



Pediatric Asthma

Muna Kilani, MD

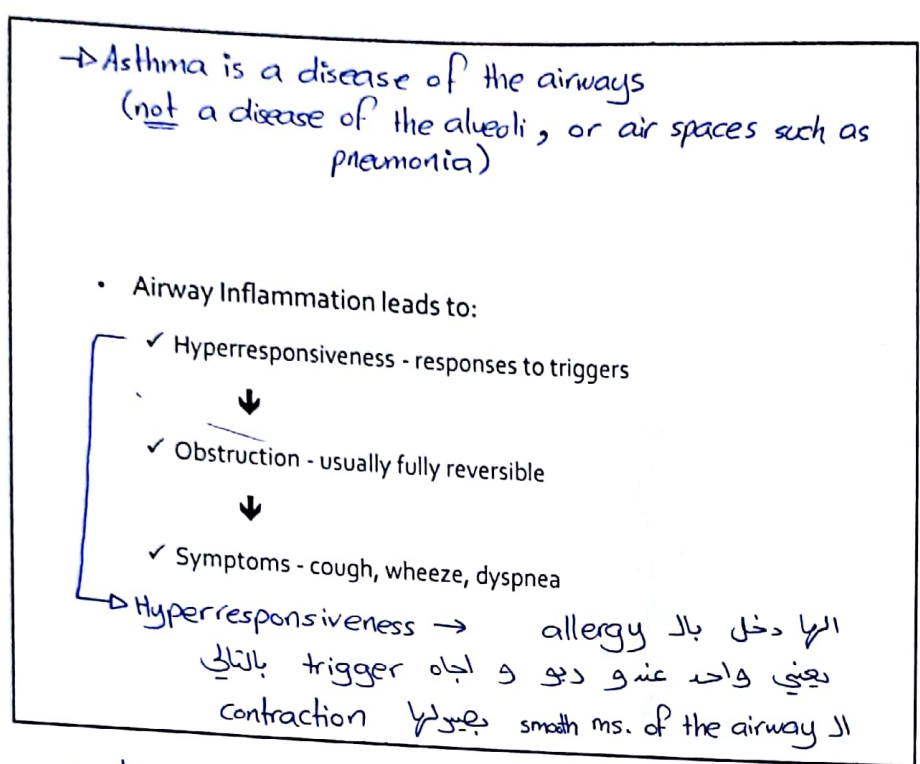
Definition of asthma

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

← بشكل عام كل شيء آدم عن wheezing و recurrent wheezing و signs of airway obstruction و ما عنو أشياء ثانية (ex. CF / infections / ...) asthma مسمى

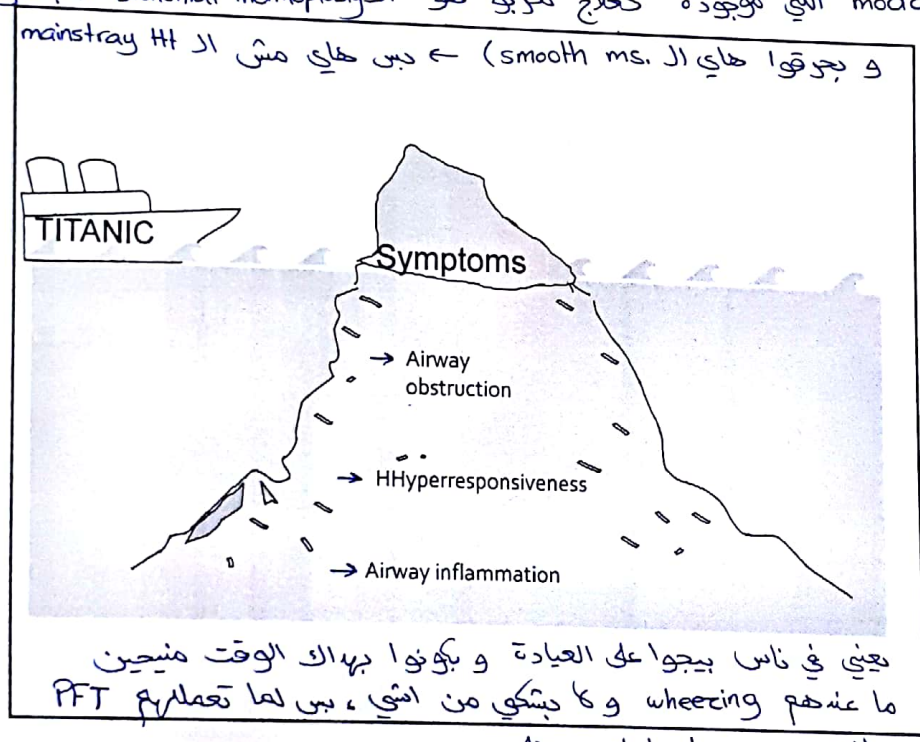
It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

GINA 2016



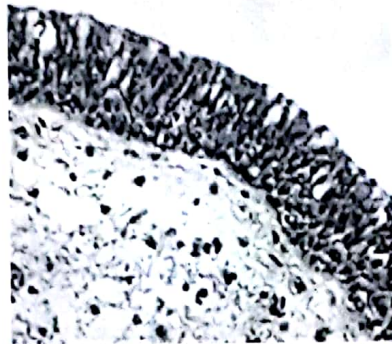
← أما واحد ما عنود ديو ، ما عنود hyperresponsiveness ← يعني ال allergin
و بقل لا muscles زي ما هي ، ما بيشكي

* بال airway في smooth ms. واحدا ما معروف ليس موجودة (ما اليا حال ال fx الريم) ، فوحدة
من ال modalities اللي موجودة كطاج للربو هو ال Bronchial Thermoplasty (بخلوا على ال bronchi

