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Immunological Lung Diseases
Asthma

Selected topics in Clinical Immunology
March, 05, 2020

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Outline

- What is asthma?
- From epidemiology to pathophysiology
- From symptoms to diagnosis
- From endotypes to phenotypes
  - Eosinophilic asthma
- Asthma exacerbation
- From assessment to treatment
  - Non-pharmacological management
  - Generic pharmacological management
  - Phenotype directed treatment
  - Biologics in eosinophilic asthma

Asthma

Heterogeneous chronic airway disease

Chronic Airway Inflammation

↓

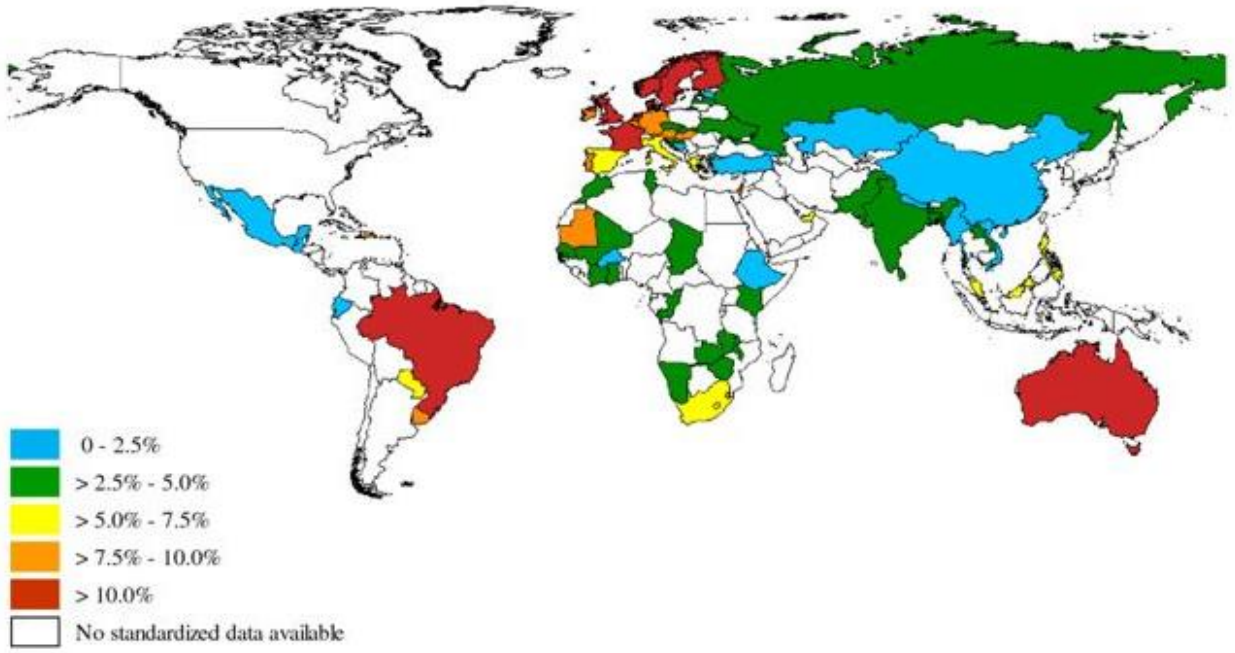
Expiratory Airflow Limitation

↓

Respiratory Symptoms

www.ginasthma.org

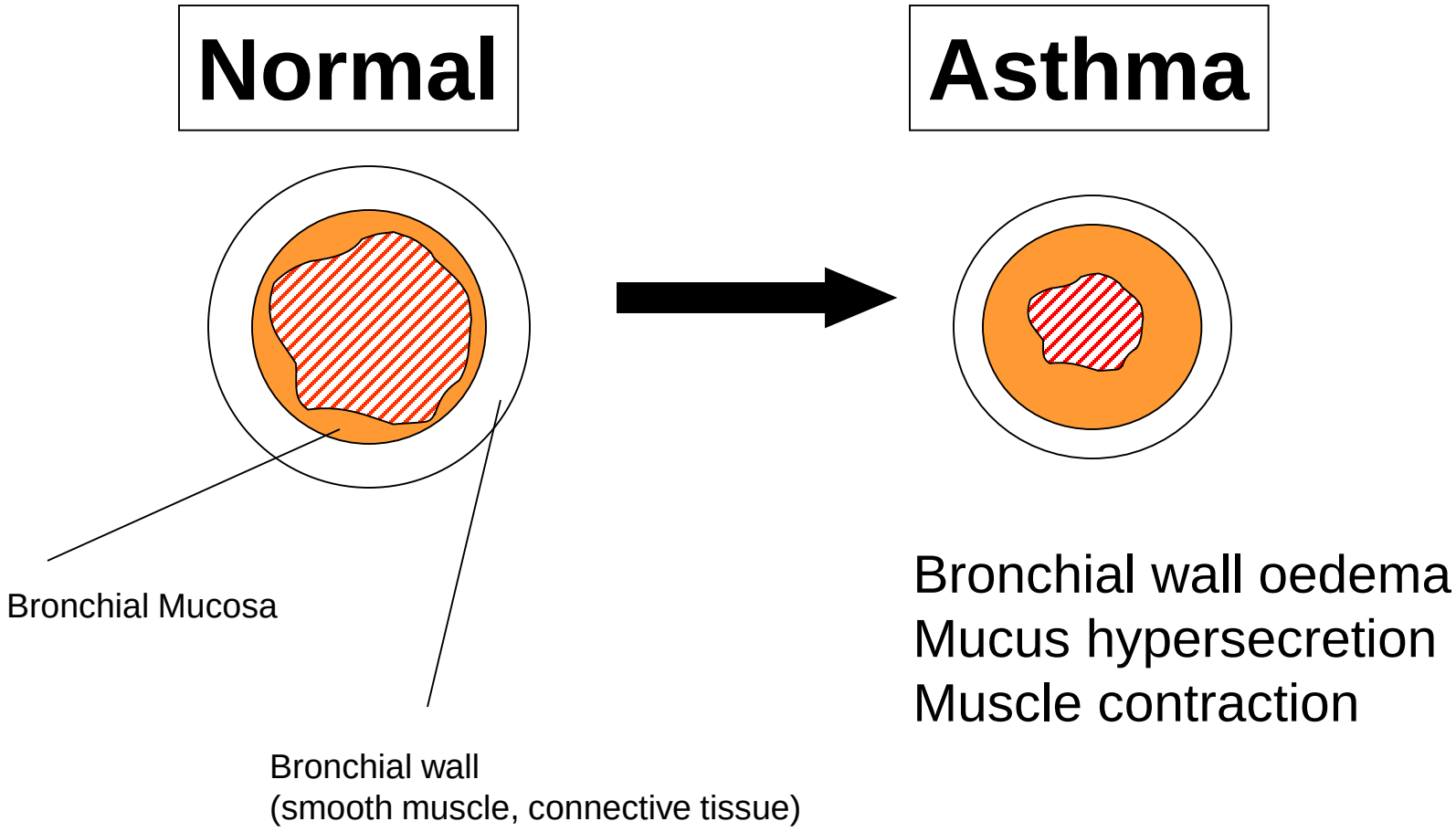
Epidemiology



- 300-400 million people worldwide affected
- Prevalence increasing
- High burden on health care system
- Major cause of school and work absence
- Early diagnosis, prevention, and treatment is cost-effective

Teresa et al. BMC Public Health, 2012

Impaired Airway Inflammatory Response → Bronchoconstriction



Allergens, Viruses, Inhalational Toxins
Environmental factors
Genetics

Dysregulated epithelial barrier

Inflammation

Airway Remodeling

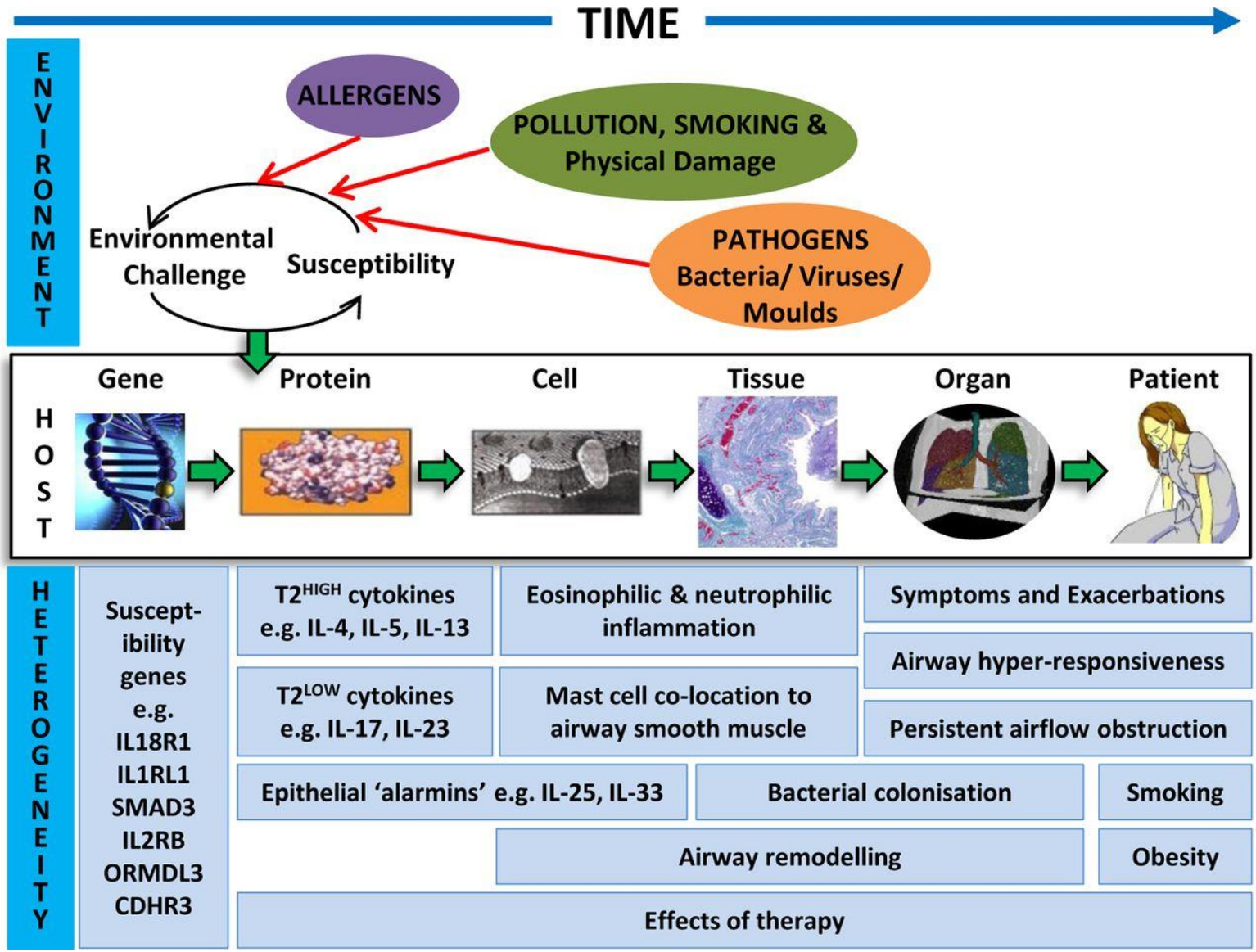
- Epithelial damage
- Cilial dysfunction
- Goblet cell hyperplasia
- Increased vascularity
- Proliferation of myofibroblasts and fibrocytes

Airway Hyperresponsiveness

Airway narrowing

Trigger

Symptoms



Richard J. Russell, and Christopher Brightling Clin. Sci. 2017

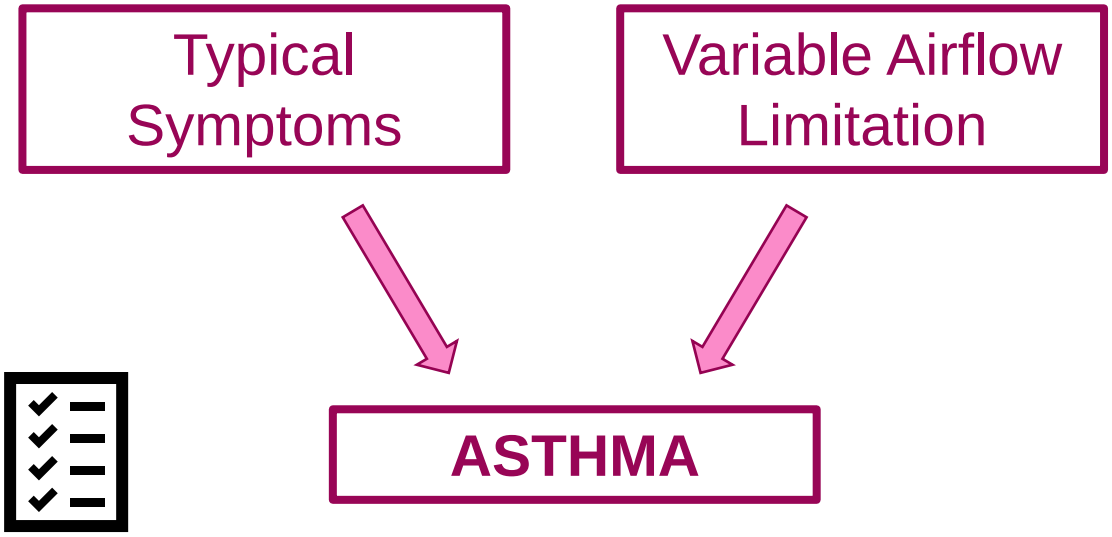
Symptoms

Variable in 1) occurrence, 2) frequency, 3) intensity

- Shortness of breath
  - Acute – chronic – at rest – at night! - at or after exercise
- Wheezing
- Chest tightness
- Cough

