APPROACH TO THE TRIPLE CROWN OF ALLERGIC DISEASE

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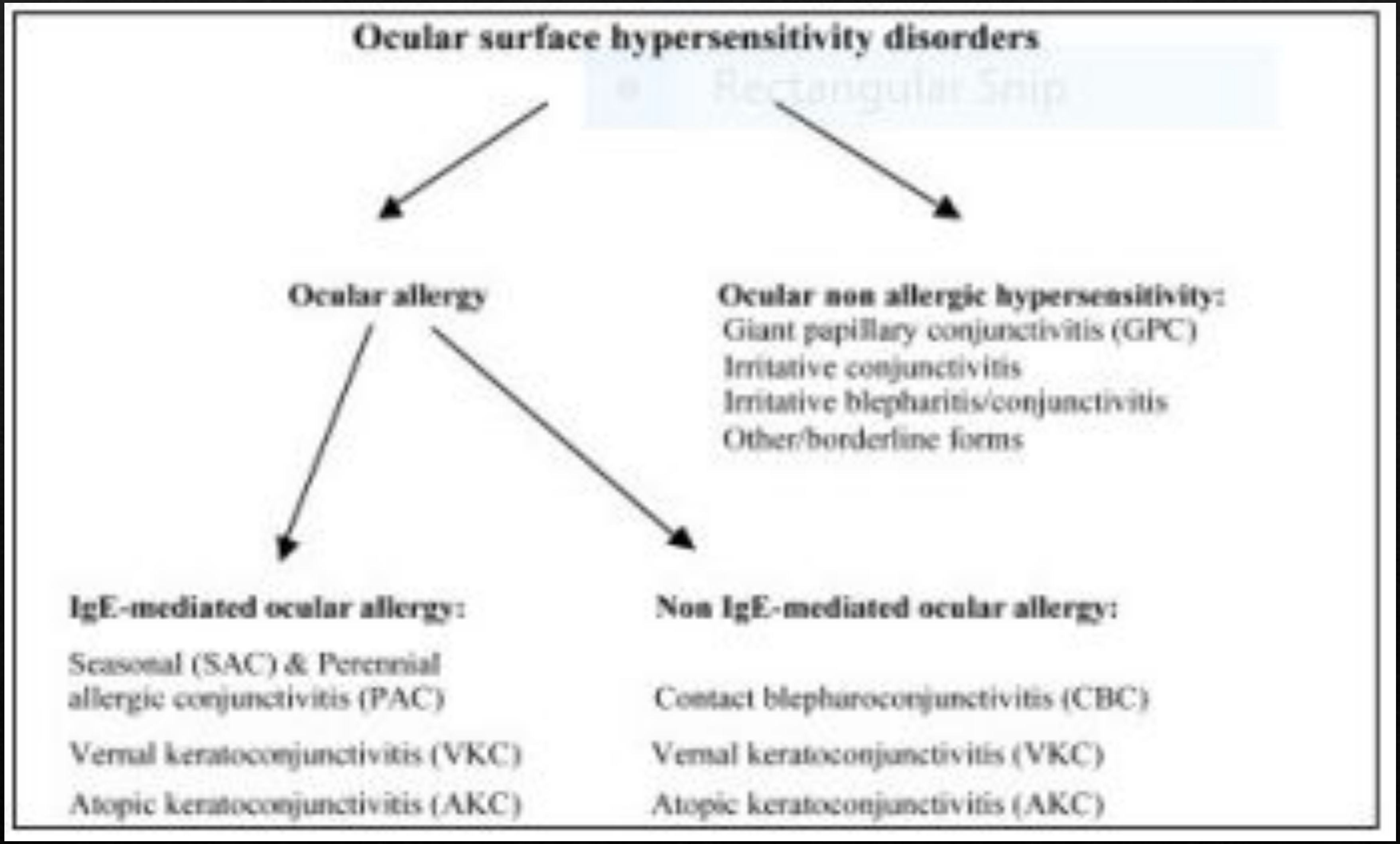
- A Tad About Ocular Allergies to Warm Up
- A Brief Overview on Asthma
- Allergic Rhinitis – When did we forget about the Nose
- The new additions to the family

A Tad About Ocular Allergies to Warm Up

- Ocular allergy - localized allergic condition that is observed as the only or dominant presentation of an allergic sensitization, or is associated with rhinitis.
- It is not a single clinical entity, but includes several conditions with different pathogenesis, hypersensitivity mechanisms, diagnostic criteria, and management.
- Approximately 15–20% of the world population is affected by some form of allergic disease;
- Ocular symptoms are estimated to be present in 40–60% of allergic patients and contribute significantly to poor quality of life
- Most of the available prevalence data encompass both ocular and nasal symptoms, making it impossible to separate ocular allergy from allergic rhinitis.
- Moreover, the frequently confusing nomenclature makes estimations of prevalence difficult.

A Tad About Ocular Allergies to Warm Up



A Tad About Ocular Allergies to Warm Up

Table 1 Clinical features of major ocular allergy syndromes, including the underlying hypersensitivity mechanism and ophthalmological presentation

	SAC	PAC	VKC	AKC	GPC	CBC
Presentation	Intermittent	Persistent	Persistent ± intermittent exacerbations	Chronic	Persistent	Chronic ± intermittent exacerbations
Allergic Mechanism	IgE-mediated	IgE-mediated	IgE- and non-IgE-mediated	IgE- and non-IgE -mediated	Nonallergic	Non-IgE-mediated
Background	Atopic	Atopic	Childhood ± atopic	Adult atopic	Atopic or nonatopic	Nonatopic
Eyelids	Edema	±Edema	Edema Pseudoptosis	Eczema + meibomitis blepharitis	–	Erythema, eczema
Conjunctiva	Follicles and/or papillae	Follicles and/or papillae	Giant papillae	Papillae ± fibrosis	Giant papillae	±Hyperemia Follicles
Limbus	–	–	±Thickened +Trantas dots	±Thickened ±Trantas dots	Hyperemia	–
Cornea	–	–	SPK ±Ulcer ±Vernal plaque	SPK Ulcer, Plaque, Opacities, neovascularization	Rare	–

SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis; GPC, giant papillary conjunctivitis; CBC, contact blepharoconjunctivitis; SPK, superficial punctate keratitis.

