Asthma update 2017
Michigan Asthma Education Day
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Objectives

- Review recent updates for clinical treatments for asthma
- Review updates of research on pathophysiology of childhood asthma
- Discuss trends in community based asthma initiatives
Clinical treatments

- Appropriate use of controller medications remain the mainstay of treatment for childhood asthma
- Although official asthma guidelines have not changed in 10 years, clinicians still rely on basically the same medications
Pharmacologic intervention

- ICS remains the mainstay treatment for chronic asthma
- ICS+LABA can be considered in refractory cases
- Long acting Anti-cholinergic medicines have been approved in asthma treatment in children for add on therapy
  - Tiotropium—6yo+
Variations on a theme

- There are multiple preparations of different ICS as well as ICS+LABA combos that are available.
- Insurance and formulary issues may dictate the options for the clinicians.
- Clinical response should generally fall within similar patterns within classes of medications.
Montelukast

- There have been concerns of behavioral issues and montelukast in children and adults for several years.
- Recently published studies suggest there could be some impact on behavior and this medication use.
- Most recent study evaluated data from a Dutch database and noted associations with depression and montelukast use.

Haarman et al. Pharmacology Research Perspectives Sept 2017
Biologics

- Several new biologics are available which target different arms of the immune system.
- All are generally given by injection.
- Cost can be prohibitive and access can be limited.
- Some have pediatric indications.
Biologics

- Dipilumab
- Omalizumab
- Mepolizumab
- Reslizumab
- Benralizumab

Diagram showing pathways and cells involved in respiratory systems, highlighting the role of biologics in respiratory health.
Enough already

Now to some of the interesting stuff....
Viruses in Asthma

- Respiratory viruses remain a key trigger of asthma exacerbations, providing insight into the evolution and pathophysiology of asthma.

- Always consider the September phenomenon in childhood asthma.
Rhinos are the culprit

- In a prospective observational cohort study involving 183 asthmatic children aged 6 to 17 years, Kantor et al found that subjects with rhinovirus infection had more severe exacerbations than those participants with virus-negative exacerbations.
- In this cohort rhinovirus-triggered asthma exacerbations became more severe as the degree of sensitization to dust mite and mouse increased.
The microbiome in asthma

- Through detailed assessments of the airway microbiome, key differences between asthmatic patients, nonasthmatic subjects, and those at risk for asthma have been characterized.

- Regarding at-risk populations, the nasopharyngeal microbiota in more than 1000 infants with bronchiolitis was analyzed as part of a large multicenter study by Masenbach et al.
Infants with bronchiolitis caused by RSV had a high abundance of Firmicutes and the genus Streptococcus and a low abundance of Proteobacteria and the genera Haemophilus and Moraxella, whereas infants with bronchiolitis caused by rhinovirus had the opposite pattern
The microbiome effects medication response

- AsthmaNet obtained bronchial brushings from 42 steroid-naive adults with atopic asthma, 21 nonasthmatic but atopic adults, and 21 healthy control adults.
- By profiling samples through gene sequencing, distinct differences in the bronchial bacterial microbiomes were appreciated in the 3 groups.
- Among asthmatic adults, the bronchial microbiome at baseline differed according to their responsiveness to inhaled corticosteroid (ICS) treatment.
Genetic influences

- DMRT1 is a novel candidate to potentially explain sex-specific asthma effects during childhood.
- A SNP on chromosome 8 was associated with early lung function decrease in asthma cohorts and was also associated with COPD risk.
- The Gly-to-Arg substitution at the 16 position in the b2-adrenoceptor gene in asthmatic children identified the increased risk of asthma exacerbation with use of LABAs in children carrying 1 or 2 alleles.
Air Quality

- Worldwide, only 12% of urban populations breathe air that complies with World Health Organization Air Quality Guidelines.
Air Pollution and Its Health Effects Are Not a New Concern!

Actios of Antiochenus (500-575 AD) wrote:

“Irritations of the eyes, which are caused by smoke, over-heating dust, or similar injury, are easy to heal; the patient being advised first of all to avoid the irritating causes…For the disease ceases without any use of any kind of medicine, if only a proper way of living be adopted.”
Definitions

- Primary – pollutants directly emitted into the atmosphere (eg. $\text{SO}_2$, some $\text{NO}_x$ species, CO, PM)

- Secondary – pollutants that form in the air as a result of chemical reactions with other pollutants and gases (eg. Ozone, $\text{NO}_2$, some particulates)
  
  *PM=particulate matter; SO2=sulfur dioxide; CO=carbon Monoxide; NO2=nitrogen dioxide; NOx=nitrogen oxides
Effects on lung function

- Inhalation of 1 ppm of SO2 for 10 minutes during moderate exercise decreased FEV1 by 23% in adolescents with asthma.
- An association between ambient ozone levels below EPA limits and asthma symptoms was found in children with asthma living in New England.
ER visits

- Numerous studies have found an association between PM 10 levels and ER visits for asthma.
- A study in Seattle noted an increase of 11 µg/m³ in fine PM was associated with an 11% increase in asthma ER visits.
- Ozone and SO2 have been associated with ER visits for asthma in Mexico in 3 long term studies.
Pollution and allergies

- Exposure to 0.12 ppm ozone decreased the amount of ragweed allergen required to provoke a 20% decrease in FEV1
- NO₂ exposure has been shown to increase airway hyperresponsiveness to tree pollen
- Exposure to PM increases total serum IgE levels
- Nasal histamine levels are increased 3-fold when diesel exhaust particles are co-administered with allergen
- Exposure to airborne endotoxin enhances response to inhaled allergen
Cars and asthma

- Physician diagnosed asthma has been reported to be more frequent among children living within 100 meters of a freeway.
- Higher rates of allergic sensitization are found in children playing more than one hour/day near major traffic thoroughfares.
Even early on

