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Review Article

Severe Pediatric Asthma Refractory to Treatment: The Ongoing Challenge of Exacerbation

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Abstract

The objective of this study was to review the last 16 years of literature on the clinical and functional risk factors for asthma exacerbation, as well as on biochemical parameters in severe pediatric asthma refractory to treatment (SPART). In searches of the Cochrane/Brazilian Virtual Library of Health, Latin American and Caribbean Health Sciences Literature, Medline, Brazilian Office for the Advancement of Higher Education, and PubMed databases, we employed the following search terms/strings: "severe asthma" or "refractory asthma" or "problematic asthma" or "difficult-to-treat asthma"; "exacerbation"; "risk factors" or "predictors"; and "pediatric" or "children and adolescents". We limited our searches to articles published between 1999 and 2016. We selected 26 original or review articles on severe pediatric asthma that addressed age, recent severe exacerbations, the level of asthma control, regular follow-up, comorbidities, behavioral factors, viral infection, and passive smoking, biomarkers of inflammation, serum vitamin D levels, and pulmonary function. However, we found very few studies dealing with SPART. Severe asthma is a heterogeneous, dynamic disease in which the various predictors of exacerbation described assess different aspects of the disease and are complementary. Such factors should be analyzed from a multifactorial and individualized perspective, because many of them are potentially modifiable.

ABBREVIATIONS

DTA: Difficult-to-Treat Asthma; FENO: Fractional Exhaled Nitric Oxide; FEV_1: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; GERD: Gastro Esophageal Reflux Disease; ICS: Inhaled Corticosteroid(s); OCS: Oral Corticosteroid(s); SART: Severe Asthma Refractory to Treatment; SPA: Severe Pediatric Asthma; SPART: Severe Pediatric Asthma Refractory to Treatment; TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (study); WHO: World Health Organization

INTRODUCTION

For most children and adolescents with access to health care, asthma can be controlled with low-dose inhaled corticosteroids (ICS). However, approximately 5% of pediatric asthma patients require treatment with high doses of ICS, in combination with a long-acting β_2 agonist, an anti-leukotriene, or an oral corticosteroid (OCS), to achieve or maintain adequate asthma control. Such patients should be referred to clinics specializing in the treatment of severe asthma, in order to confirm the diagnosis, manage comorbidities, and evaluate potentially modifiable factors [1-5].

Over the past 20 years, asthma that remains symptomatic despite current treatment with high doses of medication has been referred to variously as difficult-to-control/treat asthma, difficult asthma, severe problematic asthma, severe asthma, severe refractory asthma, and asthma resistant to treatment. The first definitions of such asthma were published in 1999 and 2000 [6,7]. In 2010, experts at the World Health Organization (WHO) proposed the standardization of the concept [1]. The WHO defined severe asthma, on the basis of the levels of current clinical control and future risks, as ". . . uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired pulmonary function or reduced lung growth in children)." The WHO experts also divided severe asthma into three groups: untreated severe asthma; difficult-to-treat severe asthma; and severe asthma refractory to treatment (SART).

For patients with asthma that is difficult to treat, control is achieved after comorbidities have been addressed, the differential diagnosis has been made, and the appropriate treatment has been administered. Patients who do not improve after all of those basic steps have been taken are classified as having SART. Among such patients, SART can have one of two presentations: partially/poorly controlled (describing cases that are relatively corticosteroid-insensitive, as well as those classified as corticosteroid-dependent, so classified because asthma control can deteriorate when the maintenance dose is reduced); and

well-controlled (describing cases in which control is maintained, albeit only with the highest recommended level of treatment). The level of treatment required to achieve control in SART suggests resistance or insensitivity to the treatment. In addition, patients with SART are at high risk of severe exacerbations when the treatment is reduced or suspended [1].

