

Allergic Respiratory Disease

ONE AIRWAY CONCEPT AND APPROACH

Agenda

- ▶ Etiology of UAD
- ▶ Definitions
- ▶ Link between Asthma and Allergic rhinitis
- ▶ Epidemiology of UAD
- ▶ Pathophysiology linking Asthma and Rhinitis
- ▶ Clinical evidences
- ▶ Management
- ▶ Summary

Asthma & Allergic Rhinitis

=

Allergic rhinobronchitis

=

United Airway Disease

=

One Airway Disease

=

Linked Airway Disease

Etiology of United Airway Disease

- ▶ Eosinophilic airway inflammation such as allergic rhinitis (AR) is often associated with lower airway diseases, such as asthma.
- ▶ The coexistence of both upper and lower airway disease is known as united airway disease, described as one airway, one disease
- ▶ Recent studies have estimated that 30% of AR patients and 70% of asthma patients have comorbid asthma and AR, respectively

Evidences of United airway disease

- ▶ SACRA study, Ohta et al. reported that asthma control was significantly impaired in AR patients and that significantly more AR patients had uncontrolled asthma than those without AR¹
- ▶ Long-term risk of developing asthma was three times higher in AR patients²
- ▶ Incidence of asthma attacks was comparatively greater in asthma patients with AR³
- ▶ Togias et al. reported an association between degree of severity of asthma and AR⁴

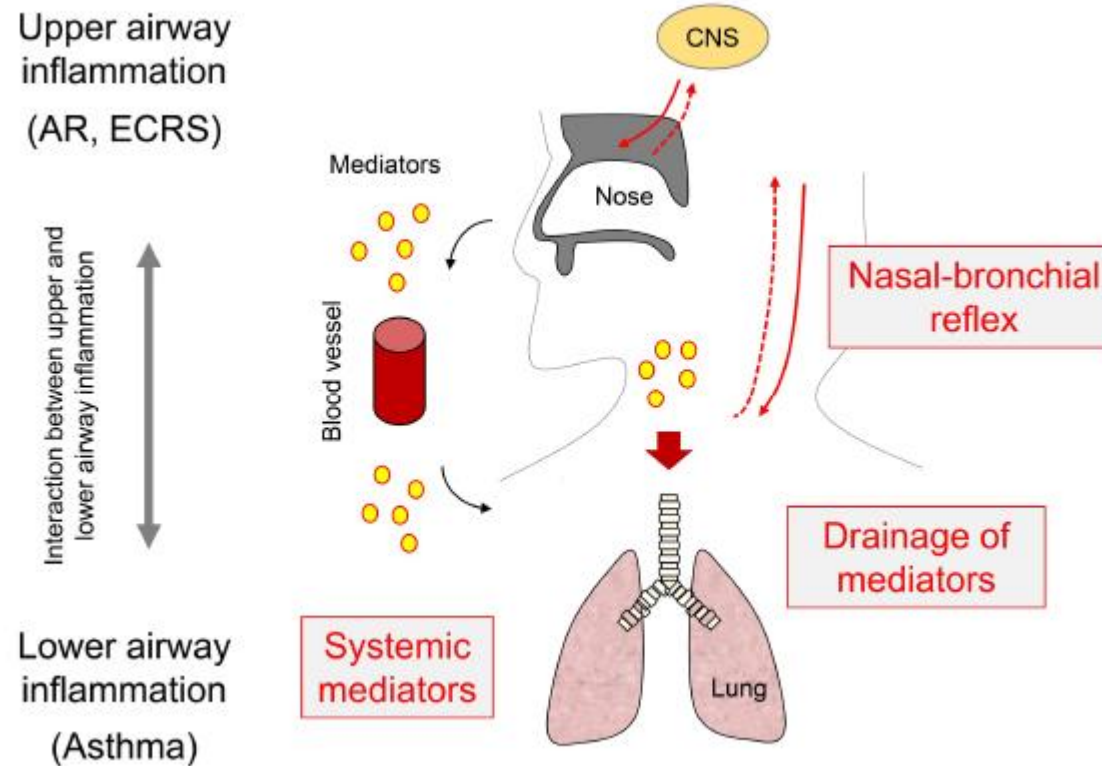
1. Ohta K. et al. Prevalence and impact of rhinitis in asthma. SACRA, a cross-sectional nation-wide study in Japan. Allergy 2011, 66, 1287–1295.

2. Settiple RJ, et al. A. Long-term risk factors for developing asthma and allergic rhinitis: A 23-year follow-up study of college students. Allergy Proc. 1994, 15, 21–25.

3. Bousquet J, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: A subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy [corrected]. Clin. Exp. Allergy 2005, 35, 723–727.

4. Togias, A. Rhinitis and asthma: Evidence for respiratory system integration. J. Allergy Clin. Immunol. 2003, 111, 1171–1183,

Relationships Among the Upper and Lower Airways and the Middle Ear in United Airway Disease



Schema of mechanisms of interaction between upper and lower airway inflammation.

Red line and dot-line indicate parasympathetic and trigeminal nerve, respectively

Definitions

Definition of allergic rhinitis

“Allergic rhinitis (AR) is an inflammatory process of the nasal mucosa, typically IgE-mediated, elicited by environmental allergens and characterized by the presence of inflammatory cells within the mucosa and submucosa”

Definition of asthma

“A chronic inflammatory disorder of the airways which manifests itself as recurrent episodes of wheezing, breathlessness, chest tightness and cough. It is characterized by bronchial hyper-responsiveness and variable airflow obstruction, that is often reversible either spontaneously or with treatment.”

Airway hypersensitivity syndrome phenotypes

- ▶ Rhinitis
- ▶ Rhinitis with airway hyper responsiveness
- ▶ Eosinophilic bronchitis
- ▶ Asthma
- ▶ Rhinitis and asthma

Note: Rhinitis can be associated with conjunctivitis.

Link between Asthma and Rhinitis

- ▶ Allergic rhinitis (AR) and asthma affect the upper and lower respiratory tracts, respectively.
- ▶ Both are characterized by inflammation of the respiratory mucosa and involve similar inflammatory cells and mediators.
- ▶ Upper and lower airways form a continuous respiratory tract
- ▶ Many inflammatory changes of allergic rhinitis is similar to those of allergic asthma
- ▶ The anatomical and immunological link between the lung and nose means that inflammation in one organ influences symptoms in the other

Epidemiologic Links between Allergic Rhinitis and Asthma

- ▶ Up to 88% of all asthmatic patients have allergic rhinitis

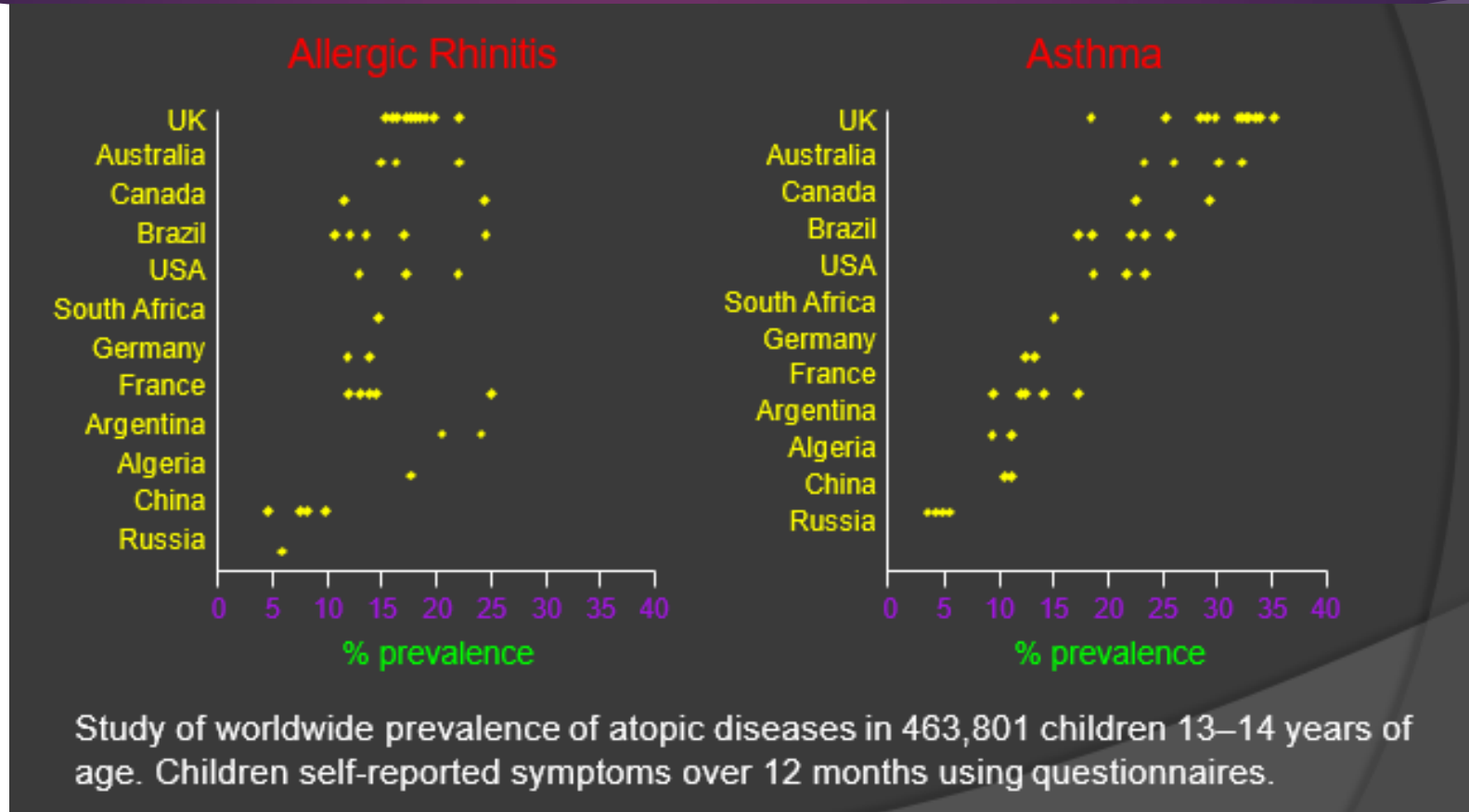
88%

Epidemiologic Links between Allergic Rhinitis and Asthma

- ▶ Up to 80% of all asthmatic patients have allergic rhinitis



Allergic Rhinitis and Asthma Have Similar Prevalence Patterns

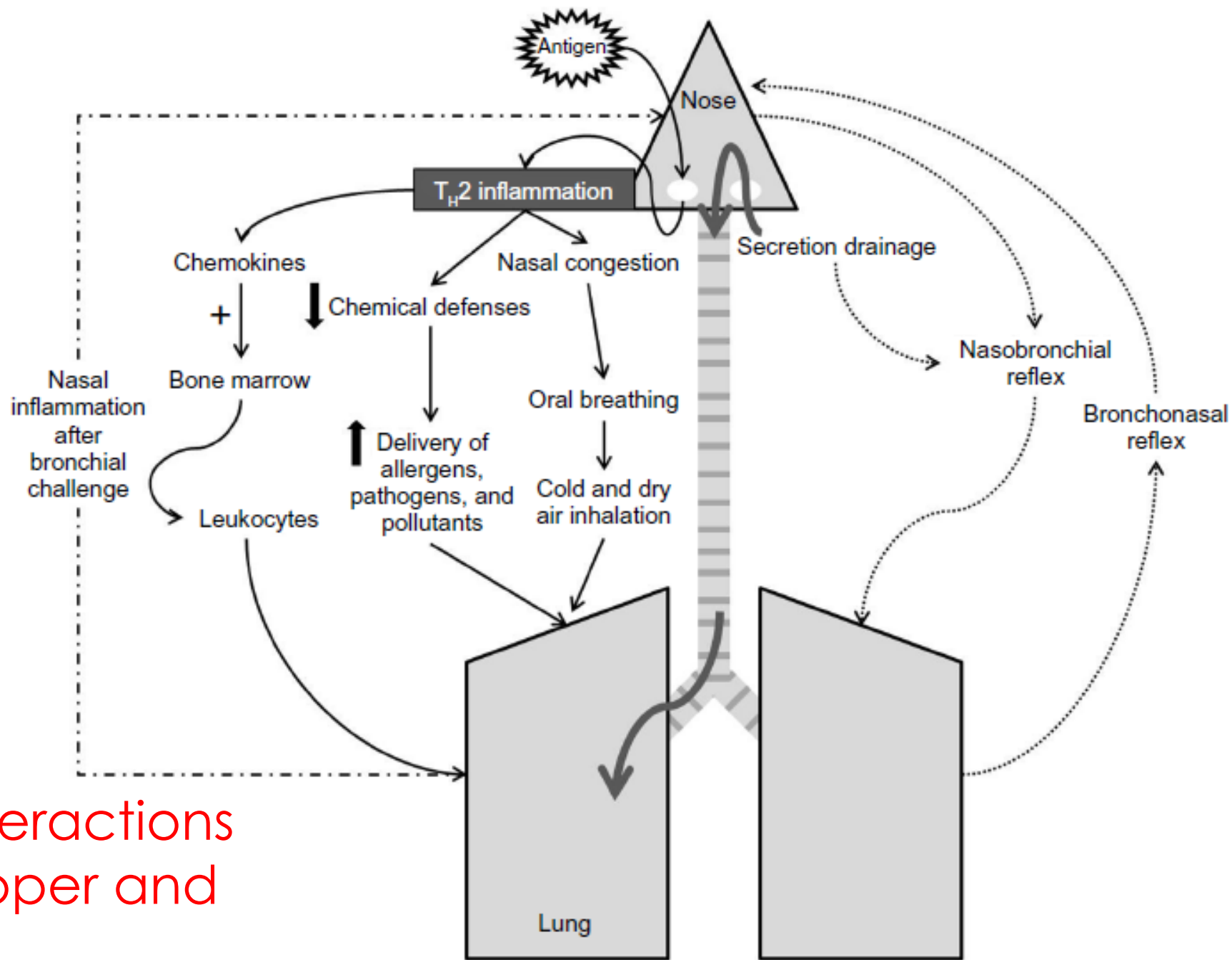


Both Asthma and Allergic Rhinitis Are Inflammatory Conditions

- ▶ Asthma is fundamentally a disease of inflammation
 - ▶ Inflammation of the lower airway causes bronchoconstriction and airway hyper responsiveness resulting in asthma symptoms
- ▶ Allergic rhinitis is an IgE-mediated inflammatory disorder
 - ▶ Inflammation of the nasal membranes in response to allergen exposure results in nasal symptoms

