Concise Clinical Review

Corticosteroids in Respiratory Diseases in Children

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We review recent advances in the use of corticosteroids (CS) in pediatric lung disease. CS are frequently used, systemically or by inhalation. Their mechanisms of action in pulmonary diseases are ill defined. CS exert direct inhibitory effects on many inflammatory cells through genomic mechanisms. There is a time lag before clinical response, and the washout of effects is also prolonged. Prompt relief in some conditions, such as croup, may be related to airway mucosal vasoconstriction through a nongenomic mechanism. CS have proven beneficial roles in the treatment of asthma, croup, allergic bronchopulmonary aspergillosis, and subglottic hemangioma. In some conditions, such as bronchiolitis, cystic fibrosis, and bronchopulmonary dysplasia, their use is controversial and is not recommended routinely. In other conditions, such as tuberculosis, interstitial lung disease, acute lung aspiration, and acute respiratory distress syndrome, CS are often used empirically despite the lack of clear evidence of their benefit. New drug regimens, including the more flexible use of inhaled corticosteroids and long-acting β-agonists in asthma, the lack of efficacy of oral corticosteroids in preschool children with acute wheeze, the severe complications of systemic dexamethasone used to prevent bronchopulmonary dysplasia and thus more restricted use, and the beneficial effect of pulse high-dose intravenous methylprednisolone in patients with allergic bronchopulmonary aspergillosis or cystic fibrosis are among the major recent developments. There is concern about adverse effects, especially growth and adrenal suppression, induced by systemic CS in children. These have been reduced, but not eliminated, with the use of the inhaled route. The benefits must be weighed against the potential detrimental effects.

Keywords: respiratory system; lung; corticosteroids; treatment

Corticosteroids (CS) are potent antiinflammatory drugs that have been used in the treatment of respiratory diseases since 1950 (1). Despite more than 60 years of use, their role is still controversial in many pulmonary conditions. We review the present role of CS in the treatment of the most important respiratory diseases in childhood, with particular focus on what is new since our previous report (1). A literature search was performed based on a predefined series of key words (corticosteroids, respiratory diseases). Searching included the Cochrane library, MEDLINE, and EMBASE, and the strategies included filters to limit the results by date range (1995–2011), age range (0–18 yr), and language (English).

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MECHANISMS OF ACTION

Molecular and Antiinflammatory Signaling Mechanisms

Most data are from adult and animal studies; there is a paucity of information on any developmental effects on these mechanisms. Endogenous cortisol passes through cell membranes and binds with high affinity to cytoplasmic glucocorticoid receptor (GCR) to form a complex that moves quickly into the nucleus. The cortisol–GCR complex inhibits inflammation through three molecular mechanisms. (*1*) It interacts with specific DNA sequences and influences nuclear gene expression, thereby increasing or decreasing gene transcription (direct genomic effect); (*2*) it blocks the activity of nuclear factor (NF)-κB, which stimulates the transcription of cytokines, chemokines, cell adhesion molecules, and receptors for these molecules (indirect genomic effect); and (*3*) it activates glucocorticoid signaling through membrane-associated receptors and second messengers (nongenomic effect) (2).

Glucocorticoids exert their antiinflammatory effect by binding to GCR through three genomic independent mechanisms: (*1*) They induce the production of annexin I (also called lipocortin-1), which, by inhibiting the synthesis of cytosolic phospholipase A2-α, blocks the release of arachidonic acid from membrane phospholipids and its subsequent conversion to eicosanoids (i.e., prostaglandins, thromboxanes, and leukotrienes); (*2*) they induce the mitogen-activated protein kinase (MAPK) phosphatase 1 that dephosphorylates and inactivates members of MAPK cascades, thereby inhibiting the transcription of inflammatory proteins or indirectly inhibiting phospholipase A2-α activity; (*3*) they antagonize the transcriptional activity of NF-κB, thereby inducing repression of cyclooxygenase 2, an enzyme essential for prostaglandin production (2) (Figure 1). The main nongenomic mechanisms involve the activation of endothelial nitric oxide (NO) synthase and NO synthesis, which is generally associated with vasodilation, and an increase of noradrenergic neurotransmission in the airway vasculature, which is associated with a reduction in airway blood flow (3).

Cellular Effects

The exact mechanisms of action of CS in pulmonary diseases are not well defined (4, 5). CS exert direct inhibitory effects on many inflammatory cells (6–8). They accelerate eosinophil apoptosis (9) and conversely inhibit neutrophil apoptosis, thus prolonging their lifespan in the airways (10). Although CS do not inhibit the release of mediators from mast cells (11), regular treatment with ICS reduces the number of mast cells within the airways (12). Many CS antiinflammatory properties may be due to inhibition of cytokine expression (13). In addition, CS may reduce airway microvascular leakage (14) and decrease mucus production (15).

