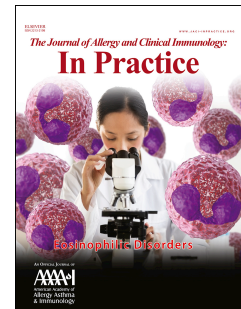


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Nidhya Navanandan, MD, Jonathan Hatoun, MD, MPH, MS, Juan C. Celedón, MD, DrPH, Andrew H. Liu, MD



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Predicting Severe Asthma Exacerbations in Children: Blueprint for Today and Tomorrow

Nidhya Navanandan^a, MD, Jonathan Hatoun^b, MD, MPH, MS, Juan C. Celedón^c, MD, DrPH,
Andrew H. Liu^d, MD

Affiliations: ^aPediatric Emergency Medicine, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado; ^bDivision of General Pediatrics, Harvard Medical School, Harvard University, Boston, Massachusetts; ^cDivision of Pediatric Pulmonary Medicine, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, Pennsylvania; ^dPediatric Pulmonary and Sleep Medicine, Breathing Institute, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora Colorado

Corresponding Author: Nidhya Navanandan, Children's Hospital Colorado, University of Colorado School of Medicine, Section of Pediatric Emergency Medicine, 13123 East 16th Avenue, Box251, Aurora, CO 80045, Email: Nidhya.navanandan@childrenscolorado.org, Phone: (847) 636-0817, Fax: (720) 777-7317.

Email addresses:

Jonathan Hatoun: jonathan.hatoun@childrens.harvard.edu
Juan Celedón: juan.celedon@chp.edu
Andrew Liu: Andrew.liu@childrenscolorado.org

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ABSTRACT

Severe asthma exacerbations are the primary cause of morbidity and mortality in children with asthma. Accurate prediction of children at risk for severe exacerbations, defined as those requiring systemic corticosteroids, emergency department visit and/or hospitalization, would considerably reduce healthcare utilization and improve symptoms and quality of life. Substantial progress has been made in identifying high-risk exacerbation-prone children. Known risk factors for exacerbations include demographics (i.e., low income, minority race/ethnicity), poor asthma control, environmental exposures (i.e., aeroallergen exposure/sensitization, concomitant viral infection), inflammatory biomarkers, genetic polymorphisms and markers from other “omic” technologies. The strongest risk factor for a future severe exacerbation remains having had one in the prior year. Combining risk factors into composite scores and use of advanced predictive analytic techniques such as machine learning are recent methods used to achieve stronger prediction of severe exacerbations. However, these methods are limited in prediction efficiency and are currently unable to predict children at risk for impending (within days) severe exacerbations. Thus, we provide a commentary on strategies that have potential to allow for accurate and reliable prediction of children at risk for impending exacerbations. These approaches include implementation of passive, real-time monitoring of impending exacerbation predictors, use of population health strategies, prediction of severe exacerbation responders versus non-responders to conventional exacerbation management, and considerations for pre-school age children who can be especially high risk. Rigorous prediction and prevention of severe asthma exacerbations is needed to advance asthma management and improve the associated morbidity and mortality.

71 **Keywords:** childhood asthma, asthma exacerbations, prediction, risk factors