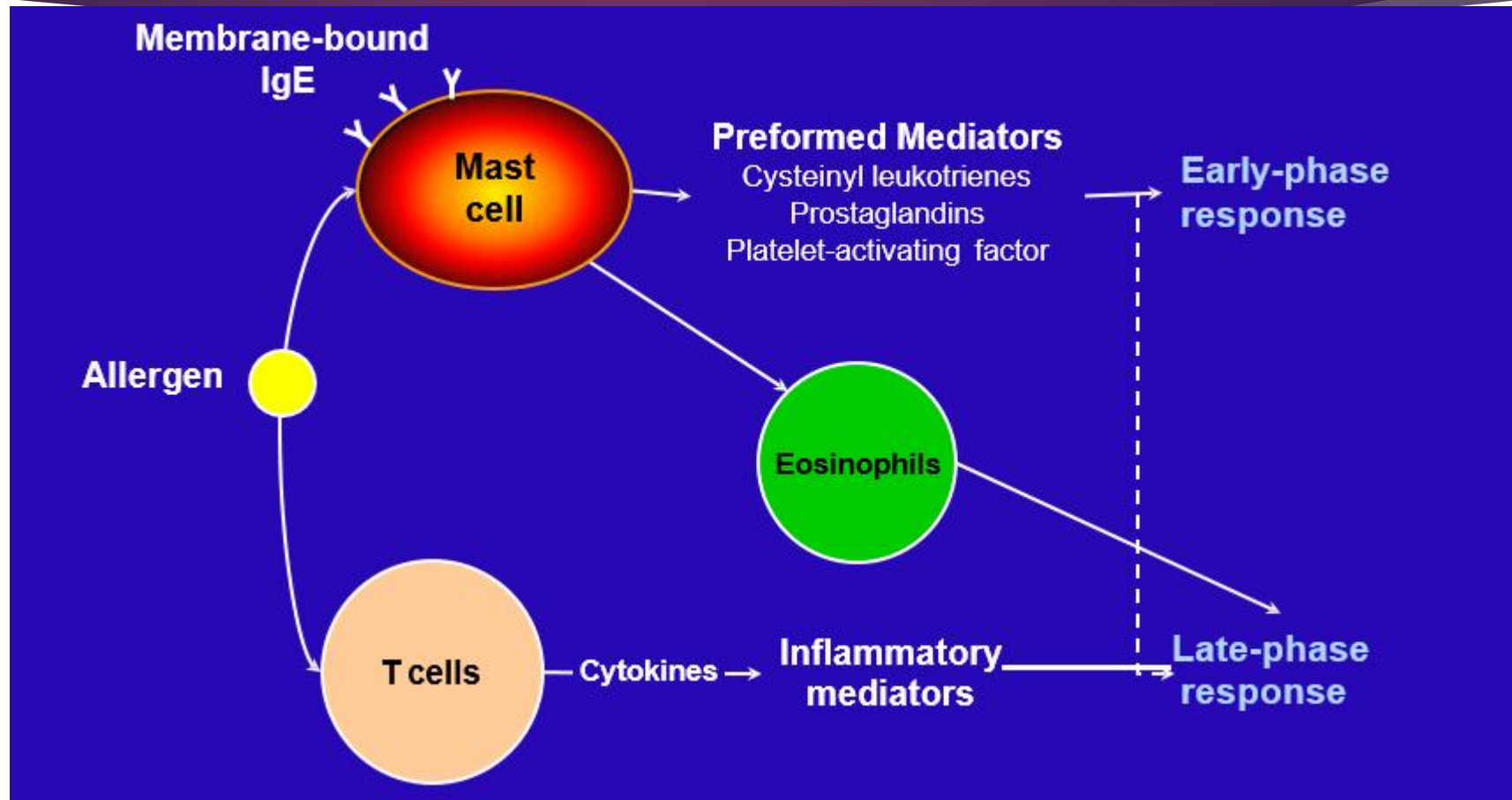
Both Asthma and Allergic Rhinitis Are Inflammatory Conditions

- ▶ In AR, one distinction is heavy vascularization of the nasal passages, which may lead to severe nasal obstruction.
- ▶ In asthma, the presence of smooth muscles from trachea to bronchioles can result in characteristic bronchoconstriction



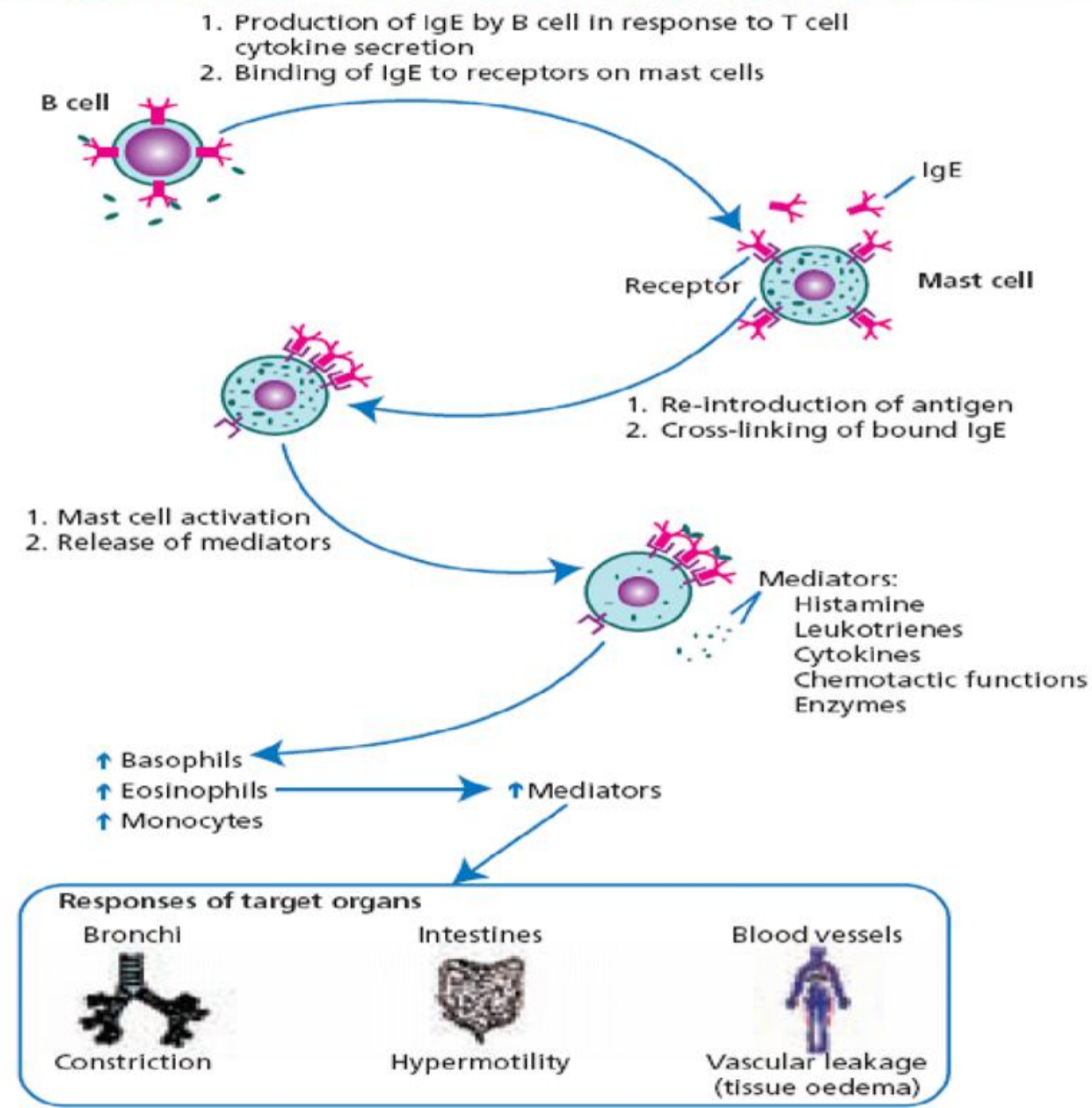
Pathological interactions
between the upper and
lower airways

Allergic Rhinitis and Asthma Share Common Inflammatory Cells and Mediators





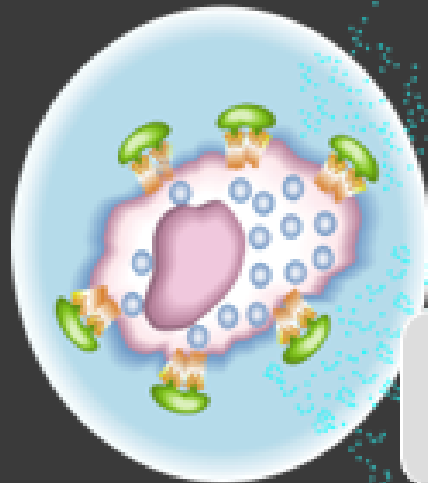
The early and late phase responses of the allergic cascade, including the inflammatory cells involved, mediators released and resulting symptoms



Allergic Rhinitis



Allergen



CYTOKINES

IL-1
IL-3
IL-4
IL-5
IL-6
IL-13
TNF- α

HISTAMINE

Leukotriene C₄
Prostaglandin D₂
Tryptase

CHEMOKINES

IL-8
Eotaxin
RANTES

ADHESION MOLECULES

P-selectin
ICAM

Early-Phase Inflammatory Response (minutes-1 hour)



Histamine binds to
H¹ receptors

Histaminic
response

- Sneezing
- Itchy, watery eyes
- Rhinorrhoea
- Nasal congestion



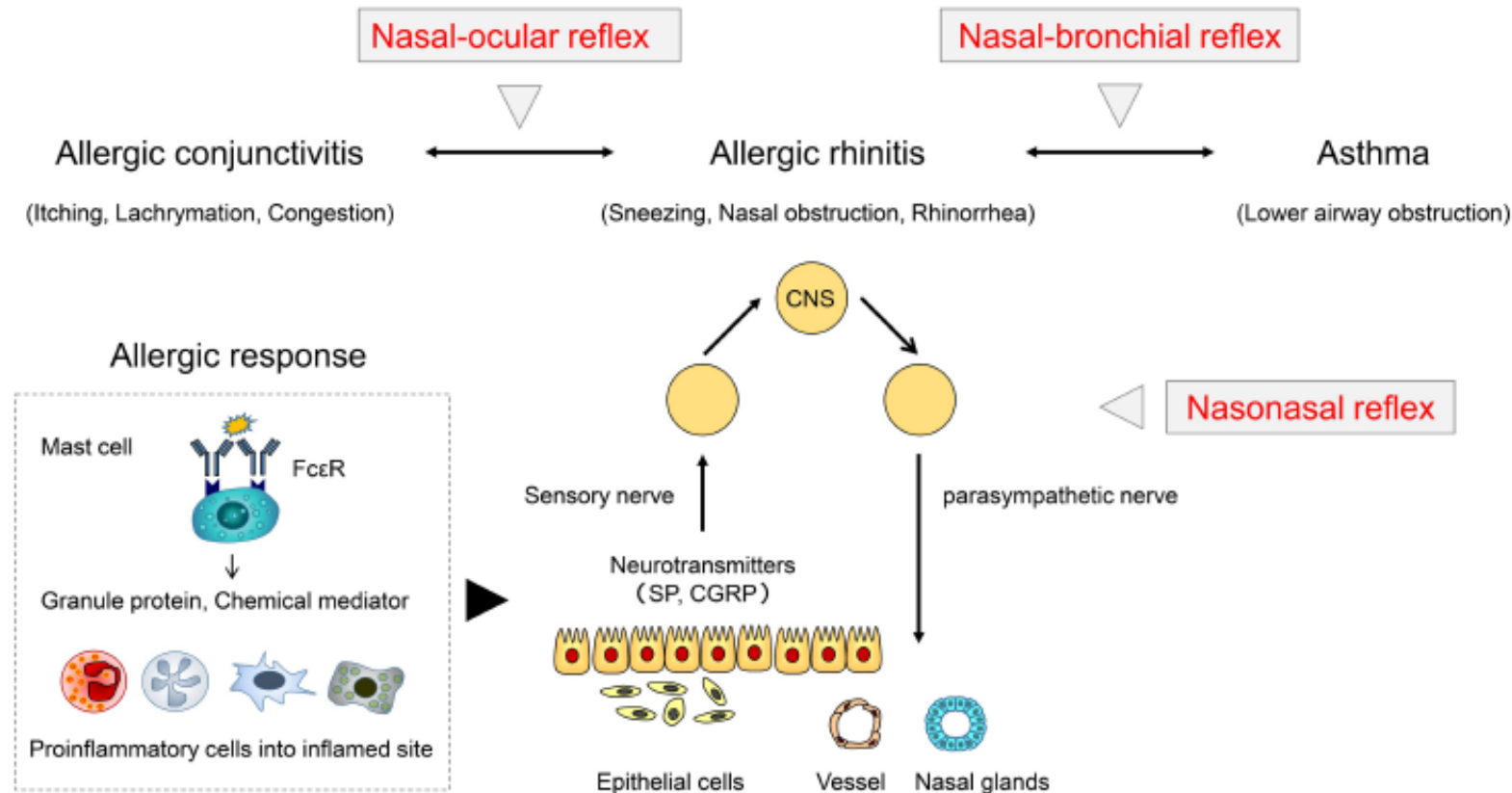
Promotes
eosinophil and
other cell migration
and infiltration