In severe asthma, exacerbations are common clinical manifestations and are associated with an increased risk of asthma-related death [8]. Compared with patients who have mild or moderate asthma, those with severe asthma use emergency care services 15 times more often and are hospitalized 20 times more often [9]. In addition, such patients are more likely to suffer the side effects of the drugs used, to consume a disproportionate amount of health care resources, to die prematurely, and to have a poorer quality of life [5,10-14]. Given the global goals of zero tolerance for asthma-related deaths and a 50% reduction in asthma-related hospitalizations in the coming years [15], addressing cases of severe asthma has become essential. In severe pediatric asthma (SPA), the predictors of exacerbation reportedly include clinical factors [16,17], functional factors [17], and biochemical parameters [18]. However, there have been few studies evaluating predictors of exacerbation in severe pediatric asthma refractory to treatment (SPART). The aim of this article was to review and discuss the predictors of exacerbation in SPA and SPART.

Exacerbation in severe asthma

Concept and classification: Asthma exacerbations are defined as episodes that cause patient discomfort, with a progressive increase in shortness of breath, coughing, wheezing, chest tightness, or a combination of those symptoms, requiring a change in the treatment. The symptoms of severe asthma can vary in a given patient or across patients, ranging from mild to life-threatening, on a daily basis and over time [1,4,10,19]. It is important to recognize episodes in which there is a transient loss of control, previously referred to as "mild exacerbation" episodes [5,19], as well as to identify exacerbations in patients who require daily doses of OCS as maintenance treatment [20,21], which is indicative of severe exacerbation. The definitions of moderate and severe exacerbations are given in Figure 1 [5,19].

The system of classifying exacerbations, as shown in Figure 1, provides considerable clarity for the recognition of moderate and severe exacerbations of asthma. However, changes in symptoms, pulmonary function, or rescue medication use vary depending on the population studied and the baseline characteristics of each patient. Therefore, there is a need for additional prospective studies to identify such criteria, especially in patients with SPA [19].

Factors predictive of exacerbation in SPA

Asthma is a dynamic disease, hence the fluctuating nature of the parameters used in monitoring its severity and control, as well as the difficulty in predicting the risk of exacerbation [4,19,22]. Among patients with severe asthma, it is important to identify those at high risk of exacerbations, because it allows the management to be individualized and informs decisions regarding prevention strategies, as well as reducing patient suffering, morbidity, and use of health care resources [23].

Given the lack of data regarding SPART, the aim of this review was to address certain relevant factors, derived from studies whose focus was on identifying the specific characteristics of SPA, as well as from studies involving adults with severe asthma or pediatric patients with moderate to severe persistent asthma. We also aimed to analyze recent efforts to identify the predictors of SPA on the basis of clinical characteristics, pulmonary function, and measures of airway inflammation. To that end, we searched the Cochrane/Brazilian Virtual Library of Health, Latin American and Caribbean Health Sciences Literature, Medline, Brazilian Office for the Advancement of Higher Education, and PubMed databases for articles published between 1999 and 2015. We employed the following search terms/strings: "severe asthma" or "refractory asthma" or "problematic asthma" or "difficult to treat asthma"; "exacerbation"; "risk factors" or "predictors"; and "pediatric" or "children and adolescents". We thus selected 26 original or review articles on severe pediatric asthma that addressed age, recent severe exacerbations, the level of asthma control, regular follow-up, comorbidities, behavioral factors, viral infection, passive smoking, biomarkers of inflammation, serum vitamin D levels, and pulmonary function (Figure 2).

