

Differential Diagnosis of Severe Asthma in Children

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TEACHING HOSPITAL

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Disclosure of Potential Conflict of Interest

I have the following relations to disclose:

Entity: UpToDate Role: Author Received: Royalty





Children's Hospital started in downtown Boston (1869) and relocated to Longwood Avenue, adjacent to the Medical School, in 1914.

Pediatric Asthma is the Most Common Chronic Respiratory Disease in the Developed World

- The highest prevalence found in the US, the UK and Australia ¹
 - The increasing prevalence previously reported appears to have plateaued or even declined
- In resource poor countries, asthma prevalence is generally increasing ² and both severity and mortality are higher ^{3,4}

1. Asher MI, et al. ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368:733-743
2. *CHEST* 2006; 130:4S-12S
3. *Lancet* 2006; 368: 733-43
4. WHO mortality database 2014 update

Asthma in Children in the US

- 4.2 million children (5.8%) currently have asthma
 - 12.3 % of African American children and 5.5 % of white children in the United States ¹
- The majority of children with asthma have mild or moderate disease
 - Small proportion (2-5%) have severe asthma
- Almost half (43%) have at least one exacerbation per year

1. Pediatric Annals • Vol. 48, No. 3, 2019

2. www.cdc.gov/asthma/most_recent_national_asthma_data.htm

Asthma in Children

- Asthma exacerbations are the number one reason for admission to children's hospitals outside the neonatal period
- Mortality from asthma, although decreasing, still occurs.
 - **204** in US (most recent data from CDC)
- Asthma care costs in the US are estimated to be \$81.9 billion per year

Asthma

- The diagnosis of asthma in children is clinical. It is based on recognising a characteristic pattern of episodic symptoms in the absence of an alternative explanation.
- Symptoms are caused by inflammation resulting in narrowing of small airways and may include:
 - wheezing
 - cough
 - difficulty breathing
 - chest tightness
- Supporting evidence includes a family history of atopy, parental asthma, a personal history of eczema, seasonal rhinitis, or food allergy.
- Response to albuterol or a short course of oral steroids is suggestive of asthma.

Severe Asthma in Children:

2007 NHLBI Guidelines for the Diagnosis and Treatment of Asthma

- Asthma severity is the intrinsic intensity of the disease process
- Based on the most severe impairment or risk category in which any feature occurs
 - Impairment domain assessed by patient's recall of previous 2–4 weeks and/or by spirometry

Case Study: 9-Year-Old Boy with Asthma

- Coughs every day
- His mother hears him cough and wake up every night
- Uses albuterol at least twice per day and sometimes more often.
- He can no longer play soccer because he gets so out of breath.
- His FEV_1 was 58% and FEV_1/FVC was 74 before treatment with albuterol.

What is the severity of his asthma?

Components of Severity		Classification of Asthma Severity → (5–11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	<ul style="list-style-type: none"> • Normal FEV₁ between exacerbations • FEV₁ >80% predicted • FEV₁/FVC >85% 	<ul style="list-style-type: none"> • FEV₁ = >80% predicted • FEV₁/FVC >80% 	<ul style="list-style-type: none"> • FEV₁ = 60–80% predicted • FEV₁/FVC = 75–80% 	<ul style="list-style-type: none"> • FEV₁ <60% predicted • FEV₁/FVC <75%

- 9 year old boy with asthma coughs every day
- Coughs a wakes up every night
- Uses albuterol at least twice per day and sometimes more often.
- He can no longer play soccer because he gets so out of breath.
- His FEV₁ was 58% and FEV₁/FVC was 74 before treatment with albuterol.

What is the Severity of his Asthma?

