Controversies in the pharmacological management of acute asthma in children

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Abstract

Objective: to present a review of controversial issues related to the pharmacological management of the treatment of acute asthma in children.

Sources: articles published in national and international scientific journals. Data were selected from Lilacs and Medline databases.

Summary of the findings: the article was organized into topics, presenting aspects on which there is consensus regarding the pharmacological treatment of asthma in children. Issues related to the use of metered dose inhaler versus nebulizers, the role of β2-adrenergic drugs administered intravenously as well as the role of methylxanthine and magnesium sulfate are approached critically.

Conclusions: inhaled β2-agonist drugs combined with corticosteroids remain the treatment of choice for acute episodes of asthma in children. Either nebulizers or metered dose inhalers connected to spacers are efficient for the relief of acute symptoms. Patients who are refractory to conventional treatment and develop severe acute asthma should receive β2-agonist drugs intravenously, provided they are properly monitored. Methylxanthine and magnesium sulfate should be considered a second choice for selected patients.


Introduction

β2-agonist bronchodilators and corticosteroids are currently widely used in the treatment of acute episodes of asthma that require hospital assistance.1-5 The administration of inhaled β2-agonist drugs is the treatment of choice for these situations. The effectiveness of this type of treatment depends on the deposition of particles (generated as aerosol) in the lungs. Several physical mechanisms are involved in this process, but central airway deposition preferably occurs by means of a “gravitational sedimentation” mechanism. For this process to occur, the mean aerodynamic diameter of particles must be less than 5 µm. All aerosol-generating devices used in the treatment of acute asthma have to work within this limit in order to be considered adequate.1,6,7

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The mechanism of action of β2-agonist drugs is related to the activation of specific receptors, which leads to an increase in the intracellular concentrations of cyclic AMP and consequently to the activation of potassium channels (maxi-K channels) by means of phosphorylation. The opening of these channels provokes cell hyperpolarization and inhibition of calcium inflow, resulting in bronchodilation.8

Therefore, from a practical point of view, in the treatment of acute asthma, β2-agonist drugs should preferably be administered through the airways. Drugs that form this pharmacological group, such as terbutaline, salbutamol, and fenoterol, present similar bronchodilator and clinical effects.9 The recommended doses usually vary according to the protocols established in each service. Once treatment through the airways (nebulizations - the administration system most frequently used in inpatients) is prescribed, different intervals of administration and dose calculations may be found: intermittent administration (from frequent to continuous), fixed doses, or doses calculated according to weight.

Corticosteroids constitute another pharmacological group that should always be considered for the management of children with asthma who require hospitalization after an acute episode.1-4 Corticosteroids act on the cell by means of binding to a specific cytoplasmic receptor. They seem to be one single class, with no evidence of subtypes, cellular differentiation or affinity. Children with acute asthma present several determinants of inflammation in the airway, and the anti-inflammatory properties of corticosteroids make them reference for the treatment of these patients.8,10

Table 1 - Antiinflammatory properties of corticosteroids in asthmatic patients

| Inhibition of cytokines (interleukin-1, interleukin-3-8, a tumor necrosis factor) |
| Inhibition of certain cytokines receptors (interleukin-2) |
| Direct action on other transcription factors that balance the cellular effect of cytokines |
| Increase of the synthesis of lipocortin-1, which presents an inhibitory effect on phospholipase A2, and, as a consequence, inhibits the production of lipidic mediators (leukotriene, prostaglandin and platelet activation factor) |
| Change of the metabolism of mediators such as bradykinin, by inducing the activity of degradation enzymes |
| Direct inhibiting effect on the expression of endothelial cell adhesion molecules, which attract other inflammatory mediators |
| Reduction of microvascular permeability |
| Reduction of mucus secretion in the airways |
in acute asthma episodes: nebulizers or metered dose inhalers connected to spacers? Should metered dose inhalers be considered for the treatment of inpatients? In cases of severe acute asthma where treatment through the airways did not prove effective, when and why should the intravenous administration of drugs be considered? Are there any known benefits associated with the use of $\beta_2$-adrenergic drugs through this route of administration? What other drugs could be used in the management of severe acute asthma? Would the use of bronchodilators, such as xanthines and magnesium sulfate, be appropriate?

