Biologics in Asthma

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Conflicts of Interest / Disclosures

- Pharma
- Personal
- NAEP / SATS / PATS

Overview

- Definitions
- Epidemiology
- GINA
- Difficult-to-treat / Severe asthma
- Phenotyping asthma
- Biologics
  - Pathophysiology
  - Options

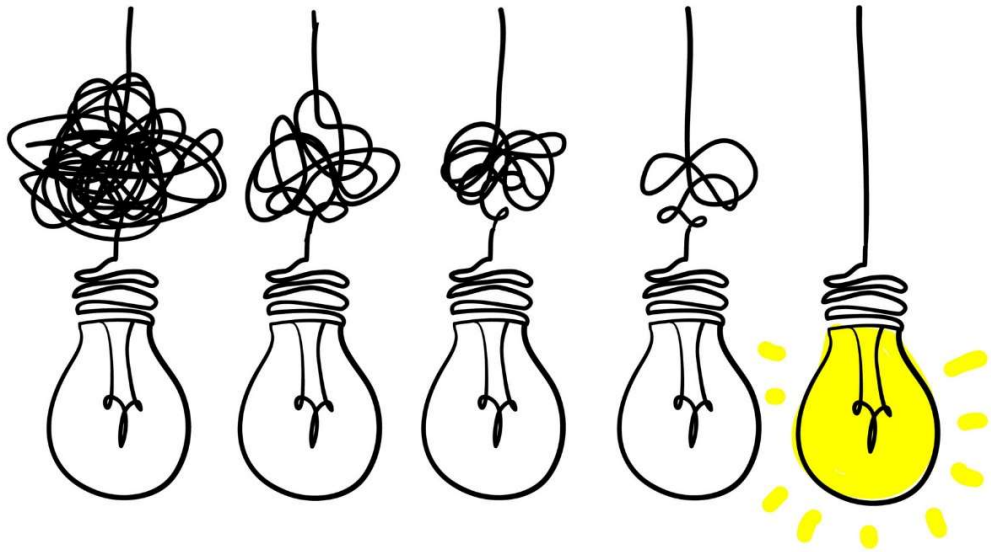
Asthma: Definitions

- GINA: chronic inflammatory disorder of the airways associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, that vary over time

- NHLBI NAEPP: Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation

Asthma: Easy definition

- **Recurrent episodes of reversible airway obstruction**
  - Components: bronchospasm, inflammation and mucous plugging
    - Asthma is a heterogeneous disease



Epidemiology

Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys

M Innes Asher, Stephen Montefort, Bengt Björkstén, Christopher K W Lai, David P Strachan, Stephan K Weiland, Hywel Williams, and the ISAAC Phase Three Study Group*

Summary

Background Data for trends in prevalence of asthma, allergic rhinoconjunctivitis, and eczema over time are scarce. We repeated the International Study of Asthma and Allergies in Childhood (ISAAC) at least 5 years after Phase One, to examine changes in the prevalence of symptoms of these disorders.

Methods For the ISAAC Phase Three study, between 2002 and 2003, we did a cross-sectional questionnaire survey of 193 404 children aged 6–7 years from 66 centres in 37 countries, and 304 679 children aged 13–14 years from 106 centres in 56 countries, chosen from a random sample of schools in a defined geographical area.

Findings Phase Three was completed a mean of 7 years after Phase One. Most centres showed a change in prevalence of 1 or more SE for at least one disorder, with increases being twice as common as decreases, and increases being more common in the 6–7 year age-group than in the 13–14 year age-group, and at most levels of mean prevalence. An exception was asthma symptoms in the older age-group, in which decreases were more common at high prevalence. For both age-groups, more centres showed increases in all three disorders more often than showing decreases, but most centres had mixed changes.

Interpretation The rise in prevalence of symptoms in many centres is concerning, but the absence of increases in prevalence of asthma symptoms for centres with existing high prevalence in the older age-group is reassuring. The divergent trends in prevalence of symptoms of allergic diseases form the basis for further research into the causes of such disorders.

Lancet 2006; 368: 733–43

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Introduction

The International Study of Asthma and Allergies in Childhood (ISAAC) epidemiological research programme was established in 1991 because of concern that asthma and allergies were increasing in prevalence and severity, but little was known about the scale of the problem worldwide or the factors affecting prevalence.[1] Until the 1990s, most studies of the prevalence of asthma and allergies had been undertaken in the UK, Australia, and New Zealand. The ISAAC investigators believed that new information would be contributed by the participation of other countries, including developing countries, with comparisons between, rather than within populations, helped by standardised methods.

The enormous participation in ISAAC Phase One, in which 700 000 children from 156 centres in 56 countries were included, demonstrated the worldwide concern about asthma and allergies. The participatory ISAAC approach with simple questionnaires enabled the collection of comparable data from children throughout the world.[2] The large variations in the worldwide prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema that were recorded, even in genetically similar groups,[3–5] suggested that environmental factors underlie the variations. Many aspects of environments have been examined in ecological analyses of data from ISAAC Phase One,[3–10] and have provided some support for hypotheses that economic development,[6] dietary factors,[7,8] climate,[9] infections,[10] and pollens,[11] might influence some of this variation.

In ISAAC Phase Two, causes are studied in more detail in 30 study centres in 22 countries, with detailed questionnaires and objective measurements of physiological variables and indoor exposure.[12] From the outset, ISAAC Phase Three was planned to assess time trends in the prevalence of symptoms by repeating the original cross-sectional study after at least 5 years. Our aim was to examine the hypothesis that the prevalence of asthma, allergic rhinoconjunctivitis, and eczema is increasing in some, but not all, regions of the world. The findings might give further clues about the causes of these conditions by revealing information about geographical variation in the rate of change in symptom prevalence for the three disorders.

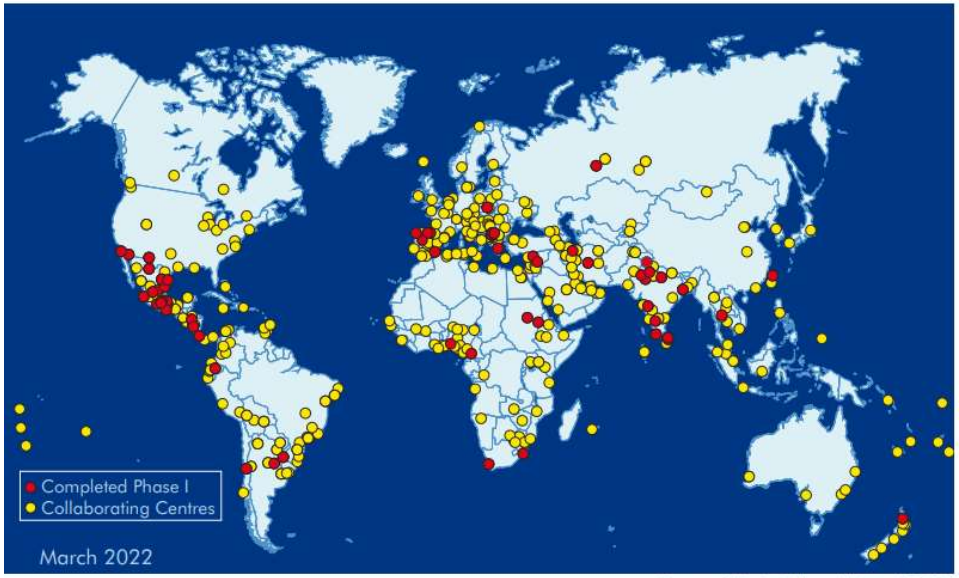
Methods

ISAAC Phase Three is a repetition of a multicountry cross-sectional survey of two age-groups of school children—6–7 years and 13–14 years—undertaken at least 5 years after the baseline survey, ISAAC Phase One. Phase One study participants were identified through random samples of schools in defined geographical areas, or by

Global Asthma Network

Epidemiology

Philippa Ellwood, Innes Asher, Karen Bissell, Chen-Yuan Chiang, Eamon Ellwood, Asma El Sony, Luis García-Marcos, Guy Marks, Refiloe Masekela, Eva Morales, Kevin Mortimer, Neil Pearce, David Strachan



Source: Global Asthma Network 2022.

Figure: Global Asthma Network Centres at March 2022

- GAN Phase 1:
  - 386 centres in 138 countries 2015-2020
  - 157 784 adolescents (13-14)
  - 101 777 children (6-7)
  - 193 192 adults

