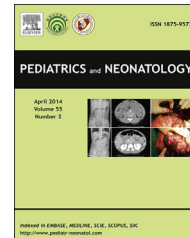




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REVIEW ARTICLE

Asthma Exacerbation in Children: A Practical Review



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Asthma is the most common chronic lower respiratory tract disease in childhood throughout the world. Despite advances in asthma management, acute exacerbations continue to be a major problem in patients and they result in a considerable burden on direct/indirect health care providers. A severe exacerbation occurring within 1 year is an independent risk factor. Respiratory tract viruses have emerged as the most frequent triggers of exacerbations in children. It is becoming increasingly clear that interactions may exist between viruses and other triggers, increasing the likelihood of an exacerbation. In this study, we provide an overview of current knowledge about asthma exacerbations, including its definition, impact on health care providers, and associated factors. Prevention management in intermittent asthma as well as intermittent wheeze in pre-school children and those with persistent asthma are discussed. Our review findings support the importance of controlling persistent asthma, as indicated in current guidelines. In addition, we found that early episodic intervention appeared to be crucial in preventing severe attacks and future exacerbations. Besides the use of medication, timely education after an exacerbation along with a comprehensive plan in follow up is also vitally important.

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1. Introduction

Asthma is the most common pediatric chronic respiratory disease, affecting 7.4% of children in central Taiwan,¹ 19.7% in northern Taiwan,² and up to 32.6% in the Western world.³

Exacerbation is a component of asthma that has a significant impact on both the child and the child's family. An exacerbation is often the initial event that precedes diagnosis of this disease and constitutes the majority of acute care events in children.⁴ Despite advances in asthma management and the introduction of guidelines specifically for pediatric asthma, acute exacerbations continue to occur and impose considerable morbidity on pediatric patients, thereby placing a considerable strain on health care resources as well as on the lives of affected children and their families.⁵

In the Asia-Pacific region, a survey conducted in 2006⁶ showed persistently poor control in asthmatic children. Compared with the results of a survey conducted in 2000,⁷ there has been no subsequent decrease in urgent care due to asthma exacerbation (44% in 2000 vs. 43% in 2006), including emergency department (ED) visits (19% vs. 19%), and hospitalization (15% vs. 17%). The urgent care rate in asthma patients may be as high as 43%. Real-world surveys conducted in the USA and Europe also revealed a considerable burden on patients and health care providers associated with asthma exacerbation.^{8,9}

Current guidelines assess asthma control based on two main facets: clinical control and future risk.¹⁰ The presence of an exacerbation has been shown to be equal to impairment in assessing the level of control. However, the two domains are not necessarily concordant. Patients may be well controlled in the impairment domain and be receiving optimal medications, yet still experience a severe exacerbation.^{11–13} The current interest in this aspect of asthma is reflected in numerous recent publications examining exacerbations from various points of view. Furthermore, the International Collaboration in Asthma, Allergy and Immunology (iCAALL), recently formed by the EAACI, AAAAI, ACAAI, and WAO, has proposed an International Consensus on (ICON) Pediatric Asthma in 2012¹⁴ and emphasizes the management of exacerbations to be a major consideration, independent of chronic treatment. iCAALL considers "improved asthma exacerbation treatment" to be "an important unmet need"; and thus recommends undertaking core research with a view to developing "new medication and/or strategies." The aim of the present study was to provide a review of recent reports on clinical practicability in asthma/wheeze exacerbation, with a particular emphasis on investigations highlighting findings that have not yet been fully discussed in the present guidelines (Table 1). Recent research on novel therapeutic modalities is not included in this review.

2. Definition of Asthma Exacerbation

Asthma exacerbation, also termed asthma "attack" or "episode", is a very common condition in pediatric practice. Although a detailed assessment of severity and treatment for exacerbation was first proposed in guidelines

many years ago, the definition of asthma exacerbation remains controversial.^{14,15} In the most recently published consensus in pediatric asthma in 2013, asthma exacerbation was defined as an acute or subacute episode of progressive increase in asthma symptoms, associated with airflow obstruction.¹⁴ The most commonly included exacerbation outcomes are the need for systemic corticosteroids, urgent unscheduled care, emergency department (ED) or urgent care (UC) visits, and hospitalizations for asthma.¹⁵

In young children, recurrent wheezing is a challenge in asthma diagnosis. In the PRACTALL consensus report published in 2008,¹⁶ the "phenotypes" of "persistent wheezing", "intermittent severe wheezing", and "non-atopic wheezing (mainly triggered by virus infection)" were proposed. These three phenotypes are very similar to asthma exacerbation in young children. It is difficult to diagnose asthma in young children and infancy; however, several publications have yielded useful findings, on prevention of severe wheezing attack and future wheezing in this age group, especially those with high asthma prediction index (API). These publications are discussed later in this review.

