On the edge of Asthma care....

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* Discuss the complexity and importance of pediatric asthma
* Review some interesting pulmonary physiology/mechanics that will help you diagnose and treat asthma
* Dissect a few interesting “controversial” topics within asthma care
* Look at current literature and classifications, and treatment based on these
* Hopefully learn something you don’t already know about this widespread and common disease.

Purpose
* The Global Initiative for Asthma (GINA) : “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.”

* The chronic inflammation is associated with airway hyper responsiveness (AHR) that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is reversible usually requiring medical treatment.

* Or: “recurrent reversible airways obstruction with/without phlegm”
Debates of the definition of asthma:

* Based on Types of Airway Inflammation (eos/neutrophilic)
* Based on Clinical Features and Age (Mild, moderate, or severe asthma, early, late, etc.)
* Based on triggers
* Based on pulmonary function
* Based on comorbid conditions

* Or... “if asthma medications work, it’s asthma”
* 2007 - 1.75 MILLION ER visits (1.11/0.64) and ~300,000/160,000 admits
* EU asthma cost at approx 40 Billion dollars with cost and lost productivity/year
* Surveyed asthmatics, 53% kids in the U.S. have missed school in the last year

* Social Burden
The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. Orange = 400/100,000 people, over lifetime.
* VIRUSES- rhino, influenza, RSV, corona, human metapneumo, parainfluenza, adeno, boca

* Atypical bacterial respiratory infections
  * Viral/bacterial interaction?

* Viral-allergen interaction—exposure to sensitizing allergens and then viral infection may have synergy?

* School “September epidemic”

* Pollution- combustion of natural gas/motor fuel outside, fireplaces or wood stoves inside. Cigarette smoke! **although these less than infections

* Stress??

What Causes???
Microbial factors
Viruses, LPS, superantigens

↓ GR nuclear translocation
↑ p38 MAPK, ↓ MKP-1, GRβ

TH17
IL-17

↓ HDAC
↑ PI3K

Corticosteroid insensitivity

↑ p38 MAPK, ↑ NF-κB, etc

Inflammation

↑ HAT
↓ HDAC

Smoking
ROS

↓ IL-10

Allergens
IL-2 + IL-4, IL-13

Vitamin D₃

↑ HAT
*School’s starting!!*
Map L1
Adult Self-Reported Lifetime Asthma
Prevalence Rate (Percent) by State: BRFSS 2011

Footnote: Ranges are based on quintiles of the overall prevalence estimates from year 2011 data.

Air Pollution and Respiratory Health Branch, National Center for Environmental Health
Centers for Disease Control and Prevention
*COUGH #1
* Recurrent wheezing; Recurrent Pna
* SOB
* Chest pain
* “anxiety”
* “Tiredness”
* Pressure on chest, “choking”
* Can’t breathe in
* COUGH again-day/night/calm/running/laughing
* Not EIA--- which most kids have
* Exercise as SOLE trigger
* Albuterol pretreat before sports, but LABA (formoterol—Dulera/Symbicort) if long practices/meets ie., swimming, gymnastics, wrestling meets.
* Some evidence that monteleukast can reduce EIB, but must dose properly
* EIB is real but probably 1-3% of all childhood wheezing

* Must demonstrate normal PFTs with reduction after exercise and NO other time.

* Most are EIA, just like some have PIA or SIA

* EIB? Real or part of continuum
-Shape of downward slope /curve is effort INDEPENDENT

-Everything else is effort DEPENDENT
* Comorbidities

* Allergic rhinitis
* GERD
* Obesity
* OSA
* Psych issues
* VCD
* Infections
Possible correlation between psychosocial stress and enhanced airways inflammation via neural and hormonal pathways

Stress → HPA axis stimulation leading to inc. corticosteroid and catecholamine levels

Chronic stress → GC insensitivity in lungs, which may lead to amplified responses to normal triggers

Social stress and Asthma
Mice were “chronically stressed” for 2 weeks

Results: inc AHR to methacholine challenge, inc BAL eos, lymphocytes, cytokines, Igs

ALSO, glucocorticoid receptor expression in the lungs significantly decreased in stressed vs vacationing mice when both groups were exposed to allergens → exaggerated responses
* Obesity is a risk factor for the development of asthma.