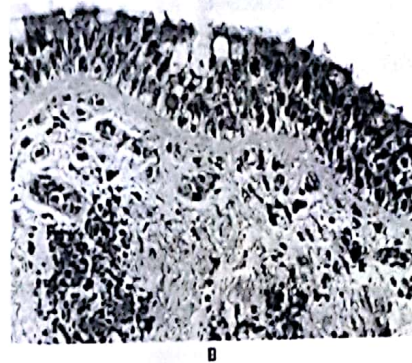


→ In asthma, airway inflammation occurs → leading to thickening of the basement membrane and infiltration of inflammatory cells (neutrophils and lymphocytes)

Normal airway



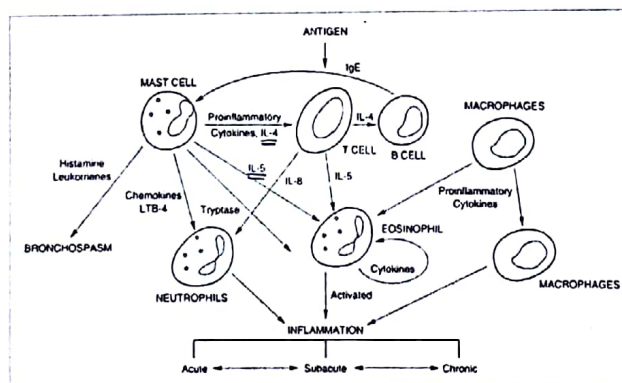
Mild Asthma



Busse et al., N Engl J Med 2001;344(5):350-362

Pathophysiology of 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

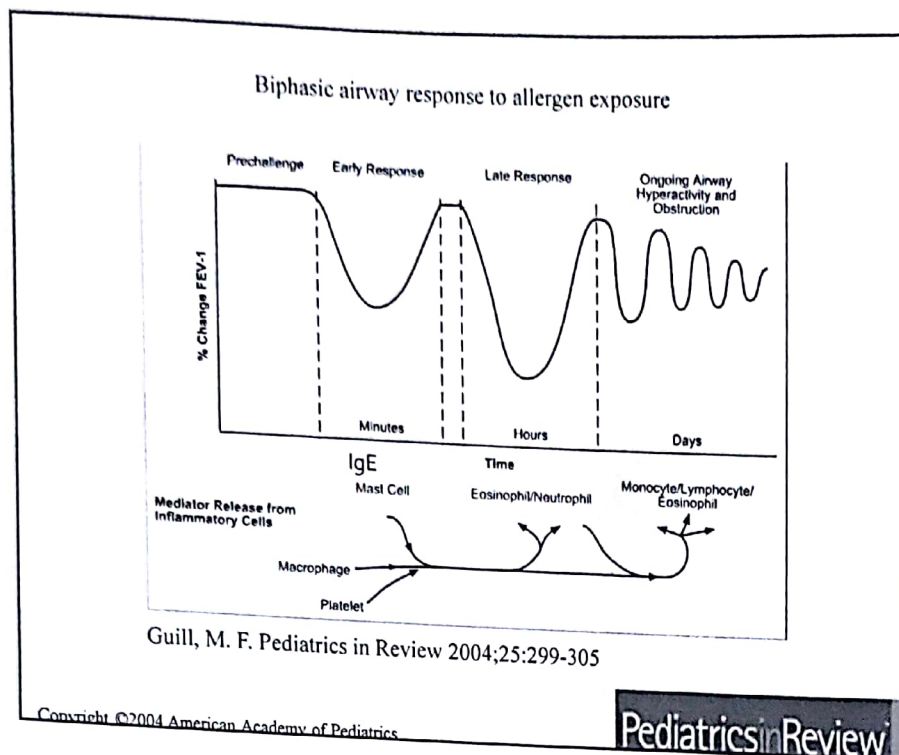
Copyright ©2004 American Academy of Pediatrics

Pediatrics in Review

Important ★

الناس التي يجب ان يكونوا
يعملوا therapies الربو
بسرعة فوا ال cytokines
وال cellular mechanisms
التي تكون involved
له مثلًا صار في

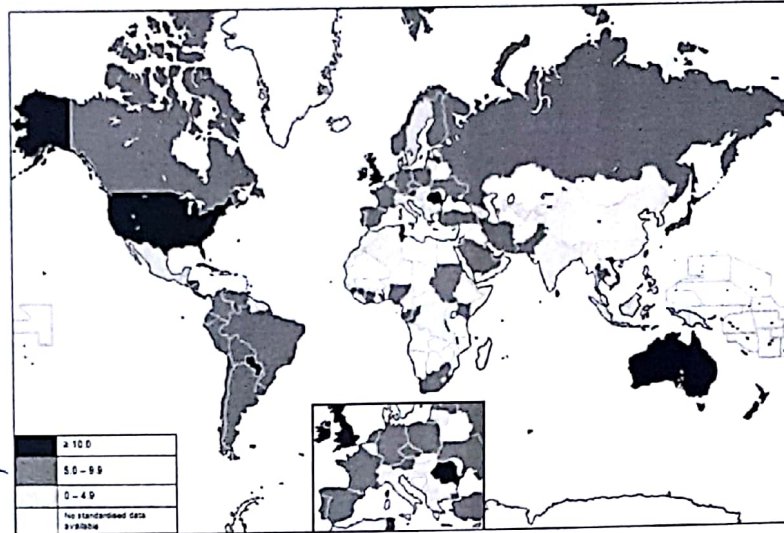
→ Anti - IL 5
→ Anti - Ig E



Burden of disease

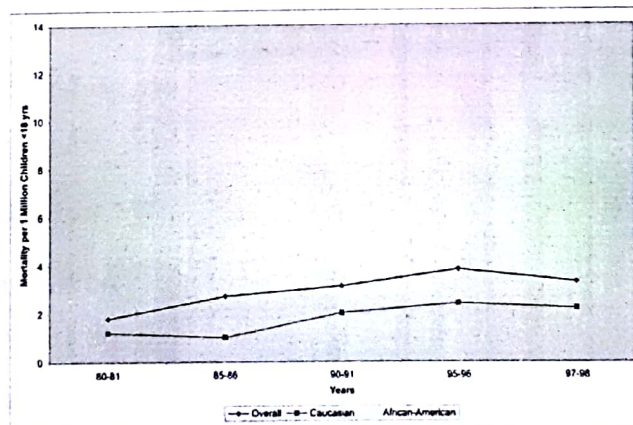
- #1 chronic illness in childhood
- #1 chronic illness causing school absence
- 78% of parents report a negative impact on family

