Asthma Exacerbation Management in Children

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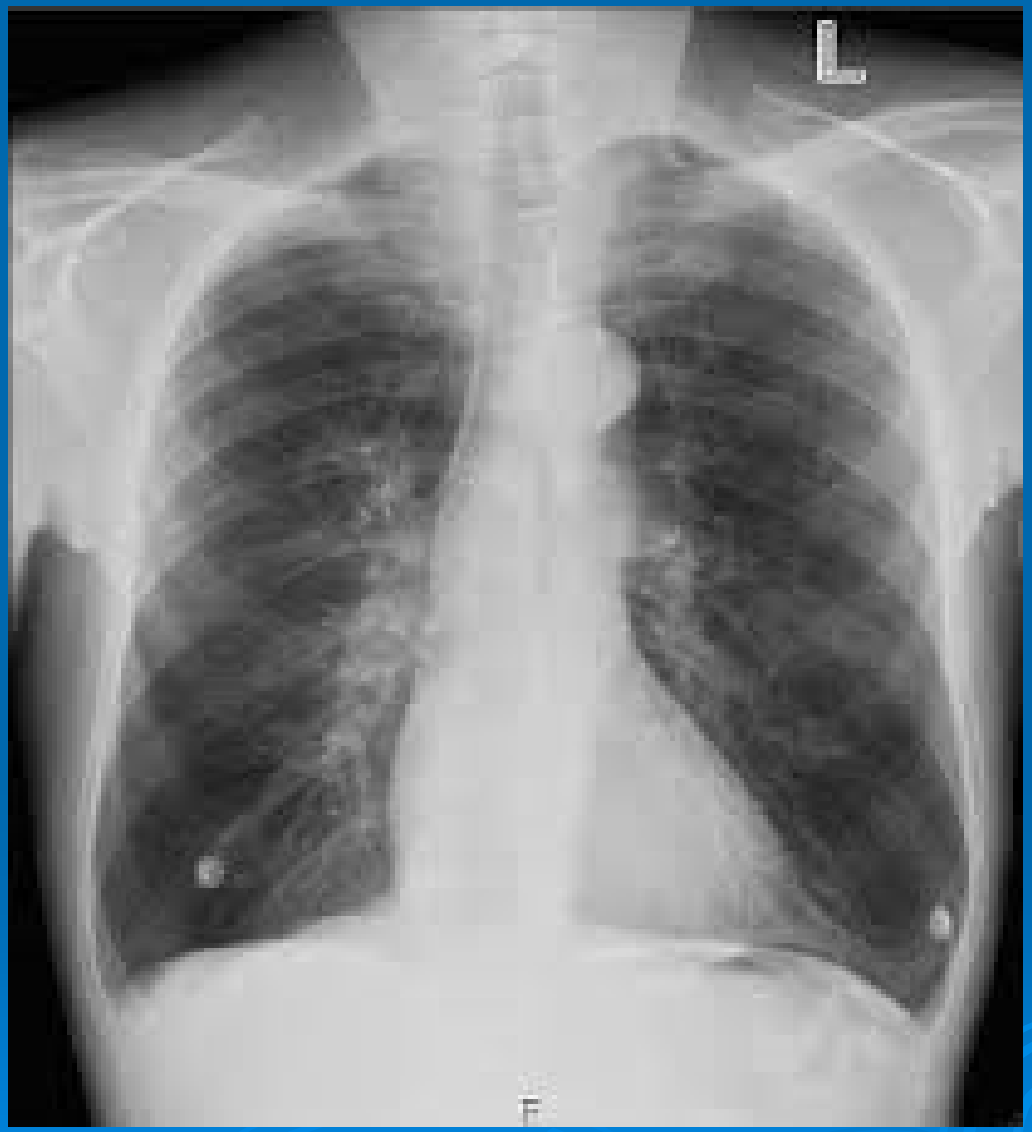
- Asthma is an airway inflammatory disease--- functional and stuctural changes--bronchial hyperesponsiveness and airflor obstructin--- airway structional change or airway remodelling ---epithelial injury, goblet cell hyperplasia, subepithelial layer thickening, airway smooth muscle hyperpklasia and angiogenesis

- It is unclear what is the best treatment identify asthma phenotype that might sepecifially respond to novel therapies such as antiIL-5, anti-IL-13 and tyrosine kinase inhibitors

Asian pac J allerrgy immnol. 2013;31(1):3-10



Hypocapnia & respiratory alkalosis due to increase resp. rate

Symptom classification

- Severe persistent
  - day: continue
  - night: frequent
- Moderate persistent
  - day: daily
  - night: >1/week
- Mild persistent
  - day: >2/week(<1/day) [3-6/week]
  - night: >2/month