These are the most important issues that still need to be defined concerning the treatment of severe acute asthma, which we will discuss from a critical and updated point of view.

**Inhalation therapy in asthma: spacers versus nebulizers**

$\beta_2$-agonist drugs administered through the airways are the treatment of choice in children suffering from acute asthma episodes. Although these drugs are more frequently administered with nebulizers, this system presents several disadvantages when compared to metered dose inhalers, such as high cost, need for electric power supply, and ineffective pulmonary deposition. In contrast, with the use of a metered dose inhaler in association with a spacer, treatment becomes more economical and hygienic, portable, and the time spent with drug administration is shorter when compared to a nebulizer. When a metered dose inhaler is connected to a spacer, drug deposition in the lower airway significantly increases, with a 10-fold decrease in oropharyngeal deposition. Due to this difference in airway deposition, it is possible to decrease the $\beta_2$-agonist dose when a spacer is used; this is not possible with nebulizers.

Schuh et al., in a study carried out with children suffering from mild acute asthma, compared the effect of treatment with one single dose of salbutamol administered through a metered dose inhaler with spacer versus the effect of salbutamol administered via a nebulizer. In that randomized, double-blind study developed in an emergency service, 90 children (5-17 years old) with baseline forced expiratory volume in one second (FEV$_1$) between 50 and 79% of the expected value were investigated; they were treated with salbutamol in 6-10 puffs (n = 30), 2 puffs (n =30), or with nebulization using 0.15 mg/kg (n = 30). Results did not show significant differences between the treatment groups in relation to FEV$_1$ improvement, clinical score, respiratory frequency, or arterial oxygen saturation. The authors concluded that the inhalation treatment with low doses was as effective as with higher doses and with nebulizers. In relation to the occurrence of adverse effects, they observed a significantly increased heart rate in the group treated with nebulizers.

Several studies in adult populations have aimed at determining the ideal dose of salbutamol to be used with metered dose inhalers to achieve effects similar to those obtained with nebulizers. The results obtained so far are considerably variable, ranging from 1:1 to 1:12 in comparisons between inhalers and nebulizers. In studies carried out with children (both out- and inpatients), the doses required for the two systems were similar, ranging from 1:1 to 1:7. Many of these studies presented methodological flaws that may compromise the validity of results, such as small sample size, no randomization, or an extremely short observation period. Most studies conclude that treatment with metered dose inhalers is clinically similar to therapy with nebulizers, and even better in some cases. Kerem et al., in a study carried out in an emergency service, assessed the efficacy of salbutamol administered through nebulizers versus metered dose inhalers with spacers in children with acute asthma. The ratio of the dose required for metered dose inhalers versus nebulizers was of 1:5. The authors concluded that spacers and nebulizers were equally effective in administering $\beta_2$-agonists in children with acute asthma. In a recent study carried out by Bowton et al., in a tertiary care hospital, over 60% of adult inpatients treated with bronchodilators administered via aerosol used metered dose inhalers with spacers in comparison with nebulizers, which represented an important saving of time and money both to the hospital and to the patients.

The main disadvantage of metered dose inhalers is that the aerosol generated by the device and the inhalation process carried out by the patient should be well-paced in order to guarantee effectiveness. Simple devices, which require minimum cooperation of the patient, are essential to assure an optimized administration of the drug to the small airways, with minimum loss in the proximal region. This is especially important in infants and preschool children, in which the doses deposited in the small airways should be known in order to allow adjustments according to the individual needs of each patient. In this sense, the use of spacers with valves and masks has shown to be very useful, since it allows spontaneous breathing maneuvers in patients younger than 4 years, who are not able to breathe deeply and slowly as older children can.