- Triggers

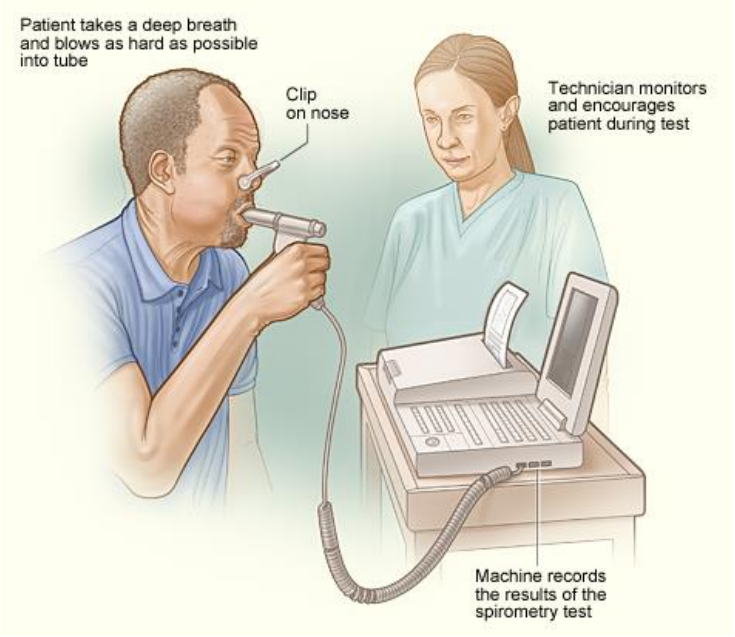
Diagnosis



- ✓ > 1 symptom
- ✓ worse at night
- ✓ variability
- ✓ triggers

- ✓ Office pulmonary function test
- ✓ Home peak-flow measurement

Measurement of airflow limitaion

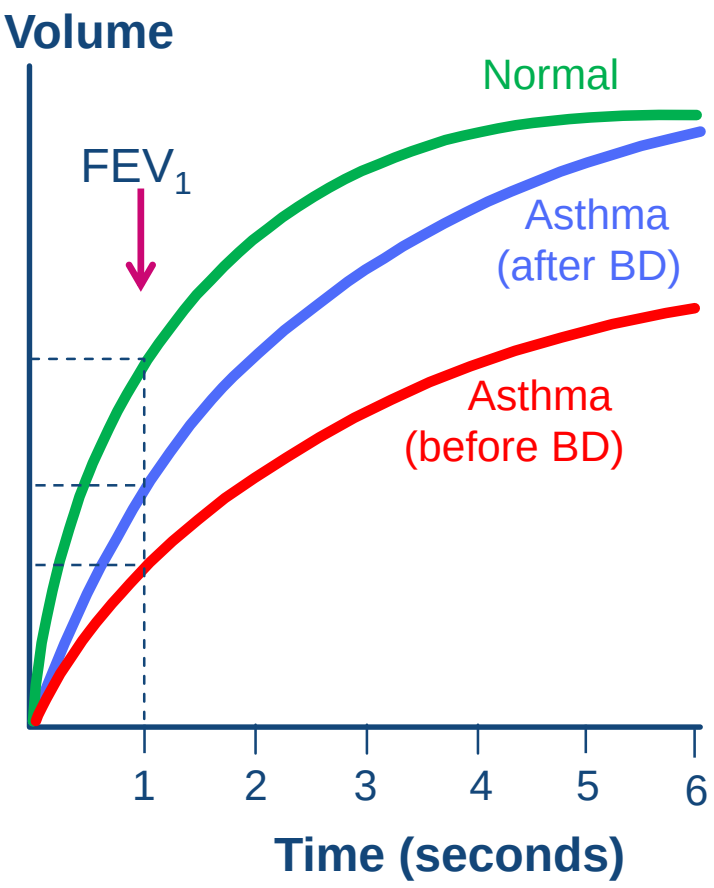


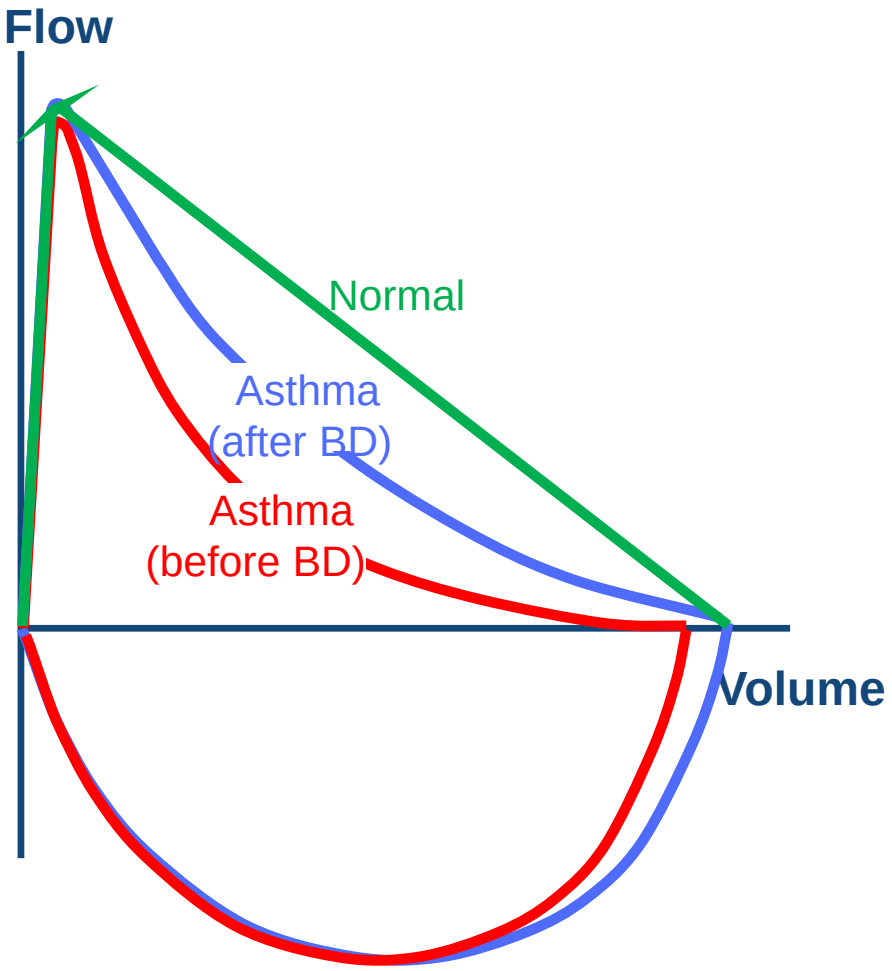
Airflow limitation & variability:

- At follow-up (spontaneous, changing triggers)
- Improvement after inhalation with bronchodilator (e.g. Salbutamol)
- Worsening after bronchoprovocation (e.g. Methacholine)

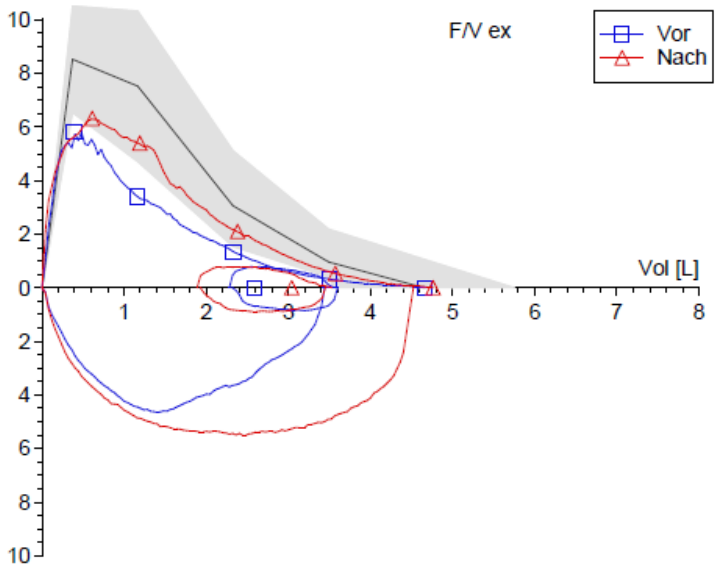
National Heart Lung and Blood Insitute (NIH)

Spirometry


Volume
Normal
FEV1
Asthma
(after BD)
Asthma
(before BD)
1
2
3
4
5
6
Time (seconds)


Flow
Normal
Asthma
(after BD)
Asthma
(before BD)
Volume

Example

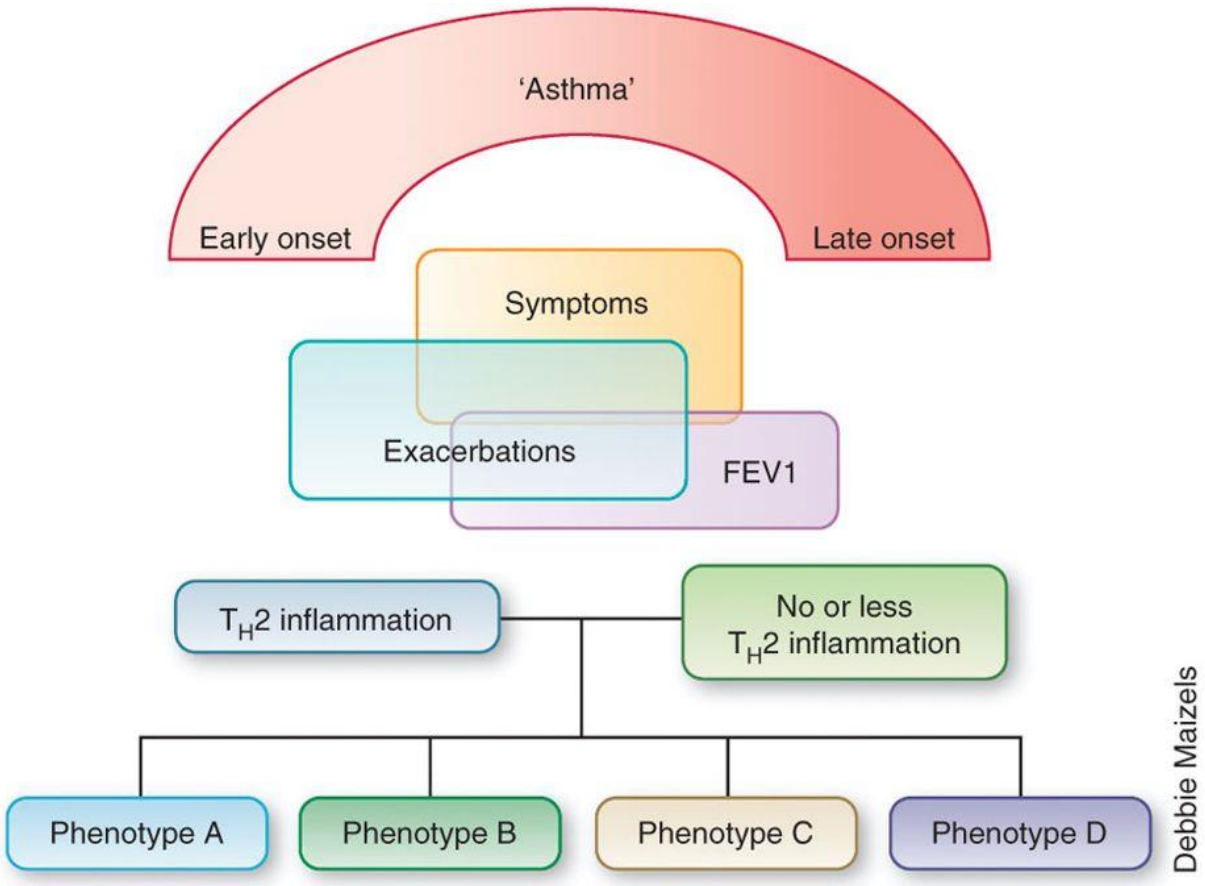


Forced Vital Capacity in 1s

Forced Vital Capacity

		Soll	Best	%-Soll	Nach	% Nach	%Änd...	Z-Score	Z-Score
Testdatum			05.07.18		05.07.18				
Besuchszeit			09:45		09:45				
VC MAX	L	4.65	4.66	100	4.76	102	2		0.03
FVC	L	4.65	4.66	100	4.76	102	2		0.03
FEV1	L	3.61	2.59	72	3.04	84	18		-1.92
FEV1%F	%	77.78	55.44	71	63.86	82	15		-2.88
FEV1%M	%	77.78	55.44	71	63.86	82	15		-2.88
FEF75	L/s	0.95	0.31	33	0.53	56	71		-2.05
FEF50	L/s	3.06	1.34	44	2.09	68	56		-1.90
FEF25	L/s	7.51	3.39	45	5.39	72	59		-2.41
PEF	L/s	8.52	5.83	68	6.31	74	8		-2.23

