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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Weaving the morning

Tecendo um(a)manhã

Emanuel Sávio Cavalcanti Sarinho[1]

The mission of the Brazilian Association of Allergy and Immunology (ASBAI) is to promote continuing medical education and disseminate scientific knowledge in the field of Allergy and Immunology, as well as to strengthen professional practice excellence in the specialty in the public and private sectors and to communicate to society the importance of prevention and treatment of allergic and immunologic diseases.

Our journal "Arquivos de Asma, Alergia e Imunologia" is an essential pillar in the mission of our association and must be increasingly valued and improved. The "Letter from São Paulo" and "Practical guide for the treatment of severe atopic dermatitis" are two special articles in this final 2022 issue, which stand out for their importance in clinical practice and equity of care for our patients.

The Letter from São Paulo entitled "Treating patients with allergic diseases in the Brazilian Unified Health System"[1] represents an important advance in demonstrating that up to one-third of the population may need care for allergic conditions. The Letter argues and consolidates the urgent and necessary action of Allergy and Immunology specialists in a more attentive and effective way in the Brazilian Unified Health System, who should always act with a focus on valuing and integrating with primary care, promoting adequate care delivery and prevention.

The second special article entitled "Practical guide for the treatment of severe atopic dermatitis"[2] is based on the best available evidence, from the perspective of precision medicine, always considering the reality of our continent-sized country. This official document has been developed jointly by ASBAI and the Brazilian Society of Pediatrics (SBP) and will be considered the gold standard guidelines for the management of severe forms of atopic dermatitis. The specialists from these two societies have done an outstanding job to offer us an experience of peer review and development of a scientific article that covers all age groups affected by the disease, consistent with the social reality of the country.

The review article "Our everyday immune system and today's pesticides,"[3] in addition to delving into the topic of possible immunological repercussions, also warns us that we are an inherent part of nature. The article "New perspectives in immunotherapy: the importance of dendritic cells in allergen-specific immunotherapy"[4] highlights the role of innate immunity, which is being progressively more investigated and better understood.

1. President of ASBAI 2021-2022.

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The original articles "Provocation tests for chronic inducible urticaria: the experience of a urticaria center of reference and excellence - UCARE,"[5] "Combination of intranasal fluticasone and azelastine for difficult-to-control allergic rhinitis in adolescents,"[6] and "Immediate adverse events to the yellow fever vaccine in egg-allergic children"[7] reveal that our journal, as it advances in scientific robustness, is becoming a new space for the dissemination of original scientific knowledge produced in the country in our field.

The articles published in "Arquivos de Asma, Alergia e Imunologia" can now be accessed in full directly via the LILACS platform, and the English version will appear in the Google Scholar search engine, which is an important step towards the internationalization of the journal with the desire to soar higher and higher.

Finally, we have reached the end of another term experiencing the joy of a successful journey and the certainty of having advanced in the process of inclusion and strengthening of the association, as well as in the improvement of scientific knowledge within the specialty of Allergy and Immunology in Brazil, because after all we are a scientific community association, and this is the mission of ASBAI.

This issue of the journal is full of relevant scientific communication, and we are therefore celebrating the Golden Jubilee of our specialty with much learning. ASBAI is growing term after term thanks to the National Board, the Regional Boards, the Scientific Departments, the Statutory and Special Committees and also to its associates, because ASBAI exists *to you*, *for you* and *with you*. And this continuous growth is the result of the joint work of everyone who weaves a morning that increasingly elevates our specialty.

"...

And growing larger, becoming cloth,
pitching itself a tent where they all may enter,
inter-unfurling itself for them all, in the tent
(the morning) which soars free of ties and ropes —
the morning, tent of a weave so light
that woven, it lifts itself through itself: balloon light."

João Cabral de Melo Neto
translated by Galway Kinnell

Thank you all for everything!

References

1. Serpa FS, de-Mello LM, Souza PS, Chiabai J, Silva EC, Mello YAM, et al. Assistência a pacientes com doenças imunoalérgicas no Sistema Único de Saúde brasileiro – Carta de São Paulo. Arq Asma Alerg Imunol. 2022;6(4):427-31.
2. Prado E, Pastorino AC, Harari DK, Mello MC, Chong-Neto H, Carvalho VO, et al. Dermatite atópica grave: guia prático de tratamento da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria. Arq Asma Alerg Imunol. 2022;6(4):432-67.
3. Saldanha CT, Rosa LGF, Uchôa SVS, Motizuki AHN, Brito TS, Lima APA, et al. Nosso sistema imune de cada dia e os agrotóxicos de hoje. Arq Asma Alerg Imunol. 2022;6(4):491-8.
4. Vigoritto MA, Pradez G. Novas perspectivas em imunoterapia: a importância das células dendríticas na imunoterapia alérgeno-específica. Arq Asma Alerg Imunol. 2022;6(4):499-503.
5. Azizi GG, Dortas-Junior SD, Bastos-Junior RM, França AT, Valle SOR. Testes de provocação para urticárias crônicas induzidas: a experiência de um centro de referência e excelência em urticária - UCARE. Arq Asma Alerg Imunol. 2022;6(4):504-10.
6. Wandalsen GF, Albuquerque CB, Calvo FP, Cunha DT, Medeiros LC, Solé D. Combinação fluticasona e azelastina intranasal no tratamento de adolescentes com rinite alérgica de difícil controle. Arq Asma Alerg Imunol. 2022;6(4):511-8.
7. Guimarães BNA, Petraglia TCMB, Marinho AKBB, Barbosa ADM. Eventos adversos imediatos à vacina febre amarela em crianças alérgicas ao ovo. Arq Asma Alerg Imunol. 2022;6(4):519-26.

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Treating patients with allergic diseases in the Brazilian Unified Health System – Letter from São Paulo

Assistência a pacientes com doenças imunoalérgicas no Sistema Único de Saúde brasileiro – Carta de São Paulo

Faradiba Sarquis Serpa[1], Luane Marques de Mello[2], Phelipe dos Santos Souza[3], Joseane Chiabai[4], Eduardo Costa Silva[5], Yara Arruda Marques Mello[6], José Luiz Magalhães Rios[7], Marilyn Urrutia-Pereira[8], Eliane Miranda da Silva[9], Marta de Fátima Rodrigues da Cunha Guidacci[10], Emanuel Sávio Cavalcanti Sarinho[11], Norma de Paula M. Rubini[12], Dirceu Solé[13]

ABSTRACT

The Brazilian Unified Health System covers all levels of health care and guarantees full, universal and free access for the entire population. The demographic and epidemiological transitions observed in recent decades have led to a higher prevalence of allergic diseases. In this context, implementing health policies to benefit these patients has become a challenge. To discuss health care for patients with allergic and immunological diseases in Brazil, the Brazilian Association of Allergy and Immunology (ASBAI) held a forum in São Paulo on August 26, 2022 called "Treating Patients with Allergic Diseases in the Unified Health System". The event's panels included members of ASBAI, representatives of the federal government, the attorney general's office, patients, and health professionals from various services with experience in successful programs for patients with allergic diseases. It was concluded that there are still many unmet health care needs for Brazilians with allergic and immunological diseases. ASBAI is contributing to the organization, implementation, and maintenance of care for these patients within the scope of the Unified Health System.

Keywords: Allergy, immunology, Brazilian Unified Health System, management, public health.

RESUMO

O Sistema Único de Saúde (SUS) abrange todos os níveis de atenção à saúde e garante acesso integral, universal e gratuito para toda a população brasileira. As transições demográfica e epidemiológica observadas nas últimas décadas trouxeram um cenário de maior prevalência das doenças imunoalérgicas. Nesse contexto, a implementação de políticas de saúde voltadas à assistência à saúde dessa população tornou-se um desafio. Com o objetivo de discutir a atenção à saúde dos pacientes com doenças alérgicas e imunológicas no Brasil, a Associação Brasileira de Alergia e Imunologia (ASBAI) realizou em 26 de agosto de 2022, na cidade de São Paulo, o Fórum sobre a Assistência a Pacientes com Doenças Imunoalérgicas no SUS. O evento foi estruturado no formato de painéis e contou com a participação de membros da ASBAI e representantes da gestão pública federal, do Ministério Público, de sociedade de pacientes e profissionais de saúde de diversos serviços com experiência em programas e projetos bem sucedidos na assistência a pacientes com doenças imunoalérgicas. Após a discussão, concluiu-se que ainda existem muitas necessidades não atendidas em relação à atenção à saúde da população com doenças alérgicas e imunológicas no Brasil. A ASBAI tem trabalhado no sentido de contribuir para organizar, implantar e manter a assistência a estes pacientes no âmbito do SUS.

Descritores: Alergia, imunologia, sistema único de saúde, gestão, saúde pública.

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Introduction

The Brazilian Unified Health System (SUS) is one of the largest and most complex public health systems in the world, covering all levels, from primary care to organ transplants, guaranteeing full, universal, and free access to health care for the entire population.[1,2]

Since its establishment in 1990, SUS has progressively expanded the health services offered to the population[2]. However, in recent decades the accelerated demographic transition has led to an increasing proportion of older adults, resulting in an epidemiological transition involving a higher prevalence of chronic diseases,[3] including immunoallergic diseases.

To address these changes, in 2011 the Brazilian Ministry of Health initiated a Strategic Action Plan for Combating Chronic Noncommunicable Diseases to promote effective public policies for the prevention and control of these diseases and their risk factors. The plan covers the four main chronic disease groups (cardiovascular disease, cancer, chronic respiratory disease, and diabetes). However, the only recognized chronic respiratory disease of allergic etiology was asthma, included in the proposal "to structure and strengthen notification of severe asthma cases".[4]

Globally, the epidemiological transition has been accompanied by great technological advances in diagnosing and treating immunoallergic diseases, which have allowed earlier and more accurate diagnosis and treatment with targeted therapies for severe and complex cases. However, uniform access to these technologies in Brazil, one of the largest countries in the world, is hampered by territorial, populational, and funding issues. To ensure the health of the Brazilian population by reducing morbidity and mortality from immunoallergic diseases, care goals must be determined and health surveillance must be increased.

Such actions could also significantly improve the use of human and financial resources in SUS. Both the Strategic Action Plan for Combating Chronic Noncommunicable Diseases and the optimization of human and financial resources in health care are objectives of the United Nations' Sustainable Development Goal (Agenda 2023) to ensure a healthy life and promote well-being for people of all ages.[5]

Since SUS was founded, little progress has been made in the standardization of care for patients with immunoallergic diseases. Although the incorporation of new technologies has not kept pace with recent developments, the following should be mentioned: the second update of the 2021 Clinical Protocol and Therapeutic Guideline for Asthma included 2 new technologies for severe cases; a clinical protocol and therapeutic guidelines for cow's milk protein allergy, as well as an oral provocation test for patients ≤ 2 years of age have been implemented; and a neonatal screening test for primary immunodeficiencies, currently called inborn errors of immunity, has been incorporated. Primary care asthma treatment guidelines have also been published recently.

However, other immunoallergic diseases remain "invisible" to SUS, especially (1) anaphylaxis, which involves the risk of death if not treated properly, (2) chronic urticaria, and (3) moderate and severe atopic dermatitis, which greatly compromise quality of life

and incur considerable health costs, both direct and indirect. Studies conducted in several countries, including Brazil, have confirmed the high cost of these and other immunoallergic diseases, such as asthma and food allergies, to the health system.[6-18] In addition, for rare diseases, including inborn errors of immunity, diagnostic and treatment resources are scarce outside of centers of excellence and the southern and southeastern regions of the country. Thus, health policies must establish a support network that includes early diagnosis by primary care professionals and the establishment of treatment flow processes.[19]

To fill in treatment gaps, local asthma programs have been developed in recent decades and have led to occasional improvements in patient care, although many have been dismantled for political or other reasons. Specialist societies have come together to demand the creation of a National Asthma Program with standardized treatment flow and access, but they were unsuccessful.[20] Similarly, a request by the Brazilian Association of Allergy and Immunology to classify anaphylaxis as a notifiable condition was rejected. Regarding atopic dermatitis and chronic urticaria, standardizing care through the development of a clinical protocol and therapeutic guidelines would facilitate adequate diagnosis and treatment and reduce judicial impediments to obtaining them.

In this context, the Brazilian Association of Allergy and Immunology, whose mission is to strengthen professional practice (both public and private) within the specialty, held a forum to discuss immunoallergic disease treatment in SUS (itinerary shown in Figure 1). The event brought together representatives of different institutions, who reviewed the unmet needs in our specialty and discussed the importance of planning care actions and health surveillance for immunoallergic diseases.

A proposal emerged from the Forum for networking between representatives of the Brazilian Association of Allergy and Immunology, the National Council of State Health Secretaries, the National Council of Municipal Health Secretaries, patient representatives, and representatives of the Public Prosecutor's Office to develop health policies for immunoallergic disease treatment. Networking was considered a viable means of collaborating to achieve a common goal.[1] After the discussion, the following strategies were proposed:

– mapping current treatments for immunoallergic diseases in different regions of the country;
– strengthening primary care for immunoallergic diseases through continuing education for health teams;
– expanding the care network by developing specialized outpatient clinics in SUS and associated networks;
– implementing sentinel registry/surveillance of chronic and/or severe allergic diseases;
– adding questionnaires on asthma and atopic dermatitis to the Chronic Disease Risk and Protective Factors Telephone Survey system[21,22];
– reviewing and updating SUS' list of immunoallergic diseases;
– promoting discussion forums on successful municipal and state experiences that can be used as models for different scenarios.

Final considerations

There are many unmet health needs among SUS users with allergic and immunological diseases. The board of directors and committees of the Brazilian Association of Allergy and Immunology have been actively positioning themselves to positively influence decisions to benefit this entire community of patients. The Forum unanimously agreed that networking could help promote health policies that organize, implement, and maintain care for SUS patients with immunoallergic diseases. The great value of a universal health system like SUS was also recognized by all, which, despite chronic underfunding and other difficulties, is ensuring the right to health for the entire population.

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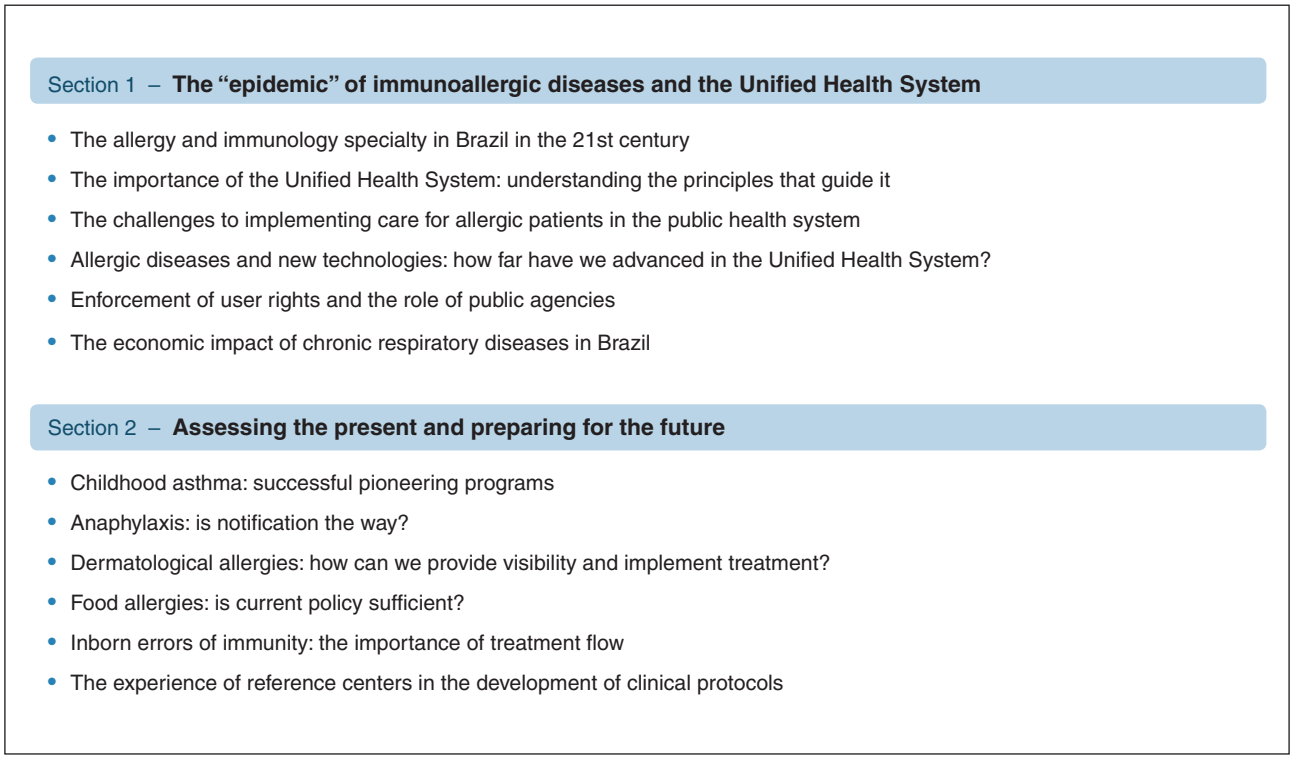

Figure 1
Itinerary of the "Treating Patients with Allergic Diseases in the Unified Health System" Forum

References

1. Mendes EV. Desafios do SUS. Brasilia, DF. CONASS, 2019, 869p. Available at: https://docs.bvsalud.org/biblioref/2020/08/1104190/desafios-do-sus.pdf. Accessed on: 10/20/2022.
2. Martins TCF, Silva JHCM, Máximo GC, Guimarães RM. Transição da morbimortalidade no Brasil: um desafio aos 30 anos de SUS. Ciênc Saúde Coletiva. 2021;26(10):4483-4496. doi.org/10.1590/1413-812320212610.10852021.
3. Duarte EC, Barreto SM. Transição demográfica e epidemiológica: a Epidemiologia e Serviços de Saúde revisita e atualiza o tema. Epidemiol Serv Saúde. 2012;21(4):529-32. doi.org/10.5123/S1679-49742012000400001.
4. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise em Saúde e Vigilância de Doenças Não Transmissíveis. Plano de Ações Estratégicas para o Enfrentamento das Doenças Crônicas e Agravos não Transmissíveis no Brasil 2021-2030. Available at: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/publicacoes-svs/doencas-cronicas-nao-transmissiveis-dcnt/09-plano-de-dant-2022_2030.pdf. Accessed on: 10/20/2022.
5. Organização das Nações Unidas (ONU). Objetivos de Desenvolvimento Sustentável da ONU. Available at: https://brasil.un.org/pt-br/sdgs. Accessed on: 10/20/2022.
6. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. J Invest Dermatol. 2017;137(1):26-30. doi: 10.1016/j.jid.2016.07.012.
7. Igarashi A, Yuasa A, Yonemoto N, Kamei K, LoPresti M, Murofushi T, et al. A Systematic Literature Review of Economic Evaluations and Cost Studies of the Treatment of Psoriasis, Atopic Dermatitis, and Chronic Urticaria. Dermatol Ther (Heidelb). 2022;12(8):1729-51. doi: 10.1007/s13555-022-00774-2.
8. Weller K, Maurer M, Grattan C, Nakonechna A, Abuzakouk M, Bérard F, et al. ASSURE-CSU: a real-world study of burden of disease in patients with symptomatic chronic spontaneous urticaria. Clin Transl Allergy. 2015;5:29. doi: 10.1186/s13601-015-0072-9.
9. Ensina LFC, Sano F, Silva EK, Rubini NPM, Solé D. Omalizumabe no tratamento da urticária crônica espontânea: análise de custo-efetividade e impacto orçamentário. Arq Asma Alerg Imunol. 2019;3(1):51-63. doi: 10.5935/2526-5393.20190010.
10. Santos PFAM, Kuschnir FC, Dias GAC, Ruiz VP, Junior SCG, Silva ECF. Carga econômica da urticária crônica no Brasil: um estudo de vida real no período de 1 ano. Arq Asma Alerg Imunol. 2020;4(4):447-57. doi: 10.5935/2526-5393.20200067.
11. Guest JF, Yang AC, Oba J, Rodrigues M, Caetano R, Polster L. Relative cost-effectiveness of using an extensively hydrolyzed casein formula in managing infants with cow's milk allergy in Brazil. Clinicoecon Outcomes Res. 2016;8:629-639. doi: 10.2147/CEOR.S113448.
12. Bilaver LA, Chadha AS, Doshi P, O'Dwyer L, Gupta RS. Economic burden of food allergy: A systematic review. Ann Allergy Asthma Immunol. 2019;122(4):373-380.e1. doi: 10.1016/j.anai.2019.01.014.
13. Alsaggaf A, Murphy J, Leibel S. Estimating cost-effectiveness of confirmatory oral food challenges in the diagnosis of children with food allergy. Glob Pediatr Health. 2019;6:2333794X19891298. doi: 10.1177/2333794X19891298.
14. Sullivan PW, Ghushchyan VH, Slejko JF, Belozeroff V, Globe DR, Lin SL. The burden of adult asthma in the United States: evidence from the Medical Expenditure Panel Survey. J Allergy Clin Immunol. 2011;127(2):363-369.e1-3. doi: 10.1016/j.jaci.2010.10.042.
15. Accordini S, Corsico AG, Braggion M, Gerbase MW, Gislason D, Gulsvik A, et al. The cost of persistent asthma in Europe: an international population-based study in adults. Int Arch Allergy Immunol. 2013;160(1):93-101. doi: 10.1159/000338998.

16. Stirbulov R, Lopes da Silva N, Maia SC, Carvalho-Netto E, Angelini L. Cost of severe asthma in Brazil-systematic review. J Asthma. 2016;53(10):1063-70. doi: 10.3109/02770903.2016.1171338.
17. Costa E, Caetano R, Werneck GL, Bregman M, Araújo DV, Rufino R. Estimated cost of asthma in outpatient treatment: a real-world study. Rev Saude Publica. 2018;52:27. doi: 10.11606/S1518-8787.2018052000153.
18. Sano F, Ensina LFC, Rubini NPM, Solé D. Avaliação de custo-efetividade e impacto orçamentário do tratamento adicional de omalizumabe em pacientes com asma alérgica grave não controlada. Arq Asma Alerg Imunol. 2019;3(1):37-50. doi: 10.5935/2526-5393.20190009.
19. Serpa FS, Cruz AAS, Neto AC, Silva ECF, Franco JM, Mello JML, et al. O atendimento médico de pacientes com doenças imunoalérgicas no Brasil: reflexões e propostas para a melhoria - Carta de Belo Horizonte. Arq Asma Alerg Imunol. 2017;1(4):327-34.
20. Silva LC, Freire LM, Mendes NF, Lopes AC, Cruz A. Carta de Salvador. J Pneumol. 2002;28(suppl 1):S2. doi: 10.1590/S0102-35862002000700002.
21. Valle SO, Kuschnir FC, Solé D, Silva MA, Silva RI, Da Cunha AJ. Validity and reproducibility of the asthma core International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire obtained by telephone survey. J Asthma. 2012 May;49(4):390-4.
22. Oliveira EF, Penedo C, Valle SOR, Kuschnir FC. Validation and reproducibility of the International Study of Asthma and Allergies in Childhood (ISAAC) Written Atopic Eczema Questionnaire for telephone survey in children aged 6-7 years. An Bras Dermatol. 2022 Mar-Apr;97(2):173-8.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Severe atopic dermatitis: a practical treatment guide from the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics

Dermatite atópica grave: guia prático de tratamento da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria

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ABSTRACT

Atopic dermatitis is a chronic, common, and complex inflammatory skin disease with a multifactorial etiology. It manifests clinically with often disabling pruritus, recurrent eczema-like lesions, and xerosis, and can progress to lichenification. Although understanding of the disease's pathophysiology has been growing in recent years, severe forms are still frequent and represent a challenge for clinicians. A non-systematic review of the literature on severe atopic dermatitis refractory to conventional treatment was conducted to develop the present guide, whose purpose is to help clarify the mechanisms involved in the disease and possible risk factors. The integrity of the skin barrier is fundamental for maintaining skin homeostasis. In addition to general care, patients should avoid triggering and/or irritating agents and moisturizers and seek emotional support, etc.; the use of topical and/or systemic anti-inflammatory/immunosuppressive agents was also reviewed. New agents, immunobiologicals, and small molecules have led to a broader range of therapies for patients with severe forms of the disease, especially cases refractory to conventional treatment.

Keywords: Atopic dermatitis, skin hydration, topical corticosteroids, calcineurin inhibitors, cyclosporine, immunobiologicals, dupilumab, JAK inhibitors.

RESUMO

A dermatite atópica (DA) é uma doença cutânea inflamatória, crônica, comum, complexa e de etiologia multifatorial, que se manifesta clinicamente com prurido muitas vezes incapacitante, lesões recorrentes do tipo eczema, xerose e que pode evoluir para liquenificação. Embora o conhecimento sobre a sua fisiopatologia venham crescendo nos últimos anos, ainda as formas graves são frequentes e representam um desafio para o clínico. Para o presente guia realizou-se revisão não sistemática da literatura relacionada à DA grave refratária aos tratamentos habituais com o objetivo de elaborar um documento prático e que auxilie na compreensão dos mecanismos envolvidos na DA, assim como dos possíveis fatores de risco associados à sua apresentação. A integridade da barreira cutânea é um dos pontos fundamentais para a manutenção da homeostase da pele. Além dos cuidados gerais: evitação dos agentes desencadeantes e/ou irritantes, o uso de hidratantes, suporte emocional, entre outros, o uso de agentes anti-inflamatórios/imunossupressores de uso tópico e/ou sistêmico também foi revisado. A aquisição de novos agentes, os imunobiológicos e as pequenas moléculas, melhorou a terapêutica para os pacientes com formas graves de DA, sobretudo as refratárias aos tratamentos convencionais.

Descritores: Dermatite atópica, hidratação da pele, corticosteroides tópicos, inibidores da calcineurina, ciclosporina, imunobiológicos, dupilumabe, inibidores de JAK.

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Introduction

Atopic dermatitis (AD) is a chronic, common, and complex inflammatory skin disease with a multifactorial etiology. It manifests clinically with often disabling pruritus, recurrent eczema-like lesions, and xerosis, and can progress to lichenification. Distribution and morphology of the skin lesions are variable, onset is generally before 2 years of age, and patients have personal and family history of atopic disease.[1]

In the absence of a conclusive diagnostic laboratory test and because of the great variation in the signs and symptoms observed in different geographic regions and at different ages, diagnosis of AD is based on the presence and distribution pattern of the lesions in combination with clinical findings and the personal and family history of atopic disease. For some time, the Hanifin-Rajka criteria have been the most widely used for diagnosis (Table 1).[2] This diagnostic definition comprises 4 major criteria and 22 minor criteria. Presence of at least three major criteria and three minor criteria identifies an AD patient.[2]

Other diagnostic criteria have been introduced since: the Williams criteria[3] (Table 2) and, more recently, the American Academy of Dermatology criteria, which added a number of exclusionary criteria that must be ruled out to diagnose AD with greater precision (Table 3).[4]

Globally, studies of AD prevalence have predominantly concentrated on the pediatric population and studies in adults are rarer. The heterogeneous nature of the samples studied, the age groups, and the criteria employed all contribute to discrepancies in the results reported.[5,6]

The study of AD prevalence that has covered the largest numbers of countries and research centers is the International Study of Asthma and Allergies in Childhood (ISAAC). It was conducted at 154 different centers in 56 countries including more than 750,000

Table 1
Principal signs, symptoms, and laboratory data used to diagnose atopic dermatitis according to the Hanifin-Rajka criteria[2]

Major criteria (≥ 3)
1. Pruritus
2. Typical morphology and distribution of lesions – Flexural lichenification or linearity in adults – Facial and extensor involvement in children
3. Chronic or chronically relapsing dermatitis
4. Personal or family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis)

Minor criteria	
1. Xerosis	12. Anterior subcapsular cataracts
2. Ichthyosis, palmar hyperlinearity, keratosis pilaris	13. Orbital darkening
3. Positive prick-test	14. Facial pallor or erythema
4. Raised serum IgE	15. Pityriasis alba
5. Tendency to cutaneous infections (*S. aureus*/Herpes)	16. Itch when sweating
6. Tendency to non-specific hand or foot dermatitis	17. Anterior neck folds
7. Nipple eczema	18. Intolerance to wool and lipid solvents
8. Cheilitis	19. Perifollicular accentuation
9. Recurrent conjunctivitis	20. Food intolerance
10. Dennie-Morgan infraorbital fold	21. Course influenced by environmental or emotional factors
11. Keratoconus	22. White dermographism

children in two different age groups (6-7 years and 13-14 years) and administering a standardized instrument at different points in time. The study reported previous 12 months AD prevalence for the 6-7 years age group ranging from 0.9 in India to 22.5% in Ecuador and prevalence in the 13-14 group ranging from 0.2% in China to 24.6% in Colombia. In Brazil, phase III of the ISAAC study reported an 8.2% mean prevalence of eczema for 6-7 year-olds and 5.0% for 13-14 year-olds.[7] The prevalence of severe forms was around 1.5% in both age groups.[7]

Among infants (12 to 15 months), the International study of Wheezing in Infants (EISL) documented elevated rates in children from Europe and Latin America, at 14.2% and 18.2% respectively.[8,9] A recent systematic review assessed 378 studies with sufficient quality for the analysis, of which 352 investigated prevalence and just 26 reported incidence of AD, the majority in children. The overall AD prevalence in children ranged from 1.7% to 32.8%, while the previous year prevalence with a physician diagnosis was from 0.96% to 22.6%. In adults, overall prevalence varied from 1.2% to 9.7% and the previous year prevalence with a physician diagnosis ranged from 1.2% to 17.1%.[10]

Table 2
UK Working Party's atopic dermatitis diagnostic criteria – The Williams Criteria[3]

Skin pruritus during the last 12 months with ≥ 3 of the following criteria:
1. Onset under the age of 2 [a]
2. History of flexural involvement
3. Visible flexural dermatitis (or photo)
4. Personal/family history of asthma and allergic rhinitis [b]
5. History of generalized dry skin

[a] Not used in children < 4 years.
[b] In children < 4 years, family history of atopic diseases.

Table 3
Essential criteria, important findings, and associated features used to diagnose atopic dermatitis by the American Academy of Dermatology[4]

Essential criteria
Pruritus
Eczema (acute, subacute, or chronic) with typical morphology and age-specific patterns and with chronic or relapsing history
Important findings – help with diagnosis in many cases
Early onset
Atopic disease – personal or family, elevated IgE
Xerosis
Associated findings – useful, but nonspecific
Facial pallor, white dermographism, keratosis pilaris, pityriasis alba, ichthyosis, hyperlinear palms, ocular/periocular changes, perioral or auricular changes, lichenification
Conditions that should be ruled out
Scabies
Seborrheic dermatitis
Contact dermatitis (irritant or allergic)
Ichthyosis
Cutaneous T-cell lymphoma
Psoriasis
Photosensitivity dermatosis
Innate errors of immunity
Other causes of erythroderma

Atopic dermatitis has a considerable impact on the quality of life of patients and their families, especially in its moderate and severe forms. It is associated with many atopic comorbidities (allergic rhinitis, asthma, food allergies, and eosinophilic esophagitis) and also with several non-atopic comorbidities, in particular those involving mental health, with frequent associations with depression and anxiety. Over recent years, innovative systemic treatments have become available, including immunobiologicals and small molecules, which act selectively to inhibit cytokines that participate in the AD inflammatory process. These new drug classes offer superior efficacy and safety compared to systemic immunosuppressants and herald a new era in treatment for severe AD. The objective of this guide is to update treatment of severe AD, with a primary focus on the rationale underlying use of biologicals and small molecules.

Clinical features: natural history and phenotypes

In all patients with AD, the characteristic lesion is eczema and pruritus is an obligatory finding.[11] However, the clinical manifestations seen in patients with severe AD are amplified expressions of the clinical presentation of AD and the signs and symptoms are hugely exacerbated. Over the course of life, AD clinical presentation is variable and can be divided into four segments, as described below.

Dermatitis of the infant (0-2 years)

Lesions have onset around 2 months after birth, involving the face (cheeks), scalp, trunk, and extensor surfaces of the limbs. Acute lesions develop vesicles, exudate, scabs, and erythema. Xerosis is common and is observed in around 42% of patients.[12,13]

Dermatitis in the child (pre-pubertal, 2 to 12 years)

The flexor surfaces become more involved, in particular the popliteal fossa and cubital fossa. Hands and wrists may be more involved. The number of subacute, dry, and thickened lesions increases. Chronic lesions with some degree of lichenification may also be observed.[12,13]

Dermatitis in the adult (12-60 years)

Lesions are more widely distributed. In addition to flexural lesions, the head, neck, and hands may be involved. Xerosis is the most common skin complication in patients with AD, and persistence of dry skin can compromise the skin's barrier function and lead to changed microbiota. Lesions are chronic and lichenified, and patients may suffer from acute crises and an increased risk of viral infections.[12,13]

Dermatitis in the elderly adult (over 60 years)

This form is primarily characterized by extensive eczematous lesions and some patients may also have erythroderma with a strong pruriginous component. Lesions can sometimes spare flexural areas. This specific subset undoubtedly merits a more in-depth analysis to define clear clinical criteria for diagnosis. It should be emphasized that as with AD of the infant, differential diagnoses must be considered in the elderly, especially in severe cases.

The natural history of AD has been changing over the years, from lesions restricted to the pediatric age group, to a disease that extends into adulthood, and nowadays there are also reports of dermatitis with onset in the sixth decade of life.

Depending on age at onset of AD lesions, the natural history of AD can progress in the ways described below.

1. *Very early onset (3 months to 2 years)* – there are no Brazilian epidemiological studies, but according to the epidemiological studies that do exist, patients with early onset AD can account for from 60% to 80% of all forms of disease onset. A substantial proportion of patients may have full remission before 2 years of age, but around 40% will continue to exhibit the disease for a long time and may constitute a population at greater risk of allergic march.[14-16]
2. *Early onset (2 to 6 years)* – these patients are also at high risk of having other allergic diseases.[14-16]
3. *Childhood onset (6 to 14 years)* – this is a small group of patients and there are few studies that offer understanding of the risks or benefits of AD with onset at this age.[14,15]
4. *Adolescent onset (14 to 18 years)* – a small group of patients with little data in the literature and little information on progression.
5. *Adult onset (20 to 60 years)* – the third largest group of patients, primarily characterized by female patients, with a very mild clinical phenotype and sensitization spectrum, generally accompanied by normal serum IgE levels.[14,15]

6. *Very late onset (> 60 years)* – this is a recently identified group, which has already been separated into two subsets: those who have had AD in the past, followed by a long remission period, and those who first had the disease very late in life. Observational studies describe patients in this group who have a very severe form of the disease and high total serum IgE levels.[14,15]

Different patterns of progression can also be observed in the clinical course and severity of the disease, which can be subdivided into five underlying types: (1) onset in childhood, progressing to remission; (2) relapsing-remitting disease; (3) persistent chronic disease; (4) long periods of remission followed by recurrence; and (5) onset in adolescence or adulthood. Types 3 and 5 are predominantly moderate and severe forms of the disease.[17]

Phenotypes

As already described, the behavior of AD can vary depending on the age at onset of symptoms, but other factors can also influence the course of the disease and define diverse phenotypes. Classifying AD by severity is another approach to delineating phenotypes, but one that involves challenges. It is important to define severity using validated and widely-adopted severity scores (see assessing severity). Attempts have been made to ensure that the two most widely used scores, SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index), can achieve equivalent results, to facilitate standardization and comparability of the population being assessed.

Presence of elevated serum IgE also defines an AD phenotype: *extrinsic* dermatitis, which is present in 80% of cases and is defined by elevated total serum IgE levels with mutation of the filaggrin gene in approximately 30%, presence of other atopic diseases, including food allergy, and a possible association with palmar hyperlinearity. In contrast, *intrinsic* AD is more common in adults, primarily women, and there is a possibility of an association with contact dermatitis, particularly when provoked by nickel.[15,16,18]

Definition of clinical phenotypes of AD also raises important issues for discussion. It must be emphasized that, in addition to the classic clinical presentation of AD, other less usual presentations can also constitute atopic stigmata. These include:[16,18]

– *nummular eczema:* coin-shaped lesions that may be atypical presentations of AD, but it is important to remember that not all patients who develop nummular eczema will actually have the same pathophysiologic basis as AD;
– *prurigo nodularis:* hyperkeratotic and extremely itchy papules, which may or may not be related to AD;
– *eczema located on the eyelids, hands and feet, or nipples or angular cheilitis.* If these clinical presentations are associated with other atopic diseases, they may be interpreted as atypical manifestations of AD. Differential diagnosis is essential in these situations,.

Table 4 lists the possible phenotypes of AD, defined on the basis of age group, age of onset, presence or absence of elevated IgE, disease severity, ethnicity, and classical clinical presentation or otherwise.

Immunopathogenesis

There is now a very large body of knowledge about the physiopathogenesis of AD and the most relevant findings appear to be those involving genetic disorders, changes to the cutaneous barrier, immunological dysregulation, and changes to the cutaneous microbioma.

For many years, it was believed that AD was an "inside-out" disease, i.e., that the inflammatory process started in the dermis, leading to damage to the barrier as a consequence. With current knowledge that the inflammation is caused by or starts with changes to the cutaneous barrier, it became recognized as a disease that is predominantly "outside-in".[20]

Cutaneous barrier

Changes to the cutaneous barrier are caused by many factors. One of the first factors known was destruction of corneocytes by excessive protease actions in corneodesmosomes (washing with alkaline soaps, increased skin pH, staphylococcal infection with production and release of enterotoxins) or because of a failure to inhibit these proteases when they exercise their excessive action. The result is a loss of cellular integrity and cohesion or disarrangement of cells. Corneocytes are keratinocytes from the corneum stratum that produce and release antimicrobial peptides, which are one of the elements of innate immune response. They are important in defense

Table 4
Clinical phenotypes of atopic dermatitis (AD), by clinical characteristics, IgE levels, and ethnicity

Differentiating feature	Classification
Clinical presentation	AD in children or AD in adults
Age at disease onset	Early or late
Presence of elevated IgE	Extrinsic or intrinsic
Severity	Mild, moderate, severe
Ethnicity	Euroamerican or Asian subtypes
Clinical presentation	Classic, nummular eczema, eczema of the hands

against microbial aggression and also produce ceramides and cholesterol, which are components of the natural moisturizing factor. We can therefore state that accelerated destruction of corneocytes increases permeability of the defensive barrier, impairing defense, and also reduces the levels of lipids in the skin.[21]

Reduced levels of filaggrin (because of mutations or acquired deficiencies) and other structural skin proteins, such as loricrin and involucrin, also change the cutaneous barrier. Filaggrins are proteins derived from pro-filaggrins that are found in the deeper layers of the skin and which migrate toward the stratum corneum under the action of keratohyalin granules. Enzymatic activity transforms them into fatty acids and they become an important component of the lamellar lipid layer. Some studies have described filaggrin as a substance that behaves as an intercellular cement that increases adhesion between cells.[22]

Junction proteins are members of the physical barrier that are located immediately below the stratum corneum. Claudins, primarily claudin-1, play an important role in these defenses. Mutations of the claudin gene reduce its expression and increase barrier permeability.[23]

All of these mechanisms, like cell disorganization and reduction of proteins such as filaggrin and claudin are important to explain how the skin defends itself from aggressions or how these changes to the level of the cutaneous barrier compromise the skin's integrity, making it possible for allergens and pathogens to penetrate.

A poor cutaneous microbioma, with low microbial diversity (dysbiosis) and deficiencies of antimicrobial peptides, contributes greatly to cutaneous infections, particularly by staphylococcal strains.[24]

Immunological dysregulation

The injured cutaneous barrier causes release of cytokines such as TSLP (thymic stromal lymphopoietin), interleukin (IL)-33, and IL-25, considered alarmins, which provoke immunological dysregulation at the level of the dermis.

TSLP activates a wide range of cell types, such as type 2 innate lymphoid cells (ILC2) and Th2, characterizing what is known as T2 inflammation.

Th1, Th2, Th17, and Th22 cells are the most important in the pathophysiology of AD because they produce and release substances capable of activating other cells or which themselves have proinflammatory primary activities. Th1 cells participate more in progression of the disease to chronicity and release interferon gamma.

Th2, Th17, Th22, and ILC2 are the cells with primary responsibility for initiating the inflammatory process. These cells release many cytokines and have different actions and play important roles in pathogenesis of the disease.[25]

Studies that have investigated participation of the different subpopulations of T lymphocytes in the inflammatory process have identified four principal endotypes – American/European, Asian, Afroamerican, and pediatric, as summarized in

Table 5. It is important to point out that participation of the Th22, Th17, and Th1 subpopulations is variable, whereas the Th2 subpopulation participates in all of the different phenotypes, defining type 2 inflammation as a fundamental element in the pathogenesis of atopic dermatitis.[26]

IL-4 and IL-13 induce formation of IgE. The higher the levels of these cytokines, the lower the expression of filaggrin, and so they also contribute to reduction of the lipid content of the stratum corneum and, indirectly, to tissue damage. IL-5 activates, differentiates, and supports survival of eosinophils. IL-17 is particular important in exacerbation of barrier injury. This cytokine degrades claudin-1, which is a junction protein that plays a barrier role between the stratum corneum and the stratum granulosum.