A Tad About Ocular Allergies to Warm Up

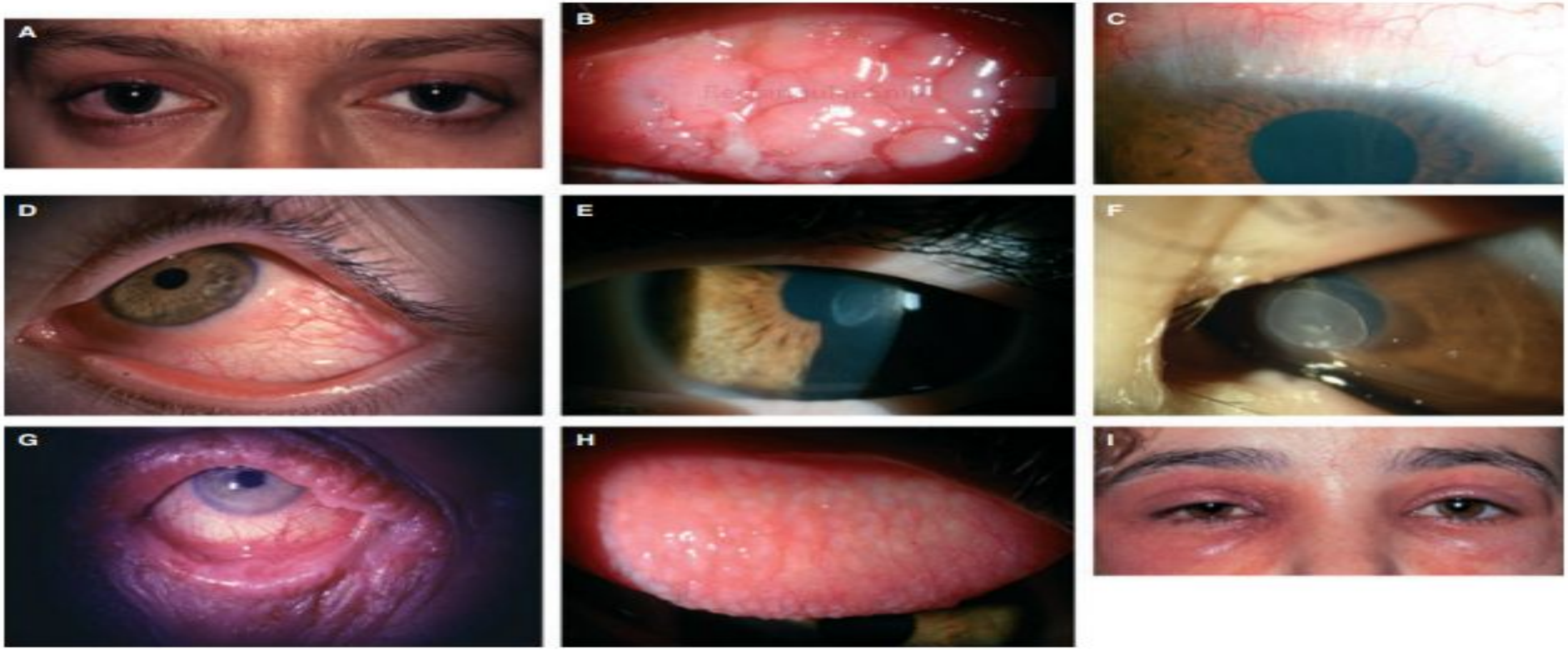


Figure 2 Clinical features of the major ocular allergy syndromes: (A) mild conjunctival redness and lid edema in perennial allergic conjunctivitis; (B) tarsal form of vernal keratoconjunctivitis (VKC) with giant papillae; (C) Trantas dots in limbal VKC; (D) limbal form of VKC; (E) central corneal ulcer in VKC; (F) corneal plaque in VKC; (G) skin lesion in atopic keratoconjunctivitis; (H) tarsal papilla in contact lens associate giant papillary conjunctivitis; (I) skin lesion in contact blepharoconjunctivitis.

A Tad About Ocular Allergies to Warm Up
Differential Diagnosis of Ocular Allergy

- Tear film dysfunction (dry eye) :Dry eye is the result of decreased tear production or increased tear evaporation
- Subacute and chronic infections - Bacterial Conjunctivitis, Viral Conjunctivitis, Molluscum Contagiosum. Chlamydial conjunctivitis chronic conjunctivitis.
- Inflammatory and Auto- Immune Conditions

A Tad About Ocular Allergies to Warm Up
Investigations of ocular allergy

- Three types of diagnostic investigations are currently used:

1. To highlight IgE-mediated hypersensitivity

- Skin prick tests (SPTs), Serum-specific IgE's, Component-resolved diagnostics

- Should be performed systematically for pollens, mites, animal dander, and Alternaria Other allergens (cockroach, molds, and latex) or food allergens should be tested, according to the suspected exposure and patient's medical history

A Tad About Ocular Allergies to Warm Up

Investigations of ocular allergy

2. To highlight a non-IgE-mediated hypersensitivity,

- Patch testing using the suspected cosmetics/triggers.
- Other batteries are used according to the patient history.
- It must be emphasized that eyelid skin is quite different from that of the back, as regards the depth of the epithelial and dermal layers.
- If a patch test is negative, a repeated open application test or use application test can be performed . If topical drugs are suspected, the patch tests for ocular drugs and ingredients in eye drops and ROAT can be performed.

