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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Editorial

Climate change, pollution, biodiversity and its influence on asthma, a collective musing!

Mudanças climáticas, poluição, biodiversidade e suas influências na asma, uma reflexão de todos nós!

Celso Taques Saldanha[1]

In recent times, the environment has been one of the most highlighted themes in global discussions, where climate change, global temperature increase, ozone layer destruction, air pollution and respective aggressions to human health are addressed, among other environmental consequences.[1] The environment presents a set of factors that maintain interactive relationships with causal agents and the susceptible individual. In this context, the physical environment, which includes and provides the means of possible anthropic life; the biological environment, which encompasses all living beings; and the social environment, place of social, political, economic and cultural interactions.[1,2]

Geographical position and its climatic peculiarities, soil, water resources, pollutants, physical agents and industrial products are the most known components of the physical environment, with climatic variables such as temperature, relative humidity, rainfall and wind speeds, those that are most closely related to diseases.[3,4] It is also known that biodiversity, a term that designates a variety of animals, plants, habitats and genes, interacts with the physical environment, which originates ecosystems, essential to life. These ecosystems have been suffering threats as a result of deforestation and burning for agricultural activities[5]. Entire ecosystems consequently become more vulnerable; for example, (previously fertile) soils are modified and that leads to climate change (over 56% of local and regional rainfall depends on forests). As such, we are most certainly living in a time of favoring epigenetic diseases.

It should also be highlighted that aggressions to the ecosystem by human activities, especially the burning of our native forest, including the Amazon Forest, the Pantanal of Mato Grosso, the Cerrado, the Atlantic Forest and other Brazilian native forests, generate serious problems, with releases of polluting gases. These pollutants, which are increasingly discharged into our atmosphere, affect local climatology and human health, triggering asthma, inflammatory rhinus-sinusopathies, eye and dermatological diseases, among other illnesses.[6]

Alto Floresta, a city located in the Amazon region of northern Mato Grosso, is recognized among Brazilian municipalities for the highest prevalence of asthma in Latin America among schoolchildren aged between 6 and 7 years old. Research on exposure to gases from forest fires in this region showed a relation of these pollutants with asthma episodes.[7] The occurrence of differences in the epidemiological profile of geographically close communities is known,

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only because of the existence of well-defined climatic characteristics (microclimate). Such consideration is relevant, since it places climatic variables as determinants for the dynamics of diseases, especially those which affect the airways.[4]

Temperature, relative humidity and rainfall stand out among climatic variables, and in humid climates with sudden drops in temperature there has been an increase in the incidence of respiratory infections and greater diffusion of aeroallergens, thus contributing to climate change for the occurrence of numerous asthma attacks[8]. It is also important to describe the correlation between climatic factors and atmospheric pollution, such as air polluted by various gases in climatic regions characterized by high temperatures, typical in an immense part of the Brazilian territory, essentially the emergence of the pollutant ozone, which is known to be harmful to the respiratory epithelium.[9]

Another environmental factor widely raised as responsible for the worsening of human health, especially respiratory, are pesticides, chemicals capable of killing and preventing the proliferation of insects, mites, molluscs, rodents, fungi and other life forms that are harmful to health and to the plantation. Growth regulating substances, synthetic fertilizers, hormones, defoliants and desiccants also fall into the category of pesticides. In research on the effects of organophosphate pesticides on asthmatic children living in certain rural regions in Brazil with intense agricultural activity, the role of organophosphate pesticides as environmental triggers in the worsening of asthma in children was evidenced. There are several mechanisms by which pesticides attack the airways, and the main one is the inhibition of the acetylcholinesterase enzyme caused by organophosphates and carbamates. Chronic exposures can lead to airway hyperresponsiveness by direct interaction with muscarinic receptors, resulting in reflex bronchoconstriction due to pulmonary irritation and mucus secretion by the airways.[10]

As asthma is a chronic airway disease with genetic predisposition and its pathological substrate is bronchial inflammation with increased airway reactivity to a variety of stimuli, environmental factors participate in the complex interaction of these various stimuli, thus influencing in the epidemiological profile of this disease.[11] It should be considered that the breathing of approximately 10 to 20 thousand liters of air per day occurs at varying degrees of temperature and humidity, which must be adequately conditioned for the lower airways with regard to filtration, humidification and heating. With each breathing movement, about hundreds of milliliters of air pass between the atmospheric air and the alveoli.[4]

The respiratory system of children up to the age of 8 years is characterized by a growth in the number of alveoli up to 10 times since birth and an increase in the number of bronchial generations. Therefore, the child population presents an anatomopathological substrate that is conducive to respiratory diseases[12] and which, associated with environmental factors, make this population group the most vulnerable to bronchial hyperresponsiveness and sensitivity to various agents in the environment.[9]

Thus, climatic variables, pollutants, irritants and air allergens affect the health of patients with asthma, intensifying and modulating the development of the disease, in addition to favoring respiratory infections,[12] having great relevance in children and adolescents, admittedly more susceptible.[13] In this environmental context of a country with geographic heterogeneity, added to climate change and aggression to our biodiversity, there is damage to health as a result of atmospheric pollutants from forest fires, among other sources of pollution. An ongoing understanding of these environmental factors that have possible repercussions on asthma should be sought.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Practical Update Guide on the treatment of asthma exacerbation in children and adolescents – Joint position of the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics

Guia Prático de Atualização no tratamento da exacerbação de asma na criança e no adolescente – Posicionamento conjunto da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria

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ABSTRACT

Acute exacerbation of asthma is a frequent condition in children and adolescents and one of the most common causes of seeking emergency care and hospitalization. It can occur in patients who have not yet been diagnosed with asthma, and even in those whose disease control is not adequate. Recognizing the exacerbation and starting its treatment from home until proper initial management in a hospital environment is essential to avoid its evolution to complications that put the patient at risk of life. Treatment comprises the recognition and treatment of hypoxemia, obstruction, and the inflammatory process, in addition to providing guidance at hospital discharge and referrals for continued treatment.

Keywords: Acute asthma, asthma exacerbation, child, adolescent, treatment.

RESUMO

Exacerbação aguda de asma é uma condição frequente na criança e no adolescente e uma das causas mais comuns de procura aos pronto atendimentos e de internações. Pode ocorrer em pacientes que ainda não foram diagnosticados como asmáticos, e mesmo naqueles cujo controle da doença não se encontre adequado. Reconhecer a exacerbação e iniciar seu tratamento desde o domicílio até o adequado manejo inicial em ambiente hospitalar é fundamental para evitar sua evolução para complicações que coloquem o paciente em risco de vida. O tratamento compreende o reconhecimento e tratamento da hipoxemia, da obstrução e do processo inflamatório, além de fornecer orientações na alta hospitalar e encaminhamentos para continuidade do tratamento.

Descritores: Asma aguda, exacerbação da asma, criança, adolescente, tratamento.

Definition of exacerbation

Asthma exacerbation is defined as an acute or subacute worsening of asthma symptoms and lung function. It is characterized by a progressive increase in shortness of breath, coughing, wheezing, or a feeling of tightness in the chest, representing a change in the patient's usual symptoms, sufficient to require

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a change in treatment.[1,2] Exacerbations may occur in patients with a pre-existing diagnosis of asthma, or occasionally as the first presentation of the disease.

The academic term "exacerbation", however, is more used in the scientific and clinical literature, while hospital studies refer more to "severe acute asthma". During care, using the term "exacerbation" is not always appropriate, as it is difficult for many patients to pronounce and remember. The term “asthma exacerbation” is easier to understand and conveys the sense that asthma is present even when symptoms are not persistent. The term “attack” is used by many patients and health professionals, but with widely varying meanings, and may not be perceived as a gradual worsening factor. In pediatric literature, the term “episode” is commonly used, but the understanding of this term by parents/caregivers is also unknown.[1]

In the United States, asthma exacerbations led to 1.7 million emergency room visits and 200,000 hospitalizations in 2016. Emergency asthma exacerbation care costs five times more than office-based care. In this context, the US Government has encouraged asthma care, intending to reduce emergency room visits and hospitalizations, as key health measures.[2]

Asthma exacerbation can be triggered by a viral infection, exposure to external agents (smoke, pollutants, inhaled allergens), medications, physical activity, psychosocial disorders, poor adherence to control treatment, among others.[1,3] However, a subset of patients has exacerbations without exposure to known risk factors. Additionally, severe exacerbations may occur in patients with mild or well-controlled asthma symptoms.

The list of most common factors (“triggers”) that increase a patient's risk of having exacerbations, regardless of their level of symptom control, includes:

– viral respiratory infections;
– exposure to allergens such as grass pollen, bean or soy dust, fungal spores;
– food allergy with systemic manifestations;
– air pollution;[3]
– seasonal changes and/or return to the school environment;
– poor adherence to inhaled corticosteroids.

Severe exacerbations that occur in an epidemic manner have been linked to storms, with high levels of airborne pollen or fungi.[4]

Epidemics of severe asthma exacerbations can occur suddenly and put high pressure on the local health care system. Such epidemics have been reported in association with spring storms with ryegrass pollen[4] or fungal spores, and with environmental exposure to soybean dust.

Treatment goals in asthma exacerbation

The main goals of the treatment of asthma exacerbations are the clinical stabilization of the child, with the suppression or reduction of its symptoms, and the prevention of complications such as hospitalization and death. During the treatment of exacerbations, the following goals should be pursued:[1,5]

– reverting airflow obstruction;
– correct hypoxemia;
– minimize the risk of recurrence of symptoms;
– prevent new exacerbations.

Patients at increased risk of severe exacerbations and even death should be identified and treated early, preferably in emergency departments. These patients include those with:[1]

– history of near-fatal asthma – need for intensive care unit (ICU) treatment, intubation with mechanical ventilation;
– hospitalization or emergency service for asthma exacerbation in the last year;
– excessive use of short-acting beta-2 agonist (SABA), especially with consumption greater than one bottle per month;
– the absence of inhaled corticosteroid use;
– The poor adherence to control treatment and no action plan;
– history of psychiatric illnesses or psychological problems;
– food allergy associated with asthma;
– lack of gravity perception;
– comorbidities such as pneumonia and heart disease.

Classification of exacerbation by severity - scores

It is important during the assessment of asthma exacerbation, to perform a brief history and physical examination while providing initial treatment according to the assessment of the condition, paying attention to the classification of the severity of the asthma exacerbation. This can be done by looking at the intensity of dyspnea, respiratory and heart rates, transcutaneous oxygen saturation (O_2 saturation), and lung function.

The assessment of severity is essential to define the best therapeutic approach, as well as to assess the risk of hospital admission, stay in emergency services, in addition to being useful in monitoring the patient during the treatment of the exacerbation. For this, the use of standardized severity scores contributes to a better follow-up of this process.

The parameters used for this assessment must take into account the age range and cognitive capacity of the child and adolescent. The objective of treating the exacerbation is to maintain O_2 saturation above 94% in room air, the presence of minimal or absent symptoms, and pulmonary function close to normal. The inability to speak sentences, agitation, presence of O_2 saturation below 90% (below 92% in children under 5 years) in room air, and peak expiratory flow (PEF) below 50% of the provided for the patient is considered a severe exacerbation.[1]

Table 1 highlights the aspects that are taken into account to assess the severity of asthma exacerbation in children under 5 years of age.

In more detail, Table 2 presents the parameters for assessing the severity of asthma exacerbation.[6]

Other instruments can be used to assess the severity of the exacerbation, some of which are described below.

Pediatric Asthma Severity Score - PASS [7,8]

Intended for patients under 18 years of age, the PASS is useful for assessing the possibility of hospital admission or prolonged stay in emergencies (Table 3).

Takes into account wheezing, respiratory effort, and prolonged expiration using the sum of all components (0 to 6); the larger the sum, the more intense the exacerbation.

Preschool Respiratory Assessment Measure - PRAM [8,9]

The PRAM was developed through a prospective study of children aged between 3 and 6 years, treated in emergency care and, after logistic regression analysis, included five variables: suprasternal retractions, scalene muscle contraction, air intake, wheezing, and O_2 saturation (Table 4). The sum of all components gives the severity, and the greater, the more intense the exacerbation.

Table 1
Initial assessment of asthma attacks in children under 5 years old.

Symptoms	Mild	Severe[a]
Altered consciousness	No	Restless, confused, or sleepy
O_2 saturation on admissions[b]	> 95%	< 92%
Speak[c]	Sentences	Words
Heart rate	< 100 bpm	> 200 bpm (0 to 3 years) > 180 bpm (4 to 5 years)
Central cyanosis	Absent	Probably present
Intensity of wheezing	Variable	Chest may be silent

[a] Any of these changes indicate severe asthma exacerbation.
[b] Oximetry before administering bronchodilators or installing O_2.
[c] The child's age and normal developmental capacity must be taken into account.
Source: adapted from GINA (2021)[1].

Table 2
Formal assessment of the severity of the asthma crisis in an urgent and emergency setting[6].

Crisis classification	Mild	Moderate	Severe	Imminent respiratory arrest
Symptoms				
Shortness of breath	While walking	At rest (infant – softer and shorter crying, difficulty feeding)	At rest (infant – stop breastfeeding)	
	Can lie down	Prefer sitting position	Sit back	
Difficulty speaking	Sentences	Phrases	Words	
Alert state	May be agitated	Usually agitated [a]	Usually agitated [a]	Sleepy or confused
Signals				
Respiratory frequency	Augmented	Augmented	Always > 30 go/minute	Poor expiratory effort, appears to be exhausted
		Normal RR values in awake children:		
		Age	Normal values	
		< 2 months	< 60/minute	
		2 to 12 months	< 50/minute	
		1 to 5 years	< 40/minute	
		6 to 8 years	< 30/minute	
Use of accessory muscles; suprasternal retraction	Usually absent	Occasionally	Generally	Paradoxical thoracoabdominal movement
Wheezing	Moderate, usually at the end of expiration	High during expiration	Usually high, during ins and exhalations	Absence of wheezing (silent chest)
Pulse/minute	< 100	100 to 120	> 120	Bradycardia
		Normal values for HR in children:		
		Age	Normal values	
		2 to 12 months	< 160/minute	
		1 to 2 years	< 120/minute	
		2 to 8 years	< 110/minute	

[a] Some children with severe acute exacerbation of asthma do not appear to be agitated.

PaO_2 = arterial oxygen pressure, PCO_2 = carbon dioxide partial pressure, PEF = peak expiratory flow, SpO_2 = oxygen saturation, BP = arterial pressure, RR = respiratory rate, HR = heart rate.

Notes:
– The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
– Many of these parameters have not been studied systematically, especially how they correlate with one another. Therefore, they only serve as general guides.
– The emotional impact of asthma symptoms on patients and family members varies, but they must be recognized and addressed and may interfere with treatment and follow-up.

Table 2 *(continuation)*
Formal assessment of the severity of the asthma crisis in an urgent and emergency setting[6].

Crisis classification	Mild	Moderate	Severe	Imminent respiratory arrest
Signals				
Paradoxical pulse	Absent at < 10 mmHg	Can be present 10 to 25 mmHg	Generally present > 25 mmHg (adult) 20 to 40 mmHg (child)	Absence suggests respiratory muscle fatigue
Others				Cyanosis
Functional assessment				
PEF predicted percentage or best personal percentage	≥ 70%	Between 40 to 69% or response to inhaled beta-2 after < 2 hours	< 40%	< 25% Note: PEF may not be needed in severe attacks
PaO_2 (in ambient air)	Normal (usually unnecessary test)	≥ 60 mmHg (usually unnecessary test)	< 60 mmHg: possible cyanosis	
PCO_2	< 42 mmHg (usually unnecessary test)	< 42 mmHg (usually unnecessary test)	≥ 42 mmHg: possible respiratory failure	
SpO_2 % (in ambient air) at sea level	> 95% (usually unnecessary test)	90 to 95% (usually unnecessary test)	< 90%	
		Hypercapnia (hypoventilation) Develops faster in younger children than in adults and adolescents		
PAN		Hypotension		

[a] Some children with severe acute exacerbation of asthma do not appear to be agitated.

PaO_2 = arterial oxygen pressure, PCO_2 = carbon dioxide partial pressure, PEF = peak expiratory flow, SpO_2 = oxygen saturation, BP = arterial pressure, RR = respiratory rate, HR = heart rate.

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Table 3
Pediatric Asthma Severity Score (PASS).

Wheezing		
(expiratory sounds heard on auscultation)	Absent or mild	0
	Moderate	+1
	Intense or absent due to little air movement	+ 2
Respiratory effort		
(use of accessory muscles or retraction)	Normal or diminished	0
	Moderate	+1
	Intense	+ 2
Prolonged expiration		
(expiration/inspiration time ratio)	Normal or slightly prolonged	0
	Moderately prolonged	+1
	Intensely prolonged	+ 2

Severity-based treatment of exacerbation

1. Hypoxia

Children, and especially infants, are at greater risk of respiratory failure during asthma exacerbations and develop hypoxemia more quickly than adults.[10] In children, O_2 saturation below 92% is a predictor of hospitalization, and below 90% signals the need for more aggressive treatment.[1]

Hypoxemia in exacerbations is correlated with the degree of airway obstruction, and consequently with the change in the ventilation-perfusion (V/Q) ratio.[11] At the beginning of treatment with bronchodilators, vasodilation may be greater than bronchodilation, resulting in an imbalance in the V/Q ratio, which may worsen the O_2 saturation by 5% or more in the first 30 minutes after administration of salbutamol.[12,13]

Most exacerbations are mild and do not require the provision of supplemental oxygen. When necessary, the offer must be titrated according to oximetry (if available) to keep it ≥ 94%. The administration of 1 to 3 L/min of O_2 is usually sufficient, and it may be through a nasal catheter or face mask.[11] The use of non-invasive ventilation should be considered in patients with severe exacerbations when initial treatments fail.[14] High-flow nasal cannulas (2-2.5 L/kg/min) have not yet demonstrated efficacy and safety in children with acute asthma exacerbations. Orotracheal intubation should be considered when there is a reduction in the level of consciousness, refractory hypoxemia, and respiratory acidosis, in addition to respiratory depression or bradycardia.[10,16]

2. Bronchospasm

Airflow obstruction resulting from bronchial smooth muscle contraction, whose main clinical expression is wheezing, is considered a central pathophysiological event in asthma exacerbation. The assessment of children with acute wheezing comprises a careful anamnesis covering the different differential diagnoses for each age group and physical examination, capable of determining the site of origin of the symptom (Table 5).[1]

However, clinical estimates of asthma exacerbation severity based solely on the presence of wheezing may result in an inaccurate assessment of the disease. For example, audible wheezing is usually a sign of moderate asthma, while the absence of this symptom can be a sign of severe airflow obstruction.[17]

Thus, in addition to pulmonary auscultation, different clinical symptoms and signs can help pediatricians to determine the severity of acute asthma. Signs of a severe exacerbation include the use of accessory muscles of breathing, chest hyperinflation, tachypnea, tachycardia, diaphoresis,

Table 4
Preschool Respiratory Assessment Measure (PRAM).

Suprasternal retractions	Absent	0
	Present	+ 2
Scalene muscle contraction	Absent	0
	Present	+ 2
Air entrance	Normal	0
	Decreased in the bases	+1
	Diffusely reduced/extended	+ 2
	Absent/minimum	+ 3
Wheezing	Absent	0
	Expiratory only	+1
	Ins and expiratory	+ 2
	Audible without stethoscope/minimal or absent air intake	+ 3
O_2 Saturation	≥ 95%	0
	92 to 94%	+1
	< 92%	+ 2

obnubilation, anxiety, inability to complete sentences, and difficulty lying down. Altered mental status, with or without cyanosis, is a warning sign for immediate emergency care and hospitalization[18] (see Tables 1 to 4).

Serial objective measurements of lung function facilitate quantification of the severity of airflow obstruction and response to treatment. The forced expiratory volume in one second (FEV_1) measured by spirometry is more sensitive and less variable than the PEF rate measurement.[19] However, the latter method provides a quick, simple, and cost-effective assessment of airflow obstruction. The evaluation of PEF before and after administration of a bronchodilator can indicate the degree of improvement in lung function that can be achieved by the instituted therapy. PEF values between 50% to 79% of predicted, or gives the personal best brand, signifying the need for immediate treatment with an inhaled short-acting beta-2 agonist (SABA) agent. Values below 50% indicate the need for immediate medical care, while values below 35% are associated with a possible serious episode with risk of life.[20,21]

When available, data related to the effectiveness of previous treatments are useful for instituting the most appropriate therapy. An exacerbation of allergic asthma is more likely to respond immediately to a SABA and inhaled corticosteroid dose adjustment, whereas a patient with an exacerbation triggered by viral infection is more likely to require systemic corticosteroids. Patients with excessive use of SABA may become refractory to inhaled beta-2 agonists and require systemic corticosteroids.[17]

Main medications used for bronchospasm reversal

Short-acting beta-2 agonists (SABA)

Inhaled SABAs are the first-line drugs for the treatment of acute asthma exacerbations in children.[1]

When administered by inhalation, these bronchodilator agents improve clinical scores, decrease respiratory rate, improve lung function and O_2 saturation, and present adverse effects comparable to those treated with placebo.[22]

Salbutamol, a selective SABA available free of charge by the Ministry of Health of Brazil, can be used in children of all ages. It is usually administered at a dose ranging from 2 to 10 jets (each jet contains 100 µg) every 20 minutes within the first hour of treatment.[23,24] According to the weight, the following can be administered: 5 to 10 kg - 4 jets; 10 to 20 kg - 6 jets; and >20 kg - 8 jets.

In a meta-analysis of 39 studies that included 1,897 children and 729 adults, the use of spacer-coupled metered-dose inhalers (MDI+ESP) was the preferred option for the administration of beta-2 agonists in children with mild and moderate asthma exacerbations. Treatment with a nebulizer may be preferred in patients who are unable to cooperate, using an MDI due to acute asthma severity or agitation.[25]

Ipratropium bromide

Ipratropium bromide (IB) is a quaternary derivative of atropine sulfate available as a nebulizer solution. It acts by competitively inhibiting acetylcholine at the muscarinic cholinergic receptor, thus relaxing smooth muscle in the large central airways.[26] A meta-analysis including four trials with 173 children concluded that it is not suitable for use as a single agent in children with asthma exacerbations, but combination therapy with SABA in more severe asthma exacerbations in children reduced the risk of hospital admission by up to 25%.[27,28]

The recommended nebulizer dose is 125-250 µg/dose (in children under 4 years of age, which corresponds to 10-20 drops) to 250-500 µg/dose (in children 4 years and older, which corresponds 20-40

Table 5
Differential diagnosis of wheezing and asthma in childhood.

Congenital diseases	Infectious diseases
Cystic fibrosis	Epiglottitis/tracheitis
Primary ciliary dyskinesia	Bronchiolitis
Immunodeficiency prhyme	Diphtheria/Pertussis
Diaphragmatic hernia	Bronchiectasis
	Abscess retropharyngeal
	Löffler's syndrome
Upper airway disorders	**Compressive syndromes**
Foreign body	Tuberculosis
Laryngotracheomalacia	Lymphadenopathy
Dysfunction of vocal chords	Vascular ring
	Pastas mediastinal
	Aspiration syndromes
Lower airway disorders	**Others**
Emphysema lobar	Gastroesophageal reflux
Bronchomalacia	
Foreign body	

Source: adapted from GINA (2021)[1].

drops) in combination with salbutamol. It should be administered up to three times every 20 minutes, for the first hour, then its dose should be reduced in 4 to 6 hours or discontinued[23] (each drop contains 0.0125 mg or 12.5 µg).

Magnesium sulfate

Magnesium sulfate ($MgSO_4$) is a bronchodilator that can be administered by nebulization or intravenously. It acts by direct relaxation of the bronchial muscles, but it has a slight additional anti-inflammatory property related to blocking the influx of calcium ions into muscle cells, thus modulating the release of histamine from mast cells and cholinergic neural transmission.[29] Its intravenous use is not routinely recommended for asthma exacerbations and may be indicated for severe exacerbations that have not responded to initial treatment in children older than 2 years of age. A recent meta-analysis showed that its intravenous administration seems to reduce the time and risk of hospitalization for asthma, and it can be considered in patients with severe, life-threatening exacerbations,

The use of inhaled isotonic magnesium sulfate at a dose of 150 mg in three doses in the first hour in children aged 2 years or older in severe exacerbations remains an option in GINA 2021, on the other hand, to date, there is no evidence of any substantial benefit of $MgSO_4$ nebulized in acute asthma.[1,30]

3. Inflammation

Systemic corticosteroids

Corticosteroids have been used to treat asthma for over 50 years, and their significant benefits are documented by several studies.[31,32] In a Cochrane review, short courses of steroids contributed to improved symptom scores, lower relapse rates, fewer hospitalizations, and less need to use beta-2 agonists.[28,32] In addition to bronchodilators, systemic corticosteroids are essential for successful therapy in asthma exacerbations, as it reduces inflammation and mucus production, as well as increasing the effectiveness of bronchodilators.[33] Although corticosteroids are routinely administered by inhalation for asthma control, during a severe exacerbation, systemic corticosteroids are preferred.[34] Regarding the mode of administration, the intravenous or intramuscular routes do not offer significant advantages over the oral route, which is preferred if the patient is able to tolerate the ingestion of oral medication and there is no concern about abnormal intestinal absorption.[35] Oral administration is as effective as intravenous, being faster, less invasive, and less costly.[1] In children, the oral solution should be preferred. The intravenous route can be used in patients with difficulty in swallowing, vomiting, or when orotracheal intubation or non-invasive ventilation is necessary.[1]

Current guidelines recommend early administration of systemic corticosteroids, preferably within the first hour of treatment[1,36], as an effective measure to control exacerbation and prevent relapse for all moderate to severe exacerbations in adults, adolescents, and children aged 6 to 11 years of age.[1] Its indication is particularly important in cases where there was no clinical improvement with the use of bronchodilators, when the exacerbation was accentuated, or when the patient has a history of exacerbations requiring the use of corticosteroids for resolution. These drugs need about 4 hours to impact clinical improvement.[1] The recommended dose is 1-2 mg/kg of prednisone or equivalent in a single dose in the morning, maximum 40 mg/day, for 3 to 5 days. Oral dexamethasone 0,6 mg/kg for 1 or 2 days has similar benefits, with a lower risk of oral intolerance, and should not be used any longer due to its metabolic effects. For still symptomatic cases, consider switching to prednisolone.[1,33] Potential side effects are a concern with the use of oral corticosteroids. However, short courses of prednisone 1-2 mg/kg per day for 5 days have been shown to not affect bone mineral density, height, and adrenal function 30 days after therapy.[37]

Inhaled corticosteroids

The use of inhaled corticosteroids (ICS) in high doses reduces hospital admissions in patients with acute asthma who are not treated with oral or intravenous corticosteroids.[38] That was the conclusion of a study that analyzed the benefit of ICS for emergency-treated asthma in 32 randomized controlled trials (RCTs: 21 RCTs evaluated 1,403 children aged 6 months to 18 years; 13 RCTs compared ICS versus placebo, and eight RCTs compared ICS versus systemic corticosteroids). The dose and frequency of use of ICS varied widely; however, in all cases, ICS was administered early in the exacerbation treatment course, usually at the time of the first bronchodilator treatment, and by nebulizer or MDI with spacer. There was a significant reduction in hospital admissions

(primary outcome) for children (n = 583) treated with ICS when compared to those treated with placebo (OR = 0.52, 95%CI: 0.33-0.80; p = 0.003; I^2 = 59%). No grouped data is available for secondary outcomes (eg, pulmonary function or clinical score) based exclusively on pediatric patients.[22] In conclusion, its use in combination with systemic corticosteroids in the emergency room seems to reduce the number of hospitalizations in children (evidence B). However, its cost can be a limiting factor and its use is still not consensual, especially regarding the choice of drug, dose, and treatment time, the latest evidence being conflicting.[1] For children aged 12 years and over, it is recommended to start ICS before discharge, if the patient has not previously used any ICS. Those who already use ICS should have their treatment intensified (up to 4 times the basal dose) for 2 to 4 weeks, and should be reminded about the importance of daily use, and the isolated use of bronchodilators is no longer indicated.[1]

Figures 1 and 2 show a suggested flowchart for managing exacerbation in children younger than 6 years and aged 6 years or more.

4. Other therapeutic alternatives

Second-line therapy for the treatment of asthma exacerbation in children/adolescents

Most children have mild or moderate asthma exacerbations and respond well to first-line therapy. Only a minority will have severe exacerbation that is unresponsive to conventional measures, requiring therapy escalation and the use of second-line medications.

There is great variability in the criteria that define second-line drugs, and the choice may vary depending on the clinical picture, the child's age, but especially regarding product availability and service experience.

Didactically we can group the second-line treatments in:[28]

– *additional inhaled bronchodilator treatment:* continuous inhaled beta-2 agonists, inhaled anticholinergics such as ipratropium bromide and nebulized magnesium sulfate;
– *parenteral bronchodilator treatment:* selective beta-2 agonists such as salbutamol and terbutaline; adrenaline (α and β receptor agonist), intravenous magnesium sulfate; methylxanthines such as theophylline and aminophylline and ketamine;
– *other treatments:* heliox, antibiotics, inhalational anesthetics, and ventilatory support.

Many of these drugs have already been discussed above, and the others will be detailed below.

Magnesium sulfate ($MgSO_4$)

First described as an adjunct to the treatment of severe asthma exacerbations in 1994, the mechanism by which the $MgSO_4$ causes bronchial smooth muscle relaxation and consequent bronchodilation is still not fully understood.[39] It is believed to act by increasing calcium uptake in the endoplasmic reticulum and/or blocking the influx of calcium ions into smooth muscle cells, acting as an antagonist.

In addition, it acts as a cofactor of adenyl cyclase and sodium-potassium ATPase, potentiating the effects of beta-2 agonist drugs.[39-41] Secondary mechanisms include inhibition of acetylcholine release by cholinergic nerves and reduction of histamine release by mast cells.[42] $MgSO_4$ has already been described for inhaled and parenteral use in children older than 2 years, and intravenous use, in a single administration, in 20 minutes, at doses ranging from 25 to 75 mg/kg/dose (maximum dose 2-2.5 g/dose) or in prolonged infusions for 4 hours, with higher doses 200 mg/kg/4 hours, presents more robust evidence than inhaled use.[40,41] Studies conclude that intravenous $MgSO_4$ reduces the chances of hospital admissions, is cost-effective, and, even in emergency care, is not associated with significant side effects or damage[40]. When pulmonary function parameters were evaluated, there was a significant improvement in FEV_1 and the FEV_1/FVC ratio in children with mild and moderate asthma, treated with intravenous MgSO4, with no adverse effects recorded.[39] Evidence suggests that the simultaneous administration of magnesium sulfate and a beta-2 agonist agent potentiates the bronchodilator effect by increasing the beta-receptor response.[30,41]

Inhaled beta-2 agonist in continuous use

For patients with severe exacerbations and who do not respond to the intermittent administration of inhaled short-acting beta-2 agonist, administration in continuous inhalation can be chosen, in this case using a nebulizer, in order to saturate all beta-2 receptors respiratory tract and reach maximum bronchodilation.[42] A meta-analysis that evaluated two

Figure 1
Asthma exacerbation management flowchart in children under 6 years old.

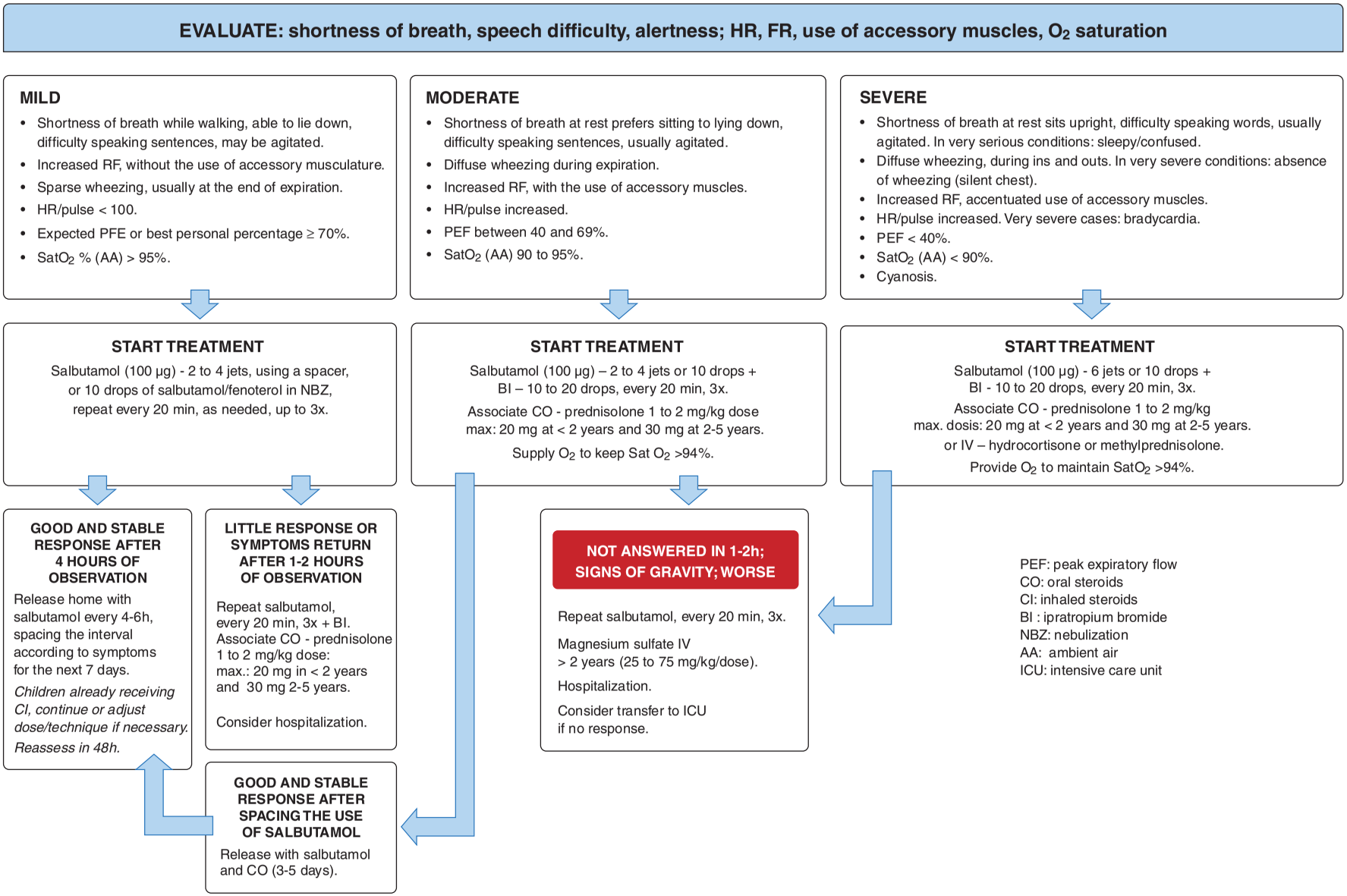
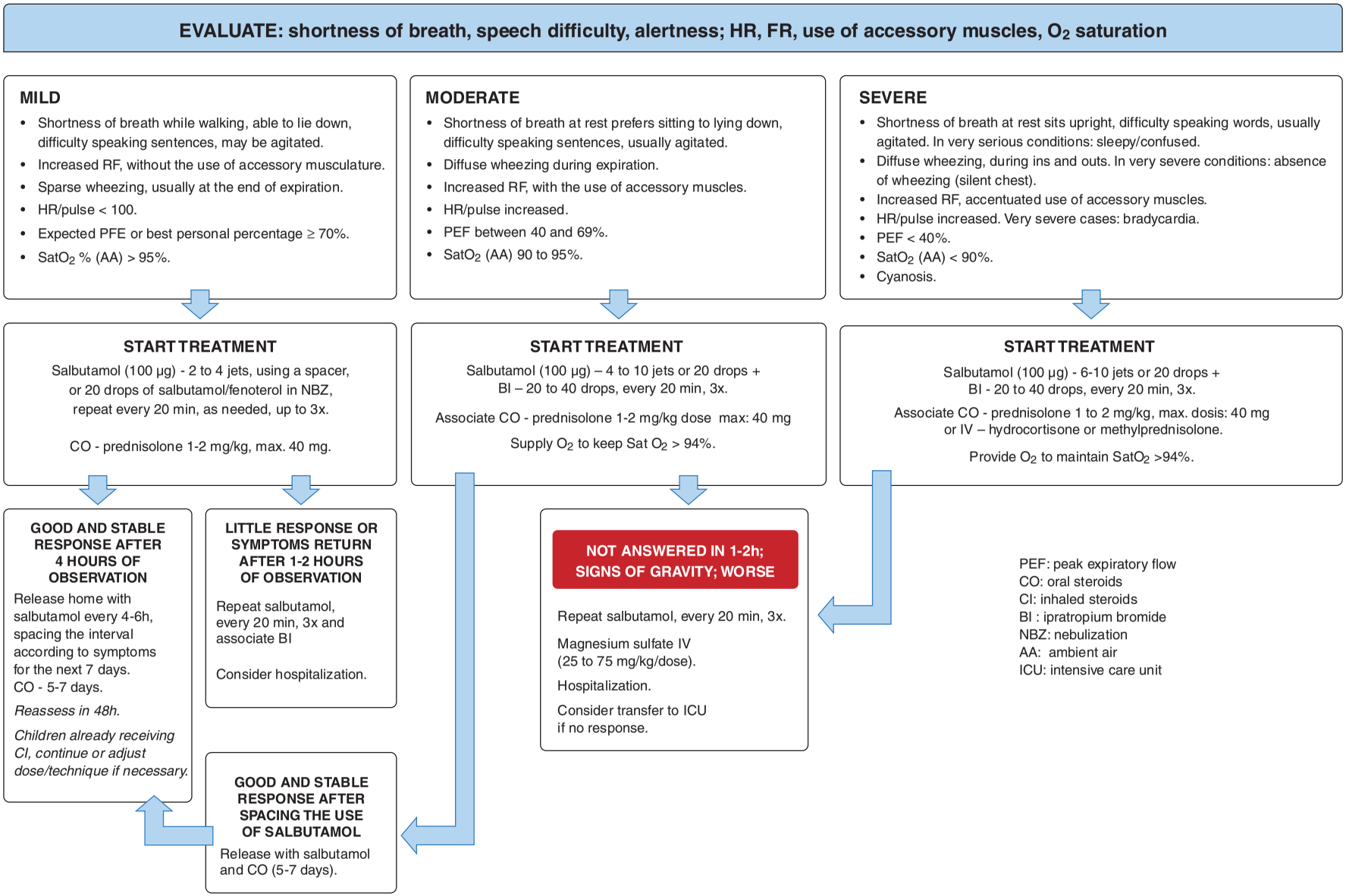


Figure 2
Asthma exacerbation management flowchart in children aged 6 years and over.



reviews showed weak evidence and no superiority of continuous use compared to intermittent (every 15/20 minutes). There was no difference in the length of stay in the emergency room and the number of hospitalizations in children, unlike what was observed in studies in adults, in which continuous nebulization was superior, especially in patients with more severe obstruction. No significant differences were observed in the side effects of the two forms of administration of bronchodilators.[43] Another fact observed was among children and adolescents hospitalized with severe asthma and submitted to continuous nebulizations with albuterol stored in bottles with benzalkonium chloride (preservative). For these patients, the duration of continuous nebulization was longer compared to those who received nebulization without the preservative (9 vs. 6 hours; RR: 1.79; 95%CI: 1.45-2.22; p < 0.001). Thus, it was concluded that benzalkonium chloride acts as a functional antagonist of salbutamol and that presentations without this product are safer for use in continuous nebulization.[44] Another fact observed was among children and adolescents hospitalized with severe asthma and submitted to continuous nebulizations with albuterol stored in bottles with benzalkonium chloride (preservative). For these patients, the duration of continuous nebulization was longer compared to those who received nebulization without the preservative (9 vs. 6 hours; RR: 1.79; 95%CI: 1.45-2.22; p < 0.001). Thus, it was concluded that benzalkonium chloride acts as a functional antagonist of salbutamol and that presentations without this product are safer for use in continuous nebulization.[44]

Intravenous beta-2 agonist

The classic idea of using intravenous beta-2 agonists in addition to or replacing inhaled beta-2 agonists stems from the concept that during a severe exacerbation, severe bronchial constriction can prevent the delivery of the inhaled drug to the distal airways.[45] On the other hand, when used systemically, they also have more adverse effects related to the interaction with beta-1 receptors outside the airways, especially tachycardia and agitation. Since the 1990s, an attempt has been made to prove the efficacy of intravenous albuterol in children with severe asthma that would refuse conventional therapy.[45] A study that compared it to placebo showed weaning from inhaled therapy and early discharge from the emergency department.