* Obesity is associated significantly with the development of asthma, worsening asthma symptoms, and poor asthma control. This leads to increased medication use and hospitalizations. In 2010, the obesity rate among adults with current asthma (38.8%) was significantly higher than the rate among adults without current asthma (26.8%).
*Obese people with asthma*
Does obesity and general diet effect the development of asthma?
* Fat mice have innate AHR
* AHR increases with degree of obesity
* Hyperresponsiveness to O3
* Decreased antiviral cytokines, NKC
* Generalized increased inflammatory markers

* Obesity/Asthma - possible mechanisms
* Effects on lung mechanics (FRC, Vt, airway closure EPP)
* Systemic Inflammation
* Hormone dysregulation - leptin, adiponectin, visfatin
* Co-morbidities: gerd, Type 2DM, hypertension → peribronchial edema, OSAS

* Obesity/Asthma - possible mechanisms
* In obese, FRC is reduced and decrease the elastic properties of the lung parenchyme on the small airways, so smooth muscle “unloaded” and shortens more than normal when activated

* Low lung volume known to airway responsiveness

* Small airway closure during TIDAL breathing, esp supine

* **Mechanical factors**
Equal pressure point

FORCED EXHALATION
Flow = 10 liters/sec

$P_{tp} = +20 \text{ cm H}_2\text{O}$

$P_{alv} = 80$

$P_{pl} = +60 \text{ cm H}_2\text{O}$
Airway closure causes hypoxia in these alveoli, leading to hypoxic pulmonary vasoconstriction → inc pulm artery pressures → peribronchial edema

Mechanical factors
* Recurrent closure small airways may break bronchiole/alveolar attachments → further airway closure
* IL6, TNF alpha, eotaxin, VEGF, MCP all increased and are known for roles in asthma
* Adipose tissue macs are source of many inflammatory cytokines
* 8-isoprostane and other oxidative stress markers increased in blood and lung

* Obesity & Chronic Systemic Inflammation
Leptin (satiety hormone) increased in obesity and very pro-inflammatory --- bad

Adiponectin, (insulin SENSITIZING hormone and anti-inflammatory) decreases -bad

Lung tissue expresses all 3 Adiponectin receptors and play a role in allergen challenges, helping balance inflammatory response - bad
• Dyslipidemia occurs in obesity and there is growing evidence this also effects asthma
• High cholesterol increases Th2 inflammation in mouse studies
• Recent studies have suggested that children with hypercholesterolemia have increased risk for asthma, with BMI factored out
• Some evidence growing that TYPE of fatty acids eaten may effect asthma and that “pro-inflammatory diet vs anti-inflammatory diet” may be worth serious consideration and research
• Omega 3 fatty acids vs Omega 6 fatty acids
Possible mechanisms explaining the relationship between obesity and asthma

Effects of obesity on lung mechanics
- ↓ FRC
- ↓ \( V_T \)
- Airway closure

Systemic inflammation
- Cytokines (TNF\(\alpha\), IL-6)
- Chemokines (eotaxin, MCP-1)
- Reactive oxygen species
- Acute phase reactants
- Other factors (VEGF)

Energy regulating hormones
- Leptin
- Adiponectin
- Visfatin

Co-morbidities
- Dyslipidemia
- GERD
- SDB
- Type 2 diabetes
- Hypertension and its sequelae (e.g. pulmonary hypertension, peribronchial edema, endothelin)

Common etiologies
- In utero conditions
- Genetics
- Exposures (e.g. sunlight)
- Dietary factors (e.g. antioxidants, omega-3 fatty acids)
• GERD/Asthma correlation

* Up to 80% of severe asthmatics have GERD
* GER can cause bronchospasm and airways inflammation and conversely, bad asthma causes GERD.
* Acid stimulation of vagus nerve increases bronchial responsiveness to other stimuli
* Direct airways irritation from microaspiration
* B-agonists can worsen GER - sometimes less is more
* Cochrane 2008, no "sig effects" but subpopulation that may benefit from medications or procedures. So...we have to actually practice the art of medicine
**Persistent asthma: daily medication**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Preferred: Low-dose ICS</th>
<th>Alternative: Cromolyn*, LTRA, or Theophylline</th>
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| Step 2   | Preferred: Low-dose ICS + LABA OR Medium-dose ICS | Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton |

