



Predicting asthma exacerbations in children

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Purpose of review

This review critically assesses recently published literature on predicting asthma exacerbations in children, while also providing general recommendations for future research in this field.

Recent findings

Current evidence suggests that every effort should be made to provide optimal treatment to achieve adequate asthma control, as this will significantly reduce the risk of severe disease exacerbations. Children who have had at least one asthma exacerbation in the previous year are at highest risk for subsequent exacerbations, regardless of disease severity and/or control. Although several tools and biomarkers to predict asthma exacerbations have been recently developed, these approaches need further validation and/or have only had partial success in identifying children at risk.

Summary

Although considerable progress has been made, much remains to be done. Future studies should clearly differentiate severe asthma exacerbations due to inadequate asthma control from those occurring in children whose asthma is well controlled, utilize standardized definitions of asthma exacerbations, and use a systematic approach to identify the best predictors after accounting for the multiple dimensions of the problem. Our ability to correctly predict the development of severe asthma exacerbations in an individual child should improve in parallel with increased knowledge and/or understanding of the complex interactions among genetic, environmental (e.g. viral infections) and lifestyle (e.g. adherence to treatment) factors underlying these events.

Keywords

asthma exacerbations, biomarkers, childhood asthma, prediction, risk factors

INTRODUCTION

Asthma, the most common chronic disease of childhood [1], affects almost 7 million children in the USA. In this country, childhood asthma is the cause of approximately 700 000 emergency department (ED) visits, approximately 200 000 hospital admissions, and almost 200 deaths [2,3]. Direct costs from disease exacerbations accounted for over 63% of the estimated \$15.5 billion total asthma costs in the USA in 2002 [4]. At an individual level, having an exacerbation is one of the most distressing events related to childhood asthma.

Identifying children at high risk for asthma exacerbations is important because it could lead to personalized and improved disease management and, ultimately, decrease suffering, morbidity, and healthcare costs. In this review, we assess recently published literature on predicting asthma exacerbations in childhood, with particular emphasis on articles published in the last 2 years. We also provide general recommendations for future research in this field.

DEFINITION OF ASTHMA EXACERBATIONS

Guidelines and recommendations for clinical trials and clinical practice have increasingly focused on how to best assess asthma control. Although this term encompasses a global assessment of asthma symptoms, lung function, medication use, and frequency of exacerbations, there is no uniform definition of adequate asthma control. Likewise, the definitions of asthma severity and asthma

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Curr Opin Pulm Med 2012, 18:63–69

DOI:10.1097/MCP.0b013e32834db288

KEY POINTS

- Adequate asthma control reduces the risk of severe asthma exacerbations in children.
- Children who have had at least one asthma exacerbation in the previous year are at highest risk for subsequent exacerbations, regardless of disease severity or control.
- Novel prediction tools using clinical information, healthcare data, and/or serial measurements of lung function have been developed but need further (e.g. prospective) validation.
- Promising biomarkers to predict asthma exacerbations include urine metabolites and serum vitamin D levels.
- Current tools to predict asthma exacerbations in childhood have had only partial success, and future studies (utilizing standardized definitions) will be more likely to identify accurate prediction tools if they account for the multiple dimensions of the problem.

exacerbations have also varied widely among different studies and guidelines [5,6].

In an attempt to standardize the definitions of asthma exacerbations for clinical trials and clinical practice, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published a consensus statement in 2009 [7¹¹]. Severe asthma exacerbations were described as ‘events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death’. Severe asthma exacerbations were defined as the occurrence of either an asthma-related hospitalization or visit to the emergency department (ED) or an urgent care facility, leading to treatment with systemic (oral, intramuscular, or intravenous) corticosteroids or use of systemic corticosteroids for at least 3 days.

The ATS/ERS consensus statement also defined moderate asthma exacerbations as the occurrence of at least one of the following events for at least 2 days (without the need for systemic corticosteroids): deterioration in symptoms, deterioration in lung function, and/or increased rescue bronchodilator use. According to this definition, ED visits for asthma not requiring systemic corticosteroids should be classified as moderate disease exacerbations.