Functional Effects on Airways

The functional effects of CS on airways have been evaluated mainly in patients with asthma. Single dose administration of

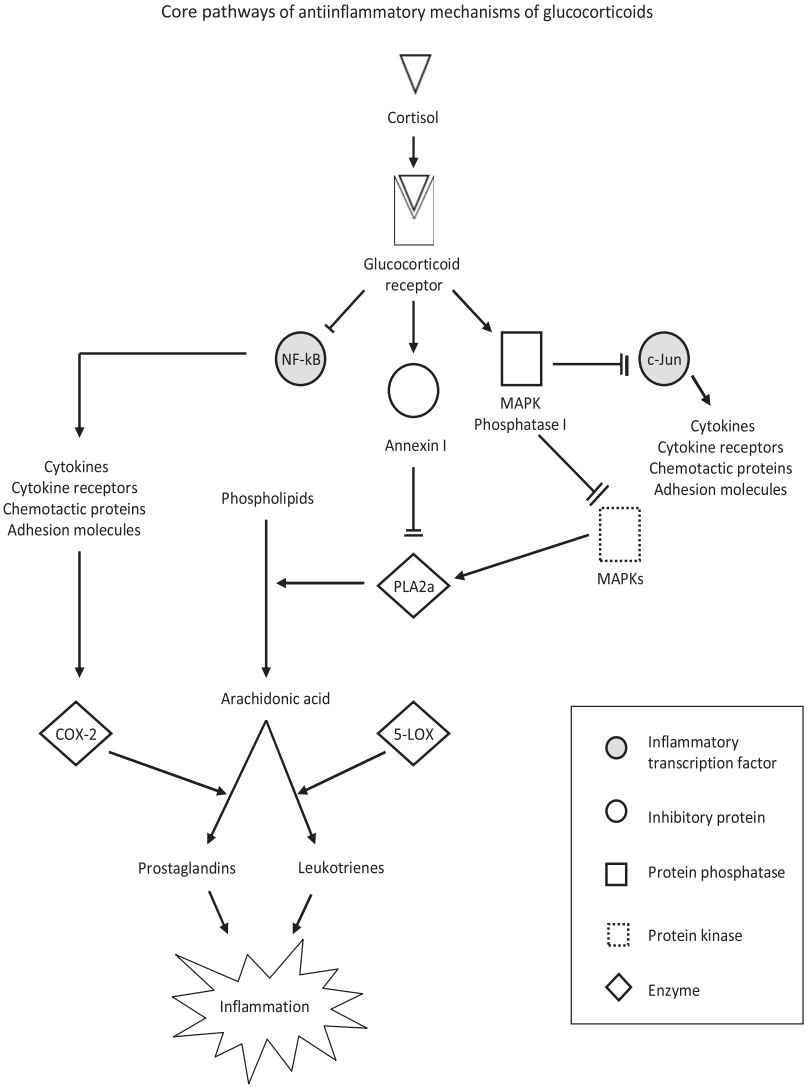

Figure 1. After binding to its receptor, glucocorticoids exert their effects through one of three pathways. (1) Via NF-κB, leading to suppression of COX-2; (2) via the induction of annexin-1; and (3) via MAPK phosphatase 1, another pathway which is anti-inflammatory. *See* text for a more detailed description of these mechanisms. *Arrow*: activation. *Double line*: inhibition. COX-2 = cyclooxygenase 2; 5-LOX = 5-lipoxygenase; MAPKs = mitogen-activated protein kinases; Nf-κB = nuclear factor κB; PLA2 = phospholipase A2.

systemic corticosteroids (SCS) (16) or inhaled corticosteroids (ICS) (17) prevents the late but not the early allergic response. However, prolonged treatment with ICS is effective in reducing even the early response to an allergen challenge in a time-dependent (18) (and probably dose-dependent [19]) fashion.

ICS do not protect against bronchoconstriction when given immediately before exercise (20). However, a single high dose of ICS improved airway responsiveness to methacholine 6 hours after administration (21). Regular treatment with ICS is effective in reducing bronchial responsiveness to direct and indirect stimuli (22) and reduces the prevalence and the severity of exercise-induced asthma (23). The effect of oral corticosteroids (OCS) on airway responsiveness in patients with asthma is negligible (24) or evident only with high doses (25). However, OCS can reverse the seasonal increase in airway reactivity in patients with grass pollen allergy, likely by reducing allergic inflammation of airways (26).

CS have negligible or no immediate effect on airway caliber in patients with asthma who have normal pulmonary function (27) or in patients with airway obstruction (28).

There is a two-way functional interaction between CS and β-2 agonists. CS enhance the expression of β-2 adrenergic receptors in a time- and concentration-dependent manner by increasing the rate of β-2 adrenergic receptor gene transcription (29). On the other hand, β-2 agonists promote the activation of the GCR by facilitating translocation into the nucleus (30), which may explain the benefits of combination therapy (31–33).

Time of Activity

The cellular effects of CS are generally immediate, but there is a time lag, usually hours, before they produce a clinical response, and the washout of effects are also prolonged (34). β-Adrenergic receptor density increases within 4 hours of SCS administration, but improved responsiveness to β2 agonists may not occur until 12 hours after administration (35). Prompt acute relief of croup or acute asthma by treatment with ICS may be related to airway mucosal vasoconstriction (36).

CLINICAL INDICATIONS

CS, administered systemically or by inhalation, have proven benefit on a variety of respiratory diseases. Asthma and preschool wheeze are discussed separately in this review because the roles of CS are different in the two conditions.