Asthma Endotype - Phenotype



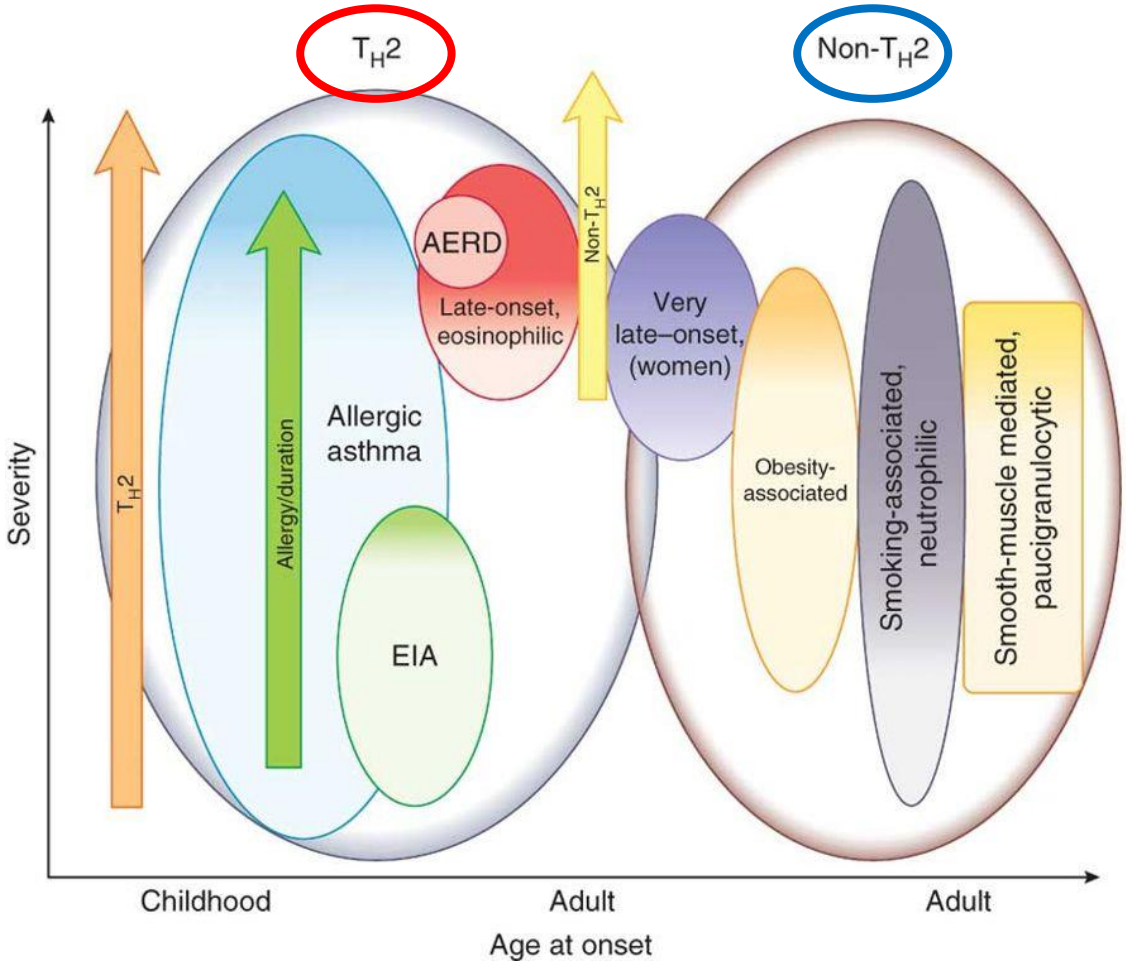
Asthma Syndrome
Symptoms
Variable airflow limitation
Bronchial hyperreactivity
Airway inflammation

Endotypes
Links molecular pathways and clinical characteristics

Phenotypes
Clinical presentation
Treatment response

Wenzel et al., NatMed 2012

Phentoypes



T_H2-Asthma:

- Allergic eosinophilic

→ early onset

- Non allergic eosinophilic

→ late onset

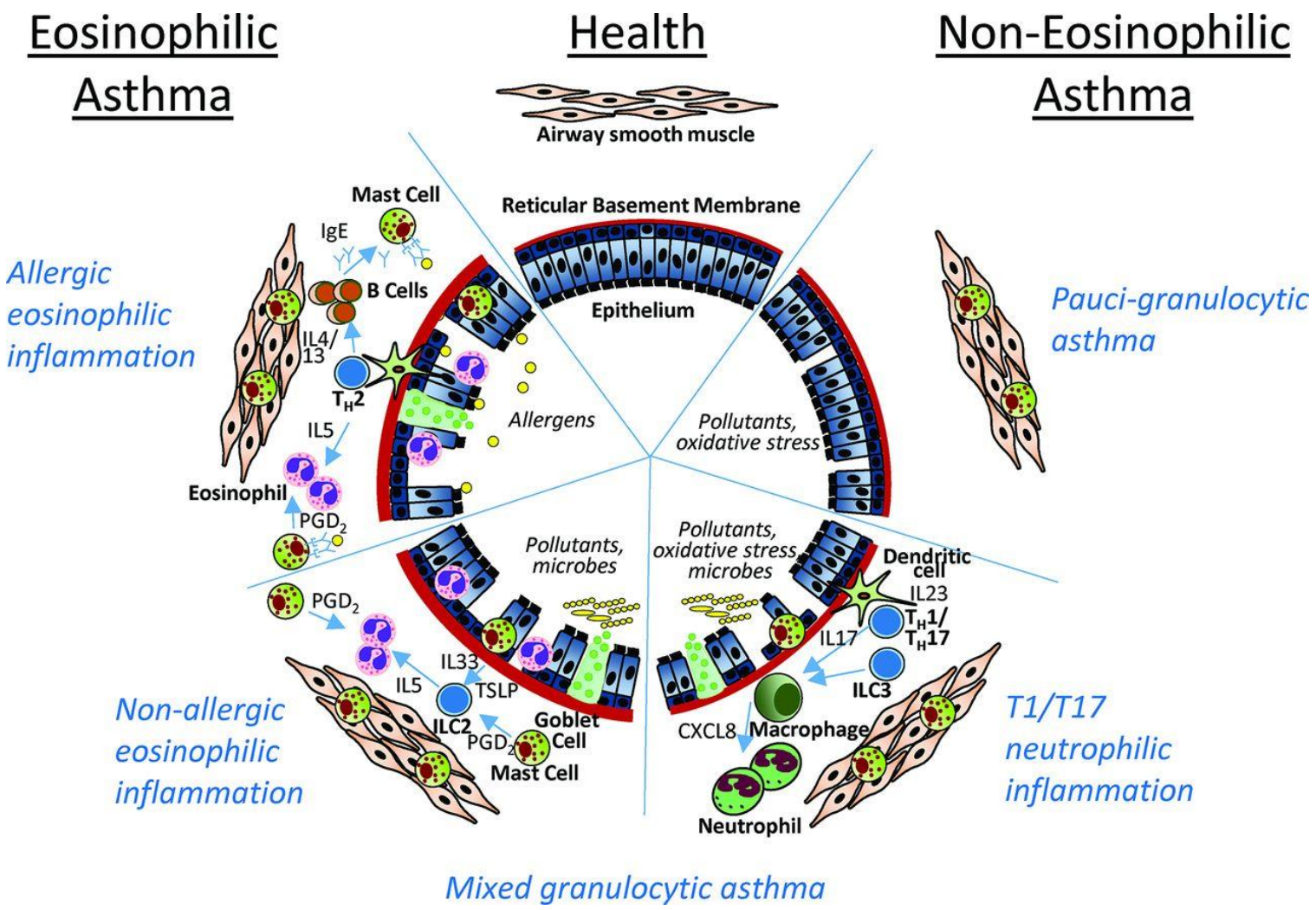
- Aspirin exacerbated
- Exercise induced

Non-T_H2-Asthma:

- Late onset
- Obesity related
- Smoking related
- Elderly (Immunosenescence)
- Neutrophilic
- Paucigranulocytic

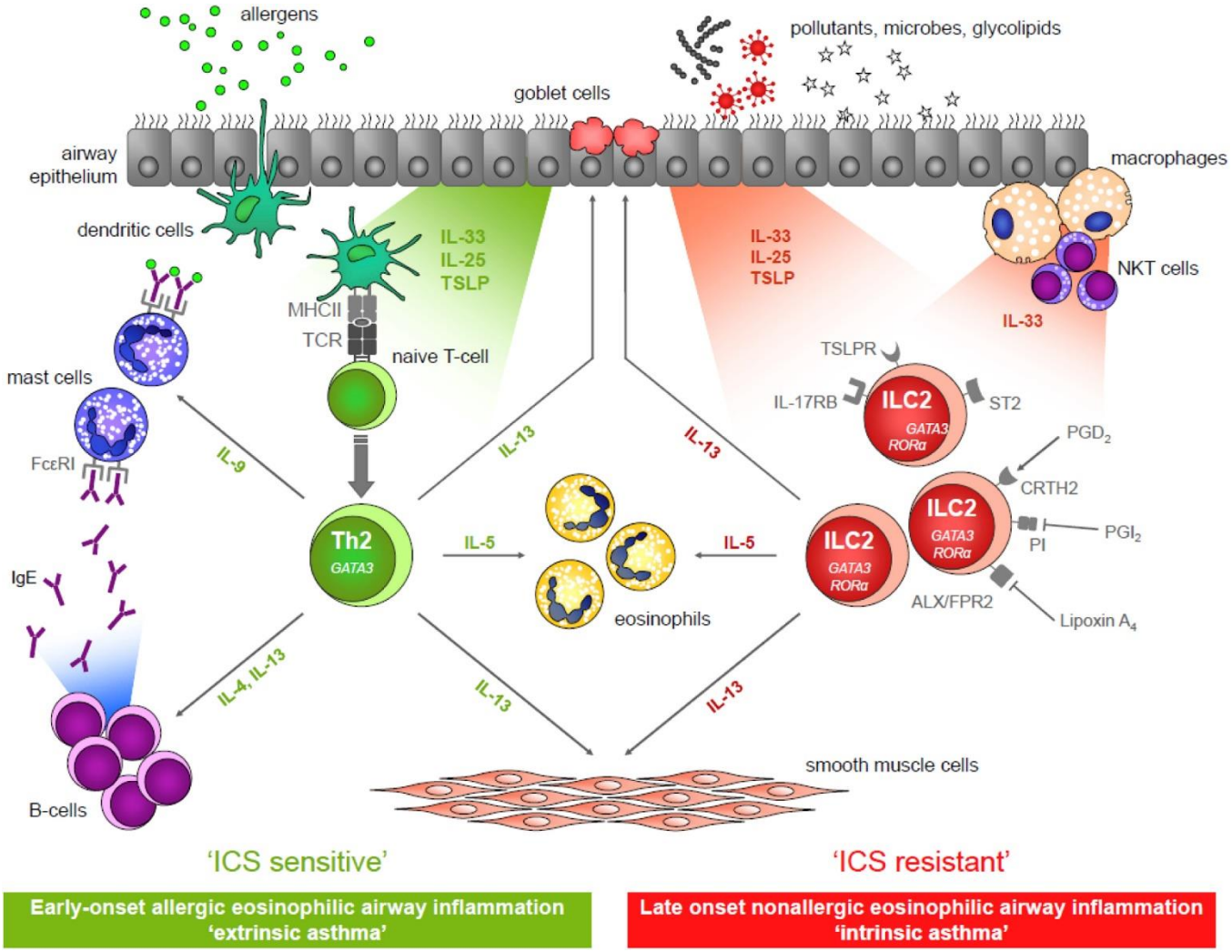
Wenzel et al., NatMed 2012

Endotypes



Richard J. Russell, and Christopher Brightling Clin. Sci. 2017

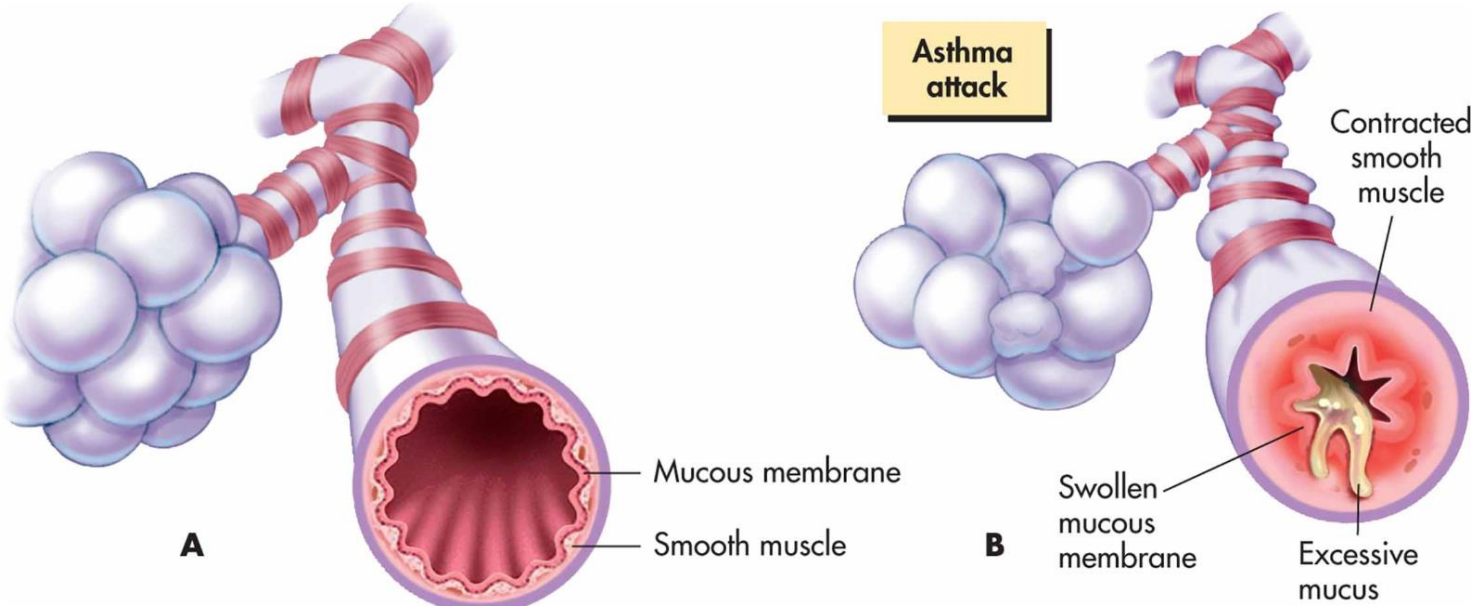
Eosinophilic Asthma



Brusselle et al., NatMed 2013

Asthma Exacerbation

- ‘Flare-up’, ‘Attack’
- Acute or sub-acute worsening of symptoms and lung function compared with the patient’s usual status
- Triggers: Viral respiratory infection, respiratory allergens, medications (β-blockers, aspirin, NSAIDs)