Prevalence of asthma in children aged 13-14 years



GINA 2016 Appendix Box A1-1: figure provided by Global Initiative for Asthma

الفكرة من حالي السلايه انه نفوق انه في mortality من الحزمة (مش كيتي بي موجودة) Asthma mortality from 1980 to 1998



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

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Pediatrics in Review

Important

★ Natural History & Prognosis

- Remains incompletely understood
- Most children do not ultimately "grow out of it"
 - However they might get better w/ age
 - "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

To know what's going on and to further understand the natural Hx of the disease we need longitudinal studies →

Asthma and Wheezing from 7 to 42 Years Melbourne Study

اللي موجودين بالعالم
عن الربو
مش كتار

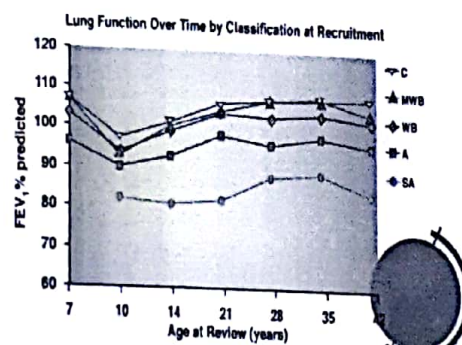


FIG 8. FEV₁ percent predicted at ages 7, 10, 14, 21, 28, 35, and 42 years in subjects in their recruitment groups. C, Control; MMB, mild/moderate bronchitis; WB, wheezing bronchitis; A, asthma; SA, severe asthma.

Phelan et al JACI 2002 109:189-196

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

Martinez et al. N Engl J Med 332:133-8, 1995.

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: ≥ 1 lung illness with wheezing before age 3

(+) Age 6: ≥ 1 wheezing episode during the year before age 6

Martinez et al. N Engl J Med 332:133-8, 1995.

هدول على عمر
ال ٣ سنين كانوا
wheezers
و على عمر ال ٦
بطلوا

True asthma

لبثوا wheezing
من هم صفار
و ضلوا على كبر

ما كانوا wheezers
و هم صفار ...
ببي صاروا لما
كبروا

* فالناس اللي يكون عندهم wheezing تحت ال ٣ سنوات
مش شرط يكون عندهم asthma

Asthma and Wheezing in the First Six Years

Categories of wheezing: Risk factors

Transient (+)Age 3, (-)Age 6	Persistent (+)Age 3, (+)Age 6	Late (-)Age 3, (+)Age 6
<ul style="list-style-type: none"> • Lung function LOW soon after birth • Maternal smoking during pregnancy 	<ul style="list-style-type: none"> ■ Atopy ■ Elevated IgE ■ Maternal smoking during pregnancy ■ Male gender 	<ul style="list-style-type: none"> ■ Atopy ■ Male gender

Martinez et al. N Engl J Med 332:133-8, 1995.

ما حكت عن
طواد السلاخ

Asthma and Wheezing in the First Six Years

Categories of wheezing: Transient

Transient: (+)Wheeze <3 y.o.; (-) Wheeze at 6 y.o.

- Lung function low after birth: "congenitally smaller airways"
- With smaller airways from birth, these children may be predisposed to wheeze during viral respiratory infections
- Wheezing was no longer present -- after sufficient lung growth had occurred -- by age 6 years

Martinez et al. N Engl J Med 332:133-8, 1995.

ما حكت عن
طواد السلاخ

Asthma and Wheezing in the First Six Years

Significance of wheezing at age 3

- 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
- Significant deterioration in lung function by age 6

Martinez et al. N Engl J Med 332:133-8, 1995.

حول بغير عدوى
viral infx
فيمكن نسمع
wheezing

حول ما يكون
asthma

rhinitis/Eczema/
skin testing to allergen

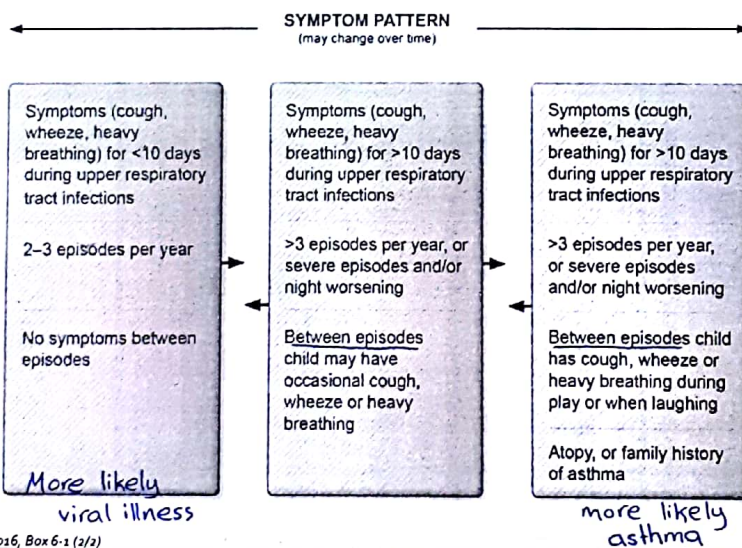
Can be tested or
evaluated by using
methacholine
(which cause smooth
ms. contraction
and obstruction)
OR by using
Salbutamol/Albuterol

