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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

The 2023 Nobel Prize and vaccine hesitancy

O Prêmio Nobel 2023 e a hesitação vacinal

Fabio Chigres Kuschnir[1]

The role of vaccines in reducing mortality and containing the spread of the COVID-19 pandemic received well-deserved recognition from the international scientific community when Hungarian biochemist Katalin Karikó and U.S. immunologist Drew Weissman, of the University of Pennsylvania, were awarded the 2023 Nobel Prize in Physiology or Medicine. Karikó and Weissman's discoveries about nucleoside base modifications made possible the development of effective mRNA vaccines against SARS-CoV-2, at an unprecedented speed, during the greatest health crisis of the century[1].

This major victory of science is especially significant for Brazil, where the National Immunization Program (PNI, from the acronym in Portuguese), a world-renowned example of success in vaccination, has faced a concerning decline in vaccination coverage rates in recent years due to vaccine hesitancy – defined by WHO as one of the main threats to the health of populations[2].

Within this context, the present issue of AAAI features a special article by Professor Dr. Jorge Kalil, one of the key figures of vaccine research and development in our country. His review covers historical aspects, different vaccine platforms, and the epidemiological situation, major challenges, and future perspectives for the development of vaccines targeting some of the most prevalent infectious diseases in Brazil. Professor Kalil's unique vantage point, reached through personal experience acquired over decades of work in the field of vaccine science, makes this review essential reading[3].

Another special document in this AAAI issue is the "Practical guide for the use of immunobiologic agents in allergic diseases", prepared by the Scientific Department on Immunobiologics of the Brazilian Association of Allergy and Immunology (ASBAI). The concept of targeted therapies and precision medicine in the treatment of patients with serious allergic conditions has already been incorporated into the daily practice of the allergy and immunology specialist. This highly objective guide was designed to aid the specialist in prescribing biologics, and covers everything from indications, dosage, efficacy, and safety to the more practical aspects of storage, administration, and how to obtain these agents. It is sure to become a valuable work of reference for all physicians who care for this patient population[4].

Also in this issue, "Starting a practice in Allergy & Immunology: what do I need?" is the first in a series of special articles prepared by the ASBAI Statute, Regulations, and Standards Committee that will be published in AAAI. Its main objective is to provide an overview and guidance on the essential steps for best

1. President of the Brazilian Association of Allergy and Immunology (ASBAI).

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practice in the clinical care of allergic patients in the private office and clinic setting. These issues are rarely addressed during specialist training in allergy and immunology, and this important document – carefully based on the most recent rules and regulations for providers and facilities involved in the practice of our specialty – has been designed to bridge this knowledge gap[5].

Among the original articles in this issue, we highlight the winner of the 2023 Oswaldo Seabra Prize, awarded at the 50th Brazilian Congress of Allergy and Immunology, held in the city of Maceió. This study by Braian et al. used a large Ministry of Health database (SIVEP-Gripe) to assess outcomes of asthma patients hospitalized with severe acute respiratory infection (SARI) during the COVID-19 pandemic. Despite the limitations inherent to cross-sectional studies and secondary, the authors were able to detect discrepancies in mortality across different age groups and regions of the country, in addition to the predominance of COVID-19 among all SARIs associated with fatal outcomes during the period of analysis[6].

We hope you will enjoy the wealth of content published in the last issue of AAAI for 2023. We wish our readers a new year filled with achievements... and vaccines for everyone!

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

The past and future of vaccines – Reflections for discussion

Vacinas passado e futuro – Reflexões para discussão

Jorge Kalil[1]

ABSTRACT

In this opinion article, I provide a brief history of vaccine development, commenting on the classic ways of producing vaccines using the infectious agent itself. I address viral vaccines, discussing their benefits and challenges and the issue of viral serotypes, as well as bacterial vaccines and their relative success. I present our studies on rheumatic heart disease and the development of a vaccine against streptococcal infection. I also discuss vaccine platforms, highlighting the success achieved with non-replicating viral vector-based vaccines and, especially, with messenger RNA (mRNA) vaccines. mRNA vaccines only became possible after the advances provided by the replacement of nucleotides that reduced the action of the innate immune system. Will all vaccines be made from mRNA in the future? Then, I address the issue of vaccine administration routes, whether subcutaneously, intradermally, intramuscularly, or intranasal. I present data from my laboratory on the development of an intranasal vaccine that induced a protective mucosal response, preventing infection and, consequently, the transmission of SARS-CoV-2. I discuss which future vaccines could be developed beyond acute infectious diseases. Finally, I discuss the advantages of developing safe, effective, multiple-use vaccines and how to make them accessible worldwide by promoting health equity.

Keywords: Vaccine, viral vaccines, infectious agent, bacterial vaccines, mRNA vaccines.

RESUMO

Neste artigo de opinião, apresento uma breve história do desenvolvimento de vacinas, comentando sobre as formas clássicas de produção de vacinas utilizando o próprio agente infeccioso. Em seguida, abordo as vacinas virais, discutindo seus benefícios e dificuldades e a questão dos sorotipos virais, bem como as vacinas bacterianas e seu relativo sucesso. Apresento nossos estudos sobre doença cardíaca reumática e o desenvolvimento de uma vacina contra infecções estreptocócicas. Também discuto plataformas vacinais, especialmente os sucessos alcançados com vacinas de vetores virais não replicantes e, acima de tudo, o grande êxito das vacinas de RNA mensageiro (mRNA). As vacinas de mRNA tornaram-se possíveis somente após os avanços obtidos com a substituição de nucleotídeos que reduziam a ação da imunidade inata. Serão todas as vacinas desenvolvidas a partir de mRNA no futuro? Em seguida, abordo a questão das vias de administração de vacinas, seja por via subcutânea, intradérmica, intramuscular ou nasal. Exponho dados do meu laboratório sobre o desenvolvimento de uma vacina de instilação nasal que induziu uma resposta de proteção da mucosa, prevenindo a infecção e, consequentemente, a transmissão do SARS-CoV-2. Posteriormente, discuto quais vacinas futuras poderiam ser desenvolvidas para além das doenças infecciosas agudas. Por fim, discuto as vantagens do desenvolvimento de vacinas seguras, eficazes e de uso múltiplo, bem como a forma de torná-las acessíveis à população mundial, promovendo a equidade em saúde.

Descritores: Vacina, vacinas virais, agente infeccioso, vacinas bacterianas, vacinas mRNA.

Vaccination began in the West with Jenner's administration of extracts of cowpox pustules (vaccinia) to humans. It was the end of the 18th century and despite the results of protection clearly observed against smallpox, much hesitation was shown in the use of this methodology, and it took the world 2 centuries to completely eradicate the disease with mass vaccination of the population. In

1. Professor of Clinical Immunology and Allergy at the Faculdade de Medicina of the Universidade de São Paulo and member of the Academia Nacional de Medicina.

* This article had previously been published in French in the journal **Bulletin de l'Académie Nationale de Médecine**, Volume 207, Number 9, December 2023, pages 1212-17. https://doi.org/10.1016/j.banm.2023.09.007

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this immunization, protection is provided through a cross-reaction between two closely related viruses: vaccinia, or cowpox, and human smallpox. While Jenner brought immunizations to the world, Pasteur, nearly a century later, laid the foundations for vaccines. Pasteur, working with animals, developed processes to attenuate the infectious agent or inactivate it, and several veterinary vaccines were developed for use. The biggest challenge, then, was to convey these principles to humans. Through multiple passages of the rabies virus in rabbits, he obtained the attenuated rabies virus, and then tested it in animal models. The opportunity to test on humans presented an opportunity when young Joseph Meister was attacked by a rabid dog and was in serious danger of death. The trial was an absolute success and was widely publicized, gaining the approval of politicians and the masses.

From that point on, much research has been done into new discoveries and many vaccines have been developed using these principles of cross-protection between similar infectious agents, or the use of an inactivated or attenuated infectious agent. We can say that for any infectious diseases for which an individual has contracted the disease once in their life and remains immunized, a vaccine can be developed. However, a scientific question arises when the disease does not directly induce protective immunity.

The most common reason for this evasion is the different serotypes of the infectious agents. Serotypes are small sequence variations in the target protein of the protective immune response, which mean that the antibodies no longer recognize this protein and, consequently, no more protection. Antibodies against this modified protein are needed, giving rise to a new serotype. A vaccine against this infectious agent should cover the various serotypes.

In this instance, finding a universal immunizer would be essential, but good results have not been achieved. For this reason, various vaccines have been developed covering the main serotypes or circulating serotypes, with the associated restrictions.

If we consider HPV, the first vaccine was made against the 4 serotypes known to be the most carcinogenic, and then a second vaccine with 9 different serotypes. This is an expensive vaccine to produce, with the inconvenience of adjustments to find a balance in the induction of a protective immune response compatible with the different serotypes.

The vaccine against influenza has to be updated every year; its composition is based on partial data on the incidence of the disease in the respective hemisphere in the previous year. Although the vaccine already has its immunogenic limitations because it is an inactivated virus, particularly in the population most in need, which is older people, its efficacy is often low due to the emergence of new strains not included in the vaccine.

The situation is even more serious with the dengue vaccine. We know that a second case of dengue tends to be more serious than the first one, due to what is known as ADE (antibody dependent enhancement), in which antibodies directed against the virus but which are not neutralizing, facilitate viral entry into the cells, increasing the viral load with important clinical consequences.

For this reason, the vaccine has to induce neutralizing antibodies in equivalent quantities, and a decline in titers over time can, instead of providing protection, induce severe disease.

This happened with a dengue vaccine produced by Sanofi Pasteur. After clinical trials, it proved to be effective in individuals who had already had the disease. Even so, after a few years it was observed that vaccinated children who contracted the disease had a more severe form of dengue than unvaccinated children, leading to a serious debate about the use of this vaccine in the general population.

As head of the Instituto Butantan, I coordinated the development of the attenuated tetravalent dengue vaccine. The viruses had been attenuated at the NIH, but the vaccine prototype had to be kept frozen and thawed immediately before use. Industrial production had very low yields and stability. From these viruses, we developed a system for mass production of the four monovalents under industrial conditions, improved their purification process and, above all, their stabilization, allowing them to be freeze-dried.

Instituto Butantan has developed a pharmaceutical product that can be used by the population from a prototype sent by the NIH. The phase II clinical trial was conducted at the Hospital das Clínicas Medical School at the Universidade de São Paulo (USP) in Brazil. It included more than 300 individuals, some had already had the disease and others had not. We then approved the phase III study, and trained 17 clinical study centers throughout Brazil, especially in regions endemic to the disease, to recruit 17,000 volunteers. The study was launched with great pomp

and circumstance in February 2016 in the presence of the President of the Republic, the Governor of the State of São Paulo and five Ministers of State, demonstrating how important this study is for the country. However, there has been a drop in the incidence of dengue in Brazil in subsequent years and, above all, there has been a decrease in the circulation of certain serotypes. As a result, it has not been possible to prove the efficacy of the vaccine for all serotypes. For the serotypes studied to date, protection is above 80%.

Despite these achievements, the development of a vaccine for the different viruses that the immune system is unable to eliminate is very difficult. The most important example is a vaccine against HIV. Despite enormous progress in our knowledge of the pathology of this disease and advances in the antiviral immune response, the characteristics of the virus elude the immune system and, despite multiple attempts with billions of dollars invested, there is still no good candidate for a vaccine. Many different antiviral therapies have been discovered, which is a great success.

However, researchers have observed that some people living with HIV for years have developed antibodies with a high neutralizing action. Several monoclonal antibodies with promising therapeutic action have been obtained from the B lymphocytes of these patients, especially if they are combined; however, they are still in clinical trials and have not been applied in clinical practice.

The epitopes recognized by these monoclonal antibodies, thus identified, may shed light on the development of an effective vaccine for the prevention of HIV, or at least for therapy to reduce viral load, drastically reducing transmission.

While vaccines for viruses are an undeniable success, antibacterial vaccines are more complex and often not as effective.

The classic BCG vaccine developed in France is widely available in Brazil, but it is not unanimously used worldwide. Difficult to mass-produce, it is now rarely available on the market. With the difficulty of a controlled phase 3 clinical trial, real-life observations of efficacy show that BCG does not prevent tuberculosis but slows it down, and cases of severe tuberculosis are rarely observed in vaccinated individuals.

Although this vaccine has been used in Brazil, the disease has resurfaced in recent years, even with constant surveillance. This resurgence is probably due to the greater susceptibility of patients living with HIV, who also produce bacilli and spread the disease.

Another classic vaccine, DTP is a great success worldwide. It has been used for decades, practically eliminating diphtheria in the countries where it is used, and greatly reducing tetanus, a significant cause of infant mortality in Brazil before the vaccine was introduced.

The pertussis component, caused by the bacterium *Pertussis*, has also had great success in preventing the disease in Brazil. In recent years, several countries, including France, have started using the acellular *Pertussis* vaccine. With new technologies using isolated proteins, this acellular vaccine avoids the adverse effects of administering the whole inactivated bacterium, but its effectiveness over the years has proved much lower, with a drop in protection over time. In the various countries that have adopted it, there has been a resurgence of the disease, especially in older people, where it can be very serious. In addition, adults can present with a mild form of the disease and carry the *Pertussis* bacterium with an enormous risk of transmission to newborns, when the disease is often fatal.

The pneumococcal vaccine is extremely important, especially for older people, but it is relatively effective and very difficult to produce. As the protective response is fundamentally against the sugars in bacterial glycoproteins, a large number of components need to be synthesized in order to obtain only partial protection.

My research group has been working for many years to understand the immunopathological mechanisms of an autoimmune disease triggered by a bacterial infection: rheumatic heart disease, triggered by pharyngitis caused by *Streptococcus pyogenes*. There are over a hundred serotypes of *Streptococcus pyogenes* due to variations in the amino acid sequence of the N-terminal region of the M protein, which is the main antigen of this bacterium. We describe how T-cells cross-recognize streptococcus M-protein and vimentin from the cytoskeleton of cardiac cells. As these lymphocytes migrate to the valves, they lose control of the regulatory cells and cause vegetative lesions, altering valve function.

We described the main susceptibility genes for the disease, in which the HLA-DR53 molecules stand out. From there, we mapped the humoral and cellular response against synthetic M protein peptides and identified a region with a T epitope, followed by another

with a B epitope, which are associated with protective responses.

We have thus described a synthetic peptide vaccine, which has been tested in various animal models and it has been possible to characterize a good cellular and humoral response. The serum of the immunized animals induces opsonization of the bacteria by macrophage cells, and they are protected against the challenge of a fatal inoculum with streptococcus. In addition, the vaccine does not induce any autoimmune manifestations in mice or minipigs, nor in mice genetically modified with the HLA DR genes, which give susceptibility to the disease.

This vaccine is due to enter a phase I clinical trial soon. If we get the expected results, we could prevent childhood angina, and above all the serious rheumatic heart disease that kills thousands of people, mainly in Africa and Southeast Asia.

If bacterial vaccines are limited both in their number and actual efficacy, anti-parasite vaccines are even more challenging. Parasites are complex organisms with multiple ways of evading the immune system. In addition to changing their form, they also alter the expression of their antigens in the multiple forms they acquire. There are some vaccines against Leishmaniasis with limited efficacy in humans, and recently some reasonable results in a vaccine against malaria. A great deal of scientific knowledge is still needed to understand how we can be successful in producing vaccines against parasites.

The vaccines using the active and inactive infectious agent that were possible to develop have already been developed. Now science has to go beyond nature to produce vaccines with ingenuity using the important part of the infectious agent, and this translates into identifying the targets of the immune response, whether through antibodies that neutralize the infectious agent, or the CD4 lymphocyte response for auxiliary effect and the CD8 response with cytotoxicity eliminating infected cells. The targets comprise the so-called antigen.

The vaccine needs a component that links the innate and adaptive immune responses, which will serve as a spark to ignite the fire of protective acquired immunity and its respective memory. For this, an adjuvant is used, which is an inflammatory chemical or the vector vehicle itself, which can be a non-replicating virus, a virus-like particle, or another type of nanoparticle that includes nucleic acids such as RNA or DNA inside, which alone activate innate immunity.

Some years ago, the international scientific community was aware of the possibility of a pandemic due to the densification of cities and the ease of transportation of people around the planet.

In February 2017, I participated in the inaugural symposium of CEPI (Coalition for Epidemic Preparedness Innovations) in which I spoke about the ZICA epidemic and its possible consequences in Brazil and around the world. The event was attended by the then French President, François Hollande, to show the importance given by France and Western countries to the possibility of a pandemic, and how to prepare for it. The meeting was a success and CEPI was given resources to invest in a major program so that the groups, through their platforms, could be more agile in developing drugs and vaccines for possible pandemics.

The most relevant platforms that were already underway and which have emerged with great force and efficacy during the COVID-19 pandemic are nonreplicating adenoviruses vectors and messenger RNA.

Adenovirus platforms have the antigen gene incorporated into the viral genome. These viruses are nonreplicating vectors because they can infect but do not multiply in human cells. This is the case with the chimpanzee adenovirus used by Oxford University, which gave rise to the vaccine marketed by Astra Zeneca. The other system used is human viruses such as the Ad26 used by Janssen or the Ad5 used by Cansino and both used by Sputnik. In these cases, one of the genes essential for viral multiplication in human cells is deleted from the virus so that it cannot multiply. For industrial production, this virus is inserted into the cell used for viral replication and once the viral mass has been produced and the virus is isolated, it no longer multiplies. When the vaccine is injected, the virus attaches to the cell, injects its nucleic acid content which will be translated into viral proteins and also into the antigen that will be secreted and induce the expected immune response. In vaccines against COVID, this platform has been used extensively, as the companies mentioned above have shown. These vaccines induce a good protective immune response and have been widely used around the world. The major problem experienced with using this platform on a large scale was the adverse effect of inducing thromboembolic thrombocytopenic purpura. This rare effect was observed mainly in young women, and raised much concern about the widespread use of this type of vaccine vector.

Undoubtedly, the greatest success that arose from this pandemic was the emergence of the messenger RNA platform. This represents the development of many years and many researchers, and humanity was fortunate that technology was at a level of advancement that allowed effective and safe vaccines to be developed in remarkable time. Treatments for both defective gene replacement and cancer and vaccines using messenger RNA have been sought for many years, yet some almost insurmountable difficulties existed, the most important of which is that RNA is extremely inflammatory. The signaling system of innate immunity through Toll receptors perceives RNA as if it were a virus and triggers an explosive response. Things have changed thanks to the efforts of Hungarian biochemist Katalin Karikó in collaboration with immunologist Drew Weissmann at the University of Pennsylvania. They showed that much of the toxicity was due to the RNA nucleotide uridine and that the use of pseudouridine, which maintained the same coding, suppressed recognition by innate immunity. The other fundamental discovery was how to encapsulate the mRNA molecule, which protected it from RNAses, allowed the nucleic acid to be fixed and incorporated into cells, allowing it to be expressed and exported extracellularly, triggering a powerful immune response. These lipid nanoparticles have various components, including cholesterol, phospholipid, and polyethylene glycol. Given the ease of synthesizing the mRNA *in vitro* and the improvement in encapsulation techniques, after the sequence of the spike protein was published, the vaccine had already been synthesized in good manufacturing practice in 66 days, all immunogenicity and toxicity tests had been conducted, and clinical trials had been started. Truly a milestone in world science. This technology will undoubtedly be improved in order to better control the length of time the RNA remains, the amount of antigen produced, and to control some adverse effects. Some of these effects are due specifically to the spike protein and should be further investigated. In 2018, in an article published before the pandemic, our group warned that PEG could trigger anaphylactic reactions when used in medicines, a fact that has been observed with these vaccines. Also, with RNA vaccines, the inconvenience is that they have to be stored at ultra-low temperatures, which poses many logistics challenges, especially in poorer countries.

In Brazil, these issues have been resolved to some extent, as the most remote populations, such as those living on the banks of the Amazon River, for example, do not have access to these vaccines.

There are other platforms being developed, many of them based on virus-like particles (VLP), in which the main antigen is included in a protein-only composition, which is uninfectious but resembles a virus and is in turn very immunogenic; other vaccines are composed of antigenic proteins that are formulated with potent adjuvants and induce a strong immune response.

These platforms had all been developed and when SARS-CoV-2 emerged at the end of 2019, and the spike protein sequence in February 2019, these different groups used the spike protein to develop their vaccines. The spike protein was known to be essential for the penetration of the virus into the cell and these findings had been described in studies conducted with the SARS-COV strain that appeared in China in 2002/2003.

In addition to vaccine production platforms, administration routes are also evolving. These rapidly developed vaccines are all intramuscular, but we know that the subcutaneous route is very important because it induces high and efficient responses. The intradermal route, using micro-needles, activates Langerhans cells. These are vaccines that, with a small amount of antigen, induce extremely high responses and, in terms of protecting mucous membranes, we need to think about other forms of immunization.

Since March 2020, our group has been working on a nasal instillation vaccine for COVID. At the very beginning of the pandemic, we recruited 250 individuals who had been infected with COVID, studied the antibody response in detail and saw that in fact a response against the RBD (Receptor Binding Domain) was sufficient. The spike did not need to be fully utilized, and this protein may be involved in the adverse reaction processes we have observed. We also studied using algorithms which were the best antigenic determinants for CD4 and CD8 cell response, synthesized 67 peptides from the 32 viral proteins and selected 14, 7 CD4 and 7 CD8, which cover the interaction with HLA molecules to be presented and induce a good T-cell response. This RBD and the peptides were placed in two types of nanoparticles after testing more than 50 formulations. The vaccine thus prepared was used through nasal instillation and induced a systemic response with a production of circulating neutralizing IgG and also T lymphocytes that also recognize the virus. Above all, however, we observed an IgA response in saliva

and bronchoalveolar lavage, which is what we were aiming for. A response of this type of immunoglobulin, which is responsible for protecting the mucous membranes. This type of vaccine, which is currently in the production phase of pilot batches for human trials, aims to produce an RBD vaccine that can be changed very easily, depending on which variant is circulating, and also to induce an IgA response that will prevent infection of the nasal mucosa, so that the disease will not spread, viral replication will be prevented, transmission among asymptomatic individuals will cease, and we think that we can therefore completely control the pandemic.

Science has achieved a new record in 11 months: after the appearance of a new disease, a vaccine was widely applied and the pandemic has been controlled, or at least the incidence and mortality of the disease has been reduced. Whether the pandemic will last is yet to be seen, as is the question of how long the protection acquired through vaccination will last. What has the medical community thinking hard is the low uptake of vaccinations in many places. The incessant work of antivaccine groups, preventing the population from getting vaccinated and presenting some adverse effects, which have in fact occurred, as if they were generalized to everyone. Different means of communication should be used to educate the population, not just the classic media such as television, radio, and newspapers, but digital media such as social networks in order to reach all strata of the population.

In the US, where RNA vaccines have been highly effective, only two thirds of the population has been vaccinated. More importantly, the unvaccinated population generally comes from the poorest and least educated backgrounds. However, antivaccine movements are important in the most educated population - this is a major problem for the advancement of vaccination worldwide and a joint effort across all academia would be very valuable.

It is worth noting that in the future with all these platforms, studies and advances in immunology; it may be possible to make vaccines against something that we are not currently considering, such as infectious diseases that invade the immune response in general, against cancer. Today we have the anti-HPV vaccine, in which the virus induces cancer, so it could be considered an anti-cancer vaccine.

In the future, we could make vaccines against specific cancer antigens, or immunotherapies against these antigens using the vaccine principle and checkpoint inhibitors together.

For allergies and asthma, we could also, in the future, have immunizations against allergens in order to induce IgG and not IgE, which causes the disease. For autoimmune diseases, we could have immunizations every time we find out which agent triggers them, as many of them are triggered through infectious agents, such as rheumatic fever, and perhaps for degenerative diseases, in many of which there is an immunological component in the degenerative mechanism.

This is a very broad field, and vaccines can be used to provide top-quality preventive medicine.

Finally, may I remind you of what vaccines bring us. A vaccine is the perfect medical act, because it prevents disease and suffering! It is easily applicable to the population and the cost is very low. It reduces infant mortality while increasing life expectancy. However, this information needs to be disseminated to the population. New technologies and new vaccines will come along and they will have to prove their benefits. Let us strive for a healthier world and greater equity, with greater access to health care to prevent the diseases that afflict humanity.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Starting a practice in Allergy & Immunology: what do I need?

Construindo o consultório do Alergista e Imunologista: o que é preciso?

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ABSTRACT

What do I need to start a practice in Allergy & Immunology? This has been a frequent concern for young specialists, one that often goes unanswered. The Statute, Regulations, and Standards Committee of the Brazilian Association of Allergy and Immunology (CERN-ASBAI) proposes the publication of a series of articles to provide guidance on the essential steps for establishing good practices in the clinical care of allergic patients.

Keywords: Allergology, immunology, good practices.

RESUMO

O que é preciso para abrir o consultório do especialista em Alergia e Imunologia? Esta é uma preocupação frequente dos jovens especialistas, que muitas vezes fica sem resposta. A Comissão de Estatuto, Regulamentos e Normas da Associação Brasileira de Alergia e Imunologia (CERN-ASBAI) propõe a publicação de uma série de artigos com o objetivo de orientar sobre os passos essenciais para o estabelecimento de boas práticas no atendimento clínico de pacientes alérgicos.

Descritores: Alergia, imunologia, boas práticas.

Introduction

The Statute, Regulations and Standards Committee of Brazilian Association of Allergy and Immunology (Comissão de Estatuto, Regulamento e Normas da Associação Brasileira de Alergia e Imunologia - CERN-ASBAI) presents a practical guide on how to structure the practice of an Allergy and Immunology specialist, based mainly on the regulations of the Brazilian Federal Board of Medicine (Conselho Federal de Medicina - CFM), including updates to the rules for supervising physicians' practices,[1] which are already in force. Other precepts deriving from ASBAI own Statutes and those of other medical organizations, such as the Brazilian Medical Association (Associação Médica Brasileira - AMB), and the Brazilian Health Regulatory Agency (Agência de Vigilância Sanitária - ANVISA), and other Brazilian public bodies.[1-3]

CFM Resolution No. 2.214/18 asserts that the enforcement department acts through its regional offices (Conselhos Regionais de Medicina/CRMs) through official acts, but also at the behest of society and the Public Prosecutor's Office (Ministério Público - MP). This enforcement department has the fundamental task of standardizing quality health care for the population. According to current regulations,

1. Associação Brasileira de Alergia e Imunologia (ASBAI) - Comissão de Estatuto, Regulamentos e Normas, administration 2023/2024.
2. ASBAI - President, administration 2023/2024.
3. ASBAI - Research Director, administration 2023/2024.

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medical practices and clinics have been categorized into three groups based on complexity of care and procedures they provide,[1] as follows.

– Group 1: practices or facilities where primary health care is provided with no procedures, local anesthesia, or sedation.
– Group 2: practices where consultations and basic allergic tests (prick and patch tests) are performed.
– Group 3: practices or facilities where local anesthesia without sedation, desensitization, and provocation tests are performed.

It should be emphasized, however, that after graduating from medical school and, as a rule, then qualifying through the AMB/scientific entities representing specialties or medical residency/Ministry of Education (Ministério da Educação - MEC),[5] doctors are repeatedly unaware of the legal and ethical rules necessary for perfectly executing their professional practice.

As a result, physicians are likely to comply with a variety of directives, fees, and regulations from time to time, both from the CFM,[1] through CRMs, and from ANVISA[2] in every state, thus requiring prior knowledge on the part of the physician in order to meet their demands.

Opening and running an allergist and immunologist's practice

"What would be necessary, regarding legal requirements, to open a medical office?"

Official documentation

It should be noted that in the private health care sector, when physicians' practice in a locality, they are required to have an official operating license, which is mandatory for this purpose. This documentation is made up of registrations with the various public bodies specified below.[2,6]

– Local operating license (ALF): Local administration.
– Local health surveillance license (may vary according to state regulations): Local administration.
– Environmental license; Fire department permit (ACVB): Local fire department.
– National registry of health facilities (CNES)[4]: Local or state health secretariat.
– Self-employed registration: Local administration.

Taxes/Individuals

Physicians should be aware of taxes such as tax on services of any kind (ISS or ISSQN), levied monthly by the local government, the National Social Security Institute (Instituto Nacional do Seguro Social - INSS), paid monthly, and the Individual Income Tax (Imposto de Renda de Pessoa Física - IRPF) or Carnê Leão, which must be paid monthly and represents the equivalent of income tax for earnings that the taxpayer (physician) receives from individuals/private patients.

Taxes/Legal entities

If the practice is a legal entity,[3-5] it can apply for federal tax through the Simples Nacional system, which is a type of tax regime based on a unified payment of taxes: Programa de Integração Social (PIS), Contribuição para o Financiamento da Seguridade Social (COFINS), Imposto sobre a Renda das Pessoas Jurídicas (IRPJ), Contribuição Social sobre o Lucro Líquido (CSLL), and ISS, also a monthly payment.

Specialist Registration/RQE

Individuals

It is essential for physicians to be registered in a particular speciality to have their RQE (Specialist Registration) – a legally binding document that certifies medical training in a speciality with the CRM.[7] An RQE in Allergy and Immunology provides primacy in the care of immunoallergic diseases of the pediatric and adult population, and can be obtained through successful completion of the annual qualifying examination held by the ASBAI/AMB.[5]

Practice/Directorate in the speciality of Allergy and Immunology

For specialized immunoallergic disease practice, in addition to availability of a technical/clinical director, an RQE in Allergy and Immunology is mandatory.[8] Therefore, it is recommended that ASBAI specialist members, in order to strengthen their speciality in Allergy and Immunology, when practicing as a legal entity, avoid assisting as a director in any activities that are not directly linked to the practice, thus ensuring that their work is ethical, in accordance with ASBAI statutory regulations.[9]

Management of allergenic extracts in the allergist and immunologist's practice

The indication, guidance, supervision and interpretation of skin tests with allergens (prick test and patch test), and the prescription, planning, and supervision of the application of subcutaneous or sublingual allergen-specific immunotherapy, are exclusive medical practices.[10]

The CFM and CRMs, the AMB, and the Brazilian National Medical Residency Commission (Comissão Nacional de Residência Médica - CNRM), through Resolution CNRM No. 12/2019, recognize that the handling of allergenic extracts is the usual practice of trained doctors, especially those qualified in Allergy and Immunology, and therefore establish that allergists and immunologists are the best prepared to handle them.[10-14]

In practices of groups 2 and 3, the CFM recognizes that the conditions of the place used to perform immediate (prick) and delayed (contact) allergic tests, dilution of allergenic extracts, and application of subcutaneous allergen-specific immunotherapy, provocation tests and desensitization with medicines and food are Allergy and Immunology practices.[10]

It should be mentioned that the journal Arquivos de Asma, Alergia e Imunologia (Archives of Asthma, Allergy and Immunology) has recently reported on the need for quality certification for prick tests in order to safeguard the health of allergic patients and guarantee the quality of the service provided to professionals.[15]

Fee-for-service earned for allergists' and immunologists' practice

When itemizing a receipt or invoice for a procedure performed in the practice, for example, handling/applying allergenic extracts, it must be stated, in accordance with CFM Resolution No. 2.215/2018, that the specialist is being paid a fee for planning and/or following up on the handling of these allergens.[8]

Informed consent form

In recent years there has been a significant increase in legal proceedings in the health system in general, including the medical sector. The importance of the Informed Consent Form in favor of medical ethics for patients has therefore arisen.

The CFM considers that the informed consent form consists of the decision-making, agreement, and approval of the patient or their surrogate, following adequate information and explanations, under the responsibility of the physician, regarding the diagnostic or therapeutic procedures recommended for the patient.

As such, allergists and immunologists should consider an informed consent form, included in the annex to CFM Recommendation No. 1/2016,[16] for procedures performed in their practices, thus demonstrating zealousness in their practices, and significantly improving standards in the services provided to their patients.

No obligation to hire health care personnel for speciality practice in medical practices and clinics

Medical practices and clinics are not required to hire other health care personnel to supervise physician aides in the professional practice of allergists and immunologists.

The CFM has even ruled that medical practices and other medical facilities are not subject to the rules of the Brazilian Board of Nursing (Conselho de Enfermagem), which apply their regulations only to nursing professionals, whereas CRMs are responsible for supervising medical services within their jurisdiction.[17]

Advertising your speciality

The speciality of Allergy and Immunology is often advertised on stamps, prescriptions, signs, and other advertisements with various names, for example: Allergology, Clinical Allergy, Allergy and Immunopathologist, Clinical Immunologist, and Allergoimmunologist. The CFM recognizes this speciality as Allergy and Immunology, in accordance with CFM Resolution No. 1.092/1983.

It is important to note that the name of the scientific organization is determined in the statutes as the Brazilian Association of Allergy and Immunology (Associação Brasileira de Alergia e Imunologia), and is included as part of ASBAI's assets. Thus, standardizing the name of the speciality in practices will certainly strengthen Brazilian Allergy and Immunology equally, and given that the speciality has its own particularities in terms of care for all age groups, ASBAI advocates advertising in practices, in addition to other advertisements of any kind, as shown below.[25]

NONONONO NONONONO, M.D.
ALLERGY AND IMMUNOLOGY - RQE 123
CHILDREN AND ADULTS
CRM-UF 1234

Allergist and Immunologist's scope of practice, according to age group in practices

In accordance with CFM Resolution No. 1.627/2001, allergists and immunologists are not, nor can they be, a fragment of a specialist who specializes in a fraction of human immune systems, but rather qualified doctors who are able to act with greater resourcefulness and capacity in allergic and immunological pathologies in all age groups. As such, the speciality is not limited to a certain age group, as acknowledged in ASBAI's own Articles of Incorporation in Article 5, item 9, AMB Secretariat Official Letter No. 123/2021, endorsed by the Brazilian Society of Pediatrics (Sociedade Brasileira de Pediatria) and also in the Diário Oficial da União (D.O.U., Federal Official Gazette) of December 3, 2018, section 1, page 231, which states that "for the exclusive care of pediatric patients, clinical responsibility is to be held by a physician with an RQE in Allergy and Immunology or an RQE in Pediatric Allergy and Immunology."

As such, there is no legal restriction on health insurance companies limiting allergists and immunologists to practice in their practices.

Follow-up appointments, according to CFM Resolution No. 1.958/2010

Appointments consist of anamnesis (interview about the patient's history and, if applicable, the disease), physical examination, drawing up diagnostic hypotheses or conclusions, requesting complementary tests (when necessary) and therapeutic prescription, and it is the doctor's prerogative to set deadlines for follow-up appointments.

In the case of tests whose results cannot be analyzed during the appointment, the medical practice will be continued at a follow-up appointment, and no additional fees should be charged.

However, if there are changes in signs or symptoms that require a new anamnesis, physical examination, formulation of diagnostic hypotheses or conclusions, and therapeutic prescription, the medical practice will be considered a new appointment and should be remunerated.

In cases of illnesses that require prolonged treatment, with follow-up examinations and therapeutic modifications, appointments may be charged for at the physician's discretion. It is also up to physicians to set follow-up appointments.

The time needed to examine the patient and their tests is determined by technical and medical criteria, rather than administratively.

Health insurance providers cannot interfere in the autonomy of the physician or in their relationship with the patient, nor can they set an interval between appointments. These institutions' technical directors will be held ethically responsible if they fail to comply with the provisions of this resolution.[22]

How to proceed when a patient is referred from another medical practitioner

According to the Code of Medical Ethics, the doctor in his practice "cannot fail to refer a patient who has been sent for a specialized procedure back to the treating doctor and, immediately afterwards, provide them with the appropriate information about what happened during the period in which they were responsible for the patient.".[23]

Thus, when a patient is referred to an allergist and immunologist, they should always seek the patient's benefit and, ethically speaking, they should provide feedback to the referral doctor by means of appropriate documentation, providing information on their practice.

Allergists and immunologists and professional advertising

It is increasingly important to communicate well with people and it is no different in medicine. In order for allergists and immunologists to disseminate information correctly and ethically in their practices, it is important to be aware of the rules of medical advertising and to keep up to date with the specific regulations on this subject, avoiding abuses that could lead to ethical and disciplinary proceedings.[25]

Each CRM has its own Commission for the Dissemination of Medical Matters (Comissão de Divulgação de Assuntos Médicos - CODAME), which is responsible for guidance, education, and supervision of physicians on issues related to advertising in their medical practice.

This body verifies whether the physician is (through posts on social media or other means

of communication, such as interviews) practicing breaches of confidentiality, undue exposure of the patient's image, promising results, unfair competition, sensationalism, among others.

Requirements for each type of practice, depending on the level of medical procedures inherent to the speciality

The requirements for establishing an Allergy and Immunology medical practice are different due to the definitions set out in the CFM classifications, although they also safeguard the privacy and confidentiality guaranteed in all instances. Within these definitions, they have been categorized into the following types of medical practice, namely Group 1, Group 2, and Group 3.[1,20]

Group 1

These are practices or facilities where basic medicine is practiced with no procedures, local anesthesia, or sedation.

In practice, they are intended for medical appointments with no procedures or immunotherapy.

According to the Manual Soma SUS of the Ministry of Health, all the items listed below that are not optional are deemed essential and should be included in the practice.

Furniture

- Two chairs or armchairs - one for the patient and one for their carer.
- A chair or armchair for the physician and a table/ desk.
- A simple padded stretcher, covered in waterproof material.
- A two- or three-step ladder for patient access to the stretcher.

If the practice has medicines subject to special control

- A lockable storage area for medicines subject to special control (essential; Ordinance MS/SVS 344/1998 art. 67).

Clinical materials

- Paper towels.
- Liquid soap for hygiene.
- Pedal garbage cans.
- Disposable sheets for stretchers.
- A sphygmomanometer.
- A clinical stethoscope
- A clinical thermometer.
- A flashlight with batteries.
- Disposable tongue depressors.
- Disposable gloves.
- A negatoscope or other digital medium that enables image reading.
- An otoscope (optional).
- An anthropometric scale suitable for each age group (optional).
- An inelastic flexible plastic tape measure (optional).
- An ophthalmoscope (optional).
- A reflex hammer for neurological examination (optional).
- Peak expiratory flow meter (optional).
- Oximeter.
- Nasal speculum.
- A sink or toilet (recommended by CENR-ASBAI) with a clinical hospital tap.
- Gel or spray sanitizer.
- Derma alcohol.