RISK FACTORS FOR ASTHMA EXACERBATIONS

Poor asthma control can lead to severe asthma exacerbations [8¹²]. Adequate management of persistent

asthma includes treatment with controller medications such as inhaled corticosteroids (ICSs), which have been consistently shown to reduce the risk of severe disease exacerbations [9–11]. However, children with persistent asthma and at least one severe exacerbation in the prior year have a two-fold increased risk of subsequent severe exacerbations despite use of controller medications [12], suggesting interindividual (e.g. genetic) susceptibility.

Viral infections have been implicated in most (>80%) asthma exacerbations in children [13¹³,14]. Although many viruses have been recovered from asthmatics, rhinovirus has been most commonly (65%) identified in proven viral-induced asthma exacerbations in children aged 2–17 years [14]. Allergen exposure can cause disease exacerbations in children with atopic asthma [15], and viral infections and allergen exposure likely have synergistic effects on exacerbations in these children [16]. Other risk factors for asthma exacerbations include nonwhite race [8¹⁴], younger age [11], season [12], environmental tobacco smoke exposure [17], and outdoor air pollution [18¹⁵].

ASSESSMENT OF ASTHMA CONTROL

Because poor disease control is a risk factor for severe asthma exacerbations (see below), standardized measures of asthma control are important for both clinical purposes and research studies of asthma exacerbations. The childhood asthma control test (C-ACT) [19¹⁶] is among the validated instruments included in the current guidelines for the diagnosis and management of asthma from the National Heart, Lung and Blood Institute (NHLBI) [20¹⁷] to assess asthma control in children ages 4–11 years. The C-ACT comprises seven questions (three are completed by the child’s parent and four are completed by the child and the parent together) that produce a score that can range from 0 to 27, in which higher scores indicate better control of asthma symptoms. A score lower than 20 indicates poor control and correlates with lower forced expiratory volume in the first second (FEV₁), need for change in the patient’s therapy, and the specialist’s rating of asthma severity. Similarly, the ACT can be used for children ages 12–18 years, with a score ranging from 5 to 25 (with higher scores also indicating better disease control). Scores from the ACT assess symptoms over an approximately 4-week period and are, therefore, flexible, relatively dynamic, and easy to administer. However, while the AUC (area under the receiver operating characteristics curve) in the initial study was 0.79, the sensitivity of the C-ACT was only 0.70, with a

positive predictive value (PPV) of 70%. Moreover, there have been concerns that the C-ACT and the ACT may underestimate the proportion of children with uncontrolled asthma, as defined by guidelines from the Global Initiative for Asthma (GINA) [21[•]].

PREDICTING ASTHMA EXACERBATIONS

We will review recent efforts that have taken different approaches to try to improve our ability to predict asthma exacerbations in children. Risk factors and current approaches to predicting asthma exacerbations in children include the following:

- (1) Exacerbation risk factors
 - (a) Poor asthma control [8[•],12]
 - (b) Recent history of prior severe exacerbation [11,12,22^{••}]
 - (c) Viral infections (rhinovirus and others) [13[•],14]
 - (d) Allergen exposure in atopic children [15,16]
 - (e) Winter season [12]
 - (f) Younger age [11]
 - (g) Nonwhite race [8[•]]
 - (h) Tobacco smoke exposure [17]
 - (i) Outdoor air pollution [18[•]]
- (2) Predictive models using clinical variables
 - (a) Childhood asthma control test [19^{••}]
 - (b) Asthma exacerbation clinical score [23^{••}]
- (3) Predictive models using computerized data
 - (a) Pharmacy data on β -agonist refills [24[•]]
 - (b) Classification algorithms [25^{••}]
- (4) Prediction using lung function
 - (a) FEV₁ and/or FEV₁/forced vital capacity (FVC) [11,26]
 - (b) Peak expiratory flow measurement (PEF) [27]
 - (c) Serial PEF and diurnal variation [28^{••}]
- (5) Prediction using biomarkers
 - (a) Exhaled nitric oxide [29,30]
 - (b) Sputum eosinophilia [31[•]]
 - (c) Urine bromotyrosine [32^{••}]
 - (d) Urine metabolome [33^{••}]
 - (e) Serum vitamin D level [34^{••},35[•]]
- (6) Prediction using genetic information
 - (a) Genetic polymorphisms [36]
 - (b) Gene expression patterns [37^{••}].