72

73 **Abbreviations:**

74 Emergency department (ED)

75 Inhaled corticosteroid (ICS)

76 Fraction of exhaled nitric oxide (FeNO)

77 IL-5 receptor α (*IL5RA*)

78 Cadherin-related family member 3 (CDHR3)

79 Human rhinovirus species C (HRV-C)

80 Machine learning (ML)

81 Area under the curve (AUC)

82 Negative predictive value (NPV)

83 Asthma Control Test (ACT)

84 Peak expiratory flow (PEF)

85

Introduction

Severe asthma exacerbations are the primary cause of morbidity and mortality in children with asthma. Severe exacerbations are a leading cause of health care utilization for asthma, accounting for 750,000 emergency department (ED) visits and 200,000 hospitalizations annually.^{1, 2} The social and economic burden of childhood asthma is also substantial, with missed school days, limitation in usual childhood activities, parental work absences, and \$50 billion in annual medical costs.³⁻⁵ Furthermore, severe asthma exacerbations are associated with progressive decline in lung function and growth, which can persist into early adulthood and portend pulmonary impairment and disability.^{6, 7} A variety of definitions are used to describe severe exacerbations in asthma clinical care and research; however, the most commonly used definition for severe exacerbation is one that requires medical intervention including systemic corticosteroid treatment, ED visit and/or hospitalization.⁸ It is notable that this common definition in clinical care and research has limitations: it is a utilization-based outcome measure and not based on a direct assessment of clinical or physiologic severity per se.⁹ Unfortunately, severe exacerbations continue to occur despite the availability of therapies to prevent or mitigate the severity of exacerbations for a majority of children. This article provides a commentary on strategies that have potential to allow for accurate and reliable prediction of children at risk for impending exacerbations. Accurate prediction of severe asthma exacerbations will allow for timely administration of effective therapies to prevent severe exacerbations and their associated morbidity.

Risk factors for severe asthma exacerbations

A variety of demographic and clinical risk factors have been identified for severe asthma exacerbations (Table 1). Young, low income, and minority children are at increased risk for severe exacerbations.¹⁰⁻¹² Exacerbation rates and health care utilization are specifically higher among boys, African American and Puerto Rican race/ethnicities, and low-income populations.¹³

Poor asthma control, as assessed by symptom questionnaires and beta-agonist use, is also a risk factor for severe asthma exacerbations.¹⁴⁻¹⁷ Studies report a 2-fold increase in exacerbation rates in children with poor asthma control as defined by the National Heart, Lung, and Blood Institute impairment domains.¹⁵ Symptom-based scores including the Asthma Control Test (ACT), Asthma Control Questionnaire and Asthma Exacerbation Clinical Score, can predict risk of exacerbation over a specified period (e.g., within months to a year), but are not effective at predicting an impending exacerbation (e.g., within a few days).¹⁶⁻¹⁸ Schatz et al¹⁶ demonstrated that the ACT was associated with an increased 12-month risk of emergency care for asthma, and oral corticosteroid and beta-agonist dispensing. However, recent studies have questioned the predictive utility of the ACT indicating that the ACT is not superior to rescue inhaler use alone in predicting severe asthma exacerbations.¹⁹ Interestingly, Wu et al²⁰ demonstrated that factors associated with worsening asthma symptoms are different than those of severe exacerbations. In their 4-year study, 14% of participants never had persistent symptoms, but had at least one severe exacerbation.²⁰

In fact, the strongest risk factor for a future severe asthma exacerbation is having had one in the prior year.^{12, 15, 20-23} Children with a recent severe asthma exacerbation have a 3-fold increase in risk of exacerbation regardless of demographics, disease severity, asthma control and medication use.²² Frequency and recency of severe exacerbations also seem to matter. In metropolitan St. Louis over a 10-year time span, the probability of hospital readmission for an asthma exacerbation in children increased from 30% after a prior first admission, 46% after a second, and 59% after a third.¹¹ In a 3-year study of adults with severe asthma, the probability of a severe exacerbation in Year 3 increased if there was a severe exacerbation in the prior year (63%), and especially if there was a severe exacerbation in each of the two prior years (82%).²⁴

Respiratory viral infections are the main trigger for severe asthma exacerbations in children. Rhinovirus, specifically, accounts for up to 80% of wheezing episodes and plays a role

in seasonal peaks in exacerbations and exacerbation severity.²⁵⁻²⁷ Aeroallergen sensitization further increases the risk of a severe asthma exacerbation after a viral infection, and such risk may be reduced by treatment with inhaled corticosteroids or anti-IgE therapy before seasonal peaks for viral illnesses (e.g., before the school year begins).^{28, 29}

Indoor and outdoor air pollutants, as well as allergen exposure, are known risk factors for severe asthma exacerbations in children. Indoor pollutants, including second-hand smoke, may trigger severe exacerbations.³⁰ Similarly, indoor allergens such as cockroach are known precipitants of exacerbations and healthcare utilization, particularly in sensitized children.³¹ Air pollution, such as that related to automobile traffic, has also been implicated in new onset of severe asthma exacerbations during childhood, either alone or in combination with allergen exposure.^{32, 33}

Although vitamin D levels below 30 ng/ml had been linked to severe asthma exacerbations in observational studies, no beneficial effects of vitamin D supplementation were demonstrated in a recent clinical trial of children with asthma and vitamin D levels between 14 ng/ml and 29 ng/ml.³⁴ However, a meta-analysis of individual data from a limited number of prior clinical trials suggests a potential beneficial effect of vitamin D against severe asthma exacerbations in children with very low vitamin D levels (e.g. below 10 ng/ml), in whom further studies are needed.³⁵

Overweight or obesity and chronic psychosocial stress have been associated with severe asthma exacerbations during childhood, with a potential common mechanism being resistance to commonly used medications for asthma. In particular, overweight or obesity has been implicated in reduced response to inhaled corticosteroids,³⁶ while high chronic stress has been associated with resistance to short-acting beta2-agonists in youth.³⁷ Moreover, chronic stress can lead to poor adherence with controller medications, a well-known risk factor for poor asthma control and severe asthma exacerbations.

