Online publication ahead of print, AJMHS Vol 57, 2021

The Role of Oral Corticosteroids in the Management of Children with Acute Respiratory Diseases

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Abstract

Respiratory diseases are the most frequent reason for children's visits to the paediatrician. They account for about 25% of paediatric consultations, 10% of which are for asthma, the others are for bronchiolitis, bronchitis and respiratory infections. Asthma is the most prevalent chronic disease of childhood and accounts for a substantial proportion of hospitalizations among children, whereas viral bronchiolitis is the leading cause of hospitalization in the first year of life. In preschool children, wheezing and croup are common respiratory conditions. Corticosteroids are often prescribed as they prevent or suppress inflammation in response to allergic or viral triggers. Oral corticosteroids are often used to treat some acute respiratory diseases. We discuss here about the management of bronchiolitis, croup, wheezing, and asthma.

Keywords: Bronchiolitis, Croup, Preschool Wheezing, Asthma, Corticosteroids

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INTRODUCTION

Acute and chronic respiratory diseases represent a global public health problem because of their increasing prevalence and severity worldwide (1). This can be attributed to several factors: 1. the significant increase in the prevalence of early allergen sensitization in childhood; 2. the frequent recurrence of viral infections; and 3. the increased survival of extremely preterm children born with bronchopulmonary dysplasia. All these factors contribute to the increased risk of acute manifestations becoming chronic. (1) In this article, we discuss issues related to the treatment of the acute respiratory diseases and to asthma, focusing on corticosteroids. We do not address forms of respiratory diseases, such as pneumonia, that have a different pathogenic basis and therefore require a very specific approach.

PHARMACOLOGICAL ASPECTS OF CORTICOSTEROIDS

Since their identification in 1935, corticosteroids application in pharmacotherapy has found a variety of uses. It is about 3 groups of steroids synthesized in the adrenal gland, respectively: 1. Mineralocorticoids in the glomerular zone, 2. Glucocorticoids in the fascicular zone, 3. Androgens in the reticular zone. (2)

Regulation, synthesis and release of the steroids are closely related with the HPA (Hypothalamus-Pituitary-Adrenal) axis. Among adrenocorticosteroids, glucocorticoids have a special position due to their involvement in a number of pathologies and their multiple effects, either therapeutic or side effects. (3,4,5)

The secretion of glucocorticoids is based on a circadian intensity, having the higher release during the morning hours and the minimal release on night hours. (6)

The pharmacological effects of glucocorticoids can be summarized in three categories:

1. Physiological effects, including the metabolic and facilitating effects.
2. Pharmacological effects, which consist of anti-inflammatory effects.
3. Immunosuppressive and anti-anaphylactic effects, anti-shock effects, hematological effects and side effects, which consist of effects on the level of muscle, bone, skin, eyes, metabolic effects, effects on central nervous system, gastrointestinal tract, cardiovascular and renal system. (7,8)

Important side effects for which glucocorticoids are blamed of are the growth inhibition in children and osteoporosis caused by the effect on calcium metabolism or by acting directly on the osteoblasts (9,10).

Glucocorticoids are classified into natural drugs (hydrocortisone, cortisone) and synthetic ones (prednisone, prednisolone, dexamethasone, betamethasone, etc.) (11).

Another classification is based upon their time-course activity: short acting (cortisone, hydrocortisone), intermediate acting (prednisone, prednisolone) and long acting (betamethasone, dexamethasone) glucocorticoids. (12, 13)

There are several pharmacokinetic aspects that a health professional should consider when prescribing these drugs. Glucocorticoids are mainly of lipophilic nature and are well absorbed during both oral and parenteral administration, but the route of administration that reaches the highest compliance in patients is the oral administration. These drugs are strongly bound to plasma proteins and represent a half-life of about 2-4 hours. The biotransformation process is of particular importance because through this process occurs the activation of several representatives (cortisone in hydrocortisone and prednisone in prednisolone). Glucocorticoids are mostly excreted through renal excretion. (14,15,16)

A serious concern with the administration of glucocorticoids is the suppression of the HPA axis, which is the base of a considerable number of side effects. The suppressive effect depends on the given drug, the dose, the administration time and the persistence of the treatment. (17)

Several studies are carried out in order to document the beneficial and adverse effects of different representatives of glucocorticoids. Studies demonstrated that application of chronotherapy in the dosing regimen of prednisolone resulted in better clinical outcomes with fewer side effects. (18)

Other studies indicated that the variations of concentration profiles depending on the time for both cortisol and ACTH were more closely to normal profiles when therapeutic doses of prednisolone were applied. Meanwhile, administering the betamethasone equivalent has made a more significant inhibition of the normal performance of these two hormones. It is considered that the suppression of HPA axis is developed by the use of betamethasone in physiological concentrations and of prednisolone in high concentrations for at least 2 weeks. (19)

The effect of drug, dose and continuation of therapy on bone metabolism has been investigated and was shown that the inhibition of intestinal calcium absorption is present during the use of betamethasone in both short-term therapy and low doses, while the inhibition is present with the use of prednisolone only at high doses. (20,21).