Group 2

These are practices or facilities where procedures are performed with no local anesthesia or sedation.

For these services, in addition to the equipment listed in the basic practice (see Group 1) for propedeutics, equipment for therapeutic procedures is also required.

These are practices where appointments and basic allergic tests (prick and patch tests)[1] are performed, and should meet the requirements below.

If the practice has medicines subject to special control[1]

- A lockable storage area for medicines subject to special control (essential; Ordinance MS/SVS 344/1998 art. 67).
- All the items contained in Group 1, plus material for asepsis/sterilization in accordance with sanitary standards and a rigid container for the disposal of sharps.

Whether immediate reading skin tests (Prick test) or contact tests (Patch test) are performed[1]

– Room tiled or covered in a waterproof material (epoxy or ceramic).
– Cold floor for easy cleaning.
– A sink or toilet (recommended by CENR-ASBAI) with a clinical hospital tap.
– A refrigerator with a minimum and maximum thermometer for exclusively storing tests and vaccines (antigens registered with ANVISA).
– Countertop and cabinets with straight lines to facilitate cleaning.

Immunotherapy with antigens (inhalants and/or insects)[1]

– Room tiled or covered in a waterproof material (epoxy or ceramic).
– Cold floor for easy cleaning.
– A sink or toilet with a clinical hospital tap, as recommended by CENR-ASBAI.
– A refrigerator with a minimum and maximum thermometer for exclusively storing tests and vaccines (antigens registered with ANVISA).
– Countertop and cabinets with straight lines to facilitate cleaning.

Medicines available[1]

– Adrenaline (Epinephrine 1:1000 - 1 mg/mL).
– Antihistamines for parenteral use (Diphenhydramine or Promethazine).
– Short-acting β2-agonist bronchodilators spray with spacer (e.g. Sabutamol 100 µg). Salbutamol solution for nebulization or flaconettes (1.25 mg/mL) and nebulizer is recommended by CENR-ASBAI.
– Glucocorticoid for parenteral use (Hydrocortisone or Methylprednisolone).
– H2 antihistamine for parenteral use (Ranitidine).
– Prednisolone (1 mL/3 mg).
– Second generation oral antihistamine.

Group 3

These are practices where, in addition to the procedures listed in groups 1 and 2, immunotherapy, desensitization, provocation tests, and intradermal allergic tests are performed.[1]

The materials described below are those required for Group 3, in addition to the materials mentioned in the previous groups.

– Allergenic extracts registered with ANVISA.
– Material for minor surgery (optional).
– Material for dressings/stitches removal (optional)
– Material for local anesthesia (optional).
– Material for asepsis/sterilization in accordance with sanitary standards.
– A rigid container for the disposal of sharps.

Safety requirements for emergency care[1]

– Within the doctor's practice or referred for appropriate care for any problems within 4 minutes.
– CERN-ASBAI recommends to take the ASBAI Advanced Life Support in Anaphylaxis and Asthma Course (AALS) for training in the appropriate medications and materials that can be used in the event of complications. We should bear in mind what is laid down in the Code of Medical Ethics: Physicians are not allowed to (...) "Art. 2 Delegate to other practitioners acts or attributions that are exclusive to the medical practice.".

Intradermal testing[1]

– Room tiled or covered in a waterproof material (epoxy or ceramic).
– Cold floor for easy cleaning.
– A sink or toilet with a clinical hospital tap, as recommended by CENR-ASBAI.
– A refrigerator with a minimum and maximum thermometer for exclusively storing tests and vaccines concentrates.
– Allergenic extracts registered with ANVISA.
– Countertop.
– Cabinets with straight lines to facilitate cleaning.

Provocation and desensitization tests[1]

– Room tiled or covered in a waterproof material (epoxy or ceramic).
– Cold floor for easy cleaning.
– A sink or toilet with a clinical hospital tap, as recommended by CENR-ASBAI.
– A refrigerator with a minimum and maximum thermometer for exclusively storing tests and vaccines.

- Antigens registered with ANVISA.
- Countertop and cabinets with straight lines to facilitate cleaning.

Medicines available, according to MS/GM Ordinance No. 2048/02, annex, item 1.3[1]

- Adrenaline (Epinephrine 1:1000 - 1 mg/mL). Antihistamines for parenteral use (Diphenhydramine or Promethazine).
- Short-acting β2-agonist bronchodilators spray with spacer (Salbutamol 100 µg).
- Salbutamol (solution for nebulization) or flaconettes (1.25 mg/mL) and nebulizer (recommended by CERN-ASBAI).
- Glucagon (recommended by CERN-ASBAI).
- Glucocorticoid for parenteral use (Hydrocortisone or Methylprednisolone).
- Prednisolone (1 mL/3 mg).
- H2 antihistamine for parenteral use (Ranitidine): see note on discontinuation of this drug by ANVISA.
- Oropharyngeal cannulas (Guedel).
- Automatic External Defibrillator (AED).
- Medicines for cardiopulmonary arrest and anaphylaxis.
- Distilled water (ampoule or floconet).
- Diazepam.
- Dipyrone or another option if the patient has a hypersensitivity reaction to it.
- Glucose 50% and Glucose 5% (recommended by CERN-ASBAI).
- Physiological saline 0.9%.
- Lactacto Ringer's Saline Solution (recommended by CERN-ASBAI).
- Oxygen supply (fixed or cylinder) with applicator mask and humidifier (essential).
- Pulse oximeter.
- Manual self-inflating balloon ventilator with reservoir and mask (essential).
- Syringes, needles and equipment for intravenous application (essential).
- Needle scalpel.
- Butterfly and intracath (with all the material for insertion).
- Gauze.
- Cotton wool.
- Crepe bandages.
- Disposable gloves.
- Rigid collection box for sharps.

Conclusion

Hence, with a view to guiding and standardizing the services provided by the Allergy and Immunology specialty, while also providing adjustments for those existing practices, this initial publication has sought to provide technical information in the light of the requirements of the supervisory bodies for professional practice, while also providing a structure for the operation of each practice classification group, guaranteeing safety for the practice of the specialty in its ethical and scientific dimension.

It also reinforces, among the various particularities of practice, that applying allergic extracts registered with ANVISA is the usual activity of the Allergist and Immunologist, recognized by the main medical entities involved in medicine, and that the specialty's practice is not fragmented and therefore has no restrictions on care by age group, thus enhancing its job market.

Finally, the guidelines described in this guide will certainly serve to answer many of the specialty's questions, in view of the care that is desired and appropriate for the environment of the Allergist and Immunologist specialist and, consequently, for patient safety.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Practical guide for the use of immunobiologic agents in allergic diseases - ASBAI

Guia prático para o uso de imunobiológicos em doenças alérgicas - ASBAI

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ABSTRACT

Monoclonal antibodies are a new class of drugs that represent a milestone in the evolution of therapy for severe allergic diseases. In addition to allowing targeted immunologic therapy, they can improve symptom control, reduce exacerbations, and increase quality of life and safety. The efficacy and safety of monoclonal antibodies in the treatment of allergic diseases are well documented in pivotal, extension, and real-life clinical studies. In Brazil, immunobiologic agents are currently licensed by the National Health Surveillance Agency (ANVISA) for use in asthma, atopic dermatitis (AD),

RESUMO

Os anticorpos monoclonais são uma nova classe de medicamentos que representa um marco na evolução da terapia de doenças alérgicas graves. Além de possibilitar uma terapia imunológica alvo específico, proporciona maior controle de sintomas, redução de exacerbações, melhoria da qualidade de vida e da segurança. A eficácia e a segurança dos anticorpos monoclonais no tratamento de doenças alérgicas estão bem documentadas nos estudos clínicos pivotais, de extensão e de vida real. No Brasil, estão licenciados atualmente pela Agência Nacional de Vigilância

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eosinophilic esophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndrome (HES), and chronic spontaneous urticaria (CSU). With the incorporation of these new therapies into the daily practice of the allergist and immunologist, practical aspects will naturally emerge and require practical guidelines in light of the most current scientific evidence in order to maintain good medical practice, with judicious and conscious use by a qualified specialist. Therefore, in this practical guide, we will address the immunobiologic agents currently approved for severe allergic diseases, aiming to assist allergy and immunology specialists in the prescription and practical management of these medications, including indications, contraindications, efficacy and safety monitoring, adverse event reporting, as well as health care factors associated with vaccination, special populations, access, transport, storage, and home use.

Keywords: Monoclonal antibodies, asthma, urticaria, atopic dermatitis, eosinophilic esophagitis, nasal polyps.

Sanitária (ANVISA) imunobiológicos para asma, dermatite atópica (DA), esofagite eosinofílica (EoE), granulomatose eosinofílica com poliangeíte (GEPA), rinossinusite crônica com pólipo nasal (RSCcPN), síndromes hipereosinofílicas (SHE) e urticária crônica espontânea (UCE). Com a incorporação do uso dessas novas terapias no dia a dia do médico alergologista e imunologista, naturalmente emergem aspectos práticos que exigem orientações práticas perante as evidências científicas mais atuais, a fim de se manter a boa prática médica, com uso criterioso e consciente pelo especialista capacitado. Assim, nesse guia prático, abordaremos os imunobiológicos aprovados até o momento para doenças alérgicas graves, com objetivo de auxiliar o especialista em Alergia e Imunologia na prescrição e manejo dessas medicações, incluindo indicações, contraindicações, monitoramento da eficácia e segurança, notificação de eventos adversos, bem como aspectos associados aos cuidados com vacinas, populações especiais, acesso, transporte, armazenamento e aplicação domiciliar.

Descritores: Anticorpos monoclonais, asma, urticária, dermatite atópica, esofagite eosinofílica, pólipos nasais.

Introduction

Progress has been made in our understanding of the pathogenesis of allergic diseases and the identification of phenotypes and endotypes, in parallel with the development of target therapies, which has allowed us to apply the concept of precision medicine to treat patients with severe allergic diseases. In parallel with the development of this knowledge, a number of practical factors have had an impact on the incorporation of these new therapies into allergists' and immunologists' routine.

Immunobiologic agents are high molecular weight molecules with a complex structure, produced in organisms or live cell cultures acting on the immune system. They comprise several classes: vaccines, serums, immunoglobulins, monoclonal antibodies, fusion proteins, and human cytokines. In this guide, we will look at monoclonal antibodies, which are the most recent class and the most widely used in severe allergic diseases.[1,2] Currently, monoclonal antibodies are an emerging class of drugs and are licensed by ANVISA in Brazil for the following conditions: asthma, atopic dermatitis (AD), eosinophilic oesophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndromes (HES), and chronic spontaneous urticaria (CSU). Among the drugs licensed in the Sistema Único de Saúde (SUS, Brazil Unified Health System), only omalizumab and mepolizumab are for the treatment of severe asthma.[3] In the supplementary health care system, 4 immunobiologic agents have been incorporated onto the Agência Nacional de Saúde (ANS, Brazil National Health Agency) list of procedures: omalizumab, mepolizumab, benralizumab, and dupilumab, covering various indications.[4] In 2022, ANVISA licensed tezepelumab for the additional treatment of patients with severe asthma and it has not yet been incorporated for use in the SUS or in supplementary health care.

The efficacy and safety of monoclonal antibodies in the treatment of allergic diseases are well documented in pivotal and extension clinical studies. In addition, real-life studies (RLS) have been conducted for most biological agents and allergic conditions. Further use in clinical practice needs to be judicious, with supervision by a trained physician, monitoring during application, continuous evaluation of the response to treatment, and any potential adverse events.[5,6]

This practical guide aims to help the Allergy and Immunology specialist with the prescription of immunobiologic agents, including: indications, contraindications, monitoring efficacy and safety, reporting adverse events, and practical details of transport, storage, and application.

Immunobiologic agents

Omalizumab

Mechanism of action

Omalizumab is a humanized IgG1 monoclonal antibody whose main mechanism of action is the neutralization of circulating IgE. This immunobiologic agent specifically binds to the Cε3 portion of the circulating free IgE molecule and thus prevents it from binding to its FcεRI and CD23 receptors on the surface of mast cells, basophils, and other cell types. As demonstrated in several studies, as a result of the formation of omalizumab-IgE complexes in the circulation, a reduction in the expression of FcεRI on the surface of mast cells and basophils is observed, with a reduction in the activation and degranulation of these effector cells and the production of IgE. As a result, the recruitment of inflammatory cells to the target tissue, especially eosinophils, is inhibited and, therefore, the use of omalizumab minimizes the T2 inflammatory cascade that characterizes the pathogenesis of allergic asthma.[7-9]

Omalizumab also reduces the number of a subtype of dendritic cells that are increased in asthma exacerbations, contributing to the control of type 2 inflammation. In addition, evidence shows that patients treated with omalizumab produce more IFN-α in response to rhinovirus and influenza infections, which could be associated with a reduction in the number of exacerbations triggered by these infectious agentes.[10]

Omalizumab is effective in severe allergic asthma, as it reduces the number of exacerbations, controls symptoms, improves quality of life, reduces the use of oral corticosteroids, and improves lung function.[11]

In CRSwNP, this immunobiologic agent has shown efficacy in reducing the size of polyps, improving symptom control and quality of life.[12]

Spontaneous chronic urticaria (SCU) is currently considered an autoimmune disease, in which the presence of IgG anti-FcεRI or IgG anti-IgE autoantibodies (type IIb autoimmunity) producing mast cell degranulation is observed. Another mechanism described is the presence of IgE class autoantibodies against autoallergens (type I autoimmunity). Omalizumab exerts its effects through serum IgE level reduction, which decreases binding to IgG class anti-IgE autoantibodies, thus reducing IgE class autoantibody levels. In addition, the expression of the FcεRI receptor in cutaneous mast cells and basophils is reduced, thus decreasing the activation of these cells and reducing the action of anti-FcεRI IgG autoantibodies.[13-15] Omalizumab has been shown to be effective in SCU through reduced onset of urticaria and angioedema, skin pruritus, and a significant improvement in quality of life.[13]

Indications and contraindications

Omalizumab is indicated as an add-on treatment for adults and children (over 6 years old) with persistent, moderate to severe allergic asthma with symptoms inadequately controlled by inhaled corticosteroids (ICS). Also, 2 other indications include complementary treatment for adults (over 18 years old) with CRSwNP in which treatment with intranasal corticosteroids has not promoted adequate control of the disease; and additional treatment for adult patients and adolescents over 12 years old with spontaneous chronic urticaria refractory to treatment with H1 antihistamines.

Omalizumab must not be used in patients who are hypersensitive to the active substance or any other component of the product. In the filled syringe presentation, the product contains natural latex and may cause allergic reactions in patients with latex allergy.[14]

Dosage regimens

In the treatment of asthma and CRSwNP, the doses of omalizumab are calculated according to the level of total serum IgE (IU/mL) and the weight of the patient (kg). The established dose is 0.016 mg/kg per IU/mL of total IgE ranging from 1 to 4 150 mg ampoules (150-600 mg) administered subcutaneously at intervals of 2 to 4 weeks. The dose is calculated according to the weight of the patient and baseline total IgE, with total IgE levels in eligible patients ranging 30 to 1500 IU/mL and body weight of 20 to 150 kg, according to the table in the patient information leaflet (PIL).[14]

In CSU, a fixed dose of 2 150 mg vials (total dose = 300 mg) every 4 weeks is recommended. However, the latest international consensus on urticaria established that, in the absence of improvement with the initial dose of 300 mg, the dose can be increased up to 600 mg with a 2-week interval between administrations.[15]

Adverse events

In general, omalizumab has a good safety profile as demonstrated in the initial and follow-up studies over almost 20 years of use in clinical practice. The most frequently reported adverse reactions in studies of adult patients with asthma were application site reaction, respiratory infection, sinusitis, headache, and pharyngitis.[14] The risk of developing anaphylaxis to omalizumab is low, around 0.09%, the majority (77%) occurring in the first 2 hours after administration of the first 3 doses.[16] Clinical studies, and RLS in the pediatric population, have also shown an acceptable overall safety profile with no evidence of an increased risk of anaphylaxis, urticaria, hypersensitivity reactions and malignancies.[17]

In chronic spontaneous urticaria, the most common adverse events described in pivotal studies were application site reactions, followed by upper respiratory tract infections and headache.[18] In RLS, an overall average of 4% (1% to 7%) of adverse events were reported, while in clinical trials these were reported at 2.9% to 8%.[19]

In the studies of omalizumab in CRSwNP, 50.4% of patients experienced at least 1 adverse event. Most of these were mild to moderate, the most common being headache, nasopharyngitis, and reaction at the site of application.[12]

Excipients

Excipients include sucrose, histidine, histidine hydrochloride monohydrate, and polysorbate. Each diluent ampoule contains 2 mL of water for injection, used to dissolve the powder.[14]

Table 1 summarizes the clinical use of omalizumab.

Mepolizumab

Mechanisms of action

Mepolizumab is a humanized IgG1/k monoclonal antibody of murine origin that binds with high affinity to human interleukin-5 (IL-5) and prevents the interaction of this cytokine with the alpha subunit of the IL-5 receptor (IL-5R). IL-5 is an important type 2 cytokine that can be produced by the activation of acquired immunity, namely T helper 2 lymphocytes (Th2) and also by the innate immunity pathway, that is, type 2 innate lymphoid cells (ILC2), playing a fundamental role in eosinophilic inflammation. IL-5 is essential for the maturation of eosinophils in the bone marrow

Table 1
Omalizumab - summary of clinical use

Mechanism of action	Blocks circulating IgE preventing binding to its high and low affinity receptors, resulting in reduced activation of the Th2 inflammatory cascade
Indications	Additional therapy for severe allergic asthma aged > 6 years old, CSU aged > 12 years old, and CRSwNP aged > 18 years old
Dosage regimen	Asthma and CRSwNP: dosage according to total serum IgE and patient weight, administered every 2 to 4 weeks CSU: 300 mg, subcutaneously, every 4 weeks
Main adverse events	Most commonly reported adverse reactions: headache and application site reactions. Anaphylaxis was described in initial studies and has an estimated occurrence rate of 0.09%

CSU = chronic spontaneous urticaria, CRSwNP = chronic rhinosinusitis with nasal polyps.

and their release into the blood. In humans, IL-5 acts on eosinophils, participating in their proliferation, maturation, recruitment, activation, and survival. IL-5 appears to modulate the development and function of basophils and mast cells, increasing the release of basophil mediators by binding to IL-5R present in basophils.[20]

The efficacy of mepolizumab is well documented in severe eosinophilic asthma, with reduced incidence of severe exacerbations, symptom control, improved quality of life, reduced use of oral corticosteroids, and improved lung function. Mepolizumab significantly reduces blood and sputum eosinophilia.[21]

Indications and contraindications

Mepolizumab is indicated for the treatment of severe eosinophilic asthma (≥ 6 years old), CRSwNP (≥ 18 years old), eosinophilic granulomatosis with polyangiitis - EGPA (≥ 18 years old) and hypereosinophilic syndrome (≥ 12 years old).[22]

Mepolizumab must not be used in patients with known hypersensitivity to the drug or any of its excipients.

Dosage regimens

The dosage regimens for the indications licensed in Brazil are described below and are differentiated according to the indication and age group:

Severe eosinophilic asthma - children aged 6 to 11 years - 40 mg, subcutaneously, every 4 weeks; adolescents and adults - 100 mg, subcutaneously, every 4 weeks.

CRSwNP - 100 mg, subcutaneously, every 4 weeks.

EGPA - 300 mg, subcutaneously, every 4 weeks.

HES - 300 mg, subcutaneously, every 4 weeks.

Adverse events

Real-world pivotal and extension studies, with follow-up for 3 to 5 years, report a good safety profile for anti-IL-5 therapy. The most frequently reported adverse events include headache, upper airway infections, application site reactions, and skin rashes.[23]

Excipients

Excipients include sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate dihydrate, and water for injections.[22]

Table 2 shows the clinical use of mepolizumab.

Benralizumab

Mechanism of action

Benralizumab is a humanized, afucosylated IgG1/k monoclonal antibody of murine origin that binds to the alpha subunit of IL-5R, preventing the receptor from forming and IL-5 from binding. As a result, IL-5 cannot exert its biological effects on the target cells. In addition to this mechanism of action, benralizumab interacts with the FcγRIIIα surface receptor of natural killer (NK) cells, via its Fc portion, inducing the death of resident and circulating eosinophils by antibody-dependent cell-mediated (ADCM) cytotoxicity.[21]

Studies on benralizumab in asthma have shown efficacy in reducing severe exacerbations, controlling symptoms, improving quality of life, reducing the use of oral corticosteroids, and improving lung function. Benralizumab rapidly and significantly reduces blood and sputum eosinophilia.[24]

Indications and contraindications

Benralizumab is indicated as an add-on treatment in patients with severe eosinophilic asthma ≥ 18 years old. It is contraindicated in patients with known hypersensitivity to benralizumab or any of its excipients.[25]

Dosage regimens

The dosage regimen in severe eosinophilic asthma is 30 mg (1 syringe), subcutaneously, every 4 weeks for the first 3 doses, and 30 mg (1 syringe) every 8 weeks thereafter.[25]

Adverse events

The main adverse events described are headache, nasopharyngitis, fever, pain at the application site, hypersensitivity reactions (anaphylaxis, angioedema, urticaria), exacerbation of asthma, and pneumonia.[26]

Excipients

Excipients include histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 20, and water for injections.[25]

The clinical use of benralizumab is summarized in Table 3.

Dupilumab

Mechanism of action

Dupilumab is a fully human IgG4 monoclonal antibody with binding affinity for the alpha chain of the IL-4 receptor (IL-4Rα), which is a common chain to the type I IL-4 receptor (IL-4α/IL-2Rγ) and the type II IL-4 receptor (IL-4α/IL-13Rα1), which are receptors for IL-4 and IL-13 respectively. Thus, this antibody has a dual inhibition action on 2 key cytokines in type 2 inflammation, and synergistic action on biological effects shared by IL-4 and IL-13, such as the switch

Table 2
Mepolizumab - summary of clinical use

Mechanism of action	Binds to interleukin-5 (IL-5) preventing the interaction of this cytokine with its cell receptors, reducing eosinophilic inflammation
Indications	Additional therapy for severe eosinophilic asthma in patients ≥ 6 years old; CRSwNP ≥ 18 years old; EGPA > 18 years old, and hypereosinophilic syndromes ≥ 12 years old
Dosage regimen	Asthma: children (6 to 11 years old) - 40 mg, subcutaneously, every 4 weeks and adolescents/adults - 100 mg, subcutaneously, every 4 weeks CRSwNP: 100 mg, subcutaneously, every 4 weeks EGPA: 300 mg, subcutaneously, every 4 weeks. Hypereosinophilic syndromes: 300 mg, subcutaneously, every 4 weeks
Main adverse events	Most commonly reported adverse reactions: headache, upper airway infections, application site reactions, and skin rashes

CRSwNP = chronic rhinosinusitis with nasal polyp, EGPA = eosinophilic granulomatosis with polyangiitis.

Table 3
Benralizumab - summary of clinical use

Mechanism of action	Binds to the alpha subunit of the interleukin-5 receptor (IL-5R), preventing conformation of this receptor and interaction with IL-5. It has an additional mechanism of interaction with the FcγRIIIα surface receptor of natural killer (NK) cells, triggering the death of eosinophils by antibody-dependent cell-mediated (ADCM) cytotoxicity
Indications	Additional therapy for severe eosinophilic asthma in patients > 18 years old
Dosage regimen	First 3 applications: 30 mg, subcutaneously, every 4 weeks Subsequent applications: 30 mg, subcutaneously, every 8 weeks
Main adverse events	Most commonly reported adverse reactions: headache, upper airway infections, fever and application site reactions

in B lymphocytes to IgE production, eosinophil chemotaxis, and bronchial hyperresponsiveness.[27]

The actions of IL-4 and IL-13 on the skin in atopic dermatitis include counter-regulation of the expression of filaggrin, loricrin, and involucrin in keratinocytes, and exacerbation of epidermal barrier dysfunction.[28]

In asthma with type 2 inflammation, IL-13 has important actions on the bronchial epithelium, promoting increased mucus production by goblet cells, thickening of the basal membrane and increased smooth muscle contractility. In addition, IL-4 acts on Th0 lymphocytes, stimulating their differentiation into Th2, aggravating the process of type 2 allergic inflammation.[27]

Indications and contraindications

Dupilumab is indicated in the severe form of atopic dermatitis (AD) in children aged 6 months to 11 years old and in the moderate to severe forms in adolescents and adults, whose disease is not adequately controlled with optimized topical treatment. Topical therapy for AD can be maintained during the use of dupilumab.

Dupilumab is also indicated for the treatment of severe asthma with type 2 inflammation (≥ 6 years old), chronic rhinosinusitis with nasal polyps (≥ 18 years old) and eosinophilic esophagitis (≥ 12 years old and ≥ 40 kg).[29]

The only contraindication to dupilumab, described in the package leaflet, refers to patients with known hypersensitivity to the drug or any of its components.

Dosage regimens

Dosage regimens in AD vary according to the clinical indication, age group, and body weight, and may include higher initial doses. Tables 4 and 5 describe the dosage regimens for use in patients with AD and asthma, respectively.[29]

In CRSwNP, the recommended regimen is 300 mg subcutaneously every 2 weeks, and in EoE 300 mg subcutaneously every week.[29]

Excipients

Excipients include histidine, arginine hydrochloride, sodium acetate, sucrose, polysorbate 80, and water for injections.[29]

Adverse events

Dupilumab has a good safety profile documented in pivotal studies and confirmed in 3-year extension studies in atopic dermatitis and asthma.[30,31]

The main adverse events reported with the use of dupilumab in AD are upper airway infections, conjunctivitis, headache, and application site reaction. The same profile of adverse events has been observed in studies of dupilumab for the treatment of asthma and CRSwNP, with the exception of conjunctivitis, which appears to be a specific adverse event in patients with AD. This conjunctivitis tends to be mild to moderate, affects around 10% to 23% of those treated and has a poorly understood pathogenesis. Several theories have been postulated, including ocular inflammation mediated by IL-17; eosinophilia after dupilumab administration; increased OX40L activity in the eyes; and systemic inhibition of IL-13, causing an indirect reduction in mucin production.[32]

Blood hypereosinophilia (> 1,500 cells/mm^3) is a laboratory adverse event observed in 4% to 15% of patients being treated for severe asthma with type 2 inflammation. It is often asymptomatic and does not indicate the need to stop treatment, tending to resolve after 6 months of treatment in most patients. However, 5 cases of eosinophilic granulomatosis with polyangiitis (EGPA) have been described.[6]

Dermatological changes not associated with atopy have been gradually described after the marketing of dupilumab. A recent systematic review showed that up to 45% of patients may develop a lesion not explained by the underlying disease, such as seborrheic dermatitis, rosacea-like rash, facial flushing, facial and neck erythema.[33]

Tezepelumab

Mechanism of action

Tezepelumab is a fully human monoclonal antibody (IgG2λ) that binds specifically to thymic stromal lymphopoeitin (TSLP), inhibiting its binding to the TSLP receptor complex on different target cells. TSLP is a cytokine of innate immunity belonging to the alarmin group, which acts as an activator of cellular and molecular pathways that promote airway inflammation. It is secreted by airway epithelial cells after tissue damage induced by various harmful agents including allergens, viruses, bacteria, and pollutants. TSLP interferes with the functions of several immunoinflammatory and structural cells that

Table 4
Dupilumab in atopic dermatitis: dosage regimens according to age group and weight

Age group/body weight	Initial dosing	Subsequent dosing	Dosing frequency
Adult (any weight)	600 mg SC (2 x 300 mg)	300 mg SC	Every 2 weeks
Adolescents 12 to 17 years old			
≥ 60 kg	600 mg SC (2 x 300 mg)	300 mg SC	Every 2 weeks
< 60 kg	400 mg SC (2 x 200 mg)	200 mg SC	Every 2 weeks
Children 6 to 11 years old			
≥ 60 kg	600 mg SC (2 x 300 mg)	300 mg SC	Every 2 weeks
30 kg to < 60 kg	400 mg SC (2 x 200 mg)	200 mg SC	Every 2 weeks
15 kg to < 30 kg	600 mg SC (2 x 300 mg)	300 mg SC	Every 4 weeks
Children 6 months to < 6 years old			
15 kg to < 30 kg	300 mg SC	300 mg SC	Every 4 weeks
5 kg to < 15 kg	200 mg SC	200 mg SC	Every 4 weeks

SC = subcutaneously.

Table 5
Dupilumab in asthma: dosage regimens according to age group, weight, and comorbidities

Age group, body weight and comorbidities	Initial dosing	Subsequent dosing	Dosing frequency
Adults and adolescents	400 mg SC (2x 200 mg)	200 mg SC	Every 2 weeks
Adults with CRSwNP and/or severe AD **Adolescents with severe AD**	600 mg SC (2x 300 mg)	300 mg SC	Every 2 weeks
Children 6 to 11 years old			
≥ 15 to < 30 kg	300 mg SC	300 mg SC	Every 4 weeks
≥ 30 kg	200 mg SC	200 mg SC	Every 2 weeks

SC = subcutaneously, AD = atopic dermatitis, CRSwNP = chronic rhinosinusitis with nasal polyps.

co-express the TSLP receptor. Together with other alarmins, such as interleukin 25 (IL-25) and interleukin 33 (IL-33), TSLP prolongs the survival of type 2 innate lymphoid cells (ILC2) and stimulates these cells to produce large amounts of IL-5, interleukin 9 (IL-9) and interleukin 13 (IL- 13).[34]

In allergic asthma, by activating dendritic cells, TSLP helps promote the differentiation of undifferentiated T helper lymphocytes (Th0) into the Th2 lineage, which secrete IL-4, IL-5, and IL-13 and target B cells, eosinophils, mast cells, and airway smooth muscle cells. In nonallergic eosinophilic asthma, TSLP stimulates type 2 innate lymphoid cells to secrete IL-5 and IL-13. In neutrophilic asthma, TSLP induces dendritic cells to stimulate the development of Th17 lymphocytes, which activate neutrophils. TSLP also interacts with mast cells and airway structural cells, including epithelial cells, fibroblasts, and smooth muscle cells.[35]

Blocking TSLP with tezepelumab reduces a broad spectrum of biomarkers and cytokines associated with inflammation, such as blood eosinophils, IgE, FeNO, IL-5, and IL-13, and promotes a reduction in the frequency of severe exacerbations, emergency room visits, and hospitalizations for asthma, an improvement in pre-bronchodilator FEV_1, symptom control, and an improvement in the quality of life of asthma patients.[36,37]

Indications and contraindications

Tezepelumab is indicated as an additional therapy to maintenance treatment for patients with severe asthma aged 12 years and over, regardless of the inflammatory phenotype of the disease (T2 or nonT2).[38] It is contraindicated in patients with known hypersensitivity to tezepelumab or any of its excipients.[39]

Dosage regimens

The recommended dosage regimen for adults and adolescents (12 years and over) is 210 mg subcutaneously every 4 weeks. No dose adjustment is necessary for individuals over 65 years old or with liver or kidney dysfunction.[39]

Adverse events

In pivotal clinical studies in patients with severe asthma, the most commonly reported adverse reactions were arthralgia, pharyngitis, rash, and application site reactions.[37,40] The safety profile during the study of the drug was not evaluated. The safety profile during the long-term extension study was broadly similar to the safety profile already identified. Hypersensitivity reactions can occur after administration of tezepelumab, but no cases of anaphylaxis have been reported to date.[39]

Excipients

Excipients include L-proline, glacial acetic acid, polysorbate 80, sodium hydroxide, and water for injection.[39]

The clinical use of tezepelumab is summarized in Table 6.

Criteria for assessing efficacy

Asthma

The main clinical outcomes, which should be achieved in the treatment of severe asthma with monoclonal antibodies, are a reduction in severe exacerbations (those requiring the use of oral corticosteroids or emergency care or hospitalization), a reduction or discontinuation of the continuous use of systemic corticosteroids, an improvement in lung function, an improvement in asthma control with a reduction in symptoms and the use of rescue medication, and an improvement in the quality of life of patients, resulting in decreased use of health services (Figure 1).[41]

No criteria have been established worldwide for assessing the response to monoclonal antibodies in asthma. Some criteria, generally defined by different methodologies, involving local or regional consensus, have been suggested by different national and international groups and societies, and have yet to be better validated in real-world studies.

Table 7 describes the recently published criteria proposed by the Global Asthma Association. According to these criteria, a good response to biological therapy is considered to be when the patient meets 3 or more efficacy criteria.[42]

According to the Protocolo Clínico e Diretrizes Terapêuticas da Asma do SUS e ANS (Brazilian Unified Health System and National Supplementary Health Agency Clinical Protocol and Therapeutic Guidelines for Asthma), the criteria are similar, although they do not include potential adverse events.

Table 6
Tezepelumab: summary of clinical use

Mechanism of action	Binds to TSLP preventing its interaction with its receptor on different target cells and blocking various pathways involved in type 2 and non-type 2 asthma
Indications	Additional therapy to maintenance treatment of patients with severe asthma aged 12 years and older, regardless of the inflammatory phenotype of the disease (T2 or non T2)
Dosage regimen	210 mg dose (autoinjector), subcutaneously, every 4 weeks
Main adverse events	The most commonly reported adverse reactions were: arthralgia, pharyngitis, rash, and application site reactions

TSLP = thymic stromal lymphopoeitin.

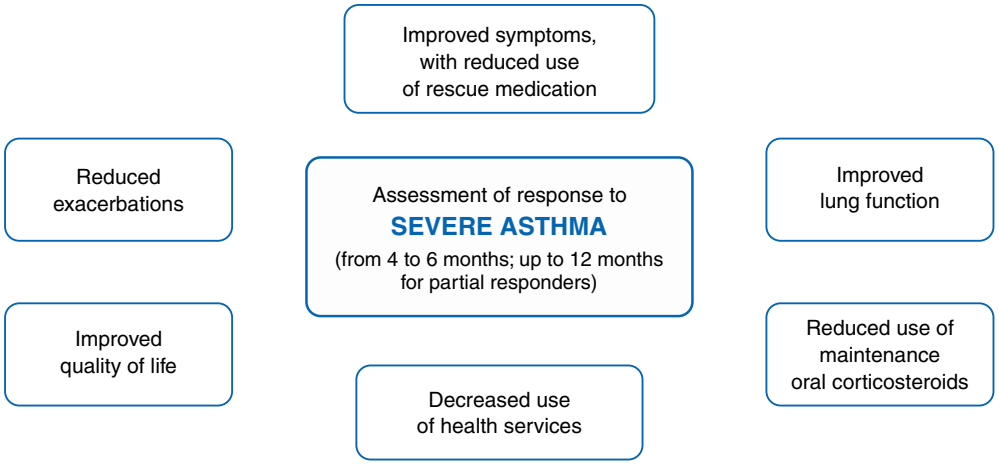

Figure 1
Objectives of biological therapy in severe asthma

The criteria proposed by Brazilian guidelines only include items 1 and 2 described in Table 7, assessed after 1 year of biological therapy.[43]

Chronic spontaneous urticaria

The main tools for assessing control and activity of CSU are the Urticaria Control Test (UCT, range 0 to 16, in which the patient is fully controlled when UCT = 16), and the 7-day Urticaria Activity Score (UAS7, range 0 to 42, in which the patient reports no urticaria activity when UAS7 = 0). The response to omalizumab should be assessed at 3 and 6 months of treatment. Around 61% of patients with CSU respond quickly to therapy within the first month of application (fast responders), and a smaller group (about 27%) responds more slowly, between month 1 and 6 of treatment (late responders).[15]

Table 7
Criteria for evaluating the efficacy of biologics in asthma

1. Reduced dose of oral corticosteroids by ≥ 50%, ideally until complete discontinuation is achieved
2. Reduced number of asthma exacerbations requiring oral corticosteroids by ≥ 50%, ideally until the absence of exacerbations is achieved
3. Minimal or no adverse events
4. Asthma control achieved: ACQ < 1.5 or ACT ≥ 20

ACQ = Asthma control questionnaire, ACT = Asthma control test.

Patients with inadequate control (UCT < 12 and/or UAS7 > 7) with the standard dosage regimen of 300 mg of omalizumab every 4 weeks should have their dosage regimen modified. The following 2 possibilities apply: reduced interval between applications to 2 weeks; or increased dose, which can be staggered, initially to 450 mg and, if necessary, subsequently to 600 mg, or increased directly to 600 mg. The treatment regimens are thus flexible and adjusted based on the assessment of disease activity and symptom control, providing patients who do not respond to the standard regimen with a better clinical response to omalizumab, with a good safety profile.[44,45]

In patients with a good clinical response to omalizumab and controlled disease, no biomarkers indicate urticaria remission. Therefore, the total duration of therapy with omalizumab in CSU has not been established, and the biological should be discontinued after complete control of symptoms to assess the possibility of disease remission. Therefore, after complete control of the CSU (UCT = 16 and UAS7 = 0) for a period of 6 months or more, the decision to discontinue treatment should follow individual medical criteria.[15]

Atopic dermatitis

Several tools are available for assessing the severity of atopic dermatitis and the response to treatment. The instruments used as primary outcomes in the pivotal studies with dupilumab were the Eczema Area and Severity Index with 75% improvement (EASI-75) and the Investigator Global Assessment Scale (IGA). Secondary outcomes included the following parameters: EASI-50, EASI-90, Severity of Atopic Dermatitis Score (SCORAD), Patient-Oriented Eczema Measure (POEM), Numerical Rating Scale for pruritus (NRS), Family Impact of Dermatitis questionnaire (FID), Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI).[46-51]

Although no worldwide consensus on parameters for assessing the efficacy of dupilumab in atopic dermatitis has been established, recommendations have been made. The Portuguese guideline for the systemic therapy of atopic dermatitis recommends evaluation after 3 and 6 months of treatment, using the EASI-50 and EASI-75, NRS of pruritus and DLQI, as described in Table 8.[52]

Rhinosinusitis with nasal polyps

The expert group on chronic rhinosinusitis with uncontrolled nasal polyps and biologics of the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA)[53] recommends that the evaluation of the response to biologic therapy in CRSwNP should be performed after 6 and 12 months of treatment, using the following tools: olfaction assessment using a validated test, Nasal Polyp Score (NPS), Nasal Congestion Score (NCS), Sinonasal Outcome Test 22 (SNOT-22) and visual analog scale (VAS), as described in Figure 2. In addition to these instruments, the need for oral corticosteroids and a surgical approach throughout the treatment should also be assessed.