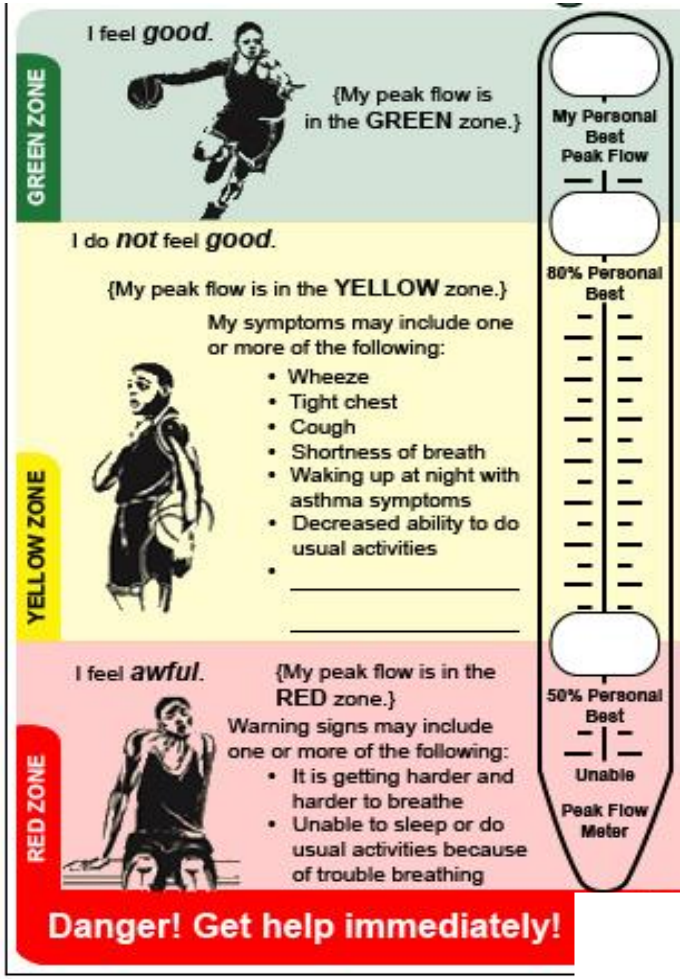
Asthma Exacerbation

Severity determines management

1) Self-management with a written asthma action plan

2) Management in primary care

3) Management in the emergency department/hospital



Asthma Treatment: Goals

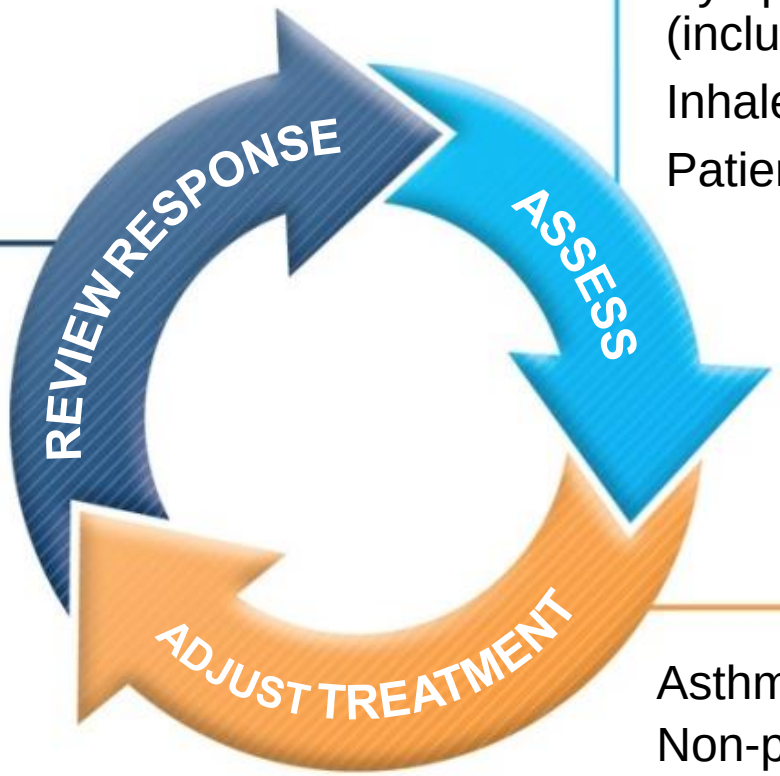
1) **Minimise symptom burden**
   - Day-to-day symptoms
     - Need no/little reliever medication
   - Disturbed sleep
   - Activity limitation
2) **Minimise the risk of adverse asthma outcomes**
   - Exacerbations
   - Persistent airflow limitation
     - Goal: normal/near normal lung function
   - Medication side-effects

Compliance/Adherence to treatment
Inhalation technique
Comorbidities/Co-factors

Shared decision making

From Assessment to Treatment

Diagnosis
Symptom control & risk factors (including lung function)
Inhaler technique & adherence
Patient preference



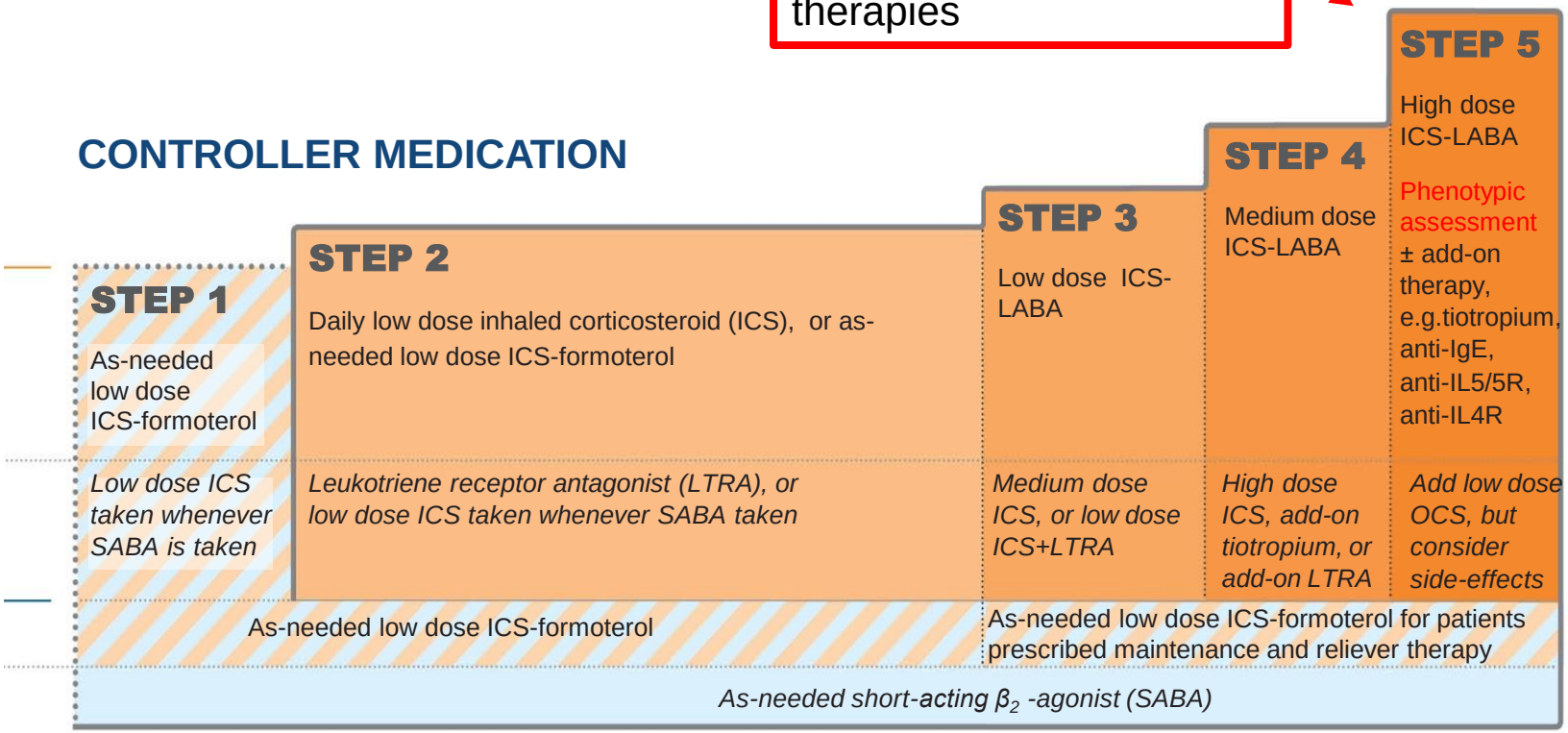
Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function

Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors

GINA 2019

Stepwise approach to control asthma symptoms & reduce risk

Phenotypic assessment
Type 2 targeted biologic therapies



RELIEVER MEDICATION

ICS inhaled corticosteroids
OCS oral corticosteroids
LABA long-acting β2 agonist

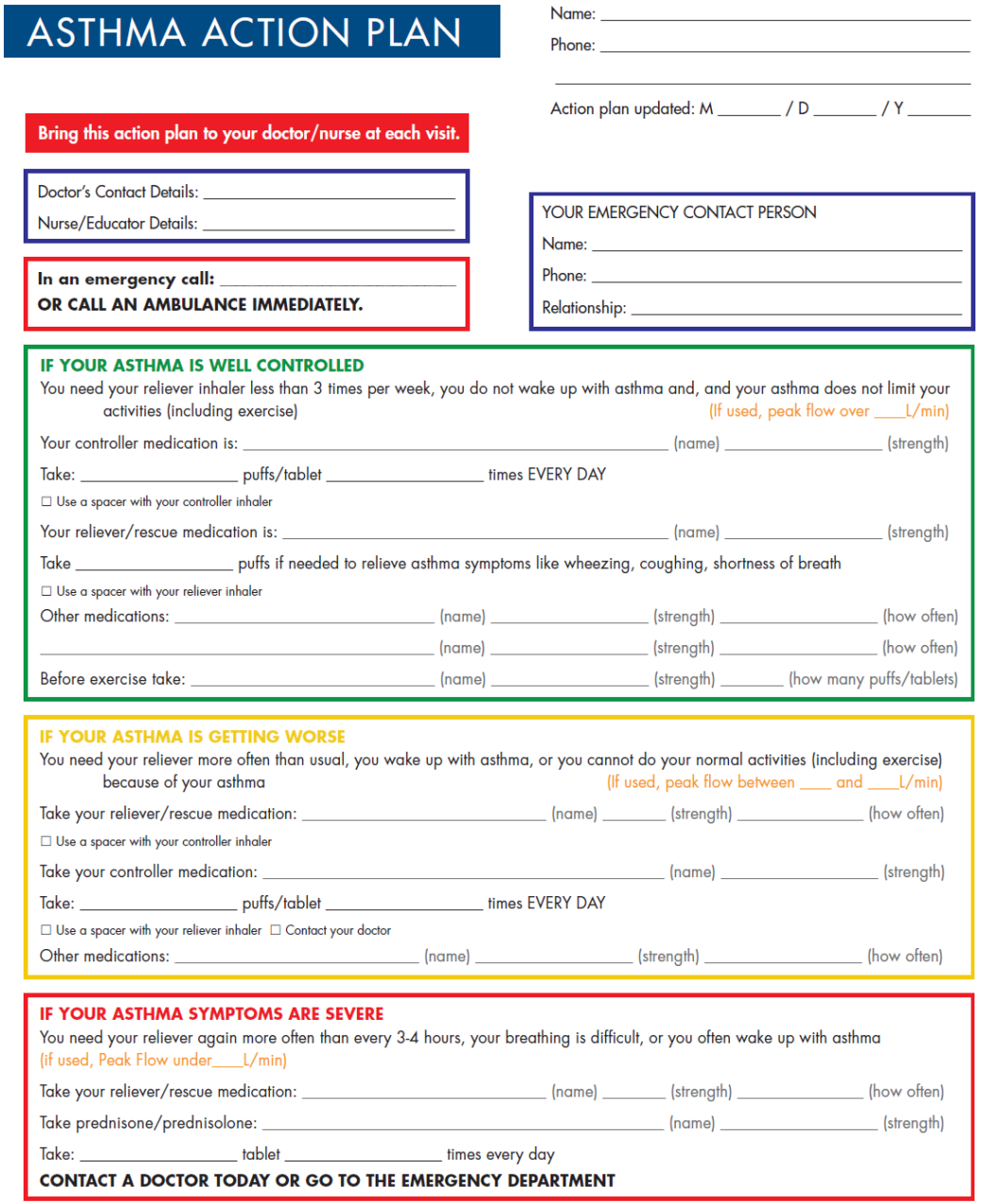
Modified from GINA 2019

Non-pharmacological interventions & management of co-factors

- Patient education
  - Self-monitoring skills, peak flow measurement, written asthma action plan
- Smoking cessation
- Assess and manage work-related asthma
- Encourage Physical activity
  - Exercise-induced bronchoconstriction
- Allergen avoidance
  - House dust mite eradication
  - Pets…
  - Sublingual immunotherapy (SLIT)
  - Availability of injectable epinephrine for anaphylaxis
- Potential intolerance to NSAIDs or beta-blockers

Assess asthma control & act accordingly

If you feel …
Then do ...



