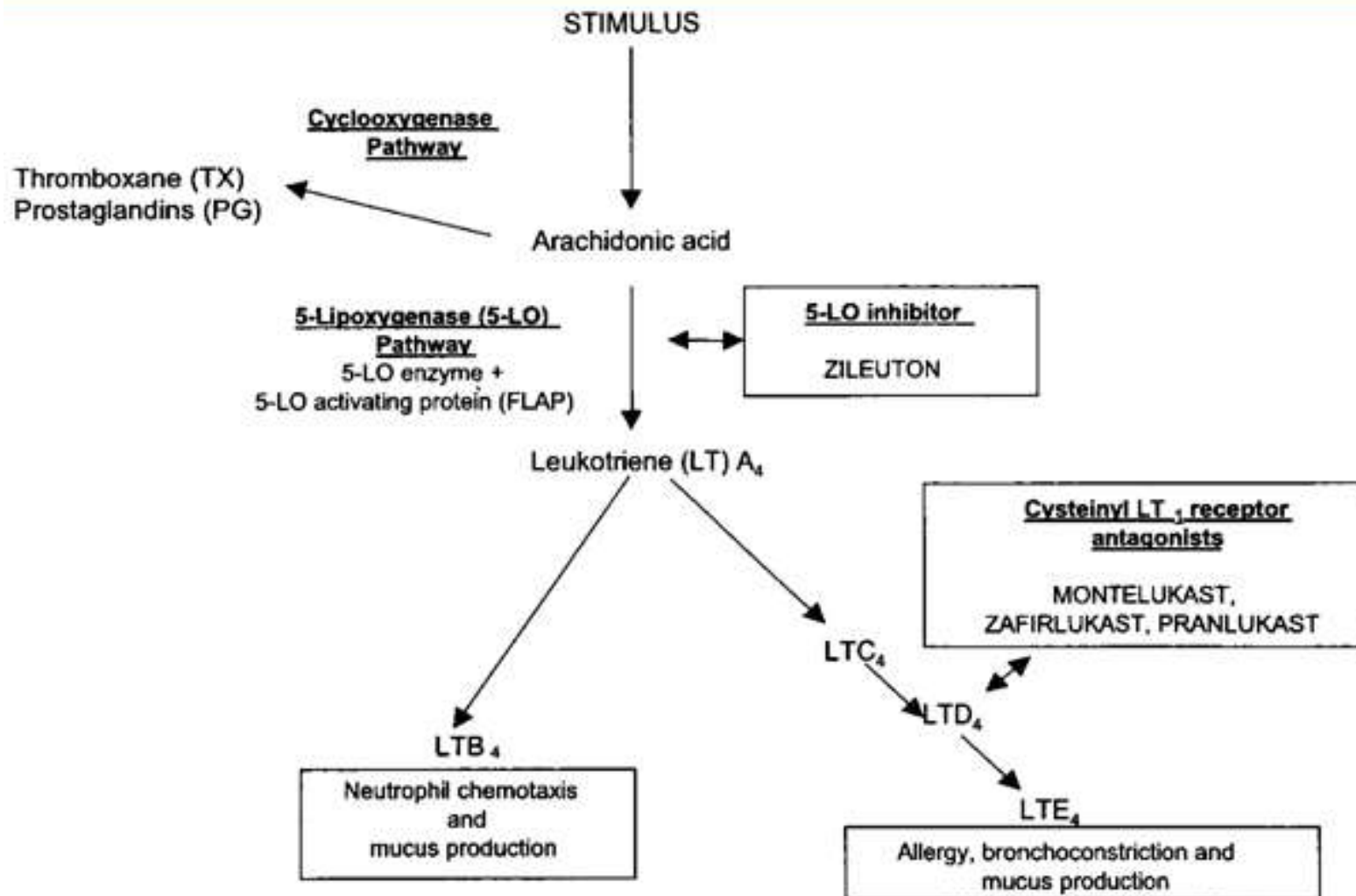
New bronchodilators

Garbo Mak and Nicola A Hanania *Current Opinion in Pharmacology* 2012, 12:238–245

