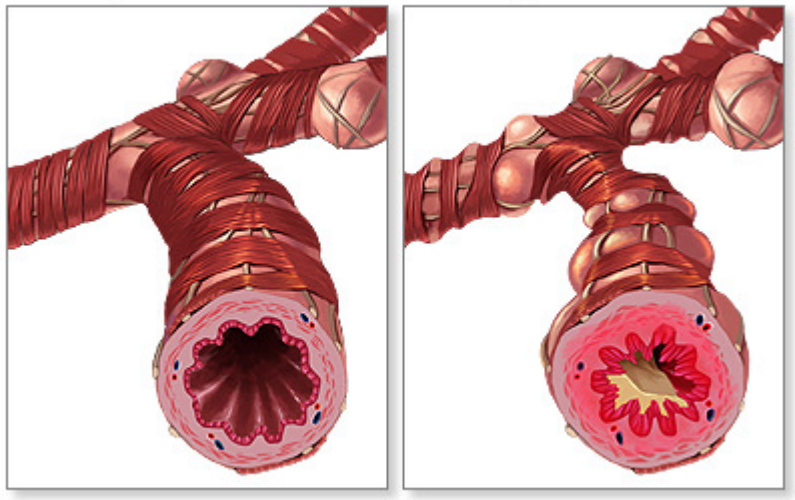
VÍA AÉREA

UN SOLO EPITELIO CON DIFERENTES RESPUESTAS

Asma

Definiciones
Fenotipos
Asma alérgica
Respuesta inmune
Severidad y control
Tratamiento
Conclusiones



ASMA: CARACTERÍSTICAS GENERALES

Definición

"El asma es una enfermedad heterogénea, usualmente caracterizada por la **inflamación crónica de la vía aérea**. Se define con la historia de síntomas respiratorios como sibilancias, disnea, opresión torácica" y tos, que puede variar en el tiempo en intensidad, junto con la limitación del flujo espiratorio"

Iniciativa Global para el Asma . GINA (2015)

Asma Severa

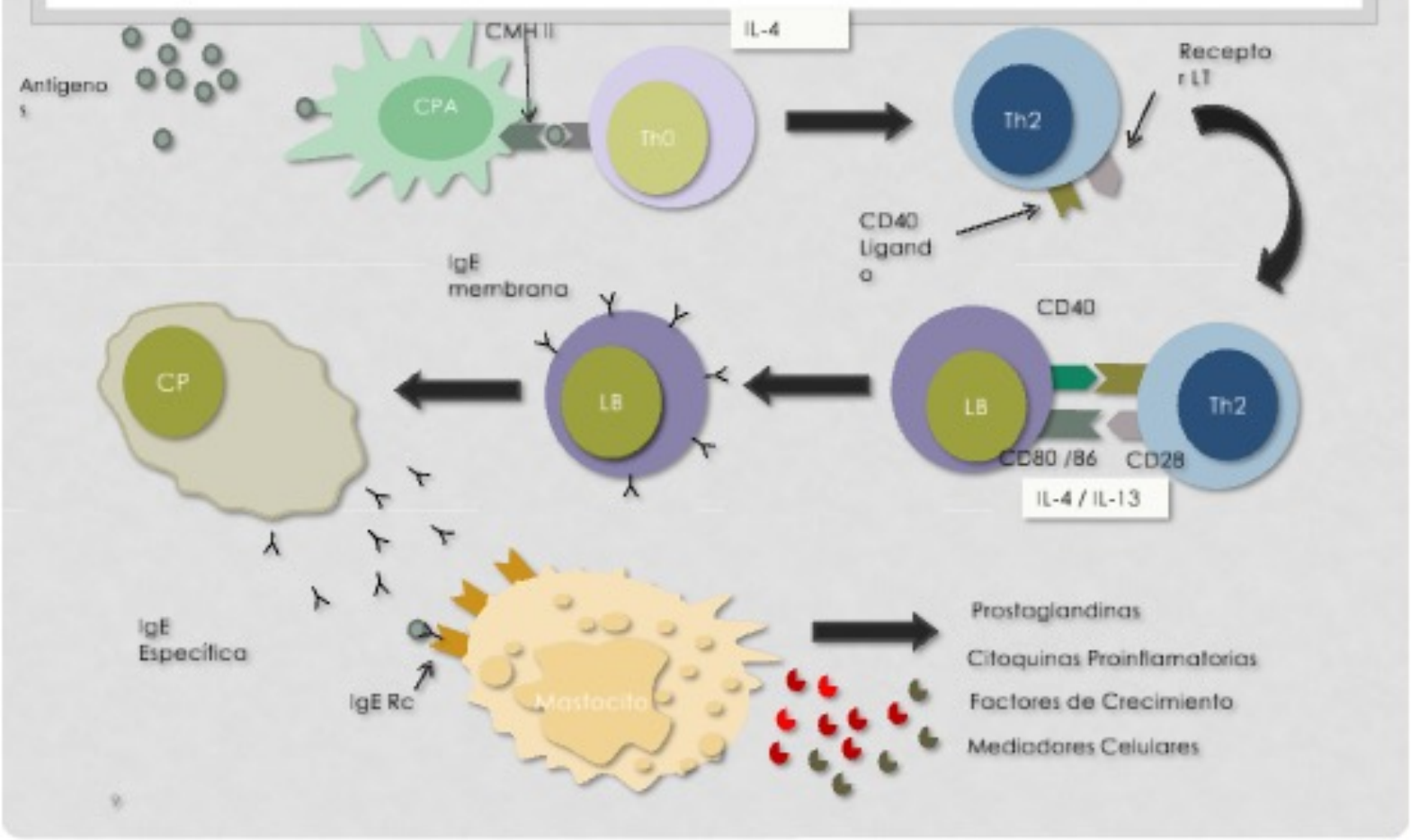
Al menos un criterio de los siguientes:

- Asma no controlada
  - Pobre control de los síntomas: ACQ > 1,5, ACT <19 o criterios de no control por GINA
  - Exacerbaciones frecuentes: 2 o mas ciclos cortos de esteroides en ultimo año
  - Exacerbaciones serias: Al menos una hospitalización, Estancia en UCI, VM
  - Limitación al flujo aéreo: VEF1 < 80% post broncodilatador
- Asma controlada, pero a expensas de altas dosis de ICS o esteroide sistémico

Eur Respir J. 2014; 43 (2): 343 - 73

RESPUESTA INMUNE ALÉRGICA

Sensibilización



ASMA ALÉRGICA

- Asma tipo I
- Resultado de una reacción inmune a los antígenos por los anticuerpos tipo IgE
- Esta hipersensibilidad inmune tipo I incluye rinitis alérgica, Asma alérgica, y alergia alimentaria.

Lancet 2006; 368: 804 - 13.

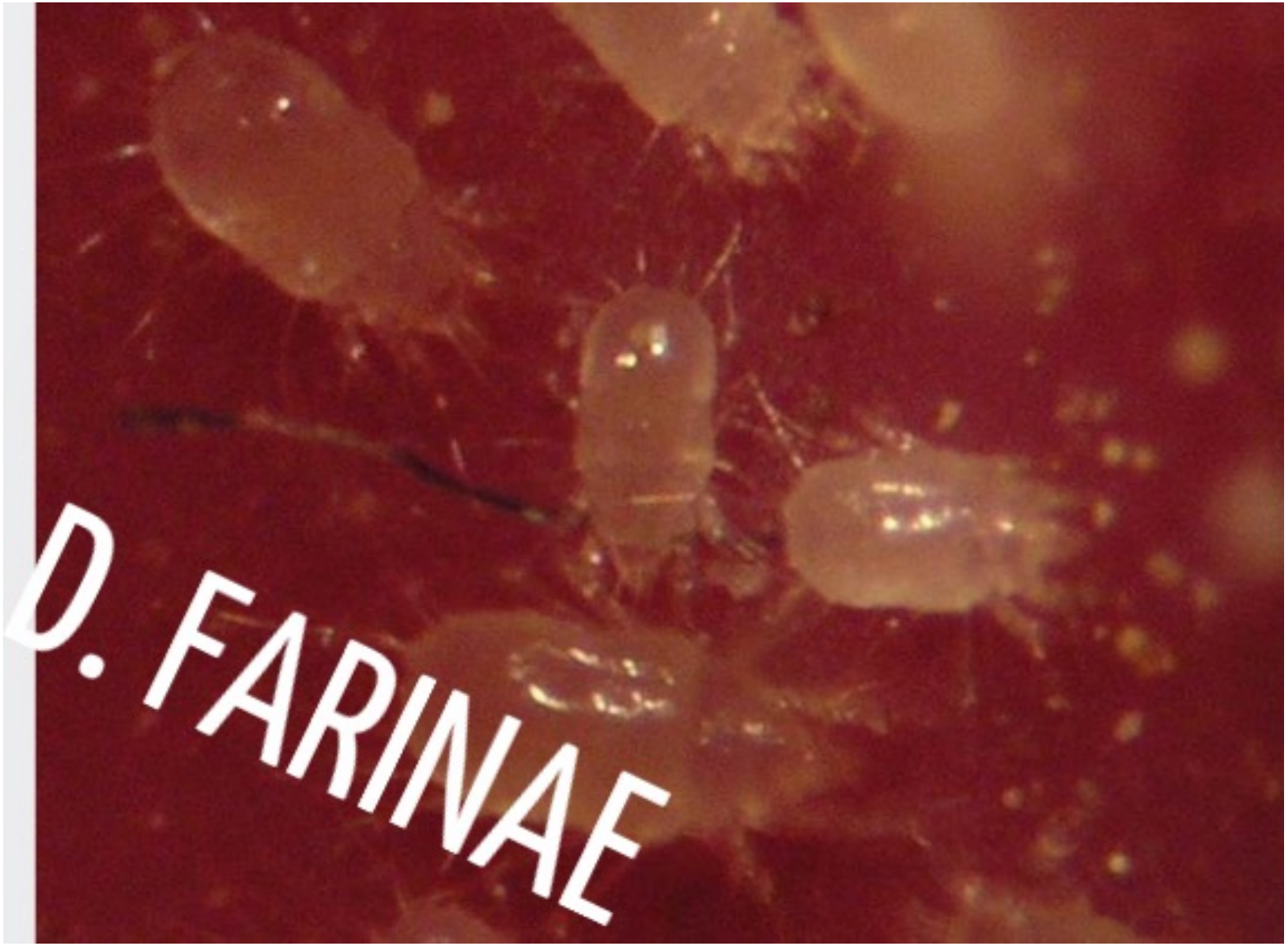

Fresas, Espárragos, Tomate, Zanahoria


ALTERNARIA

Residuos Orgánicos e inorgánicos

Aspergillus. En casa como en el exterior.