ASTHMA ACTION PLAN

Name: _____
Phone: _____
_____
Action plan updated: M _____ / D _____ / Y _____

Bring this action plan to your doctor/nurse at each visit.

Doctor's Contact Details: _____
Nurse/Educator Details: _____

In an emergency call: _____
OR CALL AN AMBULANCE IMMEDIATELY.

YOUR EMERGENCY CONTACT PERSON
Name: _____
Phone: _____
Relationship: _____

IF YOUR ASTHMA IS WELL CONTROLLED
You need your reliever inhaler less than 3 times per week, you do not wake up with asthma and, and your asthma does not limit your activities (including exercise) (If used, peak flow over ____L/min)

Your controller medication is: _____ (name) _____ (strength)
Take: _____ puffs/tablet _____ times EVERY DAY
☐ Use a spacer with your controller inhaler
Your reliever/rescue medication is: _____ (name) _____ (strength)
Take _____ puffs if needed to relieve asthma symptoms like wheezing, coughing, shortness of breath
☐ Use a spacer with your reliever inhaler
Other medications: _____ (name) _____ (strength) _____ (how often)
_____ (name) _____ (strength) _____ (how often)
Before exercise take: _____ (name) _____ (strength) _____ (how many puffs/tablets)

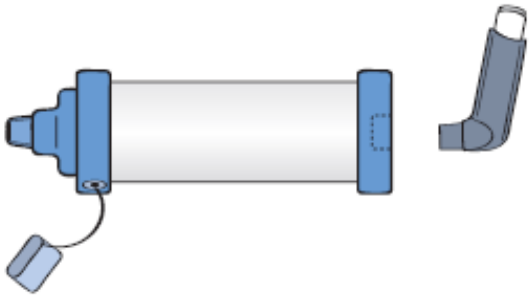
IF YOUR ASTHMA IS GETTING WORSE
You need your reliever more often than usual, you wake up with asthma, or you cannot do your normal activities (including exercise) because of your asthma (If used, peak flow between ____ and ____L/min)

Take your reliever/rescue medication: _____ (name) _____ (strength) _____ (how often)
☐ Use a spacer with your controller inhaler
Take your controller medication: _____ (name) _____ (strength)
Take: _____ puffs/tablet _____ times EVERY DAY
☐ Use a spacer with your reliever inhaler ☐ Contact your doctor
Other medications: _____ (name) _____ (strength) _____ (how often)

IF YOUR ASTHMA SYMPTOMS ARE SEVERE
You need your reliever again more often than every 3-4 hours, your breathing is difficult, or you often wake up with asthma
(if used, Peak Flow under____L/min)

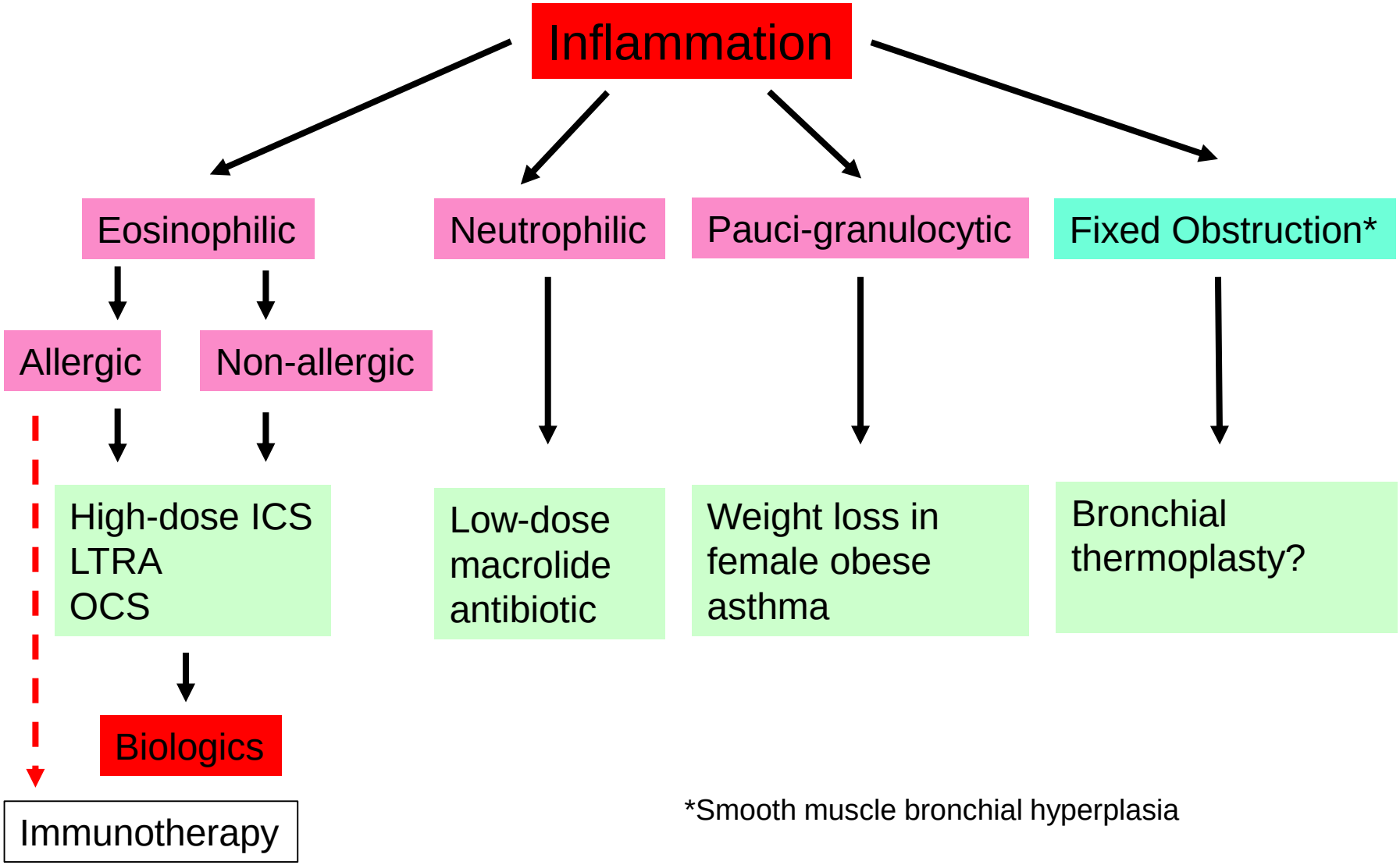
Take your reliever/rescue medication: _____ (name) _____ (strength) _____ (how often)
Take prednisone/prednisolone: _____ (name) _____ (strength)
Take: _____ tablet _____ times every day
CONTACT A DOCTOR TODAY OR GO TO THE EMERGENCY DEPARTMENT

Asthma inhalation therapy



https://www.nationaljewish.org

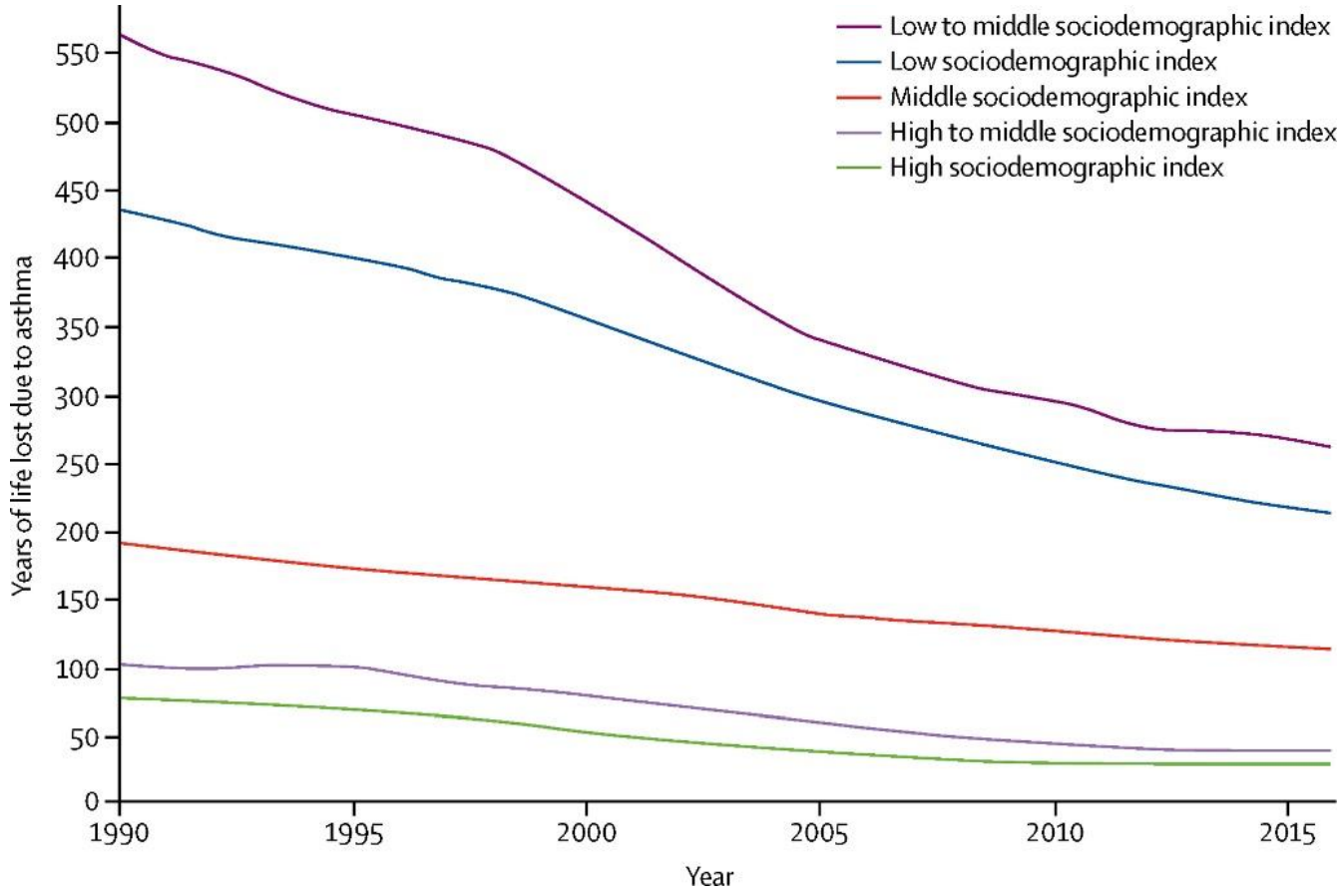
Phenotype-directed Therapy in severe Asthma