Table 8
Criteria for assessing the efficacy of dupilumab in atopic dermatitis

At 3 months of therapy
- Achieve EASI-50
- Reduced NRS by at least 3 points
- Reduced DLQI by at least 4 points

At 6 months of therapy
- Achieve EASI-75
- Achieve NRS ≤ 4 points
- Achieve DLQI ≤ 5 points

EASI-50 = Eczema Area and Severity Index with 50% improvement, NRS = Numerical Rating Scale for pruritus, DLQI = Dermatology Life Quality Index, EASI-75 = Eczema Area and Severity Index with 75% improvement.

Eosinophilic esophagitis

No standardized definition of response to the various modalities of drug therapy in EoE[54] has been established. However, the following parameters were used as primary outcomes in clinical studies of dupilumab in adolescents and adults with EoE: reduced peak eosinophil count on histopathological examination of the esophageal mucosa and reduced dysphagia symptoms assessed by the Dysphagia Symptoms Questionnaire (DSQ).[55]

The cut-off point for histological response in pivotal studies of dupilumab was 6 eosinophils/HPF (high power field). However, some authors consider 15 eosinophils/HPF to be a satisfactory response for the other therapy modalities.[56]

In studies with dupilumab, a cut-off point for reducing the DSQ score was not established, and a comparative analysis of the mean absolute reduction in the treatment group versus the placebo group was performed.[2] The DSQ evaluates a period of 14 days and the values vary between 0 and 84, with higher values indicating greater severity.[57] In clinical practice, it is necessary to set a cut-off point for a minimally significant difference. Therefore, it is reasonable to use the cut-off point proposed for other therapies, which consider a significant improvement to be a reduction of > 30% in the DSQ score.[58]

Evaluation of the clinical response to dupilumab should be performed at 3 and 6 months of treatment (the biological period in which the best response is seen).[55] In patients with a good clinical response, evaluation of histological response can only be carried out at 6 months; while in those with an absent or insufficient clinical response at 3 months, histological evaluation is also recommended at this time.[54]

In cases of discordant response between histological remission and clinical response, other parameters can be used, such as assessing inflammatory activity using endoscopy. The Endoscopic Reference Scoring System (EREFS) is the main instrument used. It assesses edema, rings, exudates, striae, and narrowing, ranging from 0 to 18, with higher scores indicating greater severity. A reduction in macroscopic inflammatory changes combined with an esophageal diameter > 15 mm has also been proposed as an outcome for clinical improvement in the endoscopic evaluation.[54,56]

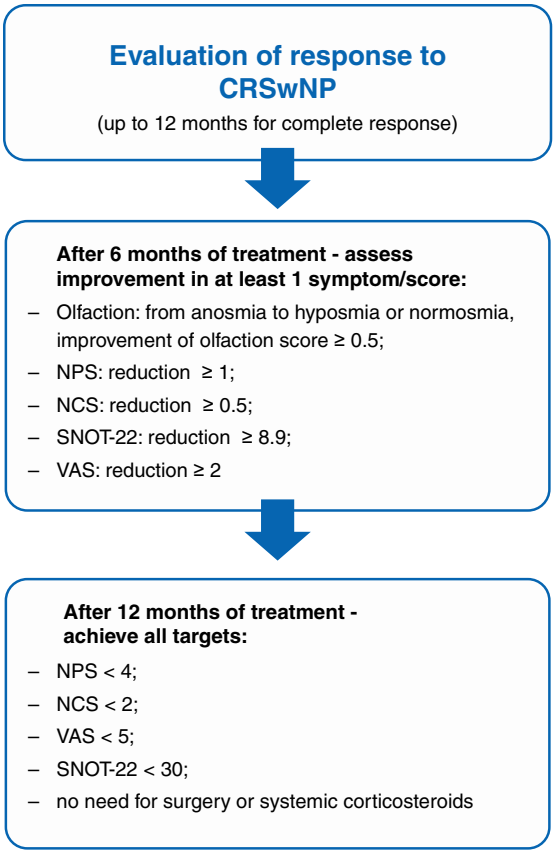

Figure 2
Assessment of response to biological therapy in CRSwNP

Olfaction = assessed by validated test (CONNECTICUT or UPSIT), NPS = nasal polyp score (Lund-Kennedy or Lund-Mackay), NCS = nasal congestion score, CRSwNP = chronic rhinosinusitis with nasal polyps, SNOT-22 (Sino-Nasal Outcome Test) = nasosinusal outcome test 22, VAS = visual analog scale.

Modified from Bachert C, et al.[53]

Hypereosinophilic syndromes

Hypereosinophilic syndromes (HSS) are a group of rare disorders characterized by high eosinophil counts in the blood (> 1,500 cells/mm^3) and/or in tissues. The clinical presentation is highly variable, involving dermatological, pulmonary, gastrointestinal, and cardiovascular manifestations.[59] Standard treatment includes corticosteroids, cytotoxic drugs, and immunosuppressive therapy. Imatinib is indicated for patients with variants sensitive to this drug. Recently, mepolizumab was approved for the treatment of patients with HSS, but criteria for response to treatment with biologics have not been established yet.[60]

However, the main primary outcomes used in the clinical studies can be applied in clinical practice as criteria for a good response, namely: 1) reduced seizures and 2) reduced dose of oral corticosteroids or maintenance immunosuppressive/cytotoxic therapy. Of course, monitoring blood eosinophilia is also important. In the pivotal clinical study, it was observed that the maximum reduction in blood eosinophil count is achieved with 8 weeks of therapy with mepolizumab.[61,62]

Monitoring, management, and reporting of adverse events

Monitoring adverse events

An adverse event (AE) with a drug can be defined as any unfavorable change to the health of the patient following their administration. They can be mild, moderate or severe, and can occur immediately after administration or after a prolonged period.[63] AEs induced by xenobiotics (traditional drugs) are mainly related to their pharmacological effects, while the adverse effects of immunobiologic agents are often related to the target molecule and the biological consequences of their actions.[26] Considering these differences, Pichler[64] proposed a special classification for adverse reactions to monoclonal antibodies, which is summarized in Figure 3.

Although pivotal and extension studies demonstrate the safety of monoclonal antibodies used in the therapy of allergic diseases and specific laboratory monitoring is not required, concerns remain about the development of adverse effects that have not been described, given the potential antigenicity of the molecules, interference with innate inflammatory response pathways, adaptive immune response and eosinophils.[5]

As for the risk of parasitosis, pre-treatment screening and monitoring during use in high-risk patients is recommended. This recommendation is based on a theoretical risk.[6]

More detailed considerations with regard to infections/parasitoses are presented in the topic developed later in this article.

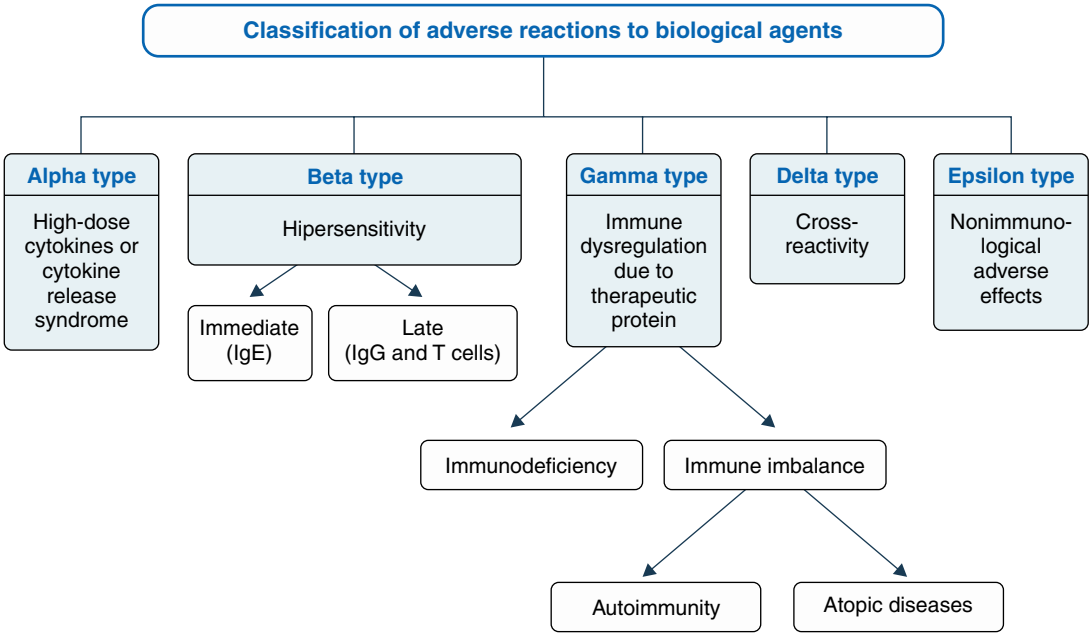

Figure 3
Classification of adverse reactions to monoclonal antibodies
Source: Pichler, 2006[64].

As for the risk of malignancy, epidemiological studies have questioned the existence of an association between cancer and some monoclonal antibodies, such as omalizumab. To date, no evidence has been found of a causal relationship between biologics used to treat allergic diseases and an increased risk of malignancies. Screening for cancer is therefore indicated according to age, sex, and specific risk factor criteria used in the general population.[6-8,11]

In summary, although no laboratory monitoring is recommended for the use of monoclonal antibodies in allergic diseases, the prescribing immuno-allergist should constantly monitor the development of the adverse events described specifically for each immunobiological (see specific section on "3 - immunobiologic agents"), and regularly update on new adverse events that may occur with the expanded use in real-world scenarios.

Table 9 compiles the most clinically relevant adverse events described to date, including systematic reviews, real-world studies, or case reports.[6,23]

Management of adverse events

Most of the adverse events (AEs) described are mild, with no need for regular laboratory monitoring or suspension of biological therapy. Local reactions in the area of application are the most common and generally do not require premedication or specific treatment.[26]

Omalizumab has an estimated risk of anaphylaxis of 0.09% and therefore prescribing physicians should talk to patients/guardians about this risk prior to treatment. Management in the event of anaphylaxis should follow guidelines established domestically and internationally.[81]

Other monoclonal antibodies have an estimated risk of nonanaphylactic hypersensitivity reactions of 1% to 2%. In mild cases, they can be managed conservatively or with symptomatic drugs such as antihistamines and/or antipyretics.[3]

Therapy with dupilumab in patients with atopic dermatitis is associated with ocular surface disease (conjunctivitis, blepharitis, and keratitis), which although frequent (14% to 23%), tends to be mild and resolve with conservative management. In some more severe or refractory cases, topical therapy should be used and joint follow-up with an ophthalmologist is recommended. Suspension of the immunobiological[66] is rarely recommended. Nonallergic skin lesions (especially on the face and neck) have been described postmarketing, but most are mild and respond to topical treatment. A systematic review estimated that 11% of these patients discontinued the medication due to this adverse event.[33]

Another concern associated with dupilumab is the presence of eosinophilia after starting treatment (up to 15% of patients). This is usually asymptomatic and tends to peak between 4-16 weeks of treatment, with a gradual decline to the baseline. Monitoring is recommended depending on the degree (see Table 9), and discontinuation is only recommended in symptomatic cases or with an alternative diagnosis (e.g. EGPA).[67,68]

As for benralizumab, it is estimated that up to 3% of patients may experience urticarial rash, although antihistamines can be used to manage this condition.[69]

Reporting adverse events

Reporting an AE is important because it allows the responsible bodies to monitor the safety of these products and identify potential risks. In general, health institutions have operational procedures for pharmacovigilance, and the physician must inform the attending pharmacist and record the AE in the medical record. In Brazil, in addition to the internal protocols of each institution, AEs involving monoclonal antibodies must be reported through the VigiMed system (available at: https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/notificacoes/vigimed), and the manufacturer of the immunobiological agent must also be notified.

Anyone can and should report an AE, but it is the physician responsibility to ensure that it is notified whenever known. Notification through VigiMed requires filling in an online form, which asks for information about the patient, the immunobiological, the AE, and the circumstances in which the product was administered.

Monoclonal antibodies and immunizations

Currently, no specific recommendations have been made in Brazil for patients taking monoclonal antibodies for allergic diseases. The calendar should be updated according to individual risk, at least 1 month before starting treatment with an immunobiological. As these are relatively new drugs, all the potential risks,

adverse effects, and interactions with the vaccines of the Programa Nacional de Imunização (PNI - Brazilian National Immunization Program)[70] are not yet known.

Because of the low theoretical risk, the monoclonal antibodies currently approved for allergic diseases can be used with inactivated vaccines (mRNA, conjugate, toxoid, and nonpathogenic viral vector

Table 9
Adverse events of biologics of major clinical importance in allergic diseases

Biologics	Systemic reactions	Other adverse events described
Omalizumab	Anaphylaxis Estimated rate - 0.09%	Case reports: – Arthralgia – Similar serum sickness – Eosinophilic granulomatosis with polyangiitis (EGPA)
Mepolizumab	Nonanaphylactic hypersensitivity reactions Estimated rate - 1% to 2% Anaphylaxis - 104 reported cases	Case reports: – Alopecia – Noncardiogenic chest pain – Histiocytic necrotizing lymphadenitis
Benralizumab	Nonanaphylactic hypersensitivity reactions Estimated rate - 1% to 3% Anaphylaxis - 63 cases Cytokine release syndrome (alpha type) - case reports	Case report: – Inflammatory disorders – Death in open-label extension study – patient developed hepatitis, *Aspergillus spp.* lung infection, and multiple organ failure
Dupilumab	Nonanaphylactic hypersensitivity reactions Estimated rate - < 1%	– Eosinophilia > 3,000 cells/mm^3 Estimated rate - 1.2% to 15% Recommendation: Patients with eosinophilia > 1,500 cells/mm^3 pre-treatment - monthly monitoring Patients with eosinophilia < 1,500 cells pre-treatment - monitoring every 3 months Note: Some patients may be diagnosed with EGPA – Conjunctivitis in patients with atopic dermatitis: Estimated rate – 14% to 23%; conservative or topical treatment. Follow-up with ophthalmologist in refractory or severe cases – Dermatological changes such as seborrheic dermatitis, rosacea, facial flushing appear in up to 45% of patients; specific treatment; discontinuation of dupilumab in refractory cases
Tezepelumab	Pivotal studies (NAVIGATOR and CASCADE): no cases. No other relevant data have been published in the literature	Case report: – Guillain-Barré syndrome

vaccines) and do not need to be suspended, as long as the application of the vaccines on the same day as the immunobiological is avoided (intervals of more than 7 days are recommended). Seasonal or periodic vaccines (flu or dTpa) should be administered without restrictions.[71]

It is important to note that although mRNA and viral vector vaccines work slightly differently to inactivated vaccines, none of them are live virus vaccines and can therefore be safely administered to patients receiving biological treatment for allergy. Thus, the vaccines currently available for COVID-19 are indicated for concomitant use with the monoclonal antibodies described here, whether they are inactivated virus vaccines (Sinovac/Butantan); mRNA vaccines (Pfizer-BioNTech; and Moderna); or viral vector vaccines (Johnson & Johnson, Oxford-Astra-Zeneca, and Verity Pharmaceuticals-Serum Institute of India).[72]

On the other hand, caution is required for live attenuated vaccines (Table 10). Although no data demonstrate an increased risk of attenuated vaccines in this context, this recommendation is based on the pivotal studies of dupilumab (SOLO 1 and SOLO 2) and tezepelumab (CASCADE AND NAVIGATOR), which did not include patients who had received attenuated vaccines in the 4 weeks prior to the start of the studies. When the benefit of an attenuated vaccine outweighs the risks, biological treatment can be interrupted based on the half-life of the drug (Table 11) and resumed as soon as the viremia of the vaccine is eliminated (e.g. the duration of viremia for the varicella virus is 14 days).[71-74]

Mepolizumab and benralizumab have been associated with a potential risk of herpes zoster reactivation (section 7 - monoclonal antibodies and infections/parasitoses). It is therefore recommended that patients with an indication for the herpes zoster vaccine (> 50 years old and/or with a risk condition) be immunized 4 weeks before starting treatment.[6,75]

Monoclonal antibodies and infections/ parasitoses

The main inflammatory response pathways to microorganisms and parasites are subdivided into type 1, type 2, and type 3 inflammation, which are directed at viruses and intracellular bacteria, parasites, and extracellular bacteria and fungi, respectively. The monoclonal antibodies used to treat allergic diseases mostly interfere with the type 2 inflammation pathway, via innate and/or adaptive immunity, which is the pathway involved in the response to allergens and eosinophilic inflammation, preserving the immune response against most microorganisms. However, mast cells and eosinophils play an important role in innate immunity and tezepelumab interferes with the top of the inflammatory cascade by blocking TSLP - an important alarmin of the innate immune system in response to various aggressions to the epithelium, including allergens, pollutants, viruses, and bacteria.

Clinical trials, extension studies, and real-world studies have generally not indicated an increased risk of infections and parasitoses. Nevertheless, specific recommendations regarding infections and parasitosis have been made for certain immunobiologic agents.[6]

Omalizumab

IgE may be involved in the immune response to helminthiases. As mentioned above (see section "Management of adverse events"), monitoring and specific treatment of patients diagnosed with helminthiasis is indicated during therapy with omalizumab. However, a Brazilian study demonstrated that omalizumab is safe in patients at high risk of helminth infections.[76]

Mepolizumab

A possible risk of herpes zoster reactivation was observed in 2 extension studies with mepolizumab in asthma. It is therefore recommended that patients eligible for the herpes zoster vaccine be immunized for this agent at least 4 weeks before starting therapy with mepolizumab (Table 11).[6]

Table 10
Live attenuated vaccines available in Brazil, 2023

BCG
Rotavirus
Measles, Mumps, Rubella (SCR)
Varicella (or SCR-V)
Yellow fever[a]
Poliomyelitis[b]
Herpes zoste[b]

[a] Consider epidemiological risk.
[b] Prefer inactivated vaccines: Poliomyelitis (IPV) and inactivated Herpes zoster.

Eosinophils participate in the immune response to helminthiases. Patients with preexisting helminthiases were excluded from the clinical trials developing mepolizumab. Patients living in areas endemic for helminthiasis should be screened pretreatment and treated if diagnosed prior to the start of therapy with mepolizumab. Patients diagnosed with helminthiasis during treatment who do not respond to anthelmintic treatment should consider temporarily discontinuing its use.[6]

Benralizumab

There have been reports of herpes zoster in studies with benralizumab, but no specific recommendations (Table 11). In relation to parasitosis, based on the theoretical risk, pretreatment screening and surveillance during therapy is recommended for patients living in or traveling to endemic areas.[6,25]

Dupilumab

Clinical trials have shown no evidence of an increase in the incidence of infections and parasitoses. In studies on atopic dermatitis, it was observed that approximately 0.4% to 1% of patients developed herpes zoster and 0.4% to 2% developed eczema herpeticum. However, these rates were no higher than those observed in the placebo group, nor are there any specific recommendations in the package leaflet.[29]

Tezepelumab

In the clinical trials of tezepelumab in asthma, no increased risk of infections has been reported. The risk of parasitosis is unknown and, considering the theoretical risk, the package leaflet recommends monitoring for helminthiases in patients being treated with this immunobiological.[39]

TSLP may be involved in the immune response to helminthiases. Before starting therapy with tezepelumab, investigation and treatment of preexisting helminthiases is recommended. If parasitosis is diagnosed during therapy and the patient does not respond to the anthelmintic, treatment with tezepelumab should be discontinued until the infestation is resolved.

Table 11
Immunization precautions, according to monoclonal antibodies

Omalizumab	No contraindications for live attenuated or inactivated vaccines
Mepolizumab	No contraindications for attenuated or inactivated vaccines
Benralizumab	No contraindications for attenuated or inactivated vaccines
Dupilumab	No contraindications for inactivated vaccines Live attenuated vaccines should be avoided. When indicated, administer 4 weeks after suspension
Tezepelumab	No contraindication for inactivated vaccines. Live attenuated vaccines should be avoided. When indicated, administer 4 weeks after suspension

Biological application in the presence of infections

No recommendations have been universally established regarding the use of biologics for allergic diseases in patients with ongoing or recent infections. However, considering that in the clinical studies the doses were not administered in the presence of viral and/or bacterial infections, it is advisable to postpone administering the dose by 7 to 14 days, or even skip an application, depending on the clinical condition of the patient and the severity of the infection.

These recommendations are also valid for the COVID-19 pandemic. During epidemic peaks, biological therapy should be maintained in patients without clinical suspicion and without household contagion, as the benefits of controlling severe allergic disease outweigh the risks of infection. In addition, the literature does not indicate that COVID-19 is more severe in patients with controlled allergic disease who are receiving biological therapy. In the event of recent exposure to SARS-CoV-2, the patient should be investigated and, if infection is confirmed, the application should be postponed.[23,70]

Use in special populations

Specific clinical trials in infants, older people, nephropaths, hepatopaths, or pregnant women are scarce. When available, they tend to be pooled with data from other patients. Literature data is limited and can be difficult to interpret. Therefore, recommending the use of immunological agents in these populations should be done with caution, bearing in mind possible risks and benefits that have not been adequately measured.

Before recommending immunological agents for women of childbearing age, patients should discuss their desire for pregnancy and contraception. For pregnant women, it should be emphasized that monoclonal antibodies are IgG antibodies and cross the placental barrier (in the order of greatest permeability: IgG1 > IgG4 > IgG3 > IgG2). Excretion in human milk generally occurs at a lower rate (1:10,000 to 1:100,000). It is important to note that even for medications considered safe during pregnancy, information on the long-term effects on the developing immune system is scarce.[77]

One important precaution when prescribing for children and adolescents is the form of application, as most drugs are parenteral. In general, nephropaths and hepatopaths tolerate monoclonal antibodies well, as the clearance of these drugs is through the reticuloendothelial system. However, these patients may have other associated conditions and their use should be monitored for worsening renal and/or hepatic function.[78] Table 12 compiles the main information available on use in special popu lations.[6,11,21,23,32,37,40,79,80] Currently, omalizumab (category B) is the only biological released for pregnant women.[77]

In summary, the use of monoclonal antibodies in special populations should be done cautiously, with due consideration for the risks and benefits involved. Specifically for pregnant women, some evidence shows that severe uncontrolled asthma increases the risk of preeclampsia, preterm birth, and gestational diabetes, in addition to the use of systemic corticosteroids and their specific risks. For CSU, no data has been provided on the risk of uncontrolled disease in pregnant women, although omalizumab appears to be effective and safe. For CRSwNP, alternative therapies are reasonable until the end of pregnancy.[79,80]

It is therefore recommended that the decision to use omalizumab in these populations be shared with the patient, discussing the limitations of the data, and warning of any theoretical risks. Comorbidities and adverse events should be monitored when indicated, and it is highly desirable to publicize these cases to share experiences.

General application precautions and guidance on home use, storage, and transportation

Biologicals for allergic diseases should be administered in a healthcare facility with the infrastructure (equipment and medicines) and healthcare staff trained to manage potential systemic adverse reactions, including orotracheal intubation and cardiopulmonary resuscitation procedures, to ensure patient safety (Table 13). In addition, transport and storage are necessary for the proper preservation of biologicals without compromising their efficacy. Therefore, Biologicals Infusion Centers are the ideal places for application, preferably in day hospital settings. Biologicals for allergic diseases can also be used in Allergy and Immunology clinics that have a type III consulting room, as provided for in CFM resolution No. 2153, available at: http://www.sbai.org.br/imageBank/resolucao-cfm-2153-consultorio-medico.pdf.

Application facilities should set up care flows, monitoring routines, and safety protocols which should be reviewed at least every 6 months. The risk of anaphylaxis and specific guidelines for medical supervision are summarized in Table 14.

The experience gained from years of using immunobiologic agents in clinical practice shows that the incidence of serious reactions during application is relatively low (< 1%), especially in patients who already use them and have no history of hypersensitivity reactions.[66]

Therefore, after the pandemic and with the advent of filled syringes, the possibility of home use of subcutaneous immunobiologic agents in low-risk patients with no history of previous reactions was considered.[6,82] Recently, the FDA authorized the use of omalizumab in a filled syringe at home in patients with no history of anaphylaxis (to any type of allergen), provided that the patient has no history of hypersensitivity reactions after receiving 3 applications initially at a health care facility. It is recommended to prescribe self-injectable adrenaline at home, a resource not readily available in Brazil.[83]

Table 12
Immunobiologic agents for special populations

Monoclonal antibodies	Pregnant women	Children	Older persons
Omalizumab	**May be recommended** Category B FDA (IgG1)	**PIL:** Asthma (≥ 6 years), CSU (≥ 12 years), CRSwNP (≥ 18 years) **Off label** CSU - retrospective study (patients ≥ 2 years)	**RCT:** up to 65 years old **RLT:** up to 83 years old
Mepolizumab	**Not recommended** Report of 1 case, with onset after first quarter	**PIL:** Severe eosinophilic asthma (≥ 6 years), EGPA (≥ 18 years), CRSwNP (≥ 18 years), HSS (≥ 12 years) **Off label:** EGPA - case report	**RCT:** up to 82 years old **RLT:** up to 80 years old
Benralizumab	**Not recommended** Not enough data	**PIL:** Severe eosinophilic asthma (≥ 12 years) **Off label:** Asthma - case report - use in 6-year-old patient	**RCT:** up to 75 years old **RLT:** up to 80 years old
Dupilumab	**Weigh risks and benefits** Report of 13 cases: no malformations; animal studies (IgG4)	**PIL:** AD (≥ 6 months), Asthma (≥ 6 years), CRSwNP (≥ 18 years), EoE (≥ 12 years) **Off label:** CSU - case report - 2 patients; Alopecia areata - case report - 2 patients	**RCT:** up to 75 years old **RLT:** up to 89 years old
Tezepelumab	**Not recommended** Not enough data	**PIL:** Severe asthma (≥ 12 years) **Off label:** HSS - case report – a 4-year-old patient	**RCT:** up to 80 years old

PIL = patient information leaflet, CSU = chronic spontaneous urticaria, CRSwNP = chronic rhinosinusitis with nasal polyps, RCT = randomized clinical trial, RTL = real-life trial, EoE = eosinophilic esophagitis, AD = atopic dermatitis, EGPA = eosinophilic granulomatosis with polyangiitis, HSS = hypereosinophilic syndrome.

Table 13
Equipment and drugs for emergencies

Equipment for ventilatory support	Stethoscope and sphygmomanometer (adult and pediatric)
	Tourniquets, syringes, needles
	Equipment for O_2 supplementation
	Equipment for venipuncture and fluid administration
	Laryngoscope and cannulas of different sizes
	Face or laryngeal/amboo mask
	Automatic defibrillator
Drugs for emergencies	Adrenaline 1:1000 - intramuscular use
	Volume expanders: saline 0.9%
	Antihistamine - injectable use
	Bronchodilator - inhalation use
	Vasoactive drugs: noradrenaline
	Glucagon: 1 to 5 mg/dose
	Corticosteroids - injectable use

Source: Brazilian Ministry of Health, 2023.[81]

The evidence supporting the use of monoclonal antibodies at home for severe allergic diseases is based on practical experience, particularly internationally. Currently, no objective criteria have been established for the indication of treatment at home, and the physician should assess the risk, considering factors such as potential anaphylaxis, the severity of the disease, cognition and comorbidities of the patient, socioeconomic and geographical conditions, among others.[84] The choice of application site should be shared, discussed exclusively in the context of the relationship between the treating doctor and the patient, with no third party involvement, such as hospital facilities or health insurers. Patients should actively participate in this decision, once they have been explained the benefits and risks. In general, patients perceive the benefits of using medication at home to include flexibility and time optimization, less exposure to infectious agents, and the possibility of traveling for long periods, among others.[84] The risks associated with application at home include the adverse events and others discussed above. Aspects associated with the form of application, storage and transportation of the medication, living close to health facilities, and an action plan to seek immediate medical care in the event of any hypersensitivity reaction or other systemic reactions should be discussed with patients.[85,86]

Should patients have understood and decided with their physician to take the medication at home, the physician must ensure that the medication is used correctly. This includes aspects of storage, application, and disposal. Theses monoclonal antibodies must be stored in a refrigerator between 2 °C and 8 °C and cannot be frozen. Almost all monoclonal antibodies for allergic diseases can be kept out of the refrigerator for up to 14 days, provided that the room temperature does not exceed 30 °C. Benralizumab, on the other hand, should not be kept out of the refrigerator for more than 24 hours.[14,22,25,29,39]

Table 14
Risk of anaphylaxis and specific guidelines for application of immunobiologic agents

Monoclonal antibodies	Product guidelines
Omalizumab	Close medical supervision during administration and observation for 2 hours after application for the first 3 doses
Low risk of anaphylaxis	
Anaphylaxis (pivotal studies: 0.1% to 0.2%);	
EAACI Task Force: 0.09%	Close medical supervision during administration and observation for at least 30 minutes from dose 4 onwards
Most cases within 2 hours of application.	
Some cases of late onset, up to 24 hours.	
It can be triggered by any dose of omalizumab.	Home use: Only possible for patients using a filled syringe, with no history of hypersensitivity reaction after the third application.
Patients with asthma: increased risk of severe allergic reactions	Preferably carry self-injectable adrenaline.
	Precaution in patients with severe uncontrolled asthma
Mepolizumab	Close medical supervision during administration and observation for at least 30 minutes, regardless of dose number
Benralizumab	Home use: Only possible for patients using a self-injectable device, with no history of hypersensitivity reaction after the third application. Precaution in patients with severe uncontrolled asthma or still taking corticosteroids
Very low risk of anaphylaxis	
Dupilumab	Close medical supervision during administration and observation for at least 30 minutes
Tezepelumab	Home use: Evaluate home use after the third application
Extremely low risk of anaphylaxis	

In addition, patients (and their families) should be taught how to recognize the signs/symptoms of anaphylaxis and a written action plan should be prescribed. A communication channel should also be available for medical contact in the event of a reaction.[6,66,85] It is worth noting that even in the event of a reaction at home, the prescribing physician must report any adverse events (see section on "reporting adverse events").

In the absence of current case law, it is essential that prescribing physicians are aware that they may be held jointly responsible in the case of home reactions. Recording details of the discussion prior to home release in medical records is recommended, with the signing of an informed consent form (ICF) and other measures to safeguard the practitioner.

The use of monoclonal antibodies at home has peculiarities in Brazil, which should be widely discussed by health personnel, managers, patients, and their families. A thorough scientifically-based analysis can enable formal recommendations to be drawn up, including criteria that define the profile of patients suitable for using monoclonal antibodies at home. These criteria include not only clinical observations, but also sociocultural context, geographic region, logistics, and access to health services (Table 15).

Access through SUS and Supplementary Health

The incorporation of medicines into the SUS and ANS enables universal access to drug treatment, which is a fundamental right of citizens and must be guaranteed.

The development of monoclonal antibodies for the treatment of serious allergic diseases has led to the need to incorporate these technologies into the SUS and ANS. Due to their high cost, the incorporation of these drugs has become a challenge for managers, medical associations, and patients. It is crucial to promote the rational use of immunological agents to ensure the sustainability of the health system.

In the context of the SUS, 2 immunological agents for severe asthma were incorporated in the latest revision of the Ministry of Health Asthma Clinical Protocol and Therapeutic Guidelines (PCDT MS), published in 2021.[87] The immunological agents provided were mepolizumab for severe eosinophilic asthma and omalizumab for allergic asthma. The inclusion criteria in the PCDT MS are listed in Table 16.

In supplementary healthcare, the ANS has made significant progress and incorporated immunological agents for asthma, atopic dermatitis, and chronic spontaneous urticaria, creating Guidelines for use (DUT) linked to the procedure "Endovenous, intramuscular, or subcutaneous immunological therapy" (DUT No. 65), providing a regulatory framework for the use of these drugs. Benralizumab, dupilumab, and mepolizumab were incorporated for severe eosinophilic asthma[88]; dupilumab and omalizumab for severe allergic asthma[89]; dupilumab for atopic dermatitis[90] and omalizumab for chronic spontaneous urticaria.[91] Table 17 shows the different diseases, immunological agents, and their respective DUTs.

The inclusion of monoclonal antibodies for the treatment of allergic diseases in the SUS and ANS is a milestone for both public and supplementary health care in Brazil. Even with the financial and logistical

Table 15
Proposal of recommendations for the application of monoclonal antibodies for allergic diseases at home

– Assess personal risk of developing serious reactions: including individual, drug, cognitive, socioeconomic and geographical factors.
– Discuss the potential related risks; discuss the form of application and the action plan, should an adverse reaction occur
– All patients must sign an informed consent form before starting treatment
– The first 3 applications should be administered in a health care facility where emergency care can be provided, including administration of epinephrine, oxygen, bronchodilators, intravenous corticosteroids, and proceeding with emergency orotracheal intubation and/or initiating cardiopulmonary resuscitation, if necessary
– In the absence of a history of hypersensitivity reaction and after clarifying the benefits and risks, the patient wishes to have the procedure administered at home: the doctor should supervise self-application, clarifying any questions, and prescribing an action plan for adverse effects. The patient should be able to recognize anaphylaxis and treat it appropriately. Ideally, the patient should have self-injectable adrenaline
– Availability for medical contact during application hours
– Notify adverse events via the VigiMed system, available on the ANVISA website

challenges involved in these additions, the advances are promising and have the potential to transform the treatment of serious allergic diseases that were previously overlooked. Nevertheless, the rational use of these high-cost drugs is an essential strategy for maintaining the sustainability of health systems, while providing a significant improvement in the quality of medical care for patients, both in public and private services.

Final considerations

It has been 2 decades now since the first immunobiologic agents treatment for allergic diseases was licensed: omalizumab for severe asthma. Over this period, there has been a great expansion in the use of biological therapy for moderate to severe allergic diseases. Recently, access to biological therapy has become a reality in Brazil with the incorporation of

Table 16
Inclusion criteria for the use of monoclonal antibodies incorporated into the SUS and included in the Asthma PCDT MS 2021[1]

	ASTHMA PCDT MS
Drug	**Inclusion criteria**
Mepolizumab	1. Age ≥ 18 years 2. Peripheral eosinophils ≥ 300 cels/mm^3 3. At least 1 severe exacerbation in the previous year requiring a course of oral corticosteroids 4. Continuous treatment with high doses of inhaled corticosteroids (≥ 1,600 µg/day of budesonide or equivalent) associated with a LABA in the same device **OR** 5. Oral corticosteroid with a dose equivalent to at least 5mg of prednisolone daily for the last 6 months. NOTE: In item 4, some practitioners prescribe tiotropium (not incorporated into the SUS, according to Conitec Recommendation Report No. 612 - May 2021) or antileukotriene (not evaluated by Conitec) instead of oral corticosteroids
Omalizumab	1. Age ≥ 6 years 2. Weight between 20 and 150 kg 3. Total serum IgE between 30 and 1,500 IU/mL 4. Confirmation of IgE-mediated allergy through skin testing or positive specific IgE to at least 1 aeroallergen 5. At least 1 severe exacerbation in the previous year requiring a course of oral corticosteroids 6. Continuous treatment with high doses of inhaled corticosteroids (≥ 1,600 µg/day of budesonide or equivalent) associated with a LABA in the same device **OR** 7. Oral corticosteroid with a dose equivalent to at least 5mg of prednisolone daily for the last 6 months. NOTE: In item 6, some practitioners prescribe tiotropium (not incorporated into the SUS, according to Conitec Recommendation Report No. 612 - May 2021) or antileukotriene (not evaluated by Conitec) instead of oral corticosteroids

PCDT MS = Ministry of Health Asthma Clinical Protocol and Therapeutic Guidelines.

Table 17
Monoclonal antibodies incorporated by the Brazilian National Supplementary Health Agency and criteria of the guidelines of use

Indication	Drug	DUT number	DUT criteria
Severe eosinophilic asthma	Benralizumab Dupilumab Mepolizumab	65.9	a. Uncontrolled asthma, despite the use of inhaled corticosteroids associated with long-acting beta 2 agonists; **and** b. eosinophil count ≥ 300 cels/mm^3 in the last 12 months; **and** c. continuous use of oral corticosteroids for asthma control in the last 6 months or > 3 asthma exacerbations requiring oral corticosteroid treatment in the last year.
Severe allergic asthma	Dupilumab Omalizumab	65.10	a. Uncontrolled asthma despite the use of inhaled corticosteroids associated with long-acting beta 2 agonists; **and** b. evidence of sensitization to at least 1 perennial aeroallergen documented by prick skin testing or *in vitro* specific serum IgE dosage; **and** c. total serum IgE, before starting treatment, > 30 IU/ml; **and** d. continuous use of oral corticosteroids for asthma control in the last 6 months **OR** > 3 asthma exacerbations requiring oral corticosteroid treatment in the last year
Atopic dermatitis	Dupilumab	65.14	Severe atopic dermatitis with indication for systemic treatment with failure, intolerance, or contraindication to cyclosporine, which meet at least 1 of the following criteria: a. Atopic Dermatitis Activity Score - SCORAD > 50; **OR** b. Eczema Area and Severity Index - EASI > 21; **OR** c. Dermatology Life Quality Index - DLQI > 10
Chronic spontaneous urticaria	Omalizumab	65.11	Urticaria and/or angioedema for a period of more than 6 weeks, if all the following criteria are met: a. 7-day urticaria activity score (UAS7) > 28; **and** b. refractoriness to treatment with second-generation antihistamines for at least 2 weeks; **and** c. prescription by a dermatologist, immunologist or allergist **Note:** – Omalizumab treatment should be discontinued if no satisfactory therapeutic response is observed up to the fourth dose; – Following dose 6, discontinue treatment to check for spontaneous remission. If the disease recurs after discontinuation, treatment with omalizumab may be restarted at the discretion of the treating physician

various immunobiologic agents into the SUS and supplementary health care.