Predictive models using clinical variables

Findings from three recent studies [11,12,22^{••}] emphasize that a history of a recent severe asthma exacerbation is a strong risk factor for subsequent exacerbations, regardless of disease severity or use of controller medications. Covar *et al.* [12] examined

factors associated with severe disease exacerbations (defined as use of systemic corticosteroids or at least one visit to the ED or at least one hospitalization for asthma) among 285 children with mild-to-moderate persistent asthma who were randomized to treatment with one of the following approaches: ICS alone, ICS and salmeterol, or montelukast. After adjustment for treatment arm and other covariates, the use of at least one course of systemic corticosteroids in the year prior to the study was associated with a two-fold increased risk of a severe asthma exacerbation during the 48-week course of the trial [95% confidence interval (CI) for odds ratio (OR) 1.4–3.1, $P=0.0008$]. In another study, Haselkorn *et al.* [22^{••}] examined factors associated with severe exacerbations (defined as recent use of systemic corticosteroids) in an observational longitudinal study of children (6–11 years old) with severe or difficult to treat asthma. After accounting for race and other covariates, both a history of at least one severe asthma exacerbation (OR 2.0, 95% CI 1.5–2.6, $P<0.001$) and very poor asthma control (OR 1.4, 95% CI 1.1–1.8, $P=0.01$) were associated with increased risk of an exacerbation during 1 year of follow-up. Similarly, Wu *et al.* [11] showed that a history of at least one ED visit or hospitalization for asthma in the prior year was associated with increased risk of at least one severe disease exacerbation over 4 years in children with mild-to-moderate persistent asthma in the Childhood Asthma Management Program (CAMP) study, even after accounting for treatment arm and other covariates. Of note, however, 22% of children without prior history of a severe asthma exacerbation had subsequent exacerbations during follow-up.

We recently aimed to construct a clinical score to predict severe asthma exacerbations based on questions that could be easily administered in a general pediatrician's office [23^{••}]. The resulting questionnaire consisted of yes/no questions (Fig. 1) [23^{••}], with a final score between 0 and 17. In our initial confirmatory sample of Costa Rican children ages 6–14 years, each one-point increase in the score represented a 1.6-fold increment in the odds of an exacerbation in the year prior to the study (95% CI for OR 1.3–2.0, $P<0.0001$), with an AUC of 0.75. When applied to North American children enrolled in a longitudinal study, the AUC to predict exacerbations up to a year later was 0.69. Importantly, we also provided a cut-off score for children at low risk, with a PPV for 'no hospitalizations' of 94–99%. Although imperfect, this score is promising, as it could allow clinicians to identify children at low and high risk for a severe asthma exacerbation. Before any application, however, this score needs to be prospectively validated in a clinical setting.

Reported asthma symptoms Symptoms for ≥ 3 months of the year ☐ Symptoms precipitated by: -colds ☐ -cold air ☐ -exercise ☐ -dust ☐	Healthcare utilization Ever hospitalized for asthma ☐ Ever admitted to ICU for asthma ☐ ≥2 courses of steroids last year ☐ ≥2 ED visits for asthma last year ☐ Doctor visits last year*: 3 or more ☐ also 6 or more ☐
Current asthma medications Short-acting β ₂ agonists ☐ Inhaled steroids ☐ Leukotriene inhibitors ☐	Medical history Personal history of eczema / hay fever ☐ Parental history of asthma or atopy ☐ Smoke exposure as infant or current ☐
Total Score = ☐ ≤ 5 (Low risk) ☐ ≥ 9 (High risk)	

FIGURE 1. Asthma exacerbation clinical score. Score instructions: one point is assigned for each question answered as yes. The score is calculated by adding all points (total score range, 0–17). For ‘doctor visits last year’, one point is assigned for at least three visits, and one more point (two total) if the patient also had at least six visits. ED, emergency department. Reproduced with permission from [23¹¹].