*Smooth muscle bronchial hyperplasia

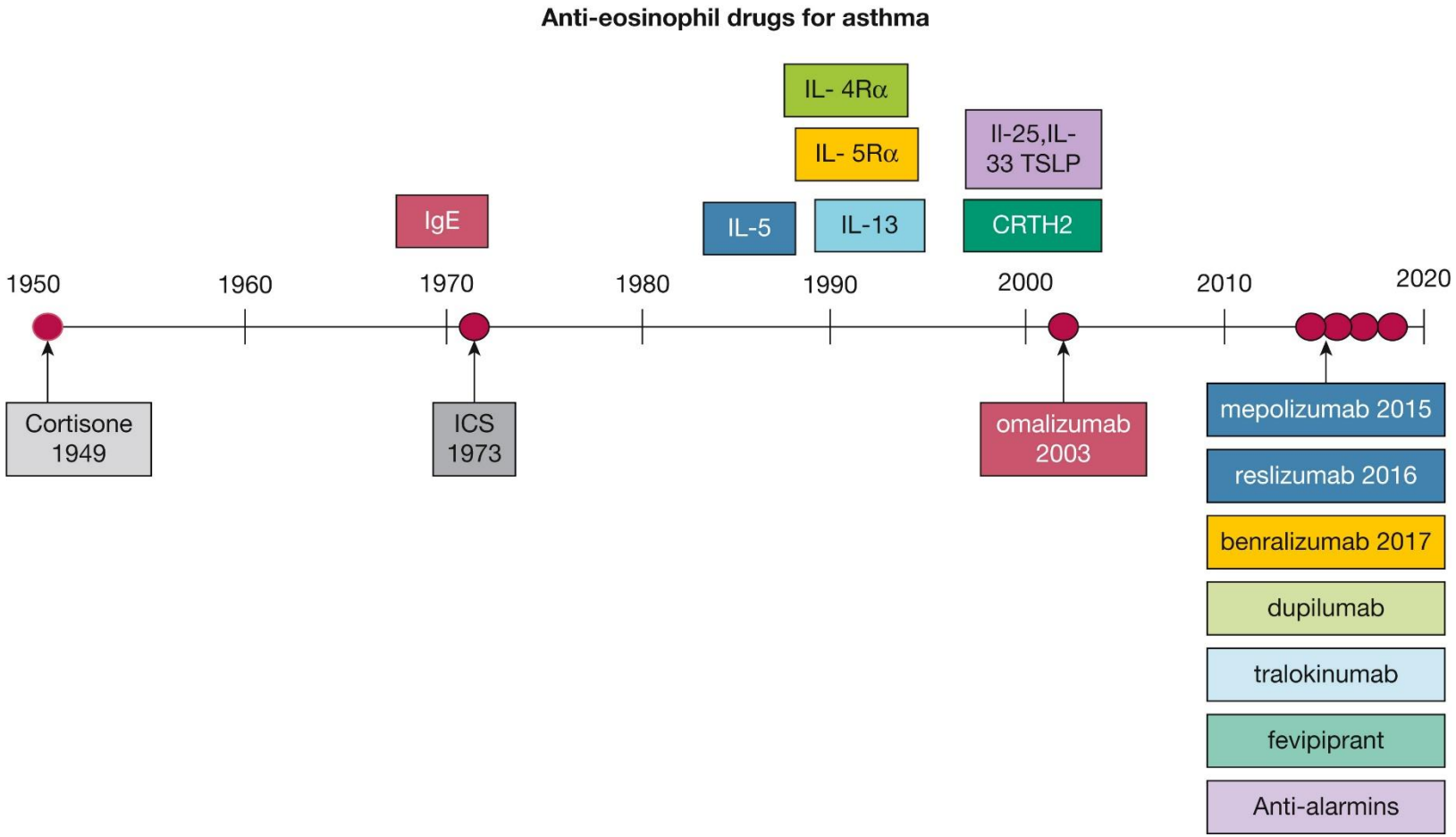
Adapted from Rothe T et al. Schweiz Med Forum 2015

Asthma therapy is effective



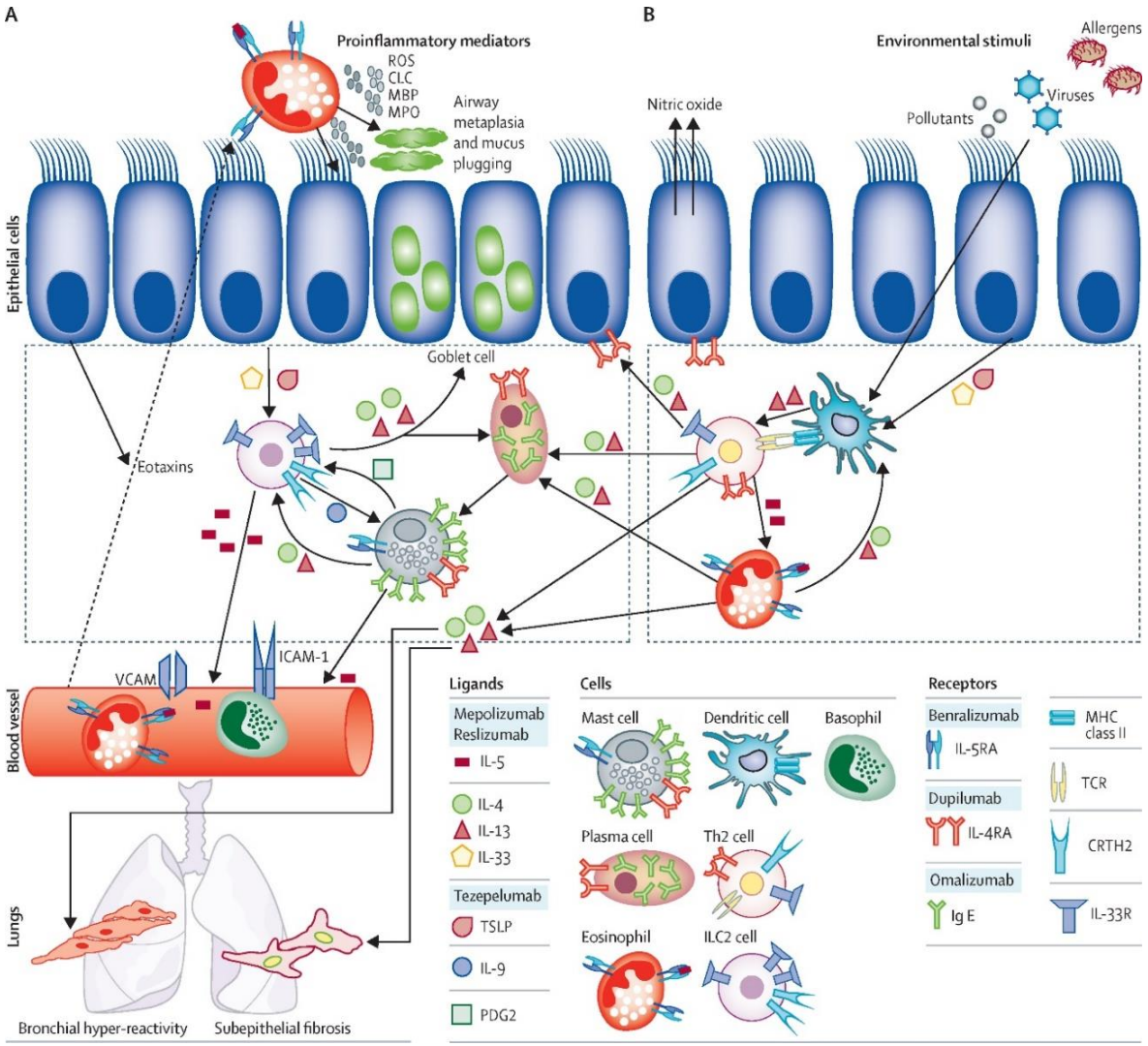
Papi et al. Lancet 2018

Asthma therapy has come a long way



Bel et al., CHEST 2017

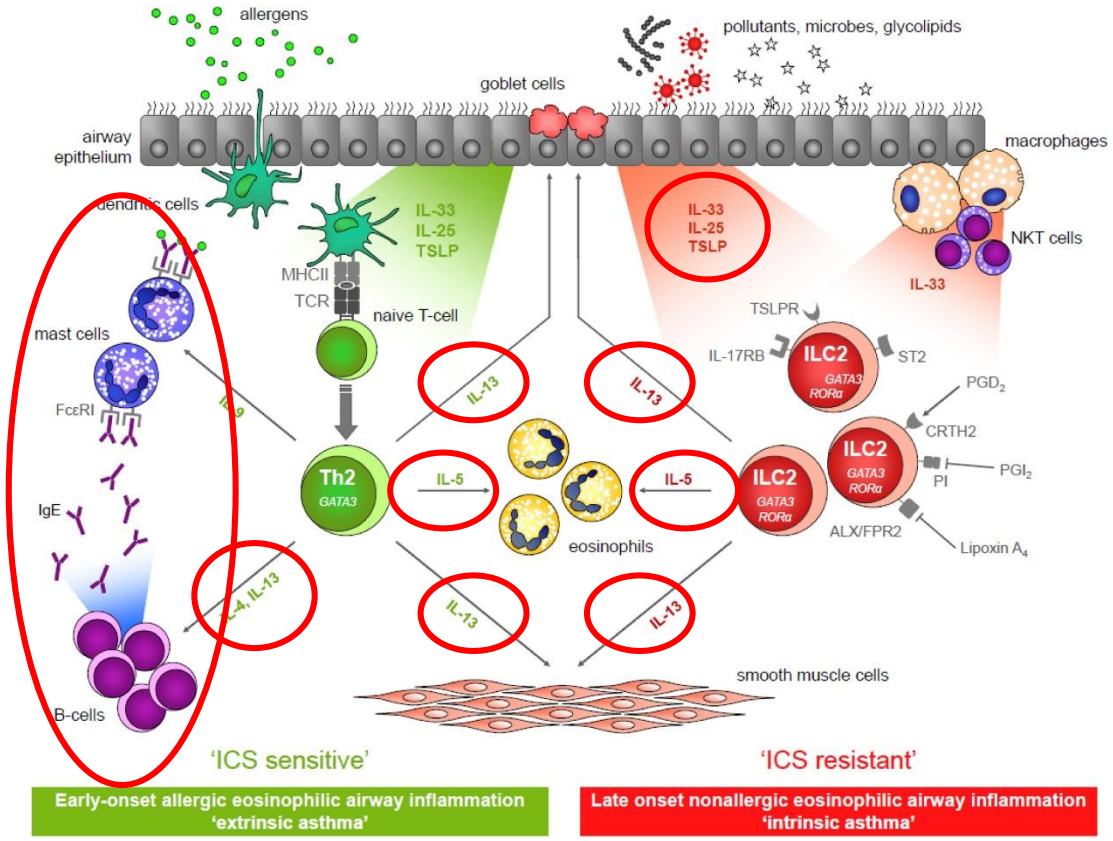
Intersection of biology and therapeutics:
Type 2 targeted therapeutics



Peters & Wenzel, The Lancet 2020

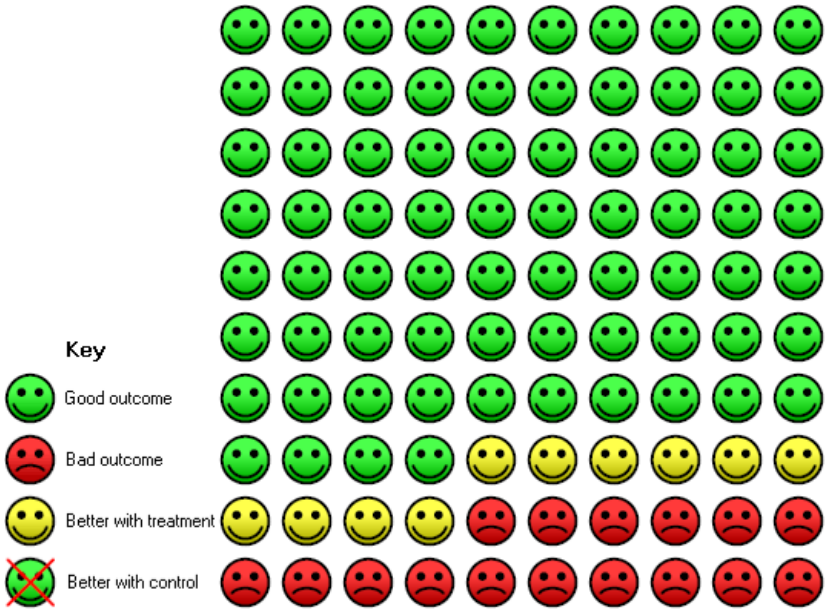
Biologics in Eosinophilic Asthma

Anti IgE	Omalizumab
Anti IL-5	Mepolizumab
	Reslizumab
Anti IL-5R	Benralizumab
Anti IL-13	Lebrikizumab
Anti IL-4R	Dupilumab
Anti TSLP Anti Alarmine	Tezelepumab