3. Burden in Asthma Exacerbation

In the United States in 2007, there were 0.64 million asthma-related ED visits by children and 157,000 asthma-related pediatric hospitalizations.¹⁷ A survey of 753 children with asthma in seven European countries revealed that 36% of children required an unscheduled urgent care visit in the past 12 months. Eighteen percent of children required one or more ED visits due to asthma in the past year.⁹ In the Asia-Pacific area, unscheduled care (UC) costs were responsible for 18–90% of total per-patient direct costs. Overall, total per-patient direct costs were equivalent to 13% of *per capita* gross domestic product and 300% of *per capita* healthcare spending,¹⁸ which do not include indirect social/economic costs. In Taiwan, the percentages of hospitalizations and ED visits for asthma patients were estimated to be 12% and 25% per year, respectively, which is equivalent to 1.2 in-patient days and 0.59 ED visits per patient per year, respectively.¹⁸ An analysis of data collected from Taiwan's National Health Insurance Research database in 2002 showed that overall health expenditure in pediatric asthma patients was 2.2 times higher than that in patients without asthma, and one-fourth of the cost for asthmatic children was attributed to hospitalization and UC.¹⁹

4. Factors Associated with Exacerbations

4.1. Poor asthma control

Poor asthma control can lead to severe asthma exacerbations.²⁰ In a study from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program, the percentage of asthmatic patients with three or more exacerbations per year was 5% in the mild group, 13% in the moderate group, and 54% in the severe group, suggesting that frequent exacerbations are related to disease severity.²¹ In

Table 1 Summary of studies for asthma exacerbation prevention.

Reference number (publication year)	Age (year)	Intervention	ER visit	Corticosteroid usage	Social: school absence, parents' work	Prevent future attack	Others
Intermittent asthma (wheezing)							
47 (2005)	2–5	Daily montelukast for 12 mo	Decrease	Decrease ICS usage	NA	Prolong the time to next exacerbation	
48 (2007)	2–14	Short course of montelukast for at least 7 d, determined by parents. Study period: 1 y	Decrease	No decrease in systemic usage	Decreased	NA	No decrease in hospitalization
49 (2008)	1–6	Early use of ICS or montelukast in URI for 7 d Study period: 1 y	No decrease	No decrease in oral usage	Not decreased	No effect	No difference in linear growth compare to placebo group
50 (2009)	1–6	Fluticasone 750 µg bid from URI onset. Maximum: 10 d Study period: 6–12 mo	NA	Decrease systemic use	NA	NA	Smaller linear growth
51 (2003)	1–4.5	Budesonide 1 mg bid from early URI for 7 d Study period: 1 y	No difference to daily budesonide use	Decrease total budesonide usage	Similar asthma control as daily budesonide	Similar to daily budesonide usage	
52 (2009)	<17	Intermittent ICS in early URI	No decrease	No decrease	NA, but parents preferred this management.	NA	Cochrane meta-analysis
53 (2009)	0.8–5	Prednisolone 10 mg or 20 mg qd from 1 st d of admission	NA	No decrease in hospital day.	NA	NA	No difference of 7-d symptoms score
54 (2010)	5–12	Prednisolone 1 mg/kg for 3–5 days, given within 6–8 h from URI onset	Decrease	Decrease	Decrease	NA	
55 (2006)	0.1–3	Budesonide 400 µg qd × 2 weeks after 3 episodes wheezing since 1 mo old. Study period: 3 y	No decrease	NA	NA	No effect	Similar linear growth to placebo group
Persistent asthma							
56 (2006)	4–11	Symbicort (80/4.5) as needed use during URI period in patients under regular budesonide controller	Decreased	Decreased	NA	NA	Better symptom score. Better linear growth than only regular budesonide group.
57 (2011)	<70	Fluticasone + salmeterol or Budesonide + formoterol as controller	No decrease	No decrease	NA	No decrease	A Cochrane meta-analysis. No decrease in hospitalization

