Predicting Severe Asthma Exacerbations in Children

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Severe asthma exacerbations are events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma (1). A joint statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) defined severe asthma exacerbations as (1) an asthma-related hospitalization or visit to the emergency department (ED) that leads to treatment with systemic (oral, intramuscular, or intravenous) corticosteroids, or (2) use of systemic corticosteroids (or an increase from a maintenance dose) for asthma, for at least 3 days (1). A similar definition was outlined by the expert panel for the Asthma Outcomes Workshop, which also recommended measuring "core exacerbation outcomes," including all deaths (from asthma and all causes) and asthma-specific ED visits requiring systemic corticosteroids, asthma-specific hospitalizations requiring systemic corticosteroids, and asthma-specific intensive care unit admissions or intubations (2). Such recommendations notwithstanding, variable definitions of severe asthma exacerbations or core exacerbation outcomes have been used in the published literature. Moreover, the ATS/ERS definition cannot be easily extrapolated to severe asthma exacerbations in preschool children, in whom there is no adequate evidence of beneficial effects of systemic corticosteroids on recurrent wheezing exacerbations (3).

In the United States, 2.1 and 10.7% of children with asthma (ages 0–17 yr) report at least one hospitalization and at least one ED visit in the previous year, respectively (4). In 2008, there were 10.5 million missed school days due to asthma among U.S. children aged 5–17 years (4). Severe exacerbations negatively impact the quality of life and education of children with asthma, while also causing enormous health care costs. Moreover, severe exacerbations are risk markers of both subsequent exacerbations and mortality from asthma (5). Thus, developing novel approaches to the prevention of severe exacerbations is a high priority in pediatric asthma.

Preventing severe asthma exacerbations requires identifying patients at high risk, to develop personalized care protocols that may prevent such exacerbations. In this review, we first assess data on risk factors (see Figure 1) and predictive tools for severe asthma exacerbations in childhood, and then discuss future directions in this field.

Risk Factors for Severe Asthma Exacerbations

Race, Ethnicity, and Socioeconomic Status

In the United States, race or ethnicity and socioeconomic status are strongly correlated, with racial or ethnic minorities disproportionately represented among the poor. In this country, asthma attacks are

more common among children who are African American, Puerto Rican, or economically disadvantaged (4, 6). Compared with non-Hispanic (NH) whites, NH blacks and Hispanics have an increased risk of ED visits for asthma, with similar findings in Asians and members of other races (7). In 2010, age-adjusted rates of hospital discharges for asthma were 29.9 per 10,000 in NH blacks, 12.6 per 10,000 in members of "other" races, and 8.7 per 10,000 in NH whites (8). Findings suggest that NH black children with severe asthma may partly be at increased risk for severe exacerbations due to resistance to corticosteroids (9).

Genetics

Whereas multiple genome-wide association studies have focused on asthma (10), few such studies have assessed severe asthma exacerbations (11, 12). One genome-wide association study identified a novel susceptibility gene for recurrent severe asthma exacerbations in children ages 2–6 years: cadherin-related family member 3 (*CDHR3*) (11). Variants in *CDHR3* may increase the risk of severe asthma exacerbations by altering the integrity of airway epithelium, thus promoting entry and replication of viruses such as rhinovirus C (13).

Viral Infections

Respiratory viral infections cause approximately 85% of severe asthma

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exacerbations in children, with human rhinovirus (HRV) being most commonly detected (14). Moreover, children with asthma exacerbations have higher total IgG₁ antibody titers to HRV compared with nonasthmatic control subjects (15). However, frequent wheezing and severe asthma exacerbations in early childhood are often due to other respiratory viruses (e.g., respiratory syncytial virus [RSV], parainfluenza, influenza, and others), acting alone or in combination (16). For example, a study of 175 children ages 2–15 years with asthma exacerbations showed that HRV was most frequently detected (73%), followed by influenza A (27%) and RSV (7.7%). In that study, coinfection with two or more viruses was present in 15% of the participants (17).