A comparative study of intravenous terbutaline with saline solution + nebulized albuterol showed a significant improvement in clinical scores, but four individuals had cardiac toxicity to terbutaline, one case of cardiac arrhythmia, and three with high levels of troponin.[46] Cochrane reviews in 2001 and 2012, including children and adults, found no significant benefit from adding intravenous beta-2 agonists to inhaled beta-2 agonists.[45,47] The route of choice for administering beta-2 agonists remains inhaled. If it is impossible to use this route, intravenous therapy must be considered, and if there is a combination of therapies, the monitoring of adverse effects must be rigorous.[45-47]

Adrenaline (epinephrine)

It is a drug with potent beta-adrenergic action and a bronchodilator effect similar to that of beta-2 agonists, but less selective. Historically, parenteral epinephrine was considered the standard therapy for asthma exacerbations in the 1970s and 1980s, but with similar clinical efficacy and the ease of use of inhaled bronchodilators proven, epinephrine was reserved as an option for critically ill patients who do not respond to first-rate inhaled therapy line.[28,48]

Methylxanthines – theophylline, and aminophylline

The bronchodilator effect of these drugs is due to the inhibition of phosphodiesterase, which leads to an accumulation of cyclic adenosine monophosphate (cAMP) in smooth muscle cells, adenosine antagonism, and catecholamine release. With proof of effectiveness and safety of beta-2 agonists of short action, the absence of additional clinical benefit of methylxanthines and, especially, the risk of side effects given the small therapeutic safety margin in the last two decades, discouraged the use of these drugs in acute exacerbations of asthma in children and adults.[28]

A systematic review from the early 2000s evaluated seven studies (380 hospitalized children with severe asthma exacerbation) and concluded that the use of aminophylline resulted in an improvement in lung function, but without a corresponding clinical improvement. In addition, there was no reduction in hospitalization time and the need for inhaled medication, with more episodes of vomiting in the groups that received aminophylline.[49]

When compared to intravenous salbutamol, in the exacerbation of severe asthma in children, a trend towards longer O_2 use (17.8 hours vs. 7.0 hours) was observed, as well as a significant increase in the length of hospital stay in the salbutamol group (85.4 hours vs. 57.3 hours), although no differences were found in the clinical score with 2 hours of treatment.[50]

It is worth remembering that aminophylline has a narrow safety margin and can cause the side effects already described. Studies have shown the occurrence of nausea, vomiting, headache, abdominal pain, and palpitations.[49,50] When considering the adverse and therapeutic effects of methylxanthines, compared to other safer classes, it is understood why methylxanthines are in the group of not recommended in most international guidelines. Currently, its use is only justified in the ICU environment, where the ability to closely monitor serum levels could mitigate the potential adverse effects of this drug.[47]

Ketamine

A drug widely used in ICU. It is a dissociative anesthetic also used for its sedative and analgesic properties.[51] The effect of inducing bronchodilation is due to sympathomimetic action or as a direct effect on bronchial smooth muscle. Other suggested effects include immunomodulation and anticholinergic action. Increased bronchial secretion and delirium are common adverse effects with prolonged use of ketamine.[28,51] For patients on mechanical ventilation, administration of ketamine was associated with an increase in dynamic compliance and a reduction in peak inspiratory pressure and $PaCO_2$[52]. There are few studies with favorable results for the use of ketamine in asthma exacerbation, and others already show little difference in the improvement of the clinical score and evolution, which places it as a drug with weak evidence compared to other adjuvant therapies. There is rational for use of ketamine in association with bronchodilators in intubated patients with respiratory failure, promoting sedation and analgesia.[28,51,52]

Heliox

It is the helium-oxygen mixture, where nitrogen (which represents approximately 79% of atmospheric air molecules) is replaced by helium. Since helium is a gas seven times lighter than nitrogen, the resulting gas is less dense and, therefore, better managed in situations of turbulent respiratory flows (as in the case of asthma), favoring a more adequate supply of oxygen. When laminar flow is achieved (when wheezing has subsided) the maximum benefit is achieved. Some studies indicate that the usefulness of heliox decreases when the need for FIO_2 falls below 0.5.[53] Heliox poses few risks, however, monitoring of the supply is recommended, as flowmeters may not accurately match the gas supply, and prolonged use of heliox may prevent turbulent flow during coughing, making pulmonary clearance difficult. Despite the relevant physical characteristic, clinical studies are controversial as to the real benefit of heliox in severe asthma exacerbation, with a tendency to show little clinical improvement and dyspnea scores, and no increase in pulmonary function values, despite gas administration have avoided intubation in a small number of patients.[53,54] The use of heliox-guided bronchodilators has been studied in children and adults with asthma,[55] and a systematic review reported increased expiratory flows and reduced hospital admissions, shorter hospital stays, and greater benefit in more severe individuals.[55,56] The use of heliox can be considered in patients who have not responded to conventional therapy, as the cost is low and the adverse event is negligible. The treatment should be discontinued if there is no clinical response.[53-56]

Non-invasive ventilatory support

Noninvasive ventilatory support (NIV) and high-flow nasal cannula (CNAF) have been increasingly used in cases of respiratory failure, including severe acute asthma. Positive pressure reduces the work of breathing by assisting the respiratory muscles and improving oxygenation by increasing mean airway pressure. With this, there is an increase in gas exchange. The use of NIV in children and adults with asthmatic status was associated with a reduction in $PaCO_2$ and respiratory rate and an increase in pH and PaO_2.[57,58] CNAF, given the characteristic of offering heated and humidified gas through a nasal cannula, in a flow that exceeds the patient's inspiratory demand and a low level of positive pressure, is usually better tolerated, especially by pediatric patients.

The use of CNAF in children with asthma exacerbation goes beyond what is observed in adult obstructive pulmonary diseases and suggests a good safety profile, but studies that prove its effectiveness

in pediatric asthma are scarce.[60] A recent study evaluated children older than 2 years of age with severe exacerbation, treated at an emergency room. The institution of CNAF did not show clinical benefits or reduction in length of stay when compared to the group treated with conventional oxygen therapy.[60]

The positive effects of CPAP (Continuous Positive Airway Pressure) and BiPAP (BI-level Positive Airway Pressure – Positive airway pressure at two levels) in children with asthma include a direct bronchodilator effect, improved alveolar recruitment, increased airflow, re-expansion of areas of collapse, hyperinflation, and reduced work of breathing.[57] Overall, scientific data suggest that NIV is safe for children with severe exacerbation and contributes to an improvement in the breathing pattern. Studies in the pediatric population, especially using the CNAF, are needed.

Antibiotics

Even given the fact that asthma exacerbations, especially in children, are mainly triggered by environmental triggers or viral infections and less commonly by bacterial infections, we often observe the prescription of antibiotics to treat the exacerbation. A Cochrane review in 2001, with randomized controlled trials, showed no clinical benefit from the addition of antibiotics during acute asthma exacerbations in children or adults.[61]

The studies that evaluated the use of macrolides in asthma are mainly in adults and are aimed at the chronic management of asthma. In a systematic review, the chronic use of macrolides was shown to have some benefit on lung function, but it was not superior to placebo in preventing hospital admissions or improving quality of life measures.[62] There are no data to support the use of macrolides in asthma exacerbations.

Inhalation anesthetics

Inhaled anesthetics such as isoflurane, halothane, and sevoflurane are powerful smooth muscle relaxants and may help relieve bronchoconstriction.[63] Isoflurane and sevoflurane are most commonly used, as halothane can cause hepatotoxicity.[63] Other adverse effects described are decreased systemic vascular resistance, leading to hypotension and malignant hyperthermia. Successful applications of inhalational anesthetics in children and young adults with refractory asthma have already been described, with a reduction in $PaCO_2$ and an increase in pH after a few hours of administration.[64] Due to the high cost of this therapy and the potential for adverse effects, inhaled anesthetics can be a choice for severe asthmatics admitted to the ICU, bearing in mind that the administration of these drugs requires specialized equipment, many of them only available in surgical rooms.[63,64]

Exacerbation monitoring

As with the initial assessment, continuous monitoring of respiratory rate, heart rate, O_2 saturation, degree of alertness, use of accessory musculature, and intercostal retractions is crucial for treatment decisions. The frequency of monitoring varies depending on disease severity and response to initial therapy, but for most patients, it is typically every 20 to 30 minutes for the first hour of treatment in all patients. It is important not to use each parameter alone.[2]

O_2 saturation with pulse oximeter should be monitored frequently (value < 92% in room air indicates severe exacerbation), especially in children ≤ 5 years. Saturation levels < 90% in adults and children indicate the need for aggressive treatment for the exacerbation.[1] Hemoglobin saturation (SpO_2 < 92%), especially after the use of bronchodilators, allows the identification of the most severe patients who should receive hospital treatment.[65] Pulse oximetry has its limitations due to movement artifacts, reading difficulties with low perfusion and should not be used in isolation as an indicator of hospital admission.[66]

For older children and adults, guidelines recommend PEF measurements (percent of predicted or best PEF) and/or FEV_1 measurements. This assessment should be performed, whenever possible, before treatment, as it is difficult to be performed in younger children and patients with severe exacerbation. Values below 40% of predicted indicate severe exacerbation.[2] According to GINA 2021, the cut-off value for a severe exacerbation is ≤ 50% of predicted or personal best value.[1] After starting treatment, sequential assessment of PEF and FEV_1 values can be used as criteria to indicate the release of the patient. Pulmonary function values (PEF, FEV_1) of 60% to 80% of predicted or the best personal value, associated with improvement in symptoms, are criteria for releasing the patient for treatment at home.[65]

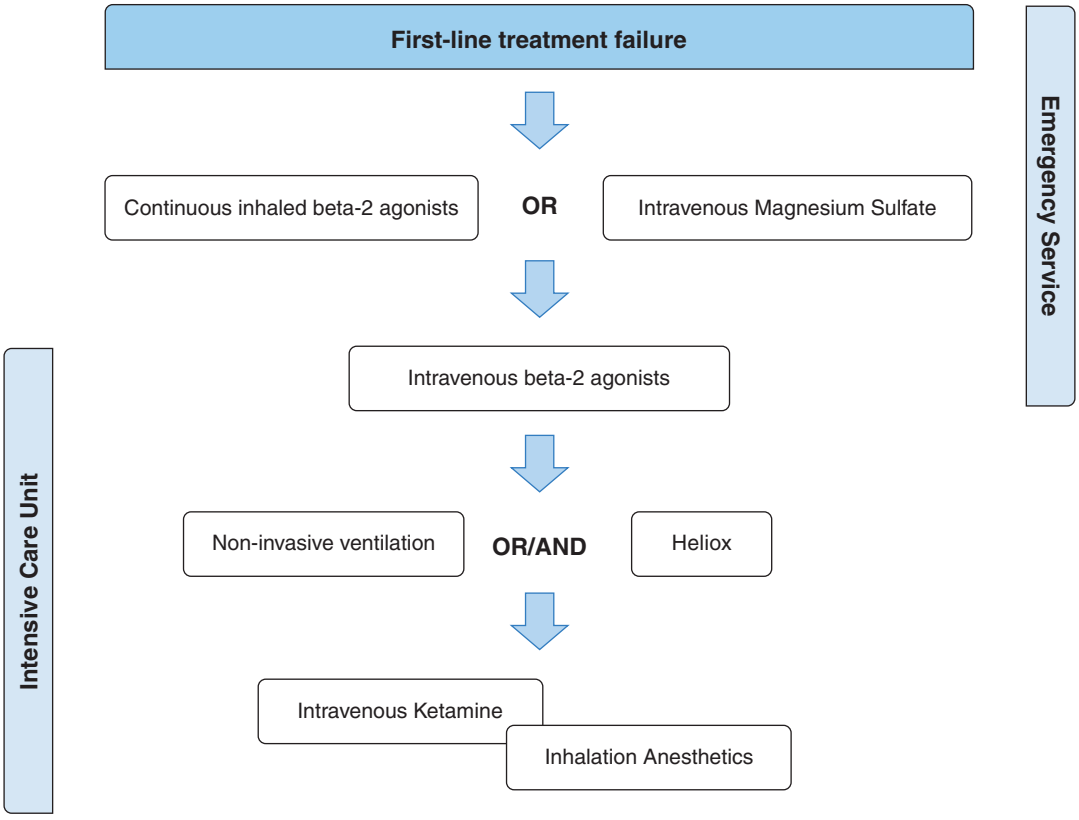


Figure 3
Suggested flowchart for asthma exacerbation management in children under 6 years old. Adapted from Rheder KJ[47].

Arterial blood gases, in general, are not routinely used and should be considered for patients with PEF or FEV_1 below 50% of predicted and/or greater personal value, or for patients who do not have a good evolution with the initial treatment,[1] or in patients with O_2 saturation below 92%. Normal or increased $PaCO_2$ levels are indicative of worsening asthma severity.[65]

Chest radiography should not be performed routinely as it rarely indicates a change in treatment. It is indicated when the patient does not respond well to treatment or when there are signs suggestive of complications, for example, pneumothorax or clinical findings of consolidation.[1,65,67]

Other laboratory tests, as well as imaging tests, are rarely useful for the treatment and are not recommended for routine assessment.[2]

Hospitalization or Intensive Care Unit – Indications

The patients who arrive at the emergency room with an acute exacerbation of asthma classified as

mild or moderate and with worsening or failure to respond to bronchodilators and corticosteroids, after two hours of initial care, will require hospitalization. Patients who arrive with an exacerbation classified as severe should be admitted to a pediatric intensive care unit (PICU).[68]

Absolute admission criteria include:[69]

– clinical deterioration observed by worsening dyspnea and/or increased respiratory effort;
– respiratory fatigue with reduced respiratory rate, reduced sternal retraction, and thoracoabdominal asynchrony;
– severe hypoventilation ("silent chest" on auscultation or the patient's inability to speak);
– need for supplemental O_2 due to low O_2 saturation on pulse oximetry for one hour or more after starting initial therapy;
– previous history of near-fatal asthma, requiring admission to the PICU, with intubation and mechanical ventilation.

Relative admission criteria include:[69]

– previous history of acute exacerbation with rapid worsening and hospitalization;
– inadequate adherence to outpatient control treatment, with frequent use of bronchodilators, especially of short duration;
– patient is in a condition of social vulnerability, and the caregiver's inability to provide necessary assistance to the patient.

The absolute criteria for admission to the PICU include:[70]

– inability to speak, confusion or drowsiness;
– hypoxemia despite O_2 additional;
– moderate to severe hypercapnia.

Intubation Indications

Absolute indications for tracheal intubation include:[71,72]

– greater severe and persistent respiratory effort, with altered mental status;
– hypoxemia (pO_2 < 60 mmHg) in the presence of high concentrations of O_2 (100%) or non-invasive positive pressure ventilation (NIV);
– progressive hypercapnia causing significant respiratory acidosis or altered mental status;
– cardiorespiratory arrest.

Treatment of asthma exacerbation outside the hospital setting

The identification of symptoms or other factors that are precursors to asthma exacerbation is essential for early treatment and prevention. The combination of increased coughing during the day, wheezing and use of beta-2 agonist at night has been shown to be a strong predictor of impending asthma exacerbation, predicting approximately 70% of exacerbations, with a low false-positive value (14%). In contrast, no individual symptom was a predictor of impending asthma exacerbation.[73]

Initial asthma exacerbation management includes an action plan that allows family members and caregivers to notice asthma worsening, initiate treatment, recognize severe exacerbations, identify when urgent care is needed, and follow recommendations for follow-up. The action plan must contain specific information about the medications, including doses and method of use.[1]

Parents and/or caregivers of children with asthma should be advised to seek medical attention immediately if:

– the child is acutely dyspneic;
– symptoms are not immediately relieved by inhaled bronchodilator;
– the period of relief after short-acting beta-2 agonist (SABA) use becomes progressively shorter;
– a child under one year of age needs SABA repeatedly.[1]

Treatment of asthma exacerbation should be started with the use of SABA (salbutamol doses ranging from 2 to 10 jets/dose or equivalent, depending on the age of the child and/or adolescent), one jet at a time, with a spacer with or without a mask. This can be repeated twice, at 20-minute intervals if necessary. The child must be watched. If there is an improvement, keep it at rest for an hour. If there is no improvement, or if more than 6 jets of SABA are needed to relieve symptoms in the first two hours, urgent medical attention should be sought.[1]

There is no evidence to support family/caregiver-initiated oral corticosteroid (OC) treatment in the home management of asthma exacerbation.[74,75] Preventive episodic treatment with high-dose nebulized inhaled corticosteroids may reduce exacerbations in children with virus-induced intermittent wheezing. However, due to side effects, especially if used inadvertently and inappropriately, this strategy should only be adopted if the physician is confident that the use will be appropriate and that the child will be monitored for adverse events.[76]

In children aged 2 to 5 years with virus-induced intermittent wheezing, a randomized controlled trial showed that a short course of leukotriene receptor antagonist (LTRA) implemented at the beginning of the exacerbation reduced symptoms, utilization of health resources, and work absenteeism of caregivers.[77] Parents should be counseled about the risk of adverse sleep and behavioral events with the use of montelukast.[78]

Asthma self-management education should include a written action plan and regular review by a health care provider of asthma control and proper use of medications. This dramatically reduces asthma morbidity in adults and children.[1] In all consultations, the technique of using inhalation devices must be re-evaluated, trained, and corrected. In young children, the focus of asthma education is on parents/caregivers, but simple measures can be taught. Asthma education is also effective when carried out by professionals from the patient's community, using understandable language and appropriate approaches.[79]

Guidance regarding the importance of long-term asthma control, side effects of repeated use of oral corticosteroids, and proper technique for the use of inhaled devices should be provided whenever possible, as they improve long-term outcomes in patients with severe asthma.[80]

Examples of action plans for children under 6 years of age or above are shown in Figures 4 and 5.

Orientation for hospital discharge

Children who experience an asthma exacerbation are at risk for future exacerbations. Studies show that caregivers have difficulty managing the instructions received at the time of hospital discharge, making medication dosage errors, in addition to poor adherence to therapy and failure to maintain an adequate outpatient follow-up.[81] Thus, we need commitment and clear strategies to modify these difficulties, taking advantage of hospitalization and guidelines given at hospital discharge to generate more impact on disease control and avoid readmissions due to exacerbations.[82]

This involves not only providing medication prescriptions but asthma education guidelines, reinforcing the importance of regular follow-up.[82,83]

Before hospital discharge, the child must be stable, that is, he has to stay out of bed without the need for supplemental O_2, with the ability to feed and ingest fluids without difficulty.

Discharge guidelines, according to GINA[1] recommendations, are described below.

Medications

1. **Short-acting bronchodilator** – should be used as needed, based on symptoms, but this daily medication requirement should be noted to assess whether the use is decreasing over the days to pre-exacerbation levels.
2. **Oral corticosteroid (CO)** – complete the treatment time, which should be 3 to 5 days in children, and 5 to 7 days in adolescents (dose of 1-2 mg/kg of prednisolone, maximum 40 mg/day).
3. **Inhaled corticosteroid (IC)** – start IC before discharge, if not previously prescribed (low dose twice a day for the first month after discharge, subsequently adjusted with the treating physician as necessary) (see Table 6). Patients who were already receiving the medication should have their treatment intensified for two to four weeks, reinforcing the importance of daily use of medication.

Education

1. **Identify risk and trigger factors that contribute to exacerbation**

   It is important to identify, before discharge, the risk factors that may have contributed to the exacerbation and establish strategies to modify them. Exacerbations severe enough to lead to hospitalization may result from exposure to allergens and irritants, respiratory viral infections, inadequate maintenance treatment, compliance

issues, and/or lack of a written asthma action plan.

2. Guide inhalation technique and action plan

Review inhalation technique and correct any errors.

Review PEF technique, if used.

Provide a written action plan or review the existing action plan (Figures 4 and 5). Patients with a plan of action and who monitor disease control using measures of PEF have better treatment outcomes after discharge.

Action plan – under 6 years old

WELL-CONTROLLED PATIENT

Breathing well
No coughing or wheezing
Sleep well at night
You can play, run

Keep medication daily

MILD SYMPTOMS

Cough or mild/moderate wheezing
Tiredness of efforts
Awakening at night by coughing
Attention!

Assess whether symptoms improve with salbutamol. If yes:

ATTITUDE:

Rescue medication: _____

Inhale _____ jets, if symptoms.

Maintain or start inhaled corticosteroids: _____

Inhale _____ jets twice a day.

Look for a health unit to make an appointment for a review, if there is no improvement within 24 hours.

MORE INTENSE SYMPTOMS

Cough/moderate/severe wheezing
Very fast breathing
Sleep interrupted by coughing
Relief medication every 2 or 3 hours
Can't speak a whole sentence
Showed cyanosis (turned purple)
Danger!

ATTITUDE:

Inhale_____ jets of salbutamol every 20/30 minutes and look for a **emergency room immediately**.

Nearest Emergency Service: _____

Mobile Emergency Service: _____

Figure 4
Suggested Action Plan for children under 6 years old.

Referrals

Ideally, schedule a return visit with the treating physician within 1 to 2 days (2 to 7 days for adolescents) and another 1 to 2 months after discharge, depending on the clinic, the practicality of scheduling, and social context. This is essential for the treatment to be continued, and for the symptoms to be well controlled.

Action plan for children aged 6 and over

WELL-CONTROLLED PATIENT

Breathing well
No coughing or wheezing
Sleep well at night
You can play, run

Keep medication daily

MILD SYMPTOMS

Cough or mild/moderate wheezing
Tiredness of efforts
Awakening at night by coughing
Attention!

ATTITUDE:

Start rescue medication: _____

Inhale _____ jets if symptoms.

Maintain or start inhaled corticosteroids: _____

Inhale _____ jets, twice a day

If it doesn't improve in 2-3 days:

Start oral steroids: _____ , in the morning, 3-5 days.

Search the health facility to make an appointment for a review.

MORE INTENSE SYMPTOMS

Cough/moderate/severe wheezing
Very fast breathing
Sleep interrupted by cough
Relief medication every 2 to 3 hours
Can't speak a whole sentence
Danger!

ATTITUDE:

Inhale _____ jets from _____ every 20/30 minutes.

Start oral corticosteroids: _____

and look for **emergency room immediately**.

Nearest Emergency Service: _____

Mobile Emergency Service: _____

Figure 5
Suggested Action Plan for children aged 6 and over.

Table 6
Low, medium, and high doses of inhaled corticosteroids, according to age group.

Inhaled corticosteroids for children under 6 years old - low dose	
Beclomethasone dipropionate	100
Budesonide	200
Nebulized budesonide	500
Mometasone	100
Fluticasone propionate	50

Inhaled corticosteroids for children aged 6 - 11 years			
Inhaled corticosteroid	**Low dose**	**Medium**	**High**
Beclomethasone dipropionate	100-200 (50-100)[a]	> 200-400 (> 100-200)[a]	> 400 (> 200)[a]
Budesonide (DPI)	100-200	> 200-400	> 400
Nebulized budesonide	250-500	> 500-1000	> 1000
Ciclesonide	80	> 80-160	> 160
Fluticasone propionate (DPI)	50-100	> 100-200	> 200
Fluticasone propionate (HFA)	50-100	> 100-200	> 200
Mometasone furoate	100	100	200

Inhaled corticosteroids for teenagers (> 12 years)			
Inhaled corticosteroid	**Low dose**	**Medium**	**High**
Beclomethasone dipropionate	200-500 (100-200)[a]	> 500-1000 (> 200-400)[a]	> 1000 (> 400)[a]
Budesonide (DPI)	200-400	> 400-800	> 800
Ciclesonide	80-160	> 160-320	> 320
Fluticasone propionate (DPI)	100-250	> 250-500	> 500
Fluticasone propionate (HFA)	100-250	> 250-500	> 500
Mometasone furoate	200-400	200-400	> 400

HFA: hydrofluoroalkane, DPI: inhalation powder device.
[a] Beclomethasone in extra-fine particle presentation.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

COVID-19 vaccines and immunological implications: a literature review

Vacinas COVID-19 e suas implicações imunológicas: uma revisão de literatura

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ABSTRACT

COVID-19 and immunological mechanisms currently are topics of great worldwide relevance. Clinical manifestations and the dangerous complications resulting from a cytokine storm motivated the creation of vaccines against SARS-CoV-2 at an accelerated pace, generating suspicions and different levels of efficacy and safety. This is a review article addressing research published in 2020 and 2021. The electronic libraries SciELO (Scientific Electronic Library Online), PubMed, LILACS (Latin American and Caribbean Literature in Health Sciences), and MEDLINE were used for specific screening with the following descriptors: COVID-19 vaccines, SARS-CoV-2, immunology of COVID-19. Issues such as the immunological mechanism, efficacy, and adverse effects of vaccines currently available on the world market are widely discussed.

Keywords: Coronavirus infections, vaccines, betacoronavirus.

RESUMO

A COVID-19 e seus mecanismos imunológicos são, atualmente, temas de grande relevância mundial. Suas manifestações clínicas e as perigosas complicações decorrentes da tempestade de citocinas motivaram a criação de vacinas contra o SARS-CoV-2 em um ritmo acelerado, gerando desconfianças e diferentes níveis de eficácia e segurança. Este estudo trata-se de um artigo de revisão que abordou pesquisas publicadas no período de 2020 e 2021, utilizando as bibliotecas eletrônicas SciELO (*Scientific Electronic Library Online*), PubMed, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde) e MEDLINE com o rastreamento específico por meio dos seguintes descritores: vacinas COVID-19, SARS-CoV-2, imunologia do COVID-19. Questões como o mecanismo imunológico, eficácia e efeitos adversos das vacinas disponíveis no mercado mundial atual foram amplamente discutidas.

Descritores: Infecções por coronavírus, vacinas, betacoronavírus.

Introduction

Reviewing immunology concepts

The defense against microorganisms, whether intracellular (such as viruses) or extracellular (such as bacteria and protozoa), occurs through reactions of innate immunity initially, followed by late responses of acquired immunity.[1]

Innate immunity (also called natural or native immunity) provides the first line of defense. The main components are physical and chemical barriers (epithelium and antimicrobial agents produced on epithelial surfaces); phagocytic cells (such as neutrophils, macrophages), dendritic cells (antigen-presenting cells) and natural killer (NK) cells; and blood proteins, including members of the complement

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system and other mediators of inflammation. These cells react to the products of microorganisms and injured cells, always responding in the same way to repeated exposures and not distinguishing the differences between them.[1]

In contrast to innate immunity, there is another immune mechanism that tends to respond and adapt to infection in a specific way: acquired immunity (also called adaptive or specific). The adaptive immune system recognizes and reacts to a large number of molecules. Its defining characteristics are the ability to distinguish between different substances (specificity) and the ability to respond more vigorously to repeated exposures to the same microorganism (memory). The unique components of adaptive immunity are cells called lymphocytes and their secreted products, such as antibodies. Foreign substances that induce specific immune responses or are recognized by lymphocytes or antibodies are called antigens.[2]

Acquired immunity is also divided into two forms of defense: represented by T lymphocytes (CD4, CD8, regulator) and known as cellular immunity; and by the response through antibodies (immunoglobulins) produced by B lymphocytes, called humoral immunity.[2]

By specifying the immune response to intracellular pathogens (such as viruses), after the antigen-presenting cells carry some viral protein to the CD4 T lymphocytes, these cells will secrete interleukin (IL)-2, which is a growth factor for the proliferation of antigen-specific T cells (clonal expansion). They aid in the recruitment and differentiation into effector T cells, which aid in the elimination of the pathogen. CD4 T cells also stimulate CD8 T cells and these also proliferate, differentiate, and kill infected cells, being very active in viral infections.[2]

As for humoral immunity, helper T cells stimulate B lymphocytes to differentiate into plasma cells, and, depending on the antigen, specific antibodies will be formed. The main antibodies or immunoglobulins formed are of the IgA class (found mainly in mucous membranes, acting on protein antigens), IgE (present mainly in allergic reactions and parasitic infections, acting on protein antigens), IgM, and IgG (acting in responses against infections; IgM acts in the active phase of the disease, that is, the individual is infected in the acute phase, and IgG means that the organism is in the chronic phase of the disease or has already been in contact with the antigen at some point in life). Antibodies act through opsonization by binding to the pathogen to phagocytosis occur.[3]

COVID-19 disease and its relation to immunity

COVID-19, caused by the SARS-CoV-2 virus, a single-stranded RNA virus, of the *Coronaviridae* family, is a new respiratory pathology, originating in China, which through rapid transmission caused a pandemic and has shown important clinical repercussions, due to its complex immunopathological mechanisms.[4] Infection by SARS-CoV-2 causes from a common cold to systemic conditions characterized by severe acute respiratory syndrome; there are also coagulopathies, neurological disorders, in addition to a severe systemic inflammatory state, in which a "cytokine storm" may occur, immunopathologically. The magnitude of clinical manifestations is related to the systemic conditions of infected individuals. SARS-CoV-2 infects cells through a structural peak protein called protein S.[5]

There are three stages of the disease:[6]

– *Viral replication phase:* occurs in the first seven days of infection; during this period, the innate immunity will act through the release of interferon (IFN) alpha and beta and stimulus of cell lessons NK, as a way to prevent the spread of the virus. The main clinical manifestations of this phase are dry cough, fever, adynamia, anosmia, and even the absence of symptoms.
– *Pulmonary phaser:* with an average duration from the seventh to the tenth day (D7-D10). At this stage, the end of the viral replication status and the start of hyperinflammation. The virus has a predilection for pneumocytes II that contain ACE receptors, preventing the action of IFN and causing an inflammatory environment, with the destruction of the basement membrane surfactant and macrophages releasing free radicals, increaseI walk to vascular permeability and predisposing to pneumonia. The destruction of alveolar surfactant with the formation of the hyaline membrane in the alveoli causes difficulty in gas exchange, inflammation, increased vascular permeability, and, consequently, a hypoxemic state, which contributes to a diffuse alveolar damage and evolution clinic for Ang's syndrome acute respiratory disease (ARDS).
– *Systemic inflammatory response syndrome phase:* observed after the D10. Initially, it is

verified the macrophage activation syndrome (MAS); and, right away, an antigenic alteration that stimulates the excessive production of IL-6, causing dysregulation of the immune response. A tumor necrosis factor (tumor necrosis factor – TNF) alpha is another cytokine that contributes to this immune dysregulation, because, in addition to not helping to fight the virus, it stimulates a systemic hyperinflammatory response, causes walk tissue damage throughout the body, and causes a reduction of TCD4 and NK lymphocytes. Nessand period, B lymphocytes stimulate the production of antibodies (mainly IgM). Another important mechanism is The HIF1-alpha synthesis, stimulated by the hypoxemic state itself, which inhibits fibrinolysis and activates tissue factors (extrinsic). Oinflammatory state (TNF-alpha, IL-6) increases platelet aggregation, stimulating prothrombotic events (coagulability), which may progress to disseminated vascular coagulation. The two main clinical manifestations are ARDS and coagulopathy (pulmonary thromboembolism, deep vein thrombosis). The cytokines involved include interleukin-1beta (IL-B), IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte, and macrophage colony-stimulating factor (GM-CSF), IFN-gamma, IP10 (interferon y-inducible protein), TNF-α, and vascular endothelial growth factor (VEGF).

Methodology

This is a review study that addressed research published between 2020 and 2021. Only original articles that investigated the topics: immunology and pathophysiology of COVID-19, vaccination, adverse effects of vaccines were selected for this review. To guide this review, the following question was elaborated: "How will the various types of vaccines help the body's immunity, as a form of defense against the SARS-CoV-2 virus?"

For the selection of articles in this review, a survey was carried out in the database of the electronic libraries SciELO (Scientific Electronic Library Online), PubMed, LILACS (Latin American and Caribbean Literature in Health Sciences), and MEDLINE between the months of January to April 2021 with specific screening using the following descriptors: COVID-19 vaccines, SARS-CoV-2, COVID-19 immunology. A total of 57 articles were selected and, among these, 30 were used to prepare the review.

Inclusion criteria for eligibility were original articles and randomized double-blind studies, which clearly described the protocols used in vaccination trials, vaccine side effects, and the trial phases each vaccine is in. Repeated articles and articles that did not fully describe the protocols used were excluded from the study.

Development of COVID-19 vaccines

The development of a new vaccine, under appropriate circumstances, is carried out by a long process that lasts from 10 to 15 years, on average.[7] In a pandemic situation, the urgency led to an overlapping of the phases, with the challenge of developing a vaccine against COVID-19 in a period of 12 to 24 months, while respecting safety standards.[8]

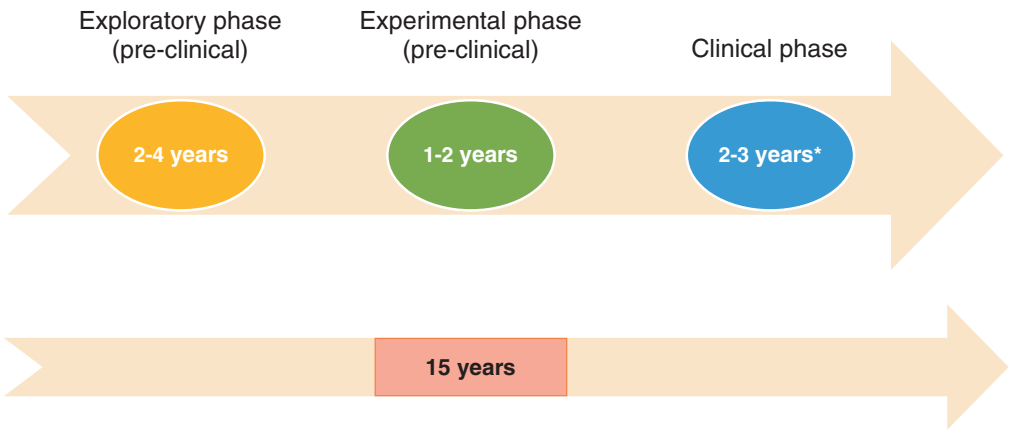
The phases are divided into pre-clinical and clinical, with their respective steps (Figure 1). The first stage of the pre-clinical phase consists of the exploratory phase, which usually lasts two to four years; it involves basic laboratory research and computer modeling to identify natural or synthetic antigens that can be used as vaccine candidates against the disease in question.[8]

The second stage (lasting from one to two years) comprises pre-clinical studies involving cell culture or tissue culture systems and tests on animals, such as mice, to assess the safety of the candidate vaccine and its immunogenicity - ability to provoke an immune response.[7,8] The study guides researchers towards an idea of the cellular responses that can be expected in humans, as well as the safest and most effective starting dose and method of application.[8]

Given the good results in animals with the issue of safety, efficacy, and immunogenicity, the process moves to the clinical phase in humans, testing in small groups and, later, in large groups, divided into three trials.[7]

Phase 1 - Safety: the vaccine is administered to a small group of healthy and immunocompetent individuals, to mainly assess safety, adequate initial dosage, and immunogenic response, as a secondary effect. The durability of 2-3 years.[7]

Phase 2 - Expanded safety: the vaccine is now administered to hundreds of participants in different age groups, re-testing safety, appropriate dosage, adverse events, the interval between doses, as well as the ability of the vaccine to stimulate the immune system.[7,8] The durability of 2-3 years.[7]



* Duration of each stage of the clinical phase.

Figure 1
The new vaccine development process.

Phase 3 - Efficacy: large-scale clinical trials begin, comprising thousands of participants, to prove safety and mainly evaluating efficacy;[8] defined as the percentage by which the disease incidence rate is reduced in the vaccinated groups compared to the placebo group,[7] obtaining more data on immunogenicity and adverse reactions.[8] The durability of 2-3 years.[7]

Phase 4 - Pharmacovigilance: monitoring of vaccine side effects with additional safety and efficacy data over time.[8] Performed after the registration of the vaccine by administrative bodies such as the FDA (Food and Drug Administration), ANVISA (National Health Surveillance Agency), and EMA (European Medicines Agency). Durability 1-2 years.[7]

The viral sequence allowed work to develop a vaccine to continue weeks after China's initial notification to the World Health Organization (WHO) on December 31, 2019, of the outbreak.[9] Coalition for Epidemic Preparedness Innovations (CEPI) funding of grants for vaccine development, announced in January 2020, along with additional funding provided by national and multinational research funders, has driven safe and effective vaccines to be developed. with a term of six to 18 months.[9] As well as the viral similarity of SARS-CoV-2 with SARS-CoV, in which there are previous studies, it contributed to the immediate search for a protective immune response.[8]

Studies have shown that protein S (spike) is the main target for the design and development of these vaccines, as it is responsible for binding the virus to the host cell surface receptor (ACE2, most likely).[10] Candidate vaccines against SARS-CoV-2 being developed around the world and currently under evaluation are based on different platforms, four of which stand out: RNA base, inactivated virus, non-replicating viral vector, and in protein subunit.[10,11]

RNA vaccines

RNA vaccines consist of messenger RNAs (mRNA) that encode viral antigens, which can be translated by human cells to produce antigenic proteins and stimulate the immune system.[12] In other words, in laboratories, vaccines use fragments of genetic material, which encode a part of the virus, such as the Spike protein (in the case of SARS-CoV-2) and, when injected into the hosts, they use the RNA instructions to make copies and trigger an immune response.[8]

The obstacle in the development of this vaccine has been the propensity of the mRNA to degrade, as stability and proper intracellular translation are necessary for the success of the vaccine. As a strategy developed to solve this problem, RNA vaccines are administered in complex with additional agents, such as protamine or nanoparticles based on lipids and polymers, aiming to increase their effectiveness.[13]

mRNA vaccines are advantageous in being safe compared to DNA vaccines as the mRNA does not integrate into the host genome, thus minimizing genotoxicity. Compared to inactivated virus vaccines or live vector vaccines, synthetic mRNA vaccine production is quality-controlled with a reduced chance of biological contamination during production.[11]

They are highly adaptable to new pathogens and capable of recapitulating the native conformation and modifications of antigenic proteins.[12] Lipid-based mRNA transporters are biodegradable. Furthermore, they demonstrate efficacy in inducing a strong humoral and cellular immune response, and their manufacture is fast and on a large scale, meeting the needs of a pandemic.[11]

However, RNA vaccines have some disadvantages, as mRNA without a proper formulation is unstable and rapidly degraded. mRNA is impermeable to cell membranes and cannot be efficiently internalized into the cytosol for translation. It can also activate the innate immune system and potentially induce inflammation and toxicity. These vaccines also require a strict cold chain condition for storage and distribution.[11]

The two main developers of SARS-CoV-2 RNA vaccines are Moderna and BioNTech / Pfizer.[12]

Both vaccines are remarkably effective, involving large randomized, placebo-controlled clinical trials with several individuals. They have evidence of some immune response 10 to 14 days after the application of the first dose of the vaccine and prevention of the severe form of the disease.[14] They require booster doses to ensure a high neutralizing antibody titer and long-term immunogenicity.[13] Overall, these impressive results place the two mRNA vaccines at the top of the most effective vaccines to date.[14]

Pfizer Inc./BionNTech SE

BioNTech (German company) together with Pfizer (an American company) developed vaccines based on mRNA. BioNTech and Pfizer's mRNA vaccine had four candidates: BNT162b1, BNT162b2, BNT162a1, and BNT162c2, of which only two advanced to the next phases.[12,13]

The nucleoside-modified mRNA vaccines are BNT162b1 and BNT162b2. BNT162b1 encodes a trimerized receptor-binding domain (RBD) of the Spike protein, while BNT162b2 encodes a full-length spike protein.[12]

After studies conducted in Germany and the USA in phase I/II, demonstrating that BNT162b1 induced neutralizing and RBD-binding antibodies with titers above that of convalescent human serum, another trial was coordinated comparing the responses to vaccination between BNT162b1 and BNT162b2.[13]

BNT162b1 and BNT162b2 have been shown to induce similar neutralizing titers in young and elderly adults. However, BNT162b2 had fewer systemic adverse reactions in older adults. In light of this, BNT162b2 was advanced instead of BNT162b1 in phase III clinical trial.[13]

On November 18, 2020, Pfizer and BioNTech announced the efficacy analysis of their Phase III clinical trial, whose evaluation showed that BNT162b2 is 95% effective against COVID-19.[13] The results of 95% of vaccine efficacy occur after the second dose, which increases the immune response and probably makes it more durable. The second dose must be administered after 21 days and is authorized for patients 16 years of age and older; there is no maximum age restriction.[14]

For now, in the United States, the Centers for Disease Control and Prevention (CDC) and the FDA recommend proceeding with the two-dose regimen whenever possible.[14]

No serious safety concerns were noted among the 43,000 enrolled participants. These data indicated that BNT162b2 is another well-tolerated and effective COVID-19 vaccine.[13]

Modern (Modern/NIAID)

Moderna is an American company based in Cambridge, Massachusetts. The Modern mRNA vaccine, mRNA-1273, encodes the spike protein so that when the vaccine is injected into the body, the immune cells that process the mRNA and the protein manufactured will subsequently be targeted for destruction.[7]

A specific antibody response appeared on the fifteenth day after the first dose, showing better efficacy in the need for a two-dose regimen.[7]

On November 16, 2020, Moderna unveiled the first interim analysis of its phase III trial, showing an estimated efficacy of 94.5% after the second dose of the vaccine, which was administered after 28 days for those over 18 and no maximum age restriction.[12,14]

His simultaneous security review also didn't notice any significant concerns. Therefore, its promising result suggested that the mRNA-1273 vaccine is safe and effective in preventing symptomatic COVID-19.[12]

Curevac

German biopharmaceutical company CureVac NV announced a clinical development collaboration for its vaccine against SARS-CoV-2 with pharmaceutical company Bayer. An mRNA-based technology platform, RNActive®, was applied to develop the vaccine, called CVnCoV.[15]

In line with pioneering work using mRNA formulated with protamine to target tumors, CureVac has established that mRNA elicits immune responses against target antigens as a prophylactic vaccine. CureVac's proprietary mRNA technology is designed to rapidly identify, produce and test stable and immunogenic mRNA molecules.[16]

CVnCoV is composed of sequence-engineered mRNA formulated with lipid nanoparticles (LNP), not chemically modified, which encodes the full-length S protein with two proline mutations (S2P). These mutations stabilize the protein's conformation, preventing the virus from binding to it and starting the viral replication process.[15,16]

In a provisional analysis, it was shown that two doses of CVnCoV ranging from 2 µg to 12 µg per dose, administered 28 days apart, are safe. Seroconversion (defined as a 4-fold increase from baseline) of virus-neutralizing antibodies two weeks after the second vaccination occurred in all participants who received doses of 12 µg.[15]

No serious vaccine-related adverse events were reported. There were dose-dependent increases in the frequency and severity of solicited systemic adverse events and, to a lesser extent, in local reactions, but most were mild or moderate and of transient duration.[15]

Non-replicating viral vector vaccine

In this type of vaccine, the antigen is cloned into a viral vector that cannot reproduce itself, that is, another known and safe virus is used, to carry specific proteins that can trigger an immune response without causing the disease.[8]

The viral vector mimics natural infection and therefore can produce stronger specific cellular and humoral immune responses compared to the recombinant protein vaccine. Furthermore, viral vectors can accept large insertions into their genome, providing a flexible platform for antigen design.[12]

Common vectors include human adenoviruses (especially, 5 and 26) or chimpanzee (ChAd), parainfluenza virus, measles virus, rabies virus, vesicular stomatitis virus, modified Vaccinia Ankara virus (MVA), and adeno-associated virus (AAV).[8,12]

Disadvantages include that the manufacturing process requires care with the optimization of cell systems and the exclusion of contaminants, which can affect the efficiency of viral vectors.[12] Finally, pre-existing immunity to the viral vector can reduce the effectiveness of the immune response.[8]

The top three candidates for this platform are AstraZeneca/ Oxford University (AZD1222), Gamaleya Research Institute (Gram-COVID-Vac), and Janssen Pharmaceutical Companies/ Johnson & Johnson (Ad26COVS2).[12]

AstraZeneca/Oxford University

AstraZeneca is an Anglo-Swedish pharmaceutical conglomerate and, in partnership with the University of Oxford, the laboratory was one of the pioneers in developing a vaccine against COVID-19, called AZD1222.[17]

The vaccine uses a viral vector of a non-replicating simian adenovirus (chimpanzee), which presents a genomic segment of the virus that expresses the

glycoprotein SARS-CoV-2 spike (S).[17] The dose of the AZD1222 vaccine was based on the previous experience of the Oxford group, which developed a similar type of vaccine for MERS-CoV using chimpanzee adenovirus (ChAdOx1).[12]

The vaccine has been shown to trigger specific antibodies to protein S and T cell responses and to induce neutralizing antibodies after the initial regimen and booster, certifying that it is well tolerated and immunogenic.[12]

The mean total efficacy evaluated, considering the joint studies of the United Kingdom, Brazil, and South Africa was 70.42% (95%CI: 54.84% - 80.63%). Administration of the second dose is indicated after four to twelve weeks, as a greater level of efficacy was observed when there was a longer interval between the first and second dose.[17]

Initially, no serious adverse effects were observed in clinical trials, demonstrating an adequate safety profile similar to other vaccines regularly used.[17] However, in March 2020, the Ministries of Health of several European countries suspended the application of the immunizing agent due to the high risk of thrombosis in vaccinated patients. According to a study carried out in Germany, among the 1.6 million doses applied, 13 demonstrated an association with thrombosis of the cavernous sinuses or cerebral veins.[18]

The Gamaleya National Center of Epidemiology and Microbiology

The COVID-19 vaccine was developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia, called Sputnik V, and registered on August 11, 2020, by the Russian Ministry of Health as Gam-COVID-Vac, is a viral vector vaccine of adenovirus.[12]

The vaccine uses a heterologous recombinant adenovirus approach in two vectors, adenovirus 26 (Ad26) and adenovirus 5 (Ad5) for peak expression of the SARS-CoV-2 protein.[19] We opted for two different adenovirus vectors administered separately in a first and second dose, 21 days apart, as using the same adenovirus for both doses can lead the body to develop an immune response against the vector and destroy it when the second dose is administered.[20] Two different vectors reduce the chance of decreasing its effectiveness.[20] That said, the use of two different serotypes, administered 21 days apart, is intended to overcome any pre-existing adenovirus immunity in the population.[19]

Results showed that Gam-COVID-Vac has an efficacy of 91.4% after the first dose. An efficacy above 95% was also verified when the interval established between the first and the second dose was 21 days.[12]

There was no unexpected adverse effect documented during the clinical trial and the promising results suggest that Gam-COVID-Vac is safe and effective in preventing COVID-19.[12]

Janssen Pharmaceutical Companies/Johnson & Johnson

Johnson & Johnson's vaccine is based on technology that involves a virus, in this case, adenovirus 26 (Ad26) as a viral vector, in which the spike protein gene SARS-CoV-2 is added to its DNA. The adenovirus is modified so that it does not multiply and, therefore, does not cause the disease.[21]

After administration of a modified adenovirus vaccine, Ad26 enters cells and releases its viral DNA. The cells use the viral DNA to produce the spike protein and thereby activate the body's immune system to produce antibodies that recognize the spike protein. If further exposure of the vaccinated person to SARS-CoV-2 occurs, the immune system initiates the recognition of the virus and prevents infection.[21]

The Johnson & Johnson vaccine initially showed the ability to produce antibodies against SARS-CoV-2 in 90% of people who received it after the first dose. Data presented by Johnson & Johnson suggest that one dose of the vaccine was 66% effective in preventing moderate to severe disease and 100% effective in preventing COVID-19-related hospitalization and death.[21]

Inactivated virus vaccine

Inactivated whole vaccines are composed of virions inactivated by heat, radiation, or chemicals so that they cannot replicate. Despite being safer than live attenuated vaccines, immunogenic epitopes of inactivated viruses can be structurally deformed during the inactivation process, impairing the protective immune response.[8,12] They tend to produce a weaker immune response than live attenuated vaccines; therefore, adjuvants are needed to enhance the immune response.[10]

SinovacBiotech Ltd.