Asthma

Long-term treatment. ICS are the most effective antiinflammatory medications for the treatment of persistent asthma (37) (Table 1). Maintenance treatment with ICS controls asthma symptoms,

reduces the frequency of acute exacerbations and the number of hospital admissions, improves quality of life and lung function, and decreases bronchial hyperresponsiveness and indirect markers of airway inflammation (38–40). Symptom control and improvement in lung function occur rapidly (after 1 to 2 wk), although longer treatment and sometimes higher doses may be required to improve airway hyperresponsiveness (41–43).

ICS do not cure the disease, and when they are discontinued deterioration of clinical control, lung function, and airway responsiveness follows within weeks in a proportion of patients (44–46). However, there may be spontaneous regression of asthma during ICS therapy, and a trial of reduction intermittently is always warranted (47). In children with mild persistent asthma, use of rescue ICS with albuterol might be an effective and safe step-down strategy after asthma control is achieved (48). Advantages of this treatment strategy include a reduced risk of ICS-related growth suppression (47, 48). It is likely that in practice this is the way parents will use ICS, whatever pediatricians may say.

The use of a budesonide/formoterol 80/4.5 μg combination four times per day for maintenance plus additional inhalations of the same combination for symptom relief (SMART [Symbicort Maintenance and Reliever Therapy] regimen) substantially reduced the frequency of asthma exacerbations and had a favorable safety profile when compared with an identical dose of budesonide/formoterol for maintenance plus terbutaline for rescue or a 4-fold higher maintenance dose of budesonide (320 μg four times per day) plus terbutaline for rescue in school-age children with asthma uncontrolled on ICS (49). This approach is a promising strategy for pediatric asthma management but needs to be confirmed in future studies (50).

Concerns about side effects with the use of ICS in children have resulted in the promotion of add-on therapy with long-acting β-agonists (LABA) as first-line treatment for persistent asthma. A recent observational study of asthma prescribing reported that a quarter of children prescribed a LABA/ICS fixed-dose combination had not received a prior prescription for an ICS, thus bypassing step 2 in the BTS guidelines (51). This strategy is not evidence based and must be discouraged. Indeed, in the PACT study, some secondary end-points were better on ICS than on LABA/ICS combination therapy (52).

A recent pragmatic trial, the results of which fly in the face of every previous double-blind, randomized controlled trial (RCT), has suggested that montelukast is not inferior to ICS as first-line treatment for asthma (53). Given the weight of opposing evidence, this study does not seriously challenge the position of low-dose ICS as the best first-line preventive treatment for asthma in children.

There is a wide variation between the available ICS in terms of lipophilicity, lung delivery profiles, and pharmacodynamics (54). Because of relatively flat dose–response relationships in asthma, significant benefit in terms of symptom and lung function improvement is usually seen at low to moderate doses of different ICS (55). Increasing the dose further provides a much smaller degree of benefit (56). In children with asthma, small-particle ICS, such as ultrafine hydrofluoroalkane-134a–beclomethasone and ciclesonide, are as effective as fluticasone on a microgram for microgram basis and are at least as effective, at half the dose, as budesonide and chlorofluorocarbon-beclomethasone (57, 58). There is no evidence that they are better in terms of clinical response at any age.

Fortunately, OCS are rarely necessary in the long-term treatment of asthma. If they are needed, the smallest dose of prednisone necessary to control symptoms should be given as a single dose every other morning. ICS should be used concurrently. In patients who are dependent on long-term OCS therapy, several "steroid-sparing" agents are available. Most treatments are unlicensed, and the evidence base is poor, with the exception of omalizumab, for which the evidence base is secure (59). More experimental therapies include oral macrolides, cyclosporin, cytotoxic drugs such as methotrexate and azathioprine, gold salts, immunoglobulins, and subcutaneous β-2 agonist treatment. Better evidence is required for all these treatment options, underscoring the need for an international and coordinated approach (60).

TABLE 1. LONG-TERM TREATMENT OF ASTHMA

What's new
• SMART (Symbicort Maintenance and Reliever Therapy) regimen is a promising strategy for pediatric asthma management.
• Use of rescue ICS with a short-acting β-agonist might be an effective and safe step-down strategy after asthma control is achieved.
• The increasing use of LABA/ICS combination therapy as first line for persistent asthma despite the lack of any evidence that this is preferable to ICS monotherapy.
• Montelukast is "non-inferior" to ICS as first-line treatment for persistent asthma in a pragmatic trial.
Recommendations
• ICS are the first-line antiinflammatory drugs for the treatment of persistent asthma in school-age children.
• In the majority of cases, asthma may be controlled with low to medium doses of ICS.
• The available ICS provide similar efficacy at low-to-medium doses.
• When ICS are discontinued, deterioration of clinical control of asthma may follow.

Definition of abbreviations: ICS = inhaled corticosteroids; LABA = long-acting β-agonist.

Acute asthma. Over the last 20 years, several studies showed that SCS are beneficial for the treatment of children with acute asthma in emergency departments (EDs) (61–64) (Table 2). A metaanalysis of 12 ED RCTs documented the efficacy of SCS by better symptom scores, improved oxygenation and pulmonary function, reduced hospital admission, earlier discharge from hospital, and reduced asthma relapse (65). Data from these studies suggest that (*1*) the benefits are greatest in patients with more severe asthma and in those not receiving SCS before ED presentation, (*2*) the improvement is not immediate and may be delayed 2 to 12 hours, (*3*) OCS and parenteral therapy appear to have equivalent effects in most patients, (*4*) a precise dose–response relationship is not evident, and (*5*) there are no substantial differences of efficacy between different SCS when given in equipotent doses (65, 66).