Antileukotriens

Medscape®

www.medscape.com



Antileukotrienes

- Antagonists of LT receptors:

Zafirlucast – ACCOLATE

2x daily from 12 years

**Montelukast – SINGULAIR, ACTAMONE,
MONTEXAL, MONTELUKAST,
SPIROMON, ASTAMASAN**

1 x daily from 6 years

- 5-LO inhibition

Zileuton – Zyflo

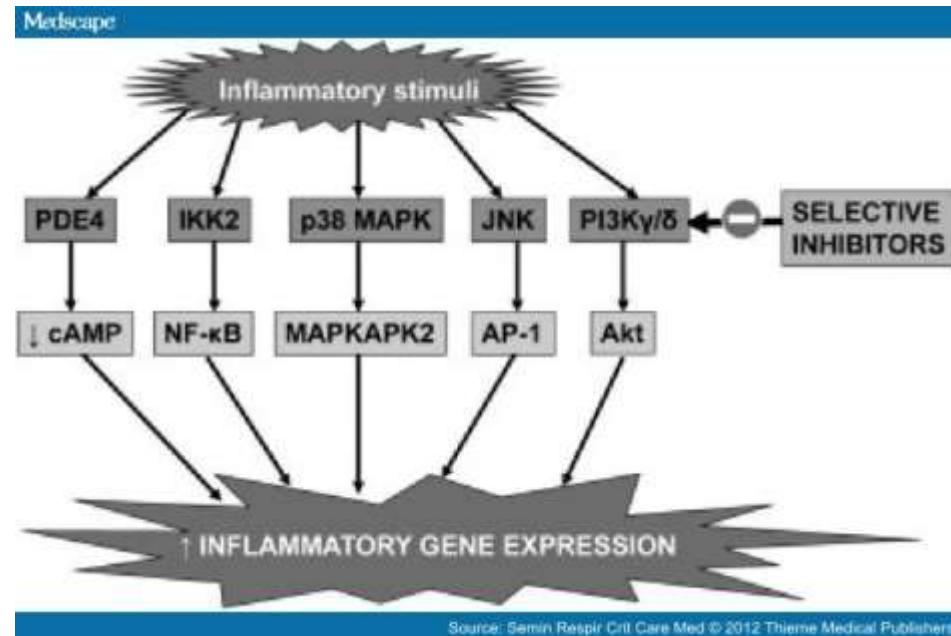
New corticosteroids

- Reducing oral bioavailability, absorption from lungs, inactivation in circulation
- Dissociated steroids – to support trans-repression and non-genomic effects and to reduce trans-activation
- Non-steroidal selective glucocorticoid receptor activators - **SEGRA** (AL-438, maprocorat)
- activators of HDAC2

New anti-inflammatory drugs

- **ICS** – golden standard
- Problem in case of concomitant rhinitis, or resistance to CS
- ICS are not so effective against neutrophil inflammation

Inhibition of signal transduction pathways that amplify inflammatory gene expression in asthmatic airways. Selective inhibitors have been developed for phosphodiesterase-4 (**PDE4**), which degrades cyclic adenosine monophosphate (cAMP); inhibitor of nuclear factor kappa B (NF- κ B) kinase (**IKK2**), which activates NF- κ B; and p38 mitogen-activated protein kinase (**MAPK**), which activates MAP kinase activated protein kinase 2 (MAPKAPK2); Jun kinase (**JNK**), which activates activator protein-1 (AP-1); and phosphoinositide-3-kinase (**PI3K**), which activates Akt. Selective inhibitors have now been developed for all of these enzyme targets