Dermatophagoides
Pteranyssinus

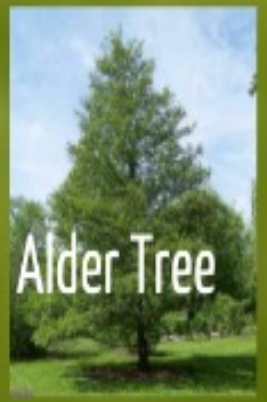

D. FARINAE


Parietaria


Birch tree


Hazel. Avellano


Ceniza


Alder Tree


Polen de Hierba Mixta


Amaranto

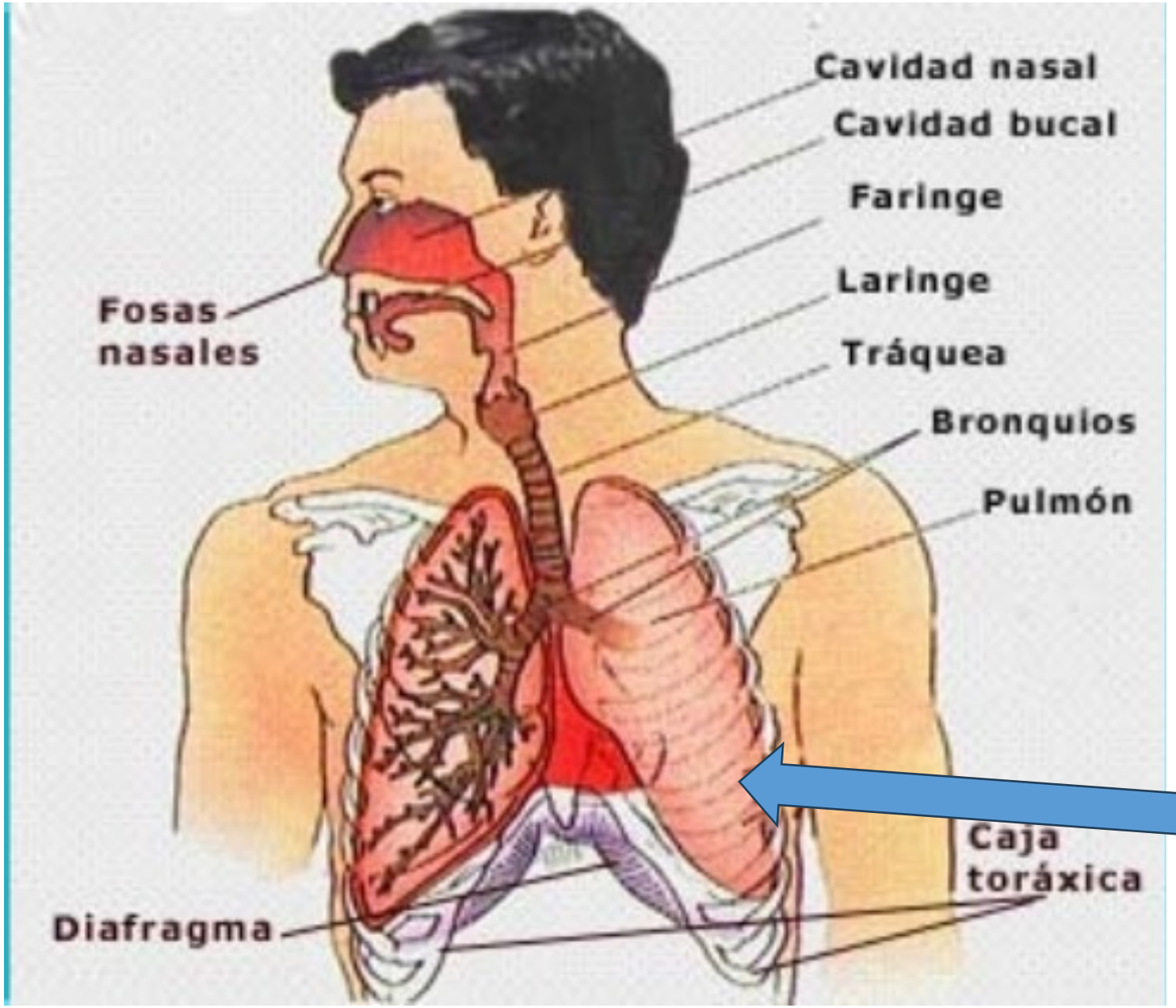

Bermudagras

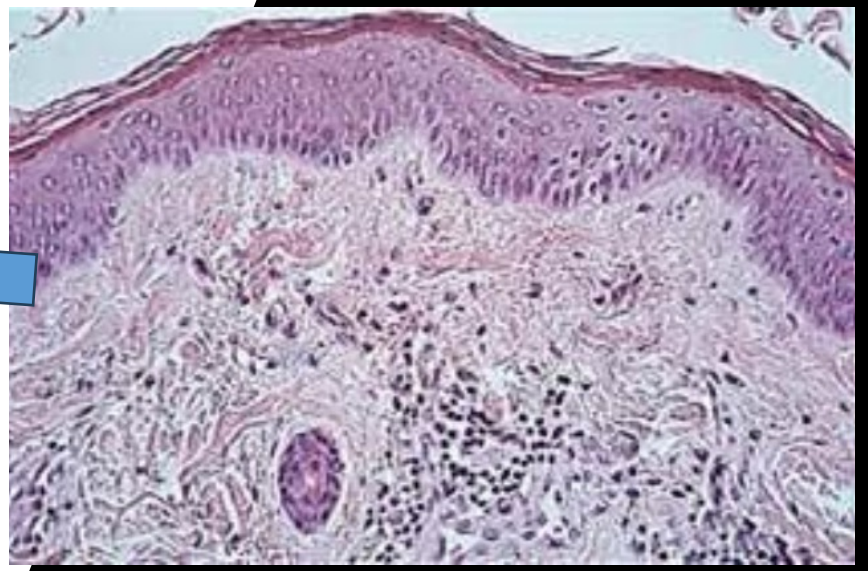
RESPUESTA INMUNE EN ASMA

Fase temprana

Table 1 Examples of biological activities of aeroallergens

Source of allergens	Identified biological activities
Grass pollen	Pectate lyase, RNase, polygalactouronase, lipid transfer protein, profilin, expansin
Tree pollen	Profilin, isoflavone reductase, pathogenesis-related protein, pectin methylesterase, peptidyl-prolyl isomerase, 1,3-β-glucanase, calcium-binding protein, pectate lyase, superoxide dismutase
Fungi	Protein disulfide isomerase, aldehyde dehydrogenase, RNase, vacuolar serine protease, alkaline serine protease, enolase, aspartate protease, dipeptidyl peptidase, subtilisin-like protease
Pet dander	Uteroglobin-like protein, cystatin, lipocalin, albumin
Mites	Cysteine protease, β-glucan moiety, trypsin, amylase, chymotrypsin, chitinase, collagenase, glutathione transferase


Cavidad nasal
Cavidad bucal
Faringe
Laringe
Tráquea
Bronquios
Pulmón
Fosas nasales
Caja toráxica
Diafragma



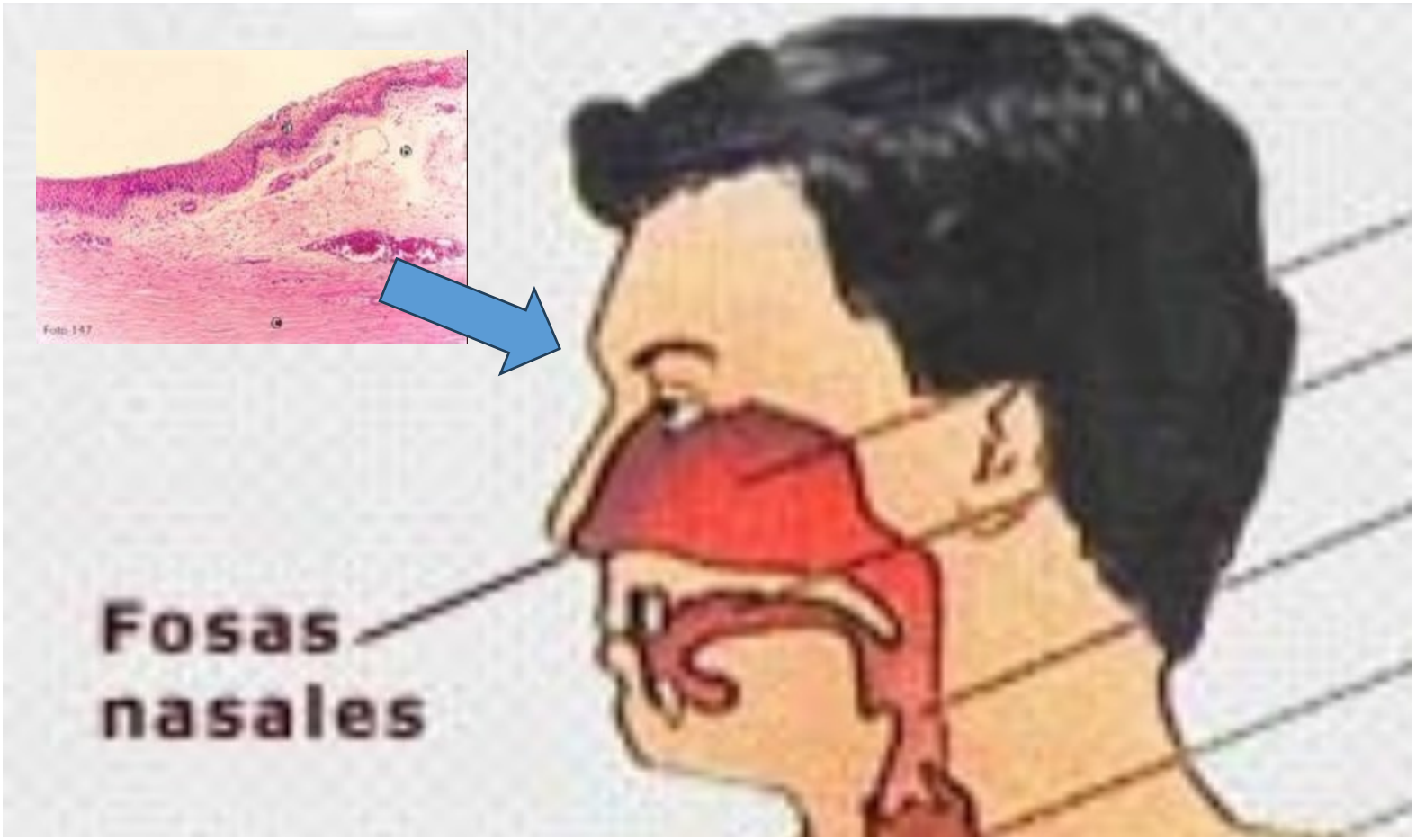
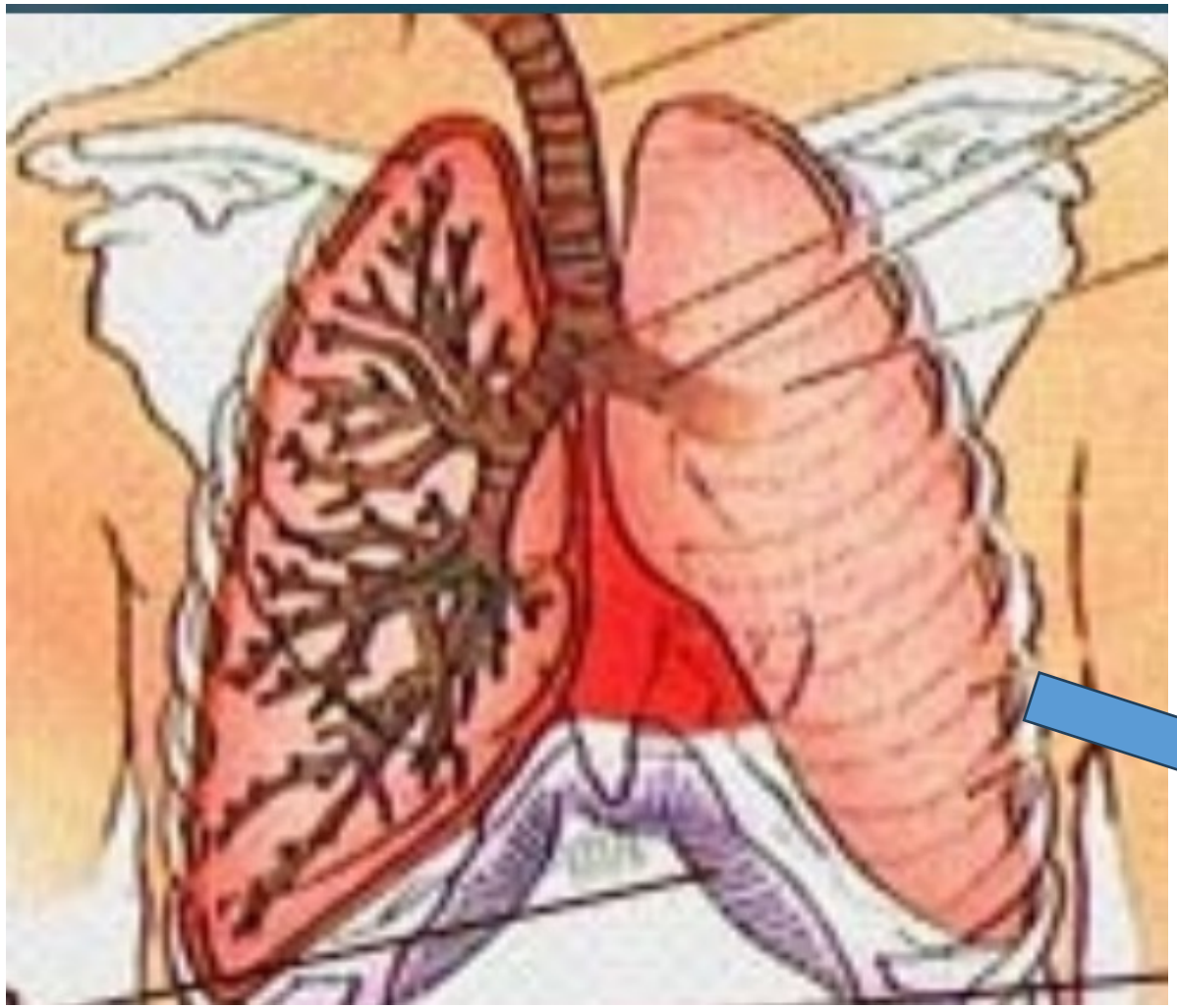
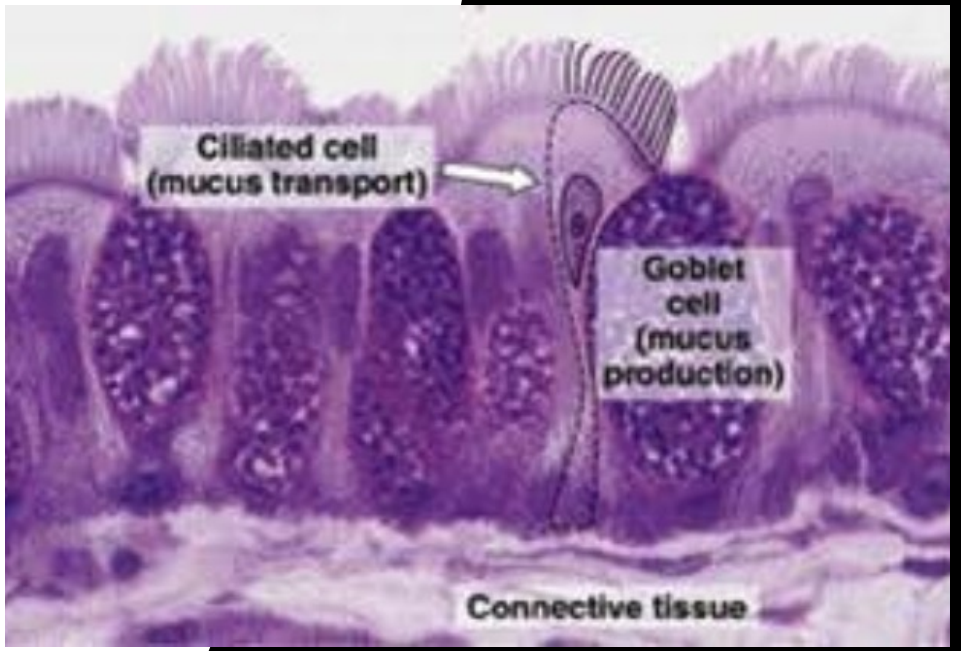


