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ORIGINAL ARTICLE

Asthma and COVID-19

Asma e COVID-19

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Keywords:
Asthma,
Coronavirus Infections,
Pandemics,
Risk Factors,
Drug Therapy,
Spirometry.

Abstract

Objectives: Highlight the asthma situation in this pandemic. Describe the safety aspects of patients and health professionals. Discuss its severity, control, risk factors, therapeutic management of chronic disease and its exacerbations. **Methods:** Data were collected from the scientific literature on the topic asthma in the context of the COVID-19 pandemic. A search was performed in PubMed databases, using the descriptors: asthma, coronavirus infections, pandemics, risk factors, drug therapy and spirometry. **Results:** Asthma has not been identified as a significant risk factor for severe COVID-19 disease, perhaps due to the lower expression of angiotensin-converting enzyme receptors in atopic asthma. Groups were identified, among severe asthmatics, with greater expression of these receptors. **Conclusions:** Nebulizers should be avoided, spacers should not be shared and spirometry or peak expiratory flow measurement is not recommended. All asthmatics should be maintained on inhaled corticosteroids. Short-acting beta2-agonist only treatment is not recommended from the age of 12. As-needed low dose inhaled corticosteroid with formoterol is the prefered reliever for this age group and can be offered together on the same device. From 6 to 11-years-old, reliever medication should preferably be short-acting beta2-agonists, associated with low dose inhaled corticosteroids and applied in separate devices. In severe asthma, tiotropium should precede the indication of the immunobiological and this, when in use, should not be interrupted.

Palavras-chave:
Asma,
Infecções por Coronavírus,
Pandemias,
Fatores de Risco,
Tratamento Farmacológico,
Espirometria.

Resumo

Objetivos: Destacar a situação da asma nesta pandemia. Descrever aspectos de segurança dos pacientes e dos profissionais de saúde. Discutir sua gravidade, controle, fatores de risco, manejo da doença e suas exacerbações. **Métodos:** Coletados dados da literatura científica sobre o tema asma no contexto da pandemia de COVID-19. Busca nas bases de dados PubMed, utilizando os descritores: asma, tratamento farmacológico, infecções por coronavírus, pandemias, fatores de risco e espirometria. **Resultados:** A asma não foi identificada como um fator de risco significativo para a doença grave COVID-19, talvez pela menor expressão de receptores da enzima de conversão da angiotensina na asma atópica. Foram identificados grupos, dentre asmáticos graves, com maior expressão desses receptores. **Conclusões:** Nebulizadores devem ser evitados, os espaçadores não devem ser compartilhados e não se recomenda a realização de espirometria ou da aferição do pico de fluxo expiratório. Todos os asmáticos devem ser mantidos com corticoide inalatório. O uso isolado de beta2-agonista de curta duração não é recomendado a partir dos 12 anos e baixa dose de corticoide inalatório associado ao formoterol, por demanda, é a opção preferencial, podendo ser aplicado em dispositivo único. Dos 6 aos 11 anos, os medicamentos de alívio devem ser preferencialmente beta2-agonistas de curta duração, associados à baixa dose de corticoide inalatório e aplicados em dispositivos separados. Na asma grave, o tiotrópio deve preceder a indicação do imunobiológico e este, quando em uso, não deve ser interrompido.

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INTRODUCTION

At the beginning of this year, the Recommendations for Asthma Management from the Brazilian Society of Pulmonology and Tisiology - were published in the Brazilian Journal of Pulmonology - 2020.[1] Pharmacological management has changed considerably. Despite these advances, the level of disease control remains low, with high morbidity, regardless of the country studied.

Asthma affects all age groups and its prevalence increases, especially in the pediatric age group, compromising the family's health. The prevalence of asthma symptoms among adolescents in Brazil was 20%, one of the highest in the world.[1] There is a high prevalence, morbidity and mortality worldwide.[2] The populations with the highest prevalence of asthma are in English-speaking countries and in Latin America. In 2013, 2,047 people died of asthma in Brazil (5 deaths/day), with Brazil being one of the countries with the highest prevalence of asthma in children and with high rates of severe asthma.3

METHOD

We collected data from the scientific literature, using the topic Asthma in the context of the Covid-19 pandemic, with a focus on the safety of patients and healthcare professionals. We searched for papers in the Pubmed database, in English, over the past 5 years, using the keywords: asthma, pharmacological treatment, coronavirus infections, pandemics, risk factors and spirometry. When we searched for Pediatric Asthma and COVID-19, we found 40 studies, with the least relevant ones being discarded[3].

