

Editorial

Asthma attacks in children are always preceded by poor asthma control: myth or maxim?

Asthma is the most common chronic disease in childhood, with a substantial burden on the healthcare system globally [1]. Asthma symptoms can be broken down into two separate domains, asthma control (day-to-day asthma symptoms such as cough or wheeze at night or with activity) and asthma attacks (significant intermittent worsening of asthma, often secondary to a trigger of some sort). A joint American Thoracic Society/European Respiratory Society task force characterised asthma attacks as a change from the patient's previous status, with moderate asthma attacks defined as "events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe. These events are clinically identified by being outside the patient's usual range of day-to-day asthma variation." Severe attacks were defined as "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." [2]. Some attack definitions include the use of systemic corticosteroids for treatment [3, 4], while other definitions include declines in lung function as a part of the definition [5, 6]. Importantly, patients may not use the terminology of "attack," but rather may call such events attacks or flare-ups [5].

Asthma attacks are a major source of both morbidity and mortality in children with asthma [7, 8]. Asthma attacks in children may be associated with decreased lung function over time [9, 10]. In addition, asthma attacks are a significant source of healthcare-related costs [11], particularly when

emergency visits or hospitalisations are required [12]. Therefore, asthma attacks are a marker for interventions targeted at decreasing many negative asthma-related outcomes.

Asthma control is a second domain of illness that is also related to substantial morbidity. The Global Initiative for Asthma defines asthma control as "the extent to which the manifestations of asthma can be observed in the patient, or have been reduced or removed by treatment" [5]. It is typically comprised of two domains: symptom control (impairment domain) and risk of future attacks (risk domain) [5, 13]. For the purposes of this article, our use of the term asthma "control" will pertain to the impairment domain, or symptom frequency, intensity and functional limitations [14].

It seems a foregone conclusion that children with poor asthma control, including worsened day-to-day symptoms, would be at higher risk for an asthma attack. However, the remainder of this article will seek to evaluate the evidence for the question: are asthma attacks in children preceded by a period of poor asthma control?

Predictors of asthma attacks

First, we will evaluate some of the known predictors of asthma attacks outside of asthma control. There are a wide range of potential predictors of asthma attacks, from demographic and historical risk factors to lung function, biomarker data and genetics (table 1) [16].

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Some, but not all, asthma exacerbations in children are preceded by poor asthma control

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Table 1 Predictors of asthma exacerbations

Demographic	History	Lung function	Biomarkers	Environmental
Children/young children	Previous exacerbation(s)	Spirometry: FEV ₁ , FEV ₁ /FVC, FEF ₂₅₋₇₅	Eosinophils: peripheral blood, sputum	Indoor allergens with sensitisation
Women	Poor asthma control	Bronchodilator response	Number of inhalant allergen sensitisations	Outdoor allergens with sensitisation
Black and Puerto Rican race/ethnicity	SABA inhaler prescription refills	Bronchial hyperresponsiveness to methacholine	Exhaled nitric oxide	Viral infections
Economically disadvantaged	Difficult-to-control asthma	Impulse oscillometry		Smoking/smoke exposure status
Overweight	Poor controller medication adherence			

FEF₂₅₋₇₅: forced expiratory flow at 25–75% of FVC; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; SABA: short-acting β -agonist. Reproduced from [15], with permission from the publisher.

Demographics

Younger age in children has been associated with an increased risk of asthma attack [17, 18], as has obesity [19]. African American and Puerto Rican race/ethnicity has been associated with a moderately increased risk of asthma attacks and emergency department visits [17, 19, 20], and this effect in African American individuals persists in some studies when controlling for poverty, healthcare provision, area of residence and level of parental education [17, 20]. However, an evaluation of readmission rates in African American children found that 80% of their increased risk could be explained after balancing biological, environmental, disease management, access to care, and socioeconomic factors, indicating that the increased risk is likely multifactorial [21]. Another study found that black children were more likely to be admitted to the emergency department for their asthma; however, statistical balancing for social variables negated this increased risk [22]. Thus, the question of the impact of race/ethnicity on asthma attacks is a complex one, and probably affected by many more factors than genetics alone. Finally, behavioural factors such as poor adherence to asthma medications may increase attack risk [23, 24].

A recent asthma attack

Perhaps the best studied and most robust predictor of an asthma attack in children is a history of a recent attack [25–31]. A systematic review of attack predictors in 5–12-year-old children found the strongest odds ratios for future attacks (2.0 to 4.1) in those who had a previous asthma attack [17].

Lung function

Decreased FEV₁/FVC ratio has been associated with increased risk of asthma attacks [28, 32], and FEV₁ <80% predicted may be associated with emergency room use, particularly in black children [20].

Biomarkers

There is some evidence that biomarkers, such as elevated serum IgE [18, 28] and eosinophils [18, 28], are associated with an increased risk of an attack. Additionally, having multiple allergic triggers for asthma may increase attack risk [26, 28].