IL-22 is a cytokine that participates in the cutaneous remodeling phenomenon, activates fibroblasts, and participates in skin hyperkeratosis and hyperpigmentation. IL-25 stimulates ILC2 and Th2 cells and eosinophils and provokes increased release of IL-31. IL-26, which is produced by Th17 cells, induces production and release of Th2 cytokines, amplifying the inflammatory process.

IL-31 is a very important cytokine in the process underlying cutaneous pruritus, because it activates nerve endings, releasing neurotransmitters such as neuropeptides (substance P and calcitonin gene related peptide [CGRP]).[27] IL-33 stimulates mast cells to release histamine and activates eosinophils and ILC2 cells, increasing IL-4 and IL-13 levels, boosting production of IgE and reducing filaggrin levels.[25] The inflammatory process triggered by the activity of these cells and cytokines reduces expression of the IL-10 released by B lymphocytes.

Bacterial infections are another factor that amplifies the inflammatory process. Staphylococcal enterotoxins, such as type B (SEB), act as superantigens and amplify lymphocyte activity, increasing release of proinflammatory cytokines.[27,28]

Trigger factors and aggravating factors

Several different studies concur that the interaction between genetic predisposition, immunological dysfunction, and environmental trigger factors contributes to the pathophysiology of AD.[29]

In addition to adherence to treatment, exposure to environmental factors, including allergens and stimuli in the workplace and at home, factors linked to lifestyle and temperature, and dysregulation of cutaneous physiology are all related to maintenance and exacerbation of AD. Feeling hot, diaphoresis, wool fibers, psychological stress, food, alcohol, and the common cold are considered particularly important factors in induction and exacerbation of pruritus in AD. Details related to factors of initiation and exacerbation and their specific features are discussed below.[30]

Table 5
Participation of T lymphocyte subpopulations in the different endotypes of atopic dermatitis

	American/European	Asian	Afroamerican	Pediatric
Th2	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Th22	↑↑↑↑	↑↑↑↑	↑↑	↑↑↑
Th17	↑	↑↑↑	absent	↑↑↑
Th1	↑↑	↑↔	absent	absent

↑ = slightly elevated, ↑↑ = elevated, ↑↑↑ = very elevated, ↑↑↑↑ = extremely elevated, ↑↔ = normal or slightly elevated.

Climate and temperature

Studies have associated increased prevalence of AD with places with low humidity, low exposure to UV radiation, and low temperature, or use of indoor heating.[31]

Household pollutants

There is still doubt with relation to the role in AD recurrence played by substances released in homes, such as tobacco smoke, combustion products (biomass, stoves, fireplaces), construction materials, biological sources, and cleaning products,[31] and also with relation to mites.[11]

Atmospheric pollutants

Cohort studies have linked exposure to air pollution to greater prevalence of AD, possibly caused by oxidative stress and damage to the cutaneous barrier caused by these external factors. Therefore, changes to climatic factors such as temperature, humidity, radiation, and air pollution can influence AD response and symptoms.[31]

Exposure to pollutants released by burning fossil fuels has been associated with increased risk of preschool children developing AD.[31] Moreover, particulate material in contact with the skin may promote skin itching, scratching and, alloknesis, an abnormal sensory state in which stimuli that would not normally evoke itching do cause it, and thereby exacerbate AD.

Diet/Food antigens

AD and Food allergy (FA) are common conditions that emerge in childhood and can be intimately linked. Approximately 30% of children with moderate to severe AD also have FA. There is evidence that patients with AD should not be put on unjustified elimination diets. Sensitization to a food (with a positive skin prick test and/or specific serum IgE test) does not signify presence of an allergy and unjustified elimination of this specific food may be prejudicial and cause loss of tolerance with a possibility of anaphylactic shock when it is reintroduced. There is strong evidence for a link between early onset of AD and development of other allergic diseases over the course of the patient's lifetime, known as the allergic march, and many preventative interventions have been suggested, such as use of emollients and early introduction of peanuts and eggs for infants at high risk, which have initially shown promising results for prevention of AD and of peanut and egg allergy.[32] A recent systematic review demonstrated that prophylactic administration of emollients started in early infancy can prevent AD, primarily if used continuously in high-risk populations, but did not prevent FA. It is still debatable whether early introduction of foods prevents FA in at-risk children.[33]

A systematic review followed by meta-analysis assessed the disparate points of view of many patients with AD and their carers. Elimination of certain foods from the diet may lead to a discrete and potentially irrelevant improvement in intensity of eczema, pruritus, insomnia, and poor sleep quality in these patients. This conduct should be evaluated in conjunction with the potential risks of indiscriminate food elimination diets for treatment of AD, especially in babies and small children at risk of developing IgE-mediated food allergy and nutritional deficiencies. Treatment focused on elimination diets leads to under-treatment, in the scenario of the growing number of treatment options now available to treat AD.[34]

Food restrictions (elimination of food allergens) should not be recommended for pregnant women or breastfeeding mothers to prevent emergence of AD. There is a possibility that AD can be exacerbated due to transfer of food allergens such as eggs to infants via breastmilk; but these infants should be carefully diagnosed on the basis of the results of tests of food elimination and food challenges via breastmilk.[35]

Aeroallergens

Aeroallergens can provoke eczematous skin lesions in sensitized patients with AD, which may be because of increased skin permeability caused by inhaled allergens in patients with cutaneous barrier defects. Positive atopic disease contact tests are associated with presence of specific IgE and a positive history of AD flare-up caused by seasonal allergens. Many aeroallergens that provoke AD are derived from *Dermatophagoides pteronyssinus* and *D. farinae* mites. The enzymatic activity of the principal mite allergens destroys the epithelial cell tight junctions in the bronchial mucosa and, therefore, can also worsen skin barrier dysfunction in patients with AD.[36] If these allergens are considered eruption exacerbation factors, they should be carefully assessed, with an in-depth evaluation of medical history, environmental changes, and changes in the characteristics of

eruptions. The evaluation should include the results of elimination tests and challenge tests, if possible, and not be based solely on clinical symptoms or specific IgE assays, or the results of skin prick tests. In common with management of food allergens, elimination of environmental allergens is an adjuvant to pharmacotherapy and skin care.[30]

Many patients report that cutaneous symptoms worsen after contact with animal hair allergens. In the past, it was recommended that patients avoid contact with pets as primary prevention of atopic disease. However, nowadays, only exposure to cat epithelium is considered a risk factor and should therefore be avoided.[29,30] There is no evidence that exposure to dogs increases the risk of AD in children; on the contrary it may even offer protection because of exposure to non-pathogenic microbes.[29,30] Once a patient has become sensitized to a pet and exhibits symptoms after contact, avoidance becomes necessary.[36]

Diaphoresis

Transpiration disorders and excess remnant sweat on the surface of skin exposed to high temperatures and humidity can worsen symptoms of AD. Allergens derived from *Malassezia sp.* found in unevaporated sweat residue can lead to worse symptoms. High temperatures and humidity on the surface of the skin obstruct sweat pores and induce transpiration. To protect against excessive diaphoresis and presence of excessive sweat on the skin, underwear made from breathable and low hygroscopy material is recommended. High temperatures and humidity should be avoided and appropriate measures such as bathing, rinsing with running water, and drying off should be adopted.[37]

Cutaneous infections

Microbiota

The skin is a habitat for a vast collection of microorganisms, including bacteria, virus, fungi, and arthropods. These microorganisms form an ecosystem associated with the favorable habitat, with an abundance of folds, invaginations, and specialized niches. The skin microbiota live in symbiosis with skin immune system factors, performing an essential and complex role in control of skin physiology and immunity.[35]

The role of bacteria

One of the characteristics of AD is that patients have greater bacterial colonization, especially by *Staphylococcus aureus*, which is found on damaged skin in more than 90% of the patients with AD. *S. aureus* plays an important role in pathogenesis of AD, to the extent that treatment to reduce colonization by *S. aureus* reduces disease severity, and this correlates with normalization of pH and transepidermal water loss. The proportion of *S. aureus* in the cutaneous microbioma increases from 35% to 90% during crises, and the severity of AD lesions is associated with the relative density of *S. aureus* colonization of the skin.

In addition to *S. aureus*, the load of other species (*S. epidermidis* and *S. hemolyticus*) is also greatly elevated in the injured skin of patients with AD. In contrast, it has been demonstrated that the inflamed skin of AD patients has notably lower concentrations of *Cutibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium*, and *Prevotella*.

Curiously, the greater concentration of *S. epidermidis* can affect the behavior of *S. aureus* by producing molecules that selectively inhibit colonization by *S. aureus* and increase production of antimicrobial peptides even further.[35]

The role of viruses

Although viral infections of the skin are relatively less common in patients with AD when compared with bacterial infections, diffuse and disseminated viral infections are observed in patients with AD and some of them can be problematic or even fatal. Viral infections that are common in AD include the viruses that cause *eczema herpeticum* (EH), *eczema vaccinatum* (EV), and *eczema molluscatum* (EM). Infection by the *Herpes simplex* virus is common in patients with AD and manifests as a disseminated and distinctly monomorphous eruption of dome-shaped blisters accompanied by fever, indisposition, and lymphadenopathy. Eczema herpeticum can cause serious complications, including keratoconjunctivitis, viremia, meningitis, encephalitis, or secondary bacterial sepsis.[35]

The role of fungi

Fungi also play a role in development and exacerbation of AD. In particular, the role played by *Malassezia* yeasts has been discussed in several studies. *Malassezia sp.* yeasts are part of the

normal cutaneous flora of humans that inhabit the superficial layers of the stratum corneum near to sebaceous glands and in the superior parts of hair follicles. Distribution and isolation of these yeasts vary in density and presence in many skin conditions and sites. It has been reported that *Malassezia* colonization is found both in patients with AD and in healthy individuals, with detection rates of 100% and 78%, respectively.[38] Among patients with AD, the head and neck are more prone to colonization than the limbs and trunk. Several different studies have indicated that *Malassezia sp.* induces production of specific IgE that is exclusively observed in patients with AD and not in patients with allergic rhinitis, urticaria, or allergic contact dermatitis.[39]

Differential diagnosis

The wide clinical spectrum of AD can frequently lead to erroneous diagnoses and treatment. Characteristics of AD including age of onset, distribution, intense pruritus, xerosis, lichenification, and association with atopic disease, can help to distinguish between AD and alternative diagnoses.[40]

Occasionally, patients with a diagnosis of AD may exhibit atypical clinical characteristics, leading physicians to question the diagnosis. In these cases, knowledge of the characteristic clinical findings of AD and recognition of possible alternative diagnoses are both important for patients, considering that management and prognosis are totally different.[41]

There is a long list of differential diagnoses for AD in children and adults, primarily comprising dermatological diseases and conditions that can manifest with cutaneous lesions and can be very similar to AD. These should be considered not only when the patient presents with an eczematous cutaneous eruption for the first time, but also when a patient diagnosed with AD does not respond to the appropriate treatment.[42] The most important diagnoses are listed in Table 6. One of the most important classes of diagnoses are the Inborn Errors of Immunity (IEI), since these are diseases that must be managed by an immunologist-allergist and careful examination is needed to make the correct diagnosis.[43]

Of note among the IEI are the Primary Atopic Disorders (PAD), which comprise a subset that are hereditary monogenic diseases that predominantly cause allergic manifestations. This makes it harder to diagnose them as IEI, because they do not exhibit the recurrent infection phenotypes seen in the majority of these diseases.[45] It is essential that physicians are able to recognize the PADs, considering the individual management of each case and impacting on patient morbidity and lethality. Table 7 lists the clinical warning signs that can facilitate diagnosis of PADs.

The principal differential diagnoses of AD and their specific morphological characteristics are described below.

Allergic contact dermatitis

Diagnosis is based on the pattern of dermatitis, normally following exposure to a specific substance, and on a positive patch test. The pattern is related to the locations of lesions in the region that comes into contact with the allergen (for example, on the face, for reactions to cosmetics). The characteristics of these lesions are very similar to AD and it is sometimes impossible to differentiate them on the bases of clinical findings alone. The most common allergens in children and adolescents are metals, fragrances, preservatives, and colorings.[44]

Seborrheic dermatitis

This is an important differential diagnosis of AD, particularly in its pediatric form, because of the similar distribution of the lesions. Diagnosis is based on clinical history and physical examination, including the distribution of eczema. Pediatric seborrheic dermatitis generally has onset within the first 3 months of life, i.e. earlier than the typical age of onset of AD. It almost always involves the diaper area, face, and scalp. In contrast, the diaper area tends to be spared in AD. Compared with AD, seborrheic dermatitis lesions tend to be less inflamed and scaling is greasier and while it can last several months, it does not last beyond 12 months of age, which also differs from the chronic character of AD. However, both diseases can occur concomitantly.[40]

Psoriasis

Although it is more common in adolescents and adults, psoriasis can occur in people of any age. It is a chronic dermatosis most often characterized by lesions in plaques and cutaneous thickening, clearly demarcated with erythema, and with presence of silver scaling in the region of the elbows, knees,

Table 6
Principal types of dermatitis/eczema and their differential diagnoses[44]

Dermatitis / Eczema	Atopic dermatitis Contact dermatitis Seborrheic dermatitis Nummular dermatitis Asteatotic dermatitis (eczema craquelé)
Other chronic dermatosis	Psoriasis Lichen simplex chronicus
Infections and infestations	Scabies Dermatophytosis Viral infections
Genetic and metabolic diseases	Netherton syndrome Ichthyosis Acrodermatitis enteropathica
Autoimmune diseases	Systemic lupus erythematosus Dermatopolymyositis
Inborn Errors of Immunity	Hyper-IgE syndrome Wiskott-Aldrich syndrome Omenn syndrome
Cancers	Langerhans cell histiocytosis Cutaneous T-cell lymphoma
Others	Drug-induced skin disorders

and scalp. There may also be ungueal and articular involvement (psoriatic arthritis). A cutaneous biopsy may be needed for diagnostic confirmation.[41]

Scabies

Differential diagnosis with AD includes both the pruriginous characteristic of *Sarcoptes scabiei* infestation and the cutaneous lesions caused by itching, with presence of erythematous papules and excoriation, predominating in interdigital areas and the flexural regions of the wrists, feet, and ankles, which could indicate an atypical eczema. Diagnosis is confirmed by observation of the mites with dermatoscopy.[40]

Table 7
Clinical warning signs of primary atopic disorders (PADs)[45]

Elevated IgE and eosinophilia
Atopic manifestations
Malignancy
Autoimmune manifestations
Short stature / growth disorders
Repeated infections
Connective tissue diseases

Ichthyosis vulgaris

This is the most common type of ichthyosis, caused by mutation of the filaggrin gene (FLG). The typical clinical status includes dry skin with fine, white scaling, very often free from erythema. Pruritus and eczematous lesions may be present, making differential diagnosis from AD difficult. It is debatable whether the eczematous lesions in ichthyosis vulgaris are actually AD, since around one third of all patients with AD are heterozygous for mutations of the FLG gene.[41]

Netherton syndrome

An autosomal recessive disease caused by mutation of the SPINK5 gene. At birth, newborns may present with erythrodermal ichthyosis. In older children, the disease is characterized by a distinct dermatitis, ichthyosis linearis circumflexa, in which the cutaneous lesions disseminate in a linear serpiginous or circinate pattern. The lesions are pruriginous and many will progress to eczematous plaques and lichenification of folds. The dermatitis may be difficult to distinguish from AD, since these children generally have elevated serum IgE and food allergies. Examination of the hair may be useful, because microscopy will reveal *trichorrhexis invaginata* (bamboo hair).[46]

Zinc deficiency acrodermatitis enteropathica

May be genetic or acquired (due to insufficient zinc intake) and is characterized by erythematous blemishes and plaques with scabs and erosions, predominantly in periorificial areas. Patients very often have other manifestations, such as diarrhea, alopecia, and growth deficiency. Diagnosis is clinical, combined with serum alkaline phosphatase and zinc assays and, very often, a skin biopsy.[45]

Hyper-IgE syndromes

These are rare inborn errors of immunity (autosomal dominant or recessive forms) and are characterized by severe eczema, recurrent skin infections (*S. aureus*), and very often pneumonia (with formation of pneumatoceles) and very high serum IgE levels (> 2000 UI/mL). Patients have characteristic skeletal features with a characteristic facial appearance (prominent forehead, wide bridge of the nose, bulbous nasal tip, and prognathism). Cutaneous changes are not limited to impetigo, but include boils and abscesses.[47]

Wiskott-Aldrich Syndrome (WAS)

This genetic syndrome is characterized by its association with eczema, although the first cutaneous manifestations are hemorrhagic lesions with petechiae, hematoma, purpura, epistaxis, oral bleeding, or bloody diarrhea. Platelets are characteristically small and autoimmune manifestations and neoplasms are common (primarily B-cell lymphomas).[44]

Omenn syndrome

This is a rare form of severe combined immunodeficiency, with early onset during the first year of life, characterized by erythroderma (similar to eczema) associated with chronic diarrhea, pneumonitis, growth deficiency, lymphadenopathy, and hepatosplenomegaly, characteristics that distinguish it from AD.[43]

Cutaneous T-cell lymphoma (fungoid mycosis)

This is a rare disease that is more frequently observed in adults, with characteristics that are similar to psoriasis or nummular eczema during the initial phases. A cutaneous biopsy should be taken from lesions that are refractory to treatment with topical corticosteroid.[42]

Assessing severity and control: evaluation scores

Assessment of the severity of AD is essential to guide treatment options and gauge the response to treatment. In the absence of a gold standard or specific biomarkers available for clinical use, several instruments have been developed and validated to measure severity and control of AD.[48,49]

For measurement of clinical severity by health care professionals, the most widely used and validated scores are Scoring Atopic Dermatitis (SCORAD) and the Eczema Area and Severity Index (EASI).[48,49] It is also recommended that patients assess their own AD severity and the most used instrument for this purpose is the Patient Oriented Eczema Measure (POEM).[49] Beyond these, the validated instrument Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) has been recommended as an instrument specifically for assessing severity in clinical trials.[50]

The SCORAD index is widely used in clinical practice, is scored from 0 to 103 points, and assesses the extent and intensity of lesions

(erythema, edema or papules, exudate or scabs, excoriation, lichenification, and cutaneous xerosis) and of subjective symptoms (itching and impact on sleep). AD is classified as mild when scores are less than 25 points; moderate at 25 to 50 points; and severe when the patient scores over 50 points.[51,52] The mean time for assessment ranges from 7 to 10 minutes. It offers the advantage of considering subjective symptoms, the intensity of xerosis, and of lesions involving the face, eyelids, neck, hands, and feet; and has the disadvantage in comparison to the EASI that it is redundant with regard to inflammatory skin symptoms, gives less weight to the extension of lesions in the final score (maximum of 20% of the value), and only assesses the intensity of the representative lesion for that patient.[48,52]

In turn, the PO-SCORAD (Patient-oriented SCORAD) is a validated score developed from the SCORAD. It has an app with a version in Portuguese that enables the patient to assess the severity of their own AD. Although it is less accurate than the SCORAD for the extent of lesions item, it covers lesions of three types of skin (white, Asian, and black) and it is easy to complete.[53]

The EASI score ranges from 0 to 72 points and covers clinical signs (erythema, edema/papules, excoriation, and lichenification) in each of four areas of the body (head and neck, upper limbs, trunk, and lower limbs) and the extent of disease in each region. It is interpreted as follows: 0 = no lesions; 0.1 to 1.0 = almost free from lesions; 1.1 to 7.0 = mild AD; 7.1 to 21.0 = moderate AD; 21.1 to 50.0 = severe AD; and 50.1 to 72.0 = very severe AD.[48,54,55] The EASI has been preferred over the SCORAD for clinical trials because it assesses all four of the fundamental clinical signs of AD, measures the intensity of lesions in the four body areas, rather than just a representative lesion, and its disease extent score is better distributed compared to the SCORAD. However, it is necessary to combine it with other scores to assess patient symptoms.[48,49]

The POEM uses seven self-administered questions to measure the extent to which patients experience their signs and symptoms over time and has been widely validated.[49] The score ranges from 0 to 28 points, where 0 to 2 points means free from lesions or almost free from lesions; 3 to 7 points, indicates mild AD; 8 to 16 points, moderate AD; 17 to 24 points, severe AD; and 25 to 28 points, very severe AD.[56] It has been translated and linguistically validated for Portuguese (in the Brazilian culture) and is freely available from the University of Nottingham website.[57]

The vIGA-AD considers the overall appearance of AD lesions as scored by an evaluator. Scores vary from 0 to 4 (0 = no lesions, 1 = almost free from lesions, 2 = mild AD, 3 = moderate AD, and 4 = severe AD) and assess the intensity of lesions (erythema, infiltration or papules, lichenification, exudate, or scabs).[3] The instrument is rapid and simple, but does not assess disease extent.[48]

Control of AD and response to treatment can be assessed using the same severity scores sequentially, or other specific instruments can be used.[48,49] For sequential use of a severity score, it is necessary to consider whether the variations exceed a minimal clinically important difference (MCID) or if there is a percentage reduction in the score, for example, the SCORAD 50 or EASI 75, with 50% or 75% reduction compared to a baseline value, respectively.[48]

Two scales were recently developed to monitor control of AD, the Atopic Dermatitis Control Tool (ADCT) and the Recap of atopic eczema (RECAP), both with similar content and validation and especially recommended for clinical trials. There is no preference between them,[49] but to date only the ADCT has been translated and undergone linguistic validation for Brazilian Portuguese.[58]

The ADCT instrument comprises six questions and has proven to be a valid and reliable tool for assessing control of AD in patients over the age of 12 years, with the capacity to detect clinically significant changes in disease control over time. Scores vary from 0 (best disease control) to 24 points (worst disease control) and AD is considered controlled if the score is less than 7 points.[59]

Other instruments for clinical symptoms perceived by the patient and the impact on health related quality of life can also be used in clinical practice and are recommended for research. The most recent update to the global Harmonising Outcome Measures for Eczema (HOME) initiative, which has the objective of standardizing clinical trials of the four principal AD outcome domains, recommends using the EASI to assess signs of severity; POEM and numerical 24-hour peak itching scale for patient-reported symptoms; disease related quality of life for quality of life questionnaires by age group (the Dermatology Life Quality Index– DLQI for adults; the Children's Dermatology Life Quality Index – CDLQI for children 5 to 16 years of age; and the Infants' Dermatitis Quality

of Life Index – IDQoL for under-fives), and the ADCT or RECAP for control of AD activity.[49]

Treatment

Considering the chronic nature of AD and the differing levels of severity, the objectives of AD treatment are as follows: to (a) reduce the extent and severity of lesions; (b) reduce itching and improve sleep quality; (c) maintain normal daily activities; (d) improve quality of life; (e) maximize disease-free periods; (f) prevent infectious complications; and (g) avoid/minimize adverse events related to treatment.

General care

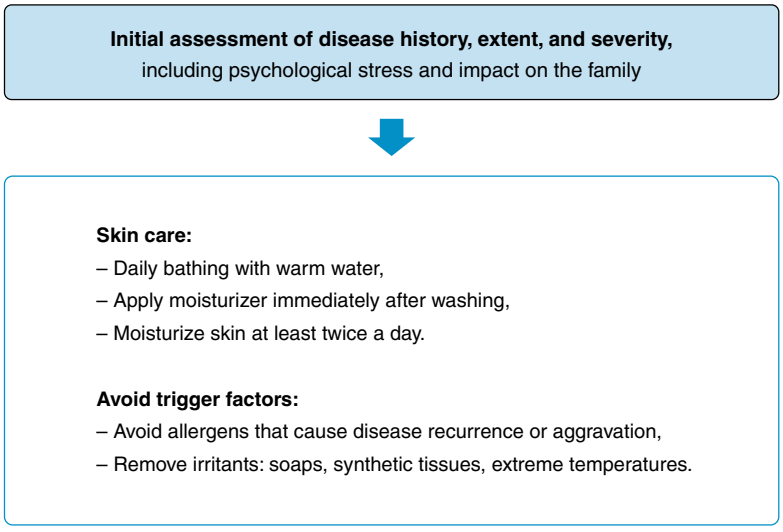
For patients with mild AD, the objectives cited above can be achieved with topical treatments alone, which is not the case of patients with moderate or severe AD, for whom treatment is challenging. The general principals include improving the cutaneous barrier, eliminating trigger factors, education and active participation of patients and family members, and treatment of inflammatory lesions (Figure 1).[1,60]

Improve the cutaneous barrier

Patients with AD have xerotic skin because of deficient barrier function and an unfavorable equilibrium between transepidermal water loss and retention.[61] If applied regularly, moisturizers improve cutaneous barrier function, increase hydration, and reduce xerosis, itching, and inflammation, reducing the need to use anti-inflammatory agents.[1] Randomized clinical studies comparing use or not of moisturizers in participants demonstrated improved SCORAD scores, longer time between crises, and reduced use of topical anti-inflammatories in the group that used moisturizer.[62]

The ideal quantity that should be applied to newborn infants, infants, children, and adolescents/adults ranges from 100 to 150, 200, or 500 grams per week, respectively.[60,63]

The moisturizers available for AD (Table 8) have varying combinations of emollients, occlusive substances, and humectants.[1] Emollients fill the spaces between corneocytes, maintaining moisturization; occlusive substances form a hydrophobic film on the epidermis that reduces evaporation of water and penetration by irritants, such as allergens and toxins;



Adapted from Kulthanan K, et al.[60]

Figure 1
Flow diagram of initial treatment for atopic dermatitis

Table 8
List of some of the moisturizing products available

Moisturizers containing urea
Cetaphil® Pro Urea 10% lotion (Galderma)
Dermovance® S (FQMmelora)
Eucerin® Urearepair 10% lotion (Eucerin)
Nutraplus® cream/lotion (Galderma)
Ureadin® cream/lotion 3%, 5%, 10% (Isdin)
Ureadin® Rx (Isdin)
Uremol® cream/fluid 10% (Stiefel /GSK)
Ureskin® cream/lotion 10% (Genon)
Moisturizers containing ceramides, cholesterol, fatty acids, phospholipids
Atoderm® cream/balm/gel (Bioderma)
CeraVe® cream/lotion (Lóreal)
Cetaphil® Advanced (Galderma)
Cetaphil® cream/lotion/serum (Galderma)
Cetaphil® Restoraderm (Galderma)
Cetaphil® pro AD (Galderma)
Dermovance® (FQMmelora)
Dersani® moisturizing cream (Megalabs)
Epidrat Corpo Intensivo® (Mantecorp)
Eucerin® pH 5 lotion (Eucerin)
Fisiogel® cream/lotion (Megalabs)
Hidrakids® (Biolab)
Hydracell® cream (Germed)
Hydraporin AI® lotion (Mantecorp)
Klaviê® cream/lotion (Theraskin)
Lipikar® lotion (La Roche-Posay)
Nutratopic® cream/lotion (Isdin)
Nutriol® lotion (Darrow)
Saniskin® lotion (Saniplan)
Stelatopia® balm/cream (Mustela)
Xeracalm® AD cream (Avène)
Moisturizers containing glycerin, oatmeal, panthenol, petrolatum
Bepantol Derma® lotion (Bayer)
Neutrogena® body care extra dry skin (Neutrogena)
Norwegian® body moisturizer (Neutrogena)
Nutriol® lotion (Darrow)
Umiditá® lotion (Libbs)
Moisturizers with anti-pruritus activity
Atoderm® SOS spray (Bioderma)
Cetaphil® pro AD fast control (Galderma)
Fisiogel® AI (Megalabs)
Lipikar® AP+M (La Roche-Posay)
Nutratopic® Rx (Isdin)
Umiditá® AI (Libbs)

Adapted from Carvalho VO, et al.[64]

and humectants increase moisturization of the stratum corneum, preserving its structure.[64] They may also contain ceramides and essential fatty acids.[1]

An ideal moisturizer should contain few ingredients, with well-tolerated preservatives, and should be free from fragrances and sensitizers (sodium lauryl sulfate, cetyl alcohol, neomycin, animal lanolin, almond oil, parabens, and methylisothiazolinone) to avoid allergic cutaneous reactions. It can often be necessary to test different products to identify the one that best achieves cutaneous moisturizing, does not sting, and fits the patient's preference for texture, lotion, cream, or balm. Lotions are preferable during the hotter months of the year because they have a more fluid consistency and are easier to spread. In cooler periods, creams and balms with thicker consistency moisturize better.[61,64] Guidelines recommend that moisturizer should be applied two or three times a day, especially with the skin still humid, during the first 3 minutes after bathing, and to areas of skin with and without lesions.[1,65]

A new era of moisturizers includes ingredients such as cannabinoids, bioactive lipids, microbioma modulators (prebiotics and probiotics) and antioxidant enzymes. These substances are intended to exert additional biological effects on the skin: regulate production of lipids, reduce sensorineural transmission of itching signals, revert oxidative stress, reduce inflammatory cell activity, and modulate skin microbiota.[66]

Bathing daily is not associated with clinical deterioration. Bathing reduces irritants, bacteria, and scabs on the skin. Warm water is recommended to avoid drying the skin when washing.[30] Patients can bathe for 5 to 10 minutes using soaps at physiological pH, i.e. slightly acid, or, preferably, using syndets.[60,61] The European guidelines recommend using cleansing oils (Table 9) during the last 2 minutes before finishing washing.[36]

Table 9
List of some cleansing oils available

Lipikar® huile lavante (La Roche-Posay)
Atoderm® cleansing oil (Bioderma)
Eucerin® pH5 body wash (Eucerin)

Identify trigger factors

a) nonspecific factors

Daily contactants such as saliva, sweat, hair, friction against synthetic clothes, and shampoo, conditioner, and soap residues can exacerbate AD.

b) Contactants

Contact dermatitis should be suspected when treatment fails or eczema location is atypical. The causative agent can be confirmed using patch tests. In general, the most common agents are topical medications, cosmetics, metal, and/or disinfectants.

c) Food allergy

A food should only be eliminated from the diet if its involvement as one of the causes of AD aggravation is proven clinically and using specific tests. Food allergies in AD are more common in children, especially during the first years of life, and are linked to the more severe forms of AD. Studies show that elimination diets (allergenic foods) for pregnant women and breastfeeding mothers do not prevent AD in their babies.

d) Aeroallergens

Domestic dust, pollens, and animal hair are considered factors in clinical deterioration, are more common after the first years of life, and allergies to them can be confirmed with prick tests and/or specific serum IgE assays.

e) Bacteria and fungi

S. aureus can be one of the factors in exacerbation of AD. Administration of antibiotics is not indicated if there is no infection. Some studies have demonstrated clinical improvement with use of topical antifungals on lesions of the head and neck, suggesting that fungi of the genera *Candida* and *Malassezia* are associated with exacerbation of AD lesions.[30,60]

Education of the patient and family members

Since AD is a chronic disease that needs long-term follow-up, patients and their relatives must be educated so that they can understand the course of the disease and how to deal with and prevent crises, improving adherence to treatment and quality of life. Interventions that include patient education reduce the number of medical consultations, facilitate the physician-patient/family partnership, and reestablish family dynamics.[67] Multidisciplinary education programs involving pediatricians, dermatologists, allergists, psychologists, and nurses help to improve the quality of life of patients and their families.[60] In Brazil, there are a number of AD support groups with this mission, which can be consulted on the aada.org.br website. The same site also provides patient-oriented information on atopic dermatitis.

Emotional stress

AD has a significant impact on the quality of life of patients and their families. Stress and emotional factors can exacerbate the disease. Psychosomatic counseling, psychotherapy, behavioral therapy techniques, and/or relaxation techniques can help with patient management.[30,60,67]

Phototherapy

Phototherapy has been used to treat many different inflammatory and immunomediated diseases since the start of the last century, primarily because of the observation that these patients improved during the summer. Treatment employs light in the ultraviolet (UV) spectrum irradiated onto the patient's skin at specific times for controlled durations. The spectra employed are ultraviolet A (UVA), UVA combined with use of psoralens (UVA+P), and ultraviolet B (UVB). The UVB category includes Broad Band UVB (BB-UVB), ranging from 280 to 320 nm, i.e. the entire UVB band, and Narrow Band UVB (NB-UVB), which uses wavelengths from 301 to 311.[36,68,69]

For treatment of AD, both of the modalities employed have similar efficacy: medium-wave UVA (340 to 400 nm, also known as UVA-1) and NB-UVB, although the latter is safer. The different spectra yield different results, and NB-UVB is indicated for chronic cases, while UVA-1 is used for acute presentations.[69]

Phototherapy is effective because it interferes in the cascade of biological events that result in suppression of the immune system linked to the T cells of the skin. Specifically in AD, it provokes suppression of the lymphocytes Th2, Th22, and Th1, improving the cutaneous barrier. It also reduces colonization by *Staphylococcus aureus*, reduces the number of

infections, and provokes reduction of toxin production by *S. aureus*.[68,69]

Phototherapy's role within the arsenal of AD treatments is as an adjuvant when topical treatments fail, before use of systemic immunosuppressant medications. Although it is recommended for adjuvant use, in some patients, SCORAD score reductions after use of phototherapy alone can exceed 50% in the first 12 weeks.[70] Its efficacy has been demonstrated in publications and NB-UVB was recommended in a recent systematic review that analyzed 32 publications that included 1,219 participants (5 to 83 years of age) and all phototherapy modalities. NB-UVB was more effective than placebo, with benefits for improvement of eczema and reduction of pruritus. The lack of uniformity of the studies, small numbers of participants, and even failure to assess patients' quality of life or employ similar severity scores interfered with interpretation of the efficacy results reported.[68,70,71]

The safety and efficacy of NB-UVB phototherapy have been demonstrated in patients up to 3 years of age, but it should be avoided in children who are unable to adhere to the safety protocols. Rates of remission over 1 year of treatment exceeded 50% for complete or near-complete remission, primarily in children with phototypes higher than III. The difficulties with conducting treatment in children, the lack of uniformity of the different publications and, primarily, the small numbers of participants in the pediatric age group are all factors that still need to be addressed.[72-74]

Phototherapy for AD is standardized, but the different types of skin, disease phenotypes, and even tolerance of treatment can all have a direct influence on the results. In cases in which UVA1+P is used for phototypes I to III, it is recommended that treatment initiates at 1 J/cm^2, while for phototypes IV to VI, 2 J/cm^2 can be used initially, with 1 J/cm^2 increments every two or three sessions. It is recommended that sessions be conducted two to three times per week. When using AD NB-UVB, the initial dose is 100 mj/cm^2, and the duration or total dose per session should be as specified in the manufacturer's standard table.[69]

The greatest problems with this treatment method are its cost and, primarily, the availability of equipment and physicians trained to use it. In some regions of Brazil, this method is not a viable option, because the equipment is only found in large urban centers or state capitals and the need for frequent sessions makes it impossible to adhere to treatment for patients who live in places far from these centers. During the COVID-19 pandemic, there were several reports of phototherapy performed at home, increasing coverage of patient care, since patients could be treated at a distance without having to travel, but the cost of the equipment and issues regarding the safety of using it at home are causes for concern. Development of new technologies and, primarily, portable and lower-cost machines are possibilities for future improvements in care of these patients.[68,73,75]

Another concern is the possibility of increased risk of skin cancer linked to exposure to phototherapy, primarily in pediatric patients, and follow-up of patients currently being treated is essential to determine the magnitude of this risk.[73]

Phototherapy offers good clinical results and is apparently safe, but the sizes of the samples of patients studied and also the cost remain factors that limit its routine adoption for the pediatric age group.

Pharmacological treatment

Control of AD requires an approach that is tailored to each phase of the disease. Treatment plans should be developed on the basis of decisions taken in conjunction with patients and their families. The plan should cover control over the short, medium, and long term, with strategies for acute crises and a roadmap for long-term control. The objective is to reduce severity and the number and duration of crises.[76] The plan should ideally be provided in writing, covering the medications to be used and the duration and times of use.[77,78]

Topical

All patients need topical treatment, irrespective of AD intensity. For severe forms of the disease, topical treatment should be combined with systemic medications.[76,77]

Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are recommended for basic therapy. Over recent years, new topical substances have been released or studied. Emerging therapies include topical phosphodiesterase-4 inhibitors and topical Janus kinase inhibitors,[76,79] but these are not yet available in Brazil.

Topical corticosteroids

The mechanisms of action of TCS include anti-inflammatory, antiproliferative, and immunosuppressant effects. They suppress inflammatory activity and reduce the number of inflammatory cells and release of cytokines, including neutrophils, monocytes, lymphocytes, Langerhans cells, IL-1α, IL-1β, IL-2, and tumor necrosis factor. Their efficacy has been demonstrated in several vehicles and at varying doses in countless randomized clinical trials.[80]

TCS are the first line treatment for acute AD crises, and efficacy is achieved with correct application, at the strength indicated for each region, and in sufficient quantity. There are seven different strength levels, varying from very weak to very strong (Table 10), and the strength should be adjusted to fit the severity of lesions and the region being treated.[77] Powerful corticosteroids should be avoided in areas with thin skin, such as the face and areas with folds. In children, corticosteroids of medium to low strength should be preferred.[81]

Application should be started as soon as symptoms of itching and erythema appear and the duration of topical treatment with steroids is guided by clinical improvement. However, their use should be restricted to areas with inflammatory lesions and periods of 7 to 14 days, or until the lesions improve.[81] They can be applied once or twice a day with similar efficacy. Proactive use is indicated in severe and difficult to control cases, i.e. after a flare up has subsided, apply 2 days a week to areas that are most resistant to treatment and, ideally, resume reactive use after 3 months.[81,82]

There is no universal standard to quantify TCS for each application. Squeezing the tube enough to cover the fingertip of an adult is sufficient to apply to a lesion the size of two hand breadths.[81]

Corticosteroids have undesirable side effects, which encourages poor compliance with treatment, caused by corticophobia, and results in insufficient clinical response. Cutaneous side effects include atrophy, telangiectasia, stretch marks, hypertrichosis, and acne eruptions.[76] The majority of these effects improve after withdrawal of the medication.[81] Side effects can be avoided if corticosteroids are used correctly and combined with skin moisturizing.[83]

Topical calcineurin inhibitors

TCI inhibit transcription of the genes for proinflammatory cytokines, such as IL-2, which are dependent on nuclear factor of activated T cells. The following have been approved for treatment of AD: tacrolimus cream 0.03% (in children from 2 to 15 years and adults) and ointment 0.1% (in over-15s and adults) for moderate to severe AD; and pimecrolimus cream 1% for mild to moderate AD in children older than 3 months. They are safe and effective for short term (3 weeks) and long term (5 years) treatment of AD.[81]

TCI are indicated for use in sensitive areas with thinner skin, such as areas with folds and the face, applied twice a day to areas with lesions. They do not cause the topical side effects observed with TCS, but there may be local itching and burning at the site of application.[83] Patients should be warned of this symptom to avoid them stopping treatment and if necessary TCS can be used for a few days beforehand and then changed for the immunomodulator, thus reducing burning sensations.[81]

Phosphodiesterase-4 inhibitors

Use of phosphodiesterase-4 inhibitors (PDE4) is founded on the intracellular function of PDE4 in keratinocytes. Circulating leukocytes in patients with AD have PDE4 activity, which is involved in production of inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13 and prostaglandin E2, by degradation of adenosine monophosphate. PDE4 reduces transcription of countless cytokines involved in acute and chronic inflammation, The PDE4 inhibitor crisaborole has been evaluated in clinical trials.[77]

Crisaborole ointment 2% was approved by the FDA in 2016 for treatment of mild to moderate AD in patients older than 2 years and in March 2020 for infants over 3 months old.[83] Several clinical trials have shown that the product is effective for improving AD lesions and disease severity and for reducing pruritus, with a favorable safety profile,[76] but it can cause burning sensations that limit its use.[83]

Topical JAK/STAT inhibitors

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is used by countless cytokines involving increased Th2 cell response, eosinophil activation, and suppression of regulatory T cells. JAK/STAT inhibitors are classified as small molecules that block intracellular targets.[77] They can prevent Th2 cytokine signaling that induces the inflammatory process in AD. Several pharmaceutical

agents targeting this group of tyrosine kinases (including JAK1, JAK2, JAK3, and TYK2) are being tested in patients with AD, in both systemic and topical treatments.[76]

Sodium hypochlorite

Sodium hypochlorite baths are an antiseptic technique for treatment of moderate to severe AD in patients with recurrent cutaneous bacterial infections. They are active against staphylococci, including methicillin-resistant *S. aureus*. They are indicated for active skin infections and maintenance therapy. The antimicrobial effect is attributed to the capacity to cause irreversible aggregation of bacterial proteins.[84] They also help improve cutaneous barrier function.[81]

The recommendation is to at 100 mL sodium hypochlorite 5% to bathwater in a 100 liter bath. Bathe for 10 minutes, rinse, and apply moisturizers. This should be done 3 days a week for a minimum of 3 months.[81]

A systematic review of sodium hypochlorite baths demonstrated that four out of five studies observed

Table 10
Classification of topical corticosteroids by strength*

Class/strength	Drug	Vehicle	Dose (%)
I - Very high			
	Clobetasol propionate	Cream and ointment	0.05
II - High			
	Betamethasone dipropionate	Cream, ointment, and solution	0.05
	Desoximetasone	Cream and ointment	0.25
	Desoximetasone	Gel	0.05
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream and ointment	0.5
III-IV - Medium			
	Mometasone furoate	Cream	0.1
	Betamethasone valerate	Cream and ointment	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream and ointment	0.025
	Triancinolone acetonide	Cream and ointment	0.1
V - Medium-low			
	Hydrocortisone butyrate	Cream, ointment	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream and ointment	0.2
	Prednicarbate	Cream	0.1
	Methylprednisolone aceponate	Cream	0.1
	Fluticasone propionate	Cream	0.05
VI - Low			
	Desonide	Cream/gel/ foam, and ointment	0.05
	Fluocinolone acetonide	Cream and solution	0.01
VII - Very low			
	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, ointment, lotion, and solution	0.5-2.5
	Hydrocortisone acetate	Cream and ointment	0.5-1
	Methylprednisolone	Cream and ointment	1%

* Adapted from Paller AS, et al. [77]

reduced AD severity.[84] The long-term efficacy and safety of this antiseptic agent is unknown, primarily with regard to continuous use.[84]

Wet Wrap Therapy

Wet wrap therapy (WWT) is an adjuvant for treatment of crises and restoration of the cutaneous barrier in refractory and severe patients who cannot tolerate TCS without bandages.[81] After bathing, moisturizers are applied in generous layers, combined or not with corticosteroids in areas with lesions. A humid bandage is applied over the moisturizer, followed by a dry bandage. WWT can be left in place for 2 to 10 hours and can be applied daily for up to 14 days. It helps to moisturize the skin, reduces pruritus, and constitutes a physical barrier that makes excoriation of the skin less likely.