The EPR 3 Guidelines on Asthma

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- Based on the most severe impairment category in which any feature occurs he has severe asthma

Determinants of Severe Asthma

- burden of symptoms
- frequency of the use of quick relief medication
- spirometry
- **the intensity of treatment required to maintain asthma control**

2020 FOCUSED UPDATES TO THE Asthma Management Guidelines

AGES 5-11 YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	Intermittent Asthma		Management of Persistent Asthma in Individuals Ages 5-11 Years			
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol [▲]	Daily and PRN combination medium-dose ICS-formoterol [▲]	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS + Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA
		Steps 2-4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy [▲]			Consider Omalizumab ^{**▲}	

Steps 5-6 are severe

GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION

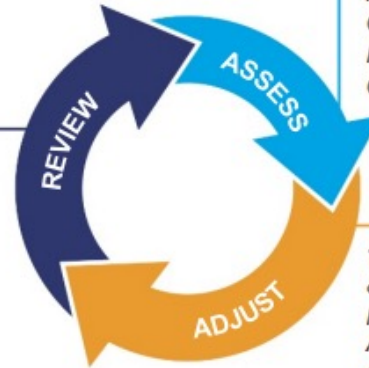
Updated 2021

Children 6-11 years

Personalized asthma management:

Assess, Adjust, Review

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training



Asthma medication options:

Adjust treatment up and down for individual child's needs

PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

RELIEVER

	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 (MART)	STEP 4 Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	STEP 5 Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE
	Consider daily low dose ICS	Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken	Low dose ICS + LTRA	Add tiotropium or add LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side-effects
	As-needed short-acting beta2-agonist (or ICS-formoterol reliever for MART as above)				

*Very low dose: BUD-FORM 100/6 mcg
†Low dose: BUD-FORM 200/6 mcg (metered doses).

-Severe asthma is asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled.

-Severity no longer references GINA steps.

Severe Asthma in Children

- The majority of children with asthma have mild or moderate disease
- A small proportion, approximately 2-5%, are considered to have severe asthma
- Those with severe asthma have chronic symptoms or recurrent exacerbations despite maximum treatment

When asthma is not well controlled: Is it severe?

-paraphrasing Prof Andrew Bush and colleagues

The most important part of managing asthma in children is, and will remain for the foreseeable future, getting the basics right.

1. Prof Andrew Bush, MD and Sejal Saglani, MD
Imperial School of Medicine, National Heart and Lung
Institute, Royal Brompton Hospital, London, UK
Lancet. 2010 September 4; 376(9743): 814–825.
2. Respirology (2017) 22, 886–897

When asthma is not well controlled: Is it severe?

-model developed by Prof Andrew Bush and colleagues

- **Not asthma**
 - exclude an alternative diagnosis

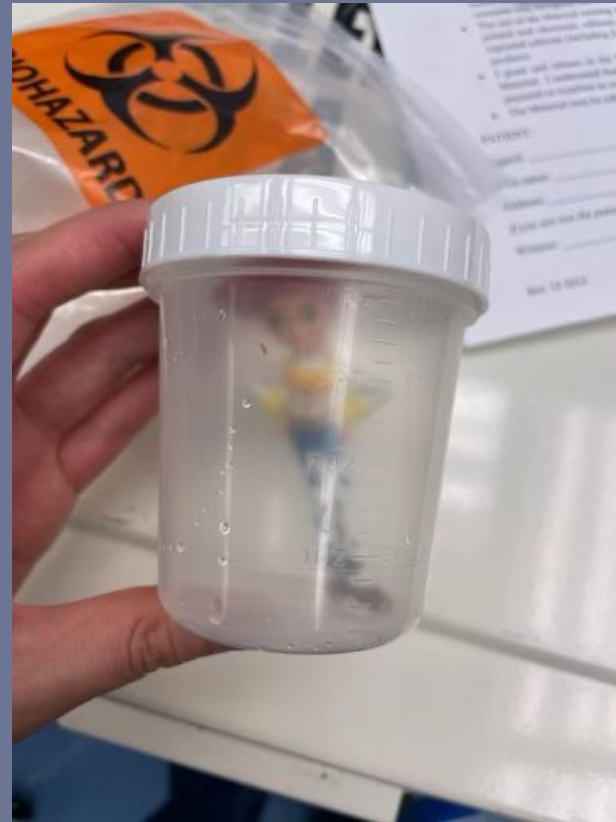
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Case 2: Acute onset of respiratory distress with wheezing