RESULTS AND DISCUSSION

Asthma is a heterogeneous disease, characterized by chronic inflammation of the airways. Respiratory manifestations, such as wheezing, coughing, chest tightness, shortness of breath, can occur sporadically, with different degrees of intensity, in episodes of exacerbation, known as seizures, but with persistent, subclinical, untreated inflammation. The disease can evolve into an irreversible sequela, which is bronchial remodeling with permanent reduction in lung function, which can be identified on physical examination, showing prolongation of expiratory time. The diagnosis can be clinical or by laboratory criteria with reversibility of the obstructive ventilatory disorder after 400mcg of salbutamol. It is very important to test lung function before starting treatment or whenever possible.[2] Currently in times of pandemic, we must avoid spirometry and peak expiratory flow measurements.

Asma and COVID-19

The Centers for Disease Control and Prevention in the United States of America lists asthma as a risk factor for severe COVID-19 disease, however, asthma and respiratory allergy have not been identified as significant risk factors for severe COVID-19 disease in a Chinese case series.[4,5]

Previous studies have reported on a lower expression of angiotensin-converting enzyme (ACE2) receptors in atopic asthma and other allergic respiratory diseases.[6]

The URECA (Urban Environment and Childhood Asthma) cohort study showed that allergic sensitization was inversely proportional to the expression of ACE2 receptors[7]. There are subgroups with higher morbidity risk by Covid 19 among patients with severe asthma, differences in the ACE2 gene expression or the or of the serine transmembrane protease 2 (TMPRSS2) in sputum cells, with greater expression of ACE2 and TMPRSS2 in male asthmatics, African descendants and diabetics, and inhaled corticosteroid (IC) was associated with lower expression of ACE2 and TMPRSS2.[8] There is still no scientific evidence regarding the benefit or impairment brought about by a previous or combined use of IC in coronavirus infections.[4]

Children with asthma were less impacted in this pandemic.[9] There is little data on whether childhood asthma is a risk factor for SARS-CoV-2 infection or COVID-19 severity.[10] Asthma was not associated with an increased risk of hospitalization and the IC, was not associated with hospitalization related to COVID-19.[11] In severe asthma, patients should maintain their use of immunobiological agent.[12] Social isolation and school leave contributed to a better control of the asthma in children.[13,14]

The spray with pediatric spacer is indicated, avoiding nebulizers, because the aerosol transmits viral particles up to more than one meter away.[15,16,17] If SpO_2 <94%, the patient should avoid humidified oxygen, reducing the risk of aerosolization, and a nasal catheter with a maximum of 4 L/min flow and a surgical mask are recommended. The high-flow nasal catheter may reduce the indication for invasive ventilation.[18]

Emotional disorders are prevalent in this pandemic.[19] We must intensify our control of SARS-CoV-2 infections, as well as tuberculosis, which are very relevant in our country.

Gravity, control and risk factors[2]

We assess severity retrospectively considering the amount of medication needed to achieve control. We control Mild asthma controlled with Steps 1 and 2.[2] Moderate asthma with Step 3 and severe asthma with Steps 4 or 5[2]. It is important to differentiate between severe asthma and uncontrolled asthma due to the presence of an error in the inhalation technique or low compliance.