In clinical trials, WWT was more effective than moisturizers alone,[85] but caution should be exercised with regard to application of high-strength TCS, because the increased absorption can lead to suppression of the hypothalamus-pituitary-adrenal axis. Low or medium strength TCS are therefore appropriate for use with WWT. It is unclear whether WWT is associated with an increased risk of cutaneous infections.[76]

Systemic

Antibiotic therapy

Patients with AD are more susceptible to cutaneous infections by bacteria, fungi, and viruses because of many reasons, such as inhibition of antimicrobial peptides. *S. aureus* is the bacteria most associated with AD, colonizing up to 90% of patients, even in areas without lesions. Colonization by *S. aureus* intensifies the cutaneous inflammatory process because of release of toxins with superantigenic activity, which accentuate the pruritus. In turn, itching promotes colonization by *S. aureus*, creating a feedback process.[81] Patients with AD may have higher rates of colonization by methicillin resistant *S. aureus* (MRSA). In two Brazilian studies, rates of colonization by *S. aureus* and MRSA were 73.6% and 0% respectively in Porto Alegre, RS, and 82.9% and 22.2% in the city of Rio de Janeiro.[86,87] In Rio de Janeiro, colonization by MRSA was positively associated with greater severity of AD and use of cyclosporine.[87]

Colonization of the skin by *S. aureus* can be reduced with effective anti-inflammatory treatment and topical use of corticosteroids or calcineurin inhibitors.[81] Sodium hypochlorite (0.005%) has antiseptic activity and can be used intermittently in the immersion baths. Presence of yellow crusting, exudate, and blisters is characteristic of bacterial infections and can be treated with topical antibiotics (fucidic acid or mupirocin). Systemic antibiotics should be used in cases with extensive bacterial superinfections, preferably with first generation cephalosporins.[81,88] Wider spectrum antibiotics can be used in cases of MRSA infections.[88] Prophylactic use of antibiotics (whether topical or systemic) for long periods is not recommended.

Immunosuppressants

Systemic immunosuppression is a resource adopted in adults and children with severe AD refractory to usual treatment. Although recent introduction of new and promising treatments such as immunobiologicals and small molecules, such as JAK inhibitors, oral immunosuppressant drugs (OIs) such as corticosteroids, cyclosporine A (CsA), methotrexate (MTX), azathioprine (AZA), and mycophenolate mofetil (MFM) are all treatment options that are established in clinical practice and are widely available for these patients.[89]

To date, cyclosporine is the only OI habitually prescribed for these purposes that is approved in Brazil, for patients over the age of 18. As a result, a significant proportion of patients with moderate/severe AD are given “off-label” prescriptions to control their disease.[90,91]

Before initiating treatment with immunosuppressants, it is necessary to study the indications, contraindications, adverse effects, and drug interactions, to be able to minimize treatment risks. The pediatric age group has a tendency to progressively improve, so it is important to evaluate the risks and benefits of these medications, which can sometimes have serious side effects.

a) Systemic corticosteroids

Systemic corticoid therapy (SCT) is limited for treatment of AD by the known side effects and lack of long-term controlled studies in adults and children. Its should therefore be used with extreme caution, restricted to exceptional cases, and the daily dose should not exceed 0.5 mg/kg body weight of prednisone or prednisolone.[67,89]

Some patients may benefit from a rapid course of SCT during severe acute crises, but clinical improvement is often associated with a high rate of recurrence of symptoms after withdrawal of the medication, resulting in difficult to control cases. Frequent use of oral corticosteroids should prompt use of other immunosuppressant treatments that avoid them.[89]

b) Cyclosporine A

CsA is a lipophilic cyclic polypeptide that inhibits the dependent pathways of calcineurin and reduces the number of activated TCD4+ and TCD8+ cells in the epidermis and, consequently, the levels of several proinflammatory cytokines, such as IL-2 and IFN-γ.[92]

Systematic reviews and meta-analyses recommend CsA as first line treatment for severe AD in adults, children, and adolescents for whom conventional treatment is ineffective or inappropriate.[89,93]

The dose habitually employed is 3-5 mg/kg/day, divided into two doses. Once clinical efficacy is achieved, it is recommended that the dose is reduced by 0.5-1.0 mg/kg/day every 2 weeks, until the maintenance dose of 2.5-3 mg/kg is reached. Treatment duration varies and should be guided by clinical criteria of efficacy and drug tolerance. Both short and long term treatments are effective, but treatment should not exceed 2 years in a continuous regimen.[67]

It is essential to monitor renal function and arterial blood pressure and if abnormal laboratory findings or increased blood pressure occur, CsA should be withdrawn or the dose reduced. Nephrotoxic effects are more likely if the dose exceeds 5 mg/kg body weight, in patients with elevated serum creatinine, the elderly, or with prolonged use of the medication. In general, the effects are reversed by withdrawal of the drug. Combining CsA with ultraviolet radiation is not recommended, because of an increased risk of cutaneous and lymphoproliferative malignancy.[93,94]

Although there are no controlled studies available that have assessed the efficacy of vaccination in children on CsA, it should be considered that attenuated vaccines may not be effective during CsA treatment.[95] Vaccines containing live attenuated microorganisms are contraindicated.

c) Methotrexate

MTX is an analog of folic acid that can competitively and irreversibly inhibit the enzyme dihydrofolate reductase, preventing conversion of dihydrofolate to tetrahydrofolate. It thus interferes in synthesis of DNA and RNA and proliferation of lymphocytes.[92]

Although there is a lack of randomized clinical trials of its use, MTX is widely used “off-label” as an accessible, low-cost treatment option for patients with serious and refractory disease.[96,97]

Studies that have assessed use of MTX in adults, children, and adolescents with severe AD have demonstrated that it is generally well-tolerated and has a good safety profile, in addition to proven clinical efficacy comparable to CsA and azathioprine.[98-100]

Compared to CsA, MTX has a slower onset of activity, but has good efficacy in prolonged treatments.[99]

Initial (5 to 10 mg/week) and maintenance dosages (7.5 to 25 mg/week) vary by age group and according to response to treatment. MTX can be administered as an oral presentation or by intramuscular route, always with weekly folic acid supplementation (5 mg) throughout treatment. The most common side effects include gastrointestinal disorders and elevated hepatic enzymes and are reversed by withdrawal. Severe adverse reactions such as myelosuppression, liver toxicity, and pulmonary fibrosis are very rare.[101,102] Since MTX is a teratogenic medication, men and women of fertile age should use effective contraceptive methods during treatment. Its use is contraindicated during lactation.[67]

d) Azathioprine

AZA is a purine analog that blocks RNA and DNA synthesis, interfering with proliferation of T and B cells, and with functioning of antigen presenting cells.[92]

Clinical trials with adults showed that when compared with placebo, it significantly improved scores for cutaneous lesions, pruritus, sleep disturbances, and interference with daily and employment activities.[103]

It is recommended as a second line treatment option for moderate to severe AD in adults, especially in cases in which CsA is ineffective or contraindicated.[67] Onset of action is slow and the benefits may not become apparent for up to 2 to 3 months after starting treatment.[104]

The most common adverse reactions to AZA are nausea and vomiting, which may occur during the first weeks of treatment and are reversed by withdrawal of the medication. Severe side effects such as leukopenia, liver toxicity, and myelosuppression may also occur. The last of these is dependent on partial or total deficiency of thiopurine methyltransferase (TPMT). Therefore, before initiating treatment, patients should be assessed for activity and/or by genotyping this enzyme to reduce the risk of myelotoxicity and to choose the safest therapeutic dose.[92]

Laboratory monitoring is essential during treatment with AZA and the recommended dose is from 1 to 3 mg/kg/day. A study realized with children with severe AD and normal TPMT levels before starting treatment did not detect myelosuppression using a dosage of 2.5-3.5 mg/kg.[105] Adult patients with moderate/severe AD, in whom the dose of AZA was adapted to TPMT activity (1.0 mg/kg per day) achieved similar clinical improvement to patients with normal TPMT activity given 2.5 mg/kg of AZA.[16] In common with CsA, AZA cannot be combined with UV treatment and effective UV protection should be used.[67]

e) Mycophenolate mofetil (MFM)

MFM is an immunosuppressant that inhibits purine biosynthesis, resulting in reduction of lymphocyte proliferation. Its utility and good safety profile have been documented in uncontrolled clinical trials in adults, children, and adolescents with refractory AD. However, it remains a third line treatment option because of the lack of large scale efficacy studies.[106,107] Adverse gastrointestinal events such as nausea or diarrhea are the most common side effects during treatment with MMF and are more common at the start of treatment. Since it is teratogenic, patients of both sexes of fertile age should use effective contraceptive methods during treatment with MFM.[67]

Table 11 summarizes the principal characteristics of the systemic immunosuppressants most frequently used for treatment of severe AD.

Immunobiologicals

Immunobiologicals are already being used in current clinical practice and have been increasingly adopted for treatment of inflammatory diseases. They constitute a class of pharmacological agents developed with genetic engineering to act on the targets/mediators of allergic inflammation. Advances in knowledge about physiopathogenesis and the arrival of target-specific treatments have triggered a revolution in treatment of immunomediated diseases.[108,109]

Current immunobiologicals are used to modify the Th2 response, blocking IgE and cytokines such as IL-4, IL-13 and IL-22, IL-32, and IL-17/IL-23, which play a fundamental role in pathogenesis of AD.[108] These are safe medications and clinical assessment (patient history/physical examination) is enough to prescribe them to patients with moderate/severe forms of AD that have not been controlled despite adequate treatment and they do not require more intense laboratory assessments, unlike the immunosuppressants.

a) IL-4 and/or IL-13 inhibitors

– Dupilumab

Dupilumab was the first immunobiological to be approved for clinical use by the FDA (US Food and Drug Administration), the EMA (European Medicines Agency) and ANVISA (the Brazilian National Agency for Sanitary Vigilance) for treatment of AD in children over 6 years of age, adolescents, and adults with moderate to severe AD that is not controlled by the usual treatments.[108,109] It is also indicated for allergic asthma and chronic rhinosinusitis with nasal polyps.[110]

Dupilumab is a recombinant human monoclonal antibody of specific IgG4 that binds to the alpha subunit of IL-4 and IL-13 receptors. This causes downregulation of the receptor which signals the JAK/STAT pathway responsible for regulation of the expression of several genes involved in pathogenesis of AD.[109]

By blocking the IL-4 and IL-13 pathway, dupilumab blocks three different relevant mechanisms of disease in AD: impairment of skin barrier function caused by downregulation of the filaggrin protein; IgE class switching caused by Th2 cytokines; and global Th2 differentiation of the inflammatory infiltrate.[109,111,112]

Investigation of the efficacy of monotherapy with dupilumab (initial dose of 600 mg, followed by 300 mg every 2 weeks, SC) for 16 weeks demonstrated an 82.5% reduction for EASI 50, 60.3% for EASI 75, and 36.5% for EASI 90. Improvement in cutaneous lesions and reduction of itching occurred 2 weeks after starting treatment and were maintained for up to 1 year when combined with TCS.[113]

Table 11
Systemic immunosuppressants for treatment of severe atopic dermatitis

	Cyclosporine	Methotrexate	Azathioprine	Micofenolato
Indication	Severe adults Off-label for children	Off-label for adults and children	Off-label for adults and children	Off-label for adults and children
	Acute intervention Mean duration 1 year	Long term maintenance	Can be used long term	Can be used long term
Onset of action	2 weeks	8-12 weeks	8-12 weeks	8-12 weeks
Relapse	< 2 weeks	> 12 weeks	> 12 weeks	> 12 weeks
Most frequent side effects	Arterial hypertension ↑ Serum creatinine	Hematological ↑ Hepatic enzymes Gastrointestinal	Hematological ↑ Hepatic enzymes Gastrointestinal	Low toxicity Gastrointestinal infections
Adult dosage Initial	3-5 mg/kg/day	5-15 mg/week	50 mg/day	[a] Depending on TPMT 1–2 g/day
Maintenance	2.5-3 mg/kg/day	15 mg/week; may ↑ to max 25 mg/week	2-3 mg/kg/day	15 / week; may ↑ to max 25 mg/week
Child dosage Initial	3-5 mg/kg/day	10-15 mg/m²/week	25-50 mg/day	[a] Depending on TPMT 20–50 mg/kg/day
Maintenance	2.5-3 mg/kg/day	↑ 2.5-5 mg/week, ↓ by 2.5 mg/week to lowest effective dose	2-3 mg/kg/day	↑ total dose by 500 mg every 2-4 weeks up to 30–50 mg/kg/day
Pregnancy	Possible (category C)	Contraindicated (category X)	Contraindicated (category D)	Contraindicated (category X)
Paternity	Possible	Few data Contraindicated	Use possible? Few data	Use possible? Few data
Vaccination [b]	3 months	1 to 3 months	3 months	3 months

[a] TPMT = thiopurine methyltransferase (see text); [b] Minimum interval for attenuated vaccines.
Table based on references 67,89, and 95.

It is recommended that the immunobiological be administered concomitantly with the underlying treatment that the patient is using daily (environmental hygiene, bathing, skin moisturizing, and topical medication, when necessary) (Table 12). Side effects of this medication are minimal, the most common being conjunctivitis (5% to 28%).[114,115]

– Tralokinumab

Not yet available in Brazil, tralokinumab is a humanized antibody that neutralizes IL-13 by inhibiting its interaction with the alpha subunit of the IL-13R receptor.[109] Tralokinumab interferes with downregulation of the filaggrin cutaneous barrier caused by IL-13. IL-13 is elevated both in skin with lesions and in skin without lesions in patients with AD and correlates with disease severity.[108] It has been documented that presence of biomarkers related to increased IL-13 is associated with better response to treatment with this biological.[116]

– Lebrikizumab

This is another specific humanized monoclonal antibody targeting IL-13, but ongoing studies do not yet enable inference of the best dosage regimens or its safety profile.[108]

b) Nemolizumab

This is a specific monoclonal antibody targeting the alpha receptor of IL-31, the principal cytokine involved in pruritus in patients with AD. It is another biological with a high likelihood of future approval for treatment of AD. Inpatients with severe/moderate AD, a double-blind study of nemolizumab *versus* placebo documented better efficacy for the biological for control of pruritus in these patients.[109]

c) Fezakinumab

Fezakinumab is a specific humanized monoclonal antibody targeting IL-22.[108,117] In acute and chronic AD lesions, an increase in IL-22 related to severity was documented. IL-22 is produced by Th22 cells and acts on keratinocytes, impairing cutaneous barrier function. A study of patients with SCORAD ≥ 50 documented significant clinical improvement in the 12th week of treatment with fezakinumab, when compared to placebo.[117] Moreover, there was also progressive improvement in all outcomes assessed up to week 20, even though treatment was ended in week 10, suggesting that the therapeutic effect is sustained after withdrawal.[117]

Immunobiologicals are modern medications and advances in knowledge about the mechanism of the disease should lead to identification of endotypes

Table 12
Dosage recommendations for dupilumab in atopic dermatitis

Body weight	Initial dose	Subsequent doses
15 to less than 30 Kg	600 mg (2 300 mg injections)	300 mg every 28 days
30 to less than 60 Kg	400 mg (2 200 mg injections)	200 mg every 14 days
60 Kg or over	600 mg (2 300 mg injections)	300 mg every 14 days

that will enable the best Candidates for these specific treatments to be chosen, contributing to personalized or precision AD medicine.

d) Small molecules

Small molecules are synthetic drugs with low molecular weight and the capacity for intracellular diffusion that can interfere with intracellular activation pathways. In comparison to the systemic immunosuppressants used for treatment of AD, these drugs have less potential for adverse effects because they enable more selective suppression of immunological pathways.[118] When compared to immunobiologicals, they have greater potential for adverse effects, because they inhibit higher numbers of inflammatory pathways, and they are not licensed for use in children. Table 13 summarizes the principal differences between the biologicals and small molecules.

Table 13
Comparison of the characteristics of biologicals and small molecules

	Biologicals	Small molecules
Molecular weight	Generally >2-5 kDa	Generally <0.5 kDa
General characteristics	Designed monoclonal antibodies	Chemical compound
	May not have a well-defined structure	Well-defined structure
	Generally made using or from live cells and organisms	Synthesized organic molecules
	Very often unstable; generally heat sensitive	Normally stable
	Catabolized into amino acids, sugars, lipids, etc.	Metabolism is by hepatic enzymes such as cytochrome P450
	Limited toxicity	May cause toxicity
	Do not penetrate cells and do not cross the blood-brain barrier	Cross the blood-brain barrier (especially liposoluble)
Route of administration	Parenteral	Oral
Half-life	Long half-life (days to weeks)	Short half-life
	Allow infrequent administration	Need frequent administration
Specificity for target	Highly selective and specific to target	Higher potential for effects beyond the target
Immunogenicity	Possible immunogenicity	Immunogenicity improbable
Cost	High development costs	High cost, but often lower than for a biological

Modified from Ahn J, et al.[118]

JAK inhibitors

JAK enzymes are important mediators of the intracellular activity of many substances, including the inflammatory cytokines (Figure 2). When their receptors are activated, signal transducer and activator of transcription (STAT) proteins undergo phosphorylation and can be transported to the cell nucleus, inducing transcription and regulation of the expression of selected genes. This stimulates expression of many different molecules and cytokines that facilitate mobilization of leukocytes and cell proliferation. The JAK/STAT pathway therefore plays a fundamental role in the function of hematopoietic and immunological cells and recent studies show that this pathway may be more susceptible to activation in patients with asthma, AD, and allergic rhinitis, which are diseases characterized by increased type 2 inflammatory IL.[119,120]

JAK inhibitors are small molecules, i.e. medications with low molecular weight, that can easily cross the cell membrane and reach intracellular targets. They thus act to inhibit signaling mediated by specific cytokines, acting on chains of specific receptors of JAK subtypes: JAK-1, JAK-2, JAK-3, and/or Tyrosine-Kinase 2 (TYK-2).[121,122]

Chronic pruritus is dependent on neuronal JAK-1 signaling, and inhibition of JAK appears to directly block neuronal transmission of itching.[123] Chronic pruritus is dependent on neuronal signaling by IL-4Ra and JAK-1 and patients for whom other immunosuppressant treatments have failed have achieved accentuated improvements when treated with JAK inhibitors. Blocking JAK/STAT can also affect eosinophil activation, B cell maturation, epidermal chemokines, and many other pathways involved in AD pathophysiology.[124]

The first JAK inhibiting drug was granted approval for clinical practice in 2011, for an autoimmune disease.[125] Their clinical applications are wide-ranging, from oncology to viral diseases, and they have great potential for allergic diseases and immune response type 2. The future prospects for JAK inhibitors in AD are increasingly being studied and they have recently been regulated in several countries, both for topical and systemic use.

Table 14 summarizes phase III studies with JAK inhibitors for AD and their efficacy and safety.

Upadacitinib is a selective JAK-1 inhibitor that blocks activity of the principal proinflammatory cytokines. It had already been authorized for use in rheumatoid arthritis in several countries. With

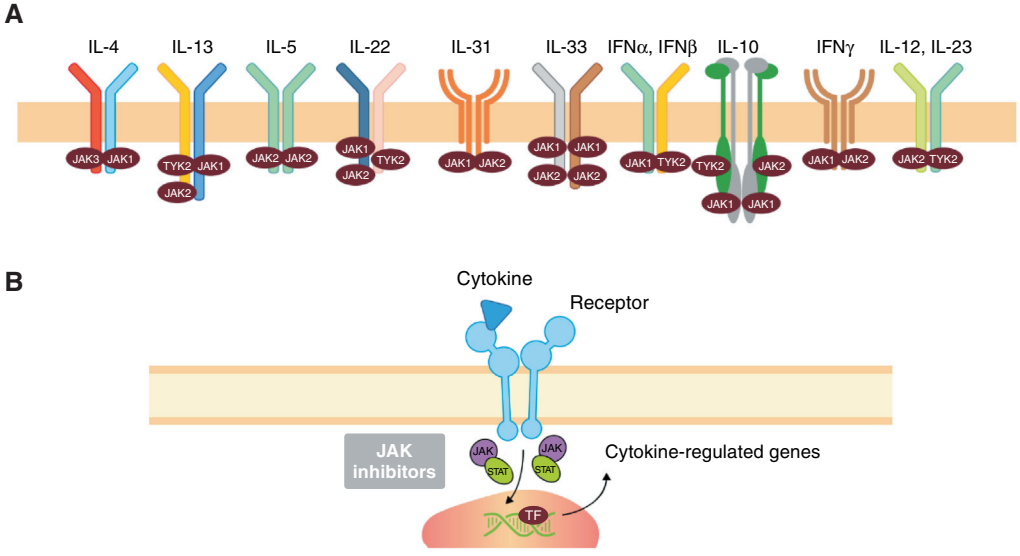


Figure 2

A) JAK signaling with cytokines involved in immune response and immunomediated diseases.

B) JAK/STAT pathway

Adapted from Ahn J, et al. [123]

Table 14
Phase 3 studies with JAK inhibitors in atopic dermatitis [a]

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Upadacitinib [127-132] (Up.) Oral route	JAK-1	MEASURE UP 1 (NCT03569293)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	847 (12 - 75 years)	16 weeks	Up. 15 mg: 69.6% Up. 30 mg: 79.7% Placebo: 16.3%	Up. 15 mg: 48.1% Up. 30 mg: 62.0% Placebo: 8.4%	Acne, URTI, nasopharyngitis, headache, increased CPK
		MEASURE UP 2 (NCT03607422)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	836 (12 - 75 years)	16 weeks	Up. 15 mg: 60.1% Up. 30 mg: 72.9% Placebo: 13.3%	Up. 15 mg: 38.8% Up. 30 mg: 52.0% Placebo: 4.7%	Acne, URTI, nasopharyngitis, headache, increased CPK
		AD UP (NCT03568318)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	901 (12 - 75 years)	16 weeks	Up. 15 mg: 64.6% Up. 30 mg: 77.1% Placebo: 26.4%	Up. 15 mg: 39.6% Up. 30 mg: 58.6% Placebo: 10.9%	Acne, nasopharyngitis, URTI, herpes oral, increased CPK, headache
		HEADS UP (NCT03738397)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4	692 (18 - 75 years)	16 weeks	Up. 30 mg: 71.0% Dup. 300 mg: 61.1%	Not reported	Acne, URTI, increased CPK, nasopharyngitis
Abrocitinib [133-140] (Ab.) Oral route	JAK-1	JADE MONO-1 (NCT03349060)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	387 (12 - 75 years)	12 weeks	Ab. 100 mg: 39.7% Ab. 200 mg: 62.7% Placebo: 11.8%	Ab. 100 mg: 23.7% Ab. 200 mg: 43.8% Placebo: 7.9%	Nausea, nasopharyngitis, headache, URTI
		JADE MONO-2 (NCT03575871)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	391 (12 - 75 years)	12 weeks	Ab. 100 mg: 44.5% Ab. 200 mg: 61.0% Placebo: 10.4%	Ab. 100 mg: 38.1% Ab. 200 mg: 28.4% Placebo: 9.1%	URTI, nasopharyngitis, headache, nausea, vomiting, acne
		JADE COMPARE (NCT03720470)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	837 (≥ 18 years)	12 weeks	Ab. 100 mg: 58.7% Ab. 200 mg: 70.3% Dup. 300 mg: 58.1% Placebo: 27.1%	Ab. 100 mg: 36.6% Ab. 200 mg: 48.4% Dup. 300 mg: 36.5%	Similar to the previous studies
		JADE TEEN (NCT03796676)	EASI ≥ 16 IGA ≥ 3 NRS ≥ 4 BSA ≥ 10%	285 (12 - 17 years)	12 weeks	Ab. 100 mg: 68.5% Ab. 200 mg: 72.0% Dup. 300 mg: 41.5%	Placebo: 14.0% Ab. 100 mg: 41.6% Ab. 200 mg: 46.2%	URTI, headache, nasopharyngitis, dizziness, acne, vomiting

* Adapted from Nogueira LB, et al.[126] URTI = upper respiratory tract infection, CPK = creatine phosphokinase.

Table 14 *(continuation)*
Phase 3 studies with JAK inhibitors in atopic dermatitis [a]

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Baricitinib [141-146] (Bar.) Oral route	JAK-1 JAK-2	BREEZE 1 (NCT03334396)	EASI ≥ 16 IGA ≥ 3	624 (≥ 18 years)	16 weeks	Bar. 1 mg: 17.3% Bar. 2 mg: 18.7% Bar. 4 mg: 24.8% Placebo: 8.8%	Bar. 1 mg: 11.8% Bar. 2 mg: 11.4% Bar. 4 mg: 16.8% Placebo: 4.8%	Nasopharyngitis, URTI, diarreia, headache
		BREEZE 2 (NCT03334422)	EASI ≥ 16 IGA ≥ 3	615 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.8% Bar. 2 mg: 17.9% Bar. 4 mg: 21.1% Placebo: 6.1%	Bar. 1 mg: 8.8% Bar. 2 mg: 10.6% Bar. 4 mg: 13.8% Placebo: 4.5%	Herpes simplex, nasopharyngitis, increased CPK, headache
		BREEZE 4 (NCT03428100)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10% Contraindication to ciclosporin	463 (≥ 18 years)	16 weeks	Bar. 1 mg: 22.6% Bar. 2 mg: 27.6% Bar. 4 mg: 31.5% Placebo: 17.2%	Bar. 1 mg: 12.9% Bar. 2 mg: 15.1% Bar. 4 mg: 21.7% Placebo: 9.7%	Nasopharyngitis, herpes simplex, influenza, headache, back and abdominal pain, diarrhea, conjunctivitis
		BREEZE 5 (NCT03435081)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	440 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.9% Bar. 2 mg: 29.5% Placebo: 8.2%	Bar. 1 mg: 12.9% Bar. 2 mg: 24.0% Placebo: 5.4%	Nasopharyngitis, URTI
		BREEZE 7 (NCT03733301)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	329 (≥ 18 years)	16 weeks	Bar. 2 mg: 43.1% Bar. 4 mg: 47.7% Placebo: 22.9%	Bar. 2 mg: 23.9% Bar. 4 mg: 30.6% Placebo: 14.7%	Folliculitis, URTI, nasopharyngitis
Ruxolitinibe [147] (Rux.) Topic	JAK-1 JAK-2	TRuE-AD 1 (NCT03745638)	IGA 2/3 BSA 3-20% (except for scalp)	631 (≥ 12 years)	8 weeks	Rux. 0.75%: 56.0% Rux. 1.5%: 62.1% Vehicle: 24.6%	Rux. 0.75%: 50.0% Rux. 1.5%: 53.8% Vehicle: 15.1%	Nasopharyngitis, URTI, headache
		TRuE-AD 2 (NCT03745651)	IGA 2/3 BSA 3-20% (except for scalp)	618 (≥ 12 years)	8 weeks	Rux. 0.75%: 51.5% Rux. 1.5%: 61.8% Vehicle: 14.4%	Rux. 0.75%: 39.0% Rux. 1.5%: 51.3% Vehicle: 7.6%	URTI, nasopharyngitis
Delgocitinib [148,149] (Del.) Topic	pan-JAK	QBA 4-1 (JapicCTI-173554)	EASI ≥ 10 BSA 10-30%	158 (≥ 16 years)	4 weeks	Del. 0.5%: 26.4% Vehicle: 5.8%	Del. 0.5%: 10.4% Vehicle: 3.8% FACE: Del. 0.5%: 22.8% Vehicle: 4.0%	Contact dermatitis
		(JapicCTI-184064)	EASI ≥ 5 IGA 2-4 BSA 5-30%	137 (2 - 15 years)	4 weeks	Del. 0.25%: 37.7% Vehicle: 4.4%	Not reported	Nasopharyngitis, folliculitis

* Adapted from Nogueira LB, et al.[126] URTI = upper respiratory tract infection, CPK = creatine phosphokinase.

publication of promising results, upadacitinib was approved for treatment of AD in patients over the age of 12 years by the European Union in August 2021,[150] by the FDA in January 2022,[151] and by ANVISA in May of the same year, for use at initial doses of 15 mg/day.[152]

Abrocitinib is a selective JAK-1 inhibitor with systemic action that is administered orally. This drug has also been approved by the FDA for use in patients with AD over the age of 18 in the United States, since January 2022.[153] This drug is still going through the regulatory process in Brazil.

Baricitinib is a JAK-1 and JAK-2 inhibitor that has been studied for use in AD since 2016, when phase 2 studies began. Although it has less efficacy than the other two oral JAK inhibitors that have had phase 3 studies for AD, baricitinib was the first JAK inhibitor approved in Europe for treatment of eczema, in September 2020,[154] and it is available in Brazil.

Ruxolitinib is a topical JAK-1 and JAK-2 inhibitor. It was developed to optimize the drug action directly on affected areas and reduce the risks of adverse systemic effects. In September 2021, ruxolitinib was approved for use with AD by the FDA and was the first JAK inhibitor approved for use in the United States, at a concentration of 1.5%, in patients over the age of 12 years.[147]

Delgocitinib is a topical pan-JAK inhibitor, i.e. it inhibits JAK-1, JAK-2, JAK-3, and TYK-2. Delgocitinib was approved for topical use with AD in Japan at concentrations of 0.25% and 0.5% for adults and for children over 2 years old in March 2021.[155]

Considering the potential for adverse events observed in pivotal clinical trials of JAK inhibitors for AD, it is necessary to conduct clinical and laboratory assessments before starting treatment to evaluate contraindications and also to monitor clinical events and laboratory findings throughout treatment. Clinical assessment must include patient history and risk factors for infectious diseases (tuberculosis, Herpes zoster, viral hepatitis, and HIV infection) and assess risk factors for thromboembolism and history of malignant cancers. The initial laboratory assessment should include full blood test, hepatic function, renal function, lipid profile, markers of viral hepatitis (B and C), and anti-HIV serology. Basic laboratory toxicity monitoring includes full blood tests, hepatic function, renal function, and lipid profile, which should be done every 3 months, and additional tests should be ordered depending on the clinical context. Investigation of active and latent tuberculosis should be conducted with PPD, chest X-ray, and interferon gamma release assay (IGRA) before treatment and over the course of treatment, if there are clinical indications. It is also recommended that immunization is up to date as scheduled before starting treatment.[156]

General recommendations for systemic treatments

According to the recommendations of national and international guidelines, systemic treatments should only be used for severe AD, i.e., for patients for whom adequate control of the disease cannot be achieved with optimized topical treatment and phototherapy. Severity should be assessed using widely used standardized and validated instruments, such as SCORAD and EASI. It is also important to assess the impact on patients' quality of life using the DLQI and the CDLQI. Patients who have moderate forms of AD, but with a major impact on their quality of life, are also Candidates for systemic treatment.[64,156,157]

Before initiating systemic treatment, it is important to revisit differential diagnosis, ruling out severe conditions that mimic AD, such as T cell lymphoma and inborn errors of immunity and evaluate adherence to treatment; investigate participation of trigger factors and aggravating factors, such as exposure to allergens (inhaled agents, foods, contactants), irritants, and psychological aspects. The choice of systemic treatment should be personalized and participatory, taking into account age group, comorbidities, adverse event profile, need for laboratory monitoring, patient preference (oral *versus* injectable medications), and the local scenario of access to the different medications. Table 15 summarizes the principal characteristics of medications for systemic treatment of AD licensed in Brazil, including those used off-label.[157]

Final comments

AD is a disease that is very prevalent in childhood and that tends to remission over time in the majority of cases. Changes to the cutaneous barrier creating the possibility of penetration by allergens and pathogens and consequent immunological dysregulation are the primary causes that explain the inflammatory process established at the level of the skin.[158]

Once epithelial damage has occurred, many different cells and cellular products are involved in the

process. We now know that Th2, Th17, Th22, and ILC-2 cells participate most actively in physiopathogenesis of AD. Several studies have shown the importance of release of many different cytokines by these cells, the direct or indirect actions of which cause greater epidermal differentiation and more severe cutaneous barrier dysfunction. It should be emphasized that many of these cytokines also function to activate cells that release products that initiate, aggravate or perpetuate the inflammatory process.[25]

Many medications have been used with the objective of inhibiting the inflammation that establishes in the dermis. Topical corticosteroids and calcineurin inhibitors are still the drugs most used as anti-inflammatory agents during the initial stages of treatment.

Table 15
General recommendations for systemic treatment of patients with atopic dermatitis [a]

	Conventional systemic treatment			Biological	JAK inhibitors		Rescue treatments
	Cyclosporine	**Methotrexate**	**Azathioprine**	**Dupilumab**	**Baricitinib**	**Upadacitinib**	**Systemic corticosteroids**
Recommendation	↑↑	↑	↑	↑↑	↑↑	↑↑	↑
Age group	≥ 16 years	Off-label	Off-label	≥ 6 years	≥ 18 years	≥ 12 years	Licensed for all age groups
Time to respond (weeks)	1-2	8-12	8-12	4-6	1-2	1-2	1-2
Basic monitoring (may be expanded depending on the context)	Complete blood count, hepatic and renal function, blood pressure	Complete blood count, hepatic and renal function, screening for chronic infections	Complete blood count, hepatic and renal function, screening for chronic infections	Unnecessary	Complete blood count, hepatic function, and lipid profile	Complete blood count, hepatic function, and lipid profile	Unnecessary for short term use Consider glycemia and adrenal suppression test with prolonged use
Most relevant adverse events	↑ Creatinine, ↑ Blood pressure	Nausea, fatigue, ↑ hepatic enzymes and myelotoxicity	Gastro-intestinal disorders, hyper-sensitivity reactions, liver toxicity, myelotoxicity	Conjunctivitis, upper airway infections	UAI, ↑ LDL-cholesterol, trombocytosis, nausea and abdominal pains, herpes, acne	UAI, acne, anemia and neutropenia, ↑ CPK, ↑ LDL-cholesterol, nausea and abdominal pains, herpes	Cutaneous atrophy, weight gain, sleep disorders, mood changes, hyperglycemia, diabetes, gastritis/peptic ulcer, osteoporosis

[a] Adapted from Wollenberg A, et al.[157]
↑↑ = higher grade recommendation, ↑ = lower grade recommendation, UAI = Upper airway infections, CPK = creatine phosphokinase.

During recent years, based on understanding of the importance of the inflammatory process, systemic immunosuppressants such as cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil have become the last resort for inhibition of this process. Their use requires special precautions because of the significant possible side effects, particularly when prescribed for prolonged periods.

It is important to point out that other medications with anti-inflammatory activity, such as systemic corticosteroids, can also be prescribed in very specific situations and for a small number of days.[75]

Addition of immunobiologicals and JAK inhibitors to the arsenal for treatment of severe to moderate AD has made safe and effective treatment possible for this population of patients. In view of the high cost of these drugs, national and international guidelines recommend their use for severe forms of AD, based on well-defined severity criteria, and after failure of optimized topical treatment.[22,159]

Immunobiologicals inhibit the activity of proinflammatory cytokines or their receptors. Dupilumab (anti IL-4/IL-13) was the first immunobiological to be used and many others are being tested in phase III clinical trials. Some are already available or will soon be approved for clinical use, such as: anti-TSLP, anti-IL-13, anti-IL31, anti-IL33, and anti-IL17.[159] Small molecules and JAK inhibitors are also being prescribed with excellent results.[83] These new drug classes attenuate disease severity, reducing the inflammatory process, improving the appearance of the skin, and relieving cutaneous pruritus, which is being proven with tools such as SCORAD and EASI.

One expectation for the coming years is that we will increase our understanding of the factors that favor development of the disease, such as genetic and epigenetic factors, external and internal exposomes, and other factors that are part of its pathophysiology.[160] We also hope that biomarkers can be identified in the future that will enable an individualized approach based on phenotypes and endotypes and also new therapeutic options that will help us to better manage this extremely complex disease.[161,162]

References

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020;396:345-60. doi: 10.1016/S0140-6736(20)31286-1.
2. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;92:44-7.
3. Williams HC, Burney PGJ, Hay RJ, Archer CB, Shipley MJ, Hunter JJA, et al. The UK Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol. 1994;131:383-96. doi: 10.1111/j.1365-2133.1994.tb08532.x.
4. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70:338-51. doi: 10.1016/j.jaad.2013.10.010.
5. Hughes AJ, Tawfik SS, Baruah KP, O'Toole EA, O'Shaughnessy RFL. Tape strips in dermatology research. Br J Dermatol. 2021;185(1):26-35. doi: 10.1111/bjd.19760.
6. Hadi HA, Tarmizi AI, Khalid KA, Gajdács M, Aslam A, Jamshed S. The Epidemiology and Global Burden of Atopic Dermatitis: A Narrative Review. Life (Basel). 2021;11(9):936. doi: 10.3390/life11090936.
7. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI; ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009;124(6):1251-8.e23. doi: 10.1016/j.jaci.2009.10.009.
8. Solé D, Mallol J, Wandalsen DF, Aguirre V, Latin American ISAAC Phase 3 Study Group. Prevalence of symptoms of eczema in Latin America: results of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3. J Investig Allergol Clin Immunol. 2010,20:311-23.
9. Mallol J, García-Marcos L, Solé D, Brand P, EISL Study Group. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. Thorax. 2010;65(11):1004-9. doi: 10.1136/thx.2009.115188.
10. Bylund S, Kobyletzki LB, Svalstedt M, Svensson Å. Prevalence and Incidence of Atopic Dermatitis: A Systematic Review. Acta Derm Venereol. 2020;100(12):adv00160. doi: 10.2340/00015555-3510.
11. Antunes AA, Solé D, Carvalho VO, Bau AEK, Kuschnir FC, Mallozi MC, et al. Guia prático de atualização em dermatite atópica - Parte I: etiopatogenia, clínica e diagnóstico. Posicionamento conjunto da Associação Brasileira de Alergia e Imunologia e da Sociedade Brasileira de Pediatria. Arq Asma Alergia Imunol. 2017;1(2):131-56. doi: 10.5935/2526-5393.20170019.
12. Pires MC, Santos RNR. Dermatites e Eczemas. In: Sittart JAS & Pires MC. Dermatologia na Prática Médica. São Paulo: Roca; 2007. p.31-62.
13. Ramírez-Marín HA, Silverberg JI. Differences between pediatric and adult atopic dermatitis. Pediatr Dermatol. 2022;39(3):345-53. doi: 10.1111/pde.14971.
14. Bieber T, D'Erme AM, Akdis CA, Traidl-Hoffmann C, Lauener R, Schäppi G, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? J Allergy Clin Immunol. 2017;139(4S):S58-S64. doi: 10.1016/j.jaci.2017.01.008.
15. Tokura Y, Hayano S. Subtypes of atopic dermatitis: From phenotype to endotype. Allergol Int. 2022;71(1):14-24. doi: 10.1016/j.alit.2021.07.003.
16. Roduit C, Frei R, Depner M, Karvonen AM, Renz H, Braun-Fahrländer C, et al. Phenotypes of Atopic Dermatitis Depending on the Timing of Onset and Progression in Childhood. JAMA Pediatr. 2017;171(7):655-62. doi: 10.1001/jamapediatrics.2017.0556.
17. Fania L, Moretta G, Antonelli F, Scala E, Abeni D, Albanesi C, et al. Multiple roles for cytokines in atopic dermatitis: from pathogenic mediators to endotype-specific biomarkers to therapeutic targets. Int J Mol Sci. 2022;23:2684-701. doi: 10.3390/ijms23052684.
18. Girolomoni G, de Bruin-Weller M, Aoki V, Kabashima K, Deleuran M, Puig L, et al. Nomenclature and clinical phenotypes of atopic dermatitis. Ther Adv Chronic Dis. 2021 Mar 26;12:20406223211002979. doi: 10.1177/20406223211002979.
19. Weidinger S, Beck L, Bieber T, Kabashima K, Irvine A. Atopic Dermatitis. Nat Rev Dis Primers. 2018;4(1):1. doi: 10.1038/s41572-018-0001-z.