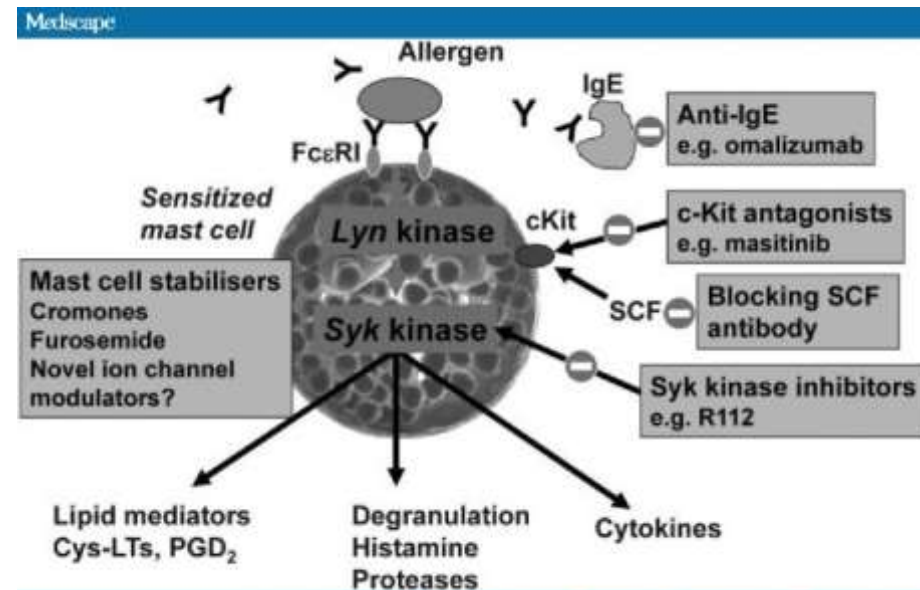


New anti-inflammatory drugs

- **PDE inhibitors – roflumilast – PDE4I**
 - Selective PDE4B inhibitors to prevent PDE4D mediated adverse effects
 - Inhalatory use
 - Dual PDE3/4 inhibitors (RPL554, inhaled)
- **Kinase inhibitors**
 - IKK – inhibitor of NF- κ B kinase
 - MAPK inhibitors
 - PI3K – also in CS resistant asthma – theophylline, or selective PI3K inhibitors (nortriptyline)
- **Adhesion molecule blockade**
 - very late antigen-4 inhibitors (VLA-4)
 - Selectine inhibitor (bimosiamose)
- **PPAR γ agonists**
 - too limited effect, approximately 15% from ICS

Anti-allergy treatment

- **Anti-IgE therapy** (omalizumab, lumiliximab – antiCD23 antibody)
- **Mast cells inhibitors**
 - cromones and nedocromil – indirect stabilizers, like furosemide
 - s-Kit and stem cell factor interaction
 - Syk kinase inhibitors



Omalizumab

- Antiallergic in allergic asthmatics
- Recombinant human monoclonal antibody IgG **against** human **IgE** – inhibits bound of IgE to receptor on mast cells and basophils
- >12 years
- Expensive (10.000 USD per year)
- **XOLAIR**

Cromoglycates

- Anti-inflammatory effects – inhibition of inflammatory cells activity
- For continual anti-inflammatory treatment of milder BA forms induced by cold air, allergens, physical and mental activity and air pollution.
- For preventive use and not for acute relieve from symptoms
- Ameliorate lung functions, decrease frequency and severity of attacks decrease airway hyperreactivity

Advantages

- **Safety tested during 50 years of use**
- **Contentment of physicians**
- **Application in children**

Cromoglycates

Disadvantages

- Weaker anti-inflammatory effect
- No prevention of remodeling
- Full action after 4-6 weeks (except nedocromil)
- Dosage 4 x daily
- No decrease of mortality
- AE – irritation

Cromoglycates

- Formulations:

Sodium cromoglycate: **NALCROM**, Cromolyn, DCNG Stada, Chomobene, Ditec (contains 1 mg of cromoglycate and 0,05 mg of fenoterol), Intal.