Recommendations regarding the use of glucocorticoids, which aim to minimize the suppression of the HPA axis, consist of:

• Using Systemic corticosteroids only in clear indications.

• Prefer the analogs with average duration of action and those protecting the steroids (steroid sparing drugs).

• Use the minimal effective dose for as short as possible by administering the drug as a single dose in the morning or on alternate days.

• Make slow discontinuation after the chronic therapy. (22, 23, 24, 25,26,27).

FREQUENT RESPIRATORY DISEASES IN CHILDHOOD

BRONCHIOLITIS

Epidemiology, clinical presentation, and treatment of bronchiolitis

Bronchiolitis is the most common viral infection of lower respiratory tract in children in their first year of life. The main etiologic virus is the Respiratory Syncytial Virus (RSV), which mainly affects children in their first 6 months of life reaching the peak in the first 30 to 60 days of life and in premature infants. RSV constitutes 60-80% of the etiologic factors (28,29) and has a seasonality nature from November to April (30). Also other viruses as human rhinoviruses, parainfluenza, metapneumovirus, etc, are frequently involved in bronchiolitis. Its clinic is preceded by a respiratory syndrome with sub febrile temperature, rhinorrhoeaand further reveals the typical clinical repertoire with cough, tachypnoea or apnoea (in premature infants), respiratory distress, expiratory wheezing and inspiratory crackles, reduction of oxygen saturation (SatO2) and dehydration due to feeding difficulties (31). Disease severity must be assessed to identify children who require hospital admission (Table 1)

Table 1. Criteria for hospitalisation (1)

	Ambulatory treatment or out of the hospital	Under observation	Hospitalization
Respiratory distress	With or without light retraction of thoracic walls	Nasal flaring, thoracic retraction	Moderate to severe respiratory insufficiency
O2 saturation	SaO2 > 95% , no need for extra O2	SaO2 90-95%	Persistent saturation <92%, O2 therapy is necessary
Feeding	Normal or slightly decreased	50-70% of normal feeding	<50%, does not feed, dehydration
Gestational age	Gestational age > 37 weeks, after birth age >12 weeks		Gestational age < 37 weeks, after birth age 6-12 weeks
Reaction and consciousness	Good reaction and the child is wake up (alert)		Weak reaction or no reaction
Socio-economic factors	Careful parents and collaborative, near to the hospital		No collaborative parents, distance from the hospital
Presence of the risk factors	Without risk factors	Pulmonary dysplasia, FC, cardiopathy, genetic defect, neuromuscular disease, Immunodeficiency.	Pulmonary dysplasia, FC, cardiopathy, genetic defect, neuromuscular disease, Immunodeficiency.

The management of bronchiolitis largely depends on the severity of the condition. Supplemental oxygen should be administered if O2 saturation levels are persistently below 90-92% at ambient air, Oxygen may be administered by means of nasal prongs, face masks or HFNC. In children who cannot maintain oral hydration is recommended rehydration with intravenous

fluids or with nasogastric tubes. Nebulizing hypertonic saline may help to decrease airway edema and improve mucociliary clearance (31). There is no convincing evidence in most of the guidelines for nebulized adrenaline, salbutamol, ipratropium bromide, antibiotics, antivirals, or inhaled and systemic corticosteroids (32). Oral salbutamol is not recommended. Systemic corticosteroids are indicated only in severe cases requiring hospitalization (33,34,35). In a randomised trial, corticosteroids in combination with salbutamol reduce 31% prolongation of symptoms especially in atopic children (36).

LARYNGOTRACHEITIS

Etiology, clinical history, and treatment of laryngotracheitis in children

Laryngotracheitis is one of the most frequent causes of acute respiratory distress in young children. The disease mainly affects children aged between 6 months and 3 years. The aetiology may be of viral origin (Parainfluenza 1, 2, 3 & 4, respiratory syncytial virus, Influenza A, B, Human metapneumoniae virus, Adenovirus) or bacterial one (H. influenza) (37). It is characterized by inspiratory stridor, severe barking cough, shortness of breath, hoarseness. The most affected age results to be 6m-3y (the highest incidence - 2nd year). According to Westley, (the clinical scoring system of croup), the gravity of croup clinical forms is scored based on the evaluation of stridor, retraction of the chest wall, the presence of cyanosis, the level of consciousness, and the air entry with points. Mild croup: WCS $\leq$ 2, Moderate croup: WCS: 3-5, Severe croup: WCS 6-11, Respiratory Insufficiency: WCS> 11(37,38).