Allergic
inflammatory
response

- Nasal inflammation
- Nasal obstruction
- Difficulty breathing
- Tinnitus

Late-Phase Inflammatory Response (4-24 hours)

Neural Modulation in United Airway Disease

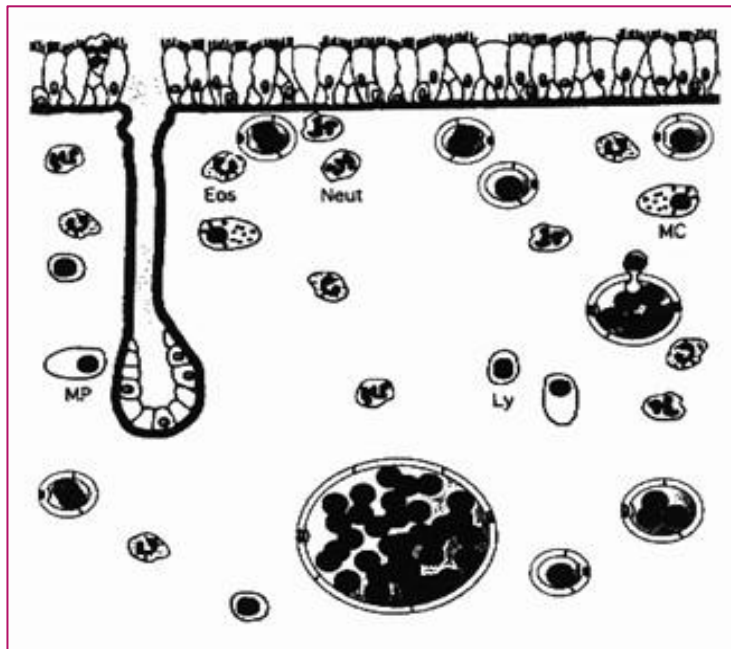


Neural pathway in allergic rhinitis; nasonasal reflex, nasal-ocular reflex, and nasal-bronchial reflex.

CGRP, calcitonin gene-related peptide; SP, substance P; Fc ϵ R, Fc epsilon receptor

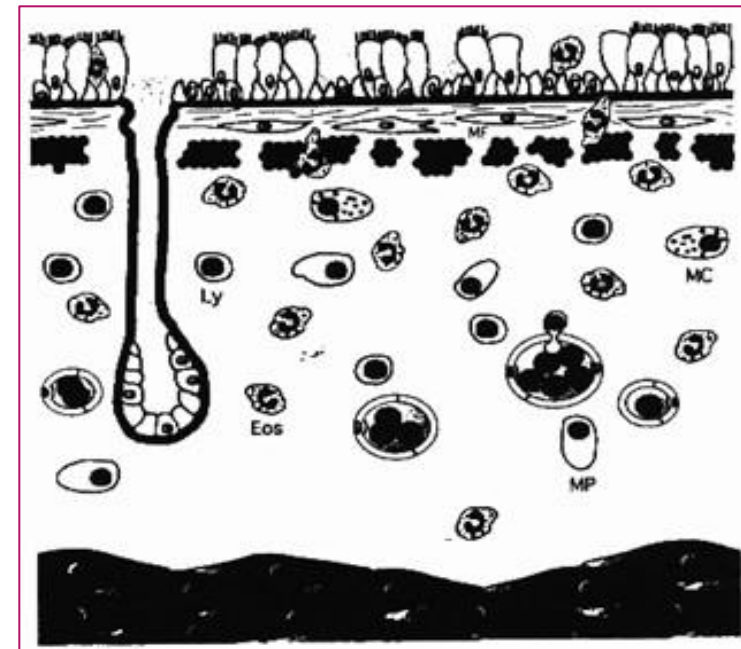
Allergic Rhinitis and Asthma Share a Similar Inflammatory Process and Occur in the Mucosa