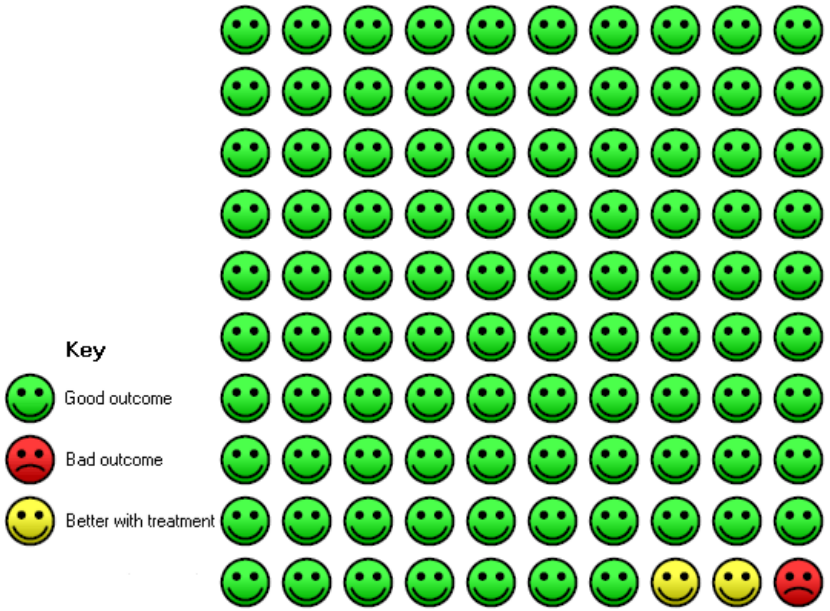


Omalizumab: anti IgE monoclonal antibody

Reduction in Exacerbations



Reduction in Hospitalisations

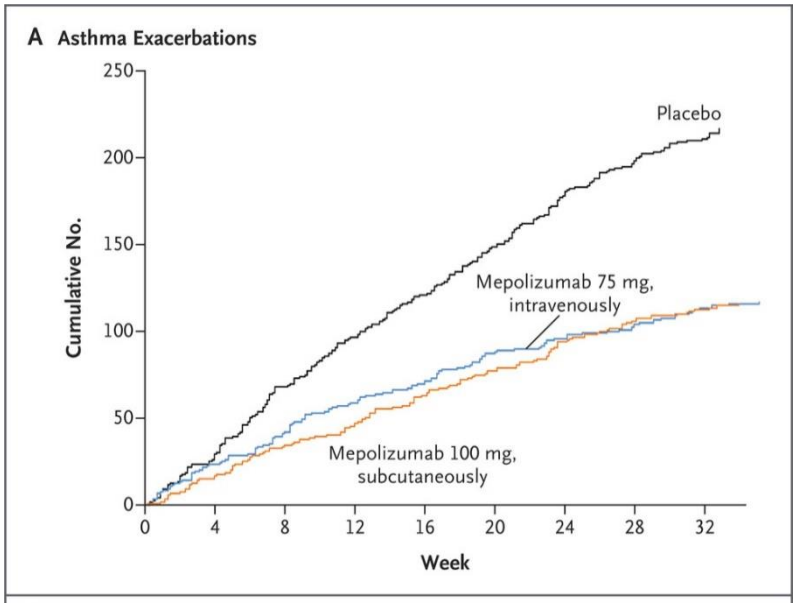


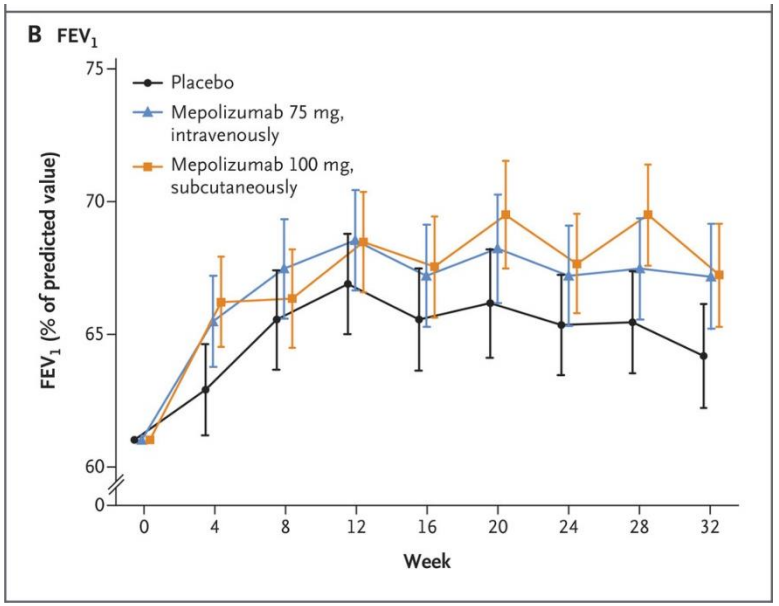
Meta-analysis including 10 studies and >3200 participants
Follow-up 4-15 months.

Normansell et al. Cochrane Database of Systematic Reviews 2014

Mepolizumab:
Humanized IgG1 monoclonal anti IL-5 antibody

- Reduction of annual exacerbation rate by >30%
- Improvement of lung function (FEV1) by 100ml
- Improved quality of life

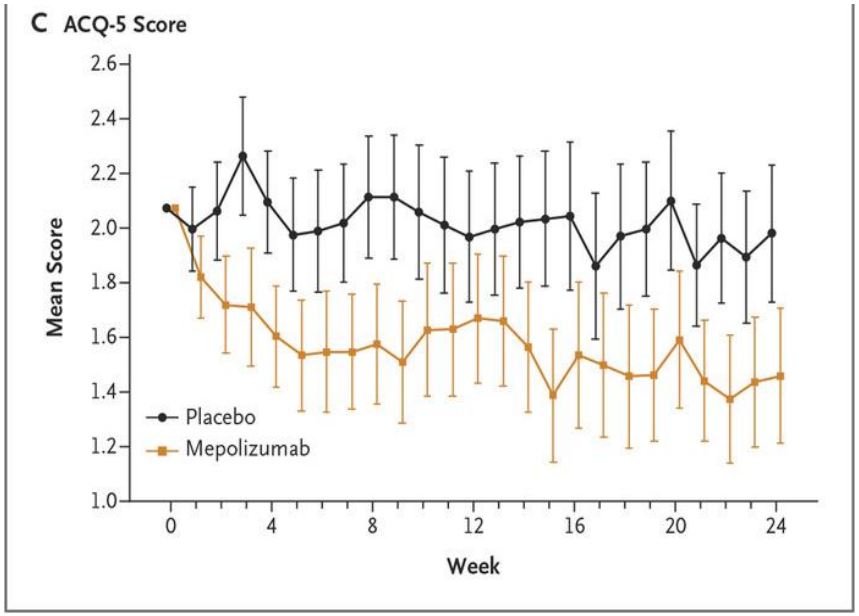


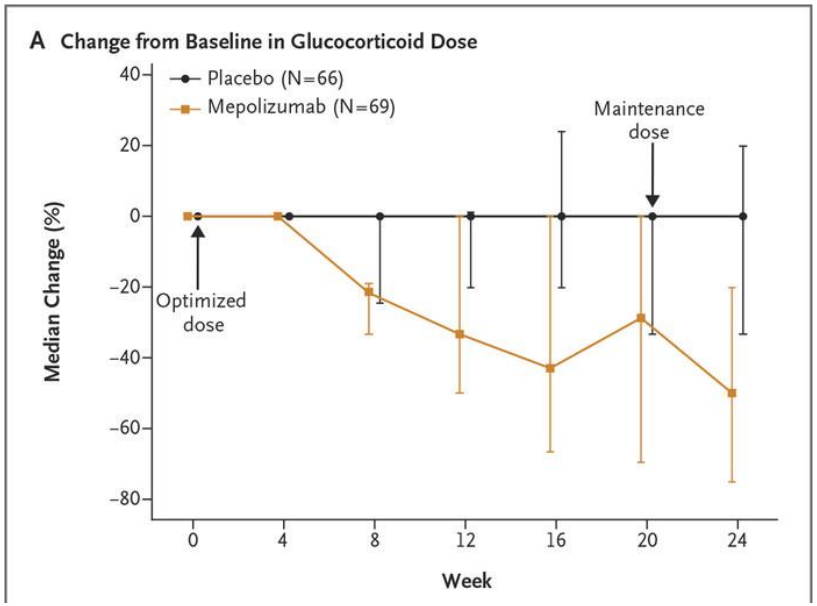


Ortega et al. N Engl J Med 2014

Mepolizumab:
Humanized IgG1 monoclonal anti IL-5 antibody

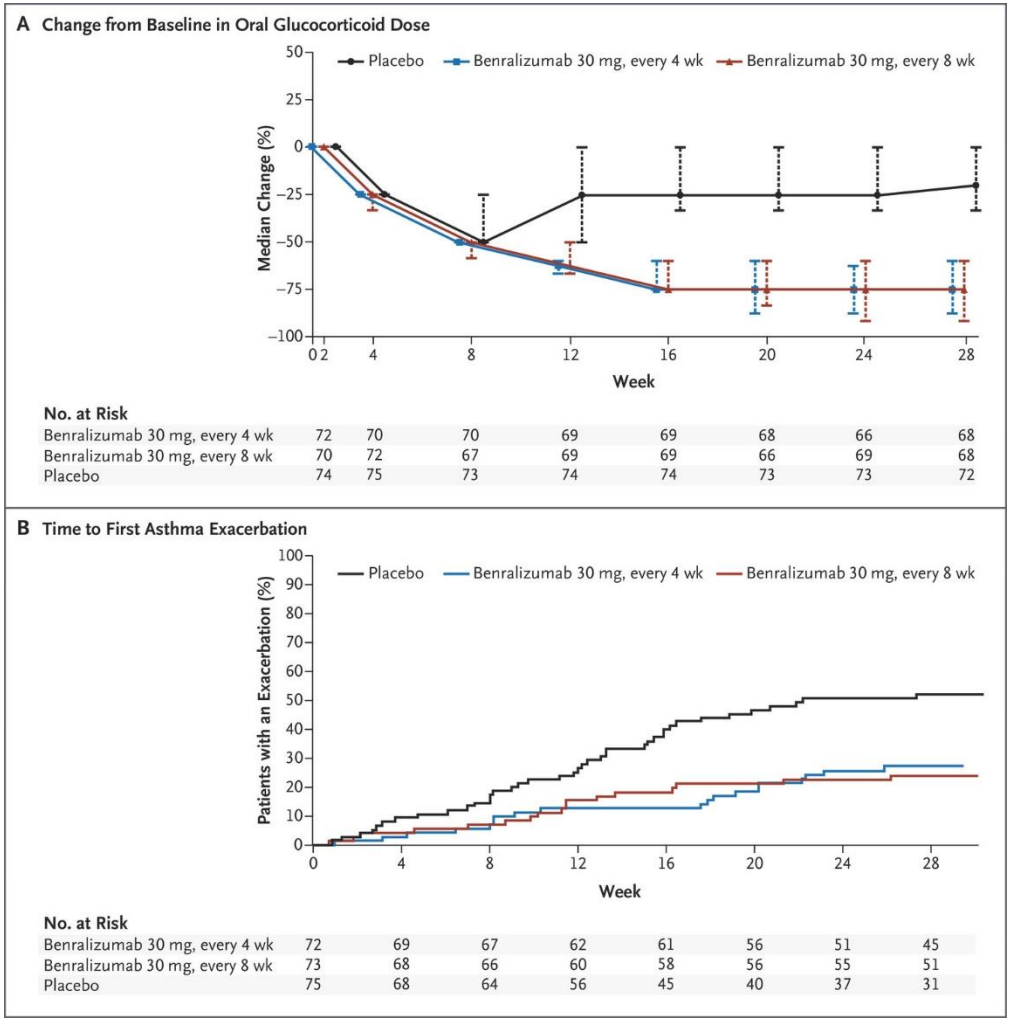
- Reduction of annual exacerbation rate by >30%
- Improvement of lung function (FEV1) by 100ml
- Improved quality of life
- Improved asthma control
- Reduction in need for oral glucocorticoids (-50%)





Bel et al. N Engl J Med 2014

Benralizumab:
Humanized monoclonal antibody against IL-5R

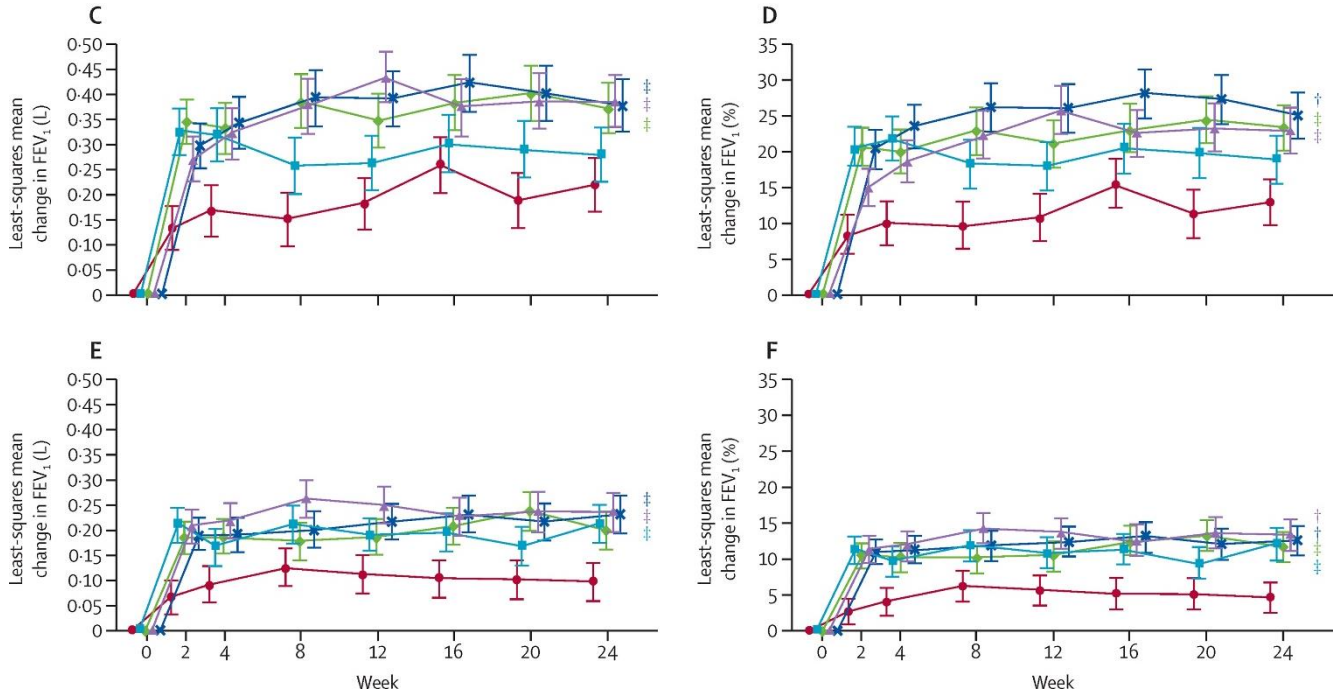


Reduction in
Oral Glucocorticoid Dose
Placebo: -25%
Benralizumab: -75%

Longer time to the first exacerbation with benralizumab:
HR 0.39 (95%CI 0.22-0.66)
HR 0.32 (95%CI 0.17-0.57)