و بنفوسا اذا صار
في قوسع بال
lung fx و تحسن ال

→ Probability of asthma diagnosis or response to asthma
Ht in children ≤ 5 years

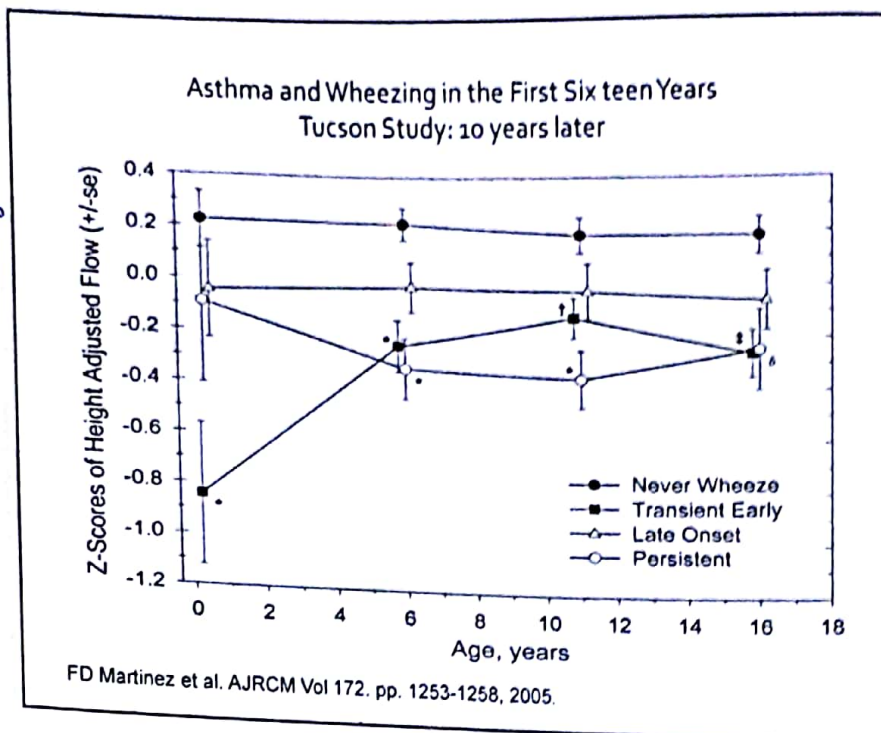
Symptom patterns in children ≤ 5 years

*** Important**



هائي الأشياء
منشأ عنها
بالرستوري

ما حكت عن
طلة السلاية



★ Important

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

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, wheezing without URI, or eosinophils $>4\%$ in peripheral bld.

Castro-Rodriguez JA. The Asthma Predictive Index: early diagnosis of asthma. Curr Opin Allergy Clin Immunol. 2011;11(3):157-161

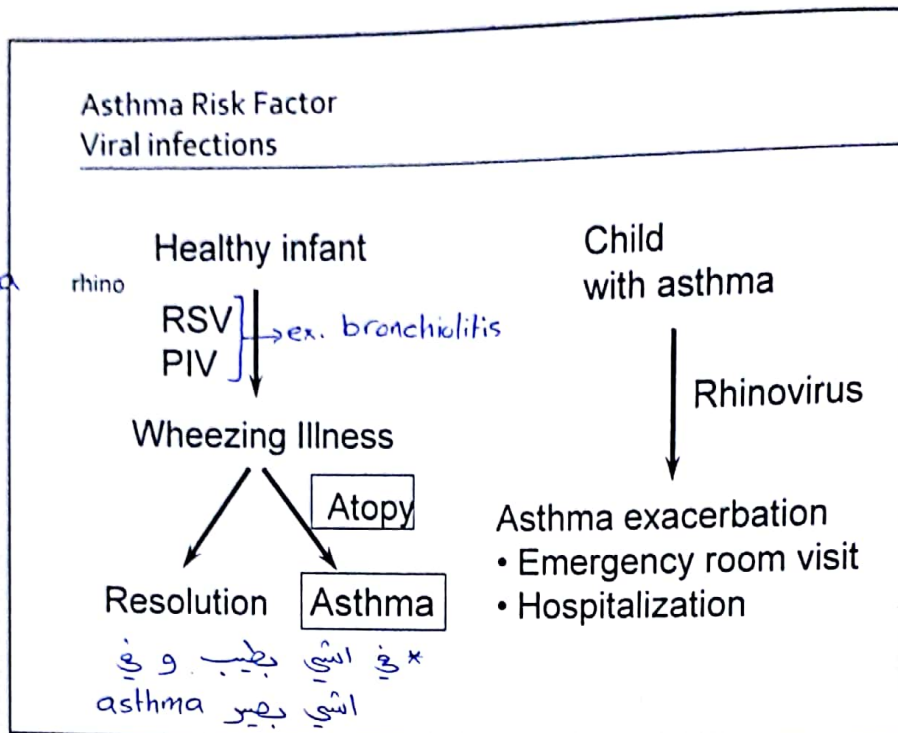
40% of asthma pts as adults started wheezing before 1 year of age

Risk factors

← هاي من سلايد
ضايقته مش
موجود هون
(بى هاد اللي
كان مكتوب فيه)

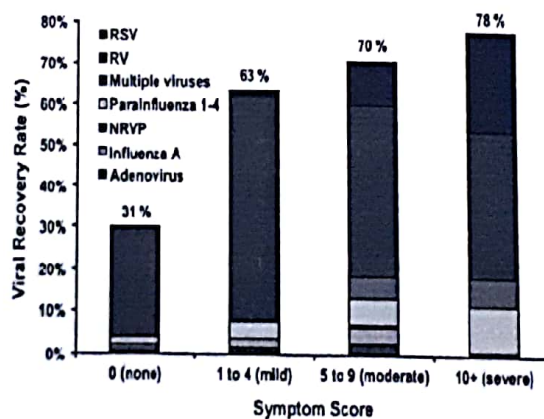
Viral infections are both a
→ Risk factor for developing asthma later in life
→ and a trigger for an asthma flare up