20. Shaker M, Murray RGP, Mann JA. The ins and outs of an 'outside-in' view of allergies: atopic dermatitis and allergy prevention. Curr Opin Pediatr. 2018;30(4):576-81. doi: 10.1097/MOP.0000000000000646.
21. Cork M, Robinson D, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, et al. News perspectives on epidermal barrier dysfunctional in atopic dermatitis: gene – environment interactions. J Allergy Clin Immunol. 2006;118(1):3-21. doi: 10.1016/j.jaci.2006.04.042.
22. Kabashima K. New concept of the pathogenesis of atopic dermatitis interplay among barrier, allergy, and pruritus as a trinity. J Dermatol Sci. 2013;70(3):3-11. doi: 10.1016/j.jdermsci.2013.02.001.
23. De Benedetto A, Rafaels NM, Mc Girl L, Ivanov A, Ivanov AI, Georas SN, et al. Tight junctions in patients with atopic dermatitis. J Allergy Clin Immunol. 2011;127:773-88. doi: 10.1016/j.jaci.2010.10.018.
24. Paller AS, Kong HH, SeedP, Naik S, Scharschmidt TC, Gallo RL, et al. The microbiome in patients with atopic dermatitis. J Allergy Clin Immunol. 2019; 143:26-35. doi: 10.1016/j.jaci.2018.11.015.
25. Simon D, Wollenberg A, Reinz H, Simon HU. Atopic dermatitis: Collegium Internationale Allergologicum (CIA) Update 2019. Int Arch Immunol. 2019; 178(3):207-18. doi: 10.1159/000497383.
26. Czarnovwicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143:1-11. doi: 10.1016/j.jaci.2018.10.032.
27. Sroka-TomaszewskaJ,Trzeciak M. Molecular Mechanisms of Atopic Dermatitis Pathogenesis. Int J Mol Sci. 2021;22(8):4130. doi: 10.3390/ijms22084130.
28. Bae JS, Da F, Liu R, He L, Lv H, Fisher EL, et al. Contribution of Staphylococcal Enteroxin B to Staphylococcus aureus Systemic Infection. J Infect Dis. 2021;223(10):1766-75. doi: 10.1093/infdis/jiaa584.
29. Yue H, Umehara Y, Trujillo-Paez JV, Peng G, Nguyen HLT, Chieosilapatham P, et al. Exogenous factors in the pathogenesis of atopic dermatitis: Irritants and cutaneous infections. Clin Exp Allergy. 2021;51:382-92. doi: 10.1111/cea.13820.
30. Katoh N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, et al. Japanese guidelines for atopic dermatitis 2020. Allergol Int. 2020;69(3):356-69. doi: 10.1016/j.alit.2020.02.006.
31. Nguyen GH, Andersen LK, Davis MDP. Climate change and atopic dermatitis: is there a link? Int J Dermatol. 2019;58(3):279-282. doi: 10.1111/ijd.14016.
32. Domíngues O, Plaza AM, Alvaro M. Relantionship Between Atpoic Dermatitis and Food Allergy. Cur Pediatr Rev. 2020;16(2):115-22. doi: 10.2174/1573396315666191111122436.
33. Zhong Y, Samuel M, van Bever H, Tham EH. Emollients in infancy to prevent atopic dermatitis: A systematic review and meta-analysis. Allergy. 2022;77(6):1685-99. doi: 10.1111/all.15116.
34. Oykhman P, Dookie J, Al-Rammahy H, de Benedetto A, Asiniwasis RN, LeBovidge J. Dietary Elimination for the Treatment of Atopic Dermatitis: A Systematic Review and Meta-analysis. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2657-2666.e8. doi: 10.1016/j.jaip.2022.06.044
35. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol.2018;16(3):143-55. doi: 10.1038/nrmicro.2017.157
36. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657-82. doi: 10.1111/jdv.14891.
37. Hiragun T, Ishii K, Hiragun M, Suzuki H, Kan T, Mihara S, et al. Fungal protein MGL_1304 in sweat is an allergen for atopic dermatitis patients. J Allergy Clin Immunol. 2013;132:608e15. doi: 10.1016/j.jaci.2013.03.047.
38. Sugita T, Suto H, Unno T, Tsuboi R, Ogwa h, Shinoda T, et al. Molecular analysis of Malassezia microflora on the skin of atopic dermatitis patients and healthy subjects. J Clin Microbiol. 2001;39(10):3486-90. doi: 10.1128/JCM.39.10.3486-3490.2001.
39. Tamagawa-Mineoka R, Katoh N. Atopic Dermatitis: Identification and Management of Complicating Factors. Int J Mol Sci. 2020;21:2671. doi:10.3390/ijms21082671.
40. Barrett M, Luu M. Differential Diagnosis of Atopic Dermatitis. Immunol Allergy Clin North Am. 2017;37(1):11-34. doi: 10.1016/j.iac.2016.08.009.
41. Fishbein AB, Silverberg JI, Wilson EJ, Ong PY. Update on Atopic Dermatitis: Diagnosis, Severity Assessment, and Treatment Selection. J Allergy Clin Immunol Pract. 2020;8(1):91-101. doi: 10.1016/j.jaip.2019.06.044.
42. Brar KK, Nicol NH, Boguniewicz M. Strategies for Successful Management of Severe Atopic Dermatitis. J Allergy Clin Immunol Pract. 2019;7(1):1-16. doi: 10.1016/j.jaip.2018.10.021.
43. Stadler PC, Renner ED, Milner J, Wollenberg A. Inborn Error of Immunity or Atopic Dermatitis: When to be Concerned and How to Investigate. J Allergy Clin Immunol Pract. 2021;9(4):1501-7. doi: 10.1016/j.jaip.2021.01.037.
44. Mortz CG, Brockow K, Bindslev-Jensen C, Broesby-Olsen S. It looks like childhood eczema but is it? Clin Exp Allergy. 2019;49(6):744-53. doi: 10.1111/cea.13381.
45. Vaseghi-Shanjani M, Smith KL, Sara RJ, Modi BP, Branch A, Sharma M, et al. Inborn errors of immunity manifesting as atopic disorders. J Allergy Clin Immunol. 2021;148(5):1130-9. doi: 10.1016/j.jaci.2021.08.008.
46. Huang E, Ong PY. Severe Atopic Dermatitis in Children. Curr Allergy Asthma Rep. 2018;18(6):35. doi: 10.1007/s11882-018-0788-4.
47. Cinicola BL, Corrente S, Castagnoli R, Lougaris V, Giardino G, Leonardi L, et al. Primary atopic disorders and chronic skin disease. Pediatr Allergy Immunol. 2022;33(Suppl 27): 65-8. doi: 10.1111/pai.13633.
48. Chopra R, Silverberg JI. Assessing the severity of atopic dermatitis in clinical trials and practice. Clin Dermatol. 2018;36(5):606-15. doi: 10.1016/j.clindermatol.2018.05.012.
49. Williams HC, Schmitt J, Thomas KS, Spuls PI, Simpson EL, Apfelbacher CJ, et al. The HOME Core outcome set for clinical trials of atopic dermatitis. J Allergy Clin Immunol. 2022;149(6):1899-911. doi: 10.1016/j.jaci.2022.03.017.
50. Simpson E, Bissonnette R, Eichenfield LF, Guttman-Yassky E, King B, Silverberg JI, et al. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. J Am Acad Dermatol. 2020;83(3):839-46. doi: 10.1016/j.jaad.2020.04.104.
51. European Task Force on Atopic Dermatitis. Severity Scoring of Atopic Dermatitis: The SCORAD Index. Dermatology. 1993;186:23-31. doi: 10.1159/000247298.
52. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-Van Der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: The SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol. 2007;157(4):645-8. doi: 10.1111/j.1365-2133.2007.08112.x.
53. Stalder JF, Barbarot S, Wollenberg A, Holm EA, de Raeve L, Seidenari S, et al. Patient-Oriented SCORAD (PO-SCORAD): A new self-assessment scale in atopic dermatitis validated in Europe. Allergy: Eur J Allergy Clin Immunol. 2011;66(8):1114-21. doi: 10.1111/j.1398-9995.2011.02577.x.
54. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001;10(1):11-8. doi: 10.1034/j.1600-0625.2001.100102.x.
55. Hanifin JM, Baghoomian W, Grinich E, Leshem YA, Jacobson M, Simpson EL. The Eczema Area and Severity Index - A Practical Guide. Dermatitis. 2022;33(3):187-92. doi: 10.1097/DER.0000000000000895.
56. Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. Br J Dermatol. 2017;176:979-84. doi: 10.1111/bjd.15179.

57. University of Nottingham. POEM – Patient Oriented Eczema Measure [Internet]. Available at: www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx. Accessed on: 07/15/2022.
58. Atopic dermatitis control tool (ADCT) [Internet]. Available at: www.adcontroltool.com. Accessed on: 07/15/2022.
59. Simpson E, Eckert L, Gadkari A, Mallya UG, Yang M, Nelson L, et al. Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol. 2019;19(1):15. doi: 10.1186/s12895-019-0095-3.
60. Kulthanan K, Tuchinda P, Nitiyarom R, Chunharas A, Chantaphakul H, AunhachokeK, et al. Clinical practice guidelines for the diagnosis and management of atopic dermatitis. Asian Pac J. Allergy Immunol.2021;39:145-55. doi: 10.12932/AP-010221-1050.
61. Waldman AR, Ahluwalia J, Udkoff J, Borok JF, Eichenfield LF. Atopic Dermatitis. Pediatr Rev. 2018; 39(4):180-91. doi: 10.1542/pir.2016-0169.
62. Van Zurren EJ, Fedorowicz Z, Arents BWM. Emollients and moisturisers for eczema: abridged Cochrane systematic review including GRADE assessments. Br J Dermatol. 2017;177(5):1256-71. doi: 10.1111/bjd.15602.
63. Eichenfield LF, Boguniewicz M, Simpson EL, Russel Jj, Block JK, Feldman SR, et al. Translating Atopic Dermatitis Management Guidelines Into Practice for Primary Care Providers. Pediatrics. 2015;136(3):554-65. doi: 10.1542/peds.2014-3678.
64. Carvalho VO, Solé D, Antunes AA, Bau AEK, Kuschnir FC, Mallozi MC, et al. Guia prático de atualização em dermatite atópica - Parte II: abordagem terapêutica. Posicionamento conjunto da Associação Brasileira de Alergia e Imunologia e da Sociedade Brasileira de Pediatria. Arq Asma Alergia Imunol. 2017;1(2):157-82. doi: 10.5935/2526-5393.20170020.
65. LePoidevin LM, Lee DE, Shi VY. A comparison of international management guidelines for atopic dermatitis. Pediatr Dermatol. 2018;36(1):36-65. doi: 10.1111/pde.13678.
66. Chandan N, Rajkumar JR, Shi VY, Lio PA. A new era of moisturizers. J Cosmet Dermatol. 2021;20(8):2425-30. doi: 10.1111/jocd.14217.
67. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32:850-78. doi: 10.1111/jdv.14888.
68. Myers E, Kheradmand S, Miller R. An Update on Narrowband Ultraviolet B Therapy for the Treatment of Skin Diseases. Cureus. 2021;13(11):e19182. doi: 10.7759/cureus.19182
69. Sociedade Brasileira de Dermatologia. Manual Prático de Fototerapia. 1ªed. Rio de Janeiro: SBD; 2020. p. 86.
70. Torres T, Ferreira EO, Gonçalo M, Mendes-Bastos P, Selores M, Filipe P. Update on Atopic Dermatitis. Acta Med Portug. 2019;32(9):606-13. doi: 10.20344/amp.11963.
71. Musters AH, Mashayekhi S, Harvey J, Axon E, Lax SJ, Flohr C, et al. Phototherapy for atopic eczema. Cochrane Database of Systematic Rev. 2021;10(10): CD013870. doi: 10.1002/14651858.CD013870.pub2.
72. Hunjan MK, Brockley JR, Buka R, Ramesh R. Treatment of paediatric eczema with narrowband ultraviolet light B therapy. Photodermatol Photoimmunol Photomed. 2021;37(2):105-10. doi: 10.1111/phpp.12615.
73. Kemény L, Varga E, Novak Z. Advances in phototherapy for psoriasis and atopic dermatitis. Exp Rev Clin Immunol. 2019;15(11):1205-14. doi: 10.1080/1744666X.2020.1672537.
74. Seccombe E, Wynne MD, Clancy C, Godfrey KM, Fityan A. A retrospective review of phototherapy in children, at a tertiary paediatric dermatology unit. Photodermatol Photoimmunol Photomed. 2021;37(1):34-8. doi: 10.1111/phpp.12604.
75. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Amer Acad Dermatol. 2014;71(2):327-49. doi: 10.1016/j.jaad.2014.03.030.
76. Diaz A, Guttman-Yassky E. Topical agents for the treatment of atopic dermatitis. Expert Rev Clin Immunol. 2019;15(4):369-82. doi: 10.1080/1744666X.2019.1564038.
77. Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology: a textbook of skin disorders of childhood and adolescence. 6ª ed. Nova Iorque: Elsevier; 2022.
78. Chisolm SS, Taylor SL, Balkrishnan R, Feldman SR. Written action plans: potential for improving outcomes in children with atopic dermatitis. J Am Acad Dermatol. 2008;59(4):677-83. doi: 10.1016/j.jaad.2008.04.025.
79. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol. 2016;175(5):902-11. doi: 10.1111/bjd.14871.
80. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess. 2000;4(37):1-191.
81. Wollenberg A, Christen-Zäch S, Taieb A, Paul C, Thyssen JP, de Bruin-Weller M, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020;34(12):2717-44. doi: 10.1111/jdv.16892.
82. Katoh N. Future perspectives in the treatment of atopic dermatitis. J Dermatol. 2009;36(7):367-76. doi: 10.1111/j.1346-8138.2009.00662.x.
83. Chovatiya R, Paller AS. JAK inhibitors in the treatment of atopic dermatitis. J Allergy Clin Immunol. 2021;148(4):927-40. doi: 10.1016/j.jaci.2021.08.009.
84. Chopra R, Vakharia PP, Sacotte R, Silverberg JI. Efficacy of bleach baths in reducing severity of atopic dermatitis: A systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2017;119(5):435-40. doi: 10.1016/j.anai.2017.08.289.
85. Devillers AC, Oranje AP. Efficacy and safety of 'wet-wrap' dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: a critical review of the literature. Br J Dermatol. 2006;154(4):579-85. doi: 10.1111/j.1365-2133.2006.07157.x.
86. Petry V, Lipnharski C, Bessa G, Silveira V, Weber M, Bonamigo R, et al. Prevalence of community-acquired methicillin-resistant Staphylococcus aureus and antibiotic resistance in patients with atopic dermatitis in Porto Alegre, Brazil. Int J Dermatol. 2014;53:731-5. doi: 10.1111/ijd.12020.
87. Abad E, Ferreira D, Cavalcante F, Saintive S, Goudouris E, Prado E, et al. High incidence of acquiring methicillin-resistant Staphylococcus aureus in Brazilian children with Atopic Dermatitis and associated risk factors. J Microbiol Immunol Infect. 2020;53:724-730. doi: 10.1016/j.jmii.2018.12.014.
88. Briscoe C, Reich P, Fritz S, Coughlin C. Staphylococcus aureus antibiotic susceptibility patterns in pediatric atopic dermatitis. Pediatr Dermatol. 2019;36:482-5. doi: 10.1111/pde.13867.
89. Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. Allergy. 2021;76(4):1053-76. doi: 10.1111/all.14631.
90. Brasil. Agência Nacional de Vigilância Sanitária (ANVISA). Bulário eletrônico [Internet]. Available at: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=CICLOSPORINA. Accessed on: 07/15/2022.
91. Simpson EL, Bruin-Weller M, Flohr C, Ardern-Jones MR, Barbarot S, Deleuran M, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. J Am Acad Dermatol. 2017;77(4):623-33. doi: 10.1016/j.jaad.2017.06.042.
92. Davari DR, Nieman EL, McShane DB, Morrell DS. Current Perspectives on the Systemic Management of Atopic Dermatitis. J Asthma Allergy. 2021;14:595-607. doi: 10.2147/JAA.S287638.
93. Roekevisch E, Spuls P I, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review. J Allergy Clin Immunol. 2014;133:429-38. doi: 10.1016/j.jaci.2013.07.049.

94. Aliaga GLC, Anagusko CLY, Gomes LS, Mamede LQ, Moraes P, Cunha PS, et al. Adverse effects of using cyclosporine in patients with severe atopic dermatitis. Arq Asma Alergia Imunol. 2020;4(1):99-102.

95. Associação Brasileira de Imunizações (SBIM). Calendários de vacinação SBIm para pacientes especiais – 2021-2022 [Internet]. Available at: https://sbim.org.br/images/calendarios/calend-sbim-pacientes-especiais.pdf. Accessed on: 08/20/2022.

96. Diniz AF, Bruscky DMV, Falcão ACA, Melo ACCDB, Peixoto DM, Sarinho ESC. Metotrexato em crianças e adolescentes com dermatite atópica: série de casos. Arq Asma Alergia Imunol. 2020;4(4):458-63. doi:10.5935/2526-5393.20200068.

97. Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to severe adult atopic eczema. Br J Dermatol. 2007;156(2):346-51. doi: 10.1111/j.1365-2133.2006.07686.x.

98. Goujon C, Viguier M, Staumont-Sallé D, Bernier C, Guillet G, Lahfa M, et al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. J Allergy Clin Immunol Pract. 2018;6(2):562-569.e3. doi: 10.1016/j.jaip.2017.07.007.

99. El-Khalawany MA, Hassan H, ShaabanD, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. Eur J Pediatr. 2013;172:351-6. doi: 10.1007/s00431-012-1893-3.

100. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol. 2011;128:353-9. doi: 10.1016/j.jaci.2011.03.024

101. Deo M, Yung A, Hill S, Rademaker M. Methotrexate for treatment of atopic dermatitis in children and adolescents. Int J Dermatol. 2014;53(8):1037-41. doi: 10.1111/ijd.12314.

102. Garritsen FM, Roekevisch E, van der Schaft J, Deinum J, Spuls PI, de Bruin-Weller MS. Ten years experience with oral immunosuppressive treatment in adult patients with atopic dermatitis in two academic centres. J Eur Acad Dermatol Venereol. 2015;29(10):1905-12. doi: 10.1111/jdv.13064.

103. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. Lancet. 2006;367:839-46. doi: 10.1016/S0140-6736(06)68340-2.

104. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/ American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. J Allergy Clin Immunol. 2006;118:152-69. doi: 10.1016/j.jaci.2006.03.045.

105. Murphy LA, Atherton DJ. Azathioprine as a treatment for severe atopic eczema in children with a partial thiopurine methyl transferase (TPMT) deficiency. Pediatr Dermatol. 2003;20:531-4.73. doi: 10.1111/j.1525-1470.2003.20617.x.

106. Murray ML, Cohen JB. Mycophenolatemofetil therapy for moderate to severe atopic dermatitis. Clin Exp Dermatol. 2007;32:23-27. doi: 10.1111/j.1365-2230.2006.02290.x.

107. Waxweiler WT, Agans R, Morrell DS. Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolatemofetil. Pediatr Dermatol. 2011;28:689-94. doi: 10.1111/j.1525-1470.2011.01488.x.

108. Reis AP, Aarestrup FM. Imunoterapia e imunobiológicos na dermatite atópica. Arq Asma Alergia Imunol. 2019;3(2):123-32. doi: 10.5935/2526-5393.20190022

109. Seegräber M, Srour J, Walter A, Knop M, Wollenberg A. Dupilumab for treatment of atopic dermatitis. Exp Rev Clin Pharmacol. 2018;11:467-74. doi: 10.1080/17512433.2018.1449642.

110. Matsuyama C. Dupilumabe: novo horizonte no tratamento da rinossinusite crônica com pólipos nasais (RSCcPN); Sanofi 2022.

111. Dupilumabe - bula disponível na Internet. São Paulo: Sanofi Medley Farmacêutica Ltda; 2022. Available at: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Dupixent. Accessed on: 08/11/2022.

112. Harb H, Chatila TA. Mechanisms of Dupilumab. Clin Exp Allergy. 2020;50(1):5-14. doi: 10.1111/cea.13491.

113. Aoki V, Lorenzini D, Orfali RL, Zaniboni MC, Oliveira ZN, Rivitti-Machado MC, et al. Consensus on the therapeutic management of atopic dermatitis - Brazilian Society of Dermatology. An Bras Dermatol. 2019;94(2 Suppl 1):67-75.

114. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156(1):44-56. doi: 10.1001/jamadermatol.2019.3336.

115. Wollenberg A, Ariens L, ThurauS, vanLuijk C, Seegräber M, de Bruin-Weller M. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab - clinical characteristics and treatment. J Allergy Clin Immunol Pract. 2018;6(5):1778-80.e1. doi: 10.1016/j.jaip.2018.01.034.

116. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 monoclonal antibody. J Allergy Clin Immunol. 2018;143(1):135-41. doi: 10.1016/j.jaci.2018.05.029.

117. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. J Am Acad Dermatol. 2018;78:872-81. doi: 10.1016/j.jaad.2018.01.016.

118. Ahn J, Grinich EE, Choi Y, Guttman-Yassky E, Simpson EL. Emerging systemic therapeutic biologics and small molecules for atopic dermatitis: how to decide wich treatment is right for your patients. J Allergy Clin Immunol Pract. 2021;9:1449-60. doi: 10.1016/j.jaip.2021.02.003.

119. Howell MD, Fitzsimons C, Smith PA. JAK/STAT inhibitors and other small molecule cytokine antagonists for the treatment of allergic disease. Ann Allergy Asthma Immunol. 2018;120(4):367-75. doi:10.1016/j.anai.2018.02.012.

120. Klein B, Treudler R, Simon JC. JAK inhibitors in dermatology – small molecules, big impact? Overview of the mechanism of action, previous study results and potential adverse effects. J Dtsch Dermatol Ges. 2022;20(1):19-24. doi: 10.1111/ddg.14668.

121. Soeberdt M, Kilic A, Abels C. Small molecule drugs for the treatment of pruritus in patients with atopic dermatitis. Eur J Pharmacol. 2020;881:173242. doi: 10.1016/j.ejphar.2020.173242.

122. Li Q, Kang C. Mechanisms of Action for Small Molecules Revealed by Structural Biology in Drug Discovery. Int J Mol Sci. 2020;21(15):5262. doi: 10.3390/ijms21155262.

123. Ahn J, Choi Y, Simpson EL. Therapeutic New Era for Atopic Dermatitis: Part 2. Small Molecules. Ann Dermatol. 2021;33(2):101-7. doi: 10.5021/ad.2021.33.2.101.

124. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. Cell. 2017;171:217-28. doi: 10.1016/j.cell.2017.08.006.

125. FDA. Ruloxitinib. Drugs@FDA: FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=215309. Accessed on: 07/10/2022.

126. Nogueira LB, Chong-Silva DC, Rosário Filho NA, Chong-Neto HJ. Inibidores de JAK no tratamento da dermatite atópica. Arq Asma Alerg Imunol. 2022;6(3):331-43.

127. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet. 2021;397(10290):2151-68. doi: 10.1016/S0140-6736(21)00588-2.

128. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, Werfel T, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2021;397(10290):2169-81. doi: 10.1016/S0140-6736(21)00589-4.

129. Mendes-Bastos P, Ladizinski B, Guttman-Yassky E, Jiang P, Liu J, Prajapati VH, et al. Characterization of acne associated with upadacitinib treatment in patients with moderate-to-severe atopic dermatitis: A post hoc integrated analysis of 3 phase 3 randomized, double-blind, placebo-controlled trials. J Am Acad Dermatol. 2022 Oct;87(4):784-791. doi: 10.1016/j.jaad.2022.06.012.

130. Simpson EL, Papp KA, Blauvelt A, Chu CY, Hong HC, Katoh N, et al. Efficacy and Safety of Upadacitinib in Patients with Moderate to Severe Atopic Dermatitis: Analysis of Follow-up Data From the Measure Up 1 and Measure Up 2 Randomized Clinical Trials. JAMA Dermatol. 2022;158(4):404-13. doi: 10.1001/jamadermatol.2022.0029.

131. Silverberg JI, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, Costanzo A, et al. Upadacitinib plus topical corticosteroids in atopic dermatitis: Week 52 AD Up study results. J Allergy Clin Immunol. 2022;149(3):977-87.e14. doi: 10.1016/j.jaci.2021.07.036.

132. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2021;157(9):1047-55. doi: 10.1001/jamadermatol.2021.3023.

133. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(8):863-73. doi: 10.1001/jamadermatol.2020.1406.

134. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet. 2020;396(10246):255-66. doi: 10.1016/S0140-6736(20)30732-7.

135. Blauvelt A, Boguniewicz M, Brunner PM, Luna PC, Biswas P, DiBonaventura M, et al. Abrocitinib monotherapy in Investigator's Global Assessment nonresponders: improvement in signs and symptoms of atopic dermatitis and quality of life. J Dermatolog Treat. 2022 Aug;33(5):2605-13. doi: 10.1080/09546634.2022.2059053.

136. Blauvelt A, Silverberg JI, Lynde CW, Bieber T, Eisman S, Zdybski J, et al. Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial. J Am Acad Dermatol. 2022;86(1):104-12. doi: 10.1016/j.jaad.2021.05.075.

137. Thyssen JP, Yosipovitch G, Paul C, Kwatra SG, Chu CY, DiBonaventura M, et al. Patient-reported outcomes from the JADE COMPARE randomized phase 3 study of abrocitinib in adults with moderate-to-severe atopic dermatitis. J Eur Acad Dermatol Venereol. 2022;36(3):434-43. doi: 10.1111/jdv.17813.

138. Alexis A, de Bruin-Weller M, Weidinger S, Soong W, Barbarot S, Ionita I, et al. Rapidity of Improvement in Signs/Symptoms of Moderate-to-Severe Atopic Dermatitis by Body Region with Abrocitinib in the Phase 3 JADE COMPARE Study. Dermatol Ther (Heidelb). 2022;12(3):771-85. doi: 10.1007/s13555-022-00694-1.

139. Shi VY, Bhutani T, Fonacier L, Deleuran M, Shumack S, Valdez H, et al. Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND). J Am Acad Dermatol. 2022;87(2):351-8. doi: 10.1016/j.jaad.2022.04.009.

140. Eichenfield LF, Flohr C, Sidbury R, Siegfried E, Szalai Z, Galus R, et al. Efficacy and Safety of Abrocitinib in Combination With Topical Therapy in Adolescents With Moderate-to-Severe Atopic Dermatitis: The JADE TEEN Randomized Clinical Trial. JAMA Dermatol. 2021;157(10):1165-73. doi: 10.1001/jamadermatol.2021.2830.

141. Reich K, DeLozier AM, Nunes FP, Thyssen JP, Eichenfield LF, Wollenberg A, et al. Baricitinib improves symptoms in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: patient-reported outcomes from two randomized monotherapy phase III trials. J Dermatol Treat. 2020;22:1-10. doi: 10.1080/09546634.2020.1839008.

142. Bieber T, Reich K, Paul C, Tsunemi Y, Augustin M, Lacour JP, et al.; BREEZE-AD4 study group. Efficacy and safety of baricitinib in combination with topical corticosteroids in patients with moderate-to-severe atopic dermatitis with inadequate response, intolerance or contraindication to ciclosporin: results from a randomized, placebo-controlled, phase III clinical trial (BREEZE-AD4). Br J Dermatol. 2022;187(3):338-52. doi: 10.1111/bjd.21630.

143. Silverberg JI, Boguniewicz M, Waibel J, Weisman J, Strowd L, Sun L, et al. Clinical Tailoring of Baricitinib 2 mg in Atopic Dermatitis: Baseline Body Surface Area and Rapid Onset of Action Identifies Response at Week 16. Dermatol Ther (Heidelb). 2022;12(1):137-48. doi: 10.1007/s13555-021-00640-7.

144. Simpson EL, Forman S, Silverberg JI, Zirwas M, Maverakis E, Han G, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy phase 3 trial in the United States and Canada (BREEZE-AD5). J Am Acad Dermatol. 2021;85(1):62-70. doi: 10.1016/j.jaad.2021.02.028.

145. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T, et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(12):1333-43. doi: 10.1001/jamadermatol.2020.3260.

146. de Bruin-Weller MS, Serra-Baldrich E, Barbarot S, Grond S, Schuster C, Petto H, et al. Indirect Treatment Comparison of Baricitinib versus Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis. Dermatol Ther (Heidelb). 2022;12(6):1481-91. doi: 10.1007/s13555-022-00734-w.

147. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol. 2021;85(4):863-72. doi: 10.1016/j.jaad.2021.04.085.

148. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kabashima K, Oda M, et al. Delgocitinib ointment in pediatric patients with atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and a subsequent open-label, long-term study. J Am Acad Dermatol. 2021;85(4):854-62. doi: 10.1016/j.jaad.2021.06.014.

149. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Murata R, Kaino H, Nagata T. Long-term safety and efficacy of delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with atopic dermatitis. J Dermatol. 2020;47(2):114-20. doi: 10.1111/1346-8138.15173.

150. European Medicines Agency. Rinvoq - european medicines agency [Internet]. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/rinvoq. Accessed on: 07/22/2022.

151. FDA. Upadacitinib - Drugs@FDA: FDA-Approved Drugs [Internet]. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed on: 07/15/2022.

152. Diário Oficial da União. Ministério da Saúde/Agência Nacional de Vigilância Sanitária/2ª Diretoria/Gerência-Geral de Medicamentos e Produtos. Resolução Re N° 1.355, de 28 de Abril de 2022. Available at: https://www.in.gov.br/web/dou/-/resolucao-re-n-1.355-de-28-de-abril-de-2022-396547245. Accessed on: 07/15/2022.

153. FDA. Abrocitinib - Drugs@FDA: FDA-ApprovedDrugs [Internet]. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed on: 07/12/2022.

154. European Medicines Agency. Olumiant - european medicines agency [|Internet]. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/olumiant. Accessed on: 07/22/2022.

155. Dhillon S. Delgocitinib: First Approval. Drugs. 2020;80(6):609-15. doi: 10.1007/s40265-020-01291-2.

156. Torres T, Gonçalo M, Lopes MJP, Claro C, Ramos L, Selores M, et al. Portuguese recommendations for the treatment of atopic dermatitis with biologic therapy and JAK inhibitors in adult patients. Drugs Contex. 2021;10:2021-9-5. doi: 10.7573/dic.2021-9-5.

157. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S, et al. European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy. J Eur Acad Dermatol Venereol. 2022;36:1409-31. doi: 10.1111/jdv.18345.

158. Ahn K, Kim BE, Leung DYM. Recent advances in atopic dermatitis. Curr Opin Immunol. 2020;16:14-21. doi: 10.1016/j.coi.2020.02.007.

159. Wu J, Guttman-Yassky E. Efficacy of biologics in atopic dermatitis. Exp Opin Biol Ther. 2020;20(5):525-38. doi: 10.1080/14712598.2020.1722998.

160. Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. Allergy. 2020;75(1):63-74. doi: 10.1111/all.13946.

161. Moyle M, Cevikbas F, Harden J, Guttman-Yassky E. Understanding the immune landscape in atopic dermatitis. The era of biologics and emerging therapeutic approaches. Exp Dermatol. 2019;28:756-68. doi: 10.1111/exd.13911.

162. Puar N, ChovatiyaR , Paller AS. New treatments in atopic dermatitis. Ann Asthma Immunol. 2021;126(1):21-31. doi: 10.1016/j.anai.2020.08.016.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Update on hypersensitivity reactions to nonsteroidal anti-inflammatory drugs – Part 2: clinical features, phenotypes, diagnosis, and management

Atualização em reações de hipersensibilidade aos anti-inflamatórios não esteroidais – Parte 2: manifestações clínicas, fenótipos, diagnóstico e manejo

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ABSTRACT

Nonsteroidal anti-inflammatory drugs are a major cause of drug hypersensitivity reactions in clinical practice. In this "Update Part 2", we discuss the clinical picture, including the main signs and symptoms, how to distinguish clinical phenotypes, how to manage affected patients, and when to indicate additional procedures, such as skin testing, challenge, and desensitization.

Keywords: Nonsteroidal anti-inflammatory drugs, drug hypersensitivity, phenotype.

RESUMO

Os anti-inflamatórios não esteroidais (AINE) são os fármacos mais frequentemente associados a reações de hipersensibilidade (RH) na prática clínica. Na parte 2 dessa atualização sobre as RH aos AINE, discutiremos os aspectos clínicos dessas reações, com foco nos sinais e sintomas, como diferenciar os fenótipos clínicos, fazer a orientação desses pacientes e quando indicar procedimentos complementares, como testes cutâneos, de provocação e dessensibilização.

Descritores: Anti-inflamatórios não esteroidais, hipersensibilidade a drogas, fenótipo.

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Introduction

In Part 1 of this review, we discuss the pharmacology of nonsteroidal anti-inflammatory drugs (NSAIDs), including the pathophysiological role of the inhibition of cyclooxygenase (COX) 1 and 2 in the genesis of most hypersensitivity reactions (HR), the genetic and epidemiological aspects of these reactions, and the mechanisms involved in their occurrence, whether they are allergic (Gell and Coombs' type I and IV) or non-allergic.[1] In Part 2, we will approach the clinical picture of each of the classical phenotypes of NSAID HRs, other possible and less frequent phenotypes, particularities in the pediatric population, and mainly the management of these patients, which includes all steps between diagnosis and treatment. Their treatment can involve adequate guidance on restricting or substituting the drugs in question or indicating desensitization.

Clinical features and phenotypes

Clinically, HRs to NSAIDs can be classified according to the timing of symptom onset into *acute* – when occurring less than 24 hours after exposure to the medication (usually immediately, less than 60 minutes after drug administration) – and *delayed*, when they occur after these 24 hours.[2] However, more than just the time between exposure and reaction, the pattern of clinical manifestations has fundamental importance when defining the phenotype.

NSAID-exacerbated respiratory disease (NERD)

In 1922, Widal and colleagues published the first study describing the association between aspirin hypersensitivity, asthma, and nasal polyps; the researchers also conducted the first aspirin challenge followed by desensitization. However, this syndrome was only recognized in the 1960s, when Samter published two studies with a condition that he named Samter's triad; it included asthma, nasal polyps, and aspirin reactions. Many other names were used for this respiratory disease, such as aspirin-induced asthma, aspirin hypersensitivity, and aspirin intolerance.[3] In 2001, Stevenson and colleagues coined the term "aspirin-exacerbated respiratory disease" (AERD), including not only asthma but also the upper airways, in addition to valuing the frequent association with an underlying respiratory disease.[4]

All these terms refer to the same untreatable inflammatory condition of the upper and lower airways; many further studies demonstrated the importance of eosinophilic inflammation of the respiratory tract in this triad. Exposure to aspirin does not initiate or even perpetuate an underlying inflammatory disease; however, after disease onset, aspirin and NSAIDs induce the liberation or synthesis of critical mediators that lead to the clinical manifestations of the characteristic respiratory reactions.[3]

Clinically, AERD is characterized by the triad: chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), asthma, and hypersensitivity to aspirin or other NSAIDs.[5,6] Therefore, the currently used acronym is "NERD," referring to "NSAID-exacerbated respiratory disease" and not just aspirin.

Other clinical features have been shown to be frequent in NERD, such as marked anosmia, atopy, alcohol intolerance, and a shorter interval between polypectomies.[6,7]

The clinical features of NERD are not usually present at disease onset; most times, they progress according to a pattern. The first clinical manifestation to appear in patients with NERD is rhinitis, considered as nasal obstruction, nasal discharge, anosmia/hyposmia, and sneezing. Anosmia/hyposmia is frequent (89%) and intense. Chronic rhinitis progresses to chronic hyperplastic eosinophilic sinusitis, which can be seen in up to 99% of patients as hyperdensity on computed tomography scans of the sinuses. The first manifestation of asthma appears on average two years after rhinitis, and hypersensitivity to aspirin or other COX-1-inhibiting NSAIDs tends to appear four years later. However, other studies demonstrated that hypersensitivity to aspirin/NSAIDs can appear at any moment during the course of the disease.[8]

The frequency of respiratory symptoms induced by alcohol consumption in patients with NERD is high; upper airway symptoms (rhinorrhea, nasal obstruction) are reported in up to 75% of the patients, and lower airway symptoms (wheezing and dyspnea) are reported by 51% of the patients.[9]

Although NERD has a characteristic presentation, including the presence of respiratory symptoms a few minutes to hours after the use of any COX-1-inhibiting NSAID (acute reaction), patients with NERD are heterogeneous[3]. Bochenek and colleagues classified patients with NERD into four subtypes. Class 1: moderate asthma, severe CRS, and peripheral blood

eosinophilia; Class 2: mild CRS, mild and relatively well-controlled asthma; Class 3: severe, poorly controlled asthma, severe exacerbations, and severe bronchial obstruction; and Class 4: poorly controlled asthma with frequent and severe exacerbations in women, normal lung function, and obesity.[10]

Another study classified NERD through an analytical strategy named latent class analysis into three subphenotypes, considering the inflammatory pathways and clinical manifestations of asthma. The subphenotypes included 16 variables: clinical characteristics such as gender, body mass index, age of asthma onset, history of asthma exacerbation, control and severity of asthma, use of inhaled and/or systemic corticosteroid, forced expiratory volume in 1 second (FEV_1), serum eosinophil count, total serum IgE, atopy (status determined by skin prick tests), and inflammatory characteristics on induced sputum (IS), such as prostaglandin (PG)D2, PGE2, and LTE4.[11]

– *Class 1:* mild to moderate asthma, with no pulmonary dysfunction, IS with low levels of eosinophils and other mediators.
– *Class 2:* severe, poorly controlled asthma with bronchial obstruction, frequent exacerbations, marked eosinophilic inflammation, and increased inflammatory markers on IS.
– *Class 3:* mild to moderate and relatively well-controlled asthma, eosinophilic inflammation and increased pro- and anti-inflammatory mediators on IS.

In this study, LTE4 levels were correlated with peripheral eosinophil counts.[11]

NSAIDs-exacerbated cutaneous disease (NECD)

NECD is characterized by patients presenting chronic spontaneous urticaria (CSU) with or without angioedema as an underlying disease, who have an acute worsening (minutes to a few hours) of cutaneous symptoms after ingesting NSAIDs, usually strong COX-1 inhibitors.[12]

Studies indicate the presence of this phenotype in 12%-30% of patients with CSU. Since CSU is a self-limited disease lasting for months to years, NECD can disappear when CSU is resolved. However, phenotypical differences arise when they are compared to patients with CSU who tolerate NSAIDs. NSAID tolerance in the presence of CSU was demonstrated to be a good prognostic factor, as these patients present shorter CSU and a lower frequency of associated angioedema.[13] Other studies demonstrated that NSAIDs that selectively inhibit COX-2 can be used in these patients as a therapeutic alternative.[14,15]

NSAIDs-induced urticaria/angioedema (NIUA)

This is the most frequent phenotype of NSAID HR. Patients present acute NSAIDs-induced urticaria or angioedema (minutes to a few hours) and do not have CSU as the underlying disease. These symptoms are manifested only after NSAID ingestion, usually with a strong COX-1 inhibitor. Patients may report urticaria only, angioedema, or a combination of both. Around 60% of all patients with NIUA have a concomitant atopic disease.[16] In a study performed in Spain, these patients were followed-up for 12 years and 62% of them developed NSAID tolerance five years after disease onset.[17] On the other hand, another study demonstrated that 33% of these patients developed CSU during follow-up[18], and this finding was not confirmed years later in a Spanish cohort[17]. This way, the theory that NIUA may be a risk factor for the development of CSU remains controversial.

Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)

SNIUAA is biologically and phenotypically different from other NSAID hypersensitivity syndromes because patients react acutely to only one NSAID class, most frequently pyrazolones (including metamizole), and tolerate strong COX-1 inhibitors of different classes (aspirin, diclofenac, or ibuprofen, for example)[2,19].

Symptoms are triggered by the Gell and Coombs' type I hypersensitivity mechanism (IgE-mediated) and reactions are usually more severe than those in the previous syndromes[20]. Similarly to classical IgE-mediated reactions, they occur immediately, usually within an hour of exposure. There are reports of cases of SNIUAA associated with NSAID classes other than pyrazolones, such as propionic acid derivatives (ibuprofen or ketoprofen), but the occurrence of specific IgE has not yet been demonstrated for other NSAID classes apart from that including metamizole as the main example available.

Single NSAID-induced delayed hypersensitivity reaction (SNIDHR)

SNIDHR has symptoms triggered by a type IV mechanism (T cell-mediated). Symptoms usually appear within 24-48 hours of NSAID ingestion.

Reactions may vary from mild symptoms such as maculopapular exanthem and localized fixed drug eruption (FDE) to severe symptoms, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and generalized bullous FDE.[2,21]

Morphologically differentiating skin lesions is fundamental for excluding other phenotypes. Dermatological findings such as lesions lasting more than 24 hours, appearance of residual lesions, multiple vesicles vesicles, skin peeling, or exudates help exclude urticaria as the diagnosis of cutaneous manifestations. Once this is performed, in case the reaction was NSAID-induced, SNIDHR can be confirmed. The next step would be to define which other delayed dermatoses can define the case. The European position paper on cutaneous manifestations of drug HR brings a simple and objective algorithm for diagnosing cutaneous drug hypersensitivity reactions and can also be used for NSAID HRs.[22]

Other phenotypes

The classification of NSAID HRs into these five clinical phenotypes (NERD, NECD, NIUA, SNIUAA, and SNIDHR) proposed 10 years ago by the European Academy of Allergy and Clinical Immunology (EAACI) was extremely helpful to the management of these cases in clinical practice.[2,23,24] Among these, non-allergic HRs with cross-intolerance between classes of COX-1 inhibitors (NERD, NECD, and NIUA) are the most frequent in all age groups. On the other hand, our incomplete knowledge of the basic mechanisms of NSAID HRs makes the definition of phenotypes and endotypes difficult and highlights the need to identify new biomarkers for improving the diagnosis and classification of these reactions.[25]

Not all patients with HRs to NSAIDs can be classified into one of these five phenotypes suggested by the EAACI. Some other phenotypes have been described: mixed or combined reactions, food-dependent NSAID-induced anaphylaxis, and selective immediate reactions to multiple NSAIDs.

Mixed or blended reactions

Non-allergic cutaneous reactions (NIUA and NECD) and respiratory reactions (NERD) can be combined and simultaneously involve cutaneous and respiratory symptoms, or even affect other organs.[26] Some studies indicate that mixed reactions are responsible for more than 25% of cross-intolerance in adults and are the second most frequent among all phenotypes.[27] The most common symptoms of combined reactions are urticaria and angioedema associated with rhinitis or bronchospasms, although other symptoms such as laryngeal edema, hypotension, and gastrointestinal symptoms have also been described. Since they simultaneously affect two organs or systems in a short period of time, these reactions end up constituting anaphylaxis, but according to the European classification, anaphylaxis would only involve the IgE-mediated phenotype (SNIUAA). The largest Brazilian case series of drug-induced anaphylaxis showed that NSAIDs were the drug class most frequently involved in this type of reaction and almost all of these patients were cross-reactive, presenting blended reactions[28].

A review of the same Brazilian group published a few years later proposed that anaphylaxis be included in the list of clinical manifestations of nonimmunologically mediated HRs, notably in the most frequent one, NIU.[29] With the increase in cases of mixed reactions in other parts of the world, EAACI classifications may face new changes in the future.

Food-dependent NSAID-induced hypersensitivity or anaphylaxis (FDNIH or FDNIA)

NSAID ingestion has been associated with food-depended anaphylaxis and has exacerbated food-dependent exercise-induced anaphylaxis (FDEIA). Diagnosis is difficult because no causal factor is identified, even with a negative provocation test (PT) for the drug if the food is not present. The basophil activation test (BAT) has been suggested to help in diagnosis. Its pathophysiology involves increased intestinal permeability caused by NSAIDs, which increases allergen absorption.[30] Another possibility is a direct effect of the drug, potentializing the activation and degranulation of mastocytes and basophils. The intensity of the IgE-mediated reaction is related with NSAID class, dose, and strength of COX-1 inhibition. A study evaluated 328 patients with suspected immediate reactions to NSAIDs; 199 (60%) confirmed hypersensitivity through a PT, and FDNIH was confirmed in 52 cases (16%); of these, 44 individuals (84%) presented sensitivity to the lipid transfer protein (LTP) Pru p 3 through skin tests and/or specific IgE measurements. World Allergy Organization (WAO) and EAACI suggest that FDNIH should be considered and food allergy tests should be included in the diagnostic evaluation of patients with HRs to NSAIDs.[31]

Selective immediate hypersensitivity reactions to NSAIDs (SIHRN)

Some studies showed that individuals may develop SIHRN while tolerating acetylsalicylic acid (ASA).[32,33] Children with paracetamol-induced urticaria and angioedema who tolerate ASA have also been described.[34]

A Spanish research group has described this phenotype and suggested that patients should not be defined as having NIUA, that is, cross-reactive patients with cross-intolerance to NSAIDs of different classes, until reactivity to ASA is confirmed (or not).[35] However, since these studies have not been replicated in other populations and the mechanisms involved in this phenomenon are not known, the possibility of patients reacting to more than one class of NSAIDs and tolerating others, including ASA, should be considered. Other aspects could influence this picture, such as cofactors, overlapping infection, drug dose or interval between doses, etc.

Advances in the knowledge of the pathophysiological mechanisms of NSAID HRs have led to the recommendation of revising the current classification, as it does not contemplate these "new phenotypes." Other important and still unknown factors are the development of tolerance over time, the role of atopy, the progression of different phenotypes, and the potential for phenotype conversion or switching.[36]

Table 1 shows a new classification proposed for NSAID HRs, including phenotypes not previously considered by the EAACI.[24]

Cross-intolerance

Most NSAIDs perform nonselective COX-1 inhibition. They interfere with arachidonic acid synthesis, leading to a blockage of PG synthesis and overproduction of the leukotriene (LT) pathway, contributing to various presentations of NSAID HRs, notably NIUA, NERD, NECD, and blended reactions.[24,37] In these phenotypes, the patient may probably present cross-intolerance between different classes of strong COX-1 inhibitors, such as virtually all carboxylic acid derivatives (ASA, diclofenac, ibuprofen, ketorolac, etc.), in addition to pyrazolones, mefenamic acid, and some oxicam drugs.[1] However, some preferential COX-2 inhibitors such as nimesulide, paracetamol, and meloxicam are tolerated by most cross-reactive patients with the aforementioned phenotypes.

Although many patients arrive at evaluation having already used these medications after their first reactions, particularly urticaria and angioedema, others do not know their tolerance to these options. Clearly, in patients who have used one of these drugs after a first reaction to another COX-1 inhibitor, their personal history of tolerance should be the main factor when evaluating whether to indicate future use of these medications. On the other hand, few studies evaluated tolerance to nimesulide and meloxicam in patients with cross-reactive NSAID intolerance. Tolerance to meloxicam (92% to 96%) appears to be slightly superior to that to nimesulide (86% to 90%) in patients with NIUA or NECD.[38-40] In an Italian study[40] evaluating patients with cross-reactive intolerance to ASA and/or other NSAIDs, when they were subjected to a PT with celecoxib, rofecoxib, or meloxicam, reactivity was only observed in individuals with cutaneous symptoms. Among those with respiratory symptoms only (NERD), all patients tolerated the three drugs.[40]

Paracetamol, on the other hand, seems to be well tolerated in a 500 mg dose in adults or an equivalent dose in children (10 to 15 mg/kg/dose) In a Turkish study, the rate of reactivity to 500 mg paracetamol was only 5.8%.[38] In children, a study could not find patients presenting reactivity to paracetamol[41]. However, this intolerance increases proportionally with the dose and can reach 25% when the paracetamol dose reaches 900 mg.[42] In a Brazilian study, 116 patients with NIUA or NECD who also reported paracetamol intolerance were challenged in a single-blind, placebo-controlled design with 500 mg of the drug. Reactivity was confirmed in only 6.9% of the patients, all of which were not severe cases; 3.4% of the individuals reacted to placebo.[42]

Considering selective COX-2 inhibitors (coxibs), tolerance seems to be even higher. In a thorough literature review published in 2019, Lilly Li and Tanya Laidlaw compiled cases published thus far and found a rate of reactivity of 3.3% to coxibs in patients with any HR to NSAIDs and highlighted that only one report of laryngeal edema was found among more than 3,000 challenges with coxibs. Moreover, no severe reaction required emergency care or adrenaline use. When specifically evaluating patients with NERD, researchers found only 0.13% of positive tests (1 positive result among 753 PTs).[44]

It is important to highlight that coxibs have been associated with increased cardiovascular risk, which took some of them off the market.[45] In

Table 1
Classification proposed for NSAID hypersensitivity reactions including phenotypes not previously considered by the EAACI*

Type of hypersensitivity	Phenotypes	Time between exposure and reaction	Underlying chronic disease	Underlying mechanism
Cross-intolerance	NIUA	< 24 hours (mostly < 1 hour)	No	COX-1 inhibition
	NECD		CSU	
	NERD		CRSwNP and/or asthma	
	Blended or mixed reactions		Yes/No	Probable COX-1 inhibition
	FDNIA		Food allergy	Unknown
Non-cross-reactive	SNIUAA		No	IgE-mediated
	SIHRN			Unknown, probably IgE-mediated
	SNIDHR	> 24 hours		T cell-mediated

* Adapted from Doña I, et al.[24] NSAID = nonsteroidal anti-inflammatory drug, NIUA = NSAIDs-induced urticaria/angioedema, NECD = NSAIDs-exacerbated cutaneous disease, NERD = NSAID-exacerbated respiratory disease, FDNIA = food-dependent NSAID-induced anaphylaxis, SNIUAA = single NSAID-induced urticaria/angioedema or anaphylaxis, SIHRN = selective immediate hypersensitivity reaction to NSAIDs, SNIDHR = single NSAID-induced delayed hypersensitivity reaction, CSU = chronic spontaneous urticaria, CRSwNP = chronic rhinosinusitis with nasal polyps, COX-1 = cyclooxygenase 1.

Brazil, etoricoxib and celecoxib remain available for oral administration and parecoxib is available for parenteral administration. We highlight that etoricoxib and celecoxib are still in the national market but at lower doses than those used when they were first launched. Etoricoxib is available at a maximum dose of 90 mg once a day, and celecoxib is available at 200 mg, twice a day. Therefore, these drugs should be avoided in older adults and individuals with cardiovascular or cerebrovascular disease.

Peculiarities in children

NSAIDs and beta-lactams are the main causes of drug HR in the pediatric age group.[46,47] Cutaneous reactions induced by infectious agents, such as viruses, constitute an important confounding factor in the context of adverse reactions to medications in children and are less likely to be confirmed than in adults.[48] In a large European multicenter study including almost 700 patients from five countries with a history of NSAID HRs, the frequency of positive PTs with the suspected agent was 19%, which allowed the exclusion of an NSAID HR diagnosis in most patients.[49]

Classification and mechanisms of HRs in children

Although most pediatric patients with HRs to NSAIDs can be phenotypically classified just as the adult patients, a fraction of them would also not be

contemplated by the five classical phenotypes. A study performed by Cousin and colleagues[50] showed that 44% of 635 pediatric patients with confirmed NSAID HRs did not fit into any of the categories as stated by the European Network on Drug Allergy (ENDA).[2] Recently, ENDA proposed a consensus for the classification of NSAID HRs directed to the pediatric population through different criteria for children under 10 years old and those older than 10 and teenagers, emphasizing differences in these age groups.[47] Data in the international literature suggest that the phenotype of mixed reactions (cutaneous and respiratory) is the most frequent in smaller children. On the other hand, CSU is uncommon in this age group and NERD can be considered rare. Therefore, in children under 10 years old, ENDA recommended the unification of NIUA, NECD, and NERD in a sole phenotype, defined in this publication as "non-allergic hypersensitivity".[42] The classification proposed by ENDA for NSAID HRs in children under 10 years old is presented in Table 2.

This proposal for a new classification was based on studies that identified that most reactions in smaller children were nonimmunologically mediated (cross-intolerance), with significant influence of cofactors. In older children and adolescents, on the other hand, the clinical picture is more similar to that in adults. Changes in the classification of NSAID reactions in children should allow a better management of these reactions, but new classifications may still be necessary as the knowledge on the pathophysiological mechanisms and natural history of the disease advances.

Diagnosis of NSAID HRs in children

The diagnosis of NSAID HRs in children relies on the analysis of a detailed clinical history, with attention to the new phenotypes and the most probable mechanism involved in the reaction. In the context of current knowledge, skin tests and *in vitro* (laboratory) tests present limited levels and low applicability due to the absence of standards and a scarcity of studies on predictive values, especially in the pediatric age group. The PT is the gold standard for diagnosis and should follow doses related with the pediatric age range and the context of risk stratification in order to be used.

Skin tests, such as the skin prick test and the intradermal (ID) skin test, can be used for immediate reactions (urticaria, angioedema, and anaphylaxis) and when there is clinical suspicion of a non-cross-reactive reaction to metamizol.[47] Although a non-irritating paracetamol concentration for immediate-reading skin tests has been described, these tests should not be performed (particularly the ID test) since no parenteral formulation of this drug is available in Brazil. Regarding selective delayed HRs, there are not enough studies in the pediatric age group, in addition to the technical difficulty of performing delayed-reading skin tests in smaller children.

In vitro tests have low applicability. The alternatives, for immediate reactions, would be serum levels of specific IgE and the BAT[51,52]; however, these do not have defined validation or accuracy, particularly in children, thus should not be performed outside of research centers.

A PT may be performed to confirm NSAID hypersensitivity, to define the clinical phenotype, or to evaluate tolerance to another NSAID (eg, a selective or preferential COX-2 inhibitor). It should only be indicated after correct risk stratification, and more than one procedure may be required in each child.[53,54] The procedure is usually open or single-blind, placebo-controlled, and must be performed in an adequate setting for the care of possible severe reactions by a certified allergy specialist. Studies recommend initial doses of 10% to 25% of the therapeutic dose adjusted to the child's weight and age, but smaller doses may be initially necessary in case of a history of severe reaction. The subsequent doses may be administered at intervals of 30 to 60 minutes or more, depending on the clinical context of the suspected reaction.[55] The observation period after full administration should be of 2 to 4 hours, or until clinical stability in case of reactions.

In some cases, additional doses may be necessary after this observation period, and these may be administered at the patient's home (extended PT). Written information on drugs that should be avoided and alternative medications with the respective doses and formulations should be provided to the child and family members. Paracetamol at low doses was shown to be well tolerated in children as an antipyretic.[56] Selective COX-1 inhibitors, despite being safe for adolescents, have not yet been approved for smaller children. In studies with children with cross-intolerance to NSAIDs, preferential COX-2 inhibitors showed to be effective and safe in more than 80% of the patients.[57] Selective COX-2 inhibitors (coxibs) are only approved for adults (over 18 years old) in Brazil, but various studies in other countries have shown the safety of these drugs, which led them to be suggested as options, even if off label, by European guidelines.[47]

The natural history of NSAID hypersensitivity is still not well understood and, in the pediatric age group, there are additional confounding factors such as the concomitant use of other medications, dose-dependency, and the coexistence of infections. The poorer knowledge on the NSAID metabolism in children, scarcity of studies on the use of skin tests in selective delayed reactions, technical difficulty, lack of standardized non-irritating NSAID concentrations, and lack of parenteral formulations for most drugs also make the management of these patients more difficult. In this context, the PT becomes fundamental for the diagnostic confirmation of NSAID HRs in children, as well as for choosing an alternative drug. Some authors report that the number of PTs required for managing children with a suspected HR is lower when they are initially treated with ASA, regardless of the reaction history.[58,59]

Recommendations for the diagnosis and management of NSAID HRs

The strategy for investigating HRs to NSAIDs initially involves a detailed clinical history of the patient, the time between exposure and symptom onset, number of reactions, and treatment. When necessary, the immediate-reading skin prick test and ID skin test are useful only for IgE-mediated HRs. The delayed-reading skin test is used for delayed HRs to NSAIDs. In non-allergic phenotypes (NIUA,

Table 2
Classification of NSAID hypersensitivity in children aged 0-10 years*

Cross-reactivity	Type of reaction	Clinical presentation	Chronology	Proposed mechanism	Influence of cofactors
Cross-intolerance reactions (non-allergic)	Non-allergic NSAID hypersensitivity (NERD, NECD, NIUA)	Urticaria, angioedema, dyspnea, rhinitis, conjunctivitis, anaphylaxis	Immediate (minutes to several hours after exposure)	COX-1 inhibition	Possible
Non-cross intolerance (allergic)	Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Urticaria, angioedema, anaphylaxis	Immediate (< 1 h)	IgE-mediated	Unknown
	Single NSAID-induced delayed hypersensitivity reaction (SNIDHR)	Involves various symptoms and envolvidos organs (FDE, SJS, TEN, nephritis)	Delayed onset (> 24 hours after exposure)	T cell-mediated	Unknown

* Adapted from Kidon M, et al.[47] NSAID = nonsteroidal anti-inflammatory drug, NERD = NSAID-exacerbated respiratory disease, SNIUAA = single NSAID-induced urticaria/angioedema or anaphylaxis, NIUA = NSAIDs-induced urticaria/angioedema, NECD = NSAIDs-exacerbated cutaneous disease, COX-1 = cyclooxygenase 1, FDE = fixed drug eruption, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.

NECD, and NERD) dependent on the AA pathway, there are no available skin or *in vitro* tests for their diagnosi.[2,23]

A PT with the suspected drug is still gold standard for diagnosis, especially when the clinical history is unclear, since no other standardized tests are available in the literature for helping with this process. The PT can be used for confirming some diagnoses or for defining if there is cross-reactivity or selectivity in the reaction to the investigated drug.[2,23] In clinical practice, the most frequent doubt usually involves differentiating patients with NSAID-induced urticaria, angioedema, or anaphylaxis, especially whether their reaction is cross-reactive or not.

When the patient has not yet presented reactions to NSAIDs of different classes, anamnesis does not allow the definition of a clinical phenotype. In these cases, the international recommendation has been a PT with ASA at an anti-inflammatory dose (500 to 1,000 mg). Patients with a positive PT should thus be considered as having NIUA and should avoid all COX-1 inhibitors. Patients with negative PTs can be non-cross-reactive or even not be hypersensitive, and confirmation might require an immediate-reading skin test or even a PT with the suspected drug.[47,60]

Although NSAIDs are one of the most frequent causes of consultations with allergy specialists due to a history of drug HR in Brazil and Latin America, no robust data are found in the literature on the frequency of each clinical phenotype among patients with NSAID reactions, or on the safety and efficacy of this investigation protocol in our population.

This way, designing a diagnostic algorithm for NSAID HRs relies on an initial phenotyping based on the symptoms reported by the patient when the reactions occurred (urticaria, angioedema, other cutaneous manifestations suggesting delayed reaction, respiratory, or mixed reactions), time between exposure to NSAID and reaction onset, and underlying disease (eg, CSU or asthma and CRSwNP). Based on these data only, most patients will be classified into one of the five classical phenotypes (NIUA, NECD, NERD, SNIUAA, and SNIDHR) or into some of the other previously mentioned phenotypes (mixed or blended reactions, FDNIA, and SIHRN), and defined as a probable cross-intolerant or non-cross-reactive patient. From this moment on, adequate investigation and management should be directed according to the clinical phenotype.

Management of SNIDHR

Patients with cutaneous manifestations other than urticaria and angioedema, such as exanthem, eczematous dermatitis, fixed eruption, etc., whose onset is characteristically delayed, should be diagnosed as having SNIDHR; in case of doubt, these patients would benefit from a classical patch test with 48h and 96h readings using the suspected medication diluted at 10% in petroleum vaseline. In case of doubt, a final reading after 7 days may be necessary. If the doubt persists, a PT may be performed with an NSAID from a different class just to confirm tolerance, or with the suspected NSAID for confirming or excluding a prior HR. This PT will be clearly contraindicated with the suspected agent or another from the same class in case of a severe delayed reaction (organ-specific, DRESS, SJS, TEN, PEGA).

Patients subjected to a PT with the suspected NSAID whose results are negative should be considered tolerant to all NSAIDs, and these drugs are considered unrelated with the previous clinical picture. However, patients with SNIDHR confirmed by a positive patch test or PT can be allowed to use NSAIDs of other classes with no need for additional investigation.

Management of NERD and mixed reactions

In case of respiratory symptoms only (bronchospasms, laryngeal edema, acute sinonasal symptoms), especially in patients with asthma or CRSwNP or in patients with a clinical picture suggesting anaphylaxis (mixed reaction), we do not recommend a PT for diagnosis (with ASA at an anti-inflammatory dose) outside of reference and research centers due to the high risk of severe reactions of difficult treatment[61].

In these cases, patient management should follow the steps of CSU and NIUA cases, focusing on allowing alternative NSAIDs such as preferential COX-2 inhibitors (paracetamol, nimesulide, meloxicam) or selective COX-2 inhibitors (etoricoxib, celecoxib), as shown in Figure 1. For AERD, coxibs can be allowed without a PT as long as the patient's underlying disease is controlled, preferably with a pulmonary function above 70% of the predicted value or the patient's highest value.

Management of NECD

In patients with CSU and possible exacerbations with the use of NSAIDs, the confirmation of NECD –

and thus of NSAID intolerance via an immunological mechanism – can only be done after a positive PT with 500 mg ASA or more. If this PT is negative, the patient can be considered tolerant to NSAIDs and no additional exclusion or restriction recommendations are necessary. In those with a positive PT or unequivocal history of exacerbation with NSAIDs, the use of 500 mg paracetamol (or an age-adjusted dose) can be allowed as an analgesic and antipyretic drug, and we recommend that other preferential or selective COX-2 inhibitors be allowed if tolerance is confirmed with a negative PT (Figure 1). Logically, in patients who report also being reactive to paracetamol at a 500 mg dose or at an unknown dose, we suggest a PT for confirming (or not) the reported reactivity.

Management of NIUA and SNIUAA

In patients who clearly, due to their clinical history, react (urticaria, angioedema, or even anaphylaxis) to more than one COX-1 inhibitor of different classes, even though the international literature recommends confirming NSAID intolerance with an ASA PT, we do not recommend this procedure as routine in the clinical practice outside of large reference centers. The doctor is authorized to recommend excluding all strong COX-1 inhibitors and allow the use of 500 mg paracetamol (or an age-adjusted dose) as an alternative analgesic and antipyretic drug. Just as in NECD, we suggest that other preferential or selective COX-2 inhibitors be allowed if tolerance is confirmed with a negative PT (Figure 1). Similarly, for patients who report also being reactive to paracetamol at a 500 mg dose or at an unknown dose, we suggest a PT for confirming (or not) the reported reactivity. Moreover, in high-risk patients with a history of severe initial reaction (anaphylaxis), even paracetamol should only be allowed after a negative PT.

However, patients with a first reaction to an NSAID or more than one reaction to the same NSAID (for example, metamizole) or to more than one NSAID from the same class (eg, ibuprofen and ketoprofen) may be non-cross-reactive cases (SNIUAA). In these cases, immediate-reading skin tests (prick and ID tests) may be used in case the drug is metamizole, but the phenotype will only be defined after a challenge with ≥ 500 mg ASA. If the patient tolerates ASA at these doses, he or she may be considered a non-cross-reactive patient (SNIUAA) and will be allowed NSAIDs of different classes from that which caused the initial reaction. In these cases, when metamizole is involved and the skin test is positive, the IgE-mediated mechanism is confirmed. Conversely, in case the PT is positive for ASA, cross-intolerance is confirmed and the previously mentioned recommendation of prioritizing alternative NSAIDs (preferential or selective COX-2 inhibitors) prevails. The same flow should be used in patients with an unclear history, where the involvement of an NSAID or even one or more different classes of NSAIDs is not certain. On the other hand, in patients whose initial reaction was induced exactly by ASA, we follow the recommendation by the Spanish group of performing an ibuprofen PT. However, other strong COX-1-inhibiting NSAIDs (eg, diclofenac, ketorolac, ketoprofen, indomethacin) might serve the same objective.

In all these groups, analgesic and/or anti-inflammatory drugs with different mechanisms of action – not acting as COX inhibitors – such as antispasmodics (scopolamine, hyoscine), opioids (tramadol, codeine, morphine), and corticosteroids should be allowed at the initial assessment, with no need to confirm their tolerance.

The algorithm suggested for managing patients with NSAID-induced immediate skin reactions (urticaria, angioedema) or anaphylaxis (NIUA and SNIUAA) is summarized in Figure 1.

Desensitization with NSAIDs

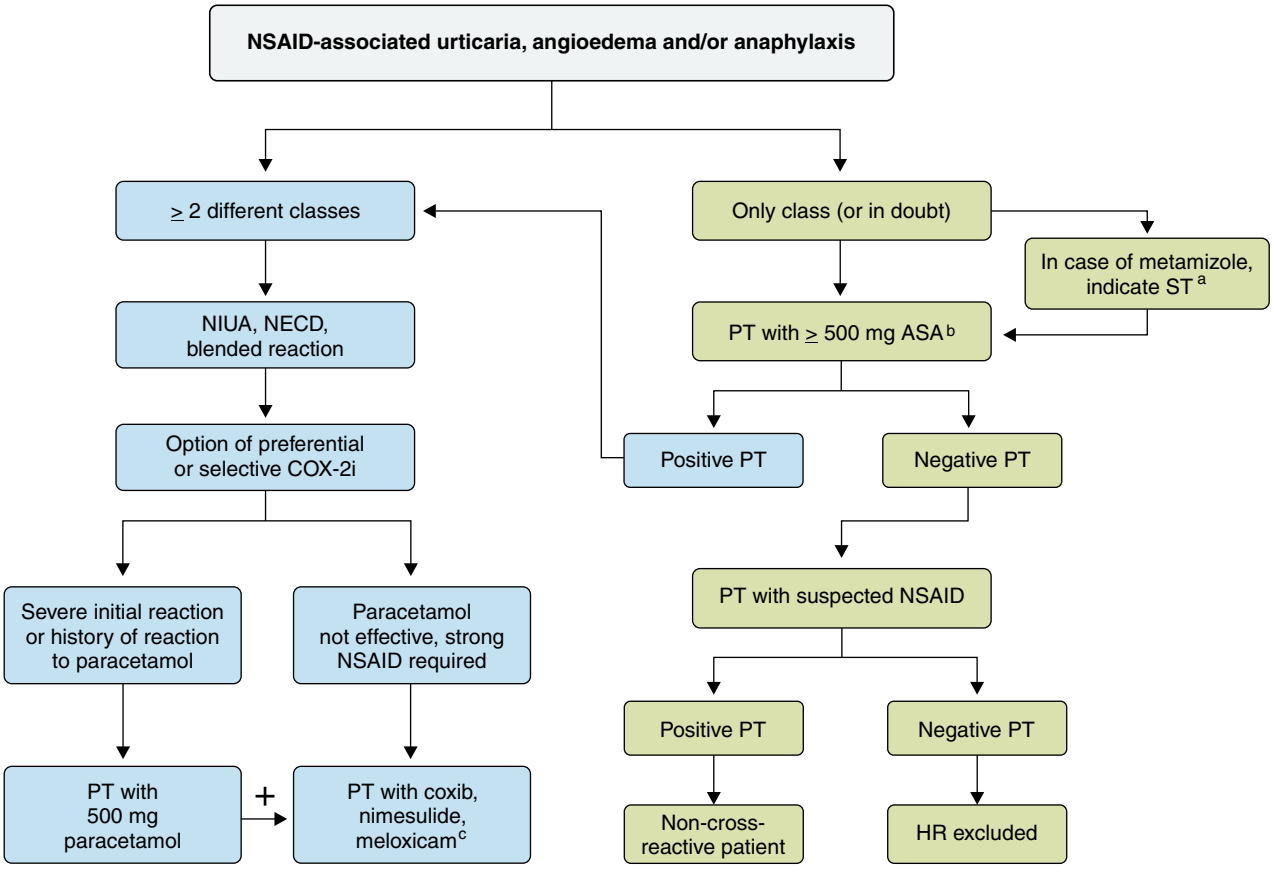
When challenging a patient with ASA, he or she is exposed to increasing doses of aspirin and the test is interrupted when the patient presents respiratory symptoms or when the maximum aspirin dose is reached. Desensitization with aspirin is the process through which aspirin tolerance is achieved, and after this period, the patient should maintain continuous and daily use of this drug. In AERD, desensitization with aspirin is achieved through the administration of high doses of aspirin after the occurrence of an initial respiratory reaction.[62]

Desensitization in cardiovascular diseases (CVD)

Patients with hypersensitivity to aspirin and CVD, with indication for this medication, are frequently not receiving adequate antiplatelet therapy. The literature presents various protocols of variable complexity for aspirin desensitization. The central role of aspirin therapy in CVD is very well established. As an irreversible COX-1 inhibitor, aspirin blocks the

biosynthesis of thromboxane A2 (TXA2), avoiding platelet aggregation. Aspirin is indicated for primary and secondary prevention in most patients with increased risk of acute myocardial infarction, stroke and cerebral ischemia, peripheral artery disease, and atrial fibrillation. Studies demonstrate that therapy with aspirin at an antiplatelet dose significantly reduced the risk of vascular events in 33%.[63]

With few exceptions, most patients with CVD and a history of aspirin hypersensitivity may be treated adequately by identifying the type of reaction to ASA and subjecting patients to challenge or desensitization



NSAID = nonsteroidal anti-inflammatory drug, NIUA = NSAIDs-induced urticaria/angioedema, NECD = NSAIDs-exacerbated cutaneous disease, COX-2i = cyclooxygenase 2 inhibitor, ST = skin test (immediate-reading prick skin test and intradermal skin test), ASA = acetylsalicylic acid, PT = provocation test, + positive, HR = hypersensitivity reaction.

[a] Non-irritating concentrations of NSAIDs other than metamizole are not known (0.1 to 4.0 mg/mL for metamizole, usually 2 mg/mL). Therefore, PTs are recommended for this drug only.

[b] When the medication involved in the initial reaction is ASA, the PT should be performed with 600 mg ibuprofen. In pediatric patients, PTs with ASA are recommended at 15-20 mg/kg/dose and, with ibuprofen, 10 mg/kg/dose[47].

[c] Maximum doses suggested for PTs with COX-2 inhibitors: 90 mg etoricoxib, 200 mg celecoxib, 100 mg nimesulide, and 15 mg meloxicam.

Figure 1
Algorithm suggested for managing patients with NSAID-induced urticaria, angioedema, and/or anaphylaxis. Patients with two or more reactions to NSAIDs of different classes should be managed as cross-reactive patients, that is, considering a nonimmunologically mediated mechanism (COX-1 inhibition), as shown in the left side of the flowchart (blue). However, in case of diagnostic doubt of if the patient reacted to only one NSAID or to more than one NSAID of the same chemical class, the algorithm should be initiated through the section to the right (green)

with ASA in a well-tolerated and practical way. Challenge and desensitization with aspirin, in CVD, can be performed both at hospital and outpatient settings.[63]

In almost all environments, the urgent need for aspirin is due to its well-known antiplatelet effect. This effect can be reached with 81 mg of ASA; using this dose as an objective is reasonable for most patients. No significant difference in 30-day outcomes was observed between a low dose (75-100 mg ASA) and a high dose (300-325 mg ASA/day) in cardiovascular death, myocardial infarction, and stroke.[63,64]

A simplified approach for ASA challenge in CDV. Symptoms should be treated with antihistamines. In case of severe symptoms, these should be treated and the dose should be repeated. Considering patients with NERD, professionals should be prepared for treatment with bronchodilators and nasal antihistamines. A dose that typically triggers symptoms in NERD is between 60 and 100 mg. Once the patient is tolerant, 81 mg/day of ASA can be initiated.[63]

Desensitization in NERD

Aspirin desensitization was performed for the first time by Widal and colleagues in 1922. In 1976, Zeiss and Lockey reported a refractory period of 72 hours after a positive oral challenge with aspirin. In 1976, Bianco and colleagues induced asthma with inhaled lysine-aspirin in a patient with NERD and, in the following 72 hours, the inhalation of the same doses of lysine-aspirin did not induce any bronchospasms (refractory period). After initiating low aspirin doses and gradually increasing them, when the target dose of 325 mg is reached, any additional doses of aspirin or other COX-1-inhibiting NSAIDs do not induce HRs. Desensitization with aspirin, followed by continuous treatment at doses of 325 mg to 650 mg twice a day, is considered standard treatment for patients with NERD after polypectomy (3 to 4 weeks prior). Aspirin can be discontinued for up to 48 hours without loss of desensitization.[64,65]

Although the clinical benefits of aspirin desensitization have been clearly demonstrated, the mechanism through which this happens remains obscure. It is not a matter of simply acquiring a state of aspirin tolerance, but the dose required for improving bronchial inflammation is usually much higher than that required for initiating a respiratory reaction or maintaining desensitization. However, a series of immunological observations have been identified in the hopes of leading to a better comprehension of the pathogenesis of this disease. In the beginning of the study, in the absence of aspirin/NSAID ingestion, patients with NERD had increased LT levels, as measured by urinary LTE4, and these levels increased proportionately to reaction severity during the aspirin challenge. Studies analyzed monocytes in the peripheral blood of patients with NERD and demonstrated a decrease in LTB4 after aspirin desensitization. Other findings include the negative regulation of cysteinyl LT receptor 1 (cysLT1) in cells of the nasal submucosa and the inhibition of IL-4 production in T cells after aspirin desensitization.[64-66]

Among many observations, the downregulation of IL-4 receptors, decrease in PGD2, decreased effects of LTE4, and effects in IL-4 expression through the downregulation of STAT-6 provide opportunities for understanding the underlying mechanism of this benefit.[65]

In a large study involving patients with NERD, surgical intervention was required every three years before desensitization; after desensitization and daily maintenance with aspirin, the mean interval increased to nine years. Some patients did not present polyp recurrence, but two complications can occur and should be monitored, as expected, after long-term treatment with aspirin: the first was gastric pain or ulcer caused by decreased PGI2 and inadequate cell repopulation of the gastric mucosa (< 15% of the patients). The second complication was bleeding in the skin (ecchymosis), but occasionally the nose, bronchi, bladder, or gastrointestinal tract.[65]

Other indications of desensitization

Desensitization is indicated for patients with NSAID-induced urticaria and/or angioedema when the clinical conditions require continuous treatment with anti-inflammatory drugs and/or in primary or secondary CVD prevention (due to the antiplatelet effect of ASA), since aspirin blocks the synthesis of TXA2 and prevents platelet aggregation.[67]

Patients who react to various NSAIDs with urticaria and/or angioedema symptoms and have a history that is consistent with chronic urticaria may be subjected to an oral PT with aspirin. Pre-medications are not usually administered before this type of challenge. Antihistamines are normally interrupted before challenges with NSAIDs, because these agents can mask the detection of initial or mild symptoms. H1-antihistamines should be discontinued at least 48 hours before the challeng.[67]

An initial dose of 81 mg or 162 mg is doubled every 90 minutes until the patient reacts or the desired therapeutic dose is reached. If the patient does not develop symptoms, he or she can safely receive an NSAID that is structurally different from the one that caused the initial reaction.[67]

Another possible indication of ASA desensitization happens during pregnancy for women with a history of HRs to ASA or other NSAIDs and with clinical suspicion of cross-intolerance. ASA may be indicated during pregnancy for preventing complications such as preeclampsia, intrauterine growth restriction, prematurity, and fetal death due to maternal thrombophilias (such as antiphospholipid syndrome) or uteroplacental insufficiency.[68] For these indications, we usually administer low doses of ASA that are similar to antiplatelet doses used in CVD. Although studies defining the adequate dose of ASA for prophylaxis against these obstetric complications are scarce[69], since the dose is usually the same as that in CVD, we recommend protocols that are similar to those mentioned in the section on desensitization in CVD.

Conclusions/final considerations

NSAIDs are the most widely used medications worldwide and, at the same time, the ones most associated with HRs, particularly in Brazil and Latin America. However, these reactions have varied clinical presentations and happen due to different pathophysiological mechanisms (nonimmunological, IgE-mediated, and T-cell-mediated). Knowing these clinical phenotypes and pathophysiology is the only way of individualizing the management of clinical cases so that we do not deny non-cross-reactive patients with an allergic mechanism a whole pharmacological class unnecessarily, while also avoiding their exposure to risks of reactions that may be severe or affect their quality of life. Only this way can we adjust the treatment of the pain, inflammation, and fever of individuals who are hypersensitive to these drugs.

References

1. Aun MV, Agondi RC, Lacerda DC, Menezes UP, Perelló MI, Rodrigues AT, et al. Atualização em reações de hipersensibilidade aos anti-inflamatórios não esteroidais – Parte 1: definições, farmacologia, epidemiologia, fisiopatologia e fatores genéticos. Arq Asma Alerg Imunol. 2022;6(3):307-17.
2. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy. 2011;66(7):818-29.
3. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. Curr Rev Allergy Clin Immunol. 2016;118:773-86.
4. Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxigenase enzymes. Ann Allergy Asthma Immunol. 2001;87:177-80.
5. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. J Allergy Clin Immunol. 2003;111:913-21.
6. Kowalski ML, Agache L, Bavbek S, Bakirtas A, Blanca M, Bochenek G, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (NERD) – a EAACI position paper. Allergy. 2019;74:28-39.
7. Kowalski ML. Heterogeneity of NSAID-exacerbated respiratory disease: has the time come for subphenotyping? Curr Opin Pulm Med. 2019;25:64-70.
8. Rodríguez-Jiménez JC, Moreno-Paz FJ, Terán LM, Guaní-Guerra E. Aspirin exacerbated respiratory disease: current topics and trends. Respir Med. 2018;135:62-75.
9. Cardet JC, White AA, Barret NA, Feldweg AM, Wickner PG, Savage J, et al. Alcohol-induced respiratory symptoms are common in patients with aspirin exacerbated respiratory disease. J Allergy Clin Immunol. 2014;2:208-13.
10. Bochenek G, Kuschill-Dziurda J, Szafraniec K, Plutecka H, Szczeklik A, Nizankowska-Mogilnicka E. Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latente class analysis. J Allergy Clin Immunol. 2014;133:98-103.
11. Celejewska-Wójcik N, Wójcik K, Ignacak-Popiel M, Cmiel A, Tyrak K, Gielicz A, et al. Subphenotypes of nonsteroidal antiinflammatory disease-exacebated respiratory disease identified by latent class analysis. Allergy. 2019;75:831-40.
12. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Aspirin-exacerbated cutaneous disease. Immunol Allergy Clin North Am. 2013;33(2):251-62.
13. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, González-Aveledo L. Aspirin-exacerbated cutaneous disease (AECD) is a distinct subphenotype of chronic spontaneous urticaria. J Eur Acad Dermatol Venereol. 2015;29(4):698-701.
14. Doña I, Blanca-López N, Jagemann LR, Torres MJ, Rondón C, Campo P, et al. Response to a selective COX-2 inhibitor in patients with urticaria/angioedema induced by nonsteroidal anti-inflammatory drugs. Allergy. 2011;66(11):1428-33.
15. Kim YJ, Lim KH, Kim MY, Jo EJ, Lee SY, Lee SE, et al. Cross-reactivity to Acetaminophen and Celecoxib According to the Type of Nonsteroidal Anti-inflammatory Drug Hypersensitivity. Allergy Asthma Immunol Res. 2014;6(2):156-62.
16. Sánchez-Borges M, Acevedo N, Caraballo L, Capriles-Hulett A, Caballero-Fonseca F. Increased total and mite-specific immunoglobulin E in patients with aspirin-induced urticaria and angioedema. J Investig Allergol Clin Immunol. 2010;20(2):139-45.
17. Doña I, Blanca-López N, Torres MJ, Gómez F, Fernández J, Zambonino MA, et al. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. Allergy. 2014 Apr;69(4):438-44.
18. Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. J Allergy Clin Immunol. 2003;111(5):1095-8.
19. Blanca-Lopez N, Soriano V, Garcia-Martin E, Canto G, Blanca M. NSAID-induced reactions: classification, prevalence, impact, and management strategies. J Asthma Allergy. 2019 Aug 8;12:217-33.