Sinovac is a biopharmaceutical company headquartered in Beijing (China), which developed a vaccine in partnership with the Butantan Institute (Brazil), called CoronaVac.[12,17]

Coronavac is composed of the attenuated whole virus of SARS-CoV-2, originated from a strain derived from a patient, cultivated in a Vero cell line (epithelial cells extracted from a primate of the genus *Chlorocebus*, known as African green monkey), inactivated with β-propionolactone, purified and adsorbed with aluminum hydroxide.[17]

The phase III clinical trial was initiated in Brazil, Indonesia, and Turkey.[12] In Brazil, the study was conducted by the Butantan Institute in 17 research centers with about 12,000 volunteers. Regarding the efficacy of CoronaVac, in the trials in Brazil, it was shown a mean total efficacy of 50.39% (95% CI: 35.36-61.98) and, concerning the prevention of mild forms, the efficacy was 77.96% (95% CI: 46.15-90.44). Thus, for the Coronavac vaccine to achieve such efficacy, it is recommended that the second dose be administered within an interval of two to four weeks after the first dose.[17]

BharatBiotech

BharatBiotech is an Indian pharmaceutical company that, in collaboration with the Indian Council of Medical Research and the National Institute of Virology, formulated its vaccine, Covaxin, based on an inactivated live virus platform. This vaccine requires two doses given intramuscularly 28 days apart.[22,23]

Live attenuated vaccines

Live attenuated vaccines involve live pathogens weakened manually by the deletion or mutation of the pathogenic component of the viral genome, not being able to induce infection, but able to stimulate humoral and cellular immune responses and, therefore, mimic characteristics of natural infection.[10,12] As a result, they are often immunogenic with a single administration without an adjuvant.[24]

This type of vaccine presents a higher risk than other technologies, especially in immunocompromised patients, as it includes the possibility of reversion to a virulent state and danger of infection. The biosafety of live attenuated vaccines needs to be carefully evaluated before proceeding to clinical use.[12]

Codagenix and the Serum Institute of India are developing a live attenuated vaccine against SARS-CoV-2, using codon deoptimization technology, based on previous experience with the respiratory syncytial virus (RSV) and influenza.[24]

Subunit protein-based vaccine

Vaccines are produced from purified pieces of the virus.[8] Antigenic fragments of a microorganism that best stimulate an immune response require multiple dosing regimens with adjuvants to achieve strong immune responses.[11]

Subunit vaccines produced by genetic engineering techniques, in which other microorganisms are programmed to produce the desired antigenic fraction, are called recombinant vaccines.[10,12] Furthermore, they are considered safe and can be used in immunocompromised patients.[8]

Novavax Inc.

Novavax is a North American company that also entered the race to develop a vaccine against SARS-CoV-2, called NVX-CoV2373.[11] Funded by CEPI and US Operation Warp Speed, it has developed a recombinant nanoparticle vaccine that exhibits the peak protein SARS-CoV-2, being genetically modified to obtain greater structural stability. Their production used baculoviruses designed to infect Sf9 insect cells.[11,24]

The use of an adjuvant to increase the effectiveness of seroconversion is warranted, so Novavax is using its saponin-based Matrix-M adjuvant.[24] In addition to the humoral response, strong cellular responses are observed after the administration of two doses.[11,24]

Preliminary clinical trial data showed that the NVX-CoV2373 vaccine was 95.6% effective against the original SARS-CoV-2 variant, while also protecting against the newer B.1.1.7 (85.6%) and variants B.1,351 (60%).[25]

The NVX-CoV2373 vaccine can be stored at 2°C to 8°C and is safe. An interim data analysis reported that serious adverse events occurred in small numbers.[25]

Vaccines based on virus-like particles

Virus-like particles (VLPs) represent an interesting approach for vaccine development, being an alternative technology as it seeks to mimic the viral structure.[8,10]

VLPs can be designed to express the surface proteins or nucleic acid sequences of the original virus without the risk of replication or infection as they lack the core genetic material. Its advantage is that, although it is categorized as a recombinant protein vaccine, it still maintains the native conformation of viral proteins, being advantageous over other subunit protein vaccines in terms of immunogenicity and antigenicity.[11]

Medicago

It is a Canadian pharmaceutical company that generated a virus-like particle vaccine (VLP) using a plant-based method – a synthetic gene containing a part of the SARS-CoV-2 genes is transferred into a tobacco species, *Nicotianabenthamiana*, using a bacterial vector. These plants then express VLPs that can be purified.[11,24]

Adverse effects of vaccines

Although there is still a need for more studies, according to Sax PE, it can already be said that, at present, there is no 100% safe vaccine.[14] However, it is worth noting that such effects have become minimal concerning the damage that SARS-CoV-2 can do to the human body. It is also known that there are three ways to guarantee the safety of a vaccine: computer simulation, animal experiments, and human trials. It is the safest method when it is replicated in humans due to its greater proximity to reality.[26]

Comparing the techniques used in the manufacture of vaccines against COVID-19, mRNA vaccines have greater safety, such as those developed by "Pfizer/BioNTech" (BNT162b2) and "Modern" (mRNA-1273), even though we know that both will cause side effects in the majority of the population that receives it, due to their exaggeratedly fast immunological response, characterizing this group as reactogenic vaccines.[27]

As for the effects, pain at the injection site of the dose can be cited as the most common, which lasts from 12 to 14 hours after administration, being characterized as severe intensity by 1% of the population. Symptoms such as headache and fatigue are also recurrent but are clinically treated with a good response to analgesics and anti-inflammatory drugs.[28]

Due to the occurrence of hypersensitivity reactions in some rare patients, including anaphylaxis, which is estimated to occur in approximately 1 in 100,000 doses, a 15-minute observation period after dose administration was determined, and for those with a previous history of severe allergies, the observation time should double to 30 minutes.[14]

There were no reports of cases of Guillain-Barré syndrome or transverse myelitis. Long-term side effects could not be studied in detail, as they were only months after the vaccine was released. However, it is worth noting that such events are commonly very rare.[14]

According to Jackson LAet al., in one of the RNAm vaccine trials, there was a report of effects with varying degrees of severity, even though the test group was mostly young and healthy.[29] Young patients had more side effects than elderly patients, and the second dose caused more effects than the first.[14]

Vaccines that use a non-replicating viral vector (Sputnik V and Johnson&Jonhson) also proved to be tolerable, in addition to a good immune response.[27] This group caused small local reactions with signs of phlogosis, headache, fever, malaise, and fatigue, which should disappear within 96 hours after administration of the dose.[30]

As for the inactivated SARS-CoV-2 viral antigen vaccine (Coronavac), a remarkable reduction in adverse effects when compared to the existing ones has already been proven. Most effects tend to disappear 72 hours after administration of the dose and are characterized by being nonspecific systemic symptoms, which, on a severity scale during phase II of the study, were classified as moderate. There were no reports of serious adverse reactions. The major effect on patients was redness and pain at the vaccine site.[30]

Novavax, produced in the United States, a vaccine based on protein subunit (NVX-CoV2373), only produced mild effects: arthralgia, fatigue, headache, myalgia, nausea, and malaise after at least 72 hours. yet there were no serious adverse effects in the study population. As previously mentioned in other vaccines, signs of redness and pain were also presented at the injection site.[13]

AstraZeneca (AZD1222), in turn, as mentioned above, after approval of its use, demonstrated a dangerous thrombotic potential that motivated the health authorities to decree its suspension. The reports of thrombosis started 4 to 16 days after the application of the dose, being 12 female patients and

1 male, aged 20-63 years. According to the explained pathological mechanism, with vaccination, there is the formation of antibodies against platelet antigens motivated by the immunological reaction. These produced antibodies will bind to the Fc receptor which causes massive platelet activation. It is noteworthy that the reason why it occurs with greater prevalence in cerebral vessels is not known.[18]

Despite not having full knowledge of the long-term effects, the application of vaccines in the vulnerable population is justified and necessary, since the effects of the disease are more devastating in certain groups.[26]

Conclusion

Following what has been described, the prerogative that not all vaccines are safe and have already been properly tested is notorious. However, due to the short period and the urgency in which the world lives due to the disease pandemic, it is essential that the population can adhere to the vaccines that have been nationally approved, as COVID-19 can bring even more damage to the population than the possible side effects. Furthermore, it is concluded that RNA vaccines have better efficacy; however, they are dangerously more associated with side effects, which, in contrast, are scarce in vaccines made from the attenuated virus.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

COVID-19-associated Multisystem Inflammatory Syndrome: a pediatric complication during the pandemic

Síndrome Inflamatória Multissistêmica associada à COVID-19: uma complicação pediátrica da pandemia

Juliano José Jorge[1], Isabella Bassetti[2]

ABSTRACT

Since the emergence of the COVID-19 pandemic, cases of late fever and systemic inflammation similar to Kawasaki Disease have appeared in the pediatric population, this entity was called Multisystem Inflammatory Syndrome associated with COVID-19. The presentation can range from just prolonged fever to severe gastrointestinal and cardiac involvement with refractory shock and multiple organ failure. Carotid aneurysms can arise in the course leading to long-term complications. The prompt recognition of this syndrome with early treatment with general support, use of Human Intravenous Immunoglobulin and other immunomodulatory drugs, can prevent progression to severe and even fatal cases, as well protect the patient from chronic complications, especially the cardiac ones.

Keywords: Systemic inflammatory response syndrome, Coronavirus infections, mucocutaneous lymph node syndrome.

RESUMO

Desde o surgimento da pandemia de COVID-19, casos de febre e inflamação sistêmica tardias, similares à Doença de Kawasaki, têm surgido na população pediátrica, sendo denominados Síndrome Inflamatória Multissistêmica associada à COVID-19. Estes quadros podem ir de apenas febre prolongada, até grave envolvimento gastrointestinal e cardíaco, com choque refratário e falência de múltiplos órgãos. Aneurismas de carótida podem surgir na evolução, levando a complicações em longo prazo. O pronto reconhecimento desta entidade com tratamento precoce de suporte geral, uso de imunoglobulina humana endovenosa e outras drogas imunomoduladoras, pode evitar evolução para casos graves e até mesmo fatais, assim como proteger o paciente de complicações crônicas, principalmente cardíacas.

Descritores: Síndrome de resposta inflamatória sistêmica, infecções por Coronavirus, síndrome de linfonodos mucocutâneos.

Introduction

Since the emergence of the Coronavirus pandemic in 2019, we have noticed that children and adolescents have been less affected. National statistics from Asia, Europe, and North America show that pediatric cases are about 2.1% to 7.8% of total COVID-19 cases.[1-3] And in those infected individuals, symptoms are milder in children than in adults, with a small proportion of children requiring hospitalization.[4] However, with the evolution of the pandemic, cases of febrile conditions began to be reported about 4-6 weeks after peaks of acute infections caused by SARS-CoV-2.[5] A study by the Centers for Disease Control and Prevention (CDC) documented the presence of 570 cases and 10 deaths, with a mean age of 8.3 years, and 99% of the cases had RT-PCR or positive serology for COVID-19.[6]

The clinical presentation is similar to other multisystem inflammatory conditions known in Pediatrics, such as Kawasaki Disease and Toxic Shock Syndrome,[7,8] but this new entity has some peculiarities, which is called "COVID-19 Multisystemic

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Inflammatory Syndrome (MIS-C)". The main symptoms are: prolonged fever, diarrhea, skin rash, conjunctivitis, edema of the extremities, mucosal changes, involvement of the central nervous system, cardiac lesions and coronary artery aneurysms, which may progress to cardiogenic shock and multiple organ failure.[9]

Unlike Kawasaki disease, which preferentially affects the Asian population and those under 5 years old, MIS-C occurs in older individuals (cases described even in patients aged 21 years old) and is more prevalent in African-American and Hispanic population.[10] Other more striking features of MIS-C in relation to other inflammatory syndromes are that abdominal symptoms, leukopenia, elevation of brain natriuretic peptide (BNP), troponin, CRP and ferritin are much more prominent.[11]

Pathophysiology

The pediatric population has a lower tendency to present severe acute cases of COVID-19, probably due to molecular alterations existing in adults and children. The primary receptor for virus entry into cells is the angiotensin-2 converting enzyme (ACE2). ACE2 is co-expressed in association with a transmembrane serine protease (TMPRSS2), which is responsible for cleaving the viral spike protein into two fragments: S1, essential for viral attachment; and S2, which guides viral fusion into the target cell.[12] Children express a lower amount of ACE2 in their pulmonary epithelium, and the expression of TMPRSS2 is regulated by levels of androgens and their receptors, which are reduced in children under 12 years of age.[13]

The emergence of MIS-C may be associated with a mechanism called antibody-dependent enhancement. It has been described in other viral infections such as dengue and Zika virus.[14] It consists of the formation of immune complexes containing the viral antigen and non-neutralizing antibodies. The FC portions of these non-neutralizing immune complex antibodies bind to specific receptors on immune cell membranes, leading to virus entry into the cell in a manner independent of traditional viral spike protein binding to ACE2. Non-neutralizing anti-spike antibodies to SARS-CoV-1 have been implicated in the worsening of inflammation in primates and in human macrophages, which leads to the hypothesis that this same type of antibodies against SARS-CoV-2 may be associated with the exacerbated inflammatory response of MIS- C.[15]

The innate immune system appears to be responsible for the inflammatory cascade that leads to tissue damage. Macrophages, stimulated by the antibody response, increase viral uptake, leading to increased production of pro-inflammatory cytokines, in a phenomenon called cytokine storm.[16] Sera from patients with MIS-C reveal elevated levels of IL-1B, IL-6, IL-8, IL-10, IL-17, interferon gamma and TNF.[5]

Immunophenotyping by flow cytometry shows B and T cell lymphopenia, with reduced CD4, CD8, gd cells.[17]

Autoantibodies have also been implicated in the pathogenesis of MIS-C. Anti-endoglin, anti-MAP2K2 (mitogen-activated protein kinase 2), anti-casein kinase, anti-Jo and anti-La antibodies were detected, as well as antibody reactivity against proteins involved in immune regulation, endothelial function and gastrointestinal biology. The generation of autoantibodies is very interesting in trying to explain part of the exaggerated immune response, but its exact role in the pathogenesis of MIS-C has not yet been determined.[5]

Neutrophils also play their role, with the formation of extracellular neutrophil traps (NET). These act as a network of free DNA, histones and neutrophil granule content, amplifying the inflammatory response and generating a prothrombotic state.[18]

Clinical condition

The case definition of MIS-C is based on the clinical presentation: evidence of involvement of two or more organs, absence of other evident infectious causes, and confirmation of infection or recent exposure to SARS-CoV-2.

The clinical spectrum ranges from a persistent febrile condition, through a situation that simulates Kawasaki Disease, to severe conditions with refractory shock and multiple organ failure.[19]

The World Health Organization criteria for the diagnosis of MIS-C are listed below.

(1) Age: 0-19 years.

(2) Signs of inflammation: fever and elevation of inflammatory markers (CRP, ferritin) for three or more days.

(3) Main features (at least two of the following items):

– bilateral non-purulent conjunctivitis or mucocutaneous rash;
– shock or hypotension;
– myocardial dysfunction, pericarditis, valvulitis or changes in coronary arteries (includes echocardiographic findings, elevation of troponin or BNP);
– evidence of coagulopathy (altered prothrombin time, KPTT, D-dimer elevation);
– acute gastrointestinal disorders (diarrhoea, vomiting, abdominal pain).

(4) Exclusion of other infectious causes.

(5) RT-PCR or COVID-19 positive serology, or recent (4 weeks) contact with patients with COVID-19.[19]

Compared to Kawasaki Disease, a greater number of patients with MIS-C present with cardiac involvement, gastrointestinal symptoms, hyponatremia, hypoalbuminemia. About 80% of patients with MIS-C have cardiac lesions, with elevated levels of troponin and BNP.[20]

Treatment

There is still no unified treatment protocol for MIS-C, but most reference centers have adopted specific protocols, based on the treatment of Kawasaki Disease, always involving a multidisciplinary team with a pediatrician, intensive care specialist, infectious disease specialist, cardiologist and immunologist.

General support is crucial, with attention to vital signs, hydration and metabolic status. Vasoactive drugs may be needed, and treatment with broad-spectrum antibiotics is recommended.

The first specific treatment option is the use of intravenous human immunoglobulin, at a dose of 2 g/kg, infused slowly for about 12 hours. Other immunomodulating drugs, such as Infliximab (anti-TNF), Tocilizumab (anti-IL-6) and Anakinra (anti-IL-1R) have shown levels of efficacy, however there is no consensus on their use, and they can be applied according to the availability and experience of using the service team.[21]

The use of steroids is recommended. Low-dose dexamethasone appears to be beneficial in suppressing the exaggerated immune response. Other drugs, such as methylprednisolone and prednisolone, have also been used, but further studies are needed to identify the true role of steroids, their optimal doses and which specific drug is most appropriate.

Assessment of coagulopathy is imperative, and if there are changes in D-dimer levels or in the coagulogram, anticoagulant therapy should be discussed with a pediatric hematologist. Low-dose aspirin (3-5 mg/kg) is used until the echocardiographic assessment excludes the presence of lesions or aneurysms in the coronary arteries.[22]

Coronary aneurysms have been identified not only in severe cases, but also in cases where the only manifestations were fever and changes in inflammatory markers. Therefore, the echocardiographic assessment and dosage of troponin and/or BNP in the initial approach is mandatory. In severe cases, follow-up with daily echocardiograms may be necessary, as well as performing this exam at the time of discharge and two and six weeks after discharge.[23] Cardiac magnetic resonance imaging can be used, but it is an exam restricted to large centers and is difficult to perform, especially in young patients and in a severe general condition.[24]

The patient can be discharged from the hospital when he is afebrile, normotensive, hydrated, without the need for supplemental O_2, and whenever the

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Relationship between exercise and the immune system

Relação entre exercício físico e sistema imunológico

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ABSTRACT

The human body always tends to seek a homeostasis state, trying to balance all systems. Physical exercise is present in the routine of individuals even with different goals, but the influence in the immune system isnt a relevant factor. The immune system is responsible for protecting the human body against some infections and diseases, and could be modulated in response by some regular physical exercise. At the moment there is a greater concern to keep efficient immunity, a practice of regular and moderate exercise can contribute to a better effectiveness of this system, thus, it can be considered a form of protection to the human body. The objective of this review was to synthesize some data from any studies presented in the literature that demonstrate the influence of physical exercise on the immune system response. Making it possible to understand the molecular mechanisms, physiological, metabolic and cellular changes that turn to a specific type of response in the human body.

Keywords: Immune system, exercise, inflammation, leukocytes.

RESUMO

O corpo humano tende sempre a procurar um estado de homeostase, buscando o equilíbrio entre todos os sistemas. O exercício físico está presente na rotina diária de indivíduos, mesmo com objetivos diferentes, porém a influência no sistema imunológico não é muitas vezes abordada como fator relevante. O sistema imune é responsável por proteger o organismo contra infecções e doenças, podendo ser modulado perante a resposta de exercícios físicos regulares. Tendo em vista que, atualmente, existe uma preocupação maior em tornar e manter a imunidade eficiente, a prática regular e moderada do exercício pode contribuir para uma maior eficácia desse sistema, dessa forma, podendo ser considerada uma proteção ao corpo humano. O objetivo dessa revisão foi sintetizar os dados de estudos presentes na literatura que demonstram a influência do exercício físico na resposta do sistema imunológico, tornando possível compreender as alterações moleculares, fisiológicas, metabólicas e celulares que levam a um tipo específico de resposta do organismo humano.

Descritores: Sistema imunológico, exercício físico, inflamação, leucócitos.

Introduction

Nowadays, sedentary lifestyle has been a habit among human beings. The increase in hours in front of computers, video games and television contributes to the increase in this population, which, consequently, reduces the time spent in physical activity, causing countless damages to health.[1] The benefit of exercise has been evident for a long time. In the fifth century BC, the physician Hippocrates already stated: "All parts of the body, if used sparingly and exercised in the work to which each one is accustomed, become healthy and well developed and age slowly; but if they are not used and are left idle, they become subject to disease, grow defective, and age rapidly." Unfortunately, in the 21st century, the belief in the value of exercise for health has faded, so much so that lack of exercise now represents a major public health problem.[2] It is of paramount importance that the population come back to believe in the benefits of physical exercise, as it is an ally to improve health and even has the ability to promote immune responses, benefiting the

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health of the individual as a whole. According to the World Health Organization (WHO), to have the health benefits, more than 300 minutes of weekly physical exercise at moderate intensity are recommended for healthy adults, or 150 minutes of weekly physical exercise at vigorous intensity, or a combination of moderate and vigorous intensity exercises.[3]

This article aims to carry out an integrative literature review relating the role that physical exercise plays on the immune system.

Immune system

The immune system is made up of several organs, cells and molecules with the purpose of adapting the organism to defend against infectious or non-infectious agents, and maintain body homeostasis.[4] Many physical stressors, such as surgery, trauma, burns, sepsis and physical exercise, induce a pattern of similar immune responses.[5] Faced with these physical stressors, our bodies mount this immune response that includes two stages: innate immunity and adaptive immunity. The first comprises physical and chemical barriers, in addition to the action of cells such as macrophages, dendritic cells (DCs), natural killer cells (NKs) and neutrophils. At this stage, several cytokines and interleukins (ILs) can also be mentioned, in addition to nitric oxide (NO). The second stage has T lymphocytes (TCD4 + and TCD8+) and B lymphocytes and their products, such as antibodies and cytokines, as a mechanism of action. This response, called adaptive, it can be subdivided into cellular immunity (mediated by cells) and humoral immunity (mediated by antibodies).[6,7] To facilitate the understanding between physical exercise and its influences on the immune system, we will present below the main soluble cells and molecules of the innate and adaptive immune system, influenced during physical exercise.

Neutrophils

Neutrophils represent about half of the total amount of circulating leukocytes, thus becoming the most abundant leukocytes in the blood, and being one of the first cells to reach the site of infection and activate the inflammatory process. This set of cells is part of the innate immune system and is essential for the host's defense, in addition to participating in several inflammatory conditions. For this response to happen, neutrophils are attracted by chemical mediators to the injury site, and this migration occurs in four steps: first, the neutrophils marginally approach the endothelium, then they roll over so that neutrophils can adhere to the endothelium and change the shape, in this way transendothelial migration takes place, and finally neutrophils leave the vessels and reach the inflamed tissues.[4] They are also important in phagocytosis, and this process is stimulated by the binding of receptors present on neutrophils to opsonins, IgG Fc, complement molecules such as C3b and Toll-like receivers(TLRs).[8] It is noted, then, that several elements are involved in the behavior of these cells, such as neuroendocrine mediators, steroid release, cytokine production and oxidation-reduction processes associated with the production of free radicals, all of these factors are influenced by physical exercise.[4]

One of the most pronounced characteristics of physical activity in immunological parameters is prolonged neutrophilia after acute exercise, of moderate intensity and long duration.[9] A study was carried out on males who underwent an indoor cycling class. In this research, acute variations in the levels of neutrophils present in the blood were verified, in which, immediately after exercise, the neutrophil count increased by 12%, and in a 24-hour recovery period the number was reduced to 19.8% and 11, 3% within 48 hours.[4] This increase in neutrophil levels is closely related to the increased expression of cell adhesion molecules after exercise, which may contribute to the extravasation of neutrophils into damaged tissue, including skeletal muscle (Figure 1).[10] A reduction in L-selectin (CD62L) expression has been reported immediately after exercise, followed by an increase during recovery.[11] The expression of CD11b also occurs in response to physical exercise.[12]

Macrophages and monocytes

Macrophages are tissue cells that bridge the gap between the innate immune system and the adaptive immune system. They act by producing cytokines, phagocytizing microorganisms, presenting antigens via MHC molecules and initiating the tissue repair process.[4,6] Exercise stress has a stimulating effect on most macrophage and monocyte functions.[13] The action of catecholamines released during exercise causes transient monocytosis, but exhaustive exercise in those individuals who have an adjacent inflammatory condition can reduce the number of macrophages recruited to the inflammatory site.[14] It

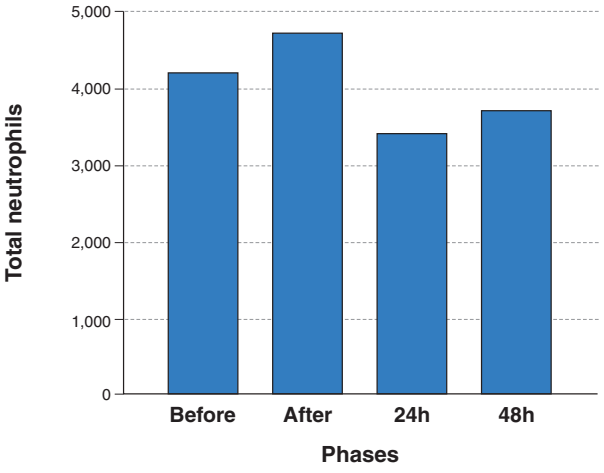

Figure 1
Total neutrophil counts at moments before, immediately after, 24h after and 48h after exercise.

has been shown that during and soon after exercise, chemotaxis, phagocytosis and cytotoxic activity are increased, possibly associated with increased secretion of cortisol, prolactin and thyroxine.[15,16] Prolonged and strenuous aerobic exercises decrease the expression of Toll-like receptors (TLRs) in macrophages and compromise the presentation of antigens to T lymphocytes, preventing, above all, the Th1 inflammatory response. This anti-inflammatory effect prevents tissue damage caused by inflammatory mediators and reduces the risk of chronic inflammatory diseases, but increases the susceptibility of infections by intracellular microorganisms.[17,18]

Dendritic cells

Dendritic cells have the ability to internalize antigens and express a large number of costimulatory molecules, being an important antigen-presenting cell for T cells, stimulating their clonal expansion.[19] They are also considered a bridge between the innate immune system and the adaptive immune system,[20] being one of the first cells to reach the site of infection.[4,6] Chiang et al. observed in rodents that, after five weeks of training on a treadmill with increments in speed and incline over the weeks, there was an increase in the number of dendritic cells, in their class II MHC expression and IL-12 production, suggesting the capacity of induction of cellular immune response.[21]

Natural killer cells

Natural killer (NK) cells are a heterogeneous population of T lymphocytes that express characteristic markers, such as CD16 and CD56,[22] and that are responsible for the recognition and lysis of cells infected by viruses, bacteria, protozoa and tumor cells, in addition to act against the spread of the tumor.[23] The cytolytic activity of these cells is increased by interferon-alpha (IFN-α)[24] and interleukin-2 (IL-2), while certain prostaglandins and immune complexes negatively regulate the function of NK cells.[22,25] This cell type is very responsive to the stimulus of physical exercise, exhibiting an increase of up to 6 times in its serum levels after physical effort.[26] This is mainly due to the responsiveness of these cells to increased levels of adrenaline and noradrenaline, which are released during exercise. This release, and consequently, the increase in serum NK cells, depends on the intensity and duration of physical exercise.[27] On the other hand, it was shown that after intense and long-term exercise, the concentration of NK cells and cytolytic NK activity tend to decrease below pre-exercise values. The maximum reduction in NK cell concentrations and, therefore, their lowest activity, occurs 2-4 h after exercise, probably due to the action of prostaglandins.[28]

Cytokines and chemokines

Cytokines are soluble glycoproteins that, in general, have a low molecular weight (between 5,000 and 30,000) and play a central role in mediating and regulating immune responses when launched at the site of inflammation.[29-31] Chemokines comprise a family encompassed by cytokines, responsible for mediating and moving leukocytes to areas of inflammation.[4] These substances have the ability to act as messengers between the cells of the immune, hematopoietic and neuroendocrine system.[32] These molecules can act as pro- or anti-inflammatory substances. The main anti-inflammatory cytokines are IL-10 and TGF-beta (transforming growth factor β) which can inhibit the production of pro-inflammatory cytokines. Among the pro-inflammatory cytokines we can mention IL-1, IL-2, IL-12, IL-18, IFN-γ and TNF-α. The production of anti-inflammatory cytokines, especially IL-10, can be regulated by a variety of factors, such as catecholamines, glucocorticoids and prostaglandin E2 (PGE2), which are produced during physical exercise.[32] IL-6, which is currently being called myokine, is a cytokine that can trigger

several modulating functions due to the change in its physiological levels, inducing pro-inflammatory, anti-inflammatory effects or even both, depending on the body and/or cell group in which they are synthesized.[9,34] IL-6, during prolonged exercise, is released in high concentrations by skeletal muscles.[35-37] The plasma concentration of IL-8 chemokine may increase in response to inflammation resulting from a physical exercise session in which eccentric muscle contractions occur.[38,39]

Lymphocytes

Lymphocytes are divided into T and B lymphocytes, in which the T cell is responsible for eradicating infections caused by intracellular pathogens and activating other cells. B cells, on the other hand, are responsible for secreting antibodies and creating memory, when transformed into plasma cells after their activation. These cells are also responsible for antigenic memory, that is, in a new exposure, a faster and more intense immune response is induced, which helps to eliminate the pathogen more effectively.[4] During moderate physical exercise, the concentration of lymphocytes increases in the vascular bed and, after strenuous exercise, it decreases to levels below the pre-exercise period.[40,41] This drop can be a consequence of an apoptosis mechanism or due to the release of adrenaline and cortisol, which inhibit lymphocyte function and are released during high-intensity exercise.[10] The ratio between CD4 + and CD8 + lymphocyte levels decreases as CD8 + T cells increase in blood relative to TCD4.[42,43]

Immunoglobulins

Immunoglobulins are products of B cells that are secreted after contact with the specific antigen.[27] After high and medium intensity exercise, an increase in serum immunoglobulins has been described. This information can be explained by the contraction of plasma volume that occurs after exercise.[13] The influx of proteins from the extra to the intravascular, mainly represented by immunoglobulin-rich lymph, could also explain the finding.[43] However, the IgA, present in the mucous membranes of the upper respiratory tract and, therefore, responsible for protecting this system, can significantly decrease after high-intensity exercise, which may explain the prevalence of respiratory diseases that affect the upper airways in athletes (URTI).[27,44]

Physical exercise

Physical activity is considered one of the main components of healthy living. It can be used to maintain health and well-being, as it is capable of modulating some neurological and endocrinological aspects in individuals who undergo regular training. The practice of physical exercise is currently used as a means of health promotion and has been proposed as a non-pharmacological intervention that brings several benefits to the individual's health.[45] In addition to the functions related to the prevention of excess body weight, systemic inflammation and non-communicable chronic diseases, it is suggested that physical exercise has a beneficial potential in reducing communicable diseases, including viral pathologies, due to the stimulation of cellular immunity.[46,47]

The ability to carry out training depends on the metabolic responses of the human body to convert chemical energy from muscle tissues in the form of adenosine triphosphate (ATP) subsequently cleaved into adenosine diphosphate (ADP) into mechanical energy, which causes it to occur muscle contraction.[48] Seeking to understand the relationship between metabolism and physical exercise, numerous studies have been carried out, with the aim of demonstrating which cellular responses would be triggered by training and which variables could interfere with this cellular response.[17] The most common variable found in the researched articles concerns the intensity of training, classifying physical exercise according to the level of effort, which can be light, moderate or intense. This classification takes into account physiological parameters of the body such as maximum heart rate, maximum oxygen consumption and exercise perception index.[50]

Physical exercise is capable of generating stress for the body. Physiologically, there is loss of homeostasis, that is, there is a systemic imbalance due to changes in blood volume, body temperature and maximum oxygen consumption.[51] Before and during exercise, some chemical, neural and hormonal agents undergo adjustments, with the objective of providing cardiovascular changes with an increase in the frequency and pumping strength of the heart, changing the blood flow in proportion to the intensity of the exercise. In response to changes, the body modifies metabolic and physiological parameters to maintain balance, thus the cellular responses in the acute phase, in the short term, are different from the chronic phase, in the long term.[49]

Acute phase

An exercise session performed in isolation can be characterized as an acute phase, and in this phase some physiological effects may already occur. These effects can be divided into immediate and late effects. The immediate effects happen right after the exercise and the late ones from 24 to 72 hours after the exercise. The immediate acute effects correspond to sweating, increased heart rate and pulmonary ventilation, and the late effects consist of improved insulin sensitivity and catecholamine secretion. At the blood level we can find a leukocytosis, and this increase in leukocytes happens due to the increase in catecholamines. These substances induce an increase in the amount of neutrophils and natural killer (NK) cells,and some experimental studies have already shown an increase in the number of macrophages and a decrease in the expression of MHC II.[52-55]

Chronic phase

The chronic phase of physical exercise occurs after numerous training sessions performed on a regular basis. In this phase, there is an adaptation, and the stimuli of the acute phase become more effective. In this phase, muscles are strengthened, cardiovascular conditioning and lipid profile improve. This regular exercise practice, especially in a moderate way, makes the individual to create tolerance to stressful stimuli. This tolerance also takes place in the immune system. It is noteworthy that these changes are related to the type of exercise, intensity and load, that is, each type of training results in the activation or inactivation of cellular and molecular mechanisms, which can directly interfere with the human immune system.[13,56]

Types of training

Resistance training

Resistance training consists of carrying out exercises with the use of weights and machines, with the objective of working against muscular resistance, generating an overload on the muscle,[56] which favors muscular resistance and, consequently, an increase in lean mass and a reduction in body fat. With the regular practice of resistance training, it also generates a reduction in fat mass, which improves the physical adaptation of the body, facilitating daily activities. Weight training and weight lifting are examples of resistance training.[57]

Aerobic training

Aerobic training consists of a greater number of repetitions, longer duration and moderate intensity. During this type of exercise there is a greater consumption of oxygen by the body, in the form of ATP to generate muscle work. The benefits for the body are increased heart efficiency, reduced fat weight, improved mental health, mood and immune system. Cycling, swimming, and walking are examples of aerobic training.[56-58]

Intensity

The exercise intensity is related to the respiratory capacity (VO_2max) and has as variables the training volume, the exercise complexity, the individual's capacity and the duration time.[58] Physical exercise is a metabolic stress for the body, intense training generates even greater stress, as it increases the intracellular formation of reactive oxygen species (ROS) promoting greater oxidative stress.[21] Moderate or low intensity physical exercise helps a healthy immune response and reduces oxidative stress after an exercise session, thus not overloading the immune system, becoming more efficient and improving the response.[59]

Intensity is directly related to immunity, as it is the main variable that defines the body's immune response to the type of training. Thus, low and moderate intensity exercises bring greater benefits related to the immune system. Immunosuppression induced by high exercise intensity has been studied since 1994, by Nieman, who proposed the J-curve, which shows the relationship between exercise intensity and the possibility of infection (Figure 2). Analyzing all parameters and variables found within the performance of physical exercise, it is noted that the frequency, intensity and volume of training are the main factors capable of influencing the individual's cellular adaptations and metabolism, which includes the immune response.[15,52,59]

Immune response to physical exercise

The immune system has a specific response to the type of stimulus that exercise provides and, along with changes in immune function, molecular, cellular and tissue changes are also noted. This difference in response is related to the level of stress that training generates, the individual's physical fitness and regularity of stimuli.[60] Considering that physical

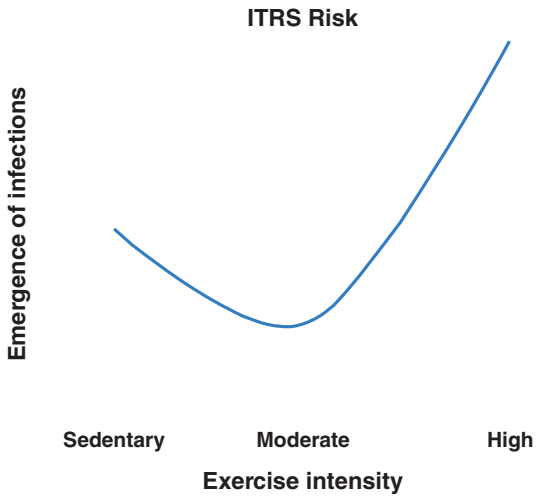

Figure 2
"J" curve model of the relationship between exercise load and the onset of upper respiratory tract infections (URTIs).

exercise induces inflammation (local and systemic), as well as tissue repair after trauma, physiological adaptations resulting from training can also be classified as acute and chronic.[61]

The acute response aims to adjust homeostasis for tissue repair right after a single or several exercise sessions. Furthermore, it can be subdivided into immediate or late, as mentioned in the previous topic.[28] Immediate acute adaptations are those that occur within a few minutes after the end of the exercise, such as increases in heart rate, blood pressure and body temperature. However, these values can change according to the type of exercise, static or dynamic, for example.[62,63] In static exercises, blood flow obstruction causes the metabolites produced during contraction to accumulate, activating muscle chemoreceptors, which promote a significant increase in sympathetic nervous activity, causing an increase in heart rate, with a decrease in systolic volume and a smaller increase in cardiac output.[28] On the other hand, blood pressure tends to increase, due to the increase in peripheral vascular resistance.[62] In dynamic exercises, there is high sympathetic nervous activity, which causes an increase in cardiac output, heart rate and stroke volume.[28] The release of muscle metabolites causes vasodilation in active muscles, which decreases peripheral vascular resistance.[62] In dynamic exercises, there is high sympathetic nervous activity, which causes an increase in cardiac output, heart rate and stroke volume.[28] The release of muscle metabolites causes vasodilation in active muscles, which decreases peripheral vascular resistance.[62]

A study in eight healthy men attempted to analyze the effects of three different types of exercise on white blood cell counts during and after exercise. The subjects were exposed to the following experiments: aerobic exercise of intensity equivalent to 90-97% of VO_2máx for 5 min, prolonged: two hours of exercise in cycle ergometry (long) completed at 60 to 65% of VO_2máx, and resistance: three sets of 10 repetitions at 60 to 70% of 1-RM strength (maximum repetition). Participants remained seated for a recovery period of 3 hours after each type of exercise, later compared with the control group, which was seated for 5 hours. During exercise, NK cells, T and B cells were recruited into the bloodstream, in addition to an increase in the amount of circulating neutrophils and monocytes. This leukocytosis occurred immediately after the exercises and persisted for 3 hours after the end.[63]

TCD3 and TCD4 lymphocyte counts showed a similar increase between aerobic and prolonged exercise. However, in the post-exercise period, after 3 hours of rest, TCD3 and TCD4 lymphocyte counts from aerobic exercise were below normal, characterizing lymphocytopenia. Circulating cells CD3 CD16+ CD56+ (natural killer) increased after aerobic exercise, a little less in prolonged exercise and even less in resistance exercise. However, all returned to baseline 3 hours later. Exercise induced few changes in B cell count (CD19+), which increased only at peak aerobics, immediately after exercise, and an increase after 3 hours in resistance exercise.[64]

The probable justifications for lymphocytopenia, caused after the end of exercise, may be related to the reduction in adrenaline levels, followed by an increase in the concentration of cortisol and growth hormone, leading to a redistribution of leukocytes and lymphocytes, thus presenting, an immunosuppressive effect.[27] On the other hand, the increase in natural killer cells is due to the greater secretion of catecholamines, especially epinephrine, and the release of some factors of the complement system, such as interferons (IFN-1), interleukins (IL-2) and beta-endorphin hormone as adjuvants in this process.[64] After 3 hours of exercise, NK cells

returned to baseline values, considering the release of prostaglandins by neutrophils and macrophages together with hormonal factors such as cortisol, which has an immunosuppressive effect.[30] Over the 24 or 48 hours after an exercise session, the acute phase that used to be immediate becomes late, in which reductions in blood pressure and increased sensitivity are observed.[62]

Chronic adaptations, on the other hand, result from systematic and regular exposure to long-term exercise sessions, so the chronic phase is the sum of the effect of acute adaptations in the neuromuscular system over a few weeks, which generate morphofunctional changes in physiological systems. As an example, resting bradycardia, muscle hypertrophy, left ventricular hypertrophy and increased aerobic power.[28,63] In addition, there is an increase in blood flow to the skeletal muscles and to the cardiac muscle, as physical exercise promotes angiogenesis.[62]

A study carried out with 28 elderly individuals with a duration of six months of moderate training showed that the absolute number of CD4+ T lymphocytes (CD28+CD4+) increased, as well as that of IFN-γ (Th1) producing cells, while the T cells, responsible for IL-4 (Th2) production, did not undergo significant changes.[63] Some other studies support these data demonstrating that the total number of T lymphocytes, CD4+ T cells, and IL-2R expression in T cells increased in patients undergoing moderate intensity exercise combined with resistance and strength, or a training program exclusively for resistance. It was concluded that the increased expression is responsible for favoring the Th1 response, which prevents infections caused by intracellular microorganisms.[31,62]

The increase in interleukin-6, IL-6, is directly related to exercise intensity,[31] given the fact that it is found in abundance in muscle tissue, which makes it more sensitive to stimuli and intensity of physical exercise.[35] On the other hand, high-intensity activities generate increased concentrations of anti-inflammatory cytokines (Th2 pattern), which can result in increased susceptibility to infections, such as upper airway infection (URTI). Athletes with low plasma concentrations of IL-10 (low concentration also in the nasal mucosa), IL-1ra and IL-8 at rest are more likely to develop respiratory diseases.[65] These data demonstrate that the immune response can be modulated to different stimuli, that is, depending on the intensity of physical exercise (Figure 3).[62]

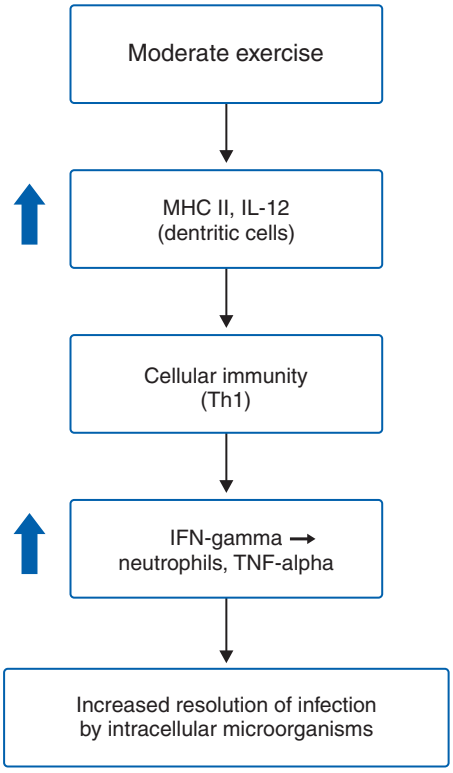

Figure 3
Summary of the effects of moderate-intensity exercise.