Whereas genome-wide association studies (GWASs) have identified susceptibility variants for asthma, less is known about susceptibility variants for severe asthma exacerbations, which may differ from those for asthma. For example, a CDHR3 (cadherin-related family member 3) gene variant was implicated in recurrent severe exacerbations in infants and pre-school aged children of European descent.³⁸ More recently, a meta-analysis of GWASs showed a significant association between a SNP in *FLJ22447* (rs2253681) and severe asthma exacerbations in 4,010 Latino youth (odds ratio [OR]=1.55, 95% confidence interval [CI]= 1.34 to 1.79, $P=6.3\times10^{-9}$), but this finding has yet to be replicated in other racial or ethnic groups. Similarly, SNPs on the genomic region for class II HLA genes were recently implicated on risk for asthma hospitalizations in a GWAS in British adults, but such findings have not been replicated in children.³⁹

Biomarkers, which have been used to identify molecular pathways for therapeutic targets, have also demonstrated association with severe asthma exacerbations. Most notably, peripheral blood eosinophil count and fractional exhaled nitric oxide (FeNO) have been used to predict response to treatment and risk of future severe exacerbations. These biomarkers indicate the well-known T2-high pathway characterized by eosinophilic inflammation and responsive to corticosteroids.⁴⁰⁻⁴² A peripheral blood eosinophil count > 300-400 cells per μL has been most consistently associated with increased risk for exacerbations. In a large retrospective analysis of individuals 12-80 years with asthma, Price et al²¹ demonstrated that individuals with blood eosinophil counts >400 cells per μL had significantly more severe exacerbations (relative risk [RR] 1.42; 95% CI:1.36-1.46) compared to those with eosinophil counts $\leq$ 400 cells per μL . In individuals with severe asthma recruited in the Severe Asthma Research Program (SARP-3), blood eosinophil counts were associated with exacerbation frequency in multivariable analysis.⁴³

FeNO has produced mixed results in prediction of future severe asthma exacerbations. Fielding et al⁴⁴ demonstrated that a large change in % FeNO was associated with poor asthma

outcomes, but not exacerbation risk. Baseline FeNO and absolute change in FeNO were also not associated with exacerbation risk or asthma outcomes questioning the utility of FeNO in identifying children at risk for exacerbations.⁴⁴ Additional prospective and longitudinal studies are needed to assess the full utility of these biomarkers in predicting severe exacerbations in children.

Omics biomarkers (i.e. genomics, transcriptomics, proteomics, metabolomics) have shown early promise as potential predictors of severe asthma exacerbations. For example, genetic variants linked to severe asthma exacerbations (e.g., CDHR-3, see above) should be assessed in longitudinal studies. Nasal airway transcriptomic (gene expression) profiling can provide fine molecular characterization of distinct asthma exacerbation processes in children at high risk for exacerbation. Altman et al⁴⁵ have leveraged nasal transcriptomics to demonstrate that baseline immune states can predict exacerbations. In their work, a higher T2/T1-Interferon ratio predicted an exacerbation in the short term suggesting a specific “at risk” immune state during which a child is most likely to experience an exacerbation.⁴⁵

Stronger prediction of severe asthma exacerbations

Considering that numerous risk factors for future severe asthma exacerbations in children have been identified, there has been a drive to determine if combining risk factors can improve prediction. Investigators have sought to identify the strongest risk factors of exacerbations, develop composite scores combining predictors, and apply iterative analytic approaches such as machine learning. As mentioned above, the most consistent risk factor for a future severe asthma exacerbation is having had one in the prior year, which has been replicated across numerous studies.^{12, 15, 20-22}