Short courses of OCS have been reported to be effective in improving symptoms and lung function in children evaluated in an ambulatory care setting (67, 68) and in decreasing the risk of health resource use when initiated by parents at home (69). Two doses of oral dexamethasone, one given in the ED and the second given the next day, were as effective as prednisolone given initially in the ED and then once daily for 4 days (70, 71). A single oral dose of prednisone/prednisolone was effective in reducing morbidity or the need for hospitalization in children with a mild to moderate asthma attack being treated in hospital (62, 63) or in an ambulatory setting (72) but did not reduce outpatient visits when independently administered by parents at home (73).

SCS may be unnecessary for treating mild attacks of asthma that respond well to bronchodilators. However, their use is mandatory in patients with a history of rapidly progressing asthmatic episodes, and in patients who previously required hospitalization or were admitted to ICU for asthma, and in patients on regular treatment with CS (74). SCS should be introduced early in addition to bronchodilators, rather than waiting for the patient's condition to deteriorate. A dosage of 1 to 2 mg/kg of prednisone is usually given in one to two daily doses, but lower dosages may have comparable efficacy (75) and fewer adverse effects (76) in

TABLE 2. ACUTE ASTHMA

What's new
• High-dose ICS in acute asthma exacerbations are not recommended.
Recommendations
• SCS should be introduced early in the treatment of acute asthma if they are likely to be needed.
• In most attacks, OCS rather than parenteral should be used.
• There is no substantial superiority of one SCS over another at equipotent doses.
• High doses of SCS are not more effective than lower doses. Suggested daily dose is 1–2 mg/kg up to a maximum 40 mg prednisone/prednisolone, in tow or three daily doses.
• Duration of treatment with SCS is 3 to 10 d, according with the severity of the attack and the clinical response.
• For duration of treatment less than 10 d, SCS may be stopped abruptly.
• SCS or ICS should be prescribed at discharge to reduce relapse of asthma.

Definition of abbreviations: ICS = inhaled corticosteroids; OCS = oral corticosteroids; SCS = systemic corticosteroids.

TABLE 3. PRESCHOOL WHEEZE

Recommendations (all new in the last 10 yr)
• OCS should be administered in preschool children with acute wheezing only when they are severely ill in the hospital by specialists; they are not a community medication.
• Intermittent use of high-dose ICS for acute wheeze is not generally recommended. High-dose ICS may be tried in individual basis, particularly in children receiving multiple courses of OCS
• Regular treatment with ICS is not effective to prevent episodic viral wheeze.
• Regular treatment with ICS may be at least partially effective in the prevention of multiple-trigger wheeze.

Definition of abbreviations: ICS = inhaled corticosteroids; OCS = oral corticosteroids.

mild exacerbations. No study has compared the relative benefits of once-daily administration versus divided doses. The duration of treatment is mainly based on the patient's response, and a 3- to 10-day course is usually sufficient (77). For treatment duration less than 10 days, SCS may be stopped abruptly with no rebound (78), provided ICS are concomitantly prescribed (79).

Several studies have evaluated the effect of ICS for the treatment of acute asthma in adjunction to bronchodilators. A meta-analysis of 17 RCTs (11 in children) treated in the ED showed that multiple, high-dose ICS administered at frequent time intervals ($\leqslant$ 30 min) may reduce the risk of admission after 2 to 4 hours of treatment (odds ratio, 0–30) but may have only a mild effect on pulmonary function (80).

Some studies compared ICS with SCS in the treatment of acute asthma. In children with mild-to-moderate acute exacerbation, inhaled fluticasone (1 mg twice daily) was as effective as oral prednisolone (81). However, oral prednisone was clearly more effective than a single high-dose of inhaled fluticasone (2 mg) in children with severe acute asthma (82). The evidence is insufficient to recommend the use of high-dose ICS as an alternative or in addition to OCS in acute asthma exacerbations (83). Furthermore, the cost of high-dose ICS is considerably greater than OCS.

Hospital readmissions after being discharged for acute asthma are greatly reduced if a short course of OCS (84) or a more prolonged course of ICS (85) is prescribed at the time of discharge.

Preschool Wheeze

The nomenclature of phenotypes in preschool children is controversial (86) (Table 3). A European Task Force has recently described two different phenotypes at this age, episodic viral wheeze and multiple-trigger wheeze (87).

Early intervention studies with ICS in young children, either intermittent courses for 2 weeks during wheezing episodes (budesonide 400 μg/d; PAC study [88]) or regular treatment (fluticasone 200 μg/d; PEAK study [89] and IFWIN study [90]), have shown no effect in preventing the progression of any phenotype of preschool wheeze to asthma in childhood. Because no disease-modifying therapy is available, treatment should be solely for the relief of present symptoms. This may be achieved by treating single acute episodes or by the administration of prophylactic treatment.