Epidemiology

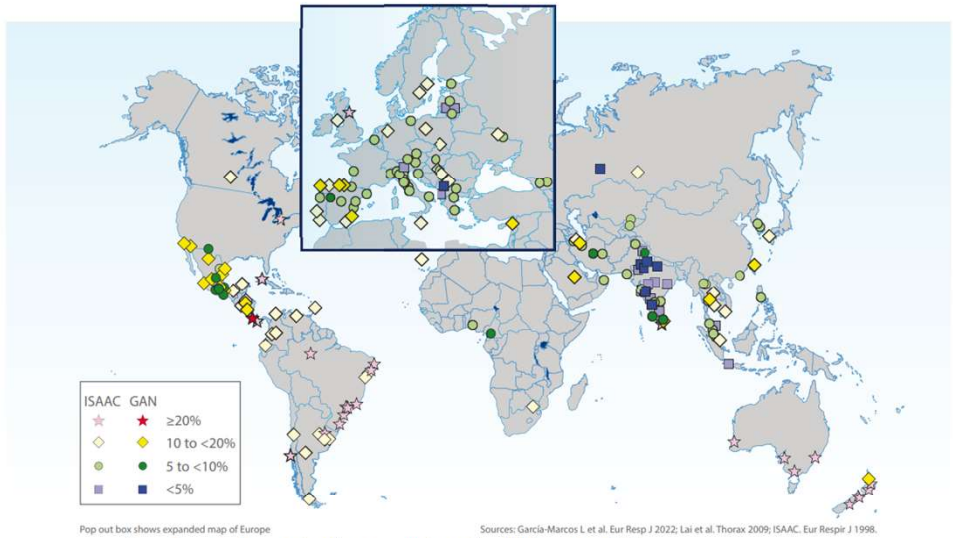


Figure 1: Prevalence of current asthma symptoms in children aged 6-7

Overall: 9.1%

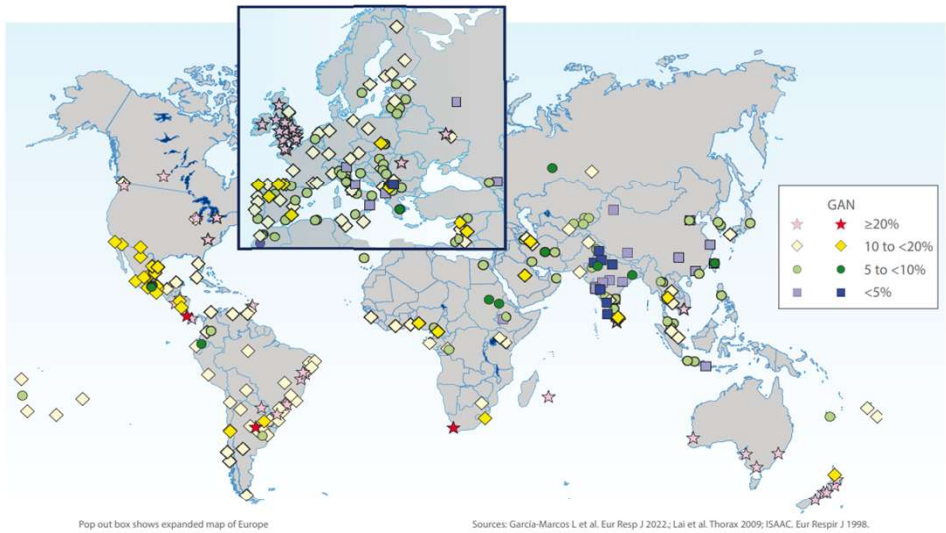


Figure 2: Prevalence of current asthma symptoms in adolescents aged 13-14

Overall: 11.0%

Epidemiology

Table: Prevalence of current symptoms of asthma (12-month prevalence rate of wheeze) by centre in South Africa 13 - 14 year age group as measured by the International Study of Asthma and Allergies in Childhood (ISAAC) Phases One, Three and the Global Asthma Network (GAN) Phase I

	13-14 Years
	N (% with asthma)
Cape Town (ISAAC One)	5178 (16%)
Cape Town (ISAAC Three)	5037 (20.3%)
Polokwane (ISAAC Three)	4660 (18%)
Cape Town (GAN Phase One)	3979 (21.7%)

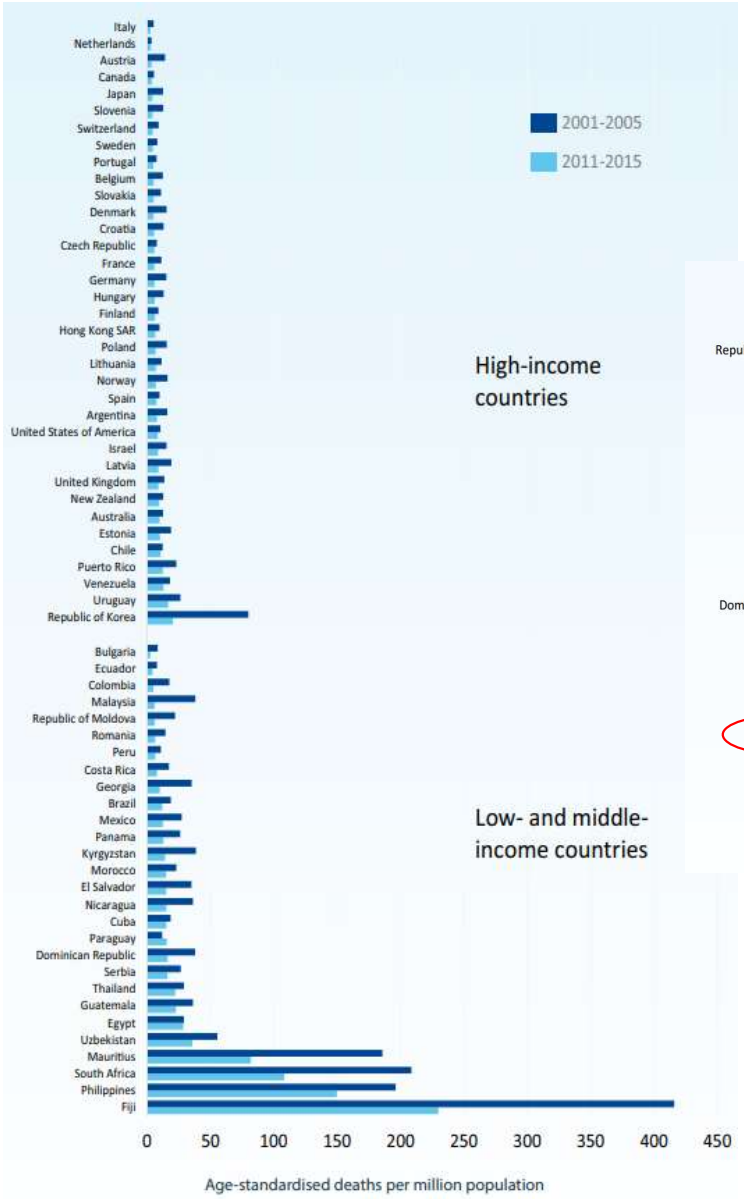
Sources: Asher MI, et al. Lancet 2021; Zar et al. Pedatric Allergy Immunol 2007.

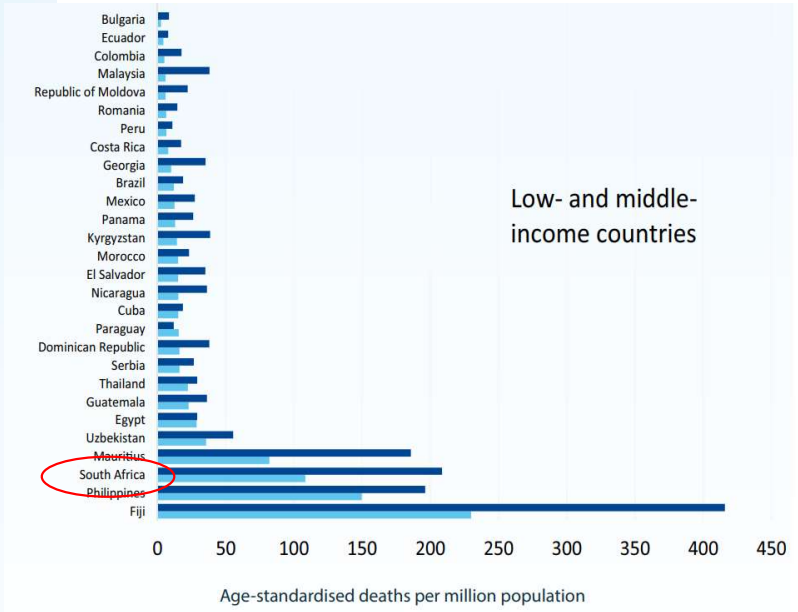
Epidemiology

Figure 1:

Age-standardised asthma mortality rates (all ages) 2001-2005 and 2011-2015 by country, ranked by 2011-2015 age-standardised mortality rate within World Bank 2014 income group

Source: WHO Mortality Database, October 2017 update. Population denominators from UN World Population Prospects, June 2017 revision. Income groups based on the World Bank 2014 definitions.





Goals of Asthma Treatment

- Simply: asthma control

- Lead a normal and physically active life:
  - Completely free from any symptoms
  - Attend school regularly and participate fully in all school activities, including sport
  - Sleep restfu[redacted]n and/or wheeze
  - Grow and d[redacted]
  - Minimise the number of attacks of acute asthma and avoid hospitalisation
  - Avoid or minimise medication-related side-effects

No deaths

Barriers to asthma management in RSA

- Poor socio-economic status
- High burden of other respiratory infections like TB
- Lack of awareness of the disease / symptoms
- Missed diagnosis / opportunities
- Lack of access to care and appropriate treatment
- Treatment factors – inhaler technique, adherence
- Environmental triggers and allergies
- Under-assessment of co-morbidities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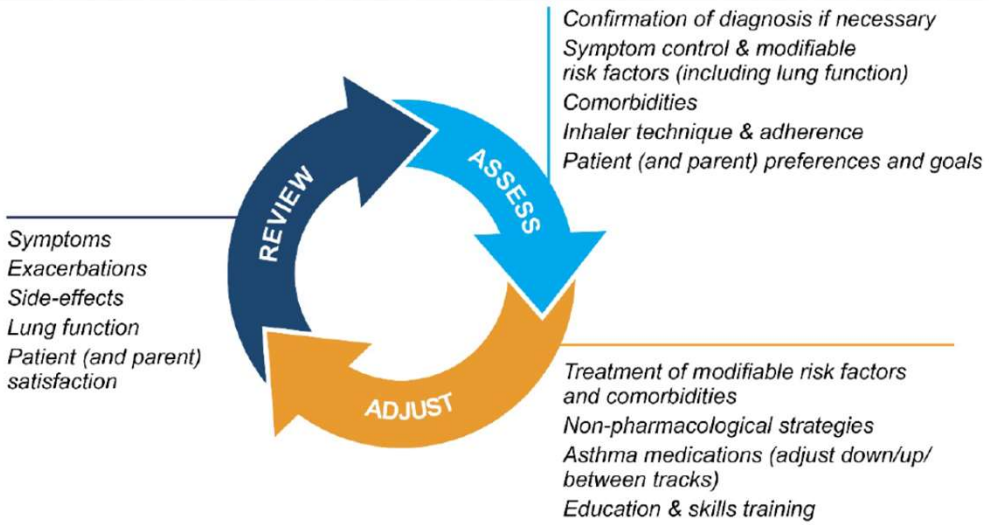
ASTHMA®