Viral infections can enhance production of proinflammatory cytokines and chemokines, which in turn induce the recruitment and activation of neutrophils and eosinophils, leading to airway inflammation and, ultimately, severe asthma exacerbations (18). Findings from *in vitro* studies suggest that the airway epithelium of subjects with asthma has defective production of type 1 and 3 interferons in response to viral infections, increasing the risk of severe exacerbations (18, 19). Moreover, RSV infection has been shown to increase the levels of histamine receptors and CC chemokines (eotaxin, RANTES [regulated upon activation, normal T-cell expressed and secreted]) in airway epithelium and fibroblasts, causing increased airway responsiveness (20).

In animal models, cross-linking of the high-affinity IgE receptor (FcεR1) by virus-specific IgE can lead to chemokine (CC motif) ligand 28 (CCL28)-mediated recruitment and subsequent activation of virus-specific helper T type 2 (Th2) memory cells, thus providing a secondary source of proinflammatory cytokines in animals with allergic airway inflammation. Consistent with experimental findings, school-aged children with allergic sensitization (atopy) are especially susceptible to the development of severe asthma exacerbations after viral illnesses (in particular, rhinovirus C) (21, 22). Indeed, findings from a United States-based clinical trial suggest that immune modulation of atopy before viral infections occur could reduce the risk of exacerbations in allergic children (23). In that randomized, double-blinded, placebo-controlled clinical trial of

513 school-aged inner-city children with persistent asthma, high total serum IgE, and one or more recent exacerbations (on a guideline-based management protocol), adding either an inhaled corticosteroid (ICS) boost or anti-IgE treatment before school began led to significantly reduced risk of severe exacerbations during the fall (odds ratio [OR] for anti-IgE vs. placebo, 0.48; 95% confidence interval [CI], 0.25–0.92) (23).

Tobacco Smoke

Second-hand smoke (SHS) is associated with worsening lung function, decreased response to treatment, and ED visits for asthma (24–26). Even though most treatment guidelines stress SHS avoidance for children with asthma, such exposure is still common, particularly among low-income families (26, 27). Given potential underreporting by caregivers, salivary or urinary cotinine may be preferred to assess SHS in children. McCarville and colleagues showed that salivary cotinine (a metabolite of nicotine with a half-life of 16–19 h) was more predictive of asthma exacerbations than caregiver-reported SHS among children aged 8–14 years (25).

Air Pollution

Outdoor air pollution, including traffic-related pollution, is a cause of severe asthma exacerbation in children (28). In a 2012 study of two communities in California (Riverside and Long Beach), the annual total (indirect and direct) costs of health care use for pediatric asthma exacerbations were estimated as \$9 million dollars (29). Other exposures (including stress, vitamin D insufficiency, and seasonality) may modify the effects of air pollution on severe asthma exacerbations (30, 31). A study of children aged 0–18 years in Orange County (California) showed that particulate matter (size, <2.5 μm; PM_{2.5}) and ozone were associated with severe asthma exacerbations in the warm season, and that PM_{2.5}, carbon monoxide, and NO_x (NO + NO₂) were associated with severe exacerbations in the cool season (32, 33).

Vitamin D Insufficiency

Vitamin D has a regulatory role in innate and adaptive immunity (34, 35). Findings from three observational studies suggest that vitamin D insufficiency (serum 25-hydroxyvitamin D < 30 ng/ml) is associated with severe asthma

exacerbations in school-aged children, and that this may be mediated by altered immune modulation of viral infections or reduced response to ICS (36–38). Two small randomized double-blinded clinical trials in Polish (n = 48) and Indian (n = 100) school-aged children reported significant reductions in loosely defined “asthma exacerbations” after 6 months of vitamin D supplementation (ranging from 500 to 2,000 IU/d) (39, 40). An ongoing clinical trial (NCT02687815; J.C.C., principal investigator) should help determine whether vitamin D supplementation prevents severe asthma exacerbations in school-aged children with vitamin D insufficiency and persistent asthma while taking ICS.

