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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Anaphylaxis: it's everyone's problem

Anafilaxia: um problema de todos nós!

Dirceu Solé[1], Fábio Chigres Kuschnir[2]

A few decades ago, anaphylaxis would make headlines in print, spoken, and televised media if it affected a notable figure such as an actor, singer, or other public personality, typically during cosmetic surgeries, and often with fatal outcomes.

Over time, the frequency of these episodes has increased significantly and has been linked to other causes such as food ingestion (cow's milk, chicken eggs, shellfish, fish, nuts), medications (nonsteroidal anti-inflammatory drugs, vaccines), insect stings (bees, wasps, hornets, ants), radiocontrast agents, among others, still often resulting in fatal outcomes.

How can we explain this increase in the incidence and severity of anaphylaxis? In addition to genetic predisposition for the development of allergic diseases, early exposure to adverse environmental conditions can determine the development of allergic diseases in their various forms.

In Brazil, information about the true extent of anaphylaxis and anaphylactic shock, as well as their mortality rates, is scarce. Moreover, little is known about the therapeutic procedures used in these conditions. Thus, under the leadership of Prof. Dr. Emanuel Sarinho (2021-2022), ASBAI created the Brazilian Anaphylaxis Registry (*Registro Brasileiro de Anafilaxia*, RBA), similar to initiatives observed in several other countries. This national registry of patients who have experienced at least one episode of anaphylaxis will allow us to improve our understanding related to the diagnosis, treatment, and follow-up of these patients, potentially saving thousands of lives.

What is the point of having a registry if the cases are not reported? In parallel with the creation of the RBA, Federal Deputy Dr. Luiz Antonio Teixeira Jr. proposed Bill 1945/21, which mandates that doctors, clinics, hospitals, and health centers across the country report anaphylactic shock occurrences to the Brazilian Ministry of Health. The bill will be conclusively reviewed by the Committee on Social Security and Family and the Committee on Constitutional, Justice and Citizenship Affairs. Once enacted into law, we will have a data record that will likely reflect reality more accurately.

Although anaphylaxis is the most severe type of allergic reactions, in some instances, an allergist may intervene to reverse it, as it is a medical emergency, and the patient must be urgently referred for hospital care. Therefore, it is crucial that emergency physicians are well-informed and prepared to provide the best treatment protocol. The treatment of choice consists of intramuscular injection of epinephrine and should be administered by health care professionals. The availability of an epinephrine autoinjector has greatly facilitated the treatment of these patients in areas where it is available.

In addition to actively participating in the public consultation on the availability of epinephrine autoinjectors on the Brazilian Unified Health System

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(SUS), ASBAI is also supporting Bill 85/2024 proposed by Deputy Geraldo Resende, which advocates for the free supply of epinephrine autoinjectors by the SUS.[1] The availability and easy access to this medication would greatly facilitate the therapeutic approach to anaphylaxis in Brazil.

In this issue, Felix MMR et al.[2] published the first results obtained from the preliminary analysis of the initial patients who experienced anaphylaxis and were included in the RBA. The study found that most episodes occurred in familiar environments, were triggered by known etiological agents, and often received inadequate emergency treatment. Few patients received injectable epinephrine.

Although some researchers suggest that mortality from anaphylaxis is low, it should be close to zero, as we are dealing with a highly preventable clinical condition.

There is a mantra that all of us specialists like to repeat: "The best treatment for anaphylaxis is prevention." To prevent it, in addition to understanding how it develops and progresses, we also need to understand how it is triggered and adequately treated.

Join us!

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Challenges and proposals for the care of patients with immune and allergic diseases within the Brazilian Unified Health System: The Maceió Charter

Desafios e propostas para a assistência aos pacientes com doenças imunoalérgicas no Sistema Único de Saúde brasileiro – Carta de Maceió

Faradiba Sarquis Serpa[1], Joseane Chiabai[2], Luane Marques de Mello[3], Eduardo Costa Silva[4], Eliane Miranda da Silva[5], José Luiz Magalhães Rios[6], Marilyn Urrutia-Pereira[7], Marta de Fátima Rodrigues da Cunha Guidacci[8], Norma de Paula M. Rubini[9], Phelipe dos Santos Souza[10], Yara Arruda Marques Mello[11], Fabio Chigres Kuschnir[12]

ABSTRACT

The Maceió Charter was based on discussions held at the 3rd Unified Health System Forum (*Fórum SUS*) of the Brazilian Association of Allergy and Immunology (ASBAI). This document highlights challenges and proposals to improve care for patients with immune and allergic diseases within the Brazilian Unified Health System (SUS). Such conditions, often chronic and debilitating, affect millions of Brazilians and require an integrated approach from primary health through to specialty care. The need for improved management of referrals and counter-referrals,

RESUMO

A Carta de Maceió foi elaborada com base nas discussões do 3º Fórum SUS da Associação Brasileira de Alergia e Imunologia (ASBAI). O documento destaca os desafios e propostas para aprimorar a assistência a pacientes com doenças imunoalérgicas no Sistema Único de Saúde (SUS) do Brasil. Tais condições, frequentemente crônicas e debilitantes, afetam milhões de brasileiros e exigem uma abordagem integrada, desde a atenção primária à saúde até a atenção especializada. Foram discutidos a necessidade de aprimorar a gestão de referência e contrarreferência, a

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the urgency of overcoming the shortage of specialists, and the challenge represented by limited access to proper diagnosis and treatment alike were discussed. Rare diseases, including inborn errors of immunity (IEI), pose an additional challenge, requiring access to high-cost technologies for diagnosis and treatment as well as multidisciplinary care. Several proposals emerged from the Forum, such as securing sufficient funding for health, strengthening early diagnosis, integrating management, continuing education for health professionals, and implementation of telemedicine. These proposed interventions seek a more inclusive, efficient, and humanized healthcare system which meets the needs of patients with immune and allergic diseases.

Keywords: Allergy and immunology, Unified Health System, health policy, rare diseases.

urgência na superação da carência de especialistas e o desafio representado pelo limitado acesso tanto a diagnóstico quanto a tratamento adequados. As doenças raras, incluindo os erros inatos da imunidade (EII), apresentam um desafio adicional, exigindo acesso a tecnologias de alto custo para diagnóstico e tratamento e cuidado multidisciplinar. Do fórum emergiram propostas como o financiamento adequado da saúde, o fortalecimento do diagnóstico precoce, a gestão integrada de cuidados, a educação continuada dos profissionais de saúde e a implementação de telemedicina. Essas ações visam um sistema de saúde mais inclusivo, eficiente e humanizado, atendendo às necessidades dos pacientes com doenças imunoalérgicas.

Descritores: Alergia e imunologia, Sistema Único de Saúde, política de saúde, doenças raras.

Introduction

The Brazilian Unified Health System (*Sistema Único de Saúde*, SUS) faces significant challenges in the care of patients with immune and allergic diseases, mostly chronic conditions that affect millions and demand an integrated and effective approach in the SUS. The care of patients with immune and allergic diseases should cover everything from diseases that are very prevalent in the population, such as rhinitis and asthma, to rare and complex diseases classified as inborn errors of immunity (IEI). Health care demands for these diseases require access to specialists, follow-up due to chronicity, and care provided by multiprofessional teams. In addition, access to diagnostic technologies and some therapies required to treat these diseases is often not available on the SUS.

In view of the current scenario of care for these patients in Brazil, the Brazilian Association of Allergy and Immunology (*Associação Brasileira de Alergia e Imunologia*, ASBAI) has brought this debate to specialists over the last few years and, since 2021, has held an annual forum, seeking to bring proposals to improve care for Brazilian patients suffering from these chronic, often debilitating conditions that generate high costs for families and the entire health system if not addressed properly.[1-5] Thus, the III ASBAI SUS Forum, held on November 17, 2023 in the city Maceió, state of Alagoas, represented a crucial moment for dialogue and proposing improvements in health policies and clinical practice relating to these diseases, addressing key issues involving comprehensive and ongoing care for patients, from primary health care (PHC) to specialized care (Figure 1).

III ASBAI SUS Forum

Opening

Fábio Chigres Kuschnir (ASBAI President)

Module 1 - Primary Health Care

Moderator: Norma de Paula Motta Rubini (ASBAI)

– Immune and allergic diseases in PHC - Luane Marques de Mello (ASBAI)
– Immune and allergic diseases in PHC from the perspective of the manager - Kátia Betina Rios Silveira (Council of Municipal Health Secretaries - COSEMS Alagoas)

Module 2 - Specialized Care

Moderator: Eduardo Costa de Freitas Silva (ASBAI)

– Allergology and immunology in specialized care: the Brazilian context - Faradiba Sarquis Serpa (ASBAI)
– Rede de Atenção à Saúde (Health Care Network): is it possible to expand access to allergology and immunology procedures? - Emanuel Sarinho (ASBAI)
– The specialty of immunology in the context of Health Policies for Rare Diseases - Natan Monsores de Sá (Brazilian Ministry of Health - General Coordination of Rare Diseases)

Figure 1
Program of the III ASBAI SUS Forum

Immune and allergic diseases in primary health care

PHC is the preferred gateway for patients with immune and allergic diseases on the SUS. Some studies, such as the one conducted by Gusso in 2009, have already indicated the high prevalence of

asthma and allergic rhinitis, placing them among the most frequent conditions treated in PHC in various locations in Brazil.[6] This reality still holds true, as shown by recent data on the global burden of asthma in 204 countries, ranking Brazil as the fourth country with the highest incidence of asthma after India, China, and the United States.[7]

PHC approaches to immune and allergic conditions can help change this reality, requiring not only qualified management, but also adequate and sufficient resources for diagnosis, treatment, and longitudinal follow-up.

In this context, the lines of care developed from the perspective of the current Brazilian public health scenario, in which PHC acts as the coordinator of the health care network (*Rede de Atenção à Saúde*, RAS) and the coordinator of health care, are aimed at systematizing care flows, favoring the quality of health care for patients with chronic diseases.[8] Figure 2 shows the lines of care for different diseases that have been drawn up and are currently available, and asthma is the only immune and allergic disease covered.[8] However, there are concerns as to whether this line of care has been implemented or whether it has been able to achieve its goals to organize and improve care through organizing pathways and communication among RAS teams, services, and users. Considering that several allergic manifestations commonly coexist in the same individual, it might be more appropriate to implement a line of care for the person with allergy.

The gap between the need for resources and their availability leads to financial and logistical problems in PHC. The discussion on health care funding highlights the lack of resources to meet the growing demand for pharmaceutical care and diagnostic tests, a scenario that challenges the sustainability and efficiency of the SUS in responding to patients' needs.[9]

It is essential to discuss health care funding to improve care for immune and allergic diseases in PHC. It is also important to promote early diagnosis and integrated care management through effective partnerships between the different levels of health care. Fundamental measures include implementing evidence-based practices, increasing access to essential medications, and providing continuing education for health professionals. Furthermore, the use of telemedicine can serve as a valuable support resource, especially in regions underserved with specialists. We believe that actions like these will result in better control of immune and allergic diseases, not to mention reduced hospitalizations for ambulatory care sensitive conditions (ACSCs).[10] A partnership between the PHC/SUS and the ASBAI, through their local offices, could help organize and deliver continuing education activities both in person and via telehealth.

Allergology and immunology in specialized care

The transition from PHC to specialized care in allergology and immunology has significant challenges. Considerable barriers include the geographical size of Brazil, shortage of specialists, and limited access to diagnostic and therapeutic procedures. Although some progress has been made, the uneven distribution of specialized services throughout the country perpetuates the difficulties in the adequate management of these diseases.[4,5]

It is imperative to develop health policies that encourage the training and equitable distribution of

Stroke in adults
Asthma
Breast cancer
Depression in adults
Type 2 Diabetes Mellitus (first version)
Chronic Obstructive Pulmonary Disease (COPD)
Chronic Kidney Disease (CKD) in adults
Low back pain
Chest pain
Viral hepatitis
Systemic Arterial Hypertension (SAH) in adults
HIV/AIDS in adults
Acute Myocardial Infarction (AMI)
Heart failure (HF) in adults
Obesity in adults
People with dementia
Childcare and Adolescent health
Smoking
Anxiety disorders in adults
Alcohol use disorders in adults
Autism Spectrum Disorder (ASD) in children
Congenital Zika virus infection syndrome (CZS)

Figure 2
Lines of care in primary health care
Source: Brazilian Ministry of Health.[8]

specialists in allergology and immunology. Expanding access to advanced diagnostic procedures and treatments, including biological therapies and immunotherapies, is essential for the provision of quality specialized care. Investments in research and development in technology are also necessary to adapt scientific innovations to the context of the SUS. Moreover, efficient management is needed to expand access to specialized services, including the regulation of referrals and counter-referrals.[11]

Health care for patients with rare diseases

The management of rare diseases, including IEI, poses a major challenge within the SUS. Diagnosis is often complex and time-consuming, aggravated by the lack of specific knowledge among health care professionals and the scarcity of specialized diagnostic resources.

In 2014, the Brazilian Ministry of Health instituted the National Policy on Comprehensive Health Care for People with Rare Diseases and approved the Guidelines on Comprehensive Health Care for People with Rare Diseases within the SUS through Ordinance GM/MS No. 199 of January 30, 2014 (consolidated in Annex XXXVIII of Consolidating Ordinance No. 2 of September 28, 2017).[12,13]

The policy has a transversal scope in the RAS and seeks to reduce mortality, contribute to reducing morbimortality, secondary manifestations, and provide opportunities to improve people's quality of life through promotion, prevention, early detection, timely treatment, disability reduction, and palliative care actions.[14]

The Brazilian Ministry of Health has so far authorized 31 referral or health care services for patients with rare diseases. However, these services are located in only 13 Brazilian states, mostly in the Southeast, and few treat patients with IEI[15] (Table 1).

In this context, it is necessary to encourage health care services for patients with rare diseases to apply for qualification as a reference or health care service for rare diseases.

The introduction of newborn screening programs and access to innovative and personalized treatments, guaranteeing more effective and humanized care, are also measures that are awaited. Multidisciplinary care and ongoing monitoring are essential to guarantee a better prognosis for these patients, creating the need for an integrated and accessible support network. Additionally, the training of health care professionals in PHC and specialized care, as well as the strengthening of specific public policies for these conditions, are necessary measures as access to these services is guaranteed.

Recommendations

Strategic recommendations emerged from the SUS Forum with the aim of improving care for patients with immune and allergic diseases within the SUS, ranging from funding and strengthening PHC, through training health care professionals, to expanding access to diagnostic and therapeutic procedures in specialized care.

Table 2 shows the barriers and proposed solutions for the comprehensive and continuous care of patients with immune and allergic diseases in PHC, specialized care, and for rare diseases.

Conclusion

Immune and allergic diseases require specialized, comprehensive, and continuous care, given their chronic nature and high impact on the quality of life of individuals. In addition, the management of these diseases is challenging and potentially costly, requiring well-defined and coordinated health care policies and strategies.

The Maceió Charter is a call for action for health managers and professionals, highlighting the urgency of moving forward in building a more inclusive, efficient, and humanized health system that also meets the needs of patients with immune and allergic diseases.

Acknowledgements

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Table 1
Centers for Rare Disease authorized by the Brazilian Ministry of Health between 2016 and 2023

Region	State	Municipality	Centers for Rare Disease	Type of accreditation	Year of accreditation
Midwest	GO	Anápolis	Associação de Pais e Amigos dos Excepcionais - APAE de Anápolis	SRDR[a]	2016
Midwest	DF	Brasília	Hospital de Apoio de Brasília	SRDR[a]	2016
Midwest	DF	Brasília	Hospital Materno Infantil de Brasília - HMIB	SRDR[a]	2019
Midwest	GO	Goiânia	Hospital Estadual de Geral de Goiânia "Dr. Alberto Rassi"	SRDR[a]	2022
Northeast	BA	Salvador	Associação de Pais e Amigos dos Excepcionais - APAE	SRDR[a]	2018
Northeast	BA	Salvador	Hospital Universitário Professor Edgard Santos - HUPES	SRDR[a]	2019
Northeast	CE	Fortaleza	Hospital Infantil Albert Sabin	SRDR[a]	2019
Northeast	CE	Fortaleza	Hospital Universitário Walter Cantídio	SRDR[a] SAEDR[b]	2019
Northeast	PE	Recife	Instituto de Medicina Integral Professor Fernando Figueira - IMIP	SRDR[a]	2021
Northeast	CE	Fortaleza	Hospital Geral de Fortaleza - HGF	SAEDR[b]	2023
Northeast	PE	Recife	Hospital Maria Lucinda	SRDR[a]	2023
North	PA	Belém	Hospital Universitário Bettina Ferro - Universidade Federal do Pará	SRDR[a]	2023
Southeast	RJ	Rio de Janeiro	Instituto Federal Fluminense	SRDR[a]	2016
Southeast	SP	Santo André	Ambulatório de Especialidade da Faculdade de Medicina do ABC	SRDR[a]	2016
Southeast	ES	Vitória	Hospital Santa Casa de Misericórdia de Vitória	SAEDR[b]	2019
Southeast	MG	Belo Horizonte	Hospital Infantil João Paulo II	SRDR[a]	2019
Southeast	SP	Campinas	Hospital de Clinicas da Universidade de Campinas - UNICAMP	SRDR[a]	2019
Southeast	SP	Ribeirão Preto	Hospital de Clinicas de Ribeirão Preto	SRDR[a]	2019
Southeast	SP	São José do Rio Preto	Hospital de Base de São José do Rio Preto	SRDR[a]	2020
Southeast	MG	Juiz de Fora	Hospital Universitário da Universidade Federal de Juiz de Fora	SRDR[a]	2021
Southeast	MG	Belo Horizonte	Hospital das Clínicas da Universidade Federal de Minas Gerais	SRDR[a]	2022
Southeast	MG	Bom Despacho	Centro de Especialidades Multiprofissionais Dr. Gê	SAEDR[b]	2023
Southeast	MG	Belo Horizonte	Hospital Julia Kubitschek	SAEDR[b]	2023
Southeast	RJ	Rio de Janeiro	Instituto de Puericultura e Pediatria Martagão Gesteira da Universidade Federal do Rio de Janeiro - UFRJ	SRDR[a]	2023
South	PR	Curitiba	Hospital Pequeno Príncipe de Curitiba	SRDR[a]	2016
South	RS	Porto Alegre	Hospital de Clínicas de Porto Alegre	SRDR[a]	2016
South	SC	Florianópolis	Hospital Infantil Joana de Gusmão	SRDR[a]	2019
South	PR	Curitiba	Complexo Hospital de Clínicas da Universidade Federal do Paraná - UFPR	SAEDR[b]	2020
South	RS	Santa Maria	Hospital Universitário de Santa Maria - HUSM	SRDR[a]	2021
South	PR	Curitiba	Hospital Erasto Gaertner	SRDR[a]	2023
South	SC	Blumenau	Associação Renal Vida	SAEDR[b]	2023

[a] SRDR *Serviço de Referência em Doenças Raras* (Reference Service for Rare Diseases),
[b] SAEDR *Serviço de Atenção Especializada em Doenças Raras* (Specialized Care Service for Rare Diseases).
Source: Brazilian Ministry of Health.[15]

Table 2
Barriers and proposed solutions for the comprehensive and continuous health care of patients with immune and allergic diseases in the Unified Health System

	Barriers	Proposed solution
Primary health care	Delay in diagnosis and access to appropriate treatment, either due to unfamiliarity with the disease or inadequate access to diagnostic screening tests and essential drugs. No integration with specialized care, which could reduce excessive referrals of mild cases and shorten waiting time for moderate and severe cases.	Implement evidence-based practices; Encourage in-person and telehealth continuing medical education in allergic diseases and inborn errors of immunity through a partnership with the ASBAI Regional Offices; Implement a Line of Care for persons with allergies; Include telemedicine in daily clinical practice, facilitating access and strengthening partnerships with specialized care; Ensuring access to essential medication.
Specialized care	Unequal distribution of specialized professionals and centers across the country; Difficulties and delays in referring patients to specialized care centers; Difficulty in accessing specialized diagnostic and therapeutic procedures in allergology and immunology.	Encourage training and equitable distribution of specialists in the SUS network through policies to encourage people management and the implementation of specialized care in regional centers in areas in need of the specialty; Ensure more efficient management of the RAS, including regulation of referrals and counter-referrals; Update outdated clinical protocols and therapeutic guidelines; Introduce clinical and therapeutic protocols for chronic diseases requiring high-cost diagnostic and/or therapeutic procedures.
Rare diseases	Complex and time-consuming diagnosis, aggravated due to the lack of specific knowledge of health care professionals; Shortage of specialized diagnostic resources; Deficiency of an integrated and accessible multidisciplinary support network.	Train health care professionals in PHC and specialized care through partnerships with the ASBAI Regional Offices; Implement newborn screening programs; Expand access to diagnostic methods to investigate inborn errors of immunity and innovative high-cost treatments; Ensure multidisciplinary care through professional development policies and fostering and supporting new reference centers in underprivileged regions of the country; Ensure access to medicines from the specialized component of pharmaceutical assistance already incorporated into the SUS.

ASBAI: Associação Brasileira de Alergia e Imunologia (Brazilian Association of Allergy and Immunology),
RAS: Redes de Atenção à Saúde (health care network).

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Caring for the environment: reverse logistics and inhalation devices

Cuidando do ambiente – Logística reversa e dispositivos inalatórios

Raphael Coelho Figueredo[1], Marilyn Urrutia-Pereira[2], Dirceu Solé[3]

ABSTRACT

Asthma is one of the most prevalent chronic diseases and represents a global public health problem, affecting more than 300 million people worldwide, with an estimated additional increase of 100 million cases by 2025. Asthma is a textbook disease of environmental origin, with exposure to infections, allergens, pollutants, and other environmental stressors implicated in its pathogenesis. The environmental impact of inhalation devices is increasingly important and has been rarely addressed and undervalued. Up to 88% of healthcare professionals are unaware that metered-dose aerosol devices contain a propellant gas that affects the ozone layer and causes global warming. Alternative treatment strategies are needed if we are to avoid worsening climate change. Given this scenario, there are excellent opportunities to make asthma treatment more effective, modern, safe, and eco-friendly.

Keywords: Asthma, metered dose inhalers, environment.

RESUMO

A asma é uma das doenças crônicas mais prevalentes e representa um problema de saúde pública global que afeta mais de 300 milhões de pessoas em todo o mundo, com um aumento adicional estimado de 100 milhões até 2025. A asma é uma doença típica de origem ambiental com exposição a infeções, alérgenos, poluentes e outros fatores estressores implicados na sua patogênese. O impacto ambiental causado pelos dispositivos inalatórios é cada vez mais importante, e pouco abordado ou valorizado. Até 88% dos profissionais de saúde não têm conhecimento que os dispositivos de aerossol dosimetrado contêm gás propelente que afeta a camada de ozônio e causa aquecimento global. São necessárias estratégias alternativas de tratamento se quisermos evitar a piora das alterações climáticas. Portanto, diante desse cenário existem oportunidades de ouro para tornar o tratamento da asma mais eficaz, moderno, seguro e ecológico.

Descritores: Asma, inaladores dosimetrados, meio ambiente.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are among the most common chronic diseases worldwide. Exacerbation of these diseases may be prevented by improving the quality of the air we breathe. The most used device to treat both is the metered dose inhaler (MDI), which uses hydrofluorocarbons (HFCs) as propellants. HFCs are greenhouse gases contributing disproportionately to the climate crisis.[1]

According to the World Health Organization (WHO), asthma will affect 262 million people and cause 455,000 deaths worldwide in 2019.[2] Because

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of its chronic nature, asthma represents a significant financial burden on public health, both for the disease itself and for its treatment.

However, unlike other chronic diseases, allergic diseases are prevalent in children and young adults. Allergic diseases can affect school, work attendance, and productivity as well as have personal, social, and economic consequences.[2]

There has been great concern for many decades about the increasing incidence and prevalence of allergic diseases in both developed and developing countries. The reasons for these increases are complex, but likely include increased exposure to indoor and outdoor air pollution (with increases in allergic disease correlating with wealth and urbanization).[2]

Inhaler devices

The impact of inhalers on the environment is a growing concern; however, it is one that is rarely addressed or evaluated. Up to 88% of health care workers are unaware that inhalers devices should be disposed of at appropriate collection points, and up to 44% of them are unaware that MDIs contain propellants that deplete the ozone layer and cause global warming[3,4], even in small quantities after disposal.[3]

In the 1990s, MDIs with chlorofluorocarbon (CFC) propellants were replaced by dry powder inhalers (DPIs) and MDIs with HFC propellants, which are potentially less harmful than previous MDIs. The annual carbon (CO_2) footprint per patient can vary from 17 kg to 439 kg for these devices.[5]

Despite the ban on the use of CFC gas in metered dose aerosols after the signing of the Montreal Protocol, HFC gas continues to be used and its impact on the environment remains high. For instance, HFC-227 (Turbuhaler) and HFC-134a (spray) can have environmental impacts equivalent to the emissions from car trips of 185 km and 120 km, respectively, after one month of use.[4,6]

In contrast, soft mist and powder devices emit less than 1 kg of CO_2 per month, while pressurized sprays can emit up to 35 kg of CO_2 per month.[2,3] Think about it on a large scale and these numbers become even more alarming. Between 2009 and 2020, over 21 million units of sprayers will be sold in Brazil.[7] From this, we can imagine the magnitude of the environmental impact they have caused on a global scale. The environmental issue is urgent, and as health care workers and citizens, we must increasingly make our decisions based on our commitment to sustainability.

Challenges

One of the great challenges of the modern world is the generation of waste and how to dispose of it in an environmentally responsible manner. Expired or unused pharmaceutical waste is potentially hazardous to the environment and public health if improperly disposed of. Brazil is the seventh largest consumer of pharmaceuticals in the world, and the Brazilian population generates over 10,000 tons of such waste per year.[8]

Reverse logistics is an important tool for improving the management of this waste. Reverse logistics should be used to direct post-consumer products and packaging, such as batteries, tires, lamps, and pharmaceuticals and their packaging, for recycling or proper final disposal. Reverse logistics is essential to minimize the impact of potential hazards from thousands of pharmaceutical residues that can contaminate people, animals, rivers, lakes, or even crops, causing damage to our ecosystem.[8]

Propellants in MDIs are potent greenhouse gases that account for up to 13% of the carbon footprint of some health care facilities. Salbutamol is the most used MDI for patients with poorly controlled disease. Strategies replacing the overuse of MDIs with treatment regimens emphasizing inhaled corticosteroids have the potential to improve asthma control while significantly reducing greenhouse gas emissions.[9]

Real-world evidence shows that a combination of a long-acting beta-2 agonist and corticosteroids in a once-daily DPI can improve adherence and asthma control while reducing the carbon footprint9. Maintenance and reliever therapy (MART) with the same combination has simplified the treatment of asthma, improved control, and reduced greenhouse gas emissions.[9] Both treatment strategies are popular with patients, most of whom are willing to change their treatment to reduce their carbon footprint.

Global efforts by environmental and health policymakers to replace currently available MDIs with DPIs for asthma control would result in substantial reductions in greenhouse gas emissions with manageable costs or potential cost savings,

depending on the health care system in each region. Policies to reduce the use of MDIs deserve worldwide attention.[10]

Laws

Since 2020, Brazil has implemented a system for reverse logistics of medicines. This initiative was launched by signing the Decree No. 10,388, which established the system for the disposal of expired or unused household medicines.[11]

Initially, the system for reverse logistics will be implemented for pharmacies in state capitals and municipalities with over 500,000 inhabitants. Participation will be optional, provided that the sector ensures one collection point per 10,000 inhabitants. If they choose to participate, pharmacies must provide a visible location to place a container dispenser (anti-return) with plastic bags for consumers to dispose of expired and/or unused medicines.[11]

Upon implementation of this law, we as a society should demand a stronger policy for widespread and conscientious compliance and call for investments in artificial intelligence to create an application with free access for the population. In this way, users will be able to locate the collection points closest to where they live, within this platform linked to the reverse logistics program.

