

# Pediatric Asthma

Muna Kilani, MD

# Definition of Asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

- Airway Inflammation leads to:
  - ✓ **Hyperresponsiveness** - responses to triggers
  - ↓
  - ✓ **Obstruction** - usually fully reversible
  - ↓
  - ✓ **Symptoms** - cough, wheeze, dyspnea

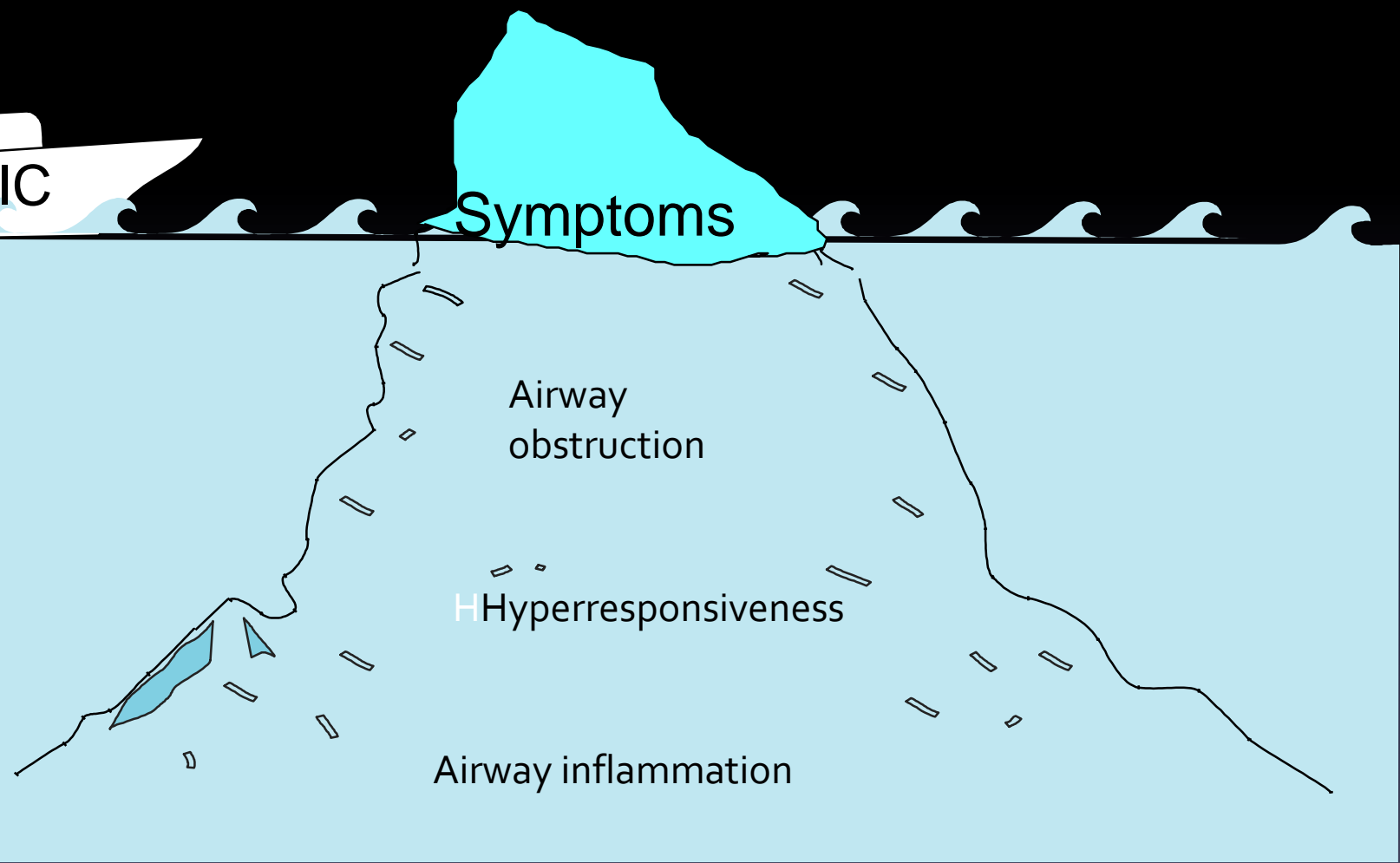


# Symptoms

Airway obstruction

Hyperresponsiveness

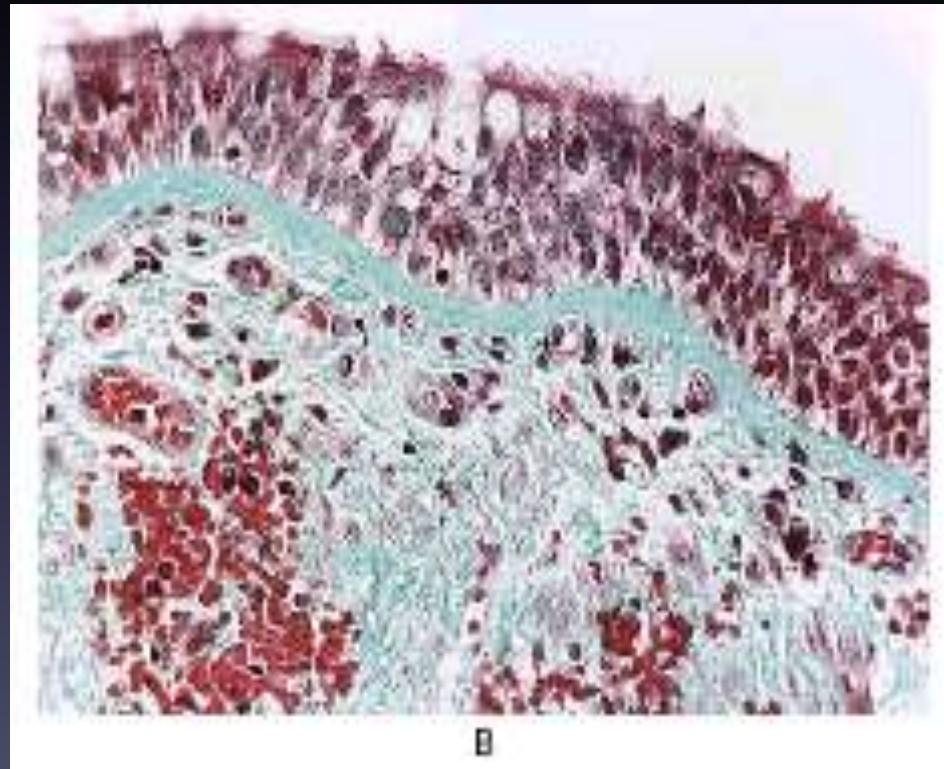
Airway inflammation