20. Woessner KM, Castells M. NSAID single-drug-induced reactions. Immunol Allergy Clin North Am. 2013 May;33(2):237-49.
21. Demir S, Olgac M, Unal D, Gelincik A, Colakoglu B, Buyukozturk S. Evaluation of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs according to the latest classification. Allergy. 2015;70(11):1461-7.
22. Brockow K, Ardern-Jones MR, Mockenhaupt M, Aberer W, Barbaud A, Caubet JC, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. Allergy. 2019;74(1):14-27.
23. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013 Oct;68(10):1219-32.
24. Doña I, Pérez-Sánchez N, Eguiluz-Gracia I, Muñoz-Cano R, Bartra J, Torres MJ, et al. Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Allergy. 2020 Mar;75(3):561-75.
25. Tanno LK, Torres MJ, Castells M, Demoly P; Joint Allergy Academies. What can we learn in drug allergy management from World Health Organization's international classifications? Allergy. 2018;73(5):987-92.
26. Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clin Exp Allergy. 2011;41(1):86-95.
27. Doña I, Barrionuevo E, Salas M, Laguna JJ, Agúndez J, García-Martín E, et al. NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. Sci Rep. 2018;8(1):16710.
28. Aun MV, Blanca M, Garro LS, Ribeiro MR, Kalil J, Motta AA, et al. Nonsteroidal anti-inflammatory drugs are major causes of drug-induced anaphylaxis. J Allergy Clin Immunol Pract. 2014;2(4):414-20.
29. Giavina-Bianchi P, Aun MV, Jares EJ, Kalil J. Angioedema associated with nonsteroidal anti-inflammatory drugs. Curr Opin Allergy Clin Immunol. 2016;16(4):323-32.
30. Matsuo H, Morimoto K, Akaki T, Kaneko S, Kusatake K, Kuroda T, et al. Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. Clin Exp Allergy. 2005;35(4):461-6.
31. Sánchez-López J, Araujo G, Cardona V, García-Moral A, Casas-Saucedo R, Guilarte M, et al. Food-dependent NSAID-induced hypersensitivity (FDNIH) reactions: Unraveling the clinical features and risk factors. Allergy. 2021;76(5):1480-92.
32. Pérez-Sánchez N, Bogas G, Cornejo-García JA, Andreu I, Doña I, Pérez-Alzate D, et al. Multiple nonsteroidal anti-inflammatory drug hypersensitivity without hypersensitivity to aspirin. J Allergy Clin Immunol Pract. 2016;4(3):524-5.
33. Bogas G, Pérez-Sánchez N, Andreu I, Doña I, Perkins JR, Blanca M, et al. Anaphylaxis to 2 NSAIDs in a Patient Who Tolerated ASA. J Investig Allergol Clin Immunol. 2016;26(4):266-8.
34. Guvenir H, Dibek Misirlioglu E, Vezir E, Toyran M, Ginis T, Civelek E, et al. Nonsteroidal anti-inflammatory drug hypersensitivity among children. Allergy Asthma Proc. 2015;36(5):386-93.
35. Pérez-Alzate D, Cornejo-García JA, Pérez-Sánchez N, Andreu I, García-Moral A, Agúndez JA, et al. Immediate Reactions to More Than 1 NSAID Must Not Be Considered Cross-Hypersensitivity Unless Tolerance to ASA Is Verified. J Investig Allergol Clin Immunol. 2017;27(1):32-9.
36. Blanca-López N, Bogas G, Doña I, Torres MJ, Blanca M, Cornejo-García JA, et al. ASA must be given to classify multiple NSAID-hypersensitivity patients as selective or cross-intolerant. Allergy. 2016;71(4):576-8.
37. Yeung WYW, Park HS. Update on the Management of Nonsteroidal Anti-Inflammatory Drug Hypersensitivity. Yonsei Med J. 2020;61(1):4-14.
38. Terzio lu K, Sancar Ö, Ekerbiçer HÇ, Öztürk RT, Epöztürk K. Tolerability to paracetamol and preferential COX-2 inhibitors in patients with cross-reactive nonsteroidal anti-inflammatory drugs hypersensitivity. Asia Pac Allergy. 2020;10(3):e29.
39. Bavbek S, Celik G, Ozer F, Mungan D, Misirligil Z. Safety of selective COX-2 inhibitors in aspirin/nonsteroidal anti-inflammatory drug-intolerant patients: comparison of nimesulide, meloxicam, and rofecoxib. J Asthma. 2004;41(1):67-75.
40. Senna G, Bilò MB, Antonicelli L, Schiappoli M, Crivellaro MA, Bonadonna P, et al. Tolerability of three selective cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib and rofecoxib in NSAID-sensitive patients. Eur Ann Allergy Clin Immunol. 2004;36(6):215-8.
41. Corzo JL, Zambonino MA, Muñoz C, Mayorga C, Requena G, Urda A, et al. Tolerance to COX-2 inhibitors in children with hypersensitivity to nonsteroidal anti-inflammatory drugs. Br J Dermatol. 2014;170(3):725-9.
42. Kim YJ, Lim KH, Kim MY, Jo EJ, Lee SY, Lee SE, et al. Cross-reactivity to Acetaminophen and Celecoxib According to the Type of Nonsteroidal Anti-inflammatory Drug Hypersensitivity. Allergy Asthma Immunol Res. 2014 Mar;6(2):156-62.
43. Zanandrea A, Mouco CC, Assis JP, Dias GMFS, Castro RB, Brugnoll RM, et al. Hypersensitivity to paracetamol: placebo effect or overdiagnosis? J Allergy Clin Immunol. 2017;141(2):AB43.
44. Li L, Laidlaw T. Cross-reactivity and tolerability of celecoxib in adult patients with NSAID hypersensitivity. J Allergy Clin Immunol Pract. 2019;7(8):2891-3.
45. El-Malah AA, Gineinah MM, Deb PK, Khayyat AN, Bansal M, Venugopala KN, et al. Selective COX-2 Inhibitors: Road from Success to Controversy and the Quest for Repurposing. Pharmaceuticals (Basel). 2022;15(7):827.
46. Lutfeali S, Khan DA. Pediatric Drug Allergies. Update on Beta-lactam, Nonsteroidal Anti-Inflammatory Drug, and Chemotherapeutic Reactions. Pediatr Clin N Am. 2019;66:1035-51.
47. Kidon M, Blanca-Lopez N, Gomes E, Terreehorst I, Tanno L, Ponvert C, et al. EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. Pediatr Allergy Immunol. 2018;29(5):469-80.
48. Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. Clin Exp Allergy. 2012;42(1):123-30.
49. Mori F, Atanaskovic-Markovic M, Blanca-Lopez N, Gomes E, Gaeta F, Sarti L, et al. A Multicenter Retrospective Study on Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Children: A Report from the European Network on Drug Allergy (ENDA) Group. J Allergy Clin Immunol Pract. 2020;8(3):1022-31.
50. Cousin M, Chiriac A, Molinari N, Demoly P, Caimmi D. Phenotypical characterization of children with hypersensitivity reactions to NSAIDs. Pediatr Allergy Immunol. 2016;27(7):743-8.
51. Gómez E, Blanca-Lopez N, Torres MJ, Requena G, Rondon C, Canto G, et al. Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. Clin Exp Allergy. 2009 Aug;39(8):1217-24.
52. Decuyper II, Mangodt EA, Van Gasse AL, Claesen K, Uyttebroek A, Faber M, et al. In Vitro Diagnosis of Immediate Drug Hypersensitivity Anno 2017: Potentials and Limitations. Drugs R D. 2017;17:265-78.
53. Zambonino MA, Torres MJ, Muñoz C, Requena G, Mayorga C, Posadas T, et al. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. Pediatr Allergy Immunol. 2013;24(2):151-9.
54. Yilmaz O, Ertoy Karagol IH, Bakirtas A, Topal E, Celik GE, Demirsoy MS, et al. Challenge-proven nonsteroidal anti-inflammatory drug hypersensitivity in children. Allergy. 2013;68(12):1555-61.
55. Ertoy Karagol HI, Yilmaz O, Topal E, Ceylan A, Bakirtas A. Nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease in adolescents. Int Forum Allergy Rhinol. 2015;5(5):392-8.

56. Kidon MI, Liew WK, Chiang WC, Lim SH, Goh A, Tang JP, et al. Hypersensitivity to paracetamol in Asian children with early onset of nonsteroidal anti-inflammatory drug allergy. Int Arch Allergy Immunol. 2007;144(1):51-6.
57. Loh W, Lim HH, Rao R, Goh A, Ong LX, Chiang WC. Tolerance to etoricoxib in children with nonsteroidal anti-inflammatory drug hypersensitivity. Asia Pac Allergy. 2015;5(1):40-6.
58. Simsek IE, Cogurlu MT, Aydogan M. Two approaches for diagnosis of nonsteroidal anti-inflammatory drug hypersensitivity in children. Ann Allergy Asthma Immunol. 2019;123:389-93.
59. Blanca-López N, Haroun-Diaz E, Ruano FJ, Pérez-Alzate D, Somoza ML, Vázquez de la Torre Gaspar M, et al. Acetyl Salicylic Acid Challenge in Children with Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs Differentiates Between Cross-Intolerant and Selective Responders. J Allergy Clin Immunol Pract. 2018;6(4):1226-35.
60. Aun MV, Kalil J, Giavina-Bianchi P. Drug-Induced Anaphylaxis. Immunol Allergy Clin North Am. 2017;37(4):629-41.
61. Khan DA, Banerji A, Blumenthal KG, Phillips EJ, Solensky R, White AA, et al. Drug Allergy: A 2022 Practice Parameter Update. J Allergy Clin Immunol. 2022:S0091-6749(22)01186-1.
62. Cahill KN. Immunologic effects of aspirin desensitization abd high-dose aspirin therapy in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2021;148:344-7.
63. Woessner KM. Aspirin desensitization for cardiovascular disease. Curr Opin Allergy Clin Immunol. 2015;15:314-22.
64. Giavina-Bianchi P, Aun MV, Galvão VR, Castells M. Rapid Desensitization in Immediate Hypersensitivity Reaction to Drugs. Curr Treat Options Allergy. 2015;2:268-85.
65. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. N Engl J Med. 2018;379:1060-70.
66. Katial RK, Strand M, Prasertsuntarasai T, Leung R, Zheng W, Alam R. The effect of aspirin desensitization on novel biomarkers in aspirin-exacerbated respiratory diseases. J Allergy Clin Immunol. 2012;126:738-44.
67. Simon RA. Diagnostic challenge and desensitization protocols for NSAID reactions. UpToDate.com. Literature review current through: Sep. 2022.
68. Benito-Garcia F, Pires I, Lima J. Aspirin Desensitization: Implications for Acetylsalicylic Acid-Sensitive Pregnant Women. Medicina (Kaunas). 2021;57(4):390.
69. Mkhize PZ, Phoswa WN, Khaliq OP, Dorsamy V, Moodley J. Aspirin in the prevention of preeclampsia: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021;100(48):e27916.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Self-reported food allergy among older Brazilians: prevalence and clinical characteristics – a study protocol

Alergia alimentar autodeclarada em idosos no Brasil: prevalência e características clínicas – Protocolo de estudo

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ABSTRACT

In recent decades, there has been a significant increase in the prevalence of food allergies, reaching an estimated frequency of 3% to 8% in adults and even higher in self-reports (from 3% to 35%). However, published data on the prevalence of food allergies among older adults are scarce, and in Brazil they are non-existent. The main objective of this study was to investigate the prevalence of self-reported food allergy among older Brazilians (≥ 60 years). This cross-sectional epidemiological study protocol involves a questionnaire that was developed, standardized, and validated in Portuguese. The investigated aspects will include the foods and symptoms most commonly associated with food allergy in this population. The data will be input into an Excel spreadsheet for statistical analysis. Obtaining this data will allow comparison of the results with previous data and help establish treatment plans for these patients.

Keywords: Food hypersensitivity, prevalence, aged, epidemiologic studies.

RESUMO

Nas últimas décadas tem se observado um aumento expressivo na prevalência de alergia alimentar (AA), com frequência estimada em adultos de 3% a 8%, sendo ainda mais relevante quando se avalia a AA autodeclarada (variação de 3% a 35%). Entretanto, são poucos os dados publicados sobre a prevalência de AA em idosos, e no Brasil tais dados são inexistentes. O objetivo principal deste protocolo de estudo é conhecer a prevalência de AA autodeclarada em idosos (≥ 60 anos) brasileiros. Trata-se de estudo epidemiológico transversal que utiliza questionário padronizado e validado para a língua portuguesa. Entre os vários aspectos investigados, serão avaliados quais alimentos e sintomas são os mais relacionados à AA nestes indivíduos. Os dados obtidos serão transcritos a planilha Excel para realização da análise estatística. A obtenção dessas informações permitirá compará-las às existentes, assim como estabelecer planos de abordagem destes pacientes.

Descritores: Hipersensibilidade alimentar, prevalência, idoso, inquéritos epidemiológicos.

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Introduction

Recent epidemiological studies suggest that the prevalence of food allergy (FA) is increasing and that the profile of sensitization to foods is subject to geographic influences.[1,2] However, the majority of studies focus on children or young adults, giving the impression that FA does not affect older adults. No studies have been conducted in Brazil investigating FA in the elderly.

The prevalence of allergic diseases in the elderly is currently estimated at 10%, with a tendency to increase over the coming years.[3] It is estimated that 20% of the world population will be considered elderly by 2030.

The phenomena of immunosenescence (which affects both adaptive and innate immunity), micronutrient deficiencies, and reduced gastric acid digestion are possible risk factors for development of FA in the elderly. However, underdiagnosis and, consequently, undertreatment is the rule in this age group, not only for FA, but also for other forms of allergic diseases.[4]

It remains unclear whether the prevalence of FA in the elderly population is similar, higher, or lower than in adults or children. The variable results are caused by the investigative methods used to assess FA frequency in different studies. Self-reported FA prevalence is known to be higher than probable FA, defined by symptoms combined with positive specific IgE assay results and/or confirmed with oral challenge tests.[5] This is clear if we compare two recent European studies of the prevalence of FA in adults. Nwaru et al.[5] describe self-reported FA prevalence in adults varying from 9.5% to 35%, whereas Lyons et al.[6] reported prevalence of probable FA at 0.3% to 5.6%. Similar results were observed in an epidemiological study with adults in general in the community.[7]

However, elderly people with immunomediated reactions to food may have symptoms that are difficult to detect, may by confused with symptoms of other diseases related to age, or may be masked by medications (polypharmacy), which makes underestimation of the FA prevalence in these people more likely.[8]

A Portuguese study developed and validated a written questionnaire for investigation of self-reported FA in adult populations, creating the possibility for its use in other countries where Portuguese is spoken, in addition to working as a screening instrument in investigations of FA.[9]

The present study was motivated by the absence of epidemiological data on FA in the elderly in Brazil and the availability of a previously validated written instrument in Portuguese and its objective is to determine the prevalence of self-reported FA, the foods involved, and the main symptoms.

Patients and method

Elderly people, over the age of 60 years, regardless of sex, will be invited to take part in this cross-sectional population study with a convenience sampling strategy. These participants will be identified by allergist/immunologist physicians affiliated to the Brazilian Association of Allergy and Immunology (ASBAI) from the 23 Brazilian states in which the ASBAI is active.

Patients will be recruited by the assisting physician during consultations at Allergy and Immunology clinics at public (University Hospitals and health care centers) or private heath care services (whether in clinics or physicians' offices), sequentially and regardless of having symptoms of food allergy.

All of the elderly participants will answer the questionnaire in person. This instrument was developed and validated in Portuguese (from Portugal) by Lozoya-Ibáñez et al.[9] and was assessed and adapted for the Brazilian culture. The data obtained will be transcribed to an excel spreadsheet for later statistical analysis.

Cross-cultural adaptation of the instrument

Since the original questionnaire was written in Portuguese from Portugal, the translation step was omitted and it only underwent analysis of its adequacy for the cultural context and lifestyle found in the target culture, in Brazil.[10] Therefore, the questionnaire was sent to 25 allergy and immunology specialist physicians from all over Brazil, who were asked about the clarity of the questions and their capacity to differentiate individuals with possible conditions related to FA. Twenty-one of these physicians agreed to assess the questionnaire's adequacy and sent back their observations.

Terms identified as uncommon in the Brazilian culture were substituted for other more appropriate ones and other specific changes were made (for example, regional foods), reaching a final instrument

which will be administered to 10 elderly people to test its comprehensibility (Figure 1).

The following changes were made to the original questionnaire after the specialists' feedback: (a) in question 2, "years of educational level" was changed to "highest educational level achieved by the elderly subject" with the following response options: no education, complete elementary education, incomplete elementary education, complete secondary education, incomplete secondary education, and others, to facilitate comprehension; (b) in question 6, "Which food or foods provoke the reaction (multiple choice MC)?" to "What is the food or foods that provoke your reaction (multiple choice)?"; "seafood or crustaceans, shrimp, crab, lobster, etc." was added in parentheses to the item "mariscos"; "mussels, octopus, squid" was added in parentheses to the item "mollusks"; "other dry fruit" was changed to "dry fruit (cashews, Brazil nuts, almonds, pistachio, hazelnuts, walnuts, etc.)"; foods in the latex group were positioned after dry fruit and "carica papaya" was specified rather than simply "papaya"; the item "fruit" was supplemented with "other than those in the latex group" and was inserted after the foods in the latex group; the item "vegetables" was supplemented with sweet corn and the explanation that "corn is considered a vegetable when fresh and a cereal when the grains are dried"; the description of the item "legumes" was supplemented with "lentils and soy"; an item "cereals (wheat, rye, barley, oats)" was added to the questionnaire after the item "legumes"; an item "do regional foods (manioc, yams, açaí, etc.) provoke reactions in you?" was inserted into the questionnaire after the item "beef"; (c) in question 7, it was made clear that more than one response could be chosen for the type of reaction after ingesting a food and the term OAS was written out in full as oral allergy syndrome; (d) for question 8, the response item "Don't remember" was added for the time taken for reactions to emerge after ingestion of the food; e) in question 10, the item "where did you receive medical treatment?", the option "INEM" (Portuguese National Medical Emergency Institute) was changed for the equivalents in Brazil: "SAMU or UPA"; and the response options "virtual or on-line consultation (Telemedicine)" and "I don't remember where I was treated" were added; a space was provided after the option "self-medication" for the respondent to state what medications were used; (e) in question 15 the item "Do you have any type of allergic disease?" was changed to "Apart from food reactions, do you have any other type of allergic disease?"; the item "asthma (coughing, pieira, shortness of breath)" (piera is a term for wheezing in Portuguese from Portugal) was changed to "asthma (coughing, chiado, shortness of breath)" (chiado is the equivalent term in Brazil); the item "rhinitis (sneezing, runny nose, and nasal comichão)" (comichão is a term for itching in Portuguese from Portugal) was changed to "rhinitis (sneezing, runny nose, coceira in the nose, and blocked nose)" (coceira is the equivalent term in Brazil); the item "conjunctivitis (lacrimejo, comichão, and red eyes)" (lacrimejo is a term for tearing in Portuguese from Portugal) was changed to "conjunctivitis (lacrimejamento, coceira, and red eyes) (lacrimejamento is the equivalent term in Brazil); the item "skin allergy (eczema, comichão, scaling, or babas na pele) (babas na pele is a term for a skin rash in Portuguese from Portugal) was changed to "skin allergy (eczema, itching, scaling, urticaria); (f) in question 16, the item "uncles" was changed to "biological uncles" and "cousins" and "children" were added; and (g) question 17 "If possible, would you like to continue the study with a Immunology and Allergy consultation at a reference Hospital?", was removed for ethical reasons.

Sample size calculation

The parameters adopted were a 95% confidence level, a 2% maximum absolute sampling error, and a 10% maximum prevalence of FA, resulting in a sample size of 865 elderly participants. Considering a 30% non-response rate, it is intended that 1,236 elderly people will be interviewed, distributed proportionally among the 23 participating Brazilian states. In order to determine the distribution of these individuals among the different states, we used the proportional distribution of elderly people in the general Brazilian population, estimated at 20,369,810, according to the most recent demographic census conducted by the Brazilian Institute of Geography and Statistics (IBGE),[11] as shown in Table 1.

The questionnaire will be made available on the Google Forms platform and should be answered by the patient during the medical consultation. The treating physician will read the questions and fill out the questionnaire. Each completed questionnaire will be identified by the participating center's code and the participant's recruitment number.

Ethical considerations

The study will be submitted to prior evaluation by the ethics and research committee for research

Questionnaire on Food allergies in elderly Brazilians

Date of administration: ____/____/_____

1) Sex

- ○ Male
- ○ Female

2) Highest educational level achieved by the elderly subject:

- ○ No education
- ○ Incomplete elementary education or equivalent
- ○ Complete elementary education or equivalent
- ○ Incomplete secondary education or equivalent
- ○ Complete secondary education or equivalent
- ○ Incomplete higher education or equivalent
- ○ Complete higher education
- ○ Postgraduate certificate
- ○ Masters degree
- ○ Doctorate

3) Age in years

Date of birth: ____/____/_____

4) Would you like to answer the questionnaire?

- ○ Yes
- ○ No

5) Have you ever had an allergic reaction to any type of food?

- ○ Yes
- ○ No

If question 5 was answered "No", go directly to questions 15 and 16 and end the interview.

6) Which foods provoke or have provoked reactions? (multiple choice)

- ○ Milk and dairy
- ○ Eggs
- ○ Fish
- ○ Seafood other than mollusks (seafood or crustaceans: shrimp, crab, lobster, etc.)
- ○ Mollusks (mussels, octopus, squid)
- ○ Peanuts
- ○ Dry fruit (cashews, Brazil nuts, almonds, pistachio, hazelnuts, walnuts, etc.)
- ○ Latex group (kiwi, banana, mango, carica papaya, figs, tomatoes)
- ○ Fruit (other than those in the latex group)
- ○ Vegetables (sweet corn, potatoes carrots, collard, etc.). NB: corn is considered a vegetable when fresh and a cereal when the grains are dried
- ○ Legumes (beans, chickpeas, peas, lentils, soy, etc.)
- ○ Cereals (wheat, rye, barley, oats)
- ○ Chicken
- ○ Pork
- ○ Beef
- ○ Regional foods (manioc, yams, açaí, etc.)
- ○ Others
- ○ Don't remember

If "Others" was chosen, specify:

Figure 1
Questionnaire on Food allergies in elderly Brazilians

7) What type of reaction did you have? (describe the symptoms provoked against the foods that caused them. If subject doesn't remember, write "Don't remember")
NB: more than one symptom can be endorsed per food.
OAS (Oral Allergy Syndrome)

	Urticaria/ Angioedema	Contact Dermatitis	OAS	Ocular	Nasal
Milk and dairy					
Eggs					
Fish					
Seafood					
Mollusks					
Peanuts					
Dry fruit					
Latex group					
Fruit (other than those in the latex group)					
Vegetables					
Legumes					
Cereals					
Chicken					
Pork					
Beef					
Regional foods					
Others					
Don't remember/ Don't know					

	Respiratory	Abdominal	Anaphylactic shock	Others
Milk and dairy				
Eggs				
Fish				
Seafood				
Mollusks				
Peanuts				
Dry fruit				
Latex group				
Fruit (other than those in the latex group)				
Vegetables				
Legumes				
Cereals				
Chicken				
Pork				
Beef				
Regional foods				
Others				
Don't remember/ Don't know				

Figure 1 *(continuation)*
Questionnaire on Food allergies in elderly Brazilians

8) How long did it take for reactions to occur after ingestion of the food? (If necessary, specify per food)
- ○ Less than 30 min
- ○ 30 min to less than 2 hours
- ○ 2 hours to 24 hours
- ○ More than 24 hours
- ○ Don't remember

9) Did you need medical treatment? (If necessary, specify per food)
- ○ Yes
- ○ No

10) If question 9 was answered "Yes", where were you treated?
- ○ Hospital emergency department
- ○ SAMU / UPA
- ○ Health center during first 24 hours
- ○ Family physician after 24 hours
- ○ Virtual or on-line consultation (telemedicine)
- ○ Seen by a specialist
- ○ Self-medication. Specify medications used: _____
- ○ I don't remember where I was treated

11) How many similar episodes have you had with the same food? (If necessary, specify per food)
- ○ Only 1 episode
- ○ 2 to 5 episodes
- ○ More than 5 episodes
- ○ Don't remember

12) How long since you last had a reaction? (If necessary, specify per food)
- ○ Less than 1 month
- ○ 1 to 6 months
- ○ More than 6 months to 1 year
- ○ 1 year to 5 years
- ○ More than 5 years
- ○ Don't remember

13) Have you ever been diagnosed with food allergy by a physician?
- ○ Yes
- ○ No

14) Have you ever had a consultation with an allergy specialist?
- ○ Yes
- ○ No

15) Other than reactions to food, do you have any type of allergic disease? (multiple choice)
- ○ Asthma (coughing, wheezing, shortness of breath)
- ○ Rhinitis (sneezing, runny nose, itching nose, blocked nose)
- ○ Conjunctivitis (eyes watering, itching, reddened)
- ○ Allergy cutaneous (eczema, itching, scaling, urticaria)
- ○ No
- ○ Others (specify): _____

16) Does anyone in your family have an allergic disease? (multiple choice)
- ○ Mother or father
- ○ Brother or sister
- ○ Grandparents
- ○ Biological uncles
- ○ Cousins
- ○ Children
- ○ No
- ○ Others (specify): _____

Thank you very much for answering this questionnaire!

Figure 1 *(continuation)*
Questionnaire on Food allergies in elderly Brazilians

Table 1
Elderly population in Brazil and numbers of research participants, by the Brazilian states in which the Brazilian Association of Allergy and Immunology is active

States	Number of elderly people (≥ 60 years)	
	Brazilian population, N (%)	Sample, n
Alagoas	276,170 (1.36)	17
Amazonas	210,173 (1.03)	13
Bahia	1,450,009 (7.12)	88
Ceará	909,215 (4.46)	55
Distrito Federal	198,012 (0.97)	12
Espírito Santo	364,861 (1.79)	22
Goiás	560,450 (2.75)	34
Maranhão	567,657 (2.79)	34
Mato Grosso	240,416 (1.18)	15
Mato Grosso do Sul	239,594 (1.18)	15
Minas Gerais	2,311,084 (11.35)	140
Pará	534,461 (2.62)	32
Paraíba	451,101 (2.21)	27
Paraná	1,172,154 (5.75)	71
Pernambuco	936,759 (4.60)	57
Piauí	331,772 (1.63)	20
Rio de Janeiro	2,079,502 (10.21)	126
Rio Grande do Norte	343,443 (1.69)	21
Rio Grande do Sul	1,461,480 (7.17)	89
Santa Catarina	656,133 (3.22)	40
São Paulo	4,771,822 (23.43)	290
Sergipe	185,999 (0.91)	11
Tocantins	117,543 (0.58)	7
Total	20,369,810 (100)	1,236

* Data from the most recent IBGE Demographic Census.[11]

involving human subjects of the Coordinating Center of the study, located at the Hospital Universitário Antônio Pedro - HUAP/UFF. All patients should sign a free and informed consent form before completing the questionnaire.

In addition to the coordinating center, the option to participate will be opened to other centers, termed coparticipants, which will follow the same procedures for study approval by their own ethics and research committees.

Statistical analysis

Initially, tables of frequency distributions will be constructed for the sociodemographic characteristics (sex, age, and educational level), presence/absence of self-report FA, foods identified as responsible for allergic reactions, types of reactions, time before appearance of symptoms after ingestion of the food, date of last allergic reaction, frequency of prior episodes of adverse reactions to the food, need for medical attention because of the reaction, and personal and family history of allergic diseases, among others). Additionally, bivariate associations will be evaluated using parametric or nonparametric tests with a 5% significance level.

Taking presence or absence of self-report FA as the point of analysis, a generalized linear model will be constructed to identify factors statistically associated with prevalence of self-report FA in elderly Brazilians, considering a 5% significance level.

Conclusions

The study objective is to collect and quantify more accurate data on the prevalence of self-reported FA in the elderly, using a validated questionnaire. These data on FA self-reported by the elderly population will also allow comparisons with data available in the world literature, such as prevalence, symptoms, and foods involved, among others.

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References

1. Wong G. Epidemiology: International point of view, from childhood to adults, food allergens. In: Ebisawa M, Ballmer-Weber BK, Vieths S, Wood RA, eds. Food Allergy: molecular basis and clinical practice. Basel: S. Karger; 2015.p. 30-6. doi:10.1159/000371662.
2. Sampath V, Abrams EM, Adlou B, Akdis C, Akdis M, Brough HA, et al. Food allergy across the globe. J Allergy Clin Immunol. 2021;148(6):1347-64. doi:10.1016/j.jaci.2021.10.018.
3. Willits EK, Park MA, Hartz MF, Schleck CD, Weaver AL, Joshi AY. Food allergy: a comprehensive population-based cohort study. Mayo Clin Proc. 2018;93(10):1423-30. doi: 10.1016/j.mayocp.2018.05.031.
4. Diesner SC, Untersmayr E, Pietschmann, Jensen-Jarolim E. Food allergy: only a pediatric disease? Gerontology. 2011;57(1):28-32. doi:10.1159/000279756.
5. Nwaru BI, Hickestein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69(1):62-75. doi:10.1111/all.12305.
6. Lyons SA, Burney PG, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, Clausen M, et al. Food allergy in adults: substantial variation in prevalence and causative foods across Europe. J Allergy Clin Immunol Pract. 2019;7(6):1920-8. doi:10.1016/j.jaip.2019.02.044.
7. Lozoya-Ibáñez C, Morgado-Nunes S, Rodrigues A, Lobo C, Taborda-Barata L. Prevalence and clinical features of adverse food reactions in Portuguese adults. Allergy Asthma Clin Immunol. 2016;12:36. doi:10.1186/s13223-016-0139-8.
8. Ventura MT, D'Amato A, Giannini M, Carretta A, Tummolo RA, Buquicchio R. Incidence of allergic diseases in an elderly population. Immunopharmacol Immunotoxicol. 2010;32(1):165-70. doi:10.3109/08923970903213735.
9. Lozoya-Ibáñez C, Belo J, Afonso RM, Pereira H, Rodrigues A, Taborda-Barata L. Development of a screening questionnaire for the study of food allergy in adults. World Allergy Organ J. 2020;13(9):100456. doi:10.1016/j.waojou.2020.100456.
10. Dortas Jr SD, Lupi O, Dias GA, Guimarães MB, Valle SO. Adaptação transcultural e validação de questionários na área da saúde. Braz J Allergy Immunol. 2016;4(1):26-30. doi:10.5935/2318-5015.20160003.
11. IBGE. Cidades@ [site na Internet]. Available at: https://cidades.ibge.gov.br/ . Acessado em 21/09/2021.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Our everyday immune system and today's pesticides

Nosso sistema imune de cada dia e os agrotóxicos de hoje

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ABSTRACT

Beginning in the 1950s, massive pesticide use began in what is called the "Green Revolution", a quest for increased agricultural productivity and modernization. In the 1960s, the Brazilian National Program of Agricultural Defense was created to facilitate the introduction of agrochemicals, leading the country to become one of the world's largest pesticide users by 2008. These substances have deleterious effects on the immune response of exposed individuals, mainly related to macrophages and B, T, and NK cells. This affects phagocytosis and antigen and antibody production, inducing production of oxygen free radicals and mitochondrial dysfunction, which results in oxidative stress and cellular DNA damage, excess apoptosis, cell cycle mutations, regulatory disorders, and, consequently, immunodeficiency. Thus, the development of immune-mediated diseases, such as asthma and chronic obstructive pulmonary disease (COPD), is closely linked to pesticides, since these varied mechanisms of toxicity to the immune system induce respiratory manifestations, such as cough, wheezing, irritation and inflammation. Pesticide use is also related to non-immune-mediated diseases because exposure alters the normal function of thyroid hormones, androgens, and estrogens. To evaluate their impact, the present study performed an integrative review of the literature, which, due to the growing and uncontrolled use of pesticides, is of great relevance and demonstrates the need for greater epidemiological, environmental, and worker health surveillance.

Keywords: Agrochemicals, pesticide exposure, immune diseases, respiratory tract diseases.

RESUMO

O uso massivo dos agrotóxicos nas lavouras deu-se a partir de 1950 com a "Revolução Verde", como resultado da busca por aumento da produtividade e modernização dos campos agrícolas. Diante disso, na década de 1960, foi criado o Programa Nacional de Defensivos Agrícolas (PNDA), que veio para facilitar a introdução dos agroquímicos, colaborando para que, a partir de 2008, o Brasil passasse a ser o país com maiores percentuais de uso destes produtos. Essas substâncias geram efeitos deletérios sobre a resposta imune dos indivíduos expostos, principalmente relacionada aos macrófagos, células B, T e NK. Isso afeta a capacidade de fagocitose, apresentação de antígenos e produção de anticorpos, além de induzir a geração de radicais livres de oxigênio e disfunção mitocondrial, resultando em estresse oxidativo e danos ao DNA celular, apoptose em excesso, mutação no ciclo celular, desordem de regulação e, consequentemente, imunodeficiência. Dessa forma, o desenvolvimento de doenças imunomediadas, como asma e doença pulmonar obstrutiva crônica (DPOC), está estreitamente ligado aos agrotóxicos, uma vez que esses variados mecanismos de toxicidade ao sistema imune induzem, dentre outras, manifestações respiratórias, tais como tosse, sibilo, irritação e inflamação. Além disso, estes pesticidas estão relacionados com doenças não imunomediadas ao alterar a função normal dos hormônios da tireoide, andrógenos e estrógenos. A fim de avaliar estes impactos, o presente estudo consiste em uma revisão integrativa da literatura e, diante da crescente utilização descontrolada dos agrotóxicos, assume grande relevância, refletindo a necessidade de maior atuação da vigilância epidemiológica, ambiental e da saúde do trabalhador.

Descritores: Agroquímicos, exposição a praguicidas, doenças do sistema imunitário, doenças respiratórias.

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Introduction

The use of chemical compounds in farming was initiated after the end of the world great wars, and started to be massively applied in the 1950s, with the so-called "Green Revolution." The quest for increased agricultural productivity and modernization resulted in the creation of the National Program of Agricultural Defense in the 1960s. This program facilitated the introduction of agrochemicals throughout the years, which led Brazil to become the world leader in the use of these products in 2008.[1-3]

Numerous types of agrochemicals are currently used in Brazil, and notably most of them are banned in European countries and in the United States. Herbicides, insecticides, fungicides, and bactericides stand out as the most used of types of agrochemicals and, despite their high impact on control of agricultural plagues, the development of resistance to the toxins applied has led to the use of increased doses and to the search for new, more potent compounds, resulting in serious impacts on human health.[1,4]

Exposure to agrochemicals produces several effects, such as impaired immune response in exposed individuals, which has drawn the attention of health care professionals.[3] Recent investigations showed that these agrochemicals affect especially macrophages, B cells, T cells, and natural killer (NK) cells, leading to changes in the cell cycle, decreased antigen presentation capacity, reduced phagocytic capacity, and induction of apoptosis.[3]

In this context, it is observed that some exposed individuals will develop an immunodeficiency state, since cell responses and antibody production will fail; therefore, these individuals will become less resistant to infectious processes. Moreover, there will be failures in immunological surveillance of tumors and immune regulation disorders, facilitating the development of neoplastic processes and immune diseases.[3]

Airway involvement caused by such chemicals also has been much observed, because they promote respiratory mucosa irritation and local epithelial inflammation, favoring the onset of diseases such as asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD).[4] Furthermore, cardiovascular, hematological, neurological, cutaneous, and ocular changes have also been correlated to the use of pesticides.[4-6]

Therefore, in view of the several impacts and damages both to workers exposed to chemical products in farming and to the general population through water, soil and air contamination, the present article aims to describe the main influences observed in the immune system resulting from exposure to pesticides.

Methods

This is an integrative literature review conducted on the following databases: National Library of Medicine (PubMed), Latin American and Caribbean Health Sciences Literature (LILACS), and Scientific Electronic Library Online (SciELO). Articles were selected using Descriptors in Health Sciences (DeCS) and Medical Subject Heading (MeSH), using the following descriptors: "agrotóxicos," "doenças do sistema imunológico," "doenças respiratórias," "exposição a produtos químicos," "agrochemicals," "immune system diseases," "respiratory tract diseases," and "chemical compound exposure." Inclusion criteria were full articles in Portuguese and English and published from January 2000 to April 2021. Exclusion criteria consisted of experience reports, opinion articles, and editorials.

Discussion

Overview of pesticides in Brazil

Agrochemicals, agricultural defensives, pesticides, medicines for plants, venom are some of the numerous terms linked to the group of chemical compounds used in the sector of production, storage, and processing of agricultural products, in pastures, in protection of forests, and in urban, water, and industrial environments. Their main purpose is to change the composition of flora and fauna in order to preserve them from harmful action of living beings and chemicals.[7]

As provided by Law n. 7,802, dated of July 11th, 1989, 3rd article, pesticides, their components, and related products may only be produced, exported, imported, marketed, and used if previously registered with a federal agency, in compliance with the directives and requirements of health federal agencies.[8]

For pesticides to be marketed in the Brazilian territory, information on their labels must be clear; therefore, the presence of specific labelling and package leaflets, written in Portuguese. In the case of accidents, there must be explicit instructions, including warning symptoms, first aid, antidotes, and recommendations for physicians.[8] Hence, for classification purposes, pesticides are divided

according to regulations provided by the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA). There were changes in 2017, and pesticides reclassified according to the level of toxicity, as shown in Table 1.[9]

In addition to the classification according to toxicity, as recommended by ANVISA, pesticides may be classified according to their chemical properties. Among them, herbicides are represented by chlorophenoxy (2,4-D; 2,3,5-T; and MCPA), urea derivatives, triazines, amide, bipyridyls, and glyphosate.[4] Insecticides are represented by organochlorines, cyclohexanes, chlorinated benzenes, cyclodienes, chlordecone, organophosphates, carbamates, pyrethroids, rotenone, Bacillus thuringiensis (protein compound).[4]

Fungicides, in turn, include dithiocarbamates, captan, captafol, pentachlorophenol, iprodione, and sulfur, and, with regard to bactericides, triazine-S-triones, chlorine-releasing agents, chlorine, and dichloronitrobenzene stand out. Rodenticides are represented by coumadin and derivatives, anticoagulants, strychnine, sodium fluoroacetate; and, finally, methyl bromide, aluminum/zinc phosphide, and sulfur are examples of fumigants.[4]

Another known classification is linked to the mechanism of action of pesticides, which may present neurotoxic properties, such as organochlorines and organophosphates, or properties similar to those of vegetal hormones, such as phenoxy herbicides. Other substances may act as endocrine disruptors, such as the herbicides atrazine and urea, or interfere with physiological processes, promoting changes in coagulation cascade by reducing vitamin K synthesis, such as coumadin, among several other types of mechanisms of action.[4]

All forms of classifying these substances show the danger of their excessive use. However, the reality of consumption shows to be contradictory since, despite the known hazards of excessive exposure, the Brazilian market occupies a prominent position in the global ranking, being the largest consumer of pesticides in the world since 2008, according to ANVISA.[1,10] Herbicides are the most commonly used products, accounting for approximately 45% of the total amount used, followed by fungicides (14%) and insecticides (12%).

In addition to intense use of registered agrochemicals, another concern is related to smuggling of these products. An analysis of samples collected in 2011 by the Program for Analysis of Pesticide Residues in Food, developed by ANVISA, showed that 78% of them were contaminated, even with two pesticides that have never been registered in Brazil, azaconazole and tebufenpyrad, which

Table 1
2017 reclassification according to levels of pesticide toxicity

Category	Toxicity	Examples
Category 1	Extremely toxic product	2,4 D and methomyl
Category 2	Highly toxic product	Chlorpyrifos and diazinon
Category 3	Moderately toxic product	Acephate, diuron, malathion, and mancozeb
Category 4	Little toxic product	Glyphosate

Sources: Brazilian Health Surveillance Agency, 2019; International Agency for Research on Cancer, 2018; United States Environmental Protection Agency, 2019.[9]

suggests lack of control of public policies on the use of agrochemicals in the country.[10]

In this context of intense production and consumption, it is worth emphasizing that the use of pesticides is a major public health problem, due to the size of the exposed population in pesticide plants and surrounding areas, in farming, in fighting endemics, in the vicinity of farming areas, and, ultimately, those who consume contaminated food,[10] requiring specialized attention for its control.