Treatment of acute episodes. The approach to the treatment of acute wheezing among preschoolers has been traditionally based on the treatment for asthma in school-age children, and SCS have been the bedrock of therapy. Three RCTs have reported a beneficial, albeit inconsistent, effect. In preschool children seen in the ED, those receiving intramuscular methylprednisolone (4 mg/kg) were discharged earlier than those receiving placebo (91). Oral prednisolone 2 mg/kg once a day for 3 days given at presentation to the ED reduced disease severity and length of hospital stay in hospitalized children (92). Some benefit of prednisolone on duration of hospitalization has also been reported in a subgroup of children with wheeze triggered by specific viruses (93). This model has been recently challenged. A parent-initiated 5-day course of oral prednisolone therapy to be given at the first sign of an attack of viral wheeze to preschool children who had had a previous admission with wheeze was not useful (94). A more recent trial found that a 5-day course of oral prednisolone in preschool children admitted to hospital with wheeze was not superior to placebo (95). Metaanalysis is therefore required to answer the question of efficacy of SCS in viral wheeze and to evaluate if there is a CS-responsive subgroup. Short-burst OCS must not be given in all cases of attacks of viral wheeze. They should be considered only in young children admitted to a hospital with features strongly suggestive of atopic asthma (e.g., a combination of multitrigger wheeze, severe eczema, and a family history of atopic asthma) or with very severe bronchodilator-unresponsive wheeze who appear to need high-dependency or intensive care.

Given that four or more courses of oral prednisolone during childhood may have adverse effects, including increased fracture risk (96), several trials have been conducted to evaluate the effect of ICS in acute viral wheeze. In infants at high risk for asthma, the intermittent use of budesonide 400 μg/d for 2 weeks after the third day of wheezing (PAC study) provided no measurable clinical benefit (88). In a systematic review (97), three high-quality studies of intermittent high-dose ICS for the treatment of the episodic viral wheeze phenotype were identified. Only a modest improvement in symptoms was achieved. More recently, a large RCT of high-dose fluticasone (750 μg twice daily by metered dose inhaler started at the first sign of a cold and continued for up to 10 d) showed a reduction in the use of rescue OCS in the active-treated patients. However, such treatment was associated with adverse events (98). Due to uncertainty regarding the long-term health effects, the preventive use of high-dose, intermittent ICS cannot be routinely recommended in children with acute wheeze. They may be tried on an individual basis, particularly in children receiving multiple courses of OCS, to try to reduce the systemic effects (99).

Regular prophylactic treatment. A systematic review (97) identified only one high-quality study of regular ICS for the episodic viral wheeze phenotype in preschool children. The effect of 4 months of regular treatment with budesonide at 400 μg daily showed no effect on symptom score, OCS use, or hospital admission (100).

The treatment of the multiple-trigger wheeze phenotype with ICS appears to be more successful than that of children with

TABLE 4. BRONCHIOLITIS

Recommendations (no relevant updates over the last 10 yr)
• SCS should not be used routinely in the management of bronchiolitis but may be used in severely ill or mechanically ventilated patients.
• ICS are not effective in modifying the acute course of bronchiolitis.
• SCS and ICS administered in the acute phase of bronchiolitis do not prevent recurrent wheezing.

Definition of abbreviations: ICS = inhaled corticosteroids; SCS = systemic corticosteroids.

TABLE 5. CROUP

What's new
• There are no substantial differences in efficacy between oral and intramuscular SCS.
• Adding ICS to SCS does not offer advantages.
Recommendations
• Any child with moderate to severe croup should receive CS at home or in the hospital setting.
• A single dose of CS is effective.
• There are no substantial differences in efficacy between SCS and ICS.
• Recommended dosage is 0.15–0.30 mg/kg (oral or intramuscular) for dexamethasone, and 2 mg (nebulization) for budesonide.
• SCS may be preferable to ICS because they are easier to administer and cheaper.

Definition of abbreviations: ICS = inhaled corticosteroids; SCS = systemic corticosteroids.

episodic viral wheeze. Two recent systematic reviews (101, 102) concluded that continuous treatment with ICS decreases the number of days with symptoms (approximately 5% vs. placebo) and the number of acute exacerbations but does not prevent the need for hospitalization. In preschool children at high risk for asthma, some phenotypic predictors of response to ICS (e.g., patients with greater disease severity) have been identified (103). There are major problems with assessing trials that have recruited a mix of phenotypes (episodic viral wheeze and multiple-trigger wheeze).

Bronchiolitis

Bronchiolitis is an acute viral-induced condition that is common in infancy (Table 4). International differences in definition make comparison of trials difficult. The optimal treatment of bronchiolitis is subject to debate (104). Neutrophilic inflammation plays a major role in the pathogenesis of airway obstruction in bronchiolitis, so CS have not proved beneficial in most studies. A recent metaanalysis including 17 RCTs concluded that there is no positive effect of SCS or ICS on the course of acute bronchiolitis (105). One study showed a beneficial effect of intravenous dexamethasone (0.15 mg/kg every 6 h for 48 h) in mechanically ventilated children (106). The recent guidelines of the American Academy of Pediatrics conclude that SCS should not be used routinely in the management of bronchiolitis (107).