In summary, we can say that moderate-intensity exercise protects against infections caused by intracellular microorganisms, as it directs the immune response to the predominance of Th1 cells, in which the type of response is cellular.[62] It is associated with increased leukocyte function, helps chemotaxis, degranulation, phagocytosis and neutrophil oxidative activity one hour after physical exercise60. High-intensity exercise, on the other hand, generates an increase in the levels of anti-inflammatory cytokines (Th2 pattern), with the objective of reducing damage to muscle tissue due to the stress generated, making the individual more susceptible to infections (Figure 4).[62] After performing just one session of intense exercise, a temporary immunosuppression takes place, known as the "immune window", and can last from 3 to 72 hours.[60]

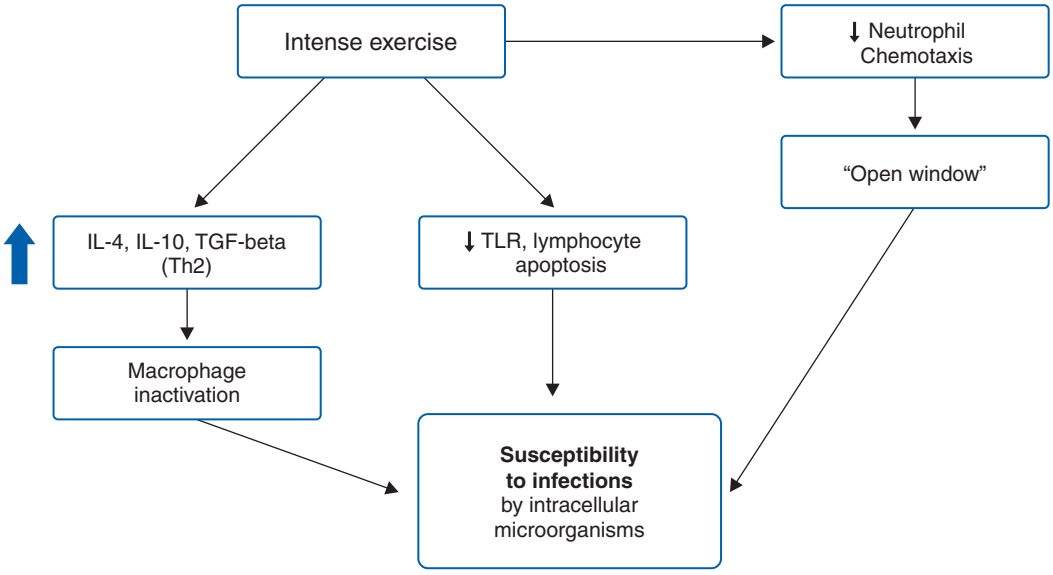

Figure 4
Summary of the effects of high intensity exercise.

Conclusion

The practice of regular physical exercise is essential for health maintenance, as it allows an adequate immune response, leads to the strengthening of the cardiovascular and respiratory system, in addition to improving the lipid profile of the individual who practices it. Science is rich in studies with evidence showing that physical exercise is capable of generating changes in the concentrations and functions of some cells of the immune system. Some aspects, such as exercise duration and intensity, influence how and what the immune response will be to the stimulus. An understanding of the immunological adaptations caused by physical exercise is necessary so that, in a future perspective, the best type of training for each person can be directed, taking into account the individuality of the practitioner.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Cross-reactivity among beta-lactams: a practical approach

Reatividade cruzada entre betalactâmicos: uma abordagem prática

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ABSTRACT

Beta-lactams are the drugs most commonly involved in hypersensitivity reactions mediated by a specific immune mechanism and are the main triggers among antibiotics. They include penicillins, cephalosporins, carbapenems, monobactams and beta-lactam inhibitors. The basic chemical structure of these drugs consist on the presence of the following components: beta-lactam ring, an adjacent ring and side chains, all of which are potential epitopes. IgE antibodies and T lymphocytes are often involved in recognizing those epitopes. Cross-reactivity depends on the stability of intermediate products (antigenic determinants) derived from the degradation of the beta-lactam ring, on the adjacent rings, and on the structural similarity of the side chains between drugs. Classically, it was believed that there was a

RESUMO

Os betalactâmicos são a classe de drogas que mais causam reações de hipersensibilidade envolvendo um mecanismo imunológico específico, e são os principais desencadeantes entre os antimicrobianos. São representados pelas penicilinas, cefalosporinas, carbapenêmicos, monobactâmicos e inibidores da betalactamase. A estrutura química básica destes fármacos consiste na presença dos seguintes componentes: anel betalactâmico, anel adjacente e cadeias laterais, sendo todos potenciais epítopos. Os anticorpos da classe IgE e linfócitos T estão frequentemente envolvidos no reconhecimento desses epítopos. A reatividade cruzada depende da estabilidade dos produtos intermediários (determinantes antigênicos) derivados da degradação dos anéis betalactâmicos, anéis adicionais e da semelhança estrutural das

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great potential for cross-reactivity within each class and even between classes, but studies from the last decade showed that individuals allergic to penicillin (with positive skin tests) reacted to cephalosporins in approximately 3% of cases, to carbapenems in about 1%, and rarely reacted to monobactams. This reactivity or tolerance seems to be linked to the degree of similarity between the side chains of these antibiotics. In this review, we emphasize the importance of systematic investigation to confirm or exclude allergy to beta-lactams, we describe the prevalence of cross-reactivity between these drugs and we suggest an algorithm for approaching these patients based on their chemical structure and on data published in the literature.

Keywords: Beta-Lactams, penicillins, cephalosporins, drug hypersensitivity.

cadeias laterais entre as drogas. Classicamente acreditava-se num grande potencial de reatividade cruzada dentro de cada classe e até entre as classes, mas estudos da última década mostraram que indivíduos alérgicos à penicilina (com testes cutâneos positivos) reagiam às cefalosporinas em aproximadamente 3% dos casos, aos carbapenêmicos em cerca de 1%, e praticamente não reagiam aos monobactâmicos. Essa reatividade ou tolerância parece estar vinculada ao grau de similaridade entre as cadeias laterais desses antibióticos. Nesta revisão, ressaltamos a importância da investigação sistematizada na confirmação ou exclusão de alergia aos betalactâmicos, descrevemos a prevalência da reatividade cruzada entre estes fármacos e sugerimos um algoritmo de abordagem desses pacientes baseados em sua estrutura química e nos dados publicados na literatura.

Descritores: Betalactamas, penicilinas, cefalosporinas, hipersensibilidade a drogas.

Introduction

Antibiotics are among the most prescribed drugs in the world in healthcare institutions.1 Beta-lactams (BL) are considered essential in the treatment for various situations such as: pharyngitis and skin infections caused by group A Streptococcus; meningitis and puerperal sepsis caused by group B Streptococcus; endocarditis by Streptococcus of the Viridans group; syphilis, particularly in pregnant women; osteomyelitis and skin infections caused by *Staphylococcus aureus*, among others.[2] Approximately 10% of the US population reports allergy to penicillin, but for the most part the signs and symptoms referred to are non-specific such as gastrointestinal symptoms, pruritus without lesions, undefined reactions that occurred more than 10 years ago or a family history of BL allergy, which rarely configure true hypersensitivity reactions. Only about 5% of all patients with a history of allergy to BL have their reactions confirmed after a systematic investigation as hypersensitivity reactions, either immediately involving IgE class antibodies or late mediated by T lymphocytes.[2,3] The BL allergy label is a public health problem with the following repercussions: increased use of second-line or broader-spectrum antimicrobials, increased microbial resistance (Multi-resistant Staphylococcus, Vancomycin-resistant Enterococcus), greater toxicity and increased costs (longer hospital stays and readmissions).[2,4] Only about 5% of all patients with a history of allergy to BL have their reactions confirmed after a systematic investigation as hypersensitivity reactions, either immediately involving IgE class antibodies or late mediated by T lymphocytes.[2,3] The BL allergy label is a public health problem with the following repercussions: increased use of second-line or broader-spectrum antimicrobials, increased microbial resistance (Multi-resistant Staphylococcus, Vancomycin-resistant Enterococcus), greater toxicity and increased costs (longer hospital stays and readmissions).[2,4]

Our group recently published a comprehensive review on BL hypersensitivity.[5] To carry out this update focused on the cross-reactivity between the antibiotics in the group, searches were performed for original articles, reviews, guidelines and consensus in the MEDLINE and Latin American and Caribbean Literature in Health Sciences (LILACS) databases, using the terms: *beta-lactams hypersensitivity*, *beta-lactam cross-reactivity*, *penicillins*, *cephalosporins*, *carbapenems*, *monobactams*, *diagnostic tests*, *risk stratification*.

Chemical structure of beta-lactams

BL are the antimicrobials most implicated in drug hypersensitivity reactions involving a specific immune mechanism.[6-8] The main classes of BL according to their chemical structures are: penicillins, cephalosporins, carbapenems and monobactams. The basic chemical structure of BLs consists of the presence of the following components: BL ring, adjacent ring and side chains; which are potential immunogenic sites capable of triggering sensitization of lymphocytes to BL. Penicillins contain the BL ring, an adjacent ring (thiazolidine) and an R1 side chain that communicates with the BL ring. Cephalosporins have the BL ring, another adjacent ring (dihydrothiazine) and two side chains R1 and R2, with R1 also binding to the BL ring (similar to penicillins) and R2 communicating with the adjacent ring. Carbapenems have the BL ring, an adjacent ring (dihydropyrrole) and two side chains R1 and R2. Monobactams, on the other hand, have only the BL ring associated with an R1 side chain. Finally, some authors consider that the clavulanic acid beta-lactamase inhibitor would be a fifth class of BL, and this antibiotic does not have an adjacent ring. As this drug is only available on the market in association with aminopenicillins, this classification into five classes is not consensual in the literature. The chemical structure of the BL classes is outlined in Figure 1.[5]

Immune mechanisms

Cross-reactivity between different BLs has been reported in studies, and its approach needs to be done in the context of knowledge of the immunological mechanisms involved. Hypersensitivity reactions to BL occur mainly through the production of IgE class antibodies, activation of T lymphocytes and also direct pharmacological interaction with protein receptors on cells (HLA and TCR).[7] It is believed that IgE class antibodies and lymphocytes T recognize as epitopes some segment of the BL chemical structure.

BL are small molecules that bind to plasma proteins forming hapten-carrier complexes. Immunoreactivity against a BL depends on the stability of intermediate products (antigenic determinants) arising from the degradation of BL rings and adjacent rings. The determinants of penicillins are stable and well defined, while the determinants of cephalosporins are not well known.[8] The main determinants or PPL (peniciloyl poly-lysine) correspond to 95% of these metabolites and the secondary or MDM (penicilloate and peniloate) to approximately 5%.

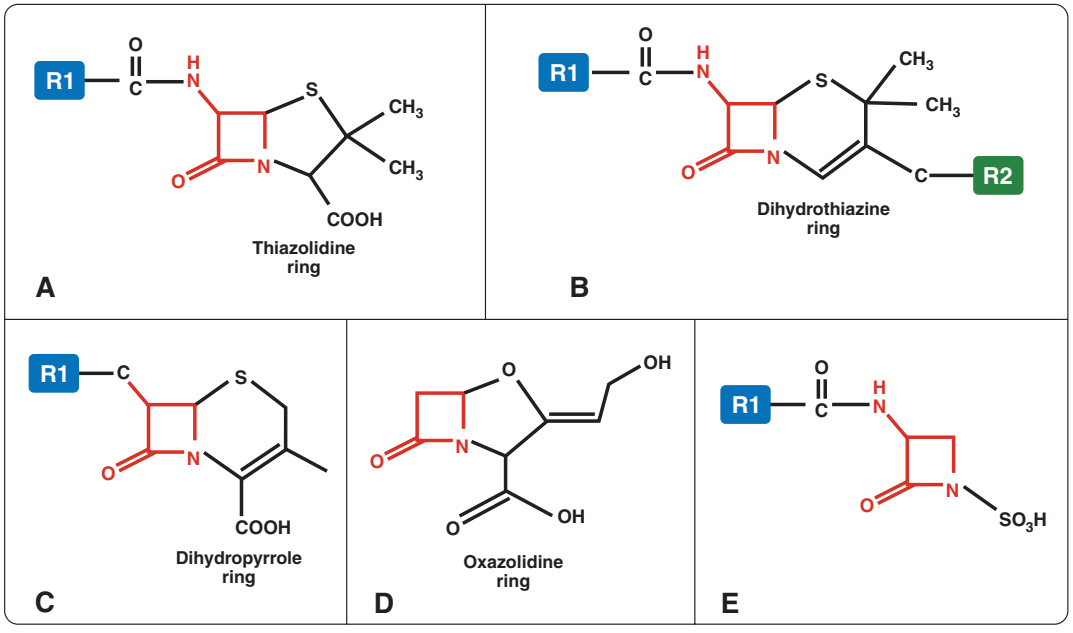


Figure 1
Basic chemical structure of the five classes of beta-lactams.
Source: Felix M. et al.[5]

It is postulated that these determinants bind to carrier plasma proteins and can stimulate the immune response.[2] Antibodies of the IgE class can bind to the BL ring, adjacent ring or side chains and form the basis of cross-reactivity involving penicillins, justifying the use of skin tests in the systematic investigation of immediate reactions to these drugs. However, more recently, it has been demonstrated that cross-reactivity between BL is mainly triggered by the similarity or structural identity between the side chains of these drugs, suggesting that this segment is the epitope in most hypersensitivity reactions.[9-12]

Penicillins and cephalosporins are the two classes of BL that most cause hypersensitivity reactions, both immediate and late, involving practically all the mechanisms described by Gell and Coombs.[12] The main immunological mechanisms involved in BL hypersensitivity are summarized in Table 1.

Clinical manifestations

Immediate reactions by IgE class antibodies usually occur within the first hour after exposure to the drug, although it may occur within 6 hours, but tends to occur earlier after re-exposure. Cutaneous manifestations such as urticaria, angioedema, pruritus and flushing-type erythema are the most frequent. Other immediate manifestations include: respiratory symptoms (rhinorrhea, nasal congestion, cough, dyspnea, hoarseness); gastrointestinal (diarrhoea, vomiting and abdominal pain); cardiovascular (hypotension, tachycardia), and more severe conditions with association of systemic signs and symptoms (anaphylaxis).[2]

Late manifestations mediated by T lymphocytes usually occur more than 1 to 6 hours after exposure to the drug, appearing more commonly after the first 24 hours of starting treatment. Maculopapular rash is the

Table 1
Immunological mechanisms in hypersensitivity reactions to beta-lactams.

Mechanism (modified Gell and Coombs)	Type of immune response	Pathological features	Clinical examples
Type I	Ige	Mast cell degranulation	Anaphylaxis, urticaria, angioedema, asthma, rhinitis
Type II	IgG and FcR	FcR-dependent cell death	Hemolytic anemia
Type III	IgG, complement and FcR	Immune complex deposition	Serum sickness
Type IVa	TH1 (IFN-gamma)	Monocyte activation	Contact eczema
Type IVb	TH2 (IL-4 and 5)	Eosinophilic inflammation	EMP, DRESS(?)
Type IVc	Cytotoxic T	CD4 or CD8-dependent cell death	SSJ/NET, EFD
Type IVd	T cell (IL-8)	Neutrophil activation	HANDLE
Type IVe	T cell (IL-12, IFN-gamma)	Activating CD4 or CD8	"Accelerated" urticaria
Undefined	T cell	TH1 and TH2 complex patterns	DRESS
Specific organ	T cell	Complex mechanisms	Hepatitis, pneumonitis

Ig = immunoglobulin, FcR = receptor for Fc fraction, TH = T-helper, IFN = interferon, IL = interleukin, EMP = maculopapular rash, DRESS = drug rash with eosinophilia and systemic symptoms, SSJ = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, EFD = fixed drug eruption, PEGA = acute generalized exanthematic pustulosis.
Modified from Blanca-Lopez N. et al.[12]

most frequent reaction, but severe manifestations such as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematic pustulosis (PEGA), drug reaction with eosinophilia and systemic symptoms (DRESS) also known as drug-induced hypersensitivity syndrome (SHID) can also occur.[2,13,14]

Diagnostic investigation

This review of current studies of cross-reactivity among BL addresses systematic investigation using the following diagnostic tools: in vitro tests where available, immediate or delayed reading skin tests, and provocation tests, which are the gold standard for confirming or ruling out the drug involved in the reaction and finding a safe alternative drug among BL.

Hypersensitivity reactions to BL should be addressed in a systematic way, through a detailed clinical history followed by immediate reading skin tests (prick and intradermal) or delayed reading skin tests (contact test and/or late reading intradermal skin test). BL contact tests are performed in 5% petroleum jelly, but the concentration for puncture and intradermal varies between medications. Table 2 summarizes the non-irritant concentrations used in puncture and intradermal tests with these drugs.[5] The negative predictive value of skin tests when using PPL and MDM is greater than 93% and the positive predictive value is around 50 to 75%.[2] Individuals with negative skin tests may be submitted to the provocation test after risk stratification.[2]

In vitro tests can be used to complement the investigation when available. In immediate reactions, the following can be used: tryptase, specific IgE dosages and the basophil activation test (BAT). Tryptase in the acute phase may indicate whether mast cell degranulation has occurred, and when elevated it indicates that there was an anaphylactic-type reaction; basal tryptase should be evaluated to rule out the possibility of increase due to systemic mastocytosis or other non-clonal mast cell disorders. Specific IgE dosages for BL have a low sensitivity and are available for some drugs (Penicillin G and V, amoxicillin, ampicillin and cefaclor). The main use of specific IgE dosage would be in patients at high risk for severe immediate reactions (anaphylaxis) before performing skin and provocation tests. BAT quantifies drug-induced CD63 or CD203c expression using flow cytometry, but it is only available in a few specialized centers and its greatest indication would also be in high-risk immediate reactions prior to the performance of the challenge test. In late reactions, lymphocyte transformation (TTL) and ELISPOT (enzyme-linked immunosorbent spot assay) tests can be useful in evaluating these reactions. The TTL

Table 2
Maximum non-irritant concentrations for skin tests (puncture and intradermal) with beta-lactams.

Hapten (drug)	Puncture and intradermal
Benzylpenicillin	10,000 UI/mL
Amoxicillin	20 mg/mL
Ampicillin	20 mg/mL
Cefepime	2 mg/mL
Other cephalosporins	20 mg/mL
Imipenem	0.5 mg/mL
Meropenem	1 mg/mL
Aztreonam	2 mg/mL

Source: Felix M. et al.[5].

measures the proliferation of T lymphocytes in the presence of the suspected drug over a period of 5 to 7 days and the ELISPOT detects cells producing antigen-specific cytokines after incubation with polymorphonuclear cells for 24 hours in the presence of the suspected drug. BAT and assays for late reactions, in our environment, are still only used at the research level.[2,13,15]

Risk stratification

Risk stratification must be approached taking into account the characteristics of the initial clinical manifestations of the suspected drug and the presence of comorbidities in the patient. It can be classified as low, moderate and high risk. Table 3 shows the main clinical aspects related to BL risk stratification.[5,15] Cardiovascular, renal and respiratory

Table 3
Risk stratification in beta-lactam hypersensitivity.

Risk level	Clinical classification of reaction	Clinical picture of the reaction
High risk	Immediate reactions	– Anaphylaxis – Hypotension – Laryngeal edema – Bronchospasm – Urticaria and/or angioedema – Generalized erythema
High risk •	Non-immediate reactions	– SSJ/NET – DRESS – HANDLE – Fixed generalized drug eruption bullous – IgA bullous dermatosis – Severe maculopapular rash (confluent rash and evolution to erythroderma; duration > 1 week; fever, eosinophilia) – Serum disease simile – Organ-specific manifestations (cytopenias, nephritis, hepatitis, pneumonitis) – Drug-induced autoimmune diseases (lupus, pemphigus vulgaris, bullous pemphigoid)
Low risk	Immediate reactions	– Isolated generalized itching – Isolated gastrointestinal symptoms (nausea, vomiting, diarrhea) – Localized urticaria
Low risk	Non-immediate reactions	– Contact dermatitis – Local reaction to IM administration – Palmar exfoliative rash – Fixed drug eruption – Late-onset urticaria – Mild to moderate maculopapular rash (especially in children) – SDRIFE

DRESS = drug rash with eosinophilia and systemic symptoms, IM = intramuscular, TEN = toxic epidermal necrolysis, IgA = immunoglobulin A, PEGA = acute generalized exanthematic pustulosis, SDRIFE = symmetrical drug-related intertriginous and flexural exanthema, SSJ = Stevens Johnson syndrome.
Source: Felix M. et al.[5].

diseases in activities; the use of drugs such as beta-blockers, antiarrhythmics, ACE (angiotensin-converting enzyme) inhibitors; Systemic mastocytosis and even the presence of pregnancy are potential high-risk situations. In the context of BL risk stratification, the two most frequent practical scenarios are also the most debated in the assessment of hypersensitivity and cross-reactivity between BL: patients allergic to penicillins or those allergic to some cephalosporins.[16-20]

Knowledge of the basic structure of BL, taking into account the similarity and identity between these drugs in the context of cross-reactivity, becomes essential in choosing an effective and safe alternative drug during the investigation, as recommended by the main studies.[17-21] Table 4 summarizes the BLs available in the Brazilian market that have similar or identical R1 or R2 side chains.

Allergic to penicillin: cross-reactivity to aminopenicillins

Despite the large number of patients labeled as allergic to penicillin, more than 95% can tolerate penicillin after systematic investigation. Due to this low prevalence of true penicillin allergy, individuals with a history of penicillin reactions should be evaluated to confirm or rule out this diagnosis, thus avoiding the use of broad-spectrum alternative drugs from other classes, such as vancomycin and quinolones, which elevate the costs, increase the selection of resistant strains such as *Enterococcus* and *Staphylococcus aureus* resistant to vancomycin and *Clostridium difficile*.[4,21,22]

Studies report a high cross-reactivity between benzylpenicillin and semi-synthetic penicillins, more precisely the aminopenicillins (amoxicillin and ampicillin), as they share the amino group in the R1 side chain.[15,17,19,23]

On the other hand, studies with individuals allergic to aminopenicillins, who presented reactions mediated by IgE or even delayed, showed negative skin tests for benzylpenicillin (penicillin G) and phenoxymethylpenicillin (penicillin V) and tolerance to provocation with these drugs. Blanca-Lopez et al. studied 58 individuals with immediate reactions to amoxicillin or amoxicillin/clavulanic acid. Of these, 7 were positive for penicillin determinantsG, 40 were positive to amoxicillin, but tolerated penicillins G and V, and 11 were positive only to clavulanic acid, tolerating penicillin G, V and amoxicillin.[24] Torres et al. diagnosed immediate hypersensitivity to penicillins in 290 patients through skin tests, specific IgE dosages or provocation tests, with amoxicillin involved in 65% of cases and benzylpenicillin in 3%. In that sample: 58% were considered selective reactors to aminopenicillins (amoxicillin or ampicillin) and the other 42% were also positive for the PPL or MDM determinants, being classified as non-selective responders.[25] Regarding late reactions to aminopenicillins, another study showed that 72% of these patients tolerated penicillin V.[26]

Table 4
Summary of beta-lactams available in the Brazilian market that share some similarity between the R1 or R2 side chains.

Similar or identical R1 chain	Similar or identical R2 chain
Benzylpenicillin, Amoxicillin, Ampicillin, Piperacillin, Cephalexin, Cefaclor and Cefadroxil	Cephalexin and Cephadroxil
Cephalotin and Cefoxitin	Cephalotin, Cefuroxime, Cefoxitin and Cefotaxime
Ceftriaxone, Cefuroxime, Cefotaxime, Ceftazidime, Cefepime, Ceftaroline and Aztreonam	

Modified from Chaudhry S.B. et al.[20]

Penicillin allergic: cross-reactivity with cephalosporins

Some previous studies showed conflicting data with current studies in patients allergic to penicillin and cross-reactive to cephalosporins. It is believed that the contamination of cephalosporins with penicillin G traces in their chemical processing led to an overestimation of the prevalence of cross-reactivity between these classes of BL.[2] In studies carried out from 1990 onwards in patients with proven IgE-mediated reactions to penicillins, the rate of positivity to cephalosporin skin tests ranged from 0 to 27%,[27] however, more recent data suggest that the rates should actually vary from according to the similarity of the R1 side chain between penicillins and cephalosporins.

Caimmi S. et al. evaluated the safety of cefuroxime in patients with proven hypersensitivity to one or more BL. Of the 143 allergic individuals evaluated, the prevalence of sensitization to cefuroxime in patients allergic only to penicillins was 4.2%, showing that it is a safe alternative drug to be used after carrying out tests in this group of individuals.[28] Importantly, cefuroxime has an R1 chain quite distinct from the R1 chains of penicillins.

In 2018, Professor Antonino Romano's group published a large series, in which they studied 252 individuals with IgE-mediated allergy to penicillins in relation to cephalosporin reactivity. To do so, they used an extensive algorithm that included IgE measurement for cefaclor, skin tests and challenge with cephalosporins of varied structures. We found 99 (39.3%) people with some positive test for cephalosporins, but almost all were positive for cephalosporins with R1 chains identical or similar to those of penicillins. No patient responded to the challenge with cefuroxime and ceftriaxone, which do not share R1 with penicillins. Therefore, it was concluded that individuals with IgE-mediated allergy to penicillins may undergo treatment with distinct R1 chain cephalosporins, but who preferentially have negative tests for these antibiotics before therapeutic administration.[27]

Confirming these findings, in a recent meta-analysis of 21 studies, Picard M. et al. included 1,269 patients who were known to be allergic to penicillin (IgE- or T-lymphocyte-mediated reactions) and showed that the cross-reactivity index varies with the degree of similarity between the R1 side chains. This risk was 16.5% for some aminocephalosporins with side chains identical to aminopenicillins, 5.6% for cephalosporins that had R1 side chains similar to penicillins, and 2.1% for other cephalosporins with a low degree of chemical similarity to the aminopenicillins.[18]

As examples, we bring two clinical cases of patients from the UPM author's personal file. In the first case, a patient with a history of immediate urticaria after exposure to amoxicillin. In the investigation, she presented a positive skin test for penicillin G and amoxicillin-clavulanate, denoting the likely cross-reactivity due to the similarity of the R1 side chains (Figure 2). The patient underwent supervised oral challenge with cefaclor, which has a similar but not identical R1 chain, and she had good tolerance to this drug. However, it is necessary to emphasize that, as it is an antibiotic with a similar chain, it was only possible to release cefaclor after complete investigation until negative provocation. The risk of reaction to this drug would be, initially, higher than that of another cephalosporin of a different R1 chain, such as cefuroxime, for example, which was the drug used in the second case – another patient, with a history of immediate urticaria and angioedema after exposure to amoxicillin. Skin tests were performed with penicillins (Figure 3), and, as an alternative, with cefuroxime, whose R1 side chain is completely different. The intradermal test with this cephalosporin was negative, and tolerance was subsequently proven with a negative challenge test.

Romano A et al. studied 131 patients with immediate reactions (mostly anaphylaxis to penicillins) confirmed with positive skin tests. All underwent skin tests with cefazolin and ceftibuten, cephalosporins that do not share the R1 chain with penicillins, and tolerance was subsequently confirmed through challenge. Only one patient (0.8%) had a positive skin test for cefazolin and ceftibuten and also for other reagents such as carbapenem and aztreonan, suggesting that, for this patient, the antigenic determinant was the BL ring itself. The findings confirm that the epitope must, in most cases, be related to the side chain. However, due to the possibility, although remote, of sensitization to the BL ring or even cosensitization to different BL, the authors maintained the recommendation to perform pretreatment skin tests with these cephalosporins in those sensitized to penicillins.[29]

Some studies evaluated cross-reactivity with cephalosporins in patients with late allergic reactions to penicillins and a cross-reactivity of up to 31.2%[15] was described, however, in a more systematic investigation, using a cephalosporin panel, Romano

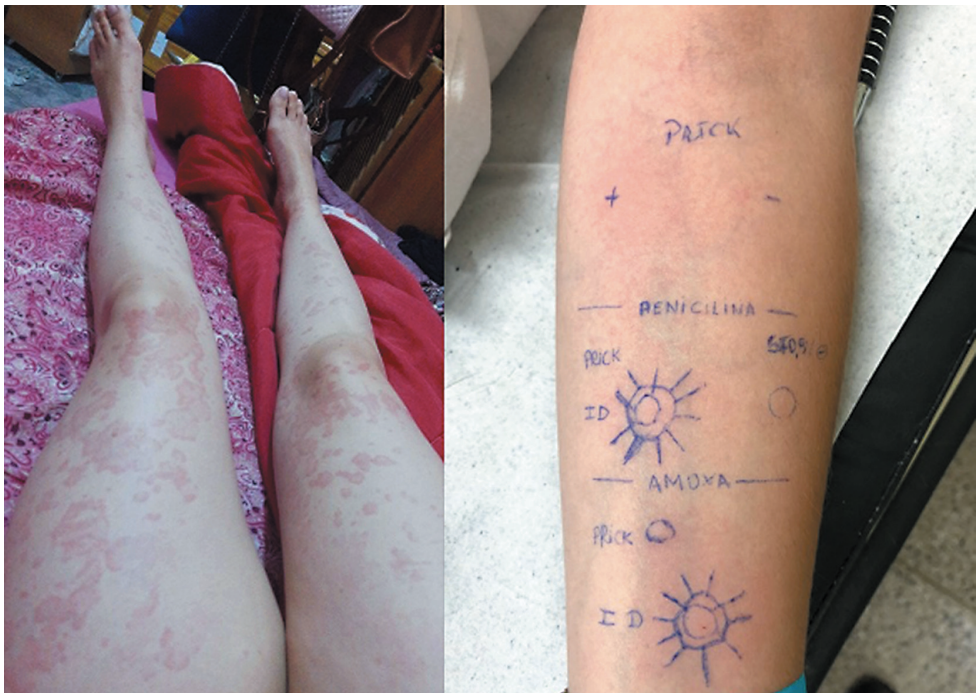


Figure 2
Immediate reaction to amoxicillin (urticaria) and positive immediate-reading intradermal test to amoxicillin-clavulanate and penicillin.

et al. studied patients with T lymphocyte-mediated reactions to penicillins confirmed by late skin prick tests, both intradermal late read and patch test. Individuals were submitted to these same skin tests with cephalosporins, and, when negative, to provocation tests. In that study, the overall cross-reactivity rate between aminopenicillins and aminocephalosporins (cephalexin, cefaclor, cefadroxil) was around 20%, but it was zero with cefuroxime and ceftriaxone. It is worth remembering that the three studied aminocephalosporins have R1 side chain similar or identical to aminopenicillins. These data corroborate the fact that, in late allergic reactions, the antigenic determinant is the side chain.[30]

Allergic to penicillins: cross-reactivity with carbapenems and monobactams

In patients with confirmed IgE-mediated reactions to penicillin, the cross-reactivity index with carbapenems was less than 1% in skin tests performed for imipenem, meropenem and ertapenem.[31] In another study involving 212 patients with confirmed IgE antibody reactions to penicillins, all had negative skin tests to aztreonan, and 211 were negative to the aztreonam challenge test.[32]

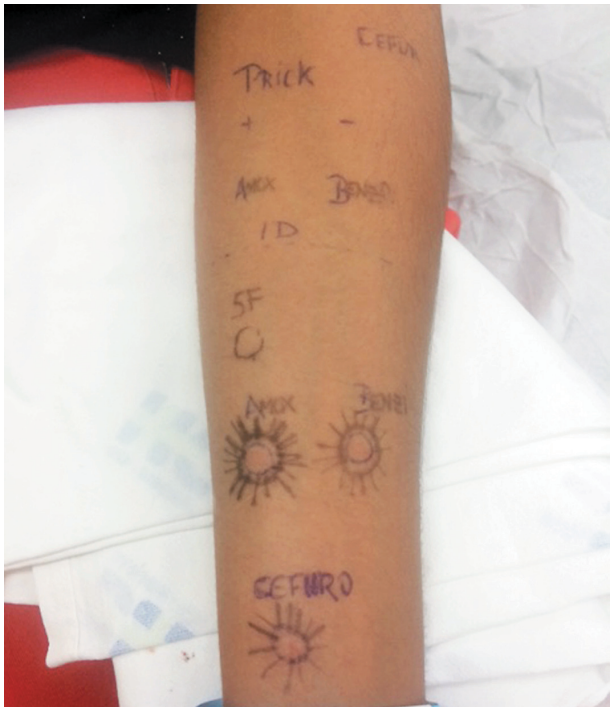


Figure 3
Positive intradermal skin tests with penicillin and amoxicillin-clavulanate and negative with cefuroxime in a patient with a history of immediate urticaria and angioedema after amoxicillin.

As for non-immediate reactions to penicillins, two studies published by the same group, in which more than two hundred patients were studied, showed 100% of negative skin and provocation tests with carbapenems and aztreonam.[30,33] These data confirm the findings that side chains must be the antigenic determinant of all late reactions to BL.

Cephalosporins: cross-reactivity with penicillins

Hypersensitivity reactions to cephalosporins are reported in about 1-3% of the population, but in Europe it accounts for 10 to 40% of all reactions to BL and also as an important cause of perioperative anaphylaxis, especially cefazolin.[8,20]

In individuals with IgE-mediated allergy to cephalosporins, few studies have evaluated cross-reactivity with other BL using challenge testing in individuals with negative skin tests. In a study with 24 patients allergic to cephalosporins, only 2 patients had positive skin tests to penicillin G, the remaining 22 patients with negative tests tolerated penicillin G challenge.[34] Another study carried out in 40 patients with anaphylaxis to cefazolin, confirmed by skin tests, without skin tests for penicillin and submitted to oral challenge with amoxicillin for 3 days, did not show any immediate reaction, and only 1 patient had a late benign rash after 24 hours of provocation.[35]

Cephalosporin allergy: cross-reactivity with carbapenems and monobactams

Few studies have studied the cross-reactivity between cephalosporins, carbapenems and monobactams. In a systematic review published in 2014, the authors compiled data from 10 studies and 12 case reports, resulting in an additional 850 individuals, but only 12 had a history, and not confirmed, of immediate reactions to cephalosporins. In this group, the incidence of reactions to carbapenemics was 25% (3 patients).[36]

In another study by prof. Romano, 98 patients allergic to cephalosporins were evaluated. The positivity for tests with these other BL was low: 2% for imipenem, 1% for meropenem and 3.1% for aztreonam, with emphasis on the latter for patients whose previous allergy was to ceftazidime, which shares R1 chain like this monobactam.[37]

In summary, in patients allergic to cephalosporins, cross-reactivity with carbapenems is less than 1%, and practically non-existent with monobactams, except in patients allergic to ceftazidime, which has a side chain identical to aztreonam.[8,16]

Cephalosporin allergy: cross-reactivity with other cephalosporins

In evaluating patients who are allergic to cephalosporins, an important question is whether they are able to tolerate other cephalosporins. In those allergic to cephalosporins, the IgE-mediated immune response is commonly directed to the R1 and R2 side chains, implying that these patients can tolerate other cephalosporins with different side chains. However, this evidence is still based on few studies of small series and case reports, in addition to having been described as cosensitization to cephalosporins, or even less frequently due to sensitivity to an antigenic determinant related to the BL ring. Cross-reactivity between cephalosporins has been demonstrated by similarity or identity mainly between the R1 side chains, but also in relation to the R2.

Few studies have been performed in patients allergic to cephalosporins who were challenged with alternative cephalosporins that showed negative skin tests. In a study involving 21 patients with immediate reactions to cefazolin, 19 with anaphylactic reactions, all had negative skin tests to cephalotin and also tolerated the challenge with this drug.[38] And in another study, patients with a history of immediate reaction to cefuroxime, and confirmed with positive skin tests, underwent skin tests for ceftazidime. All had negative results and tolerated the challenge with this drug, showing that a small structural difference between these drugs can result in a loss of cross-reactivity and present clinical tolerance.[39]

Another larger study involved 102 patients with a history of immediate reactions to cephalosporins, both anaphylaxis and urticaria. All underwent skin tests with a panel of 11 cephalosporins and were classified into 4 groups according to the response to the tests.[40]

– *Group A:* 73 patients with positive skin tests to ceftriaxone or another cephalosporin with a similar R1 side chain (cefotaxime, ceftazidime, cefuroxime, cefodizime);

- *Group B:* 13 patients who tested positive for aminocephalosporins with R1 side chains identical to amoxicillin or ampicillin (cephalexin, cefaclor and cefadroxil);
- *Group C:* 7 patients with similar R1 side chains (cefazolin, cefoperazone, cefamandole);
- *Group D:* 9 patients with cephalosporin positivity from more than one group, suggesting an immune response directed at the BL rings or dihydrothiazine, rather than the side chains.

Systematized challenge was performed with selected cephalosporins, whose skin tests had been negative, and there was no reaction. No patient was challenged with a similar R1 side chain cephalosporin or with the cephalosporin involved in the reaction. Challenges with alternative cephalosporins were, in general, well tolerated, confirming that the allergy would not be "class specific", but rather, in most cases, directed to the R1 or R2 chains. Furthermore, the authors concluded that the negative skin tests before the challenges were already an excellent biomarker of the safety of the challenge, which would later be confirmed as negative.[40]

Anyway, it is notorious that the studies that evaluated the cross-reactivity within the cephalosporin class are still scarce and should grow exponentially in the next ones, due to the growing importance of this BL class in clinical practice. In what may be the largest single-center series of patients investigated for suspected cephalosporin allergy, Touati N. et al. retrospectively surveyed data from 476 patients with a history of reactions to cephalosporins. Allergy was confirmed in only 22.3% of cases, 51.9% using skin tests and 48.1% using provocation tests. Despite being safe, provocation tests triggered anaphylaxis in 20% of cases, and even skin tests caused systemic reactions in 9.1% of individuals. Patients were investigated to confirm or exclude the causative agent and were also classified into 4 groups according to the R1 side chain, but there was no systematic investigation of cross-reactivity. Even within groups of similar or identical R1 chains, the cross-reactivity index was very low.[41]

Current recommendations - EAACI (European Academy of Allergy and Clinical Immunology)

Considering existing studies until 2020, the EAACI recently published guidelines to facilitate the management of patients with allergy to one or more BL. In that publication, sensitization to the BL ring in IgE-mediated reactions was defined as "very rare", with the side chains being the most frequent epitope. In addition, it was also described that, in reactions by cellular immunity, sensitization to the BL ring does not occur, that is, the cross-reactivity between all BLs is non-existent and, therefore, the exchange of BL for another with a different side chain is safe.[15]

As recommendations regarding the two most used classes, penicillins and cephalosporins, the European guidelines suggest that, in patients who cannot undergo a full investigation, when there is an indication for a cephalosporin in an individual with a history of immediate allergy to penicillin, that it be submitted to skin tests with cephalosporins of side chains other than penicillins and, if the results are negative, submitted to a provocation test.[15] On the other hand, in mild to moderate non-immediate reactions (rash) to penicillins in patients who require treatment with cephalosporins and there is no time to perform pre-treatment late-reading skin tests, administration of a full dose of cephalosporins with side chains other than penicillins under medical supervision, with no risk of serious reactions, but only the occurrence of rash being documented.[15]

In the Brazilian reality, where the performance of skin tests with drugs is the scope of the practice of the allergist-immunologist and taking into account that our specialty does not yet have qualified and available professionals equally distributed throughout the country, we believe that this algorithm can be adapted to our reality, in order to become more practical and feasible throughout the national territory.

Current recommendations – Scientific Department of Drug Allergy at ASBAI

Initially, in a suspected previous allergy to a BL, one should ask about the urgency of the investigation. Ideally, the investigation should be started as soon as possible, respecting the minimum interval of 4 weeks after the initial reaction, if possible.