Environmental pollution

Asthma is one of the most common chronic diseases and a global public health problem, affecting over 300 million people worldwide, with an estimated increase of 100 million by 2025.[12,13] Asthma is a typical environmental disease, with exposure to infections, allergens, pollutants, and other environmental stressors significantly increasing the risk of new-onset asthma, asthma exacerbations, or other adverse asthma-related outcomes.[14]

Inhalable air pollutants (e.g., particulate matter [PM]) with an aerodynamic diameter equal to or less than 2.5 μm ($PM_{2.5}$) and equal to or less than 10 μm (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO), have been recognized as one of the major environmental threats to human health in the latest World Health Organization (WHO) global air quality guidelines.[15] Other significant outdoor pollutants include volatile organic compounds, ammonia, methane, hydrocarbons, black carbon, and ultrafine particles of nanoscale size (less than 0.1 μm). Outdoor air pollutants are emitted by vehicles, heating systems, industry, refineries, power plants, agriculture, and more. Outdoor air pollutants can also be produced by natural phenomena such as fires, volcanic eruptions, dust storms, and erosion.[15]

Individual air pollutants have long been associated with asthma exacerbations and other adverse asthma-related outcomes, such as loss of asthma control, increased use of health care resources, decreased lung function, or reduced quality of life.[16,17]

Opportunities

Alternative treatment strategies are needed if we are to prevent the exacerbation of climate change. These strategies include promoting nonpharmacological therapies such as smoking cessation and pulmonary rehabilitation, empowering patients to achieve better disease control through written management plans, and promoting preventive therapies rather than relying solely on palliative therapies.

Pharmacological strategies include improving inhalation technique and using spacers; minimizing propellant release by using lower-volume MDIs and simpler dosing regimens; using dose counters to reduce waste; switching to inhalers with low global warming potential; and recycling inhalers.

Sales of asthma medicines in Brazil increased by 51% in the last 12 months compared to the same period last year. In 2023, between January and May, the increase was 33%. The state of Rio Grande do Sul leads the sales ranking with an increase of 38%, followed by Federal District, Paraná, and Goiás. The increase in asthma medication purchases may be related to the evolution of the market to treat it, greater patient concern about asthma, especially after the pandemic, and the increase in cases because of heat waves and increased air pollution.[18] Therefore, reverse logistics becomes even more important in the treatment of asthma.[18]

New propellants with lower global warming potential are on the horizon, and their introduction could provide an opportunity to improve the usability and sustainability of devices. This can be achieved by making them rechargeable, incorporating habits to optimize inhalation technique, adding integrated caps, optimizing materials for recycling, and adding dose counters to all MDIs.[1]

Conclusion

Control and monitoring of asthma remains a challenge worldwide. Although international guidelines recommend the interaction of secondary and primary care services as an effective strategy to control the disease, it is essential to adopt a preventive approach to improve the care of asthma patients. This starts with reducing the carbon footprint of inhalers via structural changes in inhaler manufacturing, universal implementation of reverse logistics, improved compliance with environmental controls, adoption of healthier lifestyles and correct use of prescribed medications.[19]

Therefore, there are golden opportunities to make asthma treatment more effective, modern, safe and environmentally friendly.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Management of the adverse effects of dupilumab in atopic dermatitis and prurigo nodularis

Manejo dos eventos adversos do dupilumabe na dermatite atópica e no prurigo nodular

Mara Giavina-Bianchi[1,2]

ABSTRACT

Atopic dermatitis (AD) and prurigo nodularis (PN) are inflammatory skin diseases characterized by various lesions such as eczema, papules, and nodules, with marked pruritus and, in severe cases, significant impairment of quality of life for patients and their families. Dupilumab is approved in Brazil for the management of both moderate/severe AD and PN that does not respond to topical treatments. The efficacy and safety of dupilumab have been extensively established for both conditions in clinical trials and real-world studies. This article aims to review the main adverse events (AEs) associated with the use of dupilumab in AD and PN and assist in their management. Since the introduction of dupilumab a few years ago, the main reported AEs have been injection site reactions, ocular surface disease (non-infectious conjunctivitis, blepharitis, dry eyes), eosinophilia, and facial/neck erythema. Other manifestations have also been observed in patients with AD on dupilumab, but without proven association: psoriasis, arthralgia, and alopecia areata. Although AEs very infrequently lead to discontinuation of dupilumab, it is crucial that physicians prescribing it for these conditions, dermatologists, and immunologists know how to detect and manage its possible adverse effects.

Keywords: Atopic dermatitis, prurigo nodularis, dupilumab, drug-related side effects and adverse reactions, management.

RESUMO

A dermatite atópica (DA) e o prurigo nodular (PN) são doenças inflamatórias da pele que cursam com lesões variadas, como eczemas, pápulas e nódulos, acompanhados de intenso prurido e, nos casos graves, de importante prejuízo da qualidade de vida para os pacientes e seus familiares. O dupilumabe está aprovado no Brasil para o manejo das duas condições: DA moderada/grave e PN que não responde aos tratamentos tópicos. A eficácia e segurança do dupilumabe foram amplamente estabelecidas para ambas as condições em ensaios clínicos e estudos de vida real. Este artigo tem como objetivo revisar os principais eventos adversos (EAD) associados ao uso do dupilumabe em DA e PN, e auxiliar no seu manejo. Desde o início do uso da medicação, há alguns anos, os principais EAD reportados foram: a reação no local da injeção, a doença da superfície ocular (conjuntivite não infecciosa, blefarite, olhos secos), a eosinofilia e o eritema de face/pescoço. Outras manifestações também foram observadas em pacientes com DA em uso de dupilumabe, mas sem associação comprovada: psoríase, artralgia e alopecia areata. Apesar de muito infrequentemente levarem à suspensão do dupilumabe, é fundamental que os médicos prescritores deste medicamento para estas condições, dermatologistas e imunoalergistas, saibam detectar e manejar seus possíveis eventos adversos.

Descritores: Dermatite atópica, prurigo nodular, dupilumabe, eventos adversos, manejo.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, with eczematous lesions of typical location depending on age and severity of pruritus.[1,2] The prevalence of AD is approximately 15% in children and 5% in adults, and is increasing.[3,4] AD is the primary cause of skin complaint in childhood and the second in adolescence leading patients to seek specialist care, as shown in a Brazilian

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study.[5] Living with AD can be a burden, especially for those requiring long-term systemic treatment, because the immunosuppressants used sometimes fail to control the condition and may lead to serious adverse reactions. Itch and skin lesions cause sleep disturbances, anxiety, depression, low self-esteem, and inability to perform physical, school, and work activities, compromising the quality of life of patients and family members.[6] Disease severity is associated with decreased quality of life, both for patients and their family.[7]

Prurigo nodularis (PN) is also a chronic inflammatory skin disease, very itchy and characterized by firm, isolated or confluent papules and/or nodules, most commonly seen in middle-aged patients and women. Systemic diseases such as nephritis, type 2 diabetes, and HIV infection may be associated with PN. The pathogenesis is still unclear, but immune dysregulation and neural circuits play an important role in the vicious cycle of skin itching and scratching.[8]

Traditional treatment for both diseases includes topical corticosteroids, topical calcineurin inhibitors, emollients, phototherapy, gabapentinoids, and immunosuppressants, with a wide range of adverse effects.[3,6] A few years ago, dupilumab proved to be highly effective and safe for AD, with numerous studies demonstrating its efficacy and safety in both clinical trials and real-world settings.[9-12] Recently, dupilumab was also approved as a treatment for PN in the United States[13] and in Brazil.[14] Two phase 3 randomized clinical trials (LIBERTY-PN PRIME and PRIME2) showed statistically significant improvements in itch and skin lesions in PN with dupilumab vs placebo. Adverse events were consistent with the known safety profile.[15]

Dupilumab was the first immunobiologic agent approved for the treatment of moderate-to-severe AD and PN unresponsive to topical treatments in Brazil. It is a fully human IgG4 monoclonal antibody that directly targets the shared alpha subunit of the interleukin (IL)-4 and IL-13 receptors.[16] These 2 cytokines are involved in type 2 helper T-cell (Th2) immune response, inducing allergen sensitization, promoting atopic inflammation, and reducing the function and structure of the skin barrier. The antibody inhibits the action of these cytokines and promotes changes in gene expression in AD lesions, improving their molecular signature.[17] Several studies have shown the impressive efficacy and safety of dupilumab in the treatment of AD, in different settings and age groups.[10,18,19] This new personalized treatment approach is based on the pathogenesis of the disease and is a milestone in the treatment of AD, and more recently, PN.

Potential adverse events of dupilumab

Adverse events associated with the use of dupilumab include injection site reaction, ocular surface disease (noninfectious conjunctivitis, blepharitis, dry eye), eosinophilia, and facial/neck erythema, which have been known for some years, since the beginning of medication use. A recent real-world Dutch study also included Meibomian gland dysfunction as a new drug-related adverse event in patients with AD.[20]

Injection site reaction

Local reactions were present in 11.4% of 1888 patients using dupilumab, with erythema being most common, followed by unspecified reaction, pain, and itching at the injection site. There are no reports of drug discontinuation due to local reactions, and, when necessary, treatment is symptomatic, with analgesics or oral anti-inflammatory drugs and topical corticosteroids for a few days.[21]

Ocular surface disease (conjunctivitis, blepharitis, dry eye)

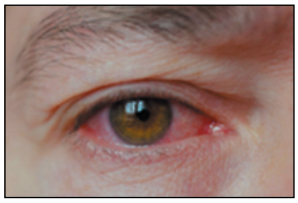
Figure 1 illustrates the differential diagnoses of ocular surface disease. Regardless of the use of dupilumab, patients with AD often present with other associated atopic diseases, such as asthma, rhinitis, food allergy, and allergic conjunctivitis, including a more chronic and severe phenotype called atopic keratoconjunctivitis. A study conducted in the United States to evaluate the association between AD and conjunctivitis in adult patients, between 2001 and 2015, compared the frequency of conjunctivitis events in patients with AD and without AD. The risk of conjunctivitis was 4 times higher in adults with AD (odds ratio [OR] = 4.38; 95% CI, 1.39-13.79; p = 0.012) and, specifically, 8 times higher for allergic conjunctivitis (OR = 8.03; 95% CI, 1.76-36.58; p = 0.007). The conclusion is that adults with AD are significantly more likely to have allergic conjunctivitis than adults without AD.[22] It is essential that physicians who care for these patients be aware of this issue and learn to recognize and manage allergic conjunctivitis. Other studies of adult patients in Iran[23] and the Netherlands[24] also showed similar results, as did other studies of pediatric patients[25-27].

Conjunctivitis is an inflammation of the conjunctiva, a thin, transparent membrane that covers the anterior part of the sclera and the inner surface of the eyelids. Allergic conjunctivitis has an estimated prevalence of 20% worldwide.[28] Symptoms include itching, tearing, hyperemia, and conjunctival edema (chemosis), as well as blurred vision in more severe cases.[29] The association between AD and allergic conjunctivitis can be explained by the fact that these diseases share common pathophysiologic mechanisms. Both involve type II immune response, most often triggered by an allergic process, but also show impairment of physical barrier functions. In addition to skin barrier dysfunction, studies suggest the existence of defects in the ocular surface epithelium in individuals with AD, which would predispose them to conjunctivitis.[30,31]

However, dupilumab-associated conjunctivitis has an unknown pathophysiology. The mean time for the development of dupilumab-associated conjunctivitis ranged from 2 to 8 weeks in clinical trials, and the number of new cases increased over time and appeared to level off around weeks 20-24.[32]

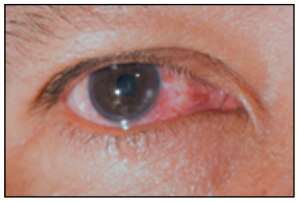
Treatment includes topical agents such as antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs, and corticosteroids. Avoiding allergens is also essential, and contact lens wearers should avoid putting on lenses during episodes to prevent contamination with infectious agents and complications.[22]

In studies on the safety and efficacy of dupilumab in AD, conjunctivitis was one of the most commonly reported adverse reactions. In pivotal studies, the incidence of conjunctivitis was statistically higher in the dupilumab-treated group (8.6%-22.1%) than in the placebo group (2.1%-11.1%). A recent real-world study, which included 29 French centers and 241 patients, showed a higher conjunctivitis rate of 38%. In this study, the development of conjunctivitis was significantly associated with a personal medical history of allergic conjunctivitis, and in 4% of cases



CONJUNCTIVITIS (inflammation of the conjunctiva)

It may be acute (red eye) or chronic (pink eye). It affects the entire conjunctiva, including the inner surface of the eyelids. The diagnosis is based on ocular discharge: serous, purulent, or mucopurulent. Infections, allergies, and physicochemical irritation are the most common causes. Foreign body sensation, burning, and itching, but no pain.

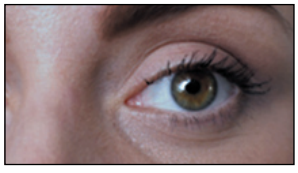


KERATITIS (inflammation of the cornea)

Always associated with severe pain. Other symptoms include foreign body sensation and photophobia. Signs: red eye, watery or purulent discharge, and decreased visual acuity (due to loss of corneal transparency). Penlight examination may reveal corneal ulceration or opacification.

BLEPHARITIS (inflammation of the eyelid)

It corresponds to inflammation of the margin of the eyelid. It is classified as anterior, with sticky plaques or scaly crusting along the eyelashes (typical of staphylococcal or seborrheic dermatitis), or posterior due to Meibomian gland dysfunction (chalazion or oily secretion). Symptoms include a sandy or gritty feeling in the eyes, which may be associated with photophobia and/or increased tear production.



DRY EYE

Due to either insufficient tear production or excessive tear evaporation.

Symptoms include foreign body sensation or eye roughness. The conjunctiva appears normal, but it may be red. Paradoxically, a perception of increased tear flow may occur. Keratoconjunctivitis sicca (Sjögren's syndrome) is characterized by filaments containing mucus with epithelial cells.

Figure 1

Examples of common ocular surface diseases in patients with atopic dermatitis

Adapted from Guex-Crosier Y, et al.[47].

it was a reason for dupilumab discontinuation.[12] In studies on PN, conjunctivitis was the most common adverse event (12.6%; n = 15/119).[8]

Therefore, physicians prescribing dupilumab should be aware of the signs, symptoms, and treatment options in cases where conjunctivitis develops. A suggested algorithm for management of dupilumab-associated ocular surface disease is shown in Figure 2.

Eosinophilia

Eosinophilia is not uncommon in patients treated with dupilumab. Approximately 20% of real-world AD cases experience an increase in eosinophil counts from baseline. Hypereosinophilia (above 1500/mm^3) occurs in 9%-11% of patients. The proposed mechanism is that the drug inhibits eosinophil migration into the tissue, but not eosinophil production in the bone marrow, thus leading to their accumulation in the blood. Eosinophilia is usually transient without clinical consequences.

Dupilumab-associated facial and neck erythema

Dupilumab-associated facial/neck erythema refers to the appearance of erythema on the face and/or neck in patients with AD who did not have lesions in these areas or whose lesions developed characteristics that are different from those of preexisting lesions. The cause remains unclear, but possible etiologies are rosacea, contact dermatitis, *Malassezia furfur* skin

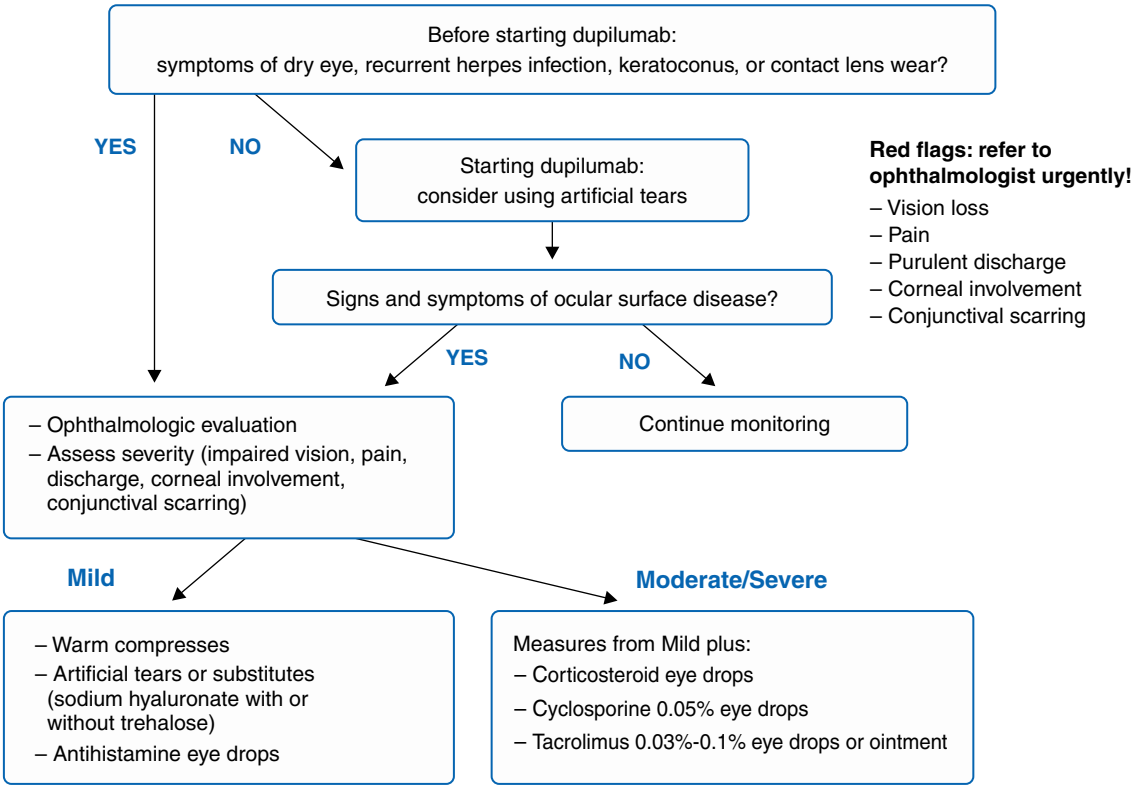


Figure 2
Algorithm for the management of dupilumab-associated ocular surface disease in atopic dermatitis and prurigo nodularis
Adapted from Guex-Crosier Y, et al.[47].

colonization, adverse effects of calcineurin inhibitors, or the discontinuation of topical corticosteroids leading to a worsening of the condition. It should be noted that the vast majority of patients with AD and preexisting lesions on the face improved with dupilumab. A study of 162 dupilumab-treated patients with AD and facial lesions showed improvement in 88.3%, whereas 6.6% remained unchanged and 4.3% experienced exacerbation.[33] In another study of 101 patients diagnosed with facial or neck erythema, 45% reported different skin symptoms from preexisting dermatitis. The most commonly used treatments were topical corticosteroids, topical calcineurin inhibitors, antifungal agents, and topical or oral ivermectin. In this study, 11% of 101 patients with facial/neck erythema discontinued dupilumab owing to this adverse event.[34] In another study of 916 dupilumab-treated patients with AD, facial/neck erythema occurred in 82 (9%).[35]

Other manifestations reported in dupilumab-treated patients with AD, but with no proven association, include psoriasis[36,37], arthralgia[38], and alopecia areata.[35]

Psoriasis

The occurrence of paradoxical psoriasiform reactions (P-PRs) in dupilumab-treated patients has been recently reported. Conversely, cases of eczema in patients treated with immunobiologic agents for psoriasis have also been described. One study identified 42 patients who developed P-PRs, 41 with *de novo* psoriasis and 1 with worsening preexisting psoriasis. All patients responded well to AD treatment with dupilumab before the development of P-PRs, which occurred, on average, 22.65 weeks after starting dupilumab. Treatment options were topical corticosteroids in 38.5%, or systemic therapy in 38.5%, or discontinuation of dupilumab in 32.5%.[36] Another study included 112 patients with AD who developed P-PRs, 101 with *de novo* psoriasis and 11 with worsening preexisting psoriasis. In the first group, patients more frequently developed lesions on the scalp and extremities, on average, 5 months after starting dupilumab, against 4 months after starting dupilumab in the second group. In the *de novo* group, dupilumab was discontinued in 38/101 patients (38%). Discontinuation and/or treatment led to complete remission of psoriasis in 30/63 (48%), incomplete remission in 3/63 (5%), recurrence in 1/63 (1.5%), persistence in 5 /63(8%), and worsening in 6/63(10%). In the second group, 50% discontinued dupilumab.[37]

Arthralgia

Cases of arthralgia as a potential adverse effect of dupilumab treatment in patients with AD have been reported, although they have not occurred during clinical trials. The onset of arthralgia ranged from days to months after the first dose. A real-world study of 4000 patients treated with dupilumab for 6 months showed no increased risk of arthralgia compared with other patients with AD using cyclosporine or mycophenolate mofetil. Therefore, the study concluded that there is no reason for growing concerns about the emergence of new cases of arthralgia associated with dupilumab treatment.[38]

Alopecia areata

In a retrospective study of 916 patients using dupilumab, 11 reported alopecia areata as an adverse event (1.2%).[35] However, other case reports indicate that dupilumab may even be effective in the treatment of concomitant alopecia areata and AD.[39,40]

Conclusion

Conjunctivitis is one of the most common adverse reactions in the treatment of patients with AD using dupilumab, and these same patients, with moderate-to-severe disease, are those who are statistically more likely to develop allergic conjunctivitis. It is important for physicians to be aware of these issues and, if possible, learn to manage conjunctivitis minimally until the ophthalmologist is consulted, according to the algorithm presented here. Several case reports have demonstrated that increasing the spacing between dupilumab injections tends to reduce this adverse effect.[41-45] However, dupilumab discontinuation due to conjunctivitis in patients who respond well to the drug is not at all desirable. Fortunately, this has rarely been required, as early diagnosis and proper treatment of conjunctivitis are often effective measures to control it, allowing patients to continue with AD treatment and to achieve the much-desired disease control.[46]

As for the other adverse events reported here, we can observe that eosinophilia, despite being relatively common, is transient and has no clinical consequences. Local reactions, if present, can be easily managed. Facial/neck erythema remains unclear, as it can have different etiologies and there are many empirical treatment options. Paradoxical reactions of *de novo* psoriasis or worsening preexisting psoriasis have been reported and, albeit infrequent,

reinforce the importance of obtaining personal and family history of autoimmune diseases in patients with AD. Arthralgia does not appear to be a concern because its association with dupilumab treatment has not been confirmed. Alopecia areata associated with AD requires further studies, as it can either be preexisting or develop after the initiation of dupilumab, or even, dupilumab may assist in hair regrowth in alopecia areata.

In conclusion, there is abundant evidence showing the efficacy and safety of dupilumab, and, in daily practice, we are pleased to see the potential improvements achieved with this drug in the lives of patients with moderate-to-severe AD and PN.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Allergic reactions to hymenopteran stings: a literature review

Reações alérgicas a ferroadas de insetos da classe Hymenoptera: uma revisão de literatura

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ABSTRACT

Insects of the order *Hymenoptera* such as bees, wasps, and ants can cause severe and even fatal allergic reactions. These insects have venom with allergenic components that they inject through their stingers, which can cause local and systemic reactions. This study aims to carry out a systematic literature review on allergic reactions to *Hymenoptera*n stings, analyzing the immune mechanisms involved, clinical manifestations, risk factors, diagnostic methods, prevention strategies, and available therapeutic options. The literature review was conducted in August 2023, in a six-stage process. Articles were obtained by searching databases using Medical Subject Headings descriptors related to the topic. Initially, 50 articles were identified; however, only 10 of these met the inclusion criteria. We found that methods for detecting reactions include skin tests with *Hymenoptera*n venoms and serum analysis for IgE specific to such venom. Risk factors that influence the outcome of anaphylactic reactions include the time interval between stings, the number of stings, the severity of the previous reaction, and the type of insect. This review provides a comprehensive overview of allergic reactions to *Hymenoptera*n stings, contributing significantly to the understanding, diagnosis, and management of these conditions.

Keywords: Anaphylaxis, insecta, bee venoms, ant venoms, wasp venoms.

RESUMO

Insetos como abelhas, vespas e formigas da ordem *Hymenoptera* podem causar reações alérgicas graves e até fatais. Esses insetos possuem venenos com componentes alergênicos e os injetam por meio de suas ferroadas, que podem causar reações locais e sistêmicas. O objetivo deste artigo é realizar uma revisão sistemática de literatura sobre as reações alérgicas às ferroadas de insetos da ordem *Hymenoptera*, com o intuito de analisar os mecanismos imunológicos envolvidos, as manifestações clínicas, os fatores de risco, os métodos de diagnóstico, as estratégias de prevenção e as opções terapêuticas disponíveis. Trata-se então de revisão sistemática de literatura realizada em agosto de 2023. O processo envolveu seis etapas. Os artigos foram obtidos pela busca em bases de dados, utilizando descritores em Ciências da Saúde relacionados ao tema. Foram identificados inicialmente 50 artigos, no entanto, apenas 10 deles atenderam aos critérios de inclusão. Para detecção das reações incluem-se testes cutâneos com venenos de *Hymenoptera* e análise do soro para IgE específica do veneno de *Hymenoptera*. Os fatores de risco que influenciam o resultado de uma reação anafilática incluem o intervalo de tempo entre as ferroadas, o número de ferroadas, a gravidade da reação anterior e o tipo de inseto. Esta revisão oferece uma visão abrangente das reações alérgicas às picadas de insetos *Hymenoptera*, contribuindo significativamente para o entendimento, diagnóstico e manejo dessas condições.

Descritores: Anafilaxia, insetos, venenos de abelha, venenos de formiga, venenos de vespas.

Introduction

The phenomenology of the reactions caused by stings from *Hymenoptera* order of insects, which includes bees, wasps, and ants, is remarkably complex, with four distinct categories: local reactions, extensive local reactions, systemic reactions, or anaphylactic reactions based on immunological mechanisms,

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and toxic or nonimmunological reactions.[1] Systemic reactions are predominantly the result of an acute response mediated by immunoglobulin E (IgE), within the context of type I hypersensitivity. Systemic reactions predominantly result from an acute response mediated by immunoglobulin E (IgE), within the context of type I hypersensitivity. A previous exposure to the allergenic components of insect venom is essential for triggering this allergic response, either through previous stings or indirect antigenic exposure through inhalation or digestion.[1-3]

Many species of insect have the ability to cause allergic reactions, usually local reactions that momentarily interfere with normal activities, causing itching, pain, or erythema at the site of the lesion. However, more serious reactions have been observed among insects of the *Hymenoptera* order, such as bees, wasps, and ants, and in severe cases they have been fatal for some individuals.[3] The *Hymenoptera* order includes a diversity of insect species that have the remarkable ability to produce venoms with different allergenic components and, in addition, are able to inoculate this venom into an individual through a sting.[3,4]

The amount of venom released during a sting varies significantly among species and even within species. For example, bees, on average, release between 50 µg and 140 µg of venom per sting, although the total content of the venom sac can reach 300 µg or more. The subfamily *Vespinae*, which includes wasps, injects smaller amounts of venom per sting, which vary among genera. This variety in venom inoculation demonstrates the complexity of these insects in terms of allergic reactions.[4-7]

Although there have been advances in the use of purified venoms, diagnosis, and treatment, allergy to the venom of *Hymenoptera* insects is still epidemiologically relevant. Between 0.15% and 8% of the general population has a personal history of systemic reactions.[1-3]

The complexity of allergic responses stands out when we consider systemic reactions, which can be varied, ranging from cutaneous manifestations to severe anaphylactic reactions. The severity of these systemic reactions, in many cases, cannot be underestimated, and *Hymenoptera* stings are responsible for a considerable number of deaths every year.[6]

Furthermore, a thorough analysis of generalized skin reactions, vasculitis, polyradiculitis, and glomerulonephritis provides a comprehensive view of the possible systemic complications resulting from these stings.[1-3]

Accurate diagnosis of these reactions is fundamental and relies on a detailed clinical assessment, including investigation of the history of the patient and specific tests, such as skin and serological tests. It is of the utmost importance that the species responsible for the sting is known, guiding appropriate treatment and prevention.[5]

In terms of treatment, this study will cover everything from local measures for simple reactions to more complex interventions for severe systemic reactions. Specific immunotherapy has emerged as an effective strategy to prevent recurrent anaphylactic reactions, thus presenting a significant advance in the therapeutic approach to these conditions.[4-6]

In summary, this systematic review of the literature aimed to provide a comprehensive overview of allergic reactions to *Hymenoptera* insect stings, underscoring the complexity of these phenomena and outlining comprehensive diagnostic, treatment, and prevention strategies. This study aims not only to contribute to the advancement of scientific knowledge in the field of insect allergy, but also to provide crucial information for clinical practice, allowing health professionals to offer more accurate and effective care to patients affected by these specific allergic reactions.[1-6]

Objective

To conduct a literature review on allergic reactions to stings from *Hymenoptera* insects, aiming to analyze the immunological mechanisms involved, clinical manifestations, risk factors, diagnostic methods, prevention strategies, and therapeutic options offered.

Methods

This is a systematic literature review conducted in August 2023. The literature review consisted of six stages: (1) identifying the topic; selecting the guiding research question and the databases; (2) establishing criteria for including and excluding studies and searching the literature; (3) defining the information to be extracted from the selected studies; (4) categorizing the studies; (5) evaluating the studies included in the review and interpreting them; and (6) presenting the review.