Persistent asthma

- Asthma sym. >/=3 days per wk or
  >/=3 nights per mo
- Inner-city children with high asthma morbidity
- Persistent asthma related to frequency of acute exacerbation
- Anti-inflammatory agents remain underused

Pediatrics. 2001;277-82

Components of asthma management

- Assessment and monitoring
- Control of factors contributing to asthma severity
- Pharmacotheray
- Education for a partnership in care

MMWR Recomm Rep.2003;52(RR-6):1-8

- Prevention of asthma exacerbation

  -framing the controller medications

  -educating the families- manage the disease & improve their domestic environment

Arch Pediar.2005;12(3):351-6

Reasons for uncontrolled asthma

- The disease process itself
- Management decisions of clinician
- Patient's perceptions of disease control or self-management behaviors
- The cost of medications

- To inform decisions about appropriate levels of asthma therapy:

  -current impairment

  -future risks of exacerbation or adverse medication effects

Eur Rev MedPharmacol Sci.2011;15(6):711-6

Difficult –to–control asthma

- 5% of the asthma population
- Level 4 or higher of GINA treatment strategy is no response
- Level 5: adding oral glucocorticoids or omalizumab

Drugs Today (Barc).2008;44 Suppl 3:1-43

- Early treatment with OCSs in children with recurrent acute asthma may decrease the severity and reduce of subsequent relapses

Pediatrics.2003;112(2):382-97

Acute asthma exacerbation

- Life-threatening in p’ts who attend accident and emergency department
- Management is not ideal- underuse of corticosteroids and inappropriate admisssion rates according to severity

Lacet.2001;358(9282) :629-35

- **Oral corticosteroid**

  - effective for out p’t treatment of acute asthma

  -early administration reduces hospitalizations

  -the critical factor for a positive outcome is early administration

Pediatrics.2003;112(2):382-97

Acute asthma exacerbation

- Systemic and inhaled corticosteroids are mainstays of treatment in the acute and sub-acute phase of an exacerbation.

Respir Med.2004;98(4):275-84

- Acute management involves severity-based treatment and implementation of clinical practice guidelines

Pediatr Clin North Am.2003;60(5):1035-48

- Steroid-phobia exists --- total control???

Triggering Factors

- -- microoganisms (viruses & bacteria)
- -- food
- -- exercise
- -- drugs (NSAIDs)
- -- ambience pollutants

Triggering Factors

(I) Virus infection----exacerbations of asthma

RV (45%) RSV (28%)
<2yr – 42%, 36%
older children – 66%, 27%
enterovirus, adenovirus, influenza and parainfluenza virus

(II)Bacterial organisms --------asthma exacerbation
Strep pneumoniae, H. influenzae
Moraxella catarrhalis--- esp. in sinusitis

Triggering Factors

(III) Atypical bacterium

(chlamydia pneumoniae, mycoplasma pneumoniae)

* asthma exacerbation
* initiate nonatopic asthma
* persistent asthma symptoms
* severity of asthma

Triggering Factors

- Prevalence of food as a cause of asthma is not known ≅ 9.5%

  Arch Pediatr. 2002 Aug;9 Suppl 3:402s-407s

  Aust N Z J Med. 1996 Aug;26(4):504-12

- Food allergy in respiratory tract symptoms rarely occur in isolation
- More common in younger children, esp. with atopic dermatitis
- Risk factor for fatal and near-fatal anaphylactic reactions

  Curr Allergy Asthma Rep. 2004 Jul;4(4):294-301

Triggering Factors

- Increase of food-induced anaphylaxis was above the overall increase in anaphylaxis
- All food-induced fatalities accompanied by respiratory problems
- Atopic individuals with asthma and prior allergic reactions to the same food are at high risk

Allergy. 2001:56 Suppl 67:102-4

- Food-induced reactions occur frequently in exercise-induced anaphylaxis

Curr Allergy Asthma Rep. 2003 Jan;3(1):15-21

Triggering Factors

- Physical activity--- main stimuli that cause
- asthma exacerbation
- Exercise-induced bronchospasm (EIB) occurs in most asthmatic.
- Trigger of persistent childhood asthma

Ann Allergy Asthma Immunol.2004 Mar;92(3):340-3

Pediatr Clin North Am. 2003 Jun;50(3):697-716

- EIA --- 40 to 90% of asthmatic, 10 to 14% of children
- Exhaled NO levels correlated with BHR & FEV1 with asthma

Chest. 2003 Aug;124(2):639-43

Triggering Factors

- NSAIDs precipitate acute asthma attack– 5-10%

  J Investig Allergol Clin Immunol. 2003;13(1):20-5

- Adverse drug reactions (ADRs) ---50% bronchospasm, pharmaceutical formulation agents, vaccines, immunoglobulins ---- asthma, atopy or drug allergy ---risk factors

