

How to prevent relapse after acute exacerbation of asthma?

Jak zapobiegać nawrotom po nagłym zaostrzeniu astmy?

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It is well known that most patients survive an acute exacerbation of asthma. This observation is in keeping with the natural tendency of acute asthma to resolve, providing treatment is prompt. Actually, for the majority of patients with an asthma exacerbation, management in the community or emergency department (ED) is adequate. Nonetheless, patients released from the ED after an acute exacerbation can relapse after discharge. The systematic review of randomized controlled trials published by Rowe et al. [1] strongly supports the use of oral or intramuscular (IM) corticosteroids (CSs) for treatment of outpatients released from the acute care setting with an exacerbation of asthma. Apparently, a short course of CSs following assessment for an asthma exacerbation significantly reduces the number of relapses to additional care, hospitalizations and use of short-acting β_2 -agonist without an evident increase in side effects. Intramuscular and oral CSs are both effective.

This is important information but, despite the proven benefit of therapy with CSs, the relapse rates for asthmatic patients released from the ED after an acute exacerbation remain high, as it has been documented by a study which combined data from two prospective cohort studies and showed that 17% of examined patients who were treated for acute asthma at an ED had relapsed by two weeks [2]. In particular, this study demonstrated that patients at increased risk for relapse had a history of numerous asthma-related ED and urgent clinic visits within the past year, and were using more outpatient asthma medications, including home nebulizers. Moreover, they also appeared to have longer duration of symptoms. In an analogous study conducted in 44 EDs, 10% of children relapsed during the 14-day period after discharge [3]. Multivariate analysis found age, use of any asthma medications other than inhaled β_2 -agonists, inhaled corticosteroids (ICSs) or CSs, and ED visits within the past year to be independently associated with relapse risk. It is likely that the onset of relapses after

ED discharge may be the result of objective stabilisation being delayed over initial symptomatic improvement, a phenomenon that can risk inducing an artificial sense of reassurance in both the patient and physician [4]. In any case, the data of these two studies emphasize the need for strategies to reduce relapse risk also because once a relapse occurs, the possibility of asthma-related morbidity and mortality rises sharply [5].

At least three variables that can be identified at the time of discharge are independently associated with relapse. They include: having made three or more visits to an ED in the prior 6 months; difficulty performing work or activities as a result of physical health in the 4 weeks prior; discontinuing hospital-based treatment for the exacerbation within 24 hours without having achieved a peak expiratory flow rate (PEFR) of at least 50% of predicted [6]. Relentless airway inflammation, poorly-resolving infection and persistent bronchial hyper-reactivity (manifesting as unpredictable swings in the PEFR amplitude) may all play a role in the pathophysiology of asthma relapse [4]. It is, therefore, likely that longer courses of prednisone might reduce relapse rates [7]. Correctly, Ornato [8] has suggested that patients given CSs should continue on oral prednisone 20 mg twice daily for 3 to 10 days after discharge, with the need for further CS treatment assessed at follow-up. Unfortunately, however, adherence to CS therapy often declines after discharge home [9], likely because of the presence of a high level of depressive symptoms that are common in adults with chronic illnesses [10]. This is a true problem because poor adherence to therapy increases the risk of adverse asthma-related outcomes, including ED visits and hospitalizations [11]. For this reason, Ornato [8] has also suggested to use a single IM injection of a CS with a depo-repository release for patients who might not adhere to traditional oral CSs regimens or for those who are unable to fill prescriptions after discharge. In effect, it has been documented that a single dose of triamcinolone diacetate, 40 mg IM, produced a relapse rate similar to that of prednisone, 40 mg/day orally for 5 days, after ED treatment of mild to moderate exacerbations of asthma [12], and, moreover, a single 1 mg/kg IM injection of methylprednisolone yielded relapse rates similar to those with an 8-day oral course of methylprednisolone [13]. The use of intravenous (IV) CSs for preventing relapses is more questionable. In general, patients with worse asthma exacerbations are more likely

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to receive IV CSs as compared with oral CSs. This is the likely explanation of the fact that patients receiving IV CSs are more likely to be admitted or experience a relapse event within 48 hours [14].