(continued on next page)

Table 1 (continued)

Reference number (publication year)	Age (year)	Intervention	ER visit	Corticosteroid usage	Social: school absence, parents' work	Prevent future attack	Others
58 (2009)	6–12	Omalizumab q2wk or q4wk Study period: 2 y	Decreased	Decreased	NA	Decreased	No significant side effect
Education 60 (2009)	Children	Follow-up education	Decreased	Decreased	NA	Decreased	A Cochrane meta-analysis
61 (2009)	1–14	Action plan for asthma in OPD follow-up	Decreased	Decreased	NA	Decreased	

terms of asthma control, in a survey of 1003 patients in the United States with uncontrolled asthma, 70% had an unscheduled visit to a physician's office, 36% had an ED visit, and 14% had a hospitalization in the last year. Even among patients with controlled asthma, 43% had an unscheduled visit to a physician's office, 10% had an emergency department visit, and 3% had a hospitalization in the previous year.⁸ Adequate management of persistent asthma includes treatment with controller medications such as inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRAs), which have been consistently shown to reduce the risk of severe disease exacerbations.^{22,23} Poor adherence to medicine is an important contributing factor to poor asthma control. A recent study²⁴ showed that children with poor adherence to ICS had a 21% increase in ED visits and a 70% increase in hospitalization.

4.2. Severe exacerbation in the previous year

One or more severe exacerbation(s) in the previous year have been proven to be an independent risk factor for future exacerbation.^{25–28} Asthmatic patients, especially children,²⁸ requiring an ED visit or hospitalization are at significantly increased risk of future exacerbations independent of demographic and clinical factors, asthma severity, and asthma control.²⁵ In a multivariate model, recent severe exacerbation is the strongest predictor for future severe exacerbation with an odds ratio (OR) of 3.08, 95% CI = 2.21–4.28.²⁷ Based on GINA guidelines,¹⁰ frequent exacerbations in the past year is also a factor associated with future risk.

4.3. Viruses

Viral infections have been implicated in most (>80%) asthma exacerbations in children.^{29,30} Upper respiratory tract viral infections have been recognized as a factor in exacerbation events, particularly in children. Such infections are sometimes referred to as the "September epidemic" due to their seasonal pattern.³¹ Khetsuriani et al conducted a study enrolling children 2–17 years of age using a panel of PCR assays. Investigators compared children experiencing an exacerbation with those who had well-controlled asthma. Respiratory tract virus infection was associated with exacerbation in 63.1% of the patients compared with 23.4% in individuals with well-controlled asthma (OR 5.6; 95% CI, 2.7–11.6).³² Although several viruses have been found in asthmatics, rhinovirus has been the most commonly identified virus in proven viral-induced asthma exacerbations in children aged 6–17 years (55%) and in infants/pre-school children (33%). Other viruses detected and associated with asthma exacerbation included respiratory syncytial virus, enteroviruses, coronavirus, and human metapneumovirus.³³

4.4. Allergen sensitization

Allergen sensitization, especially when there are more than three allergen triggers, is also associated with asthma exacerbation (OR 2.05, 95% CI = 1.31–3.20).²⁷ Simpson et al³⁴ observed that most children classified as atopic using

conventional definitions were clustered into four distinct classes: early multiple, late multiple, dust-mite, and non-dust-mite. Only the early multiple class, which comprised approximately a quarter of the atopic children, was significantly associated with risk of hospitalization with asthma. Because PRACTALL has proposed that a phenotype of asthma is allergen-induced,¹⁶ which underscores the heterogeneity in these disorders, a more detailed interpretation of allergen sensitization may provide better prediction of exacerbation.

