Systemic Corticosteroids in Respiratory Diseases in Children

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Introduction

Corticosteroids are anti-inflammatory drugs that have been used for the treatment of respiratory diseases for many decades. Despite their long use, the role of steroids in several respiratory conditions is still highly debated.

Corticosteroids inhibit the release of several cytokines and proinflammatory mediators and have a direct action on certain inflammatory cells. They accelerate the apoptosis of eosinophils and, although they are not effective in inhibiting the release of mediators from mast cells, after long-term treatment corticosteroids reduce the number of mucosal mast cells in the airways. Furthermore, glucocorticoids inhibit the increase of vascular permeability caused by inflammatory mediators with a direct effect on postcapillary venules of the respiratory epithelium and reduce the production of mucus in the airways.

Asthma

One of the most common respiratory diseases in children is asthma, which is a chronic inflammatory disease of the lower airways characterized by bronchial obstruction, usually reversible spontaneously or in response to therapy, and bronchial hyperreactivity. Systemic corticosteroids are rarely necessary in the long-term treatment of asthma in children. They should be considered only in patients with severe asthma and used at the lowest dose necessary to control symptoms. In

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children with uncontrolled asthma needing systemic steroids, other drugs can be considered, even if most treatments are unlicensed and studies of these treatments are few. An exception is omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody. The most recent asthma guidelines, such as the update of the National Institute for Health and Care Excellence guidance in 2013, the International Consensus on Asthma guidelines, and the update of the Global Initiative on Asthma guidelines in 2014, recommend omalizumab as add-on therapy in adults and children over 6 years of age with uncontrolled IgE-mediated asthma who require frequent use of oral corticosteroids [1, 2].

Many studies have shown that systemic corticosteroids are useful in the treatment of acute asthma. In fact, they improve symptoms, oxygenation, and pulmonary function and reduce hospital admissions [3, 4]. Some studies showed that systemic steroids are more effective in patients with severe asthma and that they may not be useful for treating mild attacks of asthma that respond well to bronchodilators, except for children who have been hospitalized or previously intubated or who are already treated with oral steroids.

Oral and parenteral corticosteroids seem to have the same effects in most patients, and there are no significant differences of efficacy between different systemic steroids administered in equipotent doses. In general, the dose of systemic corticosteroids given is 1–2 mg/kg of prednisone in one or two doses, and the duration of treatment is usually 3–10 days depending on the severity of the attack and the clinical response [5].

Preschool Wheezing

Oral steroids are widely used to treat preschool children with wheezing, but their efficacy is controversial. Preschool wheezing is a common condition that usually regresses in the first 6 years of life. Three randomized control trials (RCTs) showed a positive but not significant effect of systemic steroids in children with wheezing admitted to emergency departments [6, 7]. A recent study has shown that oral prednisolone given for 5 days at the beginning of an attack of viral wheeze in preschool children has no benefits [8]. A more recent trial reported that in preschool children with mild or moderate wheeze admitted to hospital, oral prednisolone is not superior to placebo [9].

Rhinovirus infection is an important risk factor for recurrent wheezing in preschool children. A recent RCT reported that oral prednisolone is not superior to placebo in preventing the recurrence of wheezing in children whose first wheezing episode was caused by rhinovirus. However, the same study reported that oral prednisolone might be useful in a subgroup of children with high viral load [10].

In conclusion, oral steroids cannot be recommended in all cases of viral wheeze. They should be given only to preschool children admitted to hospital who are not responding to bronchodilators or with risk factors for asthma such as atopic eczema or a family history of asthma [11, 12].

Bronchiolitis

Another common respiratory disease in children is bronchiolitis, which is the most common lower respiratory tract infection in the first year of life. Oxygen supplementation and other supportive treatment such as feeding, hydration, and nasal suctioning are the main therapy for bronchiolitis [13]. Systematic reviews and meta-analyses of RCTs involving 1,200 children with viral bronchiolitis have not provided sufficient evidence to support the use of steroids in this illness [14, 15]. The recent guidelines of the American Academy of Pediatrics state that systemic corticosteroids should not be used routinely in the treatment of bronchiolitis [15].

Community-Acquired Pneumonia

Systemic corticosteroids are also used in community-acquired pneumonia (CAP), another frequent disease of the lower airways in children. The benefits of corticosteroids in the treatment of CAP in adults are not clear and even fewer data are available on the use of steroids in children with CAP. A recent prospective observational study reported that treatment with corticosteroids in CAP in adults is not associated with lower mortality and does not change the length of hospital stay or the readmission rate. A randomized double-blinded clinical trial with 213 adults concluded that systemic prednisolone has no positive effects in patients hospitalized with CAP [16]. A recent study reported that systemic steroids in adult patients with CAP do not influence the mortality rate or clinical course of the disease, but seem to prolong the duration of hospitalization [17].

A further study investigated a 5-day course of methylprednisolone therapy in 29 children with severe CAP treated with imipenem. This group was compared with 30 patients treated with imipenem and placebo [18]. The authors reported that methylprednisolone significantly reduced the length of hospital stay as well as the number of severe complications and of surgical interventions [18].

A multicenter retrospective study of 20,703 children with CAP showed that systemic corticosteroids are useful only in patients with acute wheezing, in whom they reduce the duration of hospitalization, whereas in those with CAP without wheezing, systemic steroids are associated with a longer hospital stay and a greater rate of readmission [19].

Thus, currently systemic corticosteroids cannot be recommended as adjunctive treatment in children with CAP [20], but further large RCTs are necessary to investigate the efficacy and safety of systemic corticosteroids in these children.