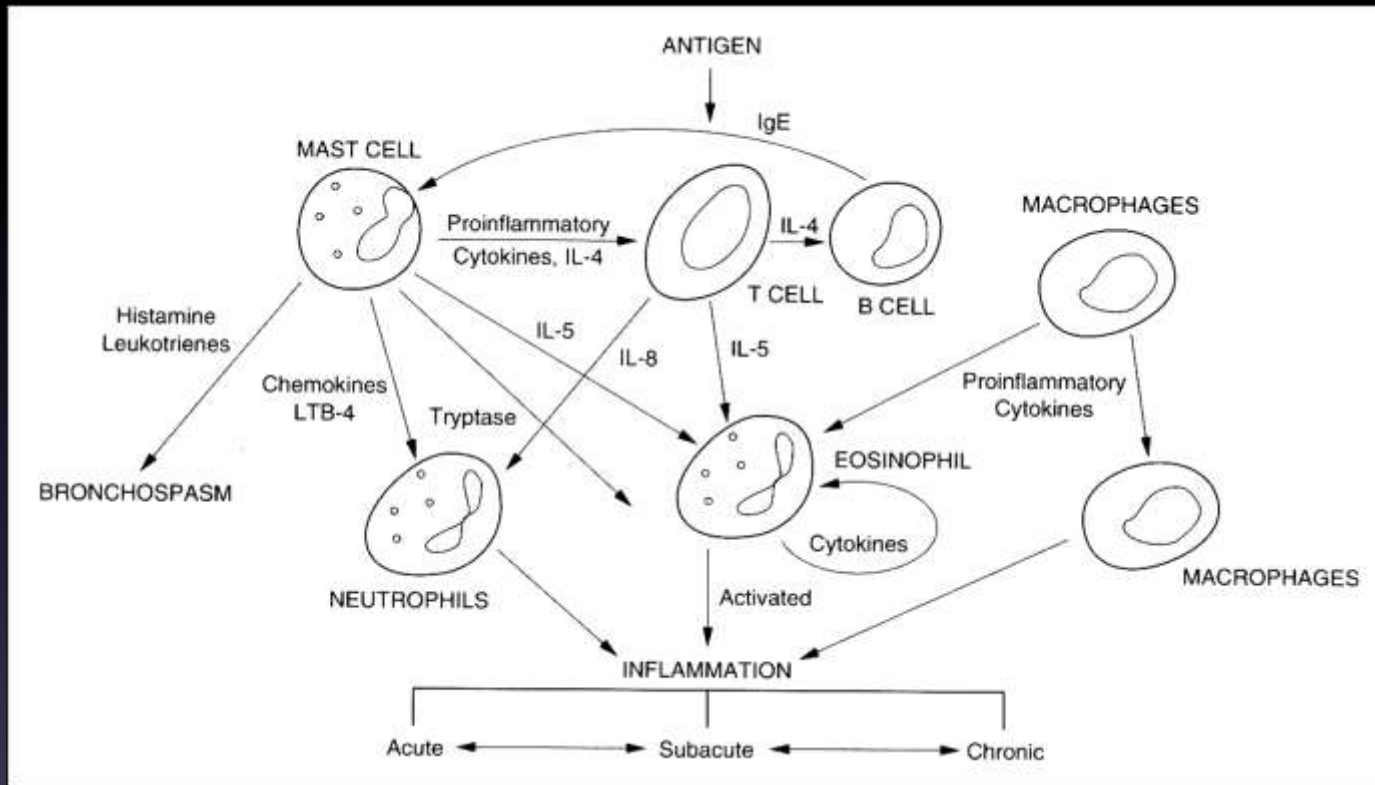
# Normal airway



# Mild Asthma



# Cellular mechanisms involved in airway inflammation and the interaction of multiple cell types and mediators in airway inflammation

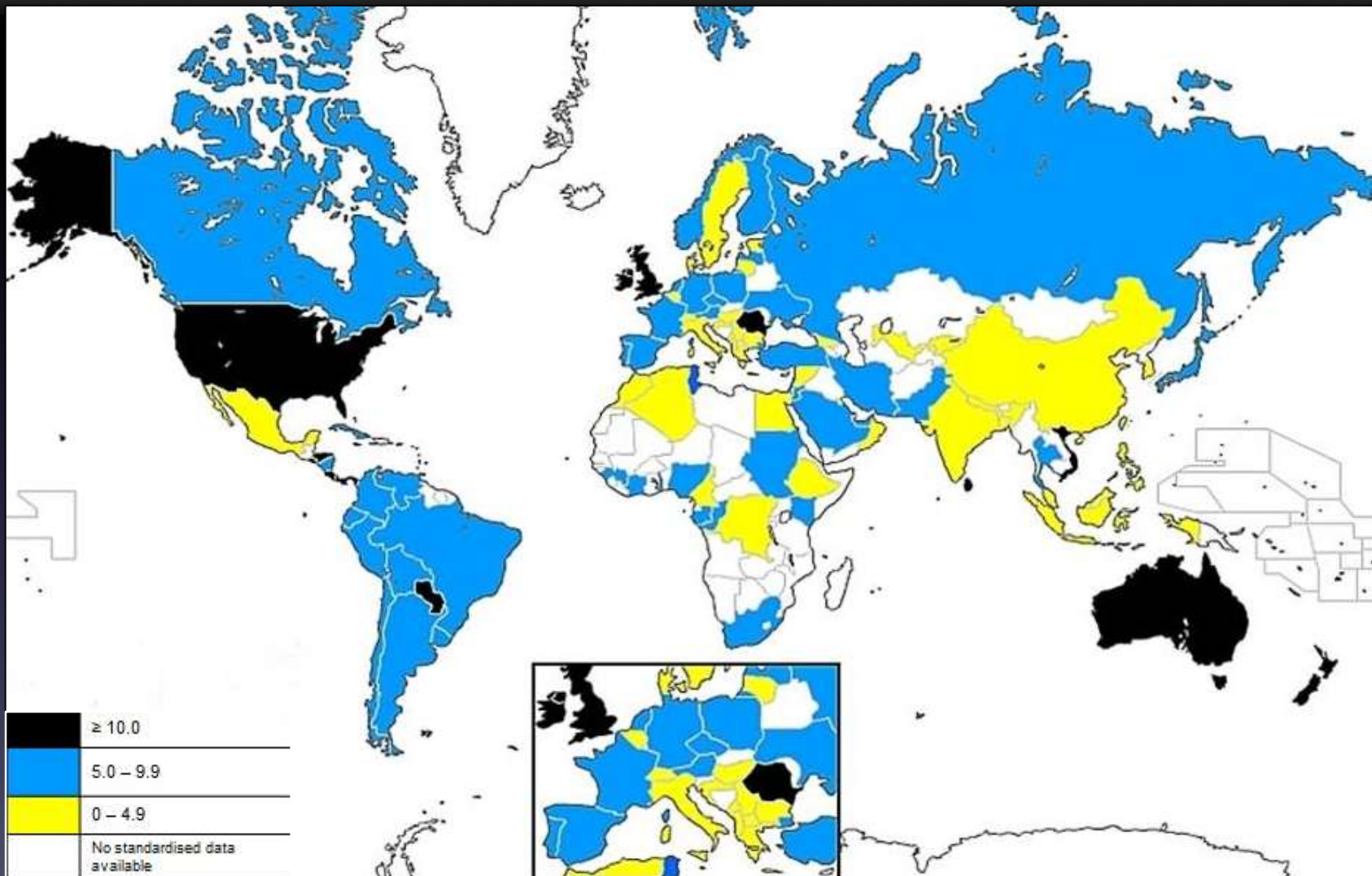


Guill, M. F. Pediatrics in Review 2004;25:299-305

# Burden of disease

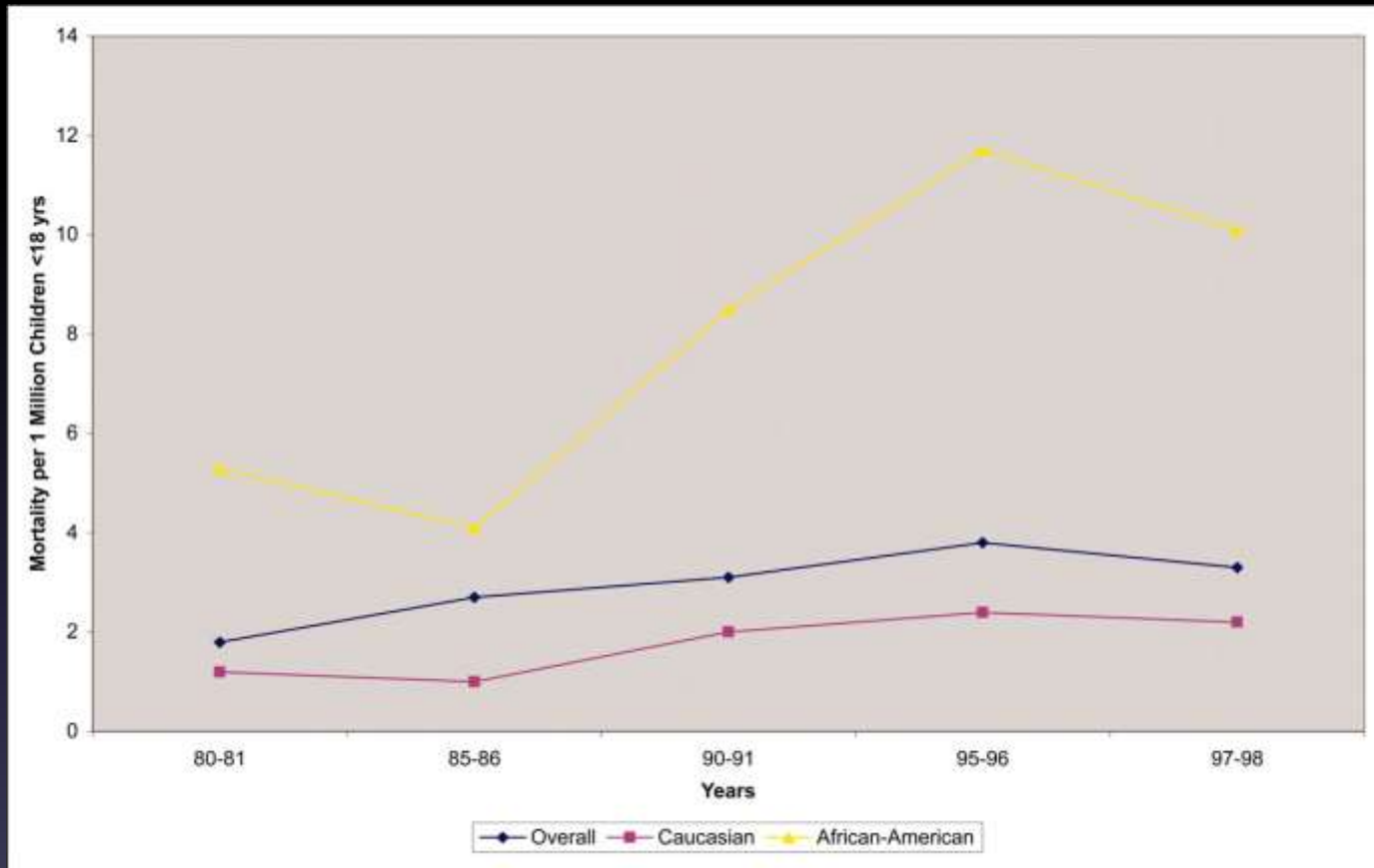
- #1 chronic illness in childhood
- #1 chronic illness causing school absence
- 78% of parents report a negative impact on family