The *Seasonal Asthma Exacerbation Index (saEPI)* is an 8-item index, ranging from 0 to 16, that was developed to determine exacerbation risk during each season.⁴⁶ Variables include age, total IgE, aeroallergen sensitization, percent blood eosinophils, exacerbation in the prior

season, treatment step, FEV1/FVC and FeNO (44). Hoch et al⁴⁷ subsequently evaluated the validity of saEPI in the PROSE (Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations) trial, which was a separate trial designed to prevent fall exacerbations with omalizumab therapy. saEPI demonstrated fair ability to distinguish those who had an exacerbation and those who do not with an area under the curve (AUC) of 0.76 and negative predictive value (NPV) of 0.88 for the guideline-based therapy group (Figure 1).⁴⁷ However, the predictive ability of the saEPI was lower in the omalizumab group with an AUC of 0.65, positive predictive value of 0.20 and NPV of 0.90.⁴⁷ The high NPV in both groups suggests that saEPI can reliably predict children unlikely to have an exacerbation but requires further refinement to predict risk of future severe exacerbation. In addition, the saEPI was not validated in children with intermittent or mild persistent asthma further limiting its generalizability.⁴⁷ Composite scores can strengthen exacerbation prediction, but must demonstrate better predictive accuracy to minimize unnecessary interventions.

Machine learning

Machine learning (ML) is becoming a commonly used analytic tool to predict outcomes for various disease processes. ML can incorporate diverse data from a multitude of sources to provide increased predictive accuracy over conventional analytic methods. ML has potential to address the poor sensitivity and specificity of current prediction models for severe exacerbations through inclusion of the numerous factors associated with exacerbations including epidemiologic, environmental and physiologic factors.⁴⁸ Using ML techniques, Luo et al⁴⁹ created a predictive model for severe asthma exacerbation (ED visit or inpatient stay) in the coming year. They initially considered 235 candidate variables chosen based on prior prediction models and expert opinion. The final model included 142 variables and achieved an AUC of 0.86 [95% CI: 0.846-0.871]. However, the positive predictive value (PPV) of their model was 22.7% [95% CI: 20.7-24.6] clearly demonstrating a substantial portion of patients identified by

the model did not require a hospital visit for asthma.⁴⁹ Their model also had a NPV of 97.8% demonstrating an ability to identify those children who are not at risk for exacerbation.

Finkelstein et al⁵⁰ demonstrated that ML techniques could be used to incorporate telemonitoring data to predict exacerbations in a 7-day window. They used daily asthma symptoms, self-reported medication administration, asthma trigger exposure and peak expiratory flow in their model and achieved a potentially actionable sensitivity.⁵⁰ However, their model could benefit from incorporating multiple data sources that combine telemonitoring data with other potentially relevant predictive factors to improve its predictive accuracy. In addition, their demonstration appeared to be limited by a low frequency of asthma exacerbations, and did not report predictive values.

Overall, ML is a work in progress, with the potential to improve the sensitivity and specificity of severe asthma exacerbation prediction needed for clinical utility and application. The current predictive accuracy of existing ML models allows for low-cost, safe preventive interventions including initiation of symptom and trigger diaries and primary care follow-up. However, to implement high-cost, high-yield and higher risk interventions such as biologic therapies to reduce asthma exacerbations, these ML-based models would benefit from achieving higher predictive accuracy. The substantial numbers of variables required for ML models is also a limitation as it is difficult to decipher which variables contribute most to the model. Also, such extensive variables are not widely available, which can limit replication of the model in other cohorts and their future potential for broad application. In addition, a majority of ML models predict exacerbation risk across a population. While informative for public health strategies, these are less beneficial in predicting an individual's risk of impending severe exacerbation. Regardless, ML's integrative approach, combining the numerous risk factors of severe exacerbations and including big data sources, has great potential to aid in real-time prediction of impending severe exacerbations.

Predicting impending severe exacerbation

Substantial progress has been made in identifying high-risk exacerbation-prone children through identification of risk factors, development of composite scores and use of innovative analytic approaches. While these tools can identify a population of children who are at risk of having a severe asthma exacerbation in the following 6 to 12-month period, they have low sensitivity and specificity for predicting impending exacerbations. In other words, these predictors identify a subset of children as high-risk; however, severe exacerbations are relatively uncommon events, and many to most children in such an at-risk cohort might not go on to have a severe exacerbation in the coming year and would actually not need preventive interventions. In such high-risk pediatric populations, a second layer of strategies for more efficient prediction of impending severe exacerbation are in development, including the development of sensitive and specific real-time monitoring tools, phenotypic understanding of exacerbation types based on triggers (e.g., virus, allergen or pollutant-induced) or responders versus non-responders to conventional exacerbation therapies, population health modeling, and special considerations for pre-school aged children.