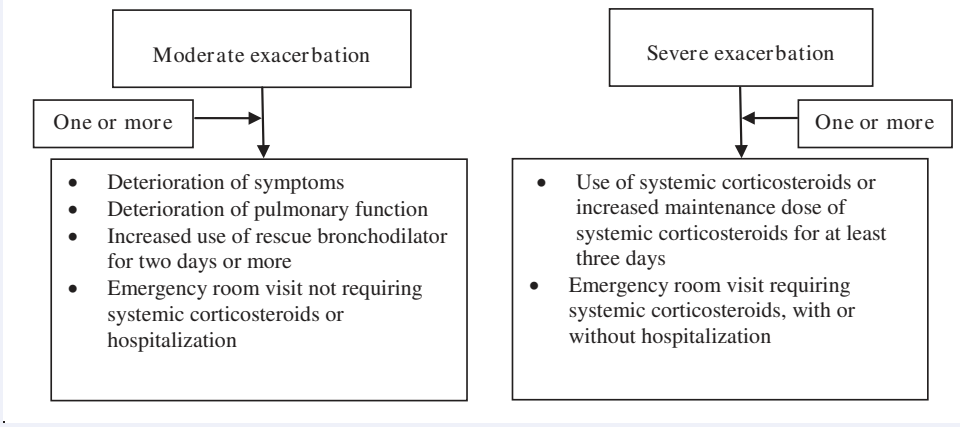

Figure 1 Degrees of exacerbation.
*Adapted from Chung et al. (5) and Reddel et al. (15).

Risk factors for exacerbation in severe pediatric asthma
Age
Recent severe exacerbations
Level of asthma control
Regular follow-up
Comorbidities
Gastroesophageal reflux disease (GERD)
Obesity
Allergic rhinitis
Behavioral factors
Inhaler technique
Adherence to treatment
Psychosocial problems
Viral infection
Passive smoking
Biomarkers of airway inflammation
Serum vitamin D levels
Pulmonary function

Figure 2 Risk factors for exacerbation in severe pediatric asthma.

Age

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study was a multicenter, cohort study involving pediatric and adult patients classified as having difficult-to-treat asthma (DTA), with an emphasis on the use of health care services [16]. The authors evaluated the patients on an annual basis over a three-year period and found the number of severe exacerbations to be equally high among children, adolescents, and adults. This authors of another study used the TENOR study data in order to evaluate the various parameters that might reduce exacerbations [17], comparing children, adolescents, and adults with severe asthma or DTA. They found that, regardless of baseline pulmonary function and long-term treatment with asthma-control drugs, severe exacerbations were two to three times more frequent in the 6- to 11-year age group. The authors emphasized the fact that, in comparison with the other patients evaluated in the TENOR study, the patients in the 6- to 11-year age group had sought emergency care for exacerbations that were significantly more severe and were more often hospitalized.

Recent severe exacerbations

In a study evaluating exclusively the portion of the TENOR study sample comprising patients in the 6- to 11-year age group with severe asthma or DTA [24], recent and "future" severe exacerbations were defined as those occurring, respectively, 3 months before and 6-12 months after one of the annual evaluations. The authors of that study found that a recent severe exacerbation was an independent risk factor for future exacerbations, regardless of the level of pulmonary function or the use of asthma control drugs. The authors suggested that the identification and more aggressive treatment of such patients could reduce the number of future exacerbations and that the investigation of recent exacerbations should be included in the evaluation of pediatric asthma.

Level of clinical control

It has been proposed that the current level of asthma control is a predictor of future exacerbations. In another study evaluating data derived from the TENOR study [25], patients with severe asthma or DTA were divided into two groups, by age: those in the 6- to 11-year age group (children; n = 82); and those in the ≥ 12 year age group (adolescents/adults; n = 725). All patients were evaluated over a period of two years. The authors also stratified the patients depending on whether the level of asthma control was always poor or improved over the study period. Despite adjustments to the treatment regimen, the risk of severe exacerbations was found to be six times higher in the poorly controlled asthma group than in the improved asthma control group. This suggests that asthma is intrinsically more serious when it is poorly controlled, which also raises the possibility of drug resistance [25].

Regular follow-up

Trying to define the clinical features of severe asthma by age, the authors of one of the studies employing TENOR study data found that the frequency of exacerbations was two to three times higher among the patients in the 6- to 11-year age group, regardless of follow-up evaluations by specialists, within or without structured programs [17]. However, that finding has not been confirmed by other authors. In a longitudinal study involving 20 patients with SPA in Argentina [26], the frequency of severe exacerbations was compared between the pre- and post-intervention periods. The authors found that, after regular follow-up treatment at a public hospital and via a specialized program for the treatment of children with severe asthma, there was a significant (55%) reduction in the frequency of exacerbations. The authors concluded that specialized follow-up is an effective strategy for the management of severe asthma in pediatric patients.