4.5. Virus–allergen interactions

A growing body of evidence supports the view that viral infection and allergy interact to increase the risk of an exacerbation. Murray et al observed synergistic interaction in children, which was even greater than the effect in adults. In his study, neither sensitization to allergens nor viral infection independently was associated with hospital admittance. It was the combination of the presence of virus and sensitization with high allergen exposure that increased the risk of admission (OR 19.4, 3.5–101.5, $p < 0.001$).³⁵

4.6. Smoking

The relationship between second-hand smoke and asthma morbidity in children is also well recognized. In the United States, more than 200,000 episodes of childhood asthma per year have been attributed to parental smoking.³⁶ Mackay et al demonstrated a reduction of 18.2% per year in the rate of asthma-related hospitalizations in children after the implementation of a public smoking ban in Scotland. Before its implementation, asthma hospitalization was increasing at a mean rate of 5.2% per year.³⁷

4.7. Pollution

Acute exposure to specific pollutants contributes to symptoms and increases the severity of asthma exacerbations, although their effects are not as pronounced as those of viruses and aeroallergens.³⁸ In children with asthma, NO₂ exposure is associated with increased respiratory symptoms,^{39,40} and increased personal level of NO₂ is associated with increased severity of virus-induced exacerbations.⁴¹

4.8. Genes

Several single nucleotide polymorphisms (SNPs) are reported to be related to asthma exacerbations. The T allele of the IL-13 gene promoter SNP (rs1800925) was associated with an increased risk of exacerbations among those receiving ICS.⁴² Three low-affinity IgE receptor gene (FcεR2) SNPs were significantly associated with elevated IgE level, and each was associated with increased severe exacerbations in white children.⁴³ Racial differences must be taken into consideration in gene studies. In Taiwan, Chen et al⁴⁴ also reported a common variant of a gene coding for the Cala cell 10 kDa protein to be a candidate determinant of asthma severity and steroid response in Chinese asthmatic children. More recently, Bisgaard et al, investigated gene

variants associated with asthma and exacerbation in early childhood. Variation at the 17q12-q21 locus was associated with an approximately twofold increased risk of recurrent wheeze, asthma exacerbations, and bronchial hyper-reactivity from early infancy to school age, but without conferring risk of eczema, rhinitis, or allergen sensitization.⁴⁵ This report adds to the growing evidence of genetic variation in susceptibility to exacerbations, particularly in non-atopic asthma, and further supports the existence of an independent presence of exacerbations. Overall, the finding that genetic variations affect severe exacerbation demonstrates the need to consider the interaction of genes with other known factors in the evaluation of children with frequent exacerbations.

5. Strategies for Preventive Management

The preventive management of exacerbation can be considered from two main perspectives in order to: (1) decrease the severity of exacerbation, and (2) avoid future exacerbation after the present attack. Here, we review updated strategies to achieve these two aims in patients with different conditions.

5.1. Intermittent asthma

Leukotriene receptor antagonist (LTRA) was reported to reduce asthma exacerbation in patients with mild intermittent asthma. A multi-center double-blind parallel group study showed daily montelukast 4 or 5 mg for 12 months significantly decreased the rate of exacerbation, the median time of first exacerbation, and the rate of inhaled corticosteroid usage.²³ An Australian randomized control trial (RCT) conducted in children with mild intermittent asthma, demonstrated that a short course of montelukast, introduced by parents at the first signs of an asthma episode for at least 7 days up to 48 hours after total symptom resolution, resulted in a significant reduction in acute health care resource utilization, symptoms, time off from school, and parental time off from work.⁴⁶ However, there were no significant effects on hospitalization rate, duration of symptoms, or use of bronchodilators and systemic steroids. The effect on future exacerbation attacks was not investigated in this study.

5.2. Intermittent wheezing in pre-school children

In pre-school age, the diagnosis of asthma is a difficult task, and a long follow-up period is often required to define the pattern of wheeze in young children. Nevertheless, during the follow-up course, there are often severe wheezing attacks that happen intermittently, especially when there is respiratory tract infection. The PRACTALL consensus proposed the concept of “virus-induced asthma” in which colds are the most common precipitating factor, and which also explains how some children can be completely well between symptomatic periods.¹⁶