Allergens and Indoor Pollutants

In the United States, children living in inner-city households in the Northeast are exposed to higher levels of certain allergens (e.g., dust mite, cockroach, and mouse) and particulate matter than those living in suburban homes. Exposure to allergens, whether indoors or outdoors, can lead to poor asthma control and severe asthma exacerbations in sensitized children (41). Similarly, indoor exposure to endotoxin, SHS, and pollutants (such as particulate matter and nitrogen dioxide) has been shown to increase the risk of severe exacerbations in children with asthma (41, 42). Multifaceted environmental control programs including reducing smoking and cockroach allergen levels, and using high-efficiency particulate arrestance filters, have shown promise in reducing exposure levels and improving asthma symptoms (41, 42). However, implementing comprehensive environmental interventions is both time-consuming and costly.

Obesity

Overweight or obesity has been associated with poor asthma control and severe asthma exacerbations in childhood (43, 44). Compared with children of normal weight, overweight/obese children have been shown to have a decreased response to ICS, measured as lung function or ED visits/hospitalizations for asthma (44, 45). For example, a study of 28,645 children with asthma (ages 6–19 yr) who were enrolled in a U.S. health maintenance organization from 2007 to 2011 showed that children who were extremely obese had 15% higher odds of developing an asthma

exacerbation within 1 year of follow-up than those of normal weight (95% CI for OR, 1.07–1.23; $P < 0.001$) (45). In addition to reduced ICS response, chronic systemic inflammation, hormonal influences, and comorbidities such as gastroesophageal reflux may underlie the link between obesity and severe asthma exacerbations (44).

Psychosocial Stress

Chronic psychosocial stress has been strongly implicated in morbidity from asthma, including severe exacerbations (46). Potential mechanisms for the detrimental effects of stress on severe asthma exacerbations include nonadherence with controller medications, decreased therapeutic responses (47), and stress-induced changes in DNA methylation or expression of genes that regulate behavioral, autonomic, neuroendocrine, and immunological responses (46). Consistent with potential stress-induced treatment resistance, chronic stress has been linked to decreased expression of the genes for the β_2 -adrenergic receptor (*ADRB2*) and the glucocorticoid receptor (*NR3C1*) in leukocytes of children and adults with asthma (48). Moreover, one study showed that high perceived stress is associated with reduced bronchodilator response in school-aged children with or at risk for asthma, likely through down-regulation of *ADRB2* by persistent secretion of catecholamines, particularly in genetically susceptible individuals (47).

Airway Microbiome

Bacterial colonization of the upper airway may predispose children to severe asthma exacerbations. In a prospective study of children monitored from birth to age 5 years, neonatal colonization of the hypopharyngeal region with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* (alone or in a combination) was significantly associated with acute severe exacerbation of wheeze and hospitalization for wheeze (hazard ratio, 3.9; 95% CI, 1.9–7.8; $P < 0.01$) (49). In another study, detection of *S. pneumoniae* or *M. catarrhalis* in nasal samples with coexisting rhinovirus infection was associated with moderate asthma exacerbations among children ages 4–12 years (50).

Poor Adherence to Treatment

A systematic review of the literature showed that poor adherence to controller medications was both common and significantly associated with severe asthma exacerbations in children (51). Yet another conclusion of that review was that the impact of adherence to treatment on severe asthma exacerbations deserves further examination in well-designed real-life prospective studies that use standardized measures for adherence (i.e., electronic monitoring) and account for competency in inhaler use (a key confounder) (51). Recognizing the key importance of treatment adherence, guidelines have emphasized educating patients on inhaler technique, followed by continuous monitoring of their adequate inhaler use (52).

In summary, viral infection is the strongest risk factor for severe asthma exacerbations in children, with markedly detrimental effects in those who are allergic. Current evidence strongly supports causal roles for genetic susceptibility, SHS, outdoor air pollution, exposure to allergens and indoor pollutants, obesity, chronic psychosocial stress, and poor adherence to treatment in the pathogenesis of severe asthma exacerbations in childhood.