In a study conducted in the Brazilian state of Bahia, at the referral center where the Feira de Santana Municipal Program for the Control of Asthma and Allergic Rhinitis is headquartered, the risk factors for asthma-related hospital admission were evaluated in 151 children and adolescents with asthma [27]. Of those 151 patients, 47 (31%) had severe persistent asthma. Among those 47 patients, the only such predictor identified was a high degree of severity, which was found to account for a 13-fold increase in the likelihood of being hospitalized for asthma exacerbation. The authors concluded that a structured follow-up plan is needed in order to reduce the number of asthma-related hospitalizations.

Comorbidities

Overview: Poor control of asthma can also be attributed to the comorbidities that are typically present in patients with asthma. Among such comorbidities, the most widely studied are gastroesophageal reflux disease (GERD), obesity, and allergic rhinitis [4].

GERD: There have been conflicting results regarding the improvement of asthma symptoms and pulmonary function after the treatment of GERD, even in review articles focusing on pediatric patients with persistent asthma [28,29]. However, the authors of those review articles suggested that there are subgroups of patients with GERD and the more severe forms of asthma that can benefit (in the form of asthma symptom improvement) from the use of GERD medication.

Obesity: Asthma and obesity are both major public health problems that have an impact on hospitalization and mortality rates, which have increased interest in studies and interventions aimed at reducing the occurrence of these two problems in the population. The interactions between obesity and asthma are complex, including changes in mechanical factors, inflammatory mediators, and immune system responses. Consequently, obesity has been identified as an major risk factor for the development of asthma, because it alters the respiratory mechanics, which has significant effects on asthma control and the response to medications. These changes appear to be independent of airway inflammation, probably representing a new phenotype of asthma [30]. In a study of 1129 patients between 4 and 12 years of age, conducted in Brazil, excess weight was found to be associated with the development of asthma and atopy in 15.3% [31].

Allergic rhinitis: It is believed that nearly 80% of pediatric asthma patients have allergic rhinitis, and the respiratory symptoms related to allergic rhinitis can often be confused with asthma symptoms, and vice versa [32,33]. A study investigating factors associated with asthma-related emergency room visits in Brazil evaluated 126 pediatric patients (between 3 and 17 years of age) with persistent asthma (moderate in 53.3% and severe in 43.7%). The authors found that 44 (34.9%) of those 126 patients experienced asthma exacerbation over a three-year treatment period [34]. During the study period, all of the patients were under specialized treatment for asthma with ICS, which was dispensed at no charge. The overall prevalence of allergic rhinitis was 74.6%, being 46.3% among the patients with severe persistent asthma. The authors reported that, in the setting of severe asthma, allergic rhinitis was the main risk factor for seeking treatment in the emergency room.

Behavioral factors

Overview: A lack of asthma control can be caused by potentially modifiable risk factors, and an efficient approach could avoid the need for further laboratory tests and changes in treatment regimens [4]. Therefore, education programs for patients with asthma, as well as written asthma action plans, should include guidelines aimed at optimizing skills for the proper management of treatment [22].

Inhaler technique: The management of asthma is increasingly dependent on treatment with inhaled medications, which requires the use of proper inhaler techniques. The incorrect use of inhalers is quite common and is associated with a lack of asthma control, as well as with adverse outcomes such as hospitalizations, emergency room visits, and the need for courses of OCS [22].

