Pediatric Asthma Care Before, During, and Almost After the Pandemic

Lessons learned and to be learned

Harvey L. Leo, MD
Michigan Asthma Partnership Forum

Learning objectives

- Discuss the impacts of COVID-19 and relationships with asthma and chronic lung disease
- Briefly review SMART therapy and its background
- Briefly review changes to NHLBI 2020 Guidelines
- Discuss preparations for asthma care post COVID-19 pandemic

Disclosures

- Commercial: None
- I will be discussing both approved and FDA investigational therapies for children

Introduction

- The past 2 years has seen the most rapid changes in public health systems and responses; the development of an efficacious vaccine platform and mass vaccination rollout in history; and reinforced factors that contribute to health disparities in all chronic disease such as asthma.
- There is no way to summarize or consider all these factors in less than 1 hour, but we should appreciate how complex health care delivery and disease interactions are.

COVID Questions to get out of the way

- There is no increased risk of vaccine reaction or allergy in allergic individuals and the overall risk of allergic reaction to the mRNA vaccines is exceedingly low.
  - Rare individuals may have reactions to components of the vaccine but it has not been more likely than other vaccines. (PEG/Polysorbate)
- Controlled asthma does not appear to be a significant risk factor for mortality
- Mask wearing in activities does not make asthma worse
- Acknowledge someone's vaccine hesitancy without judgement and work with the patient to find means to reduce concerns and answer questions as best you can. At the end, vaccination is their choice, but our hope.

COVID and nursing mothers

- Breast milk provides protection against serious childhood infections. Women are often encouraged to continue breastfeeding or provide breast milk even when they are sick with a virus, such as the flu.
- In a study of 18 women with confirmed SARS-CoV-2 infection, one breast milk sample had detectable SARS-CoV-2 RNA, but the viral culture for that sample was negative (Chambers). No other breast milk samples from the 18 women had evidence of infectious virus.
- In another study that included 24 mothers confirmed with COVID-19 and 19 with suspected infection, no breast milk samples tested positive for the SARS-CoV-2 nucleic acid (Peng).
- A review of 46 COVID-19 positive mothers whose breast milk samples were tested for COVID, 43 samples tested negative, and only three tested positive. Of the three mothers whose breast milk samples tested positive, only one infant tested positive for the virus (Centeno-Tablante).
- This suggests that breast milk may not be a potential source of infection for the infant. In fact, one group found that there was no clinical evidence of infections in infants who were breastfed with mothers wearing masks, appropriate hand and breast hygiene, and with newborns kept six feet away from mothers (Kyle).

COVID and Asthma

- There have been many studies looking at the relationship between COVID-19 and asthma.
- Thus far the vast majority of these studies have found no increased risk of COVID-19 disease severity in those with asthma.
- Further, there appears to be no indication that asthma is a risk factor for developing COVID-19 disease.
- A few studies have suggested that non-allergic asthma may be associated with more severe COVID-19 disease, although it is not clear in these studies that subjects did not have COPD, which is a well-established risk for severe COVID-19.

COVID and Asthma

- The use of systemic corticosteroids for treatment of COVID-19 lung disease in individuals without asthma is not recommended.
- There is no data at this time to support limiting or avoiding all standard asthma therapeutic measures, including systemic corticosteroids, in individuals with asthma and a COVID-19 infection.
- Patients with asthma should continue to take their controller medications and not stop them, even if they have symptoms of COVID-19.
- Also, the studies showing a potentially worse outcome with systemic steroids were in hospitalized COVID-19 patients who received the steroids as a treatment for the viral illness. Not due to asthma treatments.

COVID and Asthma

- A few studies have also suggested a higher rate of intubation in asthma patients hospitalized with COVID-19, but other studies have not replicated these findings.
- A large retrospective study involving 27,810 patients showed that ICS treatment for COPD did not increase the risk for hospitalization, ICU admission, mechanical ventilation or mortality from COVID-19.
- Early data from New York State had suggested a reduced death rate in asthma patients hospitalized with COVID-19, and recently re-reported by Mather et al in the Journal of Asthma 2021.

Can ICS help in COVID?