# Prevalence of asthma in children aged 13-14 years





## Asthma mortality from 1980 to 1998



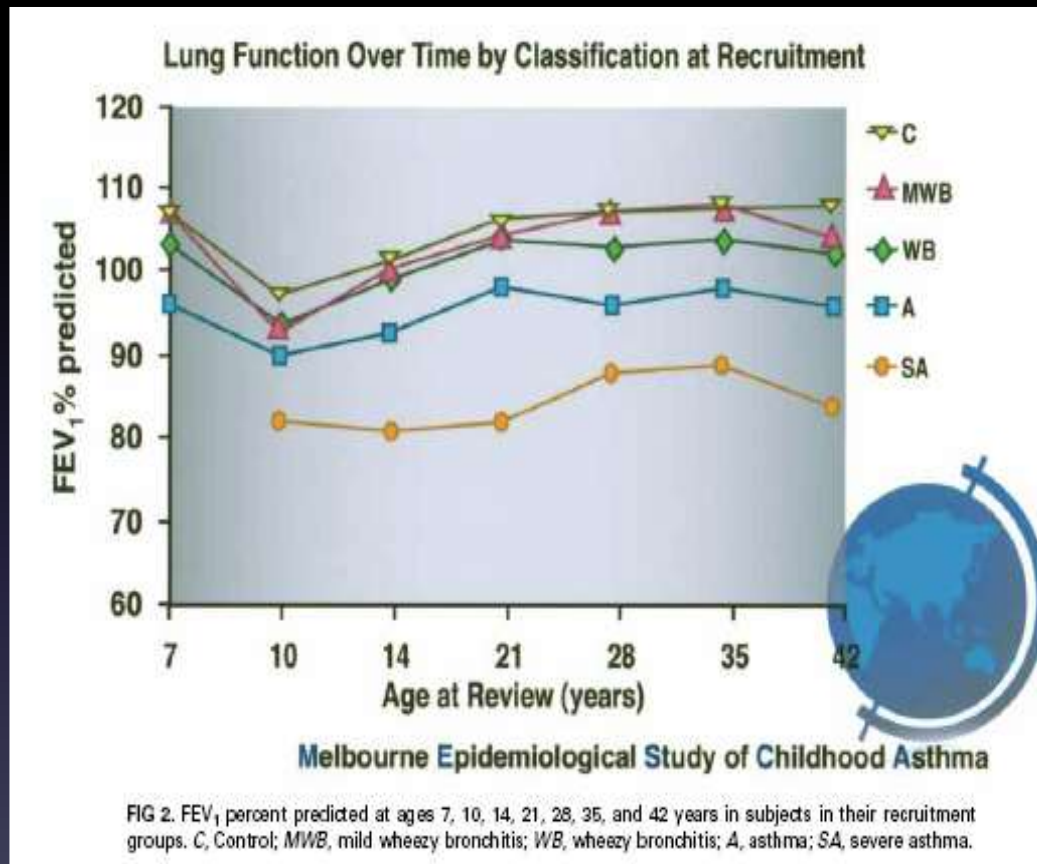
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# Natural History & Prognosis

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- Remains incompletely understood
- Most children do not ultimately “grow out of it”
  - “Loss” of symptoms may be related to growth of lungs and not due to a change of airway hyperresponsiveness.
  - Disease may go through a silent, asymptomatic period in young adulthood

# Asthma and Wheezing from 7 to 42 Years Melbourne Study



# What's Unique?

## Pediatric asthma epidemiology

- Some risk factors for asthma are common for adults and children, but some clearly differ
  - Differences are perhaps most marked in the youngest age groups
- Asthma and wheezing in the first 6 years of life
  - Studied by Martinez and colleagues
  - Results from 826 infants followed from birth through age 6

# Asthma and Wheezing in the First Six Years

## Tucson Children's Respiratory Study

Category	Age 3	Age 6
“Transient” Wheezing	(+)	(−)
“Persistent” Wheezing	(+)	(+)
“Late” Wheezing	(−)	(+)

(+) Age 3:  $\geq 1$  lung illness with *wheezing* before age 3

(+) Age 6:  $\geq 1$  *wheezing* episode during the year before age 6

# Asthma and Wheezing in the First Six Years

## Significance of wheezing at age 3

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- Of patients who wheezed before age 3, wheezing **persisted** through age 6 in **about 40%**

### Transient wheezing

- Smaller airway caliber
- No bronchial hyperresponsiveness
- Wheezing resolved by age 6

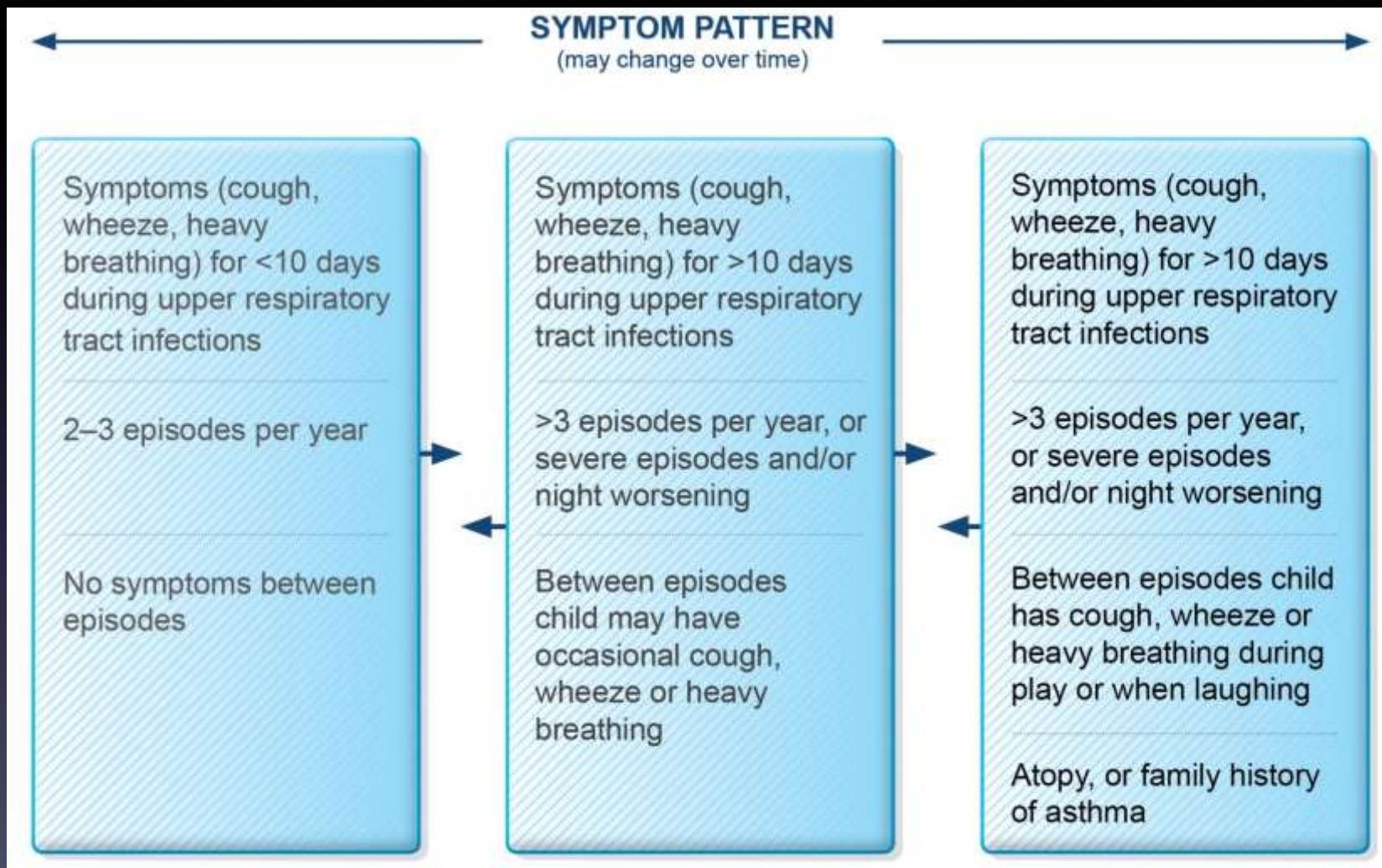
### Persistent Wheezing

- Atopy
- Bronchial hyperresponsiveness
- Significant deterioration in lung function by age 6