In a study investigating potentially modifiable risk factors in problematic asthma, 71 pediatric patients (4.5-17.5 years of age), all of whom were under follow-up treatment at a referral center for pediatric pulmonology, were evaluated in home visits [35]. The authors found that factors related to the use of asthma medication, including treatment nonadherence, use of an incorrect device, and inappropriate inhaler technique, contributed to poor symptom control in 34 (48%) of the 71 patients. The inhaler technique was considered appropriate in 44 (62%) of the patients, satisfactory in 13 (18%), and unsatisfactory in 6 (8%). (The authors did not explain the missing data.) The inhalers prescribed were considered inappropriate in 11 patients (15%), the most common inappropriate prescriptions being of a mask with a spacer, of a metered-dose inhaler without a spacer, and of a device that the patient was unable to activate through inspiration. Some very young patients used the medication improperly and did so without direct supervision. Although the authors of that study did not assess the impact of such measures on the exacerbation of problematic asthma, they concluded that this type of evaluation led to the adoption of new management strategies in 39 (55%) of the patients, which eliminated the need for further escalation of the treatment, with its consequent potential risks and costs.

Adherence to treatment: In the study cited above [35], which involved pediatric patients with problematic asthma, the data collected during home visits complemented the investigation of treatment adherence and of the home environment. Among the various causes of inadequate control, the authors identified medication-related issues, including poor adherence to treatment in 34 patients (48%). In 23% of households, the asthma medications were not found. In other households, they were in inaccessible places or were out of date. Despite the fact that their study did not focus on exacerbations, the authors showed that poor treatment adherence influenced the subsequent assessment and management of problematic asthma.

In a study conducted in Brazil, the rates of adherence to ICS treatment were assessed in patients between 3 and 12 years of age who were followed at a referral center for pediatric pulmonology, 84.9% having been diagnosed with severe persistent asthma [36]. During each of the periods evaluated, the self-reported rate of treatment adherence was higher than was that verified by consulting the pharmacy dispensing records. The authors found that 83% of the patients with severe persistent asthma had experienced one or two exacerbations per month prior to enrolling in the study. Their findings demonstrate the importance of quantifying treatment adherence and estimating its potential influence on the outcome of exacerbations.

Psychosocial problems: There is evidence that stress worsens asthma in children and that psychosocial problems can manifest as dysfunctional breathing, which can be confused with symptoms of asthma exacerbation [37]. Studies also show that stress can increase eosinophilic inflammation, thus exacerbating asthma and decreasing the expression of β_2-adrenergic receptors, as well as influencing the induction of resistance to corticosteroids, through neuroimmunological mechanisms [38].

The authors of one study compared adolescents with and without asthma in terms of the prevalence of emotional and behavioral disorders [39]. Those authors applied a psychological disorders questionnaire (the Strengths and Difficulties

Questionnaire) in adolescents between 14 and 16 years of age, with and without asthma. The subjects were randomly selected from among the student populations of public schools. The authors found that the prevalence of emotional and behavioral disorders was 20.4% among the adolescents with asthma, significantly higher than among those without. Asthma was not found to be associated with any of the socioeconomic variables evaluated. The authors emphasized the need for an interdisciplinary approach in adolescents with asthma.

In a retrospective study of a mixed sample, in which 165 (31%) of the patients were under 15 years of age, the Mortality and Severe Morbidity Working Group of the National Asthma Task Force evaluated fatal outcomes of asthma exacerbations [40]. Factors associated with an increased risk of death from asthma, such as behavioral problems, repeated absences from scheduled medical visits, and poor inhaler technique, were identified in 48% of the patients. Psychosocial problems attributed to psychosis, alcohol or drug abuse, financial problems, learning disabilities, anxiety, or the use of antidepressants, were identified in 85% of the sample.

Viral infection

In asthma, viral infection has been shown to be a major trigger for exacerbations [4,41]. A study involving 84 asthma patients between 3 and 17 years of age addressed the potentially modifiable risk factors for asthma-related hospitalization[42]. In sensitized patients, the combination of allergen exposure and viral infection was found to have an effect that was statistically more significant than was that of either condition in isolation. That study was particularly interesting because of the high frequency of atopy in the pediatric asthma patients.

Passive smoking

Considering passive smoking as a predictor of the risk for exacerbation, two studies involving pediatric patients with moderate-to-severe persistent asthma evaluated the ability of a biomarker of smoke exposure to predict an increased risk of severe exacerbations [43]. Using a urinary biomarker, the authors showed that exposure to secondhand smoke are a significant risk factor for asthma exacerbation, despite the use of ICS. In the patients not exposed to secondhand smoke, asthma exacerbation was found to be associated with advanced age and with severely impaired pulmonary function.