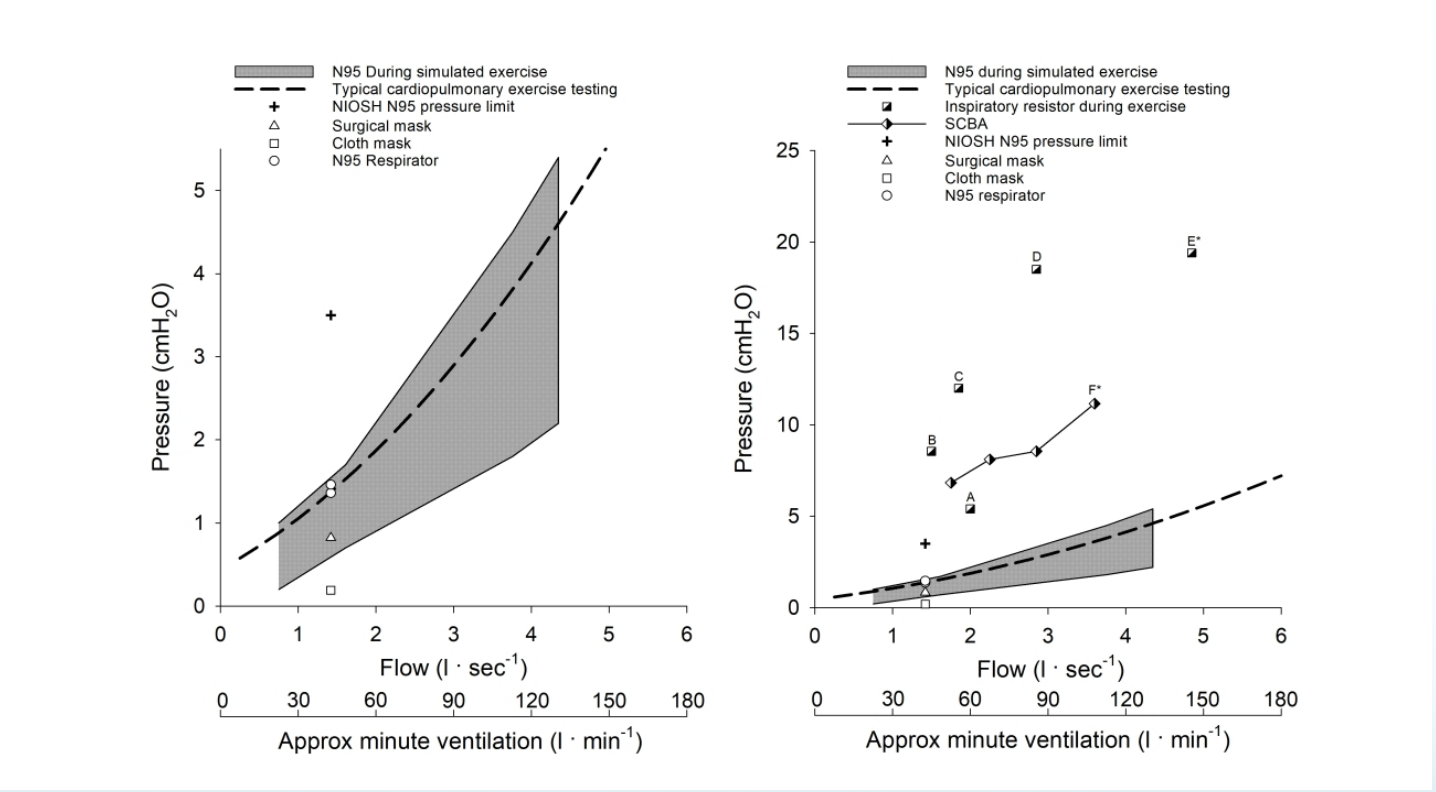
- A randomized open-label study with 146 participants in the UK found that treatment with inhaled budesonide, 1600mcg BID, within seven days of onset of mild COVID-19 symptoms was associated with reduced likelihood of needing urgent medical care and reduced time to recovery compared to regular care.
- No other studies have replicated this approach.

Ramakrishnan et al. Lancet Respiratory Medicine April,2021 (In press)

What about filters and masks?

- A study from the CDC has found that portable air cleaners with HEPA filters and masks, when used together, reduced indoor exposure to COVID-19 aerosols by up to 90%
- Overall, open air helps reduce aerosolized spread of virus more than mask and filters at their best
- We are limited since indoor activities remain the main area of transmission
  - ie birthday parties

Masks and exercise



As of mid July, CDC encourages return to school, but masking suggested for unvaccinated students.