Currently, the prescription of immunobiologic agents is part of the therapeutic arsenal of all allergists and immunologists. In addition to theoretical and technical knowledge, the prescription of immunobiologic agents in allergic diseases must involve reflection on aspects of clinical practice, such as monitoring response, adverse events, care with application and access, as well as the cost-benefit balance.

New advances are continually being made, including the development of new monoclonal antibodies, expansion of the age range for use, and new indications for monoclonal antibodies that have already been licensed. In addition, some patients may benefit from the combined use of 2 monoclonal antibodies for concomitant allergic conditions (e.g. atopic dermatitis and urticaria) or for the potentiation of effects in the treatment of a single allergic condition (e.g. asthma), involving multiple pathogenic mechanisms.[92] Furthermore, patients with allergic diseases and other illnesses are also indicated for monoclonal antibodies therapy (e.g. asthma and Crohn's disease).[93] However, experience is still quite limited, and the combination of monoclonal antibodies should be reserved for exceptional cases, based on a shared decision between the prescribing physicians and the patient.

Finally, it should be emphasized that immunobiologic agents are new drugs and, therefore, some of the recommendations contained in this guide have not reached the desired scientific robustness yet. As such, they should be interpreted in the light of current evidence and local experiences, and should be updated periodically.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Cutaneous hypersensitivity to quinolones and associated factors

Determinação da reatividade cutânea às quinolonas e fatores associados

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ABSTRACT

Introduction: Quinolones, widely used in clinical practice, are the second leading cause of antibiotic hypersensitivity. Hypersensitivity to quinolone poses a challenge for allergists, as it occurs through immunoglobulin E (IgE)-mediated mechanisms as well as nonimmunologic ones (specifically the MRGPRX2 receptor). **Objective:** To assess cutaneous hypersensitivity to ciprofloxacin at different concentrations. **Methodology:** Skin prick test (SPT) and immediate-reading intradermal test (IDT) with ciprofloxacin were performed on volunteers treated at a tertiary outpatient clinic. Concentrations of 2 mg/mL (main solution), 1:10, and 1:50 were used for the SPT, and concentrations of 1:10, 1:50, 1:100, and 1:500 were used for the IDT. **Results:** Thirty-one individuals with no history of hypersensitivity to quinolone were included, of whom 74.1% were women. Mean patient age was 40.5 years. Atopic diseases were found in 48.4% of participants, of whom 100% had allergic rhinitis, 20% had allergic conjunctivitis, 13.3% had asthma, and 13.3% had atopic dermatitis. Previous quinolone use was reported by 45.2%. SPT performed with the main solution and 1:10 dilution was positive in 25.8% and 6.5% of cases, respectively, whereas SPT with 1:50 dilution was negative in all cases. IDT performed with 1:10, 1:50, and 1:100 dilutions was positive in 96.8%, 45.2%, and 6.5% of cases, respectively, but negative with 1:500. Among the individuals who had used quinolones, SPT with main solution and 1:50 dilution was positive in 28.6% and 14.3% of cases, respectively, compared with 25% and 0% in those who had not used quinolones. Among those who had used quinolones, IDT results were positive in 100% at 1:10, 57.1% at 1:50, and 14.3% at 1:100. Among those who had not used quinolones, IDT results were positive in 93.7% at 1:10, 37.6% at 1:50, and 0% at 1:100. In atopic individuals, SPT was positive in 26.7% with the main solution and 1:10 dilution, and negative with 1:50. Among nonatopic individuals, 25% had a positive SPT with the main

RESUMO

Introdução: As quinolonas, amplamente usadas na prática clínica, correspondem à segunda causa de reações de hipersensibilidade aos antibióticos. Reações às quinolonas (RQ) são um desafio para o alergista, pois ocorrem por mecanismos IgE mediados, mas também por uma via não imunológica, o receptor MRGPRX2. **Objetivo:** Este trabalho avalia a reatividade cutânea de pessoas sem alergia ao ciprofloxacino em diversas concentrações. **Metodologia:** Foram realizados *prick tests* (PT) e testes intradérmicos de leitura imediata (ID) com ciprofloxacino em voluntários atendidos em um ambulatório de serviço terciário. No PT, foram usadas concentrações de 2 mg/mL (solução mãe), 1:10 e 1:50. No ID, 1:10, 1:50, 1:100 e 1:500. **Resultados:** Foram incluídos 31 indivíduos sem histórico de RQ. A média de idade foi de 40,5 anos, sendo 74,1% do gênero feminino. Doenças atópicas foram encontradas em 48,4% dos participantes, 100% destes com rinite alérgica, 20% com conjuntivite alérgica, 13,3% com asma, e 13,3% com dermatite atópica. Uso prévio de quinolonas foi relatado por 45,2% dos indivíduos. O PT puro e 1:10 foi positivo em 25,8% e 6,5%, respectivamente; na concentração 1:50 não mostrou positividade. O ID 1:10, 1:50 e 1:100 foi positivo em 96,8%, 45,2% e 6,5%, respectivamente, mas foi negativo na diluição 1:500. Nos que já usaram quinolonas, o PT puro e 1:50 foram positivos em 28,6% e 14,3% dos participantes, respectivamente, *versus* 25% e 0% nos que não usaram. O ID entre os indivíduos que já usaram foi positivo em 100% na diluição 1:10, 57,1% na 1:50, e 14,3% na 1:100. Entre os que não usaram, 93,7% na diluição 1:10, 37,6% na 1:50, e 0% na 1:100. Nos atópicos, o PT foi positivo em 26,7% e 13,3% na concentração mãe e 1:10; e negativo em 1:50. Nos participantes não atópicos, observou-se positividade de 25% no PT com a solução mãe e testes negativos nas demais diluições. O ID com as soluções 1:10, 1:50 e 1:100 foi positivo em 100%, 46,7% e 6,7% dos atópicos, e 93,7%,

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solution, and the remaining individuals were negative. IDT results with 1:10, 1:50, and 1:100 dilutions were positive, respectively, in 100%, 46.7%, and 6.7% of atopic individuals and in 93.7%, 43.7%, and 6.3% of nonatopic individuals. **Conclusion:** Ciprofloxacin triggers cutaneous hypersensitivity via immunologic mechanisms and the MRGPRX2 receptor. It is recommended that skin tests be performed at a dilution of 1:100 or greater to investigate immediate hypersensitivity.

Keywords: Quinolone allergy, skin tests, skin prick test, intradermal tests, ciprofloxacin.

43,7%, 6,3% nos não atópicos, respectivamente. **Conclusão:** O ciprofloxacino apresenta reatividade cutânea através de vias imunológicas e pelo MRGPRX2, sendo recomendada a realização de testes cutâneos em concentrações igual ou menores de 0,02 mg/mL para investigação de reações de hipersensibilidade imediata, pois essas concentrações apresentam boa especificidade.

Descritores: Alergia a quinolonas, testes cutâneos, teste de puntura, testes intradérmicos, ciprofloxacino.

Introduction

Quinolones are broad-spectrum antibacterial drugs that were first obtained during the synthesis of chloroquine and then chemically evolved throughout the years, leading to the development of nalidixic acid, which acts predominantly on gram-negative bacteria causing urinary tract infection, and modern antibiotics that enter into several sites, have a broad spectrum activity, and are used in the treatment of more resistant microorganisms.[1]

The basic chemical structure of quinolones consists of a 4-oxo-1,4- dihydroquinoleine ring core with a hydrogen atom at position 1 and a carboxyl acid at positions 3 and 4. Since the synthesis of the first quinolones, several chemical changes have been made, improving their efficacy, spectrum of action, bacterial activity, and tissue penetration. Quinolones have been classified into four generations, based on their chemical structure and antibacterial spectra. The chemical structure of quinolones and their classification are presented in Figure 1.[2]

The first-generation quinolones – nalidixic acid, pipemidic acid, cinoxacin, oxolinic acid – are active against gram-negative bacteria, and their penetration is restricted to the urinary tract. The second generation, developed with the introduction of the fluorine atom at position C-6, includes fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, fleroxacin, lomefloxacin, enoxacin) and has broad-spectrum activity against gram-negative bacteria g gram-positive bacteria. The addition of a halogen (fluorine or chlorine) at position 8 leads to third-generation quinolones – levofloxacin and gatifloxacin –, which have greater activity against *Pseudomonas aeruginosa*, gram-positive bacteria, and anaerobes. Finally, the fourth generation – moxifloxacin, gemifloxacin, and trovafloxacin – is more potent against gram-positive bacteria and anaerobes and less active against *P. aeruginosa*, due to a double ring derived from the pyrrolidone ring at position 7 and a methoxy group at position 8.[3,4]

Bactericidal activity of quinolones targets the bacterial enzymes DNA gyrase and DNA topoisomerase IV, inhibiting microorganism replication.[1,4,5] Currently, these antibiotics are widely used in the treatment of gram-positive and gram-negative bacteria affecting the urinary, respiratory, digestive, and cutaneous tracts, in addition to sexually transmitted infections, prostatitis, and tuberculosis.[5]

Due to the widespread use of quinolones, adverse events related to the use of these drugs have been described. Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as “any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function”. These reactions can be classified into type A – predictable and dose-dependent; and type B – unpredictable, dose-independent, and not directly associated with the effects of the drug.[6]

Drug hypersensitivity reactions (DHRs) are defined by the WHO as type B ADRs resembling allergy and reproducible in subsequent administrations. The term drug allergy should be used when there is a specific immunological mechanism associated with clinical manifestations, involving either drug-specific immunoglobulins or T cells.[6]

DHRs to quinolones are the second leading cause of hypersensitivity to antibiotics and the third leading cause of hypersensitivity to medications in general, after non-steroidal anti-inflammatory drugs

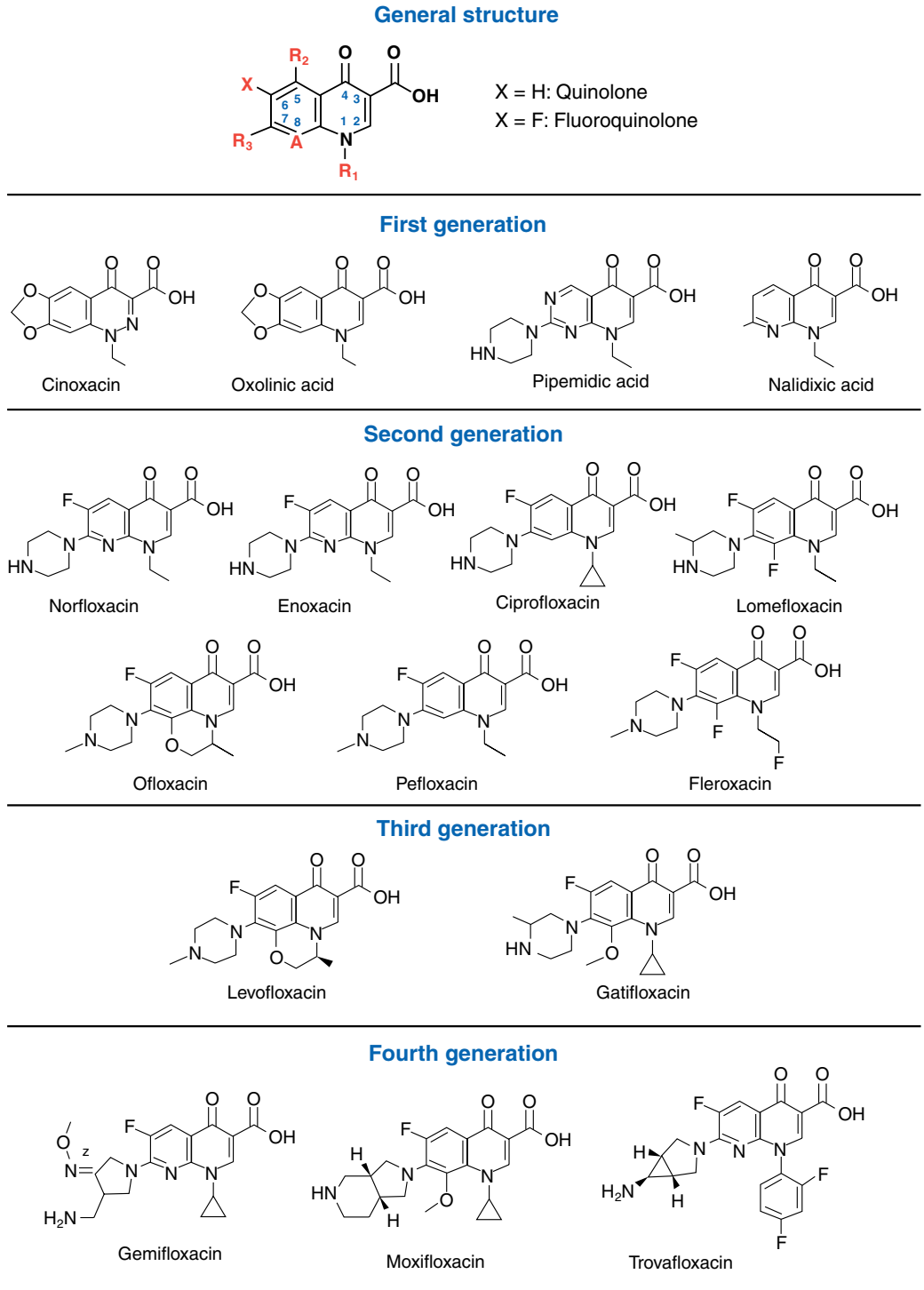

Figure 1
Chemical structure and classification of quinolones
Adapted from Doña I, et al.[2].

and beta-lactams in frequency.[7] These reactions are classified into immediate, which usually involve urticaria and other symptoms associated with anaphylaxis, or delayed T cell-mediated reactions, such as maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), or acute generalized exanthematous pustulosis.[2,8]

Immediate DHRs to quinolones, resulting from the activation of mastocytes and basophils, may occur through different endotypes, despite having the same phenotype. The presence of quinolone-specific IgE was identified in 30 to 55% of individuals with history of immediate DHRs[8-10]; however, in some individuals, these medications may trigger reactions via other mechanisms, such as agonist action at MRGPRX2 (mast-related G-protein receptor X2), present in mast cells, basophils, and eosinophils, leading to the activation of these cells.[2,11]

In clinical practice, the diagnosis of immediate DHRs to quinolones is based on detailed clinical history of the symptoms and previous use of the medication involved, which is correlated with the reaction throughout time. Additional tests, such as skin tests and provocation tests, are important investigation tools. *In vitro* tests, such as specific IgE tests and basophil activation tests may be used, despite being little available and having greater application in research.[2,12,13]

Investigation with skin tests starts with the skin prick test, or skin puncture, test. In case of a negative result, investigation continues with the immediate-reading intradermal test. Despite being widely used in clinical practice for DHRs to other drug classes, the use of skin tests for quinolones is controversial, since these drugs may generate positive results via two mechanisms – presence of specific IgE and agonistic action at MRGPRX2, depending on the concentration used.[2,14]

Determining the drug dilution concentration to be used in skin tests in essential. More concentrated solutions may induce "irritant" skin reactions in individuals with no history of DHR, or, in the case of quinolones, via MRGPRX2 present in skin mast cells. Therefore, the predictive positive value of skin tests should be interpreted in light of possible interferences.

In addition to the concentrations used to perform the skin tests, other conditions may influence the results, such as skin reactivity, presence of comorbidities, and use of antihistamines and antidepressants. Hence, knowledge of skin reactivity at different concentrations used in skin tests with quinolones, associated with analysis of possible interfering factors, may help in better understanding mast cell homeostasis, in addition to potentially predicting the most appropriate dilution to be used in the diagnostic investigation of immediate DHRs to quinolones.

This work had the primary objective of assessing reactivity of skin, epicutaneous (prick) and immediate-reading intradermal tests to quinolones in a population with no history of hypersensitivity to these medications. The study made it possible to determine the concentration of ciprofloxacin that has good specificity in skin tests to investigate immediate reactions to the antibiotic. As a secondary objective, the study analyzed possible factors associated with skin reactivity to ciprofloxacin in immediate-reading skin tests.

Methods

This work consisted of a cross-sectional analytical assessment of the study population, composed of individuals with no history of immediate hypersensitivity reaction to quinolones. Adult volunteers older than 18 years of age treated at the outpatient clinics of the Clinical Immunology and Allergy Service of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Individuals with history of hypersensitivity to quinolones were excluded, as well as those receiving antihistamine treatment in the last 7 days prior to the skin test and those who had anaphylaxis at any point in life, mast cell activation syndrome, cutaneous or systemic mastocytosis, spontaneous or induced chronic urticaria, and extensive skin disease that prevented the execution of skin tests.

Initially, an interview was conducted for collection of medical history - age, sex, previous use of quinolones, presence of atopic diseases, and personal or family history of hypersensitivity to other medications. Next, a prick test was performed to assess sensitization to aeroallergens with extract of *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, cat and dog epithelium, *Lolium perenne*, *Aspergillus sp*, *Penicillium notatum*, *Blatella germanica*, and *Periplaneta americana.*

Finally, skin reactivity to ciprofloxacin was evaluated. The puncture test was conducted with the following concentrations: 2 mg/mL (pure solution),

0.2 mg/mL (1:10), and 0.04 mg/mL (1:50). The immediate-reading intradermal test was performed with the following concentrations: 0.2 mg/mL (1:10), 0.04 mg/mL (1:50), 0.02 mg/mL (1:100), and 0.0004 mg/mL (1:500). The prick test was considered positive if the allergen produced a wheal 3 mm larger than the negative control (saline solution), whereas the intradermal test was considered positive if the difference between the initial and final size of the wheal was 3 mm larger than the difference observed in the negative control. Skin tests were performed in duplicate on the anterior surface of both forearms.

Statistical analysis was performed using the Python platform, with data from Excel® files. The data collected included patients' characteristics and test results, which were converted for binary values. All continuous variables were expressed as means and their respective standard deviations. An initial descriptive analysis was performed, followed by application of the Student's *t* test for paired samples. Categorical variables were presented as absolute numbers and percentages, and compared using the chi-square test (χ^2). P-values lower than 0.05 were considered significant. Bar graphs were created using Matplotlib and Seaborn.

Results

This study included 31 individuals with no history of hypersensitivity to quinolones. Mean age was 40.5 years (standard deviation 13.0 years), and 74.1% of individuals were female. Atopic diseases were reported in 48.4% of participants – among these, 100% reported allergic rhinitis, 20% allergic conjunctivitis, 13.3% asthma, and 13.3% atopic dermatitis. Of total participants, 45.2% reported previous use of quinolones; of these, 32.2% had contact with ciprofloxacin, 32.2% with levofloxacin, and 0.03% with moxifloxacin. These data are described in Table 1. Age distribution is shown in Figure 2.

In the total population, the prick test with pure ciprofloxacin and 1:10 dilution was positive in 25.8% and 6.5% of the sample, respectively, whereas no positive results were found with the 1:50 dilution. The intradermal test at the 1:10, 1:50 and 1:100 dilutions was positive in 96.8%, 45.2%, and 6.5% of the sample, respectively. There were no positive results with the 1:500 dilution. Therefore, specificity was 93.5% for both the prick test with the 1:10 dilution and the intradermal test with 1:100 dilution.

The prick test for aeroallergens was positive in 54.9% of the evaluated individuals. Among these, puncture with ciprofloxacin was positive in 23.5% and 11.8% for pure ciprofloxacin and 1:10 dilution, respectively. The intradermal test with the antibiotic was positive in 100%, 52.9%, and 5.8% for 1:10, 1:50, and 1:100 dilutions, respectively. Therefore, 1:100 dilution showed good specificity (94.2%) in individuals with atopy.

Patients with a negative result for aeroallergens accounted for 45.1% of the cases, of which 28.6% were positive in the prick test with pure ciprofloxacin, but negative with the other dilutions. The intradermal test with ciprofloxacin was positive in 99.9%, 35.8%, and 7.2% with 1:10, 1:50, 1:100 dilutions, respectively.

No statistical differences were observed in the results of the chi-square tests for each type and dilution of the skin test with ciprofloxacin comparing individuals with positive and negative results in the test for aeroallergens.

In the subgroup of volunteers with atopic diseases, the puncture test was positive in 26.7% and 13.3% with pure ciprofloxacin and 1:10 dilution, respectively. The intradermal test with 1:10, 1:50, and 1:100 dilutions was positive in 100%, 46.7%, and 6.7%, respectively.

Table 1
Demographic and clinical data of the population

	N: 31
Mean age	40.5 years
Female gender	74.1%
Atopic diseases	48.4%
Allergic rhinitis	100%
Allergic conjunctivitis	20%
Asthma	13.3%
Atopic dermatitis	13.3%
Previous use of quinolones	45.2%
Ciprofloxacin	32.2%
Levofloxacin	32.2%
Moxifloxacin	0.03%

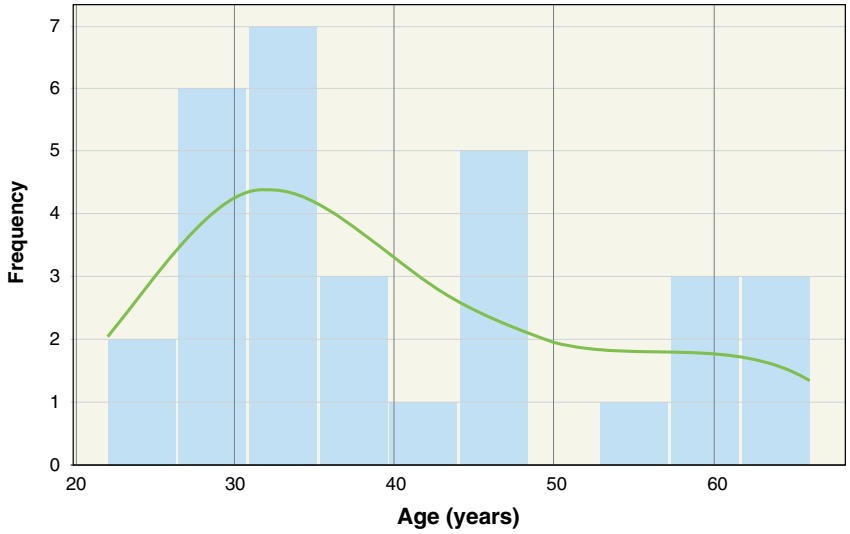

Figure 2
Age distribution in the analyzed population

Among participants without atopic diseases, 25% had a positive prick test with pure ciprofloxacin, and negative with the other dilutions. The intradermal test with 1:10, 1:50 and 1:100 dilutions was positive in 93.7%, 43.7%, and 6.3% of the nonatopic participants.

No statistical differences were observed in the assessment of the chi-square tests for skin tests with ciprofloxacin and for presence or absence of atopic diseases.

In the population that reported previous use of quinolones, the prick test with pure ciprofloxacin and 1:10 dilution was positive in 28.6% and 14.3% of the cases, respectively, vs 25% and 0% in those who did not use quinolones. The intradermal test at 1:10, 1:50, and 1:100 dilutions was positive 100%, 57.1%, and 14.3%, respectively, among those who used the antibiotic. Among those who did not use it, the intradermal test with 1:10, 1:50, and 1:100 dilutions was positive in 93.7%, 37.6%, and 0% of the cases, respectively.

Results for the chi-square tests comparing previous use of quinolones revealed a $p = 0.3$ for prick test with pure ciprofloxacin and 1:10 dilution, and $p = 0.9$, $p = 0.4$, and $p = 0.2$ for intradermal tests at 1:10, 1:50, and 1:100 dilutions, respectively.

Among all the volunteers, 74.2% denied previous ADRs to any medication; of these, 26.0% and 43% had a positive prick test with pure ciprofloxacin and 1:10 dilution, respectively, and 95.6%, 52.1%, and 4.3% showed positive skin reactivity in the intradermal test with 1:10, 1:50, and 1:100 dilutions, respectively.

The participants who reported a type A or B ADR accounted for 25.8% of the cases, of which 25.0% and 12.5% showed positive skin reactivity in the prick test with pure ciprofloxacin and 1:10 dilution, respectively. When these participants were assessed using the intradermal test with 1:10, 1:50, and 1:100 dilutions, there was reactivity in 100%, 25%, and 12.5% of the cases, respectively.

The chi-square tests did not reveal statistically significant differences between the skin test of participants with and without previous ADR.

Table 2 shows positivity rates in the general study population and according to associated factors: positive epicutaneous test for aeroallergens, presence of atopic disease, previous use of quinolones, and history of drug reactions. Tables 3, 4, 5 and 6 compare positivity rates of intradermal tests according to four associated factors: sex, positive epicutaneous test for aeroallergens, presence of atopic disease, and previous use of quinolones.

Table 2
Positivity of skin tests in the subgroups evaluated

General population - N = 31	Prick test, pure ciprofloxacin: 25.8% Prick test, 1:10 dilution: 6.5% ID test, 1:10 dilution: 96.8% ID test, 1:50 dilution: 45.2% ID test, 1:100 dilution: 6.5%
Positive prick test for aeroallergens - N = 17	Prick test, pure ciprofloxacin: 23.5% Prick test, 1:10 dilution: 11.8% ID test, 1:10 dilution: 100% ID test, 1:50 dilution: 52.9% ID test, 1:100 dilution: 5.8%
Atopic diseases - N = 15	Prick test, pure ciprofloxacin: 26.7% Prick test, 1:10 dilution: 13.3% ID test, 1:10 dilution: 100% ID test, 1:50 dilution: 46.7% ID test, 1:100 dilution: 6.7%
Previous use of quinolones - N = 15	Prick test, pure ciprofloxacin: 28.6% Prick test, 1:10 dilution: 14.3% ID test, 1:10 dilution: 100% ID test, 1:50 dilution: 47.1% ID test, 1:100 dilution: 14.3%
Other ADR - N = 8	Prick test, pure ciprofloxacin: 25.0% Prick test, 1:10 dilution: 12.5% ID test, 1:10 dilution: 100% ID test, 1:100 dilution: 25% ID test, 1:100 dilution: 12.5%

ADR = adverse drug reaction, ID = intradermal.

Discussion

Drug hypersensitivity reactions (DHRs), either allergic or not, are underdiagnosed in some scenarios, but may also be overly attributed to patients, leading to misdiagnoses of allergy in healthy individuals. This situation may hamper future therapeutic approaches, in which less effective and more expensive medications are used as alternatives.[6,15]

The execution of skin tests for betalactam antibiotics is already well established, as well as algorithms to define what portion of the molecule is more likely to be involved in sensitization. For quinolones, applicability

Table 3
Positivity of intradermal tests according to participants' sex

	Intradermal test dilutions		
Sex	**1:10**	**1:50**	**1:100**
Female	100%	45.8%	0.8%
Male	85.7%	42.8%	0

of these tests seems to be more controversial, since their concentrations are not well established, and they may lead to positive results through immunological and non-immunological (irritative) pathways.

Table 4
Positivity of intradermal tests according to positivity of epicutaneous tests for aeroallergens

Epicutaneous test for aeroallergens	Intradermal test dilutions		
	1:10	1:50	1:100
Positive	100%	52.9%	5.8%
Negative	99.9%	35.8%	7.2%

Table 5
Positivity of intradermal tests according to the presence of atopic disease or not

Atopic disease	Intradermal test dilutions		
	1:10	1:50	1:100
Present	100%	46.7%	6.7%
Absent	93.7%	43.7%	6.3%

Table 6
Positivity of intradermal tests according to previous use of antibiotic

Previous use of quinolones	Intradermal test dilutions		
	1:10	1:50	1:100
Yes	100%	57.1%	14.3%
No	93.7%	37.6%	0

HRs to quinolones, which represent broad spectrum antibiotics used in several clinical conditions, are difficult to investigate. In this work, a considerable number of individuals with no history of ADRs to these medications showed skin reactivity to different concentrations of ciprofloxacin. This result reflects the practical difficulty in performing an investigation of HRs to these medications.

Broz et al. assessed skin reactivity with ciprofloxacin through intradermal skin tests with the 1:300, 1:1000, and 1:3000 concentrations in 15 volunteers with no history of HR to quinolones. Readings in these tests were made using photograph records and analysis of wheal growth via a computational software, in addition to application of laser Doppler fluoroscopy to evaluate changes in skin perfusion. For the concentration of 1:300, no wheal growth was observed, despite the increase in blood flow; hence, this concentration was considered to be nonirritant.[16]

Venturini Díaz et al. used ciprofloxacin at a concentration of 0.02 mg/mL (1:100) for puncture and intradermal tests, levofloxacin at 5 mg/mL for the prick test and at 0.05 mg/mL for the intradermal test, and other oral quinolones (norfloxacin, ofloxacin, moxifloxacin, pipemidic acid, trovafloxacin) administered in tablets diluted in saline solution for the prick test, in 12 individuals without HR to quinolones. Of these participants, 3 had a positive prick test for ofloxacin, 1 for moxifloxacin, and 1 for pipemidic acid.[17]

In our work, both the prick test with 1:10 dilution and the intradermal test with 1:100 dilution had a specificity of 93.5%, being the most recommended concentrations for skin tests to rule out hypersensitivity to quinolones. Previous use of these drugs and ADR to other medications led to higher positivity rates at a concentration of 1:100, which may suggest previous sensitization, although the difference was not statistically significant. Atopy or presence of atopic diseases did not interfere with the results of the skin tests.

In the medical literature, there is no current consensus on the use of skin tests in the approach of HRs to quinolones, and there are authors in favor and against the use of these tests, with the latter recommending to perform only the provocation test, a procedure that carries some risks.[15,18]

Due to these limitations, skin tests are not conducted very often in individuals with a history of hypersensitivity, leading to a scarcity of data on

sensitivity in individuals subjected to the provocation test, opening the possibility for future studies.

Conclusion

In our work, the prick test with 1:10 dilution and the intradermal test with 1:100 dilution had a specificity of 93.5%, being these the concentrations recommended for skin tests to rule out hypersensitivity to quinolones. Individuals who previously used these drugs or had an ADR to other medications tended to show greater reactivity at lower concentrations; however, additional studies are needed to define sensitivity to skin tests and their clinical applicability.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Etiology, sociodemographic profile, and outcomes of patients with asthma hospitalized for severe acute respiratory illness (SARI) in Brazil from 2020 to 2022: an analysis of 83,452 hospitalizations

Perfil etiológico, sociodemográfico e desfechos dos pacientes com asma internados por síndrome respiratória aguda grave (SRAG) no Brasil de 2020 a 2022: uma análise de 83.452 internações

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ABSTRACT

Introduction: Asthma is one of the most common chronic diseases affecting the Brazilian population. We aimed to determine the etiology, sociodemographic profile, and risk factors for death in patients with asthma hospitalized for severe acute respiratory illness (SARI) in Brazil from 2020 to 2022. **Methods:** We included all patients over 5 years of age registered in the Influenza Epidemiological Surveillance Information System (SIVEP Gripe) database of the Brazilian Ministry of Health from January 1, 2020 to July 21, 2022 hospitalized for SARI. Patients had to have a history of asthma and known outcomes. As exposures, age, sex, region of residence, ethnicity, and viral etiological agent were evaluated. The outcomes measured were admission to an intensive care unit, need for mechanical ventilation, and death. We used multilevel generalized linear mixed models to calculate the odds ratio between exposure and outcomes. **Results:** A total of 83,452 hospitalizations were included, of which 14,062 were children and adolescents and 69,390 were adults. Mortality increased with age, ranging from 0.6% in those aged 5-10 years to 33% in those over 60 years. In the pediatric population, living in the north and northeast regions (OR 2.14, 95%CI 1.41-3.24) and having between 10-20 years (OR 3.73, 95%CI 2.65-5.26) were associated with higher mortality. As for etiologic agents, only SARS-CoV-2 was associated with a higher risk of death (OR 5.18,

RESUMO

Introdução: A asma é uma das doenças crônicas mais frequentes na população brasileira. O objetivo deste estudo foi determinar as etiologias, o perfil sociodemográfico e os fatores de risco para óbito entre pacientes com asma internados por síndrome respiratória aguda grave (SRAG) no Brasil entre 2020 e 2022. **Métodos:** A partir do banco de dados SIVEP-Gripe, incluímos todos os pacientes com idade maior que 5 anos registrados no banco de 01/01/2020 até 21/07/2022, hospitalizados por SRAG, com antecedente de asma e com desfechos conhecidos. Como exposições, foram estudadas a idade, sexo, região de moradia, etnia e agentes etiológicos virais isolados. Os desfechos foram internação em unidade de terapia intensiva, necessidade de ventilação mecânica e óbito. Para calcular a razão de chances entre exposição e desfechos, utilizamos modelos lineares generalizados mistos multinível. **Resultados:** Foram incluídas na análise 83.452 internações, sendo 14.062 crianças e adolescentes, e 69.390 adultos. A mortalidade aumentou com a idade, indo de 0,6% entre 5-10 anos para 33% nos maiores que 60 anos. Na população pediátrica, morar na região Norte e Nordeste e ter entre 10-20 anos foram associados a maior mortalidade (OR 2,14 IC95% 1,41-3,24 e OR 3,73 IC95% 2,65-5,26 respectivamente). Quanto aos agentes etiológicos, apenas o SARS-CoV-2 conferiu maior risco de óbito (OR 5,18 IC95% 3,62-7,42). Entre adultos, sexo feminino

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95%CI 3.62-7.42). Among adults, female sex (OR 0.87, 95%CI 0.83-0.9) and non-White ethnicities (OR 0.90, 95%CI 0.85-0.94) were protective factors against death. Older age groups, living in the north and northeast regions, and a diagnosis of COVID-19 were associated with higher mortality. **Conclusions:** There are important sociodemographic vulnerabilities in the outcomes of patients with asthma hospitalized for SARI, with higher mortality rates in the north and northeast regions, among adolescents in the pediatric age group, and among older adults. Furthermore, COVID-19 was one of the main infections associated with higher mortality.

Keywords: Asthma, COVID-19, severe acute respiratory syndrome , epidemiology.

e etnias não brancas foram protetoras (OR 0,87 IC95% 0,83-0,9 e OR 0,90; IC95% 0,85-0,94 respectivamente) para óbito. Faixas etárias mais avançadas, morar nas regiões Norte e Nordeste e o diagnóstico de COVID-19 foram associados a maior mortalidade. **Conclusões:** Há importantes vulnerabilidades sociodemográficas nos desfechos das internações de pacientes com asma por SRAG, com maior mortalidade nas regiões Norte-Nordeste, entre adolescentes na faixa etária pediátrica e entre idosos nos adultos. Além disso, destaca-se o protagonismo da COVID-19 entre as infecções associadas a maior mortalidade.

Descritores: Asma, COVID-19, síndrome respiratória aguda grave, epidemiologia.

Introduction

Asthma is one of the most common chronic diseases affecting the population in Brazil, with estimated prevalence rates between 9% and 13% in children and adolescents (C&A) and 4.4% in adults.[1,2] Although mortality has fallen dramatically since inhaled corticosteroids use has been introduced and widespread,[3] the number of deaths due to the disease has stabilized over the last decade in the country. In addition to the loss of lives, it highly burdens the health system and has an impact on society, both in the form of direct treatment costs and healthy years lost to the disease.[4,5]

From 2020, the epidemiological health scenario in Brazil and worldwide has been dominated by the emergence of COVID-19 and its aftermath. Since its onset, with the adoption of social distancing and barrier measures to the transmission of SARS-CoV-2, the pandemic has had a profound impact on the transmission dynamics of respiratory viruses, changing the seasonality and profile of the most common respiratory viral infections.[6,7] This global reality culminated in an outbreak of respiratory cases following the relaxation of isolation measures, especially in the pediatric age group.[8,9] Although chronic diseases increase the risk of poorer outcomes in COVID-19, recent studies show that controlled asthma alone does not increase the risk of hospitalization or death from the disease, and may even be a protective factor.[10,11] However, among asthma patients hospitalized for respiratory symptoms, the impact of viral infections on their outcomes is still unclear, especially considering the dynamic change in the epidemiology of viral transmission experienced in recent years.

During the 2009 influenza epidemic, the Brazilian Ministry of Health (MH) began to record all hospitalizations for severe acute respiratory syndrome (SARS), which became mandatory notification, making up the Sistema de Vigilância Epidemiológica da Gripe (SIVEP-Gripe, Influenza Epidemiological Surveillance Information System). With the emergence of COVID-19, the disease also became part of the SARS database, representing a valuable source for epidemiological studies on the evolution of hospitalizations for the syndrome, its etiology, and outcomes. This study aimed to analyze this domestic database to determine the etiologies, outcomes, and risk factors for death among patients with asthma hospitalized for SARI in Brazil from 2020 to July 2022.

Methods

This study used data from the MH-SIVEP-Gripe database, which records cases of hospitalization for SARS in the country, a compulsory notification condition. The database records multiple pieces of information about each patient, including sociodemographic data, clinical presentation, comorbidities, etiological research, outcomes, among others. The MH defines SARS for notification purposes as patients with flu-like syndrome who show signs of severity, such as dyspnea/respiratory discomfort or persistent pressure or pain in the chest, or oxygen saturation below 95% on room air or cyanosis of the lips/face.[12]

This study included all hospitalized patients older than 5 years, registered in the database from 01/01/2020 to 07/21/2022, with a history of asthma (reported by the patient or family member), and known

outcomes. As exposures, we studied age (divided into age groups and then into C&A and adults), sex, region of residence, ethnicity, and the viral etiological isolated agents. We considered patients to be adults if they were older than 20 years, according to the World Health Organisation.[13] So as to maximize contrasts, the regions of the country were grouped into Northern (North and Northeast) and Southern (Midwest, Southeast and South) macro-regions, a common strategy in population studies.[14] Similarly, ethnic groups were divided into white and nonwhite (black, mixed race, indigenous people, and yellow). The most common viral agents reported were SARS-CoV-2, influenza, rhinovirus, and respiratory syncytial virus (RSV). We also used the variable "sample collection" to describe the percentage of patients who underwent etiological research, although the form does not describe for which agent the samples were collected. We described intensive care unit (ICU) admission, need for mechanical ventilation, and death as outcomes, although only death was studied in the multivariate analyzes.