The articles were retrieved from the Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (MEDLINE), Virtual Health Library (VHL), and Google Scholar databases. Descritores em Ciências da Saúde (DeCS)/Medical Subject Headings (MeSH) were used, such as "reações alérgicas," "allergic reactions," "ferroadas de insetos," "insect bites," "Hymenoptera," "imunoterapia," "immunotherapy" combined with the commands "AND" or "OR" to search for relevant results in the titles of articles. The search included articles in Portuguese, English, and Spanish published in the last fifty years, starting on January 1, 1973.

The articles were then critically analyzed, the data were collected, the results were discussed, and the systematic literature review was presented.

The exclusion criteria included open studies, studies in which the outcome did not assess systemic reactions after the provocation test, double-blind trials randomized to receive pretreatment with antihistamines or not, or outcomes assessing changes in cytokine patterns after immunotherapy. Other exclusion criteria included the following: a history of systemic arterial hypertension, heart disease, poorly controlled lung disease, and a negative skin test.

Pathophysiology

In individuals who have previously been sensitized, a new contact with the allergen will result in the activation of mast cells and basophils, triggering the degranulation of these cells and the subsequent release of preformed mediators such as histamine, serotonin, and chemotactic factors, not to mention neoformed mediators such as prostaglandins and leukotrienes. This degranulation occurs through the interaction between IgE antibodies present on the surface of mast cells and basophils and the allergen, in this case, venoms.[4,5]

Minor local reactions are intrinsically linked to the pharmacological properties of the venom, illustrated, for example, with the formation of pustules resulting from ant stings, attributed to the toxicity of the alkaloid components present in the venom of these insects.

Several risk factors have been identified for the appearance of serious systemic reactions in response to the venom of *Hymenoptera* insects. These include age, the length of time between two stings, the species of insect, high baseline serum tryptase levels, the presence of cardiovascular disease, systemic mastocytosis, and use of beta-adrenergic blockers (which can reduce the effectiveness of adrenaline in treating anaphylaxis) and angiotensin-converting enzyme inhibitors (which can aggravate hypotension during anaphylaxis).[6,7]

A detailed comprehension of the pathophysiology of these allergic reactions resulting from *Hymenoptera* insect stings is imperative to effectively diagnose, manage, and prevent these potentially lethal conditions. Accurate clinical management and patient

Table 1
Descriptors used in database searches

Database	Descriptors	Articles found
PubMed - Search 1	*"Insects bites or Hymenoptera and allergic reactions"*	26 articles
PubMed - Search 2	*"Anaphylaxis and immunotherapy and poison"*	19 articles
SciELO - Search 1	*"Insects bites or Hymenoptera and allergic reactions"*	3 articles
SciELO - Search 2	*"Anaphylaxis and immunotherapy and poison"*	2 articles
Google Scholar	*"Insects bites or Hymenoptera and allergic reactions"*	0 articles
Biblioteca Virtual em Saúde (BVS)	*"Insects bites or Hymenoptera and allergic reactions"*	0 articles

education about risk factors play a central role in mitigating the risks associated with such allergic reactions.[8]

Types of reactions

Reactions to *Hymenoptera* stings can be divided into local and systemic reactions, which can be further divided into allergic and nonallergic. Local reactions are defined as any reaction in which the signs and symptoms are limited to the tissues adjacent to the sting site. Most people develop this type of reaction, which is not considered a form of allergic reaction as it is produced by the action of the venom at the site of the sting. The symptoms are pain, edema, and erythema, which usually disappear after a few hours.[4,9] Less commonly, patients can develop an extensive local reaction, with painful edema and erythema limited to the skin and subcutaneous tissues adjacent to the site of inoculation of the venom. The affected area is usually more than 10 cm in diameter on average. These reactions gradually worsen, peaking between 24 and 48 hours and lasting between 3 and 10 days.[9] In this case, an inflammatory reaction occurs, which can be followed by nausea, vomiting, a significant drop in general condition and secondary infection. The extensive local reaction can be considered an allergic reaction.[4] Patients with a history of an extensive local reaction most often have the same type of reaction in subsequent stings.[9]

It is not yet known whether the risk of developing these reactions changes over time or whether it is influenced as a result of the frequency of stings. The risk of a systemic allergic reaction after an extensive reaction has been estimated at approximately 7%, based on observational studies. The risk of anaphylaxis, on the other hand, is lower and is estimated to occur in less than 3% of cases. Even when more severe, these reactions are still limited to the skin (generalized urticaria and angioedema) and are therefore called systemic skin reactions.[10,11]

Systemic reactions can cause signs and symptoms far from the sting site and include a spectrum of manifestations, which range from mild to potentially fatal. Systemic reactions can be divided into reactions involving several systems and reactions limited to the skin, as already mentioned.[12]

Anaphylactic reactions are those involving signs and symptoms secondary to the release of mediators present in the mast cell, such as histamine, and which affect more than one organ system. The skin is commonly involved, but respiratory or circulatory symptoms are also prevalent, and to a lesser extent, the gastrointestinal tract can be affected. Some of the most serious reactions (for example, sudden hypotension) occur in the absence of any skin findings and can be refractory to single or multiple doses of adrenaline (the main treatment).[13,14] *Hymenoptera* stings cause at least 40 identified deaths annually in the United States, and the rates reported are similar in other parts of the world.[15-17]

A toxic (nonallergic) systemic reaction can occur when the individual is stung multiple times, causing toxic pharmacological effects to the components of the venom: phospholipase A2, melittin, apamin, hyaluronidases, vasoactive amines, etc. The clinical manifestations are similar to allergic reactions, and it is difficult to differentiate them; these reactions can even lead to death.[4,18]

Late systemic reactions can also occur. They manifest as vasculitis, polyradiculitis, and glomerulonephritis. These reactions are rare and of unknown pathogenesis.[4]

Generalized skin reactions consist of signs and symptoms limited to the skin (such as pruritus, erythema, urticaria, and angioedema), which generally involve the skin that is not close to the sting site. Reactions involving angioedema of the tongue or larynx, which can compromise the airway, are generally excluded from this category and are considered anaphylactic reactions.[9]

Diagnosis

The diagnosis of a reaction to *Hymenoptera* venom will be essentially determined according to the clinical history and the investigation of venom-specific IgE antibodies. This investigation can be either through a skin test (prick test and/or intradermal test) or an *in vitro* test. These tests can determine the previous sensitization of the patient to the venom. This sensitization occurs in more than 30% of adults within weeks of being stung. Sensitization can be self-limiting, disappearing in 30% to 50% of cases after 5 to 10 years, while it can also persist for decades, even if there is no re-exposure.[19]

Importantly, these tests should be performed at least 3 to 4 weeks after the acute event to reduce the likelihood of false-positive results within the refractory period.[3] These tests not only confirm the diagnosis, but also identify the appropriate venom to be used in

immunotherapy.[20] All patients with systemic reactions should undergo this subsequent evaluation, while patients with local reactions generally do not require these tests.

Skin tests (prick test and/or intradermal test) or *in vitro* tests ought to be performed at least 3 to 4 weeks after the acute event, to reduce the likelihood of false-positive results within the refractory period.[3]

Table 2 shows the key steps for diagnosing sensitization to *Hymenoptera* venom.

Clinical history

These stings are extremely painful, and patients easily realize that they have been stung, although often they may not have seen the insect clearly. In cases of anaphylaxis, people close to the patient may notice changes in the voice (laryngeal angioedema), mental confusion or reduced level of consciousness, skin changes, or angioedema.

A comprehensive history should review whether the patient has had similar episodes before and the risk of future stings (i.e., occupation and hobbies) and determine whether their reaction was local or systemic. Some questions should be asked during patient assessment, including the following.

- How long has the accident occurred?
- How many times have you been stung and where on your body? For example, a sting to the face can cause extensive facial angioedema as part of a local reaction, whereas the same symptom following a sting to the leg or back would indicate a systemic response.
- How long has it been between the sting and the onset of symptoms? You should actively ask what symptoms the patient has experienced.
- Which insect has stung you? (This information is often unreliable).
- Have you taken any medication that could interfere with the onset of symptoms or the response to treatment, such as angiotensin-converting enzyme (ACE) inhibitors or beta-blockers? This information is relevant for assessing the risk of more serious reactions and treatment refractoriness.
- How has the reaction been treated and have there been any late symptoms?

Table 2
Patients with a convincing history of systemic sting reaction but negative venom-specific IgE tests may be at risk of a future systemic reaction due to unclear mechanisms

Sting reaction	Skin test result or venom-specific IgE test	Is venom immunotherapy indicated?
Generalized, nonlife-threatening skin reaction: generalized urticaria, angioedema, erythema, pruritus	Positive	It may be recommended in specific cases: frequent exposure to insects and impact on quality of life
Life-threatening systemic reaction: skin symptoms associated with respiratory symptoms (laryngeal edema or bronchospasm) or cardiovascular symptoms (hypotension, shock)	Positive	Yes
Systemic reaction	Negative	No
Significant local reaction (> 4 inches or 10 cm in diameter, lasting > 24 hours)	Positive or negative	It can be considered if the test is positive
Regular reaction (≤ 4 inches or 10 cm in diameter, lasting < 24 hours)	Positive or negative	No

Adapted from Graft DF[47].

– Have you been stung before and, if so, has this resulted in any local, extensive local, or systemic symptoms?
– Have you been stung subsequently and, if so, what symptoms have you developed?
– Are you regularly exposed to insects of the *Hymenoptera* class? (as a result of occupational or recreational activities).[21]

Identifying the culprit species

Identifying the insect responsible for the allergic reaction and its habitat is of paramount importance for the diagnosis, prevention, and treatment of patients.[22] The two families of winged *Hymenoptera* responsible for most stings are the *Apidae* family (honey bees and drones) and the Vespidae family (wasps).

The family of wingless *Hymenoptera* also involved in accidents is the *Formicidae* family (fire ants).[3,23]

Hymenoptera generally sting people in self-defense or to protect their nests or hives. Their stings are extremely painful, and the patient can tell that they have been stung even though they may not have seen the insect. Identifying the species of winged *Hymenoptera* responsible can be somewhat difficult, as the resulting lesions are similar in appearance. A culprit species can sometimes be identified from the location and appearance of the nest or hive, geographical location, or body site where the sting occurred.[24]

Persons stung by bees are normally able to visualize the stinger. In wasp stings, on the other hand, it is generally not possible to identify the stinger, as most of these insects do not leave the stinger in place; however, some members of the *Vespidae* family may leave a stinger.[25] Fire ant (*Solenopsis sp.*) usually sting the lower limbs, are less painful, can be multiple, and tend to occur in the warmer months of the year.[26-28]

It is worth noting that bees generally leave their sting at the site of the lesion, as do some species of wasp. Ants, on the other hand, do not leave a stinger.[29-30]

Treatment

The type of treatment to be administered will depend on the type of reaction the person has had.

Local reactions can be treated with cold compresses to reduce local pain and swelling. Oral antihistamines and analgesics are also used to reduce local pain or itching associated with skin reactions. Oral corticosteroids are also effective in these cases. Secondary infections in immunocompetent people are rare complications, so antibiotics are not indicated in the absence of signs of acute infection.[31-37] If an ant has stung a person, the pustule that may form should be kept intact.[38]

Extensive local reactions are usually treated in the same way as local reactions, however, on some occasions they can be severe and manifest as extensive edema and erythema. Topical or oral corticosteroids and anti-inflammatories should be used to control the pain, which can be intense.[39-42]

The treatment of systemic reactions depends on the severity of the reaction. Mild generalized reactions can only be treated with antihistamines.[14] In severe cases, injectable antihistamines and parenteral corticosteroids should be administered, in addition to maintaining a clear airway and controlling blood pressure. If an anaphylactic reaction is identified, which by definition is a severe allergic reaction with a rapid onset and which can cause death, the treatment should be similar to that for anaphylaxis due to other causes, with intramuscular injection of adrenaline into the anterolateral region of the thigh being the first-line drug of choice.[31] The concentration is 1:1000 in aqueous solution, at a dose of 0.3 mL to 0.5 mL (adult dose) and 0.01 mL/kg up to a maximum of 0.3 mL (infant dose), at intervals of 5 to 15 minutes.[43]

Bees have a barbed stinger that lodges in the skin and detaches from the body of the insect with the venom sac once it has stung. The venom is released in the first few seconds following the sting,[44] so if the insect or stinger can be pulled out of the skin immediately, this can help limit the amount of venom injected. If the patient comes to the clinic a long time after being stung, it will not be necessary to remove the stinger immediately, as the venom will already have been completely expelled. However, the remaining stings should be removed because they can occasionally cause foreign body reactions. Some patients may present with ants attached to their skin,[45,46] as they can firmly grasp the patients' skin with their mandibles and inflict multiple bites and stings, so they should also be removed immediately.[27]

Prophylaxis of allergic reactions

Patients who have developed some kind of systemic reaction after a sting, essentially anaphylaxis,

should be given some extremely important information before they are discharged from hospital. They should be informed that venom allergy is a potentially fatal disorder, that further evaluation is needed, and that venom immunotherapy is available to prevent anaphylaxis from future stings. In addition, they should be instructed to purchase an adrenaline auto-injector pen, which they should carry with them at all times, as well as instructions on how and when to use this device.[28]

Patients should also be informed of certain precautions, such as avoiding the use of sweet or strong perfumes, to prevent attracting insects; not walking barefoot in gardens or near swimming pools; and wearing boots in rural areas.[4]

Patients with a suspected systemic allergic reaction following a *Hymenoptera* sting (of any severity) should be referred to an allergist and immunologist to determine whether they are candidates for venom immunotherapy.[9]

Specific immunotherapy

Immunotherapy is considered a safe and effective treatment to prevent *Hymenoptera* sting-induced anaphylactic reactions in persons with a history of systemic reactions. Immunotherapy targets T cells, modifying the TH2 response in favor of the TH1 response, and this has been the only way to change the natural course of the disease in patients who have had systemic reactions.[4,37]

Protection against recurrent anaphylactic reactions seems to be effective in most patients within a week of receiving maintenance doses.[38] Immunotherapy not only reduces the risk of recurrent systemic reactions, but also improves quality of life by reducing anxiety and allowing patients to participate in outdoor activities as they please.[39,40] The risk of the patient having a new systemic reaction is reduced to less than 5%, and even those few patients who have anaphylactic reactions after immunotherapy tend to have much milder symptoms compared to the first reaction.[41-43]

Table 1 summarizes the indications for immunotherapy, which is mostly administered through a series of subcutaneous injections.[43-47]

Practical implications

Initiating the correct management at Basic Health Units (BHU) for children or adults following an insect sting is fundamental to ensuring the health and well-being of patients. Correctly identifying the species that caused the sting is crucial for effective treatment, avoiding complications and ensuring an adequate response.

For this reason, innovative applications and ready-made forms for detecting the species of insect have become a valuable tool. These technological solutions enable rapid identification, allowing health care professionals to act with accuracy and efficiency in patient care. In addition, applications can provide useful information to parents, advising on immediate care to be taken at home before seeking professional help.

By integrating technology with health care services, not only are we speeding up the diagnostic process, but also empowering the community to deal proactively with insect stings. This innovative approach promotes prevention and education, helping to build a healthier and more informed society and reducing the progression to more serious or fatal conditions.

Conclusions

This literature review on allergic reactions to stings from insects of the *Hymenoptera* order provides a thorough overview of these complex phenomena. The comprehensive approach included the categories of reactions, immunological mechanisms, diversity in venom inoculation, and epidemiological relevance.

The importance of accurate diagnosis, supported by clinical history and specific tests, is emphasized. An analysis of the pathophysiology, types of reactions, and risk factors reveals the complexity of these allergic responses.

As for treatment, which includes local measures and interventions for anaphylaxis, the study emphasizes the importance of taking the right approach. Prophylaxis, patient education, and specific immunotherapy are prioritized as crucial strategies in preventing future reactions.

In summary, this review provides a comprehensive overview of allergic reactions to *Hymenoptera* insect stings, contributing significantly to further understanding, diagnosis, and management of these conditions. Specific immunotherapy has emerged as an effective tool for reducing the risk of recurrent anaphylactic reactions, underlining the continued importance of research and education in the field of insect allergy.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Contact urticaria syndrome – a review

Síndrome da urticária de contato – uma revisão

Sérgio Duarte Dortas Junior[1,2], Solange Oliveira Rodrigues Valle[1]

ABSTRACT

Contact urticaria syndrome (CUS), contact urticaria, and protein contact dermatitis (PCD) are entities described under the umbrella term of immediate contact skin reactions (ICSR). Generally, hives appear 20-30 minutes after contact with the offending substance, and disappear completely in a few hours, without leaving residual lesions. However, the CUS may be associated with severe systemic symptoms. A prevalence of 5-10% has been estimated among European workers; in the general population it is 1-3%. The mechanisms involved in CUS pathogenesis have not been fully elucidated. An initial approach to improving its understanding involves dividing this condition into non-immune and immune contact urticaria. The former does not require prior sensitization to the allergen, while the latter does. Diagnosis of CUS is established by a detailed history and physical examination, followed by skin tests with suspected substances. Removal of the triggering agent is the best treatment. This requires early proper diagnosis, occupational reporting, and development of preventive measures.

Keywords: Chronic urticaria, chronic inducible urticaria, angioedema, dermatitis, occupational dermatitis.

RESUMO

A síndrome da urticária de contato (SUC), a urticária de contato (UCO) e a dermatite de contato por proteínas (DCP) são entidades descritas sob o rótulo de reações cutâneas imediatas por contato. Geralmente as urticas surgem 20-30 minutos após a exposição por contato com uma substância, e desaparecem por completo em algumas horas, sem deixar lesão residual. Entretanto, a SUC pode apresentar sintomas generalizados graves. Estima-se uma prevalência, entre trabalhadores europeus, entre 5-10%, enquanto na população geral estima-se de que seja de 1-3%. Os mecanismos envolvidos na patogênese da SUC não foram totalmente elucidados. Uma abordagem inicial, para melhorar a sua compreensão, pode ser dividir esta condição em urticária não imunológica (UCNI) e imunológica (UCI). A primeira não necessita de sensibilização prévia ao alérgeno, enquanto a segunda necessita. O diagnóstico da SUC necessita de uma anamnese detalhada e exame físico seguido de teste cutâneo com as substâncias suspeitas. O afastamento do agente desencadeante é o melhor tratamento. Para isso é necessário o diagnóstico apropriado e precoce, a confecção de relatórios ocupacionais e o desenvolvimento de medidas preventivas.

Descritores: Urticária crônica, urticária crônica induzida, angioedema, dermatite, dermatite ocupacional.

Introduction

Contact urticaria syndrome (CUS), contact urticaria (CU), and protein contact dermatitis (PCD) are entities referred to as immediate cutaneous contact reactions.[1] All three of these conditions occur within minutes of exposure to an irritant that has penetrated the skin or mucous membranes.[1] Since Maibach and Johnson first described these diseases in 1975, a growing body of evidence has revealed multiple triggering factors and diverse clinical presentations. Triggers may include chemicals, foods, preservatives, fragrances, metals, and animal or plant products.[2-4] Overall, hives appear 20–30 minutes after contact with a substance

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and disappear completely within a few hours, leaving no residual lesions. However, CUS may present with severe generalized symptoms.[2,4] Hjorth and Roed-Petersen defined PCD as an immediate dermatitis induced after contact with proteins (e.g., meat, fish, vegetables, etc.).[5] Prognoses for these diseases are generally good, although there are reports of severe symptoms.[4,6] Therefore, early detection and prevention are essential in the management of these conditions.

CUS is thought to be underdiagnosed and/or inadequately diagnosed.[7] Therefore, dissemination of knowledge about this condition to allergists, dermatologists, and occupational health physicians is important.[1,7]

Epidemiology

Accurate data on the prevalence of CUS are not available, but it is estimated to be 5–10% in European workers and 1–3% in the overall population.[4]

The Finnish Register of Occupational Diseases (FROD) identifies CU as the second most common occupational skin disease (29.5%) after contact dermatitis (CD). FROD reports bovine hair, flour and grain, and latex as the three most common triggers.[8] An Australian study found the three most affected occupations were health care workers (exposed to latex), food handlers (exposed to food), and hairdressers (exposed to ammonium persulfate).[9] In Germany, cosmetics and latex were the most common triggers.[10]

Reports of CUS have increased in recent years due to the use of personal protective equipment (PPE) and hand sanitizers because of the COVID-19 pandemic. The use of legal cannabis products has led to an increase in occupational cases of CU to cannabis.[4,11]

Pathogenesis

The mechanisms involved in the pathogenesis of CUS are not yet fully understood. A first approach to a better understanding of this disease may be to divide it into nonimmunologic contact urticaria (NICU) and immunologic contact urticaria (ICU). The former does not require prior sensitization to the allergen, whereas the latter does.[12]

ICU is a type I hypersensitivity reaction that occurs in patients with specific immunoglobulin E (IgE) against a particular trigger. Thus, ICU requires prior sensitization and only after repeated exposure to the offending agent will patients exhibit symptoms. Confirmation of this mechanism is seen when skin tests are performed, as positive tests are observed in affected patients and negative in controls. ICU can be caused by two types of agents. The first group includes high molecular weight proteins (10,000 kD or more), while the second group includes low molecular weight chemical haptens (less than 10 kD).[4] Table 1 displays a proposed classification of agents causing ICU.

Table 1
Classification of ICU triggering agents

Group I	Plant proteins
Group II	Animal proteins
Group III	Grains
Group IV	Enzymes

Modified from Giménez-Arnau AM, et al.[4]

Latex is the primary example of ICU. The reaction can range from hives to anaphylaxis. Thirteen different allergenic proteins have been described, named hevein (Hev) b1 to b13.[7] Latex allergy has broader implications for patients, as those allergic to latex have a high degree of cross-reactivity with other antigens, particularly those found in fruits (banana, kiwi, avocado, chestnut), sometimes referred to as "latex-fruit syndrome".[13] Plant dyes (e.g., henna, cassia, and indigo), usually used in powder form, are potential causes of ICU in hairdressers. In addition, oxidative hair dyes are possible causes of ICU in hairdressers, particularly due to the presence of para-phenylenediamine (PPD) and its derivatives.[14-16]

NICU appears to be more common than ICU, but without the presence of systemic symptoms. Among the substances that may induce NICU are cinnamaldehyde, benzoic acid, sorbic acid and nicotinic acid esters.[4,7] In all, 10% of hairdressers in a recent study reported CU from "blonde" hair dyes.[17]

The pathogenesis of PCD is thought to involve a coexistence of type I and type IV hypersensitivity reactions to proteins, usually with high molecular weight or even low molecular weight haptens, as described for ICU. Various foods such as fruits, vegetables, meat, and seafood or nonfood proteins have been reported to be responsible for PCD.[18]

Clinical manifestations

Symptoms of CUS are determined by the nature of exposure (form, duration, and extent), the characteristics of allergen, and the individual's susceptibility.[7]

CU typically occurs within 10–30 minutes of skin contact with the inciting agent and disappears within minutes or hours (< 24 hours). It affects areas of the body that come into contact with the inciting agent, usually exposed areas.[7] Late-onset CU has occasionally been described after repeated applications of the trigger.[19] Patients present with hives, rarely angioedema, associated with itching, burning, stinging and/or pain at the site of contact with the inciting agent. The clinical appearance of the primary lesions does not differ from other types of urticaria.[7]

Volatile proteins (e.g., flour) may cause conjunctivitis, rhinitis, or asthma if they come into contact with the conjunctival mucosa or respiratory tract. Systemic symptoms, such as abdominal pain, oral itching after ingestion (oral allergy syndrome [OAS]), and diarrhea, may occur upon contact with the mucosa of the gastrointestinal tract.[7] OAS is a form of contact urticaria that occurs minutes after ingestion and presents as itching, burning, and swelling of the lips, tongue, palate, or throat and is particularly associated with hypersensitivity to fresh fruit.[7,20]

A staging system was described by Amin & Maibach in 1997[21] and is described below.

Cutaneous reaction only (stages 1 and 2)

Stage 1: Localized hives, eczema, and nonspecific symptoms (itching, tingling, and burning).

Stage 2: Generalized hives.

Extracutaneous reactions (stages 3 and 4)

Stage 3: Asthma (wheezing); rhinitis, conjunctivitis (runny nose and watery eyes), oropharyngeal symptoms (lip edema, hoarseness, dysphagia), and gastrointestinal symptoms (nausea, vomiting, diarrhea, cramping).

Stage 4: Anaphylactic reactions (shock).

Diagnosis

Diagnosis of CUS requires a detailed history and physical examination, followed by skin testing for the suspected substances. Occupational history and habits are also very important to include in the history. Physical examination is crucial in assessing the nature of the lesions (if present). *In vitro* techniques are available for some allergens, such as latex allergy, which can be investigated by using basophil activation test (BAT), radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA), or IgE for natural rubber components.[22]

Investigation with *in vivo* methods should be done cautiously, as severe systemic symptoms have rarely been described following testing.[4] A sequential order for skin testing procedures has been proposed (Figure 1).

Since patch tests are rarely positive, the diagnosis of PCD is made by means of the prick test.[24]

Many everyday cases require a differential approach, which may include tests such as patch testing and photopatch testing.[25]

Treatment

Treatment of CUS depends on identification and subsequent avoidance of the causative agent. In addition, therapies that prevent the release of mast cell mediators and possibly other mediators may suppress symptoms. Second-generation antihistamines are the drugs of choice for the treatment of hives.[26] High doses of antihistamines should be used before considering the use of alternative treatments. If eczema is present, topical immunomodulation with topical steroids and/or calcineurin inhibitors (tacrolimus and pimecrolimus) may be used. In severe cases of CUS, a short course of oral corticosteroids may be necessary.[4,23]

Antihistamines are not effective in cases of NICU, which leads to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin.[23]

Conclusions

CUS represents a significant challenge because of its occupational relevance, which is recognized in only a few countries. It may present as urticaria and/or dermatitis. Identification of CUS requires a high index of clinical suspicion, a detailed occupational history, physical examination, and ancillary testing (e.g., prick testing). Latex, cosmetics, plants, vegetables, and foods are the most common agents. Avoidance of the offending agent is the best treatment. This requires appropriate and early diagnosis, the preparation of occupational histories, and the development of preventive measures.

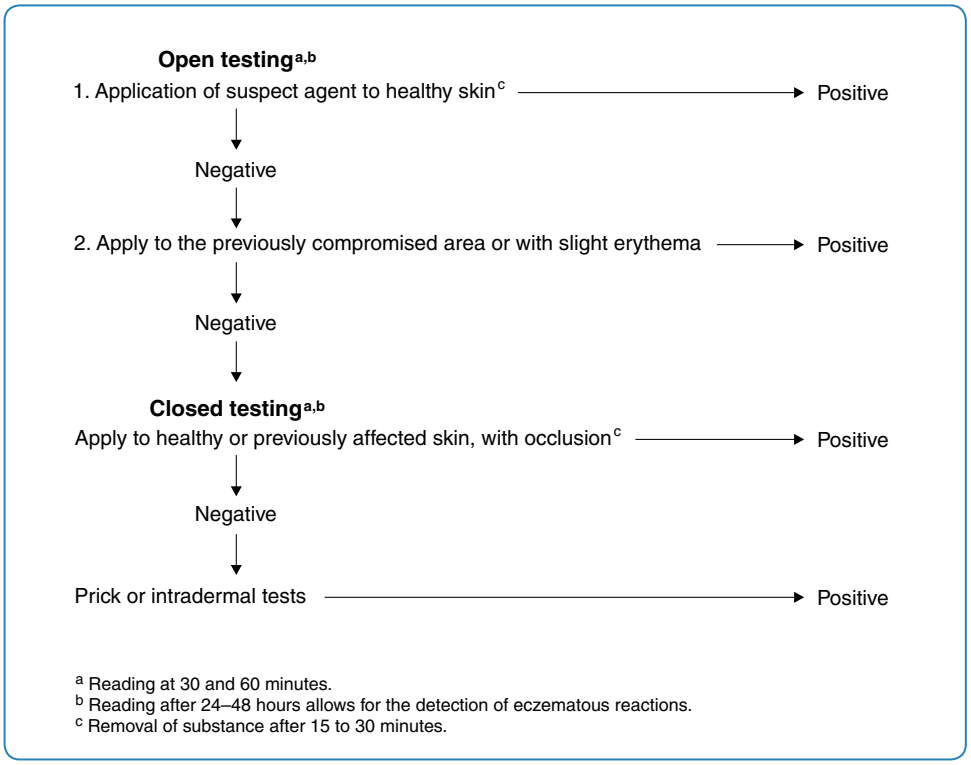

Figure 1
In vivo assessment of contact urticaria syndrome
Modified from França AT and Dortas Junior SD[23].