Passive real-time monitoring

Rapid technological advances in electronic medication monitoring devices, mobile health applications, and home biometric monitoring, including personal smart devices (e.g., smart watches), allow for passive collection of real-time data that might be useful to predict impending severe asthma exacerbations. Integration of data from these devices permits monitoring by patients, caregivers, and their care teams with the opportunity for real-time intervention to prevent impending exacerbations. As Himes et al⁵¹ describes, there are a multitude of potential benefits to these tools including the ability to collect longitudinal data on symptoms, trigger exposures, and inhaler usage, while simultaneously incorporating data from external sources such as weather, allergen and air quality reports. The aggregation of this information may allow

providers to help caregivers and patients determine when symptoms are worsening in order to implement appropriate and timely interventions to prevent exacerbations.

When monitored daily, asthma symptoms, peak expiratory flow (PEF) and rescue albuterol use change shortly before and during severe exacerbations in adults⁵² and children.²³ In the pediatric study, changes in cough and wheeze scores, albuterol rescue use, and PEF were evident 12 to 3 days before a severe exacerbation, and more abruptly within the 2 days before (Figure 2).²³ However, worsening of these measures had low sensitivities and low predictive values for severe exacerbations, either alone or in combination, that might be attributed to limitations of data collection based on diary card tracking.

Improvements in remote patient monitoring of rescue and controller inhaler medication usage and app-based home spirometers are currently available. Studies of internet-based real-time electronic medication monitoring devices demonstrate mixed results. Vasbinder et al⁵³ compared real-time medication monitoring with text message reminders for usual care in asthmatic children 4 to 11 years of age. Electronic medication devices demonstrated improved adherence to ICS treatment, but no improvement in asthma control, quality of life or exacerbations. In contrast, Morton et al⁵⁴ randomized children to an intervention consisting of a combination of an electronic medication monitoring device, daily reminder alarms, and feedback in clinic regarding ICS use, versus usual care. The intervention group had higher adherence and fewer severe exacerbations (oral corticosteroid course or hospitalization). In addition to remote medication monitoring devices, portable spirometers allow for self-monitoring of lung function to assess asthma control. Remote app-based spirometers have been shown to be feasible and safe, and provide measurements of lung function meeting American Thoracic Society/European Respiratory Society acceptability and reliability criteria.⁵⁵ However, it is currently unknown if remote spirometry measurements can indicate loss of asthma control and predict impending exacerbations.

Over the past several years, personal smart devices have become ubiquitous and have rapidly expanded in capabilities. These personal smart devices allow for real-time monitoring of physiologic parameters such as heart rate, oxygen saturation, sleep and respiratory rate, as well as activity levels and GPS location. Such devices may provide valuable insight into asthma control at home and risk of impending severe exacerbation. While existing literature regarding passive monitoring strategies is limited and mixed, these tools are worthy of consideration for impending exacerbation prediction, especially in children who are not necessarily able to advocate and seek appropriate care for themselves. For effective implementation, it will be important to consider potential barriers to use of these technologies, such as uncertainty regarding effectiveness, sustained user engagement, difficulties with data integration and interpretation, and concerns about privacy, cost and acceptability.⁵⁰

Population health models

A primary goal of population health models is to accurately identify patients at risk of a negative outcome in order to offer proven, preventive interventions. Numerous attempts have been made to predict which children will go on to be diagnosed with asthma,^{56, 57} though fewer models exist to identify children at risk of suffering a severe asthma exacerbation. Models to predict the risk of suffering a severe exacerbation in pediatric populations may draw on demographic, clinical, laboratory, pharmacy, insurance, biomarker, or home monitoring data. As all of these elements are increasingly accessible in electronic medical records (EMR), the development of predictive scores for severe asthma exacerbations that can be calculated for entire populations has become more achievable.

