Provisionally accepted for publication

Position Paper

Doi: 10.56164/PediatrRespirJ.2024.67

Position Paper on short-acting beta-2 agonists for acute wheezing episodes in children aged below 6 years. A statement proposed by the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) Asthma Committee and approved by the SIMRI Advocacy Council and Executive Committee

Raffaella **Nenna** [1, *], Grazia **Fenu** [2], Giuliana **Ferrante** [3], Maria Elisa **Di Cicco** [4], Federica **Porcaro** [5], Stefania **La Grutta** [6], SIMRI Advocacy Council [¤], Executive Committee [†]

[1] Department Maternal Infantile and Urological Sciences, Sapienza University of Rome, Rome Italy

[2] Pulmonology Unit, Meyer Children's Hospital, IRCCS, Florence, Italy

[3] Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, University of Verona, Verona, Italy

[4] Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Pisa, Pisa, Italy

[5] Pediatric Pulmonology and Cystic Fibrosis Unit, Respiratory Research Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[6] National Research Council (CNR), Institute of Translational Pharmacology (IFT), Palermo, Italy

[¤] SIMRI Advocacy Council: Giampaolo Ricci, Luana Nosetti, Maria Francesca Patria, Valentina Fainardi, Iolanda Chinellato, Sabrina Di Pillo, Valentina Agnese Ferraro, Maria Elisa Di Cicco, Anna Maria Zicari, Paola Di Filippo, Marina Attanasi

[†] Executive Committee: Stefania La Grutta, Enrico Lombardi, Fabio Midulla, Giovanni Pompeo Ciccarone, Alessandro Amaddeo, Giuliana Ferrante, Raffaella Nenna, Luana Nosetti, Giuseppe Fabio Parisi, Pierluigi Vuilleumier

* **Correspondence to**: raffaella.nenna@uniroma1.it. ORCID: https://orcid.org/0000-0001-8880-3462.

KEY WORDS

Short-acting beta-2 agonists; wheezing; children.

ABSTRACT

The term ‘wheeze’ denotes a common clinical sign observed in various respiratory obstructive diseases among pediatric patients. It affects approximately one out of every three children under the age of three. In children aged below 6 years, viral respiratory tract infections commonly trigger the episode of wheeze, although some children may wheeze in response to other triggering factors. Short-acting beta-2 agonists, that proved to be a safe and wieldy drug, represent the first-line treatment for managing acute wheezing attacks in preschoolers, regardless of the severity of wheezing.

Their bronchodilator action is established within 5 minutes and lasts for 4-6 hours. This statement outlines the role, the mechanisms of action and side effects of short-acting beta-2 agonists and reports the recommendations of the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) in treating acute wheezing episodes in children younger than 6 years.

IMPACT STATEMENT

SABA, that proved to be a safe and wieldy drug, represents the first-line treatment for managing acute wheezing attacks in preschoolers. This statement outlines the role, the mechanisms of action and side effects of short-acting beta-2 agonists in children aged under 6 years.

INTRODUCTION

The term ‘wheeze’ denotes a common clinical sign observed in various respiratory obstructive diseases among pediatric patients (1). It affects approximately one out of every three children under the age of three (2). We distinguish ‘wheeze’ that refers to a sign identified by healthcare

professionals and ‘wheezing’ that describes symptoms reported by the patient or caregiver. During chest auscultation of a patient with wheezing, a characteristic musical, high-pitched, and continuous sound is observed (3). This sound, provoked by airway obstruction regardless of the underlying etiology and mechanism, arises from the limitation and turbulence of airflow at the site of airway constriction and varies based on the degree of obstruction.

Airway narrowing in patients experiencing wheezing can stem from several underlying mechanisms, including: 1) congenital abnormalities; 2) smooth muscle constriction; 3) extrinsic or intrinsic compression; 4) mucosal swelling and mucus accumulation in the airway.

Given the different possible mechanisms involved, it is not surprising that wheezing is observed in various diseases with differing etiologies, such as asthma, cystic fibrosis, bronchiolitis, as well as bronchomalacia, endobronchial masses, aspirated foreign bodies, vascular rings (4, 5).

The features of the sound produced during airway narrowing depend on the level and severity of obstruction. Wheezing, as an indication of intrathoracic airway obstruction, typically manifests during the expiratory phase, although it may also occur during inspiration in cases of severe obstruction (1). When wheeze arises from the obstruction of larger airways, the sound is transmitted uniformly throughout the lung and is termed ‘monophonic’. Conversely, obstruction of smaller airways results in ‘polyphonic’ sounds due to variable obstruction occurring at different sites within the lung (1).