- 3 year old developed respiratory distress and audible wheezing while bouncing on their backyard trampoline
 - No recent respiratory illness
 - Has never been diagnosed with asthma
 - Family history of seasonal allergies but no asthma
-
- Parents called 911

Case 2: Acute onset of respiratory distress with wheezing

- Upon arrival in the ED he was in respiratory distress with audible wheezing
- A lateral neck X-ray was ordered



Not all
wheezing is
asthma

Do not jump
on a
trampoline
with Jessie
in your
mouth

Foreign Body Aspiration in Children

- 305,814 nonfatal injuries due to choking in children from 0 to 19 years of age in the United States ¹
 - 73 % of nonfatal injuries and 75 % of choking fatalities occur in children under five years of age
- In 2020, there were 118 deaths due to suffocation in the one- to four-year-old age group, and 21 of these (18 %) were due to FBA.
- Predisposing factors to FBA in this age group include access to improper foods or small objects, activity while eating, and older siblings (who may place food or objects into the mouths of infants or toddlers).
- The presence of wheezing does not always mean that the patient has asthma, and a proper history and physical exam are required to make the diagnosis.²

1. <https://wisqars.cdc.gov/fatal-leading> (Accessed on March 3, 2023)

2. <https://www.ncbi.nlm.nih.gov/books/NBK482454>

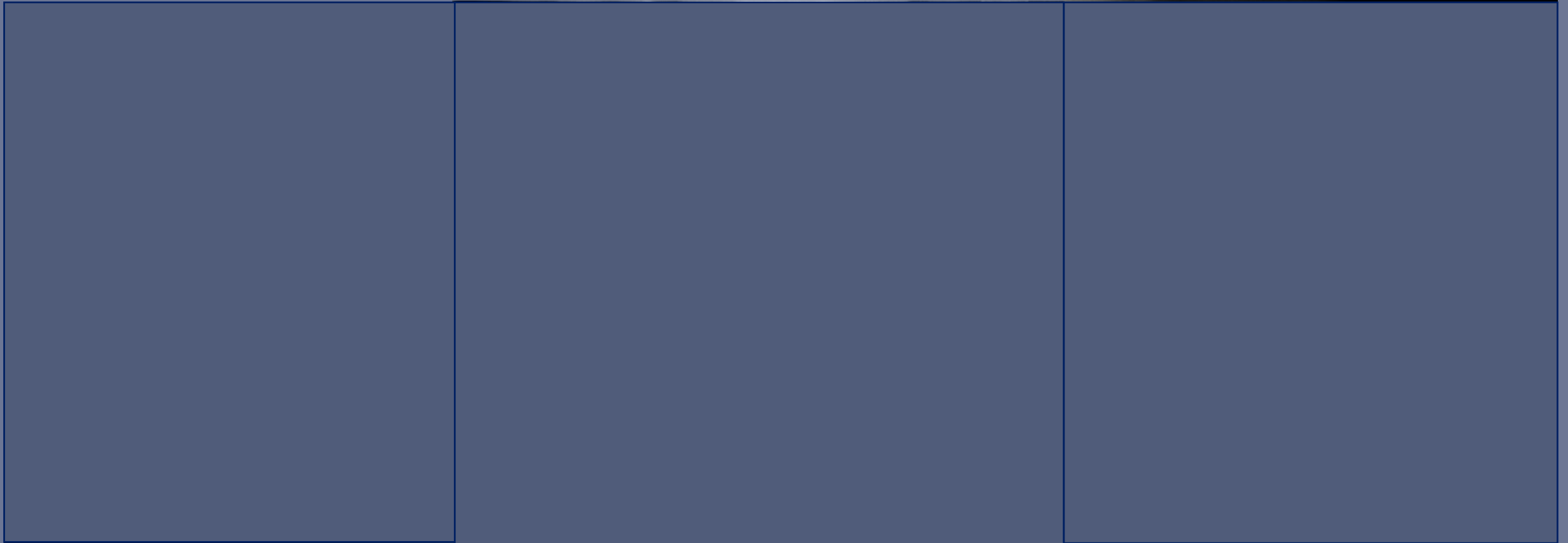
Case 3: 19 month old with cough and wheezing