Agrochemicals and non-immune-mediated diseases

Studies associate exposure to agrochemicals with hormone deregulations and diseases in humans.[11] These impacts have been studied since these products began to be used in the 1960s. Currently, it is know that agrochemicals have compounds capable of deregulating the endocrine system, inhibiting cholinesterases, such as AchE (acetylcholinesterase) and ChP (butyrylcholinesterase), and acting as a substance with carcinogenic potential.[11,12]

Deregulation of the endocrine system occurs by altering the physiological function of thyroid hormones, androgens, and estrogens. Some agrochemical compounds are capable of interrupting signaling pathways, mimicking the interaction of endogenous hormones with nuclear receptor. Consequently, they interfere with synthesis, response, and degradation of peptide and steroid hormones.[2,11,13,14] Furthermore, epidemiological data have associated exposure to agrochemicals with increased incidence of hormone-dependent tumors, which are closely linked to endocrine deregulation.[11]

Moreover, the fact that interruption of hormone synthesis may be a factor that precedes changes in human brain functions has been also an object of study.[11,14] In humans, neuronal death caused by agrochemical compounds is caused by oxidative stress, mitochondrial dysfunction, failures in endoplasmic reticulum function, damages to signaling molecules, protein degradation, and other mechanisms.[14]

Exposure to pesticides, such as organophosphates, may lead to acute and even chronic manifestations, depending on time and extent of exposure. Therefore, when a test is performed to measure biological exposure indicators, the levels of cholinesterases, AchE, and ChP are reduced. Consequently, in poisoning, people may present with muscarinic, nicotinic, motor, and neurosensory effects, as well as cognitive disorders.[12] Furthermore, studies that used epidemiological data and analyzed cell models established the relationship between exposure to agrochemicals and brain neurodegeneration, with Parkinson's disease being the main neurodegenerative disease.[14]

From this perspective, contact with toxic agents is practically inevitable, since consumption of industrialized products and interaction with nature go hand in hand with contact with several chemical entities. Therefore, it is also worth highlighting the carcinogenic potential of agrochemicals, due to the heterogeneity of compounds and chronic exposure to these substances experienced by a large portion of rural workers. However, chronic effect is linked to the several absorption pathways, such as dermal, digestive, and respiratory ones, and, when associated with fat-soluble toxins, leads to increased risks for cell mutation, due to bioaccumulation generated in the body. Thus, brain neoplasms, non-Hodgkin lymphoma, cutaneous melanomas, digestive and urinary tract cancers become the reality of the population in contact with such chemicals.[2]

Agrochemicals, immune system, and immune-mediated diseases

Immune response to pathogens and to diseases results from the joint action of several cell and hormone components. It can be divided into innate or adaptive immune responses, with the first represented mainly by neutrophils, macrophages, and NK cells, and the latter by T and B lymphocytes and antibodies.[3] The effects of agrochemicals in this system result from their immunotoxicity potential, a term first used in 1970 that covers any deleterious effect in immune function, both innate and adaptive.[15] These effects deregulate the body protective system, thus impairing defensive response.

Agricultural defensives are present in food, in fluvial waters, in the air, and in the soil; therefore, there are several forms of contamination. Moreover, since various agrochemicals are used concomitantly and each mechanism has specific actions, different cell groups are affected, resulting in multiple immunity failures.[3] These failures include deficiencies in phagocytosis capacity, in antigen presentation, and in antibody production, induction of excess apoptosis, cell cycle mutations, regulatory disorders, and, consequently, immunodeficiency.[3,15] These deleterious effects become even more intense during

spraying seasons, since inhalation of pesticides is shown to be an important contamination pathway.[3]

Organophosphorus compounds, organochlorines, carbamates, triazines, and chlorophenols are the most used chemical groups in Brazil and, as previously mentioned, each group has different mechanisms of immunotoxicity, with a direct action on cells and consequences to the development of immune-mediated diseases. Together with these mechanisms of direct action to the cells, reactive oxygen species (ROS) are produced, which results in oxidative stress and cellular DNA damage, inducing changes in signaling and proapoptotic state.[3] In this context, the effect of glyphosate was observed in tests of specific cell lines, confirming significant cell mortality resulting from mitochondrial damage due to increased amount of ROS.[16]

Furthermore, a study conducted in the United States observed a significant genotoxic effect on B and T lymphocytes caused by pesticides among farmers during one pesticide spraying season.[17] Workers were chronically exposed to several pesticides, making it difficult to attribute the genotoxic effect to one specific class or chemical compound. However, this form of exposure was shown to induce DNA damages, such as simple- and double-stranded DNA breaks, resulting in deficient B and T cell repair. Fungicides, such as chlorothalonil, carbendazim, and methyl thiophanate may play a greater role in inducing these DNA damages in T lymphocytes.[17] Chlorothalonil exhibited strong cytotoxicity against specific cell lines, resulting in high cell mortality after 24 and 48 hours of contact[18] and cytogenetic effects on lymphocytes, leading to an increased number of chromosome aberrations.[19]

Mitochondrial dysfunction, another mechanism, is characterized by damaging effects to the endoplasmic reticulum, causing deficiency in protein production and also in cell apoptosis.[3] An example of this phenomenon is the negative effect on anti-cancer proteins, specifically NK-92CI cells, which are highly cytotoxic to tumor cells. This effect is characteristic of the carbamate class, such as carbaryl (insecticide), maneb (fungicide), thiram (fungicide), and ziram (fungicide). Therefore, the findings of the study suggest that this class significantly reduces intracellular levels of proteins in this cell line, in a dose-dependent manner to their immunotoxic effect, predisposing individuals to the development of cancer.[20]

Deregulation of signaling mechanisms is also common, caused by agrochemicals such as atrazine, one of the most used herbicides in Brazil but banned in the European Union because it induces positive modulation of regulatory T cells, preventing the production of cytokines such as interferon-gamma and weakening immune response.[21] This results in toxic effects in fertility, nervous system, and fetal development.[3] Similarly, bendiocarb, a carbamate insecticide, causes dose-dependent changes in homeostasis and immune cell function, including changes in regulatory TCD4 cells and in adjustment of cytokines and chemokines.[22]

However, the most serious problem is that bendiocarb may be absorbed by pregnant women and transferred to the fetus. Therefore, intra-uterine exposure to this chemical has unequivocal effects on the fetus immune system, due to an exacerbated inflammatory response, which may be critical to maintain maternal-fetal tolerance and leads to adverse effects during pregnancy. Furthermore, it brings important biological consequences to child's development and health, since these changes are still detectable in childhood.[22]

All these mechanisms may negatively influence the potential of the body to defend itself against external pathogens, including viruses. Cellular damages may worsen clinical conditions, a fact that is particularly important in a pandemic scenario such as that of COVID-19. In this context, individuals with comorbidities such diabetes mellitus, hypertension, obesity, and immunosuppression were considered as a risk group.[3,23] Thus, it can be inferred that the impact of these chemicals on the immune system extends to the ability of responding to viral infections, including SARS-CoV-2 infection, either directly or not.[3]

Development of immune-mediated diseases is also closely linked to agrochemicals. These varied mechanisms of toxicity to the immune system induce, among others, respiratory manifestations such as cough, wheezing, and airway irritation and inflammation. These manifestations derive from immune-mediated lung diseases, and may be divided into type 1 reactions, which are predominantly IgE-mediated, such as occupational asthma, type 3 and 4 reactions, which are caused by hypersensitivity, such pneumonitis, and those mediated by innate immunity, such as CPOD.[15]

Organophosphates consist of an important chemical group extensively used worldwide since, in addition to the previously mentioned effects on the central nervous system in non-immune-mediated reactions, these compounds have also peripheral

effects, especially for airways. Their mechanism of action is based on the inhibition of acetylcholinesterase, whose function is degrading acetylcholine, resulting in accumulation of this neurotransmitter in the respiratory system. As a consequence of chronic exposure, excess muscarinic response occurs, characterized by induction of hyperresponsiveness and bronchoconstriction, justifying its relationship with asthma.[3-5,24]

Considering that the use of organophosphates is not restricted to farming areas, also including peri-urban and urban areas, their ability to worsen asthma and other immune-mediated diseases extends both rural and urban workers and residents.[5,24] Moreover, organophosphates have another mechanism of direct action on the immune system: they inhibit serine hydrolases, enzymes able to hydrolyze immune signaling chemicals. Therefore, several previously mentioned defense cells, such as neutrophils, macrophages, NK cells, antibodies, and lymphocytes, undergo negative immune modulation, generating an immunodeficiency state again.[25]

Asthma is defined as an inflammatory lung disease characterized by intermittent, reversible bronchoconstriction, hypersecretion, and airway hyperreactiveness, with repercussions in the presentation of respiratory symptoms and reduced quality of life.[5,15,24] It was shown that one fifth of cases of adult-onset asthma results from occupational factors and that, in nearly 90% of these cases, immunological factors are involved.[26] This pathophysiology is justified by the action of mastocytes, eosinophils, lymphocytes, IgE, and mediators such as histamine, which act causing edema and inflammation after exposure to allergens. However, due to low antigenicity of pesticides, asthma induced or worsened by these chemicals is possibly due to the immunological effect of Th1/Th2 imbalance, so as to induce release of ROS and cause cellular damage.[27] Therefore, exposure to vapors of chemicals may result in cough and chronic expectoration, leading to exacerbation of pre-existing disease[4] and to the development of adult-onset asthma.[4,28]

Rhinitis is, by definition, an inflammation of nasal mucosa, and may be caused by direct action of agrochemicals, also known as irritant rhinitis, or be immune-mediated, known as allergic rhinitis, which is much more common in the context of rural workers.[27] Clinical presentations of this disease include rhinorrhea, sneezing, itching, and nasal obstruction.[27,29] The use of 2,4-D pesticide was associated with development of allergic rhinitis and wheezing in the long term compared to workers not exposed to this chemical. Similar results were obtained with the use of carbamates and pyrethroids.[29]

Hypersensitivity pneumonitis (HP) is an interstitial lung disease characterized by inflammation concomitant with fibrosis resulting from constant inhalation of antigens and, consequently, sensitization.[27,30] In Brazil, it is the second most common interstitial lung disease, and inhalation of low-molecular weight chemical compounds, such as organochlorines, carbamates, and pyrethroids, are among the several causes for the development of HP.[24] One of the most remarkable forms of HP is "farmer's lung," a type of allergic pneumonitis caused by a type 3 and 4 hypersensitivity reaction resulting from inhalation of dust and agricultural products; thus, increased levels of inflammatory interleukins such as IL-1, IL-6, and TNF-alpha potentiate defensive response and cause noncaseating granulomas, alveolar destruction, and fibrosis.[15] Because of these changes, this disease is manifested as fever, chills, cough, dyspnea, and chest pain, in the acute stage, and cough and chronic expectoration when sequelae remain.[30]

Finally, COPD is characterized by chronic small airway limitation in association with inflammation and loss of lung elasticity. Occupational exposure to pesticides may be related to the development of COPD, and organophosphates, organochlorines, carbamates, and herbicides are the classes more related to chronic bronchitis.[4] Therefore, it is possible to observe the extent and severity of the influence of agrochemicals on the immune system and on the development of immunodeficiency.

Conclusion

In view of the growing and uncontrolled use of agrochemicals, this study addressed information on the existing relationship between high consumption of pesticides in Brazil and diseases they cause in the entire body, either immune-mediated or not. Therefore, it is possible to understand the relevance of the immune system with regard to the other body systems, because, in cases of immunodepression or agrochemical poisoning, the other systems are also affected and, thus, the entire physiology will be impaired, focusing, in this study, on the consequences to the nervous, endocrine, and respiratory systems.

Therefore, the main importance of the present study lies on its aim of subsidizing measures to protect the most vulnerable individuals in the context of harm to human physiology, notably to the immune system. In this sense, it bears noting the importance of developing studies and research projects involving such issues, so as to better understand the existing relationship between agrochemicals, with all their immunotoxicity effects, and the immune system, as well as the other body systems and, based on this, develop control measures regarding the use of agrochemicals in Brazil.

From this perspective, it is possible to understand beforehand that the impact of agrochemicals on the body and on the environment demonstrates the need for a better health promotion and prevention, and, concomitantly, for greater monitoring and mapping of agrochemical poisoning, either acute or chronic, in order to promote health surveillance actions, focusing on those of epidemiological, environmental, and notably worker health surveillance.

References

1. Londres F. Agrotóxicos no Brasil - um guia para ação em defesa da vida. 1st ed. Vasa. Rio de Janeiro: AS-PTA - Assessoria e Serviços a Projetos em Agricultura Alternativa; 2011. p. 190.
2. Lopes CVA, Albuquerque GSC. Agrotóxicos e seus impactos na saúde humana e ambiental: uma revisão sistemática. Saúde Debate. 2018;42:518-34.
3. Novato-Silva E, Silva JM, Pinheiro TMM. Efeitos de agrotóxicos sobre o sistema imune: considerações no contexto da pandemia da COVID-19 no Brasil. Pista: Periódico Interdisciplinar [Sociedade Tecnologia Ambiente].2021;3:8-24.
4. Ye M, Beach J, Martin JW, Senthilselvan A. Occupational pesticide exposures and respiratory health. Int J Environ Res Public Health. 2013;10(12):6442-71.
5. Rocha CB, Nascimento APC, Silva AMC, Botelho C. Asma não controlada em crianças e adolescentes expostos aos agrotóxicos em região de intensa atividade do agronegócio. Cad Saúde Pública. 2021;37:e00072220. doi:10.1590/0102-311x00072220.
6. Scharmach C, Silva JC, Campos R. Toxicidade do agrotóxico na função respiratória de agricultores. BJD. 2020;6:33740-56. doi:10.34117/bjdv6n6-069.
7. Peres F, Moreira JC, Dubois GS. Agrotóxicos, saúde e ambiente: uma introdução ao tema. In: Peres F, Moreira JC, orgs. É veneno ou é remédio? Agrotóxicos, saúde e ambiente. Rio de Janeiro: Editora FIOCRUZ; 2003. p. 21-41.
8. Brasil. Lei nº 7.802, de 11 de julho de 1989. Dispõe sobre a pesquisa, a experimentação, a produção, a embalagem e rotulagem, o transporte, o armazenamento, a comercialização, a propaganda comercial, a utilização, a importação, a exportação, o destino final dos resíduos e embalagens, o registro, a classificação, o controle, a inspeção e a fiscalização de agrotóxicos, seus componentes e afins, e dá outras providências. Diário Oficial da União, 14 jul 1989; p. 11459.
9. Reclassificação toxicológica. Agência Nacional de Vigilância Sanitária - ANVISA [Internet]. Available at: https://www.gov.br/anvisa/pt-br/setorregulado/regularizacao/agrotoxicos/copy_of_reclassificacao. Accessed on: 07/14/2022.
10. Rigotto RM, Vasconcelos DP, Rocha MM. Pesticide use in Brazil and problems for public health. Cad Saúde Pública. 2014;30:1360-2. doi:10.1590/0102-311XPE020714.
11. Luque EH, Muñoz-de-Toro M. Special issue "Health effects of agrochemicals as Endocrine Disruptors". Mol Cell Endocrinol. 2020;517:110982. doi:10.1016/j.mce.2020.110982
12. Araújo AJ, Lima JS, Moreira JC, Jacob SC, Soares MO, Monteiro MCM, et al. Exposição múltipla a agrotóxicos e efeitos à saúde: estudo transversal em amostra de 102 trabalhadores rurais, Nova Friburgo, RJ. Ciênc Saúde Coletiva. 2007;12:115-30. doi:10.1590/S1413-81232007000100015.
13. Vandenberg LN, Najmi A, Mogus JP. Agrochemicals with estrogenic endocrine disrupting properties: Lessons Learned? Mol Cell Endocrinol. 2020;518:110860. doi:10.1016/j.mce.2020.110860.
14. Silva BA, Breydo L, Fink AL, Uversky VN. Agrochemicals, α-synuclein, and Parkinson's disease. Mol Neurobiol. 2013;47(2):598-612. doi:10.1007/s12035-012-8333-2.
15. Luster MI. A historical perspective of immunotoxicology. Journal of Immunotoxicology. 2014;11:197-202. doi:10.3109/1547691X.2013.837121.
16. Chaufan G, Coalova I, Ríos de Molina MC. Glyphosate commercial formulation causes cytotoxicity, oxidative effects, and apoptosis on human cells: differences with its active ingredient. Int J Toxicol. 2014;33(1):29-38. doi:10.1177/1091581813517906.
17. Lebailly P, Mirey G, Herin F, Lecluse Y, Salles B, Boutet-Robinet E. DNA damage in B and T lymphocytes of farmers during one pesticide spraying season. Int Arch Occup Environ Health. 2015;88(7):963-72. doi:10.1007/s00420-015-1024-3.
18. Nakadai A, Li Q, Kawada T. Chlorpyrifos induces apoptosis in human monocyte cell line U937. Toxicology. 2006;224(3):202-9. doi:10.1016/j.tox.2006.04.055.
19. Santovito A, Gendusa C, Ferraro F, Musso I, Costanzo M, Ruberto S, et al. Genomic damage induced by the widely used fungicide chlorothalonil in peripheral human lymphocytes. Ecotoxicol Environ Saf. 2018;161:578-83. doi:10.1016/j.ecoenv.2018.06.047.
20. Li Q, Kobayashi M, Kawada T. Effect of carbamate pesticides on perforin, granzymes A-B-3/K, and granulysin in human natural killer cells. Int J Immunopathol Pharmacol. 2015;28(3):403-10. doi:10.1177/0394632015582334.
21. Oliveira GW. Aspectos do comportamento da atrazina no solo e potenciais efeitos ambientais [trabalho de conclusão de curso]. Cerro Largo: Curso de Graduação em Agronomia, Universidade Federal da Fronteira Sul; 2015.
22. Prahl M, Odorizzi P, Gingrich D, Muhindo M, McIntyre T, Budker R, et al. Exposure to pesticides in utero impacts the fetal immune system and response to vaccination in infancy. Nat Commun. 2021;12:132. doi:10.1038/s41467-020-20475-8.
23. Minussi BB, Paludo EA, Passos JPB, Santos MJ, Mocellin O, Maeyama MA. Grupos de risco do COVID-19: a possível relação entre o acometimento de adultos jovens "saudáveis" e a imunidade. BJHR. 2020;3:3739-62. doi: 10.34119/bjhrv3n2-200.
24. Ferreira TS, Carneiro APS, Mancuzo EV. Occupational exposure to pesticides and chronic hypersensitivity pneumonia: a case report. Rev Bras Med Trab. 2021;19(2):249-52. doi: 10.47626/1679-4435-2020-672.
25. Silverio AM, Pinheiro PB. A biociência dos agrotóxicos e seu impacto na saúde. Revista Ouricuri. 2019;9:016-33. doi: 10.29327/ouricuri.9.2-9.
26. Mapp CE. Genetics and the occupational environment. Curr Opin Allergy Clin Immunol. 2005;5(2):113-8. doi:10.1097/01.all.0000162301.74610.21.
27. Viegas CAA. Agravos respiratórios decorrentes da atividade agrícola. J Pneumol [Internet]. 2000;26(2):83-90.

28. Faria NM, Facchini LA, Fassa AG, Tomasi E. Pesticides and respiratory symptoms among farmers. Rev Saude Publica. 2005;39(6):973-81. doi:10.1590/s0034-89102005000600016.
29. Patel O, Syamlal G, Henneberger PK, Alarcon WA, Mazurek JM. Pesticide use, allergic rhinitis, and asthma among US farm operators. J Agromedicine. 2018;23(4):327-35. doi:10.1080/1059924X.2018.1501451.
30. Magalhaes EMS, Stella AKS, Corrêa FMV, Naves FES, Sabatini JO. Pneumonite por hipersensibilidade Relato comparativo de dois casos. Rev bras alerg imunopatol. 2005;28:112-7.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

New perspectives in immunotherapy: the importance of dendritic cells in allergen-specific immunotherapy

Novas perspectivas em imunoterapia: a importância das células dendríticas na imunoterapia alérgeno-específica

Maria Angela Vigoritto[1], Gustavo Pradez[2]

ABSTRACT

Allergen-specific immunotherapy is the only treatment capable of altering the natural course of allergic disease. Clinical trials have shown that immunotherapy is safe and effective for many patients. However, it still faces problems related to efficacy, safety, long treatment duration and poor patient compliance. In this context, there has been intense research into the development of adjuvant treatments that increase safety, optimize treatment regimens, and improve patient compliance. Allergens were modified (glycoconjugated) with carbohydrates derived from *Saccharomyces cerevisae* to increase their uptake and presentation through carbohydrate receptors in dendritic cells, benefiting from their ability to induce tolerance and initiate immune response. In light of the new evidence, these cells are a key therapeutic target for adequate response to allergen-specific immunotherapy and can drive innovation in the field of immunotherapy.

Keywords: Allergen-specific immunotherapy, allergy, dendritic cells.

RESUMO

A imunoterapia alérgeno-específica é o único tratamento capaz de alterar o curso natural da doença alérgica. Ensaios clínicos mostram que a imunoterapia é segura e eficaz para muitos pacientes. No entanto, ainda enfrenta problemas relacionados à eficácia, segurança, longa duração do tratamento e baixa adesão dos pacientes. Neste contexto, tem havido intensa pesquisa no desenvolvimento de adjuvantes com objetivo de aumentar a segurança, otimizar os esquemas de tratamento e melhorar a adesão dos pacientes. Alérgenos foram modificados (glicoconjugados) com carboidratos derivados de *Saccharomyces cerevisae* para aumentar sua captação e apresentação através dos receptores de carboidratos presentes nas células dendríticas, beneficiando-se da capacidade de atuarem na indução de tolerância para iniciar respostas imunes. À luz de novas evidências, essas células constituem alvo terapêutico chave para se obter uma resposta adequada à imunoterapia alérgeno-específica, com potencial de contribuição na inovação do campo da Imunoterapia.

Descritores: Imunoterapia alérgeno-específica, alergia, células dendríticas.

Introduction

Although allergic diseases may be controlled with symptomatic or emergency treatment, allergen-specific immunotherapy is the only curative treatment option with proven efficacy and safety described by several studies and meta-analyses.[1,2]

However, some limiting factors include long treatment durations, costs, poor patient adherence,

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and the risk of serious, life-threatening adverse reactions. The development of immunotherapy with modified allergens with increased antigenicity and decreased allergenicity, in combination with novel adjuvant molecules via new routes, may shorten treatment durations and possibly reduce these disadvantages.[3]

Mechanisms of allergen-specific immunotherapy

Contrary to what was previously believed, the shift from Th2 to Th1 immune response is not the key to successful treatment. Recent advances in the knowledge of regulatory T (Treg) and B cells and peripheral tolerance mechanisms were essential to explain immune alterations resulting from immunotherapy.

Immunotherapy was believed for many years to induce a shift from Th2 to Th1 immune response by reducing the levels of inflammatory cytokines (IL)-4, IL-5, and IL-13 and, consequently, increasing the levels of interferon-γ. However, this theory does not completely explain why patients undergoing immunotherapy do not have a higher incidence of diseases related to the Th1 lymphocyte population.[4]

The first studies demonstrating the role of Tregs in the mechanism of allergen-specific immunotherapy were published in 2004. Since then, immune tolerance induction has become the main target in the prevention and treatment of diseases related to immune system dysfunctions, such as allergies.[5]

Cell subsets with regulatory capabilities are induced during allergen-specific immunotherapy. IL-10 and transforming growth factor β (TGF-β) are the main suppressor cytokines, in addition to surface molecules such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) within the microenvironment. Modified T- and B-cell responses and antibody isotypes, increased activity thresholds for eosinophils, basophils and mast cells, and consequent limitation of inflammatory cascades induce and maintain a state of sustained allergen-specific unresponsiveness. Established tolerance is reflected on clinical perspectives as improvement of allergy symptoms together with reduced medication requirements and progression of disease severity.[5]

New adjuvants

Allergen-specific immunotherapy is the only treatment capable of altering the natural course of allergic disease. Although clinical trials have shown that immunotherapy is safe and effective for many patients, it has some limitations.

Although it has been evolving for more than 100 years, immunotherapy with allergen extracts is often inconvenient for patients due to disadvantages such as long-lasting treatment regimens and concerns about efficacy, treatment safety, and longevity of induced effects. For some allergies, immunotherapy is still only partially effective and may be hampered by undesirable side effects. Therefore, many research projects aim to improve immunotherapy by creating new vaccine candidates and adjuvants that increase efficacy while decreasing undesirable adverse effects.[6]

An extensive literature review found recent publications reporting new and innovative approaches aimed at increasing safety, maintaining or even increasing efficacy, and improving treatment regimens in allergen immunotherapy. To increase the effectiveness of immunotherapy, allergens were coupled to immunostimulants, and new adjuvants were introduced. Allergens were modified to increase their uptake and presentation. Hypoallergenic molecules were developed to improve the safety profile of vaccines, including peptides derived from allergens, recombinant allergens, receptor agonists and other adjuvants, among which we highlight the new adjuvants obtained from *Saccharomyces cerevisae.*[7,8]

Mannan from *Saccharomyces cerevisiae* is a polysaccharide consisting of mannose residues derived from yeast. The potential of mannan as an adjuvant for the treatment of different diseases was described by studies demonstrating enhanced dendritic cell (DC) maturation and antigen presentation, as well as enhanced immune responses with mannan.[9,10] Carbohydrate conjugation to allergens is a well-described approach to targeting antigen-presenting cells (APCs) and rendering the allergen hypoallergenic.[11]

Mannan (*Saccharomyces cerevisiae*) has been used in several studies for targeting allergens to APCs. Weinberger et al. demonstrated that mannan conjugates were efficiently taken up by DCs *in vivo*, inducing a switch from IgE to IgG production.[11] The strategy of conjugating the antigens (from mites, grass

pollens, etc.) with a carbohydrate source (mannose) extracted from the cell wall of a known yeast called *Saccharomyces cerevisiae*, which is composed of three main structures (mannan, chitin, and glucan) and is well described in the literature.[12]

The targeting of antigens to DCs to increase cellular uptake has the potential to result in more effective and efficient immunotherapy. Antigens coupled to yeast mannan, as a source of mannose, are suitable for this purpose, given that mannose-binding receptors are expressed on these cells.[12]

APC system – DCs – C-type lectin receptors

DCs are the therapeutic target of glycoconjugates that are rich in yeast mannose. These preparations benefit from carbohydrate receptors found in DCs. They are targeted to C-type lectin receptor (CLR) agonists, in which the adjuvant acts both as an immunostimulant and as an antigen delivery vector system – directing allergens to greater uptake by DCs.

Described by Ralph Steinmen, the 2011 Nobel Prize-winning immunologist, DCs are the main professional APCs. They are located in all lymphoid tissue, in primary and secondary lymphoid organs, and in the blood. They are responsible for initiating and maintaining immune responses.[13]

Glycoconjugate antigens (*Saccharomyces cerevisiae*) are suitable vaccines for allergen-specific immunotherapy, with a growing number of important publications, and may be extremely relevant for the development of therapeutic interventions in other diseases related to immune tolerance.[14] They induce potent blocking antibodies and are captured by human DCs much more efficiently than native antigens, which rely on non-integrin-mediated internalization of the mannose receptor and the specific DC. In addition, they activate human DCs to generate functional forkhead box P3 (FOXP3) Treg cells through PD-L1.[14] These adjuvant characteristics may be explained by their ability to activate CLRs, which are pattern recognition receptors normally expressed in DCs.[14]

Glycoconjugate antigens form an antigen-mannan complex that is more easily captured and internalized. Subsequently, in the presence of IL-10, DCs are activated and acquire a tolerogenic phenotype to form a new population of Treg tolerant cells.[15] Glycoconjugation has been shown to promote the generation of tolerogenic DCs capable with ability to induce FOXP3, functional Tregs both *in vivo* and *in vitro*. The presence of alum was shown to impair the tolerogenic properties of allergenic vaccines with glycoconjugate antigens (*Saccharomyces cerevisiae*).[16]

The Mannose receptor – Internalization and activation

Although there is evidence for carbohydrate conjugation to allergens (glycoconjugation) and *Saccharomyces cerevisiae* can be easily found in Brazil, the use of the mannose-rich adjuvant mannan is linked to an international patent (INMUNOTEK, Spain). However, mannose can be obtained from carbohydrate structures on the cell wall of *Saccharomyces cerevisiae*, for which the general principle of antigen glycoconjugation to mannose may be applied.

Saccharomyces cerevisiae (native) preserves its macrostructures (chitin, glucan, and mannan). The cell wall structure of *Saccharomyces cerevisiae* mainly consists of chains of glucose residues and mannoproteins. Despite having a high degree of purity, the β-glucan fraction of yeast has a mannose-rich fraction, with short or long chains with a high concentration of mannan. Thus, glycoconjugation with this fraction of *Saccharomyces cerevisiae* is capable of maintaining the carbohydrate structure intact (mannan, glucose) and its potentially associated tolerogenic properties, with adjuvant capacity for targeted delivery of allergens to DCs.

Differentials, safety, and effects in immunotherapy

The use of polysaccharides in immunotherapy regimens with one of the mannose-rich fractions of *Saccharomyces cerevisiae* was studied by Oliveira & Binnotti.[17] Although the authors considered the practice to be promising, they described it as experimental.

Current studies demonstrate that glycoconjugates (*Saccharomyces cerevisiae*) target DCs via the mannose receptor and the DC-SIGN, increasing allergen uptake, increasing IL-10 production and PD-L1 expression, and promoting the generation of allergen-specific FOXP3 T cells, both *in vitro* and *in vivo*, which are impaired by the conventional adjuvant alum.[16]

A recent literature review showed that these conjugates also reprogram monocyte differentiation and generate tolerogenic DCs through epigenetic and metabolic rewiring. Unprecedented molecular mechanisms have been discovered, through which these glycoconjugates can restore allergen tolerance during allergen-specific immunotherapy.[18]

Conclusions and future perspectives

Although the use of polysaccharides, currently best described as glycoconjugate antigens with mannose from *Saccharomyces cerevisiae*, in immunotherapy regimens has been poorly understood in the past, several international studies currently supporting its benefits, which are superior to that of native antigens, constituting a recent and important evolution in the field of immunotherapy.

The essential role of DCs is highlighted in the literature. After capturing and internalizing antigens, DCs are activated and acquire a tolerogenic phenotype to form T cells – a fundamental mechanism of allergen-specific immunotherapy. Studies have demonstrated the benefits of optimizing and improving the safety of the therapeutic regimen, as well as of increased promotion of Treg tolerant cells.[15]

DC absorption increases bioavailability and absorption, improving the dosing scheme by suppressing the induction phase and leading to increased spacing between applications, with intervals every 5 weeks. Vaccines for pollen and dust mite allergies have already been developed, but the same concept is also being studied for other allergens, including peanuts.[15]

Glycoconjugate antigens (*Saccharomyces cerevisiae*) represent a new generation of allergy vaccines, as they optimize the uptake of allergens by DCs and increase the bioavailability of administered doses while promoting safe immune responses.[15]

The emergence of new evidence elucidates the immunostimulatory activity and the allergen delivery vector system to DCs, potentiated by glycoconjugation of antigens to high mannose adjuvant from *Saccaromyces cerevisae* and its potential contribution to innovation in the field of immunotherapy.

References

1. JutelM, AgachеI, BoniniS, BurksAW, CalderonM, Canonica W, et al. International Consensuson Allergen Immunotherapy II: mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol. 2016;137:358-68.
2. Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M, et al. Perspectives in allergen immunotherapy: 2017 and beyond. Allergy. 2018;73(Suppl104):5-23.
3. Kucuksezer UC, Ozdemir C, Cevhertas L, Ogulur I, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and allergen tolerance. Allergol Int. 2020 Oct;69(4):549-60. doi: 10.1016/j.alit.2020.08.002.
4. Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. J Allergy Clin Immunol. 1998;102:157-64.
5. Pereira VAR, Aun WCT, Mello JF. Mecanismos da imunoterapia alérgeno-específica. Arq Asma Alerg Imunol. 2017;1(3):257-62.
6. Schülke S, Vieths S. Dendritic cell targeting with C-type lectins for improvement of allergen immunotherapy. J Allergy Clin Immunol. 2016 Aug;138(2):568-70.
7. Pfaar O, Creticos PS, Kleine-Tebbe J, Canonica GW, Palomares O, Schülke S. One Hundred Ten Years of Allergen Immunotherapy: A Broad Look Into the Future. J Allergy Clin Immunol Pract. 2021 May;9(5):1791-803. doi: 10.1016/j.jaip.2020.12.067. Erratum in: J Allergy Clin Immunol Pract. 2021 Oct;9(10):3851. PMID: 33966868.
8. Komlósi ZI, Kovács N, Sokolowska M, van de Veen W, Akdis M, Akdis CA. Highlights of Novel Vaccination Strategies in Allergen Immunotherapy. Immunol Allergy Clin North Am. 2020 Feb;40(1):15-24. doi: 10.1016/j.iac.2019.09.010.
9. Sheng KC, Pouniotis DS, Wright MD, Tang CK, Lazoura E, Pietersz GA, et al. Mannan derivatives induce phenotypic and functional maturation of mouse dendritic cells. Immunology. 2006 Jul;118(3):372-83. doi: 10.1111/j.1365-2567.2006.02384.x.
10. Tada H, Nemoto E, Shimauchi H, Watanabe T, Mikami T, Matsumoto T, et al. Saccharomyces cerevisiae- and Candida albicans-derived mannan induced production of tumor necrosis factor alpha by human monocytes in a CD14- and Toll-like receptor 4-dependent manner. Microbiol Immunol. 2002;46(7):503-12.
11. Weinberger EE, Himly M, Myschik J, Hauser M, Altmann F, Isakovic A, et al. Generation of hypoallergenic neoglycoconjugates for dendritic cell targeted vaccination: a novel tool for specific immunotherapy. J Control Release. 2013 Jan 28;165(2):101-9.
12. Manzano AI, Javier Cañada F, Cases B, Sirvent S, Soria I, Palomares O, et al. Structural studies of novel glycoconjugates from polymerized allergens (allergoids) and mannans as allergy vaccines. Glycoconj J. 2016 Feb;33(1):93-101. doi: 10.1007/s10719-015-9640-4.
13. Bona C, Bot A. The 2011 Nobel Prize - honoring the memory of Dr. Ralph Steinman. Int Rev Immunol. 2011 Oct-Dec;30(5-6):233-4. doi: 10.3109/08830185.2011.630972.
14. Sirvent S, Soria I, Cirauqui C, Cases B, Manzano AI, Diez-Rivero CM, et al. Novel vaccines targeting dendritic cells by coupling allergoids to nonoxidized mannan enhance allergen uptake and induce functional regulatory T cells through programmed death ligand 1. J Allergy Clin Immunol. 2016 Aug;138(2):558-67.e11
15. Benito-Villalvilla C, Soria I, Subiza JL, Palomares O. Novel vaccines targeting dendritic cells by coupling allergoids to mannan. Allergo J Int. 2018;27(8):256-262. doi: 10.1007/s40629-018-0069-8.
16. Benito-Villalvilla C, Soria I, Pérez-Diego M, Fernández-Caldas E, Subiza JL, Palomares O. Alum impairs tolerogenic properties induced by allergoid-mannan conjugates inhibiting mTOR and metabolic reprogramming in human DCs. Allergy. 2020 Mar;75(3):648-59. doi: 10.1111/all.14036.

17. Oliveira CH, Binotti RS. Uso de polissacarídeos em esquemas de imunoterapia. Rev bras alerg imunopatol. 2002;25(6):200-3.

18. Benito-Villalvilla C, Pérez-Diego M, Angelina A, Kisand K, Rebane A, Subiza JL, et al. Allergoid-mannan conjugates reprogram monocytes into tolerogenic dendritic cells via epigenetic and metabolic rewiring. J Allergy Clin Immunol. 2022 Jan;149(1):212-22.e9. doi: 10.1016/j.jaci.2021.06.012.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Provocation tests for chronic inducible urticaria: the experience of a urticaria center of reference and excellence

Testes de provocação para urticárias crônicas induzidas: a experiência de um centro de referência e excelência em urticária - UCARE

Guilherme Gomes Azizi[1], Sérgio Duarte Dortas-Junior[1], Rossy Moreira Bastos-Junior[1], Alfeu Tavares França[1], Solange Oliveira Rodrigues Valle[1]

ABSTRACT

Introduction: Urticaria is determined by mast cell activation that presents as wheals, angioedema, or both. Urticaria is classified according to its duration into two forms: acute (< 6 weeks) and chronic (> 6 weeks). Chronic urticaria includes chronic spontaneous urticaria and chronic inducible urticaria. Chronic inducible urticarias include dermographism, delayed pressure urticaria, cold, heat, solar, aquagenic, cholinergic, and vibratory urticaria/angioedema. Chronic inducible urticaria can be diagnosed through clinical history, physical examination, and the reproduction of lesions through provocation tests. **Objective:** To describe the profile of positive provocation tests for chronic inducible urticaria performed at an urticaria center of reference and excellence (GA^{2}LEN UCARE). **Methods:** We retrospectively evaluated the results of provocation tests performed between December 2017 and September 2021 in 114 patients with a history suggestive of one or more types of chronic inducible urticaria. **Results:** The sample included 88 (77%) female and 26 (23%) male patients. The following were diagnosed through positive provocation tests: 65 cases of dermographism (FricTest® and/or dermographometer); 23 cases of delayed pressure urticaria (all diagnosed with a dermographometer and 11 confirmed with the Warin test); 11 cases of cold urticaria (temperatures ≤ 27°C) and 3 cases of heat urticaria (temperatures ≥ 38°C), all diagnosed with TempTest® 4.0; 4 cases of cholinergic urticaria, all diagnosed with the Modified Test for Cholinergic Urticaria-HUCFF-UFRJ, and 1 case of vibratory urticaria. No patient tested positive for solar or aquagenic urticaria. Seven patients have been negative. **Conclusion:** Provocation tests, which use direct and safe stimuli as triggers, allow physicians and patients to confirm the disease's causative stimulus and its thresholds.

Keywords: Chronic urticaria, urticaria, angioedema, allergy and immunology.

RESUMO

Introdução: A urticária é determinada pela ativação de mastócitos que se apresenta por urticas, angioedema ou ambos. A urticária é classificada de acordo quanto a sua duração, em duas formas: aguda (UA < 6 semanas) e crônica (UC > 6 semanas). A UC compreende Urticária Crônica Espontânea (UCE) e Urticárias Crônicas Induzidas (UCInd). Entre as UCInd estão o dermografismo, urticária por pressão tardia (UPT), frio, calor, solar, aquagênica, colinérgica e urticária/angioedema vibratório. As UCInd podem ser diagnosticadas por meio da história clínica, exame físico e da reprodução das lesões através dos testes de provocação. **Objetivo:** Descrever o perfil dos testes de provocação positivos para UCInd realizados em um Centro de Referência e Excelência em Urticária (GA^{2}LEN UCARE). **Métodos:** Foram avaliados, retrospectivamente, os resultados dos testes de provocação para UCInd, realizados de dezembro de 2017 a setembro de 2021, de 114 pacientes que apresentavam história sugestiva de uma ou mais UCInd. **Resultados:** Dos 114 pacientes avaliados, oitenta e oito (77%) eram do sexo feminino e 26 (23%) do masculino. Foram diagnosticados, através de testes de provocação positivos: 65 dermografismos (FricTest® e/ou dermografômetro); 23 UPT (23 diagnosticados com o uso do dermografômetro e 11 também confirmados através do teste de Warin); 11 urticárias ao frio (temperaturas iguais ou inferiores a 27 °C) e 3 urticárias ao calor (temperaturas iguais ou superiores a 38 °C), todos diagnosticados com o TempTest® versão 4.0; 4 urticárias colinérgicas, diagnosticados através do Teste Modificado para Urticária Colinérgica - HUCFF-UFRJ e 1 urticária vibratória. Nenhum paciente apresentou teste positivo para urticária solar ou aquagênica. Sete pacientes foram negativos. **Conclusão:** Os testes de provocação, através do estímulo direto e seguro com o desencadeante, permitem ao médico avaliador e ao paciente a compreensão e a confirmação do estímulo causador da enfermidade em questão e seus limiares.

Descritores: Urticária crônica, urticária, angioedema, alergia e imunologia.