If the investigation is elective and outpatient, the priority should be to try to confirm or exclude hypersensitivity to the suspected BL. However, at the same time, investigation of other members of the same class can be used, particularly in skin tests, in which several tests can be performed at the same time and also assess tolerance to other BL antibiotics,

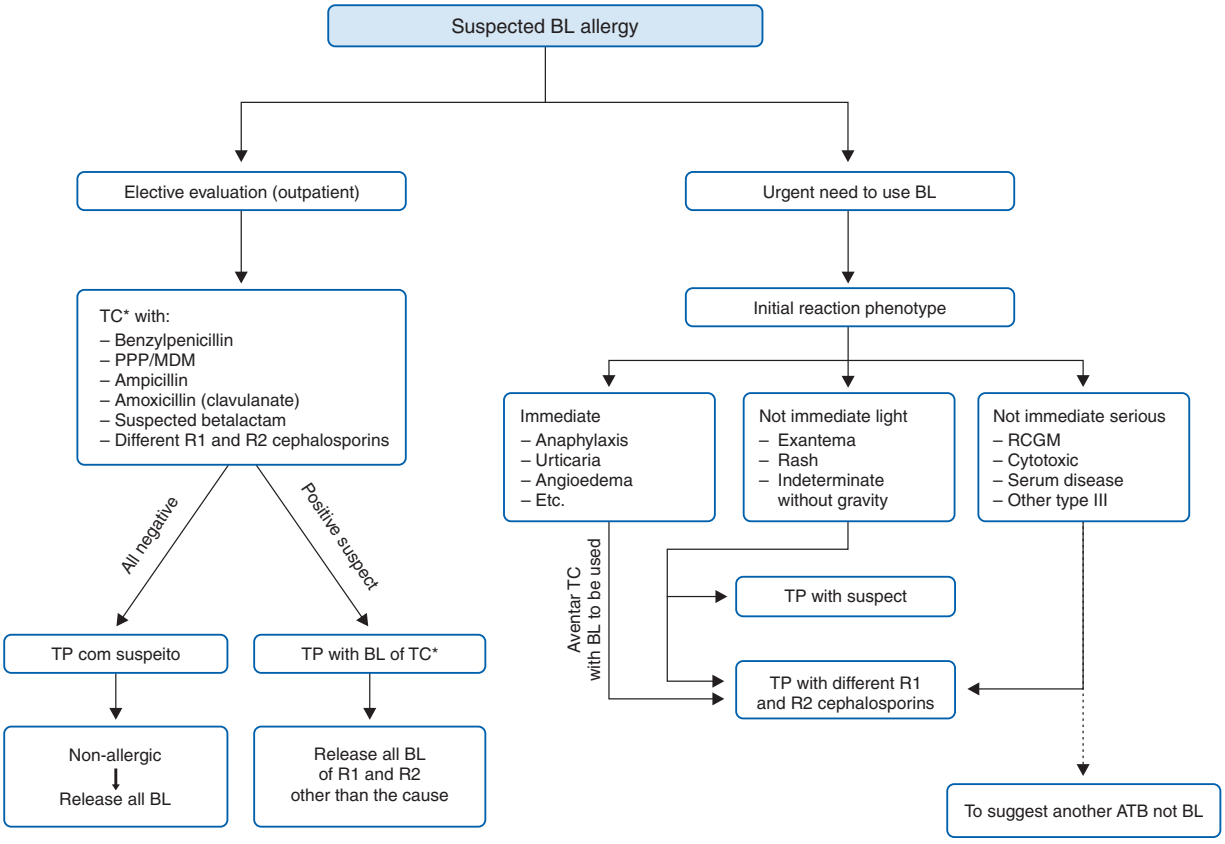
if the suspect is confirmed as guilty. For this purpose, the method of initially characterizing the phenotype of the index reaction and whether it was immediate or not immediate must be respected, in order to perform the appropriate skin test: puncture and intradermal immediate reading or intradermal semi-late reading [Arthus] or late and contact test, respectively. In addition, it is imperative to remember that to perform intradermal, medications must be used in their sterile injectable (parenteral) presentations.

If the skin tests are negative and there is no contraindication, based on the patient's risk stratification, the ideal is to carry out the challenge with the suspect, because if this is negative, the entire BL class will be free for use. We also emphasize that, in case of non-immediate mild exanthematic reactions, provocation can be used directly, without the obligation of skin tests. However, if the initial BL allergy is confirmed, either by skin or provocation test, or if there is any contraindication (severe pharmacoderma, for example), alternatives can be released with the provocation test based on the side chains of the drug.

If there is an urgent need for the use of BL in a patient not yet investigated, the systematic investigation will have to be postponed and the priority will be the release of an effective and safe BL. In this case, the rule is to use BL with a structure different from the one suspected of having caused the initial reaction (Table 4) and, ideally, to carry out the first administration with increased doses, as in a provocation test. In the case of an immediate initial reaction, particularly if it has been anaphylactic, immediate-read skin tests with the alternative BL before the first therapeutic dose may increase the safety of this challenge. At the end of treatment with this BL, a complete investigation of the suspected agent should be scheduled, in order to de-label possible non-allergic patients and release the entire BL class. The suggested algorithm for assessing tolerance to other BL in a patient with suspected allergy is outlined in Figure 4.

Conclusions

Beta-lactams are the drugs that most cause hypersensitivity reactions involving an immunological mechanism, with emphasis on the classes of penicillins and cephalosporins. Recent studies have shown that both within the same class and between beta-lactams from different classes, cross-reactivity is much lower than previously thought, and seems to be closely related to the structural similarity between the side chains of these drugs. Thus, knowledge of the chemical structure of beta-lactams is essential in this assessment. The updated approach to cross-reactivity between beta-lactams should be done through a systematic investigation, allowing for the dislabeling of patients who are not truly allergic, but at least allowing the use of an alternative beta-lactam in a safe and effective way. The development of educational programs, with the standardization of algorithms between different centers that allow specialist and non-specialist physicians to put into practice the most appropriate administration of antimicrobials in intra and extra-hospital environments.



BL = beta-lactam, TC = skin test, BP = benzylpenicillin, PPL = peniciloyl polylysine, MDM = mixture of secondary determinants, R1/R2 = side chains, TP = provocation test, TC = skin test, RCGM = severe skin reaction to drug , ATB = antibiotic.

* Before indicating the skin test, it is mandatory to define the reaction phenotype. Immediate reactions should be investigated with a puncture test and, if negative, with an intradermal test, both immediately read, with the medications properly diluted, and being used in their injectable presentations. Non-immediate reactions can be investigated by intradermal, but with semi-late (Arthus, 6 to 8 hours) or late (48 to 72 hours) readings, or by the classic patch test (48 and 96 hours readings and sometimes, 7 days). If available, major and minor determinants of penicillin can be used for puncture and intradermal.

Figure 4

Algorithm for analysing the patient with suspected allergy to a beta-lactam, in order to investigate the cause and possible tolerance to other antibiotics of the class.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

The role of biologics in eosinophilic esophagitis

O papel dos imunobiológicos na esofagite eosinofílica

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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic inflammation in the esophageal mucosa driven by an antigen-mediated abnormal immune response with apparent increasing prevalence worldwide. Genetically predisposed individuals present with a dysfunctional esophageal barrier and an abnormal immune response mediated by Th2 and IgE against certain allergens. Consequently, esophageal lesions can cause dysmotility, fibrosis and loss of esophageal barrier function. Clinical manifestations are age-related and include symptoms of esophageal dysfunction. Diagnosis is established by specific histological features associated with the presence of at least 15 eosinophils per high-power field. Management of EoE includes control of allergic diseases with diet restrictions and/or pharmacological treatment with proton-pump inhibitors and corticosteroids, not completely effective and limited by possible side effects and impairment of quality of life. Although immunological mechanisms of EoE are still less clear than other allergic diseases, biologic trials indicate some promising perspectives for EoE management. The purpose of this review is to present the current evidence of biologic drugs as options for EoE treatment.

Keywords: Biological products, diagnosis, endoscopy.

RESUMO

Esofagite eosinofílica (EOE) é uma inflamação crônica da mucosa esofágica com resposta imune antígeno-mediada anormal e com aparente aumento mundial na prevalência. Indivíduos geneticamente predispostos se apresentam com quadro de disfunção da barreira esofágica e uma resposta imune, mediada por TH2 e IGE, anormal contra certos alérgenos. Consequentemente, lesões esofágicas podem causar dismotilidade, fibrose e perda da função de barreira. O quadro clínico apresenta variação conforme idade e inclui sintomas de disfunção esofágica. O diagnóstico é estabelecido por achados histológicos específicos associados à presença de, ao menos, 15 eosinófilos por campo de alta potência. O manejo inclui controle do quadro alérgico com restrição dietética e/ou tratamento medicamentoso com bloqueadores da bomba de prótons e corticosteroides. São tratamentos sem completa efetividade, com efeitos colaterais e prejuízo na qualidade de vida. Ainda que os mecanismos imunológicos da EOE sejam menos claros que as demais doenças alérgicas, novos ensaios com imunobiológicos salientam uma perspectiva promissora de tratamento para a EOE. O objetivo desta revisão é apresentar as atuais evidências de uso de imunobiológicos como uma nova opção de terapêutica para a esofagite eosinofílica.

Descritores: Produtos biológicos, diagnóstico, endoscopia.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammation in the esophageal mucosa driven by an antigen-mediated abnormal immune response, expressed by clinical manifestations from esophageal dysfunction and histologic findings of at least 15 eosinophils per high-power field on light microscopy.[1]

Its prevalence seems to be increasing worldwide and recent data estimates to be between 10 and 57 cases/100,000 persons.[2] Likewise, the incidence

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presents with the same trend, presumably because of better clinical recognition and, therefore, an enlarged number of diagnosis.[2] Male individuals are more frequently affected and such preference suggests that an X-linked gene could be associated.[3] It is more common in children and adolescents and is frequently associated with a personal or familial history of allergic disorders, mostly represented by atopic diseases.[3]

Clinical manifestations of EoE are age-related and include a range of dyspeptic, allergic and respiratory symptoms.[1] The disease has a strong relationship with atopic diseases, such as allergic rhinitis, asthma and atopic dermatitis and is usually triggered by foods, where cow's milk represents the most common culprit food. There seems to be a relation between EoE and gastroesophageal reflux disease (GERD), although its association is complex and not well understood yet .[4] As a consequence of the nonspecific symptoms, diagnosis of EoE can be delayed, which can substantially worsen prognosis.[5]

Current management includes food restriction, proton-pump inhibitors (PPIs) and swallowed corticosteroids. Although partially effective, a considerable proportion of steroid-refractory patients can still be observed; adherence rates to daily medication, particularly in the long term, are low and response to steroids might be lost over time.[5] In parallel, and especially in childhood, restriction diets imply several issues, including quality of life and nutritional problems. Therefore, there is an urgent need for better management options, where biologics tend to be a promising expectation.[6]

Pathophysiology

The underlying mechanisms involved in the pathophysiology of EoE are vast and complex, with diverse implicated pathways, immune cells and cytokines. Although not totally elucidated yet, the basis of the disease relies on an antigen-mediated immune response capable of recruiting eosinophils into the esophagus and the consequences of a cascade of released inflammatory mediators.[7]

Genetically predisposed individuals present with a dysfunction in epithelial esophageal barrier caused by reduced expression of desmoglein 1 and genetic variants in the filaggrin gene, which enable the passage of antigens. Pursuant to, epithelial and resident cells are stimulated by food and environmental allergens to release thymic stromal lymphoprotein (TSLP) and interleukin (IL-) 33.[8] The proinflammatory mediators, named alarmins, activate leukocytes such as basophils, mast cells and lymphoid innate cells to secrete T helper (Th) 2 cytokines, especially IL-4, IL-5 and IL-13. In response to contact of allergens by antigen presenting cells (APCs), Th2 cytokines induce naive T-CD4 (Th0) cells into Th2 effector cells, which amplifies the type-2 inflammation profile cytokines. Furthermore, IL-5, eotaxin and RANTES recruit eosinophils into the esophageal mucosa. Eosinophils secrete mediators such as eosinophilic peroxidase, eosinophilic cationic protein and major binding protein, which directly cause tissue damage and esophageal dysmotility.[9]

Secondary effects of Th2 cytokines, mainly IL-4 and IL-13, include impairment of barrier function and tissue remodeling. IL-4 stimulates IgE production. Thus, an elevated number of mast cells and their degranulation in esophageal epithelium suggest that EoE is associated with type 1 hypersensitivity. Simultaneously, IL-13 seems to have a central role in EoE pathogenesis, independently of IgE and mast cells. It has been shown that IL-13 is partially responsible for esophageal eosinophilia. In addition, overexpression of IL-13 can lead to prominent esophageal remodeling with epithelial hyperplasia, angiogenesis and collagen deposition, in an eosinophilic-independent pathway.[10]

In parallel, IL-5 generates a substantial activation, proliferation, survival and chemotaxis of eosinophils to the tissue, responsible for collagen deposition, remodeling and additional tissue damage. Consequently, patients reveal esophageal lesions, extracellular matrix damages, fibrosis, dysmotility and loss of esophageal barrier function.

Although IL-4, IL-5 and IL-13 are considered major Th2 cytokines in the pathogenesis of EoE, several other cytokines play substantial roles in the inflammatory process. IL-9 seems to have an important function on epithelial barrier disruption and mast cell recruitment.[11] It has been reported that IL-15 is overexpressed in animal models of EoE.[12] Furthermore IL-33 increased expression is associated with EoE in childhood.[8] Besides them, an increasing number of different small molecules are a current focus of research and are possible targets for management interventions.[6]

Recent studies have demonstrated the potential role of IgG4 in EoE, which seems to have an increased production and can present with elevated seric and esophageal mucosal levels. Although further

studies are needed for elucidation of its role in EoE phisiopatology, dietary and pharmacological treatment appear to reduce IgG4 levels.[13] The major biological functions of IgE, IL-4, IL-13 and IL-5 in genesis of EoE are summarized in Table 1.

Genetics

EoE has a genetic background. It was described that there is a 41% risk in homozygous twins and 22% in dizygotic twins, whereas prevalence is about 0.05% in the general population. The EoE "transcriptome" comprises 574 genes expressed in healthy and affected children and the various roles illustrate the complexity of EoE pathophysiology.[9]

Genetic studies of EoE have been trying to explain the complex relationship between GERD and EoE on account of GERD being able to cause alterations of the epithelial barrier and possibly lead to EoE and the response to PPIs in both diseases. Nevertheless, no particular gene has been found to explain the impact of GERD in EoE.[9]

Knowledgement of genetic variants in EoE transcriptome provides a deep understanding of the mechanisms of EoE, but there are still many genes remaining with an unknown role in pathophysiology. Some of them which were already described might have impact in EoE pathogenesis, such as overexpression of CCL26 (eotaxin-3), which is induced by IL-13, and underexpression of filaggrin, which leads to the loss of epidermal cell differentiation and impaired barrier function.[9] The overexpression of malfunctional genes, such as CAPN14, leading to architectural changes, more antigens traffic, and variations in the microbial imbalance in esophagus can enhance imparied barrier function in patients with EoE and contribute to the esophageal inflammation.[9]

Further studies for identification of novel rare genetic variants of EoE will provide insights into the complex pathophysiology of EoE and associated diseases.

Clinical manifestations

The consequences of the wide inflammation previously described points to clinical manifestations of chronic and age-related symptoms of esophageal dysfunction, may expressed as dysphagia, inappetence, heartburn, regurgitations, vomiting, chest pain, odynophagia, abdominal pain and/or failure to thrive.[1]

Eosinophilic esophagitis is associated with atopy and other allergic conditions and patients frequently have multiple food allergies (cow's milk, egg, wheat, soy), with atopic symptoms or suggestive family history of atopic disorders.[1,4]

The broad spectrum of symptoms and associated atopic conditions directly implicate an impaired quality of life. Delayed diagnosis and difficulty in clinical management also have a major impact on the patient's life.

Table 1
Role of IgE and main Th2 cytokines (IL-4, IL-13 and IL-5) in eosinophilic esophagitis (EoE) pathogenesis.

Molecule	Role of eosinophilic esophagitis pathogenesis
IgE	Eosinophilic activation; esophageal dysmotility and remodeling; IgE mediated reactions (food allergies, atopic diseases)
IL-4	Impairment of barrier function and tissue remodeling; stimulation of IgE release
IL-13	Esophageal eosinophilia → esophageal remodeling
IL-5	Recruitment of eosinophils into the esophageal mucosa; eosinophil activation and proliferation → esophageal remodeling and collagen deposition

Due to the nonspecific symptoms of EoE, the disease usually progresses for as long as four years before diagnosis is confirmed.[5] Figure 1 summarizes the different clinical features of EoE according to age.

Diagnosis

Based on the symptoms a patient is presenting, clinical suspicion for EoE can be established and a detailed investigation can be started.

The gold standard for diagnosis of EoE is the upper gastrointestinal endoscopy (esophagogastroduodenoscopy - EGD) with esophageal biopsies from proximal, medial and distal sites.[4] Diagnostic criteria include the presence of at least 15 eosinophils per high-power field and specific endoscopic features, such as eosinophilic microabscesses, mucosal edema, exudate, longitudinal furrows, circular esophageal rings and esophageal stenosis.[4] Diagnosis can only be confirmed in the presence of signs and symptoms compatible with esophageal dysfunction associated with endoscopic and histological findings.

Besides the endoscopic findings and clinical manifestations, it is crucial to discard differential diagnosis such as GERD, achalasia, hypereosinophilic syndrome, Crohn's disease, viral and fungal infections, connective tissue disorders, hypermobility syndromes and autoimmune disorders.

Although EoE is associated with atopic diseases, mostly food allergies, specific IgE blood tests and skin prick tests show poor sensitivity and specificity. It's important to evaluate the most prevalent allergies in EoE patients to help with management and prevent anaphylaxis and in that scenario the IgE and skin tests can be useful.[4] Therefore, because of the lack of predictive positive value (44%),[14] these tests alone are not sufficient for EoE diagnosis.[4,14,15]

A suggestive algorithm for EoE diagnosis is shown in Figure 2.

Management of EoE

Diet

Dietetic management of individuals with EoE has shown to be an adequate treatment with good clinical and histological remission rates, especially in pediatric patients. Three alternatives are most used: elementary diet, allergy testing-directed elimination diet and empiric elimination diet. Although superior in efficacy, use of a strict amino acid formula has several limits, including taste, limited meal variety and cost.[14]

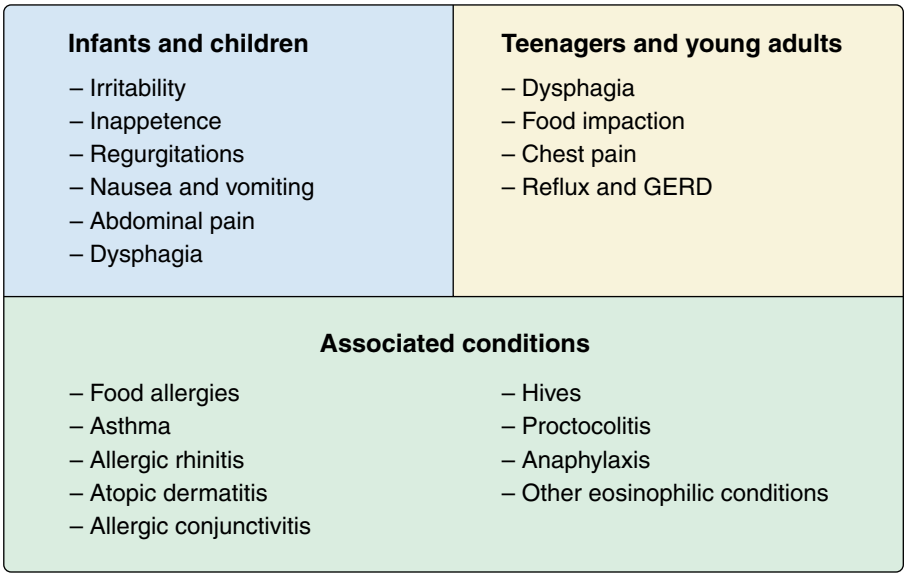

Figure 1
Clinical manifestations of eosinophilic esophagitis according to age.

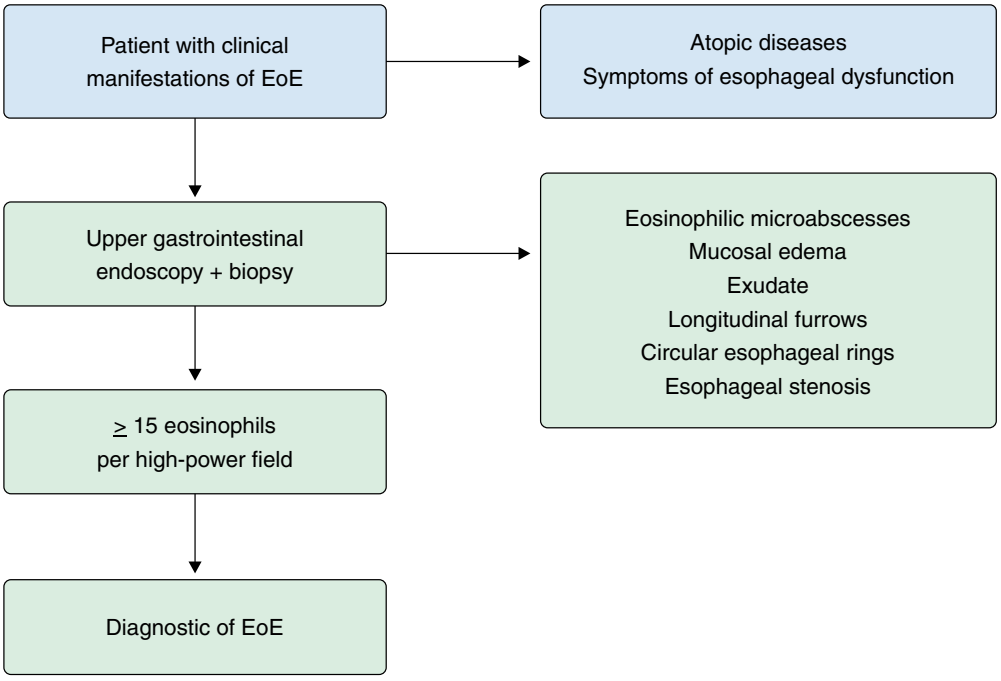

Figure 2
Suggestive algorithm for eosinophilic esophagitis diagnosis (modified from Dellon ES, et al.[20]).

Since IgE is not necessarily required for triggering EoE, restricted diets based on specific IgE tests present limited success.[15] Atopy patch testing had been analyzed for the same purposes but the lack of evidence of accuracy or validation restrain its application as restriction guidance, even if combined with skin prick tests.[16]

Empiric elimination diet consists in the elimination of the most common prevalent culprit foods in the pathogenesis of EoE and comprises six (cow's milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish), four (milk, wheat, egg, and soy), two (milk and wheat) or only milk.[17,18] After a period of 6-8 weeks, foods should be reintroduced, if possible after repeated endoscopies, which is a considerable problem in pediatric patients. Although better accepted over elemental diet and more effective than allergy testing-directed elimination diet, deprivation of several nutrients and emotional stigma make a difficult practice when maintained for prolonged time.

Corticosteroids

Both swallowed fluticasone or budesonide demonstrate efficacy in clinical and histopathology of patients with EoE.[19] Although long-term use is currently indicated for maintenance therapy, treatment is not free of side effects, especially oral and esophageal candidiasis.[20]

Proton-pump inhibitors (PPI)

A PPI should be considered as a potential early or initial treatment or if diet or steroid therapy is used as a first line therapy but is ineffective on follow-up endoscopy.[20] Differently of previous beliefs, PPI-responsive patients must be reclassified as having EoE.

Surgical treatment

Esophageal dilation is an alternative therapy for patients with remodeling processes caused by

EoE. It is especially useful in the adult population to treat associated symptoms. It has not shown any histological response and is exclusively used in severe esophageal stenosis or persistent dysphagia.

Figure 3 shows an algorithm proposed for management of EoE.

Biologics

Due to all the facts presented previously regarding worries about increasing prevalence of EoE, its clinical manifestations and limitations and/or incomplete effectiveness of current treatment options, there is an urgent need to deepen safer and more efficient tools for management of the disease.

Recently, advances in the monoclonal antibodies (mAbs) or biologics field have been allowing different therapeutic approaches for several immunological diseases. It would be reasonable to evaluate, therefore, whether biologic drugs scientifically approved for treatment of allergic diseases (e.g. asthma, atopic dermatitis, chronic rhinosinusitis)[21,22] could have some role in EoE management.

Anti IgE (Omalizumab)

Omalizumab is a humanized mAb that targets circulating IgE and which has been efficaciously used to treat allergic asthma and chronic spontaneous urticaria.[23,24] There are few case reports of successful treatment of EoE with omalizumab.[25,26] To date, only two clinical trials have been published and both demonstrated poor histological improvement and clinical remission with this drug, suggesting eosinophilic inflammation is not IgE-mediated.[27,28] A unique double blind placebo controlled (DBPC) phase 2 study including 30 adult and teenager patients(12-60) was already published and showed no histological or clinical recovery by using omalizumab.[28]

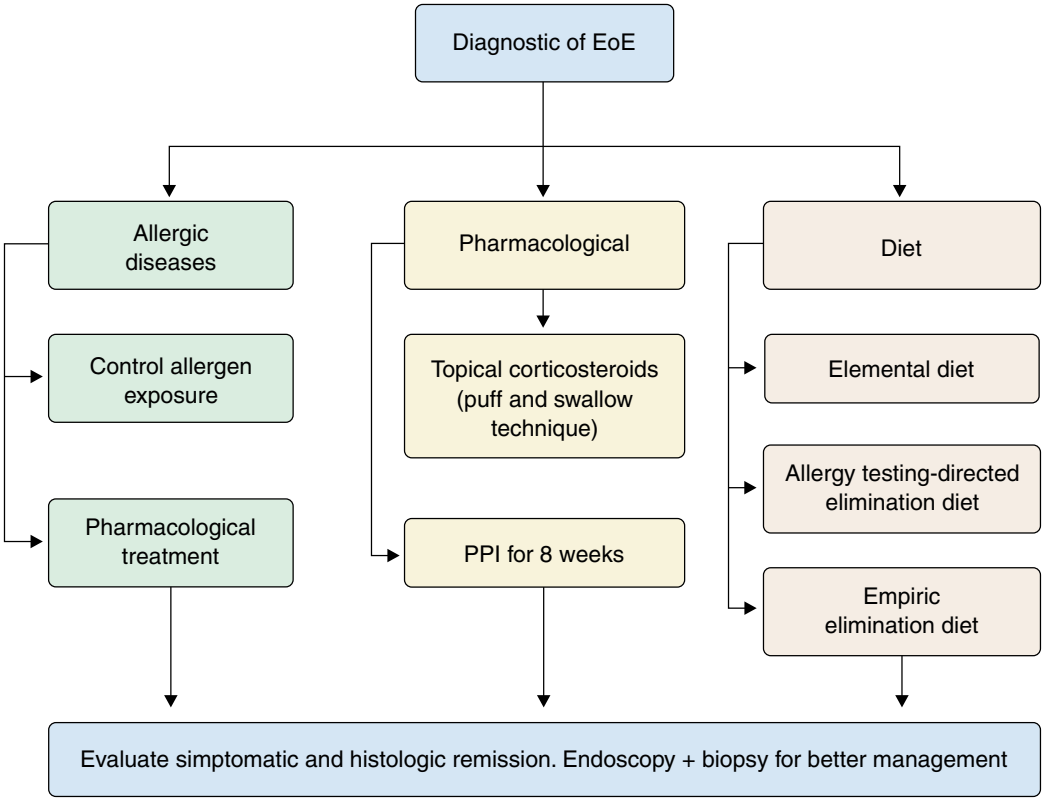

Figure 3
Algorithm for management of eosinophilic esophagitis (EoE).

Anti IL-5 (Reslizumab, Mepolizumab and Benralizumab)

Reslizumab, Mepolizumab and Benralizumab are mAbs that antagonize the IL-5 pathway. While Benralizumab blocks the IL-5 receptor that is expressed in the membrane of basophils and eosinophils and induces their death, reslizumab and mepolizumab bind to the IL-5 molecule directly, preventing activation of the IL-5 receptor.[29-31]

In a DBPC study, 226 children received Reslizumab infusion versus placebo and the results showed improvement in histological features with a 67% reduction in eosinophil counts when compared to a 24% reduction within the control group ($p < 0.001$).[32] However, no benefits in clinical symptoms were described.[32] In parallel, a retrospective 9 year study analyzed 12 patients who received reslizumab treatment for EoE and showed better control of clinical manifestations.[31] It is considered a well tolerated medication and the most common adverse effects described in large asthma clinical trials were cough and congestion.[30]

A DBPC clinical trial was conducted with 84 children with EoE using mepolizumab in different doses. There was improvement in both clinical symptoms and histological eosinophilia. However, clinical remission was only achieved in 8.8% of the kids.[33] There was a clinical trial including 11 adults with EoE[34] and although there was a decrease in mucosal eosinophilic inflammation, mepolizumab did not induce clinical benefits compared to placebo. Moreover, authors evaluated duodenal inflammation of those 11 individuals and could not find differences in eosinophilic or lymphocytic inflammation in duodenal mucosa.[35]

Despite its mechanism of action suggesting a possible role of benralizumab in EoE management, there are no case reports published with this drug to treat EoE. There is a promising phase three clinical trial in progress with 170 patients, but as it was initiated in September 2020, results are still not available.[36]

Anti IL-4 and IL-13 (Dupilumab)

Dupilumab is a fully human IgG4 mAb that targets the IL-4 receptor alpha subunit that is endogenously bound by both IL-4 and IL-13. It was approved by the FDA and Brazilian regulatory agency (ANVISA) for the treatment of moderate to severe atopic dermatitis, severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps.[37] This drug inhibits the effects of cytokines that are main factors in the Th2 response and has been studied for allergic diseases treatment for the last few years, with promising results.

Whereas EoE has an important allergic component that implies the Th2 immune response in its pathophysiology, dupilumab is considered a possible therapy for the disease. The only published study is a phase 2 randomized, double-blind, placebo-controlled clinical trial that evaluated adults with EoE and the results showed that dupilumab reduced dysphagia, histologic and endoscopic features compared to placebo.[40] There are phase 3 trials in progress trying to support the efficacy and safety of dupilumab for EoE treatment in pediatric and adult patients separately.[38,39]

Although more evidence is needed to establish efficacy and safety for EoE treatment with dupilumab, especially in children, promising results are emerging and could widen modalities and quality of EoE treatment.

Others: small molecules, IL-33, TNF alpha

Other biologics are being evaluated as add-on therapy for EoE. Studies with those biologics registered in clinicaltrials.gov or already published are summarized in Table 2.

IL-33 is an important citocine in the activation of type 2 T helper cells. Although its circulating level is not high in pediatric patients with EoE, it appears to have an important role in reducing antigenic tolerance and, therefore, favoring EoE occurrence in the pediatric population.[41] TNF-α imunoglobulin (infliximab) was tested in 3 adult patients with severe EoE in order to see if there could be any benefit in treatment. Although none of them had any important adverse events, the treatment failed to reduce activity of disease and laboratorial/endoscopic improvement.[46]

Future perspective

For the future, there is a tendency to increase studies on the efficiency of the immunobiologicals, given that there are ongoing clinical trials and published articles that foster hope for the use of this class of medication.

Considering Omalizumab, the clinical results are not so promising since they did not show histological or clinical improvement, so there may be a tendency for this drug to be left aside when it comes to the treatment of EoE.

Table 2
Most promising biologicals for eosinophilic esophagitis (EoE) treatment.

Biologic	Mechanism of action	Study phase	References
Mepolizumab	Anti IL-5	2	33-35
Reslizumab	Anti IL-5	2 and 3	30, 32
Lirentelimab	Anti Siglec-8	2 and 3	42
QAX576	Anti IL-3	2	43
Dupilumab	Anti IL-4 e IL-13	2 and 3	38-40
Omalizumab	Anti IgE	1 and 2	27,28
RPC4046	Anti IL-13	2	44,45
Infliximab	Anti TNF-α	2	46

In view of Reslizumab, there are better prospects for the future as published studies have shown a reduction in eosinophil counts and a reduction in symptoms. However, one of the studies had only 12 patients, which suggests a need for further studies to better investigate the effect of this drug.

Mepolizumab shows similar results in different studies, but it's not an elucidate result since there is clinical improvement in one study and not in another, and is also a source for new studies.

Regarding Dupilumab, we also have a good perspective for the future, as studies have shown a reduction in symptoms and histological improvement of patients receiving treatment, however more studies should be carried out to establish a safe pharmacological profile.

Thus, there is a good prospect for the future with immunobiologicals that should count on more studies to better establish the pharmacological profile and treatment efficacy. The development of studies can occur both in the drugs that already exist and in the emergence of new drugs with similar immunobiological mechanisms.[47]

The prospects of a safe and effective treatment for EoE with immunobiologicals in the future could be the key to better management and clinical control of this disease, significantly improving the quality of life of these patients.

Conclusion

Eosinophilic esophagitis represents a challenge for clinicians due to its increasing prevalence, broad spectrum of clinical manifestations, gaps in pathophysiology mechanisms and limitations of current treatment possibilities. Consequently, there is a pressing need to expand the therapeutic options and improve the quality of life. In that perspective, the emerging biological drugs could enable better management of the disease and create an innovative approach.

Despite progressive efforts for achieving the perfect drug, further studies are needed in order to establish their role as main treatment and/or adjuvant and possible benefits of association for better results.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

The specialty of Allergy and Clinical Immunology in Brazil: how do we start the second decade of the 21st century?

A especialidade de Alergia e Imunologia Clínica no Brasil: como começamos a segunda década do século XXI?

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ABSTRACT

Introduction: It is necessary to know the situation of allergists/immunologists in different scenarios of action, identifying profiles and possible difficulties. The knowledge of these data can serve as a subsidy to promote the implementation of policies that ensure comprehensive health care for patients with allergic diseases and inborn errors of immunity (IEI). **Objective:** To verify the profile of specialists in Allergy and Immunology in Brazil, concerning the place of work, access to tests, therapies, and the impact of the pandemic on their professional practice. **Methods:** Descriptive-exploratory study, with data collected through an online survey, using the Google Forms tool. All compliant Associação Brasileira

RESUMO

Introdução: É necessário conhecer a situação de alergistas/imunologistas nos diferentes cenários de atuação, identificando perfis e eventuais dificuldades. O conhecimento destes dados poderá servir de subsídio para fomentar a implementação de políticas que garantam a integralidade na atenção à saúde do paciente com doenças alérgicas e erros inatos da imunidade (EII). **Objetivo:** Verificar o perfil dos especialistas em Alergia e Imunologia no Brasil, em relação ao local de atuação, acesso a exames, terapias e o impacto da pandemia COVID-19 sobre o seu exercício profissional. **Métodos:** Estudo descritivo-exploratório, com dados coletados por inquérito *on-line*, utilizando-se a ferramenta Google

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de Alergia e Imunologia – ASBAI members were invited to participate. The questionnaire addressed sociodemographic and professional aspects. The information was analyzed using SPSS version 20.0. **Results:** Four hundred and sixty associates answered the questionnaire. Women were predominant (73%), and the median age was 47 years. Most participants work in the private sector (95%) and 47% in the public sector. Approximately 80% of those who work in the public sector reported having access to some diagnostic tests for allergic diseases and IEI. Only 35% of specialists in the public system have access to specific allergen immunotherapy, against 96% of those working in the private sector. As for immunobiological drugs, 53% and 72% of specialists working in the public and private service, respectively, reported access. More than 60% of the members participating in the survey had a reduction in the number of consultations by at least 50% and 56% have been assisted by teleconsultation during the Covid19 pandemic. **Conclusion:** ASBAI associates have incorporated advances in the therapy of immune allergic diseases into their clinical practice, but several diagnostic methods are still inaccessible. The presence of specialists in Allergy and Immunology in the Unified Health System (Sistema Único de Saúde - SUS) also needs to be expanded. The coronavirus pandemic brought the discussion of telemedicine as a method of clinical care practice in our specialty.

Keywords: Allergy and Immunology, comprehensive health care, telemedicine.

Forms. Todos os associados adimplentes da Associação Brasileira de Alergia e Imunologia - ASBAI foram convidados a participar. O questionário abordou aspectos sociodemográficos e profissionais. As informações foram analisadas no programa SPSS versão 20.0. **Resultados:** Quatrocentos e sessenta associados responderam ao questionário. Observou-se predomínio de mulheres (73%), com mediana de idade de 47 anos. A maioria dos participantes atua no setor privado (95%), e 47% no setor público. Aproximadamente 80% dos que atendem no setor público referiram ter acesso a algum exame diagnóstico para doenças alérgicas e EII. Apenas 35% dos especialistas do sistema público têm acesso a imunoterapia alérgeno específica, contra 96% dos que atuam no setor privado. Já aos medicamentos imunobiológicos, 53% e 72% dos especialistas que atuam no serviço público e privado, respectivamente, referiram acesso. Mais de 60% dos associados participantes da pesquisa tiveram redução no número de consultas em pelo menos 50%, e 56% tem realizado atendimento por teleconsulta durante a pandemia de COVID-19. **Conclusão:** Os associados da ASBAI têm incorporado na sua prática clínica os avanços na terapia das doenças imunoalérgicas, mas vários métodos diagnósticos ainda são pouco acessíveis. A presença do especialista em Alergia e Imunologia no SUS, também precisa ser ampliada. A pandemia do coronavírus trouxe a discussão da telemedicina como um método de atendimento clínico em nossa especialidade.

Descritores: Alergia e Imunologia, assistência integral à saúde, telemedicina.

Introduction

The increase in the prevalence of immune allergic diseases observed in recent decades has generated a growing demand by qualified specialist physicians, who work in both the private and public sectors, at different levels of health care, to meet the needs of the population suffering from allergic and immunological conditions.[1] In parallel to this, the advances that have taken place in diagnostic procedures and the development of targeted therapies have created the need for continuous training for specialists. Thus, the importance of the specialty society working with different spheres of the health scenario in Brazil is very clear, to improve access to diagnosis and treatment of these conditions, which affect about 30% of the population.

In this context, the Associação Brasileira de Alergia e Imunologia – ASBAI's mission is to promote permanent and continuing medical education, in addition to spreading knowledge in the area of Allergy and Immunology, to strengthen the professional practice of the specialty with excellence, both in the public and private spheres.[2] The challenges to achieving a balance in the distribution of professionals and access to diagnostic tests and therapies, in a country with a continental dimension, are countless. Therefore, it is of fundamental importance to know the situation of specialists in the different action scenarios, so that the ASBAI can identify barriers and promote policies that ensure comprehensive healthcare for patients with allergic diseases and inborn errors of immunity (IEI).

To learn about the situation of experts at the national level, in 2017, ASBAI surveyed the performance of its specialists, which provided an overview of the place of work and the availability of diagnostic tests and immunotherapy. At that time, most allergists/immunologists were young and concentrated in large centers. The access to Specialized care in Allergy and Clinical Immunology was restricted to a few services, usually university services, making it difficult to provide comprehensive care to patients affected by these diseases, especially those over 70% who depend on the SUS. Shortcomings were identified in the access to various diagnostic tests and

specific immunotherapy with allergens, a therapeutic procedure exclusive to the specialty.[3]

COVID-19, declared a pandemic in March 2020,[4,5] has been imposing many challenges for the specialist, who has needed to adopt the sanitary recommendations to contain the dissemination of the coronavirus in health units, including the reduction of consultations and elective procedures, without being absent from their responsibility to provide quality care to their patients, within the ethical precepts on which medicine is based.

Five years after such study[3] it is necessary to update the information about the performance of the specialist in Brazil. Therefore, the objective of this research was to verify the current situation of specialists in Allergy and Immunology in Brazil concerning their workplace, access to exams, therapies, and the impact caused by the COVID-19 pandemic on specialized care.

Material and methods

The study consisted of an online survey of a descriptive-exploratory nature, carried out from March to May of 2021. All ASBAI non-compliant members were invited to participate. E-mails informing about the survey and containing links to Google Forms® and access to the questionnaire (questionnaireasbai@gmail.com) were sent to all members.

The questionnaire addressed sociodemographic and professional aspects in 34 multiple-choice questions and an open answer (Figure 1). Once answered, the information was electronically and automatically transferred from Google Forms to a Microsoft Excel® spreadsheet. At the end of the collection period, a database containing information on all research participants, in Excel format, was transferred to the SPSS version 20.0 program. Data were checked for duplicity and consistency, ensuring data and results reliability. Data were cataloged as numerical (age in years) and categorical (all others) variables. Data were analyzed and results are presented as simple frequencies in the form of tables and graphs.

Results

From March to May 2021, 460 members responded to the structured online questionnaire, which corresponds to 25% of the total non-compliant members of ASBAI (N = 1,848). The analysis of the responses showed a 100% completion rate for the questionnaire. The distribution was proportionally similar to the number of members per region (Table 1, Figure 2). The comparative analysis showed a heterogeneous distribution of specialists considering the Brazilian regions, however it was similar to that of all non-compliant members of the ASBAI in 2021 (Table 1).

Regarding the demographic profile, there was a predominance of women among the survey participants (336/460; 73%). Age ranged from 27 to 82 years (mean = 47.9; median = 47) and 56.4% of specialists reported being under 50 years of age. The distribution of participants by gender and age group is shown in Figure 3.

Regarding the main area of activity, we found that more than 90% of the participating associates have Allergy and Immunology as their main specialty, followed by 36.3% who add up to Pediatrics (Table 2). Despite this, only 14.6% restrict their care to pediatric patients (Table 2). 47.2% of those who participated in the survey work in the public sector, as specialists, and 95% in the private sector (Table 2). The distribution of the place of work, by age group, is seen in Figure 4.

Among specialists working in the public service (256/460), we found that the main workplace is in the outpatient clinic of a University Hospital (49.6%). Among those who work in the private sector (437/460), 89.7% do it in a private clinic and 27.2% in an outpatient clinic of a private hospital (Table 3).

Table 1
Distribution of experts who responded to the questionnaire and ASBAI members by Brazilian geographic regions.

	Sample* (n=460) n (%)	ASBAI associates (n=1,848) %
North	17 (3.7)	4.4
North East	73 (15.9)	15.0
Midwest	44 (9.5)	7.7
Southeast	280 (60.9)	63.1
South	46 (10.0)	9.7

*Chi-square – p <0.001.