In a group of infants younger than 2 years, presenting episodes of acute bronchial obstruction and being treated in an emergency service, Rubilar et al., assessed the efficacy of salbutamol via metered dose inhalers connected to spacers in comparison with nebulizers. They studied 123 patients with moderate to severe bronchial obstruction randomly allocated to each group of treatment. In this study, the dose used in inhalers/spacers versus nebulizers ranged from 1:3 to 1:7, according to patient weight. There were no differences between the groups at admission to the service in terms of clinical evaluation or other demographic characteristics. The improvement rate (clinical score for bronchial obstruction 5) after the 1st hour of treatment was 90% in the inhaler/spacer group and 71% in the nebulizer group (p=0.01). The authors concluded that infants with acute bronchial obstruction (moderate to severe) treated with
inhaled or spacer treatments presented a quicker and more effective bronchodilator response when compared to those using nebulizers. These results confirm the findings of Closa et al., who also studied bronchodilator response in infants with acute airway obstruction, though in a smaller sample.20

Tay et al.21, assessed the deposition of Aerochamber™, administered via an inhaler connected to a spacer and a mask, in the respiratory and gastrointestinal tract of infants and preschool children with bronchial obstruction. The group included 15 children who used salbutamol labeled with Technetium 99. The investigators analyzed deposition in the oropharynx, lungs, stomach and in the spacer itself. Aerosol deposition was of 2±1% in the lungs, 1.2±0.7% in the oropharynx, and 1±2% in the stomach -the rest remained in the air chamber. The study of lung images showed that the drug was well distributed both in the central and in the peripheral airways. A comparison with two adult volunteers aimed at assessing the deposition obtained with the use an inhaler connected to a spacer resulted in 19% in the lungs and 2% in the stomach. The authors concluded that infants and preschool children with bronchial obstruction could be safely treated with inhaled medications administered by means of spacers and masks. In addition, the results suggest that medication doses, even if not completely determined yet, should be higher than those currently used, and maybe similar to those used in adults.

During several years, nebulizers were the method of choice for the treatment of acute asthma in children. Since the introduction of metered dose inhalers, over 20 years ago, several studies have shown the efficacy, acceptability, and low cost of these devices in the management of asthma in children. Currently, most consensus recommendations advocate the use of nebulizers as a second option, when metered dose inhalers cannot be used.22 Several differences have been identified between both systems, and nebulizers have usually been associated with high cost, greater difficulty of use, and need for electric power. In nebulizers, about 90% of the drug remains in the system or is released to the atmosphere23; in addition, different factors interfere with the efficiency of administration, including technical specifications (type and characteristics), as well as volume, temperature, concentration and osmolarity of the solutions used. On the other hand, metered dose inhalers connected to spacers are easier to use, more economical, compact and portable, and require a shorter administration time when compared to nebulizers.24

In an extensive review of the pediatric literature, Amirav and Newhouse25 selected 10 studies that compared treatments using metered dose inhalers with spacers and nebulizers. The protocols included 301 patients treated with inhalers/spacers and 274 treated with nebulizers. Of these studies, eight did not reveal significant differences between the two methods, while in two of them, the use of inhalers showed better results. None of these studies favored the use of nebulizers, even with a significantly higher dose of $\beta_2$-agonists. On the contrary, the authors’ conclusions advocated the use of inhalers/spacers due to their convenience, quick administration, patient preference, and low cost. In relation to patients with severe acute asthma, the literature has suggested that the administration of drugs with metered dose inhalers is more adequate than with nebulizers, both in children and in adults suffering from the disease.26,27

Recently, Cates et al.28, assessed the effects of metered dose inhalers with spacers and nebulizers in patients with asthma, including the Cochrane Group - Airway, which assessed 21 studies carried out until 2001 (880 children and 444 adults), and found no differences in hospitalization rates and pulmonary function tests, observing a significantly lower heart rate in patients using inhalers/spacers. In addition, in one of the studies involving children, hospital stay was significantly shorter in the inhaler/spacer group.

There are some questions not yet elucidated concerning the use of metered dose inhalers with spacers versus nebulizers, which include: the possibility of using inhalers at home, the variability of effects secondary to the type of spacer used, the need for more adequate ergonomics for use in infants, the importance of using spacers with valves, the optimal dose and frequency of inhalations, the breaths that are necessary to “empty” the spacer, the most appropriate type of bronchodilator to be used, among others.