Categorical variables were presented as frequencies and percentages. Chi-square was used in the initial tables to analyze the significance of differences between categorical variables. Multilevel mixed generalized linear models (GLM) were built to calculate the odds ratio (OR) and confidence intervals (95% CI) between exposure and outcome, considering the health care facility where the patient was cared for as a random effect. The multivariate analysis was adjusted for other variables with significant differences for the outcome studied, in different models for C&A and adults. It is important to emphasize that the multivariate analysis compared the effects of having a positive result for a given agent with the absence of a positive result for that agent, regardless of whether the test had been performed or not. Considering the discrepancies between age groups, the results for C&A and adults were reported separately.

The only significant loss of data among the sociodemographic variables studied was ethnicity: 17.3% of hospitalizations had no record of the patients' ethnicities. In order to preserve the reliability of the data, we decided not to perform multiple imputation techniques, so patients with missing ethnical data were excluded from the analyzes involving this variable, and ethnicity was not included as an adjustment variable in the multivariate models.

The chance of an alpha error occurring was set at 5%. The data was processed and analyzed using STATA (Data Analysis and Statistical Software) version 17.

As this study used anonymized data taken from a repository available in the public domain, no approval from an ethics committee was required.

Results

The analysis included 83,452 hospitalizations, of which 14,062 were C&A and 69,390 were adults. Most hospitalizations occurred in 2021 (47.6% in 2021, 42.4% in 2020, and 10% in 2022). As for the number of hospitalizations, a U-shaped curve can be seen, with a drop in the number among adolescents compared to children, followed by a gradual increase in the following age groups. Mortality showed a tendency to increase with increasing age: 0.6% between 5-10 years old, 2.3% between 10-20, 10% between 20-40, 18.9% between 40-60, and 33% in people over 60 (Figure 1).

Table 1 shows the sociodemographic characteristics, etiological agents, and outcomes in the pediatric age group, both in the general population studied and only deaths. The majority of children included were male, nonwhite, and from the South, Southeast, and Midwest regions. Among the sociodemographic characteristics, only to live in the North-Northeast region was associated with higher mortality ($p < 0.001$). In addition, two-thirds of hospitalizations were among children, while most deaths were among adolescents, also a significant difference. Although more than 95% of the patients underwent an etiological investigation, less than 15% had a viral etiological isolated agent. SARS-CoV-2, the etiological agent of COVID-19, was the most frequent virus in this cohort (53.4% of isolated agents), especially among deaths (83%). Around a fifth of patients required ICU admission, and approximately 5% were intubated. Mortality among C&A was 1.2%.

Table 2 describes the sociodemographic characteristics, etiological agents, and outcomes among adults, including deaths. Contrasting with the pediatric age group, among adults admissions predominated among women and white patients, and the highest number of admissions was in the Southern macro-region. Men and living in the North and Northeast were associated with higher mortality ($p < 0.001$). Most hospitalizations were among patients older than 60, as were most deaths. The majority of adults underwent viral testing, and more than half had

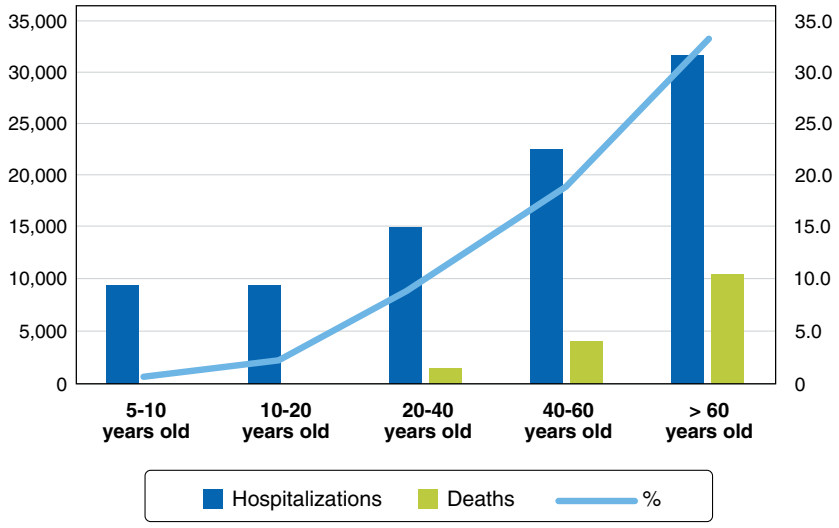

Figure 1
Number of hospitalizations, deaths, and death rate per age group among asthma patients hospitalized for severe acute respiratory syndrome (SARS) in Brazil between 2020-2022

Source: SIVEP-Gripe.

The X axis on the left represents the number of hospitalizations and deaths (bars); on the right, the death rate and each age group (line).

Table 1
Sociodemographic characteristics, etiological agents, and outcomes of children and adolescents with asthma hospitalized for severe acute respiratory syndrome (SARS) in Brazil between 2020 and 2022

Characteristics	Categories	General (N = 14,062) N (%)	Deaths (N = 163) N (%)	p
Region	North/Northeast	2,728 (19.4)	53 (32.5)	< 0.001
Sex	Male	7,664 (54.5)	78 (47.8)	0.086
Ethnicity	Nonwhite	6,402 (57)	83 (60.6)	0.395
Age	5-10	9,346 (66.5)	54 (33.1)	< 0.001
	10-20	4,716 (33.5)	109 (66.9)	
Sample collection	Collected	13,408 (95.3)	151 (92.6)	0.385
Etiological agent	Isolated	2,088 (14.8)	67 (41)	< 0.001
SARS-CoV-2	Positive	1,115 (7.9)	56 (34.4)	< 0.001
Rhinovirus	Positive	513 (3.6)	4 (2.4)	0.413
Influenza	Positive	264 (1.9)	5 (3.1)	0.260
RSV	Positive	158 (1.1)	1 (0.6)	0.534
ICU	Yes	2,946 (22.7)	101 (65.6)	< 0.001
Invasive ventilation	Yes	679 (5.3)	97 (65.5)	< 0.001

p value: results from Chi-square test.
RSV: respiratory syncytial virus, ICU: intensive care unit.

a viral agent isolated, and SARS-CoV-2 was the agent in most cases, both in the general population studied and among deaths (96.5% and 98.4% of viral agents isolated, respectively). Of the patients, one third were admitted to ICU and 18% required intubation. Mortality among adults was 23.5%.

Figures 2 and 3 show the results of the multivariate analyzes among C&A and adults, death as the outcome, and the different sociodemographic and etiological variables as the exposure. Adolescents have a risk of death almost 4-fold higher than children (OR 3.73; 95% CI 2.65-5.26), and residents in the North and Northeast regions die more than twice as often as patients living in other regions (OR 2.14; 95% CI 1.41-3.24). C&A with isolated SARS-CoV-2 also have a higher risk of death when compared to patients without this diagnosis (OR 5.18; 95% CI 3.62-7.42); this relationship is maintained in C&A in an analysis stratified by age group. Neither sex, ethnicity, nor a diagnosis of influenza, RSV, or rhinovirus were related to death. However, among adults, women were protective, 13% less likely to die than men (OR 0.87; 95% CI 0.83-0.9), as were nonwhite ethnic groups (OR 0.90; 95% CI 0.85-0.94). Similar to pediatrics, older age groups and living in the North and Northeast regions were also risk factors. A diagnosis of COVID-19 increased mortality risk almost 3-fold (OR 3.01; 95% CI 2.66-3.41), an association that was maintained when broken down into age groups. Conversely, isolation from influenza, RSV, or rhinovirus was a protective factor.

Discussion

This is the most comprehensive nationwide study to date on the epidemiology, etiology, and risk factors for death in asthma patients hospitalized for SARI. Using a population-based database, we included a large number of patients to show how these hospitalizations are distributed across the country and the impact of

Table 2
Sociodemographic characteristics, etiological agents, and outcomes in adults (≥ 20 years old) with asthma hospitalized for severe acute respiratory syndrome (SARS) in Brazil between 2020 and 2022

Characteristics	Categories	General (N = 69,390) N (%)	Deaths (N = 16,284) N (%)	p
Region	North/Northeast	10,949 (15.8)	3,121 (19.2)	< 0.001
Sex	Male	26,369 (38)	6,427 (39.5)	< 0.001
Ethnicity	Nonwhite	25,228 (43.7)	6,095 (43.6)	0.771
Age	20-40	15,050 (21.7)	1.511 (9.3)	< 0.001
	40-60	22,532 (32.5)	4,265 (26.2)	
	> 60	31,765 (45.8)	10,500 (64.5)	
Sample collection	Collected	65,942 (95)	15,513 (95.3)	0.028
Etiological agent	Isolated	34,856 (50.2)	10,645 (65.4)	< 0.001
SARS-CoV-2	Positive	33,640 (48.5)	10,478 (64.3)	< 0.001
Rhinovirus	Positive	192 (0.3)	14 (0.1)	< 0.001
Influenza	Positive	908 (1.3)	139 (0.8)	< 0.001
RSV	Positive	118 (0.2)	12 (0.1)	0.001
ICU	Yes	21,910 (33.4)	9,993 (65.6)	< 0.001
Invasive ventilation	Yes	11,439 (18.2)	7,810 (52.5)	< 0.001

p value: results from Chi-square test.
RSV: respiratory syncytial virus, ICU: intensive care unit.

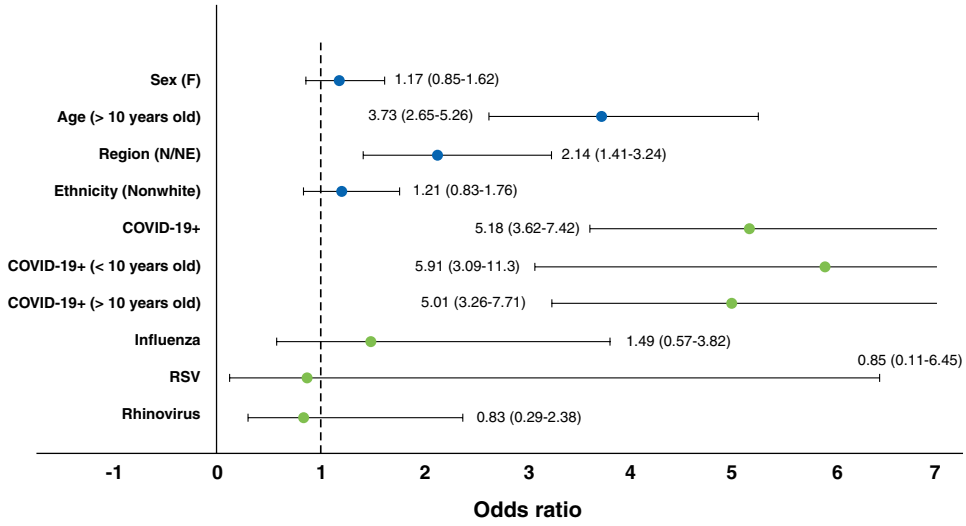

Figure 2

Demographic and etiological factors related to mortality among children and adolescents with asthma hospitalized for severe acute respiratory syndrome (SARS) in Brazil between 2020-2022

Result of generalized linear mixed models, assuming hospital of admission as a random effect. Demographic factors adjusted relative to each other (except ethnicity). Ethnicity adjusted for sex and age group. Viral etiological factors adjusted for region and age group. Results expressed as odds ratios and 95% confidence intervals in brackets. Bars represent the confidence interval. RSV: respiratory syncytial virus.

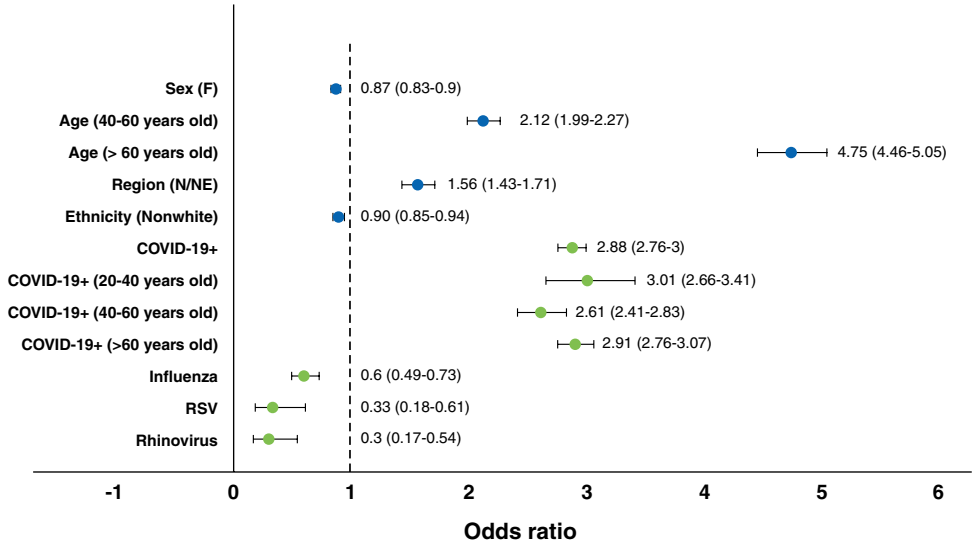

Figure 3

Demographic and etiological factors related to mortality among adults with asthma hospitalized for severe acute respiratory syndrome (SARS) in Brazil between 2020-2022

Result of generalized linear mixed models, assuming hospital of admission as a random effect. Demographic factors adjusted relative to each other (except ethnicity). Viral etiological factors and ethnicity adjusted for sex, region, and age group. Results expressed as odds ratios and 95% confidence intervals in brackets. Bars represent the confidence interval. RSV: respiratory syncytial virus.

the region of residence, sex, and age group on the outcome of death. We also assessed SARS etiology based on viral isolation of the main respiratory viruses, demonstrating the prominence of COVID-19 in the period studied and the impact of SARS-CoV-2 on patient mortality. Considering that asthma has different predominant phenotypes in different age groups, our results were reported separately between C&A and adults, and are of interest to both pediatricians and clinicians. Our results point to a complex picture and shed light on the interaction between a history of asthma and acute infectious conditions, in the context of the dynamic epidemiological evolution that has characterized the COVID-19 pandemic.

It is important to bear in mind that although this study focused on patients with asthma, the criteria for hospitalization and inclusion in the database were not based on disease exacerbation, but on the presence of SARS criteria. While the entities often overlap, with the infectious condition triggering the asthma exacerbation, it is impossible to say that all patients had poorer respiratory functional parameters and/or bronchospasm. Thus, the infectious condition and the etiological agent play a key role in the evolution and outcome of the patient. It is known that patients with asthma generally have poorer outcomes in respiratory infections,[15,16] yet this trend was curiously not demonstrated in COVID-19.[10,11,17] Our sample showed a predominance of SARS-CoV-2 isolates, showing that this was the dominant infection during the study. Thus, patient outcomes are closely linked to COVID-19 outcomes in these groups.

The analyzes showed increasing mortality as age increased in asthma patients hospitalized for SARI, in both age groups. The difference in mortality between C&A and adults is striking, with a 55-fold increase when comparing the age endpoints. This behavior is to be expected, since it has been shown that older patients die more from asthma, as epidemiological studies conducted in the country using the SUS mortality registration systems have shown.[18,19] It has also been shown that advancing age is a risk factor for mortality from COVID-19, the predominant infection in the study population, both among C&A and adults.[17,20] It is therefore no surprise that age was also a risk factor for death in the study population.

Brazil is a continental country with enormous variability in access to health care and profound socioeconomic inequalities. Our data show higher mortality among patients living in the North and Northeast regions, in both age groups, and adjusted for sex and age group. This inequality probably reflects the difficulty of access and the poorer health conditions that residents of the North and Northeast face. Social determinants of health are closely related to asthma prevalence and outcomes. A large American population study, including more than 1,500,000 C&A with asthma, showed a significant association between living in poorer regions and both emergency room visits and hospitalizations for asthma (OR 1.06 95% CI 1.01-1.12 and OR 1.1 95% CI 1.03-1.[17] respectively, in adjusted models).[21] Similarly, socioeconomic factors are also related to poorer COVID-19 outcomes, as 2 Brazilian studies have shown. The first study included 5,857 C&A with COVID-19 and showed that living in more developed towns reduced the chance of mortality with the disease by nearly 75%.[17] The second study focused on the adult population, including 228,196 patients hospitalized for the disease, and showed that living in the North and Northeast regions of the country increased the chance of death more than 2-fold (OR 2.76 and 2.05 respectively).[22]

The association between asthma and viral infection is complex and appears in different instances throughout life. In the first few years, the vast majority of wheezing episodes occur in the context of a viral infection, especially RSV and rhinovirus.[23] The latter has already been recognized as an important risk factor for developing asthma.[24] Viral infections are among the most frequent triggers of attacks in patients already diagnosed with asthma, with rhinovirus predominating as the etiological agent.[24,25] Despite high rates of etiological research, our study showed a low rate of positive results, especially in children. This result may be associated with the fact that the majority of etiological investigations in the period probably corresponded to SARS-CoV-2, a less important agent in the pediatric age group when compared to adults, a population that showed a much higher rate of positive results.

The main limitations of this study are due to the fact that it used a secondary database, so important biases should be considered. Firstly, the diagnosis of asthma was reported by patients or family members, with the scrutiny of the practitioner who filled in the notification form, and no standardized approach of proof. This self-reporting approach is common in large epidemiological studies, and it has been shown that reliance on medical diagnosis can underestimate the prevalence of asthma in the population.[1] In addition, it is impossible to guarantee that all cases of SARI have been reported, and there may have been a

selection for more severe cases, thus leading to a bias in the proportion of negative outcomes in the study population.

In the multivariate analyzes, the effects of the etiological agents compared patients with the positive agent with those without the positive agent, not including whether they had been tested or not. This conservative approach may have underestimated the size of the effects, since not all untested patients were actually negative. A selection bias may also exist for testing agents, with more severe patients more likely to be tested. In addition, the availability of tests also differs between agents: while there is greater availability of tests for COVID-19, testing for RSV and rhinovirus depends on more advanced and not so easily available tests, which has an impact on the rates of detection reported. Therefore, the proportions of etiological diagnosis should be interpreted in light of these limitations.

Ethnicity was not recorded for more than 17% of the hospitalizations included, and this loss of data was proportionally greater in the North than in the South (21.5% vs. 16.5%, $p < 0.001$). As patients with no ethnic data were excluded from analyzes of the effect of ethnicity on mortality, a higher proportion of patients from the Northern macro-region were excluded. Considering that living in the Northern macro-region represented a risk factor for mortality in both age groups, the protective effect of ethnicity among adults may have been overestimated and the result of a bias.

This nationwide analysis of asthma hospitalizations highlighted demographic vulnerabilities, with higher mortality in the North-Northeast regions, among adolescents in the C&A age group, and among older adults in the adult age group. In addition, COVID-19 is the leading cause of infections associated with mortality. Population measures should therefore be targeted at the groups most at risk to protect the population with asthma.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Main sensitizing agents involved in allergic contact dermatitis in patients of a hospital in western Santa Catarina, Brazil

Principais agentes sensibilizantes na dermatite de contato alérgica em pacientes de um hospital da região oeste de Santa Catarina

Leda das Neves Almeida Sandrin[1], Alana Olga De Avila[1], Renata Ferronato Conrado[1], Samuel Spiegelberg Züge[1]

ABSTRACT

Introduction: Allergic contact dermatitis (ACD) corresponds to 20% of contact dermatitis cases, being the most common type of occupational skin disease and a common cause of consultation with a dermatologist or allergist. **Objective:** To identify the main sensitizing agents involved in ACD at a specialized allergy center in western Santa Catarina, a state in the south of Brazil. Methodology: This retrospective, descriptive, quantitative, and observational study involved the review of medical records of all patients who underwent patch testing for ACD from 2018 to July 2020 in the allergy center. The sensitizing agents evaluated in the patch test followed the standard patch series (including the standard Brazilian patch series, cosmetic series, and regional Latin America series). Frequency analyses were performed for qualitative variables and to assess the prevalence of the main sensitizing agents. In addition, the main agents were correlated with sex and age variables using Pearson's chi-square test. **Results:** The most prevalent sensitizing agents were nickel sulfate (33.5%), PPD mix (23.2%), perfume mix (22.4%), fragrance mix (22.0%), and cobalt chloride (18, 9%). The most prevalent substances were nickel sulfate and PPD mix, which are widely used in patients' daily lives. **Conclusion:** The identification of allergens via patch testing provides patients with an opportunity to reduce ACD caused by the sensitizing agents identified.

Keywords: Allergen, allergy and immunology, eczema, hypersensitivity.

RESUMO

Introdução: A dermatite de contato alérgica (DCA) corresponde a 20% dos casos de dermatite de contato, sendo recorrente em doenças ocupacionais e causa frequente de procura por profissionais dermatologistas e alergistas. **Objetivo:** Identificar os principais agentes sensibilizantes na dermatite de contato alérgica em um centro especializado em alergia do oeste de Santa Catarina. **Metodologia:** Trata-se de um estudo do tipo retrospectivo, descritivo, quantitativo e observacional, no qual se realizou a análise por meio de prontuários médicos de 394 pacientes que realizaram o teste de contato por dermatite de contato alérgica no período de 2018 a julho de 2020 no serviço de referência do oeste de Santa Catarina. Os agentes sensibilizantes avaliados no teste de contato foram conforme as baterias padrão (bateria padrão brasileira, bateria de cosméticos e higiene e bateria regional da América Latina). Foram realizadas análises de frequência para as variáveis qualitativas e avaliação da prevalência dos principais agentes sensibilizantes. Além disso, foram relacionados os principais agentes com as variáveis sexo e idade por meio do teste de Qui-quadrado de Pearson. **Resultados:** Os agentes sensibilizantes mais prevalentes foram: níquel (33,5%), PPD mix (23,2%), perfume mix (22,4%), fragrância mix (22,0%) e cobalto (18,9%). As substâncias mais prevalentes foram o níquel e o PPD mix, que são agentes sensibilizantes usados amplamente no cotidiano dos pacientes. **Conclusão:** A identificação dos alérgenos através do *patch test* possibilita aos pacientes a oportunidade de amenizarem a DCA provocada pelos agentes sensibilizantes encontrados.

Descritores: Alérgeno, alergia e imunologia, eczema, hipersensibilidade.

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Introduction

Contact eczema occurs when the skin is exposed to an allergen capable of provoking irritation or allergy via an inflammatory reaction.[1] Contact dermatitis (CD) accounts for 90% of all occupational skin diseases and is the most common cause of these diseases.[2] Contact eczema is subdivided into allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD), which are classified according to the sensitizing agent involved.[3] ICD is responsible for the majority of CD cases, at around 80%, while ACD accounts for just 20% of cases.[3]

ACD is a disease that is caused by a Gel and Coombs hypersensitivity type IV reaction to an exogenous antigen.[4] According to Brar,[5] there is a sensitization period, during which effector T cells are produced by the body, with the result that an eczematous reaction mediated by memory T lymphocytes occurs 24 to 36 hours after a second exposure to the sensitizing agent.

Allergic contact dermatitis can present as a localized rash and is most commonly seen on the hands and face or is disseminated. During physical examination of a patient, ACD may be detected in an acute or chronic state, in the first of which it will normally present as an erythematous, eczematous, or blistered dermatitis, while in the second state it will present as lichenification, which may be cracked and flaky.[6] Other clinical signs and symptoms may also be found, such as erythema, papules, pruritus, secretions, and blisters.[5] The most common sites of ACD involvement are the hands, face, eyelids, trunk, lips, arms, and scalp.[7] The hands are the most common site of contact dermatitis and nickel, cobalt, fragrances, and rubber additives are the allergens most often responsible.[8]

Allergens are identified using the gold standard for ACD diagnosis, which is patch testing.[5] In a study by Shane et al., the main sensitivity allergens found with patch testing were Peru balsam, cobalt, chrome, formaldehyde, fragrance mixes, nickel, quarternium and thimerosal.[9]

ACD is a common complaint at consultations with specialists in allergy and dermatology.[10] It should be noted that studies demonstrating the epidemiology of contact dermatitis in Brazil are rare and even though occupational dermatitis cases are notifiable diseases, the data cannot be considered trustworthy because of major under-notification.[11] This is because workers tend not to seek medical attention and because of fear of being fired.[12]

Occupational CD can cause workers to be sent home or laid off and its prevalence is estimated at 6.7% to 10.6%.[13] ACD can also impact on daily activities and employment activities, since it can cause erythema, blisters, pustules, hemorrhage, scabbing, flaking, and erosions,[14] in addition to eruptions and intense itching.[1] Patients who develop ACD have their wellbeing compromised and may spend long periods off work because of eczema, significantly impacting them socioeconomically.[2]

Therefore, considering that there are still few studies of the epidemiology of contact dermatitis in Brazil, this study contributes to enabling health professionals to question their patients who work at high risk of contact with sensitizing agents, even those without complaints, helping to make notification more reliable.

The primary objective of this study is to identify the main sensitizing agents of allergic contact dermatitis among patients at a hospital in the West of Santa Catarina, Brazil. It also attempts to identify the main sensitizing agents by age group, in order to compare ACD rates at different ages, and also to record the prevalence of these agents by patient sex.

Materials and Methods

This is a retrospective, descriptive, quantitative, and observational study.

The study analyzed the medical records of all patients who underwent patch testing for allergic contact dermatitis from 2018 to July 2020. The study population was estimated as 1,500 patient medical records, but just 394 medical records met the study inclusion criteria. The study was conducted at a hospital in the West of Santa Catarina state and medical records missing the following data were excluded: age, sex, and site and duration of dermatitis.

Data were collected by searching for International Classification of Diseases (ICD) codes L20, L22, and L232 on the hospital computer system.

The following data were extracted from patient medical records: date of birth; sex; race; region; medications; profession/occupation; weight; height; site and duration of dermatitis; risk factors for ACD (atopic dermatitis); sensitizing agents included in the standard test series (standard Brazilian patch series, cosmetic series, and regional Latin America series) and their respective results. Additionally, the results of

patch tests for specific agents and/or biopsies were also recorded for analysis.

The criteria used for standard test result reading were as recommended by the International Contact Dermatitis Research Group (ICDRG) based on + and – symbols, as follows: (-) negative, equating to intensity 1 in Table 1; (+) discrete erythema with some papules (intensity 2); (++) erythema, papules, and vesicles (intensity 3); (+++) intense erythema, papules, and coalescing vesicles (intensity 4).

Data were collected directly into Epi info 7.0. Statistical analyses were performed using PASW Statistics® for Windows version 20.0 (Predictive Analytics Software, SPSS Inc., Chicago, US). Analyses of frequency were conducted for qualitative variables and prevalence analyses were performed for the main sensitizing agents. The main agents were also correlated with age and sex using Pearson's chi-square test. A 5% significance level was adopted for analysis of the statistical tests.

The ethical principles set out in Resolution 466/2012 were followed and the study was approved in August 2020 by the Human Research Ethics Committee – CEP/UNOCHAPECÓ, decision number 4.232.567.

Results

A total of 394 medical records were identified for patients who had undergone patch tests for sensitizing agents included in the standard Brazilian test series, the Latin American regional series, and the cosmetic series. Majorities of the patients studied were female (71.6%) and had white skin (97.2%), followed by brown (2.0%), yellow (0.5%), and not identified (0.3%).

The age group with the highest prevalence of sensitivity to allergens was from 25 to 48 years (45.9%), followed by zero to 12 years (15.2%), 13 to 24 years (13.7%), and 49 to 90 years (25.1%).

The results observed were used to identify the sensitizing agents with greatest prevalence that were considered to have provoked reactions in the patch tests: nickel (33.5%), p-phenylenediamine (PPD) mix 0.4% (23.2%), perfume mix 7% (22.4%), fragrance mix 14% (22.0%), cobalt 1% (18.9%), triethanolamine 2.5% (17.3%), chrome 0.5% (15.9%), Kathon CG 0.5% (15.6%), paraphenylenediamine 1% (15.4%), and octyl gallate 0.35% (13.9%) (Table 1).

Analysis of the main sensitizing agents by patient sex showed that only nickel was significant ($p = 0.000$). Females had a higher prevalence of positive tests for nickel than males (Table 2).

Analysis of the relationships between the ten main sensitizing agents and age showed that cobalt, paraphenylenediamine, perfume mix, and PPD mix were significant ($p < 0.05$). Among the main sensitizing agents, octyl gallate was prevalent in all age groups, PPD mix was prevalent in the 0 to 12 years group, and fragrance mix was prevalent among those 49 or older (Table 3).

Discussion

In this study, it was observed that the most prevalent agent was nickel 5% (33.5%), followed by PPD mix 0.4% (23.2%), perfume mix 7% (22.4%), fragrance mix 14% (22.0%), cobalt 1% (18.9%), triethanolamine 2.5% (17.3%), chrome 0.5% (15.9%), Kathon CG 0.5% (15.6%), paraphenylenediamine 1% (15.4%), and octyl gallate 0.35% (13.9%).

Boyvat and Yildizhan[15] published a study reporting the results of patch tests in Turkey, showing that the main sensitizing agents found were: nickel (19.6%), chrome (6.5%), cobalt (6%), Myroxylon pereirae resin (Peru balsam) (5%) and paraphenylenediamine (3.7%). As such, 4 of the 5 agents found in that study were also identified as prevalent in the present study.

A study conducted from 2002 to 2007 with 2,076 patients using a basic test series from the British Contact Dermatitis Society found nickel, fragrance mix (FM) I, *Myroxylon pereirae*, cobalt, colophony, PPD, neomycin, thiuram mix, carba mix, and FM II.[16] The high prevalence of nickel reaction found in this study, at 33.5%, confirms the scientific literature. A study conducted with patients from 13 centers in North America also reported that nickel was the most often detected allergen, at 17.5%.[17] Along the same lines, Rubins3 also found that among the patients tested, nickel was identified as the most common allergen.

In addition to being the agent with highest prevalence, nickel was also more often reactive among females (39.8%) and in the age group from 25 to 48 years (37.1%). Rubins[3] also found that the most prevalent allergen causing ACD in females was nickel. One of the reasons for this prevalence is the increased exposure of young females under the age of 18 years to jewelry.[3]

According to Rubins,[3] this early exposure sensitizes children, so that when they come into

Table 1
Sensitizing agents in the standard Brazilian patch series, the cosmetic series, and the regional Latin America series

Sensitizing agent	No reaction n (%)	Reaction n (%)	Intensity of reaction n (%)				Pr
			1	2	3	4	
Anthraquinone (n=291)	286 (98.3)	5 (1.7)	3 (1.0)	2 (20.7)	–	–	1.7
Peru balsam (n=299)	282 (94.3)	17 (5.7)	8 (2.7)	6 (2.0)	3 (1.0)	–	5.7
Benzocaine 5% (n=290)	271 (93.4)	19 (6.6)	9 (3.1)	8 (2.8)	2 (0.7)	–	6.5
Chrome 0.5% (n=327)	275 (84.1)	52 (15.9)	31 (9.5)	21 (6.4)	–	–	15.9
P–tert–butylphenol 1% (n=293)	283 (96.6)	10 (3.4)	7 (2.4)	3 (1.0)	–	–	3.4
Carba mix 3% (n=299)	274 (91.6)	25 (8.4)	8 (2.7)	12 (4.0)	5 (1.7)	–	8.3
Nickel 5% (n=340)	226 (66.5)	114 (33.5)	22 (6.5)	32 (9.4)	49 (14.4)	11 (3.2)	33.5
Cobalt 1% (n=296)	241 (81.4)	55 (18.6)	22 (7.4)	23 (7.8)	9 (3.0)	1 (0.3)	18.9
Terebenthine 10% (n=291)	275 (94.5)	16 (5.5)	7 (2.4)	7 (2.4)	2 (0.7)	–	5.5
Colophony 20% (n=314)	299 (95.2)	15 (4.8)	3 (1.0)	7 (2.2)	5 (1.6)	–	4.7
Thimerosal 0.05% (n=297)	262 (88.2)	35 (11.8)	6 (2.0)	10 (3.4)	17 (5.7)	2 (0.7)	11.8
Ethylenediamine 1% (n=297)	292 (98.4)	5 (1.6)	4 (1.3)	1 (0.3)	–	–	1.7
Thiuram mix (n=318)	305 (96.0)	13 (4.0)	2 (0.6)	8 (2.5)	3 (0.9)	–	4.1
Formaldehyde 1% (n=308)	296 (96.1)	12 (3.9)	7 (2.3)	4 (1.3)	1 (0.3)	–	3.9
Hydroquinone 1% (n=293)	268 (91.5)	25 (8.5)	12 (4.1)	9 (3.1)	3 (1.0)	1 (0.3)	8.5
Triclosan 1% (n=296)	285 (96.3)	11 (3.7)	5 (1.7)	3 (1.0)	3 (1.0)	–	3.7
Kathon CG 0.5% (n=319)	269 (84.3)	50 (15.7)	12 (3.8)	15 (4.7)	15 (4.7)	8 (2.5)	15.6
Lanolin 30% (n=304)	294 (96.7)	10 (3.3)	6 (2.0)	1 (0.3)	3 (1.0)	–	3.3
Mercapto mix 2% (n=307)	293 (95.4)	14 (4.6)	9 (2.9)	4 (1.3)	–	1 (0.3)	4.5
Neomycin 20% (n=320)	289 (90.4)	31 (9.6)	11 (3.4)	10 (3.1)	10 (3.1)	–	9.7
Nitrofurazone 1% (n=293)	284 (97.0)	9 (3.0)	6 (2.0)	2 (0.7)	1 (0.3)	–	3.1
Paraben mix (n=321)	311 (97.0)	10 (3.0)	4 (1.2)	2 (0.6)	4 (1.2)	–	3.1
Paraphenylenediamine 1% (n=330)	279 (84.6)	51 (15.4)	15 (4.5)	16 (4.8)	17 (5.2)	3 (0.9)	15.4
Perfume mix 7% (n=317)	246 (77.6)	71 (22.3)	26 (8.2)	29 (9.1)	15 (4.7)	1 (0.3)	22.4
PPD mix 0.4% (n=293)	225 (76.8)	68 (23.2)	32 (10.9)	27 (9.2)	9 (3.1)	–	23.2
Promethazine 1% (n=294)	280 (95.3)	14 (4.7)	8 (2.7)	3 (1.0)	3 (1.0)	–	4.7
Propylene glycol 2% (n=294)	287 (97.7)	7 (2.30	5 (1.7)	1 (0.3)	1 (0.3)	–	2.4
Quarternium 15% (n=296)	279 (94.2)	17 (5.8)	7 (2.4)	7 (2.4)	3 (1.0)	–	5.7
Quinoline mix (n=290)	281 (96.9)	9 (3.1)	4 (1.4)	3 (1.0)	2 (0.7)	–	3.1
Epoxy resin 1% (n=297)	285 (96.0)	12 (4.0)	6 (2.0)	3 (1.0)	3 (1.0)	–	4.0
Amerchol L–101 (n=291)	284 (97.6)	7 (2.4)	2 (0.7)	4 (1.1)	1 (0.3)	–	2.4
Tonsilamine resin Formaldehyde (n=328)	304 (92.8)	24 (7.2)	10 (3.0)	9 (2.7)	4 (1.2)	1 (0.3)	7.3

Pr = prevalence of positive reactions in the population.
ICDRG intensity 1 = (-) No reaction.
ICDRG intensity 2 = (+) Discrete erythema with some papules.
ICDRG intensity 3 = (++) Erythema, papules, and vesicles.
ICDRG intensity 4 = (+++) Intense erythema, papules, and coalescing vesicles.

Table 1 *(continuation)*
Sensitizing agents in the standard Brazilian patch series, the cosmetic series, and the regional Latin America series

Sensitizing agent	No reaction n (%)	Reaction n (%)	Intensity of reaction n (%)				Pr
			1	2	3	4	
BHT (butyl hydroxy–toluene) 2% (n=294)	288 (97.9)	6 (2.1)	4 (1.4)	2 (0.7)	–	–	2.0
Triethanolamine 2.5% (n=299)	247 (82.5)	52 (17.5)	25 (8.4)	22 (7.4)	5 (1.7)	–	17.3
Bronopol 0.5% (n=297)	282 (95.0)	15 (5.0)	10 (3.4)	3 (1.0)	1 (0.3)	1 (0.3)	5.0
Sorbic acid 0.5% (n=292)	287 (98.3)	5 (1.7)	4 (1.4)	1 (0.3)	–	–	1.7
Chloroacetamide 0.2% (n=290)	285 (98.3)	5 (1.7)	3 (1.0)	2 (0.7)	–	–	1.7
Coconut diethanolamide 0.5% (n=293)	276 (94.2)	17 (5.8)	7 (2.4)	7 (2.4)	3 (1.0)	–	5.8
Chlorhexidine 0.5% (n=295)	286 (97.0)	9 (3.0)	5 (1.7)	–	3 (1.0)	1 (0.3)	3.0
Ammonium thioglycolate 2.5% (n=292)	284 (97.2)	8 (2.8)	4 (1.4)	2 (0.7)	2 (0.7)	–	2.7
Germall 115 2% (n=294)	292 (99.3)	2 (0.7)	2 (0.7)	–	–	–	0.7
Disperse blue 124 0.50% (n=196)	170 (86.7)	26 (13.3)	15 (7.7)	9 (4.6)	2 (1.0)	–	13.2
Caine mix 10% (n=180)	172 (95.6)	8 (4.4)	4 (2.2)	4 (2.2)	–	–	4.4
Palladium 2% (n=179)	161 (89.9)	18 (10.0)	5 (2.8)	8 (4.5)	5 (2.8)	–	10.0
Diazolidinyl urea 2% (n=179)	175 (97.7)	4 (2.3)	3 (1.7)	1 (0.6)	–	–	2.2
Dialkyl Thiourea mix 1% (n=179)	175 (97.8)	4 (2.2)	2 (1.1)	2 (1.1)	–	–	2.2
Fragrance mix 14% (n=219)	171 (78.1)	48 (21.9)	19 (8.7)	12 (5.5)	17 (7.8)	–	22.0
Octyl gallate 0.35% (n=180)	155 (86.1)	25 (13.9)	17 (9.4)	6 (3.3)	2 (1.1)	–	13.9
Methylisothiazolinone 0.02% (n=212)	187 (88.2)	25 (11.8)	6 (2.8)	9 (4.2)	9 (4.2)	1 (0.5)	11.8
Methyldibromo glutaronitrile 0.50% (n=192)	176 (91.7)	16 (8.3)	4 (2.1)	9 (4.7)	3 (1.6)	–	8.3
Paraformaldehyde 1% (n=180)	166 (92.2)	14 (7.8)	7 (3.9)	6 (3.3)	1 (0.6)	–	7.7

Pr = prevalência dos reagentes positivos na população.
Intensidade 1 = nenhuma cruz na leitura dos resultados pela ICDRG. Intensidade 2 = (+) discreto eritema com algumas pápulas pela ICDRG.
Intensidade 3 = (++) eritema, pápulas e vesículas pela ICDRG. Intensidade 4 = (+++) intenso eritema, pápulas e vesículas confluentes pela ICDRG.

contact with nickel again, it provokes allergic contact dermatitis. Moreover, cellphones also contain metals, and nowadays contact with these devices starts early, facilitating onset of ACD.