Links between asthma and COVID

- There are clear links between the disease but not in the traditional sense
  - Asthma remains an inflammatory disease of the lungs with multiple triggers including viral infections
  - Asthma outcomes are just a likely to be influenced by social determinants of health as medication choices
- Severe COVID is really an inflammatory process that results in respiratory failure and immune dysregulation (cytokine storm)
  - Multiple biologic agents and anti-inflammatory agents are being used to manage disease in the acute setting

Where symptoms blur

- **Persistent Symptoms After Infection**
  - A systemic review of 45 studies including 9,751 participants with COVID-19, the median proportion of individuals who experienced at least one persistent symptom was 73%.
  - Symptoms occurring most frequently included **shortness of breath or dyspnea**, fatigue or exhaustion, and sleep disorders or insomnia.
  - Keep this in mind when patients present with new onset asthma or SOB
  - Several large centers such as the University of Michigan have post COVID Clinics housed within Divisions of Pediatric and Adult Pulmonary to address these issues.

Acute Symptoms blurring

- **Home Monitoring of Oxygen Saturation and Respiratory Rate Are Important**
  - Several studies examined mortality in hospitalized patients with COVID-19 and noted that while many had hypoxemia and tachypnea on admission, few reported shortness of breath or cough.
  - Patients with hypoxemia (O2 sat <92%) had a 1.8 to 4.0-fold increased mortality risk.
  - The authors suggest that patients with other risk factors monitor respiratory rate and oxygen saturation at home and seek medical care if O2 sat is <92% and/or respiratory rate is >23 breaths/minute, when early treatment might be most helpful.

So, a reminder

- Patients with asthma need to continue to take their controller medications and keep their asthma under control because the risk here is that they stop the medications, have an asthma flare, then present to the emergency department
- Further being in a known community with spread of COVID-19, and then they get COVID-19 from being in the emergency department—all of which could have been avoided by keeping their asthma under control in the first place.

COVID and Asthma Summary

- Taken together, it appears that there is either no risk or at most a very slight risk for more severe COVID-19 disease in non-allergic asthma patients.
- In contrast to other risk factors like uncontrolled COPD, obesity, etc., that have consistently been linked to more severe COVID-19 disease.
- Children with asthma have not been hospitalized more than their counterparts without asthma.
- We now know that for many the acute inflammatory phases and coagulopathies are major contributors to poor outcomes in severe disease.
  - This highlights many of the new biologic agents being tested

So what about after COVID

- The CDC has issued a health advisory about increased interseasonal RSV in the southern U.S. and recommends testing for that infection in patients with acute respiratory illness who test negative for SARS-CoV-2.
- ER rates for acute virally induced asthma flares in children plummeted throughout the country during the height of the COVID pandemic.
  - This supports the viral impacts of asthma exacerbations

How to tell the difference

- It is not possible to distinguish between an impending viral induced asthma exacerbation and the symptoms of COVID-19 in students who do or do not have asthma.
- Thus, all symptomatic students should be considered to have COVID-19 until testing proves otherwise.
- Children should continue their daily controller medications, including inhaled corticosteroids. These medications have not been shown to increase risk of COVID-19 infection or disease severity.
- Children should therefore continue their medications as prescribed by their asthma health provider.

COVID COVID COVID

- **Repeat Testing Not Helpful in Low Prevalence Situations**
  - In a population of 5,000 patients with symptoms in an area with a low prevalence of SARS-CoV-2 infection, repeat testing of negative patients who had persistent symptoms still yielded a negative result in 96% of cases.
- **Asymptomatic Children Have Lower Viral Load**
  - In study publish in the Journal of Clinical Microbiology, researchers noted that asymptomatic children with SARS-CoV-2 had Ct values (cycle threshold for RT/PCR) 10.3 cycles higher than children with symptoms (so less of a viral load).
- **CDC Issues New Guidance Defining "Close Contact"**
  - The new definition includes exposure to a confirmed or likely case of COVID-19 for a total of **15 minutes or more over a period of 24 hours**.