- Referred because her family was concerned that she has been coughing off and on for more than three months
- The coughing is worse when she is running around
- Birth history: She was born full-term and had an uneventful perinatal course
- Family history: Maternal grandmother has asthma
- Wheezing has noted on examination by her pediatrician
- Treatment with nebulized albuterol provided a few hours of relief from coughing but it would then return
- She was prescribed prednisolone which led to reduction, but not resolution, of daily coughing

Case 3: 19 month old with cough and wheezing

- Presents to ED with increased work of breathing
 - No fever
 - Oxygen saturation 88% in RA
 - Chest exam: No flaring/grunting/retractions. Rhonchi in all lung fields but good air movement throughout, no wheezes.
- Tests (+) for RSV
- CXR ordered

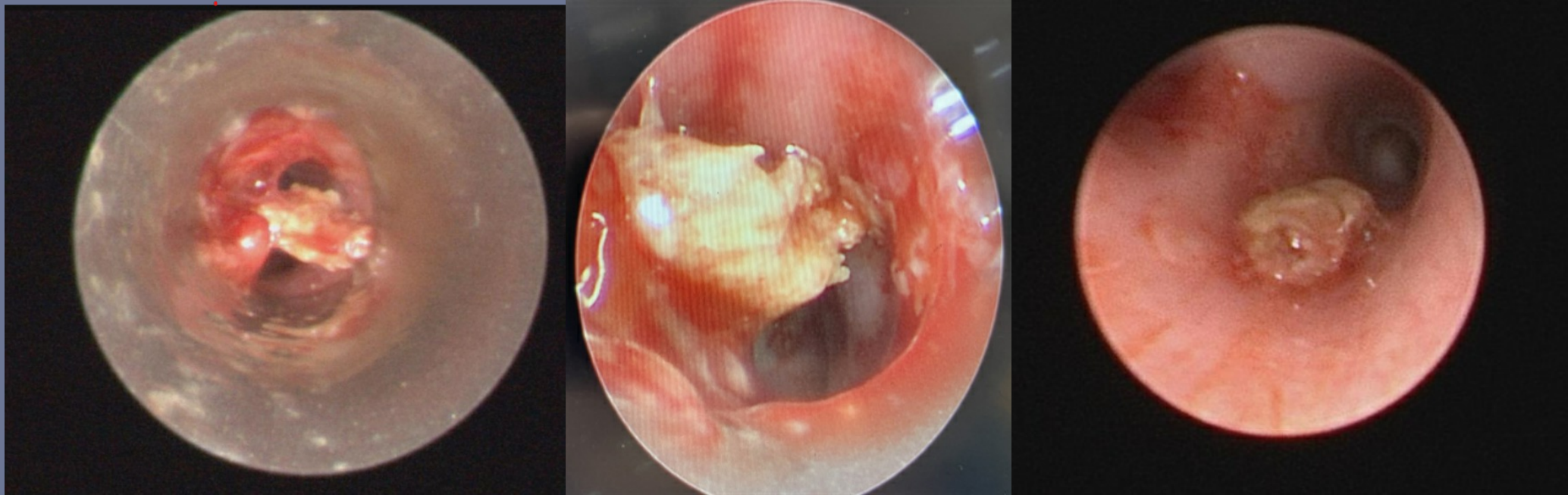
Case 3: 19 month old with cough and wheezing



Right side up

Left side up

19 month old with cough and wheezing



- Additional history - Her father recalls that she had suddenly started to cough and cry after eating chicken off a drumstick