Environmental factors

Poor access to care has been associated with increased risk of asthma attacks across multiple studies [17]. Environmental tobacco smoke may mildly increase the risk of attacks in children [17, 19, 33]. In addition, airborne pollutants including ozone and particulate matter may be a driver of attacks, especially when combined with viral and allergic exposures [19, 33–35].

Poor asthma control does not always precede an attack

Asthma attacks can and do occur in children with apparent good asthma control and no recent history of an attack [16]. A large electronic health records study including more than 51 000 adults with asthma found that of those characterised as frequent exacerbators, 58% had mild/moderate asthma [36]. Symptom tracking in a study of 285 children with asthma found a poor positive predictive value of worsening of asthma symptoms

for an attack [29]. Changes in impulse oscillometry detected peripheral airway obstruction in 4–7-year-old patients even during asymptomatic periods, and such obstruction was associated with an increased chance of an asthma attack [37]. Children who are admitted to the intensive care unit with severe attacks may experience a more rapid onset of attack symptoms than controls [38]. A secondary data analysis of the Childhood Asthma Management Program (CAMP) showed that while having persistent asthma symptoms was predictive of an attack, the predictors of poor asthma control were different than the predictors of an attack [39]. However, uncontrolled asthma at baseline certainly does not guarantee that a child will have an asthma attack [32], and asthma severity may not be associated with attack risk especially in younger age groups [40]. There may in fact be a group of children with attack prone asthma that may be a distinct clinical phenotype [41].

Viral infections are one of the most important triggers of asthma attacks in children [33, 42, 43], and importantly, it is a trigger that is not entirely predictable. Multiple factors may increase the risk of viral induced attacks, including an interplay between genetics, atopy and infection type [42, 44]. In addition to acute viral infections, a predominance of certain bacteria may predispose to asthma attacks, although the role of acute bacterial infection in asthma attacks remains unclear [45]. One adult study showed that asthmatic adults were susceptible to attacks related to infection, irrespective of level of asthma control [46]. Attacks in children follow a seasonal pattern of prevalence, with increased attack rates particularly in the autumn season [18, 47, 48], which may reflect a confluence of atopy and viral infections during that time of the year.

Poor perception of actual level of control may account for some lack of association between asthma control and attacks. Perception of asthma-related symptoms relies on a complex interplay of activation of neural pathways, transmission of information and interpretation and understanding of that information by the patient, complicated further by acknowledgement of that information by the parent or caregiver of the patient in young children [49]. There have been documented discrepancies between both parental and provider assessment of asthma control and more objective measures [50–53], and children, especially those with severe asthma, may be particularly vulnerable to poor perception [54]. One small study found that nearly 50% of children studied were unable to detect either acute obstruction or bronchodilation [55], and symptom perception may be worse in younger children [55]. Increased levels of airway inflammation may be associated with poor perception of symptoms as well, possibly due to sensory receptor destruction [54]. Dyspnoea related to obesity may cause discrepancy in the perception of asthma control as well [56].

Self-evaluation questions

- 1 Which of the following is the most robust predictor of a future asthma exacerbation in children?
 - a) serum total IgE
 - b) history of a previous exacerbation
 - c) exposure to tobacco smoke
 - d) decreased FEV₁/FVC ratio
- 2 True or false: children with mild asthma are not at risk from fatal asthma exacerbations.
- 3 Which of the following seasons have been shown to be the highest risk for exacerbations in children?
 - a) Spring
 - b) Summer
 - c) Autumn
 - d) Winter
- 4 True or false: poor day-to-day control of asthma symptoms accounts for the biggest source of asthma healthcare-related costs in children.

Perhaps one of the most concerning features of asthma attacks is the fact that fatal asthma attacks can occur at any level of asthma severity. One study of adult and child asthma deaths in Australia showed that 34% of fatal asthma victims had no significant limitation due to asthma prior to their fatal attack, and 39% had never been admitted to the hospital prior to that event [57]. When evaluating the subset of children under 20 years of age in this group, 33% had a history of mild or “trivial” asthma, and only 36% had severe asthma [58]. An evaluation of Danish children showed that children who died from asthma were more likely to be in the 15–19-year-old age group, and had few asthma symptoms and poor asthma follow-up [59].

Poor asthma control does precede an attack

Various studies have demonstrated an increased risk of asthma attack in those with poorly controlled asthma [26, 60]. A meta-analysis of 68 studies in children showed a moderately increased risk of asthma attacks (OR of 1.4 and 7.8 in various studies) in children with persistent symptoms/poor control [17]. The TENOR study, which enrolled 4756 asthmatic adults, adolescents and children, found that asthma control both as measured by validated questionnaires or by US national guideline classifications were associated with increased risk of future asthma attacks [25]. Very poorly controlled asthma may pose a higher attack risk than not well controlled asthma [61]. Increased use of rescue medications has also been associated with increased attack risk [62, 63].