In a recent RCT among infants with bronchiolitis treated in the ED, combined therapy with epinephrine and high-dose oral dexamethasone (1 mg/kg at presentation and 0.6 mg/kg for an additional 5 d) appeared to reduce the rate of hospital admission and to shorten the time to discharge and the duration of some symptoms (108). The authors state that treating infants with bronchiolitis with such combination is the most cost-effective treatment option (109). Given the small effect size of the study—11 infants would have to be treated to prevent one hospital admission—and the potential effects of these very high doses of CS on brain and lung development (110), this regimen cannot be recommended.

CS administered orally (111, 112) or by inhalation (113) during the acute phase of bronchiolitis do not prevent recurrent postbronchiolitis wheeze.

Croup

Viral croup is the most frequent cause of acute upper airway obstruction in children 6 months to 6 years of age (114) (Table 5). There is clear evidence for the effectiveness of CS, which are routinely recommended for treatment of croup (115). Metaanalyses of RCTs have consistently demonstrated significant improvements in patients treated with CS, either systemically or nebulized (116–118). CS decrease the time spent in the ED or hospital, the use of epinephrine, the number of return visits and hospital admissions, the need for intubation, and the risk of reintubation (116–119).

Trials of CS in croup have involved a variety of drugs, dosages, and routes of administration. The oral or intramuscular routes have been shown to be equivalent or superior to inhalation (120–123). Adding nebulized budesonide to oral dexamethasone offered no advantage in hospitalized children (124).

Two trials comparing oral and intramuscular SCS (mainly dexamethasone) showed no difference regarding croup score, hospital admission, need for further treatment, or return for medical care (125–127). In studies comparing oral dexamethasone to oral prednisolone, no difference was noted in the reduction of croup score (128, 129), but dexamethasone was superior in reducing return for medical care (129).

There is conflicting evidence regarding the effect of OCS dosage. In a metaanalysis (116), more children admitted to hospital responded to treatment when higher doses of hydrocortisone equivalents were used. A few small trials compared different doses of oral dexamethasone and suggested that a single dose of 0.15 mg/kg was as efficacious as 0.3 or 0.6 mg/kg (130, 131). Nebulized budesonide has been usually administered as a single 2-mg dose. It is more expensive than dexamethasone but may be preferable in the child who is having multiple attacks of spasmodic croup to reduce systemic effects of steroids.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) remains the most common severe complication of preterm birth (132) (Table 6). Given the recognized role of inflammation in the pathophysiology of BPD, CS have been used widely in preterm infants with respiratory failure.

Regarding early ($\leqslant$ 7 d) postnatal SCS administration, 20 RCTs were identified for intravenous dexamethasone (133), and eight RCTs were identified for hydrocortisone (134). Although early dexamethasone treatment facilitates extubation and reduces the risk of death from chronic lung disease, patent ductus arteriosus, and severe retinopathy of prematurity, it causes short-term adverse effects, including gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, and an increased risk of cerebral palsy. The authors conclude that early dexamethasone or hydrocortisone treatment cannot be recommended to prevent BPD. Regarding late ($>$ 7 d) postnatal SCS administration, 19 RCTs were identified for dexamethasone (135). Late dexamethasone treatment reduced neonatal mortality but not later mortality, failure to extubate, and BPD. There were clear short-term complications, including hyperglycemia and hypertension. The authors conclude that it appears prudent to reserve the use of late dexamethasone to infants who cannot be weaned from mechanical ventilation and to minimize the dose and duration of any course of treatment. A recent policy statement of the American Academy of Pediatrics recommended that clinical judgment be used when attempting to balance the potential adverse effects of glucocorticoid

TABLE 6. BRONCHOPULMONARY DYSPLASIA

Recommendations (all new over the last 10 yr)
• Early dexamethasone treatment cannot be recommended to prevent BPD.
• Late dexamethasone treatment should be reserved to infants who cannot be weaned from mechanical ventilation.
• ICS cannot be recommended for the prevention or treatment of BPD.

Definition of abbreviations: BPD = bronchopulmonary dysplasia; ICS = inhaled corticosteroids.

treatment with those of BPD (136). A recent retrospective study showed that very-low-dose dexamethasone (0.05 mg/kg/d) administered to ventilator-dependent preterm babies resulted in faster extubation and more rapid improvement in lung function and was not associated with clinically significant side effects (137). A RCT is required to further assess the efficacy and long-term outcomes of this regime (138).

Administration of ICS has been used to prevent BPD in preterm infants with the intention of reducing the risk of side effects of SCS. Metaanalysis of the results of 11 RCTs showed no reduction in the incidence of BPD development (139). An international multicenter clinical study (NEuroSIS [Neonatal European Study of Inhaled Steroids]) is ongoing with the main objective of determining whether the early inhalation of budesonide in preterm infants reduces the risk of mortality and BPD (140).

Cystic Fibrosis

Neutrophil-dominated inflammation combined with an exaggerated host response is a major contributor to lung injury in cystic fibrosis (CF) (141) (Table 7). Inflammation is detectable in infants with CF who are as young as 4 weeks (142) and is further exaggerated during pulmonary exacerbations (143).

There is evidence that neutrophils in the CF airway are not as responsive to CS as those in the circulation (144). It has been suggested that polymorphisms of the GCR gene in CF (145) or GCR down-regulation due to the chronic exposure to CS (146) could be associated with an alteration of CS efficacy.