Treating asthma in the COVID era in schools

- Nebulizers should be discouraged from being used routinely in the school setting.
- If absolutely necessary, rescue inhalers such as albuterol can be used with the student's own spacer, or appropriate disposable spacers. Disposable spacers should be discarded after use.
- Follow CDC guidelines for other considerations when treating a sick child (e.g., placing in isolation room with ad- equate medical supervision until parent arrives for pick up).
- Although CDC recommendations on the use of peak flow meters indicate that they are unlikely to generate aerosols, the accuracy of results can be questionable and the effort may produce coughing, so this is not recommended.

Myocarditis post vaccination

- Ages range from 16-66 years, mostly males
- For clinicians the presentation of chest pain or pressure and shortness of breath would not be unusual in presentation in asthma or myocarditis
  - **Symptoms include chest pain or pressure, shortness of breath, EKG abnormalities, and abnormal cardiac enzymes.**

Myocarditis

- The ACIP COVID Vaccine Safety Technical (VaST) Work group heard several presentations on this from the Department of Defense, VAERS, and Vaccine Safety Data Link (VSD).
- VaST concluded that there are relatively few reports of myocarditis and they were predominately occurring in adolescent and young adult males following mRNA vaccine, more often after dose two, occurring four days to two weeks after vaccination and most were mild.
- Within the CDC monitoring systems, these issues have been noted but agreed the benefits of vaccination out weighted any of the current risks of myocarditis.

AICP recent statement

- **Allergic reactions (including severe allergic reactions) not related to vaccines (COVID-19 or other vaccines) or injectable therapies, such as allergic reactions related to food, pet, venom, or environmental allergies, or allergies to oral medications (including the oral equivalents of injectable medications), are not a contraindication or precaution to COVID-19 vaccination.**

The ”New” Guidelines

It only took 13 years and a pandemic

NHLBI Guidelines

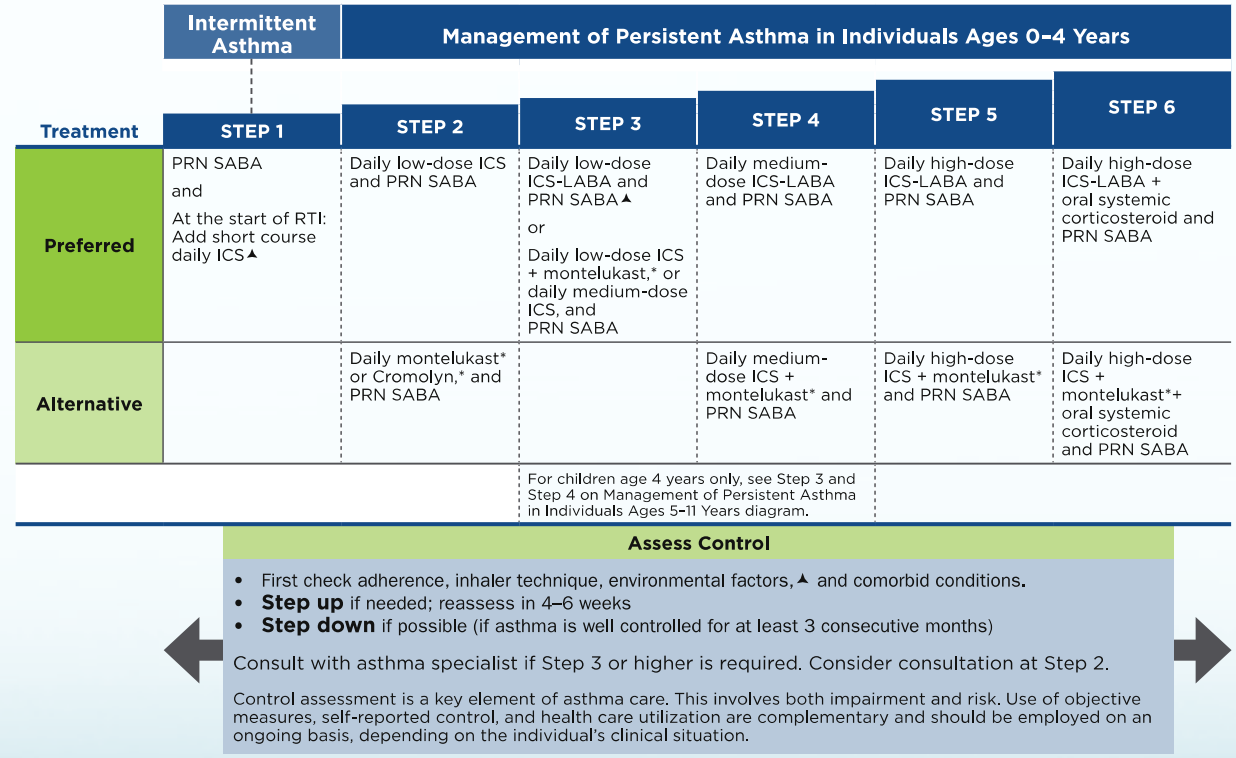
- FINALLY NEW GUIDELINES in 2020!
- The general framework of asthma management has remained unchanged for over 13 years but we might have new options now!
- Inhaled corticosteroids remain the mainstay of maintenance medication with intermittent use of short acting beta-agonist medications
- But there are some new approaches worth discussing specific to how clinicians delivery care in the community