  Respiration. 2001;68(4):345-51

- Beta-blockers, calcium antagonists can induce asthma

  Drug Saf. 2000 Aug;23(2):143-64

- Most of the drug reactions are nonallergic

Initial Assessment

Vital signs

- HR, RR, PEF (<40%) or FEV1
- O2 saturation

  poor indicator of need for adm. or prog.

  may transiently drop
- End-tidal CO2

  should be suppressed

  may predict impending resp. failure

  (specific but not sensitive)

Classifying the Severity of Acute Asthma Exacerbations in Children

Cincinnati Children's Hospital Medical Center

Sign/Symptom	Classification		
	Mild	Moderate	Severe
PEFR (% predicted)	70–90	50–70	<50
Respiratory rate	Normal to 30	30–50	>50
Alertness	Normal	Normal	May be decreased
Dyspnea	Absent or mild; can speak in complete sentences	Moderate; speaks in phrases/partial sentences	Severe; speaks in single words or short phrases
Accessory muscle use (intercostals retractions)	None to mild	Moderate; some tracheosternal retractions, chest hyperinflation	Moderate; tracheosternal retractions with nasal flaring during inspiration; chest hyperinflation
Color	Good	Pale	Possibly cyanotic
Auscultation	End expiratory wheeze	Inspiratory and expiratory wheezing	Breath sounds inaudible
Oxygen saturation (% at sea level)*	>95	90–95	<90
PCO_2*	<35	<40	>40

Recommendations for Using OCSs to Treat Acute Exacerbations of Asthma in Children From Selected Currently Used Asthma Guidelines

Cincinnati Children's Hospital Medical Center

Guidelines	Dose	When to Start
BTS (1995)[6]	5–15 y: single dose of 1–2 mg/kg prednisolone, maximum 40 mg; then 1–2 mg/kg/d, maximum 40 mg for 4 d	Patient with incomplete response to initial treatment with short-acting β_2-agonist (by nebulization or MDI + spacer ± face mask) 3–4x hourly, after 3–4 h
	1–5 y: 20 mg/d prednisolone for 1–3 d	
	<1 y: 1–2 mg/kg/d prednisolone for 1–3 d	
Canada (1999)[7]	> 5 y: single dose of 40–60 mg prednisone or equivalent; then 30–60 mg/d for 7–14 d	As soon as possible in all patients with moderate or severe asthma (ie, FEV_1 or PEF <60% of predicted)
	≤5 y: 1–2 mg/kg/d prednisone or equivalent, maximum 50 mg/d, for 3–5 d	
NHLBI (1997)[10]	Adult (>12 y): prednisone, methylprednisolone, or prednisolone, 120–180 mg/d, given as 3–4 divided doses over 48 h; then 60–80 mg/d until PEF reaches 70% of predicted or personal best; for an outpatient "burst," use 40–60 mg in single or 2 divided doses for 3–10 d	Patient with incomplete response to initial treatment with short-acting β_2-agonist, up to 3 treatments of 2–4 puffs by MDI at 20-min intervals
	Child (≤12 y): 1 mg/kg prednisone, methylprednisolone, or prednisolone every 6 h for 48 h; then 1–2 mg/kg/d (maximum 60 mg/d) in 2 divided doses until PEF reaches 70% of predicted or personal best (for children capable of performing PEF); for an outpatient "burst," use 1–2 mg/kg/d (maximum 60 mg/d) for 3–10 d	
GINA (2002)[12]	0.5–1.0 mg/kg prednisolone or equivalent during a 24-h period	If the response to initial treatment with a rapid-acting inhaled β_2-agonist (up to 3 treatments of 2–4 puffs by MDI at 20-min intervals) is not prompt or sustained (eg, PEF >80% predicted or personal best) after 1 h

Management of acute asthma in children aged over 2 years

- Acute severe

  (FEV1 or PEF< 40-50% predicted)

  - Can't complete sentences in one breath or too breathless to talk or feed
  - Pulse>125 (>5yr) or >140 (2 to 5yr)
  - Respiration>30 breaths/min (5yr) or >40 (2 to 5yr)

Management of acute asthma in children aged over 2 years

- Life threatening
  - Hypotension
  - Exhaustion
  - Confusion
  - Coma
  - Silent chest
  - Cyanosis
  - Poor respiration effort

Management of acute asthma in children aged over 2 years

- Criteria for admission

  - increase β2 agonist 2 puffs every two mins up to 10 puffs
- SpO2<92% on air after initial bronchodilator – intensive inpatient tx
- Clinical signs should be recorded

Management of acute asthma in children aged over 2 years

- Treatment of acute asthma

- O2: life threatening asthma or SpO2<94%
  should receive high flow O2

- β2 agonist:

First line tx. A pMDI + spacer is option in mild to moderate asthma

Individualize drug dosing

Single bolus dose of IV salbutamol (15 mcg/kg over 10 min) in severe case

Continue LABA when SABA is required more often than four-hourly

Management of acute asthma in children aged over 2 years

- Steroid:
  - give prednisolone early
  - 20mg for aged 2 to 5 yr
    30-40mg for >5yr
    2mg/kg up to max dose of 60mg for children already receiving maintenance steroid
  - consider IV steroid for who vomit
  - 3 days is usually sufficient.
  - weaning is unnecessary uless exceeds 14 days

Management of acute asthma in children aged over 2 years

- Other therapies
  - ipratropium bromide (250mcg/dose mixed with the nebulized β2 agonist solution)
  - Aminophylline is not recommended in mild to moderate acute asthma
  - consider aminophylline in PICU setting for children with severe or life threatening bronchospasm unresponsive to maximal doses of bronchodilator plus steroid

anrukinzumab

- Anrukinzumab is an ani-IL-13 monoclonl antibody
- Pharmacokinetics behave like a typical antibody but a higher dose levemay be required

Br J Clin Pharmacol. 2015;80(1):101-9

- IL-13 is a T-helper type 2 cytokine associated with inflammation and pathology in asthma
- Lebrikizumab exerted system effectives on markers of Th2 inflammation, reducing serum IgE chemokine ligands 13 and 17 by approximately 25%
- Improves prebronchodilator FEV1

Clin Exp Allerggy. 2014;44(1):38-46

- Anti-IL13 therapy would benefit patients with asthma who had a pretreatment profile consistent with IL-13 activity (high periostin, marker)
- 5.5% points higher in the lebrikizumab group than in the placebo

N Engl J Med, 2011;365(12):1088-98

- Aplastic anemia and eosinophilic pneumonia were reported

Lacet Repir Med. 2016;4(10):781-796

- Predictive biomarkers is urgently needed to better aply biological treatment.

Int Arch Allergy Immunol. 2016;170(2):122-31

Dupilumab

- A fully human monoclonal antibody to alpha subnit of the IL4 receptor amonoclonal antibody that blocks both IL4 and IL13 signaling

  N Engl J Med. 2018;378(26):2533-2534

- Dupipumab therapy associated with fewer asthma exacerbations when LABA and ICS were withdrawn, with improved lung function and reduced of Th2-asociated inflamatory markers.

  N Engl J Med. 2013;368(26);2455-66

- There are few asthma-related adverse events and fewer adverse events requiring beta-agonist rescue after subscutaneous administration of anti-IL4

  Lancet. 2007;370(9596):1396-8

Quilizumab

- A humanized IgG1 monoclonal antibody
- Targets the M1-prime segmentof membrane-expressed IgE
- Leadin gto depletion of IgE –switched and memory B cell
- Not sufficient for a clinically meaningful benefit for aduts wih allergic asthma unconrolled by standard therapy.

Repir Res2016;17:29

Quilizumab

- Benefits of anti-IgE in asthma maybe explained by a decrease in eosinophilic inflammationand IgE –bearing cells.

Allergy 2009;64(1):72-80

- FE(NO) can be the noninvasive marker of omalizumab treatment

Pediatrics. 2004;113(4):e308-12

Quilizumab

- Safely improves asthma control in allergic asthmatics who remain symptomatic despite regular use of ICS and simultaneous reduction in corticosteoid requirement.

Eur Respir J. 2001;18(2):254-61

Management of acute asthma in children aged under 2 years

- Assessment is difficult
- Intermittent wheezing attacks are usually due to viral infection and response to asthma medication is inconsistent
- D/D with aspiration pneumonia, pneumonia, bronchiolitis, tracheomalacia, complication of congenital anomalies
- Prematurity and LBW are risk factors for recurrent wheezing

Management of acute asthma in children aged under 2 years

- β2 agonists
  - oral form not recommended for infants
  - a pMDI + spacer for mild to moderate p't
- Steroid
  - steroid tablets early in infants with moderate and severe asthma (10mg for up to 3 days)
- Inhaled ipratropium bromide in combination with an inhaled β2 agonists for more severe case

Adjunctive Therapies for child <12 years of age

- Magnesium sulfate (IV)
  - Bolus: 50mg/kg/dose (25 to 100mg/kg/dose; max 2 gms)

- Systemic β2 agonists
  - Epinephrine (IM) 0.01mg/kg (max 0.3 to 0.5mg every 20 min for 3 doses)
  - Terbutaline
    IV- 0.01mg/kg bolus (max 0.4mg) over 10 min
    SC- 0.01mg/kg (max 0.25mg), may repeat every 15 min for 3 doses

Thank you

For

Your attention