Predictive models using healthcare data

Researchers have tried to construct predictive models to identify children at high risk for asthma exacerbations using large databases maintained by managed care organizations. In a recent study of healthcare data from 11 779 patients with asthma who were older than 11 years, O'Connor *et al.* [38¹²] confirmed previously reported associations between suboptimal asthma control and history of recent asthma exacerbations with subsequent disease exacerbations. In another study, Schatz *et al.* [24¹³] used computerized pharmacy data to create a scale for the use of β-agonists, which correlated with the risk of ED visits, hospitalizations, and courses of systemic steroids.

To the best of our knowledge, only one study has created a computer-based classification tree to identify individual children at risk [25¹⁴]. In that study, Lieu *et al.* used variables in a large managed care database to create two classification trees for prediction of asthma hospitalizations, with AUCs of 0.75 and 0.79. Interestingly, the trees involved only two to three questions referring to a history of hospitalization in the prior 6 months, the number of units of β-agonist medication used, and the number of physicians prescribing asthma medications to the patient. However, these algorithms identified only 2–7% of the population as high risk, with high specificity (94%) but low sensitivity (32%). An additional limitation of this method is that its implementation would require access to unified medication refill information linked with a detailed medical record.

Predictive models using objective measures of lung function

FEV₁ is one of the criteria used to classify asthma severity in children, and a reduced FEV₁ has been

associated with asthma attacks (defined as at least one episode of wheezing or shortness of breath) in retrospective cohort studies of children [26] and adults [39]. However, two longitudinal studies of North American children who had mild-to-moderate persistent asthma and were enrolled in a clinical trial showed no association between FEV₁% predicted at baseline and severe asthma exacerbations over 1–4 years of follow-up [11,12]. In one of these studies, baseline FEV₁/FVC was an independent risk factor for severe asthma exacerbations over 4 years of follow-up [11]. This is interesting, as a reduced FEV₁/FVC – and not FEV₁ – was associated with increased disease severity [40] and increased airway responsiveness [41] in cross-sectional studies of children with asthma in the US north-east [40] and Costa Rica [41].

Spirometric measures of lung function are not easily obtainable in certain clinical settings and/or geographic areas and, thus, although controversial [42], peak expiratory flow (PEF) has been proposed as a surrogate measure of FEV₁ [27]. Thamrin *et al.* [28¹⁵] combined serial PEF measurements with the power of computer-based simulation to predict the risk of asthma exacerbations in adults. They used 64 days of PEF data from 309 asthmatic patients, used computers to simulate 5000 PEF data points per patient, and used those models to predict risk of subsequent exacerbations. When exacerbations were defined as a drop of PEF below 80% predicted, the models were highly efficient, with AUC of 0.79–0.85; however, the AUC was substantially lower (0.61–0.66) when trying to predict clinically defined exacerbations.

Predictive models using biomarkers

Identifying a biomarker of severe asthma exacerbations is attractive, but has proven elusive. Exhaled

nitric oxide, a marker of eosinophilic airway inflammation, has been a more effective risk marker of asthma exacerbations in adults [43] than in children [29,30]. Sputum eosinophils have shown promising results in a handful of studies in adults and children with asthma [31]. However, sputum eosinophilia may not be a practical risk marker of asthma exacerbations in children because of difficulties in obtaining an adequate sputum sample and uncertain reference values for sputum eosinophil count in childhood [44].

Among 57 children with asthma, Wedes *et al.* [32] found that an elevated level of urine bromotyrosine (a side-product of eosinophil peroxidase) at baseline was associated with a four-fold higher risk of disease exacerbations (95% CI for relative risk 1.1–14.7, $P=0.03$) over 6 weeks of follow-up. Further studies will be required to confirm these findings and, if appropriate, to determine how to use urinary bromotyrosine in a clinical setting (e.g. what constitutes a significant increase/decrease in urinary levels, and how they correlate with risk of exacerbations over extended periods of follow-up). A more complex approach using arrays of approximately 20–40 metabolites detected by NMR spectroscopy on urine samples has recently shown promising results in differentiating children with asthma from healthy controls, and stable outpatient asthma versus those presenting to the ED for an asthma exacerbation [33].