What the Guidelines say

- The guidelines generally keep the same framework as before, but spend more effort supporting the recommendations with data and offer some clinician guided advice on how to present and implement the recommendations.
- There is also greater focus on adjusting treatment options based on specific patient groups as well as acknowledgements of the impacts on social determinates of health in respect to asthma and other chronic diseases.
- Treatment of asthma is NOT a one size fit all.

Ages 0-4

AGES 0–4 YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA



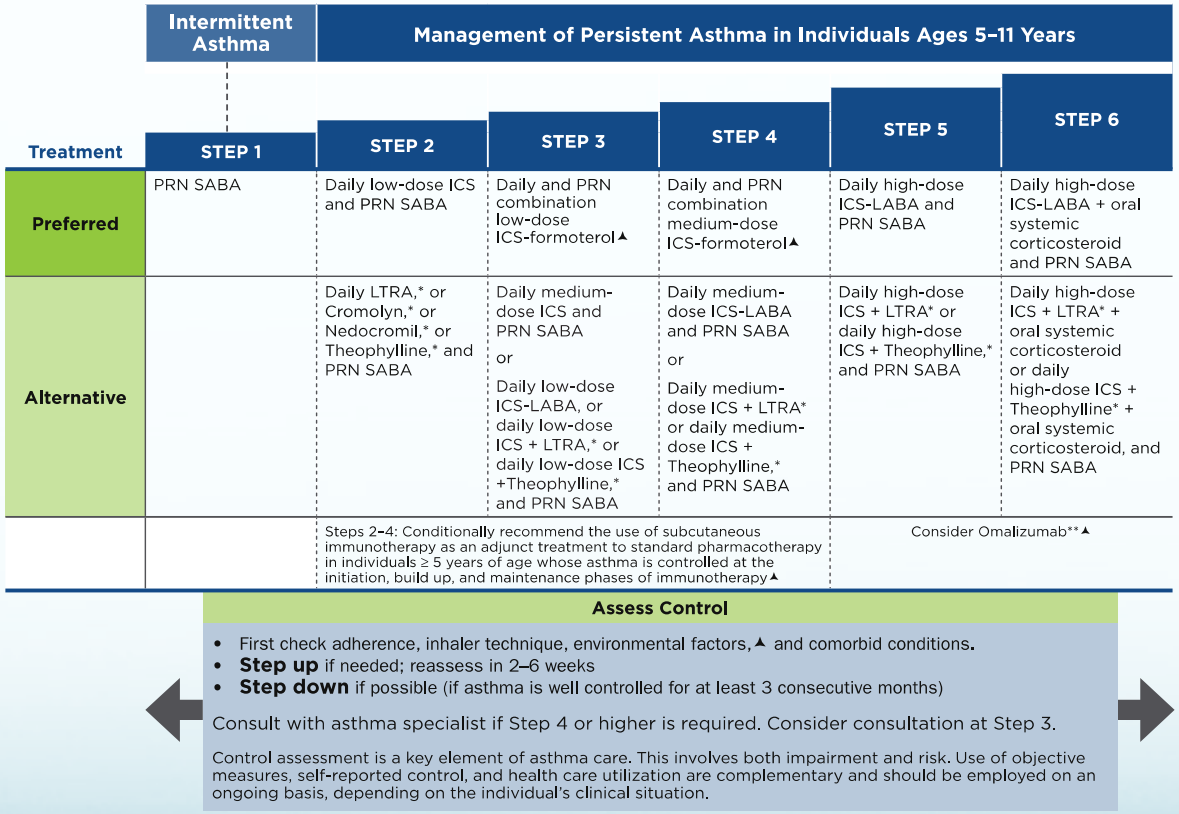
Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist; RTI, respiratory tract infection; PRN, as needed

▲ Updated based on the 2020 guidelines.