# Probability of asthma diagnosis or response to asthma treatment in children $\leq 5$ years



# Symptom patterns in children $\leq 5$ years





# Asthma Predictive Index

- Used in children younger than 3 to predict the likelihood of developing asthma in the future
  - 3 Episodes of wheezing
  - Plus 1 major criteria ( Parental history, atopy like eczema, positive sensitization to environmental allergen)
  - or 2 minor criteria like allergic rhinitis,

# Risk factors

- Viral infections are both

Risk factor for developing  
asthma later in life

A trigger for an asthma  
flare up

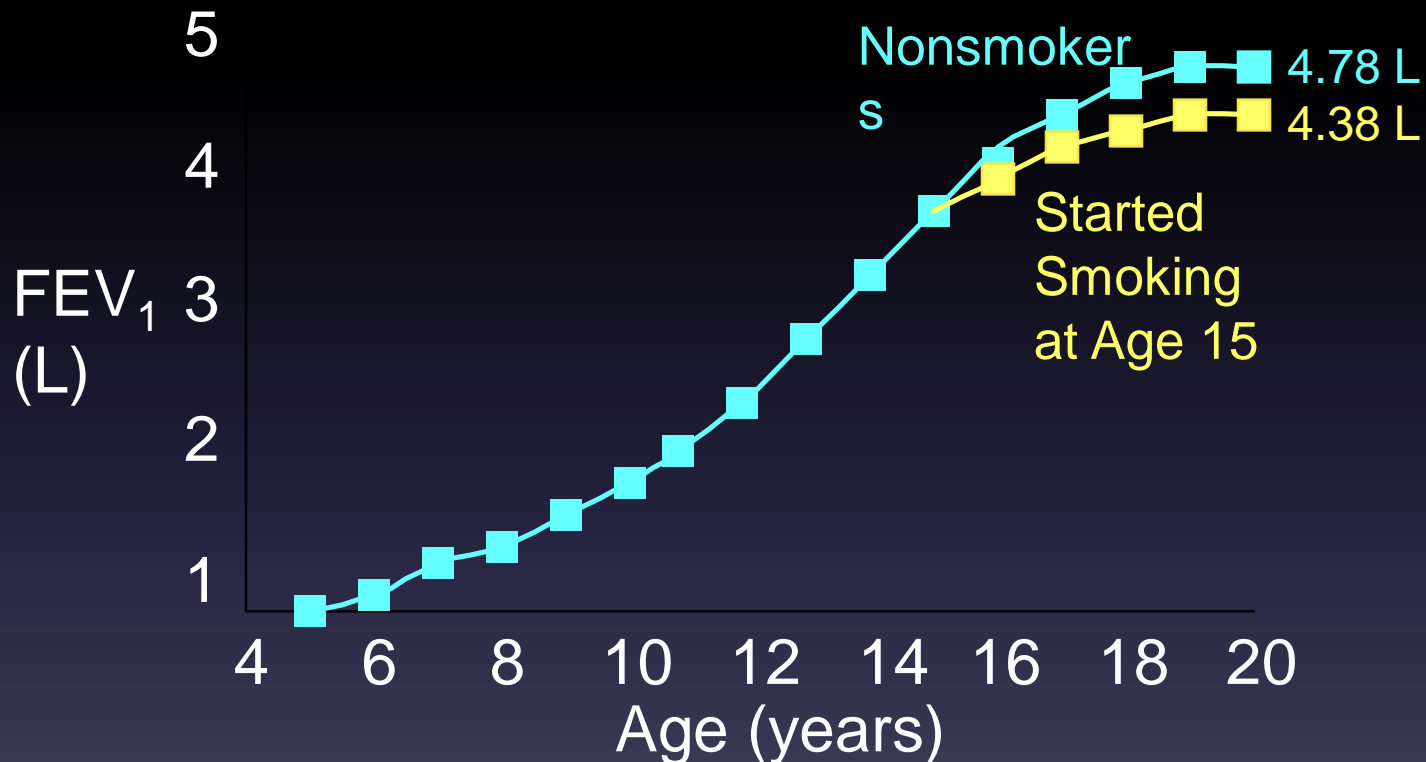
# Risk Factors

- Atopy is the most important risk factor for the development of asthma.
  - By school age 40-80% of asthmatic children have positive immediate type allergy skin tests.
  - Allergic rhinitis, eczema, high IgE levels and more than 4% eosinophils.

# Asthma Risk Factor

## Cigarette smoking in early adolescence

Active smoking reduced the growth in FEV<sub>1</sub>



- As little as 1 cigarette per day reduced the maximal growth in FEV<sub>1</sub> by 5%

# Risk Factors

- A positive family history of asthma
  - Maternal history of asthma had a stronger association with developing asthma than paternal history
  - If one parent has asthma the likelihood of asthma in their children increases by 3 times, if both parents have asthma it increases by 6 times

# Clinical Presentation

# History

## Symptoms

- ✓ Cough, wheeze, dyspnea
- ✓ Nocturnal awakenings

## Frequency & Severity

- ✓ Seasonal, perennial
- ✓ Precipitating factors / “Triggers”
- ✓ Interference with daily activities
- ✓ ER visits or hospitalizations

## Medication Usage

Short-acting beta-agonist use

## Family History

- ✓ Allergy / Atopy
- ✓ Asthma



# Precipitating / Aggravating Factors

## Asthma Triggers

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- Viral upper respiratory infections
  - Allergen exposure
  - Exercise, hyperventilation
  - Irritants (especially smoke)
  - Weather
  - Strong emotion
  - Gastroesophageal reflux???
- Symptomatic GERD benefits from treatment

# Physical exam

- Decreased air entry bilateral
- Prolonged forced expiration
- Use of accessory muscles
- Retractions
- Hyperexpansion of the chest
- Signs of other allergic diseases
  - Atopic dermatitis
  - Allergic rhinitis

Physical examination of the chest may be normal

# Wheezing

- Wheezing
  - A sign of intrathoracic airway obstruction
  - A musical sound generated by airway passing at high velocity through an airway narrowed to the point of almost closure

# When should wheezing be called asthma

- When it is recurrent
- When other wheezing conditions have been excluded
- When a number of risk factors are present
- When the child responds to anti asthma therapy

- Differential diagnosis of wheezing
  - Bronchiolitis
  - Cystic Fibrosis
  - Foreign body
  - Anatomical lesions like vascular rings, mediastinal cysts
  - GERD, aspiration
  - Heart failure

# Challenges in Treating Childhood Asthma

## Assessing airway function

Spirometry:

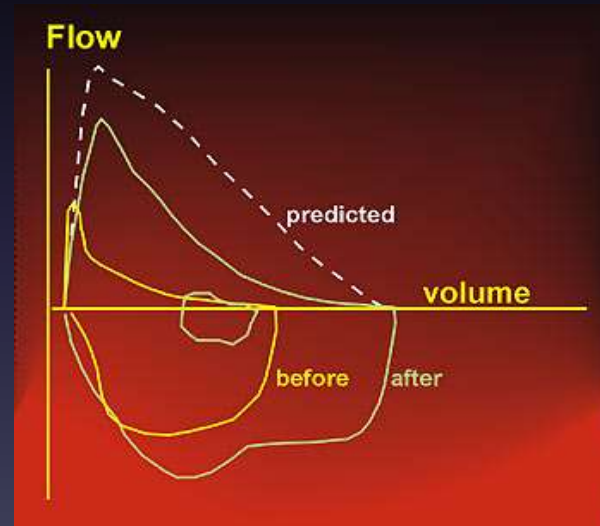
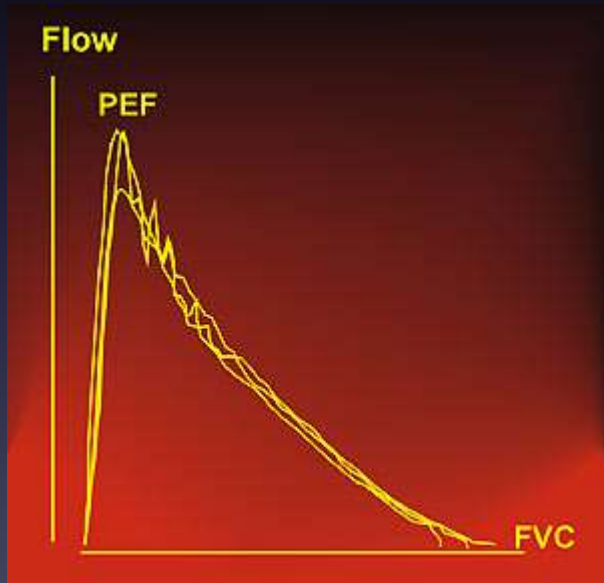
An FEV<sub>1</sub> response of <sup>3</sup>12% post-bronchodilator is suggestive of asthma

BUT,

- Spirometry is difficult in children <4 yrs
- Some children cannot perform spirometry adequately until >7 years of age

# How often? Diagnosis

- Pulmonary function testing.
  - Flow volume curves



# Diagnosis

- X rays

When?