Multiple composite risk scores have been developed in an attempt to predict asthma attacks, and many include some measure of asthma control as one factor. One such score

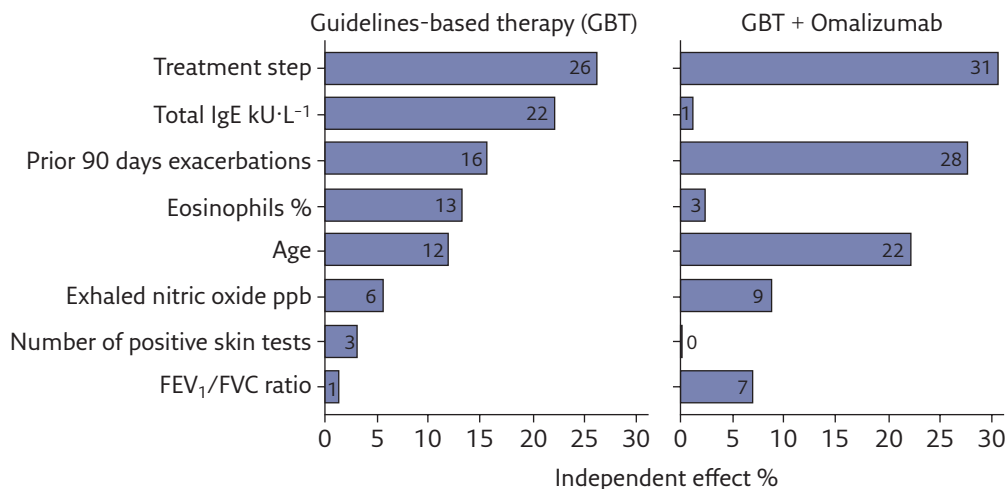


Figure 1 Relative importance of index variables for predicting exacerbations during the intervention period. Bar length represents the independent percentage of contribution of the variable in explaining exacerbations. The numbers at the end of each bar represent the independent effect of each variable. Reproduced from [18], with permission from the publisher.

was validated in the CAMP cohort and in a group of Costa Rican children and included multiple measures of asthma control including daily symptoms and exercise intolerance, and was validated for predicting risk of attacks [64]. The Seasonal Asthma Attack Predictive Index (saEPI) was developed to predict risk of asthma attack in children by season [18, 28], and included a treatment step which could be considered a proxy for asthma severity (*i.e.* a higher treatment step needed to control symptoms may indicate worsened overall severity). In a validation analysis, treatment step was the most relatively important factor in predicting attacks in children treated with guidelines-based therapy and those treated with guidelines-based therapy plus omalizumab to prevent fall attacks (figure 1) [18].

Overall opinion

Poor control of asthma is a marker of increased asthma-related inflammation, and is one of many possible predictors of asthma attacks. For many patients, poor asthma control does precede an asthma attack. However, there are also cases in which asthma control may be (or may be perceived to be) good prior to an asthma attack. Viral or atopic triggers may trigger attacks in those who are well controlled and poorly controlled alike, and unfortunately, having well controlled or mild asthma does not protect children from fatal asthma attacks. Therefore, while there is truth to the statement that poor control may often precede an asthma attack, the statement that the perception of poor asthma control always precedes an asthma attack is an overstatement.

Key points

- A previous asthma attack is the best predictor of another attack.
- Poor asthma control is often, but not always, associated with an asthma attack.
- Asthma attacks, even fatal attacks, can happen in children with well controlled or mild asthma.

Affiliations

Heather H. De Keyser, Stanley Szeffler

University of Colorado School of Medicine; Children's Hospital Colorado, Breathing Institute, Aurora, CO, USA.

Conflict of interest:

H.H. De Keyser reports consulting fees from AstraZeneca and a donation of research devices from Propeller Health outside the submitted work. S. Szeffler reports acting as a consultant for development and oversight of paediatric studies to meet regulatory requirements for new medications and oversight of a global study of this new medication as well as assistance in manuscript development (approximately \$5000 received over past 3 years, funds to his university) for Boehringer-Ingelheim, participation in two Pediatric Asthma Summit meetings to discuss asthma management worldwide (received approximately \$4000 for this work) and in two global advisory meetings for drug development including children (received approximately \$4000 for this work as well, all funds

to his university) for GlaxoSmithKline, assistance in educating investigators regarding severe asthma in children and also for guidance in new product development (approximately \$12000 over the past 3 years, funds to his university) for AstraZeneca, acting as a consultant for new drug development for childhood asthma (approximately \$4000 paid to his university in the past year) for Sanofi, acting as a consultant for new drug development for childhood asthma (approximately \$2500 paid to his university in the past year) for Regeneron, grant support from Propeller Health, and discussion of research data regarding electronic monitoring of adherence and rescue therapy and potential future research studies (approximately \$5000 paid to his university over the past 2 years) with Propeller Health, outside the submitted work.

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Suggested answers

- b.
- False.
- c.
- False.

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