* Cromolyn and montelukast were not considered for this update and/or have limited availability for use in the United States. The FDA issued a Boxed Warning for montelukast in March 2020.

Ages 5-11

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



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

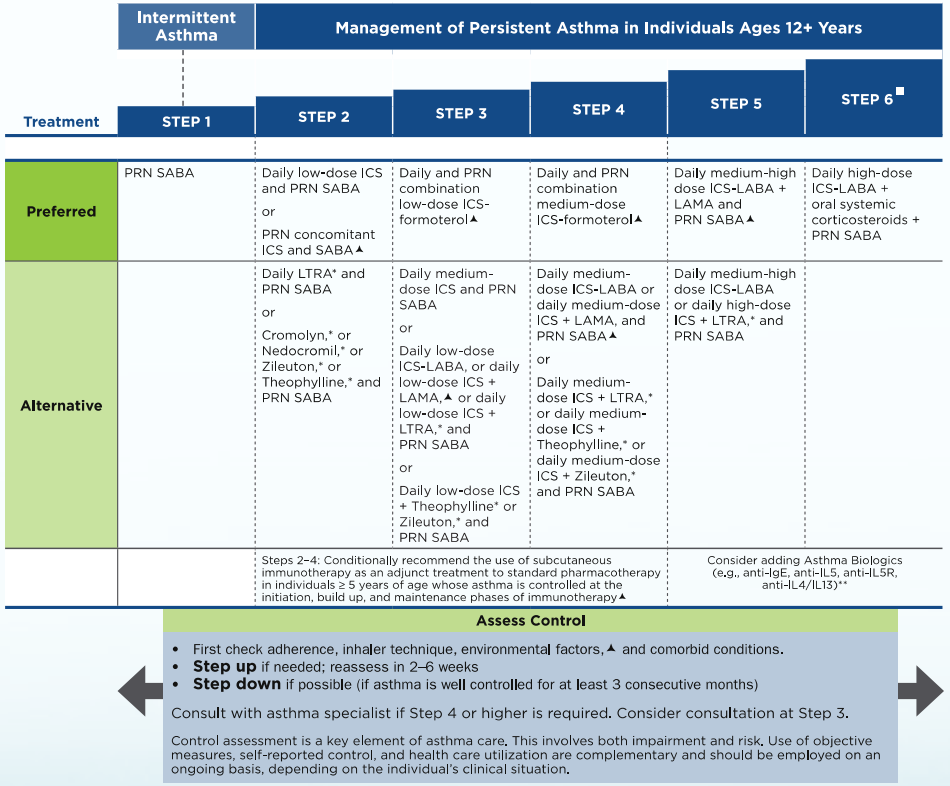
▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including montelukast, and Theophylline were not considered in this update and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** Omalizumab is the only asthma biologic currently FDA-approved for this age range.

Ages 12-Adult

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including Zileuton and montelukast, and Theophylline were not considered for this update, and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (e.g. anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6.

■ Data on the use of LAMA therapy in individuals with severe persistent asthma (Step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

Some background of SMART therapy

“On Demand” use of inhaled maintenance medication

- With the availability of approved pediatric inhaled steroids, clinicians have attempted patient initiated acute increases in dosing as a simple, available method to reduce the need for oral steroid for acute flares of asthma
- Earlier studies suggested this could reduce emergency room utilization and hospitalization
- Examples include doubling ICS dosing during viral infections and reduction once symptoms resolve

Combination therapy as acute treatment

- In clinical practice, poor adherence to asthma medications, particularly ICS as maintenance therapy, is a major problem across all severities of asthma
- Patients rely on SABAs for symptom relief, but SABAs do not address the underlying inflammatory process or protect against exacerbations
- Increased use of SABAs is associated with a higher exacerbation risk

Intermittent treatment

- O'Byrne et al utilized this potential strategy to address these issues by using of a combination of a fast-acting β-agonist and ICS taken on an as needed basis in mild/moderate asthmatics.
- On demand budesonide-fomotorol combination therapy was able to show effectiveness compared to SABA alone and reduce exacerbations of asthma as well as maintenance therapy.
- Intermittent acute combination therapy preserved lung function as well as maintenance therapy.