Allergic rhinitis



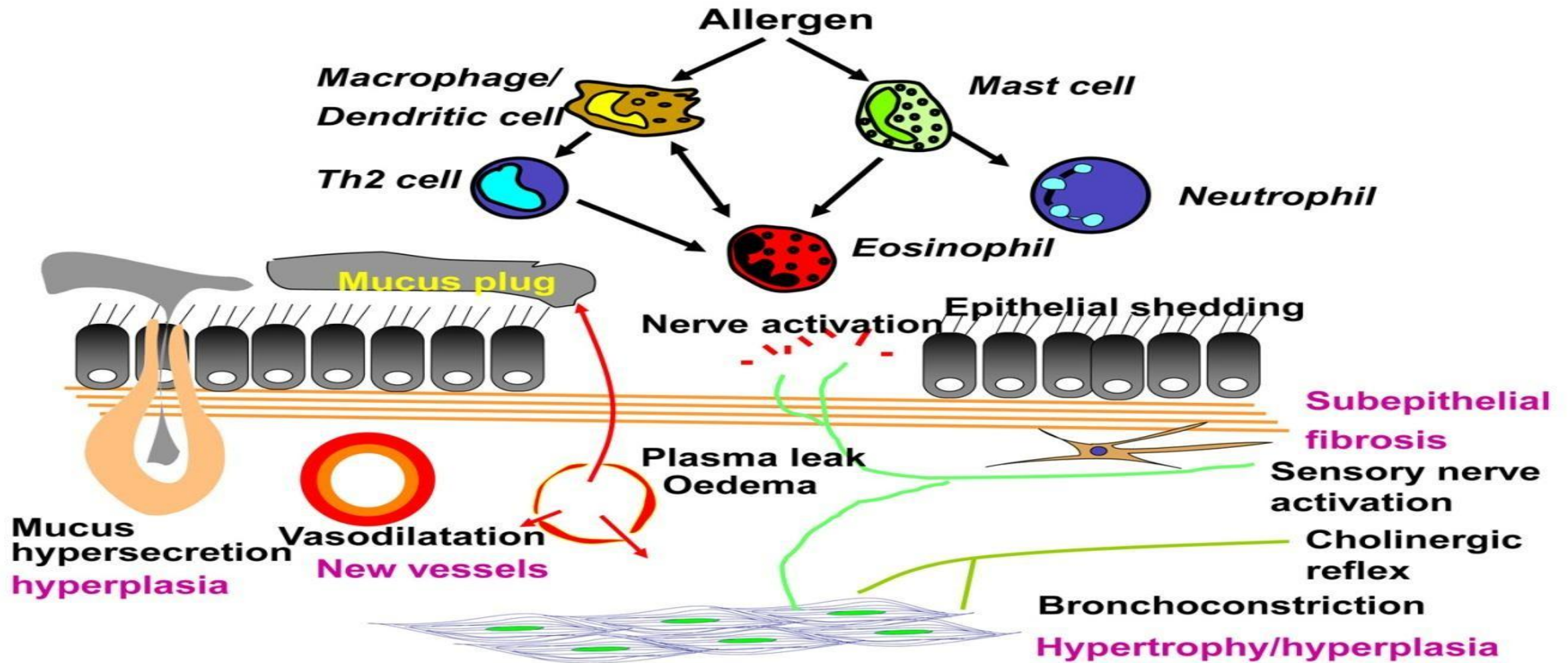
Nasal mucosa

Asthma



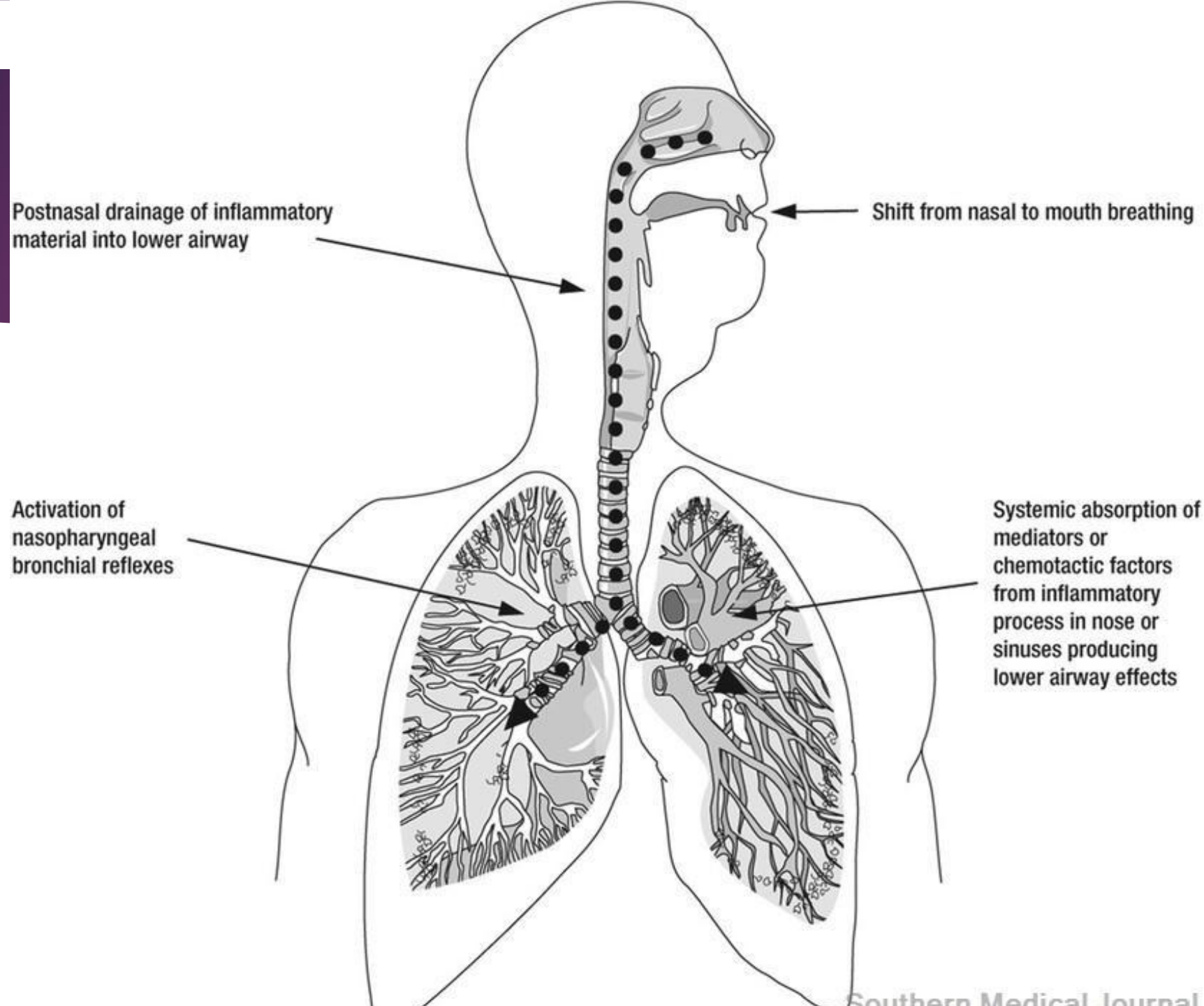
Bronchial mucosa

Asthma Inflammation



Asthmatic inflammation

Mechanisms of pathologic relationships between upper and lower airways

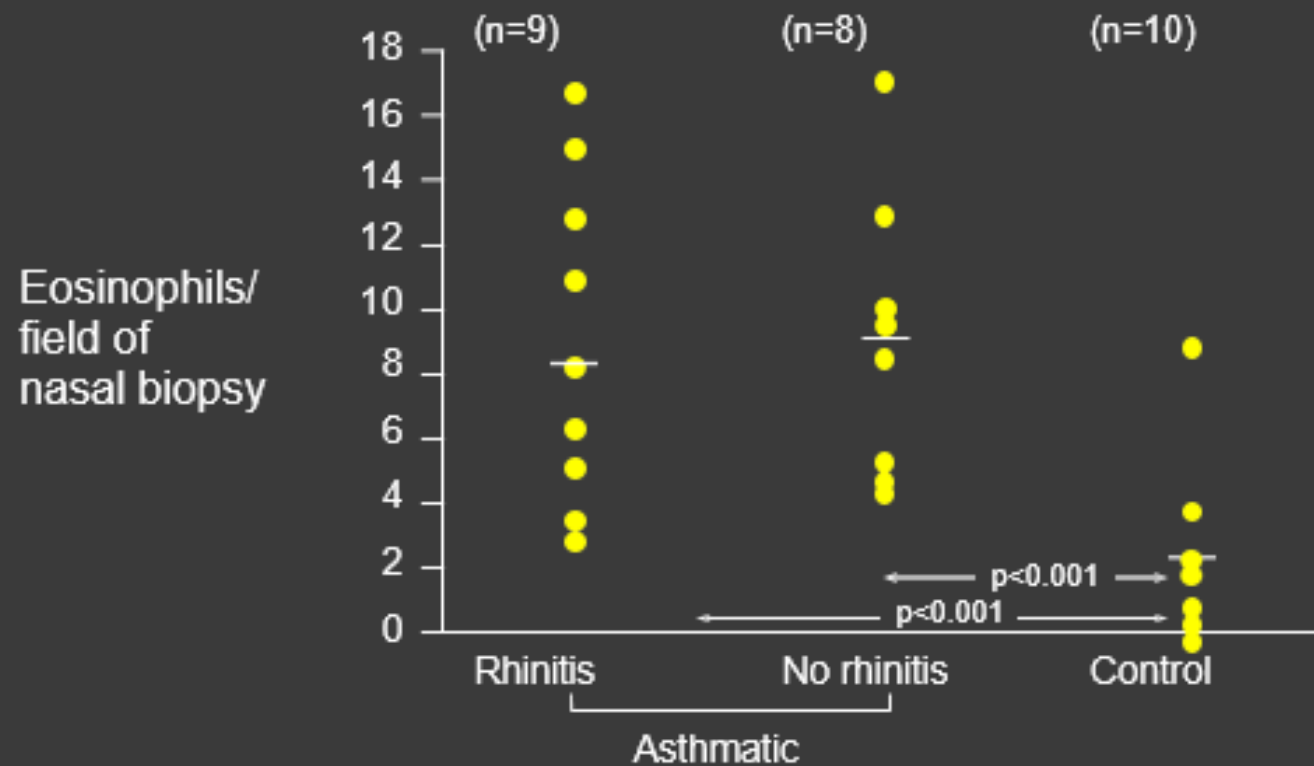


Other Proposed pathophysiologic mechanisms of asthma exacerbated by sinusitis

- ▶ Spread of inflammatory mediators and chemotactic factors to lower airways triggers Sino bronchial reflex mechanism.
- ▶ Stimulation of autonomic nervous system causes acute bronchial hyper responsiveness.
- ▶ Reversible partial beta-adrenergic blockade is enhanced.
- ▶ Depressed nitric oxide concentration promotes acute bronchial hyper responsiveness

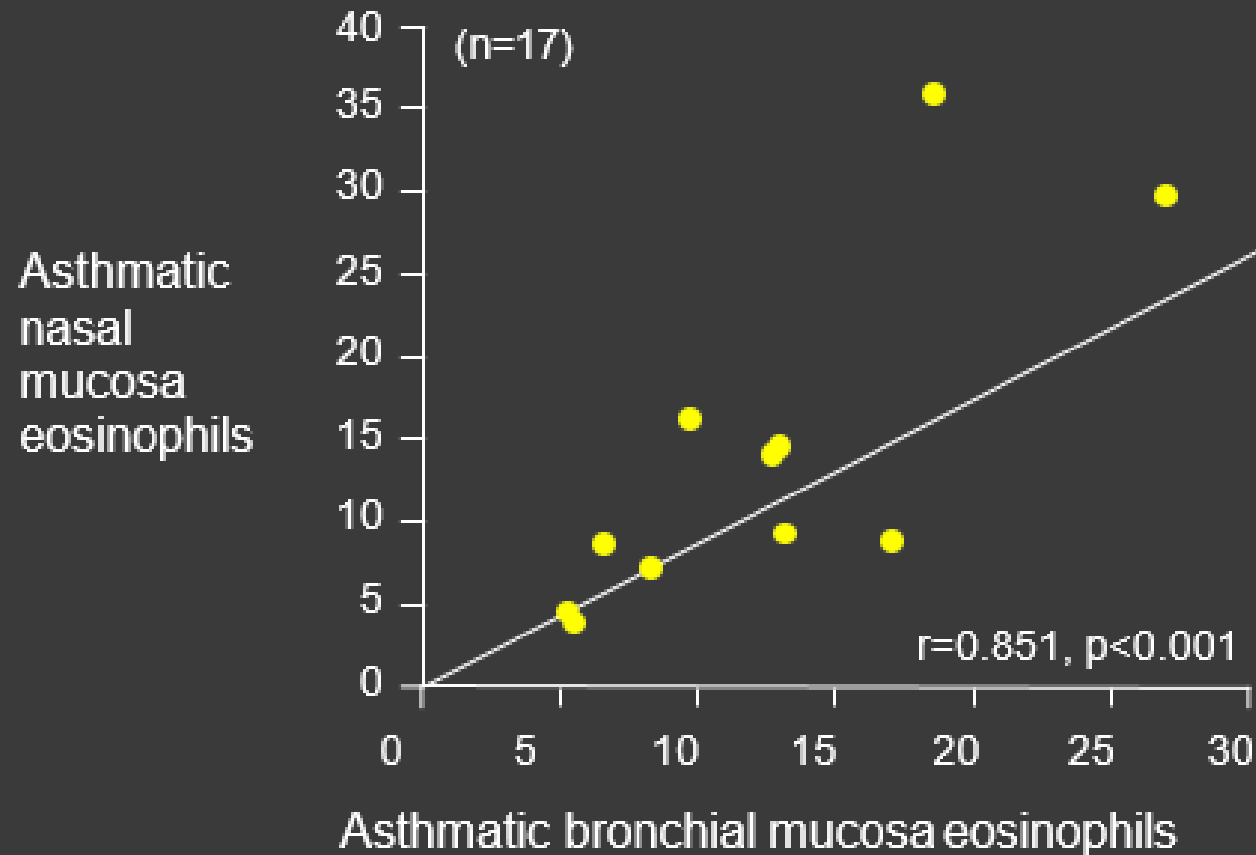
Many Patients with Asthma Have Nasal Inflammation

Eosinophil counts in the nasal mucosa



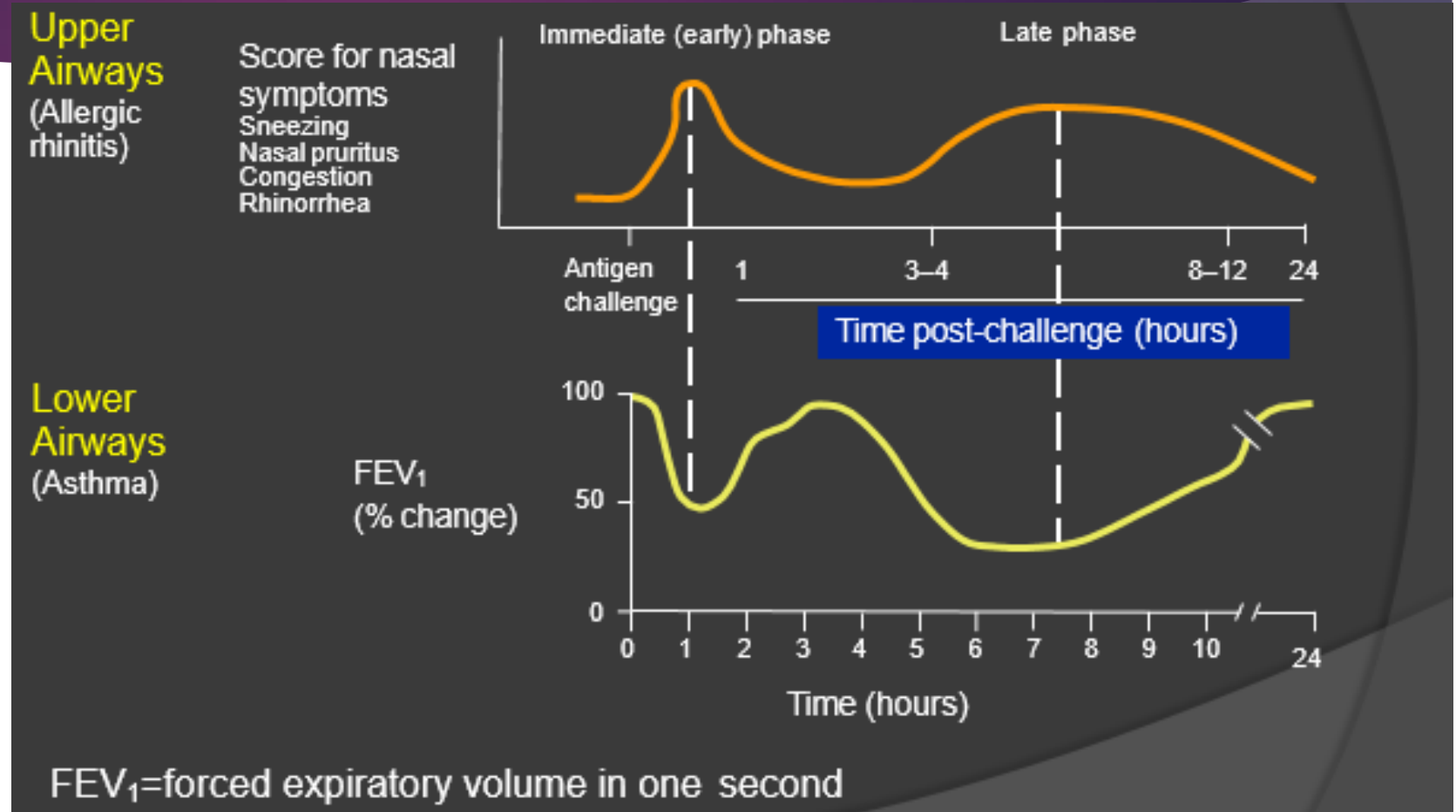
Study of whether nasal mucosal inflammation exists in asthma regardless of the presence of allergic rhinitis in atopic subjects 20 to 66 years of age
Bars represent median values.

Inflammatory Changes in the Nasal and Bronchial Mucosa Are Correlated

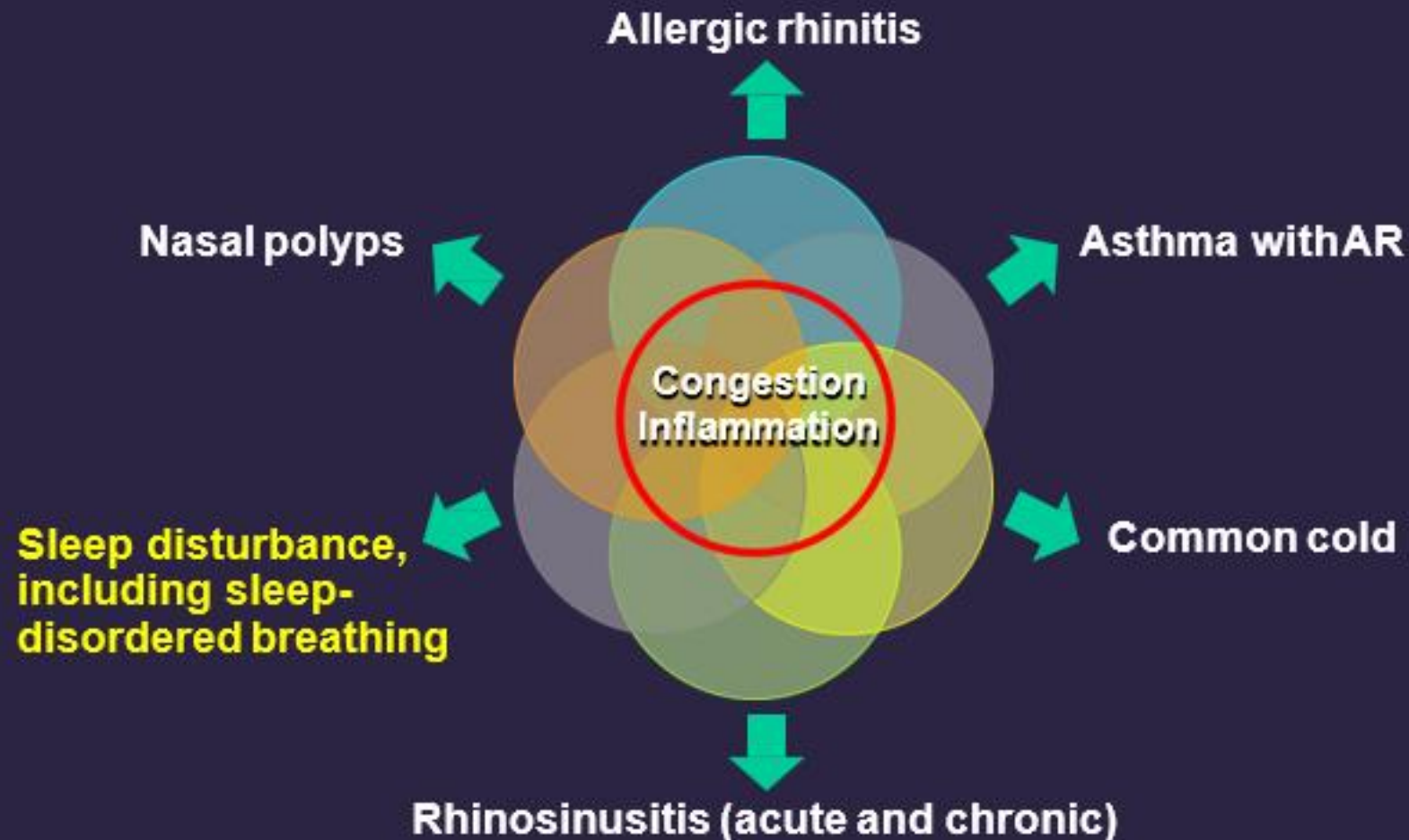


Study of whether nasal mucosal inflammation exists in asthma regardless of the presence of allergic rhinitis in atopic subjects 20 to 66 years of age