- First time wheezing
- Fever
- Unilateral Wheezing
- Sever symptoms

# Diagnosis

## Assessing airway function

- Metacholine/ Histamine/Exercise challenge test.
- Sputum eosinophils.
- Exhaled NO.
- Infant lung testing.

Peak flow??

- Test for assessment of allergic asthma
  - IgE level
  - Allergy skin testing and RAST testing for allergens
  - Blood eosinophils

- Peak Flows
  - Not routinely indicated
  - Used in moderate and sever asthma

**Table 1** Major endotypes of severe asthma in children

	Triggers	Major cellular drivers	Major molecular drivers	Related clinical features
<b>Type 2 asthma</b>				
Allergic eosinophilic	Allergens	Airway epithelial cells, Th2 lymphocytes, eosinophils	IL-25, IL-33, TSLP, IL-4, IL-5, IL-13, IgE	More common in children Good response to corticosteroids Reversible airway obstruction Associated with upper airway comorbidities
Nonallergic eosinophilic	Pollutants, microbes, glycolipids	Airway epithelial cells, ILC2s, eosinophils	IL-25, IL-33, TSLP, PGD <sub>2</sub>	Less common in children (late-onset) Significant AHR Relatively insensitive to corticosteroids No increased atopy
<b>Non-type 2 asthma</b>				
Paucigranulocytic	Environmental factors (cigarette smoke, allergens, contractile agonists)	ASM dysfunction; no cellular inflammation	High level of oxidative stress (mechanisms not known)	High AHR Insensitivity to corticosteroids
Neutrophilic	Infections	Th17 lymphocytes, neutrophils	IL-17, IL-21, IL-22	Bacterial airway colonisation Poor response to corticosteroids Severe airway obstruction

Th: T-helper cell; IL: interleukin; TSLP: thymic stromal lymphopoietin; IgE: immunoglobulin E; ILC2s: innate lymphoid cells type 2; PGD<sub>2</sub>: prostaglandin D<sub>2</sub>; AHR: airway hyperresponsiveness; ASM: airway smooth muscle cells.

Management

# Management of asthma

How important ?

- Long term goals
  - Maintain child symptom free
  - Best lung function at all times
  - Avoid need for bronchodilators
  - Prevent the restriction of childhood activities
  - Prevent the development of irreversible lung disease
  - Reduce the risk of death
  - Avoid unnecessary side effects.

# Treatmen of asthma

- Bronchodilators - $\beta$  agonist SABA salbutamol
  - Relax smooth muscle in the bronchial tree.
  - Duration of action around 4 hours, peak 10-30min
  - Can cause sympathomimetic effects
  - Available as inhalers or nebulizers



# Medications

- Dosing for albuterol
  - MDI 90mcg per puff, 2-4puffs as needed
  - For nebulize 2.5mg of albutrol/dose

# Medications

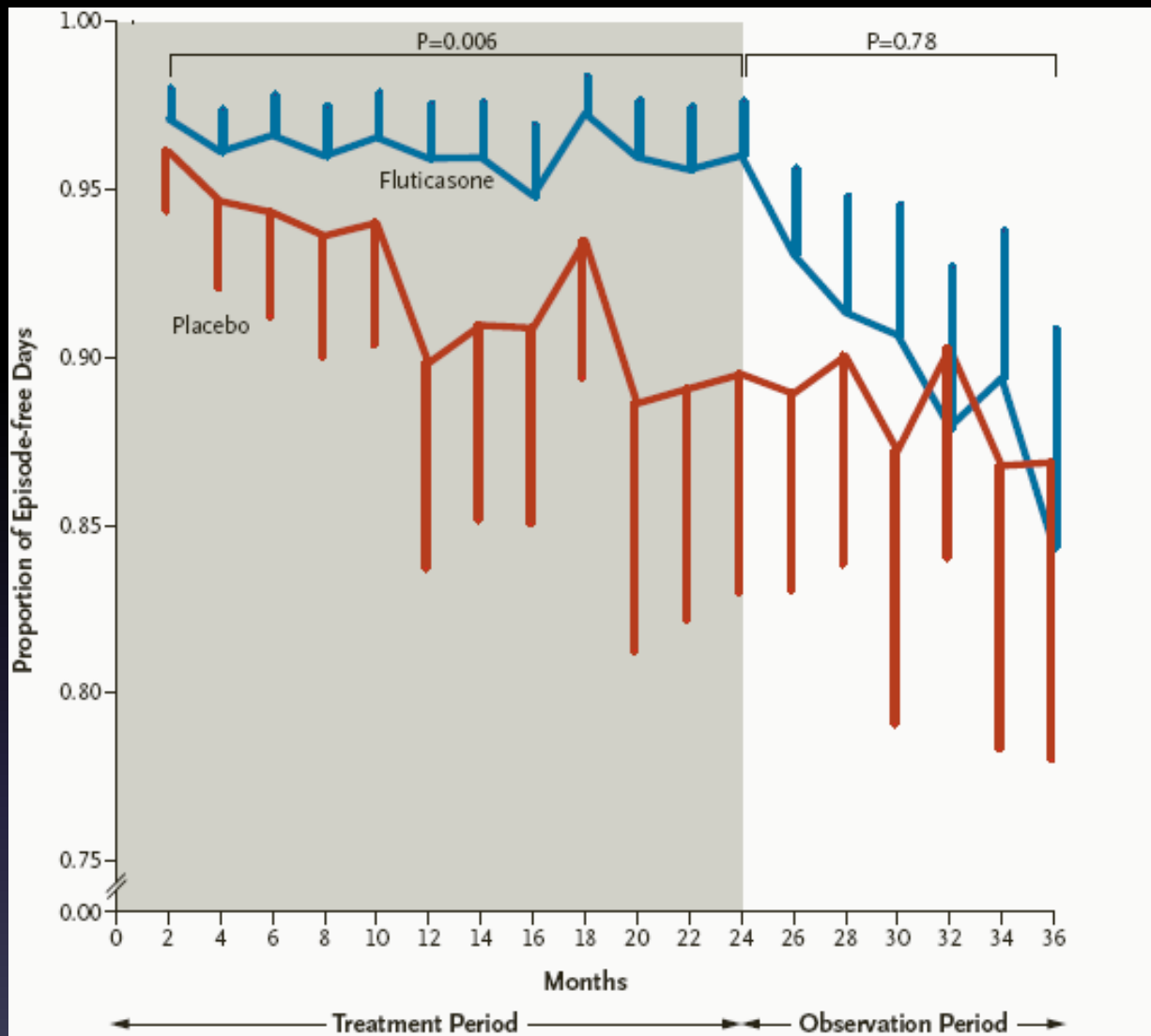
- Anticholinergic agents: ipratropium bromide
  - Blocks the postganglionic efferent vagal pathways leading to bronchodilation.
  - Additive effect to B<sub>2</sub> agonist in an acute asthma attack.
  - Effective in acute asthma management, use in first 24 hours decreased rate of hospital admission.

# Medications

- Inhaled steroids:
  - Anti inflammatory agents that lead to the modification of arachidonic acid metabolism.
  - Associated with decreased airway responsiveness.
  - Available as beclomethasone, budesonide, fluticasone, and triamcinolone, ciclosporin (Alvesco)
  - Inhaled or nebulized

# Medication

- Side effects:
  - Suppression of hypothalamic-pituitary axis, rarely doses below 800mcg.
  - Decrease in height. ( CAMP study).
  - Oral thrush, hoarseness.
  - Similar to oral steroids in high doses.
- Are not believed to prevent the development of asthma



# Medications

- Oral steroids:
  - Most commonly used in the management of an acute attack.
  - Also in children with severe chronic asthma.
  - Onset of action is after 8 hours.
  - Side effects: reduced growth, Hypothalamic pituitary axis suppression, hypertension, cataract...