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Epidemiology of anaphylaxis in Brazil: The Brazilian Registry of Anaphylaxis (RBA) of the Brazilian Association of Allergy and Immunology (ASBAI)

Epidemiologia da anafilaxia no Brasil: Registro Brasileiro de Anafilaxia (RBA) da Associação Brasileira de Alergia e Imunologia (ASBAI)

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ABSTRACT

Introduction: Anaphylaxis is a life-threatening, acute, severe multisystem allergic reaction. There is little data on its epidemiology in Brazil. The Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology (RBA-ASBAI) was devised to expand knowledge about anaphylaxis in Brazilian individuals. **Methods:** Cross-sectional observational study using an online questionnaire to collect data on demographics, suspected triggers, clinical manifestations, treatment during the reaction, diagnostic workup, and post-reaction counseling in patients who have experienced an anaphylactic reaction. **Results:** Between June 2021 and April 2023, 237 patients were included (131 female): 99 children/adolescents (<18yo), 127 adults (18-64yo), and 11 older adults (65-77yo). There was a male predominance in the pediatric group (55.5%), while females were predominant among adults (64.5%). The median age was 22 years (range, <1 to 77). The most frequent clinical manifestations were cutaneous

RESUMO

Introdução: A anafilaxia é uma reação alérgica multissistêmica grave, de início agudo e potencialmente fatal. Poucos são os dados sobre sua epidemiologia no Brasil. O Registro Brasileiro de Anafilaxia da Associação Brasileira de Alergia e Imunologia (RBA-ASBAI) teve como objetivo ampliar o conhecimento sobre anafilaxia em indivíduos brasileiros. **Métodos:** Estudo observacional transversal com questionário *online* sobre dados demográficos, desencadeantes suspeitos, manifestações clínicas, atendimento durante a reação, investigação diagnóstica e aconselhamento após a reação de pacientes que experimentaram uma reação anafilática. **Resultados:** Entre junho/2021 e abril/2023, foram incluídos 237 pacientes (131 femininos): 99 crianças/adolescentes; 127 adultos e 11 idosos. Houve predomínio de meninos entre crianças/adolescentes (55,5%), e de mulheres entre os adultos (64,5%), e mediana de idade de 22 anos (< 1 a 77 anos). As manifestações cutâneas (92,8%) foram as mais frequentes, seguidas pelas respi-

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(92.8%), followed by respiratory (70.1%), gastrointestinal (52.3%), neurological (36.3%), and cardiovascular (35.3%). The most common triggers were foods (43.0%), drugs (26.2%), venoms (21.6%), and latex (2.5%). Foods (milk, egg, peanuts/tree nuts) predominated among children, versus drugs (mostly nonsteroidal anti-inflammatory drugs and antibiotics) among adults. Regarding treatment, 61.1% received epinephrine (52.7% by a healthcare professional and 8.4% via epinephrine auto-injector [EAI]). One teenager (12yo) died due to a bee sting. Most patients received a written emergency plan (78.1%) and were taught how to use the EAI (70%). **Conclusion:** Foods were the most common triggers of anaphylaxis among Brazilian children and adolescents, while drugs predominated among adults. Epinephrine continues to be underused, highlighting the need for greater awareness of proper treatment of anaphylaxis.

Keywords: Anaphylaxis, food hypersensitivity, drug hypersensitivity, venom hypersensitivity, epinephrine.

ratórias (70,1%), gastrointestinais (52,3%), neurológicas (36,3%) e cardiovasculares (35,3%). Os principais desencadeantes foram: alimentos (43,0%), medicamentos (26,2%), himenópteros (21,6%) e látex (2,5%); os alimentos entre crianças (leite, ovo, amendoim/castanhas), e os fármacos (anti-inflamatórios e antibióticos) entre os adultos. Quanto ao tratamento, 61,1% recebeu adrenalina (52,7% por profissional e 8,4% via autoinjetor de adrenalina - AIA). Uma adolescente (12 anos) faleceu após picada de abelha. A maioria recebeu plano escrito de emergência (78,1%) e foi ensinada a usar o AIA (70%). **Conclusão:** Os alimentos foram os desencadeantes mais comuns entre crianças/adolescentes, e os fármacos entre adultos brasileiros. A adrenalina continua sendo subutilizada, reforçando a necessidade de maior disseminação do tratamento adequado da anafilaxia.

Descritores: Anafilaxia, hipersensibilidade alimentar, hipersensibilidade a drogas, hipersensibilidade a veneno, epinefrina.

Introduction

Anaphylaxis is defined a severe multisystemic allergic reaction of acute onset and potentially fatal.[1-3] Clinically, some or all of the following signs and symptoms may be present: urticaria, angioedema, respiratory and gastrointestinal involvement, and/or arterial hypotension.[1-4] The occurrence of two or more of these symptoms immediately after exposure to a likely allergen alerts to the diagnosis and the need for immediate treatment.[1,3]

The incidence of anaphylaxis has been increasing in the last years, although there are few data on its epidemiology in Brazil. In most cases, literature is limited to studies with small population groups, with variable results depending on diagnostic criteria to define cases, study site, population assessed, study duration, among others.[5-9]

Registries have been a widely used tool in the study of diseases with a low prevalence, such as anaphylaxis.[4,6,10-20] They allow for gathering and documenting, in an active and standardized manner, patients' data on predefined questions on clinical manifestations, treatment, and evolution. Registries also allows for assessing the efficacy in the clinical and laboratory medical care routine, in addition to the monitoring of patient safety as well as economic evaluation and minimum quantity (therapeutic) research required for disease control.[17] In order to obtain more representative data on a given disease and to have a broader perspective about it, records are multicenter and/or multinational.[6,10-20]

The Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology (*Registro Brasileiro de Anafilaxia da Associação Brasileira de Alergia e Imunologia*, RBA-ASBAI)[20] was developed based on the Portuguese Registry of Anaphylaxis and Adverse Reactions of the Portuguese Society of Allergy and Clinical Immunology (*Registro Português de Anafilaxia e Reações Adversas da Sociedade Portuguesa de Alergia e Imunologia Clínica*, RPARA-SPAIC)[10], with the purpose of collecting national health data that allow us to gain a broader knowledge on the profile of Brazilian individuals affected by anaphylaxis. These data will be essential for physicians who treat these patients, as well as public power and society, to understand the importance of this problem, based on greater knowledge about the matter.

Method

This is an observational cross-sectional study aimed at assessing the characteristics of anaphylaxis in Brazilian individuals, using the RBA-SBAI, which is a national anaphylaxis registry that is completed online by the attending physician of a patient with a history of anaphylaxis.[21] This questionnaire contains sociodemographic data, suspected triggers, clinical manifestations, treatment provided during the reaction, diagnostic workup, and post-reaction counseling.

The study was approved by the Research Ethics Committee (REC) of Instituto Pensi (No. 5.145.239).

In December 2021, this REC waived for mandatory signing of informed consent and assent free forms (ICF and IAF, respectively) for the inclusion of cases in the RBA-ASBAI.

Statistical analysis was performed by non-parametric tests, using the Jamovi® software (version 2.3). Categorical variables were described by frequency distribution, and continuous ones by mean and standard deviation (SD). P-values below 0.05 were considered statistically significant. The analysis included registries made from 06/28/2021 to 04/15/2023.

Results

Data from 237 patients were assessed, with a predominance of the female sex (131; 55.3%). Patients from 17 out of the 27 Brazilian states were included; state distribution ranged from 0.4% to 25.8% of the overall sample, with most patients coming from Southern and Southeastern states: São Paulo (25.8%), Paraná (19.4%), and Rio de Janeiro (15.6%). Patients were categorized as follows: 99 children/adolescents (< 18 years); 127 adults (18-64 years), and 11 older adults (65-77 years). There was a predominance of men among children and adolescents (55.5%; p = 0.005), and of women among adults (64.5%; p = 0.002). Overall median age was 22 years, and mean age was 25.6 (SD ± 20.8) years (minimum < 1 year and maximum = 77). For the female sex, mean age was 27.8 (SD ± 20) years and median was 29 years, while for the male sex, these values were 22.9 (SD ± 21.5) years and 16 years, respectively. For 97/237 (39.2%) patients, the episode included in the RBA-ASBAI was the first one and, for 61/237 (25.8%) patients, it was the third one or more.

Household was the most frequent place of occurrence of the reaction (111/237; 46.8%), followed by hospital or health unit (37/237; 15.6%), park/field (27/237; 11.4%), restaurant (19/237; 8.0%), public space (16/237; 6.8%), and workplace (10/237; 4.0%). Nearly 95% of patients received some type of treatment, 68.4% (162/237) at an urgent service, 18.6% (44/237) at the place of occurrence of the reaction, 4.6% (11/237) at an intensive care unit, 3.4% (8/237) at an outpatient service, 3% (7/237) at an in-hospital ward, and 2.1% (5/237) at another place.

Symptoms occurred within the first 10 minutes after exposure to the allergen in 38.8% of the patients; from 10 to 30 minutes in 44.7%; from 31 to 59 minutes in 7.2%; and after 1 hour in 7.1%. Biphasic reaction was observed in 10 patients (4.2%). There was predominance of cutaneous manifestations (92.8%), followed by respiratory (70.1%), gastrointestinal (52.3%), neurological (36.3%), and cardiovascular (35.3%) manifestations (Table 1). Urticaria was the most frequent cutaneous manifestation, with no differences regarding age, whereas angioedema predominated among individuals aged 65 years or older (Table 1). Respiratory manifestations predominated among those younger than 65 years, the most frequent of which was dyspnea, with no differences regarding age (Table 1). Rhinitis predominated among those younger than 18 years (Table 1). Gastrointestinal manifestations occurred similarly in the three age groups, and neurological manifestations were frequent among individuals aged from 18 to 64 years (Table 1). Hypotension was more frequent among older patients (Table 1).

For 133/137 (97.0%) patients who have had a previous episode, the previous one was more severe. Of these 133 patients, 55 were children, 71 were adults, and 7 were older adults (with no statistical difference among age groups). Only one 12-year old girl had a fatal outcome due to bee sting, a previously known allergen, because she was not treated with epinephrine.

Among the triggers, the most common were: foods (43.0%), drugs (26.2%), *Hymenoptera* sting (21.6%), and latex (2.5%) (Table 2). Foods predominated among patients younger than 18 years (27.4%), with cow's milk, egg, peanuts, and tree nuts being the most common allergens in this group, and seafood and wheat among individuals aged from 19 to 64 years (Table 2). Drug reactions predominated among adults (nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotics, and latex) (Table 2). An analysis of variance (ANOVA) was conducted to investigate the differences for the "food" and "drug" triggers among the three different age groups: children, adults, and older adults. Results for ANOVA revealed significant differences in the "food" ($F = 7.3$; $p < 0.001$) and "drug" ($F = 3.62$; $p < 0.001$) variables among the age groups. In relation to insects, there was predominance of adults (ant, wasp, and bee), followed by children (ant, bee). For 78.9% of patients, there was no cofactor associated with the condition, whereas 6.3% appointed exercise, 5.4% drugs, 1.6% alcohol, and 1.6% stress as cofactors.

In relation to the treatment received, it was observed that 61.1% of patients received epinephrine (52.7%

Table 1
Clinical manifestations presented by patients included in the Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology during their most recent anaphylaxis episode, according to age group (% in relation to the number of individuals affected in each age group)

	Age group (years)			
Clinical manifestations	**< 1 to 18 99 (%)**	**19 to 64 127 (%)**	**≥ 65 11 (%)**	**Total 237 (%)**
Cutaneous	95 (96.0)	114 (89.8)	11 (100)	220 (92.8)
Urticaria	67 (67.7)	79 (62.2)	7 (63.6)	153 (64.6)
Angioedema	65 (65.6)	70 (55.1)	2 (18.2)	137 (57.8)
Generalized pruritus	37 (37.4)	59 (46.5)	7 (63.6)	103 (43.5)
Generalized erythema	26 (26.3)	32 (25.2)	4 (36.4)	62 (26.2)
Respiratory	69 (69.7)	94 (74.0)	5 (45.5)	168 (70.1)
Rhinitis	22 (22.2)	16 (12.6)	0	38 (16.0)
Oppression sensation in the throat	13 (13.1)	33 (26.0)	1 (9.1)	47 (19.8)
Stridor	2 (2.0)	10 (7.9)	0	12 (5.1)
Laryngeal cough	19 (19.2)	18 (14.2)	0	37 (15.6)
Dysphonia	10 (10.1)	16 (12.6)	0	26 (11.0)
Dyspnea	29 (29.3)	38 (29.9)	4 (36.4)	71 (30.0)
Mild bronchospasm	16 (16.2)	12 (9.4)	1 (9.1)	29 (12.2)
Moderate bronchospasm	12 (12.1)	11 (8.7)	0	23 (9.7)
Hypoxemia ($SatO_2$ < 92%)	5 (5.0)	19 (15.0)	1 (9.1)	25 (10.5)
Respiratory arrest	0	2 (1.6)	0	2 (0.8)
Gastrointestinal	52 (52.5)	67 (52.8)	5 (45.5)	124 (52.3)
Edema labial	15 (15.2)	30 (23.6)	2 (18.2)	47 (19.8)
Oropharyngeal pruritus	5 (5.1)	25 (19.7)	0	30 (12.7)
Oppression sensation in the oropharinx	7 (7.1)	33 (26.0)	3 (27.3)	43 (18.1)
Nausea	10 (10.1)	16 (12.6)	0	26 (11.0)
Recurrent vomiting	23 (23.2)	13 (10.2)	0	36 (15.2)
Mild abdominal pain	6 (6.1)	8 (6.3)	0	14 (5.9)
Intense abdominal pain	2 (2.0)	5 (3.9)	2 (18.2)	9 (3.8)
Diarrhea	12 (12.1)	10 (7.9)	1 (9.1)	23 (9.7)
Loss of sphincter control	0	4 (3.1)	0	4 (1.7)
Neurological	28 (28.3)	54 (42.5)	4 (36.4)	86 (36.3)
Anxiety	6 (6.1)	20 (15.7)	0	26 (11.0)
Altered level of activity	10 (10.1)	10 (7.9)	0	20 (8.4)
Sensation of lipothimia	11 (11.1)	20 (15.7)	1 (9.1)	32 (13.5)
Confusion	0	9 (7.1)	0	9 (3.8)
Loss of consciousness	8 (8.1)	23 (18.1)	4 (36.4)	35 (14.8)
Cardiovascular	18 (18.2)	57 (44.9)	8 (72.7)	83 (35.0)
Tachycardia	7 (7.1)	24 (18.9)	1 (9.1)	32 (13.5)
Severe bradycardia	0	1 (0.8)	0	1 (0.4)
Dysrhythmia	0	0	0	0
Shock	0	7 (5.5)	1 (9.1)	8 (3.4)
Hypotension	13 (13.1)	35 (27.6)	8 (72.7)	56 (23.6)
Heart arrest	0	2 (1.6)	1 (9.1)	3 (1.3)

Table 2
Agents appointed as responsible for anaphylaxis in patients included in the Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology, according to age group in relation to the total sample

	Age group (years)			
	< 1 to 18	19 to 64	≥ 65	Total
Triggering agent	**99 (%)**	**127 (%)**	**11 (%)**	**237 (%)**
Foods				
Cow's milk	32 (13.5)	0	0	32 (13.5)
Egg	13 (5.5)	2 (0.8)	0	15 (6.3)
Peanuts	6 (2.5)	0	0	6 (2.5)
Wheat	4 (1.7)	5 (2.1)	1 (0.4)	10 (4.2)
Nuts	2 (0.8)	0	0	2 (0.8)
Seafood	1 (0.4)	15 (6.3)	0	16 (6.8)
Fish	1 (0.4)	0	0	1 (0.4)
Kiwi	0	1 (0.4)	0	1 (0.4)
Other	6 (2.5)	11 (4.6)	0	17 (7.2)
Total	65 (27.4)	36 (15.2)	1 (0.4)	102 (43.0)
Drugs				
NSAIDs	1 (0.4)	20 (8.4)	1 (0.4)	22 (9.2)
Antibiotics	1 (0.4)	7 (2.9)	2 (0.8)	10 (4.2)
Biological agents	0	1 (0.4)	0	1 (0.4)
Anesthetics	0	1 (0.4)	0	1 (0.4)
Corticosteroids	0	1 (0.4)	0	1 (0.4)
Proton pump inhibitors	0	1 (0.4)	0	1 (0.4)
Contrast media	0	1 (0.4)	1 (0.4)	2 (0.8)
Muscle relaxant	0	1 (0.4)	0	1 (0.4)
Vaccine	0	1 (0.4)	0	1 (0.4)
Latex	1 (0.4)	4 (1.7)	1 (0.4)	6 (2.5)
Other	2 (0.8)	12 (5.1)	2 (0.8)	16 (6.7)
Total	5 (2.1)	50 (21.1)	7 (2.9)	62 (26.2)
Insects				
Ant	11 (4.6)	9 (3.8)	0	20 (8.4)
Bee	4 (1.7)	7 (2.9)	2 (0.8)	13 (5.5)
Polistes spp. wasp	2 (0.8)	8 (3.4)	0	10 (4.2)
Vespula spp. wasp	2 (0.8)	1 (0.4)	0	3 (1.3)
Other	0	5 (2.1)	0	5 (2.1)
Total	19 (8.0)	30 (12.7)	2 (0.8)	51 (21.5)
Outro				
Exercise	5 (2.1)	9 (3.8)	1 (0.4)	15 (6.3)
Cold	0	1 (0.4)	0	1 (0.4)
Total	5 (2.1)	10 (4.2)	1 (0.4)	16 (6.7)

(%) = percent of the total.

administered by a professional, and 8.4% via the anaphylaxis emergency kit). Only 25 patients carried the kit. The use of epinephrine in the emergency event was greater in adults than in children (58.3% vs 43.4%, $p < 0.05$), respectively. Antihistamines were used by 87.3% of patients, corticosteroids by 83.1%, bronchodilator by 27.4%, oxygen inhalation therapy by 29.5%, and volume replacement therapy by 30.8%. Ten patients were intubated (9 adults/1 older adult), who more frequently had a history of a more severe previous episode, and eight were resuscitated (6 adults/2 older adults), all of whom had a history of a more severe previous episode ($p = 0.039$).

With regard to patients' workup, it bears highlighting that only 24 (10.1%) underwent serum tryptase testing, which showed high levels in two; 149 underwent other complementary tests with the following frequency: specific serum IGE testing (101/149; 67.7%), skin test (62/149; 41.6%), and/or provocation test (13/149; 8.7%). Clinical history was highly suggestive in nine patients.

A large number of patients had already been referred to a specialist (42.6%) or was referred to after the anaphylaxis episode (50.2%). Epinephrine autoinjector (EAI) was prescribed to 68.8% of patients. With regard to counseling, it was observed that most patients were taught how to use the EAI (70%) and about the trigger (95.8%), prevention strategies (96.2%), and post-reaction practices (97%). The majority of patients received a written emergency plan (78.1%), but a minority received an anaphylaxis alert bracelet or medal (20.7%). In relation to immunotherapy, 30% of patients were advised to receive it.

Discussion

This study reported the first 237 patients who presented anaphylaxis and whose data were included in the RBA-ASBAI by their allergologist physicians.

Since anaphylaxis is a very severe and potentially fatal allergic reaction, it is important to understand its clinical evolution, its triggering agents, and the therapeutic approach adopted, in order to establish guidelines that allow for providing these patients with better care.

Similar to findings observed by other researchers who analyzed data from different sources (population samples, national or international registries, among others), cutaneous manifestations, especially urticaria and angioedema, predominated.[5-19] It bears emphasizing that, although urticaria is one of the items composing several diagnostic criteria for anaphylaxis, some patients may manifest it in the absence of cutaneous symptoms.[1,3]

With regard to etiological agents, an important relationship was found according to patients' age, with foods predominating among younger patients, and drugs among the older ones, which corroborates findings from other registries.[5,19] Such fact may be justified by the life stage when individuals are exposed to the allergen. Foods that are introduced early in life, such as milk and egg, are capable of inducing reaction already early in life, whereas seafood, whose food introduction occurs lately, triggered reactions at more advanced stages of life. The same can be said for drugs. It is worth highlighting that NSAIDs stand out as the main cause of drug-induced anaphylaxis in adults, as also noted by Jares et al. in Latin America.[19]

Concerning *Hymenoptera* venoms, it is important to bear in mind some aspects related to their exposure at different ages. Among adults, professional exposure (bees) predominates, while children and adolescents are exposed during leisure time (ant, bee). Other studies also showed ants as a relevant trigger in the pediatric population[19].

With regard to the place of occurrence of the reaction, most episodes occurred at the patient's own house. This may be explained by the higher prevalence of food reactions in our sample and highlights the importance of having the EAI available and of providing proper counselling after the first reaction.

Although the treatment of choice at the acute phase of anaphylaxis was epinephrine, only 61.1% of patients in the study received it, applied mostly by a healthcare professional, less often among children and adolescents, and only 13.7% of patients used the EAI. What would justify this difference? Difficulty in establishing the diagnosis of anaphylaxis in individuals younger than 19 years? Less information by physicians who treat children at the emergency room? Less severe cases among the youngest?

Despite dissemination of recent knowledge and life support training currently received by most physicians, prescription of epinephrine, either intramuscular or subcutaneous, remains low, as opposed to the high prescription of antihistamine agents and corticosteroids.

A noteworthy finding is the fact that patients with previous history of severe episodes and need for

resuscitation were the ones who presented the most severe forms of anaphylaxis, requiring intubation and admission to the intensive care unit, all of whom were older than 19 years.

Serum tryptase testing has been one of the recommended biomarkers for anaphylaxis diagnosis and follow-up. Several factors interfere with its levels, especially at the time of collection in relation to the duration of the episode, which may justify the low incidence of positive results for this test in the present sample.

Specialized follow-up of these patients is very important to allow for identifying the etiological agent, in addition to instructing the patient with regard to the disease and its warning signs and to providing a written plan in case of emergency and, if possible, use of EAI. Fortunately, most registered patients received appropriate guidance on emergency plan and use of EAI.

Our study has limitations, because it was conducted by allergists only, with a non-random population sample, with a probable selection bias. Therefore, results cannot be generalized to the entire Brazilian population. Another weakness is recall bias, since the questionnaires were completed based on patients' reports. Despite this, it is worth highlighting the inadequate approach to which these patients were submitted. Conversely, there are some positive aspects, such as the nationwide coverage of the study and the fact that it included individuals with different dietary habits and environmental exposures, in addition to the use of a standardized questionnaire that was completed by trained professionals in recognizing anaphylaxis.

To conclude, analysis of the first patients with anaphylaxis included in the RBA-ASBAI points the need for greater awareness of cases of anaphylaxis and a more comprehensive education for lay people and other professionals, especially to prevent new episodes and provide proper treatment in case of recurrence.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Effect of environmental exposure on the perceived health status of individuals from five Latin American countries

Influência da exposição ambiental na percepção do estado de saúde de indivíduos de cinco países latino-americanos

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ABSTRACT

Objective: The relationship between environmental exposure and health outcomes is well known. We investigated this relationship in five Latin American countries with different cultural backgrounds but similar Human Development Indexes. **Methods:** This was a cross-sectional study involving 3,016 individuals (18 to 75 years old) from Argentina (n=878), Brazil (n=1030), Mexico (n=272), Paraguay (n=508), and Peru (n=328). Participants were randomly selected and responded to a standardized questionnaire (including sociodemographic and environmental factors and lifestyle habits) derived from a clinical screening tool for air pollution risk. Based on their current health status, participants were categorized as having regular/bad/very bad or excellent/good health. Multivariate analysis was conducted, and data were presented as likelihood ratios and 95% confidence intervals (95%CI). The significance level was set at 5%. **Results:** Living in any of the study countries; indoor humidity (OR=1.68; 95%CI: 1.33-2.12); driving with the windows open (OR=1.31; 95%CI: 1.03-1.65); low family income (OR=1.59; 95%CI: 1.26-2.01); incomplete education (OR=1.54; 95%CI: 1.22-1.94); personal/family history of hypertension (OR=2.25; 95%CI: 01.64-3.09), chronic obstructive pulmonary disease/asthma (OR=1.74; 95%:CI: 1.28-2.36), diabetes (OR=3.74; 95%CI:2.23-6.29), obesity (OR=1.84; 95%CI: 1.84-3.19), or ocular comorbidities (OR=1.89; 95%CI: 1.55-2.30); and exercising outdoors (OR=1.60; 95%CI: 1.31-1.96) were significantly associated with a worse perceived health status. **Conclusions:** Despite the different exposures to

RESUMO

Objetivo: A relação entre exposição ambiental e risco à saúde é amplamente reconhecida e a avaliamos em cinco países da América Latina com condições culturais distintas, mas com Índices de Desenvolvimento Humano semelhantes. **Métodos:** Estudo transversal envolvendo 3.016 indivíduos (18 a 75 anos) oriundos de: Argentina (n = 878), Brasil (n = 1.030), México (n = 272), Paraguai (n = 508) e Peru (n = 328). A seleção foi aleatória e todos responderam questionário padronizado (fatores sociodemográficos, fatores ambientais e hábitos de vida) derivado do *Clinical Screening Tool for Air Pollution Risk*. Segundo o estado atual de saúde, foram categorizados em: saúde regular/má/péssima ou excelente/boa. Tendo-a como desfecho, realizou-se análise multivariada. Os dados foram apresentados como razão de verossimilhança (RV) e intervalos de confiança de 95% (IC 95%), tendo-se 5% o nível de significância. **Resultados:** Foram significantemente associados a pior percepção de situação de saúde: morar em qualquer um dos países, ter umidade na residência (OR = 1,68; IC 95%: 1,33-2,12), dirigir automóvel com janelas abertas (OR = 1,31; IC 95%: 1,03-1,65), ter baixa renda familiar (OR = 1,59; IC 95%: 1,26-2,01), nível educacional incompleto (OR = 1,54; IC 95%: 1,22-1,94), histórico pessoal/familiar de hipertensão arterial (OR = 2,25; IC 95%: 01,64-3,09), doença pulmonar obstrutiva crônica/asma (OR = 1,74; IC 95%: 1,28-2,36), diabete melito (OR = 3,74; IC 95%: 2,23-6,29), obesidade (OR = 1,84; IC 95%: 1,84-3,19) ou comorbidades oftalmológicas (OR = 1,89;

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which participants were subjected, some factors remain very significant. Low family income, exposure to pollution, and a history of chronic diseases were associated with the perception of a poor health condition.

Keywords: Environmental pollution, health, noncommunicable chronic diseases, smoking, asthma, cardiovascular diseases.

IC 95%: 1,55-2,30); realizar exercícios ao ar livre (OR = 1,60; IC 95%: 1,31-1,96). **Conclusões:** Apesar das diferentes exposições a que foram submetidos, alguns fatores permanecem muito significativos, e ter baixa renda familiar, expor-se à poluição e ter antecedentes de doenças crônicas foram associados à percepção de condição ruim de saúde.

Descritores: Poluição ambiental, saúde, doenças crônicas não transmissíveis, tabagismo, asma, doenças cardiovasculares.

Introduction

Air pollution is increasingly recognized as the greatest environmental threat to human health and well-being.[1] Air pollution is estimated to be responsible for millions of deaths, years of healthy life lost, and billions of dollars lost each year.[1-3]

There is ample scientific evidence linking pollution and socioeconomic and educational levels to health outcomes in the most vulnerable populations. This disparity is a risk factor that amplifies the health effects of pollution.[3-8]

Outdoor air pollutants, whether released from stationary sources (e.g., industrial facilities) or mobile sources (e.g., motor vehicles), and indoor air pollutants (tobacco smoke, biomass burning, volatile organic compounds [VOCs], etc.), pose a significant threat to air quality.[1,9]

Furthermore, housing quality plays a critical role in exposure to pollutants and allergens. Homes with inadequate infrastructure, prone to leaks and infiltration, create ideal conditions for the growth of allergens such as mold. Low-income populations and ethnic minorities are more likely to live in substandard housing, thereby increasing their exposure to these allergens.[8,10-12]

Approximately 70% of the 9 million deaths caused by air pollution each year are related to noncommunicable diseases (NCDs) such as heart disease, stroke, chronic obstructive pulmonary disease (COPD), lung cancer, etc.[4,5,13,14]

A pilot study conducted in the city of Uruguaiana, state of Rio Grande do Sul, Brazil, documented an association between exposure to outdoor air pollution and an increased risk of systemic arterial hypertension, chronic respiratory disease, and low socioeconomic status.[14]

The purposes of the present study were to assess the relationship between environmental conditions (e.g., exposure to environmental pollutants) and the perceived health status of individuals living in Latin America by using a standardized instrument.