Foto 147
Fosas
nasales



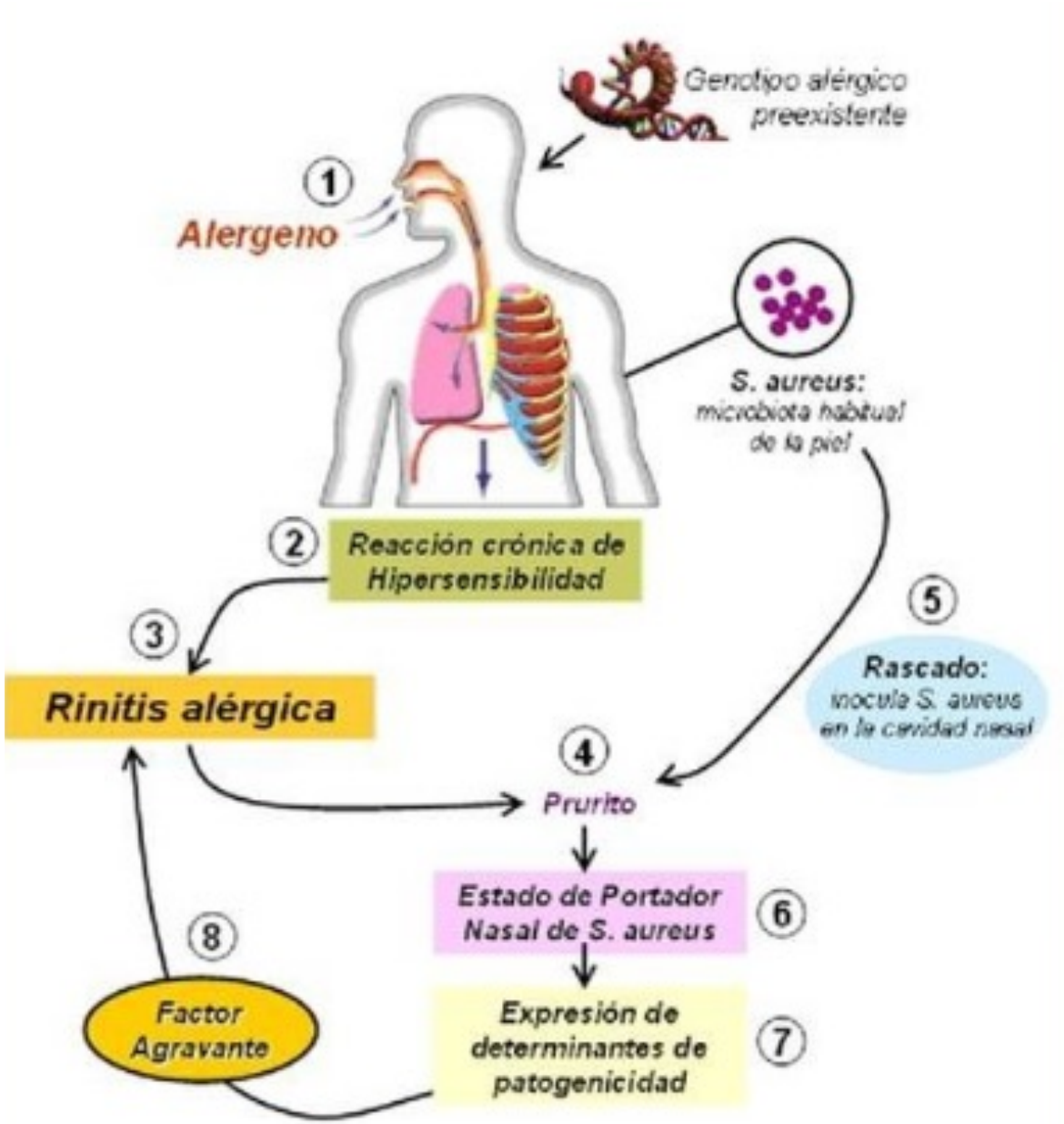

Ciliated cell
(mucus transport)
Goblet
cell
(mucus
production)
Connective tissue

La mayor parte de los pacientes con asma tienen rinitis (80-95%)

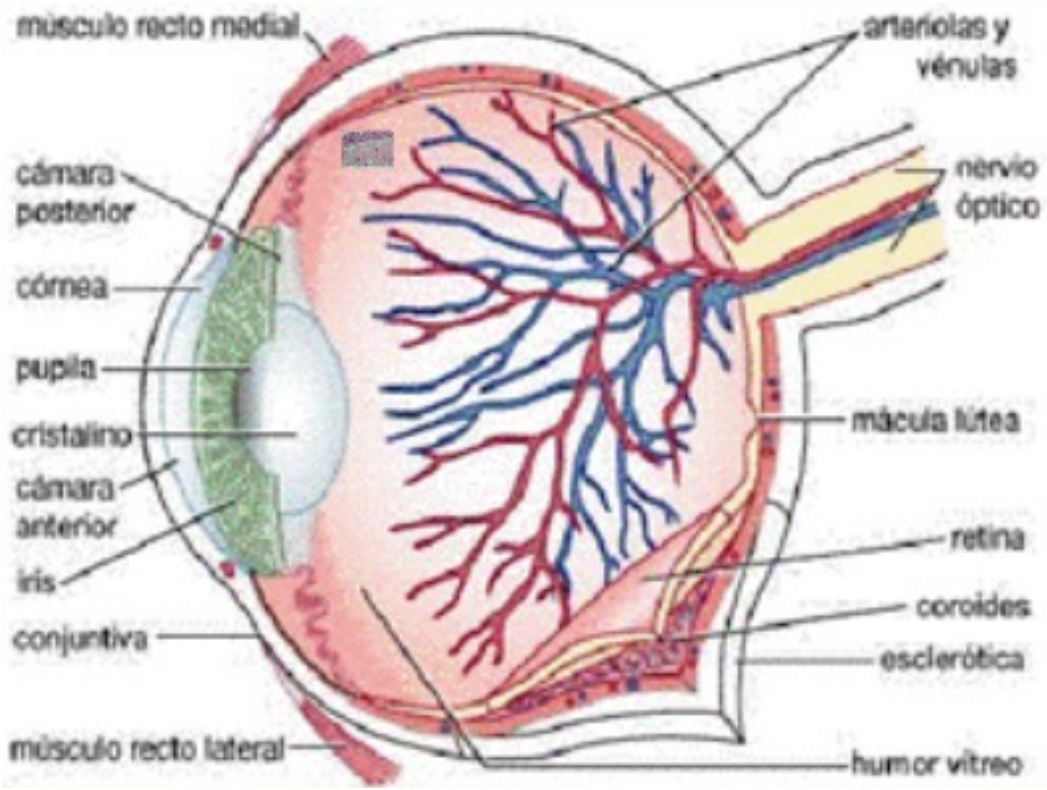
la rinitis alérgica es un factor

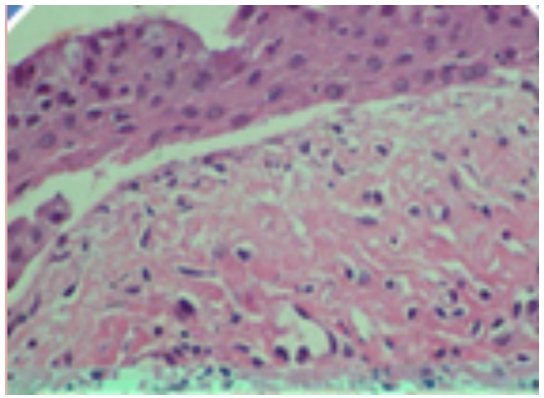
de riesgo importante para el desarrollo de asma y comparten un proceso inflamatorio común

El asma puede afectar al 20-50% de los sujetos con rinitis alérgica y esta a su vez puede complicar el tto para el Asma

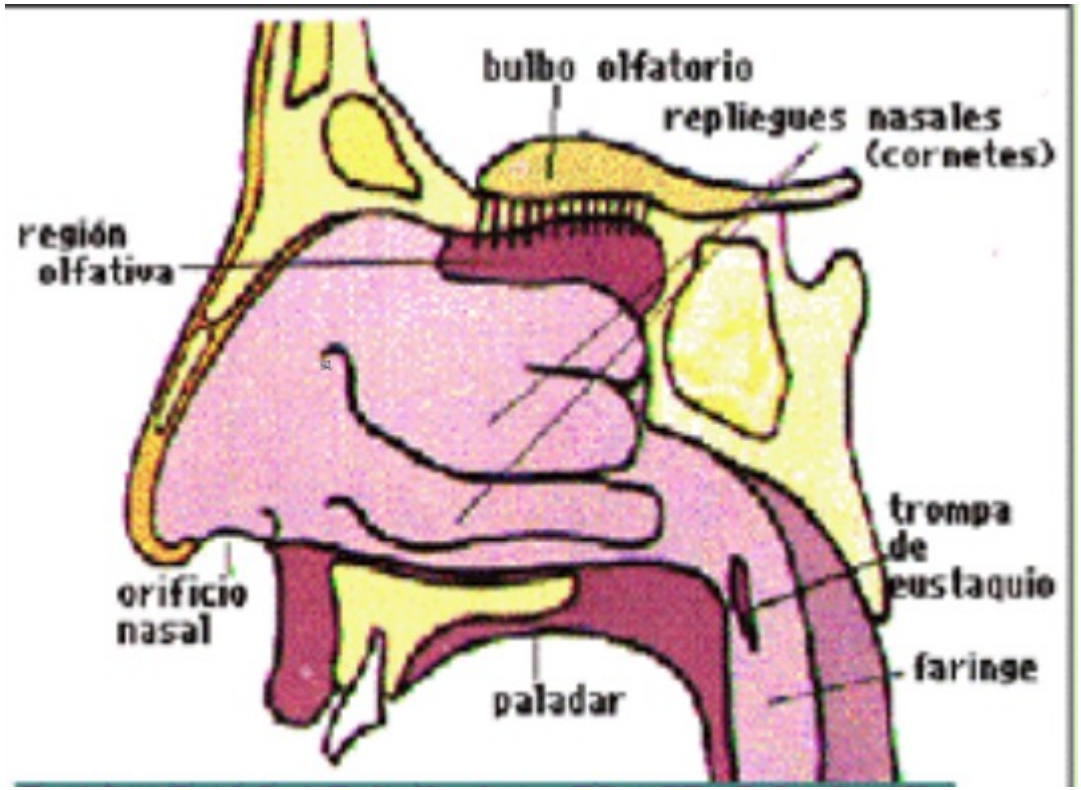

Genotipo alérgico preexistente
1
Alergeno
S. aureus:
microbiota habitual de la piel
2
Reacción crónica de Hipersensibilidad
3
Rinitis alérgica
5
Rascado:
inocula S. aureus en la cavidad nasal
4
Prurito
Estado de Portador Nasal de S. aureus
6
Expresión de determinantes de patogenicidad
7
8
Factor Agravante