Using data from the Chicago Initiative to Raise Asthma Health Equity study, McCarville et al. [44], evaluated the difference between measured and self-reported exposure to secondhand smoke in 71 asthma patients between 8 and 14 years of age, 15% of whom had severe persistent asthma. The authors found that the level of salivary cotinine (a biomarker of nicotine exposure) was predictive of the frequency of exacerbations, although self-reports of household smoking were not considered predictive of such.

Biomarkers of airway inflammation

It has been suggested that the biomarkers of airway inflammation constitute a sensitive indicator of changes that occur early in the exacerbation process. In a study on the risk of asthma exacerbation, involving 55 patients with SPA, symptom-guided conventional management (a control condition) was compared with management based on the proportion of eosinophils in induced sputum [45]. The number of exacerbations (total and cumulative) was lower in the latter group (comprising patients receiving treatment based on the inflammatory pattern), although the difference was not statistically significant. Although there was no significant difference between the two groups in terms of the total number of asthma-related hospital admissions, management based on the proportion of eosinophils in induced sputum reduced exacerbations in the short term, suggesting that the proportion of eosinophils should be determined more frequently if such evaluations are to have a clinically useful effect. This indicates that the control of inflammation plays an important role in certain SPA subgroups.

Serum levels of vitamin D

In a study involving 36 pediatric patients with SART, the serum level of vitamin D was evaluated in terms of its relationship with asthma severity and airway remodeling [18]. Acute exacerbations in the last six months were found to be more common among the patients with low serum levels of vitamin D, which were also found to be associated with increased use of OCS and ICS and a more pronounced bronchodilator response. In addition, the serum level of vitamin D showed a positive association with forced expiratory volume in one second (FEV_1), expressed as a percentage of the predicted value, and with forced vital capacity (FVC), expressed as an absolute value.

Pulmonary function

In studies with pediatric patients, pulmonary function does not show a strong correlation with asthma symptoms. However, even after having been adjusted for the frequency of symptoms, low FEV_1, especially FEV_1 < 60% of the predicted value, is an independent predictor of exacerbations [4].

In a longitudinal study involving 28 asthma patients, 16 of whom had SPA, the frequency of exacerbations was found to be associated with the baseline characteristics of pulmonary function and markers of early airway obstruction [46]. Pre- and post-bronchodilator FEV_1 < 80% of the predicted value was identified as a significant predictor of exacerbations, as was an FEV_1/FVC ratio < 0.8. In addition to showing greater impairment of pulmonary function, the patients with SPA were found to need rescue medication more often than were those with less severe forms of asthma.

CONCLUSION

Asthma exacerbations continue to be a common occurrence, resulting in significant morbidity, with an impact on pulmonary function and lung growth in pediatric patients, as well as on quality of life, together with adverse drug reactions and increased use of health care resources. The goals of asthma management should include the identification of clinical, functional, and biochemical risk factors, in order to facilitate prevention. However, there have been only a few studies investigating such factors in patients with SPART [4,5,7].

In other forms of asthma, various factors have been associated with the risk of exacerbation. In the studies of SPA evaluated

here, the following variables were identified as risk factors for exacerbation: being between 6 and 11 years of age [17]; having a recent history of severe exacerbations [24]; having uncontrolled asthma [25]; having psychosocial problems [40]; and showing an obstructive pattern of pulmonary function [46]. Strategies that have yielded promising results include regular follow-up by specialists [26] and asthma management based on the proportion of eosinophils in induced sputum [45].

We identified only one study involving exclusively patients with SPART, who are subject to severe and frequent exacerbations. In that study, a low serum level of vitamin D was found to be a predictor of asthma exacerbation. There is an ongoing need for studies aimed at characterizing the effects that exacerbations have on asthma control and identifying interventions to reduce the impact of asthma exacerbations.

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