# Emerging targeted treatment for moderate to severe uncontrolled asthma

**Table 1.** Main Biologic Drugs currently approved in the pediatric population.

Biological Drug	Structure	Action	Dosage	Age (Years)	References
<b>Omalizumab</b>	Humanized IgG1	Anti-IgE	<ul style="list-style-type: none"> <li>In moderate to severe allergic asthma:                             <ul style="list-style-type: none"> <li>SC 75 to 375 mg SC/2-4 wk</li> </ul> </li> <li>In CRSwNP and CSU</li> </ul>	<ul style="list-style-type: none"> <li>≥6 (AIFA)</li> <li>≥6 (EMA)</li> <li>≥6 (FDA)</li> <li>≥18 in CRSwNP</li> </ul>	[39,40]
<b>Mepolizumab</b>	Humanized IgG1	Anti-IL-5	<ul style="list-style-type: none"> <li>In severe eosinophilic asthma:                             <ul style="list-style-type: none"> <li>SC 100 mg/4 wk ≥ 12 yo</li> <li>SC 40 mg/4 wk ≥ 6 yo</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>≥6 (AIFA)</li> <li>≥6 (EMA)</li> <li>≥6 (FDA)</li> </ul>	[50,51]
<b>Reslizumab</b>	Humanized IgG4	Anti-IL-5	<ul style="list-style-type: none"> <li>In severe eosinophilic asthma:                             <ul style="list-style-type: none"> <li>IV 3.0 mg/kg/4 wk</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>≥18 (AIFA)</li> <li>≥18 (EMA)</li> <li>≥18 (FDA)</li> </ul>	[62,63]
<b>Benralizumab</b>	Humanized IgG1	Anti-IL-5Rα	<ul style="list-style-type: none"> <li>In severe eosinophilic asthma:                             <ul style="list-style-type: none"> <li>SC 30 mg/4 wk</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>≥18 (AIFA)</li> <li>≥18 (EMA)</li> <li>≥12 (FDA)</li> </ul>	[67]

Biological Drug	Structure	Action	Dosage	Age (Years)	References
Dupilumab	Human IgG4	Anti-IL-4R $\alpha$	<p>In moderate-to-severe eosinophilic asthma, CRSwNP &amp; moderate-to-severe atopic dermatitis</p> <ul style="list-style-type: none"> <li>Initial dose of SC 600 mg, then 300 mg/2 wk in OCS treat. or + AD</li> <li>initial dose of SC 400 mg, then 200 mg/2 wk</li> </ul>	<p><math>\geq 12</math> (AIFA)  <math>\geq 12</math> (EMA)  <math>\geq 12</math> in asthma  <math>\geq 6</math> DA (FDA)</p>	[72,73]
Tezepelumab	Human IgG2	Anti-TSLP	<p>In severe asthma, especially with:</p> <ul style="list-style-type: none"> <li>high blood eosinophil counts (<math>\geq 300</math> cells per microliter) and</li> <li>FeNO levels (<math>\geq 25</math> parts per billion)</li> <li>SC 210 mg/4 wk</li> </ul>	<p>Phase 3 RCTs (NAVIGATOR, SOURCE) ongoing <math>\geq 12</math></p>	[80,81]



# Treatmen of asthma

- Long acting  $\beta$  agonist LABA
  - Salmeterol—up to 12 hours
  - Formoterol—observed in most patients to last up to 12 hours
  - Are steroid sparing
  - Black box warning

# Medications

- Leukotriene-receptor antagonist (Zafirlukast, montelukast), and Leukotriene-receptor inhibitors (Zileuton)
  - Block airway response to challenges, lead to improved lung function.
  - Oral medication taken **ONCE** daily.
  - *Have a role in mild asthma.*
  - Some pharmaco-genetics involved

# Medications

- Theophyllin (Methylxanthines): A phosphodiesterase inhibitor, increases intracellular cAMP, decreases inflammation
  - Narrow therapeutic index, multiple drug interactions, needs drug levels
- Cromolyn sodium: Mast cell stabilizer
- Nedocromolil Sodium: Long acting mast cell stabilizer
- Magnesium sulphate: Inhibits smooth muscle contraction, stabilizes mast cells, inhibits acetylcholine release.
  - A cochrane review 2160, showed that it may reduce the need for hospital admission in children with acute moderate to severe asthma, but the evidence is extremely limited
  - Omalizumab: Anti IgE (Xolair)
  - Anti IL 5 antibodies

# Treating asthma to control symptoms and minimize risk



## GINA Global Strategy for Asthma Management and Prevention 2016

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# GINA Guidelines

Table 3.

GINA classification of asthma severity by clinical features before treatment

	Symptoms /Day	Symptoms /Night	PEF or FEV1	PEF variability
<b>STEP 1 Intermittent</b>	< 1 time a week Asymptomatic and normal PEF between attacks	≤ 2 times a month	≥ 80%	< 20%
<b>STEP 2 Mild Persistent</b>	> 1 time a week but < 1 time a day Attacks may affect activity	>2 times a month	≥ 80%	20 - 30%
<b>STEP 3 Moderate Persistent</b>	Daily Attacks affect activity	> 1 time a week	60% -80%	> 30%
<b>STEP 4 Severe Persistent</b>	Continuous Limited physical activity	Frequent	≤ 60%	> 30%

# NAEPP (American guidelines)

Table 1.

NAEPP classification of asthma severity

Symptoms Severity	Days with Symptoms	Nights with Symptoms	PEFR FEV1	PEF Variability
Step 4 Severe Persistent	Continual	Frequent	$\leq 60\%$	$> 30\%$
Step 3 Moderate Persistent	Daily	$> 1 / \text{week}$	$> 60\% - < 80\%$	$< 30\%$
Step 2 Mild Persistent	$> 2 / \text{week}$ , but $< 1 / \text{day}$	$> 2 / \text{month}$	$\geq 80\%$	20-30%
Step 1 Mild Intermittent	$\leq 2 / \text{week}$	$\leq 2 / \text{month}$	$\geq 80\%$	$< 20\%$

# GINA assessment of asthma control in children $\leq 5$ years



## A. Symptom control

### Level of asthma symptom control

In the past 4 weeks, has the child had:

- Daytime asthma symptoms for more than few minutes, more than once/week? Yes  No
- Any activity limitation due to asthma? (runs/plays less than other children, tires easily during walks/playing) Yes  No
- Reliever needed\* more than once a week? Yes  No
- Any night waking or night coughing due to asthma? Yes  No

Well-controlled

Partly controlled

Uncontrolled

None of these

1-2 of these

3-4 of these

# Risk factors for poor asthma outcomes in children $\leq 5$ years



## Risk factors for exacerbations in the next few months

- Uncontrolled asthma symptoms
- One or more severe exacerbation in previous year
- The start of the child's usual 'flare-up' season (especially if autumn/fall)
- Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens (e.g. house dust mite, cockroach, pets, mold), especially in combination with viral infection
- Major psychological or socio-economic problems for child or family
- Poor adherence with controller medication, or incorrect inhaler technique

## Risk factors for fixed airflow limitation

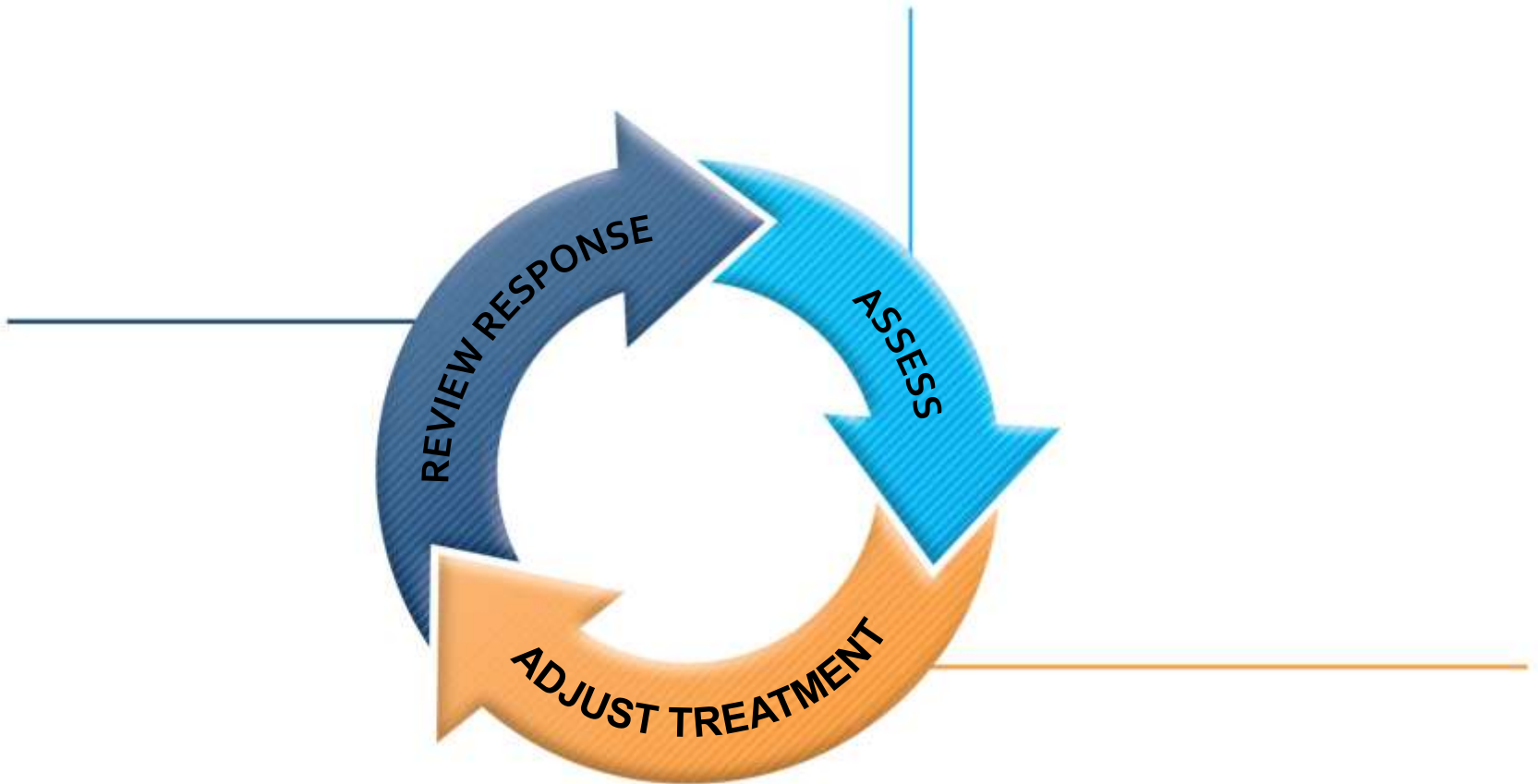
- Severe asthma with several hospitalizations
- History of bronchiolitis