A Tad About Ocular Allergies to Warm Up

Investigations of ocular allergy

3. Specialized ocular investigations - necessary when traditional allergy test results are negative

- Conjunctival Cytodiagnosis/ Impression cytology can assess conjunctival inflammation in the active phase and can be performed using different methods: tear cytology, conjunctival scraping, and brush cytology (a modification of the Cytobrush).
- Total tear IgE levels
- The level of Eosinophil cationic protein (ECP) in tears

A Tad About Ocular Allergies to Warm Up

Practical treatment for ocular allergy

- IgE-mediated diseases: Seasonal allergic conjunctivitis, Perennial allergic conjunctivitis
- Avoidance of clinically relevant allergens.
- Topical antihistamines, mast cell stabilizers, or double-action drugs are the first choice of treatment.
- Avoid topical corticosteroids, as they are rarely needed.
- Topical vasoconstrictors should be used with caution.
- Systemic antihistamines should be used in acute forms or when ocular symptoms are associated with other allergic comorbidities.
- Consider specific immunotherapy when specific sensitization is the main cause of ocular allergy.

A Tad About Ocular Allergies to Warm Up

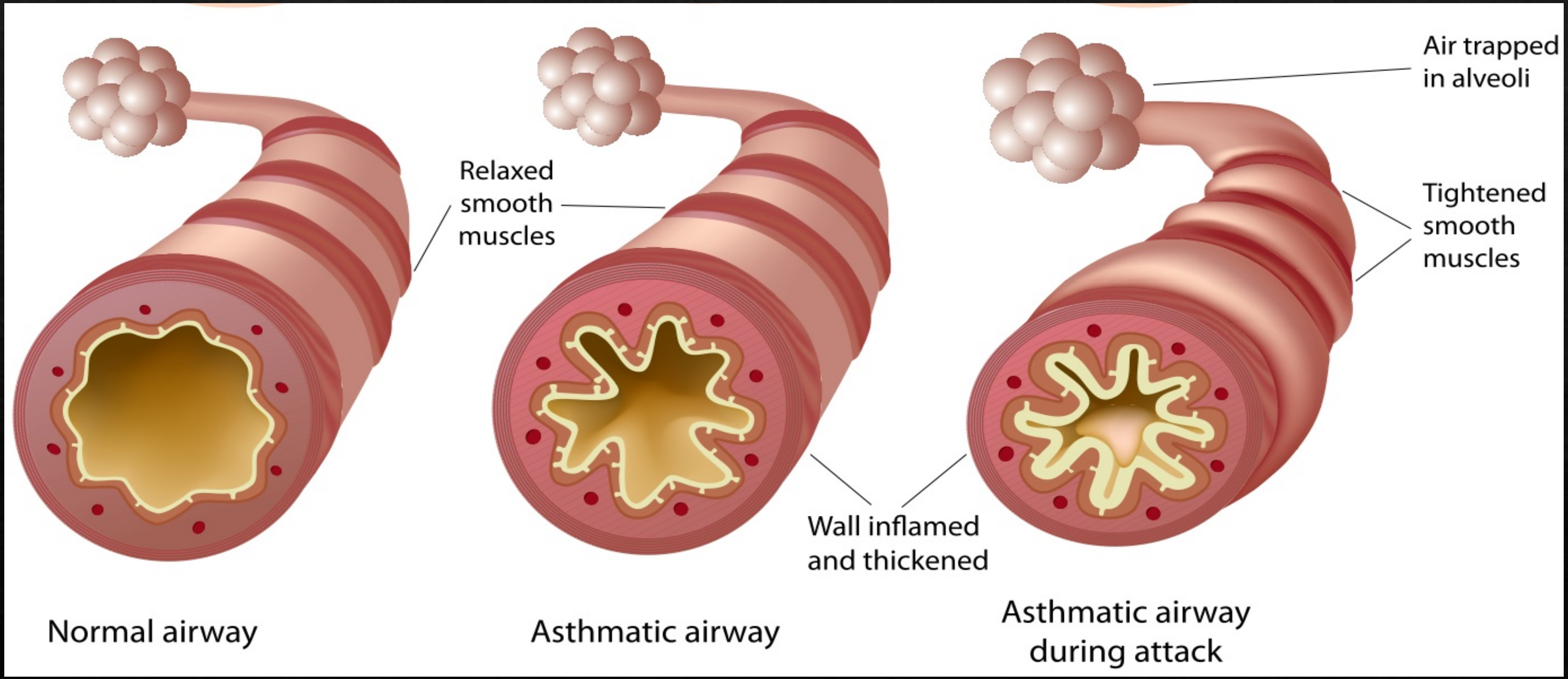
Practical treatment for ocular allergy

- Persistent/ Chronic forms (IgE/Non-IgE mediated):Vernal Keratoconjunctivitis/atopic Keratoconjunctivitis
- Avoidance of specific and nonspecific triggers
- Use cold compresses, good eyelid hygiene, and lubricants.
- Topical antihistamines, mast cell stabilizers, or double-action drugs are the first treatment choice, but may need to be used in combination. They should be used frequently during the day and during the whole season.
- Topical corticosteroids should be used as short, pulsed therapy, when the cornea is involved.
- Topical calcineurin inhibitors may be used in patients followed in specialized centers (off-label treatment in the EU).
- Systemic anti-allergic drugs should be used when ocular symptoms are associated with other allergic comorbidities