Material and method

The present cross-sectional, quantitative study was conducted on 3016 individuals (aged 18 to 75 years) from 5 Latin American countries: Argentina (n = 878), Brazil (n = 1030), Mexico (n = 272), Paraguay (n = 508), and Peru (n = 328). All participants were randomly selected (convenience sample) and volunteered. They duly completed the standardized questionnaire on sociodemographic factors and exposure to environmental factors and lifestyle habits adapted from the Clinical Screening Tool for Air Pollution Risk.[15]

Data collection was conducted between June 2021 and June 2022 during medical consultations in primary care facilities, regardless of the reason for the visit. Individuals were asked about their sex, race, education level, marital status, employment, household income, place of residence, health status, diseases, alcohol consumption, exposure to pollution sources at work and home, exposure to fuel combustion (e.g., biomass, fossil fuels, etc.), alcohol consumption, home ventilation, cleaning products, cigarette smoking, regular exercise, etc.

In terms of economic level, patients were categorized according to whether their income was up to 2 minimum wages (MW) or more than 2 MW, as defined by government authorities in each country. Participants were categorized according to their current health status (self-defined): fair/poor/very poor health or excellent/good health.

Table 1 compiles the main socio-demographic characteristics of the countries participating in the study. Data for Brazil have already been published separately.[16]

Data analysis

Data were entered into an Excel® spreadsheet, and categorical variables were presented as frequency distributions and proportions. Nonparametric tests (chi-square or Fisher's exact test) were used for group comparisons. With health status (excellent/good vs. regular/poor/very poor) as the outcome, multivariate analysis followed by logistic regression was performed by considering each country individually and collectively. Data were presented as odds ratio (OR) and 95% confidence intervals (95% CI). Geographical, environmental, sociodemographic, health, and lifestyle variables were considered. A 5% significance level was used to reject the null hypothesis in all analyses. SPSS software (version 20) was used for statistical analysis.

The study was approved by the local research ethics committee at each participating center. All participants agreed to and signed the informed consent form.

Results

Table 2 presents the affirmative responses to the different questions that make up the questionnaire, provided by the participating individuals and distributed according to their country of origin. In all countries, except for Brazil and Peru, there was a preponderance of females, individuals under the age of 60, and self-identified whites.

In Mexico and Brazil, there was a preponderance of individuals with a high level of education. Most patients reported living in stable partnerships or marriages, being employed or self-employed, and having a satisfactory average income, except in Peru (27.7%). Urban dwellers predominated in all countries except Peru. The HDIs of the countries were similar, except for Argentina, which had the highest value (Table 1).

Table 3 shows the factors identified by univariate and multivariate analysis of variance for all the countries evaluated together. Table 3 shows the following factors were significantly associated with poorer health status: living in any of the countries studied, humidity in the home, driving a car windows open, low family income, incomplete schooling, personal/family history of hypertension, chronic obstructive pulmonary disease/asthma, type I or type II diabetes mellitus, obesity, ocular comorbidities, and exercising outdoors.

Table 4 shows the factors associated with poor health that were identified by multivariate analysis in each of the participating countries. Table 4 shows several factors were identified as risks, but not universally. Humidity in the home; living near a source of pollution; having paints, waxes, or incense at home; driving a car windows open; and systemic arterial hypertension, COPD/asthma, type I or type II diabetes mellitus, obesity, ocular comorbidities, smoking, and exercising outdoors were identified as risk factors in most countries. Other factors had mixed results,

Table 1
Sociodemographic characteristics of the countries included in the present study

Characteristics	Argentina	Brazil	Mexico	Paraguay	Peru
Estimated population (2023) in millions of people[17]	45.8	216.4	128.4	6.9	34.4
Human Development Index (HDI) (2021)[18]	0.842	0.754	0.758	0.717	0.762
Infant mortality (2021) in deaths per thousand live births[19]	9.0	15.88	10.65	16.91	16.69
Gross domestic product (GPD) per capita (2021) in millions of US dollars[20]	922.1	3.248	2463	88.91	430.3
Life expectancy at birth (years)[21]	77.82	74.74	76.69	77.9	74.7
GPD growth rate (2021) in %[22]	0.85	0.66	1.02	1.16	0.91

Table 2
Distribution of respondents with positive responses to the various items of the environmental health questionnaire by country of origin (N = 3016)

Variables	Argentina 878 (%)	Brazil 1,030 (%)	Mexico 272 (%)	Paraguay 508 (%)	Peru 328 (%)
Sociodemographic factors					
Family income of up to 2 minimum wages	214 (24.4)	380 (36.9)	67 (24.6)	104 (20.5)	237 (72.3)
Female	664 (75.6)	651 (63.2)	192 (70.6)	306 (60.2)	232 (70.7)
Age group (years)					
Up to 25 years old	152 (17.3)	238 (23.2)	11 (4.0)	61 (12.0)	52 (15.8)
25 to 59 years old	673 (76.6)	725 (70.5)	242 (88.9)	371 (73.1)	255 (77.8)
Over 60 years old	53 (6.0)	65 (6.3)	19 (7.0)	76 (15.0)	21 (6.4)
Higher education degree or more	294 (33.5)	527 (51.2)	218 (80.1)	220 (43.3)	97 (29.6)
Race/skin color – white	803 (92.1)	415 (40.4)	148 (55.0)	473 (93.1)	88 (26.9)
Marital status – married/stable relationship	517 (58.9)	562 (54.6)	170 (62.5)	257 (50.6)	217 (66.2)
Unemployed	239 (27.2)	292 (28.3)	72 (26.5)	176 (34.6)	150 (45.7)
Environmental factors					
Spends most of the day in traffic/exposed to areas with heavy vehicle circulation	130 (14.8)	145 (14.1)	34 (12.5)	93 (18.3)	39 (11.9)
Uses a wood/charcoal/kerosene/solvent/other furnace	1 (0.4)	92 (18.4)	7 (3.7)	7 (3.7)	7 (3.7)
You are the household cook	7 (4.7)	510 (49.5)	168 (61.8)	161 (31.7)	194 (59.1)
Cooks for up to 2 hours	690 (83.0)	744 (78.8)	190 (75.1)	429 (89.4)	130 (43.8)
Humidity on the walls	216 (24.6)	176 (17.1)	62 (22.8)	318 (62.6)	60 (18.3)
Mold on the walls	122 (13.9)	171 (16.6)	19 (7.0)	260 (51.2)	16 (4.9)
Paints, waxes, repellents, or incense in the house	622 (70.8)	441 (42.8)	90 (33.1)	444 (87.4)	117 (35.7)
Bleach for house cleaning	728 (82.9)	675 (65.5)	16 (5.9)	380 (74.8)	231 (70.4)
Degreaser for house cleaning	250 (28.5)	262 (25.4)	45 (16.5)	89 (17.5)	24 (7.3)
Disinfectant for house cleaning	335 (38.2)	548 (53.2)	89 (32.7)	130 (25.6)	130 (25.6)
Source of pollution near the house	331 (37.7)	434 (42.1)	115 (42.3)	345 (67.9)	223 (68.0)
House in unpaved area	141 (16.1)	110 (10.7)	11 (4.1)	81 (15.9)	41 (12.5)
Open sewage near the house	36 (10.9)	76 (17.5)	7 (6.1)	21 (6.1)	0 (0.0)
Source of pollution near the place of work	187 (21.3)	301 (39.2)	84 (30.9)	217 (42.7)	53 (16.2)
Materials burned in the home	108 (12.3)	83 (8.1)	10 (3.7)	32 (6.3)	187 (57.0)
House in rural area	31 (3.5)	78 (7.6)	16 (5.9)	19 (3.7)	194 (59.1)
Open car windows while driving	237 (27.5)	4 (4.1)	71 (26.3)	55 (10.8)	48 (14.8)
Health-related factors					
Perceives health as fair/poor/very poor	123 (14.0)	296 (28.7)	65 (23.9)	166 (32.7)	79 (24.1)
Systemic arterial hypertension	77 (8.8)	80 (7.8)	36 (13.2)	122 (24.0)	10 (3.0)
Chronic obstructive pulmonary disease (COPD)/Asthma	52 (5.9)	86 (8.3)	34 (12.5)	104 (20.5)	17 (5.2)
Allergic rhinitis	178 (20.3)	337 (32.7)	97 (35.7)	275 (54.1)	38 (11.6)
Diabetes mellitus	15 (1.7)	21 (2.0)	13 (4.8)	62 (12.2)	11 (3.4)
Obesity	109 (12.4)	73 (7.1)	51 (18.8)	106 (20.9)	25 (7.6)
Ocular comorbidities	397 (45.2)	509 (49.4)	173 (63.6)	421 (82.9)	104 (31.7)
Itchy eyes	205 (23.3)	372 (36.1)	77 (28.3)	172 (33.9)	39 (11.9)
Dry eyes	257 (29.3)	226 (21.9)	83 (30.5)	75 (14.8)	20 (6.1)
Lifestyle habits-related factors					
Exercises outdoors	521 (59.3)	549 (53.3)	93 (34.2)	258 (50.8)	82 (25.0)
Exercises once a week	128 (14.5)	178 (17.2)	24 (8.8)	79 (15.6)	27 (8.2)
Current/former smoking	283 (32.2)	145 (14.1)	102 (37.5)	151 (29.7)	88 (26.8)
Lives with a smoker	181 (20.6)	182 (17.7)	60 (22.1)	69 (13.6)	25 (7.6)
Consumes alcohol	587 (66.9)	577 (56.0)	171 (62.9)	399 (78.5)	264 (80.5)
Consumes alcohol at least once a week	272 (31.1)	163 (15.9)	43 (15.8)	75 (17.5)	32 (9.8)
Consumes more than one liter a week	61 (10.3)	167 (27.1)	16 (9.2)	52 (24.8)	132 (50.2)

Table 3
Factors associated with self-reported poor health (fair/poor/very poor) among individuals from 5 Latin American countries: univariate and multivariate analysis (N = 3016)

	Univariate		Multivariate	
			OR (95% CI)	
	OR (95% CI)	p	N = 2854 LR = -1252.57	p
Geographical aspects				
Country				
Peru	1.95 (1.42–2.67)	< 0.001	1.81 (1.08–3.03)	0.024
Paraguay	2.98 (2.28–3.89)	< 0.001	1.73 (1.23–2.43)	0.002
Mexico	1.93 (1.38–2.70)	< 0.001	1.73 (1.16–2.59)	0.008
Brazil	2.48 (1.96–3.13)	< 0.001	3.00 (2.19–4.11)	< 0.001
Argentina	1.00		1.00	
Environmental factors				
Place of residence				
Urban	0.86 (0.67–1.12)	0.263	1.03 (0.70-1.51)	0.890
Place where most of the time is spent				
Indoors	0.76 (0.60–0.98)	0.035		
You are the household cook				
Yes	0.93 (0.79–1.11)	0.428		
Mold on the walls				
Yes	1.57 (1.29–1.92)	< 0.001		
Humidity on the walls				
Yes	1.91 (1.60–2.28)	< 0.001	1.68 (1.33–2.12)	< 0.001
Source of pollution near the house				
Yes	1.68 (1.42–1.99)	< 0.001	1.21 (0.99–1.49)	0.065
Source of pollution near the place of work				
Yes	1.15 (0.96–1.38)	0.142	1.15 (0.96–1.38)	0.142
Materials burned in the home				
Yes	0.88 (0.69–1.12)	0.296		
Paints, waxes, repellents, or incense in the house				
Yes	1.23 (1.04–1.46)	0.017	1.10 (0.90–1.36)	0.355
Bleach for house cleaning				
Yes	0.91 (0.76–1.08)	0.290		
Open car windows while driving				
Yes/sometimes	1.54 (1.27–1.88)	< 0.001	1.31 (1.03–1.65)	0.025
Sociodemographic factors				
Family income (SM)				
Up to 2 minimum wages	1.47 (1.24–1.75)	< 0.001	1.59 (1.26–2.01)	< 0.001
Sex				
Male	0.95 (0.79–1.14)	0.571		
Age group (years)				
60 or more	1.21 (0.67–2.20)	0.524		
Incomplete higher education				
Yes	1.49 (1.26–1.77)	< 0.001	1.54 (1.22–1.94)	< 0.001
Race/skin color				
Black/brown	1.43 (1.18-1.73)	< 0.001	1.27 (0.98–1.65)	0.070

OR: odds ratio, LR: likelihood ratio, CI: confidence interval.

Table 3 *(continuation)*
Factors associated with self-reported poor health (fair/poor/very poor) among individuals from 5 Latin American countries: univariate and multivariate analysis (N = 3016)

	Univariate		Multivariate	
			OR (95% CI)	
	OR (95% CI)	p	N = 2854 LR = -1252.57	p
Health-related factors				
Systemic arterial hypertension				
Yes	3.67 (2.90–4.65)	< 0.001	2.25 (1.64–3.09)	< 0.001
Chronic obstructive pulmonary disease/asthma				
Yes	2.37 (1.85–3.04)	< 0.001	1.74 (1.28–2.36)	< 0.001
Type I or type II diabetes mellitus				
Yes	7.71 (5.20–11.42)	< 0.001	3.74 (2.23–6.29)	< 0.001
Obesity				
Yes	2.95 (2.35–3.70)	< 0.001	2.43 (1.84–3.19)	< 0.001
Ocular comorbidities				
Yes	1.80 (1.52–2.14)	< 0.001	1.89 (1.55–2.30)	< 0.001
Lifestyle habits-related factors				
Smokes				
I smoke/have smoked	1.21 (1.00–1.45)	0.050	1.15 (0.91–1.46)	0.251
Consumes alcohol at least once a week				
Yes	0.68 (0.54–0.85)	0.001	0.86 (0.66–1.13)	0.276
Exercise outdoors				
Yes	1.99 (1.68–2.36)	< 0.001	1.60 (1.31–1.96)	< 0.001

OR: odds ratio, LR: likelihood ratio, CI: confidence interval.

including both protective and risk factors, such as being woman and having incomplete education.

Discussion

The present study was conducted in 5 Latin American countries (Argentina, Brazil, Mexico, Paraguay, and Peru), as they represent about 70% of Latin America,[17] with mostly similar sociodemographic factors and HDIs but different cultural conditions[18] (Table 2).

Although there is evidence of the impact of environmental pollution on respiratory health in Latin America,[23] we are not aware of any studies conducted in primary care settings, such as the present one, that clearly show an association between perceived poor health and the environmental factors studied.

Of the factors associated with poor health revealed by multivariate analysis in each of the participating countries, several risk factors were identified, but not in a generalized way (Table 4).

Our study showed a significant association between the perception of poor health quality and both indoor and outdoor pollution factors. Living near a source of pollution, driving a car windows open, and exercising outdoors were identified as outdoor risk factors. Similarly, the use of candles, paints, waxes, repellents, and incense indoors was significantly

Table 4
Multivariate analysis of factors associated with self-reported poor health conditions among individuals living in 5 Latin American countries (N = 3016)

	Argentina		Brazil		Mexico		Paraguay		Peru	
	N = 854 LR = -281.2		N = 1021 LR = -519.8		N = 267 LR = -113.6		N = 428 LR = -178.84		N = 324 LR = -115.6	
Variables	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Environmental factors										
House in urban area			0.55 (0.34–0.89)	0.014						
Place where most of the time is spent										
You are the household cook			1.37 (1.04–1.79)	0.024						
Mold on the walls	2.07 (1.29–3.33)	0.003								
Humidity on the walls	3.11 (2.09 –4.62)	< 0.001			2.14 (1.15–3.97)	0.016	1.68 (1.13–2.49)	0.011	1.95 (1.07–3.57)	0.031
Source of pollution near the house	1.58 (1.07–2.31)	0.020	1.79 (1.37–2.35)	0.001			1.85 (1.22–2.82)	0.004		
Source of pollution near the place of work							0.57 (0.39–0.84)	0.005		
Materials burned at home			1.62 (1.02–2.58)	0.041						
Paints, waxes, repellents, or incense in the house			1.50 (1.15–1.98)	0.003	2.10 (1.18–3.72)	0.011				
Open car windows while driving	2.07 (1.25–3.43)	0.005					3.13 (1.44–6.78)	0.004	4.01 (1.39–11.55)	0.01
Sociodemographic factors										
Family income of up to 2 minimum wages	1.92 (1.28–2.88)	0.002	1.78 (1.35–2.34)	< 0.001						
Female			0.60 (0.45–0.81)	0.001					1.97 (1.16–3.35)	0.013

OR: odds ratio, LR: likelihood ratio, CI: confidence interval.

Table 4 *(continuation)*

Multivariate analysis of factors associated with self-reported poor health conditions among individuals living in 5 Latin American countries (N = 3016)

	Argentina		Brazil		Mexico		Paraguay		Peru	
	N = 854 LR = -281.2		N = 1021 LR = -519.8		N = 267 LR = -113.6		N = 428 LR = -178.84		N = 324 LR = -115.6	
Variables	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Sociodemographic factors										
Over 60 years old							16.36 (7.00-38.2)	< 0.001	17.6 (5.02-61.76)	< 0.01
Incomplete higher education	0.25 (0.07-0.91)	0.001	1.53 (1.17-2.01)	0.002			1.68 (1.14-2.46)	0.008		
Black race	–	–	–	–	–	–	3.88 (1.3-11.47)	0.014	–	–
Health–related factors										
Systemic arterial hypertension	2.57 (1.49–4.42)	0.001	2.30 (1.45–3.65)	< 0.001			8.20 (5.2–12.91)	< 0.001	7.97 (2.01–31.62)	0.003
COPD/Asthma	3.30 (1.79–6.1)	0.001	1.80 (1.14–2.83)	0.011	2.21 (1.04–4.72)	0.040	2.42 (1.56–3.76)	< 0.001		
Type I or type II diabetes mellitus	4.25 (1.49–12.16)	0.007	2.79 (1.17–6.65)	0.020	4.04 (1.31–12.5)	0.015	15.14 (7.4–30.79)	< 0.001	9.24 (2.39–35.75)	0.001
Obesity	2.76 (1.72–4.43)	< 0.001	1.93 (1.19–3.13)	0.008	2.52 (1.32–4.84)	0.005	5.55 (3.51–8.77)	< 0.001	3.89 (1.70–8.93)	0.002
Ocular comorbidities	1.89 (1.19–3.00)	0.007	2.21 (1.59–3.07)	< 0.001	3.90 (1.87–8.16)	< 0.001	–	–	–	–
Factors related to lifestyle habits										
Current/past smoking	1.98 (1.33–2.96)	0.001	2.18 (1.64–2.90)	< 0.001	3.03 (1.62–5.68)	0.001			1.97 (1.18–3.29)	0.009
Exercising outdoors	2.07 (1.41–3.05)	< 0.001	1.32 (1.01–1.74)	0.042			4.64 (3.08–6.97)	< 0.001	2.18 (1.11–4.28)	0.023

OR: odds ratio, LR: likelihood ratio, CI: confidence interval.

associated with poor health quality. Our findings are similar to those of other researchers who have demonstrated the strong impact of environmental pollution on health quality.[24]

Low- and middle-income populations suffer disproportionately from the effects of transport pollution, in part because they use older and inefficient diesel vehicles, or because they live or work in densely populated, high-traffic areas near sources of pollution.[14]

A recent systematic review found moderate to high levels of evidence for an association between long-term exposure to traffic-related air pollution (TRAP) and adverse health outcomes, including all-cause mortality, circulatory disease, ischemic heart disease, lung cancer, and asthma. This suggests that exposure to TRAP continues to be a significant public health concern and deserves greater attention from the public and policymakers.[25]

Storing paints, waxes, and burning incense or candles at home were also considered risk factors. The generation of aerosol particles can result from various combustion activities, such as cooking, smoking, and burning candles and incense.[26] Burning incense and candles, typically indoors, produces ultrafine particles larger than those produced by smoking, frying meat, or cooking on an electric stove. These particles tend to deposit in the alveolar region.[27]

The presence of humidity and mold on walls, often associated with low socioeconomic status and poor household sanitation, are significant risk factors for chronic respiratory diseases such as rhinitis and asthma, which significantly affect quality of life.[28]

Within the spectrum of elements that increase the risk of poor health, we have also identified the incidence of NCDs such as hypertension, chronic obstructive pulmonary disease/asthma, type I and type II diabetes mellitus, obesity as well as adverse ocular conditions and tobacco use.[29,30] In addition, air pollution may be responsible for the generation of reactive oxygen species, which can disrupt the methylation and demethylation cycle in the nucleus, causing widespread and localized epigenetic modifications. These modifications can directly alter methylation of CpG sites or affect the activity of the enzymes involved. This process can lead to metabolic disorders characterized by conditions such as dyslipidemia and increased insulin resistance.[29,30]

The link between pollution and NCDs is real and complex, especially considering that indoor air pollution is responsible for 25% of all deaths from stroke, 15% of ischemic heart disease deaths, and 33% of chronic obstructive pulmonary disease cases.[31] A systematic review and meta-analysis of the association between air pollution and cardiovascular disease (CVD) concluded the strongest evidence was observed between higher short- and long-term exposure to air pollution and all-cause mortality and morbidity from CVD, stroke, blood pressure, and ischemic heart disease.[32]

A systematic review of the health effects of TRAP and diabetes in the adult population indicates an increased risk of disease with higher exposure to NO_2, associated with a higher prevalence of diabetes (RR = 1.09; 95% CI: 1.02–1.17 per 10 μg/m^3).[33]

Ocular comorbidities stood out from another risk factors. Exposure to particulate matter was associated with significant thickening of the epithelial layers of the cornea and conjunctiva. These effects, if prolonged, may cause irreversible changes in corneal refractive power and visual processes. When exposed to PM, corneal epithelial cells release pro-inflammatory cytokines: interleukin (IL)-6, IL-8, tumor necrosis factor-alpha, IL-1, and monocyte chemoattractant protein-1 (MCP-1). In addition, there is a reduction in cell viability and proliferation and altered production of mucin.[34,35]

The presence of diesel exhaust particles (DEP), tobacco smoke, and biomass burning has been associated with oxidative stress in corneal epithelial cells and cataracts, particularly in women.[36,37]

The strong association between obesity, chronic respiratory disease, cardiovascular disease, environmental pollution, and poor quality of life found in the present study is explained by a complex mechanism involving mechanical, metabolic, and epigenetic factors, the release of pro-inflammatory ILs and the respiratory and intestinal microbiota.[38,39]

Because of this complexity, the treatment and prevention of this current epidemic, with its significant implications for the future, is an enormous challenge.[38,39]

In the present study, smoking was associated with poor health perception. Cigarette smoking, which is increasingly prevalent in lower social classes, has a significant impact on chronic respiratory diseases (e.g., asthma and COPD), cardiovascular diseases, high morbidity and mortality, with economic consequences for the patient and a high-cost burden for health care systems.[40,41]

Our study has limitations. First, as a cross-sectional study, it does not allow causal interpretation; however, our study provides a snapshot of the environmental factors that influence the perception of health status among adults in 5 South American countries within a small-time window. Second, the data were obtained through a questionnaire, which is a simple and inexpensive method of identifying environmental risk factors to which patients are exposed.

The assessment of potential health risks posed by a specific pollutant does not, by its very nature, reflect the multiple environmental and social stressors faced by vulnerable communities, which may interact to cause adverse health effects.[42]

Conclusion

In this context, the objective of this study was to identify possible sociodemographic, socioeconomic, environmental and lifestyle factors associated with adverse health outcomes in adults from 5 Latin American countries. More equitable environmental policies, continued research on the effects of these exposures, and public education are essential to mitigate adverse health effects and promote a healthier and more equitable environment for all communities.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Incidence of vaccine-related anaphylaxis from Brazil's National Immunization Program

Incidência de anafilaxia relacionada às vacinas do Programa Nacional de Imunizações

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ABSTRACT

Vaccine-related anaphylaxis is a rare health event, and its incidence requires further investigation in Brazil. The objective of this study was to describe the incidence of anaphylaxis as an event supposedly attributed to vaccination and immunization (ESAVI) associated with the Brazilian National Immunization Program (PNI). A retrospective study was conducted with data extracted from the PNI ESAVI notification system between January 2021 and May 2023, with ethical approval and registration in Plataforma Brasil. Among 290,101 adverse events reported, 84 cases closed with the descriptor "anaphylaxis" or "anaphylactic shock" were identified, mainly concentrated in the South and Southeast regions. Children aged 0 to 9 years were predominantly affected, with a higher incidence in women and white individuals. In absolute numbers, anaphylaxis was associated mainly with the AstraZeneca/Fiocruz (viral vector), Pfizer Comirnaty (mRNA), and CoronaVac (inactivated virus) COVID-19 vaccines, while the highest relative incidence was with the anti-rabies vaccine (2.8 cases per million doses administered). The overall incidence was 0.14 per million vaccine doses. No deaths were reported. Underreporting of vaccine-related anaphylaxis is relevant and highlights the importance of maintaining robust systems for surveillance and management of allergic reactions within vaccination programs. This study corroborates global trends in the rarity of vaccine-related anaphylaxis. The low incidence of this event, regardless of recipient demographics, provides further evidence of the safety of COVID-19 vaccines and other vaccines included in the PNI.

Keywords: Vaccination, anaphylaxis, immunization programs, vaccination hesitancy, immediate hypersensitivity.

RESUMO

A incidência de anafilaxia pós-vacinal é um evento de saúde raro e carece de melhor detalhamento no Brasil. Neste estudo, objetivou-se descrever a incidência de anafilaxia como evento supostamente atribuído à vacinação e imunização (ESAVI) das vacinas do Programa Nacional de Imunizações (PNI). Foi realizado estudo retrospectivo com dados extraídos do sistema de notificação de ESAVI do PNI entre 01/2021 e 05/2023 com aceitação na Plataforma Brasil e aprovação ética. Foram identificados 84 casos encerrados com o descritor "anafilaxia" ou "choque anafilático" entre 290.101 eventos adversos notificados, concentrados principalmente nas regiões Sul e Sudeste. Crianças de 0 a 9 anos foram predominantemente afetadas, com maior incidência em mulheres e indivíduos brancos. A anafilaxia associou-se em números absolutos principalmente às vacinas COVID-19, destacando os fabricantes AstraZeneca/Fiocruz (vetor viral), Pfizer Comirnaty (RNAm) e CoronaVac (inativada), e a maior taxa de incidência foi com a vacina antirrábica (2,8 por milhão de doses aplicadas). A incidência global foi de 0,14/milhão de doses aplicadas. Entre os desfechos não foi relatado óbito. A subnotificação de casos é relevante e sublinha a importância de manter sistemas robustos de vigilância e manejo de reações alérgicas em programas de vacinação. Este estudo segue tendências mundiais da raridade da anafilaxia relacionada às vacinas. Os dados reforçam a segurança das vacinas COVID-19 e demais vacinas existentes no PNI, independente da demografia analisada.

Descritores: Vacinação, anafilaxia, programa de imunização, hesitação vacinal, hipersensibilidade imediata.

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Introduction

Anaphylaxis is a serious hypersensitivity reaction that can be fatal if not treated appropriately. This is part of the definition proposed in 2020 by the World Allergy Organization, which characterizes anaphylaxis as a sudden, severe event that can involve the upper and lower airways and/or cardiocirculatory system, occurring with or without skin lesions and with or without circulatory shock.[1]

Depending on the definition, method, and geographic area, the estimated lifetime prevalence of anaphylaxis is 0.3-5.1%, with a 26.5-54% chance of recurrence over a follow-up period of 1.5-25 years.[2] The most common causes are medications, foods, and poison from insects of the *Hymenoptera* order.[3]

Vaccine-related anaphylaxis is a rare event, with an incidence of 1 in 100,000-1,000,000 administered doses.[4] McNeil et al. found an incidence of 1.31 per million (95% CI 0.90-1.84), i.e., only 33 cases of anaphylaxis occurred in 25 million doses, with no age group being predominant. The highest incident rates were for the trivalent influenza vaccine (1.35; 95% CI, 0.65-2.47), followed by monovalent influenza (1.83; 95% CI, 0.22-6.63), and there was an 85% prevalence of allergic comorbidities in these patients.[5] Regarding COVID-19 vaccines, a recent systematic review found a combined incidence rate of 5.58 per million doses (95% CI, 3.04-8.12) for the Pfizer-BioNTech mRNA vaccine and the Moderna vaccine and 9.31 per million doses for the Pfizer-BioNTech vaccine alone.[6]

In allergic reactions (with a type I hypersensitivity reaction mechanism), other vaccine components may be involved in addition to the antigen, such as suspension medium, which could may contain remnants of vaccine production culture media (eg, eggs), adjuvants to enhance antibody production (eg, aluminum hydroxide), stabilizers (eg, gelatin, sugars, and amino acids), preservatives (eg, 2-phenoxyethanol and thimerosal), antibiotics, yeast, and latex.[5,7,8] This also includes substances that increase vaccine solubility, particularly in COVID-19 vaccines. Both the Pfizer-BioNTech and Moderna vaccines contain polyethylene glycol (PEG), a substance previously implicated in immediate IgE-mediated reactions.[9] The AstraZeneca/Fiocruz vaccine contains polysorbate 80, a substance used in many medications and biological therapies, which can sensitize the patient, resulting in subsequent post-vaccination reactions.[8]

Because post-vaccination health events are not always due to the vaccine itself and a causal relationship cannot always be determined at the time of notification, they have been called "events supposedly attributable to vaccination or immunization" (ESAVI) by the Pan American Health Organization. ESAVI may be related to variables, such as vaccine batch quality, application scheduling error, other health conditions, or to the vaccine itself, which could include its components, the application device, or the personal protective equipment of those who administer the vaccine.[10] Establishing causality requires a systematic investigation of individual and populational evidence surrounding the event based on a structured methodology[11] following World Health Organization criteria.[12]

If an immediate hypersensitivity reaction is confirmed, subsequent procedure can then be determined, which could include contraindication for subsequent doses, vaccination under supervision, changing to a formulation without the implicated component, dose fractionation, or vaccination without additional precautions.[13] Increased knowledge of allergens and vaccine reactions and appropriate investigation can also affect vaccine hesitancy[14], a complex phenomenon[15] that World Health Organization has classified as one of the top 10 threats to global health since 2019.[16]

The Brazilian National Immunization Program, which was founded 5 decades ago, was designed to reduce deaths from preventable diseases. Brazil has been an innovator in investigating post-vaccination adverse events[17], including surveying and cataloging anaphylactic reactions, and providing safety data on routinely used vaccines to health professionals and the population. Pursuant to these goals, we investigated the incidence of anaphylaxis as an adverse event of vaccines used in the National Immunization Program and demographically characterized anaphylaxis cases, describing the comorbidities and reported symptoms, classifying cases according to Brighton criteria, describing the causality of anaphylactic events, and reporting the outcomes and conduct upon receiving the final notifications.