Symptoms Correlate with the Early and Late-Phase Responses in Allergic Rhinitis and Asthma



Congestion and Inflammation: Adverse Clinical Impact in Upper Respiratory Disease



Impact of allergic rhinitis on lung function

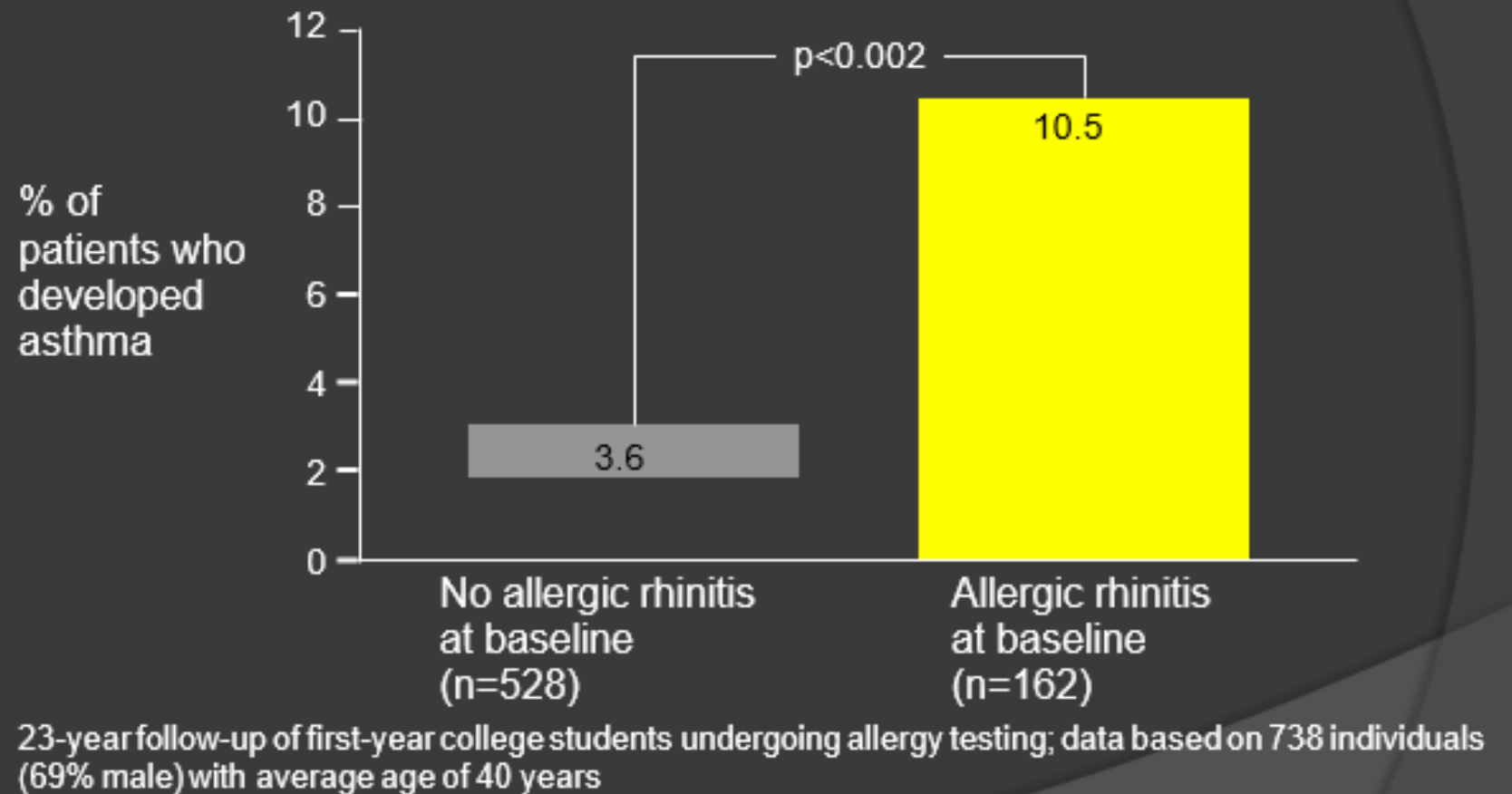
- ▶ Both AR and asthma have airflow limitation as the main functional consequence
- ▶ The forced expiratory volume in 1 second (FEV1), a measurement of exhaled volume during the first second of a forced expiratory maneuver, may be impaired in approximately 5% of patients with AR who report only nasal symptoms.

How Allergic rhinitis affects asthma

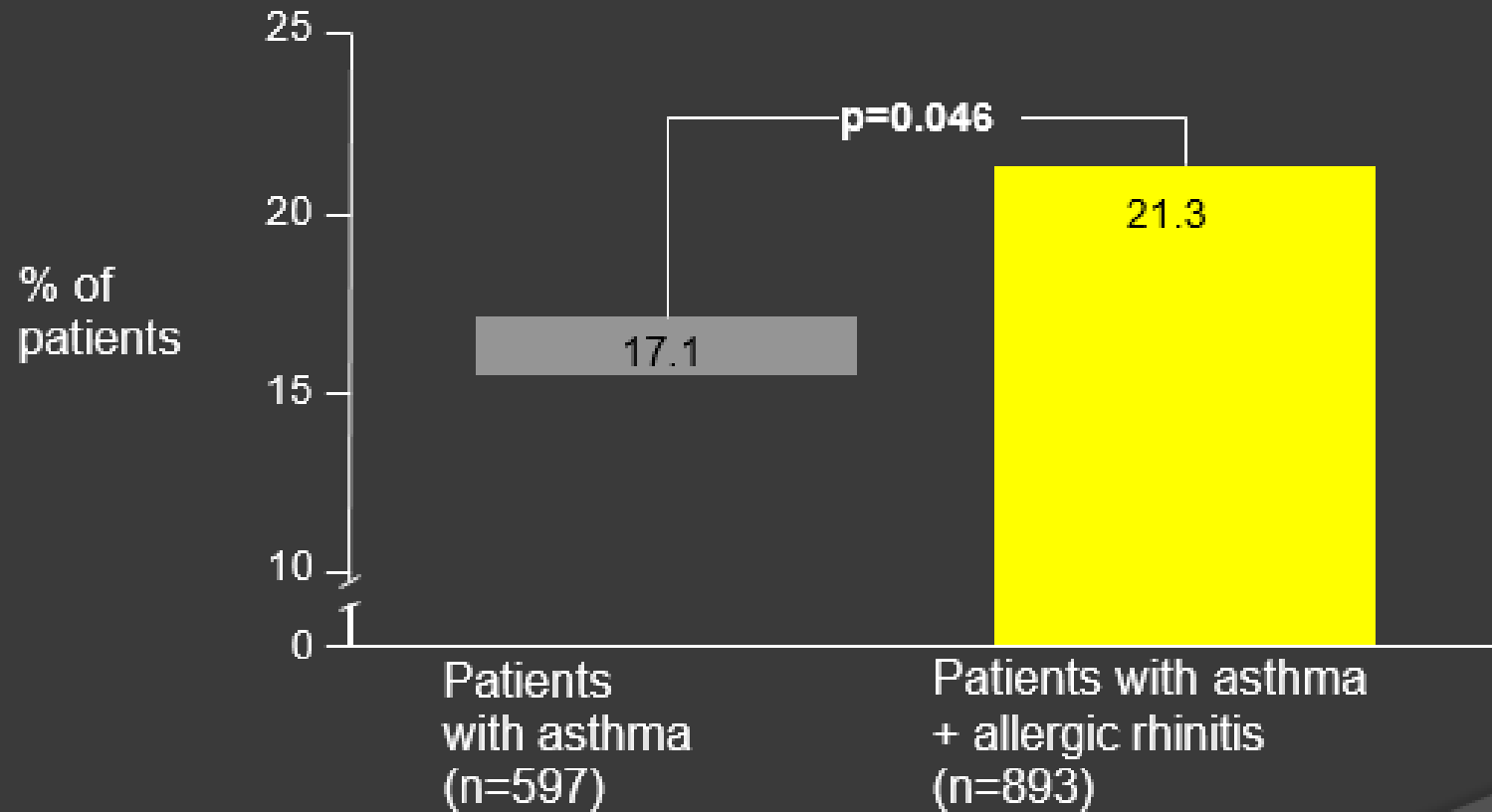
- ▶ Allergic rhinitis may promote or exacerbate asthma through several physiologic mechanisms that link the disorders.
- ▶ These include :
 - ▶ The vagal (rhinobronchial) reflex, which causes
 - ▶ nasal stimulation to induce bronchoconstriction.
 - ▶ Systemic release of mediators and cytokines. 3- Postnasal drip and resulting irritation.
 - ▶ 4- The need for oral respiration caused by nasal obstruction, which causes dry, cold air to penetrate into the bronchi and promote bronchial hyper reactivity

