Objectives

- Discuss research findings in the last year about factors contributing to the development and morbidity of asthma
- Describe new research involving asthma therapeutics
- Outline publications describing asthma-related educational interventions

Factors Contributing to Asthma Development and Morbidity
Comorbidities contribute to poorly controlled asthma

Improved understanding of risk factors can help improve asthma care

Patients with prescription for high dose fluticasone (>1000ug) or oral steroids from pharmacy database were sent questionnaires about asthma symptoms and comorbidities.

- 92% of patients with difficult to control asthma had 1 comorbidity
- Comorbidities were associated with older age, female, + smoking history and chronic prednisone use
- Limitations include use of questionnaires to gather data, limited patient population
- Conclusion: “Patients with difficult to control asthma, in particular older women, prior smokers and those on chronic prednisone should be thoroughly screened” and treated for complicating comorbidities


- Ontario Asthma Surveillance Information System (registry of 2.1 million patients with physician-diagnosed asthma in Ontario, Canada)
- Asthmatics aged 5-99 with ED visit for asthma between 2008-2014 included
- Compared characteristics of those with/without ED return in one year for asthma
- 58,364 patients met criteria
- Weaknesses include one study site, could miss patients not in the health system, based on visit codes
Within 1 year, 12.1% returned to the ED for asthma at least once
Age associated with highest risk of return to ED
20-49 had 18% increased risk
5-19 had 13% increased risk
Comorbid COPD increased risk of return by 14%
Low SES/materially deprived increased risk by 14%
Small increased risk in those without follow-up appt within 3 days of ED visit
Sex was not a significant risk factor


Identifying and targeting those at highest risk for return visits to the ED for asthma may help prevent return visits, reduce cost, improve quality of care and match up inventions with those who could benefit from them the most.


Physical activity and exercise lead to better health outcomes in the general population and sedentary lifestyle is associated with impaired health.

Some studies have observed that decreased exercise and increased sedentary time is more prominent in obstructive airway disease populations. Further these behaviors have been independently associated with worse outcomes but this link has not been established in asthma.

However, some studies have revealed better asthma outcomes in patients with greater physical activity routine.
Few studies have objectively measured sedentary time in a severe asthma population.

Cross-sectional characterization study

122 adults with severe asthma and age/sex matched controls in Australia

Differences in two populations

Clinical measurements included:
- Height, weight, skin prick test, serum IgE, comorbidities, smoking status
- Exercise capacity measured via 6-min walk test (distance achieved calculated)
- Asthma control via ACQ and AQLQ
- Airflow limitation via spirometry
- Airway inflammation via BAL and sputum eosinophils
- Systemic inflammation via hs-CRP
- Physical activity and sedentary time via actigraph

More steps improved exercise capacity.

More sedentary time negatively impacted asthma control reports.

No relationship was observed between behavioral variables and eosinophilic inflammation markers.

Increased steps did significantly reduce systemic inflammation markers.

Clinical applicability: Walking and activity are important to overall health and mobility in severe asthma (which is common) results in lower asthma control scores.
Assessment of lung function is an important component of managing asthma. Obtaining accurate results of lung function testing in preschool children can be a challenge and is often not attempted. Part of this study evaluated the technical acceptability of spirometry and impulse oscillometry in children aged 3-5 years old.

- Spirometry requires maximal forced expiration and is effort-dependent.
- Impulse oscillometry uses application of oscillatory pressure to the lungs and does not require maximal effort as tidal breathing is used, so it is less effort-dependent. Pressure waves are applied at the mouth to measure resistance and reactance of the total respiratory system.
URECA (Urban Environment and Childhood Asthma Study) is a multicenter birth cohort study investigating the development of allergies and asthma in inner-city children.

- Pregnant women were recruited in areas with high rates of poverty (>20% of population area with annual income below poverty level)
- >2000 families screened, 609 enrolled in study
- At age 33 months, there was an educational and practice session for the breathing tests
- Then at age 3, 4, and 5 both spirometry and IOS were performed (>400 tests completed at each age group)

For IOS, an acceptable test required 15 seconds of normal tidal breathing with at least 4 breaths in 30 seconds. IOS was performed first.