Methods

This was an observational, retrospective, descriptive study of national ESAVI notifications registered on the Unified Health System's electronic

notification platform (*e-SUS Notifica*). Anonymized data were obtained from all ESAVI notifications made between January 2021 and May 2023 by the Department of Immunization and Vaccine-Preventable Diseases. To complement the analyses, other data were also obtained from the Unified Health System[18] regarding the total number of doses administered by each immunizer during the same period. For COVID-19 vaccines, the number of administered doses were also made publicly available on the *Vacinômetro* (Vaccinometer) platform, developed by the Secretariat of Information and Digital Health's Department of Monitoring and Evaluation.[19]

The sample consisted of 290,101 ESAVI notifications, which were searched using the descriptors "anaphylaxis" and "anaphylactic shock" in the "post-investigation diagnosis" and "investigation closure" column. Relevant notifications were included in the analysis. It should be noted that all cases of anaphylaxis were closed with an ICD-10 code of unspecified anaphylactic shock (T78.2) or unspecified allergy (T78.4: in these, the term "anaphylaxis" was found in the investigation tab's reaction field). ESAVI notifications whose investigation closure column did not include the aforementioned descriptors were excluded. The National Immunization Program uses the criteria of Brighton et al.[20] to determine whether a notification describes a case of anaphylaxis.

Based on the results, we performed a demographic analysis of the population, including state, age group, sex, race, comorbidities, symptoms, the incidence of confirmed cases of anaphylaxis and/or anaphylactic shock (both overall and for each immunization agent), and the attributed causality, including reclassification according to the Brighton criteria.

It should be noted that, in the state of São Paulo, data on COVID-19 vaccinations (including ESAVI reports and the total number of doses) were recorded in its own information system, separate from the federal system. Thus, any other COVID-19 data from that state found in parallel systems (such as the *Vacinômetro* platform) were also removed from the analysis.

This study's ethics committee approval is registered on Plataforma Brasil (CAPPesq/SGP decision 6.083.162; CAAE 69358023.3.0000.0068), including exemption from informed consent.

Results

Of the 290,101 notifications during the study period, 84 were confirmed as anaphylaxis or anaphylactic shock, of which 2 duplicates and 12 notifications with inconsistent data were excluded. The majority of the notifications (56 [66%]) were from the southern and southeastern regions and the Federal District, as shown in Figure 1. Not counting São Paulo (due to the aforementioned data system discrepancy), the state with the most cases was Rio de Janeiro (19%).

The predominant age group for anaphylactic events was 0-9 years of age (20 [24%]), especially 0-5 years (15 [17.8%]), followed by 40-49 years (16 [19%]), as shown in Figure 2. Most events (56 [67%]) events occurred in females. Regarding self-reported race, the cases were mainly White (41 [49%]) or of mixed race (26 [31%]), as shown in Figure 3.

The most frequently reported comorbidity was allergy (9), including asthma (2 cases), allergy to analgesic agents (2 cases), allergy to drugs, medications, or biological substances (1 case), and unspecified allergy (5 cases).

Of the 84 notifications confirmed as anaphylaxis, 69 (82%) occurred after isolated vaccine applications and 15 (18%) after combined immunization. Of the cases due to an isolated vaccine, 54 (65%) were COVID-19 vaccines (Figure 2), with the highest absolute number for Oxford-AstraZeneca-Fiocruz (21 [25%]), followed by Pfizer-BioNTech (15 [18%]), (14 [17%]) and Pfizer-BioNTech pediatric (4 [5%]). Three cases occurred due to arachnid (1 [1%]) and scorpion (2 [2%]) antivenom (Figure 4). Of the anaphylaxis cases associated with isolated vaccines, the majority occurred after the first/only dose (52 [75%]), followed by the second (11 [16%]), and third dose/booster (6 [9%]).

The overall incidence of post-vaccination anaphylactic events was 0.14 per million doses. Among isolated vaccines, the rabies vaccine had the highest incidence rate: 2.80 per million (Table 1), followed by the 23-valent pneumococcal polysaccharide vaccine (1.53 per million), and the Pfizer–BioNTech pediatric COVID-19 vaccine (0.31 per million). Among adult COVID-19 vaccines, the Oxford-AstraZeneca-Fiocruz and CoronaVac (Sinovac-Butantan) vaccines had the same incidence (0.18 per million), followed by Pfizer-BioNTech (0.10 per million) and Janssen (0.05 per million). The overall incidence rate for all COVID-19 vaccines was 0.14 per million (Table 1).

A total of 65 different symptoms were reported among the 84 event notifications. The most frequent

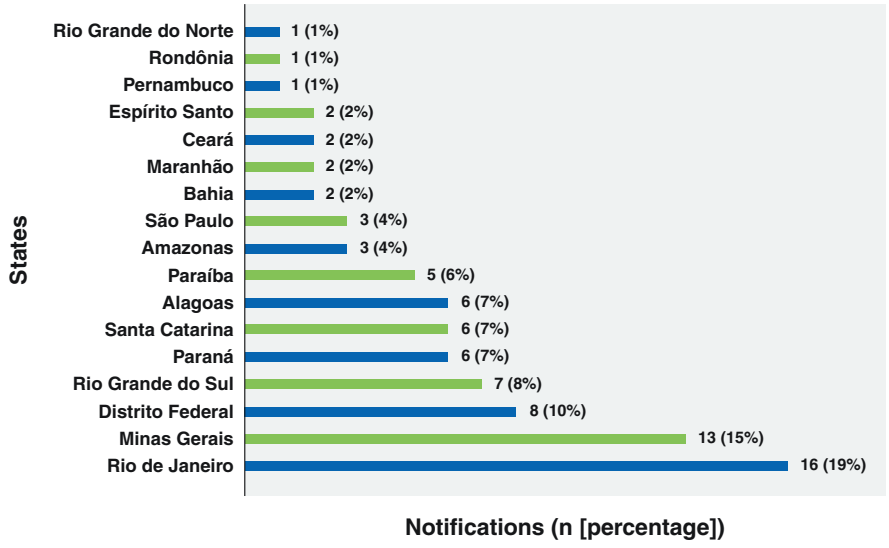

Figure 1
Distribution of anaphylaxis cases reported to the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

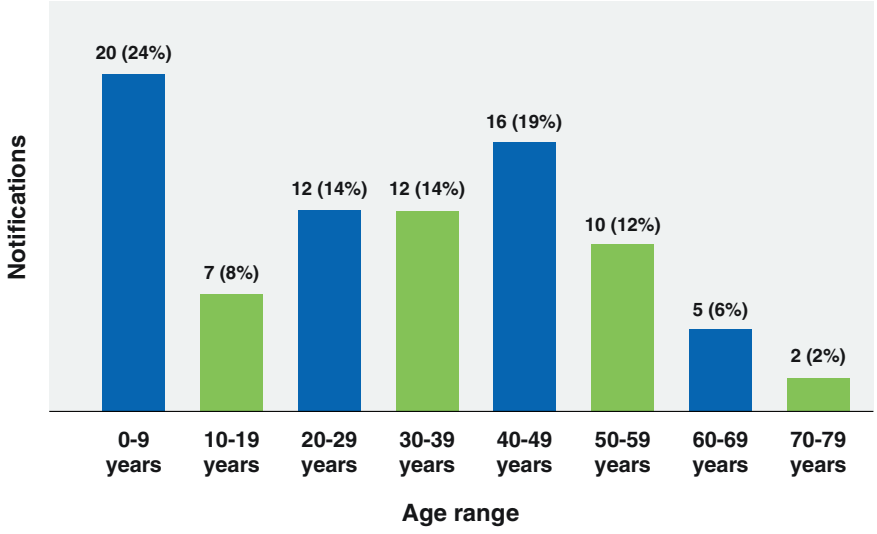

Figure 2
Age distribution of anaphylaxis cases reported to the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

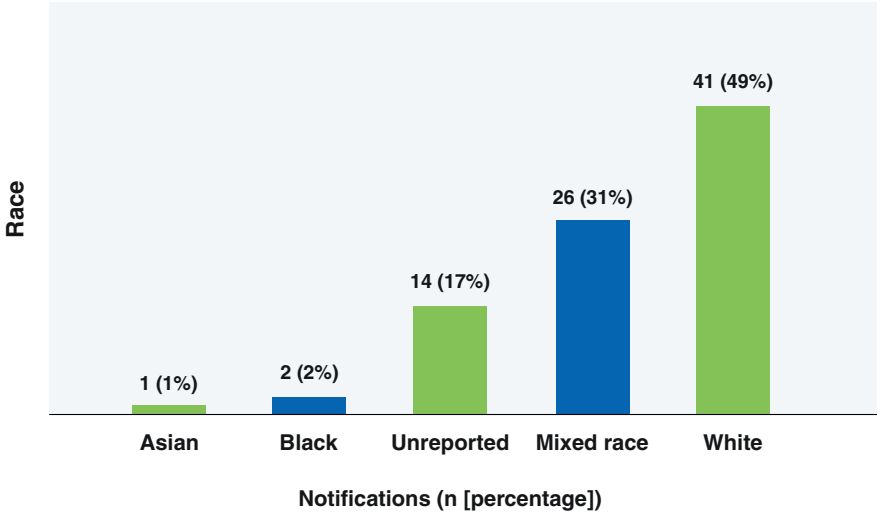

Figure 3
Distribution by race of anaphylaxis cases reported in the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

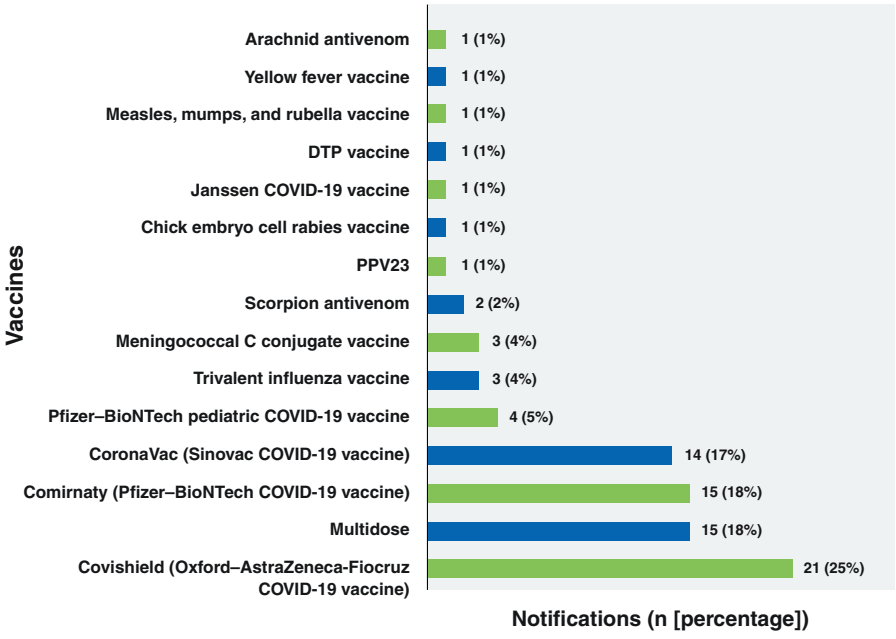

Figure 4
Percentage of confirmed anaphylaxis cases for each Brazilian National Immunization Program vaccine between January 2021 and May 2023, excluding cases of multidose anaphylaxis (n = 84)

DTP= diphtheria, pertussis, and tetanus; PPV23 = 23-valent pneumococcal polysaccharide vaccine.

Table 1
Incidence rate (IR) of anaphylaxis per million doses for Brazilian National Immunization Program vaccines, except for COVID-19 vaccines in the state of São Paulo and cases due to antivenom or multidose application (in descending order by IR)

Vaccine	Doses	Cases	IR per million
Rabies	357,271	1	2.80
PPV23	654,479	1	1.53
Comirnaty (Pfizer–BioNTech) COVID-19, pediatric	13,102,289	4	0.31
Meningococcal C conjugate	14,826,616	3	0.20
Oxford-AstraZeneca-Fiocruz	117,597,423	21	0.18
CoronaVac (Sinovac-Butantan)	76,235,510	14	0.18
DTP vaccine	10,157,454	1	0.10
Comirnaty (Pfizer–BioNTech) COVID-19	153,684,896	15	0.10
Measles, mumps, and rubella	16,845,804	1	0.06
Yellow fever	16,833,464	1	0.06
Janssen COVID-19	22,049,722	1	0.05
Trivalent influenza vaccine	135,344,321	3	0.02

DTP = diphtheria, pertussis, and tetanus; PPV23 = 23-valent pneumococcal polysaccharide.

were anaphylaxis (23), dry cough (13), dyspnea (12), anaphylactic shock (10), glottis edema (8), allergic reaction (7), pruritus (7), urticaria (6), edema (6), facial edema (6) and headache (5).

Based on the described symptoms, the event notifications were classified according to the Brighton criteria. The majority of cases (41 [49%,]) were certainty level 1, followed by level 4 (32 [38%]), level 5 (5 [6%]), level 3 (4 [5%]), and level 2 (2 [2%]).

Regarding the location and type of care offered to patients during the event, the facilities and complexity varied. Many patients underwent observation at a basic health unit for ≤ 24 hours (31 [37%]), followed by outpatient care at a clinic or doctor's office (14 [17%]), hospitalization for > 24 hours (13 [15%]), and admission to an intensive care unit (2 [2%]). This information was not reported in 24 (29%) cases.

The outcome was reported in 65 (77%) of the event notifications, including 81% reported as cured without sequelae and 19% still in follow-up at the time of study completion. No deaths were reported among the cases. The decisions regarding future vaccination at case closure are shown in Figure 5.

Discussion

As far as we know, this was the first national survey on anaphylaxis incidence based on Brazilian National Immunization Program data. The low number of ESAVI notifications during the study period is relevant, since it could indicate underreporting. The study data were from a critical phase of the COVID-19 pandemic, during which treatment seeking would have been somewhat limited. Due to the focus on COVID-19 vaccines during the pandemic, other vaccination coverage was reduced. Health care professionals may also have failed to recognize the signs and symptoms of anaphylaxis, resulting in a lower number of diagnoses

and notifications. Training health professionals to recognize anaphylaxis in a timely manner will ensure greater notification, adequate treatment, and favorable outcomes.

The 84 cases of post-vaccination anaphylaxis were mainly concentrated in the southern and southeastern regions and the Federal District, especially the state of Rio de Janeiro, where 19% occurred. However, since these are absolute numbers, this could merely be indicative of the greater population in these regions. There could also be regional variation in anaphylaxis awareness in different health care networks, in addition to heterogeneous notification routines in different states and municipalities.

The most affected age group was children 0-9 years of age, especially the 0-5 year sub-group, although occurrences were very rare. At this age, patients are more frequently exposed to vaccines and their immune system is still immature. This group also has a higher prevalence of allergies to vaccine components and a higher incidence of infections, which can influence reactions.[21] Furthermore, young children are closely and consistently observed by a caregiver, which increases the chance of noticing an adverse reaction. The rarity of anaphylaxis in this age group is another endorsement for the safety of National Immunization Program vaccines.

In line with the findings of a previous cohort, women and girls were predominantly affected[5], which also agrees with other studies that have confirmed sexual dimorphism in antigenic response and adverse reactions to certain vaccines.[22,23] However, the number of doses applied to each sex and whether this would affect the incidence rate is unknown.

There was a higher prevalence of cases among Whites, followed by individuals of mixed race, confirming previously documented trends.[5,24] This demographic profile could indicate either a greater tendency to report adverse events or some as yet unknown biological susceptibility.

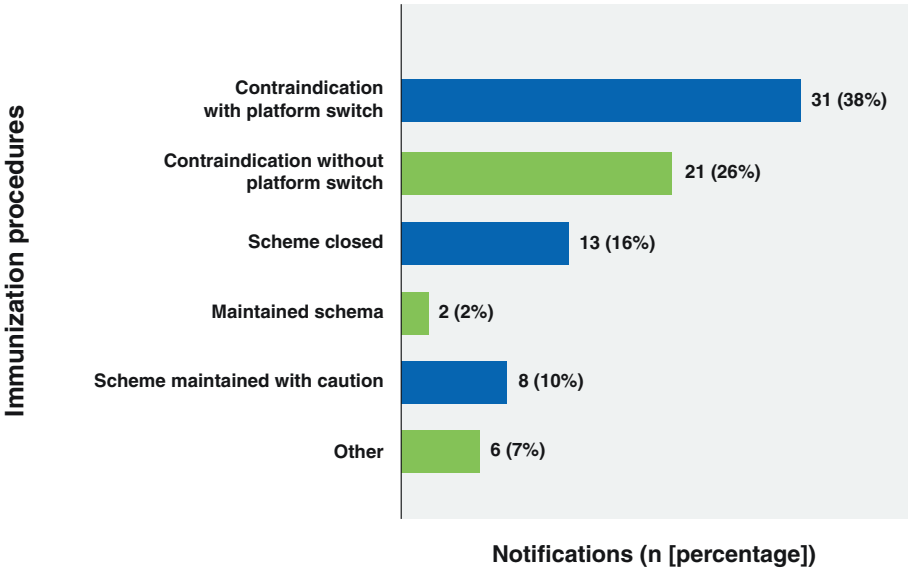

Figure 5
Immunization conduct upon closing anaphylaxis cases reported to the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

Regarding comorbidities, 25% of the event notifications mentioned pre-existing conditions, with allergies being the most common (10%). Atopy has been reported as a factor in individuals with an immunoglobulin E-mediated systemic reaction to vaccine components such as diphtheria and tetanus toxin, although the association was not statistically significant.[25] An ongoing clinical trial[26] is evaluating vaccine reactions among atopic and non-atopic populations, which may shed more light on this risk factor, especially regarding COVID-19 vaccines. In any case, our results reinforce the importance of carefully evaluating atopic patients prior to vaccination. This is especially true for asthmatic patients: due to the association between poor asthma control and severe anaphylactic reaction, this group has shown worse outcomes in all age groups.[27]

Post-vaccination anaphylaxis is a very rare adverse reaction. The incidence rate in our sample was 0.14 per million doses, which is lower than that in a pre-pandemic study (1.31 per million). In this study, the inactivated influenza vaccine had the highest number of events, (although similar to other vaccines) and the rabies vaccine had the highest incidence rate (86 per million)[5], as it did in our sample (2.8 per million).

Rabies vaccines may contain gelatin[4], which is one of the main anaphylaxis-related antigens, having a proven immunoglobulin E-mediated type I allergic response. Regarding alpha-gal syndrome, it is still controversial whether the amount of gelatin contained in vaccines could elicit a reaction.[28,29] The anti-rabies vaccine involved in the reported event was produced by the Butantan Institute and is preferred by the National Immunization Program. This innovative vaccine is Vero cell-derived and free from any animal products, having an excellent safety profile.[17]

The preponderance of anaphylaxis cases associated with COVID-19 vaccines should be interpreted with caution. These were the most frequently applied vaccines during the study period and, despite the highest absolute number of cases, the incidence rate was low (0.045-0.31 [mean 0.14] cases per million). Our incidence rate for COVID-19 vaccines was significantly lower than that reported by the U.S. Centers for Disease Control data (5 per million)[30], which might be explained by underreporting or a lack of investigation into reported cases, which were thus never confirmed as anaphylaxis. This highlights the need to strengthen the surveillance system and improve the notification and training systems for health professionals.

Regarding individual COVID-19 vaccines, the Oxford-AstraZeneca-Fiocruz vaccine was the most commonly associated with reactions (25%), followed by Pfizer-BioNTech (18%), and CoronaVac (17%). These vaccines include components such as polysorbate 80 (Oxford-AstraZeneca-Fiocruz) and PEG 2000 (Pfizer-BioNTech), which many reports have identified as the cause of allergic reactions, especially PEG 2000. However, it was later found that the risk of reaction to this vaccine, even among patients who previously reacted to PEG, is extremely low. Thus, due to the strong level of evidence according to Grading of Recommendations, Assessment, Development and Evaluation criteria, vaccination is indicated.[31] Other reactions to PEG with mechanisms involving mast cell activation have been described, such as complement activation-related pseudoallergy, in which IgG and IgM antibodies against PEG activate the complement and lead to mast cell degranulation.[28] CoronaVac uses aluminum hydroxide as an excipient, which has been associated with late local reactions but is not usually involved in immediate reactions.[13] There has also been considerable discussion of non-immunological reactions to vaccines, which can mimic anaphylactic reactions, such as vasovagal response, and immunization stress-related response, which can involve both physical and emotional symptoms and typically has a benign outcome.[4,17,28] Anamnesis and a review of the medical records are essential in the investigation and can guide allergists in differentiating the response type. Skin tests with the vaccine and/or component have low sensitivity and high specificity for stratifying individuals who may have a serious reaction in the second dose. There is no formal recommendation regarding these tests, and they can be performed at the specialist's discretion.[32] The second dose of COVID-19 vaccine is generally well tolerated, even without switching platforms; no clear benefits have been determined from taking gradual doses or premedication.[31] The decision should depend on patient choice in a shared decision model.[32]

In cases of anaphylaxis after combined vaccination, skin tests and component diagnosis may be the only way for patients to continue following their vaccination schedule. The allergist's role is crucial to avoid unnecessary vaccine restriction, thus leaving patients susceptible to vaccine-preventable diseases.[13] However, further evidence is needed to guide such decisions.

The majority (75%) of ESAVI in this study occurred after the initial dose. Other authors have also found this to be the case with COVID-19 vaccines, hypothesizing possible non-allergic causes. When the second dose was administered without changing the platform, a lower frequency of anaphylaxis was observed, and the symptoms that did occur were tolerable.[33]

It should be noted that the majority of cases were classified as Brighton level 1, indicating a high probability of true anaphylaxis, which indicates the importance of surveillance and preparation for serious allergic reactions in vaccination centers. However, our reclassifications were based solely on data from the notification form. For example, in 2 cases classified as Brighton level 5 (i.e., not anaphylaxis) and another 32 cases classified as level 4 (i.e., indeterminate), the notification forms were investigated by the surveillance service according to National Immunization Program protocols, and additional information (from medical records, for example) led to confirmation of anaphylaxis. Such data discrepancies highlight the importance of correct notification procedures: health professionals must add as much clinical information as possible at the time of notification to strengthen subsequent epidemiological studies based on notification data. In a study of COVID-19 vaccines, Basili et al. reported no significant difference in certainty between Brighton and World Allergy Organization classifications.[34] However, due to a lack of clinical data in the notification forms, we did not undertake such a comparison.

Regarding the World Health Organization's Causality Assessment Protocol for adverse events following immunization, reports in the A1 category were the most contraindicated for future doses of the vaccine. No deaths from anaphylaxis occurred in our sample, and the majority of cases were resolved without sequelae, which aligns with the literature since, despite being a potentially serious event, fatalities are extremely rare.[5,21,35]

Including ICD-11 codes that address various differentials could improve future epidemiological research on vaccine-related anaphylaxis, given that the current classification systems limit the correct description of events, due to which some cases may not be investigated.[36]

As study limitations, in addition to possible underreporting, we highlight the non-inclusion of ESAVI data from the state of São Paulo, since it is the most populous state in the country, thus reducing the absolute number of reported cases.

Conclusions

The incidence rate of anaphylaxis associated with National Immunization Program vaccines was 0.14 cases per million doses during the study period, which reinforces the rare nature of such events and highlights the safety of the program's vaccines. The rabies vaccine had highest incidence rate, whereas COVID-19 vaccines had the highest absolute number of cases. Underreporting was probably relevant and may have impacted the absolute number of events.

Demographic characterization of confirmed anaphylaxis cases revealed a higher incidence among children, women, and Whites. The main type of comorbidity was allergy, which underscores the importance of consulting an allergist when making immunization decisions.

Indication/contraindication for subsequent doses or the decision to switch platforms must be made after rigorous analysis of the facts and possible reaction mechanisms. Our data corroborate the need for robust surveillance and management of allergic reactions in vaccination programs.

Acknowledgements

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Analysis of the clinical and epidemiological profile of hospitalizations due to asthma in the period 2020-2021 in a hospital in southern Santa Catarina, Brazil

Análise do perfil clínico e epidemiológico das internações por asma no período de 2020 a 2021 em um hospital do sul de Santa Catarina

Alice Assis Pacheco[1], Kelser de Souza Kock[1]

ABSTRACT

Introduction: Bronchial asthma is a chronic inflammatory disease with a high worldwide frequency, especially in Brazil, where more than 100,000 asthma-related hospitalizations occur annually according to DATASUS data. Identifying patients upon hospital admission who may require an ICU bed or mechanical ventilation due to an asthma attack is a challenge for healthcare professionals. It is important to analyze clinical variables that may predispose to deterioration and evaluate more vulnerable patients to ensure that effective interventions are instituted promptly. **Objective:** To analyze the clinical and epidemiological profile of patients admitted due to asthma in a hospital in southern Brazil and evaluate predictors of longer hospital stay. **Methods:** Observational epidemiological study with a cross-sectional design. The source of information were secondary data obtained from medical records of patients admitted to a hospital in southern Brazil. **Results:** Overall, 261 medical records were analyzed. Patients were predominantly under the age of 40, representing 57% of hospitalizations. In terms of gender and ethnicity, most patients were female (63%) and white (87%). Three patients (1.1%) required ICU admission, approximately 6.9% had prolonged hospitalizations (>3 days), and 2 (0.8%) died. Low oxygen saturation and elevated heart rate correlated significantly with prolonged hospitalization. **Conclusion:** Vital signs at the time of hospital admission and the epidemiological profile of patients should be analyzed, so that the most prevalent populations and predictors of severe outcomes can be monitored, and appropriate and effective measures can be taken.

Keywords: Asthma, hospitalization, vital signs, prognosis.

RESUMO

Introdução: A asma brônquica é uma doença crônica inflamatória de alta frequência mundialmente, e em especial no Brasil, onde ocorreram mais de 100.000 internações por ano, segundo dados do DATASUS. Identificar pacientes em admissão hospitalar que poderão necessitar de leito em UTI ou uso de ventilação mecânica por conta de crises asmáticas é um desafio ao profissional de saúde, portanto, faz-se importante analisar variáveis clínicas que possam predispor agravos e avaliar pacientes mais vulneráveis, para que as condutas realizadas sejam efetivas e rápidas. **Objetivo:** Analisar o perfil clínico e epidemiológico de pacientes internados em um hospital do sul do Brasil e avaliar os preditores relacionados ao maior tempo de internação. **Métodos:** Estudo epidemiológico observacional, do tipo transversal, que utilizou como fonte de informação dados secundários, os quais foram obtidos através de prontuários de pacientes internados em um hospital do sul do Brasil. **Resultados:** Foram analisados 261 prontuários. Verificou-se que a população menor de 40 anos de idade teve maior prevalência, representando 57% das internações. Além disso, em relação a gênero e etnia, mulheres e caucasianos foram as populações com maiores taxas de hospitalização, sendo 63% e 87% das admissões hospitalares, respectivamente. A necessidade de internação em UTI foi encontrada em 1,1% dos casos (3 pacientes), cerca de 6,9% tiveram internações prolongadas (maiores de 3 dias), e 0,8% vieram à óbito (2 pacientes). Identificou-se que a baixa saturação de oxigênio e a alta frequência cardíaca tiveram relação significativa com internação prolongada. **Conclusão:** É importante analisar sinais vitais no momento das admissões hospitalares e o perfil epidemiológico dos pacientes para que as populações mais prevalentes e os fatores preditivos de desfechos mais graves possam ser acompanhados e a conduta a ser tomada seja adequada e efetiva.