Nair et al., NEJM 2017

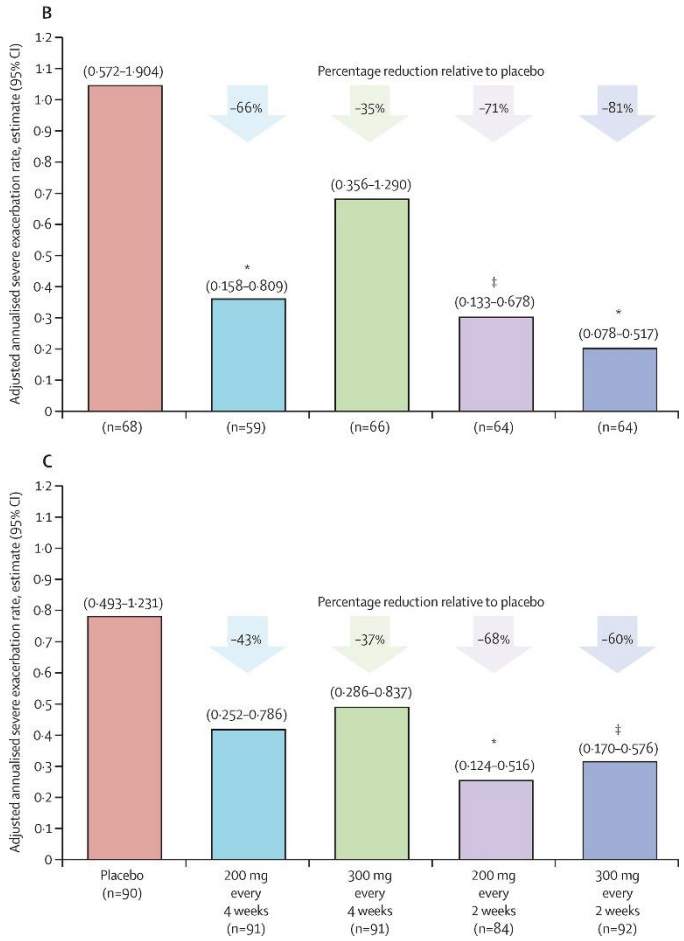
Dupilumab:
Humanized monoclonal antibody against IL-4R
Inhibits IL-4 and IL-13 signalling



C/D: Eosinophilic (≥300 cells/mcl); E/F: Non-eosinophilic (<300 cells/mcl)
Primary endpoint: Improvement in FEV1 after 12 weeks for both groups met
Larger effect size in eosinophilic group.

Wenzel et al., Lancet 2017

Dupilumab:
Humanized monoclonal antibody against IL-4R
Inhibits IL-4 and IL-13 signalling

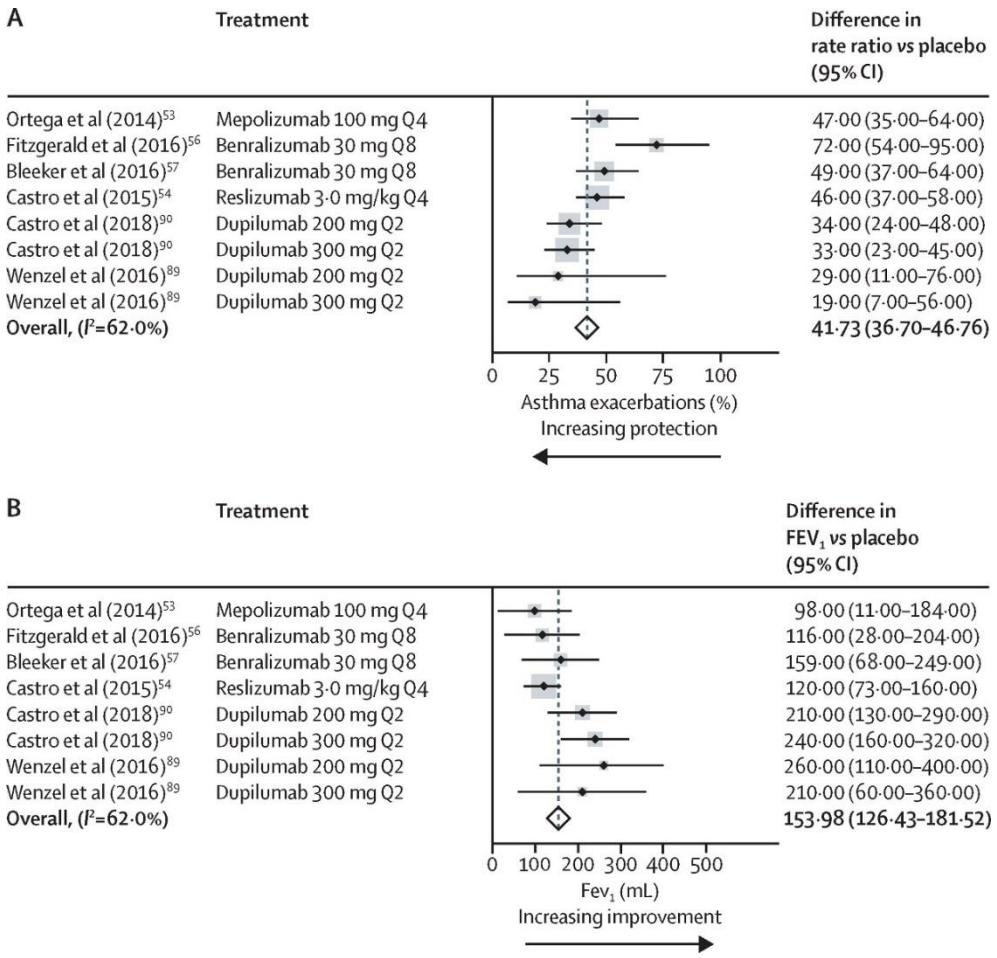


Severe exacerbations event rates/year
B: Eosinophilic (≥300 cells/mcl)
C: Non-eosinophilic (<300 cells/mcl)

- Significant reduction in frequency of severe exacerbations.
- Better effect in patients with high eosinophil blood count

Wenzel et al., Lancet 2017

Treatment effect of type 2 biologic agents in patients with eosinophilic asthma



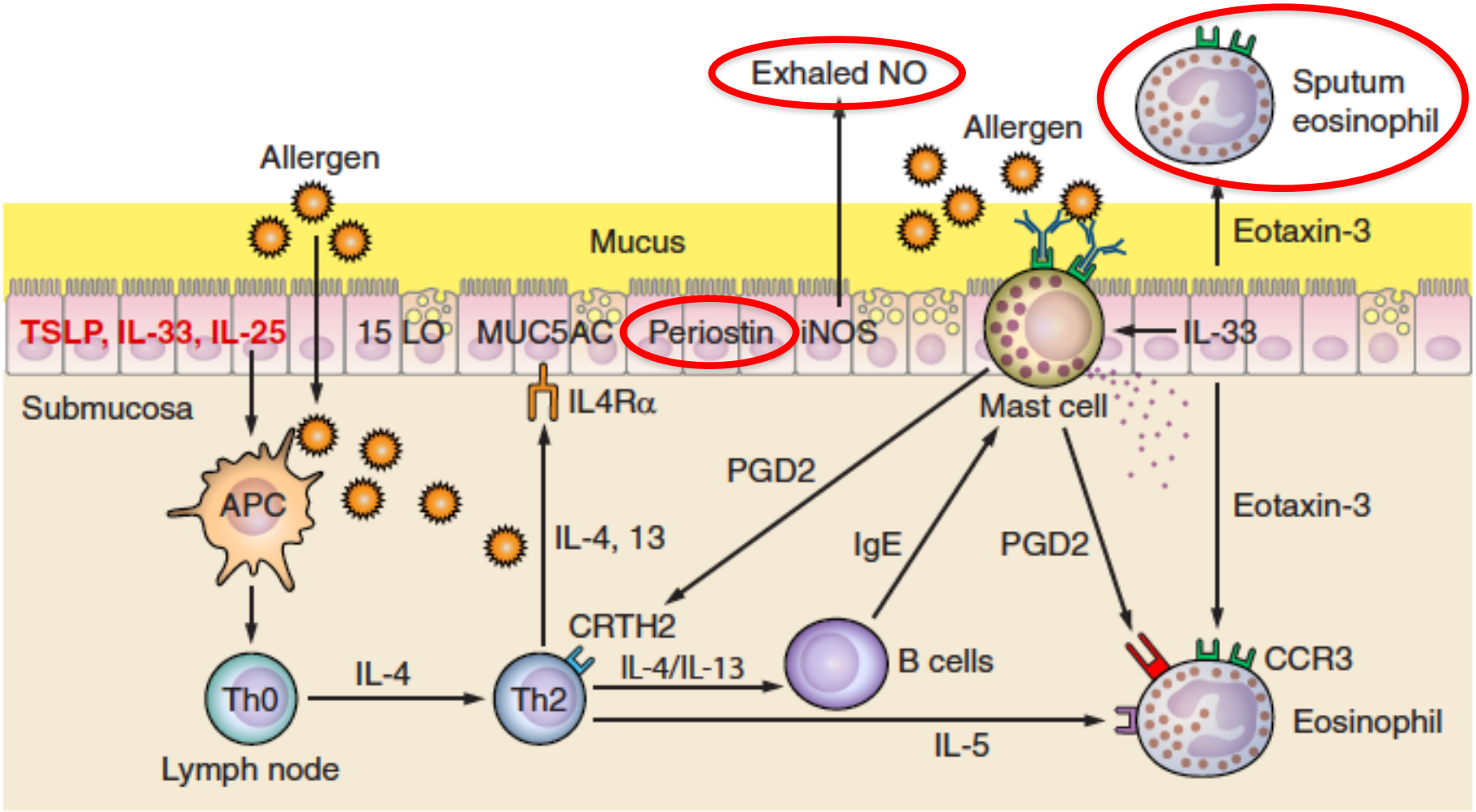
Peters & Wenzel, The Lancet 2020

Asthma biologics: Indications and limitations

	Exacerbations (prev. year)	Blood eosinophils	Price
Mepolizumab (Nucala®)	≥ 2 & GINA Step 5 ≥ 2 & OCS ≥ 6 months/year ≥ 4 & GINA Step 4	≥ 0.4G/L	1409 CHF/month
Reslizumab (Cinqaero®)			Ca. 1300 CHF/month
Benralizumab (Fasenra®)			1429 CHF/month
Omalizumab (Xolair®)	Severe, allergic Asthma. Management by pulmonologist or allergologist.		1000-2000 CHF/month
Dupilumab (Dupixent®)	Severe atopic dermatitis (not approved for asthma yet)		3033 CHF/month

www.swissmedic.ch
http://www.spezialitätenliste.ch/

Biomarkers for asthma diagnosis & treatment response



Ray A et al. Am J Physiol Lung Cell Mol Physiol. 2015

Emerging therapies for non-eosinophilic (Th2 low) asthma

Tezepelumab:

- Human monoclonal antibody for thymic stromal lymphopoietin (TSLP)
- Phase 2 study (Corren et al. NEJM 2017)
- Lower rates asthma exacerbations (-62 to -71%) and higher FEV1 independent of baseline blood eosinophil counts

IL-33 Inhibitors:

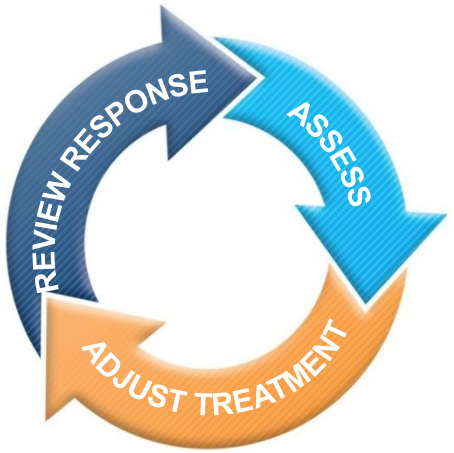
- Involved in ILC2 activation: Little clinical effect in Phase 2

Other potential pathways:

- Targeting systemic (IL-6 high) inflammation in obesity and age-associated asthma
- Treatment to restore inflammation resolution
- Treatment of microbial dysbiosis

Take away

- Asthma is a common and potentially severe chronic disease with variable degree of airway inflammation and obstruction.
- Pathophysiology is based on complex gene–environment & host-environment interactions.
- Respiratory symptoms include shortness of breath, cough, wheezing and chest tightness.
- Presentation is heterogeneous as there are several different phenotypes and underlying endotypes of asthma.
- Therapy includes non-pharmacological, generic pharmacological, and phenotype directed medication in severe asthma.
- Asthma can be controlled – not cured.




It ain't
easy
being
wheezy