Management: The child should be examined in the quietest conditions preferably in the parent's arms. In the mild form there is no need for special therapy except of informing the parents, the follow-up is performed as outpatient. Conventionally, croup is treated with corticosteroids and epinephrine. Dexamethasone and prednisolone are the most effective for mild-to-moderate croup, recommended dosages for oral prednisolone 1mg/kg and dexamethasone 0.6mg/kg (if oral administration is impossible, apply im), the child is monitored and followed for 2-4 hours: In case of deterioration, the patient is hospitalized, otherwise is sent home with the respective recommendations. The severe cases should always be hospitalized, and if child is in respiratory distress is administered oxygen therapy, nebulized epinephrine is applied 0.5 ml/kg (or adrenaline 1: 1000, 4 ml insoluble sol. under O_2 therapy) (39). It is important to maintain the child's hydration. He/she should be observed in hospital conditions and in cases of improvement, for a further period of 3-4 hours for any possibility of recurrences. (39)

PRESCHOOL WHEEZING

Classification, diagnosis and treatmentof Preschool Wheezing

Wheezing is one of the most common symptoms of child presentation for paediatric consultation. 1/3 of preschool children are presented with

wheezing before 5 years of age (1 in 3 children have at least one episode with wheezing before the age of 5 years old). The wheezing clinical phenotypes are very heterogeneous, while there is few evidence of its physiopathology and treatment. The most important risk factor for persistent symptoms at school age is the atopy: the more allergens and the greater the level of sensitization, the greater the possibility that wheezing persists even in school age (40)

Classification of the preschool wheezing

In 2008, ERS task Force proposed classification **according to the etiologic stimuli**:

1. **Episodic wheezing vs Multiple-trigger wheeze**: Episodic wheezing (viral) which lasts for a short period of time, is accompanied by a viral infection of upper respiratory tract, and there is no evidence of wheezing between the episodes. Multiple-trigger wheeze (wheezing from multiple stimuli), children make severe exacerbations, have also symptoms between episodes. Important stimuli are considered the tobacco smoke, exposure to allergens, physical strain, such as weeping, laughter, etc. (41). Several other classifications of wheezing have been proposed but still there is no complete consensus on the classification and used terminology (42,43,44):

2. Atopic wheezing vs.non atopic wheezing: Atopic wheezing (or allergic asthma): if the patient does ≥ 3 episodes with dyspnoea and wheezing AND sensibility confirmation to inhaled or nutritional allergens. Non atopic wheezing (viral) is considered when thepatient does ≥ 3 episodeswith dyspnoea and wheezing, which happens during the viral infections, AND there is no evidence for allergy from pneumoallergens or nutritional allergens. (41)

3.Wheezing **by frequency and gravity**: Mild form of Wheezing is not common, in cases when no affects on the daily life, and have rare episodes

Table 2. Aetiologies of Atypical wheeze

Warning sign	Possible underlying causes
Persistent symptoms from birth	Tracheobronchomalacia and PCD
Productive wet cough as a main symptom	PCD, CF, immune deficiency and TB
Never completely symptom free	Tracheobronchomalacia, vascular ring, foreign body aspiration and neonatal chronic lung disease
Failure to thrive	CF and immune deficiency
Recurrent pneumonia	CF and immune deficiency

(<1 episode /month). Severe form of Wheezing, is common, in cases when there is considerable impact on daily life (presentation in the urgency or hospitalization), as well the episodes are frequent (≥2/ months). (41)

Diagnostic approach to wheezing… Wheezing is a non-specific symptom, which occurs in several diseases. The initial assessment aims to exclude serious pathologies which are presented as "Atypical Wheeze" (40). After the exclusion of aetiologies as in below table, the majority of pre-school children with wheezing have "Typical Wheeze". In children where "typical wheeze" is confirmed, the only useful diagnostic test is skin prick test and/or specific Ig E for atopic wheezing confirmation (allergic pre-school asthma). Allergic asthma is the most common chronic childhood disease, which begins in early childhood (1/2 of asthma patients refer for symptoms since in childhood). The most important risk factor considered is the atopy (45).