The concept of asthma control comprises two distinct domains: the control of symptoms, the need for relief medication and the preservation of physical activities; and reduction of future risks, such as exacerbations, accelerated loss of lung function and adverse effects of treatment. Lung function is useful as an indicator of future risk.[2]

Asthma control expresses the frequency and intensity of asthma symptoms that should be suppressed by treatment, varying in days or weeks. The control diagnosis is obtained after 2 to 3 months of treatment, and it is evaluated according to the frequency of asthma symptoms in the last four weeks, being divided into two age groups: under 6 years of age and from 6 years on. There are 4 parameters evaluated: daytime symptoms, nighttime awakening, relief medication and activity limitation. The frequency of symptoms and the use of relief medication for children under 6 years of age is considered when > 1 x week and in the older > 2x week. Any activity limitation or night awakening is considered a criterion of lack of control. Therefore, the presence of one or two uncontrolled characteristics represents partial control of asthma and when there are 3 or more characteristics, asthma is uncontrolled.[2]

The risk factors must be investigated; the medications are represented by the use of a fast-acting B2 agonist (short-acting beta2-agonist-SABA) greater than 1 metered-dose aerosol bottle per month, no IC prescription, low compliance, and incorrect inhalation technique. The greater the bronchodilator response, the worse the obstructive ventilatory disorder and the greater the risk of exacerbation. Low forced expiratory volume of the first second (FEV1), as well as blood or sputum eosinophilia, are risk factors for fixed airway limitation. They must be investigated at each reevaluation. Uncontrolled asthma is an important risk factor. Any exacerbation indicates a review of treatment maintenance.

Treatment Maintenance

Asthma treatment aims to achieve symptom control, maintain normal physical activities, minimize future risks such as loss of lung function, decrease morbidity and mortality, avoid fixed airway limitation by bronchial remodeling and the adverse effects of treatment.

A written action plan should be guided, individualized and developed in partnership with the person in charge of the minor, specifying the maintenance treatment, guidance for early recognition of exacerbation, with home treatment of mild crises and a clear indication of when to look for an emergency service.[2]

At each reassessment visit, the doctor should check for compliance with the treatment prescribed, because approximately 50% of asthmatics undergoing inter-crisis treatment, do not use the medication regularly, and many have errors in the inhalation technique. A cross-sectional study with one hundred adolescents aged twelve to nineteen, identified a compliance rate of 53%, when questioned away from their guardians; compared to 89% compliance when in front of their guardians. There was also an error in the inhalation technique in 89% of these adolescents.[20] Environmental control and aggravating factors must be evaluated at each visit.

Key points in preventing asthma in pediatric patients, with high quality evidence:

- Avoid tobacco in pregnancy and in the first year of life of the baby.
- Stimulate vaginal delivery and breastfeeding.
- Avoid paracetamol and broad-spectrum antibiotics in the first year of life.

Important points in the treatment:

1. From 12 years of age, the use of SABA alone is not recommended.
2. Everyone from 12 years and older should receive IC to reduce exacerbations and better control of symptoms; and when in crises, formoterol + IC to relieve asthma symptoms.
3. Before increasing the treatment dose, make sure that there is no error in the inhalation technique and that the compliance is good.
4. Before decreasing the treatment dose, make sure that the asthma has been under control for 3 months and that there is no risk factor.
5. The leukotriene receptor antagonist is less effective than IC, and patients should be aware of the serious risk of adverse effects on mental health with the regular use of montelukast.

The therapeutic arsenal is divided into 3 groups:

1. Control medications: useful for reducing the inflammatory process, better controlling symptoms, reducing attacks and minimizing lung function loss.
2. Relief medications: they are prescribed for all asthmatics, avoiding the use of SABA alone. Prescribed also for the prevention of exercise-induced bronchospasm.
3. Complementary therapies for severe asthma: they are considered when symptoms are persistent with frequent exacerbations, despite the optimized treatment with high-dose controlling drugs and with treatment of modifiable risk factors.

Treatment ≥ 12 years[2]:

Initial treatment is based on the frequency of symptoms

- **Step 1:** < 2 x month, low dose IC + formoterol on demand, the data being only with the budesonide-formoterol presentation, as an alternative: low IC whenever using SABA.
- **Step 2**: ≥ 2 x month, low dose IC or low dose IC + formoterol on demand, as an alternative: Leukotriene Receptor Antagonist (LTRA) daily or low dose IC whenever using SABA.
- **Step 3:** almost daily or with nightly awakening ≥ 1 x week, low dose IC + long-acting beta2-agonist (LABA), as an alternative: medium dose II or low IC + LTRA.
- **Step 4:** almost daily or with nightly awakening ≥ 1 x week or with low lung function, medium dose IC + LABA, alternatively, high dose IC, add tiotropium or LTRA.
- **Step 5**: not controlled with Step 4, IC high dose + LABA. Refer to the Phenotyping Specialist. Add tiotropium, anti IgE, anti IL5/R, anti IL4, as an alternative: OC low dose.