ASTHMA: Definition

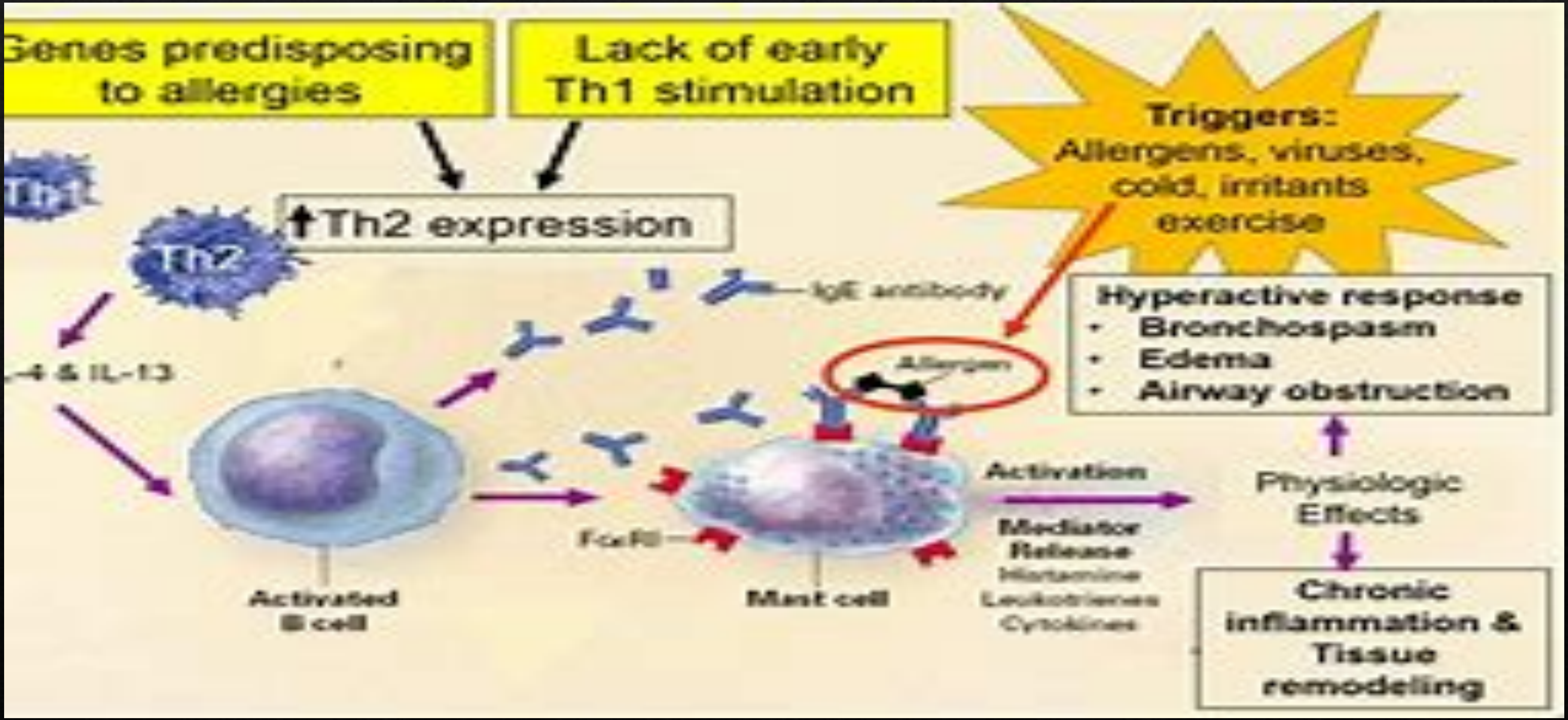
- It is heterogenous disease with multiple phenotypes characterized by chronic inflammation
- Chronic inflammation causes increased airway responsiveness
- Leads to recurrent wheezing, breathlessness, chest tightness and coughing
- It is widespread with variable airflow obstruction that is often reversable spontaneously or with treatment

DEFINITION



Air trapped
in alveoli
Relaxed
smooth
muscles
Tightened
smooth
muscles
Wall inflamed
and thickened
Normal airway
Asthmatic airway
Asthmatic airway
during attack

PATHOGENESIS



PATHOGENESIS

- Characterized by hallmark features including Eosinophilic Inflammation and many other inflammatory Cytokines(IL4,IL5,IL13)
- Can have both IgE and Non-IgE based pathological features
- Associated with structural changes(Remodelling) which are associated with irreversible loss in lung function that begins in early childhood
- Poorly studied in infants and shown that Bronchial Epithelial thickening and Eosinophilic inflammation are absent in wheezy infants with reversable airflow but subsequently present later in preschool aged children
- The persistence of wheezing and progression of Asthma results from a Complex relationship between Genetics, Environment Exposures and Host Genotypes

RISK FACTORS FOR WHEEZING

- Prenatal

  Maternal Asthma, Maternal Obesity and Weight Gain, Smoking
- Perinatal

  C/S
- Genetics

  Specific Genetic Phenotypes
- Postnatal

  Infection – RSV, Rhinovirus(Causes remodelling secondary to VEGF, Gene upregulation in Interferon Pathway

  Smoke Exposure

  Rapid Weight gain in first 3 months of life

DIAGNOSIS

- History and Examination NB - Suspected on basis of symptoms and signs , particularly if there is variability
- Consider differential diagnosis specific to age groups(Will discuss later)
- Not every child who wheezes has Asthma
- Search for associated Risk Factors

  - Related Atopic Disorders (AR, Allergic Conjunctivitis, Atopic Dermatitis)
  - Family History of Asthma and Other Allergic Disorders
  - Symptom onset (specifically in childhood)
  - Identifiable triggers of deterioration(eg Exercise, Environmental Allergens)

DIAGNOSIS

- Seek objective evidence for reversable airflow obstruction
  - PEFR and Spirometry
  - PEFR > 15 % or FEV1/FVC > 12 % post bronchodilatation
  - PEFR Variability of 20% on diurnal assessment
- Optional Testing to Assist Diagnosis(Normally Costly)
  - FBC to check Eosinophil count
  - Skin Prick Testing or Specific IgE’s
  - Methacholine, Histamine or Exercise challenge
  - Measurement of Exhaled Nitric Oxide
- Review response to therapeutic trials also can assist in diagnosis (Specifically in younger children)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis Wheezing

- Asthma
- Congenital Anomalies with airway impingement: Vascular rings, tracheobronchial obstruction, mediastinal mass
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Gastroesophageal reflux
- Aspiration
- Foreign Body Aspiration
- Heart Failure
- Sinusitis and allergic rhinitis
- Bronchiolitis
- Pertussis
- Tuberculosis
- Immune system Disorders