Regarding the daily adherence and possible adverse effects of daily inhaled corticosteroid (ICS), several studies have investigated the effects of intermittent therapy for this phenotype in recent years and the results have been

instructive in pediatric clinical practice. For children aged 12–59 months with moderate to severe intermittent wheezing, early use of budesonide inhalation or montelukast in addition to albuterol for 7 days showed a modest reduction in trouble breathing and interference of activity compared with the placebo group, and the effects were particularly significant in those with positive asthma predictive indices. The effects were comparable in these two groups. However, neither episodic budesonide (1 mg twice daily, via nebulizer), nor montelukast (4 mg daily) showed differences in event-free days, oral corticosteroid use, health care use, quality of life, or linear growth when compared with the placebo group.⁴⁷ Another study from Canada⁴⁸ enrolled children aged 1–6 years with at least 3 previous wheezing attacks and at least one moderate to severe attack in the past 6 months in order to investigate the pre-emptive use of inhaled fluticasone for virus-induced wheezing. The study group received fluticasone 750 µg twice daily at the onset of upper respiratory infection and continued for a maximum of 10 days. In the 6–12-month study period, the fluticasone group showed decreased rescue systemic corticosteroid usage (OR 0.49, 95% CI = 0.3–0.83), but they suffered from smaller gains in height and weight. Therefore, its long-term benefits require further clarification.

Zeiger et al compared intermittent and daily budesonide therapy for preventing severe exacerbation in children between the ages of 12 and 53 months who had positive values on the modified API, recurrent wheezing episodes, and at least one exacerbation in the previous year but a low degree of impairment. Intermittent high-dose (1 mg) budesonide given twice daily for 7 days, started early during a predefined respiratory tract illness, showed a comparable effect of daily budesonide (0.5 mg nightly) with respect to the exacerbation frequency (0.95 vs. 0.97 per patient year).⁴⁹ There were also no significant between-group differences in several other measures of asthma severity, including the time to the first exacerbation, or adverse events. The mean exposure to budesonide was 104 mg less with the intermittent regimen than with the daily regimen. A meta-analysis from the Cochrane database also addressed this issue in a study on the use of inhaled steroids for episodic viral wheeze in childhood.⁵⁰ It concluded that episodic high-dose inhaled corticosteroids provide a partially effective strategy for the treatment of mild episodic viral wheeze in children. There is no current evidence to favor maintenance of low-dose inhaled corticosteroids in the prevention and management of episodic mild viral-induced wheeze.

The effects of early oral corticosteroid usage have also been evaluated in recent years, but the results have been inconsistent. For young children with previous wheezing attack, a 5-day course of oral prednisolone (10 mg daily for children aged between 10 and 20 months, 20 mg daily for those between 20 and 60 months) was instituted on their admission. Compared with the placebo group, there were no differences in the duration of hospitalization, 7-day symptom score, or albuterol usage.⁵¹ Another study of children aged 5–12 years with a history of recurrent episodes of acute asthma used the strategy of parent-initiated prednisolone when parents suspected imminent onset of a severe asthma attack based on their previous experience or

the absence of improvement in symptoms within 6–8 hours. Prednisolone 1 mg/kg/day was used for 3–5 days depending on the persistence or resolution of their child's asthma symptoms. There was some reduction in asthma symptoms ($p = 0.023$), health resource use ($p = 0.01$), and school absenteeism ($p = 0.045$).⁵² Overall, the present data suggest that early institution of oral corticosteroid for prevention of severe exacerbation is not recommended.

In an investigation of wheezing attack prevention, Bisgaard et al assigned infants to a treatment group with a 2-week course of inhaled budesonide (400 µg/day), which was initiated after a 3-day episode of wheezing, or to a placebo group which received conventional care. There was no decrease in the proportion of symptom-free days, percentage of persistent budesonide use, or acute episode duration compared with the placebo group during the 3-year follow-up, and there was no decrease in height or bone mineral density in the study group.⁵³

5.3. Persistent asthma

Controlled persistent asthma patients do have fewer exacerbations than patients with uncontrolled persistent asthma. However, even among controlled asthma patients, 43% have an unscheduled visit to a physician's office, 11% visit an ED, and 3% are hospitalized due to an exacerbation each year.⁸ Therefore, an additional regimen before or in the early stage of exacerbation is a recommended strategy for better asthma control.