Given the key role of inflammation in the pathophysiology of CF, antiinflammatory therapy was considered a rational approach to slow down deterioration in lung function (147). The use of SCS in CF has been evaluated in a series of studies (148). A Cochrane review identified three long-term RCTs with OCS (149). Two of these trials had a 4-year duration, and one had duration of 12 weeks. A prednisone equivalent dose 1 to 2 mg/kg alternate days appeared to slow the progression of lung disease in patients chronically infected with *Pseudomonas aeruginosa*, but this benefit needs to be weighed against the development of cataracts and the effect on linear growth. In a follow-up study of children who had participated in a 4-year trial, boys, but not girls, had persistent growth impairment after treatment was discontinued (150). In light of these studies, long-term use of OCS in patients with CF is not routinely recommended.

Treatment of acute pulmonary exacerbations with short pulses of CS was hypothesized to have a better risk–benefit ratio than long-term administration. In a pilot study, adding a 5-day course of oral prednisone to standard therapy for acute pulmonary exacerbations did not show a significant effect on lung function or sputum markers of inflammation (151). In a 10-day RCT in infants with CF hospitalized for lower respiratory illnesses, intravenous hydrocortisone (10 mg/kg/d) did not lead to changes in pulmonary function but induced a greater improvement in lung function 1 to 2 months after discharge (152). In a pilot report on young children with CF hospitalized for respiratory distress, a 3-day course of methylprednisolone (1 g per 1.73 m^2) dramatically improved patients' conditions without adverse effects (153).

TABLE 7. CYSTIC FIBROSIS

What's new
• A short course of high-dose intravenous methylprednisolone may be an efficient and safe treatment for uncontrolled pulmonary exacerbations.
Recommendations
• Long-term use of OCS is not routinely recommended
• ICS are not recommended in patients with cystic fibrosis who do not have asthma

Definition of abbreviations: ICS = inhaled corticosteroids; OCS = oral corticosteroids.

In an attempt to gain the benefit of SCS without the side effects, ICS have increasingly been studied in CF. A recent update to the original Cochrane review identified 13 RCTs (154). Evidence from these trials was insufficient to establish whether ICS are beneficial in patients with CF. There was some evidence that they may cause harm in terms of growth. Withdrawal of ICS in a selected group of those already taking them was safe (155). A recent analysis of the CF registry data from North America found that ICS therapy in children with CF was associated with a significant reduction in the rate of decline of lung function but at the cost of decrease in linear growth and increase in antidiabetic drug use (156). An expert committee assembled by the Cystic Fibrosis Foundation recently advised against the use of ICS as antiinflammatory agents in adults and children older than 6 years who do not have asthma or allergic bronchopulmonary aspergillosis (ABPA) (157).

Despite the absence of evidence, physicians continue to prescribe ICS to many patients with CF (158). A recent registry analysis in Belgian patients with CF revealed that ICS use was associated with a decrease in lung function decline in children 6 to 12 years of age but not in adults (159). It was believed biologically plausible that ICS would decrease airway inflammation in young, relatively healthy subjects and that the effect of the drug was not seen in older subjects with lower lung function and likely a larger burden of bacterial infection.

Allergic Bronchopulmonary Aspergillosis

ABPA most often occurs in patients with CF, at least in childhood (160, 161) (Table 8). ABPA is defined by a constellation of clinical, laboratory, and radiographic criteria that include active asthma, serum eosinophilia, an elevated IgE level, fleeting pulmonary opacities, bronchiectasis, and evidence for sensitization to *Aspergillus fumigatus* (162).

Therapy for ABPA has two main targets. The first is the attenuation of the inflammation and the immunological activity, using CS. The second is the attenuation of the antigen burden arising from fungal colonization, for which antifungal agents have been prescribed (163). None of the medications tried in the treatment of ABPA, including SCS, ICS, and antifungal agents, has been subject to a large RCT (164).

SCS are the mainstay of therapy for ABPA. Treatment leads to decreased wheezing, serum total IgE levels, and eosinophilia and to reduction or resolution of parenchymal opacities. A number of dosing regimens have been recommended. Some experts think a more aggressive regimen with high doses of OCS may result in the best long-term outcomes (165), but a more conservative approach may be used (166). With either regimen, remission is defined by improvement in clinical symptoms, decrease in total serum IgE level, resolution of radiographic opacities, and improvement in lung function. Cases of invasive pulmonary aspergillosis and central nervous system disease have been reported in patients receiving SCS for the treatment of ABPA (167, 168).

TABLE 8. ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

What's new
• Pulses of high-dose intravenous methylprednisolone combined with oral antifungals may be effective in patients with cystic fibrosis and ABPA and are generally better tolerated than OCS.
Recommendations
• SCS are the mainstay of therapy for ABPA.
• Proper controlled trials of safety and efficacy are awaited with new agents in patients with ABPA.

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; OCS = oral corticosteroids; SCS = systemic corticosteroids.