Predicting Severe Asthma Exacerbations

Predictive Scores

Consistent, poorly controlled asthma (requiring urgent care, unscheduled care, hospitalization, or intensive care unit admissions) is associated with future asthma exacerbations (53). Well-known and validated questionnaires are often used in clinical practice to assess asthma severity or control, including the Asthma Control Questionnaire, the Asthma Control Test, the Asthma Therapy Assessment Questionnaire, and the Global Initiative for Asthma (GINA) Questionnaire. Although these questionnaires are useful in assessing asthma control during a specified period of time, none can accurately predict a forthcoming asthma exacerbation in an individual child.

We aimed to construct a clinical score to predict severe asthma exacerbations based on a questionnaire that could be administered in a general pediatrician's office (54). The resulting questionnaire

yielded a final score between 0 and 17 points (based on yes/no questions). In their initial sample of Costa Rican children ages 6–14 years, each 1-point increase in score was associated with a 1.6-fold increment in the odds of an exacerbation in the previous year (95% CI, 1.3–2.0; $P < 0.001$), with an area under the curve (AUC) of 0.75. When applied to North American children enrolled in a longitudinal study, the AUC to predict exacerbations up to 1 year later was 0.69. Importantly, the cutoff score for children at low risk had a positive predictive value for “no hospitalizations” of 94–99%. Although imperfect, and in need of refinement and validation in larger (and more diverse) populations, this score is promising, as it could eventually allow clinicians to identify children at low and high risk for a severe asthma exacerbation.

Using data from 7,446 subjects in three studies, Bateman and colleagues investigated predictors of failure to achieve good asthma control on treatment, while also attempting to develop a simple risk score for exacerbation for clinical use (55). In a multivariable analysis, GINA step 4 versus 3 (OR, 1.33; 95% CI, 1.20–1.47), reliever use (OR per one occasion of higher use per day, 1.22; 95% CI, 1.16–1.28), postbronchodilator FEV₁, and the five-item Asthma Control Questionnaire score were dominant predictors of both uncontrolled asthma and severe exacerbations ($P < 0.001$ in all instances); smoking status and body mass index also predicted severe asthma exacerbations. Moreover, an exponential increase in risk was observed with increments in risk score for exacerbation based on five selected predictors for exacerbations (55). In another study, the severity of an asthma attack 1 hour after arriving at the ED (determined according to GINA criteria) was associated with subsequent hospitalizations for asthma (56). Other researchers have tried to develop predictive models on the basis of health care data and objective measures of lung function.

Biomarkers

Asthma monitoring is challenging in children with frequent exacerbations. Such monitoring is often based on symptoms, exacerbation frequency, need for rescue treatment or systemic steroids, and lung function. With better understanding of the pathophysiology of asthma, novel biomarkers have been tested for their ability

to predict severe exacerbations. A few of these biomarkers are described below.

Fractional exhaled nitric oxide (Fe_{NO}) is a noninvasive biomarker of eosinophilic airway inflammation. To date, a number of studies have concluded that Fe_{NO} has low power to predict asthma exacerbations, even when combined with clinical characteristics and symptom assessment (57). In a study by van der Valk and colleagues, repeated measures (three to five measurements in 3 wk) of Fe_{NO} predicted moderate asthma exacerbations (worsening daily symptoms not requiring oral steroids or hospitalizations) but not severe asthma exacerbations (58).