Wheeze is categorized as mild, moderate, or severe based on the degree of airflow limitation. This categorization takes into account the presence or absence of respiratory distress signs (such as nasal flaring, prolonged expiration, tachypnoea, and intercostal muscle engagement) and the association with red flag signs (including desaturation, cyanosis, inability to speak, and confusion) (6).

Various types of wheezes can be identified based on the onset time and duration of signs and symptoms. The unexpected and sudden onset in an otherwise healthy patient defines ‘acute wheeze’, while experiencing two or more episodes within a six-month period defines ‘recurrent wheeze’ (5). In both cases, wheeze is a very common clinical issue which most practitioners must face.

In children aged below 6 years, viral respiratory tract infections are commonly the *primum movens* of wheezing (episodic viral wheeze), although some children may wheeze in response to other triggering factors (multiple-trigger wheeze) (1).

Although microbiologic diagnostic tests are rarely performed in clinical practice (particularly in an outpatient setting) (7), Respiratory Syncytial Virus (RSV), Rhinovirus (RV), human Bocavirus, Metapneumovirus, Parainfluenza virus, Influenza virus, Adenovirus and Coronavirus are frequently involved in starting the inflammatory response in the airways (8).

Inflammation causes cellular infiltration of the peribronchiolar tissue, oedema of the bronchioles, mucus overproduction, and inefficient mucous clearance. These factors collectively contribute to varying degrees of airway obstruction, bronchospasm and air trapping.

This statement outlines the role of short-acting beta-2 agonists (SABA) in treating acute wheezing episodes in children younger than 6 years.

Mechanisms of short acting β 2 agonists

Since their introduction in clinical practice in 1968 (9), β2 agonists have been widely used to treat acute episodes of bronchoconstriction caused by asthma as well as other respiratory diseases.

The β2 agonists are bronchodilator drugs acting on β2-adrenergic receptors (β2-AR) (G-protein-coupled receptors) present on bronchial smooth muscles. They are also called β2-mimetics (10).

The stimulation of β2-AR, activating adenyl cyclase and producing an increase in intracellular cyclic adenosine 3′,5′-monophosphate (cAMP), leads to smooth muscle relaxation and inhibition of smooth muscle contraction in the airways (11). They can promote the release of the bronchial muscles, increasing the caliber of the bronchi and bronchioles aimed at reducing resistance within the airways (12). More precisely, the activation of these receptors leads to a decrease in the levels of calcium ions (Ca++) in the cells of the bronchial smooth muscle. Calcium ions are responsible for bronchoconstriction; therefore, it is clear how a reduction in their concentration can favor the reverse process, i.e. bronchodilation. Therefore, β2 agonists, as agonists of the β2-AR, stimulate them and induce bronchodilation.

The β2AR-mediated vasorelaxation, and potentially bronchodilation, decline with age due to decreased affinity for agonists, sub- optimal receptor signaling and reduced cAMP production (13).

Prolonged exposure to the agonist desensitizes G-protein-coupled receptors through a downregulation leading to a net loss of receptors after hours of agonist exposure. The receptors can only be replaced by re-synthesis of new receptors through transcription of the β2AR-gene (14, 15). It takes hours to days to overcome downregulation. Corticosteroids increase β2AR-gene transcription and regulate both the number of receptors and the coupling to adenylate cyclase, reversing β2AR downregulation (14).

The pharmacologic actions of β2 agonists differ mainly with respect to their potency due to relative binding affinities and duration of action based on their ability to be retained in the lung tissue. The drugs belonging to the class of β2-AR agonists can be divided into three groups depending on their duration of action: 1) short-acting β2-agonists (SABA): the bronchodilator action is established within 5 minutes, and they have a duration of action of 4-6 hours. Salbutamol belongs to this category; 2) long-acting β2-agonists (LABA): these drugs are used primarily to prolong the control of symptoms of asthma. They have a slow onset of action (20-30 minutes), but the bronchodilation they induce lasts 8-12 hours. LABA has larger side chains, which make them more lipophilic, thereby increasing lung retention, giving them a longer duration of action. This category includes salmeterol and formoterol. Formoterol is moderately lipophilic with most of the inhaled dose being retained in cell membranes and gradually released. Some molecules remain in the aqueous phase outside the cells allowing immediate interaction with β2-receptors and thus, a rapid effect (16); and 3) ultra long-acting β2-agonists (ultra-LABA): the bronchodilator action lasts 24 hours allowing for a single daily administration. Abediterol, indacaterol, olodaterol and vilanterol belong to this category of drugs (17,18).