Treatment from 6 years to 11 years of age[2]:

- **Step 1:** <2x month, as an alternative: low dose IC whenever using SABA, with separate inhalers or low dose IC.
- **Step 2:** ≥ 2 x month, low dose IC, as an alternative: LTRA or low dose IC whenever using SABA.
- **Step 3:** almost daily or at night ≥ 1 x week, low dose IC + LABA or medium dose IC, as an alternative: low dose IC + LTRA.
- **Step 4:** almost daily or with nightly awakening ≥ 1 x week and with low lung function, medium dose IC + LABA. Refer to the specialist, alternatively, high dose IC + LABA or add tiotropium or add LTRA.
- **Step 5:** Uncontrolled asthma with Step 4. Refer to the specialist for Phenotyping. Add anti IgE; alternatively, anti IL5 or low dose OC.

The diagnosis of asthma in children under 5 years of age is likely when:

- Wheezing or coughing occurs with physical exercise, laughter, crying or in the absence of viral infections.
- There is a history of other allergic diseases such as atopic dermatitis, allergic rhinitis, sensitization to allergens or diagnosis of asthma in first-degree relatives.
- There is clinical improvement during 2 to 3 months of treatment and it worsens after its suspension.

Treatment in ≤ 5 years[2:]

- **Step 1**: viral wheezing or rare symptoms, SABA on demand.
- **Step 2**: symptoms consistent with partially controlled asthma or ≥ 3 x seizures per year, low dose IC, as an alternative: LTRA or low dose IC + SABA on demand.
- **Step 3**: poorly controlled asthma with low dose IC, double the IC dose, as an alternative: low IC + LTRA. Consider referring to the specialist.
- **Step 4:** uncontrolled asthma with Step 3, continue treatment and refer to the specialist, alternatively, add LTRA or increase the IC dose or add intermittent IC.

Treating exacerbation from the age of 6 (Figures 1 and 2).[2]

A brief history, physical examination concomitantly with the immediate start of therapy.

History: investigate factors that increase the risk of asthma-related death

- Asthma requiring intubation or mechanical ventilation.
- Hospitalization or emergency in the last 12 months.
- Recent use of oral corticosteroids or lack of regular IC treatment.
- Excessive use of SABA, more than one flask per month.
- Psychiatric illness or psychosocial problems.
- Low compliance, absence of a written action plan and no food allergy.
- Physical examination: vital signs, level of consciousness, use of accessory respiratory muscles, audible wheezing.
- Complications: pneumonia, pneumothorax, anaphylaxis.
- Other diagnoses: heart failure, laryngospasm, foreign body, pulmonary embolism.

Approach to the asthma spell in patients ≤ 5 years of age (Table 2).[2]

In this age group, the initial symptoms are represented by the aggravation of cough, especially at night, lethargy, reduced exercise tolerance, impaired daily activities such as food and poor response to relief medications.

Table 1. Dose equivalence of inhaled corticosteroids licensed to be used in Brazil.[a]