Management

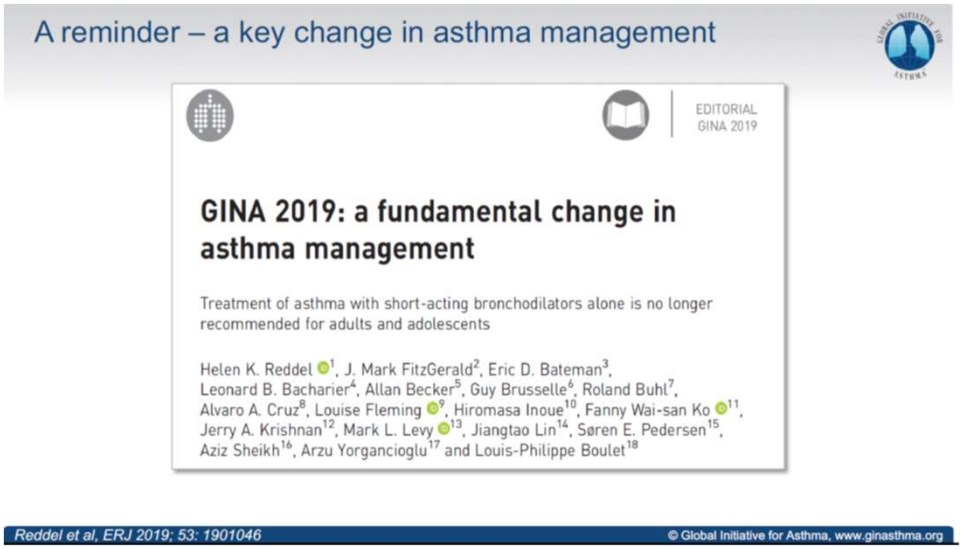
Personalized asthma management

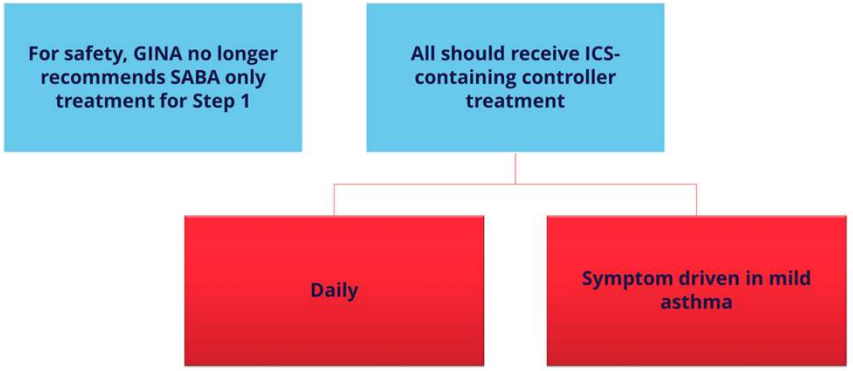


- NOT just about medications, NOT one-size-fits-all

GINA 2021 Box 3-2

Gina 2019 – landmark changes in asthma management in adults and adolescents





Global Initiative for Asthma (GINA)

What's new in GINA 2021?

GINA Global Strategy for Asthma Management and Prevention

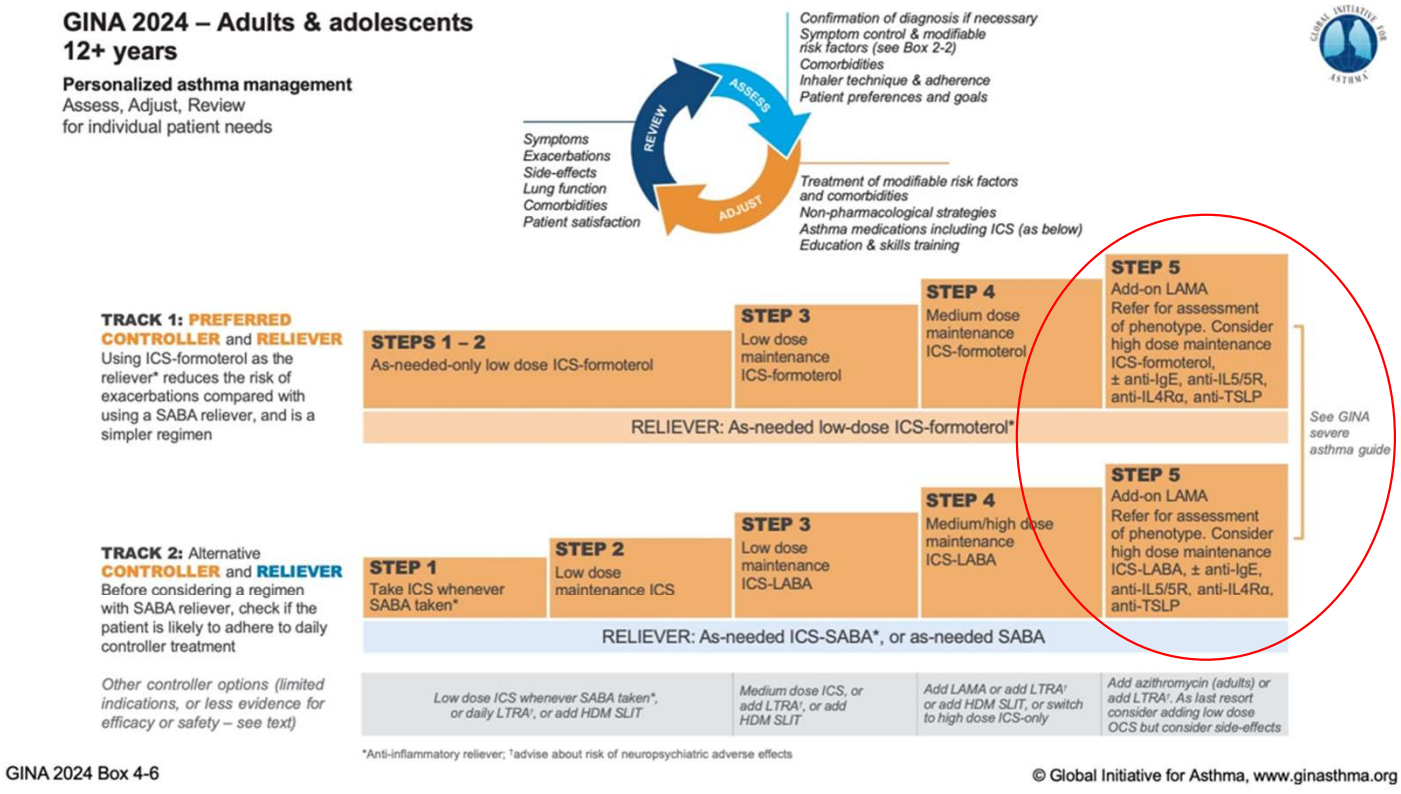
What's new in GINA 2024?

GINA 2024 update published 22 May 2024

Download from ginasthma.org

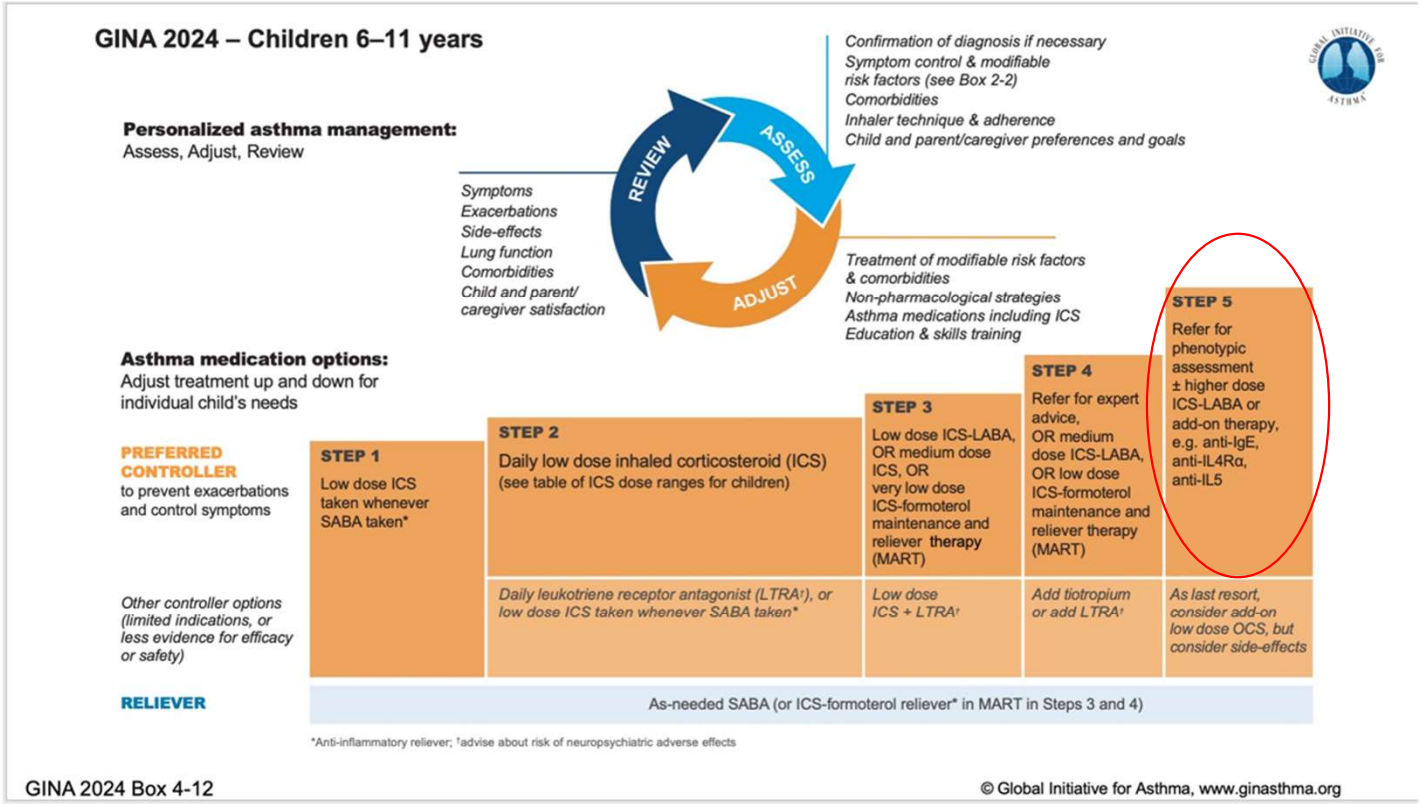
GINA Global Strategy for Asthma Management and Prevention