Formoterol is a full agonist at the β2-receptor and results in more than 80% of maximal β2-receptor activation, on the other hand, salmeterol and salbutamol are partial agonists at the β2-receptor and therefore they do not result in maximal bronchodilation (16).

While salbutamol is one of the most effective and safest drugs available, currently included in the World Health Organization list of essential drugs (19), it may cause adverse effects mostly by stimulating extra-respiratory β2-receptors found in the vessels, heart, muscles, brain, and liver. Side

effects depend on the dosage (they are not very common at recommended doses) and the route of administration. They are more frequent when salbutamol is administered intravenously or orally. Nebulized administration is a safer option, achieving high drug concentrations and faster bronchodilation effect in the airways while minimizing systemic absorption (17, 19).

The most reported side effect is tachycardia with or without palpitations, which is more common when salbutamol is administered by an inhaler, due to the inhaled portion rather than the swallowed one (20). Tachycardia is caused by direct stimulation of β receptors in the atria and ventricles, some of which are β2, but this effect is transient and usually not life threatening. Moreover, tachycardia may be caused by the response to vasodilation caused by stimulation of β-receptors in the vessels (20). Also, angina and arrhythmias have been reported, especially in those with severe hypoxemia and hypokalemia. As a matter of fact, salbutamol may cause or worsen hypokalemia, especially at high doses administered intravenously or by nebulizer, due to stimulation of intracellular accumulation of potassium in the skeletal muscle (21). Due to such effect, salbutamol has been used to treat hyperkalemia in intensive care units in both adults and children.

Tremor is another common adverse effect of salbutamol which seems to be caused by direct stimulation of β-receptors on the skeletal muscle or may be correlated with hypokalemia (22).

Among side effects, even respiratory symptoms might be reported, including chest heaviness and paradoxical bronchoconstriction (23). Finally, β2-receptors stimulation in the liver causes glycogenolysis and increase in blood sugar levels (24) and in the nervous system, it may cause hallucinations and anxiousness (25, 26). To our knowledge, there are few data on the incidence of salbutamol's systemic side effects, especially in childhood (27-29). Notably, a recent systematic review and meta-analysis evaluated the risk of cardiovascular system adverse events in salbutamol users showing that the only reported cardiovascular system adverse event in 2097 subjects was tachycardia or palpitations, and its pooled incidence was 16% (95%CI: 11% - 22%) (30).

Short-acting β2-agonists: action plan in wheezing children aged below 6 years

SABA is considered the first-line treatment for managing acute wheezing attacks in preschoolers, regardless the severity of wheezing (31). Oral administration of bronchodilators is not recommended;

indeed, delivery by inhalation achieves high concentration in the airways, more rapid onset of action, and fewer systemic adverse effects. Spacers (with mask in the first 3 years of life or mouthpiece in children aged 3 years and over) are the preferred device through which administering such drugs, while nebulizers are considered an alternative option (32). In particular, SABA should be administered via a pressurized metered-dose inhaler (pMDI) with a spacer in mild-to-moderate attacks or via nebulization driven by oxygen in severe attacks. For most children pMDI plus spacer is the preferred choice as it is more efficient and faster than a nebulizer for drug delivery; moreover, the use of nebulizers can be associated with spreading of infectious particles, so local infection control measures must be followed (33).

Noteworthy, correct inhalation technique and education are essential, when using a spacer. Most children aged 3 years and older can use a mouthpiece. Treatment must be administered during quiet awake breathing, due to the risk that no medication will be deposited in the lower airways during crying or sleep (34). The only possible inhalation technique in infants and preschoolers is tidal breathing. The number of breaths required to empty the spacer depends on the child's tidal volume, volume of the spacer, and dead space; however, usually 5-10 breaths per actuation are considered sufficient. The optimal use of spacers is crucial to deliver an efficient treatment. Therefore, it should be considered that:

- young children can use spacers of all size, but a lower volume spacer (< 350 ml) is preferred in very young patients;
- priming of the spacer by firing waste puffs is not necessary (since even 15 waste puffs would not affect significantly the half-life of the drug in the spacer) (35);
- a single pMDI actuation should be delivered at a time, after shaking the inhaler; multiple actuations before inhalation may dramatically reduce the amount of medication inhaled;
- inhalation should start as soon as possible after actuation, which should be delivered when the child is ready, and the spacer is in the mouth;
- when a mask face is used, it must be fitted tightly around the child's mouth and nose;

- caregivers should ensure that the valve is moving while the child is breathing through the spacer;
- plastic spacers should be washed weekly with detergent, without rinsing, and allowed to air dry, to reduce static charge and increase lung delivery.