	Adults	**Adolescents**	**≥ 12 years**	
Corticosteroid	Type of device	Low doseb	Medium dose	High dose
	µg/day	µg/day	µg/day[c]	µg/day[c]
Beclomethasone dipropionate	DPI, HFA	100-200	> 200-400	> 400
Budesonide	DPI, HFA	200-400	> 400-800	> 800
Fluticasone propionate	DPI, HFA	100-250	> 250-500	> 500
Fluticasone furoate	DPI	n d	100	200
Mometasone furoate	DPI	110-220	> 220-440	> 440
	Children	**6 to 11 years of age**		
Corticosteroid	DPI, HFA	Low dose[b]	Medium dose	High dose[c]
Beclomethasone dipropionate	DPI	50-100	> 100-200	> 200
Budesonide	Plastic vials	100-200	> 200-500	> 500
Budesonide	HFA	250-500	> 500-1.000	> 1.000
Fluticasone propionate	DPI	100-200	> 200-500	> 500
Fluticasone propionate	DPI	100-200	> 200-400	> 400
Mometasone furoate	DPI	110	≥ 220-440	≥ 440
	Children	**< 6 years of age**		
Corticosteroid	Type of device	Dose baixa µg/dia	Idade	
Beclomethasone dipropionate	HFA	100	≥ 5 years	
Budesonide	Plastic vials	500	≥ 6 Months	
Fluticasone propionate	HFA	50	≥ 4 years	
Mometasone furoate	DPI		≥ 4 years	

DPI: dry powder inhaler; HFA: hydrofluoroalkane; and na: not available. [a]Dose listed in the drug label. [b]Standard dose to start and maintain treatment for most patients. [c]Increase substantially the frequency and intensity of systemic side effects. Source: SBPT, 2020.

Parents or guardians should receive a written action plan with the SABA doses and intervals, without the inclusion of OC, and should seek medical assistance to evaluate the prescription of corticosteroids.

Before treatment, we must assess the exacerbation severity (Table 2).[2]

CONCLUSIONS:

1. Avoid nebulizers.
2. Don't share the spacers.
3. Maintain IC for all asthmatics.
4. In controlled asthmatics, there is no need to increase IC.
5. Isolated SABA is no longer recommended from age 12.
6. Low dose of IC associated with formoterol, on demand, is the preferred option, in asthmatics ≥ 12 years, and can be applied from a single device.
7. The maximum dose of formoterol is 72 mcg/day when combined with budesonide and 48mcg/day when associated with beclomethasone.
8. SABA associated with low IC, should preferably be applied from separate devices, in exacerbations in asthmatics aged 6 to 11 years.
9. In severe asthma, from 6 years of age, tiotropium must precede the indication of the immunobiological agent, which, when in use, must not be interrupted.
10. Do not perform spirometry or measure the peak expiratory flow.