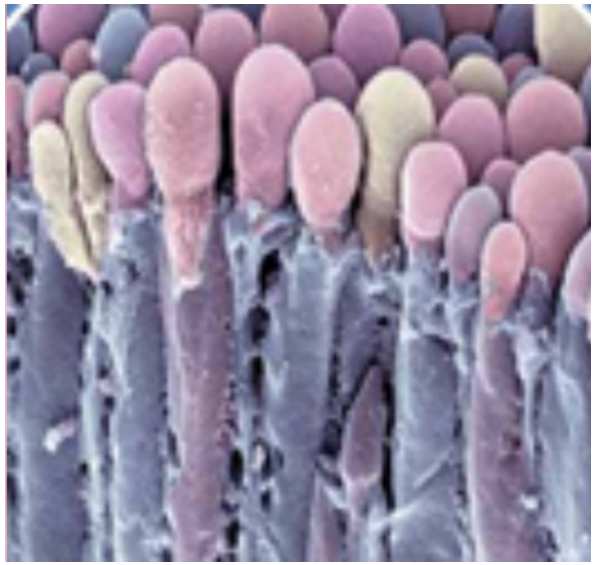
Conjuntival Nasal Bronquial



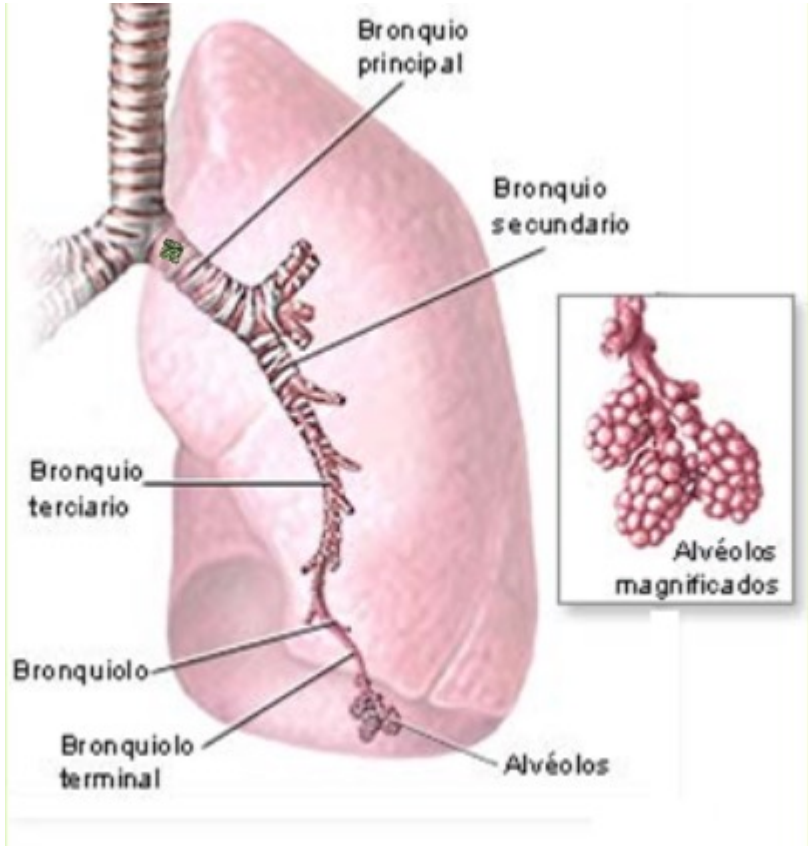


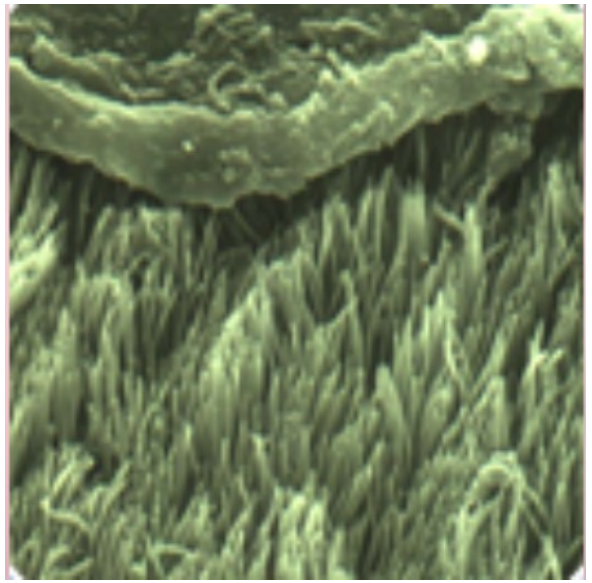
Conjuntival Nasal Bronquial





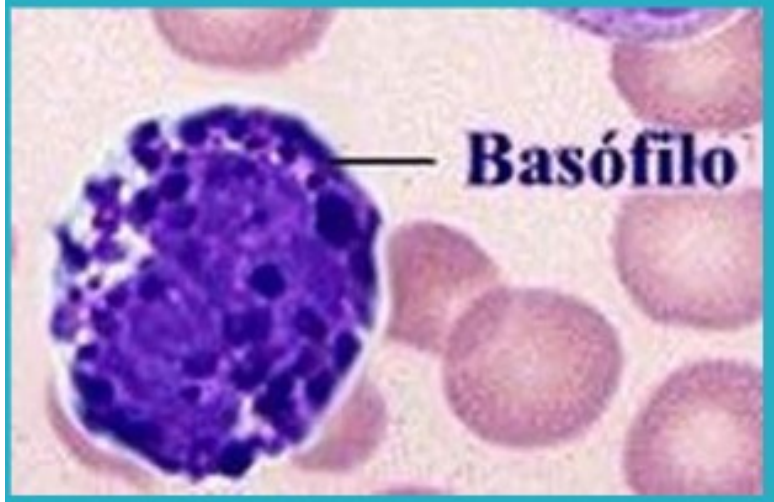
Conjuntival Nasal Bronquial

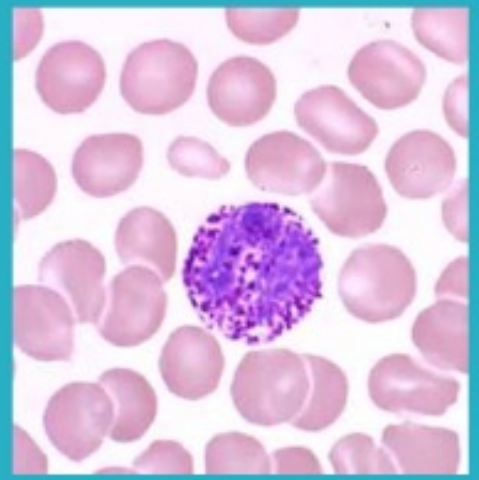


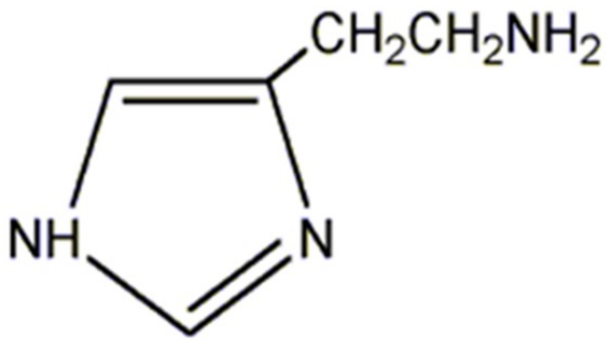



Ciliated cell
(mucus transport)
Goblet
cell
(mucus
production)
Connective tissue
A
B