1. Gender:	Masculine Feminine
2. Age (full years):	
3. City of residence:	
4. State of residence:	
5. Main acting specialty (you can check more than one option):	Allergy/Immunology Pediatrics Medical clinic Family Health Other:
6. What is the age group of your patients considering the area of expertise?	Children and teenagers All age groups Teenagers and adults Adults
7. Do you work as an allergist in public service?	Not Yes
8. Where do you work as an allergist in the public service? (check as many as needed)	Basic Health Unit General Hospital Outpatient Clinic University Hospital Outpatient Clinic (teaching) Other
9. Do you work with patients with allergic diseases in the public service?	Not Yes
10. Do you work with patients with immunodeficiency or with suspicion in the public service?	Not Yes
11. In which place do you work with patients with immunodeficiencies (innate error of immunity - IEI) or suspected in the public service?	Basic Health Unit General Hospital Outpatient Clinic University Hospital Outpatient Clinic (teaching) Other
12. Do you work with patients hospitalized for allergic diseases in the public service?	Not Yes
13. Do you work with hospitalized patients with allergic diseases in the private service?	Not Yes
14. Do you work with hospitalized patients with innate error of immunity (IEI) in the public service?	Not Yes
15. Do you work with hospitalized patients with innate error of immunity (IEI) in the private service?	Not Yes
16. Do you have access to diagnostic tests for allergy in the public service where you work?	Not Yes I don't work in the public service
17. What diagnostic allergy tests do you have access to in the public service? (check as many as needed)	Immediate-read skin tests Contact tests Total IgE dosage Specific serum IgE dosage Oral food provocation test Oral drug challenge test None I don't work in the public service
18. Do you have access to diagnostic tests for immunodeficiencies (IEI) in the public service in which you work?	Not Yes I don't work in the public service
19. What diagnostic tests for immunodeficiency (IEI) are available in the public service? (check as many as needed)	Dosage of serum immunoglobulins (G, A, M, and E) IgG subclass dosage Antibodies to vaccine antigens (rubella, polio, among others) Antibodies to polysaccharide antigens (pneumococcus) Late Reading Skin Tests Immunophenotyping and quantification of T lymphocytes (CD4, CD8) Immunophenotyping and quantification of B lymphocytes (CD19, CD20) NK lymphocyte immunophenotyping (CD56) Evaluation of phagocytes (Rhodamine) Complement and fractions Quantitative and qualitative C1 inhibitor Newborn Screening - TRESs/KRECs Others I don't work in the public service

Figure 1
Questionnaire on the specialty of Allergy and Immunology at different levels of health care.

20. Do you have access to immunotherapy in the public service?	Not Yes I don't work in the public service
21. Do you have access to immunobiologicals for the treatment of immune allergic diseases for public service patients?	Not Yes I don't work in the public service
22. Have you ever prescribed immunobiologicals for the treatment of immune allergic diseases for public service patients?	Not Yes I don't work in the public service
23. For which disease have you already prescribed immunobiologicals in the public service?	Asthma Urticaria atopic dermatitis chronic rhinosinusitis Primary Immunodeficiency (IEI) None
24. Which immunobiological do you have access to for the patients you work within the public service? (check as many as needed)	Omalizumab Dupilumab Mepolizumab Benralizumab Human immunoglobulin Others I don't attend the public service None
25. Do you work in the private sector? *	Not Yes
26. Where do you work in the private sector? (check as many as needed)	Clinic Multispecialty clinic private hospital Supplementary health service clinic I don't work in the private sector
27. Do you prescribe immunotherapy in the private sector? *	Not Yes I don't work in the private sector
28. Do you have access to immunobiologicals for private sector patients?	Not Yes I don't work in the private service I don't have patients in use
29. For which disease have you already prescribed immunobiologicals in the private service? (check as many as needed)	Asthma Atopic dermatitis Urticaria Chronic rhinosinusitis Primary Immunodeficiency (IEI) Other indications
30. How does the patient attending the private service have access to treatment with immunobiologicals? (check as many as needed)	Via health operator Own resource Via the Unified Health System Judicialization I don't have patients in use
31. Which immunobiological do you have access to by health care providers? (check as many as needed)	Omalizumab Dupilumab Mepolizumab Benralizumab Human immunoglobulin Others None
32. What percentage did the pandemic reduce the number of consultations in the private practice?	Not Reduced Reduced below 25% Reduced between 25 and 50% Reduced between 50 and 75% Reduced above 75% I don't answer in private
33. Are you taking Telemedicine?	Yes Not
34. If you had the opportunity, would you like to work in the Unified Health System (Sistema Único de Saúde - SUS)? *	Not Yes I don't have an opinion I already work at SUS
35. Leave your comment here:	

Figure 1 *(continuation)*
Questionnaire on the specialty of Allergy and Immunology at different levels of health care.

State of operation – n (%)	
AC	1 (0.2%)
AL	6 (1.3%)
AM	3 (0.7%)
BA	11 (2.4%)
CE	15 (3.3%)
DF	26 (5.7%)
ES	17 (3.7%)
GO	11 (2.4%)
MA	4 (0.9%)
MG	35 (7.6%)
MS	2 (0.4%)
MT	5 (1.1%)
PA	11 (2.4%)
PB	5 (1.1%)
PR	21 (4.6%)
PE	23 (5.0%)
PI	2 (0.4%)
RJ	83 (18.0%)
RN	1 (0.2%)
RS	15 (3.3%)
SC	10 (2.2%)
SP	145 (31.5%)
SE	6 (1.3%)
TO	2 (0.4%)

Figure 2
Distribution of survey participants, according to housing status.

Table 2
Distribution of specialists according to sociodemographic characteristics, the main specialty of activity, age group of patients, and place of work.

Feature	Total n=460 (%)
Main specialty in which he works	
Allergy and Immunology	449 (97.6)
Allergy, Immunology, and Pediatrics	169 (36.7)
Allergy, Immunology and Clinical Medicine	23 (5.0)
Allergy, Immunology and Family Health	10 (2.2)
Others	14 (3.0)
The age range of your patients in Allergy and Immunology	
All tracks	373 (81.1)
Children and teenagers	67 (14.6)
Teenagers and adults	21 (4.6)
Others	32 (6.6)
Do you attend to allergic diseases in public service?	
Yes	256 (55.7)
Do you work in private service?	
Yes	437 (95.0)

In the public sector, 78.5% (201/259) of specialists work with patients with a diagnosis or suspicion of IEI, 54.3% (139/256) work with patients hospitalized for allergic diseases, and 46.9% (139/256) work with patients hospitalized for IEI. In the private sector, 53.1% (232/437) of the specialists treat patients hospitalized for allergic diseases, and 61.6% (269/437) treat patients hospitalized for IEI (Table 3).

Approximately 82% of specialists who work in the public sector have access to diagnostic tests for allergic diseases (Table 4). Among the tests, we highlight the measurement of total serum Immunoglobulin E

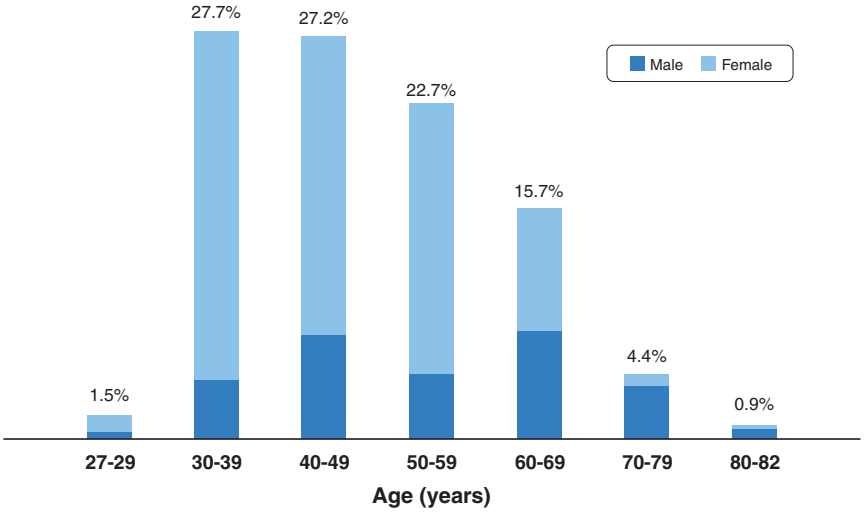

Figure 3
Distribution of research participants, according to gender and age group.

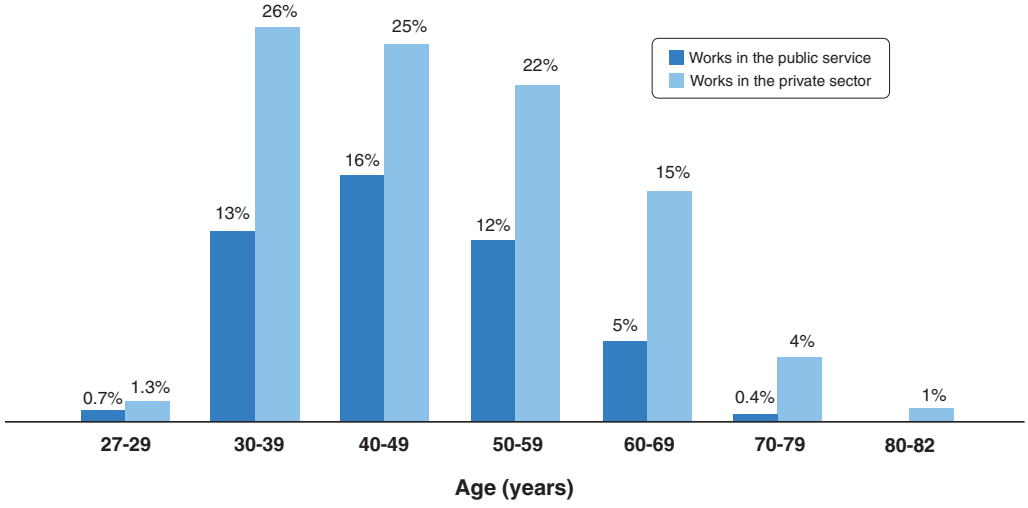

Figure 4
Distribution of participants, according to the place of professional activity, according to age group.

(IgE) (226/256; 88.3%), specific serum IgE (163/256; 63.7%), and immediate hypersensitivity skin tests (135/256; 52.7%) (Table 4). The provocation tests with food or drugs were mentioned by less than 50% of the experts. Regarding tests to assess possible IEI, we observed that 80.1% (205/256) of specialists have access to diagnostic tests, with special emphasis on serum immunoglobulin dosage (225/256; 87.9%), antigen antibodies vaccines (166/256; 64.8%), immunophenotyping and quantification of T lymphocytes (155/256; 60.5%), the dosage of complement and fractions (165/256; 64.4%), among others (Table 4).

Regarding allergen-specific immunotherapy(ASIT), in the public system, only 35.5% (91/256) of specialists report having access to it, against 95.9% (419/437) of those working in the private sector. As for immunobiological agents, 52.7% (135/256) and 71.9% (314/437) of specialists working in public and private services, respectively, reported having access to it. Among specialists working in the public service, 61.3% (157/256) reported having already prescribed at least one of these agents (Table 5).

As for the diseases for which immunobiological drugs have been prescribed by professionals working in the public service, hives, IEI, asthma, and atopic dermatitis stand out, in descending order. In the private sector, the main prescriptions were for urticaria (hives), atopic dermatitis, asthma, and IEI (Table 5).

Omalizumab and dupilumab were the most used immunobiologicals both in the public system [142/256 (55.5%)] and [66/256 (25.8%)], and in the private sector [265/437 (60.6%) and [122/437 (27.9%)], respectively (Table 5). About human immunoglobulin, 47.3% (121/256) of specialists from the public service and 38.9% from the private sector (170/437) reported its use (Table 5). As for patient access to immunobiologicals in the private sector, health

Table 3
Distribution of specialists according to where they work: public or private.

Specialist	Public n=256 (%)	Private n=437 (%)
The location where you work		
Basic Health Unit	27 (10.5)	–
General Hospital Outpatient Clinic	46 (18.0)	–
University Hospital Outpatient Clinic	127 (49.6)	–
Clinic	–	392 (89.7)
Multispecialty clinic	–	96 (22.0)
Private Hospital Outpatient Clinic	–	119 (27.2)
Supplementary Health Clinic	–	30 (6.9)
Other	96 (37.5)	–
Do you treat patients with Inborn Errors of Immunity or suspicion?		
	201 (78.5)	–
Do you work with hospitalized patients with allergic diseases?		
	139 (54.3)	232 (53.1)
Do you work with hospitalized patients with Inborn Errors of Immunity?		
	120 (46.9)	269 (61.6)

Table 4
Distribution of specialists, according to the availability of subsidiary tests used in the assessment of patients with immune allergic diseases in the public sector (n=256).

Laboratory investigation	n=256 (%)
Access to allergy diagnostic tests?	
Yes	210 (82.0)
Which exams do you have access to?	
Immediate reading skin tests	135 (52.7)
Contact tests	92 (35.9)
Total serum IgE dosage	226 (88.3)
Specific serum IgE dosage	163 (63.7)
Oral food provocation test	116 (45.3)
Oral drug challenge test	103 (40.2)
None	23 (9.0)
Access to diagnostic tests for Inborn Errors of Immunity?	
Yes	205 (80.1)
Which exams do you have access to?	
Serum immunoglobulins (G, A, M and E)	225 (87.9)
IgG Subclasses	94 (36.7)
Vaccine antigen antibodies (rubella, polio, others)	166 (64.8)
Antibodies to polysaccharides (pneumococci)	55 (21.5)
Late Reading Skin Tests	68 (26.3)
T lymphocyte immunophenotyping (CD4, CD8)	155 (60.5)
B lymphocyte immunophenotyping (CD16, CD20)	111 (43.4)
NK lymphocyte immunophenotyping (CD56)	87 (34.0)
Evaluation of phagocytes (dihydro-rhodamine)	23 (9.0)
Complement and fractions	165 (64.4)
Qualitative and quantitative C1 inhibitor	73 (28.5)
Newborn Screening - TRECs/KRECs	23 (9.0)
Others	20 (7.8)

care providers (245/316; 77.5%) and judicialization (253/316; 80.1%) have been the most frequently used access routes (Table 5).

We found, among specialists participating in the survey, that when asked about the disorders caused by the pandemic in private care, more than 60% of them had a reduction in the number of consultations by at least 50%, and 56% have been attended by teleconsultation. Another relevant fact was that approximately half of the specialists who answered the questionnaire work in the public service and that 29.5% of those who do not work would like to do so (Figure 5).

Discussion

The trajectory of the specialty of Allergy and Clinical Immunology in Brazil is intertwined with the history of the Associação Brasileira de Alergia e

Imunologia.[2] The entity emerged from the successful union of two pre-existing scientific societies intending to join efforts to strengthen the specialty in the country. Due to their common scientific objectives, on November 18, 1971, the merger of Sociedade Brasileira de Alergia (RJ/1946) and the Sociedade Brasileira de Investigação em Alergia e Imunologia (SP/1960), which took place in the following year, in 1972, giving rise to the Sociedade Brasileira de Alergia e Imunopatologia (SBAI). In 2005, SBAI became an association and came to be called the Associação Brasileira de Alergia e Imunopatologia (ASBAI). Years later, another change took place, and the entity was renamed Associação Brasileira de Alergia e Imunologia in 2013.[6]

In the early 1970s, the creation of the Pediatric Allergy subspecialty represented another important milestone in the history of the specialty in Brazil, definitively changing the lives of countless children with allergic and immunological diseases, by improving the quality of care and professional training.[7]

Tabela 5
Access to allergen-specific immunotherapy and biological agents for patients in the public and private sectors, according to expert responses.

Variable	Public n=256 (%)	Private n=437 (%)
Access to Immunotherapy?		
Yes	91 (35.5)	419 (95.9)
Access to immunobiologicals?		
Yes	135 (52.7)	314 (71.9)
Have you ever prescribed immunobiologicals?		
Yes	157 (61.3)	–
For which diseases did you prescribe immunobiologicals?		
Asthma	88 (34.4)	188 (40.9%)
Urticaria	119 (46.5)	259 (56.3%)
Atopic dermatitis	74 (28.9)	195 (42.4%)
EII	97 (37.9)	52 (11.3%)
What immunobiologicals do you have access to?		
Omalizumab	142 (55.5)	265 (60.6)
Dupilumab	66 (25.8)	122 (27.9)
Mepolizumab	14 (5.5)	24 (5.5)
Benralizumab	–	23 (5.3)
Human immunoglobulin	121 (47.3)	170 (38.9)
Others	31 (12.1)	13 (3.0)
None	43 (16.8)	128 (29.3)
In the private sector, how do you have access to immunobiologicals? *		
Health Unic System	–	82 (25.9)
Via Health Operator	–	245 (77.5)
Judicialization	–	253 (80.1)
Own resource	–	58 (18.4)
I don't have a patient in use	–	121 (38.3)

* Considering only those who prescribed (n=316).

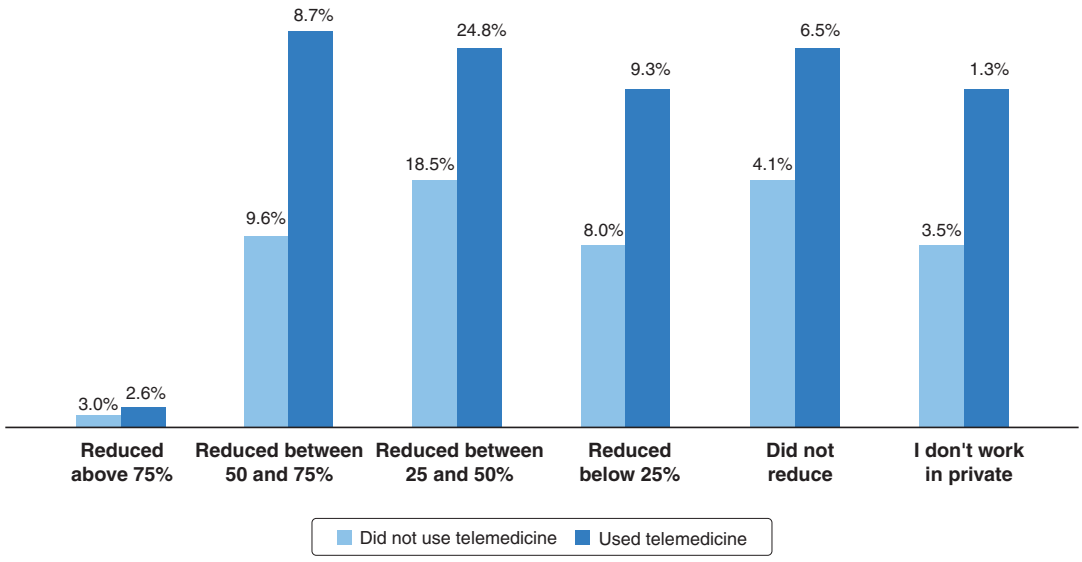

Figure 5
Distribution of participants (n=460) according to the reduction in consultations in private clinics and the option for telemedicine care.

Since then, ASBAI has been developing and expanding, through actions aimed at the permanent and continuing education of the associate, valuing the specialist and professional defense. Today, at the door of the celebration of its 50 years of existence, the specialty of Allergy and Immunology is in its most prominent and representative position on the national and international scene, most notably, in Latin America. However, despite the many achievements already accomplished, there is still much to be done.

In the international context, the specialty has been facing challenges, such as the unavailability of specialists to meet the demands in different locations, the limitations imposed by its recognition only as a subspecialty in some countries, and the reduction in the training time of new specialists, paving the way for the weakening of the specialty.[8]

The results of the present study provided relevant information regarding the profile of the Brazilian specialist in Allergy and Immunology today. The completion rate of the structured questionnaire was 100%, meaning that all participants who started the survey completed it properly. Regarding the response rate, although it reached 25%, this percentage is within the expected range for the research strategy adopted. Furthermore, the studied sample adequately represents the target population, which minimizes the risk of non-response bias, ensuring the reliability of the results.[9] When verifying the response rates, we observed an increase of 5% in this study when compared to the study previously carried out.[3]

The results showed that Brazilian allergists/immunologists are young, mostly women, and more concentrated in the Southeastern region of the country, with São Paulo, Rio de Janeiro, and Minas Gerais being the three states with the highest number of specialists. This data is in agreement with those of the previous study and shows that there has been no change in the demographic profile of the population of specialists in recent years.[3]

The specialty continues to attract more young people every year, professionals starting their careers, which may explain the maintenance of the mean age in relation to the previous study.[3] The distribution of professionals in the territory is still heterogeneous, being absent in several cities in the country, which results in an unequal specialist/patient relationship between regions. As a result, the access of patients with allergic and immunological diseases to adequate care can be quite compromised and

limited to some locations in the country, generating higher costs.

The dissemination of information about allergic diseases and the importance of specialized care in treating patients; professional qualification through matrix support programs for medical professionals from other specialties, especially those in Primary Care; specialized support via telemedicine for non-specialist professionals from distant locations; in addition to encouraging the creation of new ASBAI Regional Offices, these are strategies that have been discussed and implemented to promote and expand the specialty throughout Brazil.

Allergic diseases and IBS, formerly known as primary immunodeficiencies, often negatively impact the lives of patients and their families, whether due to the high prevalence of some of them or the high burden resulting from the morbidity and mortality associated with this group of diseases. This generates a demand for specialized care to meet the health needs of children and adults affected by immune allergic conditions, which, in turn, makes it imperative not only to train specialist professionals in Allergy and Immunology with appropriate skills and competences but also to facilitate access to this type of specialized care.[7] This can be achieved through programs to encourage migration and allocate professionals in places lacking specialists.

Another important issue is the need for the presence of specialists at all levels of the health care network, which could be achieved through public tenders aimed at the area of Allergy and Immunology. Greater insertion of specialists is also much awaited in undergraduate courses in Medicine, where they would contribute to the formation of a profile of graduates who are more prepared to recognize and manage the most frequent allergic diseases. The insertion and strengthening of syllabi related to allergic diseases and immunodeficiencies in the medical curriculum are essential for the dissemination of the specialty among undergraduates, awakening vocations, alongside the implementation of postgraduate courses and scientific research in the area of Allergy and Immunology.

The present study showed that the vast majority of research participants work as an allergist/immunologist, preferably in the private sector, and care for patients of all age groups. Although the place of work of the allergist/immunologist is predominantly in private offices, more than half of them reported working in the public service, which means a trend towards greater equity in access to specialized care. However, when verifying the main place of action in the public service, almost all reported being in outpatient clinics of University Hospitals, which means that the specialist is concentrated in highly complex SUS services. As these are regulated access services, that is, they are not of the "open gate" type, the flow depends on the loco-regional regulation system. Thus, the patient's journey to reach the specialist depends on a well-organized health care network, where all service points (primary care units, specialized care units, high-complexity hospitals, and service providers, such as units of diagnostic services) act in a coordinated manner and where the regulatory system works properly, aspects that directly depend on the local management of the SUS. The difficulties encountered in the journey of patients with severe allergic diseases and IBS can result in delayed diagnosis, irreversible damage to health, and death. Thus, it is necessary to encourage this discussion with local managers, which can result in improved flows to access our specialty.

When evaluating the type of care, both those working in the private sector and those working in the SUS provide care to patients hospitalized for allergic diseases and IEI, revealing the level of complexity that specialists have to deal with in any sector in which they are linked. In this sense, permanent and continuing education strategies are essential to guarantee the updating of specialist professionals.

However, the quality of the care provided does not only depend on the specialist's skills and competences. It also depends on the diagnostic and therapeutic resources made available by the different sectors, whether public or private. The present study identified that about 80% of specialists have access to complementary tests, especially laboratory tests, for the diagnosis of both allergic diseases and IBS in both sectors. Regarding the in vivo tests, the Immediate Reading Skin Test was cited as the most available to specialists in the SUS, while the Contact Test was the least available, compromising the proper approach to cases suspected of contact dermatitis, unlike the previous study, where 45.6% of the participants reported having access to this patch test.[3]

Likewise, the tests to assess the response mediated by antibodies and the complement system were the most frequently mentioned as tests available for the investigation of suspected cases of IEI in the current study, in agreement with the data from the previous study.[3] Regarding the (ASIT), its availability in the SUS is referred to as being three times smaller

than in private services, indicating the inequality of access to this important therapeutic resource, exclusive to the allergy specialty.

As for immunobiologicals, even though they are recent and costlier options, the data from the present study reveal that more than 60% of specialists report having already prescribed them for patients with allergic diseases and IBS, both in the public and private service. This suggests that Brazilian professionals are aware of the rapid changes in clinical protocols and new therapeutic options for their patients. Omalizumab, which was approved by ANVISA more than 10 years ago for severe asthma and later for chronic spontaneous urticaria (CSU); dupilumab, more recently approved for atopic dermatitis, asthma, and chronic rhinosinusitis (CRS) with nasal polyps; and intravenous human immunoglobulin for IEI were the most prescribed. Hives, asthma, atopic dermatitis, and IEI were the indications most frequently cited by specialists for the group of biologicals. These drugs came to fill a gap and solve a demand generated by the CSU unresponsive to antihistamines and by severe asthma, atopic dermatitis, and CRS with nasal polyps, consolidating this new era of personalized medicine and individualized therapeutic regimens. As they are, in general, of high cost, few patients, for whom immunobiologicals are indicated, manage to use them. Thus, the use of these products by most patients depends on subsidized availability. Judicialization and funding via health care providers are the forms of access most frequently reported by research participants.

Recently, the Clinical Protocol and Therapeutic Guideline (CPTG) for asthma were updated and now includes two immunobiologicals for the treatment of severe asthma. In addition, a new resolution from the Agência Nacional de Saúde Suplementar (ANS) was published, updating the List of Procedures and Events in Health, making mandatory the coverage of private health care plans for a series of procedures, including immunobiological therapy intravenous, intramuscular, or subcutaneous, as long as properly guided by the Guidelines.[10] These measures represent a great achievement, guaranteeing the patient a better quality of life, through the opportunity to access effective and safe medications for the treatment of severe forms of some allergic and immunological diseases.[10]

Differently, despite being a well-known therapeutic resource indicated in the treatment of antibody replacement in IEI in which there are humoral immunity problems and in the control of several inflammatory and immunological diseases, human immunoglobulin (HumIg) has been less used, according to data from research participants. It is second in frequency. A possible explanation for this difference is the lower prevalence of IEI in the population compared to allergic diseases, and the smaller number of specialists and services dedicated to the treatment of these conditions compared to the prevalence of allergic diseases, for which immunobiologicals are indicated and locations that make them available. Encouraging young specialists to also work with IEI can contribute to changing this scenario.

Perhaps the lower use of IgHum is due to compromised production. IgHum is an IgG concentrate extracted from human plasma, dependent on blood donation, which suffered a large reduction in the number of blood donations due to the COVID-19 pandemic. In Brazil, this scenario is even more worrying because there is no national production of the product, which makes us dependent on imported products to meet local demand. The concern with the possibility of a shortage of the product at a level that interferes with the treatment of patients with IIE worries specialists and has stimulated discussions on the subject.

The COVID-19 pandemic has also significantly affected the routine of allergists/immunologists. Approximately 60% of specialists reported a reduction in attendance by more than 50%, reaching in some cases a reduction of more than 75%. However, more than half of the affected professionals reported using, in a very timely manner, the resource of telemedicine as a way to reduce both the negative financial impact and to maintain the continuity of specialized care for the patient who was complying with the recommendations of the national and international health authorities of social isolation.[11] The pandemic seems to have consolidated the essential role of connectivity in several sectors, such as medicine, and it seems that telemedicine consultations will become an important option for people's health care.

At present, ASBAI has had as its motto to support the member and offer alternatives that guarantee their continued education, offering information with updated and relevant content. The online model has allowed specialists greater access to information and should have an impact on the specialist's daily practice.

In conclusion, ASBAI members have followed the growth of the specialty of Allergy and Immunology, seeking to incorporate the new therapies proposed in clinical practice. Access to exams has been

expanding, but the investigation of food and drug allergies, which depend on oral provocation tests, and several exams for investigation of IEI need health policies that enable their incorporation into services, which in health supplementary, includes forms of remuneration appropriate to the complexity and risk of these procedures. ASBAI has been engaged and actively participating in the processes of incorporation of new health technologies in public and private health, through the available channels; including the updating of the ANS Procedures List and public consultations by Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC) – Ministry of Health. it is still necessary to sensitize government authorities to expand health care for patients with allergic diseases and immunodeficiencies in the SUS. Public tenders specifically created for specialists in Allergy and Immunology are the definitive way to guarantee access and quality care aimed at this public. Greater access to area-specific diagnostic and therapeutic resources would help to improve patient care more immediately.

The COVID-19 pandemic impacted the entire health sector, affecting the practice of the specialty, especially during the period when elective face-to-face care was restricted, but it brought up the discussion and accelerated the process of incorporating telemedicine into the specialists' routine.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Translation and cross-cultural adaptation of the Congestion Quantifier Five-Item questionnaire to Brazilian Portuguese

Tradução e adaptação transcultural do questionário Congestion Quantifier Five-Item *para o português brasileiro*

Carolina Stefany da Silva[1], Eduarda Lubambo Costa[2]

ABSTRACT

Background: Allergic rhinitis (AR) is considered the most prevalent disease among chronic respiratory diseases, although it is a benign disease, could impact the quality of life of affected individuals, with nasal congestion being the most bothersome symptom reported by patients. Congestion Quantifier Five-Item (CQ5) questionnaire was validated in American English, and was developed to assess the severity and the impact of nasal congestion in adults with AR. The present study aimed to translate and to perform a cross-cultural adaptation of the CQ5 questionnaire to Brazilian Portuguese and to verify if this translated version can be understood by individuals with AR. **Methods:** Following the guidelines of International Society for Pharmacoeconomics and Outcomes Research (ISPOR), CQ5 questionnaire was translated and adapted to Brazilian Portuguese. The Portuguese version was applied with a comprehension questionnaire to volunteers with allergic rhinitis. **Results:** These steps of: preparation; forward translation; reconciliation; back-translation; back-translation review; harmonization; cognitive debriefing; review cognitive debriefing results and finalization; proofreading; and final report proposed by ISPOR were carried out. The final version was applied in 41 volunteers (32,2 ± 7,8) with good understanding of all items. **Conclusion:** The CQ5 questionnaire was translated, and cross-culturally adapted to Brazilian Portuguese with good understanding in individuals with AR.

Keywords: Nasal obstruction, allergic rhinitis, patient health questionnaire.

RESUMO

Introdução: A rinite alérgica (RA) é considerada a doença de maior prevalência entre as doenças respiratórias crônicas, e embora seja uma doença benigna, interfere na qualidade de vida dos indivíduos afetados, sendo a congestão nasal o sintoma mais incômodo relatado pelos pacientes. O questionário *Congestion Quantifier Five-Item* (CQ5), validado em inglês americano, foi desenvolvido para avaliar a gravidade e o impacto provocados pela congestão nasal em indivíduos adultos com RA. O presente estudo teve como objetivo traduzir e adaptar transculturalmente o questionário CQ5 para o português brasileiro e verificar se esta versão traduzida pode ser compreendida por indivíduos portadores de RA. **Métodos:** Seguindo as diretrizes da *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR), o questionário CQ5 foi traduzido e adaptado para o português do Brasil. Esta versão em português foi aplicada em voluntários com rinite alérgica juntamente com um questionário de compreensão. **Resultados:** As etapas de preparação, tradução direta, reconciliação, retrotradução, revisão da retrotradução, harmonização, análise cognitiva da tradução, revisão dos resultados da análise cognitiva e finalização, revisão, e relatório final propostas pela ISPOR foram realizadas. A versão final foi aplicada em 41 voluntários (32,2 ± 7,8) com boa compreensão em todos os itens. **Conclusão:** O questionário CQ5 foi traduzido e adaptado para o português (Brasil) com boa compreensão em indivíduos com RA.

Descritores: Obstrução nasal, rinite alérgica, questionário de saúde do paciente.

Introduction

Allergic rhinitis (AR) is defined as a symptomatic disorder of the nose, induced by an Immunoglobulin E (IgE)-mediated inflammation of the nasal lining mucosa.[1] Rhinitis symptoms include rhinorrhea, nasal congestion, itchy nose and sneezing, which improve spontaneously or with treatment.[1] The clinical

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manifestations of AR occur after the susceptible individual is exposed to a sensitizing allergen.[2]

Rhinitis is considered the most prevalent disease among chronic respiratory diseases, being considered a global public health problem.[3] The World Health Organization (WHO) estimates that 400 million people worldwide suffer from AR.[4] Although it is a benign disease, AR interferes with the quality of life of affected individuals, with high economic costs related to health care.[5,6]

Among the symptoms of AR, nasal congestion is the most characteristic and uncomfortable.[7] In general, there is a gradual worsening of nasal congestion, which can contribute to daytime fatigue, drowsiness, decreased productivity and difficulty concentrating at school and at work.[8,9] Furthermore, it is a symptom considered a risk factor for respiratory and sleep disorders, including snoring and obstructive apnea.[10]

To assess nasal congestion in individuals with allergic rhinitis, Stull et al. (2007)[11] developed the Congestion Quantifier Seven-Item (CQ7) questionnaire. It is a self-administered instrument in which a simplified version and with the same objective was created by the same authors, the Congestion Quantifier Five-Item (CQ5) questionnaire. The CQ5 has been validated for the American adult population and has similar reliability and responsiveness to the CQ7.

This instrument helps individuals to monitor the evolution of their symptoms and guides health professionals in relation to the clinical and drug treatment of AR. For the CQ5 to be applied in Brazil, it is necessary to translate its items into the local language and semantic and cultural adaptation in a language that can be understood by the general population. Therefore, the general objective of this study is to translate and cross-culturally adapt the Congestion Quantifier Five-Item (CQ5) to Brazilian Portuguese and to verify whether this translated version can be understood by individuals with AR.

Methods

It is a methodological study translation and cross-cultural adaptation of the CQ5 questionnaire into Brazilian Portuguese, which was carried out after approval by the Research Ethics Committee (CEP) of the Instituto Aggeu Magalhães/Fundação Oswaldo Cruz - PE, with a favorable opinion (number 4,529,536). In addition, the translation and adaptation of the CQ5 questionnaire was authorized by the tool's developer, Dr. Donald Stull.

The translation and cross-cultural adaptation process of the CQ5 was carried out in accordance with the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[12] for translation and cultural adaptation of patient-reported outcome measures (Patient-Reported Outcomes - PRO). The final version was applied to volunteers with allergic rhinitis to check their understanding of the CQ5 questionnaire.

Items from the original CQ5 questionnaire were kept confidential for copyright preservation, as the original article is not available to the general public, only to subscribers. The study was carried out in the city of Recife (Pernambuco), between August 2020 and June 2021. The application of the questionnaire for cognitive analysis of volunteers was carried out in March 2021.

Participants were recruited through dissemination on electronic means of social networks. Adult individuals, aged between 18 and 60 years, of both genders, diagnosed with AR by a specialist (alergologist or pulmonologist), Brazilian, literate, with a minimum level of education of completed elementary school and who accepted to participate in the research by signing the Informed Consent Form (FICF).

The exclusion criteria applied were: individuals with other upper respiratory tract diseases or nasal structural abnormalities such as polyps and septal deviation, and cognitive disorders or neurological diseases that made it impossible to understand the questionnaires.

The translation and cross-cultural adaptation were carried out according to the ISPOR steps,[12] described below.

(1) Preparation: an initial contact was made with the main author of the CQ5 questionnaire requesting authorization for its use.

(2) Direct translation: after authorization from the developer and approval of the project by CEP, two direct translations of the questionnaire from the source language (American English) to the target language (Brazilian Portuguese) were carried out independently by two bilingual translators, native speakers of Portuguese and fluent in American English, being a sworn translator of English and a guest researcher, health professional, Master in Health Sciences. The translators were previously clarified so that they

could carry out a translation based on the conceptual meaning of the items, capable of being understood by the target population and not an exclusively literal translation. The translations were developed independently without any contact or consultation between the translators.

(3) Reconciliation: the translations produced by the translators were compared to detect possible differences between them. A reconciled translation version was prepared by the researcher and the project coordinator, with input from the second translator, as provided for in the ISPOR guidelines.

(4) Reverse translation: the reconciled version was submitted to a back-translation. At this stage, the Portuguese version of the questionnaire was translated into American English by a native US teacher who was fluent in Brazilian Portuguese. This translator was not involved in any of the previous steps.

(5) Review of the reverse translation: the back-translated version was reviewed and made available to the author of the original instrument for analysis, and he consented to continue the research.

(6) Harmonization: harmonization was performed by the researcher and project coordinator, who compared the reconciled version and the back-translation with the original instrument in order to identify conceptual differences between the original instrument and the translated version. After completing this step, volunteers with allergic rhinitis were recruited to answer the questionnaire.

(7) Cognitive analysis: study participants were recruited through the dissemination of a "folder" containing basic information on the inclusion criteria on social media. Volunteers with allergic rhinitis who volunteered to participate in the study were duly informed about the research and signed the consent form. Data were collected in person or through the multi-platform WhatsApp messaging application.

Initially, data were collected on personal identification, age, gender, education level, time since diagnosis of allergic rhinitis, regular physical activity (defined as physical activity equal to or greater than 3 times a week) and medications in use for the treatment of RA and general purpose. After collecting general data, the cognitive analysis began and the participants answered the CQ5 questionnaire, consisting of five items and five response options.

To assess the participants' understanding of each item of the CQ5 questionnaire, a questionnaire called the understanding questionnaire was applied. The response options for the comprehension questionnaire contained the following options: "I understand well", "I understand a little" and "I don't understand" and the option for written suggestion of word changes from CQ5. Only items with more than 80% comprehension would be included in the final version. If 20% or more of the participants checked the options "I understand little" or "I don't understand", these items would be reformulated and a new version of the CQ5 questionnaire would be reapplied until reaching the 80% comprehension level, previously defined.

(8) Review of cognitive analysis results and completion: The completed questionnaires were analyzed and reviewed.

(9 and 10) Review and final report: the researcher and the project coordinator performed the final review of the questionnaire to correct spelling or grammatical errors. Finally, a final report was prepared by the researcher with a detailed description of all the steps.

The collected data were organized in a database using the Microsoft Office Excel 2016 software, with double data entry and frequent checks to correct typing errors. In the statistical analysis, descriptive statistics (mean and standard deviation) and frequency distribution of the collected data were used.

Results

The CQ5 questionnaire was translated and adapted to Brazilian Portuguese according to ISPOR recommendations. Figure 1 shows the direct translations (Translation 1 and Translation 2), and the reconciliation version of the five items of the CQ5 questionnaire.

The version was back-translated and sent to the developer for review. There were not pointed out by him, items to be modified. Thus, the final version of the questionnaire was completed.

After the final version of the consolidated questionnaire, the instrument was submitted to a cognitive analysis in a group of 41 volunteers with allergic rhinitis. Table 1 shows the clinical characteristics of the sample.

Thirteen participants responded to the survey in person, and 28 responded through the WhatsApp application, in which all files were sent for reading, knowledge and filling in data, and the files were sent back after completion by the participants. All participants marked "I understand well" for items 1, 2, 4

and 5, totaling 100% of understanding for these items. Regarding item 3, four participants (corresponding to 10% of the sample) indicated “I understand little”. All items were answered by all participants.

Of the four participants who marked "I understand little", one participant suggested a modification in item 3. The suggestion was to remove the preposition "from" in the excerpt "even after blowing it" in the sentence "How often did you have difficulty cleaning completely your nose, even after blowing it several times?”.

Item 3 was changed to “How often did you have difficulty cleaning your nose completely, even after blowing it several times?”. The item modification was incorporated into the final version of the questionnaire, as shown in Figure 2.

Discussion

In the present study, the CQ5 questionnaire was translated and cross-culturally adapted to Brazilian Portuguese. Adult volunteers with AR who participated in the study reported understanding of all items in the Portuguese version.

To carry out the translation of this tool, all steps were followed according to the guidelines proposed by ISPOR in order to obtain semantic and conceptual equivalence between the original version and the

Item	Tradução 1	Tradução 2	Reconciliação
1	Com que frequência você teve entupimento, bloqueio ou congestão nasal?	Com que frequência você teve entupimento, obstrução ou congestão nasal?	Com que frequência você teve entupimento, obstrução ou congestão nasal?
2	Com que frequência você precisou respirar pela boca porque não conseguia respirar pelo nariz?	Com que frequência você teve que respirar pela boca porque não conseguia respirar pelo nariz?	Com que frequência você teve que respirar pela boca porque não conseguia respirar pelo nariz?
3	Com que frequência você teve dificuldade de limpar completamente o nariz, mesmo após assoá-lo diversas vezes?	Com que frequência você teve dificuldade para limpar completamente o nariz, mesmo após assoar repetidamente?	Com que frequência você teve dificuldade de limpar completamente o nariz, mesmo depois de assoá-lo diversas vezes?
4	Com que frequência você acordou de manhã com entupimento, bloqueio ou congestão nasal?	Com que frequência você acordou de manhã com entupimento, obstrução ou congestão nasal?	Com que frequência você acordou de manhã com entupimento, obstrução ou congestão nasal?
5	Com que frequência o seu sono foi afetado por causa de entupimento, bloqueio ou congestão nasal?	Com que frequência seu sono foi afetado em decorrência do entupimento, da obstrução ou da congestão nasal?	Com que frequência seu sono foi afetado em decorrência do entupimento, da obstrução ou da congestão nasal?
Escala de respostas	(0) Nenhuma vez, (1) poucas vezes, (2) algumas vezes, (3) quase o tempo todo, ou (4) o tempo todo.	(0) Nunca, (1) Um pouco, (2) Algumas vezes, (3) Na maioria das vezes, ou (4) Sempre.	(0) Nunca, (1) Poucas vezes, (2) Algumas vezes, (3) Na maioria das vezes, ou (4) Sempre.

Figure 1
Translations 1 and 2 and reconciliation version of the CQ5 questionnaire.

Table 1
Clinical characterization of the sample.

Variables	Evaluation n=41
Age (in years)	32.3 ± 7.8
Sex	
Masculine	10 (24%)
Feminine	31 (76%)
Education level	
Complete high school	09 (22%)
Complete higher education	18 (44%)
Specialization/Graduate	11 (27%)
Master's degree	03 (07%)
Diagnosis of allergic rhinitis (years)	
Less than 1 year	00 (00%)
Between 2 and 5 years	07 (17%)
Between 5 and 7 years old	07 (17%)
More than 10 years	27 (66%)
Regular physical activity	
Yes	23 (56%)
Not	18 (44%)
Allergic rhinitis medications	
Yes	32 (78%)
Not	09 (22%)
Other medications in regular use	
Yes	11 (27%)
Not	30 (73%)

Data expressed in average numbers ± standard deviation or absolute numbers (%).

translated version, ensuring the adaptation of the instrument to the local culture and maintenance of properties psychometrics of the questionnaire, aiming at its subsequent validation.[12]

ISPOR's translation and cultural adaptation guidelines recommend the development of at least two direct translations, performed by two independent translators, avoiding the risks of a translation that includes a translator's own writing style and reducing individual speech preferences.[12,13] Thus, two translators were included to perform the direct translation.

The titles independently translated into Portuguese were “Quantificador de Congestão com Cinco Perguntas (CQ5)” (in english: Congestion Quantifier with Five Questions (CQ5)) and “Cinco Itens do Quantificador de Congestão (CQ5)” (in english: “Five Items of the Congestion Quantifier (CQ5)”). We chose to keep the second option because it was considered by the researcher and coordinator to be easier to understand. In the initial section containing the questionnaire instructions, “last week” was replaced by “last 7 days” to avoid interpretations between individuals regarding the period to which the questionnaire referred.

Some items, in particular items 1, 2, 4 and 5, required a discussion in the translation process, as a literal translation of the instrument would recommend the use of “nasal block”. However, this expression was replaced by “nasal obstruction” (suggested by translator 2), since this common expression is more used in Brazilian daily life.