## Risk factors for medication side-effects

- Systemic: Frequent courses of OCS; high-dose and/or potent ICS
- Local: moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect skin or eyes when using ICS by nebulizer or spacer with face mask



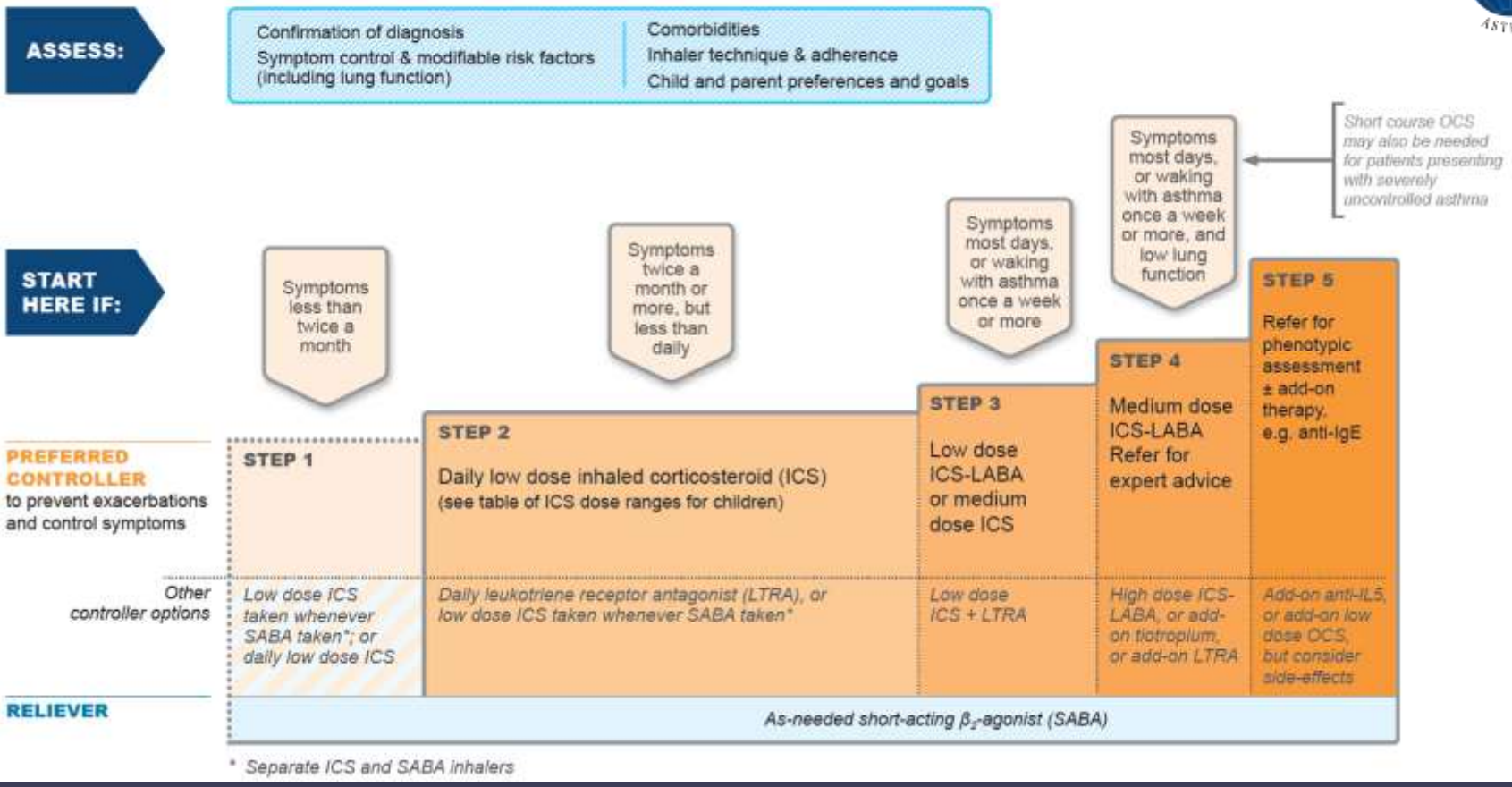
# The control-based asthma management cycle



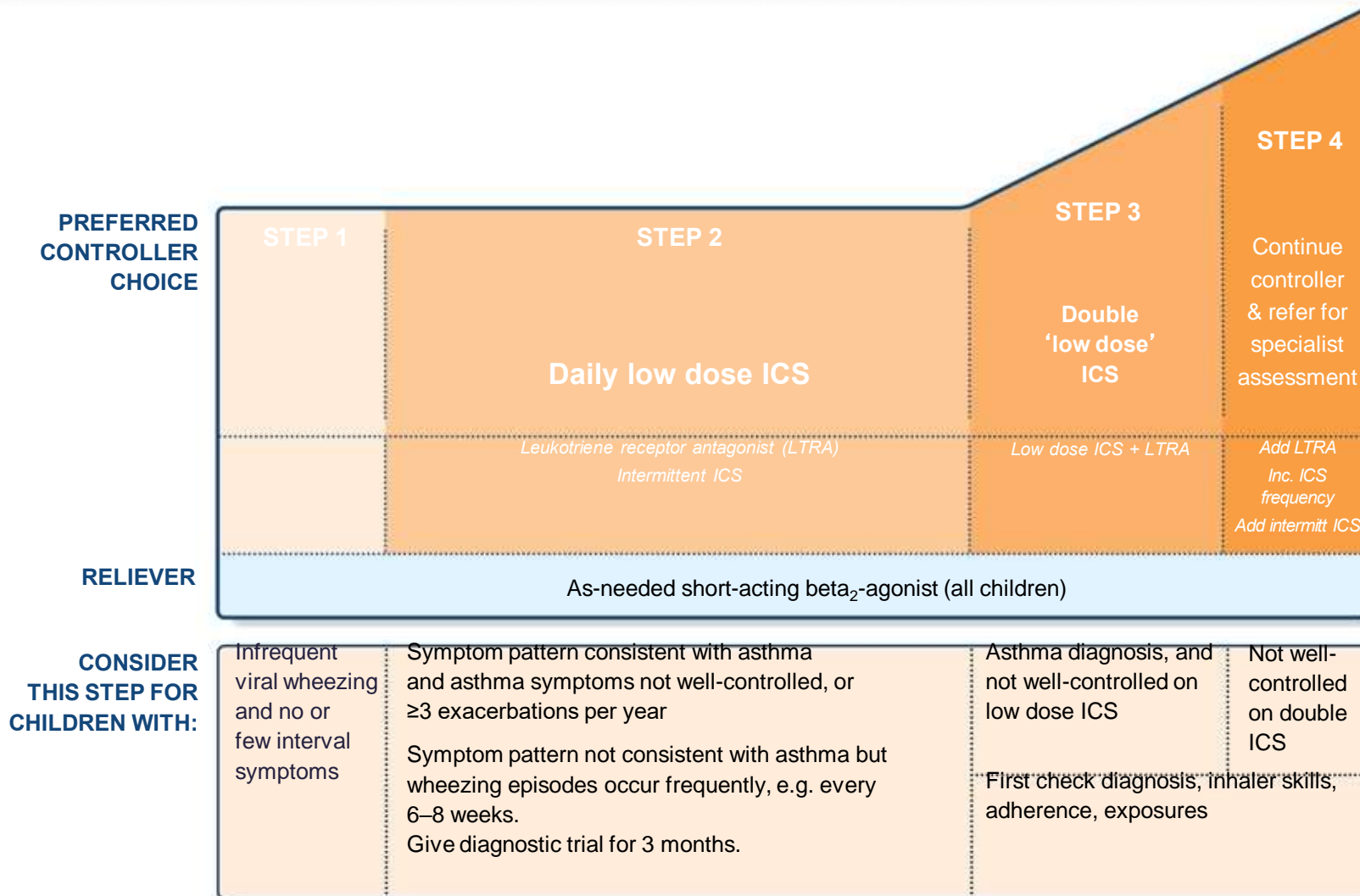
Treat modifiable risk factors



**SUGGESTED INITIAL CONTROLLER TREATMENT IN CHILDREN 6-11 YEARS WITH A DIAGNOSIS OF ASTHMA**



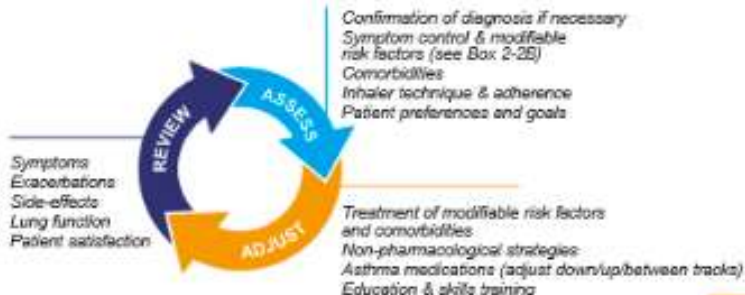
# Stepwise approach – pharmacotherapy (children ≤5 years)