Retained foreign body



“...keep in mind that chicken drumsticks, depending on how they're cooked, can become brittle and easily breakable, especially at the edges.” ¹

- Retrospective single institution study over 20 years ²
 - 3557 children had foreign bodies
 - 35 children had occult foreign bodies
 - 71.4% of retained FBAs occurred around the age of 3 years.
- Cough is almost universal
 - 50% has wheezing
- Radiological findings included pneumonia, atelectasis, and lung consolidation but air trapping was not observed (in contrast to acute).
- Complications include bronchiectasis, bronchopleural fistula, recurrent pneumonia, lung abscess, atelectasis and even death

1. <https://solidstarts.com/foods/chicken/>

2. Liu et al. BMC Pulm Med (2020) 20:320

When asthma is not well controlled: Is it severe?

- Not asthma
 - exclude an alternative diagnosis
- **Difficult asthma**

1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.
2. Respirology (2017) 22, 886–897

Difficult asthma

- Limited access to healthcare
- Limited access to medications
 - cost of medications
- Not taking them regularly
- Not taking properly

➤ Asthma control improves when the basic management needs, such as adherence and inhaler technique, are corrected

When asthma is not well controlled: Is it severe?

- Not asthma
 - exclude an alternative diagnosis
- Difficult asthma
 - improves when the basic management needs, such as adherence and inhaler technique, are corrected
- Asthma plus



1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.
2. Respirology (2017) 22, 886–897

Gas stoves and asthma: Ripped from the headlines!



- “Comments by the Consumer Product Safety commissioner set off a **fiery** debate over gas stoves”
- “The Gas Stove Debate Is **Heating Up** Again After Government Proposes New Standards”
- “Federal Commission Seeks Data on Gas Stoves’ Health Impact”
- Consumer Product Safety Commission says it isn’t planning new regulations or seeking a ban
 - Wall Street Journal 3-2-2023

Gas stoves and asthma

- States with a higher percentage of children living in households with gas stoves have higher proportions of current childhood asthma.
- Gas cooking stoves produce **nitrogen dioxide** (NO₂)*
- Exposure to even low levels of NO₂ may cause increased bronchial reactivity and make young children more susceptible to respiratory infections.

* NO₂ primarily forms from emissions from cars, trucks and buses, power plants, and off-road equipment.

NO₂ causes oxidative injury to the airways, leading to inflammation and remodeling that, in a genetically predisposed individual, could result in asthma development.

Gas stoves and asthma

- 35% of households in the United States have indoor gas stoves
- 12.7% (95% CI = 6.3–19.3%) of current childhood asthma in the US is attributable to gas stove use
- The proportion of childhood asthma that could be theoretically prevented if gas stove use was not present in Massachusetts is 15.4%

Gas stoves and asthma: What can be done?

- Ventilate the stoves outdoors
 - Increase air exchange in the home
 - Avoid a continuously burning pilot light
 - Do not use gas stoves for heating the home
 - Switch to electric
- There is certainly more to come on this topic...

Blame it on the pandemic:
Childhood asthma and COVID-19

Childhood asthma outcomes during the COVID-19: The Pediatric Asthma in Real Life (PeARL) multinational cohort

- 1,054 children with asthma and 505 non-asthmatic children aged between 4 and 18 years from 15 countries
- Compared pandemic vs. preceding year in regard to
 - respiratory tract infections
 - episodes of pyrexia
 - asthma exacerbations
 - lung function
 - emergency visits
 - hospital admissions