GINA 2024



GINA 2024 Box 4-6

GINA 2024


GINA 2024 – Children 6–11 years
Personalized asthma management:
Assess, Adjust, Review
Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Child and parent/caregiver preferences and goals
REVIEW
ASSESS
ADJUST
Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Child and parent/ caregiver satisfaction
Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications including ICS
Education & skills training
Asthma medication options:
Adjust treatment up and down for individual child's needs
PREFERRED CONTROLLER
to prevent exacerbations and control symptoms
STEP 1
Low dose ICS taken whenever SABA taken*
STEP 2
Daily low dose inhaled corticosteroid (ICS)
(see table of ICS dose ranges for children)
STEP 3
Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever therapy (MART)
STEP 4
Refer for expert advice, OR medium dose ICS-LABA, OR low dose ICS-formoterol maintenance and reliever therapy (MART)
STEP 5
Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4Rα, anti-IL5
Other controller options (limited indications, or less evidence for efficacy or safety)
Daily leukotriene receptor antagonist (LTRA†), or low dose ICS taken whenever SABA taken*
Low dose ICS + LTRA†
Add tiotropium or add LTRA†
As last resort, consider add-on low dose OCS, but consider side-effects
RELIEVER
As-needed SABA (or ICS-formoterol reliever* in MART in Steps 3 and 4)
*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects
GINA 2024 Box 4-12
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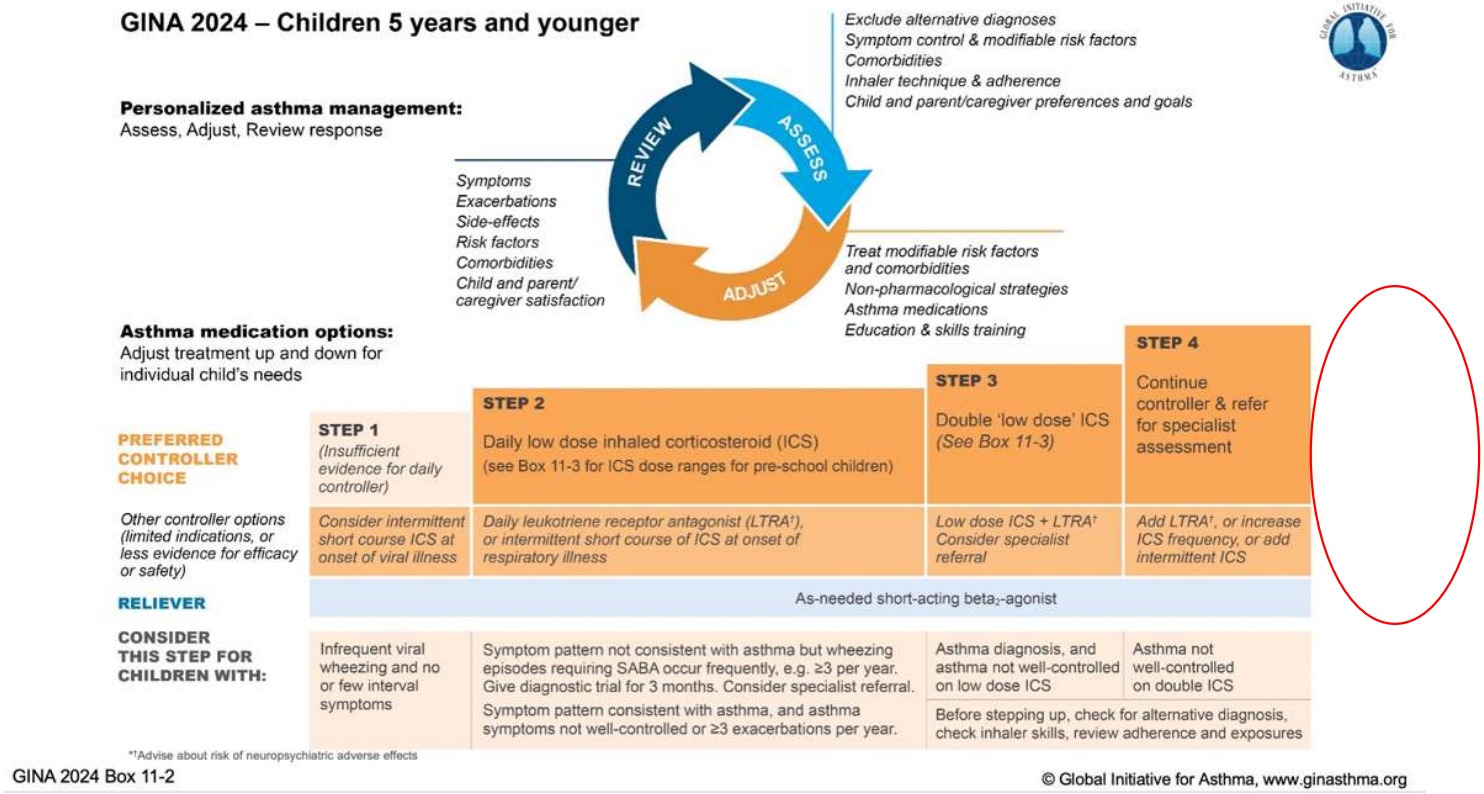
GINA 2024 – Children 5 years and younger
Personalized asthma management:
Assess, Adjust, Review response
Exclude alternative diagnoses
Symptom control & modifiable risk factors
Comorbidities
Inhaler technique & adherence
Child and parent/caregiver preferences and goals
REVIEW
ASSESS
ADJUST
Symptoms
Exacerbations
Side-effects
Risk factors
Comorbidities
Child and parent/ caregiver satisfaction
Treat modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications
Education & skills training
Asthma medication options:
Adjust treatment up and down for individual child's needs
STEP 1
(Insufficient evidence for daily controller)
STEP 2
Daily low dose inhaled corticosteroid (ICS)
(see Box 11-3 for ICS dose ranges for pre-school children)
STEP 3
Double 'low dose' ICS
(See Box 11-3)
STEP 4
Continue controller & refer for specialist assessment
PREFERRED CONTROLLER CHOICE
Other controller options (limited indications, or less evidence for efficacy or safety)
Consider intermittent short course ICS at onset of viral illness
Daily leukotriene receptor antagonist (LTRA†), or intermittent short course of ICS at onset of respiratory illness
Low dose ICS + LTRA†
Consider specialist referral
Add LTRA†, or increase ICS frequency, or add intermittent ICS
RELIEVER
As-needed short-acting beta2-agonist
CONSIDER THIS STEP FOR CHILDREN WITH:
Infrequent viral wheezing and no or few interval symptoms
Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral.
Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.
Asthma diagnosis, and asthma not well-controlled on low dose ICS
Asthma not well-controlled on double ICS
Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures
*†Advise about risk of neuropsychiatric adverse effects
GINA 2024 Box 11-2
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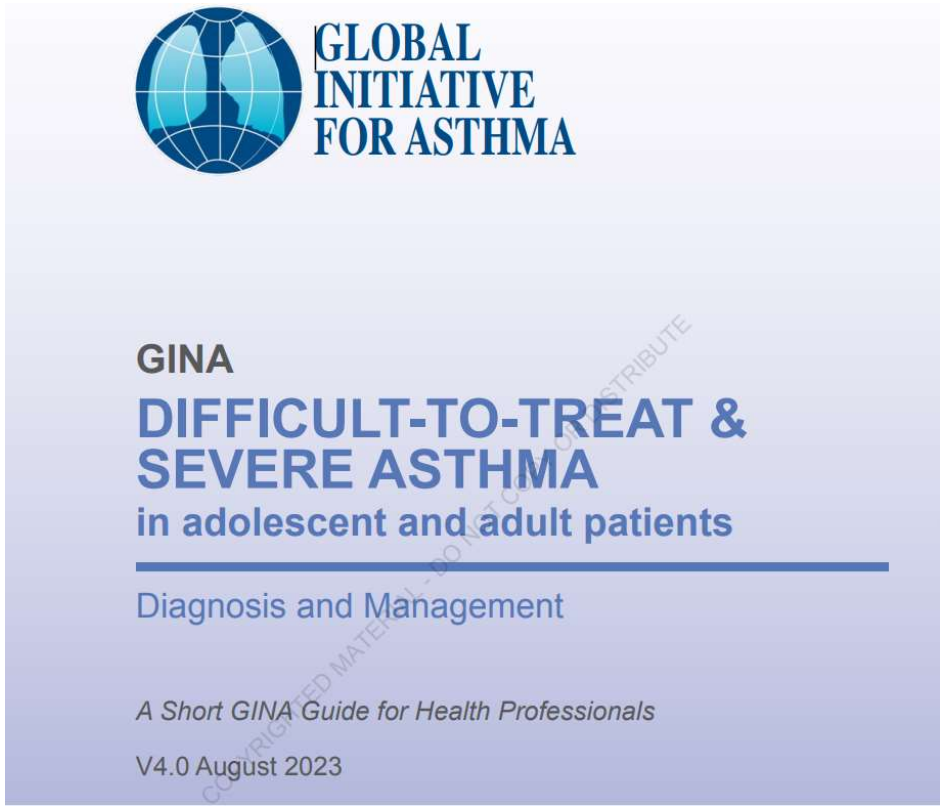
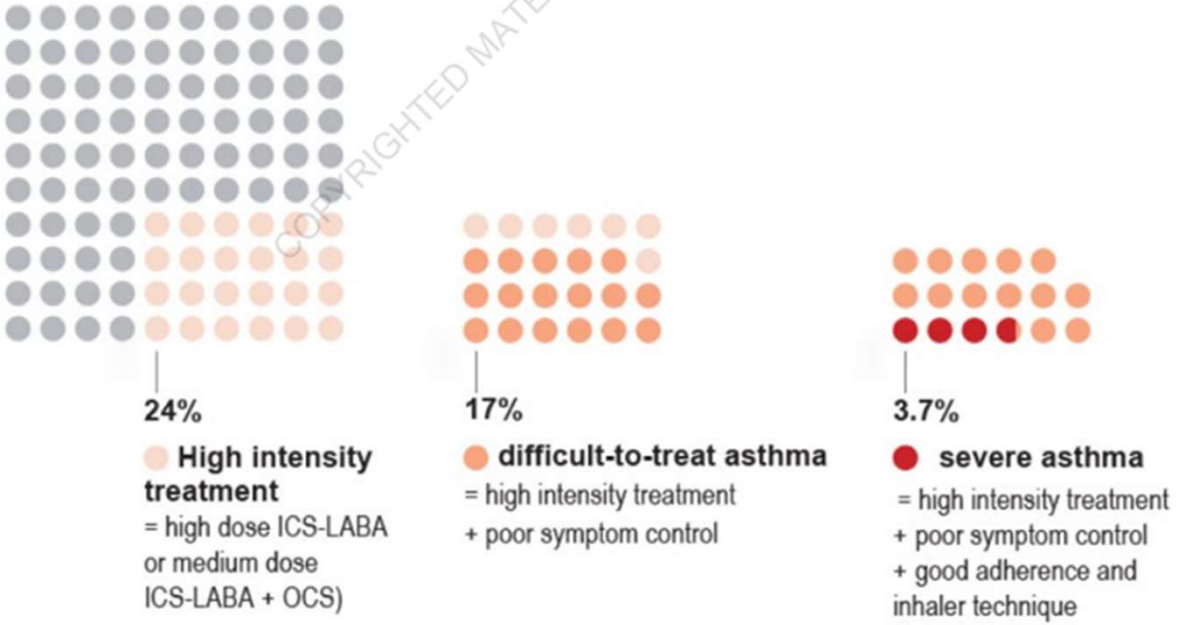