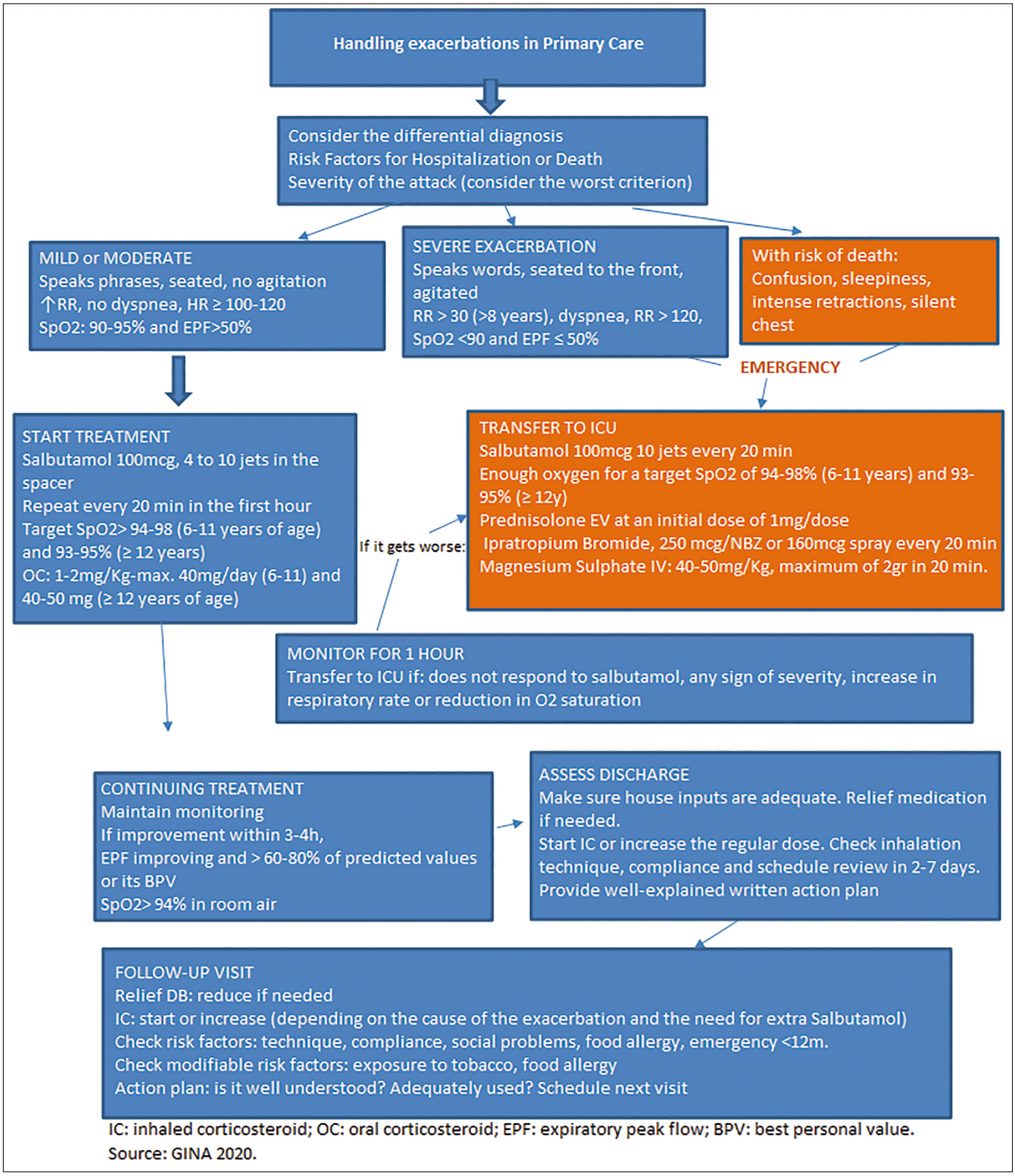


Figure 1. Handling exacerbations in Primary Care ≥ 6 years of age.

