



Complex pathways leading to future paediatric asthma exacerbations

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Childhood asthma studies to identify additional risk factors, triggers and biomarkers may reveal novel pathways leading to exacerbation <https://bit.ly/3BOhSWy>

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LOWDEN and TURNER [1] have published their study entitled “Past asthma exacerbation in children predicting future exacerbation: a systematic review” in this issue of *ERJ Open Research*. This systematic review of the asthma literature provides an analysis and relevant findings in a challenging and complex area of clinical importance.

Paediatric asthma exacerbations: clinical phenotypes at risk

Asthma exacerbations are associated with significant childhood morbidity, mortality and healthcare utilisation. Recurrent exacerbations may be associated with progressive decline in lung function and structural changes to the lung. The study by LOWDEN and TURNER [1] contributes additional knowledge to the understanding of clinical risk factors for a second exacerbation following an index case among children. The study contributes to current knowledge in the field by highlighting that the severity of the index exacerbation is not directly related to the risk of the second exacerbation [1].

The authors report their findings of a systematic review of 19 studies identified after database search and an additional seven studies identified by review of citations. They included studies with a mean age ranging from 5–18 years of age, to identify the risk of future asthma exacerbation, based on an index case of exacerbation.

One key finding of this paediatric study is that an index case of exacerbation is a risk factor for a second exacerbation, supporting close clinical monitoring of all paediatric asthmatics who experience an exacerbation. The authors describe a wide range of risk, depending on the study included, and whether the index case resulted in an emergency visit, hospital stay or paediatric intensive care unit (PICU) admission. For index cases resulting in hospital stay, the odds ratio of a subsequent exacerbation ranged from 1.89 to 5.36, based on the inclusion of data from five studies.

The degree of severity of an index case, unlike similar studies from the adult literature, did not result necessarily in a corresponding proportional increase in the odds ratio of future exacerbation. This finding is also important in the recognition that the development of asthma in children is complex and risk factors for exacerbation among adults are not consistently translatable to children.

Study limitations: complex pathophysiology leading to exacerbations

The study though did not, though, consider biomarkers or lung function in the analysis and the authors acknowledge that more studies are needed to better understand the role of biomarkers such as exhaled nitric oxide fraction (F_{ENO}) and exhaled breath compounds [2] in children. In another study, by ROBROEKS *et al.* [3], exhaled breath condensate (EBC) from 38 asthmatic children ranging in age from 6 to 16 years revealed that the combination of clinical score and EBC interleukin-5 level was useful in predicting asthma exacerbation.



In addition, there is a limited number of studies included involving subjects who required PICU admission. With respect to severe asthmatic exacerbation risk, therefore, the results may be more limited. The addition of lung function data, exhaled and blood biomarker panels may lend further insight. Another aspect to consider is the younger child with recurrent wheezing and the developing immune system. The current study did not study children <5 years of age.

Additional related citations

In a review by DI PALMO *et al.* [4], the authors describe that childhood asthma exacerbations result from not only lack of recognition and treatment, but also from complex interactions between susceptibility factors. These include genetic, environmental, infectious disease and immune responses. If unrecognised and left without adequate treatment, the developing lung may develop chronic inflammation, cellular infiltrates and progressive loss of lung function.

A study in adult patients with severe asthma has identified associated clinical and gene signatures related to the frequency of exacerbation [5], and may lend insight as to the risk factors among children with more than one exacerbation. The study reported that among severe asthma patients who experienced persistent frequent exacerbations, eczema, higher short-acting β_2 -agonist use, and higher bronchial tissue expression of type 1 and type 2 activation pathways were present [5]. A relevant analysis of the features associated with persistent frequent and infrequent exacerbations was included. The authors compared patients with exacerbations in the past and in the following year during the study. Atopic biomarkers such as serum IgE, blood eosinophil percentage and exhaled nitric oxide were lower among the persistent frequent exacerbation cohort compared with the persistent infrequent exacerbation cohort. The blood neutrophil percentages were not significantly different. The study though included adult patients and smokers, in contrast to the study by LOWDEN and TURNER [1].

A study by KRAFT *et al.* [6] utilised data pooled from the placebo groups of seven phase 2 and 3 randomised control trials (RCTs) of biologic therapies in adult patients with severe uncontrolled asthma. The findings revealed that there was no relationship between baseline serum IgE concentrations and annualised exacerbation rates (AERs). Persistent eosinophilia and F_{ENO} elevation were associated with greater AER. A subgroup analysis of subjects with the highest levels of type 2 inflammatory markers, $F_{ENO} \geq 50$ ppb and eosinophil counts ≥ 300 cells per μL experienced the highest AERs in comparison to the other subjects. Notably, among the RCTs analysed, children were not specifically included and most subjects did not have early onset asthma before the age of 6 years, highlighting the urgent need for similar studies in the paediatric population.

Another circulating biomarker which has been studied among children prior to the use of inhaled corticosteroids is circulating microRNAs, which have been studied in serum samples from 153 children enrolled in the CAMP study. The authors report a combined microRNA–clinical score model to predict exacerbations in children subsequently treated with ICS [7].

Studies that relate genetic predisposition to environmental triggers are of special relevance in understanding the pathways leading to childhood asthma and exacerbation risk. In studies of viral triggers, human rhinovirus C is noted to be a common trigger of childhood asthma exacerbations and severe attacks [8]. It is noted that genetic polymorphisms affecting the receptor expression of cadherin-related proteins may render a younger host more susceptible. Other studies of the upper airway reveal a relationship between nasopharyngeal microbiome profiles and the risk of childhood asthma exacerbations [9].

Another consideration is the developing immune system and the current study spans a wide age range, 5–18 years. In a study by EISENLOHR *et al.* [10], a study of 127 younger children, mean age 47 months (32–65 months), reveals that low vaccine antibody responses may identify a younger population at risk for asthma exacerbation or wheezing with illness.

Mild asthma and potential for severe exacerbation

Mild asthma may be associated with severe exacerbations and subjects with mild asthma are at risk for future asthma exacerbation. LOWDEN and TURNER [1] reported that there was no direct association between the degree of asthma severity and risk for future asthma exacerbation. This is similar to the finding in adults with one study reporting that up to 22% of mild-to-moderate asthmatic have required hospitalisation or had a severe exacerbation in the past year [11]. The study by LOWDEN and TURNER [1] supports the emphasis the Global Initiative for Asthma guidelines 2021 (www.ginasthma.org) put on close management of mild asthmatics who remain at risk for future exacerbations.

In terms of biomarkers in mild asthma, PAVORD *et al.* [12] report that higher blood eosinophil counts among adult mild asthmatics were associated with risk for future severe exacerbation. Again, similar studies are needed in the paediatric population.

Conclusions

In summary, the published study by LOWDEN and TURNER [1] highlights the importance of close management of children with an index case of exacerbation, regardless of asthma severity. Future studies should focus on investigating the pathophysiology of paediatric asthma exacerbations, and hopefully the identification of clinical, genomic and proteomic markers among children with an index case of exacerbation early in the disease will lend further mechanistic insight into paediatric asthma exacerbations.

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