## Adults & adolescents 12+ years

### Personalized asthma management

Assess, Adjust, Review  
for individual patient needs

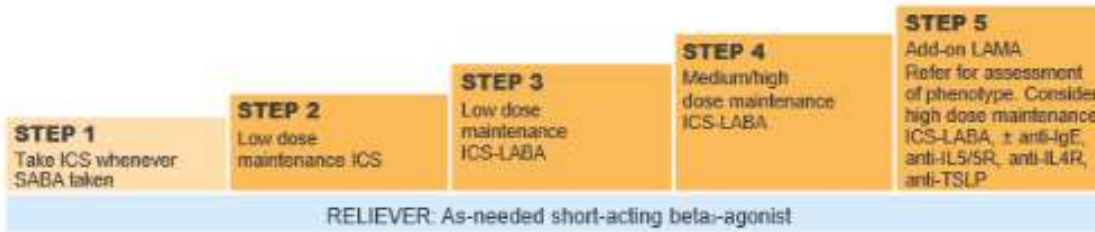


**CONTROLLER and PREFERRED RELIEVER**  
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

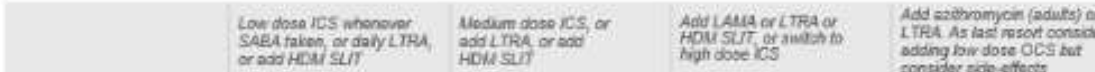


See GINA severe asthma guide

**CONTROLLER and ALTERNATIVE RELIEVER**  
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller



Other controller options for either track (limited indications, or less evidence for efficacy or safety)



- For children with intermittent viral-induced wheeze and no interval symptoms, if as-needed SABA is not sufficient, consider intermittent ICS. Because of the risk of side-effects, this should only be considered if the physician is confident that the treatment will be used appropriately.

# Assessing asthma severity

- How?
  - Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations
- When?
  - Assess asthma severity after patient has been on controller treatment for several months
  - Severity is not static – it may change over months or years, or as different treatments become available
- Categories of asthma severity
  - *Mild asthma*: well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
  - *Moderate asthma*: well-controlled with Step 3 (low-dose ICS/LABA)
  - *Severe asthma*: requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment

# Acute asthma flare up

Starts at home

Asthma management plan

# Acute asthma management

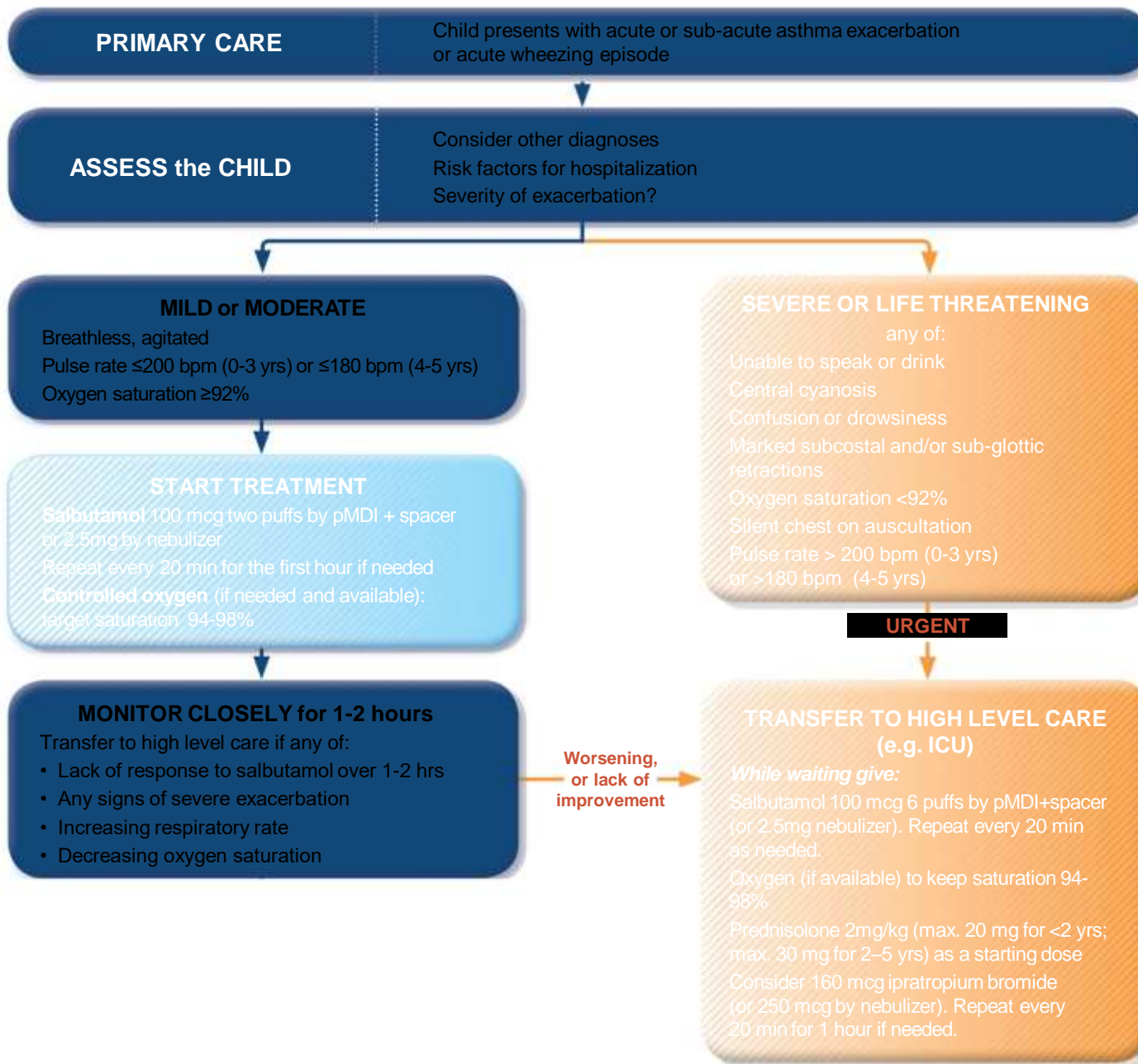
- Inhaled albuterol, continuous, frequent
- Inhaled anticholinergics
- If no improvement consider
  - Subcutaneous terbutaline
  - Theophyllin
  - Magnesium sulphate
  - Heliox
  - Intubation and ventilation
  
- Systemic steroids----- Oral or IV



# Initial management of asthma exacerbations in children $\leq 5$ years



Therapy	Dose and administration
Supplemental oxygen	24% delivered by face mask (usually 1L/min) to maintain oxygen saturation 94-98%
Inhaled SABA	2–6 puffs of salbutamol by spacer, or 2.5mg by nebulizer, every 20 min for first hour, then reassess severity. If symptoms persist or recur, give an additional 2-3 puffs per hour. Admit to hospital if >10 puffs required in 3-4 hours.
Systemic corticosteroids	Give initial dose of oral prednisolone (1-2mg/kg up to maximum of 20mg for children <2 years; 30 mg for 2-5 years)
Additional options in the first hour of treatment	
Ipratropium bromide	For moderate/severe exacerbations, give 2 puffs of ipratropium bromide 80mcg (or 250mcg by nebulizer) every 20 minutes for one hour only
Magnesium sulfate	Consider nebulized isotonic $MgSO_4$ (150mg) 3 doses in first hour for children $\geq 2$ years with severe exacerbation







# Medication delivery devices

- Inhalers
- Nebulizers
  - Both used with mask if under 4 years and mouth piece after that.
  - Always review technique with patient

- Dry powder inhalers

## Multidose dry powder inhalers



Accuhaler®



Turbuhaler®



Genuair®



Easyhaler®



Twisthaler®



Nexthaler®

Thank you!!!!!!