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<th>Step 3</th>
<th>Preferred: Medium-dose ICS + LABA</th>
<th>Consider Omalizumab for patients who have allergies</th>
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<tr>
<th>Step 4</th>
<th>Preferred: High-dose ICS + LABA AND Consider Omalizumab for patients who have allergies</th>
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| Step 5   | Preferred: High-dose ICS + LABA + oral corticosteroid AND Consider Omalizumab for patients who have allergies |

| Step 6   | Step up if needed (first, check adherence, environmental control, and comorbid conditions) |

Each step: patient education, environmental control, and management of comorbidities.
Steps 2-4: consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see footnotes).

**Quick-relief medication for all patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Assess control
Step down if possible (and asthma is well controlled at least 3 months)
ASTHMA ACTION PLAN:

* -

* Take EVERY day: QVAR 80, 2 puffs twice a day; Singulair 5mg once a day;

* -

* Take only AS NEEDED: Albuterol inhaler: Use 2-4 PUFFS IF COUGHING, SHORT OF BREATH OR WHEEZING.

* -

* WHEN SICK: AT THE FIRST SIGN OF ANY RESPIRATORY ILLNESS OR COLD, START ALBUTEROL 2-4 PUFFS EVERY 3 TO 4 HOURS FOR THE DURATION OF THE ILLNESS.

* -

* IF HAVING MORE SEVERE SYMPTOMS, YOU MAY USE 4 TO 6 PUFFS EVERY 2-3 HOURS FOR 24 HOURS. IF NOT BETTER, START ORAL STEROIDS. (maximum of 6 puffs every 2-3 hours)

* -

* IF VERY SEVERE, (EMERGENCY ZONE), YOU MAY USE 6 PUFFS or ONE NEB DOSE, wait 5 minutes, then ANOTHER SIX PUFFS or SECOND NEB DOSE. --START ORAL STEROIDS, Call your doctor, call 911 or go to ER if you are needing to do this.

* -

* STEROID DOSING: If symptoms are getting severe and you are considering an urgent care/ER visit, first start your steroid dosing. If symptoms are moderate but lasting a long time you may start the steroid dosing.

* -

* DOSING: 50 mg once a day for 3 to 5 days.

* ER initiation of ICS??
Glucocorticoids affect various cell types and tissues in the respiratory system:

- **Macrophage**: Downregulation of mediators and numbers.
- **Dendritic cell**: Downregulation of numbers.
- **Lymphocyte**: Downregulation of mediators.
- **Eosinophil**: Downregulation of numbers.
- **Mast cell**: Downregulation of numbers.

- **Smooth muscle cells**: Upregulation of β₂R expression and decrease in remodelling?
- **Capillary endothelium**: Decrease in microvascular leak and angiogenesis.
- **Respiratory epithelial cells, goblet cell**: Decrease in mediators, mucus secretion tight junction remodelling.
* Formoterol/ICS vs B-agonist in for exacerbations/relief medication 2009 Cochrane
* Formoterol fast acting
* ? When symptoms arise, patients increase dosing
* Has potential to treat both bronchospasm and airways inflammation in early exacerbation
* 3 trials, 5905 subjects
* Mild asthmatics - no advantage,
* mod/severe showed less adverse events (exac) when kids already on daily ICS, ICS/LABA used for symptoms
* Intermittent vs daily ICS for persistent asthma

* 6 trials, 1211 subs
* No difference in adverse events
* Intermittent had fewer symptoms free days, more use of B-ag, inc eNO
* No diff in QOL, hospitalisations, ER
* Intermittent use showed greater growth
**Macrolides for Asthma**

* 7 studies, 416 subs
* Macrolide Rx x 4 weeks for chronic asthma
* Significant reductions in eosinophilic airways inflammation and asthma symptoms
* Decreased airways hyper responsiveness
* One study showed large increases in morning peak flow
* More studies needed-- ? Up the sleeve
* Now, even MORE education re: use of antibiotics in chronic cough/asthma symptoms
Omalizumab (Xolair)