BASOFILOS Y MASTOCITOS

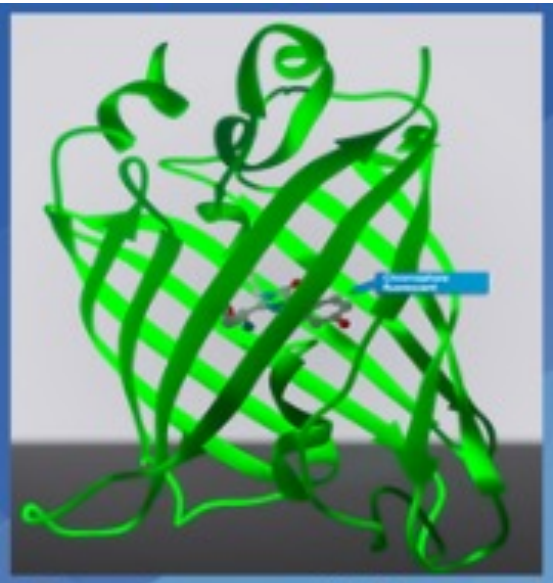




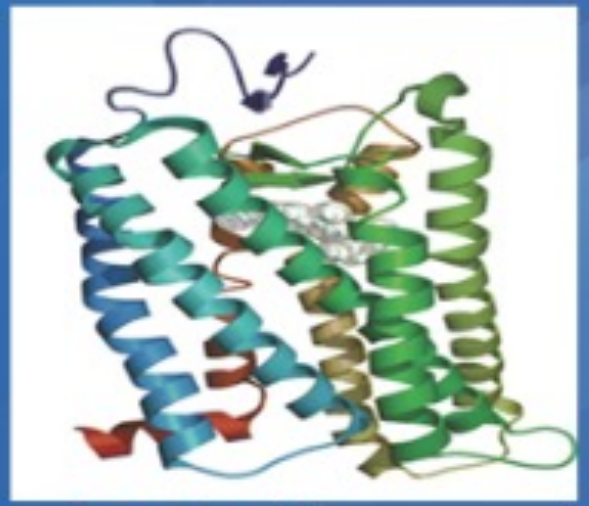


Histamina

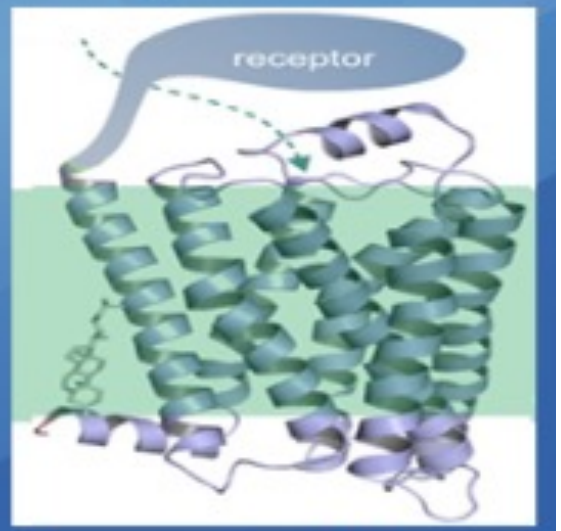
- Receptor H1



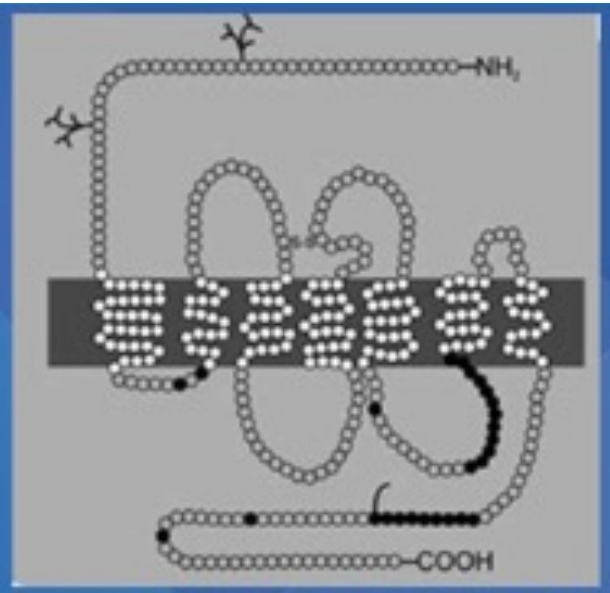
- Receptor H2



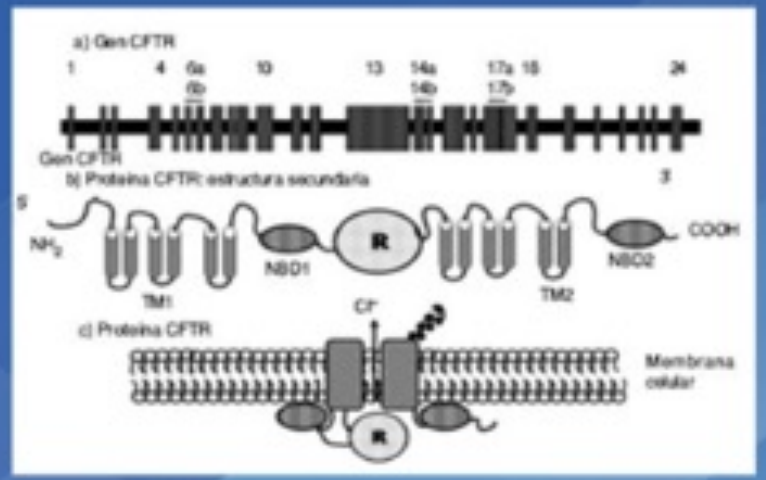
- Receptor H3



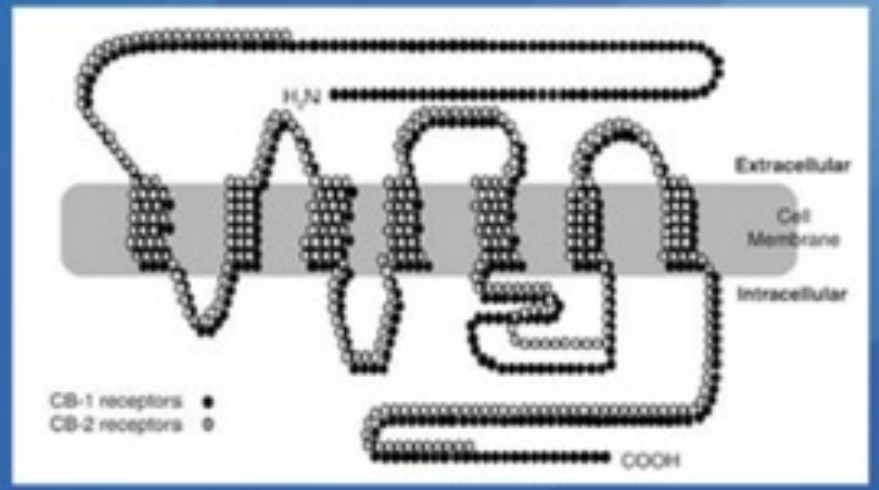
- Receptor H4



Receptor Muscarínico

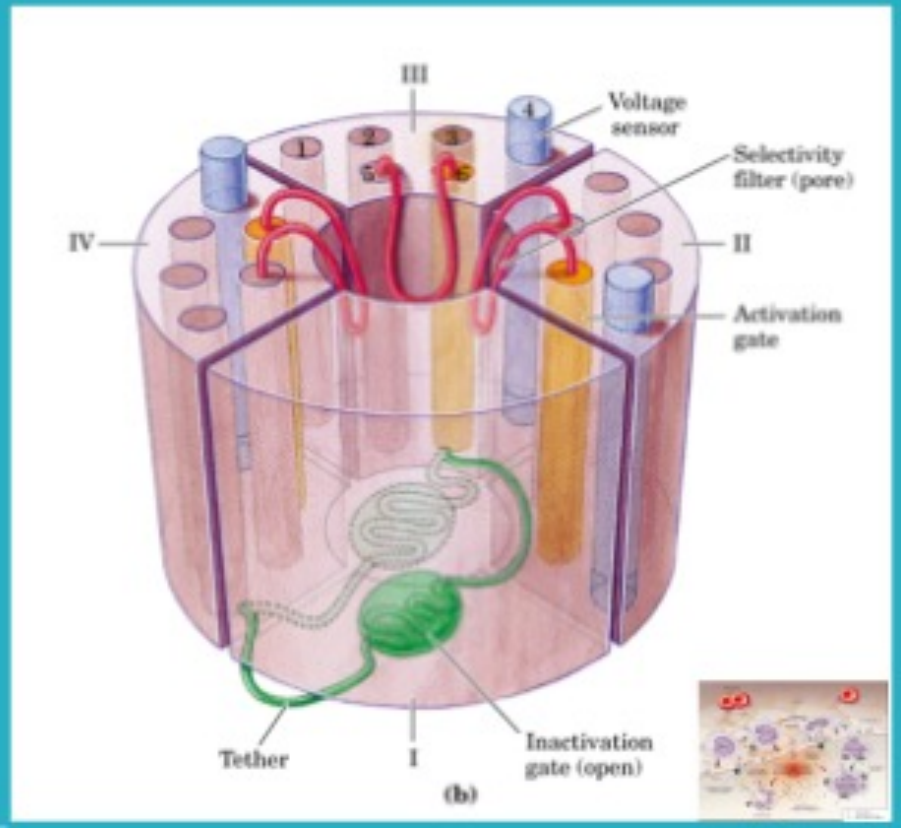


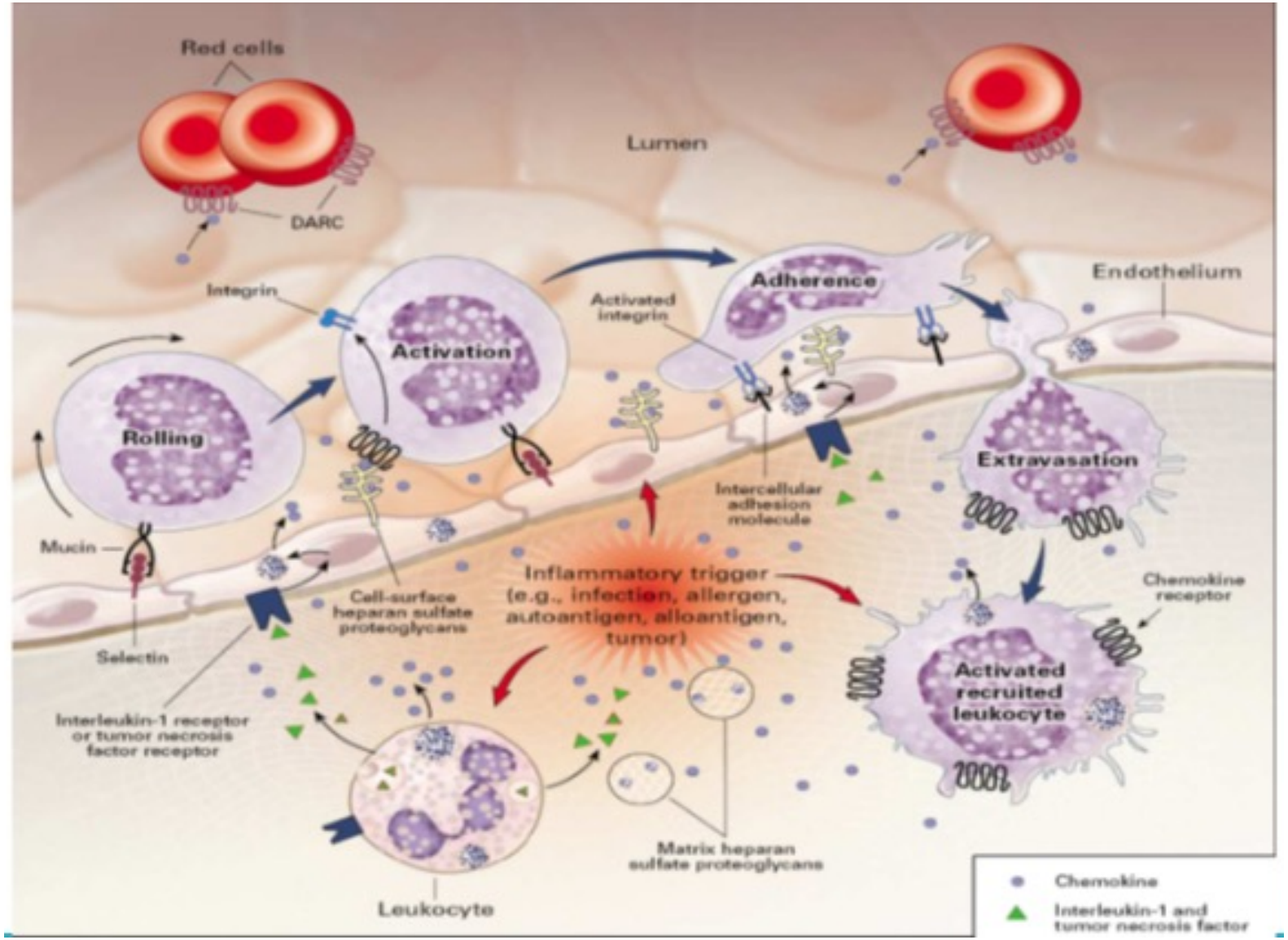
Receptor Alfa-Adrenérgico

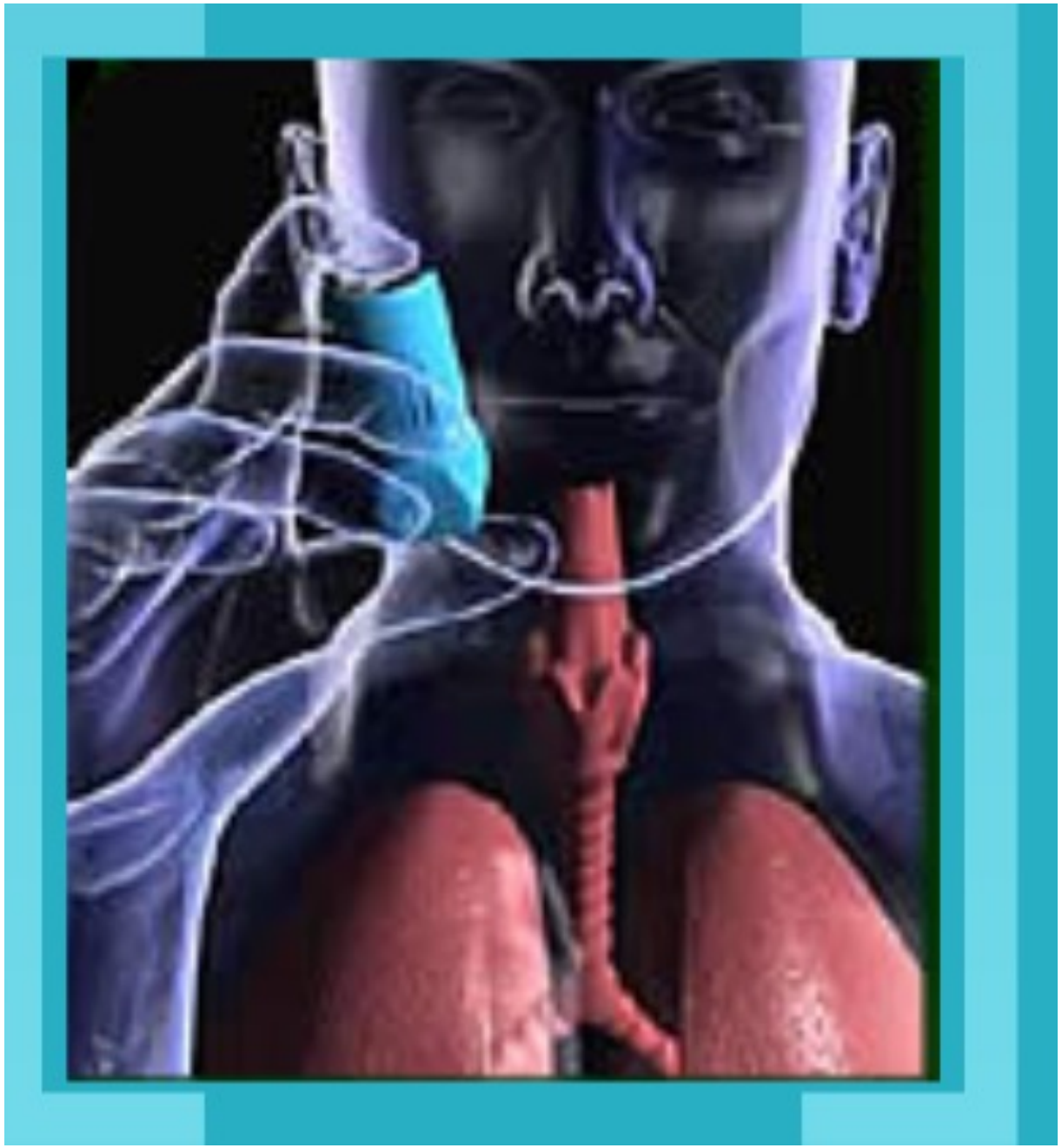


Receptor de Serotonina

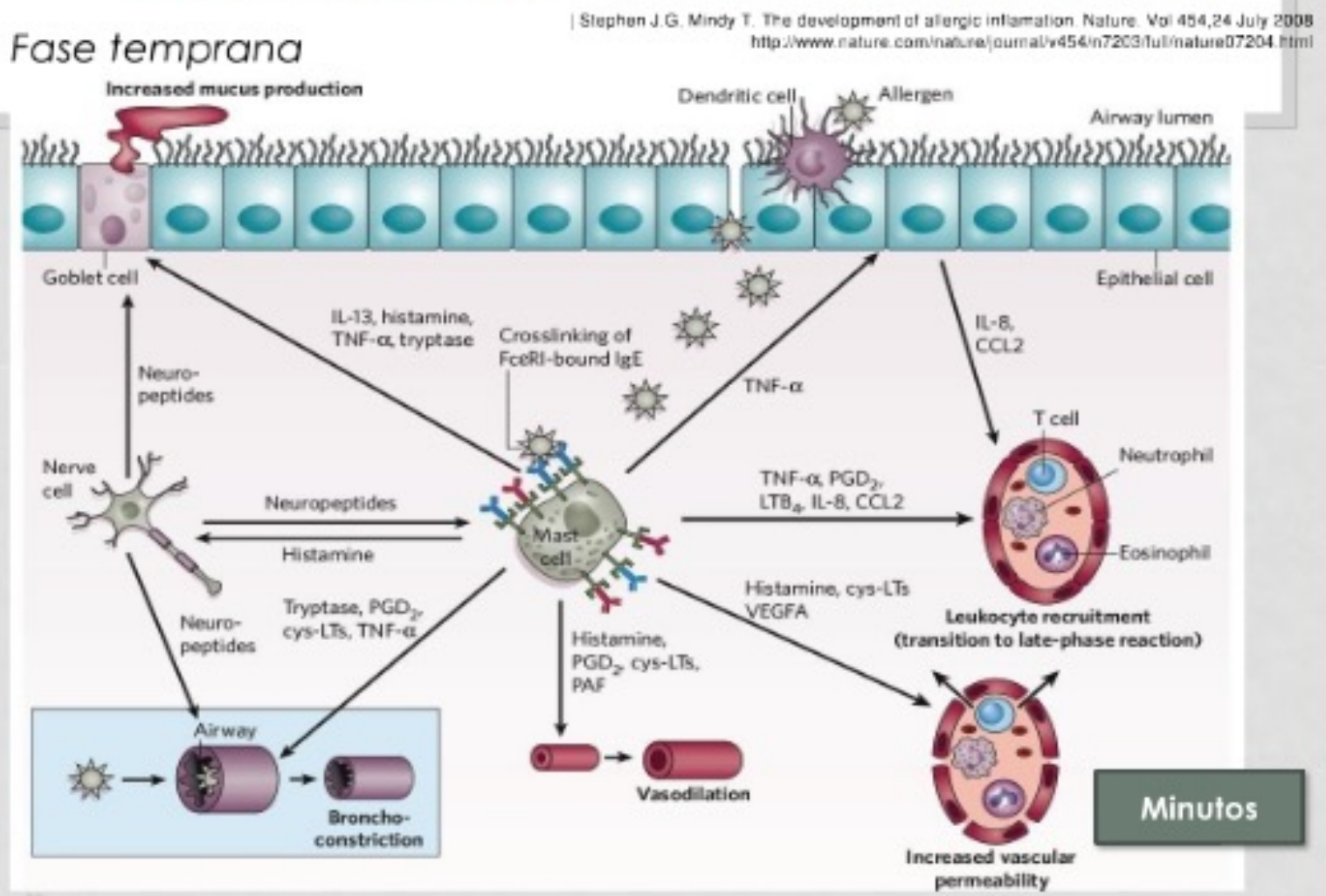
CANALES IONICOS




Red cells
DARC
Lumen
Endothelium
Integrin
Activation
Activated integrin
Adherence
Rolling
Extravasation
Intercellular adhesion molecule
Mucin
Selectin
Cell-surface heparan sulfate proteoglycans
Inflammatory trigger (e.g., infection, allergen, autoantigen, alloantigen, tumor)
Chemokine receptor
Activated recruited leukocyte
Interleukin-1 receptor or tumor necrosis factor receptor
Matrix heparan sulfate proteoglycans
Leukocyte
Chemokine
Interleukin-1 and tumor necrosis factor