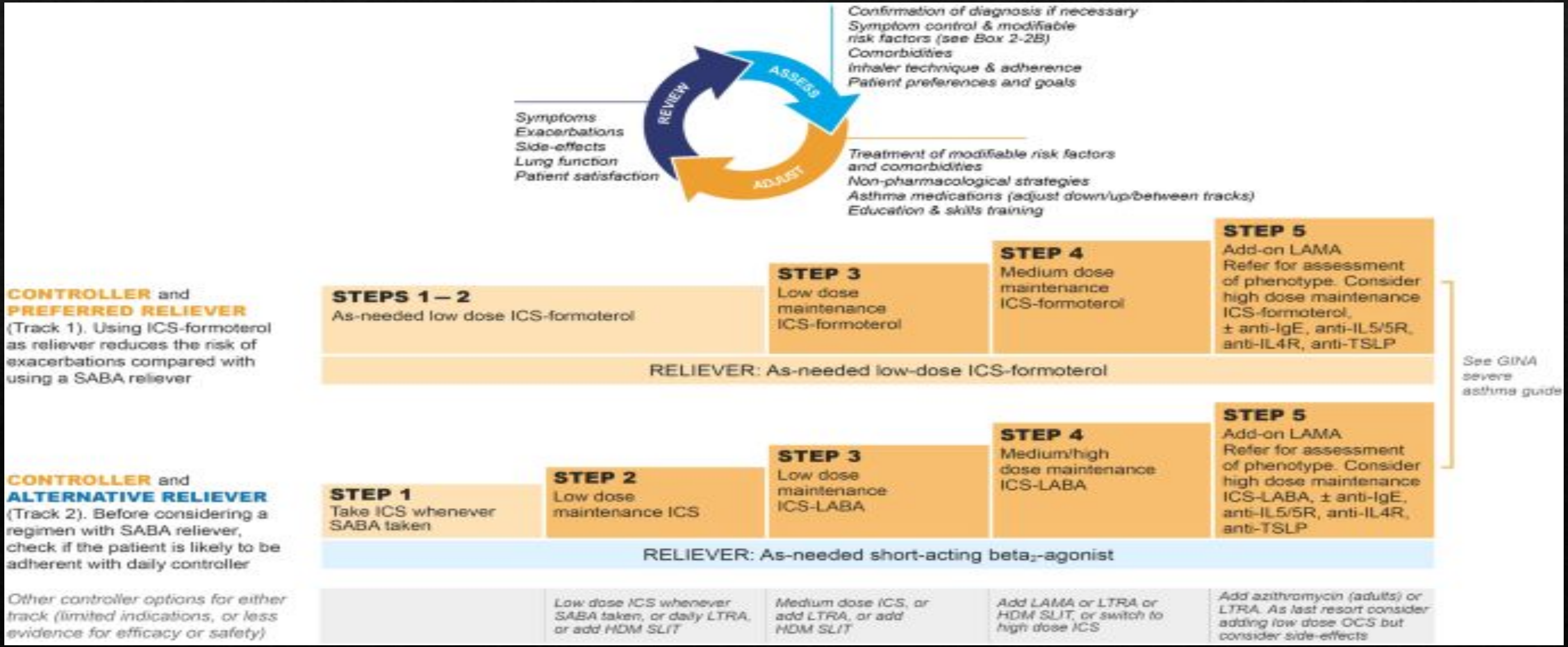
ASSESSMENT OF ASTHMA: SEVERITY ASSESSMENT

to the Expert Panel Report 2 National Asthma Guidelines

			Children >5 y Who Can Use a Spirometer or Peak Flowmeter, %	
Asthma Classification	Days With Symptoms	Nights With Symptoms	FEV_1 or PEF (Predicted Normal)	PEF Variability
Severe persistent	Continual	Frequent	≤60	>30
Moderate persistent	Daily	≥5/mo	>60 to <80	>30
Mild persistent	>2/wk	3-4/mo	≥80	20-30
Mild intermittent	≤2/wk	≤2/mo	≥80	<20

Abbreviations: FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow.

Asthma : Management



Asthma : Management

Box 3-5B. Personalized management for children 6–11 years to control symptoms and minimize future risk

Children 6-11 years

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

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

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

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

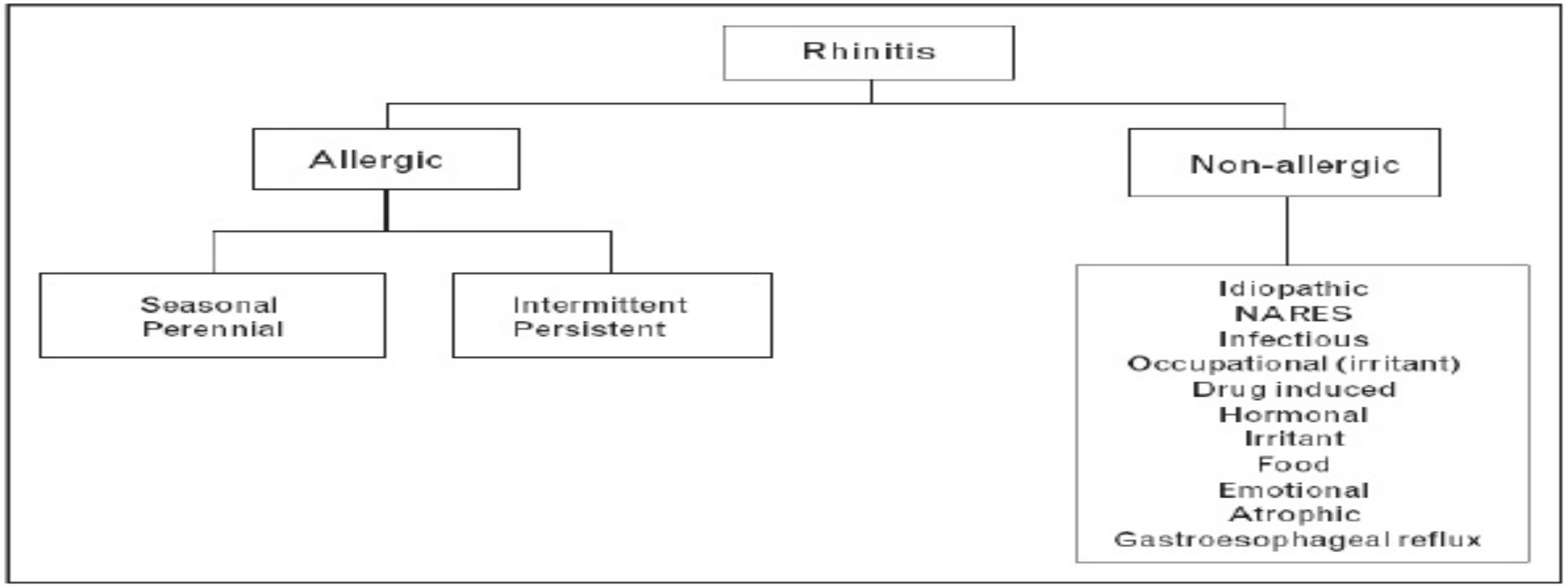
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol 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 for MART as above)				