The PeARL cohort



Asthma
N=1054



Non-Asthma
N=505



Multinational

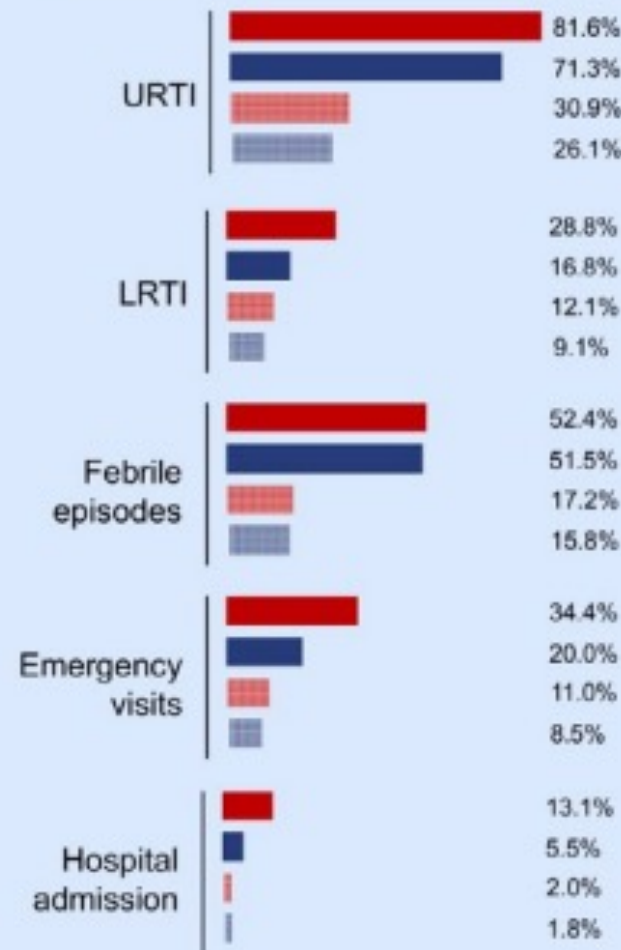


Longitudinal



Children with asthma **are not** disproportionately affected by COVID-19

Children with asthma have improved outcomes



Asthma attacks



Asthma control



FEV₁
PFR

Acute events observed during:

■ 2019
■ Pandemic

The Pediatric Asthma in Real Life (PeARL) multinational cohort

Acute events	Children with asthma			Controls			Between-group differences
	2019	Pandemic	Frequency change during pandemic	2019	Pandemic	Frequency change during pandemic	
URTI	2 [1-4], 81.6%	0 [0-1], 30.9%	<i>p</i> < 0.001 73 fewer*	2 [0-3], 71.3%	0 [0-1], 26.1%	<i>p</i> < 0.001 35 fewer*	<i>p</i> = 0.005, favoring control
LRTI	0 [0-1], 28.8%	0 [0-0], 12.1%	<i>p</i> = 0.12	0 [0-0], 16.8%	0 [0-0], 9.1%	<i>p</i> < 0.001 18 more*	<i>p</i> = 0.09
Pyrexia	0 [0-2], 52.4%	0 [0-0], 17.2%	<i>p</i> < 0.001 24 fewer*	0 [0-2], 51.5%	0 [0-0], 15.8%	<i>p</i> < 0.001 20 fewer*	<i>p</i> = 0.08
Emergency visit	0 [0-1], 34.4%	0 [0-0], 11.0%	<i>p</i> < 0.001 9 fewer*	0 [0-0], 20.0%	0 [0-0], 8.5%	<i>p</i> = 0.79	<i>p</i> = 0.31
Hospital admission	0 [0-0], 13.1%	0 [0-0], 2.0%	<i>p</i> < 0.001 17 fewer*	0 [0-0], 5.5%	0 [0-0], 1.8%	<i>p</i> = 0.29	<i>p</i> = 0.08
Need for additional treatment	2 [0-4], 74.0%	0 [0-1], 29.5%	<0.001 165 more*				
Acute asthma	0 [0-1], 40.7%	0 [0-0], 9.6%	<i>p</i> < 0.001 31 fewer*				
Hospitalization for acute asthma	0 [0-0], 9.8%	0 [0-0], 1.2%	<i>p</i> < 0.001 9 fewer*				

Why did asthma control improve during the pandemic?

- home sheltering
- reduced school days
- social distancing
- masks
- avoidance of outdoor allergens
- fewer viral infections
- reduced physical exercise
- less air pollution exposure
- increased treatment adherence

➤ In vitro models have shown that ICS may suppress both coronavirus replication and cytokine production.