Dosage up to 4x2 inhalations

Sodium nedocromil: Tilade, **TILADE MINT.**

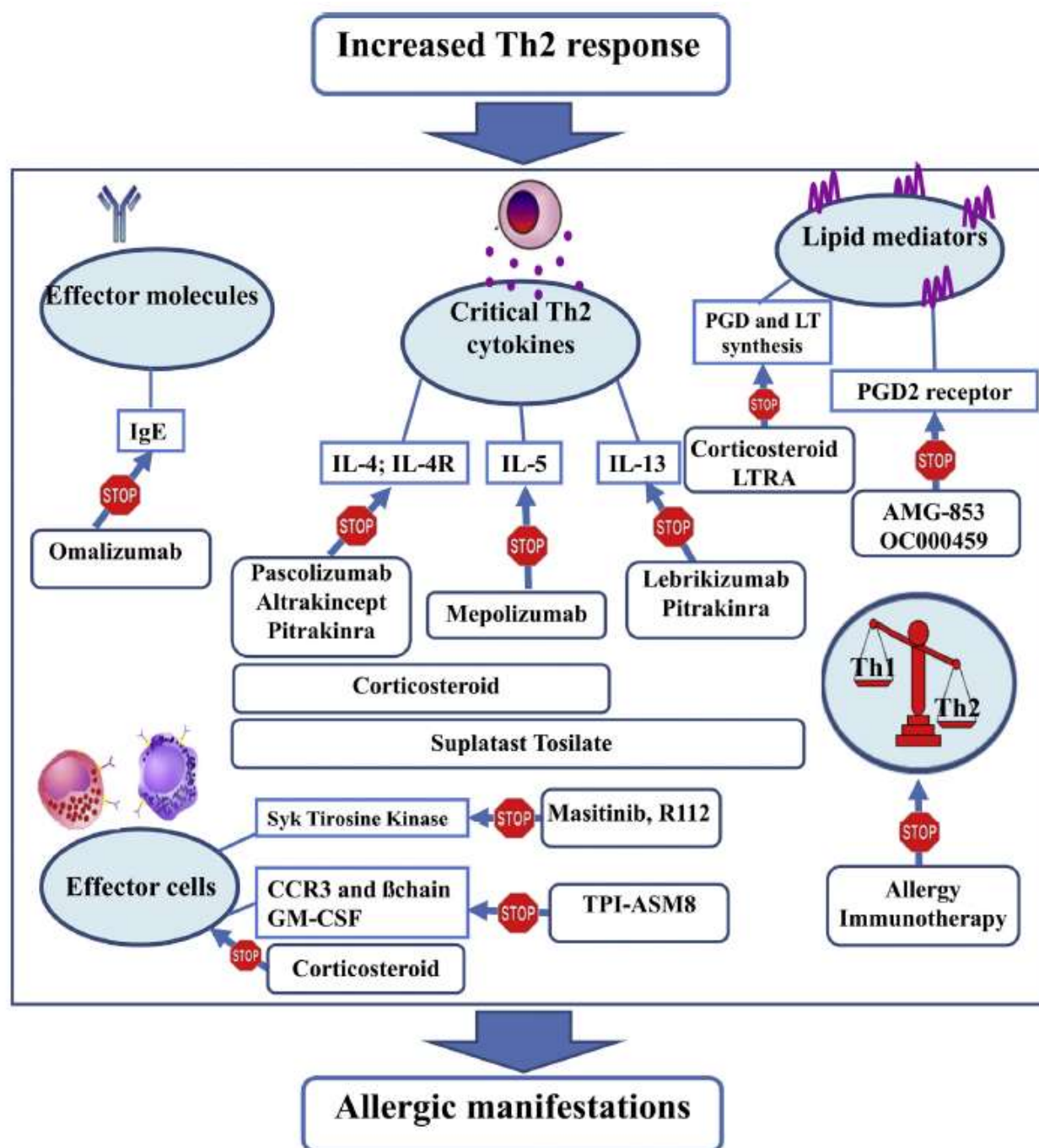
Dosage 2x2 inhalations

Asthma therapy – future challenges

- **Inhibiting key effector cells**
 - **Mast cells inhibitors** (like chromones)
 - c-Kit receptor and stem cell factor interaction – masitinib
 - Anti-Syk (Syk ASO) – inhibitor of tyrosine kinase Syk activated by binding of IgE on mast cell
 - **Eosinophil inhibitors**
 - TPI-ASM8 - blocker of CCR3 chemokine receptors and common beta chain of GM-CSF, IL-3 and IL-5 receptors

Asthma therapy – future challenges

- **Anti-Th2 cytokine therapy**
 - **IL-4 antagonists** – together with IL-13 (pitrakinra)
 - **IL-13 antagonists** (lebrikizumab)
 - **IL-5 inhibitors** (mepolizumab, reslizumab)
 - **Suplatast tosilate** – Th2 cytokine inhibitor (Japan)
 - **OX40L antagonists** –antagonists of special TNF receptor (R0498991)
 - **Block of lipid mediators** – CRTH2 receptor for PGD_2



New immunomodulatory drugs

Drug	Mechanism of Action	Route of administration	Development status	Clinical efficacy
Pascolizumab	IL-4 antagonist	Intravenous	Phase II	Unfavorable data
Altrakincept	Blocks interaction between IL-4 and its cellular receptors IL-4Rα	Nebulized	Phase III	Poor effectiveness in moderate persistent asthma
Mepolizumab	IL-5 antagonist	Intravenous	Phase II	Potential efficacy on specific eosinophilic refractory asthma subphenotype
Lebrikizumab	IL-13 antagonist	Subcutaneous	Phase II/III	Improvement of FEV1 in moderate-to-severe asthma with poor responsiveness to ICS.
Pitrakinra	Antagonist of IL4 and IL13 through Blocking IL-4Rα	Nebulized or Subcutaneous	Phase III	Improvement of FEV1 and reduction of asthma exacerbations