- RSV → respiratory syncytial virus
- PIV → Para influenza virus



* Note: Viral inf_x is the most common trigger for asthma

Impact of Viral LRIs Before Age 3 Years



Lemanske et al JACI 116(3):571-577 2005

Asthma Risk Factor

Atopy

- 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.
- FAMILY HISTORY

symptoms or manifestations of atopy

Asthma Risk Factor

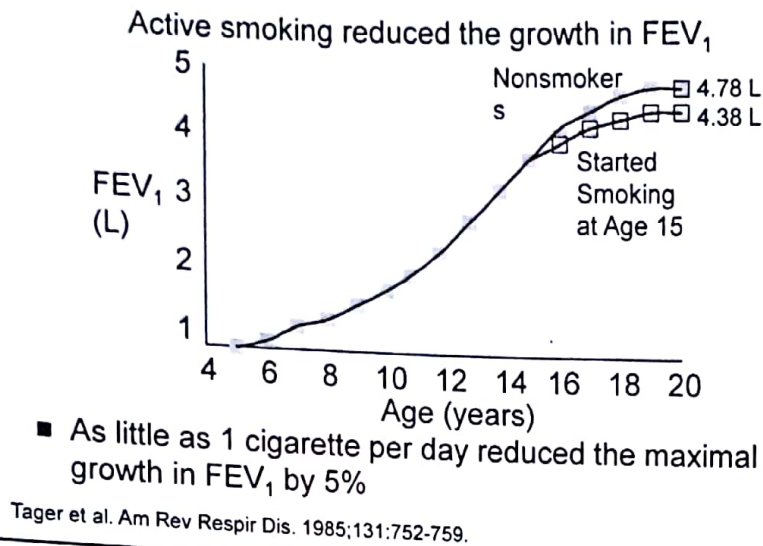
Male gender

- In general,
 - Female lungs are smaller than male lungs
 - Female airways are smaller than male airways
- However, relative to lung size, male airways are smaller than female airways
 - This may explain the greater incidence of asthma in boys than in girls
 - It is certainly clear from epidemiology that asthma is more common in boys than in girls

ما انشئ عن حاد السلايد

Asthma Risk Factor

Cigarette smoking in early adolescence



Asthma risk factors

There is a genetic component
بني ما منتوف بالورب
شو هو.

- A positive family history of asthma
- Maternal history of asthma had a stronger association with developing asthma than paternal history
فأول اشي دبسال إذا الام عندها أزمة
و بعدين دبسال عن الأب.
- 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

Presentations of Wheezing

- The most common cause of wheezing in young children is viral respiratory infection

BUT

- The strongest *predictor* for wheezing that develops into asthma is ATOPY
 - About 70–90% of children with asthma are atopic (i.e., positive skin tests)

#

Making the diagnosis: History

Symptoms

- ✓ Cough, wheeze, dyspnea
- ✓ Nocturnal awakenings

طبي حرقه ... بعض
بالليل متى عارف
يتنفس

Frequency & Severity

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

Medication Usage

→ ex. salbutamol / Albuterol

Short-acting beta-agonist use

Family History

- ✓ Allergy / Atopy
- ✓ Asthma

Precipitating / Aggravating Factors Asthma Triggers

* food allergy
rarely causes
an asthma attack

→ examples on
allergins:

- Cats are a
strong allergin

- Pollen

- ~~Moss~~ mold

- Grass

* Dust and

Smoke are
irritants not
allergins

■ Viral upper respiratory
infections

→ Causing bronchospasm

■ Allergen exposure

→ The passage of air causes friction of the airway

■ Exercise, hyperventilation

■ Irritants (especially smoke)

→ Dust is also an allergin

■ Weather

■ Strong emotion (rare)

■ Gastroesophageal

reflux???

Very cold air
can cause
bronchospasm

Hot air causes
inflammation

Change in the

weather or in
the pressure
can also be a
trigger

→ Can cause bronchospasm and trigger wheezing

← برأي الحالة، معالج ال GER
فيحسن المريض

(مثلا كان يمكن حامي و دخل
على مكان سخن ...)

Making the diagnosis: Exam

(Physical exam)

- 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

* Not every wheeze is asthma
But every wheeze is narrowing of the
airways

* Important

- Differential diagnosis of wheezing
 - Bronchiolitis
 - Cystic Fibrosis
 - Foreign body
 - Anatomical lesions like vascular rings, mediastinal cysts
 - GERD, aspiration
 - Heart failure
 - ↳ How?! via pulmonary edema.

Making the diagnosis: 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

Challenges in Treating Childhood Asthma

Assessing airway function

For Dx

Spirometry: Pulmonary function test

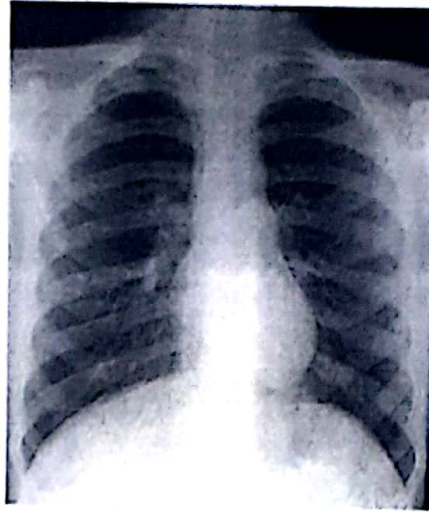
An FEV₁ response of $\geq 12\%$ post-bronchodilator is suggestive of asthma

BUT,

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

Diagnosis

- X rays



When?

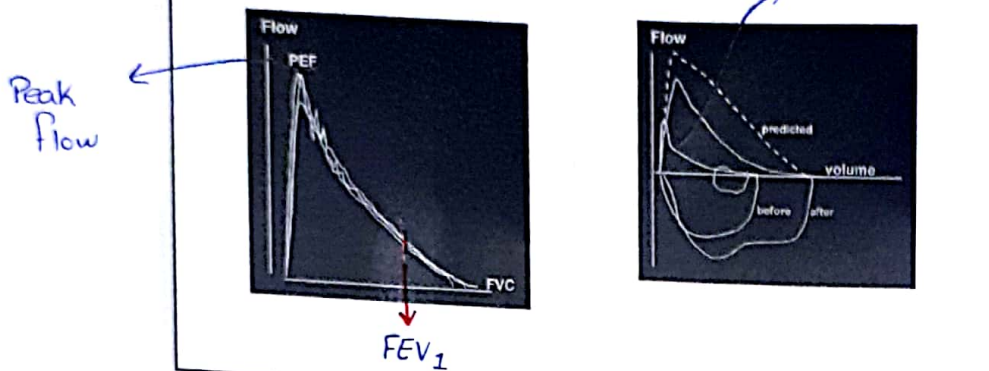
- May be normal
- May show hyperinflammation hyperinflation (but this is not diagnostic)

- First time wheezing
- Fever (to rule out pneumonia)
- Unilateral Wheezing
- Severe symptoms (ex. if pt enters ICU)

How often? Diagnosis

- Pulmonary function testing.