Bisgaard et al proposed symbicort maintenance and relief therapy (SMART) as a new strategy in pediatric asthma in 2006.⁵⁴ SMART involves the use of symbicort 80/4.5 µg qd plus additional doses as needed. In this 12-month, double-blind, randomized study, 341 children aged 4–11 years with uncontrolled asthma received regular ICS with an average daily dosage up to budesonide 320 µg. SMART showed 70% and 79% ($p < 0.001$) reductions in exacerbation compared with groups receiving high-dose budesonide (320 µg qd) + terbutaline 0.4 mg as rescue and symbicort 80/4.5 µg qd + terbutaline 0.4 mg as rescue, respectively. The SMART regimen also reduced mild exacerbation days and nighttime awakening. The yearly height growth was better than that of the high-dose budesonide group. The good result consequently led to several trials using the SMART approach in several countries. In 2011, Cochrane published a meta-analysis of combined fluticasone and salmeterol versus fixed dose combination of budesonide and formoterol for treatment of chronic asthma in adults and children.⁵⁵ In the present analysis, the SMART regimen was not found to significantly decrease severe exacerbations. The conclusion of this meta-analysis was that the imprecise estimates of exacerbation indicate that further research is warranted. Indeed, more recent studies on the SMART regimen have yielded different results.

With regard to the safety of LABA usage in children, guidelines in recent years recommend increasing ICS dosage in uncontrolled asthma rather than adding LABA. The SMART regimen was first proposed in 2006, before the availability of guidelines specific for children, so even the "maintenance" component of SMART is not the first choice for children with persistent asthma.

The development of mAbs directed against molecular targets identified as important in patients with allergic asthma has shown some early potential in preventing asthma exacerbations. In a randomized trial of 6–12-year-olds with multiple exacerbations despite ICS treatment, a 43% reduction in clinically significant exacerbations was observed in the Omalizumab-treated group over a 1-year period.⁵⁶

To the best of our knowledge, a short course of ICS + LTRA combination for preventing pediatric asthma/wheeze exacerbation has never been previously reported, although ICS+LTRA was reported in a systemic review to be superior to ICS alone for the prevention of future exacerbation.⁵⁷

6. Education and Comprehensive Follow-up Plan

Aftercare of exacerbation events is a necessary component of exacerbation care. Many physicians feel that families need to be educated to recognize an imminent exacerbation and to enhance controller medication adherence. A Cochrane review published in 2009 found that educational programs significantly reduced risk of subsequent ED visits and hospital admissions, and also fewer unscheduled doctor visits compared with controls. They concluded that asthma education aimed at children (and their caregivers) who present to the ED for acute exacerbations can result in lower risk of future ED presentation and hospital admission.⁵⁸ Schatz et al also reviewed evidence of the effectiveness of follow-up after acute asthma episodes.⁵⁹ Recommendations based on their findings are listed below: (1) telephone reminders of appointments should be used to improve the effectiveness of patient follow-up after the ED visit, and if possible, appointments should be made before leaving the ED; (2) patients' chronic severity should be characterized by items in asthma guidelines; (3) specific elements should be included in the follow-up visit, such as controller, inhaler technique, self-monitoring, individualized asthma action plan, trigger identification, avoidance instruction, and further follow-up plans; (4) patients should be referred to a specialist when indicated.

7. Conclusion

One of the primary goals in the management of asthma is to minimize the severity and future risk of exacerbations, which also improves asthma control. Respiratory viruses are now well accepted as the main trigger of these exacerbations, and rhinoviruses remain the most commonly detected pathogens. The interaction of virus and sensitized allergen in pediatric asthma/wheeze patients needs further clarification, which should include the role of genetic variation. At present, early episodic treatment modalities provide some benefit, albeit to a limited extent, in reducing the impact of exacerbation, but more research needs to be done, especially with regard to identifying subgroups of response. In our review of the literature it is apparent that patients with previous severe exacerbation, positive asthma predictive indices, and multiple allergen sensitization require special attention and need to be

educated about these aspects of their disease. Pediatricians must be capable of identifying the signs and symptoms of patients with chronic asthma so that families can be educated to detect imminent exacerbation and adhere to the asthma control plan. Referral to a pediatric allergy specialist is indicated in pediatric patients with recurrent exacerbations and persistent asthma.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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