Childhood asthma outcomes during the COVID-19: The PeARL multinational cohort

- Improved outcomes attributed to reduced exposure to asthma triggers and increased treatment adherence.
- The decreased frequency of acute episodes does not support the notion that childhood asthma may be a risk factor for COVID-19.
- The potential for improving childhood asthma outcomes through environmental control becomes apparent.

But then...

- The rise of the highly infectious Delta variant coincided with the return of millions of unimmunized students to in person classrooms with highly variable mitigation strategies.
- Previously observed lower rate were likely due to physical distancing, masks, and perhaps other factors such as decreases in air pollution.
- Hospitalization rates for children with asthma with COVID-19 began to rise.

Asthma as a risk factor for hospitalization in children with COVID-19

- Using data from prospective clinical registries studied:
 - children with COVID-19 and asthma
 - children with COVID-19 without underlying disease
 - children with asthma without COVID-19

- Results:
 - Asthma severity was not associated with higher risk of COVID-19 in children
 - SARS-CoV-2 was not a strong trigger for asthma exacerbations
 - Asthma was a risk factor for hospitalization in children with COVID-19, but not for worse COVID-19 outcomes.

- These results suggest that the increased hospitalization rate may have been due to a different threshold to admit children with asthma rather than truly because of a more severe presentation.

When asthma is not well controlled: Is it severe?

- Not asthma
 - exclude an alternative diagnosis
- Difficult asthma
 - improves when the basic management needs, such as adherence and inhaler technique, are corrected
- Asthma plus
 - consider comorbidities

1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.
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Case 4: 11 year old with frequent asthma exacerbations

- She was full term
- Food allergies including egg, tree nuts, and sesame
- Family history of asthma and food allergies
- At age 4 years she presented with cough, wheezing and respiratory distress requiring admission to the PICU for management
- Discharged on treatment with low dose inhaled steroids and albuterol as needed

Case 4: 11 year old with frequent asthma exacerbations

- Occasional exacerbations managed at home.
- No ED visits and no subsequent admissions.
- When she began remote learning she had no symptoms so her mother stopped her asthma therapy.

Case 4: 11 year old with frequent asthma exacerbations

- When she began to cough both day and night her mother restarted asthma therapy
- When her symptoms persisted her therapy was escalated to the use of a combination of inhaled corticosteroid and long-acting β_2 -agonist both as the controller and the quick relief therapy (SMART)
- This did not lead to improvement...

Case 4: 11 year old with frequent asthma exacerbations

- Additional history...
- They went a breeder and purchased a “hypoallergenic” dog
- She was tested and found to be allergic to dog
 - **Her asthma plus**
- They decided to undergo desensitization rather than re-home the dog