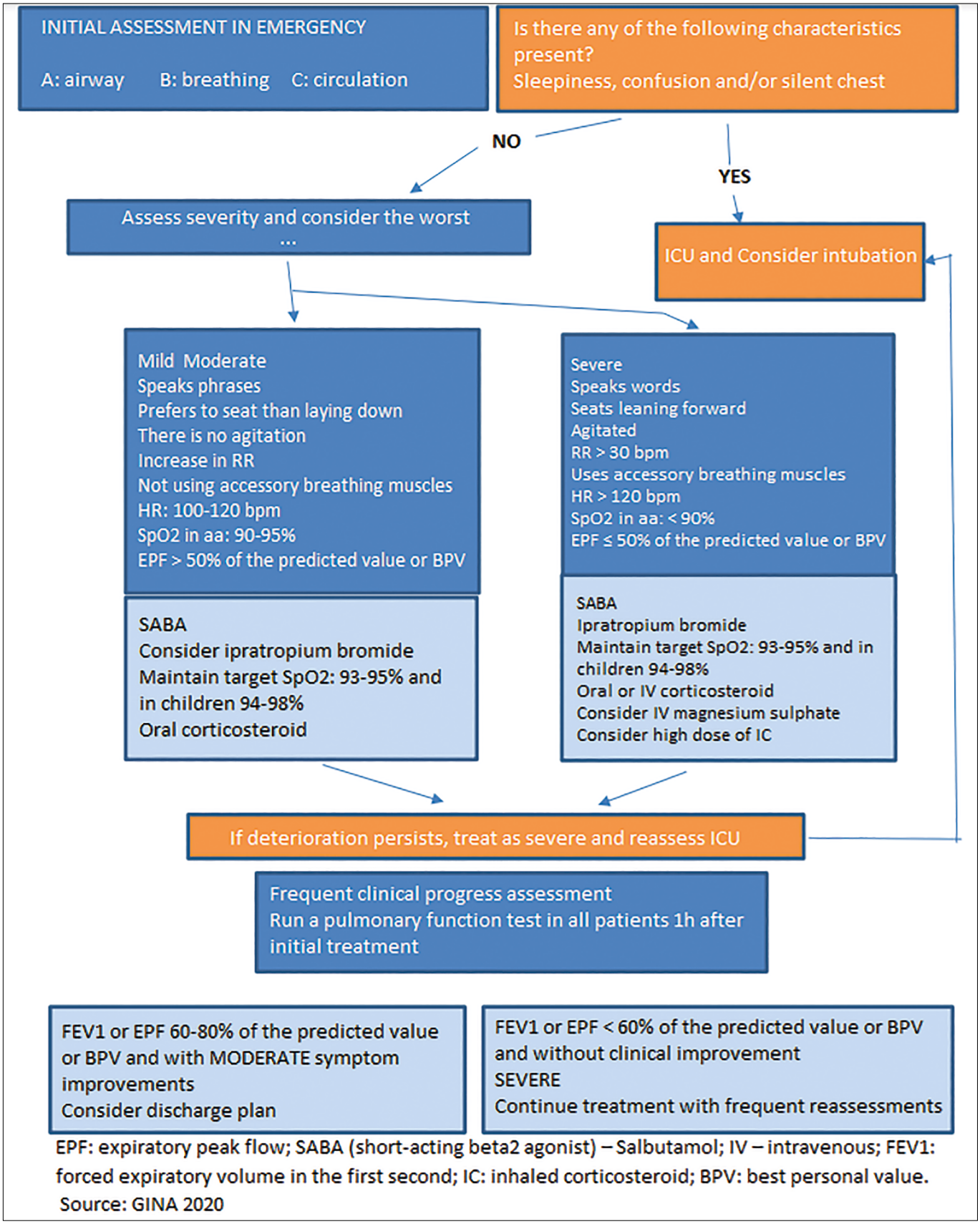


Figure 2. Handling exacerbations in emergency care ≥ 6 years of age.

Table 2. Assessing disease worsening and handling in patients ≤ 5 years.

	Disease worsening assessment in patients ≤ 5 years
MILD	**SEVERE***
No change in level of consciousness	Agitation, confusion or sleepiness
SpO2 >95%**	<92%
Speaks phrases #	Speaks words
HR<100 bpm(0-3a)	>180 bpm (0-3 years)
HR<100 bpm(4-5a)	>150 bpm (4-5 years)
RR ≤40 bpm	>40 bpm
No central cyanosis	Probable central cyanosis
Variable sibilance intensity	Probable silent chest
	Disease worsening handling in patients ≤ 5 years
Treatment	**Doses and means of administration**
Oxygen therapy	By mask (usually 1L/minute) to maintain oxymetry between 94-98%
SABA	2-6 sprays with spacer, or 2.5mg of salbutamol in the nebulization, every 20 minutes in the first hour ##. If symptoms persist, administrate an additional dose of 2-3 sprays per hour. Hospitalization is indicated if patients need more than >10 sprays in 3-4 hours
Systemic corticosteroid	Oral prednisolone (1-2 mg/Kg up to a maximum of 20 mg < 2 years; 30 mg between 2-5 years. Or methylprednisolone 1 mg/Kg every 6 hours in the first 24 hours
	Additional treatment in the first hour
Ipratropium bromide	In moderate to severe worsening, 2x 80mcg sprays (or 250mcg in the nebulization) every 20 minutes only in the first hour of treatment
Magnesium sulphate	Consider nebulization with magnesium sulphate (150mg) 3 doses in the first hour of treatment in patients ≥ 2 years with severe worsening

*Any of these characteristics indicates a severe exacerbation. ** Oxymetry before treatment with oxygen or bronchodilator. #Take into account the normal development of the patient. ## If inhalation treatment is not possible, a bolus of Terbutaline Sulfate 2 mcg/Kg can be applied intravenously in 5 minutes, followed by a continuous infusion of 5mcg/Kg/hour (Evidence level C). This child should be monitored and the dose adjusted according to the improvement and side effects. SpO2: Pulse oxymetry; HR: heart rate; RR: respiratory rate; bpm: beats per minute; bpm: breaths per minute; SABA: (short-acting beta2- agonist) -Salbutamol. Source: GINA, 2020.

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