Another important aspect that should be mentioned is that nickel is involved in orthopedic surgical procedures. According to Nassau and Fonacier,[7] sensitization to nickel increased after joint replacement, since as the metal undergoes wear, free ions are released and deposited in the area around the prosthetic joint. The same authors also explain that nickel can be found in elevated concentrations in some foods, such as chocolate, vegetables, nuts, figs, peanut butter, chocolate spreads, and breakfast cereals.

PPD mix 0.4% contains 3N-phenyl-N-isopropyl-p-phenylenediamine and N-N-diphenyl-p-phenylenediamine, each at 0.2%.[18] The current study observed a 23.2% overall prevalence of positive reactions, which were more prevalent among females (23.4%) and most common in the age group from zero to 12 years (26.3%).

A Brazilian study with 630 patients, 69 of whom had occupational contact eczema, found that PPD mix 0.4% was one of the main allergens linked to occupational contact dermatitis clinical status.[18] Moreover, the same authors state that PPD is primarily used in hair dyes, make-up, the textile industry, and henna tattoos. These uses are more common among women, which coincides with the research findings.

The allergens perfume mix and fragrance mix are combinations of several perfumes and have similar components, which is why they had similar prevalence, at 22.4% and 22.0%, respectively. Each of the two mixes were tested on different numbers of patients, 317 in the case of perfume mix and 219 for fragrance mix.

Additionally, these two sensitizing agents are part of different test series, fragrance mix is part of the regional Latin America series and perfume mix is part of the standard Brazilian patch series. Moreover, Geier and Brans[19] state that the frequency of positive reactions to fragrance mix II has been reducing over recent years.

Table 2
Main sensitizing agents by sex

Sensitizing agents	Sex		p	Pr	
	Female n (%)	Male n (%)		F	M
Chrome 0.5%					
Reaction	36 (15.5)	16 (16.8)	0.766	15.5	16.8
No reaction	196 (84.5)	79 (83.2)			
Cobalt 1%					
Reaction	39 (18.1)	16 (19.8)	0.750	18.1	19.8
No reaction	176 (81.9)	65 (80.2)			
Fragrance mix 14%					
Reaction	30 (19.7)	18 (26.9)	0.240	19.7	26.9
No reaction	122 (80.3)	49 (73.1)			
Octyl gallate 0.35%					
Reaction	15 (11.8)	10 (18.9)	0.212	11.8	18.9
No reaction	112 (88.2)	43 (81.1)			
Kathon CG 0.5%					
Reaction	40 (17.2)	10 (11.5)	0.209	17.2	11.5
No reaction	192 (82.8)	77 (88.5)			
Paraphenylenediamine 1%					
Reaction	33 (14.0)	18 (19.1)	0.241	14.0	19.1
No reaction	203 (86.0)	76 (80.9)			
Perfume mix 7%					
Reaction	51 (22.5)	20 (22.2)	0.962	22.5	22.2
No reaction	176 (77.8)	70 (77.5)			
PPD mix 0.4%					
Reaction	50 (23.4)	18 (22.8)	0.917	23.4	22.8
No reaction	164 (76.6)	61 (77.2)			
Nickel 5%					
Reaction	98 (39.8)	16 (17.0)	0.000	39.8	17.0
No reaction	148 (60.2)	78 (83.0)			
Triethanolamine 2.5%					
Reaction	34 (15.5)	18 (22.5)	0.159	15.5	22.5
No reaction	185 (84.5)	62 (77.5)			

Pr = prevalence of positive reactions by sex, male (M), female (F).

Table 3
Prevalence of sensitizing agents by age

Sensitizing agent	Patients with reactions n (%)	Patients without reactions n (%)	Prevalence	p
Chrome 0.5%				
0-12 years	15 (28.9)	37 (71.1)	28.8	0.038
13-24 years	7 (16.6)	35 (83.4)	16.6	
25-48 years	21 (13.9)	131 (86.1)	13.8	
49 years or older	9 (11.1)	72 (88.9)	11.1	
Cobalt 1%				
0-12 years	8 (22.2)	28 (77.8)	22.2	0.040
13-24 years	4 (10.0)	36 (90.0)	10	
25-48 years	35 (24.2)	110 (75.8)	24.1	
49 years or over	8 (10.6)	67 (89.3)	10.6	
Fragrance mix 14%				
0-12 years	5 (14.2)	30 (85.8)	14.2	0.107
13-24 years	3 (9.7)	28 (90.3)	9.67	
25-48 years	24 (24.3)	75 (75.7)	24.2	
49 years or over	16 (29.7)	38 (70.3)	29.6	
Octyl gallate 0.35%				
0-12 years	1 (5.9)	16 (94.1)	5.88	0.216
13-24 years	1 (3.8)	26 (96.2)	3.70	
25-48 years	16 (17.8)	74 (82.2)	17.7	
49 years or over	7 (15.3)	39 (84.7)	15.2	
Kathon CG 0.5%				
0-12 years	3 (12.5)	35 (87.5)	7.8	0.068
13-24 years	12 (26.7)	33 (73.3)	26.6	
25-48 years	20 (13.0)	134 (87.0)	12.9	
49 years or over	15 (18.3)	67 (81.7)	18.2	
Paraphenylenediamine 1%				
0-12 years	6 (16.3)	31 (83.7)	16.2	0.302
13-24 years	5 (11.2)	40 (88.8)	11.1	
25-48 years	21 (13.2)	138 (86.8)	13.2	
49 years or over	19 (21.4)	70 (78.6)	21.3	
Perfume mix 7%				
0-12 years	10 (26.4)	28 (73.6)	51.7	0.640
13-24 years	7 (15.6)	38 (84.4)	27.8	
25-48 years	34 (22.6)	117 (77.4)	34.8	
49 years or over	20 (24.1)	63 (75.9)	33.3	
PPD mix 0.4%				
0-12 years	21 (56.8)	16 (43.2)	26.3	0.000
13-24 years	11 (26.9)	30 (73.1)	15.5	
25-48 years	23 (16.2)	119 (83.8)	22.5	
49 years or over	13 (17.8)	60 (82.2)	24	
Nickel 5%				
0-12 years	16 (30.2)	37 (69.8)	30.1	0.358
13-24 years	10 (23.3)	33 (76.7)	23.2	
25-48 years	59 (37.1)	100 (62.9)	37.1	
49 years or over	29 (34.2)	56 (65.8)	34.1	
Triethanolamine 2.5%				
0-12 years	2 (5.4)	35 (94.6)	5.4	0.065
13-24 years	9 (21.5)	33 (78.5)	21.4	
25-48 years	32 (21.7)	116 (78.3)	21.6	
49 years or over	9 (12.5)	63 (87.5)	12.5	

Fragrance mix had greatest prevalence in the over 49 years age group (29.6%), which is in line with the findings of a review by Garg, McDonagh, and Gawkrodger,[16] in which fragrance allergy increased with age. Also according to these authors, this rise could be because of cumulative exposure to personal hygiene products and increased use of medications or impaired epidermal barrier function, because of aging.

In the same study by Garg, McDonagh and Gawkrodger,[16] which patch tested 2,076 patients with the British Contact Dermatitis Society basic test series, women predominated in all sensitizing agent age groups. However, in the present study, it was observed that the prevalence of reaction to fragrance mix was higher among males (26.9%) than females (19.7%). Nevertheless, the prevalence of perfume mix reaction was higher among females (22.5%), than males (22.2%).

Fragrances are found in personal hygiene products, cleaning products, and aromatherapy products and the rate of allergic reactions in the general population is in the range of 0.7% to 2.6%.[20] Additionally, fragrances and many other ingredients are defined as commercial secrets by the Fair Packaging and Labeling Act, which explains why many products labelled as hypoallergenic or perfume free contain these fragrances.[7] According to Rubens et al., their study showed that the majority of reactions to ACD occur after exposure to fragrances, preservatives, and hair dyes; which could also be a reason for the higher incidence of ACD among women.[3] While reactions tend to be seen in older women, children also tend to become sensitized by this agent. This takes place not just by exposure of children themselves to the agent, but also by products used by their parents.[21]

Cobalt 1% had a prevalence of 18.9%, and was the second most common metal allergen detected. This allergen was most prevalent among patients aged 25 to 48 years (24.1%), and so both metals – cobalt and nickel – are among the main sensitizing agents in this age group. Cobalt 1% is found in many dental alloys, paints, and pigments used in porcelain and glass.[3] With relation to patient sex, men exhibited a prevalence of 19.8% compared to 18.1% of women, whereas a multicenter study by the Swedish Contact Dermatitis Research Group found a higher proportion of women with positive tests for cobalt 1%.[22]

The allergen triethanolamine is an emulsifier in cosmetic products and is widely used in sunscreen and moisturizers in Brazil, where it had a prevalence of 17.3%, being more common among men and in the 25 to 48 years age group.[23]

Chrome had a higher prevalence of positive tests among males (16.8%) and the 0 to 12 years age group (28.8%). However, the highest proportion of sensitization occurs in adult males and can be attributed to contact with cement and wearing leather footwear.[24]

Kathon CG had a 15.6% prevalence of positive results and was also more common among females (17.2%), while the age group with the highest prevalence of Kathon reactions was 13 to 24 years (26.6%). In comparison, in a Brazilian study conducted in São Paulo with 297 patients, Kathon CG sensitivity had a prevalence of 15.1%, predominantly among women,[25] which results are in line with those of the present study.

Kathon is formed by combining methylisothiazolinone and methylchloroisothiazolinone.[5] Kathon CG is a highly effective preservative and was released onto the market in the 1970s, triggering a global epidemic of ACD caused by this agent.[26]

The main products that contain Kathon are cosmetics, cleaning products, personal care products, glue for use in schools, and wet wipes.[5] Women are probably more affected by allergic contact eczema caused by this allergen because they use more products containing Kathon in their daily lives than men do, which agrees with the results of the present study.

Paraphenylenediamine had a prevalence of 15.4%. It is a component used in permanent hair dyes, temporary henna tattoos, to darken the tone and reduce drying time, leather, furs, textiles, and industrial rubber products.[7] In the present study, it was positive more often in males (19.1%), which may be more related to occupational contact dermatitis, as shown by Nassau and Fonacier,[7] which is also consistent with the age group of greatest prevalence in the current study, which was 49 years or over.

A study that investigated the most prevalent allergens in allergic contact cheilitis found that octyl gallate was in third place.[27] This sensitizing agent was most prevalent in the 25 to 48 years age group and among males, with an overall prevalence of 13.9%. Octyl gallate is used as an antioxidant in cosmetics and medications and by the food industry.[28]

When conducting this study, certain limitations were identified, primarily related to the scarcity of research into the subject, particularly in Brazil. Another

limiting factor is the use of countless different terms for the same sensitizing agents, which makes searching for literature on these products difficult.

It is clear that this study contributes to increasing the body of data on sensitizing agents that cause ACD, describing their relationships with age groups and sex, which could be used to support future research and debates.

Final comments

The main sensitizing agents found in the study population were nickel 5%, PPD mix 0.4%, perfume mix 7%, fragrance mix 14%, cobalt 1%, triethanolamine 2.5%, chrome 0.5%, Kathon CG 0.5%, paraphenylenediamine 1%, and octyl gallate 0.35%. The most prevalent among males were chrome, cobalt, fragrance mix, octyl gallate, paraphenylenediamine, and triethanolamine. Among females, Kathon CG, perfume mix, PPD mix, and nickel predominated. In the 0-12 years age group, PPD mix, perfume mix, and chrome were prevalent. Among the 14-24 years age group, only Kathon CG was prevalent. The predominant agents in the 25-48 years age group were nickel, cobalt, octyl gallate, and triethanolamine. Finally, fragrance mix and paraphenylenediamine were prevalent among patients aged 49 years or older.

Therefore, it is concluded that these test series (standard Brazilian patch series, cosmetic series and regional Latin America series) are important to help patients identify the agent causing their allergic contact dermatitis so they can avoid using these products or becoming exposed to these allergens. It is also suggested that the name of each sensitizing agent should ne standardized to facilitate searching of published data. This would make it possible for patients to avoid agents to which they have become sensitized.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Environmental exposure and health risks in Brazil

Exposição ambiental e risco à saúde - Brasil

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ABSTRACT

Objective: To identify potential sociodemographic, socioeconomic, health, environmental, and lifestyle factors associated with adverse health effects in residents of 3 Brazilian cities. **Methods:** This cross-sectional study with a quantitative approach was conducted in the cities of Imperatriz (Maranhão), Palmas (Tocantins), and Salvador (Bahia). A total of 975 patients aged 18 to 75 years treated at primary health care units from June 2021 to June 2022 were selected via convenience sampling. A standardized questionnaire on sociodemographic characteristics, exposure to environmental factors, and lifestyle habits was administered. The outcome measured was health status (excellent/good vs fair/bad/very poor). Multivariate analysis was performed using logistic regression, respecting each municipality individually and collectively. Data were presented as odds ratios (OR) and 95%CIs. **Results:** Women predominated in all cities: 58.3% in Imperatriz, 67.5% in Tocantins, and 65.4% in Salvador. The prevalence of smoking (present and/or past) was significantly higher in Salvador, as was the prevalence of alcohol consumption. Despite Salvador having the highest rate of comorbidities, residents of Imperatriz reported more instances of fair/poor/very poor health. Environmental factors significantly associated with poor health conditions in both analysis models included exposure to wood/coal/kerosene/other stoves during childhood, spending more than 2 hours in the kitchen with a working stove, and living close to a pollution source. Residents of Imperatriz were 1.8 times and 1.7 times more likely to have poor health compared with residents of

RESUMO

Objetivo: Identificar possíveis fatores sociodemográficos, econômicos, de saúde, ambientais e de hábitos de vida associados a efeitos adversos sobre a saúde de moradores em três cidades brasileiras. **Método:** Estudo transversal com abordagem quantitativa realizado nas cidades de Imperatriz (Maranhão), Palmas (Tocantins) e Salvador (Bahia). Participaram 975 pacientes (18 a 75 anos) atendidos em unidades básicas de saúde no período de junho de 2021 a junho de 2022. Esses indivíduos foram selecionados aleatoriamente (amostra de conveniência). Foi aplicado o questionário padronizado sobre fatores sociodemográficos e exposição a fatores ambientais, assim como o de hábitos de vida. Empregou-se a situação de saúde (excelente/boa x regular/má/péssima) como desfecho, foi realizada análise multivariada seguida por regressão logística respeitando-se cada município individualmente e o seu coletivo. Os dados foram apresentados como *odds ratio* (OR) e intervalos de confiança de 95% (IC95%). **Resultados:** Em todas as cidades houve predomínio de pacientes do sexo feminino: 58,3% em Imperatriz, 67,5% em Tocantins e 65,4% em Salvador. A prevalência de tabagismo (presente e/ou passado) foi significantemente mais elevada em Salvador, assim como a de consumo de álcool. Houve maior referência de saúde regular/má/péssima entre os moradores de Imperatriz, apesar de em Salvador haver o maior relato de comorbidades. Os fatores ambientais associados à condição precária de saúde, em ambos os modelos de análise, foram: ter sido exposto durante a infância a fogão a lenha/carvão/querosene/outro; passar mais de duas horas

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Salvador (a more developed center with more health resources) and Palmas, respectively. **Conclusions:** Health professionals should guide the population regarding socio-environmental issues affecting health indices. Demographic, environmental, and economic data can impact health conditions.

Keywords: Environmental exposure, environmental pollution, hypersensitivity.

na cozinha, com fogão em funcionamento; e residir próximo a uma fonte poluidora. Morar em Imperatriz revelou chance 1,8 vezes maior de ter saúde debilitada quando comparado aos moradores de Salvador, e de 1,7 vezes para os de Palmas. **Conclusões:** Profissionais de saúde deverão orientar a população quanto as questões socioambientais que interferem nos índices de saúde. Os dados demográficos, ambientais e econômicos podem interferir nas condições de saúde.

Descritores: Exposição ambiental, poluição ambiental, hipersensibilidade.

Introduction

Exposure to environmental pollutants has consistently been associated with adverse consequences for health, triggering a series of pathological conditions.[1,2] This phenomenon is especially evident in low-income communities and among ethnic minorities, which are subject to higher rates of exposure to these pollutants as a consequence of unfavorable social and historical structures.[1,2] One of the most worrying results of this exposure is the increased prevalence of allergic diseases in these populations, creating a worrying interface between environmental pollution and allergy.[1,2]

Emissions from fixed sources such as industrial plants release harmful substances such as sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate material (PM).[1,3,4] These pollutants have been extensively studied for their role in the incidence and exacerbation of respiratory diseases such as asthma, in reduced pulmonary function, and in increased mortality.[5,6] Vulnerable populations, very often living in low-income areas, are particularly susceptible to these adverse impacts. Emissions from mobile sources, such as motor vehicles, represent a significant threat to air quality.[1,7] Traffic-related air pollution is made up of gasses and particles released by combustion of fossil fuels. This type of pollution has been associated with a range of health problems, including respiratory morbidity, cancer, and heart disease. Ethnic minority and low-income communities very often live in areas with greater exposure to these pollutants, intensifying their risk of developing allergic diseases.[1,7,8]

In turn, poor quality housing plays a crucial role in exposure to pollutants and allergens. Houses with inadequate infrastructure, subject to leaks and seepage, provide the ideal conditions for growth of allergens, such as mold. Low income and ethnic minority populations are more likely to live in environments with poor housing, increasing their exposure to these agents that trigger allergies.[1,9-11]

This panorama highlights the complex interconnection between pollution and allergic diseases, emphasizing the need for immediate action. More equitable environmental policies, continuous research into the impacts of these exposures and public education are essential to mitigate the adverse effects on health and promote a healthier and fairer environment for all communities.

Against this background, the objective of this study was to identify possible sociodemographic, socioeconomic, health, environmental, and lifestyle factors associated with adverse effects on the health of residents of three Brazilian cities, with the objective of identifying risk factors that can be targeted in future prevention campaigns.

Methods

A cross-sectional study with a quantitative design was conducted in the cities Imperatriz (Maranhão) and Palmas (Tocantins), both in the North region of Brazil, and in Salvador (Bahia), in the Northeast region of Brazil. Patients (18 to 75 years of age) who were seen at primary care health centers in these three Brazilian cities, irrespective of the reason for their consultation, were invited to take part from June 2021 to June 2022. Participants were selected at random (by convenience sampling) and voluntarily and appropriately answered a standardized questionnaire on sociodemographic factors, exposure to environmental factors, and lifestyle habits, adapted from the Clinical Screening Tool for Air Pollution Risk.[12]

Individuals were asked about sex, race, educational level, marital status, employment, family income, whether they were recipients of the Bolsa Familia

welfare program, place of residence, health status, diseases, alcohol consumption, exposure to sources of pollutants at work, housing, exposure to fuel burning including biomass, fossil fuels and others, ventilation of domestic environments, cleaning products, cigarette smoking, and regular exercise, among other questions. With relation to economic level, patients were divided into those whose income was less than or equal to twice the minimum monthly wage (MMW, approximately US$ 450)[13,14] or greater than twice the MMW.[15] Participants were categorized by current health status as having regular/poor/very poor health or very good/good health.

Table 1 lists the main sociodemographic characteristics of the three cities participating in the study,[16] two of which, Palmas and Salvador, are state capitals.[15] This study is part of a larger research project also conducted in other parts of Latin America.

Analysis of the data

The data collected were input to an Excel® spreadsheet. Categorical variables were expressed as frequency distributions and proportions and comparisons between groups were performed using nonparametric tests (Chi-square or Fisher's exact test). Taking health status as the outcome (very good/good vs. regular/poor/very poor), a multivariate analysis was conducted, followed by logistic regression, taking each city individually and all three together. Data were expressed as odds ratios (OR) and 95% confidence intervals (95%CI). Two analytical models were employed. Model 1 used environmental variables only and model 2 included environmental, sociodemographic, health, and lifestyle variables, plus comorbidities (diseases included in the questionnaire) and ophthalmological comorbidities. For all analyses, the cutoff adopted for rejection of the null hypothesis was 5%.

Table 1
Some sociodemographic characteristics of the cities studied[16]

Characteristic	Imperatriz	Palmas	Salvador
Estimated population [2021], number of people	259,980	313,349	2,900,319
Area of city territory [2021], km^2	1,369.039	2,227.329	693,453
Biome [2019]	Amazônia; Cerrado	Cerrado	Atlantic Rain Forest
Per capita GDP [2019], R$	28,830.95	34,933.66	22,213.24
Mean monthly salary of registered workers [2020], MMW [a]	2.0	3.9	3.3
Percentage of 6-to-14-year-olds in school [2010], %	98.4	98	95.9
Infant mortality [2020], deaths per thousand live births	10.64	12.13	14.76
Municipal Human Development Index (HDI) [2010]	0.731	0.788	0.759
Latitude – South	5° 31' 33"	10° 11' 04"	12° 58' 16"
Longitude – West	47° 28' 33"	48° 20' 01"	38° 30' 39"
Altitude, meters	95	260	8.3

[a] Multiples of the Minimum Monthly Wage; approximately US$ 225.[4,5].

The study was approved by the Research Ethics Committee at the Universidade Federal do Pampa and all participants signed a free and informed consent form (No. 31930620.0.0000.5323).

Results

In all three cities, majorities of the patients were female: 58.3% in Imperatriz, 67.5% in Tocantins, and 65.4% in Salvador. With the exception of Palmas, majorities of the sample self-identified as of non-White races. Except for Imperatriz, high educational level predominated. The majority of patients stated they were married or in a stable relationship and were employed or self-employed. In Imperatriz, the prevalence of individuals with family income less than or equal to 2 MMW (56.1%) was significantly higher than in the other two cities and 28.1% of the sample received government benefits.

Residents of urban areas predominated in all three populations assessed. Despite the differences observed in sociodemographic characteristics, we found that all three cities had very similar HDIs (Table 1).

Table 2 presents the results of the univariate and multivariate analyses (models 1 and 2) based on the entire patient sample and the outcome of poor health. These results show that environmental factors that were significantly associated with poor health status, in both analytical models, were as follows: having been exposed to a wood/charcoal/kerosene/other stove during childhood, spending more than 2 hours in the kitchen with the stove lit, and living close to a source of pollution. When sociodemographic, health, and lifestyle variables and presence of comorbidities were also analyzed in addition to environmental variables, we found that having income of up to two MMW, living in Imperatriz or Palmas, having comorbidities, having ophthalmological comorbidities, and exercising outside were also associated with worse health status.

Table 3 shows that having been exposed to a wood/charcoal/kerosene/other stove during childhood, spending more than 2 hours in the kitchen, living close to a source of pollution, having income of up to two MMW, having comorbidities, including ophthalmological comorbidities, and exercising outside were associated with increased health risk. Living in Imperatriz was associated with a 1.8 times greater likelihood of poor health when compared to living in Salvador (a more developed city with more health care resources) and 1.7 times greater than living in Palmas.

Discussion

The present study assessed residents of three cities in Brazil: Salvador, Imperatriz, and Palmas. Although these three cities have very similar HDIs, there are differences between them in terms of *per capita* GDP (lower in Salvador); mean monthly salary of registered workers (lower in Imperatriz) and infant mortality (higher in Salvador) (Table 1).

Analysis of factors associated with worse health status identified the following as significantly associated with worse health status: early exposure to stove burning wood/charcoal/kerosene/other, spending more than 2 hours in the kitchen with the stove lit, living close to a source of pollution, having income of up to two MMW, living in Imperatriz or in Palmas, having comorbidities, having ophthalmological comorbidities, and exercising outside.

Several different studies have confirmed that populations living in extremely poor regions, without adequate refuse collection, with inadequate sanitation, and with open sewers, in areas where people are exposed to pollutants, and to biomass burning have worse health indicators, with increased morbidity and mortality, impacting on the life expectancy of these populations.[17,18]

Many pollutants are the main factors in diseases affecting humans, including particulate material (PM^{10}, $PM^{2,5}$, $PM^{0,1}$), nitric oxide, sulfur dioxide, volatile organic compounds (VOC), dioxins and polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, ozone, primarily in soil, and heavy metals. The diseases caused by exposure to the substances listed primarily include respiratory problems, such as chronic obstructive pulmonary disease (COPD), asthma, lung cancer, cardiovascular events, central nervous system dysfunctions, and cutaneous and ophthalmological diseases. Additionally, climatic changes caused by environmental pollution affect the geographical distribution of many infectious diseases, in addition to natural disasters.[17,19]

Pollution is responsible for 9 million premature deaths/year worldwide, accounting for one in six deaths all over the planet. Deaths caused by pollution are an unintentional consequence of industrialization and urbanization and these mortality rates have increased 7% since 2015 and more than 66% since

Table 2
Logistic regression assessing factors associated with self-reported poor health[a]

Variables	Univariate model				Multivariate model 1 N = 895 LR = -123.91				Multivariate model 2 N = 892 LR = -445.26			
			95%CI				95%CI				95%CI	
	OR	Value p	Minimum limit	Maximum limit	OR	Value p	Minimum limit	Maximum limit	OR	Value p	Minimum limit	Maximum limit
Environmental factors												
Type of stove used												
Wood/charcoal/kerosene/solvent/other	1.28	0.276	0.82	2.00	0.79	0.376	0.48	1.32				
Natural gas/GLP	1.00				1.00							
Type of stove at home when a child												
Wood/charcoal/kerosene/other	1.88	< 0.001	1.40	2.52	1.86	< 0.001	1.32	2.63	1.54	0.028	1.05	2.25
Natural gas/GLP	1.00				1.00				1.00			
Number of hours spent in the kitchen with the stove lit												
More than 2 hours	1.66	0.004	1.18	2.34	1.48	0.026	1.05	2.08	1.51	0.034	1.03	2.20
Up to hours	1.00				1.00				1.00			
Has damp environments at home												
Yes	1.29	0.172	0.89	1.87	1.31	0.162	0.90	1.91				
No	1.00				1.00							
Lives close to a source of pollution												
Yes	1.75	< 0.001	1.32	2.33	1.73	0.002	1.23	2.43	1.55	0.010	1.11	2.16
No	1.00				1.00				1.00			
Works close to a source of pollution												
Yes	1.25	0.158	0.92	1.69	0.99	0.940	0.69	1.42				
No	1.00				1.00							
Burns any type of material inside the house												
Yes	1.63	0.044	1.01	2.62	1.45	0.204	0.82	2.55	1.61	0.121	0.88	2.92
No	1.00				1.00				1.00			
Place of residence												
Urban	0.57	0.024	0.34	0.93	0.77	0.388	0.42	1.40	1.12	0.720	0.60	2.12
Rural	1.00				1.00				1.00			
Sociodemographic factors												
Family income (MMW)												
Up to 2	1.82	< 0.001	1.36	2.42					1.85	0.008	1.17	2.91
More than 2	1.00								1.00			
Sex												
Female	1.50	0.008	1.11	2.03					1.39	0.066	0.98	1.98
Male	1.00								1.00			

[a] Regular/poor/very poor.
RV: 95%CI: 95% confidence interval, LR: likelihood ratio, OR: odds ratio, MMW: multiples of monthly minimum wage.

Table 2 *(continuation)*
Logistic regression assessing factors associated with self-reported poor health[a]

Variables	Univariate model				Multivariate model 1 N = 895 LR = -123.91				Multivariate model 2 N = 892 LR = -445.26			
			95%CI				95%CI				95%CI	
	OR	Value p	Minimum limit	Maximum limit	OR	Value p	Minimum limit	Maximum limit	OR	Value p	Minimum limit	Maximum limit
Sociodemographic factors												
Age group (years)												
60 or over	0.41	0.041	0.17	0.96					0.33	0.066	0.10	1.08
40 to 59	0.49	0.042	0.25	0.97					0.45	0.111	0.17	1.20
25 to 39	0.38	0.004	0.19	0.74					0.26	0.006	0.10	0.68
18 to 24	0.42	0.017	0.21	0.86					0.27	0.008	0.10	0.71
0 to 17	1.00								1.00			
Educational level												
Up to end of elementary	2.57	0.001	1.47	4.51					1.46	0.345	0.67	3.19
Secondary education	1.53	0.027	1.05	2.24					1.01	0.968	0.57	1.81
Started higher education	1.29	0.240	0.84	1.97					1.04	0.890	0.60	1.80
Graduated higher education	1.22	0.354	0.80	1.87					1.16	0.550	0.71	1.90
Postgraduate	1.00								1.00			
Race/Color												
Not white	1.20	0.217	0.90	1.61					1.09	0.609	0.77	1.55
White	1.00								1.00			
Region in Brazil												
Imperatriz	1.24	0.336	0.80	1.92					1.70	0.045	1.01	2.85
Palmas	1.80	0.001	1.28	2.53					1.81	0.015	1.12	2.92
Salvador	1.00								1.00			
Factor related to health												
Presence of comorbidities (except ophthalmological)												
Yes	1.69	< 0.001	1.27	2.24					2.35	< 0.001	1.63	3.40
No	1.00								1.00			
Presence of ophthalmological comorbidities												
Yes	2.10	< 0.001	1.57	2.83					2.07	< 0.001	1.44	2.98
No	1.00								1.00			
Factors related to lifestyle habits												
Exercises outside												
Yes	1.23	0.155	0.93	1.63					1.46	0.022	1.06	2.02
No	1.00								1.00			
Smokes												
Yes	1.43	0.070	0.97	2.11					1.53	0.072	0.96	2.44
No	1.00								1.00			

[a] Regular/poor/very poor.
RV: 95%CI: 95% confidence interval, LR: likelihood ratio, OR: odds ratio, MMW: multiples of monthly minimum wage.

Table 3
Logistic regression assessing factors associated with self-reported poor health status[a]

	Multivariate model N = 892 LR = -445.26			
Factors	**OR**	**Value p**	**95%CI minimum**	**95%CI maximum**
Environmental				
Type of stove used				
Wood/charcoal/kerosene/solvent/other	0.79	0.376	0.48	1.32
Natural gas/GLP	1.00			
Type of stove at home when a child				
Wood/charcoal/kerosene/other	1.54	0.028[b]	1.05	2.25
Natural gas/GLP	1.00			
Number of hours spent in the kitchen with the stove lit				
More than 2 hours	1.51	0.034[b]	1.03	2.20
Up to 2 hours	1.00			
Lives close to a source of pollution				
Yes	1.55	0.010[b]	1.11	2.16
No	1.00			
Burns any type of material inside the house				
Yes	1.61	0.121	0.88	2.92
No	1.00			
Place of residence				
Urban	1.12	0.720	0.60	2.12
Rural	1.00			
Sociodemographic				
Family income (MMW)				
Up to 2	1.85	0.008[b]	1.17	2.91
More than 2	1.00			
Sex				
Female	1.39	0.066	0.98	1.98
Male	1.00			
Age group (years)				
60 or over	0.33	0.066	0.10	1.08
40 to 59	0.45	0.111	0.17	1.20
25 to 39	0.26	0.006[b]	0.10	0.68
18 to 24	0.27	0.008[b]	0.10	0.71
0 to 17	1.00			
Educational level				
Elementary school or less	1.46	0.345	0.67	3.19
Secondary education	1.01	0.968	0.57	1.81
Started higher education	1.04	0.890	0.60	1.80
Graduated higher education	1.16	0.550	0.71	1.90
Postgraduate education	1.00			

[a] Regular/poor/very poor.
[b] Significant.
95%CI: 95% confidence interval, LR: likelihood ratio, OR: odds ratio, MMW: multiples of monthly minimum wage.

Table 3 *(continuation)*
Logistic regression assessing factors associated with self-reported poor health status[a]

	Multivariate model N = 892 LR = -445.26			
Factors	**OR**	**Value p**	**95%CI minimum**	**95%CI maximum**
Sociodemographic	1.00			
Race/color				
Not white	1.09	0.609	0.77	1.55
White	1.00			
Region in Brazil				
Imperatriz	1.70	0.045[b]	1.01	2.85
Palmas	1.81	0.015[b]	1.12	2.92
Salvador	1.00			
Related to health				
Presence of comorbidities (except ophthalmological)				
Yes	2.35	< 0.001[b]	1.63	3.40
No	1.00			
Presence of ophthalmological comorbidities				
Yes	2.07	< 0.001[b]	1.44	2.98
No	1.00			
Lifestyle habits				
Exercises outside				
Yes	1.46	0.022[b]	1.06	2.02
No	1.00			
Smokes				
Yes	1.53	0.072	0.96	2.44
No	1.00			

[a] Regular/poor/very poor.
[b] Significant.
95%CI: 95% confidence interval, LR: likelihood ratio, OR: odds ratio, MMW: multiples of monthly minimum wage.

2000. With relation to economic losses, the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD) demonstrated that pollution was responsible for an economic loss of US$ 4.6 trillion (6.2% of global economic output) in 2015. Moreover, the study found that 92% of deaths related to pollution and the greater part of the burden of economic losses caused by pollution occurred in low and middle income countries. The 1.55 odds ratio observed in our study for populations that live close to a source of pollution is striking.

A study conducted in Palmas in 2014 observed that environmental factors have a causal relationship with increased admissions for respiratory diseases to a public pediatric referral hospital in the city. The study demonstrated a negative relationship between rainfall and the total number of admissions for respiratory diseases ($R = 0.606$; $p < 0.03$), especially pneumonia ($R = 0.375$; $p < 0.01$). It is known that months of extreme drought are a risk for respiratory disease exacerbation because of the increase in airborne pollutants and the reduction in the relative

humidity of the air.[20] In Tocantins state, the number of fires is particularly high during the months of the dry season, compromising the Cerrado biome, with a mean of 44 foci of fire/1,000 km^2, from 2002 to 2011.[21] The issues of airborne pollution, foci of fire, and admissions of children for respiratory diseases may be related to the factors observed in our study, such as exposure during to childhood to stoves that burn wood/charcoal/kerosene/other fuels, spending more than 2 hours in the kitchen with the stove lit, living close to a source of pollution, having comorbidities, including ophthalmological comorbidities, and exercising outside.

The social determinants of health encompass individuals' quality of life. Inequalities in social, economic, and environmental factors impact on overall health and on visual health. Williams et al. explain that factors such as income, educational level, access to health care, environmental issues, and social conditions can interfere with ophthalmological care and eye health.[22] Low socioeconomic status is associated with severe visual deficiencies or blindness (OR 2.55; 95%CI 1.36-4.79).[23]

In our study, self-reported ophthalmological comorbidities were significant (odds ratio of 2.07; $p < 0.001$). The number of people who reported having other, non-ophthalmological comorbidities was also relevant (OR 2.35 $p < 0.001$).

In China, a study that analyzed data from the 2013 Chinese General Social Survey to investigate the impact of the mechanisms of environmental problems and social inequalities on health found that, in addition to environmental pollution (both airborne pollution and contamination or pollution of food), low income, low educational level, and lack of green spaces also had negative impacts on the population's health.[24] The same was observed in our study, which documented a positive relationship between low income (up to two MMW) and poor health status (OR: 1.85, $p < 0.008$).

When we compared the residents of the three cities studied, we found that those living in Imperatriz were most exposed to environmental pollutants (passive smoking, heavy vehicle traffic, biomass burning, and exposure to paints and varnishes, and people living in the rural zone of the municipality also live near to open sewers and work close to sources of smoke and dust) and exhibited poor health status. In Salvador, there was a higher number of active smokers, a higher proportion of alcohol consumption, and a higher proportion of working close to sources of pollution and roads with heavy traffic. In Palmas, a higher proportion of individuals were aware of the harm caused by smoking and a lower proportion of people rated their health as good or very good.

It is well known that there is a direct relationship between educational level and health status, because access to information is essential for access and adhesion to disease treatment and prevention. Of the three cities, Imperatriz had the lowest educational level and the lowest income and these data may partially explain why living in Imperatriz was associated with a 1.8 times greater chance of poor health compared to living in Salvador (a more developed center with more health care resources) and 1.7 times greater than living in Palmas. If we analyze the Basic Education Development Index from 2022, Palmas was in second place in the list of state capitals in terms of performance in the first years of primary education (Year 1 to year 5), with an average of 6.1. In the second phase (years 6 to 9), Palmas was in first place of all Brazilian capitals. It should be pointed out that Palmas is a new city where a large proportion of the economically active population are public workers or service providers.[25]

In addition to studying the pathophysiology of diseases and new treatments, health professionals should also understand and teach and provide guidance to the population about socio-environmental issues, thereby intervening in health indicators within a holistic view of their patients in any given region. It is based on this knowledge that public policies are enacted with the objective of reducing morbidity and mortality, increasing life expectancy, and reducing the economic costs of public health. We have presented demographic, environmental, and economic data on the risks of harm to health in three Brazilian cities with similar HDI, located in the North and Northeast regions of Brazil.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

The 2023 South America report of The Lancet Countdown on health and climate change: trust the science. Now that we know, we must act

Relatório Lancet Countdown South America 2023 - saúde e mudanças climáticas: confie na ciência. Agora que sabemos, devemos agir

Marilyn Urrutia-Pereira[1], Herberto José Chong-Neto[2], Dirceu Solé[3]

ABSTRACT

The Lancet Countdown Report has made significant contributions by exposing the main impacts on environmental health caused primarily by increasingly intense anthropogenic action. Deforestation, increasingly uncontrollable forest fires, drought, fossil fuels, and nonrenewable energy contribute to the onset of climate change. This change is characterized by heat waves, increasingly intense storms, and floods that, consequently, compromise human health. The South America report of The Lancet Countdown highlights the alarming changes occurring in the continent and urges action to stop these changes while there is still time.