For spirometry, an acceptable test followed guidelines per ATS statement on pulmonary function testing in preschool children:
- Full return to baseline
- FEV<sub>0.5</sub> in place of FEV<sub>1</sub>
- 8 attempts allowed

### Reasons for Unacceptable Spirometry

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<th>Age 3</th>
<th>Age 4</th>
<th>Age 5</th>
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<tr>
<td>Poor effort</td>
<td>37%</td>
<td>57%</td>
<td>71%</td>
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<tr>
<td>Glottic closure</td>
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<td>Short expiration</td>
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<td>0%</td>
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<tr>
<td>2+ reasons</td>
<td>7%</td>
<td>6%</td>
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Figure 1


- Chronic cough is one of the most common conditions treated in pulmonary medicine.
- Cough Variant Asthma (CVA) accounts for up to 29% of chronic cough.
- CVA is diagnosed by bronchial challenge tests and existence of bronchial hyperresponsiveness (BHR), typically attained by tests such as methacholine or histamine challenges.
- Such tests can be expensive, time consuming, hard to access and risky for some patients.


- Limitations include select patient population, not all children attempted the breathing tests.
- Much higher % of preschool children were able to perform acceptable spirometry than previously reported.
- All participants completed a practice session at 33 months which likely increased their ability to perform the tests.
- We should consider starting to “practice” spirometry at an early age to hasten our ability to obtain interpretable tests.


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Fractional Exhaled nitric oxide (FENO) can provide a noninvasive biomarker for airway inflammation (eosinophilic) that predicts responsiveness to corticosteroids in asthma.

Eosinophilic inflammation is often present in CVA.

Studies have demonstrated FENO values are higher in patients with CVA than healthy controls, suggesting a role for FENO in diagnosis of chronic cough.

Though Asthma is classified as a large airway disease, there is evidence revealing the importance of the inflammatory cascade in smaller airways.

Small airway dysfunction (as predicted by forced expiratory flow rate at 25-75%), may contribute to lack of disease control, exacerbations (general and exercise-induced) and night time symptoms.

Greater BHR has been associated with lower FEF 25-75.

FEF 25-75 may be a good marker for early bronchial dysfunction, especially in patients with normal FEV1, mild asthma, allergic rhinitis or CVA.

Retrospective, cross-sectional study

Analyzed diagnoses made by spirometry and bronchial provocation test results

290 patients with chronic non-productive cough of at least 2 months

Pulmonary outpatient clinic in China
Of 290 patients: 97 had positive Broncho provocat testing, 193 had negative
FEV1, FVC and FEF 25-75 were all significantly lower in MCH positive patients.
FENO and EOS% were higher in positive challenge patients.

FENO alone and FEF 25-75 alone did not reveal a statistical correlation with increased BHR.
However... There was a correlation when these two tests were combined.
"There was an increased likelihood of BHR positivity associated with FENO >43 and FEF 25-75 <78%.

Clinical applicability: FENO has low sensitivity and this can limit use, however when added to other testing tools, it may have better utility in diagnosing certain types of asthma.

Asthma Treatment
Guidelines recommend step down therapy once asthma controlled

This study evaluated the different approaches for step down therapy in those >12 years old with well controlled asthma (for at least 30 days) taking ICS/LABA

Excluded if smoked in past year (or smoking hx of >10pack-years)

Controlled/stable asthma was defined as ACT >19, no acute visits, pre-bronchodilator FEV1 >70% and <16 puffs of SABA per week

After an 8 week run in period (total of 3 months of controlled asthma) a total of 459 subjects were randomized into 3 parallel treatment groups

Followed subjects for 48 weeks

Primary outcome was time to treatment failure (composite of need for acute visits, oral steroid use, need for rescue/reliever use, and lung function)

- Time to treatment failure was the same in all groups
- In the group that removed the LABA, there were greater lung function declines and increased hospitalization rates
- High rates of treatment failure in all 3 step down therapy groups
- Step down strategies for those on ICS/LABA must take into account risks and benefits of therapy, but with any strategy, early recognition of loss of control is crucial given high rates of treatment failure


- Cough can be one of the most distressing symptoms of asthma
- There are numerous mediators of cough in asthma including inflammation, airway hyper-responsiveness and bronchoconstriction
- Cough can also be triggered by neurogenic mediators
- M3 (muscarinic receptor) involved with mucous secretion, inflammation and bronchoconstriction
- Tiotropium is an inhaled M3 receptor antagonist used in asthma
Recently demonstrated that in patients with acute URI induced cough, that neurogenic triggers through the capsaicin cough reflex contribute to symptoms.

Tiotropium has been shown to attenuate this neurogenic-mediated cough in acute URIs.

The aim of this study was to evaluate the effects of tiotropium on capsaicin cough reflex, lung function and asthma control in patients with asthma and symptomatic cough despite ICS/LABA therapy.