In summary, in view of the increased clinical benefits, lower cost, quicker and easier administration, decreased need for professional assistance, and similar (or maybe even better) clinical effects obtained with inhalers in comparison with nebulizers, the literature currently recommends the use of metered dose inhalers connected to spacers for most cases of acute asthma in the pediatric population, although some questions still need to be investigated.

Intravenous therapy: the role of $\beta_2$-agonists

Although inhalation is the route most commonly used for the administration of $\beta$-agonists in patients with acute asthma, in some situations these drugs have been administered intravenously.

Bohn et al.29, in a non-controlled clinical study, were the first to publish results related to the intravenous use of salbutamol for the treatment of pediatric patients suffering from severe acute asthma. With a sample of 14 children (16 acute episodes), the authors showed that the drug was able to significantly reduce $\mathrm{PaCO}_2$ in 69% of cases in a period of four hours. In only five patients (11%) the drug was not able to prevent the need for mechanical ventilation. In that study, unwanted side effects related to the use of the drug were not observed. The authors concluded that this form of treatment was safe and able to revert cases of severe bronchospasm in most children that might require mechanical
ventilation. Almost 20 years have elapsed since that publication, and up to the present days, there is no consensus defining the exact moment in which inhalation should be replaced with the intravenous route. In theory, there are only two main indications for intravenous treatment: (a) intense or more severe crises, manifested through eminent respiratory fatigue, sensorial alterations, worsening of the breathing pattern, CO$_2$ retention, decrease in oxygen saturation, among others; and/or (b) cases showing poor response to inhalation therapy.

It is estimated that less than 10% of β-agonist doses inhaled by children with severe acute asthma reach the lower airways. This great loss is related to factors such as: (a) mean diameter of the particles inhaled, which should be lower than 5 μm; (b) type of flow in the airways, since quick and turbulent flows, such as those observed in asthmatic patients, cause the impaction of particles in larger airways; (c) degree and severity of obstruction, since more obstructed airways result in less air flow and, consequently, in lower deposition of the drugs in this region; and (d) no cooperation of the patient and/or use of inadequate inhalation techniques.

It is believed that about 30% of patients with asthma may be genetically resistant to β-agonists. Alterations in the genetic code would change the response and sensitivity of β-agonist receptors.

Based on these concepts and on the experiences published so far, the use of intravenous β-agonist is not an exception anymore; on the contrary, it is now more deliberately used (and in earlier moments) in children with severe acute asthma. Browne et al., in a double-blind study comparing the addition of one 15 μg/kg dose of intravenous salbutamol administered during 10 minutes with the same volume of placebo added to the standard treatment (oxygen, inhaled - agonists and corticoids) of children admitted to the emergency room due to asthma crises showed that patients receiving intravenous salbutamol were discharged earlier, and that the use of oxygen and inhalation therapy was shorter. In our setting, Santana obtained similar findings and that the use of oxygen and inhalation techniques usually related to factors such as: (a) mean diameter of the particles inhaled, which should be lower than 5 μm; (b) type of flow in the airways, since quick and turbulent flows, such as those observed in asthmatic patients, cause the impaction of particles in larger airways; (c) degree and severity of obstruction, since more obstructed airways result in less air flow and, consequently, in lower deposition of the drugs in this region; and (d) no cooperation of the patient and/or use of inadequate inhalation techniques.

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In addition to the alterations observed in the indication of intravenous β-agonists, changes have also occurred in their form of administration. In the past, an initial dose of 1 μg/kg/min (10 minutes) was recommended, followed by the slow infusion of 0.2 μg/kg/min, which should be increased by 0.1μg/kg/min every 20 minutes, according to clinical response. The maximum dose referred to in the literature is of 4 μg/kg/min. Currently, once infusion is initiated at 1 μg/kg/min rates, the dose is increased at short intervals, until the desired clinical response is obtained, or until the appearance of signs related to patient non-tolerance; in these cases, infusion rates can reach 10-15 μg/kg/min. Recently, based on the pharmacokinetics and pharmacodynamics of these drugs, Shan proposed a new infusion protocol. The author advocates the administration of salbutamol at 5 μg/kg/min during 1 hour, and after that, a reduction in infusion to 1 μg/kg/min. In the use of terbutaline, the initial dose should be of 3 μg/kg/min during 1 hour, and then it should be reduced to 1 μg/kg/min.