The word "blocking" is defined as "Act or effect of blocking" and "blocking" means "Preventing the movement or movement of", and "obstruction" is defined as "Partial or total, mechanical impediment, due to various causes, of the free transit of organ light; occlusion.”[14] In addition, DeCS/MeSH defines “nasal obstruction” as: “Any impediment to the passage of air into or out of the nose. The obstruction can be unilateral or bilateral, and can involve any part of the nasal cavity”, the descriptor being “nasal obstruction”.[15,16] In this case, it is highlighted that "nasal blockage" and "nasal obstruction" are synonymous terms.

A literature review[17] that included 31 articles with different methods for cross-cultural adaptation of questionnaires shows that although back-translation is a commonly used step, there is no convincing evidence that this step improves the target language version. However, as the objective of the back-translation is to control the quality of the translated version and whether it has the same meaning when translated back into the original language,[12] the step was included in this study and was analyzed by the study developer with a satisfactory opinion.

Among the limitations, it is noteworthy that this study did not assess the degree of nasal congestion of the participants to compare with the information provided by the volunteers, as this was not the objective of the study. This work was also not intended to assess the validity of the questionnaire and the psychometric properties of all of its items.

As perguntas a seguir referem-se aos últimos 7 dias. Para cada pergunta, selecione apenas uma resposta marcando a caixa apropriada.

1. Com que frequência você teve entupimento, obstrução ou congestão nasal?
   (0) Nunca (1) Poucas vezes (2) Algumas vezes (3) Na maioria das vezes (4) Sempre

2. Com que frequência você teve que respirar pela boca porque não conseguia respirar pelo nariz?
   (0) Nunca (1) Poucas vezes (2) Algumas vezes (3) Na maioria das vezes (4) Sempre

3. Com que frequência você teve dificuldade de limpar completamente o nariz, mesmo após assoá-lo diversas vezes?
   (0) Nunca (1) Poucas vezes (2) Algumas vezes (3) Na maioria das vezes (4) Sempre

4. Com que frequência você acordou de manhã com entupimento, obstrução ou congestão nasal?
   (0) Nunca (1) Poucas vezes (2) Algumas vezes (3) Na maioria das vezes (4) Sempre

5. Com que frequência seu sono foi afetado em decorrência do entupimento, da obstrução ou da congestão nasal?
   (0) Nunca (1) Poucas vezes (2) Algumas vezes (3) Na maioria das vezes (4) Sempre

Figure 2
CQ5 questionnaire translated into Brazilian Portuguese.

The CQ5 questionnaire was translated and cross-culturally adapted to Brazilian Portuguese and was well understood by individuals with AR. Future research may assess the psychometric properties and validate this version for use in clinical practice in individuals with AR.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Response to dupilumab in severe atopic dermatitis without prior use of systemic immunosuppressive agents during the COVID-19 pandemic

Resposta ao dupilumabe na dermatite atópica grave sem uso prévio de imunossupressor sistêmico durante a pandemia de COVID-19

Mara Morelo Rocha Felix[1,2], Laira Vidal da Cunha Moreira[1], Ana Carolina de Moura Rocha Teixeira Miranda[1], Nathalia Mota Gomes Almeida[1]

ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and recurrent eczema. It mainly affects childhood but has become quite prevalent in adolescents and even adults. Despite being generally non-fatal, it has an important psychosocial burden for patients and their families. AD treatment involves skin hydration and anti-inflammatory medications. In severe cases, systemic therapy with immunosuppressive agents such as cyclosporine, methotrexate, and azathioprine may be necessary. More recently, some biologicals are being developed to control AD. Dupilumab is a monoclonal antibody with anti-IL-4/IL-13 dual-action, approved for the treatment of children from 6 years of age with severe AD and adolescents/adults with moderate to severe AD. This article aimed to report a case series of adolescent and adult patients with severe AD and their response to dupilumab during the COVID-19 pandemic. These are four patients (three female), with a significant worsening of AD during the year 2020. All had a history of AD since childhood, with complementary exams showing IgE-mediated sensitization to mites. They had already undergone several topical and systemic treatments, including courses on oral corticosteroids. None of them had received systemic immunosuppressive agents, but they were refusing this type of treatment due to fear of the pandemic. All had a good response to dupilumab, evidenced by a reduction in the number of skin lesions and pruritus, with few side effects. Two patients had symptoms suggestive of COVID-19 during treatment with dupilumab (one confirmed by PCR) with a good outcome.

RESUMO

A dermatite atópica (DA) é uma doença inflamatória crônica da pele, caracterizada por intenso prurido e eczema recorrente. Acomete principalmente a infância, mas tem se tornado bastante prevalente em adolescentes e até em adultos. Apesar de ser geralmente não fatal, apresenta uma carga psicossocial importante para os pacientes e seus familiares. O tratamento da DA envolve a hidratação cutânea e medicações anti-inflamatórias. Em casos graves, pode haver necessidade de terapia sistêmica com imunossupressores como ciclosporina, metotrexato e azatioprina. Mais recentemente, alguns imunobiológicos estão em desenvolvimento para controle da DA. O dupilumabe é um anticorpo monoclonal com ação dupla anti-IL-4/IL-13, liberado para tratamento de crianças a partir de 6 anos com DA grave e adolescentes/adultos com DA moderada a grave. O objetivo deste artigo foi relatar uma série de casos de pacientes adolescentes e adultos com DA grave e sua resposta ao dupilumabe durante a pandemia do COVID-19. Trata-se de quatro pacientes (três do sexo feminino), com piora significativa da DA durante o ano de 2020. Todos tinham história de DA desde a infância, com exames complementares evidenciando sensibilização IgE-mediada para ácaros. Já haviam sido submetidos a diversos tratamentos tópicos e sistêmicos, inclusive a cursos de corticosteroides orais. Nenhum deles havia recebido imunossupressor sistêmico, porém estavam recusando este tipo de tratamento devido ao medo da pandemia. Todos apresentaram boa resposta ao dupilumabe, evidenciada pela redução do número de lesões cutâneas e prurido, com poucos efeitos colaterais. Dois pacientes apresentaram sintomas

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In conclusion, patients with severe AD have a great impact on quality of life and, during the COVID-19 pandemic, many had a significant worsening of their dermatological condition. In this context, dupilumab proved to be an effective and safe therapeutic option for the treatment of these patients.

Keywords: Atopic dermatitis, monoclonal antibodies, immunosuppressive agents, quality of life, COVID-19.

sugestivos de COVID-19 durante o tratamento com dupilumabe (um com confirmação por PCR), com boa evolução. Concluindo, os pacientes com DA grave possuem grande impacto na qualidade de vida e, durante a pandemia de COVID-19, muitos apresentaram piora significativa do seu quadro dermatológico. Nesse contexto, o dupilumabe se mostrou uma opção terapêutica eficaz e segura para tratamento destes pacientes.

Descritores: Dermatite atópica, anticorpos monoclonais, imunossupressores, qualidade de vida, COVID-19.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching and recurrent eczema.[1] It mainly affects children, but it has become quite prevalent in adolescents and even adults.[2] Despite being generally non-fatal, it has an important psychosocial burden for patients and their families.

The severity of AD can be assessed using a score called Scoring Atopic Dermatitis (SCORAD).[3] The index considers the extent of the disease, the severity of the lesion, and the presence of subjective symptoms such as itching and sleep loss. The SCORAD is an objective measure that allows the assessment of the patient over time and comparison between different studies.[1]

The impact on the quality of life (QoL) of patients with AD can be measured using different instruments.[4] One of the most used is the Quality of Life Index in Dermatology Questionnaire (DLQI-BRA).[5] The risks to QoL arising from AD have been recognized, but this impact is still little explored in the adult population.[6-8]

AD treatment involves skin hydration and anti-inflammatory medications.[4] Among the anti-inflammatory drugs, the most used are topical corticosteroids and calcineurin inhibitors.[4] In severe cases, there may be a need for systemic therapy with immunosuppressants such as cyclosporine, methotrexate, and azathioprine.[4] More recently, some immunobiologicals are being developed to control AD.[9] Dupilumab is a monoclonal antibody with anti-IL-4/IL-13 dual-action, approved for the treatment of children from 6 years of age with severe AD and adolescents/adults with moderate to severe AD.[9]

The aim of this article was to report a case series of adolescent and adult patients with severe AD and their response to dupilumab during the COVID-19 pandemic.

Case report

Case 1

I.B.P., 28 years old, male, with AD since 5 years old. He had partially controlled asthma using combined therapy (inhaled corticosteroids and long-acting beta-agonists), allergic rhinitis, allergy to shrimp, and amoxicillin-clavulanate. He reported a significant worsening of the skin lesions in 2020. He was under regular use of bilastine (double dose), moderately potent topical corticosteroids (mometasone), topical tacrolimus on the eyelids, skin moisturizer, in addition to frequent use of topical and systemic antibiotics and corticosteroids systemic. Exams (09/22/2020): Total IgE: 4588 KU/L; *Blomia tropicalis* specific IgE > 100 KU/L; *Dermatophagoides pteronyssinus* > 100 KU/L; *Dermatophagoides farinae* > 100 KU/L; dog epithelium 1.98 KU/L; cat epithelium 0.16 KU/L; *Aspergillus fumigatus* 0.36 KU/L; shrimp 48 KU/L. The DLQI-BRA was applied, totaling 15 points out of a maximum of 30 points, which indicates a high compromise in the patient's quality of life, and the initial SCORAD of 74 on 09/22/2020 was calculated, which indicates severe dermatitis. He had already been submitted to specific immunotherapy with mites on previous occasions. The patient refused to start treatment with a systemic immunosuppressant for fear of the side effects of the drugs and a possible more serious evolution of COVID-19 during the pandemic. Considering the severity of the AD picture and the impact on QoL, in addition to partially controlled

asthma, it was decided to start dupilumab in December 2020. The patient returned on 01/26/21, after 4 applications of dupilumab, with a SCORAD of 24,2 and significant improvement in pruritus. Regarding side effects, reported only occasional mild facial erythema and ocular pruritus. He maintains the use of dupilumab and is currently with her asthma controlled using combination therapy. He was suspected of having COVID-19 during the use of dupilumab (suggestive symptoms, in addition to intra-household contact with positive PCR), but no PCR was collected. He had a good evolution, with no need for hospitalization.

Case 2

M.M.S.R, 19 years old, female, with AD since she was 6 months old. She had rhinitis but had no other allergic comorbidities. She reported a significant worsening of the skin lesions in 2020. She was under regular use of bilastine (double dose), moderately potent topical corticosteroids (mometasone), topical tacrolimus on the eyelids, skin moisturizer, in addition to frequent use of topical and systemic antibiotics and corticosteroids systemic. Exams (11/08/2020): Total IgE 5000 KU/L; *Dermatophagoides pteronyssinus* specific IgE > 100 KU/L; *Dermatophagoides farinae* > 100 KU/L. The DLQI-BRA was applied, totaling 15 points out of a maximum of 30 points, which indicates a high compromise in the patient's quality of life, and the initial SCORAD of 62.6 on 08/04/2020 was calculated, which indicates severe dermatitis. She had already been submitted to specific immunotherapy with mites on previous occasions. She refused the use of systemic immunosuppressants due to possible side effects. It was decided to start dupilumab in January 2021 due to the severity of the condition and the patient's QoL, even without the use of systemic immunosuppressants. The patient returned on March 31, 21, after 5 applications of dupilumab, with a SCORAD score of 18.5, with substantial improvement in skin itching (approximately 90%). In June 2021, the patient complained of conjunctivitis after applying duplilumab, being prescribed eye drops with lubricants, and being referred to Ophthalmology. Repeated the DLQI-BRA in August 2021, totaling 2 points. It was decided to start dupilumab in January 2021 due to the severity of the condition and the patient's QoL, even without the use of systemic immunosuppressants. The patient returned on March 31, 21, after 5 applications of dupilumab, with a SCORAD score of 18.5, with substantial improvement in skin itching (approximately 90%). In June 2021, the patient complained of conjunctivitis after applying duplilumab, being prescribed eye drops with lubricants, and being referred to Ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points. It was decided to start dupilumab in January 2021 due to the severity of the condition and the patient's QoL, even without the use of systemic immunosuppressants. The patient returned on March 31, 21, after 5 applications of dupilumab, with a SCORAD score of 18.5, with substantial improvement in skin itching (approximately 90%). In June 2021, the patient complained of conjunctivitis after applying duplilumab, being prescribed eye drops with lubricants, and being referred to Ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points. the patient complained of conjunctivitis after the application of duplilumab, being prescribed eye drops with lubricants, and referred to ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points. the patient complained of conjunctivitis after the application of duplilumab, being prescribed eye drops with lubricants, and referred to ophthalmology. The DLQI-BRA was repeated in August 2021, totaling 2 points.

Case 3

M.S.S.A.A., 19 years old, female, with AD since 6 years old, without other allergic comorbidities (asthma, rhinitis, or food allergy). She reported a significant worsening of the skin lesions in 2020. She was under regular use of bilastine (double dose), moderately potent topical corticosteroids (mometasone), skin moisturizer, in addition to frequent use of topical and systemic antibiotics and systemic corticosteroids. Exams (11/12/2020): Total IgE: 897 KU/L; *Dermatophagoides pteronyssinus* specific IgE 56.8 KU/L; *Dermatophagoides farinae* 54.8 KU/L; *Blomia tropicalis* 10.5 KU/L; ant 4.7 KU/L; dog epithelium; cat and negative fungi. The DLQI-BRA was applied, totaling 29 points out of a maximum of 30 points, which indicates a very serious compromise in the patient's quality of life, and the initial SCORAD of 83.5 was calculated, which indicated severe dermatitis on 01/06/2021. She had already been submitted to specific immunotherapy with mites in 2020, with worsening of the lesions, being suspended after two series. She refused the use of systemic immunosuppressants due to possible side effects and fear of progressing to severe COVID-19. It was decided to start dupilumab due to the seriousness of the condition and the impact on

the patient's quality of life, even without the use of systemic immunosuppressants. The patient returned on March 24, 21, after 4 applications of dupilumab, with a SCORAD score of 21. She had many residual hypertrophic lesions, especially in the lower limbs, and was seeking treatment with Dermatology.

Case 4

M.E.T.N.O., 16 years old, with AD since 2 months of age. She had asthma and allergic rhinitis. She reported a significant worsening of the skin lesions in 2020. She was in regular use of phototherapy (no response). In addition, she was already using bilastine (double dose), moderately potent topical corticosteroids (mometasone), and skin moisturizer. She frequently used topical and systemic antibiotics and systemic corticosteroids. Exams (12/17/2020): Total IgE: 875 KU/L; (06/24/2018): total IgE 279 KU/L; *Dermatophagoides pteronyssinus* specific IgE 15.2 KU/L; *Dermatophagoides farinae* 7.31 KU/L; *Blomia tropicalis* 32.1 KU/L; ant 1.13 KU/L; negative dog and cat epithelium. The DLQI-BRA was applied, totaling 29 points out of a maximum of 30 points, which indicated a very high compromise in the patient's quality of life, and the initial SCORAD of 76.3 was calculated. which indicated severe dermatitis on 03/02/2021. She had already been submitted to specific immunotherapy with mites in 2018, with worsening of the lesions, and was suspended. She refused the use of systemic immunosuppressants due to possible side effects. It was decided to start dupilumab due to the severity of the condition and the impact on the patient's QoL, even without the use of systemic immunosuppressants. Dupilumab started in May 2021 with SCORAD falling to 24.9 in August 2021, as shown in Figures 1, 2, and 3. Repeated the DLQI-BRA in August 2021, totaling 3 points. She had mild COVID-19 in July 2021, confirmed by PCR, without the need to go to the Emergency Room or hospital. She report that during the picture she only presented odynophagia. Delayed

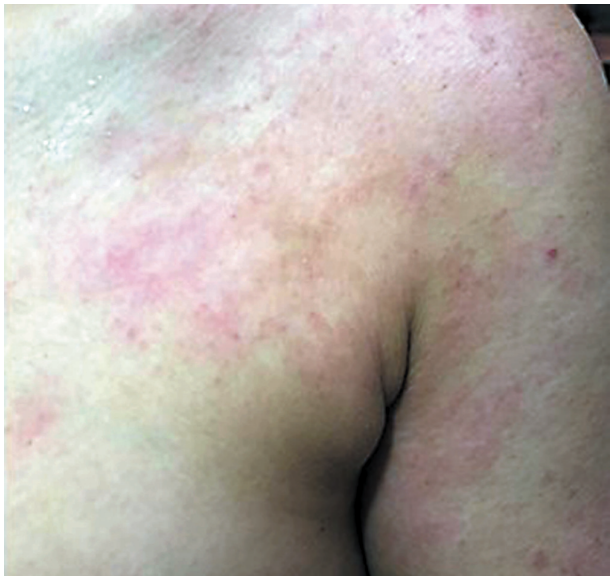

Figure 1
Case 4: left shoulder (before starting dupilumab).

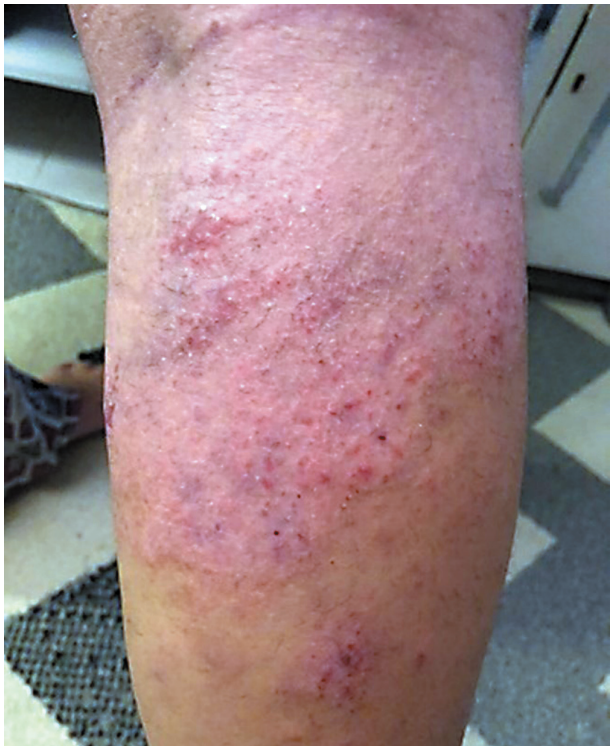

Figure 2
Case 4: popliteal region (before starting dupilumab).

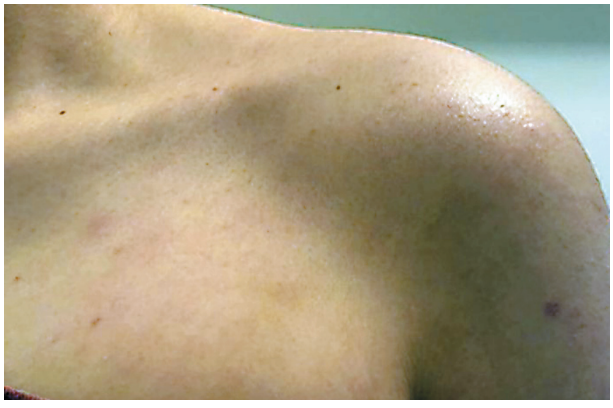

Figure 3
Case 4: left shoulder (after starting dupilumab).

the application of dupilumab due to the condition of COVID-19.

Discussion

In all reported cases there was a significant worsening of AD during 2020, coinciding with the COVID-19 pandemic period, highlighting the importance of the emotional agent as an aggravating factor in AD cases.[1] On the other hand, after starting dupilumab there was a substantial improvement in the patients' QoL as evidenced by the DLQI-BRA.[4] Thus, it is clear that the use of different instruments can be useful to better measure the impact of AD on patients' lives.

Another important aspect is the long evolution of the disease, with a severe condition, all with SCORAD above 50. The SCORAD is a widely used tool to assess the severity of AD, as it considers the extent of the disease, the intensity of the lesions, and the presence of subjective symptoms.[1,3] All patients had significant improvement in SCORAD after starting dupilumab, both in subjective criteria such as pruritus and in the intensity and extension of the lesions. Other tools can be used to measure the severity of AD, such as the EASI and the IGA.[1] We chose to use SCORAD because it is the simplest, with measurement through an application.

The frequent use of systemic corticosteroids to control AD exacerbations was observed in all reported cases, and it is a very common practice in our country. On the other hand, it should be noted that it increases the risk of infections, in addition to serious, often irreversible, side effects. A meta-analysis (10 studies, n = 6,548 patients) has already shown that the use of corticosteroids in patients with Influenza pneumonia was associated with higher mortality, longer intensive care unit stay, and a higher rate of secondary infection.[10] Thus, especially in times of COVID-19 pandemic, the use of oral corticosteroids should be avoided, always making gradual and slow reduction if the patient is with prolonged use, being careful with the risk of adrenal insufficiency in abrupt withdrawal.

Finally, the discussion on the scaling of treatment steps deserves to be highlighted. Topical therapy is usually sufficient to manage patients with mild to moderate AD. However, in moderate to severe cases, especially when there is a refractory disease, it may be necessary to introduce therapy with systemic immunosuppressants. Cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil have shown positive results in the treatment of patients with severe AD. On the other hand, they are medications that cannot be used for a long time due to their potential toxic effects. Furthermore, many of these drugs are not licensed for use in AD in Brazil and are not distributed free of charge by the health network. Methotrexate and cyclosporine are among the most used drugs, but both are associated with an increased risk of infections. The BIOBADADERM registry (Spanish Registry of Adverse Events for Biological Therapy in Dermatological Disease), which included 2,153 patients with psoriasis, showed a higher infection rate for cyclosporine versus methotrexate of 58%.[11] In a comparison of methotrexate (n = 50) versus cyclosporine (n = 47) in adults with moderate to severe AD, infection rates were 32% and 24%, respectively.[12] Another consideration is the potential impact of these immunosuppressants on the susceptibility/severity of SARS-CoV2 infection. Patients in our series refused to use immunosuppressants for fear of side effects. These are effects that can be controlled and monitored through periodic examinations. Before starting to use this type of medication, we need patients' consent. Benefits versus risks must be explained so that we can make a shared decision.

Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 by binding to IL-4 subunits α and IL-13α-1 of the receptor, inhibiting the JAK-STAT signaling pathway.[13] Thus, there is a reduction in the production of Th2 cytokines, IgE, and an improvement in the skin barrier function.[13] It was the first biologic approved for use in AD, with proven efficacy in patients with moderate to severe AD, as observed in our patients. An analysis of seven randomized controlled trials showed that adult AD patients treated with dupilumab had a lower risk of serious infections, skin infections, and herpetic infections (eczema herpeticum or herpes zoster) compared to placebo.[14] Furthermore, through the concomitant treatment of asthma, in theory, there would be better evolution during an infection in the COVID-19 pandemic.

The side effects observed in our series were conjunctivitis and facial erythema. These effects are similar to those described in the literature and generally do not prevent the continued use of the medication. The reason why dupilumab causes conjunctivitis is still not completely known.[13] In any case, it remains a much safer therapeutic option when compared to systemic immunosuppressants

that can lead to pancytopenia, hepatotoxicity, or renal failure.[13] It is important to consider that during treatment with dupilumab, there is a contraindication for the application of vaccines with live components, but vaccines with inactivated components, such as those of SARS-CoV2 can be applied.

There are few studies on the evolution of COVID-19 in patients using dupilumab. In our sample, one patient had an unconfirmed suspicion of infection and evolved well, with no need for hospitalization. Another patient had confirmed infection with good evolution. A recent publication showed a series of 71 adult AD patients in Lombardy using dupilumab and only 2 had infection confirmed by COVID-19 (one of these patients had comorbidities and needed to be hospitalized, but did not have sequelae).[15] In Milan, among 245 patients using dupilumab, only 2 developed COVID-19 (without complications).[16] In a retrospective study in Toronto, of 162 patients using duplilumab, only 1 had to discontinue treatment due to patient concerns, but not because of infection.[17]

In conclusion, patients with severe AD have a great impact on QoL and, during the COVID-19 pandemic, many had a significant worsening of their dermatological condition. In this context, duplilumab proved to be an effective and safe therapeutic option for the treatment of these patients. Further studies are needed to assess the safety and efficacy of immunosuppressants compared to immunobiologicals, such as dupilumab, during the COVID-19 pandemic.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

BCG reactivation after COVID-19 vaccine: case report

Reativação da BCG após vacina contra COVID-19: relato de caso

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ABSTRACT

BCG reactivation can occur in different contexts: associated with infectious conditions, immunosuppression, autoimmunity and post-vaccinations. Also, especially in children below of 5 years of age, should be valued as a finding present in about 50% of cases of Kawasaki disease. In this article, we report the first case published in the literature of a young adult patient, who manifested a reactivation of BCG after receiving the first dose of vaccine against COVID-19 (AztraZeneca/Oxford/Biomanguinhos). Within the first 24 hours after the administration of the vaccine, the patient developed high fever, sweating, local pain, diffuse myalgia and headache. After 2 days, erythema and induration at the site of the BCG vaccine scar began. she has how comorbidity to chronic spontaneous urticaria, but she was asymptomatic without crises for more than 1 year. The relevant family history is maternal death due to the complex syndrome of autoimmunity overlap (systemic lupus erythematosus, Sjögrens syndrome, and anti-phospholipid antibody). After being medicated with NSAID and moderate topical corticosteroid therapy potency for 3 days, there was complete resolution of BCG reactivation. The patient, after 3 months, received the 2nd dose of the vaccine and had no symptoms. It is believed that the reactivation of BCG occurs due to a cross-reaction mechanism between the individuals HSP, elicited as mediators of innate immunity against vaccine inflammation, with some epitopes of *M. bovis*. It is recommended that any immunosuppressive or autoimmune condition be investigated in patients that manifest BCG reactivation, especially in adults, in which Kawasaki disease is quite rare. Vaccines, including those against COVID-19, can also trigger of this immunological phenomenon still poorly understood.

Keywords: BCG vaccine, COVID-19 vaccines, autoimmunity.

RESUMO

A reativação da BCG pode ocorrer em diversos contextos: associada a quadros infecciosos, imunossupressão, autoimunidade e pós-vacinações. Além disso, especialmente em crianças abaixo de 5 anos de idade, deve ser valorizada como um achando presente em cerca de 50% dos casos de Doença de Kawasaki. Neste artigo, relatamos o primeiro caso publicado na literatura de uma paciente adulta jovem, a qual manifestou uma reativação de BCG após receber a primeira dose de vacina contra COVID-19 (AztraZeneca/Oxford/Biomanguinhos). Dentro das primeiras 24h após a administração da vacina, a paciente desenvolveu febre alta, sudorese, dor local, mialgia difusa e cefaleia. Após dois dias, iniciou eritema e enduração no local da cicatriz da vacina BCG. Ela tem como comorbidade a urticária crônica espontânea, porém estava assintomática sem crises há mais de 1 ano. Tem como antecedente familiar relevante o óbito materno por síndrome complexa de sobreposição de autoimunidade (lúpus eritematoso sistêmico, síndrome de Sjögren e síndrome do anticorpo antifosfolípide). Após ser medicada com anti-inflamatórios não esteroides (AINE) e corticoterapia tópica de moderada potência por 3 dias, houve resolução completa da reativação da BCG. A paciente, após 3 meses, recebeu a segunda dose da vacina e não manifestou nenhum sintoma. Acredita-se que a reativação da BCG ocorra devido a um mecanismo de reação cruzada entre HSP do indivíduo, elicitadas como mediadores da imunidade inata frente à inflamação vacinal, com alguns epítopos do *M. bovis*. Recomenda-se que seja investigada alguma condição imunossupressora ou autoimune nos pacientes que manifestem reativação da BCG, principalmente em adultos, na qual a doença de Kawasaki é bastante rara. As vacinas, incluindo as contra COVID-19, também podem desencadear o surgimento deste fenômeno imunológico ainda pouco compreendido.

Descritores: Vacina BCG, vacinas contra COVID-19, autoimunidade.

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Introduction

BCG reactivation consists of an inflammatory process located in the region of vaccine administration (in the right deltoid region), which can manifest from mild local hyperemia to more exuberant reactions, with formation of eczema, ulceration with exudation and crusts on the skin. This process can occur temporarily years after the administration of BCG (in Brazil, it is applied to newborns right at birth). Some literature references also call itBCGitis, although this term more commonly encompasses satellite adenomegaly type reactions.

It is described as occurring in various contexts, such as after infectious conditions, usually of viral etiology (upper airways or gastroenteritis, in addition to published reports on measles and HHV-6), in addition to immunosuppressive conditions (use of immunosuppressive drugs, chemotherapy, infection by HIV or post-transplantation). It is also described as a process that occurs after several vaccinations and as a clinical sign indicative of Kawasaki disease in about 50% of cases, despite not being included in the diagnostic criteria for this disease.

In this article we report the first case published in the literature of a young adult patient, who was vaccinated against COVID-19 (AztraZeneca/Oxford) and developed a reactivation of BCG.

Case report

A 23-year-old patient, student of Medicina, received the vaccine against COVID-19 and about 12 hours later, she developed chills and burning in her eyes, but without hyperemia or ocular secretion. Two hours after the onset of the condition, he developed a fever of 39.4°C and sweating, associated with pain at the site of vaccine administration and diffuse myalgia, especially on the back, and frontal headache. The next day, he observed mild hyperemia at the site of the vaccine and started inappetence. After 2 days, he observed redness and induration at the site of the scar from the BCG vaccine (which he had received in childhood, Figure 1). She was seen by the team from the Post-Vaccine Adverse Events Outpatient Clinic of a tertiary referral hospital, and an erythematous plaque measuring 2 cm in diameter was observed at the site of vaccine administration. Other changes were excluded, such as adenomegaly or signs of systemic involvement.

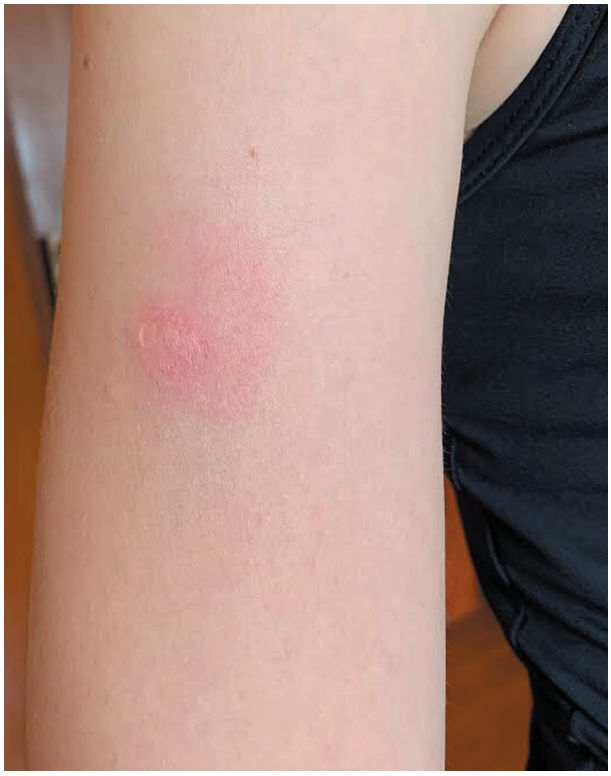

Figure 1
BCG reactivation after COVID-19 vaccine.

She presented from comorbidity a condition of spontaneous chronic urticaria, which had been diagnosed since the age of 10 years, and had been under control, without medication, for more than 1 year. In the reported crises, he presented some episodes of urticaria accompanied by angioedema (on the face and extremities of the hands and feet), associated with arthralgia in the knees. Despite extensive investigation of autoimmune etiologies, the patient did not meet criteria for any other specific disease.

The patient had been investigated, when she was diagnosed with chronic urticaria, with biochemical tests, search for some tumor markers and serological tests to search for autoantibodies – she had a family history of a mother who died of complex autoimmune overlap syndrome (systemic lupus erythematosus, Sjögren's syndrome and anti-phospholipid syndrome). At the time it was evaluated by BCG reactivation, some of these tests were repeated (Table 1). The use of oral NSAID (nimesulide) and topical corticotherapy (mometasone cream 0.1%) were prescribed for 3 days, with complete resolution of the skin condition.

She did not have a recurrence of urticaria or any other systemic manifestation, with follow-up and subsequent contact being carried out until 1 month after vaccination. The patient received the second dose, scheduled after 3 months, and did not develop any reaction, remaining asymptomatic.

Discussion

The pathophysiological mechanism involved in BCG reactivation is still controversial in the literature. A mechanism is suggestedimmune-mediated, through cross-reactions between mycobacterial epitopes with certain chaperones called HSP (heat shock protein).

Tabela 1
Exams performed in the diagnosis of chronic urticaria and BCG reactivation.

Initial exams (2018-2019)	Current exams (2021)
Hb: 13.4 g/dL Ht: 40.9% Platelets: 354 thousand/mm^3 Leukocytes (/mm^3): 11530 - Neutrophils: 6930 - Lymphocytes: 3430 - Monocytes: 820 - Eosinophils: 310 - Basophils: 40	Hb: 12.7 g/dL Ht: 36.1% Platelets: 283,000/mm^3 Leukocytes (/mm^3): 5920 - Neutrophils: 2469 - Lymphocytes: 2611 - Monocytes: 480 - Eosinophils: 349 - Basophils: 12
Anti-nucleus ac (Hep2) NR Ac gastric parietal cells NR Anti-native DNA Ab (double helix) NR Anti-endomysial IgA ac NR Antimitochondrial Ac NR Anti-smooth muscle ac NR Antithyroglobulin NR Ab Anti-Sm Ac/RNP NR Ac anti-Ro and anti-La NR Anticardiolipin NR IgG Anticardiolipin NR IgM Ab C3=90 (VR 67-149 mg/dL) C4=16 (VR 10-38 md/dL) C 15.3=8.2 (VR < 28 IU/mL) C 19.9=6.5 (VR < 37 IU/mL) CA-125=11 (VR < 35 IU/mL)	Anti-nucleus ac (Hep2) NR 1st hour VHS=1 C-reactive protein=negative D-dimer 0.45 (VR < 0.5 µg/mL) Antithyroglobulin NR Ab Anti-TPO Ab (microsomal) NR C4=18.4 (VR 12-36 mg/dL) Autologous Serum Test=negative
IgA=266 mg/dL IgG=827 mg/dL IgM=187 mg/dL IgE=31 kU/L	IgA=262.5 mg/dL IgG=782 mg/dL IgM=161.5 mg/dL IgE=25.02 IU/mL Immunophenotyping: - CD3/CD4=1176 (40.3%) - CD3/CD8=821 (28.1%) - CD4/CD8=1.4 - CD19=325 (11.2%) - CD16/56=413 (14.2%)
Free T4: 0.9 nd/dL Basal TSH: 1.3 mIU/L	T4L: 1.17 ng/dL Basal TSH: 2.33 mIU/mL

Chaperones are a family of proteins that are involved in the post-translational processing of proteins synthesized in cells, ensuring the correct folding of the polypeptide chain, preventing aggregation and ensuring that disulfide bonds are established between the sulfated amino acids. Among the chaperones, there are the so-called HSP (heat shock protein) – heat shock proteins, involved in the folding, assembly and transport of essential proteins for cell survival. Its synthesis increases in the presence of cellular stress, including infections, ischemia and other physical stresses. Its role has been included within the innate immune response.

In the illness of Kasawaki, the cross-reaction between HSP 63 and HSP 65 with mycobacterial antigens is cited explaining the BCG reactivation described in this disease. Another possible mechanism described in the literature is the reactivation of quiescent M. bovis maintained adjacent to the site of vaccine administration under certain conditions of immunosuppression, including a theoretical risk of systemic dissemination of the infection, called BCGose.

In the case reported in this work, the only comorbidity presented by the patient is spontaneous chronic urticaria, a disease now considered autoimmune in more than 50% of cases. Two possible current mechanisms to explain the onset of the disease are described: first, there is the abnormal synthesis of IgG against specific IgE molecules or their receptors, present on the surface of mast cells and basophils (autoimmune urticaria); second, there is the possibility that the individual will develop specific IgE molecules that recognize a particular autoantigen (autoallergic urticaria). Regardless of the associated mechanism, mast cells and basophils end up being activated, culminating in the release of pre- and newly formed inflammatory mediators, responsible for the symptoms of the condition and the emergence of wheals.

It is suggested that the COVID-19 vaccine may have caused an unspecific stimulation of innate immunity, which interfered with the balance maintained between the presence of bovisquiescent and the individual's immune system. In the literature, it is speculated that infections associated with transient immunosuppression, such as measles, may disrupt this balance, explaining the reported cases of BCG reactivation after this wild virus infection. Interestingly, the patient did not have urticaria exacerbation and/or angioedema, keeping her underlying disease under control, suggesting that BCG reactivation itself may not have a direct relationship with spontaneous chronic urticaria. She also did not meet criteria for Kawasaki disease, which is rare over 5 years old.

Therefore, it is imperative to investigate any immunosuppressive/autoimmune condition in individuals who present BCG reactivation after different contexts, such as infections or vaccine reactions, although there is none in the literature suggested investigation protocol. In children, especially under 5 years of age, especially infants, it is essential to remember the possibility of Kawasaki disease in the presence of this immunological phenomenon that is still poorly understood.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Atypical presentation of X-linked hyper-IgM syndrome simulating inflammatory bowel disease

Apresentação atípica de síndrome de hiper-IgM ligada ao X simulando doença inflamatória intestinal

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ABSTRACT

We report the case of a male patient, who started with ulcers in the gastrointestinal tract, associated with recurrent fever and diarrhea with mucus and blood at 10 months of life, initially suspected of inflammatory bowel disease, however, he did not improve the condition with immunosuppressive therapy, being investigated for inborn error of immunity. In laboratory tests, he had low levels of IgG and IgA and high levels of IgM and persistent neutropenia. Therefore, a genetic test was performed and confirmed the diagnosis of X-linked hyper IgM syndrome. Inborn errors of immunity can manifest relatively frequently with diseases of the gastrointestinal tract, and should be included as a differential diagnosis of chronic diarrhea. Included in this group of diseases, hyper-IgM syndromes constitute a heterogeneous group of diseases, having in common significantly low or absent levels of IgG and IgA and normal or high levels of IgM, which predispose to infections and recurrent fever; in addition to other laboratory alterations, such as neutropenia, which may be associated with ulcers in the gastrointestinal tract and proctitis, simulating the clinical presentation of inflammatory bowel disease. For the reported patient, therapy with immunoglobulins was started periodically, in addition to antibiotic prophylaxis for infections, evolving with a satisfactory clinical response. The main objective of the article is to alert to the differential diagnosis of inborn errors of immunity in view of the presented condition, aiming at early diagnosis and the institution of adequate therapy.

Keywords: Primary immunodeficiency diseases, immune system diseases, hyper-IgM immunodeficiency syndrome type 1.

RESUMO

Relatamos o caso de um paciente do sexo masculino, que iniciou quadro de úlceras em trato gastrointestinal, associado a febre recorrente e diarreia com muco e sangue aos 10 meses de vida, suspeitado inicialmente de doença inflamatória intestinal, no entanto, não apresentou melhora do quadro com terapia imunossupressora, sendo realizada investigação para erro inato da imunidade. Nos exames laboratoriais, apresentou níveis baixos de IgG e IgA e níveis elevados de IgM e neutropenia persistente. Diante disso, foi realizado teste genético que confirmou diagnóstico de síndrome de hiper-IgM ligada ao X. Os erros inatos da imunidade podem se manifestar com doenças do trato gastrointestinal, de forma relativamente frequente, devendo entrar como diagnóstico diferencial de diarreia crônica. Inclusa nesse grupo de doenças, as síndromes de hiper-IgM constituem um grupo heterogêneo de doenças, possuindo em comum níveis significativamente baixos ou ausentes de IgG e IgA e níveis normais ou elevados de IgM, o que predispõe a infecções e febre recorrente; além de outras alterações laboratoriais, como neutropenia, que pode estar associada a úlceras no trato gastrointestinal e proctite, simulando apresentação clínica de doença inflamatória intestinal. Para o paciente relatado, foi iniciada terapia com imunoglobulinas de forma periódica, além de antibioticoprofilaxia para infecções, evoluindo com resposta clínica satisfatória. O artigo possui objetivo principal de alertar para o diagnóstico diferencial de erros inatos da imunidade diante do quadro apresentado, visando o diagnóstico precoce e a instituição da terapia adequada.

Descritores: Doenças da imunodeficiência primária, doenças do sistema imunitário, síndrome de imunodeficiência com hiper-IgM tipo 1.

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Introduction

Inborn errors of immunity (EII) are genetic disorders that affect different components of the immune system. Currently, due to the improvement of genetic diagnosis methods, more than 400 diseases are described. However, late or incorrect diagnosis is still common.[1,2] Clinical manifestations are very diverse, being characterized by severe recurrent or prolonged infections, autoimmune/inflammatory disease, allergy or malignancy.[3,4]

EII can affect the gastrointestinal tract at a frequency ranging from 5% to 50%.[1] The intestine-associated lymphoid tissue is the largest lymphoid organ in the body, with varied mechanisms of immune regulation. Diarrhea and malabsorption are common in many EII. Recurrent or treatment-refractory gastrointestinal diseases should be a warning sign for a possible immunodeficiency.[5]

Hyper-IgM syndrome (HIGM) can be congenital or secondary to other underlying diseases (multiple myeloma, leukemia, nephrotic syndrome, and chronic infections, such as congenital rubella syndrome and use of medications such as phenytoin).[6] Congenital forms are very rare, accounting for 0.3 to 2.9% of all primary immunodeficiencies, with an estimated incidence of 1/130,000 live births and with heterogeneous genetic defects, which may present X-linked, autosomal recessive inheritance or dominant.[3,7,8] In HIGM, there is a defect in immunoglobulin class switching due to genetic defects in the CD40 (B lymphocyte)/CD40 binding (CD40L; T lymphocyte) signaling pathway or in the DNA repair system responsible for class switching. Therefore, there is a loss in the signaling necessary for activated T lymphocytes to induce B lymphocytes to convert immunoglobulin M (IgM) into other immunoglobulins (IgG, IgA and IgE).[2,9,10] In addition, CD40L also participates in the maturation of antigen-presenting cells, in stimulating the effective function of macrophages and in the enhancement of T lymphocyte antigens.[8,11,12]

Depending on the associated genetic defect, HIGM can be classified into five subtypes: type 1, occurs due to CD40L deficiency, is X-linked autosomal dominant hereditary, exclusive to males and the most common form, corresponding to 65% of cases;[5] type 2, corresponds to the autosomal recessive form with mutations in the gene that encodes a cytidine deaminase that participates in the intracellular activation cascade of the B lymphocyte.[5] These patients may have adenoid hyperplasia with defects in the germinal centers, representing about 15% of cases; type 3, the mutation occurs in the gene that specifically codes for the CD40 molecule essential in lymphocyte development, growth, and differentiation; type 4, whose molecular mechanisms are still unknown; and type 5, produced by mutations in the gene for a glycosylase (uracil DNA glycosylase), the last two being recessive forms.[6] All these syndromes have similar clinical characteristics and only through molecular and genetic studies is it possible to make a differential diagnosis.[1,13] The patients have as characteristics significantly low or absent levels of IgG and IgA and normal or high levels of IgM, in addition to a weak or non-protective IgG response to vaccinations.[14] Neutropenia is the most common hematological alteration in type 1 HIGM, but its cause remains unknown, and it may be due to the presence of antineutrophil antibodies and/or delay in myeloid maturation in the marrow.[15] Some studies suggest that CD40-ligand may also act to stimulate the endogenous production of granulocyte colony stimulator,[15] and bone marrow biopsies from these patients may show delay in myeloid lineage maturation.[14]

Most patients with HIGM have increased susceptibility to infections, especially sinopulmonary, such as pneumonia, sinusitis and acute otitis media, developing symptoms during the first year of life; and almost all during the first four years.[16] Pneumocystis is the most prevalent infection and in half of the cases it is caused by *Pneumocystis jirovecii*.[16] Infectious complications of the respiratory tract, such as bronchiectasis, are common.[9] Infectious diarrhea has been associated with infection by cryptosporidium, giardia, salmonella or entamoeba.[2] Aphthous ulcers, gingivitis and rectal ulcers may be associated with chronic or intermittent neutropenia.[2] Central nervous system infection, sepsis, hepatitis and/or sclerosing cholangitis, cellulitis and/or subcutaneous abscesses may also occur.[16] Due to recurrent infections, these patients may have growth and development failure.[16,17] There is an increased risk of neoplasms, especially of the liver and biliary tract, and of autoimmune complications, such as sclerosing cholangitis, which may be associated with chronic infection by *Cryptosporidium parvum*.[9,16,18]

We report the case of a male patient who presented warning signs of innate immunity error, with severe infection, in addition to recurrent fever, chronic diarrhea, oral ulcers and neutropenia, initially being managed as an inflammatory bowel disease, however,

with confirmed later diagnosis of type 1 HIGM, with the aim of reminding us of this diagnostic hypothesis in the face of similar conditions.

