Asthma Exacerbations

David B. Peden, MD, MS
Chief, Division of Allergy, Immunology, Rheumatology and Infectious Diseases, Department of Pediatrics
&
Director, Center for Environmental Medicine, Asthma and Lung Biology
University of North Carolina at Chapel Hill
Chapel Hill, NC

Disclosures

David B. Peden, MD, MS

- **Personal financial interests in commercial entities that are relevant to my presentation(s)**

No relevant commercial interests.

Committee Members

- Anne Fuhlbrigge, M.D., M.S. (Co-chair)
- David Peden, M.D. (Co-chair)
- Andrea Apter, M.D.
- Homer Boushey, M.D.
- Carlos A. Camargo, Jr., M.D., Dr.P.H.
- James Gern, M.D.
- Peter Heymann, M.D.
- Fernando Martinez, M.D.
- David Mauger, Ph.D.
- William G. Teague, M.D.
- Carol Blaisdell, M.D. (NIH Liaison)

DRAFT Recommendations: Ages ≥ 12

	Characterization of Study Population for Prospective Clinical Trials (i.e. baseline information)	Prospective Clinical Trial Efficacy /Effectiveness Outcomes	Observational Study Outcomes
Core Outcomes	Events in the 12 months prior to study entry: 1. Systemic corticosteroids for asthma* 2. Asthma-specific hospital admissions 3. Asthma-specific Emergency Department visits	1. Systemic corticosteroids for asthma* 2. Asthma-specific hospital admissions 3. Asthma-specific Emergency Department visits (includes Urgent Care [UC] visits where these can be differentiated) 4. ICU/intubations 5. Death (all cause & asthma-related)	1. Systemic corticosteroids for asthma* 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (includes Urgent Care [UC] visits where they can be differentiated)
Supplemental Outcomes	1. For trials of acute management of exacerbations (ED setting): FEV_1 2. Any prior exacerbation 3. Any prior ICU admission/intubation 4. Socioeconomic Status (SES)	1. For trials of acute management of exacerbations (ED setting): FEV_1	NONE

* For patients on a stable maintenance dose, an increase in the dose of systemic corticosteroids

DRAFT Recommendations: 0-4 and 5-11 years of age

	Characterization of Study Population for Prospective Clinical Trials (i.e. baseline information)	Prospective Clinical Trial Efficacy /Effectiveness Outcomes	Observational Study Outcomes
Core Outcomes	Events in the 12 months prior to study entry: 1. Systemic corticosteroids for asthma* 2. Asthma-specific hospital admissions 3. Asthma-specific Emergency Department visits	1. Systemic corticosteroids for asthma* 2. Asthma-specific hospital admissions 3. Asthma-specific Emergency Department visits (includes Urgent Care [UC] visits where these can be differentiated) 4. ICU/intubations 5. Death (all cause & asthma-related)	1. Systemic corticosteroids for asthma* 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (includes Urgent Care [UC] visits where they can be differentiated)
Supplemental Outcomes	**1. For trials of acute intervention (ED setting): validated tools such as PASS, PS, PRAM, CAS, PI, ASS** 2. Any prior exacerbation 3. Any prior ICU admission/intubation 4. Socioeconomic Status (SES)	**1. For trials of acute intervention (ED setting): validated tools such as PASS, PS, PRAM, CAS, PI, ASS**	NONE

* For patients on a stable maintenance dose, an increase in the dose of systemic corticosteroids

DRAFT Recommendations: Ages ≥ 12

	Characterization of Study Population for Prospective Clinical Trials (i.e. baseline information)	Prospective Clinical Trial Efficacy /Effectiveness Outcomes	Observational Study Outcomes
Emerging Outcomes	1. Biomarkers of exacerbation: (FeNO, sputum, exhaled breath condensate analytes)	1. Stratification of exacerbations by severity 2. Short course of high dose ICS as a definition of an asthma exacerbation. 3. SABA use as a definition of an asthma exacerbation. 4. Biomarkers of exacerbation: (FeNO, sputum, exhaled breath condensate analytes) 5. Total corticosteroid dose	NONE