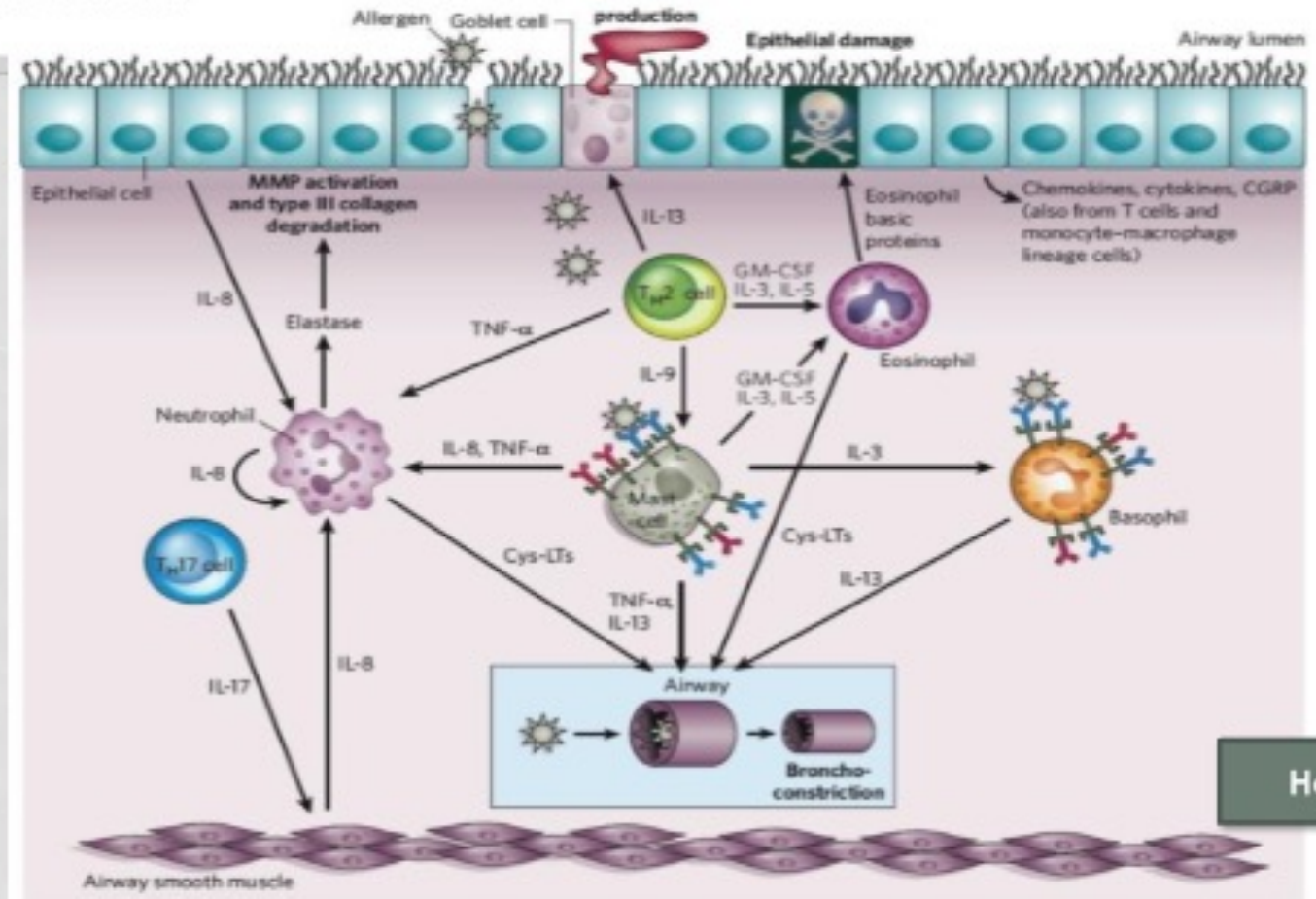


RESPUESTA INMUNE EN ASMA



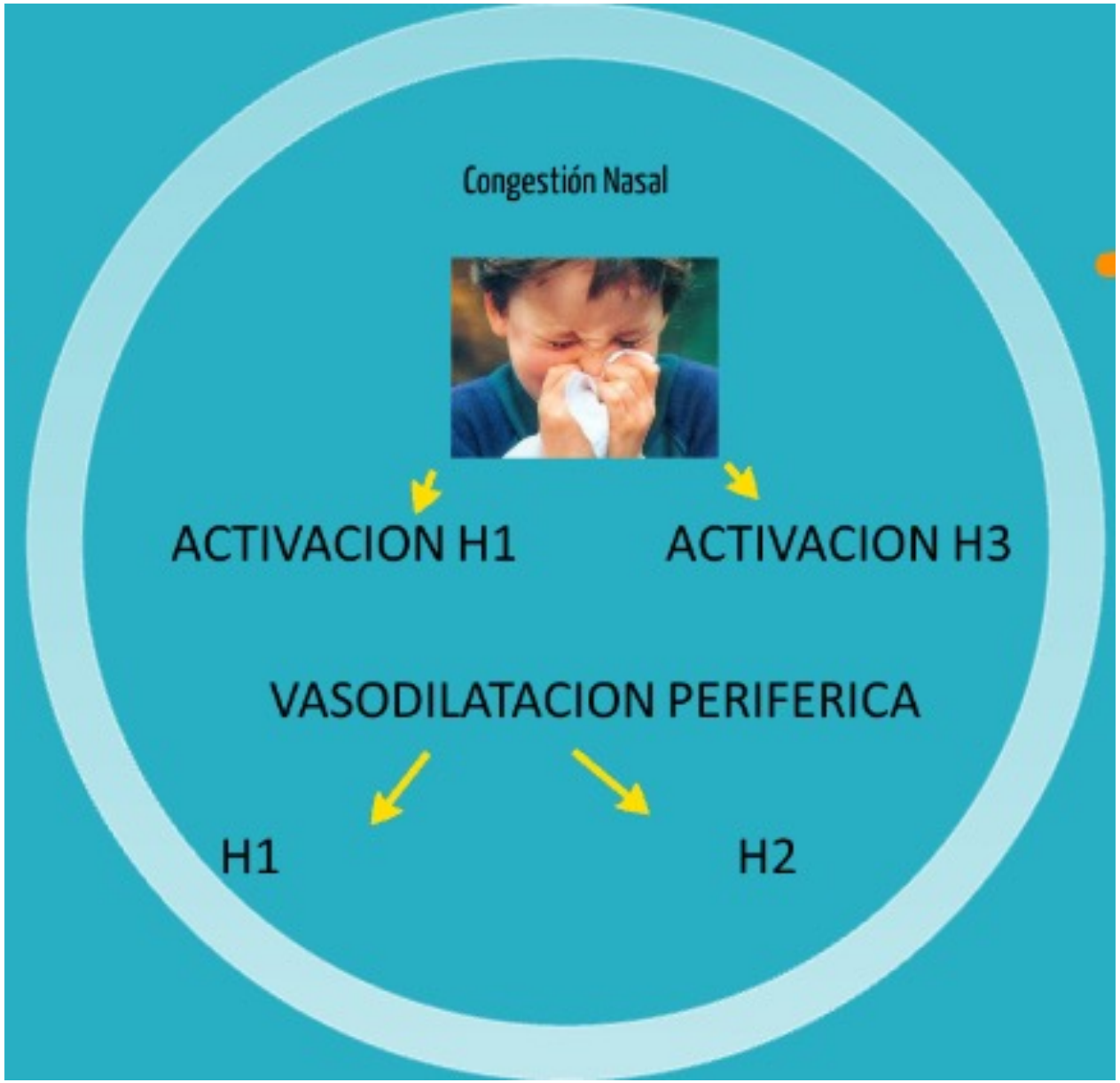
RESPUESTA INMUNE EN ASMA

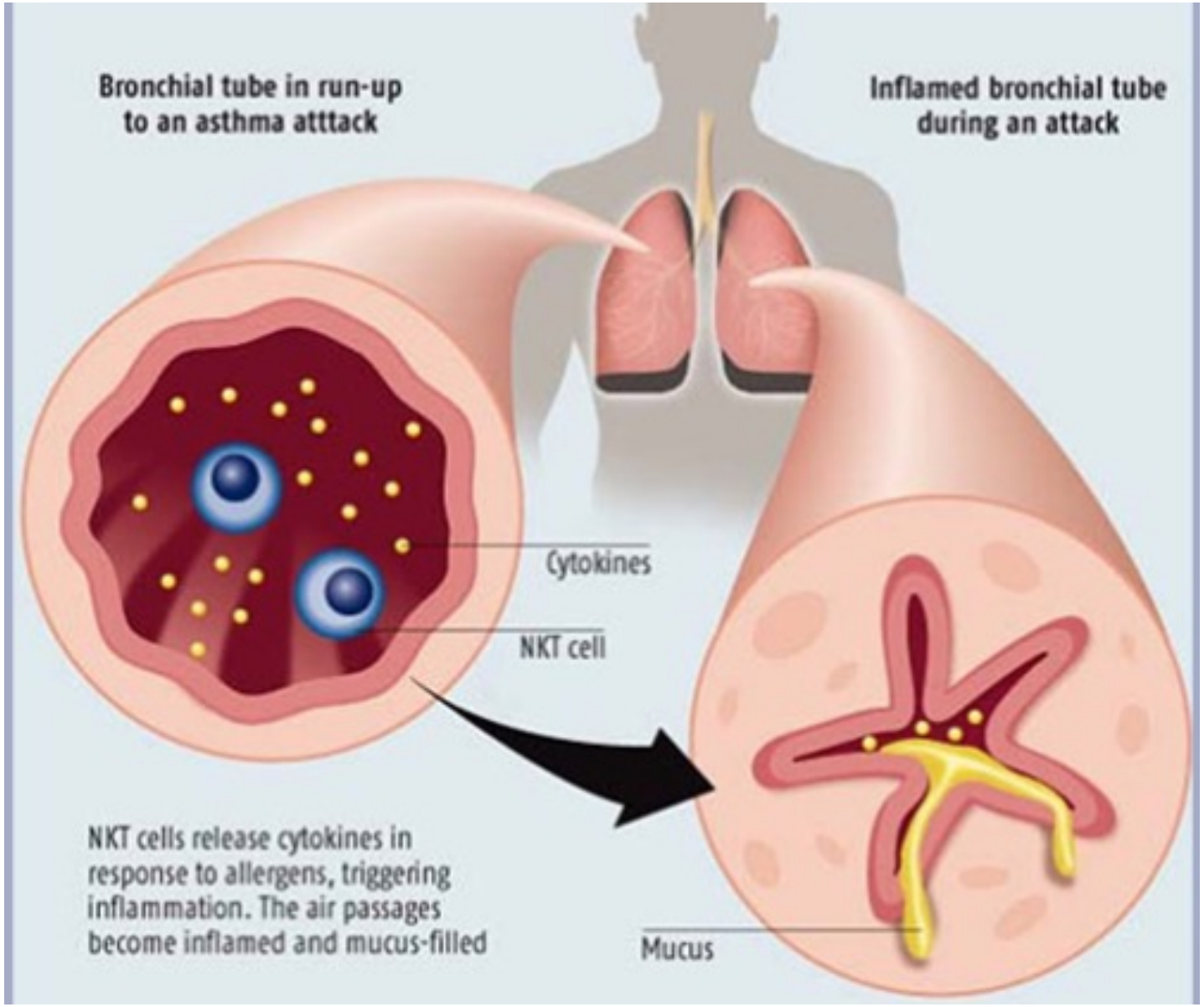
Fase Tardía



Stephen J.G. Mindy T. The development of allergic inflamation. Nature. Vol 454.24 July 2008
http://www.nature.com/nature/journal/v454/n7203/full/nature07204.html

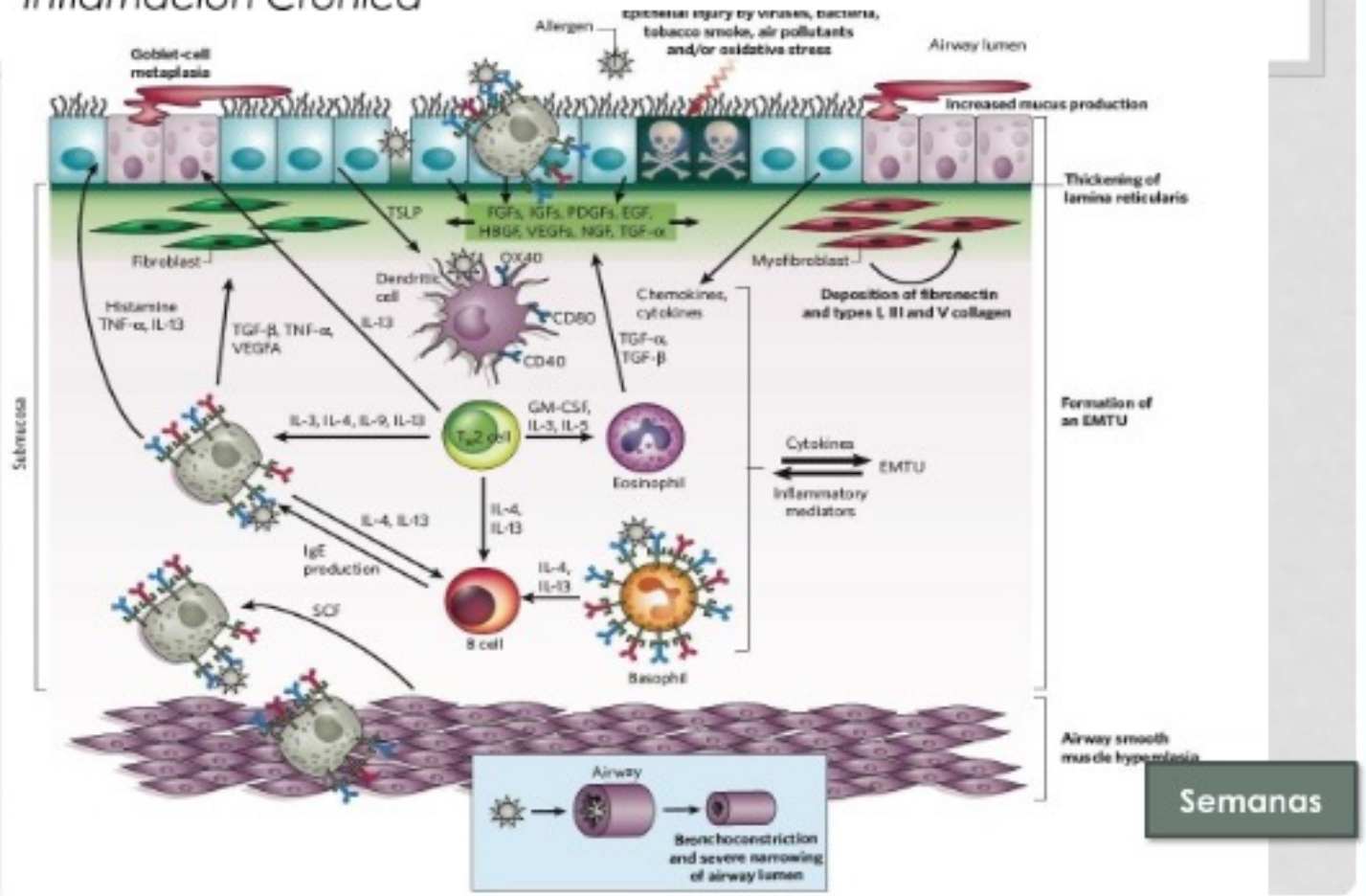
Horas


Congestión Nasal
ACTIVACION H1
ACTIVACION H3
VASODILATACION PERIFERICA
H1
H2


Bronchial tube in run-up to an asthma atttack
Inflamed bronchial tube during an attack
Cytokines
NKT cell
NKT cells release cytokines in response to allergens, triggering inflammation. The air passages become inflamed and mucus-filled
Mucus