- Uncontrolled asthma
  - Poor symptom control
  - Frequent exacerbations (x2/year)
  - Serious exacerbations (x1/year)
- Difficult-to-treat-asthma
  - Uncontrolled
    - Med-high dose ICS + 2nd controller
    - Maintenance OCS
    - Possibility of modifiable factors
- Severe Asthma
  - Uncontrolled
    - Max high-dose ICS/LABA
    - Modifiable factors removed

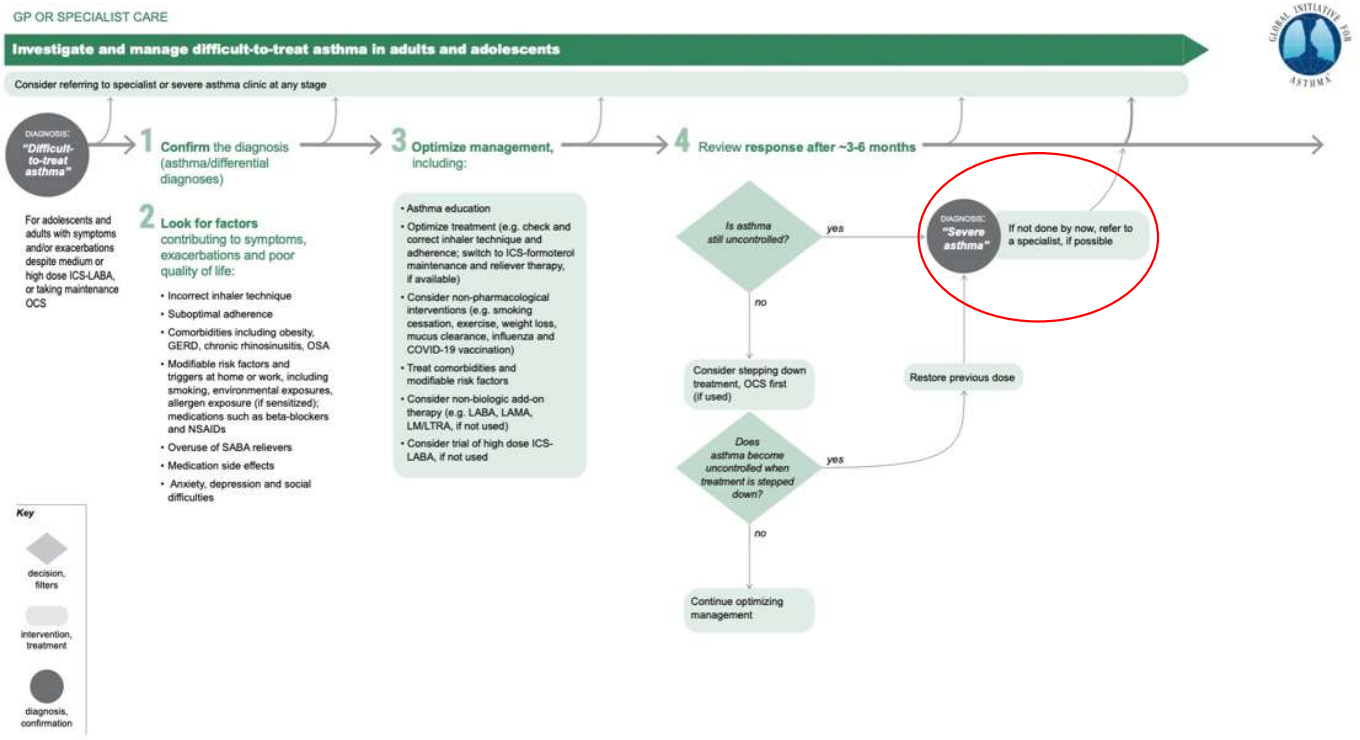
GINA 2024

Box 1. What proportion of adults have difficult-to-treat or severe asthma?

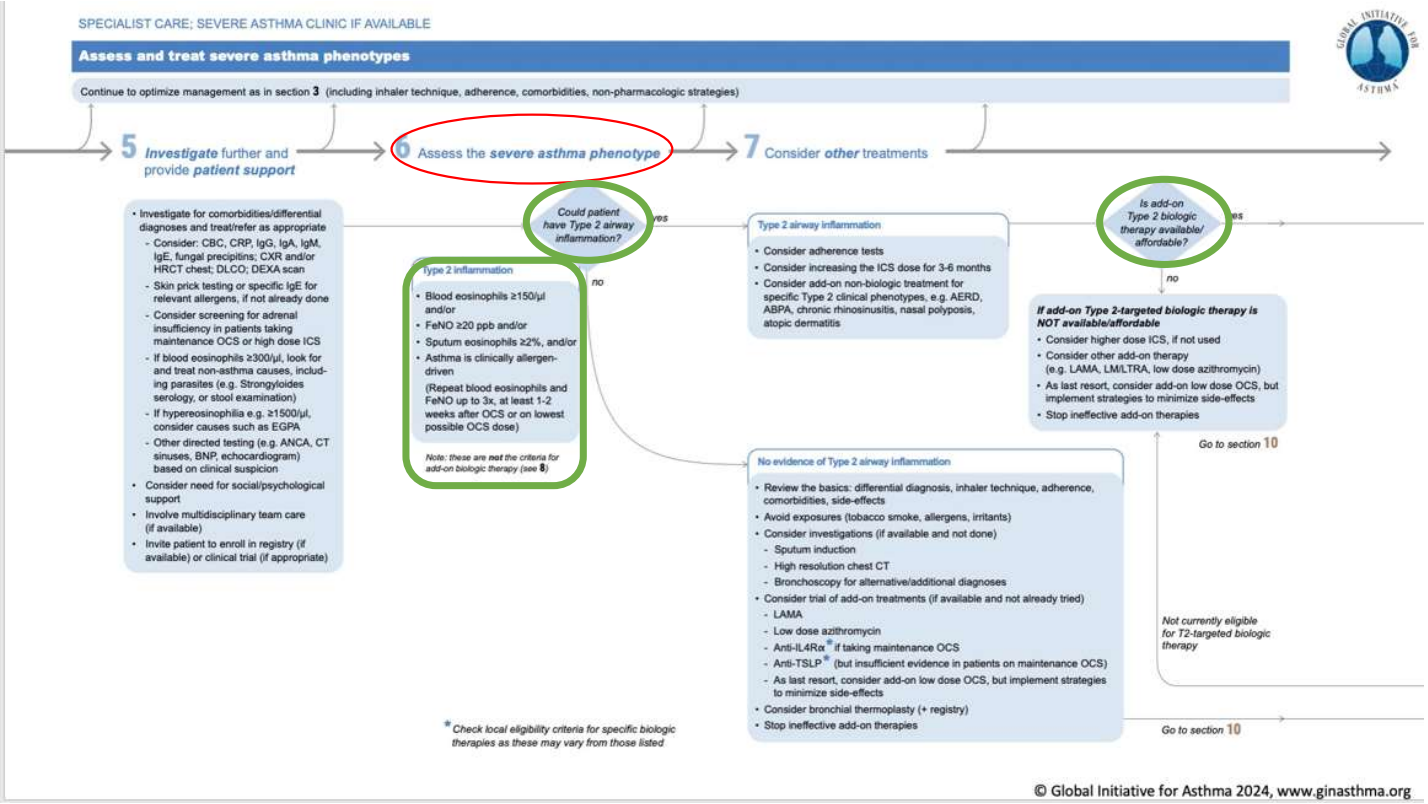


Data from the Netherlands, reported by Hekking et al (2015)[2]