Allergic Rhinitis Is a Risk Factor for Asthma

Allergic rhinitis increased the risk of asthma about threefold

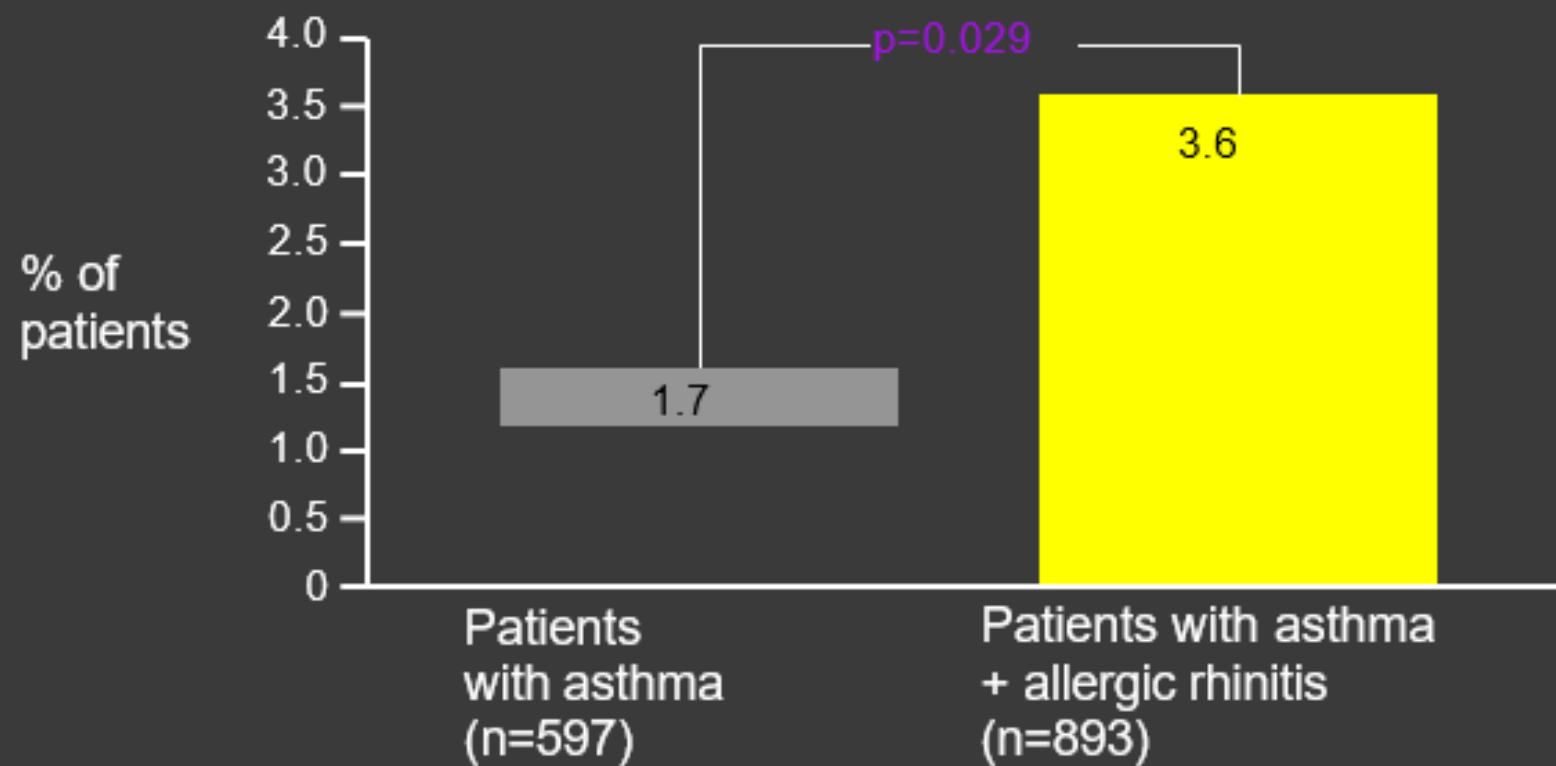


Allergic Rhinitis Increased the Risk of Asthma Attacks



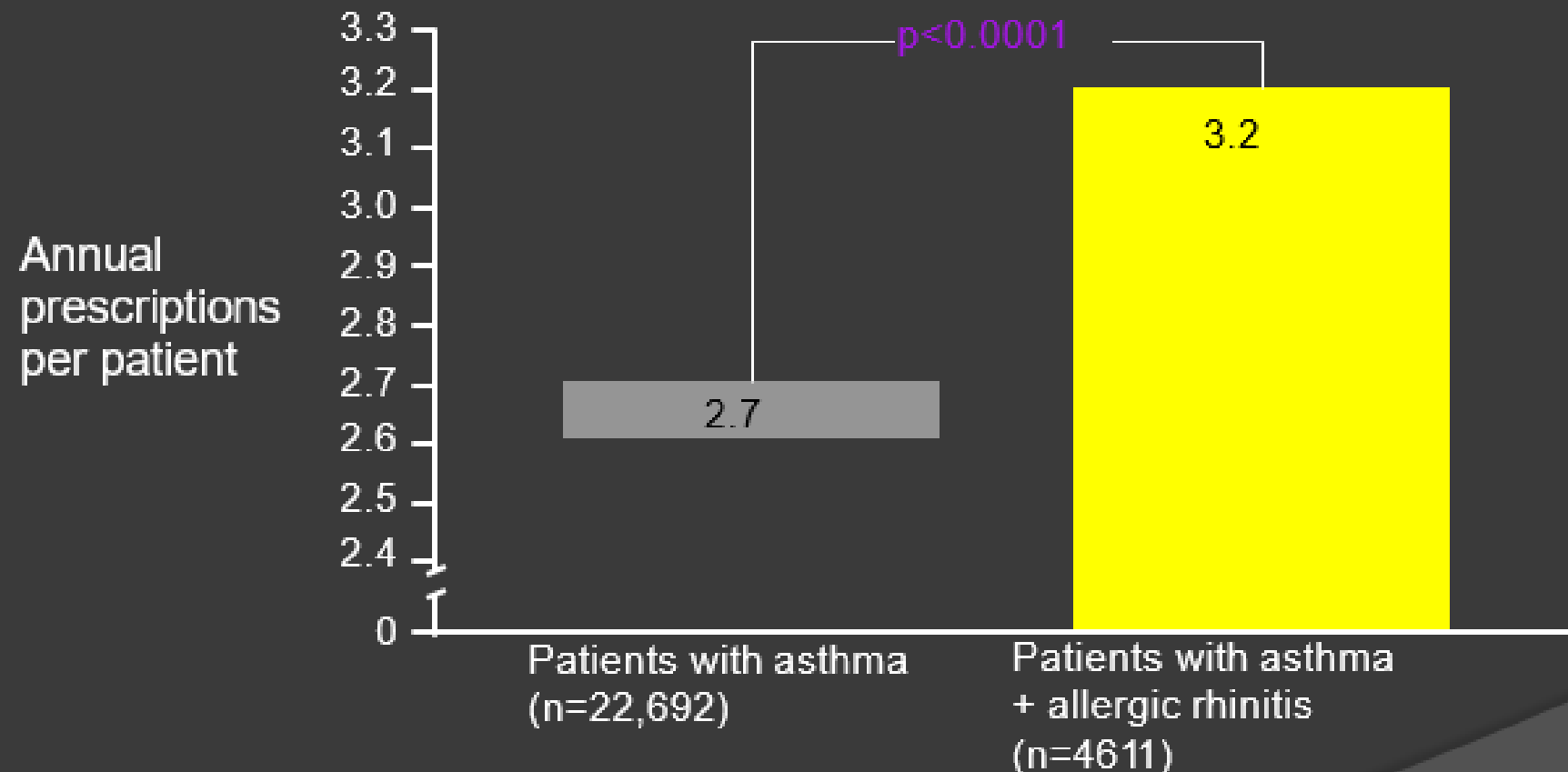
Post hoc analysis of medical resource use/asthma attacks in asthmatic patients with and without concomitant allergic rhinitis over 52 weeks

Allergic Rhinitis Doubled the Risk of Emergency room Visits in Patients with Asthma



Post hoc analysis of medical resource use/asthma attacks in asthmatic patients with and without concomitant allergic rhinitis over 52 weeks

Allergic Rhinitis Increased the Number of Prescriptions for Rescue Therapy (SABA) in Patients with Asthma



Analysis of health-care resource use in adults 16 to 55 years of age with asthma and allergic rhinitis in general practice in the UK
SABA=short-acting beta₂-agonists

Treating Rhinitis May Help Asthma

- ▶ The key to successful therapy for rhinitis and asthma is the prevention or suppression of inflammation
- ▶ Treatment of rhinitis has been shown to be beneficial to the lower airways
- ▶ Treating inflammation in the upper airways indirectly improves asthma symptoms and decreases bronchial hyper reactivity

Management of UAD

- ▶ Therapy for UAD includes
 - ▶ Avoidance of relevant allergens and irritants,
 - ▶ Pharmacotherapy,
 - ▶ Allergen-specific immunotherapy (SIT).

Management of UAD

- ▶ **Allergen avoidance** has been suggested to prevent
 - ▶ UAD onset and progression
 - ▶ Reduce its burden,
 - ▶ Improving symptoms and
 - ▶ Quality of life

Triggers of Asthma and AR

Common allergens

- ▶ House dust mites
- ▶ Pollen and spores
- ▶ Animals
- ▶ Work-related allergens

Like wood dust, flour dust or latex.

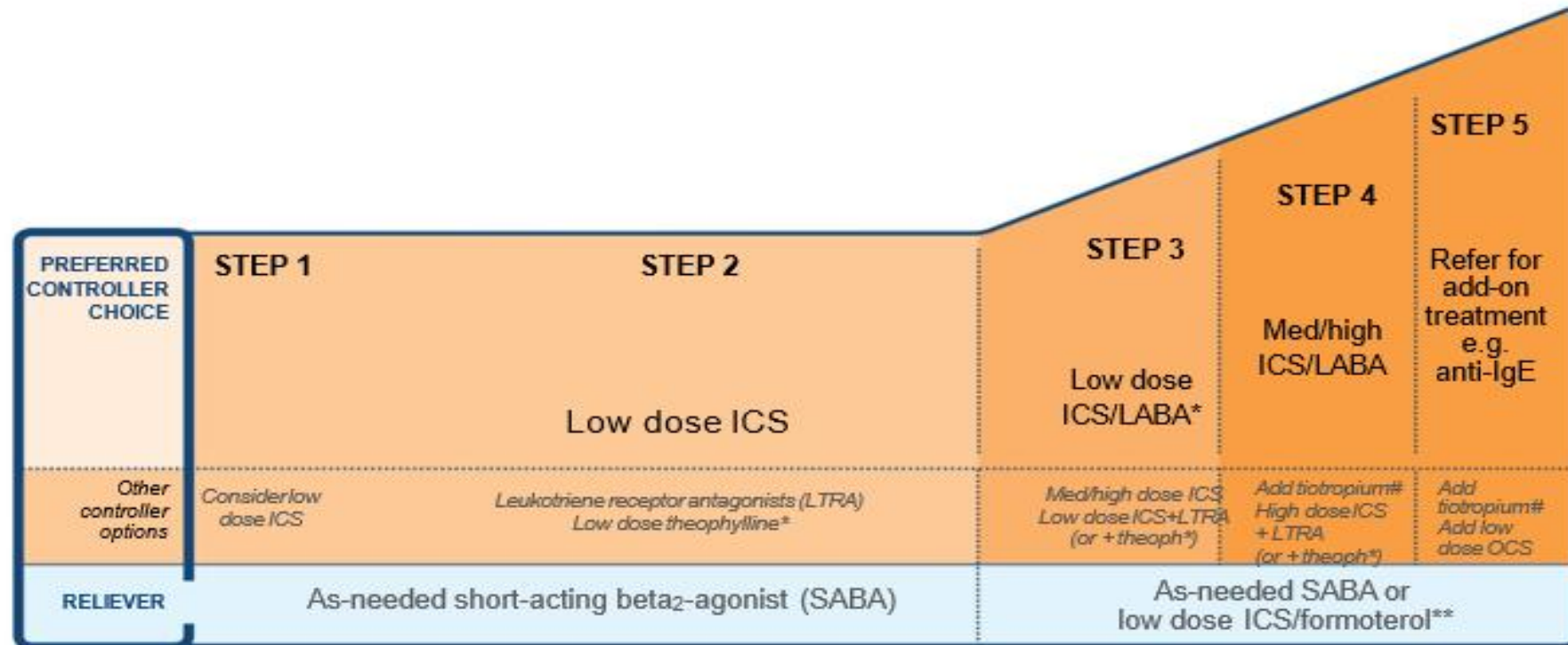
Management of UAD

- ▶ The **pharmacologic approach** includes
 - ▶ Antihistamines,
 - ▶ Oral leukotriene antagonists, and
 - ▶ Intranasal corticosteroids (considered the most efficacious) drug¹.
 - ▶ Oral and intranasal antihistamines, as well as leukotriene antagonists, are less effective than intranasal corticosteroids²

1. Bousquet J, et al. Allergy. 2008 Apr; 63 Suppl 86:8-160.

2. Benninger M, et al. Ann Allergy Asthma Immunol. 2010 Jan; 104(1):13-29.

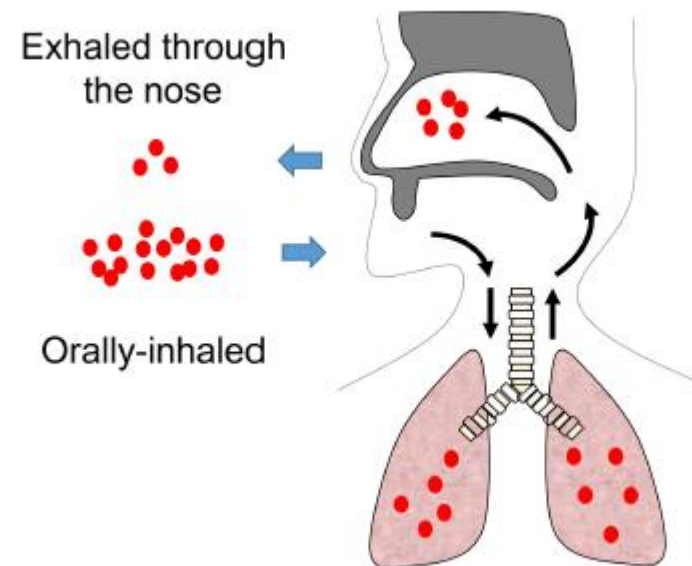
Inhaled short-acting beta2-agonist (SABA)



*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 # Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.

A Novel Therapeutic approach to United Airway Disease



Schema of HFA-BDP ETN treatment; hydrofluoroalkane-134a-beclomethasone dipropionate (HFA-BDP) exhaled through the nose (ETN) treatment.

Red dots indicate corticosteroids.