The possibility of switching patients to high-dose ICS therapy instead of continuing oral CSs after discharge has also been evaluated, taking into consideration that, although short-term use of CS is generally very safe, there are concerns about possible long-term effects in asthmatics requiring frequent courses of CS, as well as rare complications, and nuisance side effects [15]. Interestingly, a recent study has documented that a 2-weeks treatment with high-dose-inhaled fluticasone has at least similar effects on sputum eosinophilia as well as a traditional course with oral prednisone during exacerbations of asthma [16]. The effect of an ICS on sputum eosinophilia might have potential benefit as regards the rate of recurrence of asthma exacerbations. In fact, several direct and indirect observations suggest that eosinophils can be relevant in the long-term persistence of the airway abnormalities and in the remodelling process [17]. Furthermore, it has been demonstrated that a therapeutic strategy aiming to control sputum eosinophilia is more effective than traditional strategy based on symptoms and pulmonary function in preventing severe asthma exacerbations [18]. A meta-analysis of seven randomized, controlled studies in 1204 patients showed that high-dose ICS therapy at ED discharge was as effective as oral CSs in preventing relapse within 7 to 10 days of discharge [19]. In particular, it has been documented that in patients discharged from the ED after having been treated with CSs for severe acute exacerbation of asthma, home use of inhaled budesonide 2400 µg/day given in 3 inhalations of 200 µg 4 times per day and oral prednisone 40 mg/day given once in the morning for 7–10 days led to similar rates of relapse [20]. Nonetheless, considering that the cost of a treatment with an ICS is much higher than that of a CS, the cost differences between the two pharmacological approaches are an important consideration and, in particular, their cost/benefit ratio need to be always evaluated [16,19]. We completely agree that, if further trials in this area support a conclusion of equivalence between these two options, there would need to be evidence of other compelling reasons to use ICS in place of CS therapy, such as side effect profile, symptom control, or compliance.

On the contrary, we believe that strong consideration should be given to sending patients home on low- to moderate-dose ICS in addition to oral CSs, especially those who were not on controller medication before the asthma exacerbation episode and had a moderate to severe presentation. This our opinion strongly fits with the clear recommendations from all international guidelines for the treatment of asthma after an ED visit [21–24]. Studies have shown that patients discharged from the ED on 1 to 2 months of ICS have a significantly lower relapse rate and a reduction in subsequent ED visits [25,26]. Nonetheless, two large retrospective cohort studies documented that a large proportion of patients did not use ICS after discharge and this was even more important among adolescents [27,28].

Of concern is the finding that many patients with clear markers of uncontrolled or severe asthma, such as prior ED visits and hospital admissions for asthma, did not have a valid prescription for an ICS after discharge.

Obviously, in those in patients whose symptoms persist despite treatment with low-dose ICS, maintenance therapy with long-acting β_2 -agonists (LABAs), such as formoterol and salmeterol, in combination with ICS is an effective alternative to higher doses of ICS [29,30]. Intriguingly, add-on LABA therapy can reduce the risk of exacerbations by 3–14% compared with higher doses of ICS [31,32]. Although, to our best knowledge, no single study has explored the possibility of preventing relapse after acute exacerbation of asthma using an ICS/LABA combination, the findings that patients poorly controlled on low-dose ICSs have shown striking improvements in daily control and a 76% reduction in exacerbations when using maintenance plus as-needed budesonide-formoterol compared with a higher dose of ICSs alone [33] and, moreover, maintenance plus as-needed budesonide-formoterol reduced the risk of severe exacerbations and events resulting in ED visits or hospitalisations compared with maintenance budesonide-formoterol plus either formoterol or terbutaline as needed [34], provide insights into our understanding of how to use ICSs and LABA therapy optimally to prevent the risk asthma exacerbations and, likely, relapses. It is vital to emphasize that approaches that rely on a significant deterioration in asthma symptoms and action plans that instruct patients to double their ICS dose without an increase in dose frequency have been demonstrated to be wholly ineffective at preventing exacerbations [35,36], and it is likely that the same is true for relapses after acute exacerbation of asthma. Actually, as lung tissue concentrations of ICS decline between maintenance doses [37,38], as-needed ICS may restore concentrations when the level of ICS can be suboptimal. The importance of this approach has been confirmed by Kuna et al. [39] who documented that budesonide/formoterol maintenance and relief patients used less ICS vs. salmeterol/fluticasone and fixed-dose budesonide/formoterol patients reducing asthma exacerbations and maintaining similar daily asthma control at a lower overall drug load. In any case, we do not believe that differences in the ICS present in a combination ICS/LABA might be crucial, but we cannot exclude the value of formoterol in this type of combination. In fact, formoterol, a full β_2 -agonist, is more efficacious than salmeterol, a partial β_2 -agonist, during periods of increased inflammation or challenge [40,41]. Another factor may be the beneficial effects on neutrophilic inflammation that have been described for formoterol but to a lesser extent for salmeterol [42].