RESPUESTA INMUNE EN ASMA

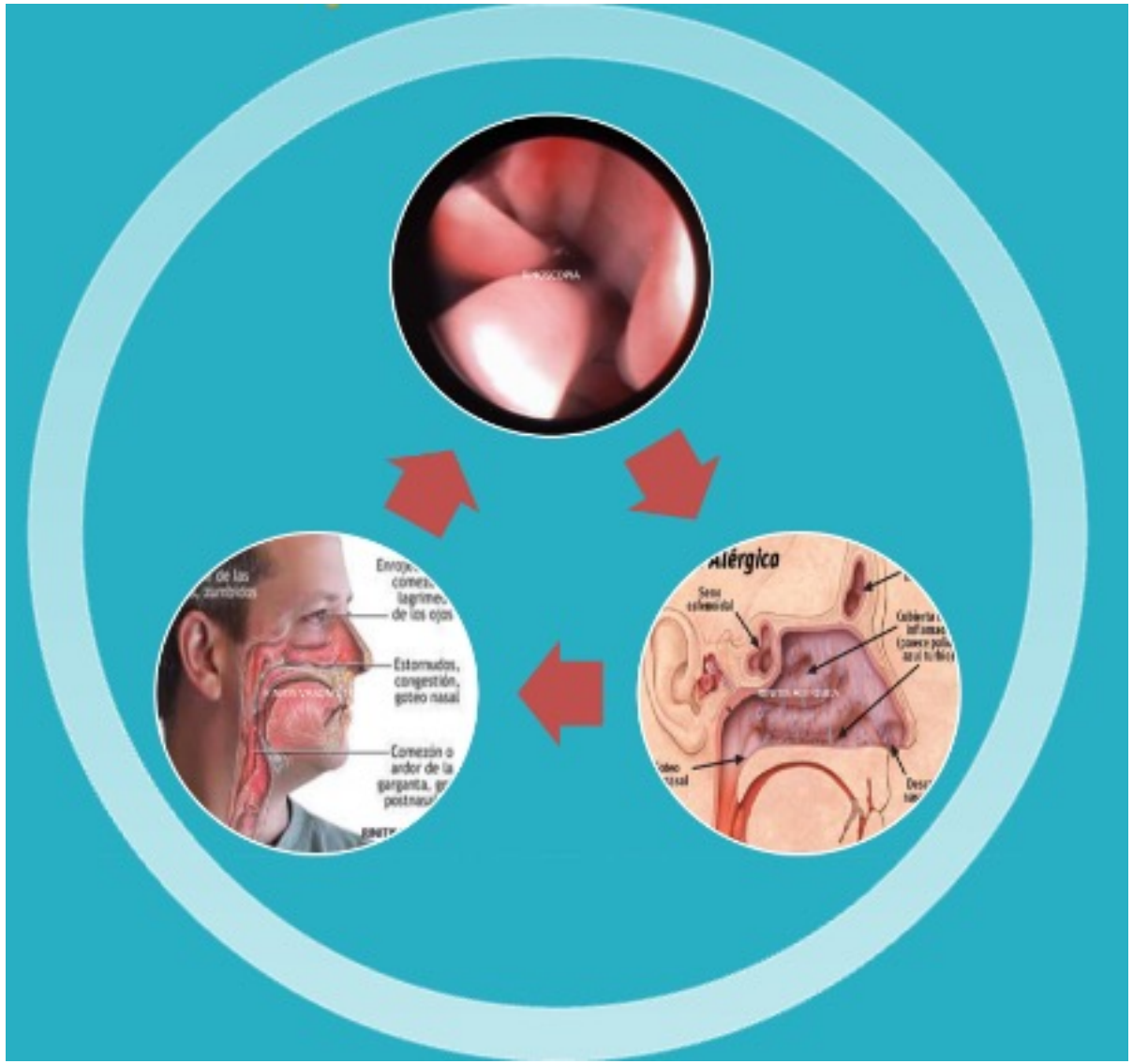
Inflamación Crónica



Semanas


RECEPTOR H1
RECEPTOR
MUSCARINICO
45% DE HOMOLOGIA

valoración clínica


Estornudos,
congestión,
goteo nasal
Comezón o
ardor de la
alérgico

RINITIS

- Rinitis alérgica
- Rinitis vasomotora
- Rinitis eosinofilica no alérgica
- Rinitis pos infecciosa
- Rinitis alérgica FUNGICA
- Sinusitis
- Rinitis por anormalidades anatómicas
- Rinitis química (ocupacional)
- Rinitis medicamentosa
- Rinosinusitis crónica

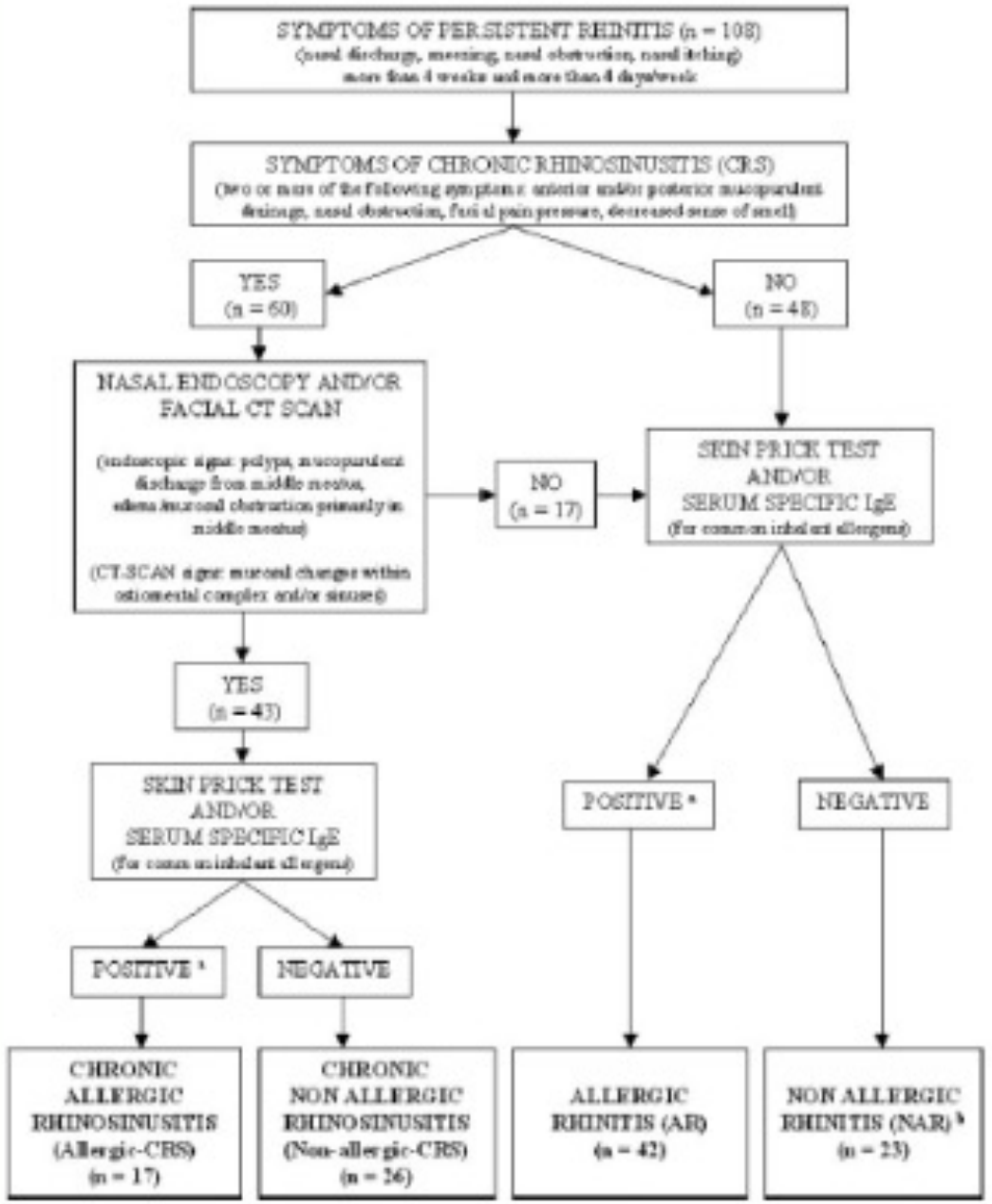
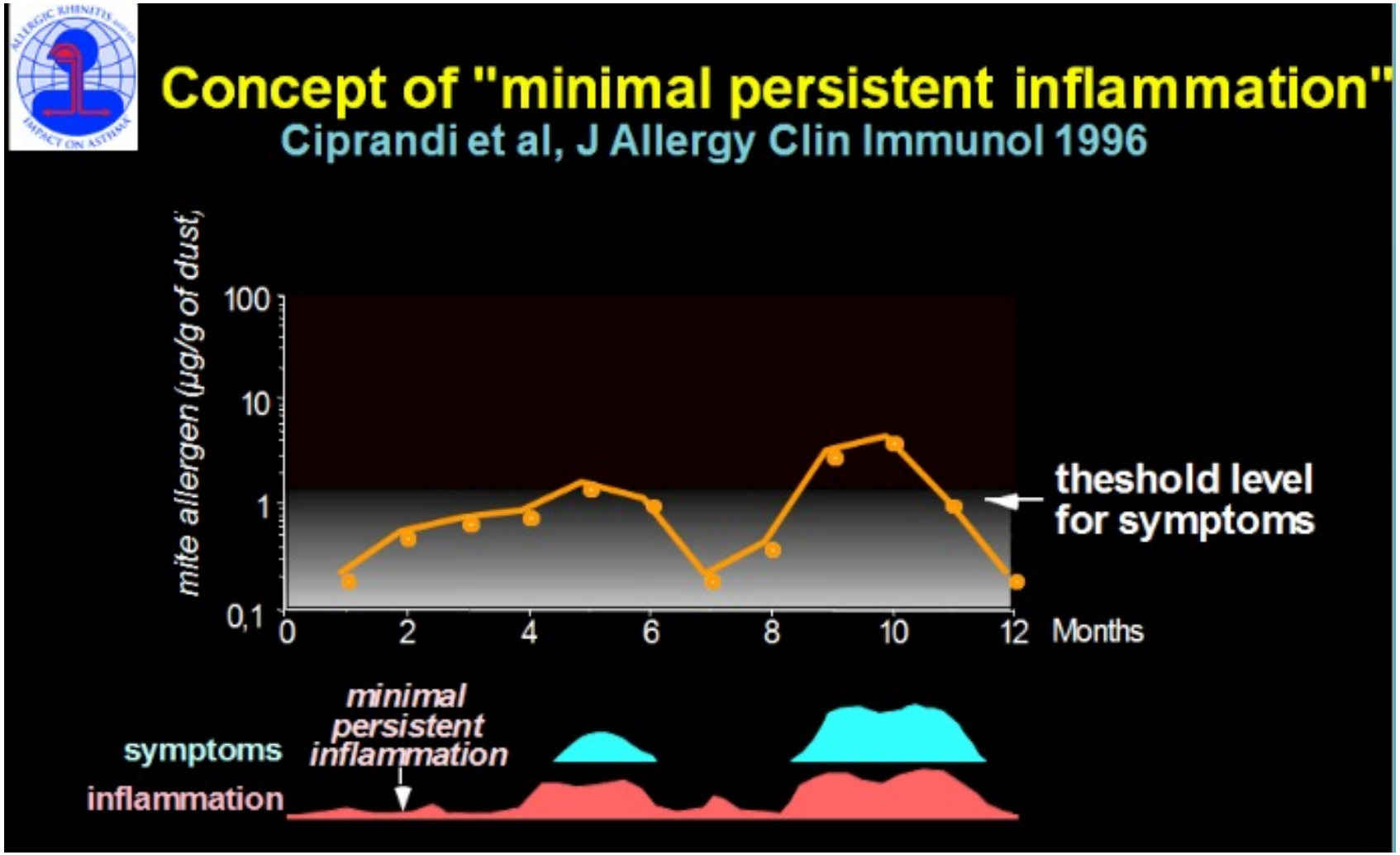

SYMPTOMS OF PERSISTENT RHINITIS (n = 108)
(nasal discharge, sneezing, nasal obstruction, nasal itching)
more than 4 weeks and more than 4 days/week
SYMPTOMS OF CHRONIC RHINOSINUSITIS (CRS)
(two or more of the following symptoms: anterior and/or posterior mucopurulent
drainage, nasal obstruction, facial pain/pressure, decreased sense of smell)
YES
(n = 60)
NO
(n = 48)
NASAL ENDOSCOPY AND/OR
FACIAL CT SCAN
(endoscopic signs: polyps, mucopurulent
discharge from middle meatus,
edema/mucosal obstruction primarily in
middle meatus)
(CT-SCAN signs: mucosal changes within
ostiomeatal complex and/or sinuses)
NO
(n = 17)
SKIN PRICK TEST
AND/OR
SERUM SPECIFIC IgE
(for common inhalant allergens)
YES
(n = 43)
SKIN PRICK TEST
AND/OR
SERUM SPECIFIC IgE
(for common inhalant allergens)
POSITIVE [a]
NEGATIVE
POSITIVE [a]
NEGATIVE
CHRONIC
ALLERGIC
RHINOSINUSITIS
(Allergic-CRS)
(n = 17)
CHRONIC
NON ALLERGIC
RHINOSINUSITIS
(Non-allergic-CRS)
(n = 26)
ALLERGIC
RHINITIS (AR)
(n = 42)
NON ALLERGIC
RHINITIS (NAR) [b]
(n = 23)

Figura n.º 1. Prueba intradérmica con ciprofloxacina. Reacción inflamatoria (eritema y habón mayor de 3 mm) del medicamento en la piel del paciente y su control con solución salina, donde no se aprecian signos inflamatorios.


Concept of "minimal persistent inflammation"
Ciprandi et al, J Allergy Clin Immunol 1996
mite allergen (µg/g of dust)
100
10
1
0,1
0
2
4
6
8
10
12
Months
theshold level
for symptoms
minimal
persistent
inflammation
symptoms
inflammation