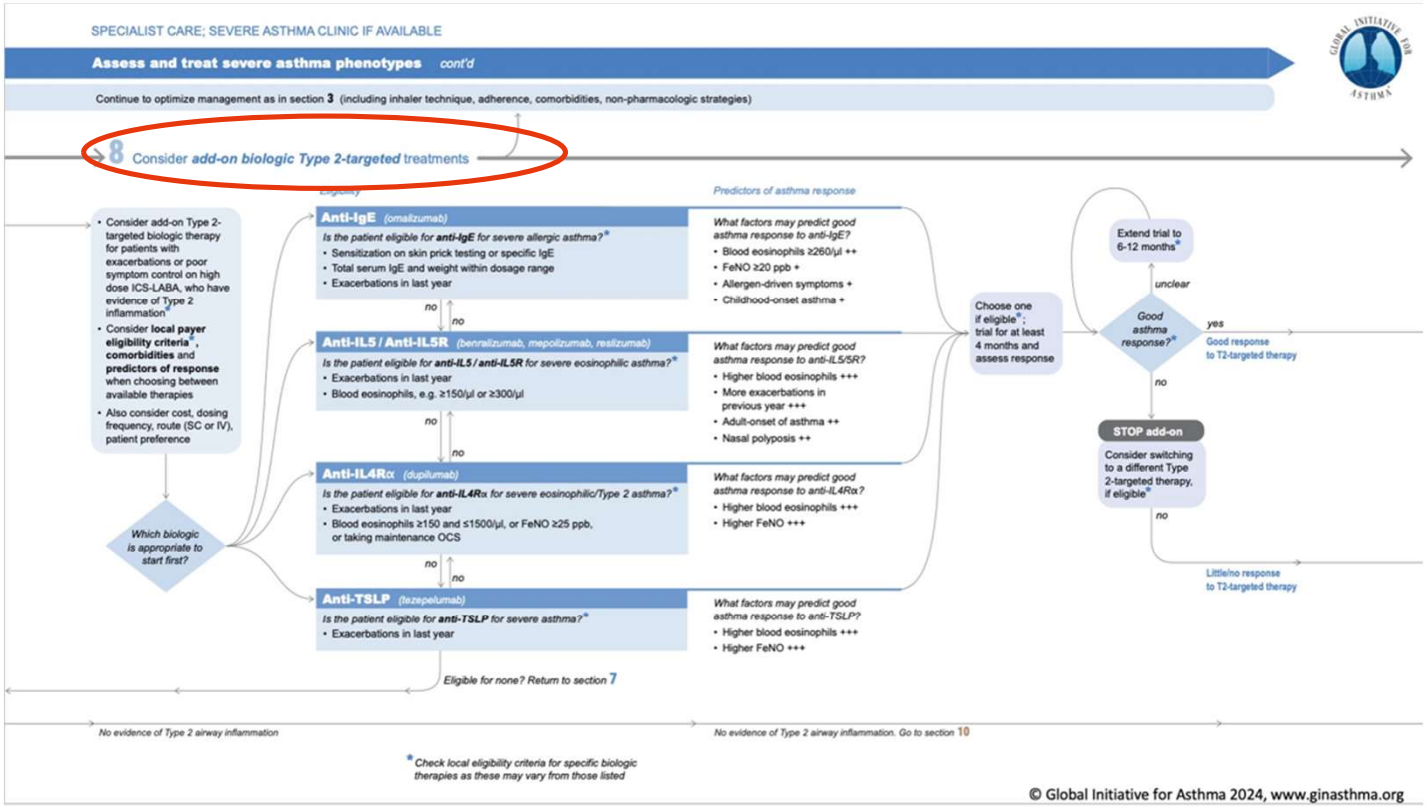
Difficult-to-treat Asthma



Severe Asthma



Biologics


SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE
Assess and treat severe asthma phenotypes cont'd
Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)
8 Consider add-on biologic Type 2-targeted treatments
Predictors of asthma response
Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
Consider local payer eligibility criteria*, comorbidities and predictors of response when choosing between available therapies
Also consider cost, dosing frequency, route (SC or IV), patient preference
Which biologic is appropriate to start first?
Anti-IgE (omalizumab)
Is the patient eligible for anti-IgE for severe allergic asthma?*
Sensitization on skin prick testing or specific IgE
Total serum IgE and weight within dosage range
Exacerbations in last year
What factors may predict good asthma response to anti-IgE?
Blood eosinophils ≥260/µl ++
FeNO ≥20 ppb +
Allergen-driven symptoms +
Childhood-onset asthma +
Anti-IL5 / Anti-IL5R (benralizumab, mepolizumab, reslizumab)
Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?*
Exacerbations in last year
Blood eosinophils, e.g. ≥150/µl or ≥300/µl
What factors may predict good asthma response to anti-IL5/5R?
Higher blood eosinophils +++
More exacerbations in previous year +++
Adult-onset of asthma ++
Nasal polyposis ++
Anti-IL4Rα (dupilumab)
Is the patient eligible for anti-IL4Rα for severe eosinophilic/Type 2 asthma?*
Exacerbations in last year
Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS
What factors may predict good asthma response to anti-IL4Rα?
Higher blood eosinophils +++
Higher FeNO +++
Anti-TSLP (tezepelumab)
Is the patient eligible for anti-TSLP for severe asthma?*
Exacerbations in last year
What factors may predict good asthma response to anti-TSLP?
Higher blood eosinophils +++
Higher FeNO +++
no
Eligible for none? Return to section 7
Choose one if eligible*; trial for at least 4 months and assess response
Extend trial to 6-12 months*
unclear
Good asthma response?*
yes
Good response to T2-targeted therapy
no
STOP add-on
Consider switching to a different Type 2-targeted therapy, if eligible*
Little/no response to T2-targeted therapy
No evidence of Type 2 airway inflammation
No evidence of Type 2 airway inflammation. Go to section 10
*Check local eligibility criteria for specific biologic therapies as these may vary from those listed
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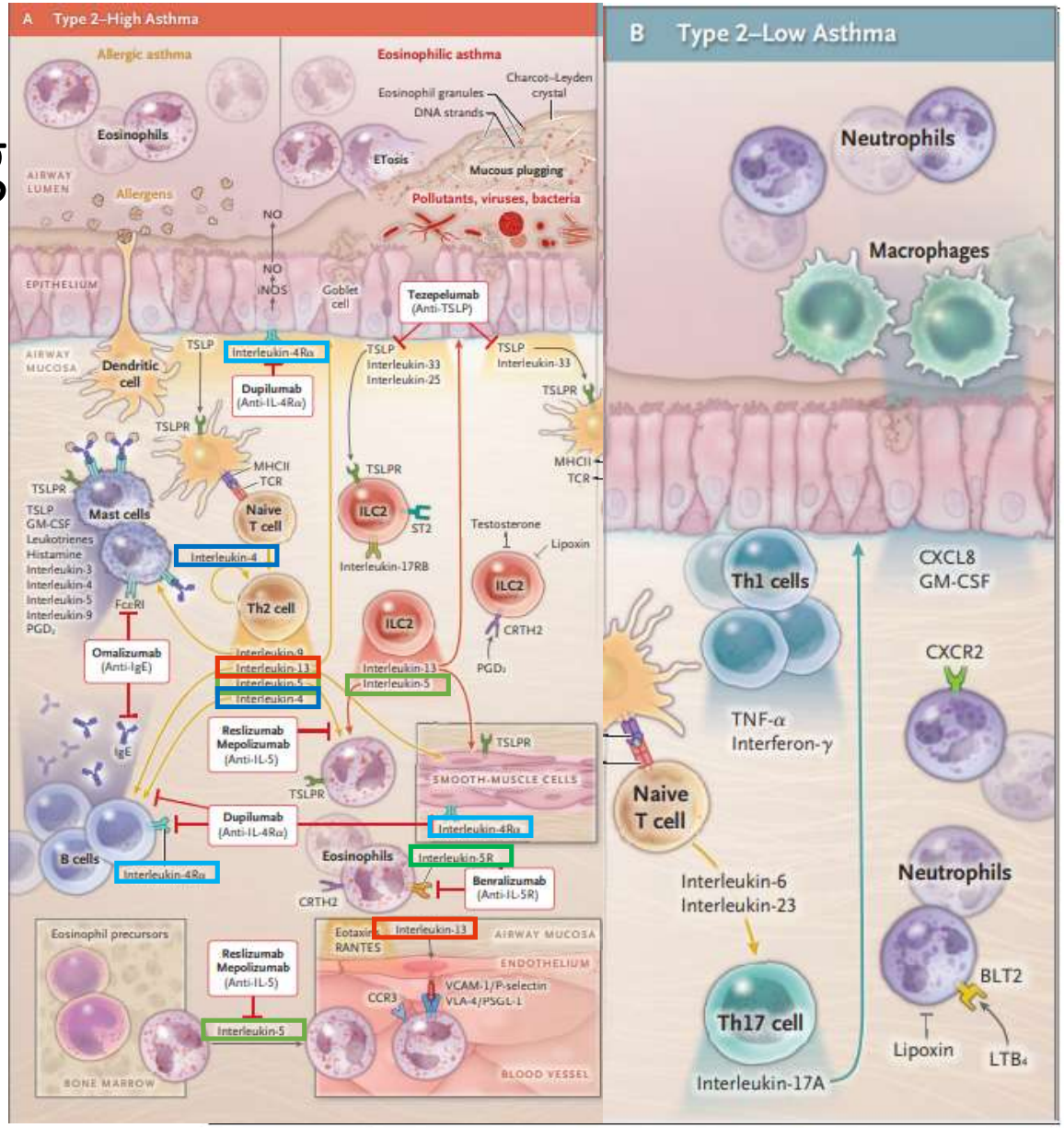
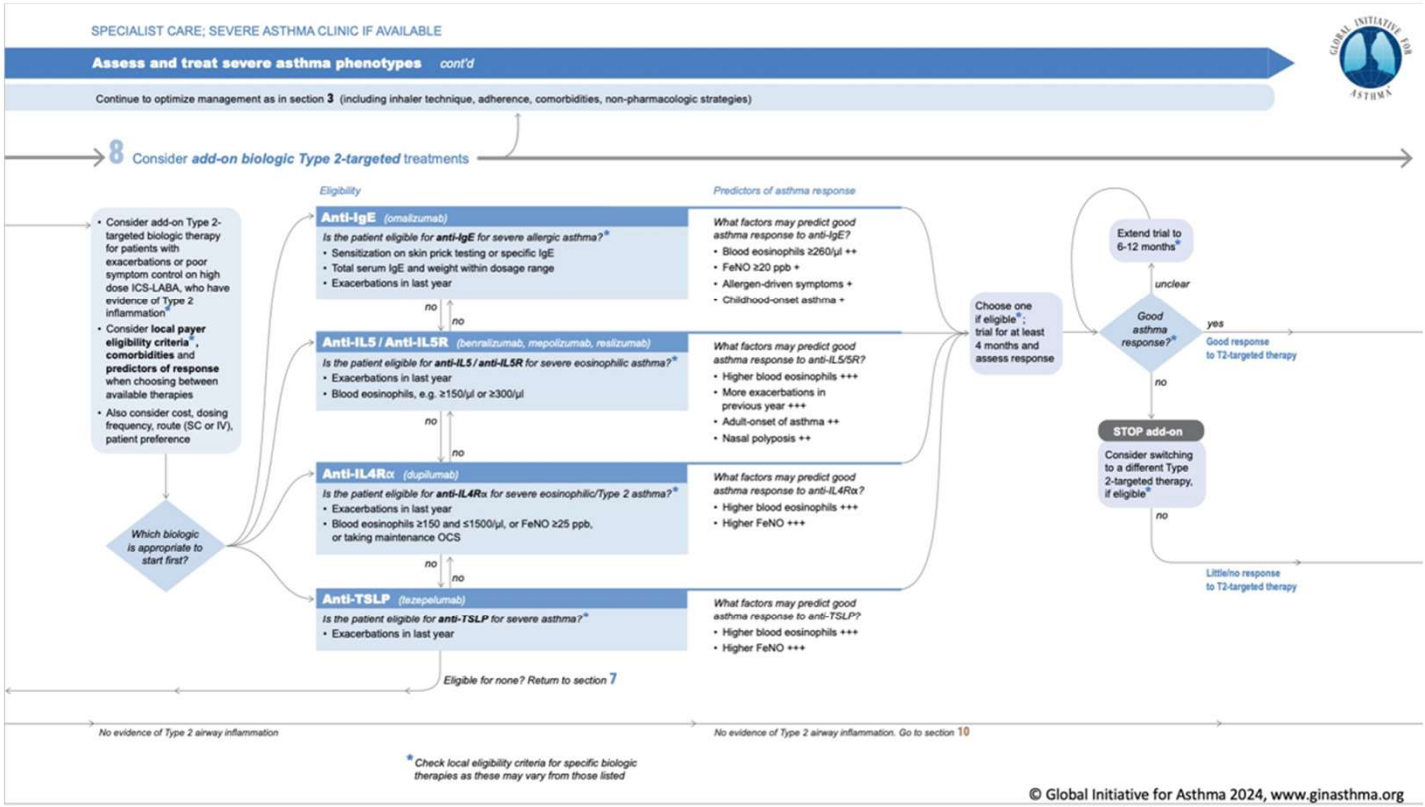
Pathophysiolog