- Tiotropium significantly reduced cough scores, improved asthma control as measured by ACT, decreased capsaicin cough reflex sensitivity but did affect FEV1.


- Historical data has revealed improvement in asthma with combined diet and exercise interventions in obese patients.
- A few observational studies show a correlation between physical activity, diet, and asthma outcomes that are independent of obesity.
- The authors’ question: Can diet and change in sedentary habits improve asthma in non-obese patients?

- Danish: 8 week single-center, randomized controlled parallel-group study.
- 4 randomized groups:
  - 1) exercise group (high intensity).
  - 2) diet group (low glycemic/high protein/low anti-inflammatory index).
  - 3) exercise + diet group
  - 4) control group with usual care.
125 patients completed the study, no significant characteristics between intervention and control groups.

Glycemic index was reduced in all treatment groups but urine urea excretion was increased from pre intervention to post intervention in the diet and diet + exercise groups.

Maximal Oxygen uptake and body composition (VO2max), improved in the exercise and exercise + diet groups.

Sputum Eosinophil Counts: exercise + diet group had a modest decrease but wasn’t statistically significant.

Blood eosinophils count: modest decrease in diet group but not significant.

Spirometry: no Significant change.

Fractional Exhaled Nitric Oxide: no significant change.

Low grade systemic inflammation: no significant change in hs CRP or IL-6.

There was a weak correlation between improved ACQ scores and decrease in eosinophilic cell counts.

Asthma control and QOL: ACQ and ACQL scores improved in all treatment groups but when compared with control, only the exercise + diet group had a statically significant improvement.
Patients in the exercise group and diet group did experience some non-statistical improvements in asthma control and quality of life. However, the only statistically significant improvement in asthma was associated with ACQ and ACQ5Q scores in the exercise + diet group.

Clinical Applicability: Exercise and healthy diet may benefit quality of life in the asthmatic patient and can be discussed in the clinical setting as a potential intervention.

Poor diet can impact the immune system via T-helper immune response and can lead to airway inflammation. Human and murine studies have suggested a link between high-fat/low-fiber diet and increase in pro-inflammatory cytokines (IL-17).

Further research has supported the protective effects of fruits and vegetables against allergic conditions via downregulation of T-helper cells. One study found plant-based choices were associated with a 14-46% decreased risk of wheeze and asthma in children and adults.
8,175 US children
22,294 US adults
Dietary Inflammatory Index (DII): "score that categorizes an individual’s diet on a continuum from the most anti-inflammatory to the most pro-inflammatory. The higher the score, the more inflammatory potential.
Hypothesis: a pro-inflammatory diet is associated with increased asthma or wheeze, and worsened lung function.

NHANES survey: demographic, socioeconomic, dietary, and health-related questions
Exam component: physical measurements, spirometry, FENO, lab testing
DII was developed and validated by peer-reviewed literature published between 1950-2010

The Journal of Allergy and Clinical Immunology: In Practice 2018 6, 834-841.e2 DOI: (10.1016/j.jaip.2017.12.029)
DII was significantly higher in adults with current wheeze than those without wheeze.

The authors examined if the effect of DII on current asthma/wheeze was modified by allergic airway inflammation.

In regards to DII and lung function measurements:
- In adults with current wheeze there was no association between DII and FEV1/FVC.
- In adults without current wheeze there was a association between increased DII and lower FEV1/FVC values.
- No association between DII and lung function was made in children.
- Higher DII was associated with greater BHR in those with obstruction on PFT.

There were generally negative findings in regards to DII being associated with current asthma. Positive findings were however associated with active wheezing. Clinical applicability: Children with high FENO may be some of the most susceptible to pro-inflammatory diets. Adults with wheeze with low and high FENO levels may be equally susceptible to pro-inflammatory diets. Whole diet studies in asthma are scare however it wouldn’t be detrimental to trial low inflammation diet in patients with active wheeze.

Asthma Education


- Asthma Adherence Pathway (AAP) application is an internet based program that combines patient and provider education strategies to enhance adherence.
- Study evaluated whether use of the AAP application improved adherence and subsequent asthma control.
AAP application "guides patients and clinicians through adherence interventions"

- Patient completes the AAP survey which helps identify attitudes, behaviors and barriers of disease management.
- Patient receives written feedback and a brief 30-60 sec video response.
- Provider receives patient information and also gets recommendations for MI based responses to address these identified barriers.