– Flow volume curves



When doing spirometry we usually use a

- short acting β agonist such as salbutamol

← بي إذا واحد علىه spirometry وطلع فورمال ولسانك

شاكك ← بيقطيه واحد من الأشياء اللي بالنقطة الأول و بيقع ال spirometry

Diagnosis Assessing airway function

- Metholine/ Histamine/Exercise challenge test.
- Sputum eosinophils. → to assess inflammation in the airway
- Exhaled NO.
- Allergy testing.
- Infant lung testing.

→ These cause more contraction (constriction of the smooth ms)

Peak flow??

↳ Next slide

- It is effort dependent
* However FEV_1 is NOT effort dependent
- Peak Flows
 - Not routinely indicated
 - Used in moderate and severe asthma
(in teenagers or adults who can do this test)

Management

Management of asthma

- Long term goals How important ?
 - 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.

سأله فاسية
ما تفتي عليه س. س.

Treatmen of asthma

- Bronchodilators - β agonist * Important SABA (Salbutamol / Albutarol)
 - 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

طارد السعال
أو
أدوية

Medications

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

Medications

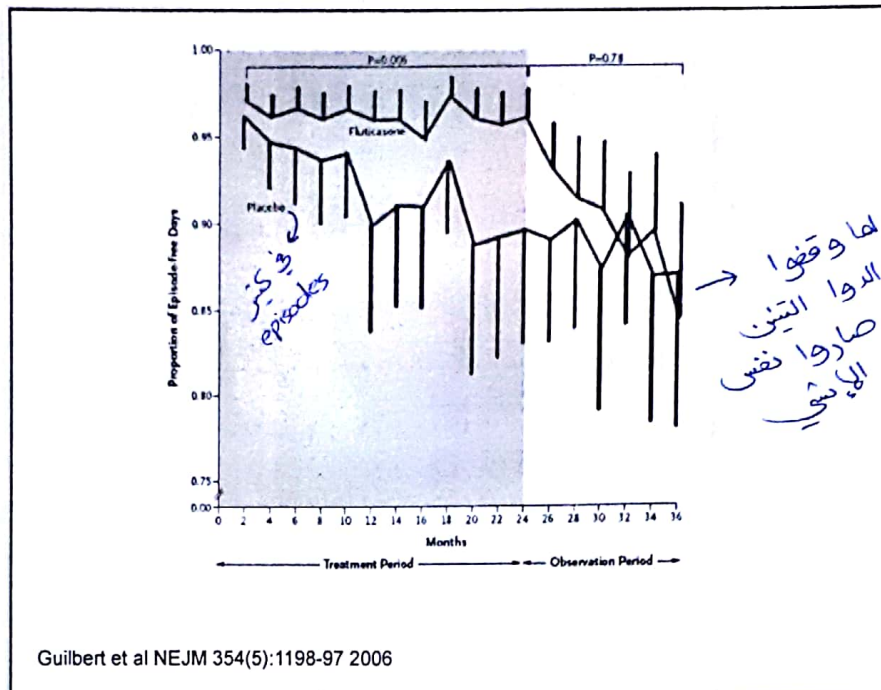
- Anticholinergic agents: (Atrovent)
 - Blocks the postganglionic efferent vagal pathways leading to bronchodilation.
 - Additive effect to B₂ agonist in an acute asthma attack.
 - Effective in acute asthma management, use in first 24 hours decreased rate of hospital admission.

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
 - Inhaled or nebulized

Medication

- Side effects:
 - Suppression of hypothalamic-pituitary axis, rarely doses below 800mcg.
 - Decrease in height. (CAMP study). → بنقصوا في سم أو سم (مضاد حيوي معوز)
 - 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. → ما يذبط بالطوارئ
 - Side effects: reduced growth, Hypothalamic pituitary axis suppression, hypertension, cataract...

Treatment of asthma

- Long acting β agonist LABA
 - Salmeterol—up to 12 hours
 - Formoterol—observed in most patients to last up to 12 hours
 - Are steroid sparing
 - Black box warning
 - ↳ They may cause death because of overstimulation of the heart

اول ما يوضحوا
جسوا انهم
حسنوا فوراً

LABA Labeling 2006

WARNING: Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including FORADIL AEROLIZER. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta₂-adrenergic agonist), the active ingredient in FORADIL AEROLIZER (see WARNINGS).

#

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

← استجابة الناس للدواء يختلف حسب الشخص

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
- Nedocromil 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

← الى دور بجلالات
الحد من acute asthma attacks

New and Emerging Therapies Being Evaluated for Asthma.

Therapy	Target	Reference or ClinicalTrials.gov Number
Anticholinergic agents	Acetylcholine receptor	Kerstjens ⁸
Chemokine receptor antagonists	CXCR2, CCR3	Nair, ⁹ NCT01180224
	CCR3 (antisense)	NCT00822861
Cytokine mediators	Interleukin-4 receptor α	Wenzel, ¹⁰ NCT00801853
	Interleukin-5	Pavord, ¹¹ Nair, ¹² Haldar, ¹³ Castro, ¹⁴ NCT01691508, NCT01285123
	Interleukin-5 receptor	NCT00659659
	Interleukin-13	Corren, ¹⁵ Piper, ¹⁶ NCT01345440, NCT01402986
Leukotriene inhibitors	5-Lipoxygenase activating protein	NCT01471665
	Leukotriene A ₂ hydrolase	NCT01241422
Mast-cell inhibitors	Tyrosine kinase	Humbert, ¹⁷ NCT01449162, NCT01097694
Once-daily beta agonists and inhaled glucocorticoids	B ₂ adrenergic receptor and multiple targets	Busse, ¹⁸ NCT01686633, NCT00556673
Prostaglandin D ₂ receptor antagonists	CRTH2	Busse, ¹⁹ Barnes, ²⁰ NCT01545726, NCT01561690, NCT01197794
Toll-like receptor agonists	Toll-like receptor 9	Beeh, ²¹ NCT01673672

* This list is not exhaustive but represents a sample of therapies being investigated for asthma. CCR3 denotes chemokine (C-C motif) receptor 3, CRTH2 chemoattractant receptor expressed on type 2 helper T cells, and CXCR2 chemokine (C-X-C motif) receptor 2.