Teach et al^{46, 47} created a validated risk score from seven factors associated with exacerbation in patients enrolled in a study, and also demonstrated that there was seasonal variability in the predictors most associated with an exacerbation. The Healthcare Effectiveness Data and Information Set (HEDIS) definition of patients with persistent asthma identifies patients

with prior severe exacerbations, recent office visits, and/or multiple medication dispensing events and is more widely accessible because it relies on insurance claims information.⁵⁸ However, numerous patients not identified by the HEDIS criteria go on to have exacerbations in the subsequent year.⁵⁹ Studies that accurately derive risk models for the general population are needed. Biagini Myers et al⁵⁷ recently demonstrated the use of a stepwise regression to weight predictors of developing asthma, an approach that could be applied to determine the predictors most associated with severe exacerbations.

Severe exacerbation management: predicting responders and non-responders

In addition to identification of children at risk for severe exacerbations, treatment response prediction is an important part of the prediction continuum for severe exacerbations in children. It would be useful to predict severe asthma exacerbation responders versus non-responders to conventional exacerbation therapies in urgent circumstances and settings. While progress has been made in the outpatient setting through improved phenotypic understanding of exacerbation types responsive to treatments,^{40, 41} such critical advances have not been made in the ED setting where severe exacerbations are prevalent. Current ED treatment of acute asthma exacerbations is based on clinical scoring tools including the Pediatric Asthma Severity Score (PASS) and Pediatric Respiratory Assessment Measure (PRAM).⁶⁰⁻⁶² While demonstrating initial promise as tools to predict ED treatment response and disposition, these scores are limited by insufficient validation, incorporation of subjective variables (e.g., auscultation), and have not proven effective at predicting treatment response.⁶³⁻⁶⁵ In addition, existing clinical prediction rules are limited by use of predictor variables with poor inter-rater reliability, insufficient external validation, and absence of response-to-treatment measures that are critical drivers of ED decision-making.⁶⁶⁻⁶⁸ Thus there is considerable variability in ED treatment of severe exacerbations contributing to prolonged ED lengths of stay, hospitalizations and relapse.^{63, 66, 69-71} Thus, similar to the outpatient setting, there is a need to evaluate the utility

of physiologic and biologic markers in predicting response to therapies during severe exacerbations to improve exacerbation management strategies.

Airwave oscillometry (AOS) is a non-invasive physiologic measure of lung function that may be useful in children presenting to the ED with acute asthma exacerbations. A feasibility study of AOS in the pediatric ED found that oscillometry is safe and feasible to use in children as young as 4 years of age with acute exacerbations.⁷² AOS measures are responsive to ED treatment, demonstrating significant changes in respiratory impedance measurements before and after nebulized bronchodilators and systemic corticosteroid administration. AOS can accurately and sensitively measure peripheral airway impairment in asthma exacerbations. AOS can also be portable and quickly tested without provoking asthma, making it ideal for clinical application in the ED. Additional AOS studies are needed to determine its utility in ED management of exacerbations as a physiologic measure of exacerbation severity and treatment response in children.

The transcriptome of children during acute severe asthma exacerbations, similar to the outpatient setting, has potential to elucidate the biologic pathways driving ED treatment response. Nasal transcriptomics have been able to discern exacerbation-prone phenotypes of asthma, molecular pathways leading to exacerbations, and pathways responsive versus unresponsive to oral corticosteroid treatment.^{42, 45} The development of minimally invasive methods to collect respiratory epithelia samples from the nasal passage for advanced transcriptomics and analysis makes this work feasible and clinically applicable in the ED setting and should be explored.⁷³

Pre-school aged children

Pre-school aged children account for an exceptionally high burden of asthma and thus require particular attention regarding prediction of severe asthma exacerbation risk. In fact, nearly 50% of pre-school aged children experience a wheezing episode before age 6.⁷⁴

Bacharier et al¹⁰ demonstrated that 71% of pre-school aged children with recurrent wheeze had ≥ 4 wheezing episodes, 52% missed school or daycare, 40% had an ED visit and 8% required hospitalization over the course of a year. In comparison to older children with asthma, pre-school aged children with recurrent wheeze have twice the rate of ED visits and more than five times the rate of hospitalization for wheezing episodes.¹⁰ Pre-school aged children pose a substantial management challenge for providers due to the diversity in phenotypic presentations and indeterminate diagnosis of asthma in this age group.⁷⁴⁻⁷⁶ Thus, pre-school aged children are unfortunately treated similarly to older children with persistent asthma in regard to management and prediction of exacerbation risk.