The toxicity of long-term OCS has led to an ongoing search for safe and effective regimens. Disease control without important side effects was obtained in three of the four patients by high-dose intravenous methylprednisolone (15–20 mg/kg/d for 3 days, with an initial dosing interval of 3 or 4 wk) (169). Monthly pulses of intravenous methylprednisolone (10–15 mg/kg/d for 3 d) in association with itraconazole also showed clinical and laboratory improvement and fewer side effects (170). This therapeutic regimen is considered the first-line treatment for ABPA in many centers, although the evidence base is not secure. For patients who cannot tolerate SCS, there are case reports that omalizumab may represent a beneficial treatment (171, 172), but controlled studies in children are lacking. Itraconazole inhibits cytochrome p450, and, in patients prescribed ICS, the risk of iatrogenic Cushing's syndrome must be remembered (173, 174).

ICS have been also evaluated in the treatment of ABPA. A RCT in patients with non-CF ABPA failed to demonstrate any benefit of beclomethasone 400 μg daily in asthma score and lung function (175). High-dose ICS were successfully used in two patients as a replacement therapy for OCS in the maintenance treatment of ABPA (176). Recently, the combination of nebulized budesonide (1 mg twice a day) and nebulized amphotericin B (5 mg twice a day) was reported as a safe and effective treatment of ABPA in three patients with CF (177).

Tuberculosis

CS therapy may be indicated for the treatment of specific pulmonary complications of TB (178). A recent review found six RCTs comparing any CS with no treatment or placebo in patients with tuberculous pleurisy. CS use was associated with less residual pleural fluid and reduced pleural thickening at 4 weeks. Data are insufficient to give evidence-based recommendations regarding the use of adjunctive CS in TB pleurisy (179).

In patients with advanced pulmonary TB, SCS therapy resulted in significant clinical and radiological benefits but had no effect on the rate of bacteriologic conversion of sputum cultures (180).

Tubercular lymph nodes adjacent to bronchi can infiltrate the airways, causing ulceration and granulation tissue formation and eventually leading to atelectasis or bronchial perforation. If started early and continued for 6 to 12 weeks, prednisone (1–2 mg/kg/d) can prevent fibrous tissue formation and may be a useful adjuvant to antituberculous drugs (181). Rifampicin induces the hepatic enzymes that catabolise CS, effectively reducing bioavailability by 50%.

Primary Ciliary Dyskinesia and Other Non-CF Causes of Bronchiectasis

These diseases are characterized by neutrophilic airway inflammation and chronic infection with a similar range of microorganisms, as is found in CF. There are no RCTs of steroids by any route in these conditions, and indications are often extrapolated from CF (182). However, the pathophysiology is different (e.g., probable airway surface liquid reduction in CF versus reduced mucociliary clearance in primary ciliary dyskinesia), and this approach is fraught with danger.

Interstitial Lung Disease

SCS are the traditional treatment for a wide variety of interstitial lung diseases, including pulmonary hemorrhagic syndromes and surfactant protein deficiencies (183), but the diversity of the pathology in children means that there are no RCTs of treatment. Many pediatricians prefer to use pulsed methylprednisolone on a monthly basis rather than oral prednisolone (184). Although in adults steroids are used for some of the more inflammatory interstitial lung diseases, such as sarcoid and nonspecific interstitial pneumonitis, but are not recommended for the fibrotic disorders such as usual interstitial pneumonia (185), in children there is no evidence to support these extrapolations from adult disease. A more detailed account of the evidence (or lack of it) for the various treatment options in childhood interstitial lung disease has recently been published (186).

Prevention of Postextubation Airway Obstruction

Intubation of the airway can lead to laryngotracheal injury, resulting in extubation failure from upper airway obstruction (187). A metaanalysis of five RCTs (three in neonates and three in children) showed that a single administration of intravenously dexamethasone before elective extubation has not proven effective in reducing the prevalence of postextubation stridor or the rate of reintubation (188). However, given the consistent trend toward benefit, this intervention merits further study.

Subglottic Hemangioma

Subglottic hemangioma is a rare cause of pediatric upper airway obstruction that can be potentially life threatening (189). SCS could have an adjuvant role to other treatments, such as laser (190) or oral propanolol, which is considered first-line therapy (191). Steroid treatment for croup may mask these lesions (192).

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a devastating disorder of overwhelming pulmonary inflammation and hypoxemia, resulting in high morbidity and mortality (193). A definitive role of SCS in the treatment of ARDS in adults is not established, and preventive SCS possibly increase the incidence of ARDS in critically ill adults (194, 195). There have been no studies of SCS for the treatment of ARDS in children (196).

Acute Lung Aspiration

The use of SCS in acute lung aspiration is controversial, with some studies proving efficacy and others the opposite. Given the uncertainty, their use is not generally recommended (197).

CONCLUSIONS

CS have an important role in a variety of respiratory diseases. CS have revolutionized the management of certain conditions, such as asthma or croup, and their value cannot be questioned. In some conditions, such as bronchiolitis or CF, their use is controversial and is not recommended routinely. In other rarer conditions, CS are sometimes used empirically despite a lack of clear evidence of their benefit. There is obvious concern about the adverse effects, especially growth, induced by CS in children. These

effects have been reduced but not eliminated with the use of ICS. Physicians must weigh the benefits against the potential detrimental effects. It is recommended that standard protocols for the use of CS available in the literature should be followed, and physicians should be alert to the potential hazards of prolonged use.

Author disclosures are available with the text of this article at www.atsjournals.org.

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