Keywords: Pollution, heat waves, human health, floods, climate change.

RESUMO

O Relatório *Lancet Countdown* tem feito importantes contribuições ao denunciar os principais agravos à saúde ambiental, graças à ação antropogênica, cada vez mais intensa. O desflorestamento, os incêndios florestais, cada vez mais incontroláveis, a seca, o consumo de combustíveis fósseis, o uso de energia não renovável, propiciam o aparecimento de alterações climáticas caracterizadas por ondas de calor, tempestades cada vez mais intensas, inundações e o consequente comprometimento da saúde dos humanos. A versão *Lancet Countdown South America* apresenta de forma clara e chocante as alterações no continente e faz chamamento para que essas alterações sejam bloqueadas, pois ainda há tempo.

Descritores: Poluição, ondas de calor, saúde humana, enchentes, alterações climáticas.

Introduction

Human health is the principal sphere in which climate change will affect the wellbeing of the population. These impacts will have economic implications that result from the individual losses: years of life lost, falling work productivity, and reduced capacity to create income, accumulate human capital, and invest in environmental education, resulting in reduced consumption, lower growth, greater poverty, and the need to allocate more resources, both public and private, to adapt the population to climate risks.[1]

Anthropogenic climate change impacts South America significantly, triggering many environmental transformations of natural ecosystems and human

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societies. South American countries are highly vulnerable, on different levels, because of their limited preparedness and capacity to respond to the dangers of climate change and its impacts on human health and wellbeing, primarily because global estimates very often mask significant differences at regional and local levels.[1]

Understanding the direct relationship and indirect routes of exposure to climatic dangers and the effects on health and wellbeing is essential to successfully conceive effective plans and policies for evidence-based mitigation and adaptation.[1]

The 2023 Lancet Countdown South America (LCSA) is the result of collaboration between 21 academic institutions and United Nations (UN) agencies and 28 researchers covering a wide range of fields, to develop expertise and understanding of the links between health and climate change at the regional level.[1]

The data and results for the 12 countries in the region presented in this report cover 25 indicators summarized in four key messages that provide evidence to support targeted response strategies to help decision-makers facing the consequences of climate change.[1]

Although the countries of South America (SA) generate less than 10% of global emissions of greenhouse gases (GHG), they contribute to amplifying heat waves, droughts, forest fires, diseases transmitted by vectors, and other dangers. These adverse effects of climate change are accelerating and disproportionately impact the most vulnerable people in SA.[1]

The LCSA analyzes and discusses current regional evidence on health and climate change in five major domains (i) Health risks, exposures, and impacts; (ii) Adaptation, planning, and resilience for health; (iii) The economic impact of climate change and its mitigation; (iv) The economic impact of climate change and finance; and (v) Public and political commitment. These domains will be presented below.[1]

Section 1: Health risks, exposures, and impacts[1]

Ambient temperature and heat waves are an elevated risk to the health of more vulnerable people, resulting in increased heat-related mortality.

The elevated danger of forest fires increases the risk of potentially fatal injuries, respiratory diseases, and corneal injuries, while loss of infrastructure, interruption of essential services, and additional environmental degradation can cause indirect harm to health.

The high ambient temperatures threaten crop yields, with negative effects on the agricultural industry, on food security, and on nutrition. Cyclic climatic variability causes unique sub-regional scenarios that present situations of different climatic health risks.

Mental health and climate change

Climate change wears down the social, economic, and environmental determinants of psychosocial wellbeing, causing far-reaching and interrelated impacts on mental health.

These impacts range from common mental disorders to severe mental disorders and suicide, representing a greater threat to underprivileged populations in a context of historic social inequalities. From 1990 to 2019, tropical Latin America had the highest mental disease-related disability-adjusted life years (DALYS) in the world.

Climate change promises to work to amplify even further these preexisting risks to mental health, particularly among populations affected by structural inequalities and marginalized groups, creating an urgent need to implement monitoring of reliable global and regional indicators.

Section 2: Adaptation, planning, and resilience for health[1]

Few countries in the region have conducted vulnerability analyses to guide adaptation interventions, which limits the scope for producing specific health policies and intervention policies and the capacity to allocate resources.

As a result, there is a profound lack of financing on the national level and limited implementation of adaptation actions, as demonstrated by some countries. Resources allocated to this purpose could spill over to many areas of society.

Science can support plans for adaptations for health, identifying best practices and barriers to implementation of action and also the benefits of encouraging more investigation.

Resilient health systems

Guaranteed equitable access to high quality health services is a basic human right. However, this right

is threatened by social inequalities and by health care disparities between and within the countries of South America, which primarily affect more vulnerable populations.

The growing impact of climate-related diseases on sensitive communities puts pressure on the region's already overloaded and fragmented health systems.

In South America, the priority is to guarantee universal access to health care; services essential to health installations, such as water and sanitation services, electricity supply, and Internet connectivity; a sufficient number of health professionals per capita, access for all to local health care; reinforcing climate-related technical capabilities on the local level, and education of local health care providers and health professionals; investing in reinforcement and adaptation of infrastructure for health and climate change.

Section 3: Actions for mitigation and health benefits[1]

Accelerating actions to transition to a low carbon economy could yield significant benefits for South America in the short and long term. The health benefits of mitigation of climate change are a critical component and include: better health with healthier and carbon emission free diets; sustainable farming practices and land management; healthier and people-centered urban planning; reduced dependence on motorized transport; improved air quality; and reduced dependence on volatile international markets.

Loss of tree cover and climate change

South America is known for its important natural areas, such as the Amazon Forest and the Patagonian ecosystems. Trees and vegetation are key components in the carbon cycle and can help to prevent CO^2 from building up in the atmosphere, transforming it into biomass by photosynthesis.

Deforestation is a risk factor for health and can lead to: increased propagation of infectious diseases; exacerbated food insecurity in nearby communities; reduced local availability of potable water; and increased degradation and erosion of the soil, which in turn exacerbates dust pollution and increases the risk of flooding.

Intense production of basic goods associated with deforestation also leads to increased health risks, including those resulting from use of agricultural chemicals and displacement of local and Indigenous communities.

Urbanization and expansion are other factors that drive loss of forests in the region. Sustainable urban planning can benefit mitigation of climate change while yielding benefits for health.

Section 4: The economic impact of climate change and its mitigation[1]

Available data on the countries of South America suggest that the costs for health of climate change have increased over the last 20 years. Deaths linked to heat and air pollution have increased faster than the global averages.

The transition to a zero carbon economy, which is essential to protect human health, demands the political willpower to eliminate subsidies for fossil fuels in combination with well-planned policies to avoid possible energy price increases affecting vulnerable populations.

Such policies could include redirecting expenditure, implementation of green tax reforms, generation of new sources of income from fossil fuels, and increasing availability of and access to sources of accessible and carbon-free energy.

Understanding the costs related to transmission of dengue

Dengue is endemic in the greater part of South America; with 16 million cases recorded in 2011-2021. In the highly urbanized countries of the Southern Cone (Argentina and Uruguay) vulnerability to severe dengue cases has increased, disproportionately affecting children, with rising mortality and morbidity and overloading local health care systems.

Understanding and quantifying the economic costs of dengue in terms of the value of the mortality linked to the disease and of the cost of treatment is essential to support precise cost-benefit analyses capable of guiding public health policies for prevention and intervention to reduce propagation of the disease and lighten the socioeconomic burden of this climate-sensitive disease.

Section 5: Public and political commitment[1]

Commitment from the multiple parties interested in health, especially governments, business,

communication media, the scientific community, and citizen communities is essential to fuel demands that measures be taken that are proportional to the risk, creating opportunities for acceptance of climatic interventions to prevent and reduce the current impacts on health.

In this respect, public opinion plays a fundamental role in influencing political decision-making. Communication media coverage of scientific and business commitments will reach its highest level in 2023.

However, despite progress, the level of commitment does not yet match the magnitude of the challenge. Indicators to measure public and governmental participation are the first step to understanding the true situation in South America. Access to information, especially for specific groups, is an essential step in reducing social inequalities and in empowering less favored populations to act.

Public commitment to the sanitary dimension of climate change

Measuring public engagement is essential to understand how people interact with crucial aspects of health and climate. However, quantifying public participation involves unique challenges because of cultural and regional differences.

Taking these first results into consideration, the LCSA research team recently published a series of articles about the gap in scientific information about health and climate change in the region. The thematic axes chosen were "Governance and public engagement research", "Economy and finances", "Mitigation", "Adaptation", and "Impacts".[2-7]

The results of this new analysis demonstrated that South America suffers the impacts of climate change, including extreme climatic events and changes in temperature and rainfall precipitation patterns. These effects interact with the region's existing social vulnerabilities, with severe consequences for the health and wellbeing of populations.

The authors highlight four principal messages from the series, which discussed important gaps from five different perspectives on health and climate. First, there is a general need for local analyses of priority subjects to support public policies, so that national and regional evidence can be included to adequately strengthen the responses, preparation, and adaptation to the dangers of climate change and tackle relevant social vulnerabilities in the countries of South America.

Second, investigations of health and climate are undertaken separately and the intersection is unclear in terms of responsibility and leadership. Multidisciplinary research and actions are therefore essential. There is an urgent need for more action from the communication media and for academic and public coverage of the climate.

Third, climate investigation, policies, and measures should be reflected in effective financing plans, which are currently very limited. For adaptation and mitigation policies to be effective, they need a solid and long-term financing framework.

Finally, climate action is a huge opportunity for more healthy and prosperous societies in South America, taking advantage of the opportunities offered by political climate strategies to meet the challenges of climate change and deal with preexisting social inequalities.

Conclusions of The Lancet Countdown South América on health and climate change – 2023[1]

This inaugural report of the LCSA follows 25 issues of health and indicators of climate change for 12 South American countries, centered on systematic monitoring of the effects of climate change on health and the responses at the regional level.

The risks for health resulting from climate change that affect South America include increased temperatures, heat waves, and more frequent and intense forest fires, lower agricultural yields, and greater exposure to climate-sensitive diseases,

South America has seen an accentuated increase in the climate's suitability for dengue, which is a disease that constitutes an important public health problem in the region, with a mean increase of 35.3% in all countries, except Chile.

Although the entire population is affected to a certain extent, those families that are already living in poverty are more vulnerable, less resilient, and, therefore, more affected.

So far, knowledge of the quantifiable effects of climate change on the health of South American populations is limited among political leaders and the general public. Even in cases in which knowledge exists, action has not been proportional to the threats and opportunities.

Although several countries in South America include health in their National Contributions (NC), the actions are being taken slowly, if at all. This delay has contributed to thousands of deaths related to internal and external pollution by particulate material with diameter less than 2.5 µg (PM2,5) and to carbon and to intensive and unhealthy diets throughout the region. Brazil is the only country that has drawn up a National Adaptation Plan (NAP), up to 2020, allocating appropriate resources to implement and execute it.

The slow pace of action on health and climate matters is reflected in low levels of commitment to interrelated issues from the principal parties involved in society. For a long time, the level of participation in involvement and coverage of health and climate changes in social communication media (which is crucial to provoke change on the individual and political levels) has been one of the lowest in the world.

This report highlights immediate threats to health, the lack of plans for adaptation for health, and the inadequate financing allocated by the different countries to deal with the burden of climate change. The current trajectory of climate inaction will only lead to even greater inequality, poverty, and vulnerability.

SA must step up its efforts, create resilient health systems, and prepare for the changes, demanding that local politicians construct a successful response, defining clear paths to face current challenges and those to come.

The message from the 28 LCSA investigators is clear. Trust the science. Now that we know what is happening, we must.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Hereditary angioedema with C1 inhibitor deficiency: traps in the diagnosis, treatment, and understanding

Angioedema hereditário com deficiência do Inibidor de C1 – Armadilhas no diagnóstico, tratamento e compreensão

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ABSTRACT

Hereditary angioedema (HAE) is a rare, underdiagnosed condition with high morbidity and mortality due to the characteristics of its clinical presentation. HAE differs from histaminergic angioedema by not responding to antihistamines, corticosteroids, or epinephrine. Therefore, early diagnose is crucial to initiate adequate therapy. HAE is suspected in patients with a clinical history of unpredictable and recurrent episodes of edema. When laryngeal edema occurs, it can lead to death from asphyxiation if not treated properly. We report the case of an 18-year-old patient previously diagnosed with HAE type 1 who sought emergency care during an angioedema attack. However, the patient was not taking any specific medication and did not have an action plan to manage attacks. This case highlights the importance of increasing awareness about the disease, educating patients and their families about the disease and potential attacks, and ensuring access to medications.

Keywords: Emergency care, angioedema, hereditary angioedema, hereditary angioedema types I and II, respiratory failure.

RESUMO

Angioedema hereditário (AEH) é uma condição rara, subdiagnosticada e de elevada morbimortalidade, devido ao caráter de suas manifestações clínicas. O AEH se diferencia do angioedema histaminérgico por não responder aos anti-histamínicos, corticosteroides ou epinefrina. Por esse motivo, é extremamente importante o diagnóstico dessa situação, a fim de instituir a terapia adequada. Tal afecção deve ser suspeitada a partir da história clínica de episódios imprevisíveis e recorrentes de edema que quando se manifesta sob a forma de edema laríngeo, pode levar a óbito por asfixia, se não for adequadamente tratado. Relatamos o caso de uma paciente de 18 anos que, apesar de previamente diagnosticada com AEH tipo 1, ao procurar um serviço de emergência devido a crise de angioedema, não dispunha de medicação específica nem apresentou plano de ação com as opções possíveis para crises. Este caso reforça a necessidade de maior divulgação da doença, além da conscientização de pacientes e familiares sobre a doença e eventuais crises, assim como o acesso as medicações.

Descritores: Emergência, angioedema, angioedemas hereditário, angioedema hereditário tipos I e II, insuficiência respiratória.

Introduction

Hereditary angioedema (HAE) with C1-INH deficiency is an autosomal dominant genetic disease that affects around 1:67,000 people.1 There is excessive activation of the contact (kinin–kallikrein), coagulation, and fibrinolysis system, with consequent increase in bradykinin (BRA), which is the main mediator.[1,2]

Clinical manifestations may have onset during the first or second decade of life. Patients present with recurrent and transitory angioedema (duration

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2- 5 days), without hives, involving the mucosa or submucosa of any part of the body, but primarily the extremities, face, genitalia, and digestive and respiratory tracts.[1,3] Episodes typically do not respond to treatment with antihistamines, corticosteroids, and epinephrine.[4] The most common reasons for seeking at emergency departments include angioedema of intestinal loops, which presents with strong abdominal pains and can lead to unnecessary exploratory laparotomies as a result of the difficulty in establishing diferencial diagnosis in order to rull out other causes of surgical acute abdomen,[5] and laryngeal edema, which is the most serious event, because of the possibility of progression to asphyxia and death if not promptly reversed.[6,7]

Laryngeal edema crises demand particular attention and rapid access to an emergency unit must be guaranteed, to enable early treatment. Laryngeal angioedema must not be mistaken with other causes of angioedema often seen at emergency services, which are mediated by histamine.[4,7] Warning signs that indicate the need for immediate intervention include feelings of a tight chest, discomfort in the oropharynx, and/or difficulty swallowing.[6]

Despite advances in understanding of the disease in recent years, significant delays in diagnosis are still described, confirming that this condition remains unknown to many health professionals.[8,9] Lack of knowledge about the disease has been linked to unnecessary invasive procedures and incorrect treatments, worsening patient quality of life and increasing morbidity related to the disease.[9]

Case report

The patient was an 18-year-old, Black, unmarried female with recurrent angioedema involving limbs and genitalia from 2 years of age that later progressed to include recurrent abdominal pains. Episodes receded spontaneously in 3 to 5 days. The crises increased in frequency after menarche, at 11 years, and were associated with emotional stress. There was a family history of HAE; both her father and a brother had a history of recurrent angioedema and the brother had died from laryngeal edema at the age of 23. When the patient was 13 years old, laboratory investigation identified reduced C4 and C1-INH levels and she was diagnosed with HAE with quantitative C1-INH deficiency.

Long term prophylaxis was initiated with antifibrinolytics, but satisfactory control of symptoms was not achieved, and they were withdrawn and replaced with attenuated androgens, despite the patient's age. The patient was also prescribed plasma derived C1 inhibitor specifically for the crises, but she was unable to obtain access to it. She was also instructed to avoid possible trigger factors, such as taking estrogens (oral contraceptives), trauma, and, as far as possible, emotional stress. An action plan for HAE crises was provided and she was instructed to seek emergency medical care in the event of crises.

At the age of 18 years, the patient was using long-term prophylaxis irregularly and during a period of considerable emotional stress she suffered a sudden episode of oropharyngeal discomfort with dyspnea and was taken to emergency by family members. Based on a clinical suspicion of laryngeal edema and not having been told about the crisis action plan, the care team administered antihistamines and intravenous corticosteroid and told her to stay for observation. Despite this recommendation, the patient left the emergency service and later developed acute respiratory failure, followed by convulsive crisis, and was taken back to emergency. She was subjected to oral endotracheal intubation (OEI) to try and provide ventilatory support. At this point, the local team contacted the specialists and were informed of the diagnosis of HAE. The hospital did not have especific crisis drugs available or even fresh frozen plasma. Despite the local team's efforts, the patient died.

Discussion

Hereditary angioedema is a complex condition that has a considerable impact on the quality of life of patients and their families. This disease should always be considered in patients with a history of recurrent edema without hives, especially if there is a family history of similar crises. It can present with sudden episodes of angioedema involving any part of the body.[1,2] It is estimated that approximately half of HAE patients will have at least one episode of laryngeal edema in life.[6] As seen in the case presented here, airway compromise is the most important medical emergency, with the potential to cause death and requiring early intervention.[4,7] In this scenario, faced with involvement of the upper airways, uvula, or tongue, the first step is to guarantee airway patency. Patients at imminent risk of asphyxia must immediately undergo OEI.[1,4,7]

In a case of suspected HAE crisis, particularly if there is involvement of the face and abdomen, patients

should always be encouraged to seek an emergency service.[7] It should be pointed out that during hospital admission, it is not uncommon for diagnostic confusion to occur with other conditions that also present with angioedema, such as those caused by histamine-mediated anaphylactic reactions. Unlike histaminergic angioedema, HAE does not respond to antihistamines, corticosteroids, and adrenaline.[4,7] This failure to respond to conventional treatment and a lack of knowledge of the treatment options available for HAE and how to access them underscore the need for better dissemination, particularly among emergency professionals.[4,9,10] Once HAE has been diagnosed, an action plan should be prepared and given to the patient, attempting to significantly reduce the extent to which the disease interferes in the daily activities of patients and their families, in addition to facilitating dealing with crises.[11] Against medical advice, the patient did not comply with the recommended regular use of medication and did not have her action plan with her on the day she had the crisis. Unlike what actually happened in this case, the action plan should be shown to the emergency care team.[11] As a result, the patient was given drugs that are not indicated for management of an HAE crisis.

The crisis action plan is prepared by the health professionals involved in caring for the patient with HAE and is designed to help the emergency team make treatment decisions.[2,11] The majority of crises are spontaneous, but some triggers have been described and so to prevent them patients are instructed about individual conditions that they should pay particular attention to for management of the disease, such as surgical and dental procedures, pregnancy, avoiding use of antihypertensive medications, certain oral hypoglycemics (gliptins), and medications containing estrogen, as part of a process known as "shared decision making".[1,12] Assessment of the frequency and severity of crises is intended to identify any need for long term prophylaxis to prevent recurrence, and continuous monitoring of these patients is necessary.[1,2,12]

Hereditary angioedema significantly compromises patients' quality of life and these measures are intended to reduce the significant morbidity and mortality associated with HAE, since a strategy based on careful treatment of crises and crisis prevention is essential for adequate management of patients.[11]

One recent study found that digital action plans help to reduce care delays in emergency situations and enable administration of appropriate treatment. Moreover, having a specialist available to communicate with the patient and the emergency team during crisis episodes helps with treatment adherence and facilitates management of this condition that is still unknown to many health professionals.[12,13] In the case described, even though a specialist and an action plan were available, because the patient and her family did not show the action plan to the emergency team, there was inadequate communication at the initial point of care, delaying knowledge of the diagnosis and measures essential to reverse the situation.

In addition to all of the aspects already mentioned, the unpredictability of crises has been linked to significant psychosomatic harm to HAE patients.[14] Despite all the family's efforts to avoid conditions that caused the patient emotional discomfort or stress, she reported considerable emotional stress, which is a known trigger factor for HAE crises. Living with a rare disease that is still unknown to many people, compounded by the difficulties of accessing crisis medications are the greatest challenge faced by these patients.[9,11]

Several studies have assessed the impact of emotional disorders on the population with HAE.[14,15] One of them, conducted in several countries, reported that anxiety and depression were described in 38% and 17.4% of patients respectively.[15]

Savarese et al. also linked emotional disorders and lack of knowledge to poor adherence to treatment.[16] According to Graffigna et al., when a patient is given an important diagnosis, he or she may not be as actively engaged in their treatment because of the emotional instability inherent to the process.[17]

The psychological processes associated with HAE are extremely important because they can act as triggers of crises and interfere in disease management by affecting patients' quality of life. Depression and anxiety have not only been described as frequent comorbidities caused by the disease, but are also listed as important crisis trigger factors.[17] A growing body of research has linked depression to angioedema via common neurobiological factors.[18]

Stress is described as the principal trigger and also appears to modify disease activity.[19] According to Felger et al., chronic exposure to inflammatory cytokines can lead to persistent changes to neurotransmitters and consequently to psychiatric disorders, such as depression.[20] Additionally, psychic stress alters the functional activity of the

complement cascade, intensifying the inflammatory process. Increased production of bradykinin in stressful situations may explain the correlation between dysfunctions of the autonomic nervous system and activation of the contact/complement system.[21] Metabolites of bradykinin, such as des-arg-9-bradykinin and IL1beta, which are responsible for increased vascular permeability, have also been associated with depression in experimental models.[18] Therefore, it is essential to study the interface between immunopathological disorders such as angioedema and these emotional disorders.[18]

Another disorder being studied currently is alexithymia, or augmented stress perception, which is more frequent among children and young adults with HAE. People with alexithymia have difficulties coping with stress and with recognizing and regulating emotions. One study reported that alexithymia affects 84% of children with HAE-C1-INH, and may also be associated with severity of the disease.[22] However, these data were not confirmed in adults, according to Savarese et al.[16]

These findings demonstrate how important managing psychological wellbeing is for the course of HAE. Its interference in the disease should be assessed individually, and it is very important to conduct periodic assessments of the frequency and severity of symptoms and of the efficacy of prophylactic treatment, when this is prescribed. A quality-of-life questionnaire such as the Hereditary Angioedema Quality of Life Questionnaire (HAE-QoL) is routinely administered, to achieve early identification of disease control and of the impacts of the disease on patients' daily lives and any possible associated psychiatric disorders.[11,23]

Furthermore, with this objective, specialist centers in several countries have set up non-profit support groups for patients with HAE, with the objective of providing support and representing patients' interests, in order to reduce morbidity and potential deaths, when not treated adequately. In Brazil, the Brazilian Hereditary Angioedema Association (Abranghe - Associação Brasileira de Angioedema Hereditário) represents this group of patients, working with education about recognition of the disease and crisis triggers, screening of family members, and lobbying for public policies, since access to expensive medications is a challenge that is faced constantly.[11]

Access to/availability of medications such as plasma derived C1 inhibitor or B2 bradykinin receptor inhibitor is essential for adequate management of an HAE crisis.[2,4,7,11] However, when these are not available, fresh frozen plasma replacement is recommended (2-4 units).[2,4,7,11] In the case described here, when the emergency team communicated with the assisting physician, they were informed of the ideal treatment options for management of the crisis, but the unit did not have these options available and so OEI was indicated. When crisis medications are not available, invasive ventilatory support should be provided immediately, to prevent rapid progression to asphyxia.[4,7,11] The procedure should preferably be performed by a qualified medical professional, since any mechanical manipulation of these patients' airways could provoke exacerbation of the edema, and the airway is generally difficult to access.[7,24] In some cases, tracheostomy or cricothyroidotomy can be attempted to speed up ventilatory support in order to stabilize the patient.[7,24]

According to current guidelines, it is recommended that patients should keep at least two doses of medication at home in case of crises.[2,11,25] All of the medications approved for crises in Brazil permit home self-administration and are of fundamental importance for early treatment of crises and prevention of fatal events, avoiding exposing patients to health care services that are still substandard in our country. However, because of their high cost, a large proportion of patients in Brazil cannot access these drugs and continue using inadequate treatments, both for prophylaxis and to treat crises.[11] In this scenario, it is important that public policies be adopted to improve access to especific medications by including them on the Ministry of Health's therapeutic guidelines clinical protocol. In the absence of these drugs, the emergency physician must be aware of the option of treating crises with fresh frozen plasma, in addition to being well trained in airway management. However, in some regions of Brazil, access to transfusion of plasma is not available, as in the case described. Therefore, we highlight the need to make specific, effective, and self-administrable treatments available.[11] Moreover, patients should be educated about possible trigger factors, regular use of prophylactic medication, when appropriate, when to seek emergency care to treat crises, and the importance of showing the emergency physician the action plan with treatment guidelines and the specialist's contact.[2,4,11,15]

Hereditary angioedema is a rare condition that causes considerable morbidity and can be fatal. Although it is better publicized and better known among specialists, a lack of knowledge among

pediatricians, general practitioners, and emergency physicians and underdiagnosis are still obstacles that need to be overcome.[9,10] Hereditary angioedema is a treatable disease and so we hope that over the coming years knowledge about it will spread, both among health professionals and patients and their families, so that more positive outcomes can be achieved.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Anaphylactic reaction to ondansetron in a pediatric patient: a rare case report

Anafilaxia a ondasetron em idade pediátrica: um caso clínico raro

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ABSTRACT

Although ondansetron is a widely used antiemetic medication, hypersensitivity to ondansetron is rare. We report a clinical case of a child who had an anaphylactic reaction after a single oral dose of ondansetron. An immunoglobulin E-mediated mechanism was determined by positive intradermal tests.

Keywords: Anaphylaxis, case reports, antiemetics, pediatrics.

RESUMO

Ondansetron é um medicamento antiemético amplamente utilizado, mas a hipersensibilidade ao mesmo é rara. Apresentamos um caso clínico de uma criança com anafilaxia após tomar dose única de ondansetron, via oral, onde se demonstra um mecanismo mediado por IgE através de testes intradérmicos positivos.

Descritores: Anafilaxia, relatos de casos, antieméticos, pediatria.

Introduction

Ondansetron, an antiemetic drug that acts as a 5-hydroxytryptamine (5-HT3) receptor antagonist, is commonly used to treat or prevent chemotherapy-induced nausea and vomiting and as a prophylactic treatment for nausea and vomiting in perioperative settings. The most commonly reported adverse effects include headache, feeling hot, and constipation. Hypersensitivity reactions to ondansetron appear to be rare. Only a few cases have been reported in the literature, including systemic reactions[1-7] and isolated cutaneous reactions.[8]

Only 7 cases of anaphylaxis have been documented[1,2 9-13], with an IgE-mediated mechanism confirmed by skin tests in 3 cases[1,9,10], 2 of which were pediatric.[10,11]

The authors describe a rare case of immediate hypersensitivity to ondansetron in a 9-year-old boy who presented with anaphylaxis. A suspected IgE-mediated mechanism was validated by positive intradermal tests.

Case report

A 9-year-old boy presented to the emergency department with a 2-day history of nausea and vomiting. He had no fever or other gastrointestinal symptoms and denied other associated symptoms or complaints. He was given ondansetron 4mg per os, but 20 minutes after administration a generalized urticarial rash appeared with associated pruritus but no angioedema or associated respiratory or cardiovascular symptoms. He was administered an antihistamine (hydroxyzine 25mg per os), which resulted in clinical improvement, and he was discharged after 2 hours.

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However, he returned 2 hours after discharge due to renewed vomiting and progression of the skin rash. In addition to the previous cutaneous symptoms, he had angioedema of the lower and upper lips and wheezing. Vital signs were within normal limits. He was treated with adrenaline (0.3mg/0.3mL, IM), methylprednisolone 20mg IV, clemastine 2g IV, and 400µg of nebulized salbutamol, which resulted in clinical improvement. Four hours later the skin lesions worsened and wheezing recurred, so adrenaline, methylprednisolone, clemastine, and salbutamol were administered again. Treatment with methylprednisolone 20mg IV and clemastine 2g IV was repeated four hours later due to the recurrence of cutaneous symptoms. The patient remained under surveillance and was discharged 12 hours later with a prescription of oral prednisolone 20mg and levocetirizine 5mg for 3 days. He was referred to the allergy department for diagnostic investigation. No information on tryptase levels was provided. The patient had no other medical history apart from a previous diagnosis of asthma and allergic rhinitis (controlled with daily fluticasone furoate 27.5µg and levocetirizine 5mg, with salbutamol 100µg/dose as needed) and had never been exposed to ondansetron.

Despite the nonexistence of validated concentrations, given the severity of the reaction, a basophil activation test was performed (Basotest®, ORPEGEN Pharma, Heidelberg, Germany) with an ondansetron solution (2mg/mL), the result of which was negative.

The patient also underwent skin testing with ondansetron (Figure 1). The recommended concentrations found in literature for both prick and intradermal tests were used.[1] In addition, 4 control tests (2 exposed patients, 2 non-exposed volunteers) were also performed to exclude possible false positive results.

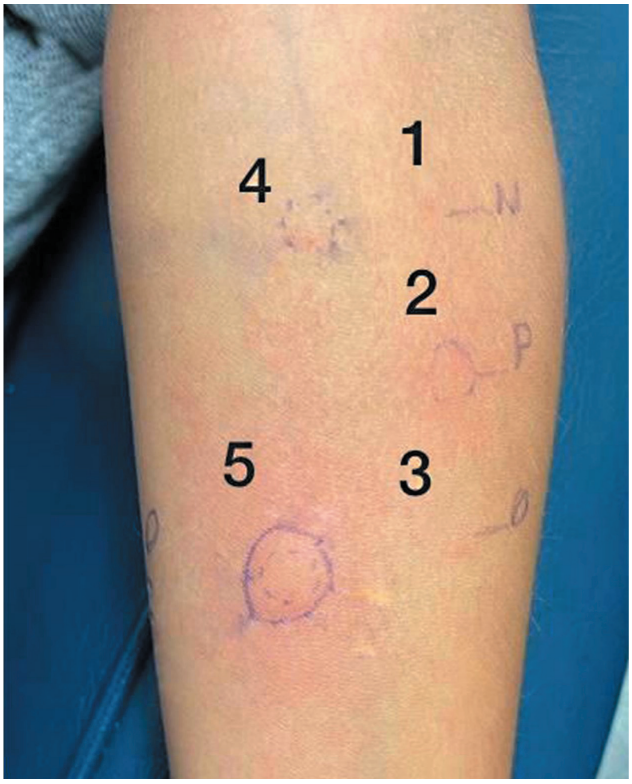

Figure 1
Skin tests with ondansetron: 1) skin prick test with saline solution; 2) skin prick test with histamine; 3) skin prick test with ondansetron at a concentration of 2mg/mL; 4) intradermal test with ondansetron at a concentration of 0.002mg/mL; 5) intradermal test with ondansetron at a concentration of 0.02mg/mL

The skin prick test results for ondansetron at a concentration of 2mg/mL were negative; the intradermal test results for ondansetron at a concentration of 0.002mg/mL was negative, but the patient tested positive in an intradermal test at a concentration of 0.02mg/mL: the initial wheal diameter increased 8 mm and erythema increased 6mm. None of the 4 controls had a positive wheal reaction at this concentration.

Due to the severity of the initial reaction, no oral provocation test with ondansetron was performed. The patient was told to avoid ondansetron and has not had similar episodes to date.

Discussion

Although ondansetron is commonly used, hypersensitivity reactions seem to be rare. Still, life threatening reactions can occur.[2] Chen et al. analyzed U.S. Food and Drug Administration records, identifying 24 reports of adverse anaphylactoid-anaphylactic reactions associated with ondansetron.[5] Sapkota et al. described the case of an anaphylactic reaction to ondansetron with a rapid and severe onset, which unfortunately was fatal despite prompt medical treatment.[2]

We found 7 cases reports of allergic reactions to ondansetron in the literature,[1,2,9-13], of which 3 involved an IgE-mediated mechanism confirmed by skin prick and/or intradermal tests.[1,9,10] Two of these 3 occurred in pediatric patients. Tan et al. described a case of anaphylaxis after initial sublingual administration of ondansetron in a 12-year-old child, and an IgE-associated mechanism was confirmed through intradermal tests.[10] Demir et al. reported a case of anaphylaxis after the fourth dose of ondansetron in a 1-year-old child undergoing chemotherapy for neuroblastoma.[11]

Our case involved a similar clinical presentation, with cutaneous symptoms appearing in the first few minutes after exposure and progression to anaphylaxis. As in the case reported by Tan et al., the patient had no previous exposure to the drug.

This is a rare case of immediate hypersensitivity to ondansetron in a pediatric patient, in which an IgE-mediated mechanism was confirmed by a positive intradermal skin test, as also described by Tan et al.[10].

Skin prick/intradermal tests for other 5-HT3 antagonists were not performed, since the patient did not require recurrent treatment with antiemetics. Since the basophil activation test results were negative, it was not useful for diagnosis in this case. The mechanism by which the patient became sensitized to ondansetron remains unknown, given that this was most likely his first contact with the drug.

Some authors suggest that a class effect, possibly involving cross-reactivity, may be involved in ondansetron anaphylaxis.[14] However, other authors reported successful ondansetron use in a patient allergic to granisetron.[15] This would suggest a drug-specific effect rather than a class effect. The authors do not recommend using ondansetron or other 5-HT3 receptor antagonists in patients who have had a severe hypersensitivity reaction to another 5-HT3 receptor antagonist.

For ondansetron-allergic patients indicated for long-term antiemetic treatment, allergological study with a skin prick/intradermal test and, if necessary, a drug provocation test for alternative drugs under medical supervision seems advisable.

We highlight the importance of using ondansetron with caution, especially in children. Healthcare professionals must be prepared to identify and manage uncommon, but severe, adverse effects, including anaphylactic reactions.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Rapid induction of oral tolerance to allopurinol: a case report

Indução oral rápida de tolerância a alopurinol: um relato de caso

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ABSTRACT

Continuous oral allopurinol use is the first-line treatment for hereditary glycogen disorders. While hypersensitivity reactions to allopurinol are uncommon, they can pose challenges when this medication is the only available option for the long-term treatment of the underlying disorder. In such cases, desensitization emerges as a viable alternative. We report the case of a patient with glycogen storage disease type I who developed a generalized pruritic rash due to allopurinol. Drug intolerance was successfully managed using a rapid oral desensitization protocol, which allowed an uneventful long-term use of allopurinol.

Keywords: Drug hypersensitivity, immunologic desensitization, glycogen storage disease.

RESUMO

O alopurinol, de uso contínuo oral, é o tratamento de escolha para os distúrbios hereditários do glicogênio. Apesar de não ser comum, a reação de hipersensibilidade ao alopurinol se torna um problema quando esta é a única medicação disponível para o controle da doença de base. Nestes casos, a dessensibilização é uma alternativa viável. No presente relato, descrevemos o caso de um paciente com diagnóstico de doença de depósito de glicogênio tipo I, com exantema pruriginoso generalizado ao alopurinol, tratado com um protocolo de dessensibilização oral acelerado. Este tratamento permitiu o uso contínuo deste medicamento sem novas reações em longo prazo.

Descritores: Hipersensibilidade a drogas, dessensibilização imunológica, doença de depósito de glicogênio.

Introduction

Glycogen storage diseases (GSDs) are hereditary metabolic disorders resulting from defects in glycogen synthesis or degradation.[1] Of various known subtypes, glycogen storage disease type I (GSD I) is so named as it was the first to have its mechanism identified. It has an autosomal recessive inheritance pattern, with an incidence of 1 per 100,000 population. Its underlying etiology is a deficiency of one of two enzymes, either glucose-6-phosphatase (subtype GSD-Ia) or glucose-6-phosphate translocase (subtype GSD-Ib). GSD-I may present with growth restriction, intermittent hypoglycemia, hepatomegaly, progressive renal failure, hyperlactatemia, hyperuricemia, hyperlipidemia, anemia, and neutropenia.[2] Around 71% of those affected will develop metabolic changes, including hyperuricemia, which occurs secondary to decreased renal clearance and increased production of uric acid as a byproduct of adenine nucleotide degradation.[3] Given the well-established association of hyperuricemia with kidney

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disease, cardiovascular diseases, diabetes, and gout, treating this condition is key to preventing or at least mitigating such complications.[4,5] The current treatment of hyperuricemia consists of dietary restrictions (with various types of diet being studied, including the DASH diet, the Mediterranean diet, and a low-purine diet) and allopurinol.[6]

Allopurinol is widely used in the treatment of patients with hyperuricemia and/or gout. It is inexpensive and is considered a first-line therapy of choice. Most of the action of allopurinol is the result of its main active metabolite, oxypurinol, inhibiting xanthine oxidase, the enzyme responsible for catalyzing the oxidation of hypoxanthine and xanthine into uric acid; inhibition decreases production of uric acid and, consequently, reduces its levels in blood and urine.[7,8] Although widely used and generally well tolerated, allopurinol can lead to hypersensitivity reactions, and is a significant cause of severe cutaneous adverse reactions worldwide. Allopurinol-related reactions can range from a mild maculopapular rash to life-threatening severe cutaneous reactions such as the Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).[7] In recent decades, investigators have attempted to identify a relationship between genetic predispositions and allopurinol-induced adverse cutaneous drug reactions. One study with Chinese patients demonstrated a strong relationship between HLA markers and the risk of developing SJS/TEN.[9] To date, some risk factors identified for this association are female sex, advanced age, chronic kidney disease or cardiovascular disease, initiation of therapy at high doses of allopurinol, and HLA-B 58:01 carrier status.[7]

An adverse drug reaction (ADR) can be defined as any non-therapeutic effect resulting from the use of a drug in usually therapeutic doses. ADRs can be classified as predictable or unpredictable. Predictable, or type A, reactions are those caused directly by the medication administered. Unpredictable, or type B, reactions are those not directly related to the effects of the medication, but rather due to intolerance or hypersensitivity; these may be allergic or result from a direct interaction of the drug with immune cell receptors. Hypersensitivity ADRs are due to stimulation of the immune system by potentially immunogenic particles. In some cases, a small-molecule drug – a hapten – binds to a carrier protein, thus forming an allergenic complex. Allergy to beta-lactams is one example of this mechanism. Pseudoallergic reactions are mediated by activation of inflammatory mechanisms without involvement of the adaptive immune system, causing a clinical picture resembling that of IgE-mediated reactions. This process occurs through activation of cellular inflammation receptors or inhibition of enzymes leading to an increase in pro-inflammatory mediators. Examples include direct activation of Mas-related G protein-coupled receptor-X2 (MrgprX2) in mast cells and the inhibition of cyclooxygenase by non-steroidal anti-inflammatory drugs (NSAIDs). The pharmacological interaction with immune receptors (p-i) concept describes a phenomenon that occurs through non-covalent bonding between a drug and immune-system cell receptors (HLA or TCR), eliciting a T cell-mediated immune response and triggering alloimmune hypersensitivity. This mechanism does not require a second signal to trigger a strong T cell-mediated reaction. Some ADRs to allopurinol are an example.[10,11]

Treatment of ADRs involves immediate discontinuation of suspected medications, symptom management, and supportive care as necessary. In anaphylaxis, epinephrine is the only treatment with proven effectiveness and must be administered promptly. Drug desensitization should be considered in patients with confirmed or high likelihood of a hypersensitivity reaction to a medication whose use is essential and where no other treatment options are available. Desensitization involves administering the culprit medication in increasing doses until the therapeutic dose is reached.[12] When treatment with allopurinol is necessary and the initial hypersensitivity reaction is not severe, desensitization may be an appropriate therapeutic option.[13]

The present report describes oral desensitization to allopurinol with a rapid protocol, designed to ensure that effective treatment can be resumed promptly in patients for whom this medication is indispensable.