Management of UAD

- ▶ **Allergen-SIT (Speicifc immunotherapy)** is defined as

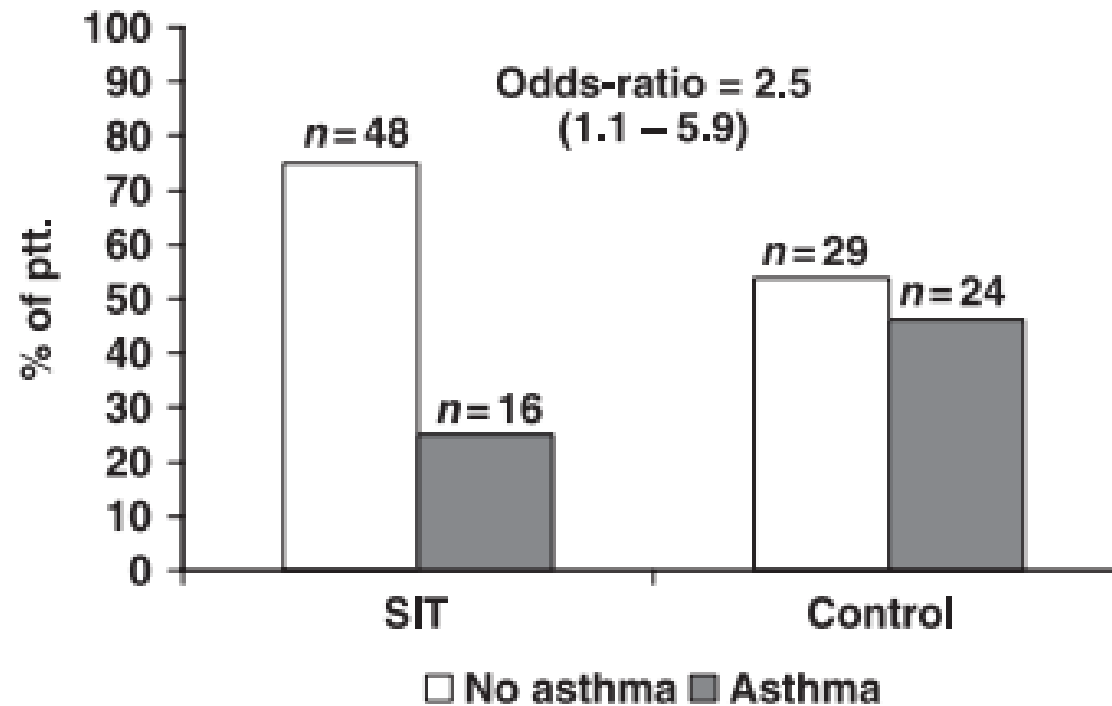
“a procedure to administer increasing amounts of specific allergens in patients diagnosed with IgE-mediated disease, in order to induce immune tolerance”.

- ▶ Subcutaneous and sublingual IT can reduce symptoms of AR and need of reliever medication, as well as improve the control of comorbid conditions

Allergen-SIT

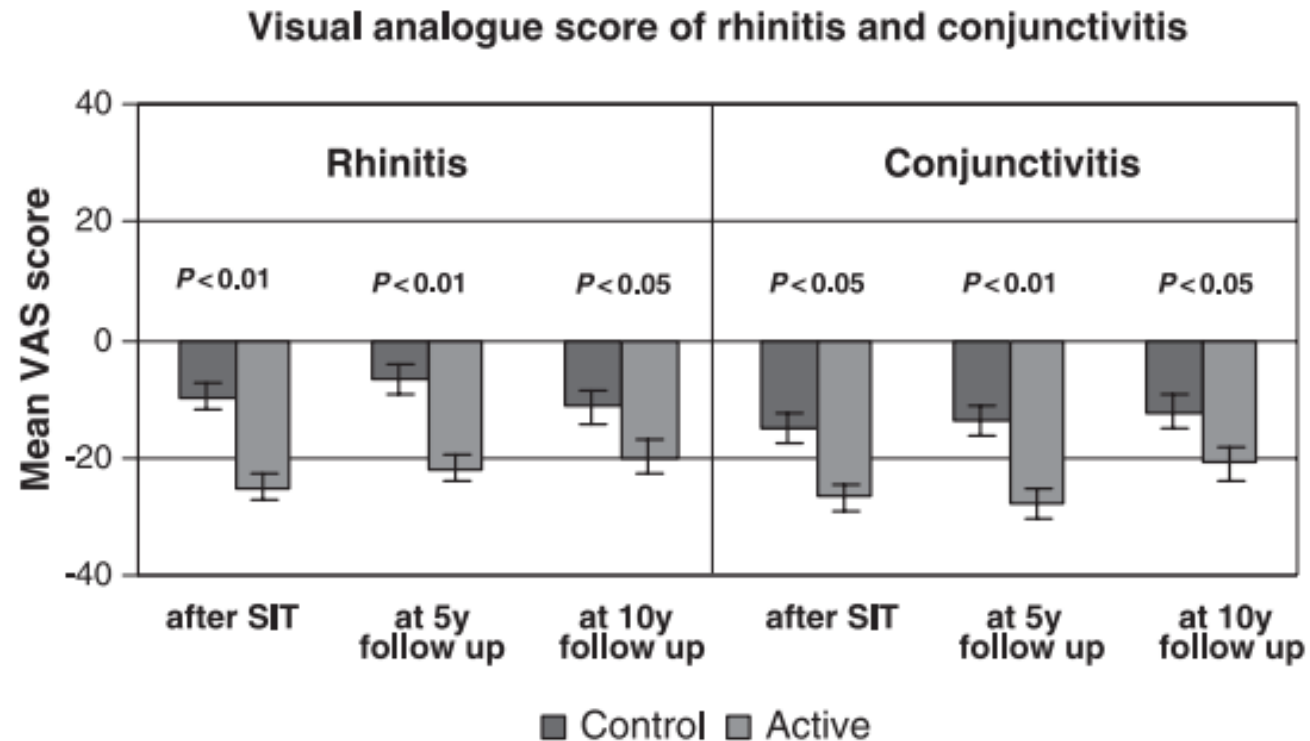
- ▶ Allergen-SIT is indicated in
 - ▶ Moderate/severe AR for which response to pharmacotherapy is inadequate.
 - ▶ Adverse effects of medications,
 - ▶ Coexisting allergic asthma,
 - ▶ Bad adherence to therapy, and
 - ▶ Patient preference for it instead of pharmacotherapy

Allergen-SIT



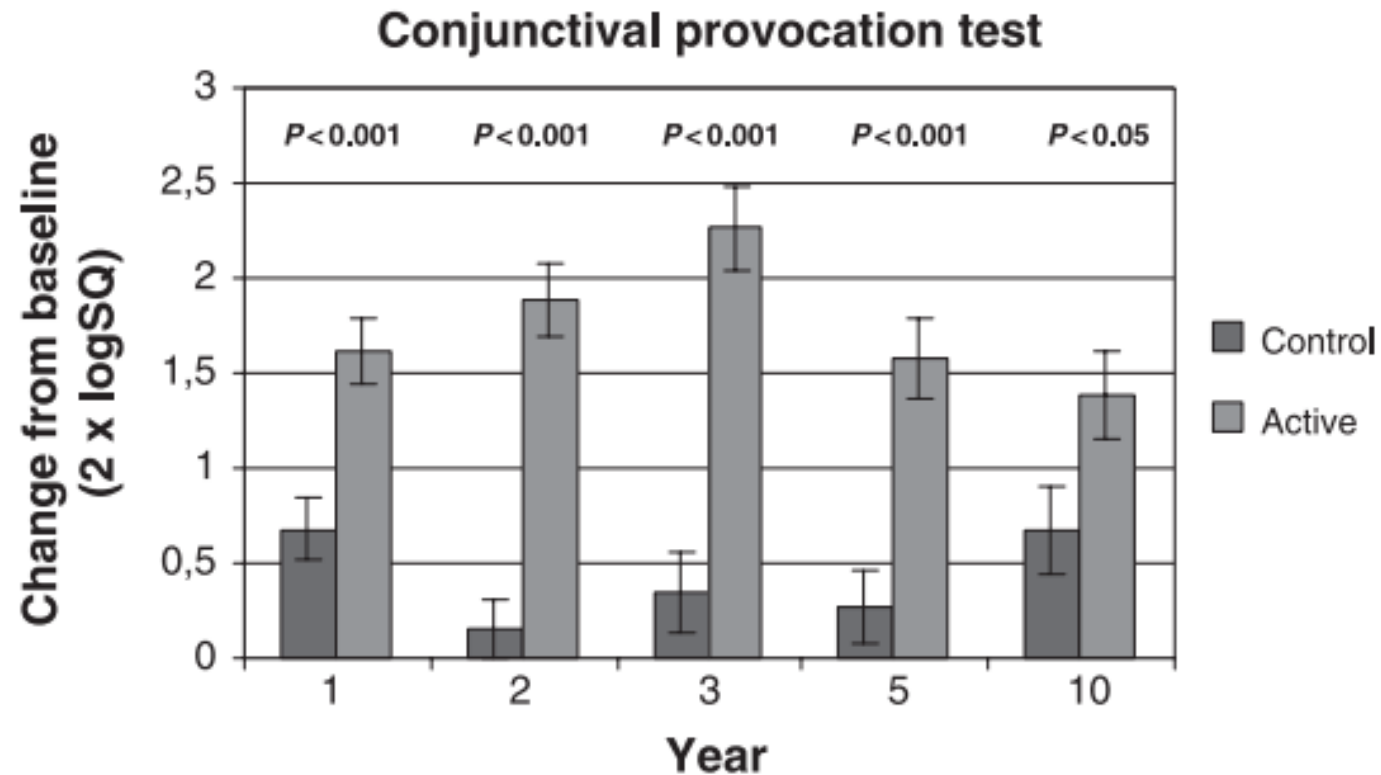
The percentage of children with and without asthma 7 years after termination (10-year follow-up) of specific immunotherapy.

Allergen-SIT



Change from baseline for rhinitis and conjunctivitis visual analogue scores at the end of specific immunotherapy, 2 and 7 years after termination.

Allergen-SIT

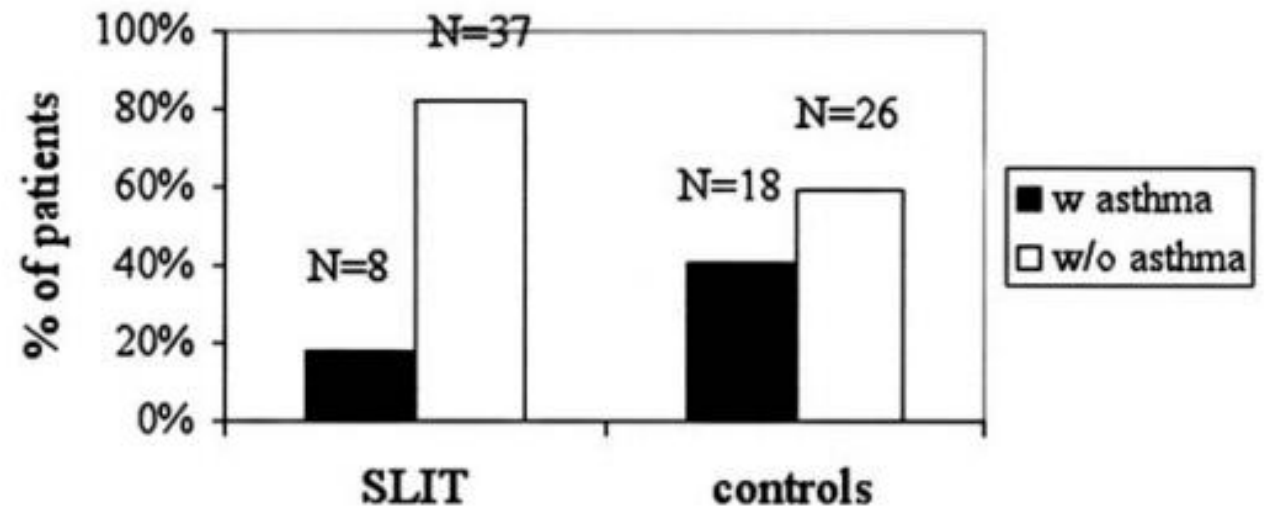


Change from baseline for the conjunctival provocation test. For children allergic to both grass and birch, the challenge with both allergens is included.

Allergen-SIT

- ▶ After 3 years of **sublingual grass-pollen IT** in children with AR, 3.8-fold more frequent development of asthma in the untreated patients

Age and centre adjusted odds-ratio = 3,8 (1,5-10,0)



The percentages of children with and without asthma after 3 years of immunotherapy

Novel targeted therapeutic approaches using biological agents

- ▶ **Omalizumab**, a humanized monoclonal antibody that binds circulating IgE and prevents its attachment to high-affinity IgE receptors
- ▶ Omalizumab improves both upper and lower airway diseases, reducing nasal and asthma symptoms, decreasing exacerbations, and improving quality of life

Novel targeted therapeutic approaches using biological agents

- ▶ **Mepolizumab**, a monoclonal antibody that blocks the binding of IL-5 to eosinophils,
- ▶ It has shown a beneficial effect on severe eosinophilic airway diseases, such as asthma and nasal polyposis in adults

ARIA and **IPAG** Guidelines Recommend a Combined Approach to Managing Asthma and Allergic Rhinitis

- ▶ Patients with allergic rhinitis should be evaluated for asthma
- ▶ Patients with asthma should be evaluated for allergic rhinitis
- ▶ A strategy should combine the treatment of upper and lower airways in terms of efficacy and tolerability

ARIA=Allergic Rhinitis and its Impact on Asthma; IPAG=International Primary Care Airways Groups

A reminder – the key change in GINA 2019



EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel ¹, J. Mark FitzGerald², Eric D. Bateman³,
Leonard B. Bacharier⁴, Allan Becker⁵, Guy Brusselle⁶, Roland Buhl⁷,
Alvaro A. Cruz⁸, Louise Fleming ⁹, Hiromasa Inoue¹⁰, Fanny Wai-san Ko ¹¹,
Jerry A. Krishnan¹², Mark L. Levy ¹³, Jiangtao Lin¹⁴, Søren E. Pedersen¹⁵,
Aziz Sheikh¹⁶, Arzu Yorgancioglu¹⁷ and Louis-Philippe Boulet¹⁸



@ERSpublications

GINA no longer recommends treating adults/adolescents with asthma with short-acting bronchodilators alone. Instead, they should receive symptom-driven (in mild asthma) or a daily corticosteroid-containing inhaler, to reduce risk of severe exacerbations. <http://bit.ly/310LLzE>

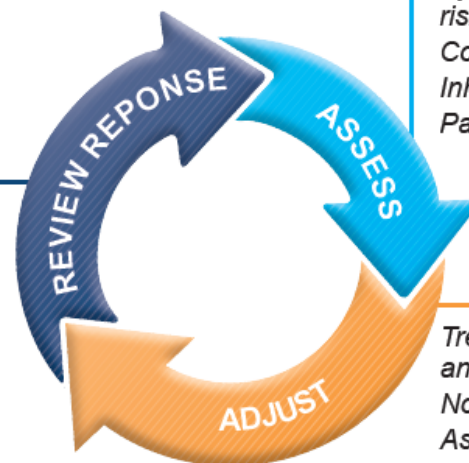
Cite this article as: Reddel HK, FitzGerald JM, Bateman ED, *et al.* GINA 2019: a fundamental change in asthma management. *Eur Respir J* 2019; 53: 1901046 [<https://doi.org/10.1183/13993003.01046-2019>].