Case report

Male patient, born by cesarean section, at term, non-consanguineous parents, one healthy sister, uneventful in the perinatal period, mixed breastfeeding from birth and introduction of food at 6 months, with normal growth and development. First admission at 6 months of age due to severe pneumonia, evolving with hyposaturation and severe respiratory distress, requiring admission to the intensive care unit, with orotracheal intubation and good response to broad-spectrum antibiotic therapy (piperacillin-tazobactam and vancomycin). He remained asymptomatic for up to 10 months of life, when he started a condition of ulcers in the oral cavity associated with daily fever, especially at night, seeking medical care sometimes, with antibiotic therapy with amoxicillin and amoxicillin-clavulanate, and the condition was reported according to the mother. with antibiotic therapy, however, return soon after the end of the medication. During this period, he even presented a condition described as dental abscess, as a complication of ulcers, which improved after the use of antibiotics. At 12 months of age, he started with episodes of diarrhea with blood and mucus, 3-4 times a day and reddish plaques evolving to more intense hyperchromic spots on the lower limbs and knees, and was interrogated arthralgia (difficulty in resting feet on the floor). He was treated with antibiotics and steroids, with a good response.

He was hospitalized twice due to oral ulcers, fever and bloody diarrhea, being treated with antibiotic therapy. He was submitted to a cow's milk protein exclusion diet, however, he did not show improvement, and after reintroduction of this protein, there were no changes in the intestinal condition.

Thus, the gastroenterology service raised the hypothesis of inflammatory bowel disease, and upper digestive endoscopy was performed, which showed shallow esophageal ulcer, without significant microscopic changes, and colonoscopy that showed isolated, shallow ulcers, with adjacent enanthematic and edematous mucosa in the transverse colon, left colon, sigmoid and rectum, without inflammatory activity on microscopy. Therapy for inflammatory bowel disease was started with prednisone, azathioprine, sulfasalazine and adequate enteral formula. However, he persisted with fever of an intermittent pattern, oral and perianal ulcers, and diarrhea with blood and mucus, requiring hospitalization during the period for intravenous antibiotic therapy, with improvement in the condition. At 15 months of age, he was hospitalized for colitis-like diarrhea, suspected of EII and an evaluation was requested from the Immunology service, with the initial hypothesis being a deficiency of IL10/IL10 receptor and a genetic panel for EII was requested. At the same time, other immunoglobulin tests and immunoglobulin dosage were requested, showing IgG and IgA below the 3rd percentile and IgM above the 97th percentile. The immunoglobulin dosage was repeated, keeping IgA and IgG below the 3rd percentile (P3) for age and normal IgM, intravenous immunoglobulin replacement was started, steroids and immunosuppressants were suspended, and antimicrobial therapy was maintained, with clinical and laboratory improvement. The review of blood counts showed intermittent anemia and persistent neutropenia since 12 months of life. Myelogram with bone biopsy was also performed, showing erythroid and granulocytic hypocellularity with moderate delay in myeloid maturation. The patient received granulocyte colony stimulator therapy, with significant improvement in neutropenia. Vitamin B 12 and folic acid levels were normal and other tests had already been performed, such as serology for Epstein-barr virus and cytomegalovirus with negative IgG and IgM, negative anti-HIV, in addition to pANCA and cANCA, fecal calprotectin, anti- fecal trypsin, HLAB51 negative. During hospitalizations, *Campylobacter jejunii* was isolated by multiplex PCR from feces, *Klebsiella* and *Citrobacter freundii* in urine cultures.

At 19 months of age, the result of the genetic panel for EII (407 genes investigated - Invitae laboratory) indicated a mutation in the CD40 ligand (Figure 1). Subsequently, flow cytometry was performed, which showed an alteration in the expression of the CD40L protein (Figure 2), and the amplification of the PCR product on an agarose gel showed absence of amplification of exons 4 and 5 (Figure 3), confirming the diagnosis of X-linked HIGM. No pathogenic mutations were observed in the other genes.

Discussion

X-linked HIGM or type 1 is characterized by CD40L deficiency, which affects males, in general, children of mothers who carry the mutation in one

RESULT: POSITIVE

One Likely Pathogenic variant identified in CD40LG. CD40LG is associated with X-linked hyper-IgM syndrome.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CD40LG	Deletion (Exons 4-5)	hemizygous	Likely Pathogenic
IL17RA	c.355C>A (p.Leu119Met)	heterozygous	Uncertain Significance
PIK3R1	c.*1del (Non-coding)	heterozygous	Uncertain Significance
VPS13B	c.4329T>G (p.His1443Gln)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 207 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Figure 1
Genetic panel for Inborn Errors of Immunity (EII - 407 genes).

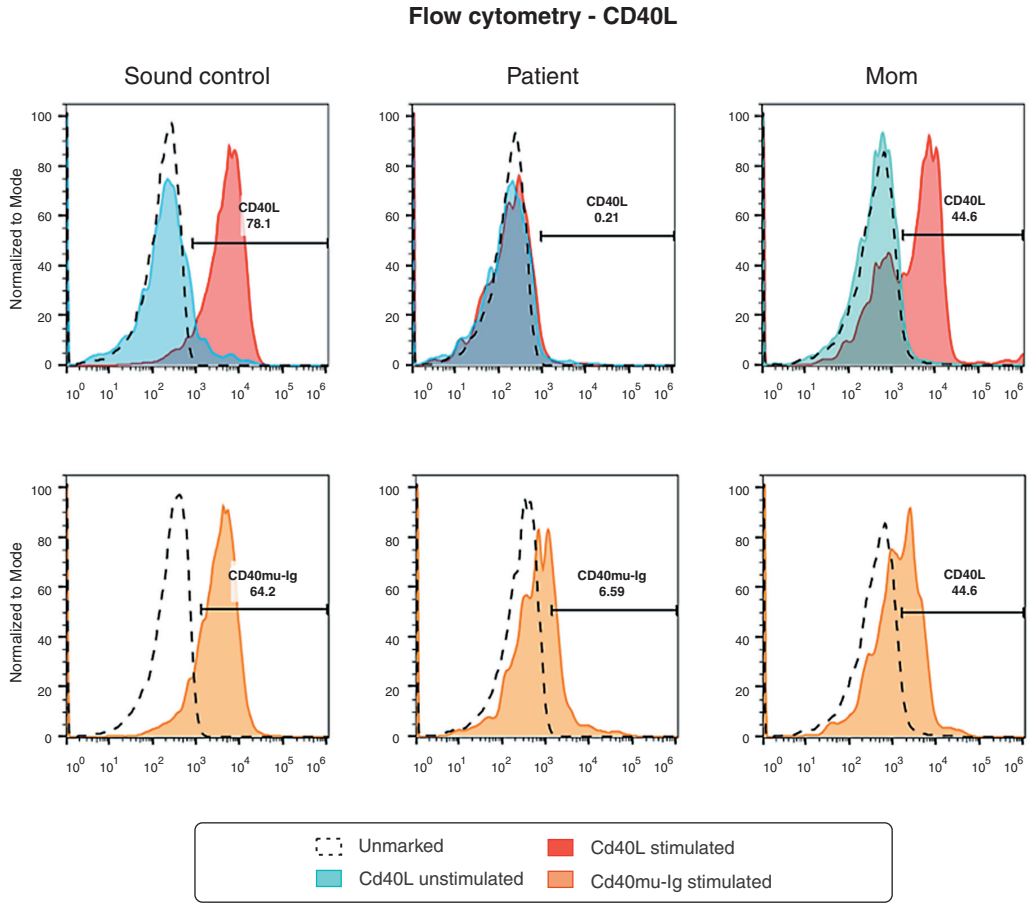

Figure 2
CD40 Ligand Protein expression by flow cytometry.

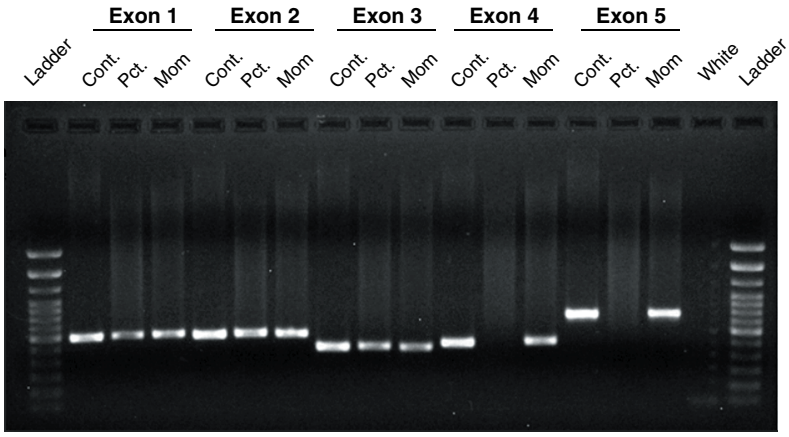

Figure 3
Amplification of CD40LG exons on agarose gel.

of the X chromosomes.[19] These patients have a defect in the function of B cells and T cells, which is considered a primary combined immunodeficiency.[20] The patient in the case reported is male and presented signs of primary immunodeficiency during the first year of life, due to severe pneumonia, requiring orotracheal intubation. Sinopulmonary infections, especially pneumonia, are present in 80% of patients with X-linked HIGM, occurring during the first year of life.[16] Approximately half of patients with HIGM have pneumonia caused by *P. jirovecii*.[16] As it is a combined immunodeficiency, these patients, in addition to being susceptible to infections by opportunistic bacteria, such as *P. jirovecii* and histoplasmosis, are also more prone to infections by encapsulated bacteria, such as Streptococcus pneumoniae or *Haemophilus influenzae*, which are likely to cause pneumonia presented by the patient. besides presenting a picture of recurrent fever with improvement after the use of antibiotic therapy and multiplex PCR of feces isolating bacteria, confirming the greater predisposition to infections.[16,17]

The patient also had chronic diarrhea, being a common manifestation of the X-linked Hyper-IgM syndrome and more commonly resulting from cryptosporidium infections.[16] Diarrhea associated with ulcers of the gastrointestinal tract could also be justified by persistent neutropenia, considered a common hematological finding present in this syndrome, present in two-thirds to half of patients, and may be episodic or recurrent, being associated with ulcers in the gastrointestinal tract, stomatitis and proctitis, in addition to increasing the risk of infections.[12,14,16] Bone marrow biopsy in these patients may show a delay in the maturation of the myeloid lineage, as in the case reported.[14]

Initially, inflammatory disease was suspected.early-onset intestinal ia; however, the patient did not have inflammatory markers compatible with inflammatory diarrhea, such as calprotectin and fecal alpha-1-antitrypsin, in addition to not presenting suggestive microscopy in ulcer biopsies and not showing a good response with the use of immunosuppressants. Furthermore, laboratory tests showed normal to high levels of IgM and low levels of IgE, IgG and IgA, in addition to neutropenia. Therefore, primary immunodeficiency was suspected, and the diagnosis of X-linked HIGM was confirmed through genetic testing.

The therapeutic options used include intravenous immunoglobulin replacement, antibiotic prophylaxis for *P. jirovecii* infection with sulfamethoxazole-trimethoprim, use of granulocyte colony stimulator for neutropenia and bone marrow transplantation, with

varying degrees of success[3,4,15,16,20]. In addition, it is not recommended that these patients receive live virus vaccines, and prevention of cryptosporidium infection (water contamination) should be recommended, with hygienic measures such as drinking only filtered water, not having contact with faeces and avoiding bathing in lakes, ponds, and in non-chlorinated pools.[7,12,14] The only curative therapy is allogeneic hematopoietic cell transplantation, with better results in young patients, without liver disease at the time of transplantation, and with good spinal cord suppression, which should be a considered therapeutic option.[9,14] In the case of the reported patient, clinical and laboratory improvement was observed with regular use of intravenous immunoglobulin IgG, in addition to good control of diarrhea, ulcers in the gastrointestinal tract and neutropenia with the use of granulocyte colony stimulator and prophylactic trimethoprim sulfamethoxazole; hygienic measures were also oriented to the mother.

Conclusion

X-linked HIGM should be remembered when there is increased susceptibility to infections, which may manifest as recurrent fever, chronic diarrhea and/or multiple hospitalizations for infectious conditions, associated with a reduction in IgG, IgA and IgE immunoglobulins, with IgM immunoglobulin normal or increased and neutropenia, especially in male patients. The main cause of death for these patients is opportunistic infections, hence the importance of early diagnosis and the institution of adequate prophylaxis, in addition to being able to program curative therapy with allogeneic hematopoietic cell transplantation earlier.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Current changes in agriculture in Southern Brazil: Lolium and polinosis in "a new vision"

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Dear Editor,

Lolium multiflorum (LOM), called annual ryegrass, is an exotic grass, native to the European Mediterranean region. It has adapted perfectly to the geo-climatic conditions of southern Brazil, serving as an excellent pasture and forage, especially in the autumn/winter period.[1]

When cultivated, it maintains a seed bank in the soil, which grows spontaneously over the years, with natural reseeding.

LOM, also referred to as ryegrass, is characterized by making a prodigious allergenic pollen production. When dispersed in the air, it produces rhinoconjunctivitis and/or seasonal bronchial asthma, during spring, in previously sensitive individuals.[2]

Such grass was initially selected in some regions of southern Brazil as winter pasture, following its use for another purpose, the so-called "direct planting in straw", a new conservationist agricultural practice.[1] It was considered one of the bases for covering the soil without its revolving (maintaining physical, chemical and biological properties) essentially in summer crops, such as soybeans and corn.

LOM can also be ecologically considered an invasive grass, which can exist on the outskirts of cities, in abandoned land, along highways, among other places. It has an anemophilious pollen, highly allergenic which affects the atopic population especially in the spring period, in southern Brazil.[2,3]

It was previously characterized through epidemiological studies, which associated agriculture/soybeans with the presence of ryegrass. In Santo Ângelo (Missions region – RS), a 22.1% prevalence of pollinosis was obtained in the adult population.[4] In parallel and identical methodology, through a written questionnaire (International Study of Asthma and Allergies in Childhood), validated in Curitiba, a population of Brazilian Army soldiers (n= 3,028) was studied in two large regions (Missões and Pampa - RS). A prevalence rate of 21.6% was obtained in the region of Missões, where extensive soy farming (summer), intercropped with ryegrass (winter) predominated. In the Pampa region, there was a prevalence of 3.2%, with a predominance of extensive cattle raising (borders with Uruguay and Argentina), in natural vegetation.[5] It is assumed that there are no skin testing for grass pollen and/or quantification of grass pollen specific IgE, which could confirm the diagnosis. However, the similar prevalences of pollinosis (22.1% and 21.6%) would not simply be a matter of chance.

Modifications in agricultural practices, including wheat cultivars with high genetic improvement and productivity, and high consumption in the Brazilian market, reactivated its cultivation by agricultural producers in extensive areas in southern Brazil, in the winter period. It was found that that could replace ryegrass with the advantage of also producing straw for soil protection in soybean crops. The same happens with black oats (*Avena strigosa*), a type of grass that has characteristics of self-pollination, that is, without pollen dispersion. The ryegrass is now "unwanted" because, through a bank of residual seeds in the soil, it behaved like a "weed" competing with summer crops such as soybeans and corn and/or also with wheat itself in the following year.[6] In addition, rye grass has become resistant to herbicides in some areas, including glyphosate, being an important fact for farmers.

One consideration, from an ecological point of view, is that there would be a potential for the growth of various types of vegetation, including ryegrass, in fallow areas (without crops), during the winter period, waiting for the land to be later planted with soybeans or corn in the summer. Current agronomic information invalidates this hypothesis, as farmers have machines and land to use for an extra gain with winter crops such as wheat, eliminating all kinds of "weeds" before cultivation.

In 2019, the state of Rio Grande do Sul (RS) was the largest wheat producer in Brazil, responsible for more than 42% of production (Source: *Radiografia da Agropecuária*

Gaúcha, 2020). These facts are similarly verified in the State of Paraná, a great producer of wheat and soybean, often surpassing RS.

We had the opportunity to observe new changes in the cultivation of wheat, in personal contact with rural producers in the region of Missões, on field days, adding a route of approximately 300 km on inland roads, bordering crops.

Although, from an ecological point of view, we have the opportunity to relate this to the possible decrease in the prevalence of pollinosis and pollen dispersion in wheat areas, previously taken up with ryegrass, there is no aerobiological data that could be analyzed together to confirm the hypothesis.

Doctors, especially allergists, with the current changes in wheat agriculture, would have some "good news" associated with pollinosis sufferers, not only because of sensitization to grass pollen, but mainly because of the intensity and incidence of symptoms. A practical visit to the field could be "planned" together with agronomists or rural producers.

Special thanks for the information and current field practices in agriculture, received from:

Gilmar Vione, agronomist at EMATER - Santa Rosa, RS, Brazil.

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Food-dependent exercise-induced anaphylaxis without IgE sensitivity – A rare challenging condition

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Dear Editor,

Exercise-induced anaphylaxis displays 4 different categories (Table 1).[1] The modality food-dependence without IgE sensitivity is rare and not documented extensively in the literature.[2,3] We therefore are herein presenting 3 illustrative cases.

Table 1
Categories of exercise-induced anaphylaxis

– Primary food-independent
– Food-dependence with IgE
– Food-dependence without IgE
– With drug-dependence

Case 1

A 31-years-old caucasian male with atopic dermatitis and allergic rhinitis refers recurrent anaphylaxis since the age of 4 years old. After eating wheat containing foods, such as pizza, sandwiches and cakes, and exercising afterwards, he always has pruritus, generalized urticaria, angioedema, diarrhea, and frequent fainting episodes. He is able to exercise normally if not eating wheat products previously and he can eat wheat containing foods if not exercising afterwards. The combination of both factors triggers the referred symptoms. The patient has a positive family history for atopy. Laboratory evaluation showed 541 eosinophils/mm^3 (8,2%), total serum IgE of 142,1 IU/mL (normal: below 100 IU/mL), specific serum IgE negative for wheat, gluten, and omega-5-gliadin (performed twice). The patient is sensitized to house dust mites Dermatophagoides farinae and Dermatophagoides pteronyssinus. He was advised to wait for 4 to 6 hours after having eaten wheat to initiate aerobic exercises. An epinephrin autoinjector was supplied.

Case 2

A 41 years-old healthy caucasian female, with a positive family history for atopy, refers that after eating crab and shrimp followed by aerobic exercises she develops severe generalized pruritus and diffuse urticaria, with large coalescent wheals. Emergency intravenous or oral antihistamines relieves her symptoms. She can eat shellfish without difficulties if not exercising afterwards. She also states that while exercising daily, there are no symptoms if she abstains from eating shellfish. Applying positive (histamine) and negative (diluent) controls, prick testing to shrimp, crab, oysters, scallops and clams were negative. She was advised to wait for 4 to 6 hours after having eaten shellfish to initiate aerobic exercises. An epinephrin autoinjector was supplied.

Case 3

A 39 years-old caucasian female, with rhinitis, bilateral nasal polyps, and a positive family history for atopy, refers that exercising on a treadmill after eating shrimp, she develops laryngeal edema requiring emergency administration of intramuscular epinephrin. Curiously, this does not happen with the other shellfish. She can eat shrimp without difficulties if she does not exercise afterwards. She also states that while exercising daily, there are no symptoms if she abstains from eating shrimp. Laboratory evaluation showed a normal serum tryptase, and twice negative specific serum IgE for shrimp, crab, lobster, oysters and clams. She was advised to wait for 4 to 6 hours after having eaten shrimp to initiate aerobic exercises. An epinephrin autoinjector was supplied.

The most common presentations of exercise-induced anaphylaxis are the food-dependent with IgE sensitization. The non-allergic modalities are uncommon and probably underreported.[4,5] Three documented cases of food-dependence without IgE sensitization are described with the following foods: wheat, shellfish and solely to shrimp. The underlying mechanisms of this entity are still unknown. More reported cases in the literature are needed

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Atypical and unusual clinical presentation of atopic dermatitis: A case report

Apresentação clínica atípica e incomum de dermatite atópica: relato de caso

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ABSTRACT

Atopic Dermatitis, also called atopic eczema, is a complex systemic inflammatory disease with heterogeneous clinical morphologies. Common features are eczematous lesions, intense pruritus and chronic or relapsing disease course. Eczematous lesions typically show an age-related distribution. However, this disease can present different phenotypes, like follicular/papular dermatitis and prurigo nodularis. We reported a male, 22 years old, phototype IV, African descent, with personal and familial history of atopy. He reported pruritus, xerosis and lesions on skin since he was 2 years-old, with relapsing and chronic course. Clinical examination showed disseminated perifollicular accentuation and rough follicular papules. Extensor surfaces of the legs showed excoriated papules and nodules, beside generalized post-inflammatory hypopigmentation. He had lichenified plaques on the back, neck, hands and foot. Skin biopsy showed spongiosis, parakeratosis and irregular acanthosis at the epidermis. The diagnosis was late and occurred only in adulthood. Due to the extensive and relapsing presentation, he received Cyclosporin 3 mg/Kg/day, associated to steroids and emollients, with improvement of pruritus, xerosis and lechinification. But he maintained perifollicular accentuation. The patient presented common features of Atopic Dermatitis, like chronic and relapsing lesions, history of atopic, dry skin, pruritus, and early disease onset. However, atypical morphologies were presented, exemplified by prurigo nodularis and follicular/papular dermatitis. Other relevant finding it was the fact that the lesions occurred outside the classic areas, with prevalence on extensor surfaces and trunk. These atypical morphologies and unusual location of lesions are prevalent on adults with high phototypes, as seen in this case. It is essential to identify these challenging phenotypes, because the diagnosis of Atopic Dermatitis is clinical. Given the diversity of clinical presentation and difficult to recognize some cases, this article will contribute to demonstrate atypical manifestations and common features in non-white patients, facilitating correct diagnosis and early treatment.

Keywords: Atopic dermatitis, phenotype, african americans, skin diseases, clinical diagnosis.

RESUMO

A dermatite atópica, também chamada de eczema atópico, é uma doença inflamatória sistêmica complexa, com morfologias clínicas heterogêneas. As características comuns são lesões eczematosas, prurido intenso e curso crônico ou recidivante. Lesões eczematosas geralmente mostram uma distribuição relacionada à idade. No entanto, essa doença pode apresentar diferentes fenótipos, como dermatite folicular/papular e prurigo nodular. Relatamos um homem, 22 anos, fototipo IV, afrodescendente, com história pessoal e familiar de atopia. Referia prurido, xerose e lesões na pele desde os 2 anos, com recidiva e curso crônico. O exame clínico mostrou acentuação perifolicular disseminada e pápulas foliculares ásperas. As superfícies extensoras das pernas apresentavam pápulas e nódulos escoriados, além de hipopigmentação pós-inflamatória generalizada. Notaram-se placas liquenificadas no dorso, pescoço, mãos e pés. A biópsia de pele demonstrou espongiose, paraqueratose e acantose irregular na epiderme. O diagnóstico foi tardio e ocorreu apenas na idade adulta. Devido ao quadro clínico extenso e recidivante, recebeu Ciclosporina 3 mg/Kg/dia, associada a esteroides e emolientes, com melhora de prurido, xerose e liquenificação, mas manteve a acentuação perifolicular. O paciente apresentava características comuns de dermatite atópica, como lesões crônicas e recidivantes, história de atopia, pele seca, prurido e início precoce da doença, no entanto, foram apresentadas morfologias atípicas, exemplificadas por prurigo nodular e dermatite folicular/papular. Outro achado relevante foi o fato das lesões localizarem-se em áreas não clássicas da doença, com predomínio nas superfícies extensoras e tronco. Essas morfologias atípicas e localizações incomuns são prevalentes em adultos com fototipos elevados, como visto neste caso. É essencial identificar esses fenótipos desafiadores, porque o diagnóstico de dermatite atópica é clínico. Devido à diversidade de apresentações clínicas e dificuldade de reconhecimento de alguns casos, este artigo contribuirá para demonstrar manifestações atípicas e características comuns em pacientes não brancos.

Descritores: Dermatite atópica, fenótipo, afro-americanos, dermatopatias, diagnóstico clínico.

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Introduction

Atopic Dermatitis (AD), also called atopic eczema, is a complex systemic inflammatory disease with heterogeneous clinical morphologies.[1,2] Essential features are eczematous lesions, intense pruritus and chronic or relapsing disease course. Eczematous lesions typically show an age-related distribution. Infants often present with acute lesions characterized by poorly defined erythema with oedema, vesicles, excoriations and serous exudate on the face, cheeks and trunk. In childhood, eczema becomes chronic (lichenification), commonly affecting flexor surfaces.[1] In adolescent and adult, often lichenified and excoriated plaques are found, particularly at flexures.[2] Hands and feet become a concerning focus for atopic dermatitis.[3]

However, this disease can present different morphologies, like follicular/papular dermatitis and prurigo nodularis.[1-3] These atypical forms are difficult to recognize, with prevalence on adults with high phototypes.[1]

There are several genes associated with AD, depending on the ethnicity. For example, the association between Filaggrin mutations and AD is less clear in people of African ancestry. This finding may explain some clinical features more common on this type of patient. Given the race specific genetic polymorphism associated with AD, particularly with regard to the Filaggrin mutations, there are likely differences in epidermal structure among ethnic groups. Some studies suggesting a lower rate of transepithelial water loss in African American, despite an overall greater severity of this disease on this group. Patients of African descent less commonly develop flexural dermatitis, being more common the involvement of the extensor surfaces. Perifollicular accentuation and scattered papules on the extensor and trunk are also more common in darker skin. This type of skin favors the development of post inflammatory dyspigmentation.[3] Moreover, in terms of disease severity, studies have found that African Americans tend to have greater AD severity compared with whites.[3,4]

The AD diagnosis is clinical and there are many criteria that try to reach all forms of presentation, like Hanifin and Rajka diagnostic. However, the recognition of atypical presentations of AD is challenging, because they do not present accurate criteria.[4,5]

Case presentation

Male, 22-Year-old, natural from São Paulo (Brazil), phototype IV, African descent, with personal history of rhinitis and asthma, besides family history of atopic dermatitis. He reported pruritus, xerosis and lesions on skin since he was 2 years-old, with relapsing and chronic course. Initially, the lesions were localized on the cubital and popliteal fossae. At 8, this eczema evolved to current locations. The patient received multiple diagnosis, like pityriasis rubra pilaris and generalized keratosis pilaris. He previously used topic steroids and emollients, with no improvement.

Clinical examination revealed intensely dry skin and diffuse lichenification. The main feature observed was the disseminated perifollicular accentuation. The skin demonstrated widespread rough follicular papules, post-inflammatory hypopigmentation (Figures 1 and 2), beside severe lichenified plaques on the back, neck, hands and foot (Figures 3 and 4). Extensor surfaces of the legs showed excoriated papules and nodules (Figure 5). On the face, we noticed Dennie – Morgan fold.

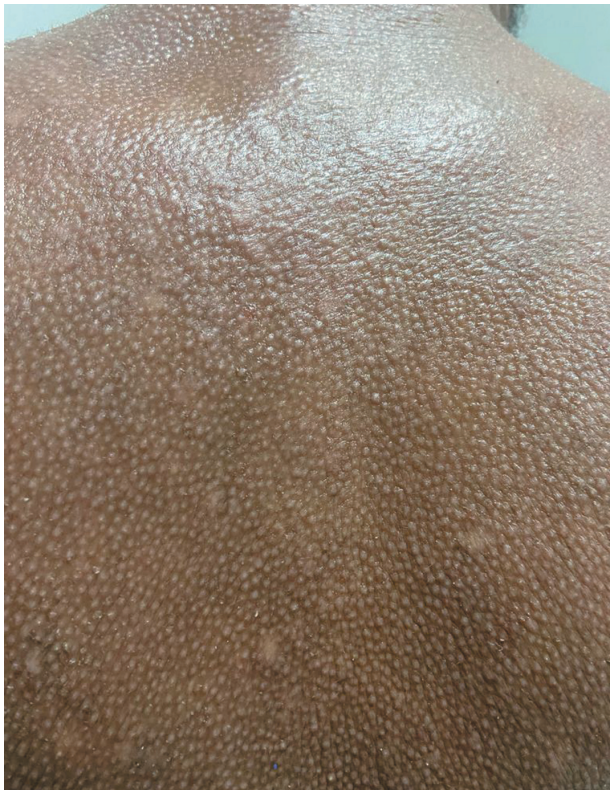

Figure 1
Skin lesions on the back: perifollicular accentuation, rough papules and post-inflammatory hypopigmentation.

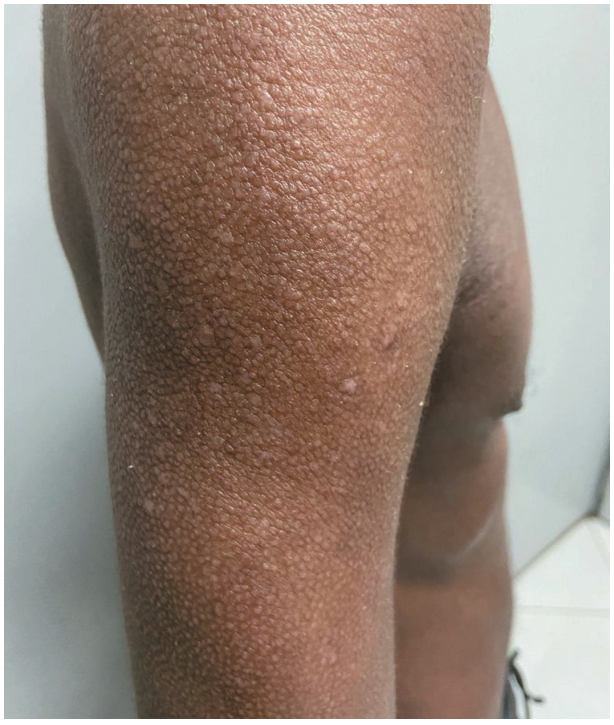

Figure 2
Skin lesions on the extensor surface of the upper limb: perifollicular accentuation, rough papules and post-inflammatory hypopigmentation.

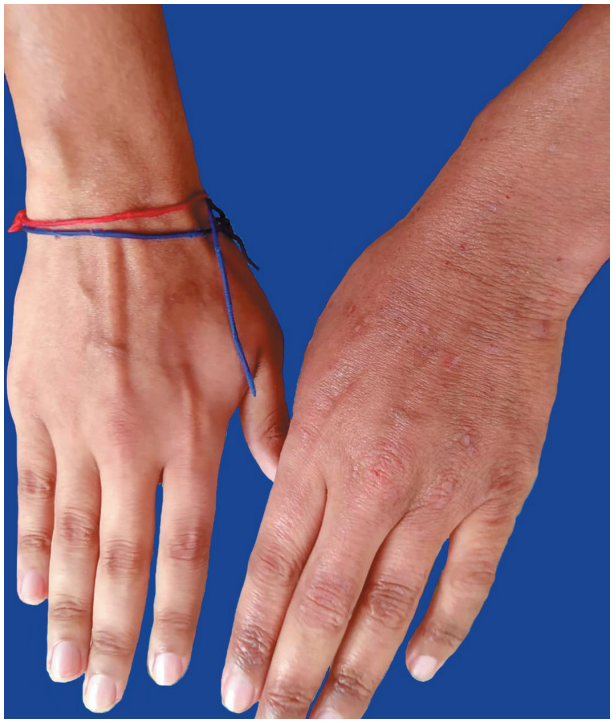

Figure 4
Hand eczema: lichenified plaques on the back of left hand.

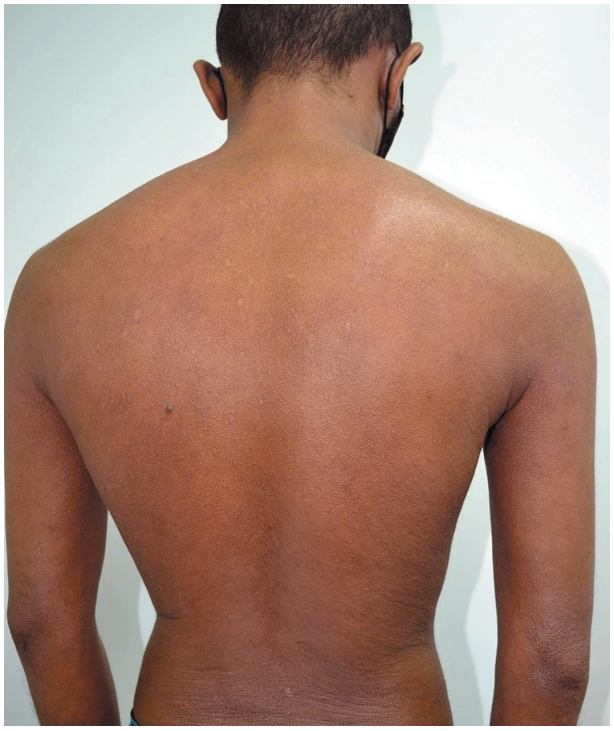

Figure 3
Skin lesions widespread on the back: perifollicular accentuation, rough papules, post-inflammatory hypopigmentation and lichenified plaques.

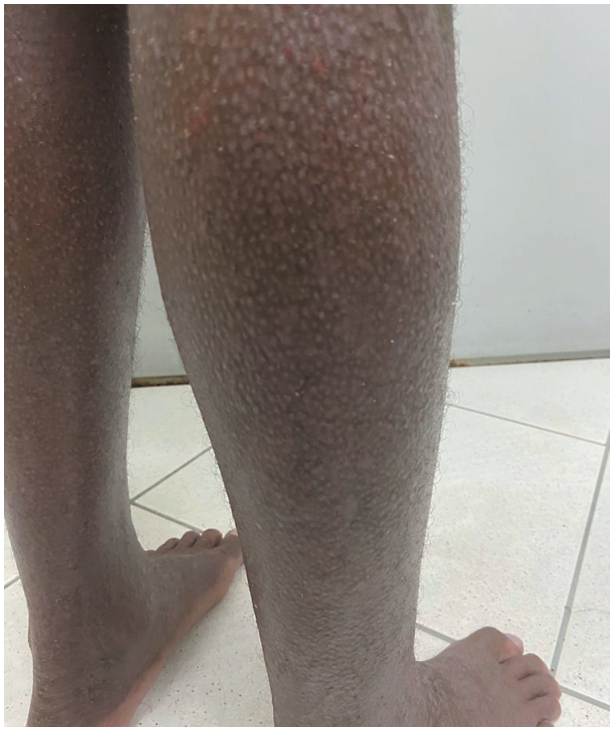

Figure 5
Extensor surfaces of the legs shows xerosis, excoriated papules, perifollicular accentuation, rough papules.

The skin biopsy was performed, that showed spongiosis, parakeratosis and irregular acanthosis at the epidermis (Figure 6). The dermis demonstrated papillary fibroplasia, verticalization of collagen fibers and perivascular infiltrates dominated by lymphocytes and eosinophils. These findings were compatible of AD.

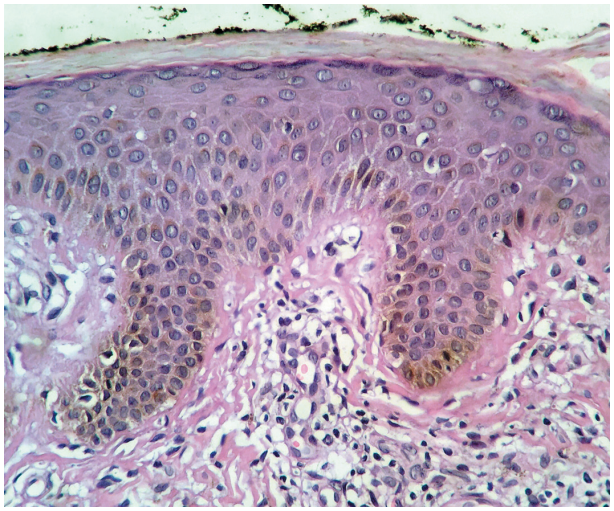

Figure 6
The skin biopsy showed spongiosis, parakeratosis and irregular acanthosis.

Blood laboratory analysis revealed eosinophilia (790/microliter), increased levels of total Immunoglobulin E (1.000 IU/ml) and high serum specific Immunoglobulin E to house dust - mite (3,5 kU/l). We performed patch testing with Brazilian standard series (Immunotech Company™), that showed strong positivity to nickel sulfate (+++).

Based on anamnesis and clinical characteristics, the patient received the diagnosis of AD, that was late and occurred only in adulthood.

Due to the extensive and relapsing presentation, he received Cyclosporin 3 mg/Kg/day, associated to steroids and emollients, with improvement of pruritus, xerosis and eczematous lesions. But he maintained perifollicular accentuation.

Discussion

The patient presented common features of AD, like chronic and relapsing lesions, history of atopic, dry skin, pruritus and early disease onset.

However, atypical morphologies were presented, exemplified by prurigo nodularis and follicular/papular dermatitis, both intensely itchy. Other relevant finding was the fact that these lesions less commonly developed on classical flexural areas, being more prevalent on the extensor surfaces and trunk.

These atypical morphologies and unusual location of lesions are more common on adults with high phototypes,[3,4] as seen in this case.

Follicular/papular eczema is commonly observed on the extensors and trunk,[3,4] like noticed in this case, instead of the classic flexural involvement, in adults.[1-3]

Besides this, the prurigo nodularis, represented by excoriated papules and nodules, is also more prevalent in non-classic areas of AD, mainly on the extensor surfaces,[1] as seen in this article.

The patient showed important post-inflammatory dyspigmentation. This is common in patients of darker skin color,[3,4] like noticed in this case.

Other classic findings in high phototypes include diffuse xerosis and Dennie-Morgan fold, being both features presented on this report.

Another important aspect was the presence of lichenified plaques on the neck, hand and foot. This type of lesions are minor criteria of Hanifin and Rajka's diagnostic and are more common on adults,[4,5] as observed on this article.

Previous studies also observed that African Americans patients have a higher tendency to present with prurigo nodularis and lichenification than other ethnic groups,[3,5] being these findings observed on this report.

Some aspects difficulted the diagnosis of AD in our patient. The first is related to poor recognition of the erythema, due to dark skin. This can present a challenge to make the diagnosis and assessing the severity of AD.

Erythema is a feature that is included in several scoring tools, like Scoring Atopic Dermatitis and Eczema Area and Severity Index. Erythema on darker skin is more likely to appear violaceous or may be missed completely.[3,4]

Second, the atypical localization of lesions, that occurred mainly on the extensor surface, back and chest.

Third, related to morphologic variant, with the follicular/papular and prurigo patterns being the main phenotypes.

It is essential to identify these challenging patterns because the diagnosis of AD is clinical.[4,5]

Given the diversity of clinical presentation and difficult to recognize some cases, this article will contribute to demonstrate atypical manifestations and common features in non-white patients with AD, facilitating correct diagnosis and early treatment.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Fixed pigmented erythema to secnidazole

Eritema pigmentar fixo à secnidazol

Mario Geller[1]

ABSTRACT

Rare description of drug fixed eruption induced by secnidazole.

Keywords: Atopic dermatitis, phenotype, skin diseases, clinical diagnosis, secnidazole.

RESUMO

Descrição rara de eritema pigmentar fixo induzido por secnidazol.

Descritores: Dermatite atópica, fenótipo, dermatopatias, diagnóstico clínico, secnidazol.

A 71 years-old male received 2g of secnidazole orally, for the second time, as treatment for an intestinal infection caused by the protozoan *Blastocystis hominis*. About a week later, he developed a non-pruritic isolated fixed drug eruption in the inframammary region (Figure 1). The drug was discontinued, and the lesion was treated with fludroxycortide cream twice a day. Within 10 days, the fixed pigmented erythema progressively subsided and in 2 weeks it has completed disappeared. Only one similar case has been reported in the literature.[1]

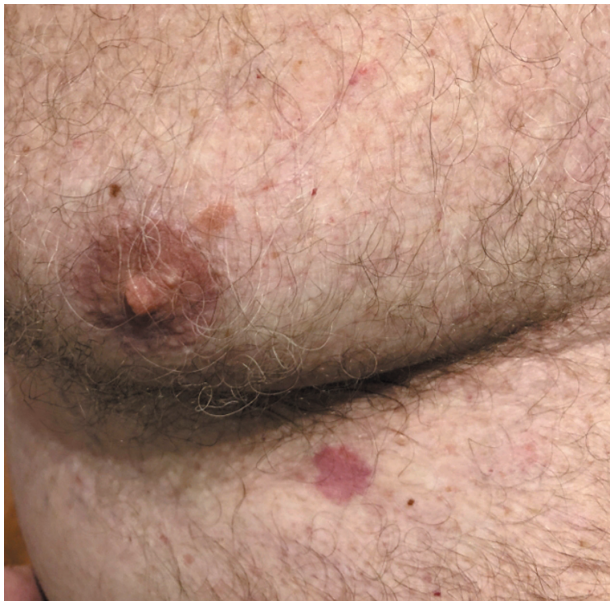

Figure 1
Secnidazole-induced fixed pigmented erythema in the inframammary region.

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