DRAFT Recommendations: 0-4 and 5-11 years of age

	Characterization of Study Population for Prospective Clinical Trials (i.e. baseline information)	Prospective Clinical Trial Efficacy /Effectiveness Outcomes	Observational Study Outcomes
Emerging Outcomes	1. Biomarkers of exacerbation: (FeNO, sputum, exhaled breath condensate analytes) **	1. Stratification of exacerbations by severity 2. Short course of high dose ICS as a definition of an asthma exacerbation. 3. SABA use as a definition of an asthma exacerbation. 4. Biomarkers of exacerbation: (FeNO, sputum, exhaled breath condensate analytes)** 5. Total corticosteroid dose	NONE

** Age 5-11 years only, the ability to perform the technique for some biomarkers, such as FeNO and EBC, is age-dependent and difficult to use reliably in young children

Standardized Reporting: Exacerbation Rates

- Preferred methodology
  - # Events requiring systemic corticosteroids/ per participant/per time interval
  - Annual rates are preferred
    - Extrapolation to annual rates from studies of shorter duration is not recommended
  - Calculated as weighted mean rate of occurrence
    - Total exacerbations/ total person time
- Additional methodology
  - Time to first exacerbation
  - Percentage of study group with an exacerbation

Key Discussion Points

- Tremendous variation exists in the literature regarding the terminology for asthma “exacerbation”
  - 15 different terms in use to refer to an asthma exacerbation
    - No dominant definition of asthma exacerbation
- Makes comparison across studies problematic
  - Exacerbation is rarely defined by a single component
    - Treatment with systemic corticosteroids is most commonly used
  - Variation in how subjects with asthma present supports the use of a definition that includes multiple components
    - Yet little evidence exists to support a specific set of components or the thresholds for any individual component within a given definition

Key Discussion Points

- Variation exists in how the severity of an exacerbation is classified
  - Most studies do not distinguish levels of severity
- The ability to distinguish between poorly controlled asthma and an "moderate" exacerbation is difficult and characterized by vague and inconsistent terminology
  - Limits the ability to reliably classify levels of severity for exacerbations

Key Discussion Points: Pediatrics

- The use or the increase in the use of SABA is a more commonly used criterion/factor in defining exacerbation in children
  - The threshold criterion for distinguishing between loss of control and an asthma exacerbation has not been defined

Call for New Outcome Measures

- Component-based definition of exacerbations
  - Defines threshold values for each component used to collectively define an exacerbation
    - Can levels of severity be distinguished by such component measures?

Key Discussion Points: Pediatrics

- Physiological measures (i.e. FEV1) are age-dependent and difficult to use reliably in young children, and as such are not useful to define exacerbations
- Currently, biomarkers are not useful in defining exacerbation
  - For older children, age 5-11 years, they may be useful in better understanding the biology/mechanisms of exacerbation and in defining the population at risk for exacerbation
  - The ability to perform techniques, such as FeNO and EBC, is age-dependent and difficult to use reliably in young children

Key Discussion Points: Pediatrics

- Asthma exacerbations in children ages 0-4 years of age are particularly difficult to identify for several reasons
  - The differentiation of changes in daily symptoms from a potential cluster of symptoms sufficient to be termed an exacerbation is based on the perception of the caregiver and not the child
  - The threshold for symptom identification and initiation of therapy depends on the education level and personality of the caregiver

Call for New Outcome Measures

- Characterization of exacerbation by precipitating factor
  - Viral illness
  - Allergen exposure
  - Pollutant exposure
  - Medication non-adherence
- Characterization of factors that contribute to the decision to use systemic corticosteroids or seek urgent health care utilization are especially variable for children
  - A checklist or standard format to define those factors is needed

Summary

- An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome
  - For patients on a stable maintenance dose, an increase in the dose of systemic corticosteroids
- This recommendation is the same for Adult/Adolescent and Pediatric populations
- Emphasis on standardized methodology and reporting