Case report

A 31-year-old white man diagnosed with GSD-I was referred to our service after developing a generalized pruritic maculopapular rash 1 hour after oral intake of 300 mg allopurinol. As allopurinol is the only medication available for the treatment of hyperuricemia associated with his underlying disease, we considered drug desensitization the best option for this patient.

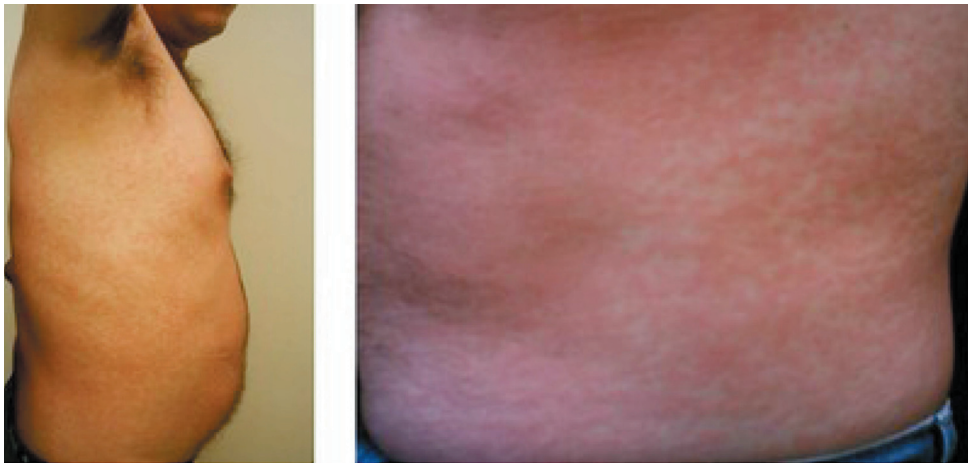
We initially proposed oral desensitization based on a 30-day protocol[14] involving daily administration of the medication at 3-to-5-fold dosage increments from one day to the next. The starting dose was 0.01 mg, with the aim of reaching 300 mg on day 30 of the protocol. However, at the 1-mg dose, the patient developed slightly pruritic erythema on his hands, and at 3 mg, the rash spread to his feet. These reactions were adjudicated as mild, and the decision was made to continue the protocol. Upon reaching the 100-mg dose, the patient developed a generalized pruritic maculopapular rash, although it was mild in severity. The 300 mg dose was reached and maintained for 1 week, at which point the rash worsened and the patient discontinued daily allopurinol (Figures 1 and 2). The rash was treated with a 21-day course of prednisone 60 mg once daily plus fexofenadine 180 mg twice daily. Prednisone was then tapered off uneventfully.

At the time we encountered this patient, there was only one report in the literature of a rapid desensitization protocol for allopurinol[15]; however, it required intravenous allopurinol, which is no longer commercially available. Therefore, we decided to adapt the reported protocol to use the oral formulation instead, administered in a hospital environment. The rapid protocol consisted of administering progressive doses of allopurinol at 15-minute intervals, with a starting dose of 0.01 mg and a target dose of 100 mg, as shown in Figure 3.

At first, the patient was advised to continue allopurinol at 300 mg per day, divided into 3 doses (100 mg every 8 hours), so as to keep the interval between doses under 12 hours. However, only a few hours later, the patient again developed a generalized pruritic rash. We then decided to continue allopurinol 100 mg every 8 hours but add on prednisone 40 mg daily and cetirizine 10 mg twice daily. After 3 days, the patient reported complete resolution of the rash.

After 2 weeks of the aforementioned regimen, a prednisone taper was started at a decrement of 5 mg/week. Once a daily dose of 20 mg prednisone was reached, the tapering rate was reduced to 2.5 mg per week. However, upon reaching a dose of 15/10 mg every other day, the rash recurred once more. This required an increase in prednisone dose back to 40 mg daily for 1 week, then 30 mg daily for another week and, finally, 20 mg daily for a further 2 weeks. From this point onwards, the dose was tapered more slowly, at a rate of 2.5 mg every 3 weeks. Once the patient had been stable on 2.5 mg every other day for 3 weeks, prednisone was discontinued. Two months later, cetirizine was also discontinued.

The patient has had no further recurrences of the rash since 2009. He has taken allopurinol 100 mg every 8 hours uninterruptedly since, and at the time of writing has not required corticosteroids or antihistamines. Laboratory tests, including complete blood counts and liver enzymes, were performed



Figures 1 and 2
Generalized pruritic maculopapular rash after a daily dose of 300 mg allopurinol

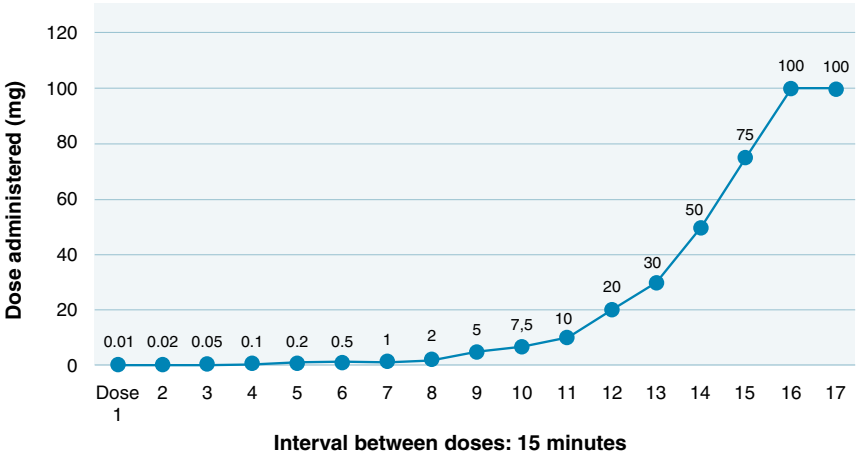


Figure 3
Rapid allopurinol desensitization protocol

periodically. All remained within normal limits before, during, and after the desensitization period. Figure 4 shows the extent of the patient's articular involvement before starting treatment, while Figure 5 shows the reduction in tophi after long-term allopurinol therapy.

Discussion

Drug desensitization is a procedure performed with the aim of temporarily reducing hypersensitivity, whether to allow chronic (continuous) drug treatment or to allow completion of a time-limited regimen or course of therapy.[16] Various mechanisms have been implicated in drug tolerance achieved through desensitization, such as hapten inhibition, IgE consumption, depletion of mast-cell and basophil mediators, and mast-cell desensitization.[17]

Although intolerance to allopurinol is uncommon, approximately 2% of patients who take this medication experience hypersensitivity reactions. Newer medications for the treatment of hyperuricemia have been developed, but access is difficult in Brazil, and options thus remain limited. Desensitization should be considered for most patients with hypersensitivity to allopurinol, except those who presented with severe reactions.[17] For the patient described in this report, we chose to pursue desensitization as his reactions were mild and there were no alternative treatments available.

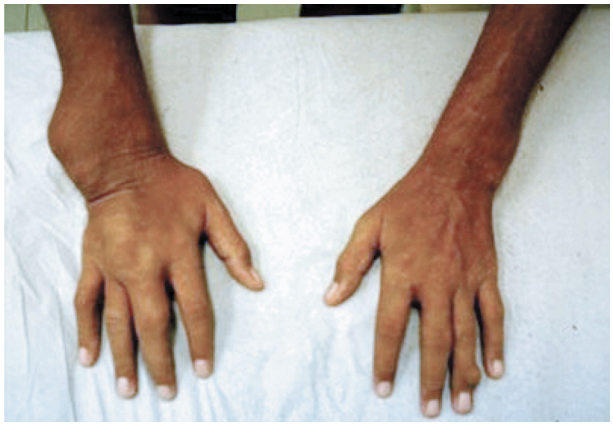


Figure 4
Articular findings before institution of long-term allopurinol therapy

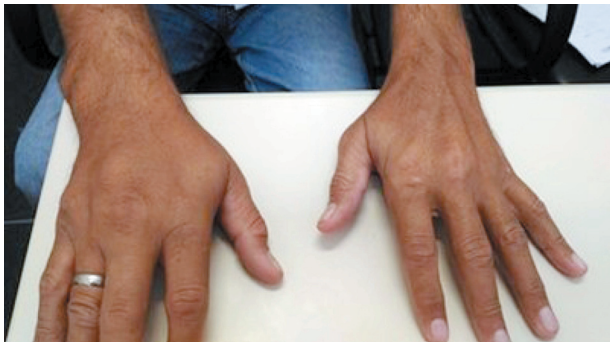


Figure 5
Reduction in gouty tophi after long-term allopurinol therapy

We found several allopurinol desensitization protocols in the literature, ranging from 28 to 81 days in duration until the desired therapeutic dose is reached. Such prolonged protocols aim to minimize potential risks; however, if there is an urgent clinical need to resume therapy with the culprit drug, they can be adapted.[17]

At the time of our treating this patient, there was only one published report of rapid desensitization with intravenous (IV) allopurinol, but IV formulations are no longer commercially available.[15] Therefore, we decided to adapt the rapid IV protocol for the oral route. Allopurinol was administered orally under medical supervision in a hospital setting, initially at a dose of 0.01 mg, increasing progressively at 15-minute intervals so a final target dose of 100 mg could be reached in a single day. The patient was then instructed to continue this 100-mg dose every 8 hours, thus avoiding the risk of a prolonged interval off the dose achieved during desensitization.

Drug desensitization protocols generally involve the administration of increasing doses of the culprit medication at regular intervals to reduce the frequency and severity of reactions. Although our patient developed several reactions throughout the desensitization process, none was considered serious. Furthermore, he responded well to the anti-allergy measures instituted during these mild reactions, which allowed desensitization to proceed safely. The impact of ceasing allopurinol treatment on his gout and known risk of involvement of other vital organs secondary to hyperuricemia was also taken into account.[18] On the basis of these considerations, pursuing desensitization proved to be the best option despite repeated reactions. The protocol was subsequently re-adapted to the patient's needs, in order to minimize reactions and increase tolerance, with administration of antihistamines and systemic corticosteroids for as long as necessary until clinical stability was achieved with oral allopurinol at the desired dose. It bears stressing that regular, ongoing intake of the drug is of the utmost importance to prevent loss of the tolerance induced by desensitization.

Most published protocols for desensitization to oral allopurinol are slow and gradual, with the 28-day oral protocol being that most frequently employed and tolerated by patients. The maintenance dose achieved with this protocol is 100 mg/day.[13,19] Contrary to what is reported in these studies, our patient developed a reaction to low-dose oral allopurinol during the conventional long (30-day) protocol we initially pursued[14], before we decided to attempt the adapted rapid protocol. Although it is still rarely used, rapid desensitization in a hospital environment (or even in an outpatient setting when appropriate) should be considered, with risks and benefits weighed on a case-by-case basis.[20]

More recently, other authors have reported induction of tolerance to oral allopurinol using accelerated protocols, with the objective of reaching the desired dose in a shorter time. The duration of desensitization in these reports ranged from 1 to 16 days, with no increase in the frequency of reactions.[17,21]

Conclusion

In glycogen storage diseases, treatment of hyperuricemia is essential to preventing metabolic and cardiovascular complications and improving quality of life. In patients intolerant to allopurinol where no alternative treatment is available, desensitization should be considered. When carried out in a safe environment by a team of specialized, experienced professionals, it can allow adaptation of therapy so that optimal treatment is provided. The rapid desensitization protocol with oral allopurinol proved successful in the case described herein, allowing treatment to resume, and enabling short- and long-term clinical stability.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Effectiveness and safety of an algorithm for the treatment of pregnant women with syphilis and a history of penicillin allergy

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Science provides vast opportunities for academic advancement and is essential for the development of any society. Thanks to the daily encouragement I received during my training as an allergist and immunologist, I had the great honor of presenting my master's thesis, "Algorithm for treatment of pregnant women with syphilis and history of allergy to penicillin – effectiveness and safety", at the World Allergy Congress (WAC) 2023, held by the World Allergy Organization in Thailand. The WAC had 148 speakers and 1,336 participants from 57 countries, and our study was the only one conducted outside Asia to win an award for best oral presentation.

In addition to the academic importance it holds for the first author personally, this work should be socially relevant as well, given its contribution to patients who have enrolled in the study and those who will enroll in future.

During pregnancy, syphilis treatment must be started immediately after a positive (reactive) test, regardless of the type of test or the titer detected. Immediate treatment should also be initiated in cases where there is no clear confirmatory evidence of infection and in pregnant women who have had sexual contact with a person known to have syphilis. Congenital syphilis is a preventable condition, provided the infection is detected during pregnancy (through effective prenatal care) and treated appropriately.[1-6]

The only effective treatment for gestational syphilis is administration of benzathine penicillin (BP), which is bioavailable to the fetus and thus ensures treatment of both mother and child. It bears stressing that there is no evidence of resistance of *T. pallidum* to penicillin in Brazil or elsewhere in the world, and that the first-line treatment of choice for syphilis in non-pregnant patients also involves penicillin antibiotics. The Brazilian Ministry of Health recommends that all pregnant women with a proven allergy to benzathine penicillin be referred to a specialized tertiary care center for desensitization in accordance with existing protocols.[2,3,5]

Penicillins are among the most common causes of drug-induced allergy. Reactions can manifest as a wide range of clinical conditions, from mild rash, urticaria, or angioedema to full-blown anaphylaxis.[7] However, the consequences of penicillin allergy mislabeling (PAM) are well documented and occur at both the individual and public-health levels.[8] Pregnant women also experience adverse health effects associated with self-reported penicillin allergy, including increased risk of cesarean section and increased length of hospital stay.[9] PAM must therefore be viewed as a threat to individual and public health, and detailed clinical histories must be obtained from all patients with alleged reactions to a penicillin antibiotic.[10]

The purpose of the detailed clinical history is to identify patients at high versus low risk of immediate reactions to antibiotics and thus determine how further investigation should proceed. A combination of detailed clinical history assessment with *in vivo* and *in vitro* testing is the safest approach to guide penicillin rechallenge.[10]

In cases of suspected immediate hypersensitivity reactions, we continue the clinical workup to confirm or rule out the diagnostic hypothesis with the aid of an algorithm. This algorithm involves administering a specific clinical questionnaire developed by the authors (with standardized scoring for previously defined clinical criteria, taking into account: clinical manifestations compatible with an immediate hypersensitivity reaction; first immediate hypersensitivity reaction 10 years or less before the date of assessment; history of exposure/re-exposure to beta-lactam antibiotics), followed by *in vivo* (immediate skin-

prick and intradermal) tests and, if possible, *in vitro* tests (detection of penicillin G-, penicillin V-, and amoxicillin-specific serum IgE).

The combination of a clinical history consistent with an immediate hypersensitivity reaction and positive *in vivo* or *in vitro* test results is diagnostic of penicillin allergy, and the patient must be referred for desensitization. If the clinical history is questionable or inconsistent with immediate hypersensitivity (i.e., suggesting low risk of a further reaction) and both *in vivo* and *in vitro* tests are negative, a drug provocation test can be carried out to confirm or rule out the diagnosis of penicillin allergy.[2,3,5]

Drug provocation testing is considered the gold standard for ruling out a diagnosis of allergy. Its main objective is de-labeling, given the aforementioned negative implications of PAM, which include heightened risk of antimicrobial therapy failure, antimicrobial resistance, adverse drug reactions secondary to the use of broader-spectrum or alternative antibiotics, and increased health expenditure.[14]

Rapid drug desensitization (RDD) is indicated for any immediate hypersensitivity reaction, whether allergic or non-allergic, thus representing an important advance in improving the treatment and prognosis of patients with such reactionss.[11] RDD is a safe, effective process in which a temporary state of mast-cell and basophil hyporesponsiveness is induced through incremental administration of suboptimal doses of the culprit drug until the desired therapeutic dose is reached.[12] Desensitization allows patients to receive antimicrobial treatment of choice for their infections, and its success has been demonstrated in several clinical studies. To date, there is no universal or consensus drug desensitization protocol for hypersensitivity reactions to beta-lactam antibiotics. Desensitization for BLs must always be performed by specialized teams, led by physicians specializing in allergy and immunology, in a hospital setting with resuscitation equipment readily available.[11-13]

Our study has already enrolled approximately 200 pregnant women. Interim analysis of 165 participants identified 81 (49.1%) with a clinical history of high risk for anaphylaxis, all of whom were desensitized; the remaining 84 had a low-risk clinical history and negative skin tests and underwent challenge. Intradermal tests were positive in 11 of 165 patients (6.7%), all with a high-risk clinical history. Positive intradermal tests were significantly associated with the development of reactions during desensitization ($p < 0.0001$). Indeed, only one patient with a negative test reacted during desensitization. Only two patients had positive allergen-specific IgE: one had a reaction to penicillin rechallenge, while the other did not. All 84 patients (50.9%) considered low-risk were subjected to provocation testing. Only three reacted: two (2.4%) had immediate hypersensitivity reactions, while one had a delayed reaction (1.2%). The diagnosis of penicillin allergy was confirmed in 9.7% of our patients. The algorithm showed 98.8% efficacy, and only two patients could not have their infection treated with penicillin. The overall safety of the algorithm was 92.1%, considering that only 13 patients developed hypersensitivity reactions upon re-exposure to penicillin, 10 of whom had mild reactions.

We invite the readers of AAAI to learn more about this project. Should you be interested in having your department, clinic, or practice participate, we will be happy to answer questions and assist with implementation, as we are seeking to conduct a multicenter study. Science extends far beyond classrooms and laboratory benches, as clinical studies allow us to confirm our hypotheses in a reproducible manner. We hope this message and our study will encourage readers to become investigators.

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Patients with chronic rhinosinusitis and serum IgE greater than 1,000 ng/mL have a higher prevalence of allergic bronchopulmonary aspergillosis (ABPA) and nonsteroidal anti-inflammatory drugs exacerbated respiratory disease

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Chronic rhinosinusitis (CRS) is defined as a mucosal inflammation associated with tissue remodeling that persists for ≥ 12 weeks.[1] There are different phenotypes and endotypes of CRS patients. According to EPOS,[1] phenotypes are organisms distinguishable from others by clinical features, such as having or not having polyposis, while endotypes are features within an individual, such as elevated serum IgE. Elevated serum IgE is a T2 response marker of the nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) phenotype, as well as other diseases, such as hyper-IgE syndrome and allergic bronchopulmonary aspergillosis (ABPA).

When eosinophilic nasal polyps are related to asthma or respiratory reactions to aspirin or other nonsteroidal anti-inflammatory drugs, the patient may present N-ERD. The prevalence of N-ERD varies from 1.8% to 44%.[2] Ingesting aspirin or other COX-1 inhibitors triggers upper and lower airway symptoms. Patients with N-ERD are more likely to have severe disease and rapid recurrence of nasal polyps, and their cases are difficult to manage.[3]

Another disease associated with type 2 immunity is ABPA, which is described as an allergic pulmonary condition caused by hypersensitivity to *Aspergillus allergens*, commonly *A. fumigatus*.[4] Symptoms are characterized by difficult-to-treat asthma, hemoptysis, cough, fever, weight loss, and potential death. The community prevalence of ABPA as a complication of asthma is about 5%,[5] while the prevalence of ABPA in patients with severe acute asthma admitted to an intensive care unit can be as high as 39%.[5] In 2019 Patel & Greenberger[6] established a set of minimal essential criteria for ABPA: asthma, immediate cutaneous reactivity to *A. Fumigatus*, and total serum IgE > 1000 ng/mL, plus one of the following: elevated specific IgE or IgG-A. Fumigatus or central bronchiectasis in the absence of distal bronchiectasis. The immune response leads to airway remodeling, inflammation, bronchiectasis, and fibrosis.

Our evidence was collected from a sample of adult patients diagnosed with CRS, but not cystic fibrosis, whose IgE serum was measured and who were followed up in a university hospital. Patients with IgE > 1000 ng/mL underwent diagnostic investigation for ABPA, including: prick test reactivity to *A. fumigatus*, specific IgE *A. fumigatus* measurement, spirometry with a bronchodilator test, anamnesis for asthma diagnosis, and chest computed tomography. To diagnose N-ERD, patients underwent anamnesis and, if needed, an oral aspirin challenge test.[3]

Out of a group of 135 patients diagnosed with CRS whose serum IgE was measured, 13 had IgE > 1000 ng/mL and followed the algorithm (Figure 1). Those with ABPA (3 men and 1 woman) were > 45 years of age at the time of diagnosis. Pulmonary symptoms included cough, wheezing, and purulent sputum. In 2 cases, asthma was confirmed with a pulmonary function test and bronchodilator challenge, with the results ranging from moderate to severe obstructive lung disease. The diagnosis of the other 2 patients was based on clinical history. *A. fumigatus*-specific IgE was measured at admission, with results ranging from 0.35 to 15 µg/mL (median = 4.95). Bilateral bronchiectasis was diagnosed in lung computed tomography in all 4 patients.

The age range of those diagnosed with N-ERD (3 women and 1 man) was 47 to 68 (median = 58) years. Clinical symptoms included nasal manifestations of CRS, with asthma-related nasal polyps, in addition to respiratory symptoms induced by aspirin or other nonsteroidal anti-inflammatory drugs. A pulmonary function test and bronchodilator challenge showed obstructive lung disease in 3 patients. An oral celecoxib challenge test was needed to confirm diagnosis in 1 patient.

Of the 135 patients in the sample, 3% were diagnosed with ABPA. We could find no articles in English or Portuguese describing the prevalence of ABPA in patients with CRS, indicating that it is not suspected, and thus not

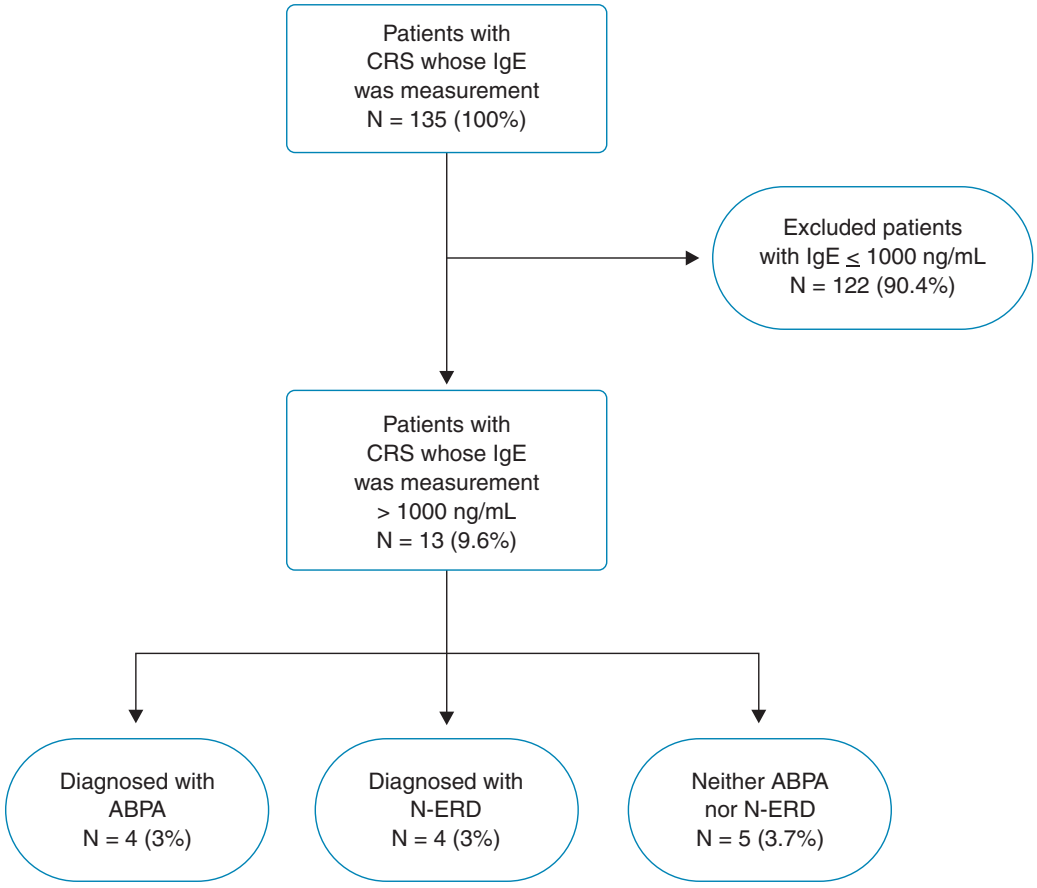

Figure 1
Flowchart of the diagnostic evaluation of patients with chronic rhinosinusitis and serum IgE >1000 ng/mL
ABPA: allergic bronchopulmonary aspergillosis; CRS: chronic rhinosinusitis; IgE: immunoglobulin E; N-ERD: nonsteroidal anti-inflammatory drug-exacerbated respiratory disease.

investigated, among these patients. Of the 13 patients with CRS and IgE > 1000 ng/mL, 30.8% were diagnosed with ABPA. Requesting an affordable blood test and IgE measurement could lead to an active search for ABPA and early treatment, preventing potentially fatal pulmonary lesions.

Since the overall prevalence of N-ERD in this CRS clinic was 10%, the prevalence of N-ERD was 3 times higher in patients with IgE > 1000 ng/mL. This illustrates the importance of an active investigation for the disease, since this diagnosis influences treatment and prognosis.

As a result of the analysis, considering that 61.6% of the patients with IgE > 1000 ng/mL were diagnosed with 1 of the 2 comorbidities, we encourage the measurement of IgE in all patients diagnosed with CRS, as well as careful investigation for ABPA and N-ERD.

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Perioperative anaphylaxis: beyond the operating room

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Dear Editor,

We read with great interest Geller and Wolf's letter to the editor titled “Collaboration between Allergy and Anesthesia”, published in a recent issue of AAAI.[1]

For any patient who has experienced a perioperative hypersensitivity reaction, the safety of any subsequent exposure will depend on the coordinated action between the allergist and the anesthesiologist.

As expressed in CFM Resolution 2174/2017[2] and echoed by Harper[3], it is the duty of the perioperative anesthesiologist to diagnose and treat any critical events, including perioperative hypersensitivity reactions in their varying degrees of severity.

This duty encompasses making a differential diagnosis with other conditions, providing prompt and appropriate with the pharmaceutical armamentarium available at hand, and informing the surgeon of the patient’s true condition so they can decide together whether the procedure can continue as scheduled or should be shortened or terminated. It is also the anesthesiologist’s duty to refer the patient for appropriate further care, whether in the intensive care unit or inpatient ward.

However, the work of this specialist is not done until he or she has drafted a clear, standardized report to be sent to the physician in charge of conducting the post-event workup and leading the case to its ultimate outcome: the allergist.

Garvey and Hopkins[4] published a timely and relevant work regarding the joint work of the allergy and anesthesiology specialties in 2019.

It is paramount that clinicians be aware of where we in Brazil stand on this topic.

In 2018, during the 45th Brazilian Congress of Allergy and Immunology in Recife, the Brazilian Society of Anesthesiology (SBA) requested a meeting with the Board of Directors of the Brazilian Association of Allergy and Immunology (ASBAI) to discuss joint work on the topic of perioperative anaphylaxis, a request which was promptly and kindly granted.

Several initiatives have been undertaken since:

2018 - ASBAI and SBA meet and begin joint work.

2019 - A working group is established to prepare a joint ASBAI and SBA document on perioperative anaphylaxis, which becomes the Update on Perioperative Hypersensitivity Reactions.

2020 - The joint document is published in the journals of both societies.[4-7]

2021 - The ASBAI/SBA Anaphylaxis Project (Projeto Anafilaxia), which seeks to appoint at least one allergist and one anesthesiologist with a special interest in the topic of perioperative anaphylaxis in each state of Brazil, is created.

2022 - The preliminary list of experts and their locations across Brazil is published (Figure 1).

2023 - The Presidents and representatives of both societies meet at the SBA headquarters in Rio de Janeiro to align their goals and publish a Joint Technical Recommendation on tryptase testing.

With their Letter to the Editor focusing on such a relevant topic, Geller and Wolf provided a unique opportunity to raise awareness of the work being carried out jointly by ASBAI and SBA.

Further activities are already in the pipeline for 2024.

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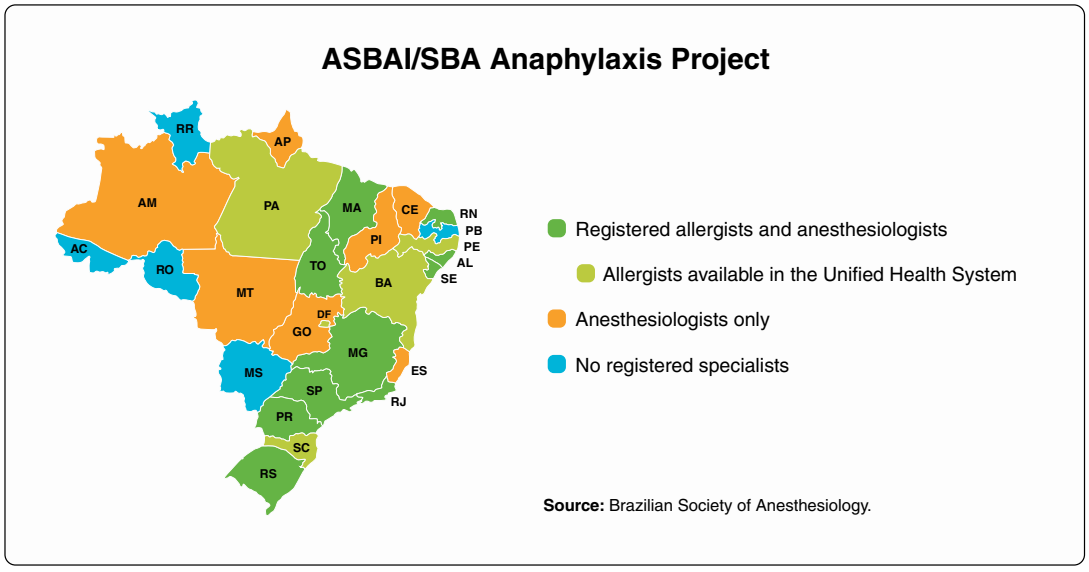

Figure 1
Distribution of specialists across Brazil

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Parabens for allergists

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Dear Editor,

What are parabens?

Parabens are esters derived from para-hydroxybenzoic acid used as preservatives in cosmetics, medicines, personal hygiene and cleaning products, shampoos, and foods. The fungicidal and bactericidal properties of parabens provide protection against microorganisms that may damage product integrity. They are tasteless, odorless, and colorless; furthermore, due to their good availability, efficacy, and low cost, can be combined with other types of preservatives in the same product.[1]

Commercially available parabens include methyl paraben (MP), ethyl paraben (EtP), propyl paraben (PrP), butyl paraben (BuP), and benzyl paraben (BeP). Human exposure to parabens occurs via topical contact or intake of products containing parabens.[2,3]

Due to their water solubility, parabens are the most frequent ingredient in cosmetics and may have a cumulative effect because of continuous dermal exposure.[4] Human exposure to parabens leads to their wide distribution within the body, being detected in samples from several origins, such as urine, serum, breast milk, placental tissue, and amniotic fluid.[5-7]

In Brazil, the Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, Anvisa) establishes the allowed maximum concentrations of each paraben in cosmetics, personal hygiene products, and perfumes.[8]

Balbani, Stelzer and Mantovani selected 35 medications, both over-the-counter and prescription drugs, marketed in Brazil, including several antihistamines in liquid form, to investigate labeling information on preservatives, dyes, sweeteners, and flavorings. The most common preservatives found in these medications were MP and PrP (43% and 35.6%, respectively).[9]

Safety and effects of parabens on the body

Although parabens were classified as "generally recognized as safe" by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA),[10] their safety has been questioned over the last decades, especially because they can cause endocrinological disorders by changing the activity of endogenous hormones and also hormone synthesis, transport, and metabolism, and by having weak estrogenic and antiandrogenic activity.[11] Epidemiological studies showed an association between urinary parabens and adverse health effects, including toxicity in human reproduction, oxidative stress (which may contribute to contact sensitization), immunomodulation, and even breast cancer.[11-13]

Urinary parabens, including MeP, EtP, PrP, BuP, and BeP were measured in 436 children in a birth cohort using gas chromatography with tandem mass spectrometry, in order to the association of exposure to parabens with age, weight z-score, height, weight for height, and body mass index. Significant associations were observed only in boys, suggesting that exposure to parabens may impair physical growth in 3-year-old boys. Further prospective studies are warranted to understand the toxicological mechanisms of paraben exposures and potential risk of children.[14]

Relationship between parabens and allergic diseases

Reactions to parabens are little frequent and usually irrelevant, and the most identified type are allergic contact dermatitis due to the topical use of cosmetics or medicines containing the product. Among the currently used preservatives, parabens are the least allergenic ones.[1]

Exposure to parabens was positively associated with aeroallergen sensitization, an important risk factor for the development, morbidity, and severity of asthma and allergic diseases.[15-17]

Anaphylactic reactions to parabens are uncommon, but urticaria and angioedema have been described in individuals with acetylsalicylic acid intolerance.[18]

The relationship between exposure to parabens and asthma was examined in a cross-sectional study in children aged from 6 to 18 years, and the findings obtained showed significantly higher odds of aeroallergen sensitization with increased urinary PrP and BuP concentrations.[19]

Currently, it is not clear whether parabens induce or aggravate allergies, in addition to contact allergy. A study that examined the relationship between exposure to parabens and prevalence of allergic diseases in Japanese children showed that the prevalence of atopic dermatitis was significantly greater in children with high

urinary concentrations of parabens than in those with low concentrations.[20]

The association between parabens and asthma morbidity was investigated among children with asthma, and with a prevalence of asthma among 4,023 children in the overall U.S. population that participated in the 2005-2014 National Health and Nutrition Examination Survey. Urinary concentrations of paraben biomarkers BuP, EtP, MP, and PP were analyzed with regard to asthma crises and emergency care visits in children with asthma.[21]

Among children with asthma, no associations were observed between any of the parabens and reports of asthma crises or emergency care visits. However, exposure to MP and PP was associated with greater likelihood of reporting emergency care visits due to asthma in the last 12 months among boys with asthma, although boys had lower concentrations of MP and PP biomarkers. Other studies had previously observed a higher frequency of aeroallergen and food sensitization in boys.[21]

Sexual dimorphism was also reported for pediatric asthma and for emergency care visits, with boys showing higher prevalence of asthma and emergency care visits due to asthma exacerbation, which would bias the interpretation of this association though the action of parabens.[22,23]

No consistent association was identified between prenatal and early-life triclosan or paraben concentrations and childhood asthma, recurrent wheeze, or allergic sensitization, but again male individuals are usually at greater risk than female individuals.[24,25]

Increasing urinary triclosan, MP, and PrP concentrations were associated with increased odds of aeroallergen sensitization and risk of asthma in a representative sample of children aged 6 to 18 years. These chemicals are nonpersistent in the body; therefore, urine concentrations are reflective of exposure at a single time.[25]

These studies of the relationship between allergic sensitization and asthma are cross- sectional, and these associations do not determine causality. Atopic dermatitis was excluded from some studies. Urinary paraben concentrations vary throughout time, and a single determination may result in misinterpretation. In general, the presence of asthma and eczema was based on information from parents and on a standardized questionnaire, and other environmental exposures, besides parabens, may have interfered with the described observations.[26,27]

The history of preservatives dates back to the 1930s and, ironically, parabens, which the industry sought to replace with “safer” alternatives, are still the most used biocides in cosmetics and seem to be much less sensitizing than newer agents. The frequency of sensitivity to this widely used biocide has remained low and notably stable for many decades, despite its extensively and progressively expanding use worldwide.[26,27]

Conclusion

Parabens are preservatives used in foods, medicines, and cosmetics, being considered safe by the Brazilian regulatory agency and by agencies of other countries. Parabens cause allergic contact dermatitis, and other reactions are rare, despite their growing use. Further studies are warranted to establish some association between parabens and asthma/atopic dermatitis, as well as endocrinological disorders and others.

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