- A median regression analysis of patients in a large birth cohort showed a significant association between increased exposure to traffic nitric oxides in the first year of life and increased adolescent airways resistance and reactance.
Pollution and allergies are a bad combo

- Traffic related air pollution (TRAP) can affect steroid sensitivity.
- In a mouse model of allergen-induced asthma with diesel exhaust particle (DEP) exposure, 4 days of dexamethasone treatment only partially reduced airway hyperresponsiveness (AHR) in mice exposed to both house dust mite and diesel exhaust.
- These HDM plus DEP-exposed mice were noted to have greater airway neutrophilia compared with mice exposed to HDM only.
Air pollution affects DNA

- Pollution is associated with DNA methylation variation.
- Cross-sectional data from non-twin siblings discordant for asthma who were born and raised in the same household showed an association between asthma status and demethylation of a CpG site in the promoter region of the TET1 gene.
- This study showed that methylation of the same CpG site was associated with TRAP exposure.
Dirty air is just bad

- Increased asthma severity was associated with high concentrations of allergenic species, high total fungal concentrations, and increased bacterial richness in children.

- Fungal and bacterial community composition shared more similarities in homes of patients with severe asthma compared with those with mild asthma.
What really does it...

- A causal network analysis on an inner-city asthma cohort demonstrated that the 2 biggest drivers of asthma severity appear to be
  - Allergy pathway starting with allergic sensitization (The Atopic March)
  - Environmental tobacco smoke pathway.
What makes asthma worse

- Rhinovirus-triggered asthma exacerbations become more severe as the degree of sensitization to dust mite and mouse increases.
- Co-exposure of respiratory virus and cockroach allergen induced a biphasic IL-33 response and impaired antiviral interferon production.
Allergies do play a role

- Analysis of an Australian longitudinal birth cohort demonstrated that allergic sensitization by 12 months of age was associated with increased risk of wheeze during young adulthood, as well as lower FEV1, FEV1/FVC ratio, and FEF25-75 at 24 years of age.
- Thus why allergists still care about allergies.
What is this?
Cochineal bugs...ie carmine allergy or real red dye #40
Maternal stress

- After adjusting for confounders in a pregnancy cohort, a dose-response relationship emerged with an increase in the odds of asthma diagnosis in children for each increase in maternal stress category both prenatally and postnatally.
- Clearly these additional in utero factors are exacerbation in certain at risk populations.
Can we get any help?
Maybe biomarkers can lead the way
Phenotyping for treatment

- Children and adolescents with difficult-to-control asthma (requiring high-dose ICSs) are distinguishable from those requiring only low-dose ICSs
  - FEV1 bronchodilator responsiveness
  - rhinitis severity
  - atopy
Some useful Biomarkers

- In patients with severe uncontrolled asthma 12 years and older, a high blood eosinophil count (\(\geq 400 \text{ cells/mm}^3\)) was an independent risk factor for \(\geq 2\) asthma exacerbations or any asthma ER visits or hospitalization.

- Some newer biologics may target these areas of inflammation and vulnerability.
A path forward

- Phenotyping with allergen sensitization and a blood eosinophil count of 300 cells/mm³ or greater identifies children with a high exacerbation probability for whom treatment with a daily ICS is beneficial despite risks of growth suppression.
- A combined high exhaled nitric oxide level and blood eosinophil count is related to a higher likelihood of AHR and uncontrolled asthma in young asthmatic patients.
The most vulnerable

- A cluster analysis defined phenotypes of inner-city children with asthma, including one phenotype of severe asthmatic children that is highly allergic.
- These children were often sensitized to both cockroach, mouse, and dust mite.
Beyond giving meds
There are many other ways to make meaningful impact
Compliance

- A study using reimbursement data noted only 24% of adults and pediatric patients maintained regular ICS adherence 1 year after a period of regular ICS use.
- Another study showed use of an electronic monitoring device system, decreased short-acting β-agonist (SABA) use, and increased SABA-free days in children and adults.
Compliance and technique

- In a population-based cohort study only 33% of pediatric patients demonstrated high ICS adherence.
- Use of an acoustic recording device attached to an inhaler found that only 20% of patients used their inhaler in the correct manner at the correct interval,
- This emphasizes the need to address not only the number of actuations but also technique errors
Maybe it’s schools

- Several studies noted a multidisciplinary school-based program can increase
  - the number of asthma action plans
  - increase rescue and controller medication use in schools
  - improve asthma knowledge scores
  - improve inhaler technique
  - reduce asthma exacerbations

I acknowledge I am preaching to the choir
The Step Up Asthma Program

- Step-Up Asthma Program used asthma counselors as a bridge between subspecialty asthma care, primary care providers, school nurses, and families.
- The program demonstrated improvement in multiple outcomes.
What schools can do

- The School-based Asthma Management Program identified 4 essential components to create this partnership with families and schools:
  - a circle of support between these groups
  - asthma management plans
  - comprehensive asthma education for school personnel
  - assessment and remediation of school-based asthma triggers.
Summary thoughts

- The 2 biggest drivers of asthma severity were an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway.
- Wheezing illnesses with onset in early life have a greater influence on lung function than wheezing duration.
Summary thoughts

- Ability to list asthma medications is associated with higher levels of health literacy
- Biomarkers, including exhaled nitric oxide levels and eosinophil counts, have potential as indicators of endotypes
- Allergen sensitization and blood eosinophil counts can be used to select medications for management of asthma in young children
Finally the truth

- Asthma educators are likely primed to be the major driving factor in community asthma improvements.
- Although medications and science can help, encouraging and guiding proper health skills and advocating for healthy environments may yield the best outcomes.
- Community asthma educators are the key.
Questions??