Biologics


SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE
Assess and treat severe asthma phenotypes cont'd
Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)
8 Consider add-on biologic Type 2-targeted treatments
Eligibility
Predictors of asthma response
Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
Consider local payer eligibility criteria*, comorbidities and predictors of response when choosing between available therapies
Also consider cost, dosing frequency, route (SC or IV), patient preference
Which biologic is appropriate to start first?
Anti-IgE (omalizumab)
Is the patient eligible for anti-IgE for severe allergic asthma?*
Sensitization on skin prick testing or specific IgE
Total serum IgE and weight within dosage range
Exacerbations in last year
What factors may predict good asthma response to anti-IgE?
Blood eosinophils ≥260/µl ++
FeNO ≥20 ppb +
Allergen-driven symptoms +
Childhood-onset asthma +
no
Anti-IL5 / Anti-IL5R (benralizumab, mepolizumab, reslizumab)
Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?*
Exacerbations in last year
Blood eosinophils, e.g. ≥150/µl or ≥300/µl
What factors may predict good asthma response to anti-IL5/5R?
Higher blood eosinophils +++
More exacerbations in previous year +++
Adult-onset of asthma ++
Nasal polyposis ++
Anti-IL4Rα (dupilumab)
Is the patient eligible for anti-IL4Rα for severe eosinophilic/Type 2 asthma?*
Exacerbations in last year
Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS
What factors may predict good asthma response to anti-IL4Rα?
Higher blood eosinophils +++
Higher FeNO +++
Anti-TSLP (tezepelumab)
Is the patient eligible for anti-TSLP for severe asthma?*
Exacerbations in last year
What factors may predict good asthma response to anti-TSLP?
Higher blood eosinophils +++
Higher FeNO +++
Eligible for none? Return to section 7
Choose one if eligible*; trial for at least 4 months and assess response
Extend trial to 6-12 months*
unclear
Good asthma response?*
yes
Good response to T2-targeted therapy
no
STOP add-on
Consider switching to a different Type 2-targeted therapy, if eligible*
no
Little/no response to T2-targeted therapy
No evidence of Type 2 airway inflammation
No evidence of Type 2 airway inflammation. Go to section 10
*Check local eligibility criteria for specific biologic therapies as these may vary from those listed
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Biologics

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?**

- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

Anti-IL4Rα *(dupilumab)*

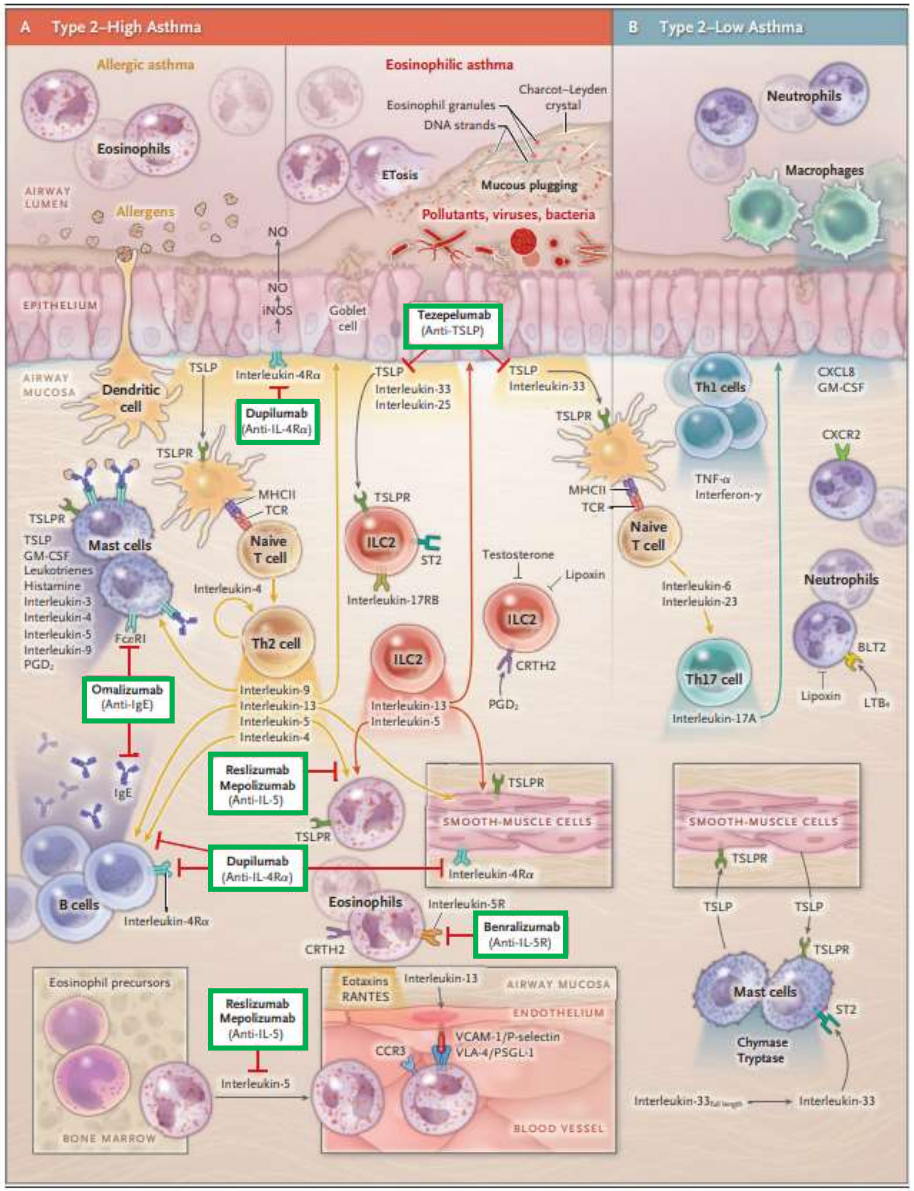
*Is the patient eligible for **anti-IL4Rα** for severe eosinophilic/Type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

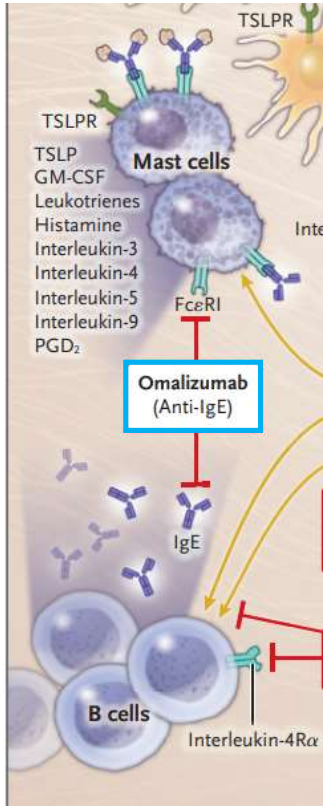
Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year



Omalizumab



Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**

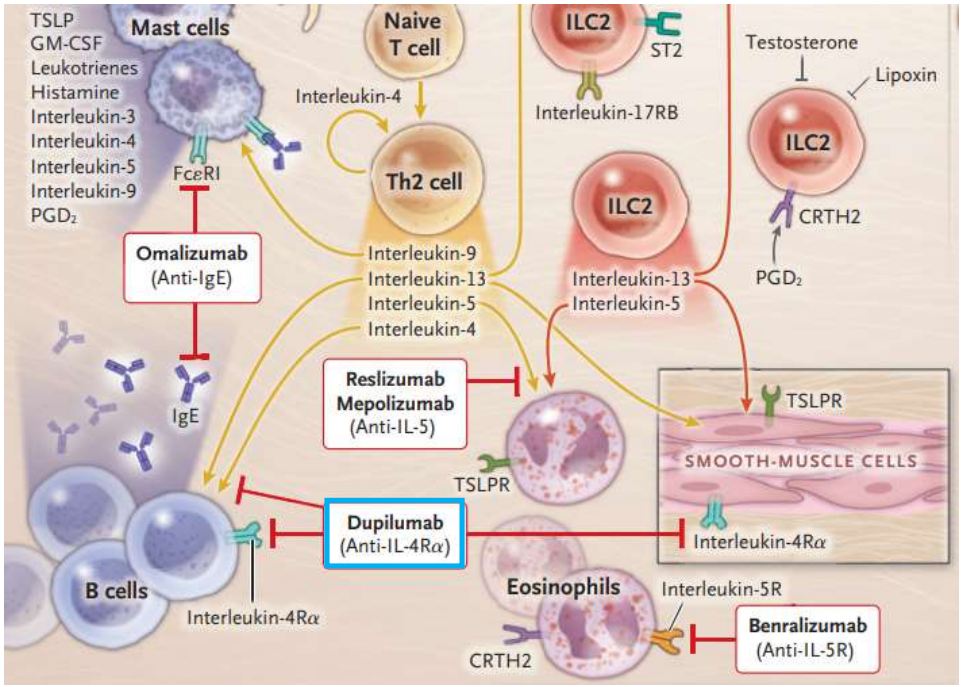
- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

- Private sector: R7500
- State sector: R2600

Dupilumab



Anti-IL4Rα *(dupilumab)*

*Is the patient eligible for **anti-IL4Rα** for severe eosinophilic/Type 2 asthma?**

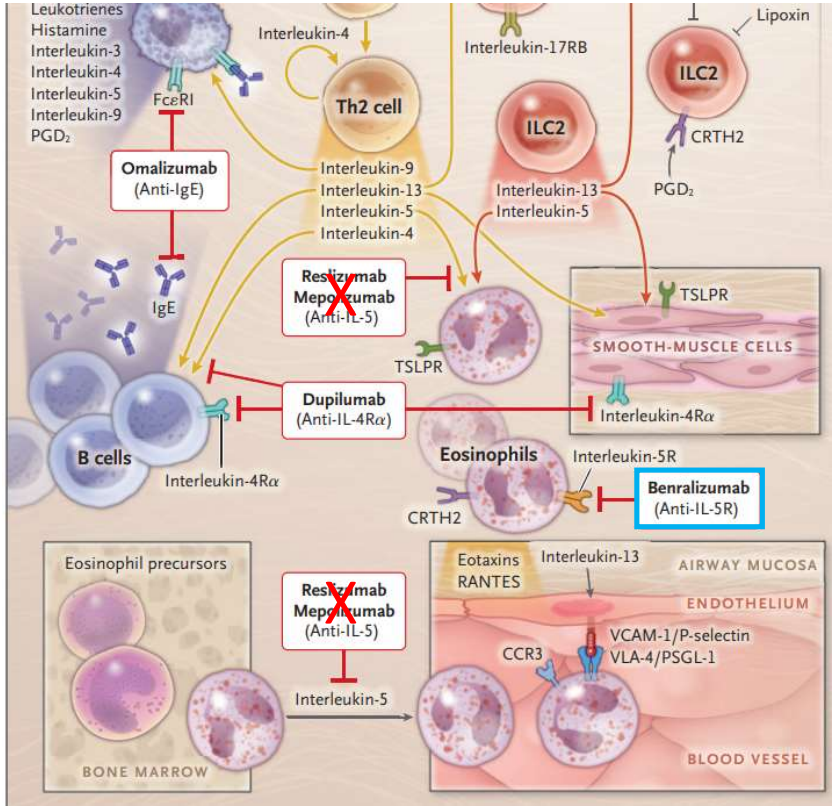
- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

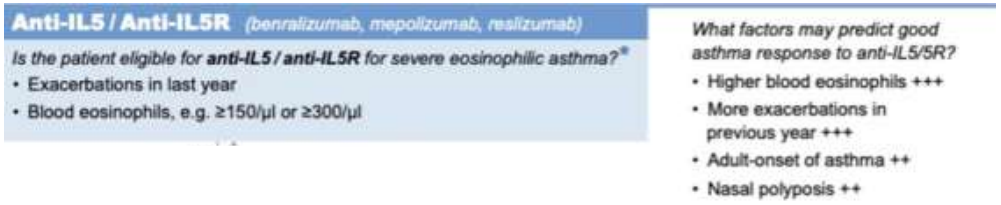
What factors may predict good asthma response to anti-IL4Rα?