Wechsler ME. N Engl J Med 2013;368:2511-2513.

Treating asthma to control symptoms and minimize risk

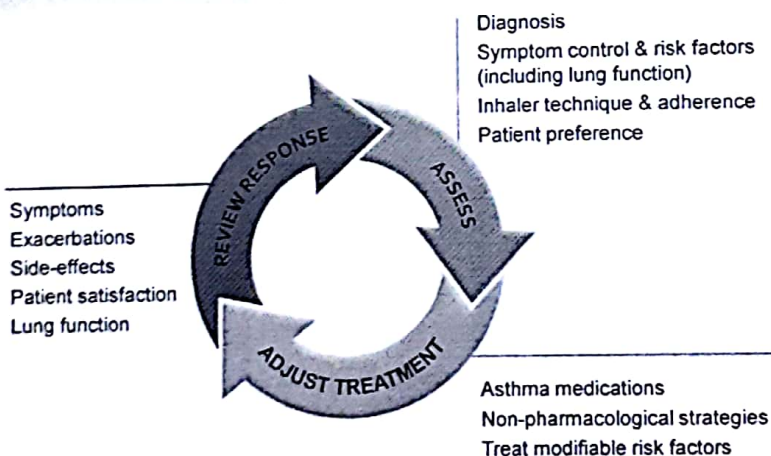
GINA Global Strategy for
Asthma management and
Prevention 2016

Assessing asthma severity (mild/mod/severe)

- 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

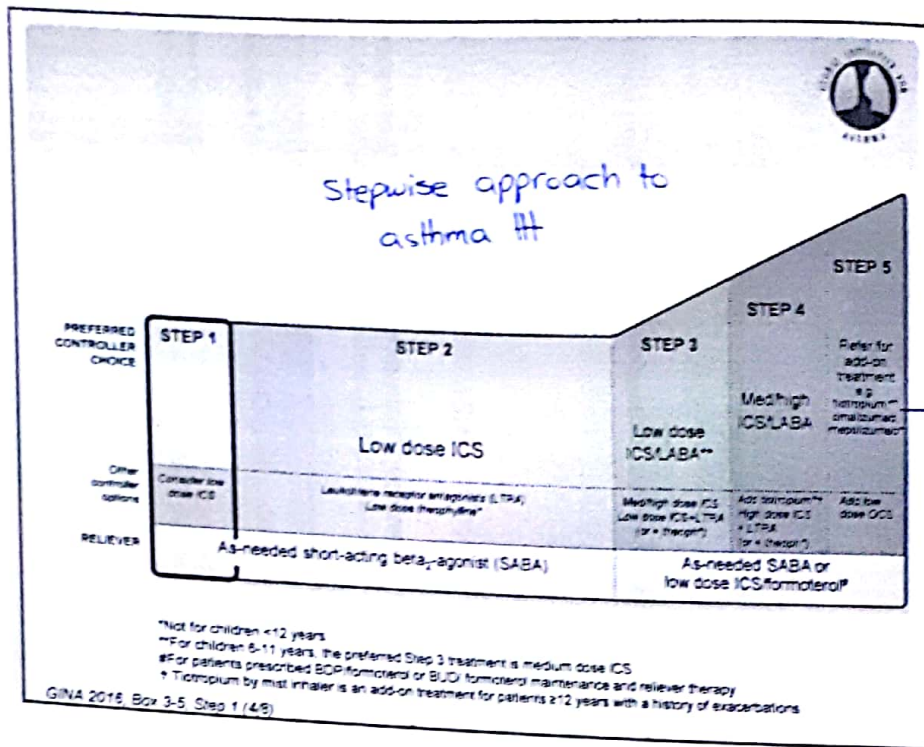
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The control-based asthma management cycle