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

GINA 2022, Box 3-5B

Allergic Rhinitis: Introduction

Classification of rhinitis



Allergic Rhinitis and its Impact on Asthma (ARIA) 2008

Allergic Rhinitis

- Allergic Rhinitis(AR) is a symptomatic disorder of the nose, induced after allergen exposure, by an IGE-mediated inflammation of the nasal membranes
- Common, often trivialised and regarded as a nuisance rather than serious condition
- Large effect on patients quality of life (School, Work and Social)
- Worldwide Prevalence between 10 to 40%
- In SA according to ISAAC, 20 % in children in 6-7 year old group and 40 % in 13-14 year old group
- Commonly associated with other allergic based diseases and family history

History

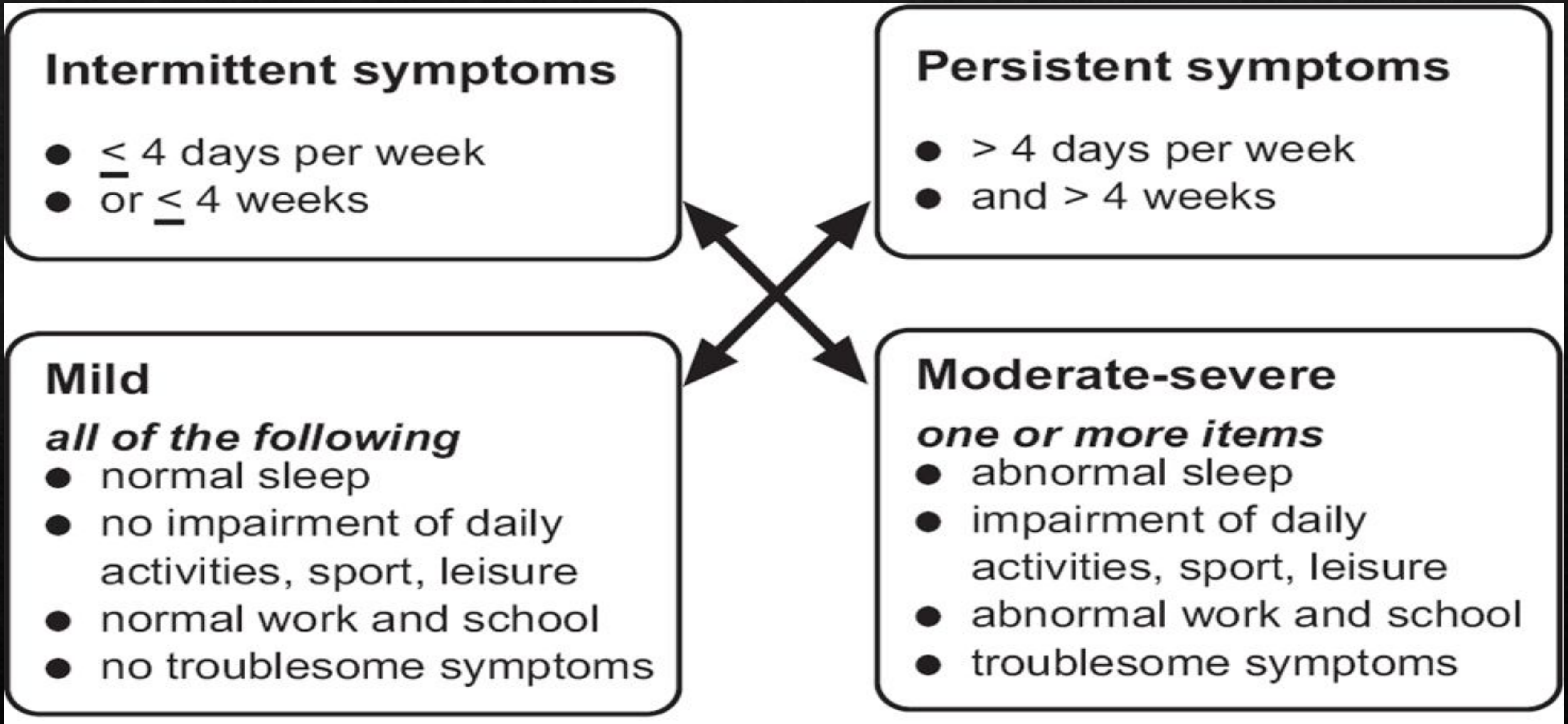
- Symptoms include rhinnorrhoea, nasal congestion or blockage, nasal itching sneezing and post nasal drip

- Nasal congestion is most troublesome symptom occurring in 90% of patients

- Hyposmia(Decreased ability to smell) occurs frequently and often overlooked

- Ocular symptoms of very common

History
Classification



Adapted from http://www.whiar.org (full permission obtained)