Adults & adolescents 12+ years

Personalized asthma management:

Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction



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

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

Asthma medication options:

Adjust treatment up and down for individual patient needs

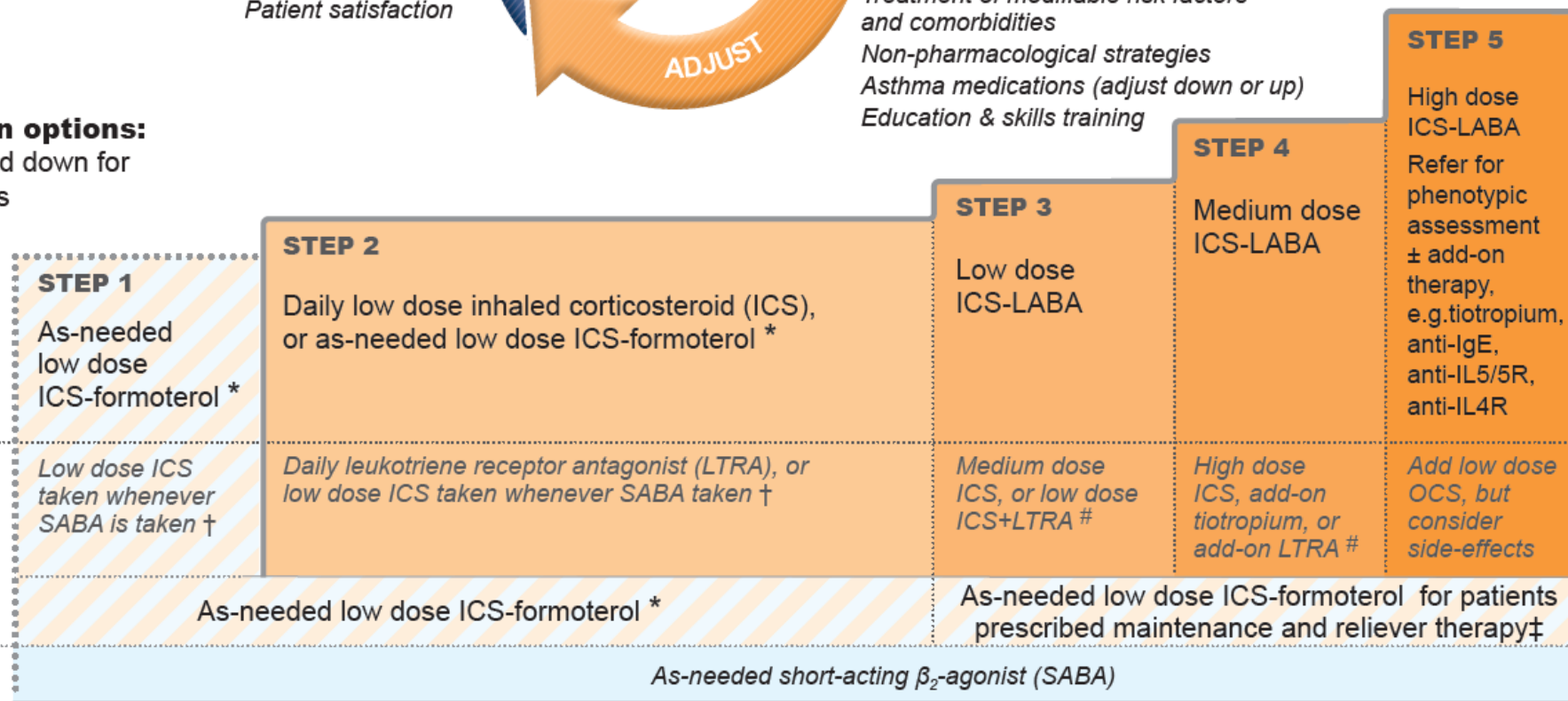
PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER

Other reliever option



* Data only with budesonide-formoterol (bud-form)

† Separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁ >70% predicted

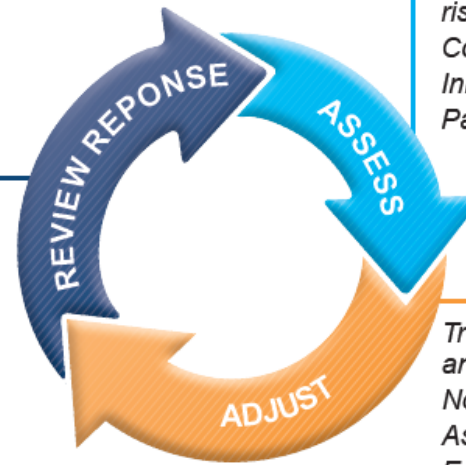


Adults & adolescents 12+ years

Personalized asthma management:

Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction



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

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

Asthma medication options:

Adjust treatment up and down for individual patient needs

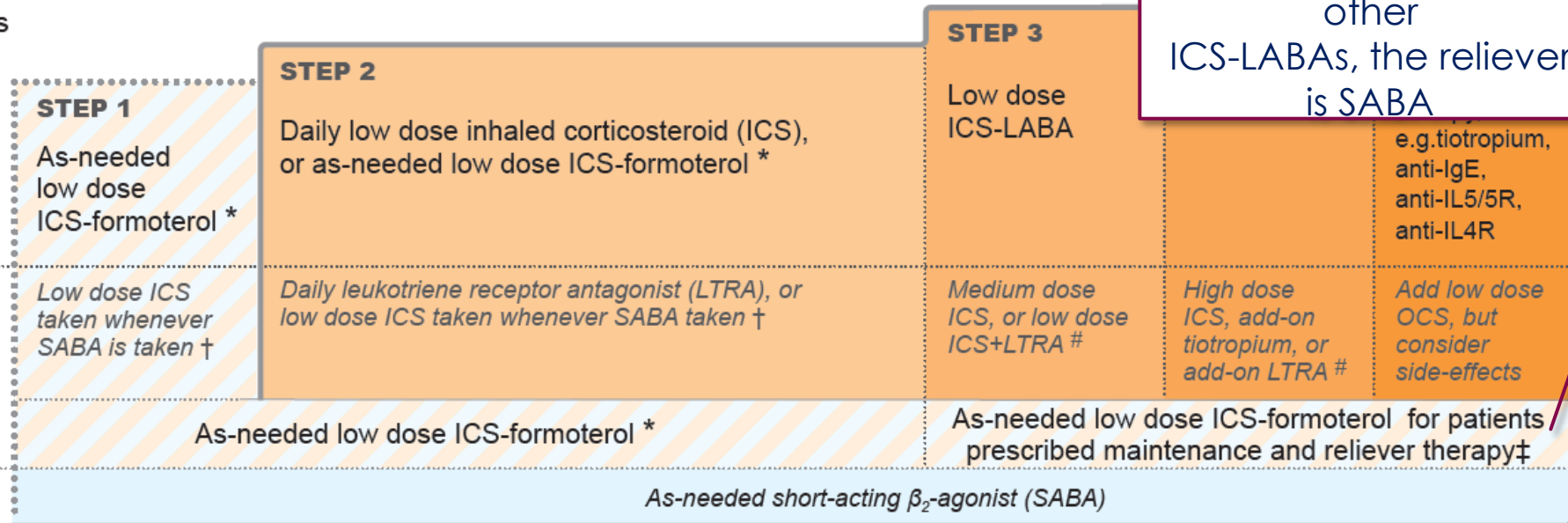
PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER

Other reliever option



* Data only with budesonide-formoterol (bud-form)

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‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

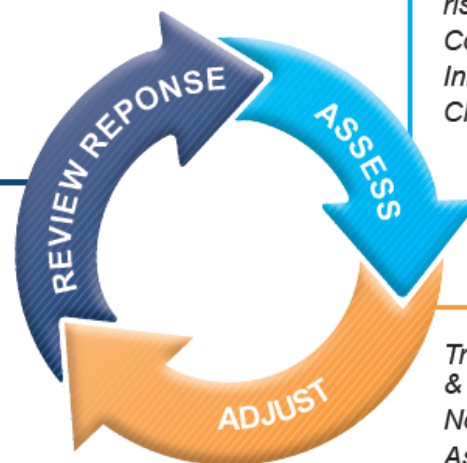
ICS-formoterol is the preferred reliever for patients prescribed maintenance and reliever therapy. For other ICS-LABAs, the reliever is SABA

Children 6-11 years

Personalized asthma management:

Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction



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

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

PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

RELIEVER

STEP 1

Low dose ICS taken whenever SABA taken*; or daily low dose ICS

STEP 2

Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)

Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*

STEP 3

Low dose ICS-LABA or medium dose ICS

Low dose ICS + LTRA

STEP 4

Medium dose ICS-LABA
Refer for expert advice

High dose ICS-LABA, or add-on tiotropium, or add-on LTRA

STEP 5

Refer for phenotypic assessment ± add-on therapy, e.g. anti-IgE

Add-on anti-IL5, or add-on low dose OCS, but consider side-effects

As-needed short-acting β_2 -agonist (SABA)

* Separate ICS and SABA inhalers

SUGGESTED INITIAL CONTROLLER TREATMENT IN ADULTS AND ADOLESCENTS WITH A DIAGNOSIS OF ASTHMA



ASSESS:

Confirmation of diagnosis
Symptom control & modifiable risk factors
(including lung function)

Comorbidities
Inhaler technique & adherence
Patient preferences and goals

START HERE IF:

Symptoms less than twice a month

Symptoms twice a month or more, but less than daily

Symptoms most days, or waking with asthma once a week or more

Symptoms most days, or waking with asthma once a week or more, and low lung function

Short course OCS may also be needed for patients presenting with severely uncontrolled asthma

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

STEP 1

As-needed low dose ICS-formoterol *

Other controller options

Low dose ICS taken whenever SABA is taken †

STEP 2

Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *

Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

STEP 3

Low dose ICS-LABA

Medium dose ICS, or low dose ICS+LTRA #

STEP 4

Medium dose ICS-LABA

High dose ICS, add-on tiotropium, or add-on LTRA #

STEP 5

High dose ICS-LABA
Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

Add low dose OCS, but consider side-effects

PREFERRED RELIEVER

Other reliever option

As-needed low dose ICS-formoterol *

As-needed short-acting β_2 -agonist (SABA)

As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy‡

* Data only with budesonide-formoterol (bud-form)

† Separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted

SUGGESTED INITIAL CONTROLLER TREATMENT IN ADULTS AND ADOLESCENTS WITH A DIAGNOSIS OF ASTHMA



FIRST ASSESS:

Confirmation
of diagnosis

Symptom control &
modifiable risk factors
(including lung function)

Comorbidities

Inhaler technique
& adherence

Patient preferences
& goals

IF:

START WITH:

Symptoms most days,
waking at night $\geq$ once a week
and low lung function?

YES

Medium dose
ICS-LABA (MART or
maintenance-only)

STEP 4

*Short course OCS may
also be needed for patients
presenting with severely
uncontrolled asthma*

NO

Symptoms most
days, or waking at night
 $\geq$ once a week?

YES

Low dose
ICS-LABA (MART or
maintenance-only)

STEP 3

NO

Symptoms twice a
month or more?

YES

Daily low dose
ICS or as-needed low
dose ICS-formoterol

STEP 2

NO

As-needed low dose
ICS-formoterol

STEP 1

Summary

- ▶ Several epidemiological findings suggests the link between asthma and allergic rhinitis as well as the worsening effect of allergic rhinitis on asthma:
 - ▶ AR coexists in the majority of asthma patients
 - ▶ Asthma patients with concomitant AR experience more asthma attacks and use more resources to control their asthma than patients with asthma alone.
 - ▶ Asthma patients with concomitant AR experience worse quality of life (physical functioning) than patients with AR alone during the pollen season.
 - ▶ Allergen avoidance, pharmacotherapy and allergen specific immunotherapy should be used to treat AR and asthma in a combined manner