Suplatast Tosilate	Presumed block of Th2 cytokines (IL-4, IL-5, IL13)	Oral	Approved in Japan since 1995	Decreased peripheral blood eosinophils and eosinophil cationic levels in serum and sputum. Reduced allergen-induced goblet cell metaplasia. Reduced ICS doses.
RO498991	OX40L inhibition	Subcutaneous	Phase II	Decreased allergic symptoms
Omalizumab	Anti IgE	Subcutaneous	Since 2003 and 2005 approved in USA and Europe, respectively	Reduced asthma exacerbations Improvement of PEF and FEV1 Reduced onset of allergic reactions combined to SCIT
AMG-853 OC000459	PGD2 receptor (CRTH2) Antagonist	Oral	Phase II	Reduced vasodilator and bronchoconstrictor effect
Masitinib	Inhibits c-Kit and PDGF receptors.	Oral	Phase II/III	Reduced bronchial inflammation and airway remodeling
Syk ASO R112 R343	Inhibit tyrosine kinase Syk	Nebulized Intranasal Nebulized	Phase II	Reduced tracheal smooth muscle contraction and lung inflammation.
TPI-ASM8	Blocks CCR3 chemokine and β chain of GM-CSF	Nebulized	Phase II	Reduced early inflammation and sputum hypereosinophilia

Immunotherapy

- treatment targeting the immune deviation
- **specific immunotherapy**
 - s.c. injection of specific allergen – not very effective
 - sublingual immunotherapy with house dust mite
 - with peptides from T-cell epitopes from cat allergen (increased IL-10 from Treg)
 - Vaccination of *Mycobacterium vaccae* (shift from Th2 to Th1)
- targeting **Tregs** – increase of IL-10 expression, suppression of IgE synthesis via shift of Th2 to Th1 (vitamin D3)
- targeting **dendritic cells** – iloprost, fingolimod (analogue of sphingosine-1-phosphate (S1P))