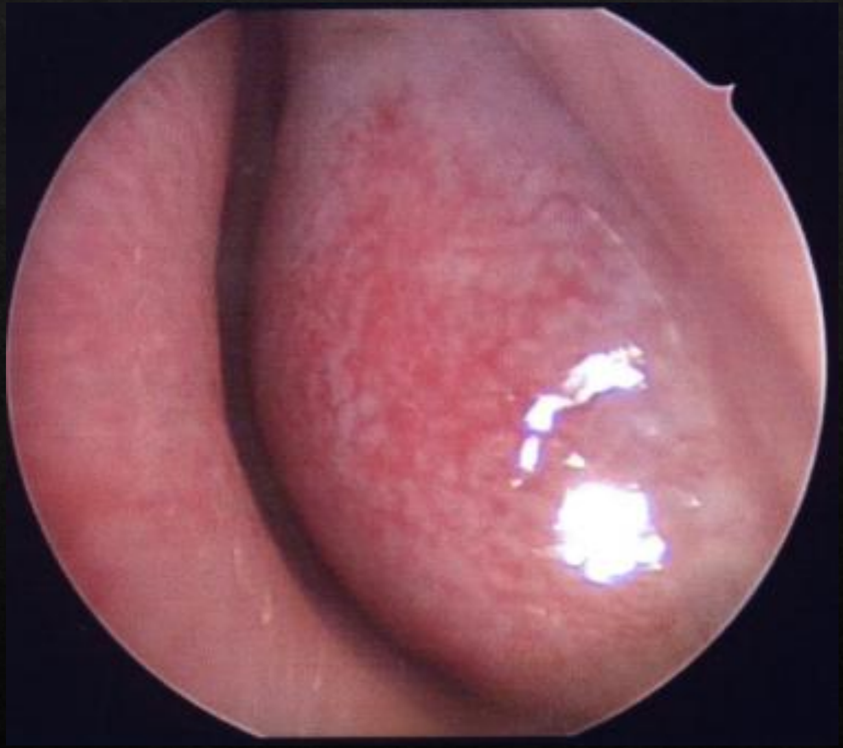
Examination

Examination

Examination

- Palor
- Allergic Shiners
- Dennie-Morgan Lines
- Mouth Breathing (Always have a look at Teeth and Jaw)
- Elongated Facial Structure (But not always)
- Always examine for other atopic diseases such as Asthma or Eczema

Examination



Examination

Diagnosis

- History
- Clinical Examination
- Allergen Sensitisation by skin prick testing or Specific IgE measurements (Be careful of costs and does it effect the outcome)
- Awareness of prevalent Aeroallergens in the area
- Not all forms for Rhinitis is Allergic Rhinitis

Co-Morbidities

- Asthma occurs in 15 – 38% of AR patients
- Nasal symptoms are present in approximately 75% of Asthmatics
- Conjunctivitis
- Still controversy around the topic of Otitis Media and AR
- Dsyphonia
- Malocclusion
- Sleep Disorders
- OSA (Later in life HPT, Cardiac disease)
- Psychiatric disorder (Specifically Depression and Anxiety)

Differential Diagnoses of Allergic Rhinitis

Allergic rhinitis	**Nonallergic rhinitis (continued)**	**Conditions that may mimic symptoms of rhinitis**
Episodic rhinitis	Gustatory rhinitis	Cerebrospinal fluid rhinorrhea
Occupational rhinitis	Hormone-induced rhinitis	Inflammatory or immunologic conditions
(allergen)	Hypothyroidism	Midine granuloma
Perennial rhinitis	Menstrual cycle	Nasal polyposis
Seasonal rhinitis	Oral contraceptives	Sarcoidosis
Nonallergic rhinitis	Pregnancy	Sjogren's syndrome
Atrophic rhinitis	Infectious rhinitis	Systemic lupus erythematosus
Chemical-or irritant-induced rhinitis	Acute (usually viral)	Wegener's granulomatosis
Drug-induced rhinitis	Chronic rhinosinusitis	Relapsing polychondritis
Antihypertensive medications	Nonallergic rhinitis with eosinophilia	Structural or mechanical conditions
Nonsteroidal anti-inflammatory drugs	syndrome	Choanal atresia
Oral contraceptives	Occupational rhinitis (irritant)	Deviated septum
Rhinitis medicamentosa	Perennial nonallergic rhinitis	Enlarged adenoids
Emotional rhinitis	Vasomotor rhinitis	Foreingn bodies
Exercise-indued rhinitis	Postural reflexes	Hypertrophic turbinates
	Primary ciliary dyskinesia	Nasal tumors
	Reflux-induced rhinitis or	
	gastroesophageal reflux disease	

Treatment
Non-Drug Treatment

- Patient Education
  - Condition education, Treatment and Adherence
  - Awareness on the fact of chronicity
- Allergen Avoidance and Environmental Control
  - Based on allergen sensitivity testing
  - Common allergens in the area
  - No single intervention strategy adequate to control disease purely

Treatment
Drug Treatment

- Intranasal Corticosteroids (INCS) (For Moderate to Severe AR)
- Combination nasal therapy(INCS in combination with Mast Cell Stabiliser)
- Antihistamines (Can be used as monotherapy in Mild AR)
- Leukotriene-receptor Antagonists (LTRAs)
- Cromones (Sodium Cromoglycate)
- Anti-Cholinergics
- Nasal Irrigation (Don’t forget about this simple assisted Rx Method)
- Decongestants
- Systemic Corticosteroids (For severe acute flares, not long term therapy)
- Specific Immunotherapy

Treatment
Drug Treatment

Table III. Relative efficacy of pharmacologic treatments for allergic rhinitis: effects on symptoms[a][17,28]

Drug class/ formulation	Sneezing	Itching	Congestion	Rhinorrhea
Oral antihistamines	+++	+++	±	++
Intranasal antihistamines	+++	+++	++	++
Intranasal corticosteroids	+++	+++	+++	+++
Oral decongestants	–	–	+	–
Nasal decongestants	–	–	++++	–
Antileukotrienes	+	+	++	+

a Ratings based on data from independent, published studies, not direct comparisons.

– indicates no effect; ± indicates questionable effect; + indicates mild effect; ++ indicates good effect; +++ indicates very good effect; ++++ indicates excellent effect.