* Cochrane 2014
* Monolconal antibody that binds free serum IgE
* 25 trials, 6382 subjects studied as an adjunt therapy to ICS compared to placebo
* Sig reduction exacerbations, oral and inhaled steroid use. On average 21 vs 40/100 STOPPED ICS usage over ~8 months
* Inc QOL, virtually no side effects
* Downsides- SQ injection every 2-4 weeks, expen$ive; constrained indications (age and IgE)
Leuven Children’s Hospital, Belgium:

*OBJECTIVE: The aim of this study is to investigate the effect of the current T&A practice in Belgium on the use of respiratory medication in subjects aged 0-15.

*METHODS: Insurance database compared the use of respiratory medication 12 months before and 12 months after T&A

*RESULTS: the median respiratory medication use reduced by 32% in the year after surgery.

*CONCLUSION: Compared with the year before surgery, the median use of respiratory medication in subjects aged 0-15 drastically reduces in the year after (A)TE.
*METHODS: All children who underwent adenotonsillectomy at our institution from 2002-2007 were identified from a medical records database. Of the 560 charts reviewed, 93 of the patients had the diagnosis of asthma from a pediatric pulmonologist. Outcome measures of asthma control were analyzed one year preoperatively and one year postoperatively and included: hospital visits, systemic steroid use, asthma medication use, and asthma control test scores.
RESULTS:
There was a statistically significant improvement in postoperative asthma severity in all measures including mean hospital visits, systemic steroid administration, asthma medication use, and childhood asthma control test scores (p<0.01).

CONCLUSION:
This study suggests that adenotonsillectomy, which provides improvement in the upper airway of children, may in turn lead to improvement of the lower airways of children, especially those with bronchial asthma.
Particle size

9 - 30 µm
5.5 - 9 µm
3.3 - 5.5 µm
2 - 3.3 µm
1 - 2 µm
0.3 - 1 µm
0.1 - 0.3 µm

Fate

visual pollution
settle in nose/throat
lodge in main breathing passages
lodge in small breathing passages
lodge in bronchi
penetrate to bronchioles and alveoli
penetrate to bronchioles and alveoli
- Particle size is important: those that are too small may be exhaled; those that are too large experience inertial impaction in the oropharynx and large conducting airways.

- Increased aerosol particle speed increases the probability of deposition by impaction in the oropharynx and large conducting airways; slow aerosol particle speed allows more particles to penetrate the peripheral bronchial tree.

- Increasing the inhalation volume allows the aerosol to penetrate peripheral bronchioles.

- Breath-holding increases gravitational sedimentation
particle density: $1 \text{ g cm}^{-3}$
respiratory flow rate: $300 \text{ cm}^3\text{s}^{-1}$
respiratory cycle period: $5 \text{ s}$
Standard Inhaler

Lung deposition of radio-labelled aerosol

11% (percentage of dose)
1. Inertial impaction  
   90%

2. Sedimentation  
   9%

3. Diffusion  
   1%

- Trachea
- Bronchi
- Bronchioles
- Direction of flow
- Impact

Beclamethasone CFC - 3.5-4.0
Asmanex DPI - 2.6-3.3
Advair HFA - 2.7
Flovent HFA 2.4-2.6
Alvesco - 1.5
QVAR - 1.1
All Micrometers
All in Mass Median Diameters
Debated first by Hypocrines in Athens Gr.

pMDI with spacer- pros: portability, cheap, low fungus/bact

Multiple studies have found (=), with less side effects since OP deposition IS lower

One neb dose 2 puffs! (6)

Why does neb work better?

* Poor MDI/spacer technique
* Incorrect dosing
* Child has bronchiolitis and saline is beneficial
* Child needs spaced out dosing to allow for opening of small airways and better medication delivery (6/5/6)
* Child and family have reduced anxiety seeing and feeling the large non-efficacious particles
Medications on the horizon

- Short acting B-ag with ICS
- Breath accuated albuterol
- Dry powder B-agonist
- More small particle size ICS, novel for ICS/LABA
- New turbohalers with better deposition
- Once a day LABAs
- Once a day ICSs