O'Byrne et al. N Engl J Med 2018;378:1865-76.

Could this work?

- The effects with budesonide–formoterol used as needed occurred at a median daily dose of ICS that was only 17 to 25% of that in the regular maintenance group.
- This was a significant decrease in ICS exposure.
- Intermittent use of combination therapy was NOT as effective as maintenance therapy in controlling daily symptoms.
- Mortality and hospitalizations were similar in both groups.
- Broader healthcare costs and public health outcomes may be supported by this approach.

SMART

- Single maintenance and reliever therapy (SMART) has been proposed as a new mechanism to address asthma control in certain individuals.
- Formotorol has been the only LABA examined with this technique since it has a rapid onset of action and is allowed to be used more than twice daily
- Maximal doses 8 puffs or 36ug (ages 4-11) or 12 puffs or 54ug
- In the studies budesonide+fomotorol was the studied drug and mometasone+fomotorol should be equivalent

Does SMART work

- Multiple reviews note that individuals who underwent the SMART approach could reduce the overall burden on inhaled steroid use, ER visits, oral steroid use, and night time wakenings compared to individuals using ICS alone or no controller medication.
- The relative risk of exacerbations decreased anywhere from 27-77% with children on SMART therapy.
- Outcomes on SMART therapy were as good as more intense therapies in children > 12 and adults.

An Example of being SMART

- 13 year old boy with moderate persistent asthma on controller medication (Symbicort 80 2 puffs BID)
- The SMART approach is to coach the child to use his Symbicort 80 as both a maintenance and rescue medications “replacing” the albuterol MDI with Symbicort during his acute exacerbation.
- In theory if the boy needs rescue medications he may be taking Symbicort 80 2 puffs at 8am and 8pm in addition to taking 2 puffs at noon and 4 pm if he’s having more wheezing. His albuterol nebulizer and MD are set aside.
- The boy would reduce his Symbicort dosing once his exacerbation is better in 2-3 days.

Applying SMART

- You cannot use SMART with salmetrol ie Advair or Airduo or Breo
  - This is due to the slower onset of action of salmeterol and vilanterol
- Data is more robust in children >12 years of age versus younger children at this time.
- This does not work well in children/teens with poor symptom perception and often need parent/guardian coaching to identify symptoms and appropriate intervention

Too late! Need to act!

What can you do when the house starts to burn!

Dexamethasone in exacerbations

- Dexamethasone has been proposed as an equivalent therapy to prednisone/prednisolone for acute asthma exacerbations in pediatric patients.
- Oral (PO) or intramuscular (IM) dexamethasone has been proposed as an equivalent therapy.
- Potential advantages
  - Longer half-life requiring a shorter course
  - Increased compliance with a single dose,
  - Less vomiting with dexamethasone.

Dexamethasone

- Compared with prednisone or prednisolone, dexamethasone is a long-acting corticosteroid with a half-life of 36 hours to 72 hours, which, when administered as a single dose or 2 doses over a 2-day period, is equivalent to a 5-day course of prednisone.
- As opposed to dexamethasone, many patients prescribed several day courses of prednisone were not adherent in filling their prescription, thus leading to a return to an emergency department.
- In the inpatient setting, dexamethasone reduced overall length of stay for exacerbations compared with prednisone, and there was no significant difference between dexamethasone and prednisone in all cause readmission rates.

Meta-analysis of dexamethasone

- Keeny et al in 2014 completed a meta-analysis involving children noting that PO/IM dexamethasone could be an equivalent alternative to standard oral steroids
- The majority of the studies within this meta-analysis were preformed in the emergency room setting and not standard outpatient clinic.

Keeny et al. Pediatrics 2014;133;493

So to finish

- COVID will likely impact how we manage asthma for a while
- There are other viral triggers to asthma beyond COVID, don't forget those
- Many families and clinicians have become rusty managing the acute exacerbations of asthma over the past year
- New methods of asthma care may yield improved outcomes despite the impact of COVID including biologic therapies

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