Although β$_2$-agonists are frequently used in the management of pediatric patients carrying severe obstruction, a systematic review of the literature did not find enough evidence to support their real benefits. A review of the Cochrane Library Group sought to assess the benefits of β$_2$-agonists administered intravenously for the treatment of severe cases of asthma treated in emergency services. In a sample of 584 patients (from 15 randomized clinical studies), any difference was found neither in the clinical outcomes assessed nor in the occurrence of side effects. The authors concluded that there is no evidence supporting the use of β$_2$-agonists in the management of patients with severe asthma, and were not able to identify any subgroup that could benefit from their use. However, it is important to emphasize that great part of the selected patients originated from studies carried out with adult populations. Only three studies involved children, which makes the establishment of conclusions or the extrapolation of findings for this subgroup - namely, our interest group - more difficult.

Considering β$_2$-agonist side effects, tachycardia could be a possible limiting factor to the intravenous infusion of these drugs. However, studies have shown that, after infusion is initiated, a mean increase of 15% in heart rate is observed, becoming stable again after some hours and returning to normality as ventilation improves. The mark of 200 bpm has been taken as the limit for new increases in the infusion of β$_2$-agonists. Special attention should be given to serum potassium levels, since β$_2$-agonist agents reduce potassium concentrations very quickly.

With some improvements, such as bronchospasm reversion, improvement in the tidal volume pattern, and decrease in respiratory dysfunction, the inhalation therapy could be reconsidered in association with the progressive reduction in intravenous β$_2$-agonist infusion. This reduction and withdrawal are directly related to the reversion status of each case. Younger patients usually require a longer administration time (lower reversibility).

**Other bronchodilators: methylxanthines and magnesium sulfate**

Since the description of the use of methylxanthines as bronchodilators for the treatment of asthma crises, at the beginning of the 20th century, these drugs were widely prescribed for the treatment of severe acute asthma up to about two decades ago. In the beginning of the nineties, some randomized clinical assays carried out with pediatric
populations suffering from acute asthma did not show clinical benefits that could justify the use of methylxanthines in cases where an optimized crisis treatment with β2-agonists and corticosteroids was used. Carter et al., considered this hypothesis and assessed 21 children (5-18 years old) admitted to a tertiary care center. In that study, a group of 12 children (with serum control of the drug being administered intravenously) was compared to nine children receiving placebo. All patients included in the study received β2-agonist treatment with frequent doses (albuterol), in addition to intravenous methylprednisolone. The groups did not present differences in terms of demographic characteristics. The authors were not able to find differences in clinical score and function evaluation along 36 hours. Both groups were similar concerning the amount of β2-agonists administered, hospital stay, and frequency of adverse effects, mainly those associated with the drug. In addition to the small number of patients assessed, the main limitation attributed to that study was the exclusion of patients with more severe cases. A systematic review of the literature published at the beginning of the nineties included 164 children (age ranging from 1.5 to 18 years), selected out of six randomized clinical assays (Medline, 1966-1994), and did not find benefits related to the intravenous administration of aminophylline in the routine treatment of acute asthma.

More recently, two clinical assays presented different results, suggesting the advantage of the use of aminophylline in patients with severe acute asthma. Yung et al., in a population of 163 patients (43% admitted to an intensive care unit) with age ranging from 1 to 19 years, showed an improvement in FEV1 after 6 hours, less need for oxygen during 30 hours (6 hours in the aminophylline group versus 18 hours in the placebo group, p = 0.015), and a reduction in the probability of intubation (0% in the aminophylline group versus 6% in the placebo group, p=0.03). Positive results were also found by Ream et al., in their evaluation of the benefit associated with the addition of aminophylline in the treatment of 47 children admitted to a pediatric intensive care unit due to severe acute asthma. All patients received inhaled salbutamol at short intervals, ipratropium bromide and intravenous methylprednisolone. Twenty-three children received theophylline intravenously. Although the need for mechanical ventilation was equal in the two groups, all patients who required mechanical ventilation in the theophylline group did so before the administration of the pharmaceutical. Considering only patients who did not require ventilation (n = 41), clinical improvement was quicker in the theophylline group (18.6 ±2.7 hours versus 31.1±4.5 hours, p < 0.05). No differences were observed in terms of stay in the intensive care unit and total incidence of side effects.