Airway eosinophilia is a well-defined inflammatory characteristic of Th2-driven (corticosteroid-responsive) asthma, and sputum eosinophils have been correlated with increased asthma severity and airway responsiveness. However, inducing sputum in children is challenging. Moreover, a study of school-aged children with severe asthma showed that a management approach accounting for both symptoms and sputum eosinophils was not superior to one using symptom management alone in reducing disease exacerbations (59). Serum periostin (a biomarker of allergic eosinophilic asthma) holds promise in predicting response to Th2-directed therapies for asthma (60), but there is limited evidence to suggest that the serum periostin level predicts asthma exacerbations, particularly in children (61). A marker of eosinophil activation (urinary bromotyrosine) was associated with poor asthma control and asthma exacerbations in a 6-week study of 57 children, but those findings have yet to be replicated in a larger study with longer duration of follow-up (62).

Cysteinyl leukotrienes LTC_4 and LTD_4 play a role in airway inflammation and are converted in plasma to cysteinyl leukotriene LTE_4 , which is partly excreted in urine. Indeed, children with acute asthma exacerbations have significantly higher LTE_4 than do healthy children (63). In a 5-month study of 44 school-aged children with moderate to severe asthma, the urinary LTE_4 level was associated with visits to urgent care or the ED by children who were exposed to SHS, but not by those unexposed to SHS (64).

Biomarkers in exhaled breath condensate (EBC) include low pH, cytokines, chemokines, NO-related products, leukotrienes, and volatile organic compounds. In a 1-year

prospective study of 40 children with asthma, both IL-5 in EBC and asthma control score best predicted disease exacerbations (Wald scores of 4.44 and 7.19; $P = 0.035$ and $P = 0.007$, respectively) (65). A combination of various biomarkers in the EBC, or a combination of EBC markers with clinical characteristics, might be a better predictor of asthma phenotypes than any single marker.

Future Directions

In spite of progress in our understanding of the pathophysiology of asthma and its phenotypes, we lack reliable instruments or biomarkers to predict severe asthma exacerbations. Most biomarkers are still confined to research use. High-throughput “omics” technologies (including genomics, transcriptomics, proteomics, lipidomics, and metabolomics) need to be increasingly standardized for discovery of biomarkers of severe asthma exacerbations.

Because no current predictive model (including clinical or biological markers) has been shown to be highly predictive of severe asthma exacerbations in children, the hope is that affordable “omics” and nanotechnologies lead not only to better predictors of severe asthma exacerbations, but also to individualized therapy. Future predictive models of severe asthma exacerbations should include a combination of epidemiological/clinical data and objective biomarkers, and target

specific asthma phenotypes (e.g., “obese asthma,” Th2-driven asthma, nonatopic asthma). Before any clinical application, such models will need to be prospectively validated in large and well-designed studies employing a standardized definition of severe asthma exacerbation (i.e., from the ATS/ERS joint statement) (1) as their primary outcome.

To date, the best predictor of future severe asthma exacerbations remains having had one recent severe exacerbation. For example, children with persistent asthma and at least one severe exacerbation in the prior year have a 2–2.5 times increased risk of subsequent severe exacerbations despite use of controller medications, supporting a strong role for individual susceptibility (53, 66, 67).

Findings from a retrospective study of 400 inner-city children and adolescents (ages 6–20 yr) with moderate to severe persistent (predominantly atopic) asthma treated according to standard guideline-based protocols for disease management (i.e., receiving ICS) further suggest that whereas some risk factors for asthma exacerbations are perennial (i.e., a reduced FEV_1/FVC), others vary by season (67). In particular, a severe asthma exacerbation in the previous season was the strongest predictor of an exacerbation in the fall or winter, but a higher requirement for ICS was the strongest predictor of an exacerbation in the spring or summer (67).

What can clinicians do with the available evidence? Children who have had a

Figure 1. Risk factors for severe asthma exacerbations in children.

severe asthma exacerbation in the prior year should be closely monitored, particularly before viral infections are likely to occur (as when school begins), so that their controller medications can be adjusted according to their asthma control. This

may be particularly relevant to allergic children who had a severe exacerbation in the previous year (23). More importantly, education, avoidance of exposure to SHS, and adherence to controllers such as ICS deserve

particular emphasis in the treatment of children at high risk for future severe asthma exacerbations. ■

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