- Higher blood eosinophils +++
- Higher FeNO +++

- R24000/month

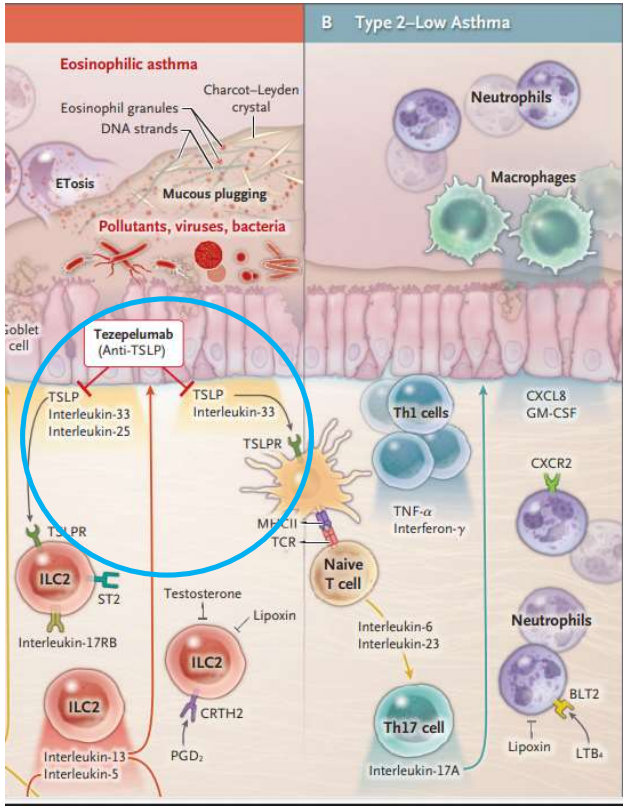
Benralizumab





- R25000/month

Tezepelumab



Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

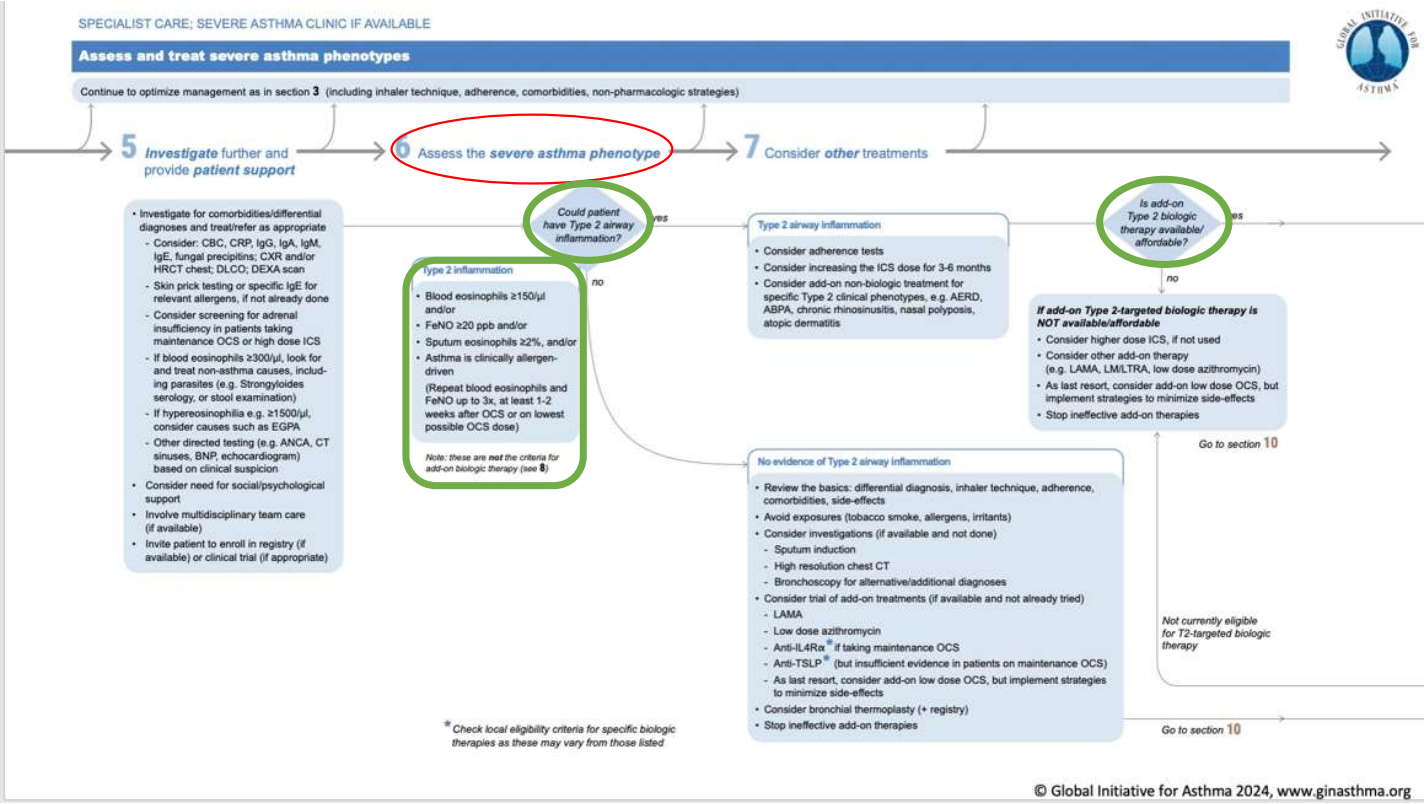
- Exacerbations in last year

What factors may predict good asthma response to anti-TSLP?

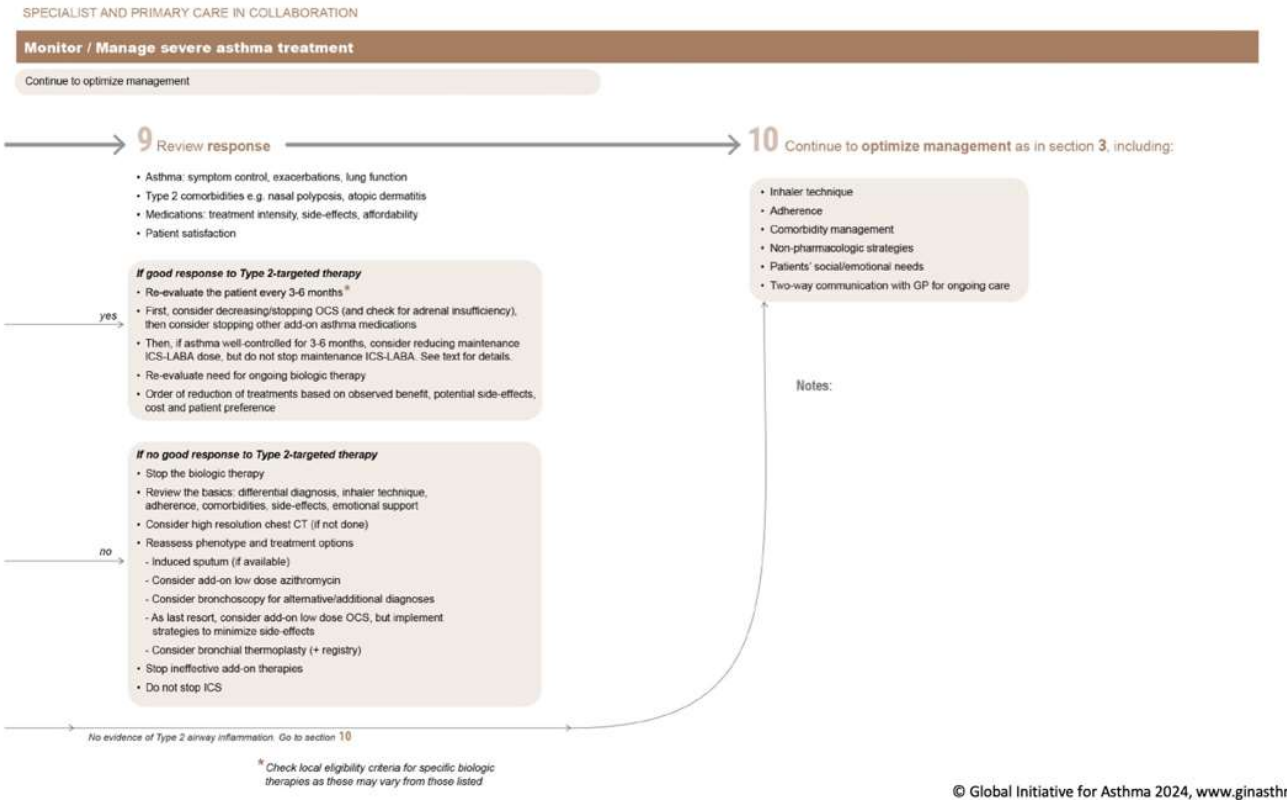
- Higher blood eosinophils +++
- Higher FeNO +++

- Not available in SA

Severe Asthma



Biologics



Conclusion

- Biologics
  - Available…expensive
  - Not for everyone
  - Specialised centres
    - Rigorous process of screening
    - Phenotyping
    - Choosing best one
    - Monitoring

- Thank you!