GINA 2016, Box 3-2

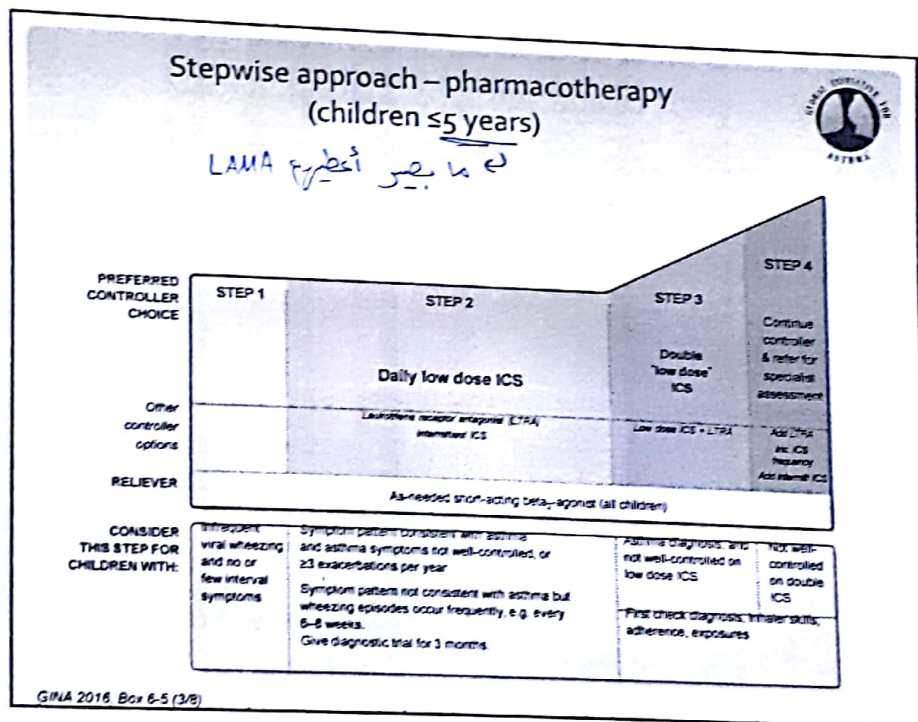
#



مدون
السلاسل
من

حققة

→ LAMA
بشكل عام
مدون مستخدم
للحبار (الصغار)
ما مستخدم
كثير



الأطفال التي أقل من ٣ سنين التي يكون شكاة فيهم
(يجروا)

✱ Important

- 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.

GINA 2016

✱ Important

Risk factors for poor asthma outcomes in children ≤ 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

GINA 2016 Box 6-4B (3/3)

GINA assessment of asthma control in children ≤ 5 years

A. Symptom control

In the past 4 weeks, has the child had:		Level of asthma symptom control		
		Well-controlled	Partly controlled	Uncontrolled
1. Daytime asthma symptoms for more than few minutes, more than once/week?	Yes <input type="checkbox"/> No <input type="checkbox"/>	None of these	1-2 of these	3-4 of these
2. Any activity limitation due to asthma? (runs/plays less than other children, tires easily during walks/playing)	Yes <input type="checkbox"/> No <input type="checkbox"/>			
3. Reliever needed* more than once a week?	Yes <input type="checkbox"/> No <input type="checkbox"/>			
4. Any night waking or night coughing due to asthma?	Yes <input type="checkbox"/> No <input type="checkbox"/>			

GINA 2016 Box E-1A

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 \pm add-on), or remains uncontrolled despite this treatment

GINA 2016

Very Very Important

Acute asthma flare up

Starts at home

Asthma management plan

Acute asthma management

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

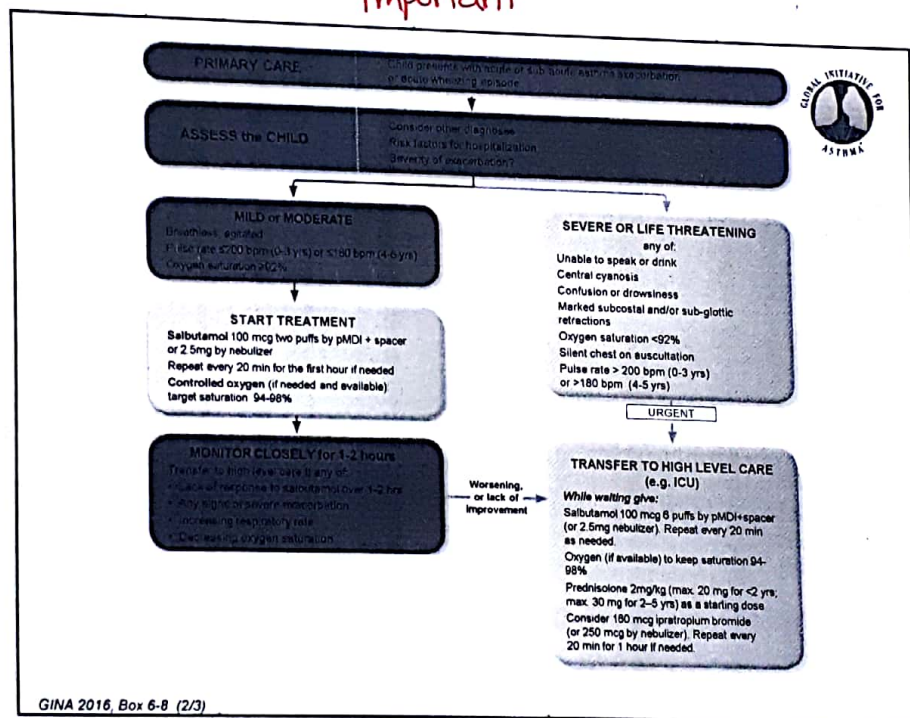
*** Important**

Initial management of asthma exacerbations in children ≤ 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 ≥ 2 years with severe exacerbation

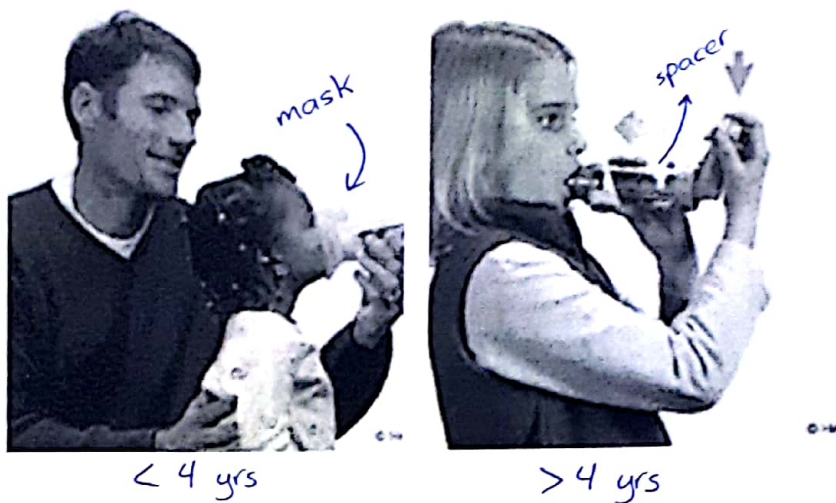
GINA 2016, Box 6-11 (2/2)

Important



GINA 2016, Box 6-8 (2/3)

Inhalers



Nebulizer



Medication delivery devices

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

* كالت - حبة جود ع
Dry powder inhalers ج

Thank you!!!!!!