Fitzpatrick et al⁷⁷ performed latent class analysis on children age 12-71 months old with recurrent wheeze to identify latent classes of wheeze and their association with both future exacerbations and inhaled corticosteroid (ICS) treatment. Their group identified four latent classes of recurrent wheeze in pre-school aged children that were distinguished by allergen sensitization and/or exposures. The annualized exacerbation rate was highest (0.93 ± 0.10) for class 2, which was characterized by "sensitization with indoor pet exposure." Interestingly, daily ICS treatment improved exacerbation rates only in class 2 and class 4 ("multiple sensitization and eczema") (Figure 3).⁷⁷ This study demonstrates the need to predict risk of severe exacerbation in pre-school aged children and establishes that sensitization and exposure might be useful predictors for future exacerbations and response to daily ICS treatment in younger age groups.

Conclusion

While substantial progress has been made in identifying risk factors for severe asthma exacerbations in children, much work remains to be done at the individual level to identify children in need of clinical interventions prior to an impending severe exacerbation. Innovations in novel biomarkers and real-time prediction of impending exacerbations may allow for timely

422 and efficient interventions at the individual level for children at risk. Integrating these innovative
423 strategies with our foundation of existing knowledge of risk factors for severe asthma
424 exacerbations holds promise for a better and safer future for children with asthma.
425

Figure Legend

Figure 1. The association between saEPI and the probability of an asthma exacerbation. [Hoch et al⁴⁷]. Risk score on the x-axis is composite saEPI score, y-axis represents the probability of having an exacerbation in the 90-day PROSE treatment period. The shaded areas represent the 95% confidence interval. The saEPI successfully predicts exacerbations in the fall treatment period.

Figure 2. Daily monitoring of symptoms, rescue albuterol use, and PEF and impending asthma exacerbations in the PACT study [Covar et al²³]. Plots of cough/wheeze severity score (scale 0 – 3), rescue albuterol use (# inhalations/day), and AM PEF (% predicted) relative to an exacerbation (prednisone course initiation = Day 0). Warning signs in these measures occurred one day or less prior to exacerbations. Patterns did not differ significantly in participants receiving different daily controller therapies as part of the study: montelukast (blue), inhaled fluticasone propionate (orange) or inhaled fluticasone/salmeterol combination (green).

Figure 3. Annualized rate of severe exacerbations in pre-school aged children by latent classes (Fitzpatrick et al⁷⁷). Annualized rate (mean $\pm$ SEM) of exacerbation in the PEAK study placebo (solid bar) and daily inhaled corticosteroid (ICS, hatched bar) treatment arms. Latent class groups (1 = minimal sensitization, 2 = sensitization with indoor pets, 3 = sensitization with tobacco smoke exposure, 4 = multiple sensitization with eczema).

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Table 1. Predictors of severe asthma exacerbations.

Predictors of Severe Asthma Exacerbations				
Demographics	History	Environmental	Lung Function	Biomarkers
• Pre-school age • Black • Male • Hispanic • Puerto Rican • Low-Income	• Prior exacerbation • Poor asthma control • SABA use • Difficult-to-control asthma • Poor controller medication adherence	• Aeroallergen sensitization and exposure • Tobacco smoke • Air pollution • Viral infections • Diet • Folate deficiency • Vit D deficiency • Overweight • Obesity	• Spirometry • FEV1 • FEV1/FVC • FEF 25-75 • Bronchodilator response • Oscillometry	• Eosinophils • FeNO • Allergen sensitizations • IgE levels • Genetic polymorphisms