Although theophylline has been widely used in the treatment of acute asthma crises, its mechanism of action has not been totally elucidated yet. The following aspects seem to be relevant: inhibition of the phosphodiesterase enzyme, antagonism with adenosine receptors, increased secretion of catecholamines, and modulation of the transmembrane calcium inflow in muscle cells. Both theophylline and its soluble salt - aminophylline - provoke relaxation of the bronchial smooth muscle. In addition, these drugs present other potentially beneficial effects on respiratory obstruction, diaphragm function, ventilatory drive, mucociliary clearance, antidiuretic hormone secretion, and inflammation.

In situations where β-receptor desensitization is identified, followed by response attenuation, the response persists. From a practical point of view, the role of β-receptors in the management of severe acute asthma remains undefined. The benefits of their association with an optimized β-agonist drug therapy are not clear. Systematic literature reviews have not been able to show the advantages of this association, although most clinical settings have not included adequate comparisons with more severe cases. In our service, the use of aminophylline has not been used as a routine in severe acute asthma patients. However, once this hypothesis is considered, it is important to reinforce that the drug has a narrow therapeutic window. So, aminophylline can be safely prescribed provided precautions are taken in relation to the dose administered, monitoring of serum concentrations, presence of associated diseases and/or medications, and appearance of side effects due to its use. In the treatment of severe acute asthma has been assessed more systematically. Its mechanism of action has not been totally clarified. The occurrence of bronchial smooth muscle relaxation secondary to a competitive inhibition carried out by calcium channels has been advocated. Magnesium is also involved in the inhibition of mast cell degranulation, which is the first step for the resulting release of inflammatory mediators (thromboxanes and leukotrienes). The main triggering factor for this release is the increase observed in intracellular calcium, which is antagonized by magnesium. Magnesium sulfate has been known for decades, but only very recently its role in the treatment of severe acute asthma has been assessed. From a practical point of view, the role of β-agonists in the pharmacological management of the disease has been assessed. Considering only patients who required mechanical ventilation in the theophylline group did so before the administration of the pharmaceutical. Considering only patients who did not require ventilation (n = 41), clinical improvement was quicker in the theophylline group (18.6 ±2.7 hours versus 31.1±4.5 hours, p < 0.05). No differences were observed in terms of stay in the intensive care unit and total incidence of side effects.

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severe) is responsible for a significant improvement in the lung function assessment performed at the beginning of the treatment of these patients.\textsuperscript{51}

Scarfone et al.\textsuperscript{52}, in a similar study, assessed the efficacy of magnesium sulfate in 54 patients (1-18 years old) assisted in an emergency service due to moderate/severe acute asthma crises. Differently from the study of Ciarallo et al.\textsuperscript{51}, these authors administered a higher dose of the drug (75 mg/kg) and determined that the main outcome to assess response would be the alterations observed in clinical score (pulmonary index) at 120 minutes. No significant differences were found in their analysis: 2.83 for the magnesium group versus 2.66 for the placebo group (\(-19\%\) to \(34\%\); 95\% confidence interval - CI). Other outcomes, such as the need for hospitalization and minimum time required for hospital discharge were not significant either. The authors concluded that the use of high doses of magnesium for the treatment of moderate/severe acute asthma does not present advantages when a \(\beta_2\)-agonist and corticoid therapy is associated.\textsuperscript{52}