The initial dose of SABA in children aged below 6 years is two puffs of salbutamol (100 mcg per puff) or equivalent; however, in severe acute attacks six puffs should be administered (36). When using a nebulizer, a dose of 2.5 mg salbutamol solution is recommended. If symptoms persist after the initial treatment, a further administration of SABA may be repeated at 20-minute intervals for an hour. Further SABA, i.e. additional 2-3 puffs up to a total of 10 puffs per day or additional 2.5 mg salbutamol via nebulizer up to a total of five administrations per day, should be given each hour if symptoms persist or recur. Importantly, patients must be admitted to hospital if: 1) they require more than 10 puffs or more than four administrations of 2.5 mg salbutamol via nebulizer in 3-4 hours; 2) they are unresponsive to 6 puffs of SABA (2 puffs, repeated 3 times) or to 2.5 mg salbutamol via nebulizer repeated 3 times for more than 1-2 hours; 3) they show persistent tachypnoea despite 3 administrations of SABA, regardless of other clinical signs of improvement (33).

Given the risks of only SABA-based treatment, the combination of low doses of inhaled corticosteroids (ICS) whenever SABA is used should be evaluated, even in patients with not sufficient evidence to start a daily controller (33, 37). Indeed, the frequent use of SABA can lead to increased inflammation, bronchial hyperreactivity and reduced bronchodilation capacity; it can also mask the worsening of symptoms (38).

An educational program should be provided to caregivers of wheezy children aged below 6 years. This program should include training on correct inhalation technique and a written action plan. The action plan should cover how to recognize symptoms, administer medications and when and how to seek medical assistance, including urgent hospital treatment (33).

Conclusion

Pediatricians often face wheezing in children aged under 6 years. Viral respiratory tract infections, allergens, exercise, or crying may suddenly trigger unexpected acute episodes with a wide range

of severity. Increasing evidence supports early airway remodeling in recurrent preschool wheezing. SABA, that proved to be a safe and wieldy drug, represents the first-line treatment for managing acute wheezing attacks in preschoolers, regardless the severity of wheezing. The bronchodilator action is established within 5 minutes and lasts for 4-6 hours. In recurrent wheezing children aged below 6 years, the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) recommends a starting dose of two puffs of salbutamol (100 mcg per puff) that can be repeated every 20 minutes for an hour and anyhow 4-5 times a day during acute wheeze episodes. SABA via nebulization at a dose of 2.5 mg driven by oxygen should be used during severe attacks. Low doses of ICS whenever SABA is used should be prescribed.

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Figure 1. 10 rules on short-acting beta-2 agonists (SABA) for acute wheezing episodes in children aged below 6 years

1. Pediatricians must be aware that wheeze is caused by airway obstruction, arises from the limitation and turbulence of airflow at the site of airway constriction and varies based on the degree of obstruction.
2. SABA promote the release of the bronchial muscles, increasing the caliber of the bronchi and bronchioles aimed at reducing resistance within the airways.
3. Prolonged exposure to the SABA desensitizes β2 receptors through a downregulation mechanism. Corticosteroids, reverse β2 receptors downregulation.
4. SABA exert the bronchodilator action from 5 minutes, up to 4-6 hours.
5. The most reported side effects of SABA are tachycardia and tremors.
6. SABA are considered the first-line treatment for managing acute wheezing attacks, regardless the severity of wheezing.
7. pMDI with a spacer is the preferred strategy through which administering such drugs, while nebulizers are considered an alternative option.
8. Young children can use spacers of all size, but a lower volume spacer is preferred in very young patients; priming is not necessary; a single pMDI actuation should be delivered immediately after having shaked the inhaler; inhalation should start as soon as possible after actuation; when a mask face is used, it must be fitted tightly around the child's mouth and nose; caregivers should ensure that the valve is moving while the child is breathing through the spacer; plastic spacers should be washed weekly with detergent, without rinsing, and allowed to air dry, to reduce static charge and increase lung delivery.
9. The initial dose of SABA in children aged below 6 years is two puffs of salbutamol (100 mcg per puff) (2.5 mg salbutamol solution using a nebulizer) or equivalent; however, in severe acute attacks six puffs should be administered. If symptoms persist after the initial

treatment, a further administration of SABA may be repeated at 20-minute intervals for an hour. Further SABA, i.e. additional 2-3 puffs up to a total of 10 puffs per day or additional 2.5 mg salbutamol via nebulizer up to a total of five administrations per day, should be given each hour if symptoms persist or recur.
10. The combination of low doses of inhaled corticosteroids whenever SABA is used should be considered, including in patients with not sufficient evidence to start a daily corticosteroid controller.