Figure 1

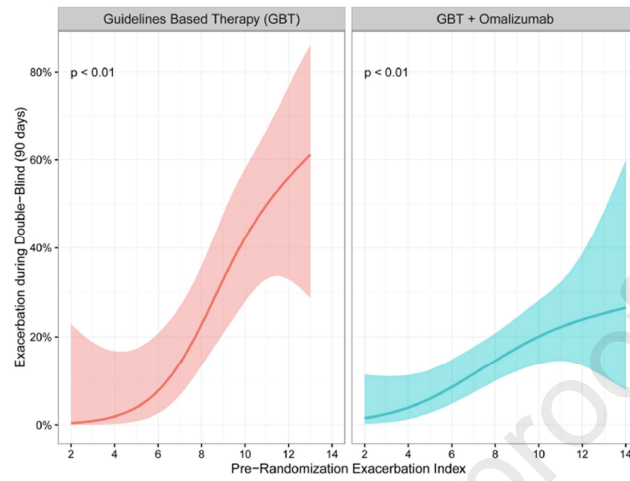


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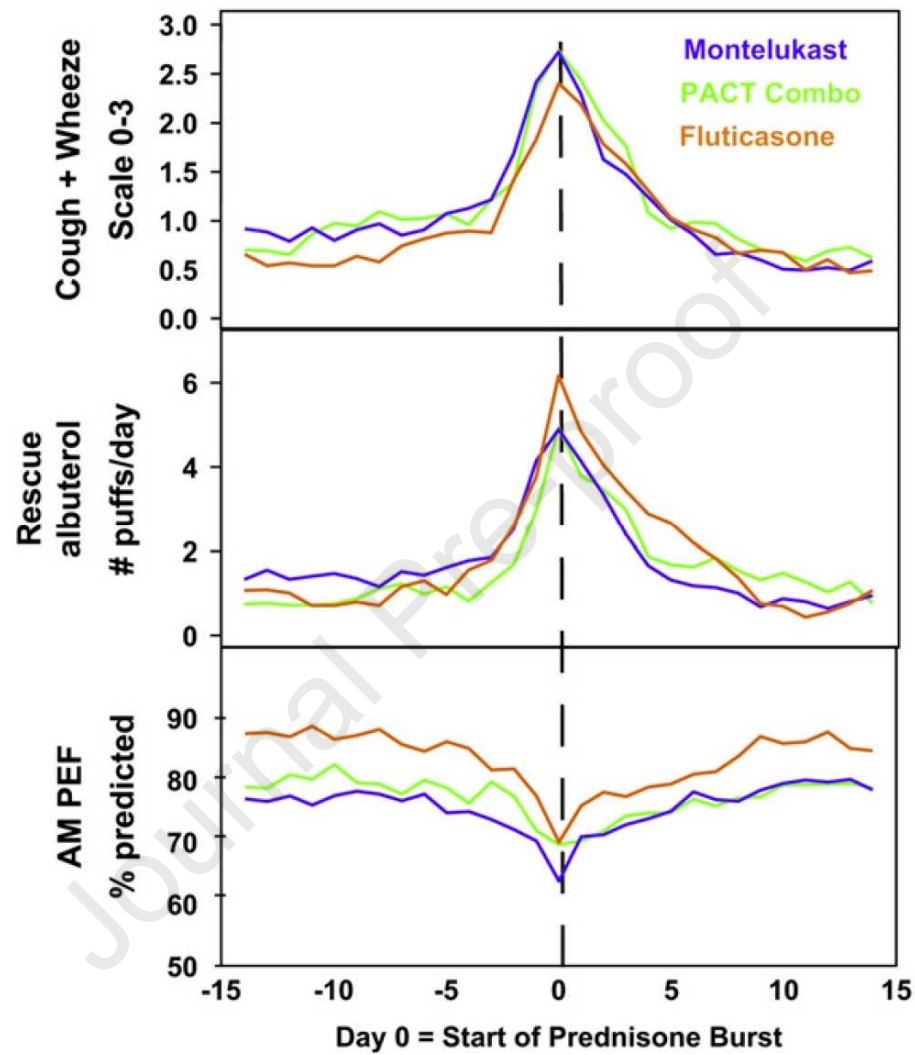
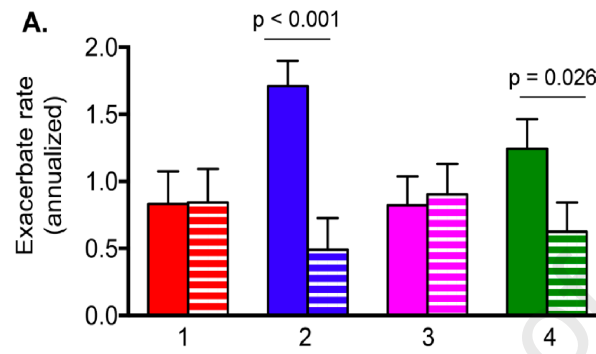


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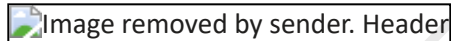
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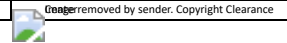
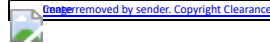
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