Similarly, a systematic review of the literature\textsuperscript{53} published prior to the studies mentioned above was not able to provide evidence to support the use of magnesium sulfate in acute asthma patients. A total of 665 patients - originated in seven randomized clinical assays (five with adult populations and two with children) - were included. Significant clinical differences favoring the use of magnesium sulfate were observed only in the subgroup of more severe cases and considering the outcome of decreased need for hospitalization (OR: 0.10, 0.04-0.27; 95\% CI). The same was not observed in the population as a whole, and there were also no differences in the clinical assessment and in the appearance of side effects between the two groups. Therefore, according to the authors, there is no evidence in the literature supporting the use of magnesium sulfate in all patients with acute asthma assisted at emergency services. However, the drug showed to be safe and beneficial in patients with severe acute asthma.\textsuperscript{53}

So, from a clinical point of view, patients presenting a functional evaluation of <50\% of the expected value and showing poor response to bronchodilator therapies (first option), are the best candidates to this form of treatment, although no studies have proven its advantages in comparison with other therapies also used in such patients (e.g. intravenous \(\beta_2\)-agonists). Anyway, magnesium sulfate may be considered as an alternative therapy to severe and refractory patients found in emergency rooms, and also to the initial management of patients in intensive care units.

Magnesium sulfate presents several advantages: easy administration, possibility of use in association with other therapies, and manifestation of clinical effects within 1 or 2 hours. In our setting, it has only been used in selected situations. Recommended doses range between 25 and 75 mg/kg administered intravenously (20 minutes); the maximum dose allowed is 2g. In addition, it can be considered a safe drug, since its main adverse effects are skin reddening and nausea, usually during infusion. Weakness, areflexia, and respiratory depression may also occur, but only in extremely high serum concentrations (>12 mg/dl). These side effects have not been reported so far in the management of patients with acute asthma.\textsuperscript{1,3,5,36}

Conclusions

Inhaled \(\beta_2\)-agonists, prescribed in association with corticosteroids, remain the treatment of choice for acute episodes of asthma in the pediatric population. They are found in most protocols and therapeutic consensus recommendations for this disease. However, when the use of inhalation is considered, it should be reinforced that pulmonary deposition depends on particle size (<5 m). In our study, both nebulizers and metered dose inhalers connected to spacers were effective in the generation of aerosol. So, from a clinical point of view, it is difficult to determine which of these two systems is most effective. On the other hand, from an operational point of view, the advantages of inhalers are evident, mainly in terms of practicality, hygiene and economy. Except for local peculiarities, the literature has already provided support for the recommendation of these devices as the first choice in cases of acute asthma assisted at home and in the initial management of patients in emergency rooms. Patients that are refractory to the conventional therapy (use of inhaled \(\beta_2\)-agonists associated with corticosteroids) should obligatorily consider other pharmacological options, otherwise the crisis may progress to respiratory failure. In these situations, \(\beta_2\)-agonist drugs administered intravenously constitute the final resource prior to the indication of mechanical ventilation. Although \(\beta_2\)-agonist drugs are acknowledged for their use in intensive care units, several questions still need to be clarified. There are divergences in relation to adequate infusion doses, moment in which this form of treatment should be indicated, and also in relation to the real clinical benefits of intravenous drug administration when compared to inhalation. Systematic literature reviews have not recommended \(\beta_2\)-agonists, since not enough evidence that justifies their use has been obtained. However, the hesitation to prescribe \(\beta_2\)-agonists in severe acute asthma cases, previously observed in several protocols, has not been mentioned anymore. In summary, these drugs have been used as part of the routine treatment of severe and refractory cases of acute asthma in emergency and intensive care units, provided patients are continuously and adequately monitored.

Other therapeutic options are still being investigated. Methylxanthines and magnesium sulfate, in spite of having their bronchodilator action acknowledged for several decades, can be considered as alternative methods for the treatment of severe acute asthma, since the literature has advocated their inclusion in the general treatment of patients.
carrying the disease. Their indication still refers to exceptions, and usually occurs when the response to conventional treatment fails to present the expected results.

However, in addition to new drugs, the advances observed in the treatment of severe acute asthma in the past 20 years have resulted in treatment optimization, such as prescription of higher $\beta_2$-agonist doses, changes in administration intervals, use of new aerosol-generating devices, availability and safety in the intravenous administration of drugs, in addition to the early use of corticosteroids in all patients requiring hospitalization due to an acute episode of the disease.

References


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