Descritores: Asma, hospital dia, sinais vitais, prognóstico.

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Introduction

Asthma is a condition that results from the interaction of various external factors, such as exposure to allergens, and intrinsic factors related to the individual genetics of each patient. Asthma is a chronic, inflammatory disease characterized by the presence of hyperreactivity of the upper airways. Clinically, asthma manifests as episodes of dyspnea, cough, wheezing, and recurrent chest tightness, which tend to worsen during the night and early morning. The need for hospitalization indicates decompensation of asthma or an absent or inadequate response to treatment, increasing the patient's susceptibility to associated complications.[1,2]

According to DATASUS, the database of the Brazilian Unified Health System, in 2011 there were more than 100,000 hospitalizations due to asthma in Brazil.[3] In southern Brazil, 20% of school-age children have asthma, and most of them severe, uncontrolled cases affecting their school performance and leading to hospitalizations.[4] Asthma is therefore a problem that negatively influences the daily lives of those affected, as it is a physically, emotionally and socially limiting condition. Some studies suggest that the severity of asthma can be considered inversely proportional to quality of life; in other words, the more severe the condition and the higher the disease activity, the greater the limitation and the poorer the patient's quality of life.[5]

According to the Brazilian Society of Pulmonology and Phthisiology (SBPT), asthma is a significant cause of hospitalization in the Brazilian Unified Health System (SUS), ranking among the third and fourth leading causes. Although asthma mortality has decreased in the last decade, asthma management in Brazil is still limited and a considerable proportion of the population remains untreated.[6] However, hospitalizations for exacerbation of asthma attacks are associated with a significant number of deaths.[6]

In Brazil, between 1996 and 2015, there were more than 5000 deaths due to asthma, the majority of which occurred in children under the age of 5. Most of these deaths occurred in the hospital setting (about 80% of cases).[7] Because of the recurrent nature of childhood asthma, it has a significant impact on quality of life.[8]

Health care workers are challenged to identify patients who will be admitted to the intensive care unit (ICU) or will require mechanical ventilation because of asthma attacks. Identifying the clinical profiles most likely to require these interventions is therefore important. By evaluating factors that predispose to the exacerbation of asthma, elevated heart and respiratory rates as well as low oxygen (O_2) saturation were found to be significantly associated with admission to the pediatric ICU (PICU) in asthmatic children.[9,10]

At-risk patients can be effectively and quickly identified by monitoring vital signs at the time of admission to an emergency department.[9,10] The Modified Pulmonary Index Score (MPIS) has been found to be useful for prognostic evaluation during patient triage and, when elevated, is associated with prolonged PICU stay.[9-11]

Therefore, the aim of the present study was to analyze the clinical and epidemiological profile of patients hospitalized in a hospital in southern Brazil and to evaluate the predictors associated with prolonged hospitalization.

Methods

This is an observational, epidemiological, cross-sectional, single-center study that used secondary data as a source of information. This study was conducted by reviewing electronic medical records (Philips Tasy® system) provided by Hospital Nossa Senhora da Conceição (HNSC), a hospital located in the southern state of Santa Catarina, Brazil. We analyzed male and female patients of all ages who were hospitalized between January 2020 and December 2021 for asthma classified under ICD J45 as the cause of admission. We included patients hospitalized at HNSC between January 2020 and December 2021 whose electronic medical records were available at HNSC, and whose cause of hospitalization was due to asthma exacerbation. Dyspnea was the admission criterion considered by the on-call hospital staff. Patients whose records were so incomplete that data registration was impossible, and patients who were hospitalized during the data collection period were excluded from the study.

The present study was conducted by means of a research form. The form was designed to include sociodemographic variables, variables related to hospitalization, and vital signs of the participating patients. Clinical data were collected at the time of patient admission to the hospital. The variables included age (described numerically and categorized as 0–9 years, 10–19 years, 20–39 years, 40–9 years, and ≥ 60 years), ethnicity, sex, associated respiratory

comorbidities, COVID-19 status, smoking status, need for ICU admission, need for mechanical ventilation (MV) or O_2 therapy during hospitalization, length of stay, mortality, and vital signs at patient admission (i.e., systolic blood pressure [SBP], diastolic blood pressure [DBP], peripheral O_2 saturation [SpO_2], heart rate [HR], and respiratory rate [RR]).

Data collection began only after approval by the research ethics committee of Universidade do Sul de Santa Catarina (UNISUL). This study was approved under opinion no. 5.542.011, signed on July 24, 2022. No informed consent was required for this study.

Data were organized by using Microsoft Excel and then exported to SPSS version 20.0 for analysis. Quantitative variables were described by using measures of central tendency and data dispersion, while qualitative variables were described by using absolute and percentage frequencies. Differences in proportions were tested by using the chi-square test. Bivariate and multivariate logistic regression were used for odds ratios (ORs). In multivariate analysis, variables with $P < 0.2$ were included by using the backward method. The level of significance was set at 5% ($P < 0.05$).

Results

In this study, a total of 261 patients hospitalized with asthma at HNSC from January 2020 to December 2021 were evaluated. Mean (SD) age was 39.9 (16.8) years. The age range of the patients was evaluated in 3 categories: <40 years, 40-60 years, and >60 years.

Table 1 shows the relationship between age group and the need for hospitalization, as more than half (57.1%) of the cases involved patients under 40 years of age. Table 1 also shows women were more affected than men, accounting for 62.8% of hospitalizations. In addition, Table 1 shows the white population was much more likely to be hospitalized than other populations, representing 87% of the cases of hospitalization due to worsening asthma attacks.

Preexisting respiratory comorbidities were found to be present in approximately 15% of cases, with chronic obstructive pulmonary disease (COPD) being the most common, affecting 4.6% of patients. Overlapping respiratory comorbidities were rare, with only 1.2% of hospitalized patients having more than one concurrent respiratory condition. In addition, although most records lacked information on whether the patient was a current or former smoker (74.7%), it was still possible to associate smoking with hospitalizations. Of the 66 patients whose records contained information on smoking, 5.8% of them reported being former or current smokers. This was the only variable with missing data and was therefore excluded from further statistical analyses.

Of the 261 patients evaluated, 6.2% of them required O_2 therapy, and the use of nasal cannula was the most common method. Regarding the clinical outcome of hospitalizations, most patients were discharged in stable condition. However, in this study, 1.1% of cases (3 patients) required ICU admission, approximately 6.9% had prolonged hospitalization (longer than 3 days), and 0.8% (2 patients aged ≥ 60 years) died.

Figure 1 shows the distribution of vital signs at the time of hospital admission. Figure 1 shows the average SBP was 132 mm Hg and the DBP was 80 mm Hg, thereby indicating a degree of hypertension at the time of admission. Regarding RR, approximately 97% of patients were within normal parameters (RR = 20 breaths per minute). In addition, Figure 1 shows O_2 saturation levels also tended to be within normal parameters, with 96% of patients having saturation levels between 98% and 100%. HR values were more variable, with some patients having normal HRs between 60 and 100 bpm, while others had HRs of 100 bpm or higher, thereby indicating tachycardia at the time of admission.

When comparing patients who were hospitalized for 3 or more days, 93.1% of the 261 patients were discharged in less than 3 days, while longer stays (3 days or more) accounted for 6.9%.

Analysis of Table 2 shows there was no statistically significant difference between sex and length of hospital stay, indicating men and women are equally likely to be hospitalized for longer periods.

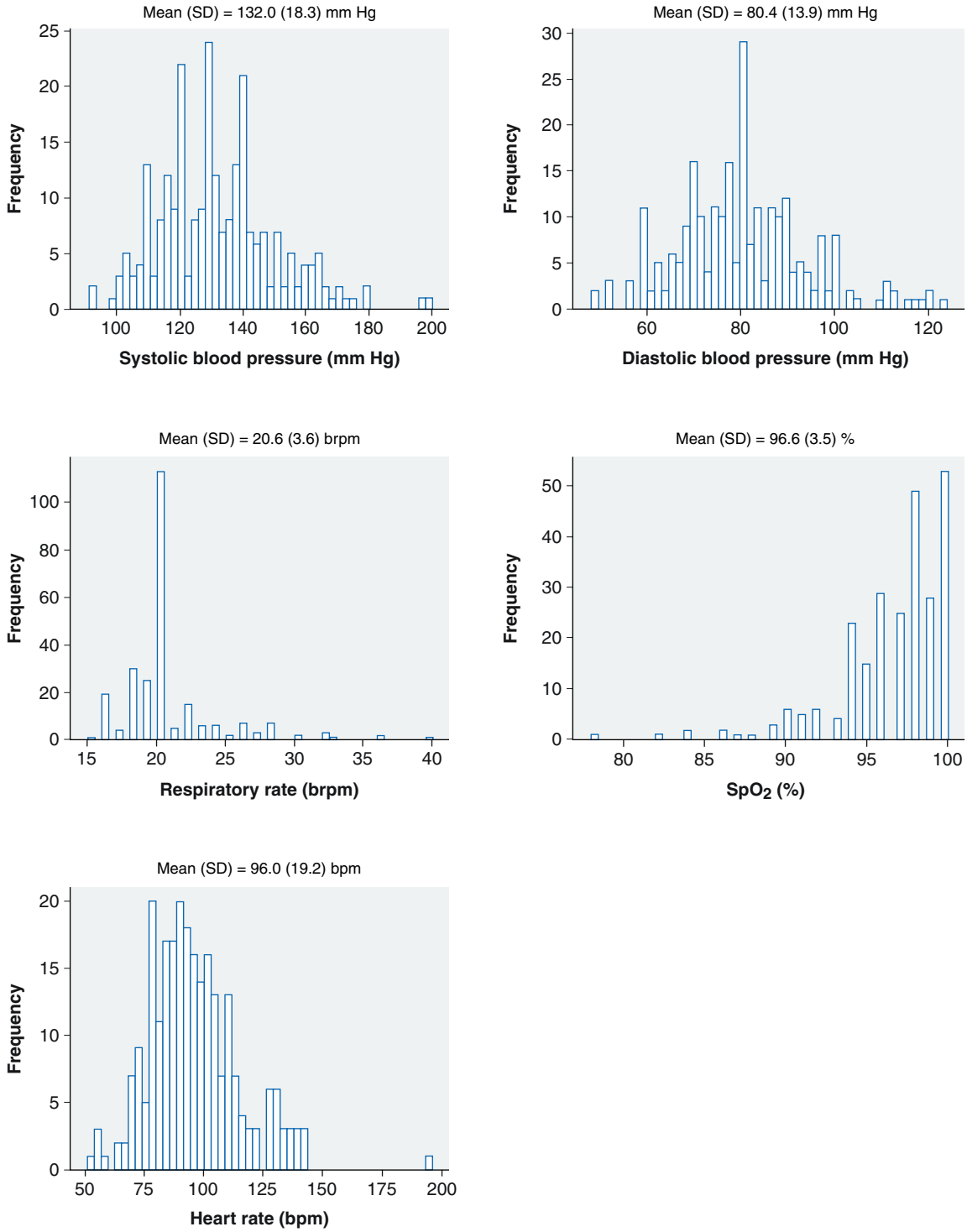
In addition, patients aged 10–19 years had a higher likelihood of prolonged hospitalization compared to patients aged 20–59 years. For comorbidities associated with asthma attacks, there was a trend toward statistical significance ($P = 0.086$), which implies individuals with respiratory disease were more likely to have longer hospital stays.

In the analysis of vital signs, SBP and HR were higher in patients hospitalized for more than 3 days. Conversely, SpO_2 was lower during longer hospital stays.

Table 1
Profile of patients hospitalized with asthma from January 2020 to December 2021 in a hospital in southern Santa Catarina

	n	%
Sex		
Male	97	37.2
Female	164	62.8
Age group		
0-9 years	1	0.4
10-19 years	6	2.3
20-39 years	142	54.4
40-59 years	73	28.0
≥ 60 years	39	14.9
Ethnic group		
White	227	87
Black	11	4.2
Mixed race	21	8.0
Other	2	0.8
Respiratory comorbidity	38	14.8
Lung decortication	1	0.4
COPD	19	7.6
Acute pulmonary edema	1	0.4
Pulmonary fibrosis	1	0.4
URTI	3	1.2
Pulmonary malformation	1	0.4
Pulmonary nodules	1	0.4
Pneumonia	4	1.6
Rhinosinusitis	4	1.6
OSAHS	2	0.4
Influenza	1	0.4
Smoker		
Yes	15	5.8
No	51	19.5
Not reported	195	74.7
Length of hospital stay ≥ 3 days	18	6.9
Need for O_2	16	6.2
Nasal cannula	15	5.8
Non-rebreather mask	1	0.4
Did not use O_2	245	93.8
Need for ICU	3	1.1
Need for MV	3	1.1
Death	2	0.8

COPD = chronic obstructive pulmonary disease, OSAHS = obstructive sleep apnea-hypopnea syndrome, URTI = upper respiratory tract infection.



SpO_2 = peripheral oxygen saturation.

Figure 1
Vital signs at admission of patients hospitalized for asthma from January 2020 to December 2021 in a hospital in southern Santa Catarina

In the multivariate regression analysis, the variables included in the model were SBP, HR, RR, SpO_2, age group, and presence of respiratory comorbidities. Only HR (OR = 1.030, 95% CI 1.005–1.057, P = 0.021) and SpO_2 (OR = 0.787, 95% CI 0.698–0.886, P < 0.001) were significant for the outcome of length of hospital stay ≥3 days.

Discussion

Asthma is a comorbidity characterized by chronic inflammation of the lower respiratory tract associated with a range of clinical conditions that may vary according to severity, risk factors, response to treatment, and genetics.[12] Between 2008 and 2013, asthma hospitalizations in Brazil totaled 1,054,184 patients, which underlines the significant prevalence of asthma among Brazilians as well as the need to evaluate predictive and associated factors to determine appropriate management strategies.[13]

Among the main findings of the present study, asthma hospitalizations were more common in women, particularly in the age group of 40 years, and in Caucasian patients. In addition, SpO_2 at the time of hospitalization was often above 90%, and patients often presented with mild tachypnea and tachycardia, although these variables were not predisposing factors for more severe hospitalizations. A target population requiring more attention during hospitalization was identified, characterized by low SpO_2 associated with tachycardia and its association with more severe hospitalizations.

The present study analyzed 261 medical records of patients hospitalized for severe asthma attacks and found a predominance of Caucasian patients. This finding differs from a study conducted in Northern California,[14] USA, which examined 242 patients hospitalized for asthma and found hospitalization rates were higher among other races. A study conducted in New York City, USA, also reported that the white population was less common, with 81.8% of hospitalized patients being black or Hispanic.[15] However, research in the United States assessing national asthma hospitalization costs was consistent with the findings of this study, showing a prevalence of Caucasian patients hospitalized for asthma.[16] This suggests the most affected population is not a fixed factor and is influenced by the region where patients are analyzed; the white are more prevalent in southern Brazil.

In terms of sex, females were found to have a higher prevalence of hospitalization than males (62.8%). This result differs from the findings of a study in the USA,[16] which showed a preponderance of hospital admissions among males up to 18 years of age. However, studies conducted in New York[17] and Pennsylvania,[18] found similar results to this study, with the female population requiring hospitalization more frequently.[17] Therefore, women often have higher hospitalization rates for asthma, although there are variations in certain regions and some age groups where the opposite is true.[19] This is due to the pathophysiology of asthma, which is an inflammatory disease characterized by an increase in CD4+ Th2 cells, mast cells, basophils, and innate immune cells.[19] Ovarian hormones such as progesterone and estrogen strengthen innate and adaptive immune responses, leading to airway inflammation in asthma. In contrast, androgens such as testosterone and 5-alpha-dihydrotestosterone suppress the immune response, thereby reducing the inflammatory state.[19]

Regarding sociodemographic data, the mean age in this study was 39.9 years, which is consistent with studies where the hospitalized population was predominantly in the age range of 36 to 64 years.[17,18] However, these data differ from the findings in Finland,[20] where studies have shown a higher hospitalization rate among patients over 70 years of age. This discrepancy can be explained by examining the age demographics of the 2 countries. According to the Brazilian Institute of Geography and Statistics, people over 60 years of age represent about 14% of the population of Brazil, while in Finland this age group represents about 24% of the population.[21,22] Thus, the higher rate of hospitalization among older people in Finland is consistent with the population data and the large proportion of people over 60, as Finland is a country with a significant focus on its growing older population. Therefore, the high rate of hospitalization among older individuals in Finland is proportional to the percentage of the population in this age group. This indicates the age profile of hospitalizations varies and, except for the most severe or mild cases, asthma hospitalization does not correlate with age.

Regarding outcomes followed during this study, most patients were discharged from the hospital. However, approximately 6.9% required prolonged hospitalization, 1.1% were admitted to ICU, and 0.8% died. In a New Zealand study of approximately

Table 2
Comparison of the length of hospital stay of patients admitted for asthma from January 2020 to December 2021 in a hospital in southern Santa Catarina

	Length of hospital stay < 3 days N (%) - 243	Length of hospital stay ≥ 3 days N (%) - 18	Odds ratio	p
Sex				
Female	153 (93.3)	11 (6.7)	1.00	0.875
Male	90 (92.8)	7 (7.2)	1.082 (0.405-2.890)	
Age group				0.035
0-9 years	1 (100.0)	0 (0.0)	–	
10-19 years	4 (66.7)	3 (33.3)	1.00	
20-39 years	136 (95.8)	6 (4.2)	0.088 (0.013-0.581)	
40-59 years	68 (93.2)	5 (6.8)	0.147 (0.021-1.008)	
≥ 60 years	34 (87.2)	5 (12.8)	0.294 (0.042-2.046)	
Respiratory comorbidity				0.086
No	211 (94.2)	13 (5.8)	1.00	
Yes	32 (86.5)	5 (6.9)	2.536 (0.847-7.591)	
Systolic blood pressure [a]	131.3 (±18.2)	141.2 (±17.1)	1.027 (1.003-1.052)	0.026
Diastolic blood pressure [a]	80.1 (±13.9)	83.7 (±13.5)	1.017 (0.984-1.052)	0.306
Respiratory rate [a]	20.5 (±3.5)	21.8 (±3.8)	1.080 (0.972-1.201)	0.147
SpO_2 [a]	96.9 (±2.9)	91.6 (±6)	0.750 (0.666-0.844)	< 0.001
Heart rate [a]	94.6 (±17.5)	114.6 (±29.3)	1.046 (1.021-1.071)	< 0.001

[a] mean (±SD), SpO_2 = peripheral oxygen saturation.

270 medical records, the number of patients who died was also considered small (17%). However, this study only looked at deaths in patients with severe asthma who had previously been hospitalized for asthma. Therefore, the 17% mortality rate should be analyzed carefully because it cannot be compared with patients whose condition is moderate or mild.[23] In California, although asthma mortality has decreased in recent years, it is still common and occurs mainly with increasing age, especially in patients over 60 years of age. This finding also supports the results of this study, as the 2 deaths observed in the medical records occurred in patients in this age group.[24] Regarding sex and its relationship to mortality, the present study was not able to test for an association. However, the study conducted in California, which analyzed all deaths from asthma exacerbations between 1960 and 1989, found no significant difference in mortality between the sexes.[24]

The need for ICU admission was also rare in this study. Despite the increase in asthma hospitalizations in several countries, the incidence of severe exacerbations has decreased. This has been attributed to improved access to health care and advances in management strategies and therapies. A study conducted in the United States found of 33,000 patients with asthma requiring hospital care, only 10% required an ICU bed and 2% required invasive mechanical ventilation.[25] These findings are consistent with the present study, as only 3 (1.1%) of the 261 patients evaluated required invasive MV. Regarding ICU admissions, our data were lower compared to the study conducted in the USA, in which only 1.1% of cases required ICU care. However, despite the decline in ICU admissions, there remains a significant association with mortality. For every 3 ICU admissions in this study, 2 resulted in death, meaning that 66.6% of patients admitted to the ICU died. Furthermore, the total number of patients who died in the present study represented 0.8% of the hospitalized cases; in both cases of death, there was a prolonged hospital stay and a prior ICU admission.

The patient's vital signs at the time of admission were critical in predicting the likelihood of prolonged hospitalization. We found in most cases, patients with O_2 saturation above 95% were more likely to be discharged within 3 days of admission. Conversely, patients with longer hospital stays had significantly lower O_2 saturations at the time of hospital arrival. A study conducted in Europe found comparable results, with hospitalized asthma patients having an average SpO_2 of 89.8%.[26] The mean values for HR (96 beats per minute) and RR (20.6 breaths per minute) are considered slightly elevated compared to clinical parameters. However, in the European study, patients were found to be tachypneic and tachycardic on admission.[26] Studies evaluating pediatric asthma hospitalizations are also consistent with the findings of this study and show evidence of decreased O_2 saturation at the time of hospital arrival.[9,27]

Analyzing patients' smoking profiles was challenging because this information was lacking from many medical records, making it difficult to determine a possible association between smoking and clinical outcomes after hospitalization for asthma. Similarly, the present study could not establish an association between more severe asthma attacks and past or current COVID-19 infection because this information was also lacking from the medical records. However, a systematic review found a 7.46% prevalence of bronchial asthma in patients who tested positive for COVID-19.[28] In addition, non-severe cases of asthma were found to be more common than severe cases among COVID-19-infected patients.[28] Among patients who were not infected, those with asthma were 14% less likely to become infected, indicating some resistance to the virus.[28]

Finally, vital signs are important predictors of clinical outcomes in patients and should be carefully evaluated to propose appropriate and individualized management for hospitalized patients.[9,10,27] The present study demonstrated the combination of low SpO_2, and tachycardia were factors associated with prolonged hospital stay. In addition, the profile of patients hospitalized for asthma in this study was of low severity, as evidenced by the good clinical outcomes in most cases.

This study has certain limitations regarding the medical records analyzed, as many patient health details were missing. For most hospitalizations, the patient's COVID-19 infection status was not documented, nor was the patient's smoking history, which was often not asked. In addition, incomplete records further limited this research, as variables analyzed at the time of hospital admission were sometimes not recorded in the hospital system. Moreover, as a single-center study, the profile of the hospital influences the selection of patients included in the sample. Therefore, the extrapolation

of the studied population as representative of other socioeconomic and geographic contexts should be done with caution. The state of Santa Catarina and the southern Brazil as a whole have a different demographic composition compared to the rest of Brazil.

Conclusion

An analysis of the medical records of patients hospitalized for severe asthma attacks in a hospital in southern Brazil found hospital admissions occurred predominantly in white patients, women, with a mean age of 40 years, mild tachycardia and tachypnea, and SpO_2 greater than 90% at the time of admission.

Tachycardia and low SpO_2 were found to be predisposing factors for prolonged hospitalization.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Allergic contact dermatitis to flowers: the importance of personalized patch testing

Allergic contact dermatitis to flowers: the importance of personalized patch testing

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ABSTRACT

Plant contact dermatitis is a very common occupational problem. Flowers and leaves are reported to cause primary irritant dermatitis (both chemical and mechanical), allergic contact dermatitis, and phytophotodermatitis. Given the variety of plants that could potentially cause dermatoses and the way in which the diagnosis was established, we report a case of allergic contact dermatitis caused by the genus *Chrysanthemum* in a florist who had sought a diagnosis for more than 10 years. Fragments of the petals and leaves most frequently handled by the patient were used to create a personalized patch test that allowed conclusive diagnosis and, finally, appropriate management. We highlight the importance of carrying out personalized patch testing, especially in cases of suspected allergic contact dermatitis in which the standard test battery was negative and/or did not cover the suspected substances.

Keywords: Occupational dermatitis, allergic contact dermatitis, plants, *Chrysanthemum*.

RESUMO

A dermatite de contato por plantas é um problema ocupacional muito comum. Flores e folhas são relatadas como causadoras de dermatite irritativa primária, tanto química como mecânica, dermatite de contato alérgica e fitofotodermatites. Frente à variedade de plantas potenciais causadoras de dermatoses e o modo como foi concluído o diagnóstico, relatamos um caso de dermatite de contato alérgica pelo gênero *Chrysanthemum* em uma paciente florista que buscou seu diagnóstico por mais de 10 anos. Fragmentos das pétalas e folhas de manuseio mais frequente pela paciente foram utilizados para confecção de um teste de contato personalizado que permitiu a conclusão diagnóstica e correta condução da paciente. Assim, ressaltamos a importância da realização do teste de contato personalizado, em especial nos casos suspeitos de dermatite de contato alérgica, onde o teste (bateria padrão) resultou negativo e/ou as substâncias suspeitas não se encontraram contempladas.

Descritores: Dermatite ocupacional, dermatite alérgica de contato, plantas, *Chrysanthemum*.

Introduction

Plants are highly valuable in medicine for both their adverse and beneficial effects. Beneficial effects include treatment of ulcers, infectious diseases such as acne, herpes, and scabies, and inflammatory diseases such as psoriasis. However, plant can be responsible for several dermatoses.[1]

Contact dermatitis from plants is a very common occupational problem,[2] and it is estimated that 50% of dermatoses among farm workers are due to plants, whereas reactions to pesticides and other chemical products account for less than 20%.[1,2]

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The plants mostly involved in cases of dermatitis include those of the family *Asteraceae* (or *Compositae*), which has 1,535 genera and nearly 23,000 species. These plants are cultivated as ornamental, medicinal, apicultural, oleaginous, aromatic, insecticidal, and edible plants.[3,4]

Given the wide variety of plants that could potentially cause dermatoses, the long patient journey to diagnosis, and the way in which it was established, we report a case of allergic contact dermatitis (ACD) from flowers of the genus *Chrysanthemum* in the family *Asteraceae*, highlighting the importance of personalized patch testing.

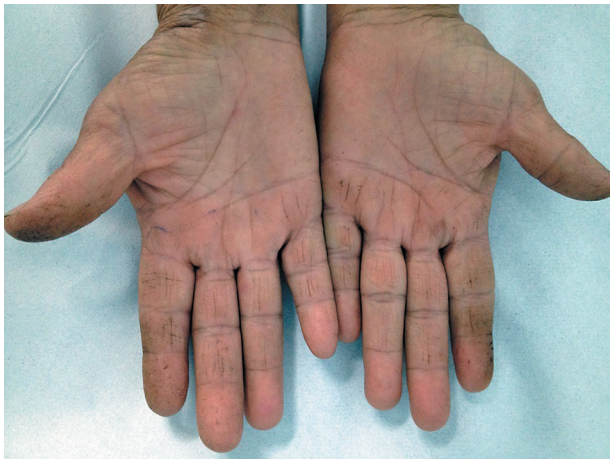

Figure 1
Palms of the hands: skin thickening with accentuation of palm lines (lichenification)

Case report

A 63-year-old female patient, florist, has complained of "body allergies" for 10 years. On dermatological examination, she presented with lichenification on the palm of her hands (Figure 1), excoriated brownish erythematous papules on her face, forearms (Figure 2A), and back in addition to erythema, fine desquamation, and hyperchromia on the right periorbital region (Figure 2B). The patient reported suffering from itching and erythema of the hands for 10 years, with worsening in the last two years and dissemination to other body sites. She told she had previously consulted six professionals and, at the request of one of them, had undergone the patch test with a standard battery, which resulted negative. When asked about her occupation, she said she had worked with flowers for 25 years. Based on this information, we decided to perform a personalized

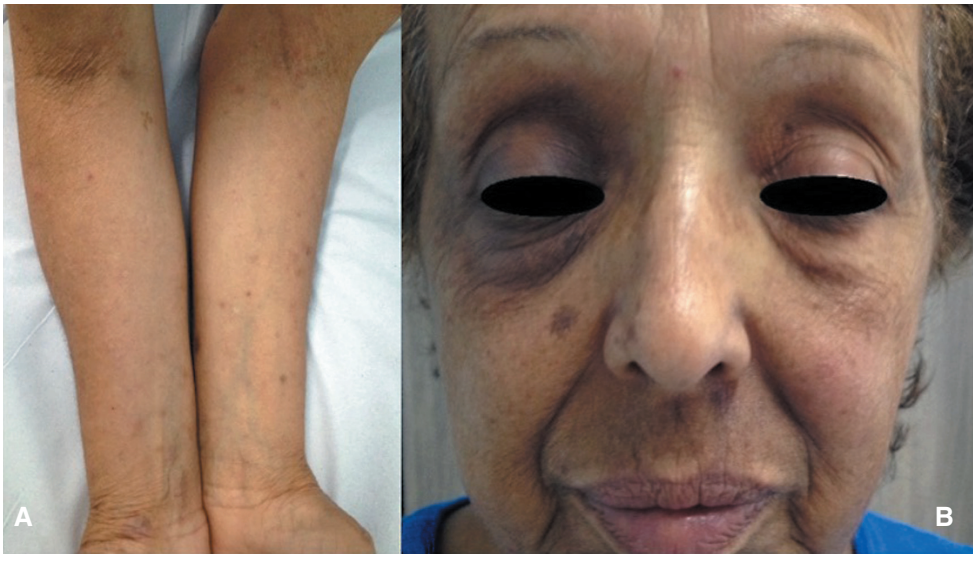

Figure 2
(A) Forearms: brownish erythematous papules, with some excoriations. **(B)** Right periorbital region: hyperchromia and fine desquamation

patch test using flowers and leaves most often handled by the patient.