- Additional web resources are available to both patient and provider.
- Adherence barriers include:
  - Management issues
  - Negative beliefs about treatment
  - Symptoms caused by emotional triggers
  - Lack of understanding about plan of care
  - Reduction in QOL
  - Lack of co-creation of mutually agreed upon plan
  - Cost
  - Side effects
  - Ambivalence/forgetfulness

Patients 18 and older were recruited from allergy and pulm clinics if they had asthma that was not well controlled who were on ICS or ICS/LABA therapy.

- Exclusion criteria were intermittent asthma, exacerbation in past 3 months, serious/uncontrolled medical condition or COPD.
- Before randomization, patients had complete PE, spirometry, assessment of control and were treated with mometasone/formoterol 100mcg 2 puffs bid + albuterol/PRN.
- Reassessed at 2 weeks and if doing well, were randomized to either continued current care vs. current care of AAP intervention.
- SmartTrack devices attached to the controller and reliever inhalers which recorded date and time of all actuations
- Control patients seen monthly x 4
- Intervention patients seen at weeks 2, 4 and then monthly
- At each follow-up visit, patients completed control questionnaires and adherence data (only in intervention group) was reviewed with patient
- If not well controlled, the dose of controller was increased
- If not adherent (<60% use of controller), barrier-specific interventions employed

Figure 2
Primary outcome measured was change in ACQ score over 3 months.

Secondary outcomes include adherence to controller therapy.

Mean adherence to controller in the intervention group was 81%.

Intervention group had greater improvement in ACQ than control group (defined as >0.5 units on ACQ) P=0.016.

Limitations include very small sample size, lack of adherence monitoring in control group.


Preliminary study using Asthma Adherence Pathway (AAP) helped promote adherence and improve asthma control.

Multifactorial web based interventions which incorporate technology, discussion prompts and in person interactions may improve asthma care.


Asthma guidelines recommend assessment of the patient's inhaler technique at each visit.

Incorrect inhaler technique is associated with poor asthma control/outcomes.

Incorrect use can be device related, patient related or HCP related.

First systematic review looking at HCPs proficiency of inhaler use.
Published studies from 1975-2014 that evaluated HCPs knowledge of inhaler use were included:
- Total of 55 studies included
- 6304 HCPs encounters
- 9996 inhaler demonstrations performed
- The majority were pulmonologists, allergists, general practitioners, nurses, pharmacists, nurses and RTs
- Direct observation of MDIs, MDIs + chambers and DPI inhaler use
- Weaknesses of study include heterogeneous studies, non-randomized trials and lack of consistent criteria for assessing inhaler use knowledge

**Pressurized metered dose inhaler (pMDI)**
1. Preparation: take off the cap, shake the inhaler (canister vertical, mouthpiece down, and horizontal)
2. Breathe out completely
3. Place teeth and lips around the mouthpiece, with the tongue flat under it and fire the device while beginning a slow inhalation
4. Inhale slowly and deeply, without stopping
5. Hold the breath for 5 to 10 s or as long as possible

**pMDI with inhalation chamber (pMDI+IC)**
6. Preparation: take off the cap, shake the inhaler while holding it vertically
7. Connect pMDI mouthpiece to the back of the spacer
8. Exhale completely until residual volume
9. Place the spacer mouthpiece between teeth and close lips around it, then, hold the breath for 5 to 10 s or as long as possible
10. Preparation: operate the inhaler according to manufacturer instructions
11. Turn away from the canister and breathe out completely
12. Place teeth and lips around the spacer to form a seal
13. Breathe in with one brisk, forceful and deep inhalation
14. Hold the breath for 5 to 10 s or as long as possible

**Dry powder inhaler (DPI)**
11. Preparation: uncap; prime the inhaler according to manufacturer instructions
12. Turn away from the inhaler and breathe out completely
13. Place teeth and lips around the mouthpiece to form a seal
14. Breathe in with one brisk, forceful and deep inhalation
15. Hold the breath for 5 to 10 s or as long as possible

Only 15.5% correct inhaler technique

**Common MDI errors**
- Not breathing out completely before inhalation
- Lack of coordination
- Exhaling into the inhaler

**Common DPI errors**
- Inconsistent preparation
- Not inhaling deep and completely
- Exhaling into the inhaler
Overall, HCPs had poor knowledge of correct inhaler use

Those tasked at educating patients on how to use inhalers often are not proficient themselves.

“Urgent need to design efficient strategies to improve training of HCPs in the appropriate use of inhalers”

References