Bronchopulmonary Dysplasia

Another disease of the lower airways in children is bronchopulmonary dysplasia (BPD), an alteration of lung development as a result of multiple insults to the lung of the fetus and the premature newborn. An important role in the pathogenesis of BPD is played by persistent lung inflammation, and corticosteroids have been administered widely in preterm infants with respiratory failure. There are many studies in which both systemic and inhaled corticosteroids have been used for the treatment and prevention of BPD. A Cochrane Review of 28 trials showed that systemic steroids administered in the first week of life facilitate extubation and decrease the incidence of BPD, but cause significant adverse effects such as gastrointestinal hemorrhage, bowel perforation, cardiomyopathy, and cerebral palsy [21]. Another Cochrane meta-analysis revealed that the use of steroids after the first 7 days is associated with a decreased risk of BPD and accelerated weaning from oxygen and mechanical ventilation with no increase in long-term adverse effects such as cerebral palsy [21, 22]. The European Association of Perinatal Medicine, the American Academy of Pediatrics, and the Canadian Pediatric Society stated there is no sufficient evidence to recommend routine use of steroids in preterm infants after the first week of life; however, a short course of dexamethasone can be considered in patients with BPD in whom weaning from mechanical ventilation and oxygen therapy is difficult or whose respiratory conditions are quickly worsening [21].

Allergic Bronchopulmonary Aspergillosis

Systemic corticosteroids, together with antifungal drugs, are the mainstay of therapy for allergic bronchopulmonary aspergillosis, which occurs often in patients with cystic fibrosis (CF). Several studies reported that systemic steroids in this condition decrease serum IgE levels and total eosinophil count and improve clinical symptoms and lung function. Oral corticosteroids are useful in allergic bronchopulmonary aspergillosis, but the adverse effects of a long-term treatment have led to a search for safer regimens. Some studies showed that monthly high doses of intravenous methylprednisolone led to improved clinical conditions and laboratory parameters with fewer side effects compared with oral steroids [23, 24]. Moreover, there are case reports that omalizumab may have beneficial effects in allergic bronchopulmonary aspergillosis, but RCTs in children are needed.

Cystic Fibrosis

The use of corticosteroids has also been investigated in the treatment of acute exacerbations in patients with CF. In a study of children with CF hospitalized for severe respiratory distress, the clinical conditions of the patients were improved by the administration of a high dose of methylprednisolone intravenously for 3 days; the authors concluded that this therapy could be an effective treatment for children with uncontrolled pulmonary exacerbations [25].

Given the role of lung inflammation in the pathogenesis of CF, systemic steroids have also been studied as long-term therapy in patients with this disease. A recent Cochrane Review identified three RCTs on oral corticosteroids given for more than 30 days in patients with CF. The authors concluded that long-term use of oral steroids at prednisolone-equivalent doses of 1–2 mg/kg on alternate days seemed to reduce the progression of lung disease, although often at the cost of adverse effects such as cataracts and growth retardation. Hence, long-term use of systemic steroids in patients with CF is not recommended [26].

Primary Ciliary Dyskinesia and Interstitial Lung Disease

Another disease of the lower airways characterized by lung inflammation and frequent infections is primary ciliary dyskinesia, which is defined as a group of congenital pathological conditions due to the abnormal structure and/or function of cilia, with altered mucociliary transport leading to several respiratory disorders.

There are no RCTs on the use of corticosteroids in this condition, and therefore indications are often based on expert opinion or are extrapolated from evidence available from CF studies. Inhaled or oral steroids together with bronchodilators are only prescribed if the child is thought to also have airflow obstruction [27]. Systemic corticosteroids are used for many interstitial lung diseases including surfactant protein deficiencies but there are no controlled trials in children; treatment is based on uncontrolled studies, case reports, and observations [28].

Bronchiolitis Obliterans

Another rare but severe chronic lung disease in children is bronchiolitis obliterans (BO). The most common presentation is the postinfectious variant, related to a viral lower respiratory tract infection in the first years of life [29]. BO is characterized by inflammation and fibrosis of bronchioli resulting in narrowing and obliteration of the small airways. There are few RCTs focusing on treatment of BO in children, and therapeutic decisions are often based on empirical evidence [29]. Inhaled corticosteroids are widely used in patients with BO; oral steroids are used

during respiratory obstructive exacerbations for variable periods or in patients with severe oxygen-dependent BO [29]. Currently, the use of systemic corticosteroids in the treatment of BO is controversial. A recent study suggested that intravenous pulse corticosteroids could be a useful and relatively safe treatment option in children with BO, with fewer adverse effects compared with continuous therapy with oral steroids. New prospective controlled trials are required to confirm this therapeutic regimen [30].

Croup

A common disease of the upper airways in which corticosteroids are widely used is croup, characterized by acute obstruction. Viral croup mainly affects children between 6 months and 6 years of age. Many RCTs have demonstrated significant benefits of corticosteroids in patients with croup; systemic or nebulized steroids decrease the need for other drugs, the duration of hospital stay, and the need for intubation [31].

Conclusion

Systemic corticosteroids are used in various respiratory diseases in children. However, the role of systemic steroids in children is limited by their side effects. Physicians must always weigh the benefits against the potential adverse effects when they decide to use corticosteroids in children.

Steroids are useful in the treatment of acute asthma and croup. In conditions such as bronchiolitis, preschool wheezing, bronchopulmonary dysplasia, and community-acquired pneumonia, their benefits are uncertain and they cannot be recommended routinely. In other rare respiratory diseases, systemic corticosteroids are used despite the lack of scientific evidence of their benefits.

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