Treatment of wheezing & pre-school asthma

It is recommended to use short-acting beta2 agonists (as needed) for all patients with wheezing exacerbation. Prophylactic therapy with ICS is recommended in children who have 1.recurrent episodes of wheezing, 2.frequent and/or severe episodes, 3.persistence of the symptoms even between episodes (40,45). OCS (oral corticosteroids) are more effective in children with asthma compared to pre-school children with acute wheezing episodes. In pre-school children with wheezing, it is recommended to use OCS in cases of hospitalization need, O_2need and in atopic wheezing (1): prednisolone 1-2 mg/kg/day max. Dose of 20mg/day in children ≤2 years old, and 30 mg/day in children 2-5-year-old (Evidence A). It is recommended the treatment duration of 3-5 days, it may be discontinued immediately. (Evidence D) (45).

ASTHMA CRISIS

Treatment of Asthma crisis

Asthma is the chronic disease with the highest prevalence in children> 5 years old, affects 5-20% of children of school age. Asthma is characterized by chronic inflammation of respiratory airways, bronchialhyperactivity, and variable expiratory obstruction. Clinically is presented with wheezing, cough, dyspnoea, chest tightness. Factors that can provoke asthma crisis are the effort, allergens, atmospheric changes, viral infections, etc. (45)

Pharmacological treatment of crisis: It is recommended O_2 therapyif SatO2 ≤ 92% in air. Short-acting beta2 agonists (SABAs) 2-4- 10 puffs Salbutamol 100 mcg (through pMDI + aero chamber). If needed repeat every 20-30 minutes during the first hour of the treatment and then every 1-4 hours as needed. Ipratropium bromide (anticholinergic) is given together with salbutamol, to treat children with a moderate-to-severe asthma attack who respond poorly to SABAs.250mcg/dose, its use improves FEV_1 and clinical scoring. In the asthma crisis, which does not respond to SABA therapy, it is recommended

to use Corticosteroids. The use of CS is associated with a rapid improvement in pulmonary function, shortens the time of hospitalization, minimizes the number of hospitalization, reduces the chances of relapse after emergence, and reduces the need for SABA. Current guidelines such as Gina 2020, British guidelines 2019, recommend oral use of CS;ivCS are recommended only when the condition is severe and the child cannot drink from the mouth (33,34). CS in children <12 years old: **Prednisolone:** 1-2 mg/kg/day, divided into 2 doses (max: 60 mg/day), until PEF is 70% of the estimated one, with a treatment duration of 3- 10 days. The duration of treatment is determined based on the removal of symptoms or PEF 80%, usually requires 3-10 days of treatment (on average 5 days); It may be neededfor a longer-term treatment. In cases where longer-term treatment is required, the use of prednisolone 0.25-2 mg/kg/day is recommended, a single dose in the morning or on an alternative day (as far as asthma control is concerned); Dose max: 60 mg/day. Use of IV methylprednisolone (1-2 mg/kg/6-8 h, up to max dosage 40 mg) is reserved for severe crises and children who cannot receive oral medication (45,46,47). Dosage of CS in children ≥12 years old: **Prednisolone:** 40-80 mg/day, 1-2 times/day until PEF 70% of the estimated, with a treatment duration of 3-10 days; In cases where longer-term treatment is required, prednisolone 7.5-60 mg/day, single dose in the morning or on alternate day as needed for asthma control. (45)

COMPLIANCE OF DRUGS IN CHILDREN

Drug compliance/adherence is a major concern nowadays. It can directly influence the therapy outcomes. Trying to address this problem, doctors are advised to apply measures that help in minimizing the non-adherence such as: counselling, simplified regimens, use appropriate dosage forms ecc. (48)

The advantage of using oral corticosteroids and solution form

- They are well absorbed
- They act as fast as the parenteral forms
- They achieve good results since the first doses
- They have fewer side effects (36).
- They are applied easily without causing pain to the child
- The effect is realised in short term period, which is not associated with the “rebound” phenomenon
- It affects slightly the hypothalamus – pituitary axis. Minimal effect in the child growth (in bone metabolism, bone mineralization and adrenal gland function)
- Oral solution of prednisone has good absorption (peak concentrations 1-2 hours after administration: 20% higher and 15 minutes earlier than tablets), avoids swallowing difficulties in children, has a better compliance/adherence (37).

CONCLUSIONS

Glucocorticoids represent an important class of drugs being used successfully in the treatment of different respiratory syndromes in childhood. They can be effective in respiratory diseases as acute laryngotracheobronchitis, bronchiolitis, asthma and respiratory insufficiency. The physician should closely monitor their use aiming to achieve the best therapeutic effects and to avoid eventual side effects.

Acknowledgments:

None declared.

Conflict of interest:

None declared.

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