Two leaves popularly known as "Guaricana" and "Avencão" (*Geonoma gamiova* and *Rumohra adiantiformis*, respectively) were included, as well as the petals and respective leaves of four flowers popularly known as "Chrysantemum Calabria" (*Dendranthema grandiflorum*), "Chrysantemum Rage" (*Dendranthema grandiflorum cv. Rage*), "Rose" (*Rosa spp.*), and " Canada goldenrod" (*Solidago canadensis*), totaling 10 possible allergens (Figure 3).

Specimens (leaves/flowers) were extracted, macerated, and applied directly on the skin, fixed with micropore tape.

In the first reading (48 hours) mild erythema was observed in test specimen number 1, and erythema and papules in test specimens number 3, 4, 5 and 6. In the final reading (96 hours) intense erythema, papules, and vesicles were observed in test specimens number 3, 4, 5 and 6, corresponding to Chrysanthemum Calabria petals, Chrysanthemum Calabria leaves, Chrysanthemum Rage petals, and

Plant	Popular names	Scientific name	Genus	Family	No. of test specimen
	Guaricana, Rabo-de-peixe	*Geonoma gamiova*	*Geonoma*	*Arecaceae*	1
	Avencão, Leatherleaf fern	*Rumohra adiantiformis*	*Rumohra*	*Dryopteridaceae*	2
	Calabria, Chrysanthemum Calabria	*Dendranthema grandiflorum cv. Calabria*	*Chrysanthemum*	*Asteraceae*	3
	Chrysanthemum Calabria leaf	–	–	–	4
	Chrysanthemum, Red daisy, Chrysanthemum Rage	*Dendranthema grandiflorum cv. Rage*	*Chrysanthemum*	*Asteraceae*	5
	Chrysanthemum Rage leaf	–	–	–	6
	Red rose	*Rosa spp.*	*Rosa*	*Rosacea*	7

Figure 3
Possible allergens tested

Plant	Popular names	Scientific name	Genus	Family	No. of test specimen
	Red rose leaf	–	–	–	8
	Canada goldenrod	*Solidago canadensis*	*Solidago*	*Asteraceae*	9
	Canada goldenrod leaf	–	–	–	10

Figure 3 *(continuation)*
Possible allergens tested

Chrysanthemum Rage leaves, respectively (Figure 4).

In view of the result obtained, which is strongly suggestive of a causal relationship between patient's dermatitis and the tested plants, the diagnosis of ACD from flowers and leaves of the genus *Chrysanthemum* was established.

The patient was instructed on the need to avoid contact with the causative agent (*Chrysanthemum* genus plants) and/or using personal protective equipment such as mask and gloves. No topic or systemic medications were prescribed, only emollients. After one year of follow-up, the patient improved significantly, reporting only sporadic accidental contacts with symptom recurrence.

Discussion

Flowers and leaves are reported as causing primary irritant dermatitis, both chemical (e.g., venoms) and mechanical (e.g., thorns), ACD, and phytophotodermatitis.[1-3,5] Furthermore, contaminants such as insecticides, agrochemicals, and arthropods may also be the responsible for dermatitis.[5]

Despite the small number of studies, a high incidence of ACD and phototoxicity from the family *Compositae/Asteraceae* are reported, with alantolactone, arteglasin A, arbusculin A, and other sesquiterpene lactones being the most commonly associated allergens.[3-5]

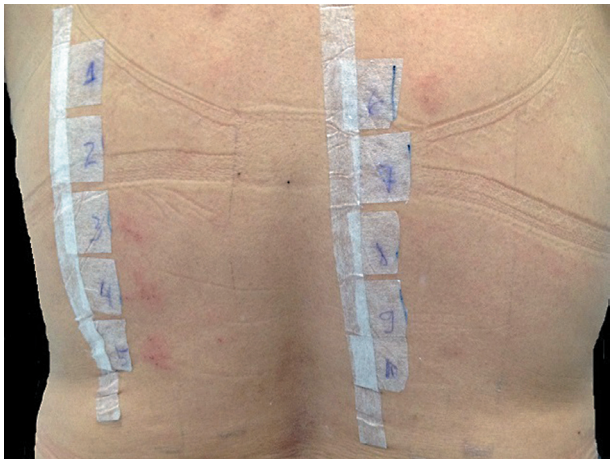

Figure 4
Personalized patch test: positivity for allergens 3, 4, 5 and 6 (Chrysanthemum Calabria petal, Chrysanthemum Calabria leaf, Chrysanthemum Rage petal, and Chrysanthemum Rage leaf, respectively)

Positive results in the personalized test for two flowers and their respective leaves of the genus *Chrysanthemum*, which is reported as an important causative agent of respiratory and cutaneous allergies within the family *Asteraceae*, corroborate current literature on the topic.[4] In line with the present report, face and hands are the most involved sites.[6]

For the diagnosis of these dermatoses, the standard patch test may be useful, since there may be a possible cross-reaction between certain allergens and some substances used in the standard test battery (e.g., paraphenylenodiamine), contributing to diagnostic reasonong.[5] A more effective alternative uses a mixture of sesquiterpene lactones or of *Compositae* plant extracts, detecting up to 90% of cases of allergy to this family. However, in daily clinical practice, these products are usually unavailable; therefore, the only feasible alternative is performing the patch test with the potential causative agents by applying them directly on the skin.[4]

The ethiopathogenic mechanism of the patch test is the same as that of ACD. Assuming a previous sensitization to the plant, the afferent pathway of ACD to the antigen was elicited. The performance of the patch test with the likely causative agents induces the formation of the afferent pathway by sensitized T lymphocytes and causes local injury. Reading of test results after 48h and 96h is justified by the time required for lymphocyte infiltration into the epidermis. The patch test was only indicated in this report because it was a case of ACD. In irritant contact dermatitis, the immunological phenomena described in ACD do not occur.

This report highlights the importance of a detailed history taking, especially in chronic/long cases, in which patients had already consulted several medical specialties, underwent different treatments, and are sometimes skeptical about their problem. Furthermore, it is worth emphasizing that plants can cause dermatosis, especially those of the genus *Chrysanthemum*, which are widely used in floriculture. Finally, this report emphasizes the importance of personalized patch test, particularly in highly suspected cases and when the likely causative agents are not included in the standard test battery.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Efficacy of midostaurin in systemic mastocytosis: a case report

Eficácia da midostaurina na mastocitose sistêmica – um relato de caso

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ABSTRACT

A 63-year-old female presented with an approximately 20-year history of systemic mastocytosis, which had become aggressive over the past 10 years. She experienced almost daily episodes of gastrointestinal and vasomotor manifestations. After multiple treatment attempts, she was started on midostaurin, a multikinase inhibitor. At 6 months of therapy, satisfactory control of symptoms was achieved, with a nearly 50% reduction in serum tryptase and complete resolution of cutaneous lesions.

Keywords: Systemic mastocytosis, tryptases, anaphylaxis, osteolytic lesions, malabsorption syndromes, multikinase inhibitor, midostaurin.

RESUMO

Paciente do sexo feminino, com 63 anos de idade, portadora de mastocitose sistêmica há cerca de 20 anos, sendo agressiva há 10 anos. Crises quase diárias com manifestações do trato gastrointestinal e vasomotoras. Após diversas tentativas de tratamento, iniciou uso de midostaurina, um inibidor multiquinase. Depois de 6 meses de uso, observou-se bom controle dos sintomas, diminuição em quase 50% da triptase sérica e desaparecimento completo das lesões cutâneas.

Descritores: Mastocitose sistêmica agressiva, triptase, anafilaxia, lesão osteolítica, síndrome de má absorção, inibidor multiquinase, midostaurina.

Introduction

Mastocytosis encompasses a group of disorders characterized by an abnormal proliferation and accumulation of clonal, neoplastic mast cells in several organs. Among these, systemic mastocytosis is the most severe form. It primarily affects adults, presenting with extracutaneous involvement and sometimes leading to dysfunction of one or more organs.[1-2] The estimated incidence of this condition is 4-5 cases per 1 million people annually.[3] Clinical manifestations are triggered by the release of vasoactive mediators and the damage caused to organs due to the infiltration of neoplastic mast cells.[4]

Most cases of systemic mastocytosis are associated with somatic gain-of-function mutations in the *KIT* gene, predominantly the D816V mutation. CD117 is a type III receptor tyrosine kinase that plays a crucial role in the normal development of mast cells. The interaction between *KIT* and its ligand (the stem cell factor) is fundamental in regulating mast cell proliferation, maturation, adhesion, chemotaxis, and survival.[4]

The aggressive form of systemic mastocytosis can manifest with a range of symptoms, including malabsorption syndrome with weight loss, hepatomegaly and/or splenomegaly with dysfunction of these organs, severe cytopenias, and osteolytic lesions, typically accompanied by significantly elevated serum tryptase levels. This condition is associated with

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a poor prognosis, with a median overall survival of only 3.5 years.[5]

The therapeutic approach for systemic mastocytosis should be individualized. Symptomatic treatment involves the use of H1 and H2 histamine receptor antagonists, leukotriene receptor antagonists, and mast cell stabilizers and aims to control symptoms and prevent recurrence of crises. Topical corticosteroids and calcineurin inhibitors can minimize skin lesions.[4]

Midostaurin is an oral multikinase inhibitor that inhibits D816V-mutated *KIT* and has proven efficacy in controlling systemic mastocytosis.[6] Additionally, this medication also inhibits IgE-dependent histamine release by acting on protein kinase C.[7] Serum tryptase levels and bone marrow involvement are used to monitor the effect of therapy.[8] The most common side effects of this medication are nausea, vomiting, diarrhea, and fatigue, with myelosuppression being the most limiting. Studies show that medication doses are often reduced due to adverse effects.[1]

Imatinib, a competitive inhibitor of a few tyrosine kinases (including *KIT*), does not perform as well as midostaurin, as it inhibits the growth of *KIT* V560G but does not act on cells carrying the *KIT* D816V mutation. Interferon-α (IFN-α), although associated with many side effects and poorly tolerated by many patients, shows only partial control of the disease in the majority of cases.[4]

Case report

A 63-year-old female domestic worker from the city of Osasco, state of São Paulo, Brazil, presented at 39 years of age with a diffuse hyperchromic maculopapular rash, predominantly on the back, which became erythematous with skin friction, heat, and stress, and sometimes was accompanied by pruritus. At age 50, she developed weekly episodes of gastrointestinal symptoms characterized by diarrhea and vomiting, associated with vasomotor symptoms such as flushing and hypotension. The condition worsened with the use of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), leading to multiple visits to the emergency room. At 56, she was hospitalized for anaphylaxis without a defined trigger, requiring orotracheal intubation. She denied being stung by an insect of the *Hymenoptera* order.

After being hospitalized at 58, a hypothesis of systemic mastocytosis was raised. A skin biopsy of the back was performed, and immunohistochemistry revealed regions in the dermis with dense infiltration of cells suggestive of mast cells, which were positive for CD117 (c-kit) and negative for CD2. To complete the diagnosis, a bone marrow biopsy was performed on the same occasion, which revealed hypercellular marrow (90%) with peritrabecular spindle cell infiltrate (40%) suggestive of mastocytosis, which was positive for CD117 (c-kit) and negative for CD2.

Three months later, the patient was admitted to a tertiary hospital under the care of the Clinical Immunology and Allergy team for further diagnostic workup. A positron emission tomography-computed tomography scan (Figure 1) for staging revealed glucose hypermetabolism in the axial and appendicular skeleton, with altered bone texture and both lytic and blastic lesions (SUVmax: 3.1 in the left proximal tibia). Abdominal ultrasound with Doppler showed parenchymal liver disease with signs of portal hypertension and portosystemic collateral pathways, as well as homogeneous splenomegaly. Liver biopsy revealed septal and perisinusoidal fibrosis with increased mast cells, which were positive for CD20, CD3, CD30, and CD117. Upper endoscopy and colonoscopy were normal. Finally, bone myelogram revealed an infiltrate of mast cells positive for CD117, CD25, and CD2 on immunohistochemistry.

The diagnosis of aggressive systemic mastocytosis was confirmed, involving the liver, bone marrow, skin, and bones. Treatment was proposed to control symptoms with loratadine 10 mg every 12 hours and ranitidine 150 mg every 12 hours. The patient was also advised to avoid medications such as opioids and NSAIDs and given an anaphylaxis action plan. However, the patient continued to experience daily episodes of diarrhea, vomiting, flushing, and hypotension, along with severe bone pain, and frequently used celecoxib.

At follow-up, the patient had developed a challenging cutaneous condition,[8] characterized by an erythematous papular rash with pruritus on the upper and lower limbs and the areolar, cervical, and abdominal regions, which also affected her husband. Skin scrapings confirmed the presence of *Sarcoptes scabiei* in both of them. Treatment with two doses of ivermectin 6 mg given 14 days apart and topical permethrin lotion 50 mg/mL led to complete resolution of scabies (Figure 2).

For the aggressive systemic mastocytosis, the Hematology team first attempted treatment with the tyrosine kinase inhibitor imatinib 400 mg/day

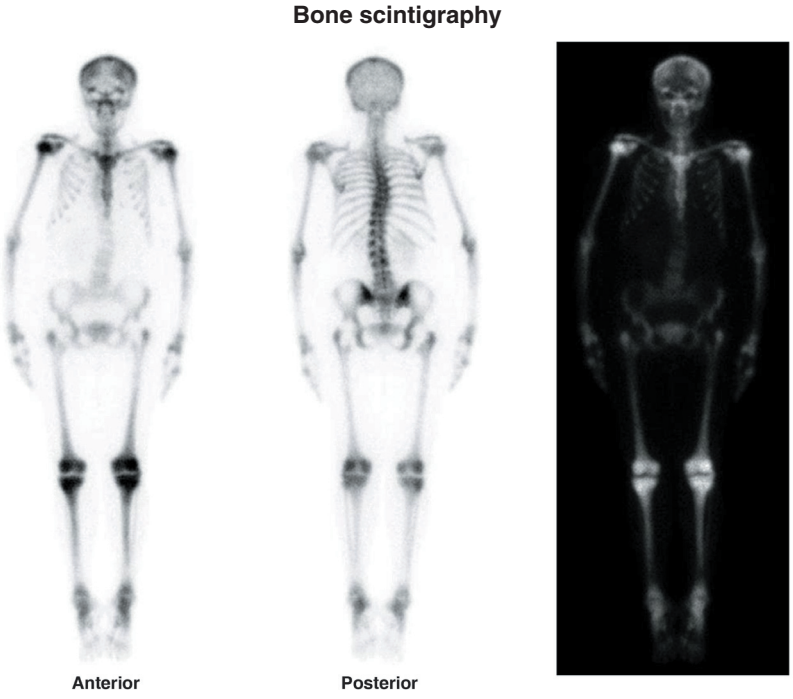

Figure 1
Anterior and posterior whole-body scan images with 99mTc-MDP revealing, in addition to hypointense areas in the proximal thirds of the femurs compatible with metal prostheses, diffuse hyperconcentration of the radiotracer in the axial and appendicular skeleton, suggestive of infiltration lesions

orally, which was discontinued after 4 months due to worsening gastrointestinal symptoms, anemia, asthenia, and lack of appetite. Subsequently, treatment with 3 million units of interferon-α 2b administered subcutaneously twice a week was started but stopped after 1 year and 7 months due to unavailability of the medication. The patient underwent a course of oral prednisone 60 mg/day but continued to have daily symptoms of flushing, hypotension, holocranial headache, and pruritus, along with weekly episodes of abdominal pain. The level of serum tryptase during this period was 200 µg/L.

In October 2022, at age 61, the oral multikinase inhibitor midostaurin (25 mg every 12 hours) was introduced. Three months later, the patient showed significant improvement, with milder and less frequent symptoms and a reduction in skin lesions. Attempts to increase the dose to 200 mg/day, as suggested for the treatment of advanced mastocytosis, were met with gastrointestinal intolerance characterized by severe nausea. A dose of 150 mg/day, taken twice daily, was tolerated by the patient.

After 6 months of continuous medication use, serum tryptase levels decreased to 118 µg/L. The patient experienced complete remission of skin lesions (Figure 3) and significant clinical improvement, with episodes characterized by mild symptoms of nausea, abdominal pain, flushing, and holocranial headache occurring every 10-15 days without the need for emergency care (Table 1).

Discussion

Midostaurin was shown to be effective in the treatment of patients with aggressive systemic mastocytosis due to its action as a multikinase inhibitor, including mutated KIT receptor and protein kinase C. Our patient had significant symptom improvement, a nearly 50% reduction in tryptase levels, and complete remission of skin lesions after

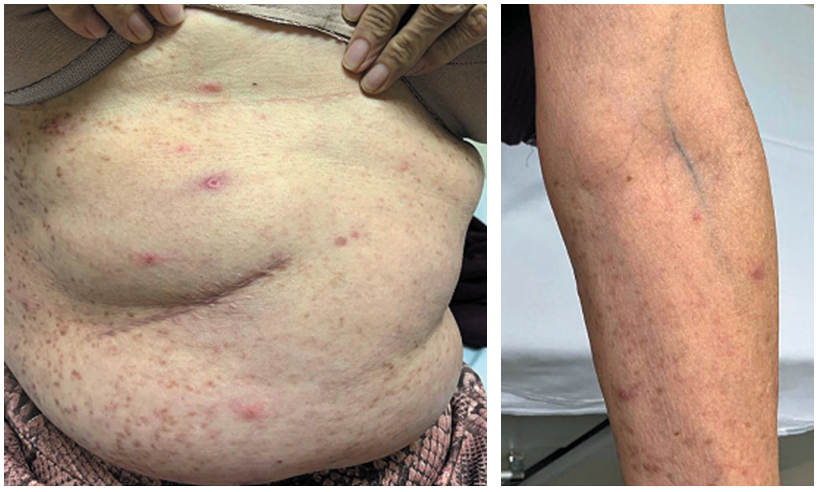

Figure 2
Erythematous papules with microvesicles in the abdominal region and left upper limbs (scabies) and brownish erythematous maculopapular rash (mastocytosis)

6 months of medication use, with management of side effects by dose reduction. The case described in this report illustrates the short-term efficacy and safety of midostaurin in treating aggressive systemic mastocytosis.

Although there are no direct treatment comparisons, a review of scientific evidence suggests the superiority of midostaurin in the survival of patients with advanced systemic mastocytosis compared with other traditionally used cytoreductive agents.[9] A real-world study from France reported a 1-year overall survival rate of 83%.[10] Additionally, studies have demonstrated the capacity of midostaurin to reverse organ damage, reduce splenomegaly and bone marrow mast cell burden, and provide benefits regarding patient-reported symptoms and quality of life.[11] Nausea, vomiting, and diarrhea are the most commonly encountered adverse effects of this medication, usually managed with symptomatic treatment and administration of midostaurin with meals.[11]

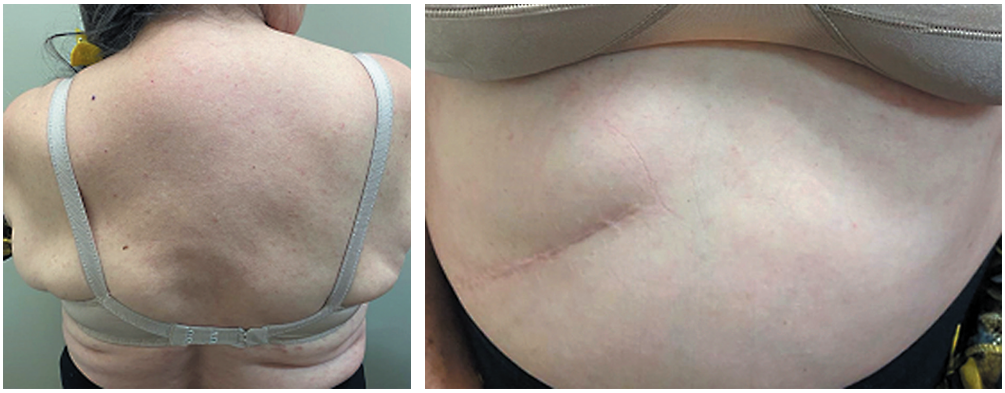

Figure 3
Skin of the back and abdomen showing remission of mastocytosis lesions after treatment with midostaurin

Table 1
Clinical and laboratory characterization before the use of midostaurin and after 6 months of using the medication

Parameter	Pre-medication	6 months after midostaurin use
Skin examination	Disseminated brownish erythematous maculopapular lesions	Absence of skin lesions
Symptoms	Daily gastrointestinal tract symptoms and vasomotor symptoms	Mild gastrointestinal symptoms that improved with symptomatic treatment
Tryptase (µg/L)	200	118

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ASBAI
Arquivos de Asma, Alergia e Imunologia

Opportunity screening for inborn errors of immunity: what is calculated globulin?

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Dear Editor,

It is estimated that more than 100 medical appointments are necessary for patients with inborn errors of immunity (IEI), formerly known as primary immunodeficiencies, to be diagnosed.[1] This delay significantly impacts the patient, who often develops sequelae that could have been avoided with earlier detection.

Some laboratory tests are related to immunodeficiencies and can help identify patients who may have undiagnosed IEI. In this context, opportunistic screening is invaluable to reduce the diagnostic delay of IEI.[2]

Immunoglobulin G (IgG) plays a key role in the diagnosis of many IEI, and low IgG levels affect several routine medical laboratory tests, such as protein electrophoresis and the measurement of total proteins and protein fractions.

Calculated globulin (CG) is defined as the plasma total protein minus albumin and is reduced in patients with primary or secondary antibody deficiency.[3]

Recent studies in different populations have demonstrated that CG can be used as a low-cost method for screening quantitative antibody deficiency in adults, as it shows good correlation with serum IgG levels. Jolles et al.[3] examined the use of CG as a screening tool in Wales, using the Architect Biuret method for total protein and the colorimetric bromocresol green method for albumin estimation.

The cut-off value for CG was defined as < 18 g/L, with a sensitivity of 0.82 and specificity of 0.71 for an IgG < 3 g/L (or 300 mg/dL).

Yegit et al. used automated results of CG and protein electrophoresis of patients seen at a tertiary hospital for various reasons. They selected 550 patients with CG levels between 15 g/L and 25 g/L. The cut-off value for CG to predict patients with IgG < 6 g/L (or 600 mg/dL) was determined to be < 20 g/L, with a sensitivity of 83.8% and a specificity of 74.9%.[4]

In our studies using protein electrophoresis, we evaluated 886 adults and 1,215 children and adolescents seen at two allergy and immunology services. In adults, for the detection of hypogammaglobulinemia (i.e., IgG levels below the normal laboratory value of 6 g/L), the CG cut-off value of 24 g/L showed a sensitivity of 86.2% and specificity of 92%.[5]

In children and adolescents, the sensitivity and specificity of CG in detecting IgG levels below normal laboratory values were 93.1% and 81.8%, respectively. The CG cut-off values for detecting hypogammaglobulinemia were determined for patients aged 1 to 17 years and varied according to the age group studied, ranging from 23.1 g/L (1-3 years) to 24.8 g/L (4-9 years). The accuracy of this test could not be confirmed in children under 1 year of age.[6]

In clinical practice, the measurement of total proteins and protein fractions is a simple and widely used test for investigating serum protein abnormalities in general pediatrics, internal medicine, and other specialties such as gastroenterology, rheumatology, nephrology, pulmonology, oncology-hematology, and intensive care.[7-9] Additionally, the severity of the diseases serves as an alert for possible cases of immunodeficiency.[10]

Overall, CG values provide relevant data on humoral immunity, as these fractions are mainly composed of IgG.[11,12]

Strategies for implementing opportunistic screening should be encouraged and coordinated in both public and private services. The CG tool is easy to obtain and can be readily implemented in clinical laboratories. Recognizing individuals with reduced CG increases the possibility of diagnosing IEI and other causes of hypogammaglobulinemia, such as those secondary to losses and medication use, due to its close correlation

with serum IgG results. Furthermore, it serves as an additional identification method in medical services that lack immunoglobulin measurements.

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Pharmacological treatment of pollinosis: has the late-phase allergic response been forgotten?

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Dear Editor,

The pathophysiology of allergic rhinitis is complex, comprising an early and late phase of allergic response. In the case of pollinosis, symptoms can become evident after exposure to pollens in nature.[1] In both allergic rhinitis and allergic asthma, the allergic response can show biphasic kinetics in susceptible individuals.[2]

The early-phase reaction is characterized by mast cell degranulation caused by allergen recognition by surface immunoglobulin E, leading to the rapid onset of nasal symptoms (i.e., sneezing and rhinorrhea) and the emergence of ocular symptoms (i.e., itching, hyperemia, and tearing). This is due to the release of histamine, together with the effects of other pro-inflammatory cytokines (e.g. leukotrienes and prostaglandins).[1,2]

The second phase, termed late allergic response (LAR), occurs 2 to 8 hours after allergen exposure in certain patients. Approximately 50% of patients with allergic rhinitis experience a symptomatic LAR.[1]

The LAR is characterized by nasal obstruction after initial recovery, associated with an increase in interleukin 13 (IL-13).[2] Nasal obstruction often leads to breathing and sleep disturbances, resulting in decreased quality of life and productivity, daytime sleepiness, fatigue, and stress.[3]

Aerobiology studies initiated in past decades have confirmed the presence of a grass pollen season in southern Brazil. It begins in September and starts to decline in December, confirming a pattern of seasonal symptoms, which is characteristic of pollinosis.[4,5] This pattern repeats year after year in sensitized patients during the spring season in Brazil.

It is known that there is a higher concentration of pollen in the air during the early morning and late afternoon. However, data regarding specific times are conflicting, as they depend on meteorological conditions, vegetation location, and species.

Because of ground and urban heating, pollen present in the air during the morning reach higher atmospheric levels. Conversely, during the late afternoon cooling, a descending current brings pollen to lower atmospheric levels, increasing its concentration and, consequently, the symptoms in patients.

In Brazil, we lack data on grass pollen concentrations at different times of the day. This may make it difficult for physicians to establish an association between possible LAR and the nocturnal nasal obstruction experienced by some patients. However, this association should be investigated particularly in patients with atopy, considering that the late afternoon on sunny, warm, dry, and windy days is when there is greater pollen dispersion in the air.

Patients with increased IL-13 concentrations in nasal secretion may be at higher risk for experiencing LAR. This could mean, in the future, a move toward personalized treatment for patients with pollinosis.[2]

Commonly used antihistamines are highly effective in mast cell degranulation, i.e., the early-phase response, but have not shown efficacy on LAR symptoms. Glucocorticoids provide greater symptom relief in this phase.[1]

Prophylactic treatment with nasal corticosteroids is more effective than oral antihistamines for pollinosis, particularly during the LAR phase.[2,6]

The use of fluticasone furoate or mometasone furoate nasal sprays is recommended, which can also control ocular symptoms.[6-9]

When asymptomatic patients are exposed to low pollen concentrations, the presence of a minimal persistent inflammation can already be detected, exacerbated by repeated exposure to pollen, known as the “priming effect”.[7]

When administered at recommended doses, topical nasal corticosteroids are generally not associated with systemic side effects, such as increased intraocular pressure or the development of subcapsular cataracts. Children should use the lowest effective dose and have their growth monitored.[8]

Antihistamines are probably the most common medication used for allergic rhinitis among the general population. They are easily accessible and distributed in Brazil through the public health system.

Pollinosis is distinguished from chronic rhinitis by the presence of acute symptoms of rhinoconjunctivitis at the beginning of the pollen season, which are often difficult to tolerate. Possible associated bronchial asthma should be investigated.

Patients who perform outdoor activities or exercise are more likely to develop symptoms. For the allergic population, avoiding pollen is challenging.

A detailed clinical history and physical examination, together with complementary diagnostic and therapeutic procedures, can make a significant difference in morbidity, quality of life, and distinguish allergists in the eyes of their patients.

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