Treatment
Drug Treatment

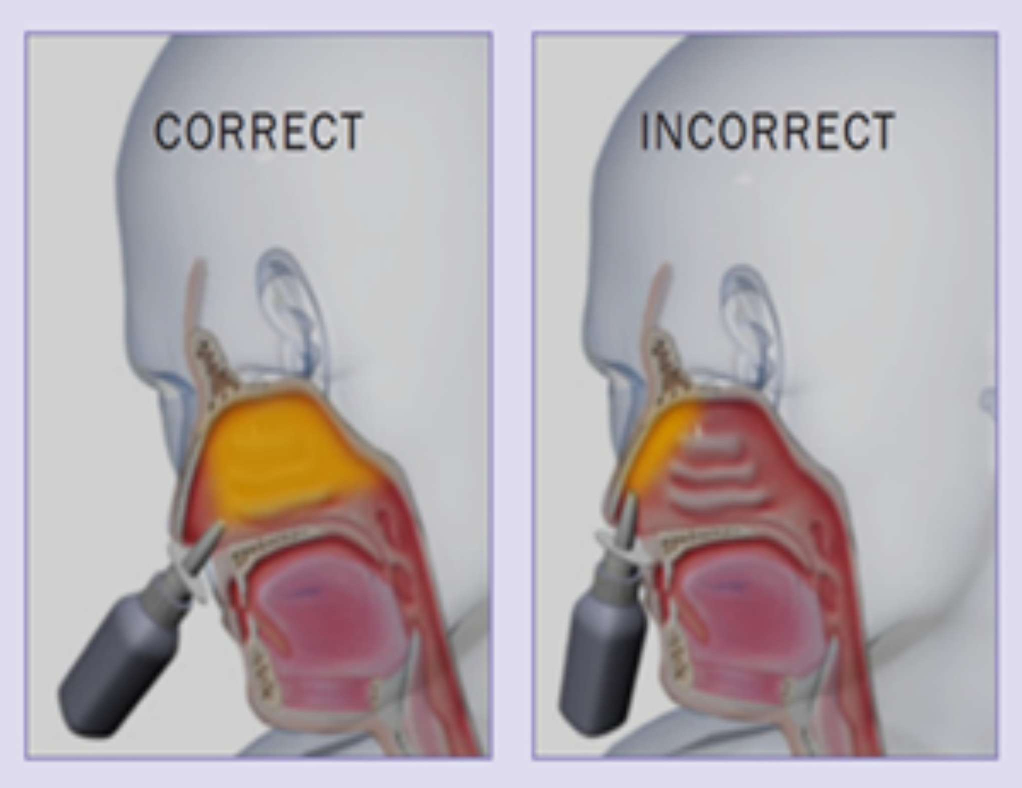
- INCS
- Single most effective class of medications for AR, treating all symptoms
- Low incidence of adverse effects
- Superior to Anti-histamines and LTRAs
- Assist with ocular symptoms
- Cost Effective in comparison to other modalities
- Education on duration and technique is key

Treatment
Drug Treatment

	Fluticasone propionate	Momentasone	Budesonide	Ciclesonide	Fluticasone furoate
Bioavailability (%)	<2	Minimal	34	<1	1.26
Protein binding (%)	91	99	85	99	99
Excretion	Feces 95%; Urine 5%	Feces 55%; Urine 45%	Feces 34%; Urine 66%	Feces 66%; Urine 20%	Feces 90%; Urine 1%
Half life (hours)	7.8	5.8	2-3	6-7	15.1
Relative receptor affinity[15]	1775	900	855	120	2989
Age of FDA approval (Years)	4	2	6	6	2
Onset/time (hour)	12	11	4	1	6-8
Dose spray (µgm)	50	50	32	50	27.5
FDA approval (year)	1994	1997	1999	2006	2007

FDA: Food and Drug Administration

Treatment
Drug Treatment



Treatment
Drug Treatment

- Oral Antihistamines
- Relieve nasal and ocular symptoms
- Most effective for Rhinnorea, sneezing and nasal itching
- Not very effective for nasal congestion
- Use of newer generation vs old generation preferred (S/E’s)

Treatment
Drug Treatment

H_1 receptor antagonists

- 1^{st} generation antihistamines

  are more likely to
  - cause sedation in therapeutic doses
  - affect autonomic receptors (cholinergic and adrenergic)
- 2^{nd} generation antihistamines
  - are sometimes called “non-sedating” antihistamines
  - But better call it low-sedating
- 3^{rd} generation antihistamines
  - are the active metabolites of 2^{nd} generation agents

Treatment
Drug Treatment

THIRD GENERATION ANTIHISTAMINE:

Action:

Third generation antihistamines formally labelled because the active enantiomer (Levocetirizine) or metabolite (Desloratadine) derivatives of second generation drugs intended to have increased efficacy with fewer adverse drug reactions.

Examples:

1) Norastemizole (Metabolite of astemizole)

2) Descarboethoxy loratadine (Metabolite of loratadine)

3) Levocetirizine (Active enantiomer of cetirizine)

Treatment
Drug Treatment

- LRTAs
- Have decongestant effect but less effective than INCS
- Similar efficacy to oral anti-histamines
- Better suited for night time symptoms
- Considered in severe congestion who are inadequately treated with INCS
- Good efficacy in comorbid disease of AR and Asthma

Leukotrienes and Montelukast

- Mast Cell Mediators
- Secreted from mast cell upon Antigen-Antibody exposure
- 1000 times more potent in inflammatory responses than histamine
- Montelukast is a drug used as a control and maintenance therapy for Asthma
- It also relieves symptoms of seasonal allergic rhinitis
- It’s a Leukotriene receptor antagonist(LRTA)
- It Binds with Cysteinyl Leukotriene Receptor in the lungs and smooth muscle of the bronchial airways and thus blocks the action of LTD4 – Bronchial constirciton, accumulation of mucosa and infiltration of inflammatory cells in the airways


Ryaltris™
NDC 72657-100-29
(olopatadine hydrochloride and mometasone furoate)
Rx only
NASAL SPRAY
665 mcg/25 mcg* per spray
*calculated on the anhydrous basis
FOR INTRANASAL USE ONLY
Glenmark
Therapeutics
240 Metered Sprays
29 g net fill weight
NDC 72657-100-99
Ryaltris™
Professional Sample Not for Sale
(olopatadine hydrochloride and mometasone furoate)
Rx only
NASAL SPRAY
665 mcg/25 mcg* per spray
*calculated on the anhydrous basis
FOR INTRANASAL USE ONLY
56 Metered Sprays 9 g net fill weight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THE FIRST ANTIHISTAMINE/
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(LTRA) fixed dose combination 2
JOINING THE DOTS
OF COMPLEMENTARY COMBINATION THERAPY
Montelukast + levocetirizine is superior to monotherapy with either medication in the treatment of seasonal allergic rhinitis 4
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Thank You