PRUEBAS DE FUNCIÓN PULMONAR

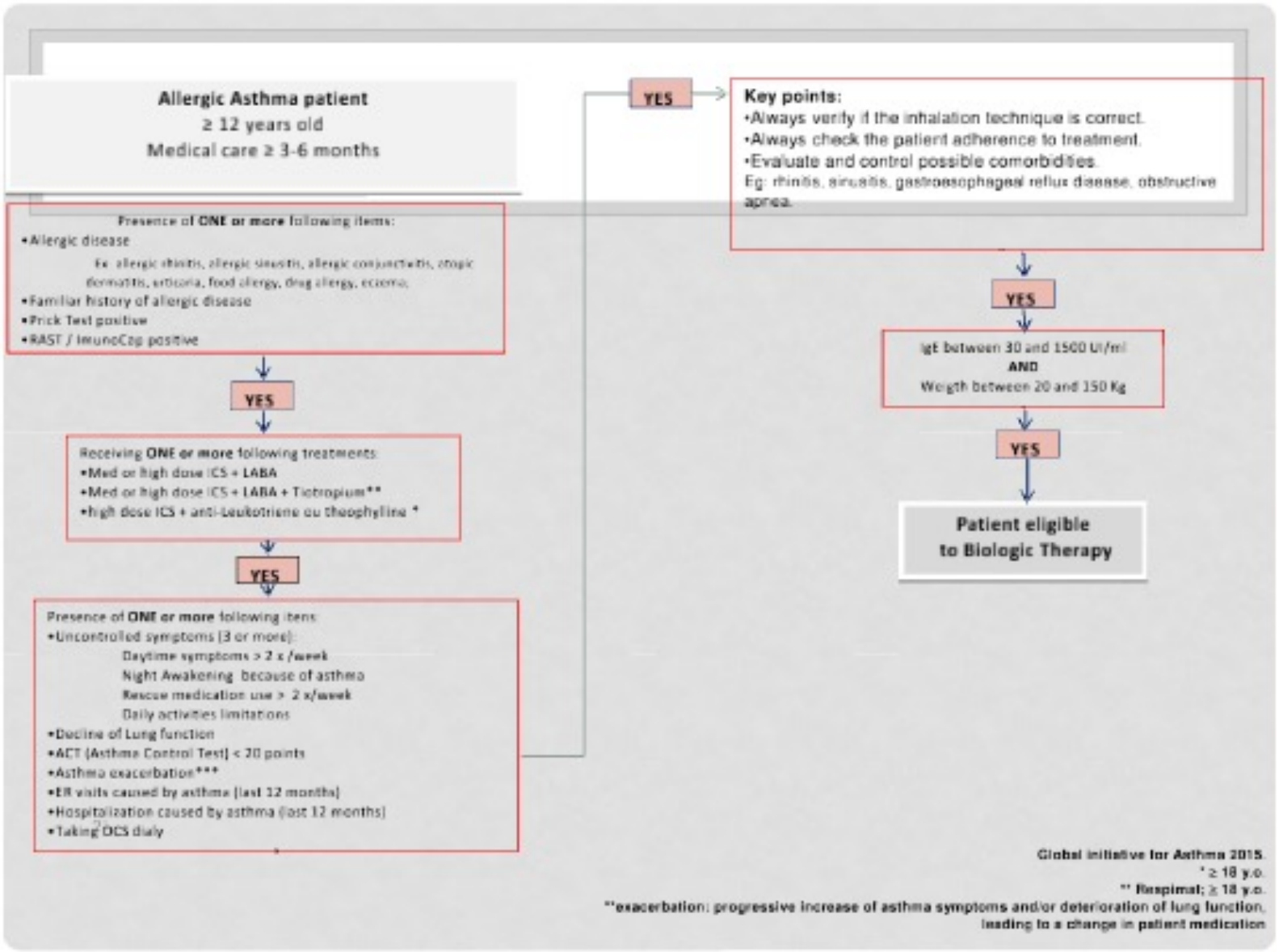
FENOTIPOS

ASMA: CARACTERÍSTICAS GENERALES

Fenotipos

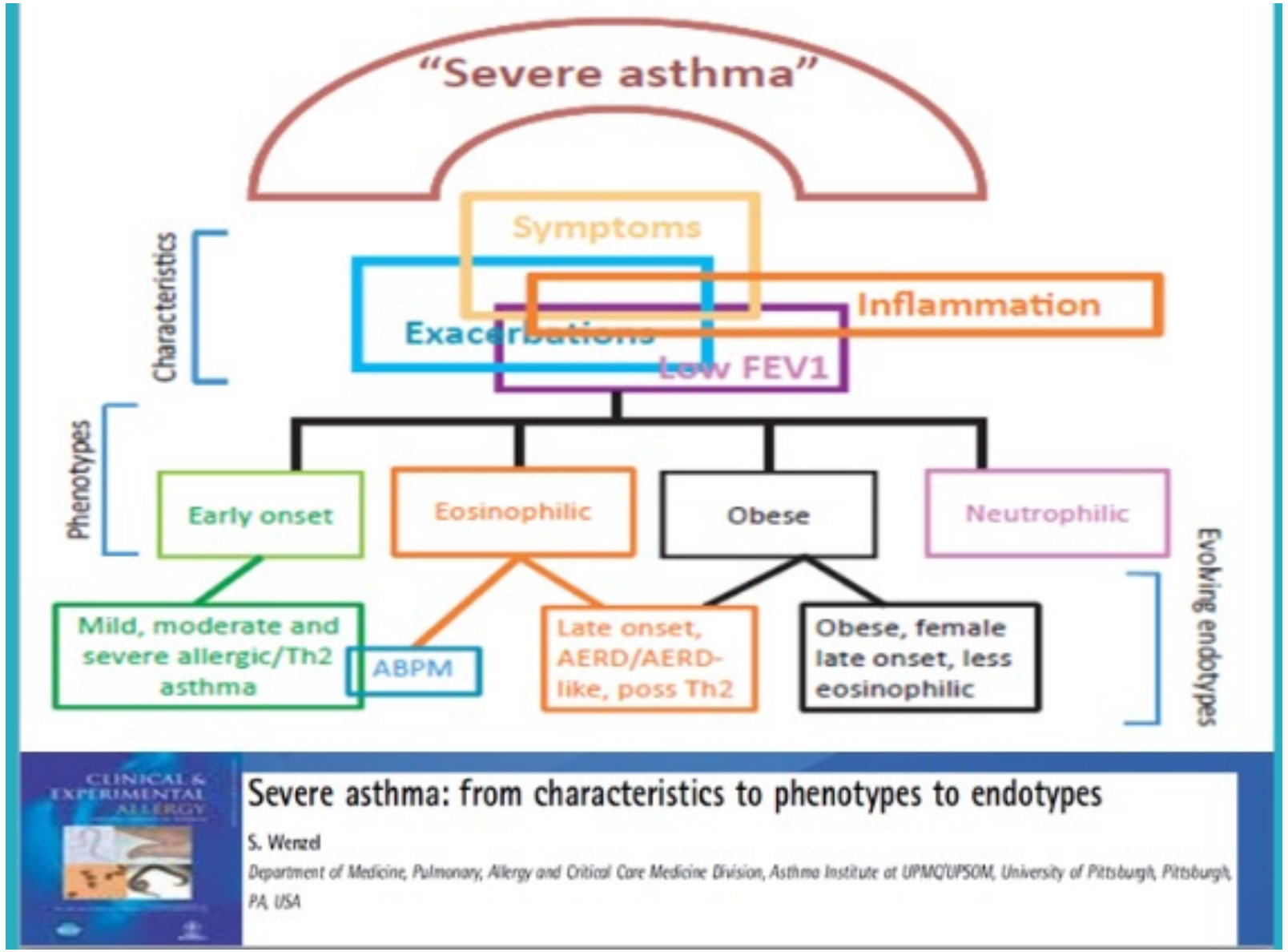
- Agrupaciones reconocibles de características demográficas, clínicas y/o fisiopatológicas

[1, 2, 3]


Allergic Asthma patient
≥ 12 years old
Medical care ≥ 3-6 months
Presence of ONE or more following items:
•Allergic disease
Ex: allergic rhinitis, allergic sinusitis, allergic conjunctivitis, atopic dermatitis, urticaria, food allergy, drug allergy, eczema,
•Familiar history of allergic disease
•Prick Test positive
•RAST / ImunoCap positive
YES
Receiving ONE or more following treatments:
•Med or high dose ICS + LABA
•Med or high dose ICS + LABA + Tiotropium**
•high dose ICS + anti-Leukotriene ou theophyline *
YES
Presence of ONE or more following items:
•Uncontrolled symptoms (3 or more):
Daytime symptoms > 2 x /week
Night Awakening because of asthma
Rescue medication use > 2 x/week
Daily activities limitations
•Decline of Lung function
•ACT (Asthma Control Test) < 20 points
•Asthma exacerbation***
•ER visits caused by asthma (last 12 months)
•Hospitalization caused by asthma (last 12 months)
•Taking OCS daily
YES
Key points:
•Always verify if the inhalation technique is correct.
•Always check the patient adherence to treatment.
•Evaluate and control possible comorbidities.
Eg: rhinitis, sinusitis, gastroesophageal reflux disease, obstructive apnea.
YES
IgE between 30 and 1500 UI/ml
AND
Weigth between 20 and 150 Kg
YES
Patient eligible
to Biologic Therapy
Global initiative for Asthma 2015.
* ≥ 18 y.o.
** Respimat; ≥ 18 y.o.
***exacerbation: progressive increase of asthma symptoms and/or deterioration of lung function, leading to a change in patient medication

FENOTIPOS

- Describen características clínicas observables sin relación directa a patofisiología .
- Clínicamente relevantes en términos de presentación , disparadores y respuesta a tratamiento , pero no necesariamente se profundiza en mecanismos patológicos


"Severe asthma"
Characteristics
Symptoms
Exacerbations
Inflammation
Low FEV1
Phenotypes
Early onset
Eosinophilic
Obese
Neutrophilic
Evolving endotypes
Mild, moderate and severe allergic/Th2 asthma
ABPM
Late onset, AERD/AERD-like, poss Th2
Obese, female late onset, less eosinophilic
CLINICAL & EXPERIMENTAL ALLERGY
Severe asthma: from characteristics to phenotypes to endotypes
S. Wenzel
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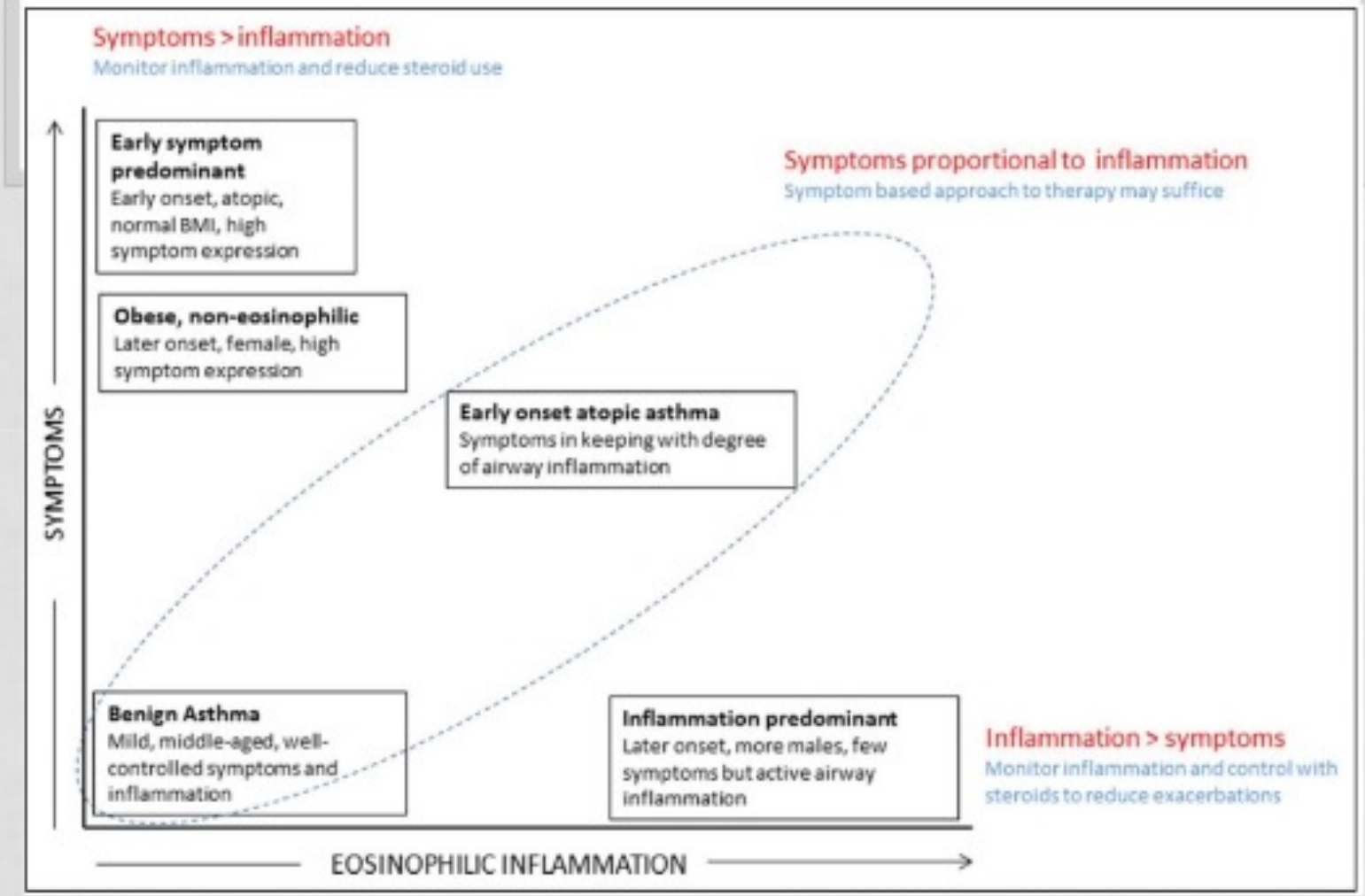

Chronic Respiratory Disease 2015; 12 (1): 69 – 77

ENDOTIPO

- Enfermedad definida por distintos mecanismos patogénicos

Basados en subtipos celulares y moleculares , que incluye

cambios en las estructuras celulares

Esto podría eventualmente permitir individualizar la terapia

Table 2 Asthma endotypes and response to inhaled corticosteroids

Biomarkers	Surrogate marker predicting response	Subphenotype	Prediction	Strength of association
Eosinophilic inflammation (10, 76)	Sputum eosinophils ?Exhaled NO	Pediatric and adult allergic asthma	Good response	+++
		Aspirin-intolerant asthma	Good response	+/–
SERPINE1 gene (79)	?Fast FEV1 decline	?	Good response	+
TSLP gene (77)	?	Allergic asthma	Good response	+
GLCCL1 variant (78)	–	?	Poor response	+
Neutrophilic inflammation (37, 39, 80)	Sputum neutrophils	Neutrophilic asthma	Poor response	++
Airway remodeling (81)	HRCT; lack of inflammation	Severe asthma with extensive remodeling	Poor response	?

NIVELES DE CONTROL DEL ASMA

Guías GINA

Características	Asma controlada (todas las siguientes)	Asma parcialmente controlada (cualquier medición presente en alguna semana)	Asma no controlada
Síntomas diurnos	Ninguno (dos veces o menos por semana)	Más de dos veces por semana	Tres o más características de asma parcialmente controlada presentes en alguna semana
Limitación de las actividades	Ninguna	Alguna	
Síntomas nocturnos/Se despierta por los síntomas	Ninguno	Alguno	
Necesidad de medicamento para aliviar los síntomas/Tratamiento de rescate	Ninguno (dos veces o menos por semana)	Más de dos veces por semana	
Función pulmonar (PEF o VEF_1)*	Normal	< 80% del esperado o del mejor del paciente (si se conoce)	
Exacerbaciones	Ninguna	Una o más por año**	Una en alguna semana ***

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. http://www.ginasthma.com/GuidelinesResources.asp , 2015.

PARA TENER EN CUENTA

- Importante definir asma alérgica severa
- Identificar Factores de riesgo
- Evaluar posibles diagnósticos diferenciales
- Los fenotipos son útiles en los casos de asma de difícil control
- Los tratamientos con terapia biológica tienen utilidad en pacientes muy bien escogidos