Serum vitamin D level is a novel and modifiable potential risk marker for severe asthma exacerbations. In a cross-sectional study of 616 Costa Rican children, Brehm *et al.* [45] showed that serum 25(OH)D level was inversely associated with having had at least one hospitalization for asthma in the previous year [OR for each log₁₀-unit increase in serum 25(OH)D 0.05, 95% CI 0.004–0.71]. Conversely, vitamin D deficiency [a 25(OH)D level <20 ng/ml] was associated with nearly 10-fold increased odds of a severe exacerbation in the year prior to the study. In a follow-up longitudinal study of North American children, the same group reported that a baseline serum 25(OH)D of 30 ng/ml or less was associated with at least one severe asthma exacerbation during 4 years of follow-up (OR 1.5, 95% CI 1.1–2.0) [34]. These findings are supported by findings from a small clinical trial [35] and may be mediated by effects of vitamin D on responsiveness to ICS [34,46] and/or viral illnesses associated with asthma exacerbations [47]. Ongoing longitudinal studies and clinical trials should help ultimately establish whether serum vitamin D level should be routinely measured, and when and in whom vitamin D

supplementation should be used to reduce the risk of severe asthma exacerbations.

Genetics

Asthma has a significant hereditary component. A genetic contribution to severe asthma exacerbations has not been formally tested but is plausible, given the interindividual susceptibility to exacerbations among children with asthma. Xu *et al.* [36] used genome-wide genotypic data [~550 000 single nucleotide polymorphisms (SNPs)] to attempt to identify children at risk for severe asthma exacerbations. A predictive panel was first constructed using data from 417 children, and then validated in a second sample of 164 children. In the validation sample, adding a panel of 160 SNPs increased the AUC for a model using clinical parameters only from 0.54 to 0.66. Consistent with other attempts to use relatively few SNPs as predictors of disease risk, this approach did not achieve optimal results, but could be further refined once our understanding of how to best assess interactions among genetic variation and environmental factors is improved.

Gene expression is more 'proximal' to a disease phenotype and, thus, of great interest. A recent study identified two distinct gene expression signatures [one for innate immunity (including interferon alpha-1 (IFN α_1), IFN β_1 , toll-like receptors, and IL-15) and another for adaptive immunity (including genes related to B-cell and T-cell antigen receptors)] associated with severe asthma exacerbations [37]. In a multivariate analysis, only two clinical factors were associated with the specific gene expression signatures: BMI and time between collection of the baseline blood sample and the exacerbation. These findings suggest that increased BMI is associated with a 'different type' of asthma exacerbation, and that the two gene expression signatures of interest may be related to different degrees of acuity of asthma exacerbations.

CONCLUSION

Substantial effort has been invested in how to best identify children at risk for asthma exacerbations. Although considerable progress has been made, much remains to be done. Currently available data suggest that every effort should be made to provide optimal treatment to achieve adequate asthma control, as this will significantly reduce the risk of severe disease exacerbations. Among children on anti-inflammatory medications whose asthma is well controlled, those who have had at least one disease exacerbation in the previous year are at highest risk for subsequent exacerbations. It should

be recognized, however, that severe asthma exacerbations do occur among children with optimal asthma control and no recent history of exacerbations.

Novel and promising biomarkers for severe asthma exacerbations (e.g. serum vitamin D) must be rigorously assessed before their use is recommended for clinical purposes.

Future studies should clearly differentiate severe asthma exacerbations due to inadequate asthma control from those occurring in children whose asthma is well controlled, utilize standardized definitions of asthma exacerbations, and use a systematic approach to identify the best predictors after accounting for the multiple dimensions of the problem (e.g. medical history and clinical variables, genetic/genomic information, biomarkers, and viral infections).

As for other complex diseases or their complications, predictive models of asthma exacerbations are intended to estimate average risk for a population of interest and, thus, cannot perfectly predict risk for a given individual (which is 0 or 100% – the event will either occur or not). Ultimately, our ability to correctly predict the development of severe asthma exacerbations for an individual patient should improve in parallel with increased knowledge and/or understanding of the complex interactions among genetic, environmental (e.g. viral infections, allergen exposure), and lifestyle (e.g. adherence with prescribed treatment) factors underlying these events.

Acknowledgements

This study was funded by grant HL079966 from the US National Institutes of Health.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 93).

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