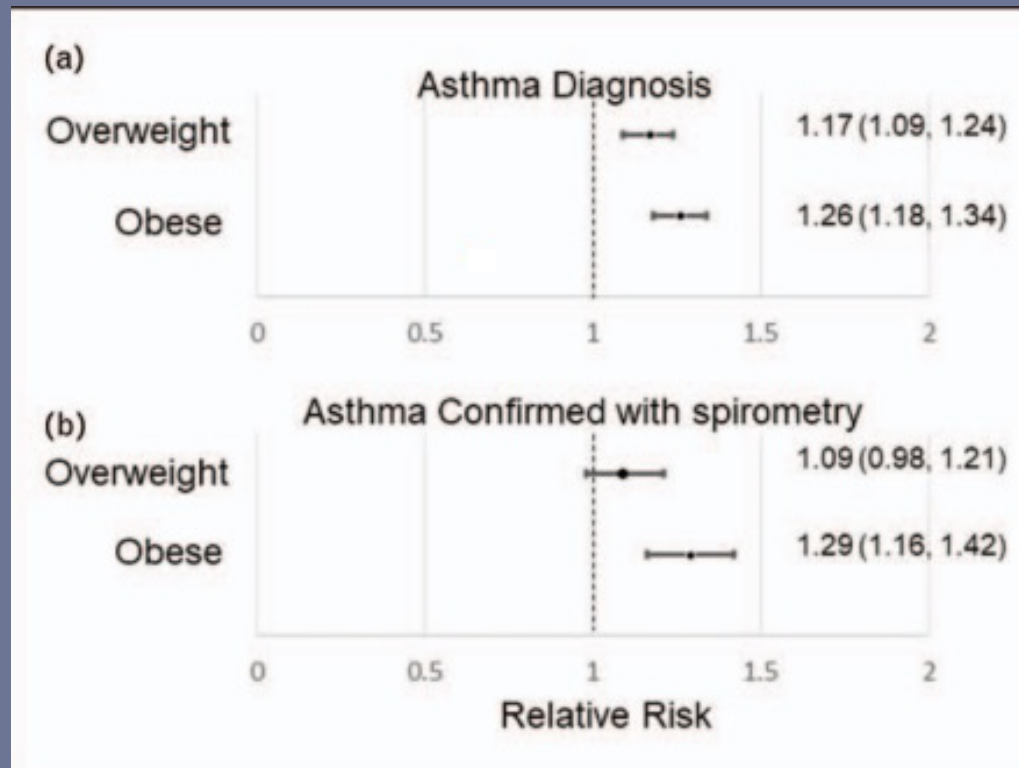
Common Comorbidities Associated with Severe Asthma

Rhinosinusitis	cough, upper-airway wheeze, and sputum production
Stress	the links between the airway and brain are complex and bidirectional
Exercise-induced laryngeal obstruction	wheeze, shortness of breath, with chest and/or throat tightness
Food allergy	high prevalence of food allergy in children with asthma admitted to PICU
Obesity	shortness of breath with exercise

Asthma and Obesity

- Compared to children of healthy weight, children with obesity are
 - at higher risk of having asthma

Obesity and the Risk of Asthma



- Increased relative risk of incident asthma diagnosis among overweight (BMI-percentile 85–94%) and obese (BMI 95th%) children without asthma at baseline.

(a) without spirometry

(b) with spirometry confirmation

Asthma and Obesity

- Compared to children of healthy weight, children with obesity are
 - at higher risk of having asthma
 - Have increased risk for asthma exacerbations

Asthma and Obesity:

Meta-analysis including 52,147 children with asthma in 14 studies

Poor asthma control	1.23 (95% CI 0.99–1.53; I ² : 0.0%)	p=0.06
Exacerbations	1.17 (95% CI 1.03–1.34; I ² : 54.7%)	p=0.02
ED visits	1.04 (95% CI 0.98–1.11; I ² : 0.0%)	p=0.21
Hospitalizations	1.18 (95% CI 0.91–1.53; I ² : 0.0%)	p=0.22

In children with asthma, obesity is associated with **an increased risk of asthma exacerbations** but not with poor asthma control, ED visits or hospitalizations.

Asthma and Obesity

- Compared to children of healthy weight, children with obesity are
 - at higher risk of having asthma
 - have more frequent asthma exacerbations
- Associated with decreased response to inhaled corticosteroids and possibly to systemic steroids
- Higher plasma IL-6 levels in children that are significantly associated with elevated body mass index, greater asthma severity with risk for both asthma exacerbations and lower lung function.¹

Differential Diagnosis of Severe Asthma in Children¹

- Not asthma
 - exclude an alternative diagnosis
- Difficult asthma
 - improves when the basic management needs, such as adherence and inhaler technique, are corrected
- Asthma plus
 - consider comorbidities
- Therapy resistant
 - if uncontrolled despite optimized treatment it is time to step-up care

1. Prof Andrew Bush, MD and Sejal Saglani, MD Imperial School of Medicine, National Heart and Lung Institute, Royal Brompton Hospital, London, UK Lancet. 2010 September 4; 376(9743): 814–825.

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