Leukotriene receptor antagonists (LTRAs) as adjunctive therapy in acute asthma should also be considered, because they might further reduce relapse rates after discharge. It is well documented that activation of leukotriene pathways in acute asthma is correlated with the degree of airflow obstruction, and resolution of the asthma exacerbation is associated with a reduction in leukotriene levels [43]. Some studies have

shown that urinary levels of leukotriene E_4 were not altered by continued treatment with ICSs in children with moderate to severe asthma [44], or by treatment with CSs in the ED in patients with acute asthma [45]. It is not surprising, therefore, that adding a LTRA to standardized ED therapy and routine discharge medication decreases the need for extended care in the ED and improves the outpatient relapse with fewer treatment failures and readmissions for patients with acute asthma [46]. Although the evidence is limited, it suggests that treatment with LTRAs provides additional bronchodilator effect to nebulised and inhaled β_2 -agonists. It has shown that IV montelukast 7 mg or 14 mg, in addition to standard treatment, gave a more rapid recovery in forced expiratory volume in the 1st second over a two hour period than did placebo [47]. Montelukast treated patients also needed less β_2 -agonist, and fewer treatment failures occurred compared with placebo. In another study, Silverman showed that addition of zafirlukast to the standard care of patients with acute asthma reduced the risk of relapse over one month compared with placebo [48]. Further studies of LTRAs, however, are needed before they can be recommended at discharge for reducing relapse risk.

It is clear that effectively treating acute asthma in the ED requires rapid reversal of airway obstruction and prevention of early relapse after discharge [8]. Treatment for discharged patients should include CSs for 5 to 7 days for all but the mildest asthma. Addition of ICSs should be considered for most patients, because evidence suggests that ICSs may reduce the rate of relapse. Improved and stable physiological measurements, sustained clinical well-being and smooth conversion to regular inhaled therapy together with an agreed asthma care plan are some of the factors that will help ensure safe discharge from hospital [4]. In any case, fundamental unanswered questions remain as to how best to prevent relapse after acute exacerbation of asthma, although it is clear that the clinician cannot expect the current pharmacotherapy to completely avoid the risk of relapses. Patients present for treatment of acute asthma for a variety of reasons, including undertreated or unrecognized disease, exacerbations of stable disease (usually caused

by recent exposure to triggers of exacerbations), and severe disease states unresponsive to conventional therapy [49]. It is likely that recognition of these phenotypes of acute asthma could enhance the management of these patients and reduce the risk of relapses.

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From the Editor

Synopsis: Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, et al. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev.* 2007; 3: CD000195.

In this systematic review with meta-analysis of 6 randomised controlled trials including together 374 participants, efficacy of administering systemic corticosteroids (*p.o.*, *i.v.* or *i.m.*) in comparison with placebo was assessed in patients discharged from emergency department following acute exacerbation of asthma. At 7–10 days in the group receiving corticosteroids the risk of relapse of asthma exacerbation was lower (RRR 62%, NNT 10, the risk was also lower at 21 days), hospitalizations were less frequent (RRR 65%, NNT 11), patients reported less need for β_2 -agonists, while the adverse event risk was not increased.

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