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Introduction

Urticaria is a disease determined by mast cell activation and presents with wheals, angioedema, or both.[1] Urticaria is classified according to its duration into two forms: acute (AU) and chronic (CU). CU is characterized by persistence of symptoms for 6 weeks or more. CU comprises chronic spontaneous urticaria (CSU) and chronic inducible urticarias (CIndU), which include physical and nonphysical urticarias.[1-3]

CIndU are defined as a group of diseases characterized by wheals and/or angioedema induced by external stimuli, including dermographism, delayed pressure urticaria (DPU), cold urticaria, heat urticaria, solar urticaria, aquagenic urticaria, cholinergic urticaria, and vibratory urticaria/angioedema.[2,3]

The prevalence of physical urticarias (PU) ranges from 20% to 30% of the cases of urticaria in adults, and from 6.2 to 25.5% in children. PU are estimated to be present in up to 5% of the general population; additionally, they are present in 10 to 50% of patients with CU, with symptomatic dermographism and DPU being the most common in our setting.[4] Patients with both CSU and PU usually show worse prognosis and longer duration of these diseases.[5,6]

CIndU may be diagnosed through clinical history, physician examination, and the reproduction of lesions through provocation tests.[7]

Dermographism is the most frequent CIndU among the general population (2-5%) and are responsible for 30-50% of cases of PU.[2] This type of PU is characterized by the occurrence of wheals after local pressure or shearing force on the skin, manifesting especially after scratching or rubbing, with the development of local itchy lesions.[8,9]

Some instruments, such dermographometer, calibrated at pressures from 20 to 160 g/mm^2 (196-1569 kPa), and Fric Test® (Moxie, Berlin, Germany), a plastic device with four pins measuring 3.0, 3.5, 4.0 and 4.5 mm in length, respectively, were developed to test dermographism and determine the symptomatic threshold. In addition to these instruments, blunt and smooth objects, such as a closed ballpoint pen tip or a spatula, may be rubbed on the volar surface of the forearm or superior surface of the back.[10]

Studies describe a low prevalence of DPU, which occurs in less than 5% of cases of CIndU.[11] Patients with DPU develop wheals and/or angioedema 4 to 6 hours after the skin is exposed to sustained pressure stimulation. Lesions may appear up to 12-24 hours and may last up to 72 hours.[12,13] The reaction is not usually associated with itching, but may be accompanied by pain and/or burning. It is essential to differentiate symptomatic dermographism from DPU, and time of appearance of lesions is one of the characteristics that differentiate these CIndU. Another characteristic is that DPU presents with painful and non-itchy lesions. It is worth highlighting that these forms may be associated.[14,15]

Provocation tests to assess DPU aim to simulate pressure to the skin during a given sustained time, to then evaluate the skin reaction at stipulated time points. Test methods include the suspension of weights over the shoulder, the application of rods, lowered vertically onto the skin and supported in a frame, on the back, thigh, or forearm, or the use of a dermographometer.[7]

Cold urticaria is defined by the appearance of wheals after exposure to cold, either by solid objects, air, or cold liquids. These lesions are caused by the release of histamine, leukotrienes, and other pro-inflammatory mediators from mast cells.[2,5,16] According to some authors, cold urticaria is the second most common type of physical inducible urticaria. Its annual incidence is estimated at 0.05%, its frequency ranges from 5 to 30%, with a predominance in the female sex (2:1), and the most affected age group is 20 to 30 years old.[2,17,18]

Lesions are usually limited to the site of contact with cold (wheals and angioedema), but they can be generalized and accompanied by systemic manifestations, including progression to acute respiratory failure and anaphylaxis. These mainly occur in situations such as carrying refrigerated objects, swimming in ice water, staying, or entering a refrigerated environment.[19]

Challenge methods for cold urticaria include the classic "ice cube test" and the TempTest®.[7]

Heat urticaria is a rare form of CIndU characterized by wheals appearing soon after exposure to heat. Due to its rareness, there are no robust data on its prevalence. Most cases occur in women (82%). The mean age of onset of heat urticaria is 34.4 ± 19.5 years, ranging from 4 to 78 years.[20]

It may occur in two forms: localized and generalized, depending on whether the reaction is limited to the directly exposed portion of the skin or affects distant sites, respectively.[21]

Wheals appear 2-15 minutes after exposure and may last for approximately 1-3 hours. A burning sensation on the site of the lesion may also occur.

Some patients may present systemic manifestations such as syncope, fatigue, nausea, vomiting, abdominal pain, fever, and dyspnea. These manifestations occur especially if extensive areas are involved. Challenge methods for heat urticaria include the classic "ice cube test" and TempTest®.[7,22]

Patients with solar urticaria develop wheals shortly after exposure of skin to sunlight (UVA, 320-400 nm; or visible wavelengths, 400-600 nm). Less frequently, lesions are induced by UVB (280-320 nm) or infrared radiation (> 600 nm). Solar urticaria accounts for 7% of all photodermatoses. The prevalence of this CIndU ranges from 0.4–0.5% of patients with CUs.[7,23,24]

Solar urticaria is classified into two types: type I occurs in patients who have precursors located in the serum, plasma or cutaneous tissue fluid that become photoallergens once activated by the appropriate wavelength and bind to IgE receptors, resulting in degranulation of mast cells and other inflammatory mediators. Type II is also IgE-mediated, but precursors are found in both healthy individuals and patients with solar urticaria.[5,25]

The diagnosis of solar urticaria is made by testing the individual for several wavelengths to simulate provocation of urticaria.[7]

Patients with vibratory urticaria/angioedema present itching and wheals minutes after the skin is exposed to vibratory stimuli, such as riding a motorcycle, riding a horse, practicing mountain bike, using a gyratory crusher or a lawn mower, and playing musical instruments such as the electric guitar. This subtype of urticaria may have a familial etiology, with a dominant autosomal inheritance. Its prevalence is approximately 0.1% of patients with CU. Vibratory urticaria may be tested by standardized challenge with a mixer vortex.[2,7,10]

Aquagenic urticaria is a rare condition resulting from contact with water, regardless of its temperature. Approximately 30 minutes after contact with water, patients develop wheals measuring 1-2 mm. These are mostly isolated cases, although familial cases were reported.[26,27]

Its fisiopatogenia is not well understood; however, there is evidence that water would act as a carrier for an epidermal antigen that is able to activate mast cells.[28,29] Provocation test for aquagenic urticaria consists of using a compress soaked in water at a temperature close to body temperature.[7]

Cholinergic urticaria was first described by Duke in 1924[9] and is characterized by the appearance of micropapular lesions related to an increase in body temperature from physical exercise or local application of heat; in addition to emotional stress, spicy foods, or hot drinks. The lesions are approximately between 1 and 3 mm, located on the trunk and upper limbs.[7,30,31]

Cholinergic urticaria is more common between the second and the third decades of life. Furthermore, its prevalence ranges from 4 to 11% in the general population.[32]

Four subtypes of cholinergic urticaria were proposed, based on its pathogenesis and clinical characteristics: the first type refers to cholinergic urticaria related to sweat allergy and without angioedema, with possible hypersensitivity to sweet after it is released from ducts; the second type is named follicular-type cholinergic urticaria with a positive autologous serum skin test is hypothesized to be caused by mast cell activation through acetylcholine and/or specific antigens located on the epidermis, inducing urticaria around the follicles; the third type consists of cholinergic urticaria with palpebral angioedema; and the fourth type is known as cholinergic urticaria with acquired anhidrosis and/or hypohidrosis.[33]

Lesions tend to last 15 to 60 minutes and may be associated with local angioedema. If cholinergic urticaria is suspected, it is important to differentiate it from exercise-induced anaphylaxis, aquagenic urticaria, adrenergic urticaria, and cold-induced cholinergic urticaria.[33,34]

We have recently reported a case in which the patient underwent challenge test for cholinergic urticaria, using a flight of stairs (13 steps) and parameters similar to a previously described standardized protocol. A frequency meter (Polar F11®) was used to measure and control heart rate (HR). The patient was instructed to go up and down in order to increase his HR by 15 bpm each 5 minutes, being intensified, so as to reach 90 bpm over base HR 30 min later. After 15 min and 45 bpm over baseline, he showed micropapular lesions and erythema on his face, chest, and limbs, and a positive test in mild exercise (57% of HRMax).[35]

CIndU are diseases that visibly impair patient's quality of life, especially due to limitations in environmental exposure, often including the work environment.[36]

Therefore, the aim of this study is to describe the profile of positive provocation tests for CIndU

performed at an Urticaria Center of Reference and Excellence (GA²LEN UCARE).

Methods

We retrospectively evaluated the results of provocation tests for CIndU performed between December 2017 and September 2021 in 114 patients with a history suggestive of one or more types of CIndU.

Results

Of the 114 patients evaluated, 88 (77%) were female and 26 (23%) were male. The following forms of CIndU were diagnosed through positive provocation tests: 65 cases of dermographism (Fric Test® and/or dermographometer); 23 cases of DPU (all diagnosed with a dermographometer and 11 confirmed with the Warin test); 11 cases of cold urticaria (temperatures ≤ 27°C); 3 cases of heat urticaria (temperatures ≥ 38°C), all diagnosed with TempTest® 4.0; 4 cases of cholinergic urticaria, all diagnosed with the Modified Test for Cholinergic Urticaria – HUCFF-UFRJ; and 1 case of vibratory urticaria. No patient tested positive for solar or aquagenic urticaria (Figure 1).

We found associations between different types of CIndU in 17 patients tested in the study period, including 11 associations between dermographism and DPU, 4 between DPU and cold urticaria, 1 between cholinergic and vibratory urticaria, and 1 tripe association between dermographism, DPU, and heat urticaria (Figure 2). Seven patients tested negative.

Discussion

CIndU are diseases that visibly impair patient's quality of life, due to limitations in environmental exposure, often including the work environment.

Our data corroborate findings from other epidemiological studies showing a higher prevalence of CIndU in females (2:1 ratio); however, the female-male prevalence ratio in our sample (4:1) was higher than that of published data.

The prevalence of CIndU is variable, and dermographism (10-50%) and cold urticaria (5-30%) are reported to be the most prevalent, followed by DPU, which accounts for 5% of CIndU. In our sample, the prevalence of dermographism (60%) and DPU (21%) was higher than that previously reported; and cold urticaria showed a similar prevalence, despite being close to the lower threshold (9%).

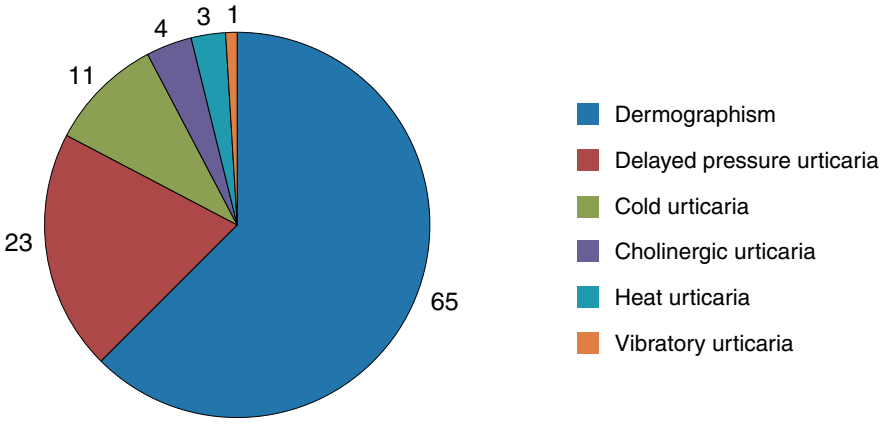

Figure 1
Positive provocation tests

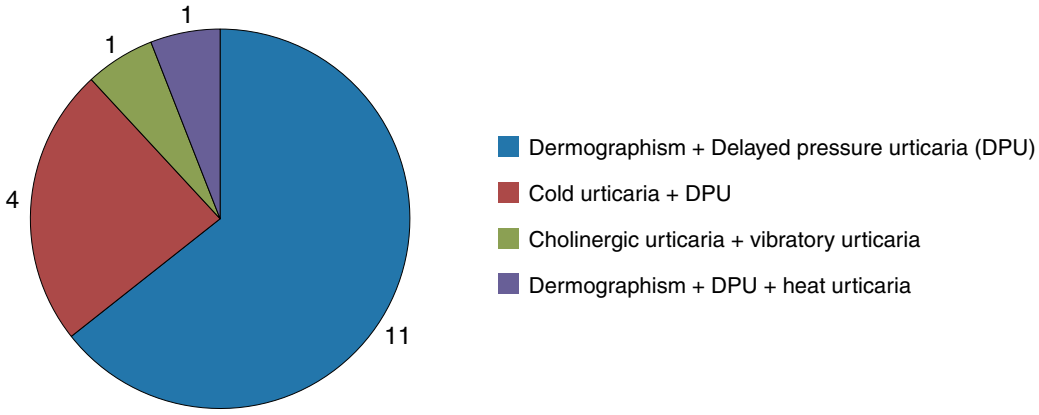

Figure 2
Associations between CIndU diagnosed through specific provocation tests

Data on the prevalence of heat urticaria are rare. In the sample evaluated, we found 3 cases (2.7%) among the 114 testes performed.

With regard to urticarias defined by exposure to temperature variations (cold and heat), we should carefully analyze the reason for these findings, i.e., why cold urticaria presented a prevalence close to the lowest values found in the literature, and heat urticaria showed opposite results. Therefore, the location of Brazil and, specifically, the place of residence of the study population, which has a subtropical climate, is linked to positive natural selection with regard to heat and negative with regard to cold.

Cholinergic urticaria has a prevalence from 4 to 11% in the general population, and was found in 4 individuals (3.5%), a percentage close to that reported in the literature. Once again, climate local conditions are linked to practice of outdoor sports and work activities, a fact that makes the population considerably more exposed to increased body temperature, and thus, to symptoms of this CIndU. However, it is worth investigating the low accurate diagnosis of cholinergic urticaria and referral to specialized care, which is essential in the subsequent management of these cases.

Similar to cholinergic urticaria, tests for vibratory urticaria resulted in only one 1 positive test in the study sample, which is closely consistent with other studies, because this CIndU is rare, with a prevalence < 1%.

It is not common for an individual to present more than one form of CIndU; however, 17 associations between CIndU were observed in our sample, including a patient who presented three forms of CIndU.

These differences in prevalence and associations described between different CIndU should be critically analyzed, since the University Hospital where provocations tests were performed provides tertiary care, and, consequently, has a greater number of referrals to specialized care.

Regarding the divergence between the two methods used to diagnose DPU in our service, a greater accuracy was observed in the use of dermographometer (23) than in the Warin Test (11). We believe that this discrepancy is associated with standardization of the latter method, due to the lack of robust studies, while the first method has accurate calculations aimed at selecting proper pressure for specific stimulus, as previously described.

Conclusion

Provocation tests, which use direct and safe stimuli as triggers, allow physicians and patients to confirm the disease's causative stimulus and its thresholds. Therefore, encouraging the use of available validated methods for diagnosis and proper monitoring of CIndU has an inestimable value for good medical practice.

Additional studies are necessary to assess the prevalence of CIndU in the local population, as well as studies aiming to develop new cost-effective challenge techniques.

References

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018 Jul;73(7):1393-414.
2. Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016 Jun;71(6):780-802. doi: 10.1111/all.12884.
3. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022 Mar;77(3):734-66. doi: 10.1111/all.15090.
4. Weller K, Altrichter S, Ardelean E, Krause K, Magerl M, Metz M, et al. Chronic urticaria. Prevalence, course, prognostic factors and impact. Hautarzt. 2010 Sep;61(9):750-7.
5. Sánchez-Borges M, González-Aveledo L, Caballero-Fonseca F, Capriles-Hulett A. Review of Physical Urticarias and Testing Methods. Curr Allergy Asthma Rep. 2017 Aug;17(8):51.
6. Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. J Am Acad Dermatol. 2001 Sep;45(3):387-91.
7. Dortas SDJ, Azizi GG, Sousa ACM, Lupi O, França AT, Valle SOR. Urticárias crônicas induzidas: atualização do tema. Arq Asma Alerg Imunol. 2020;4(3):305-16.
8. Dice JP. Physical urticaria. Immunol Allergy Clin North Am. 2004;24:225-46.
9. Duke WW. Urticaria caused specifically by the action of physical agents (light, cold, heat, freezing, burns, mechanical irritation, and physical and mental exertion). J Am Med Assoc. 1924;83(1):3-9.
10. Sánchez-Borges M, González-Aveledo L, Caballero-Fonseca F, Capriles-Hulett A. Review of Physical Urticarias and Testing Methods. Curr Allergy Asthma Rep. 2017 Aug;17(8):51. doi: 10.1007/s11882-017-0722-1.
11. Kulthanan K, Ungprasert P, Tuchinda P, Chularojanamontri L, Charoenpipatsin N, Maurer M. Delayed Pressure Urticaria: A Systematic Review of Treatment Options. J Allergy Clin Immunol Pract. 2020 Jun;8(6):2035-49.e5. doi: 10.1016/j.jaip.2020.03.004.
12. Lawlor F, Black AK, Ward AM, Morris R, Greaves MW. Delayed pressure urticaria, objective evaluation of a variable disease using a dermographometer and assessment of treatment using colchicine. Br J Dermatol. 1989;120:403-8.
13. Ryan TJ, Shim-Young N, Turk JL. Delayed pressure urticaria. Br J Dermatol. 1968;80:485-90.
14. Lawlor F. Cellular, molecular and therapeutic aspects of the physical urticarias. MD theses, 1990.
15. Black AK, Lawlor F, Greaves MW. Consensus meeting on the definition of physical urticarias and urticarial vasculitis. Clin Exp Dermatol. 1996 Nov;21(6):424-6.
16. Magerl M, Pisarevskaja D, Staubach P, Martus P, Church MK, Maurer M. Critical temperature threshold measurement for cold urticaria: a randomized controlled trial of H(1) - antihistamine dose escalation. Br J Dermatol. 2012 May;166(5):1095-9.
17. Siebenhaar F, Weller K, Mlynek A, Magerl M, Altrichter S, Vieira Dos Santos R, et al. Acquired cold urticaria: clinical picture and update on diagnosis and treatment. Clin Exp Dermatol. 2007 May;32(3):241-5.
18. Katsarou-Katsari A, Makris M, Lagogianni E, Gregoriou S, Theoharides T, Kalogeromitros D. Clinical features and natural history of acquired cold urticaria in a tertiary referral hospital: a 10-year prospective study. J Eur Acad Dermatol Venereol. 2008;22:1405-11.
19. Sánchez JM, Ramírez RH, Tamayo LM, Chinchilla CF, Cardona R. Urticaria por frío: serie de casos y revisión del tema [Cold urticaria: case series and literature review]. Biomedica. 2011 Jun;31(2):168-77.
20. Pezzolo E, Peroni A, Gisondi P, Girolomoni G. Heat urticaria: a revision of published cases with an update on classification and management. Br J Dermatol. 2016 Sep;175(3):473-8.
21. Doeglas HM, Rijnten WJ, Schröder FP, Schirm J. Cold urticaria and virus infections: a clinical and serological study in 39 patients. Br J Dermatol. 1986 Mar;114(3):311-8.
22. Rodrigues-Valle S, Azizi G, Duarte-Dortas S Jr. TempTest®: un instrumento de precisión en las urticarias físicas. Rev Alerg Mex. 2021 Jan-Mar;68(1):2-6.
23. Jong CT, Finlay AY, Pearse AD, Kerr AC, Ferguson J, Benton EC, et al. The quality of life of 790 patients with photodermatoses. Br J Dermatol. 2008 Jul;159(1):192-7.
24. Chong WS, Khoo SW. Solar urticaria in Singapore: an uncommon photodermatosis seen in a tertiary dermatology center over a 10- year period. Photodermatol Photoimmunol Photomed. 2004;20:101-4.
25. Pérez-Ferriols A, Barnadas M, Gardeazábal J, de Argila D, Carrascosa JM, Aguilera P, et al. Solar urticaria: Epidemiology and clinical phenotypes in a Spanish series of 224 patients. Actas Dermosifiliogr. 2017 Mar;108(2):132-9.
26. Seize MB, Ianhez M, de Souza PK, Rotta O, Cestari CS. Familial aquagenic urticaria: report of two cases and literatura review. An Bras Dermatol. 2009;84:530-3.
27. Shelley WB, Rawnsley HM. Aquagenic urticaria. Contact sensitivity reaction to water. JAMA. 1964;189:895-8.
28. Czarnetzki BM, Breetholt KH, TraupeH. Evidence that water acts as a carrier for an epidermal antigen in aquagenic urticaria. J Am Acad Dermatol. 1986;15:623-7.
29. Sibbald RG, Black AK, Eady RA, James M, Greaves MW. Aquagenic urticaria: evidence of cholinergic and histaminergic basis. Br J Dermatol. 1981;105(3):297-302.
30. Czarnetzki BM. Ketotifen in cholinergic urticaria. J Allergy Clin Immunol. 1990;86:138-9.
31. Illig L. On the pathogenesis of cholinergic urticaria. I. Clinical observations and histological studies. Arch Klin Exp Dermatol. 1967;229:231-47.
32. Maurer M, Fluhr JW, Khan DA. How to Approach Chronic Inducible Urticaria. J Allergy Clin Immunol Pract. 2018 Jul-Aug;6(4):1119-30. doi: 10.1016/j.jaip.2018.03.007.
33. Fukunaga A, Washio K, Hatakeyama M, Oda Y, Ogura K, Horikawa T, et al. Cholinergic urticaria: epidemiology, physiopathology, new categorization, and management. Clin Auton Res. 2018 Feb;28(1):103-13.

34. Kawakami Y, Gokita M, Fukunaga A, Nishigori C. Refractory case of adrenergic urticaria successfully treatedwith clotiazepam. J Dermatol. 2015;42(6):635-7.

35. Azizi GG, Ontiveros CM, Zylbersztejn SRS, Dortas Junior SD, Valle SOR. Teste de urticária colinérgica modificado e teste de urticária vibratória em hospital universitário. Arq Asma Alerg Imunol. 2019;3(Supl 1):S209.

36. Dortas-Jr SD, Azizi GG. Síndromes imunológicas e alérgicas induzidas ou exacerbadas por exercício: o que o profissional de saúde do exercício precisa? Rev Bras Fisiol Exerc. 2021;20(3):388-402. doi: 10.33233/rbfex.v20i3.4562.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Combination of intranasal fluticasone and azelastine for difficult-to-control allergic rhinitis in adolescents

Combinação fluticasona e azelastina intranasal no tratamento de adolescentes com rinite alérgica de difícil controle

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ABSTRACT

Introduction: Allergic rhinitis has a high prevalence and is responsible for a significant impact on the quality of life of affected individuals, reflecting negatively on school performance, social life, and work. An association of fluticasone propionate and azelastine hydrochloride (FP+AZE) has been recommended for patients with difficult-to-control allergic rhinitis. **Objective:** To evaluate treatment response to FP+AZE in adolescents with difficult-to-control moderate/severe persistent allergic rhinitis (MSPAR). **Methods:** This was a prospective, open-label, uncontrolled clinical trial for a therapeutic intervention in adolescents with difficult-to-control MSPAR treated at a specialized outpatient clinic. **Results:** There was significant improvement in all studied variables, showing better MSPAR control with FP+AZE. Using the minimal clinically important difference as an evaluation parameter, 83% of the patients improved. There were no reports of serious adverse events; a bitter taste was reported by 38.5% of patients, and 2 discontinued use due to an adverse event. **Conclusion:** FP+AZE was a well-tolerated, safe, and effective treatment for MSPAR. The most commonly reported adverse events were local.

Keywords: Allergic rhinitis, steroids, nasal obstruction.

RESUMO

Introdução: A rinite alérgica (RA) tem prevalência elevada e é responsável por impacto significativo da qualidade de vida destes pacientes, refletindo-se negativamente no desempenho escolar, na vida social ou no trabalho. A associação de propionato de fluticasona e cloridrato de azelastina (PF-AZE) tem sido recomendada no tratamento de pacientes com rinite alérgica de difícil controle. **Objetivo:** Avaliar a resposta ao tratamento com PF+AZE administrado a crianças e adolescentes com RA persistente moderada-grave (RAPMG) de difícil controle. **Métodos:** Ensaio clínico aberto não controlado prospectivo com intervenção terapêutica em que participaram adolescentes (n = 65) com RAPMG de difícil controle acompanhados em ambulatório especializado. **Resultados:** Houve melhora estatisticamente significante de todas as variáveis estudadas, o que mostrou melhor controle da rinite com a combinação PF+AZE. Utilizando-se a diferença mínima clinicamente importante como parâmetro de avaliação, 83% dos pacientes tiveram melhora da doença. Não houve relato de evento adverso grave, gosto amargo foi relatado por 38,5% dos pacientes e dois interromperam o esquema por evento adverso. **Conclusão:** A combinação PF+AZE foi bem tolerada, segura e eficaz no tratamento de pacientes com RAPMG. Eventos adversos locais foram os mais comumente relatados.

Descritores: Rinite alérgica, corticosteroides, obstrução nasal.

Introduction

Allergic rhinitis (AR) is a frequent inflammatory disease of the mucosal lining of the nasal cavity whose clinical manifestations may have a great impact on the quality of life of affected patients, in addition to negatively impairing sleep, school or work performance, and social life, among others.[1] In Brazil,

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an epidemiological study identified a prevalence of AR ranging from 25% and 30% among children and adolescents.[2]

Pharmacological treatment of AR includes the following drugs: topical or oral H1-antihistamines, intranasal corticosteroids (INCS), leukotriene receptor antagonists, and, occasionally, oral corticosteroids.[1,3,4]

INCS are the most effective and safe drugs to control allergic inflammation and AR, when administered at recommended doses in adults and children for the treatment of persistent forms. However, patients with severe forms may remain symptomatic even with a treatment combining INCS and another control medication.[1,3,4]

Recently, the combination of an INCS (fluticasone propionate) and an antihistamine (azelastine hydrochloride) (FP+AZE) became available for topical intranasal use in patients with moderate/severe persistent AR (MSPAR)[5], which was subsequently extended to all forms of AR, regardless of its type and severity.[1,6,7]

The use of FP+AZE in patients with AR, compared to fluticasone alone, showed to be a clinically more effective combination in controlling symptoms since the first day of treatment, and remained effective during the 1-year follow-up.[8] In a previous study, 75% of patients treated with FP+AZE experienced symptom relief and a positive impact on quality of life and treatment adherence. Furthermore, good tolerance and low incidence of adverse events were observed, similar to what occurred with fluticasone alone.[8] Thus, FP+AZE began to be recommended to patients with MSPAR aged over six years and with uncontrolled disease.[1,9]

Therefore, the aim of this real-life study was to evaluate treatment response to intranasal FP+AZE for four weeks in adolescents with MSPAR that remained uncontrolled despite being effectively treated.

Methods

This open-label, uncontrolled study included adolescents (12 to 20 years) with uncontrolled MSPAR for at least six months followed at a specialized outpatient clinic. The diagnosis of MSPAR was made by an allergist physician[1], and allergic sensitization to at least one aeroallergen (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, *Blatella germanica*, *Periplaneta americana*, cat dander, dog epithelium, pollen mixture, fungal mixture) was confirmed by positive specific serum IgE and/or prick test (diameter of wheal at least 3 mm greater than the negative control).[10]

All adolescents had uncontrolled MSPAR (medical opinion), because they remained symptomatic despite treatment with INCS and/or oral antihistamine.

Patients diagnosed with uncontrolled asthma, upper airway anatomical malformation, systemic diseases, cognitive deficit, active or recent (within the last three weeks) respiratory infection, as well as those using systemic corticosteroid in the last 30 days and/or allergen-specific immunotherapy, or receiving immunosuppressant therapy, were not included in the study.

Once patients were admitted, their current drug regimen was interrupted, and they started a new drug regimen with a combination of a fixed dose of intranasal FP (50 µg/ spray) and AZE (137 µg/spray) (1 spray/nostril twice a day) for 30 (± 5) days.

The following variables were measured at the beginning and at the end of the study: nasal symptom score (NSS), extra-nasal symptom score (ENSS), a questionnaire named RCAT (Rhinitis Control Assessment Test), a visual analogue scale (VAS) on nasal allergic rhinitis control, and peak nasal inspiratory flow (PNIF).

The NSS was calculated from the sum of the scores given by adolescents for: nasal obstruction, nasal itching, runny nose, sneezing, and post-nasal drip, whose intensity in the previous week was quantified with scores ranging from 0 (absent) to 3 (intense).[11] Therefore, NSS ranged from 0 to 15 points, and rhinitis was classified into mild (0 to 4 points), moderate (5 to 10 points), or severe (11 to 15 points).[11] The ENSS (0 to 12 points) was calculated similarly for the following symptoms: ocular itching, eye tearing, ocular hyperemia, and pharyngeal itching.[11]

The RCAT, a self-administered instrument translated and validated to Brazilian Portuguese[12], consists of six questions related to symptoms experienced in the previous week, and each question received scores, according to frequency of reporting, ranging from: 5 for never, 4 for rarely, 3 for sometimes, 2 for often, and 1 for very often. The sum of all questions gives the final score, and adolescents with a total score ≤ 22 were classified as having uncontrolled rhinitis.[12]

Control of nasal symptoms in the previous week was also assessed by the VAS (0 mm = no discomfort to 100 mm = maximum discomfort).[13] An objective

assessment of nasal function was performed by measuring PNIF in liters per minute (L/min), using a peak nasal inspiratory flow meter (Clement Clark®, UK), and the best of three measurements was considered, with a variation of less than 10%.[14]

Medical opinion about AR control (controlled, partially controlled, or uncontrolled) was recorded at the beginning and at the end of the study. The presence of adverse events was investigated in the final assessment of the study.

Individual clinical response for each outcome was defined according to the minimal clinically important difference (MCID), which was established as 23 mm for the VAS[13]; 3.0 points for RCAT[5]; 4.5 points for the NSS[15]; 3.6 points for the ENSS[13]; and 20 L/min for PNIF.[16]

Mean difference in the values obtained at the beginning and at the end of the study was compared using the Student's *t* test for paired samples. A level of significance of 5% was established to reject the null hypothesis.

The study was approved by the Research Ethics Committee of Universidade Federal de São Paulo, and all patients signed an Informed Consent Form.

Results

Seventy-one adolescents were included in the study, of which six did not return to the final visit, and two withdrew treatment due to adverse events. Mean age of the 63 adolescents (55.6% female) who completed the study was 14 ± 2 years, ranging from 12 to 20 years. With regard to the presence of other allergic manifestations, 81% had asthma, 57% had atopic dermatitis, and 46% had allergic conjunctivitis. All participants had been treated with INCS, and 25% received oral systemic antihistamine without achieving AR control. Eighty-five percent of patients reported to be adherent to this treatment.

During initial assessment using the NSS, 21 (33.4%) adolescents were classified as having severe AR; 38 (60.3%), moderate AR; and 4 (6.3%) mild AR. According to RCAT scores, 48 (76.2%) patients had a score equal to or lower than 22 (uncontrolled AR); according to the VAS, 52 (82,5%) patients were graves/uncontrolled (VAS ≥ 50 mm); and finally, according to medical opinion, 71% had uncontrolled AR, and 29% had partially controlled AR. The average interval between assessments was 33 days.

Table 1 presents the values obtained by the different instruments used, at the two time points of the study. There was a significant reduction in NSS, ENSS, and VAS scores, as well as in increase in PNIF and RCAT.

The separate analysis of nasal and extra-nasal symptoms at the two study time points revealed a significant reduction in all of them at the end of the study (Figure 1). Figure 2 presents the individual variations in VAS, RCAT, and NSS scores.

Table 1
Clinical and functional outcomes assessed at the beginning and at the end of treatment with a combination of fluticasone and azelastine (n = 63)

Variable	Initial	Final	Mean difference	95%CI	p
RCAT	19.4	24.2	4.8	3.6 – 6.1	< 0.001
NSS	9.0	4.1	4.9	4.0 – 5.7	< 0.001
ENSS	5.1	2.4	2.7	1.8 – 3.5	< 0.001
VAS (mm)	58	29	29	23 – 35	< 0.001
PNIF (L/min)	88	106	18	8 – 29	0.01

RCAT = rhinitis control assessment test, NSS = nasal symptom score, ENSS = extra-nasal symptom score, VAS = visual analogue scale, PNIF = peak nasal inspiratory flow, 95%CI = 95% confidence interval.

Table 2 describes the percentages of patients who showed improvement (values higher than MCID) or worsening (values lower than MCID) in the different parameters, according to the MCID for each of them.

Similarly, it was found that, after treatment with FP+AZE was initiated, there was an increase in the number of patients classified by the physician as having controlled AR (0 *vs.* 71%), as well as a decrease in the number of those with uncontrolled AR (71% *vs.* 11%) (Figure 3).

Adverse events were reported by 56% of adolescents, with a predominance of bitter taste in the mouth (38%), and there were no serious events (Table 3). Six patients did not return to the final visit, and two discontinued therapy due to an adverse event (3.1%).

Discussion

In our real-life study, we confirmed the results observed by other investigators showing that intranasal FP+AZE is effective in controlling uncontrolled MSPAR among adolescents, despite treatment with INCS and/or oral H1 antihistamine H1.[11,17-28]

Regardless of the instrument used to assess efficacy of treatment with FP+AZE (VAS, NSS, RCAT, PNIF), a high rate of AR control was observed in our patients, considering the MCID, i.e., 87% experienced improvement in at least one instrument.

In a recent review on the treatment of moderate/severe AR with FP+AZE, this combination achieved a 44% and 64% greater nasal symptom improvement, respectively, compared to its components administered alone.[29] Although the patients treated in our study had not satisfactorily responded to treatment with INCS

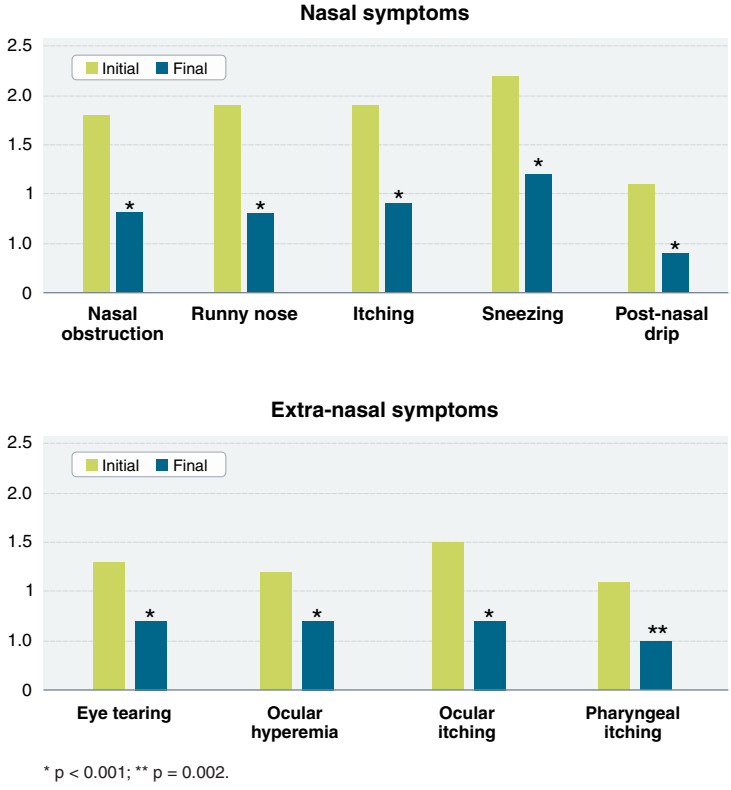

Figure 1
Mean individual scores for nasal and extra-nasal symptoms (ranging 0 to 3 points) at the beginning and at the end of the treatment with a combination of fluticasone and azelastine (n = 63)

alone or associated with systemic anti-H1, it is not possible to infer that combination was better than INCS alone, since patients had been using different products. However, when assessing patients *per se*, there was a significant reduction in the intensity of nasal and extra-nasal, consistent with findings reported by other authors.[11,17-28] (Figure 2).

Nasal obstruction, one of the most frequent symptoms of AR, is certainly one of the most bothersome for patients.[30] An assessment of PNIF, an objective measure of nasal patency, it was found that the group as a whole showed a significant improvement in PNIF after treatment with the combination and that 50% experienced an increase greater than 20 L/min, the MCID defined for this instrument.[16]

Another interesting data observed among our patients was the decrease in ENSS. Considering the MCID as the evaluation parameter, it was found that

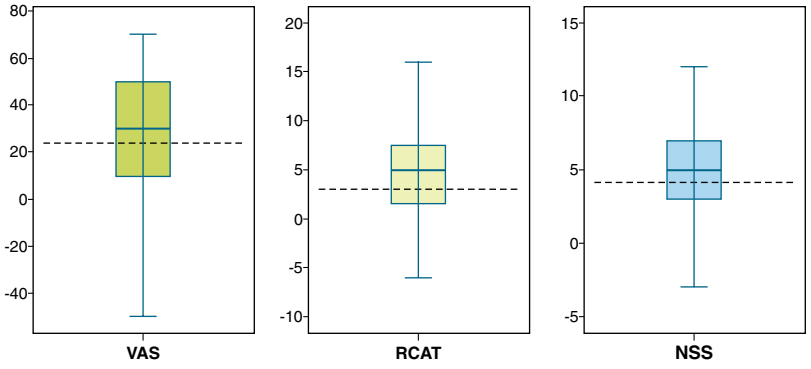

Figure 2
Individual variation of visual analogue scale (VAS), Rhinitis Control Assessment Test (RCAT), and nasal symptom score (NSS) at the end of treatment with a combination of fluticasone and azelastine compared to baseline (n = 63). Minimal clinically important difference for each outcome is shown by the dashed line

Table 2
Percentage of adolescents with clinical improvement and worsening after treatment with a combination of fluticasone and azelastine according to the MCID (n = 63)

Variable	MCID	Improvement		Worsening	
		n	(%)	n	(%)
RCAT	3.0	32	(50.8)	4	(6.3)
NSS	4.5	32	(50.8)	0	
ENSS	3.6	26	(41.3)	3	(4.8)
VAS (mm)	23	38	(60.3)	4	(6.3)
PNIF (L/min)	20	33	(52.4)	3	(4.8)

RCAT = rhinitis control assessment test, NSS = nasal symptom score, ENSS = extra-nasal symptom score, VAS = visual analogue scale, PNIF = peak nasal inspiratory flow, MCID = minimal clinically important difference.

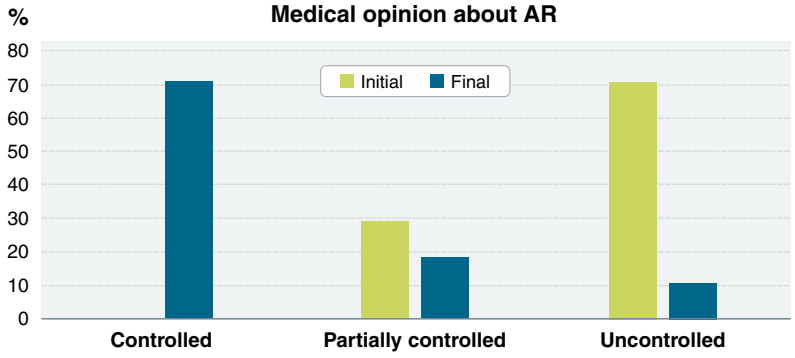

Figure 3
Percentage of adolescents classified as having controlled, partially controlled, and uncontrolled allergic rhinitis (AR) by the physician at the beginning and at the end of treatment with a combination of fluticasone and azelastine (n = 63)

more than 40% of patients experienced a decrease in ENSS, especially ocular itching. INCSs are believed to reduce ocular symptoms due to a class effect, because, when these drugs bind to glucocorticoid receptors, they promote increased expression of anti-inflammatory molecules and of beta-adrenergic receptors, in addition to decreased expression of pro-inflammatory cells and molecules, which increases the benefits of adding antihistamines.[31]

Table 3
Adverse events reported during treatment with a combination of fluticasone and azelastine (n = 65)

Adverse event	N	%
Bitter taste in the mouth	25	38.5
Pharyngeal discomfort	12	18.4
Nasal burning	8	12.3
Bad smell sensation	8	12.3
Headache	3	4.6
Epistaxis	1	1.5

Adverse events resulting from use of FP+AZE have been little frequent, with no reports of serious adverse events.[25] The most frequent adverse events have been: dysgeusia, nausea, sneezing, nasal discomfort, and epistaxis, all of them having low or very frequencies.[25] Although adverse events, mostly local reactions, were reported by a significant portion of our patients, only two discontinued the therapeutic regimen and withdrew the study.

Except for PNIF, all outcomes assessed here have a subjective component, because they depend on information provided by patients themselves. Therefore, the MCID was adopted in this study to assess results that are meaningful to patients and may be either self-reported or measured objectively. The MCID corresponds to the smallest change in outcome score that represents a significant change to patients.[32,33] Several methods are available to measure the MCID, but principal is that the change should be greater than the measuring error of the instrument that is being used to assess the outcome, and should be great enough for patients to perceive a clinical change.[32,33] Therefore, in the assessment of our outcomes, although few of those we used were validated to our population, we adopted cutoffs established by other authors.[5,13,15,16]

It is importantly to highlight that the percentage of patients with clinically important improvements

in the NSS and in the ENSS was much probably underestimated in our study. Due to the lack of specifically defined criteria for these scores, we decided to define more conservative values of 30% of the total for each score.[16]

The present study has some limitations. Since it was a real-life study, there was no comparison with a placebo group. Furthermore, there were no study arms assessing use of the drugs (fluticasone and azelastine) alone, thus hampering of these with FP+AZE.

In conclusion, INCS+AZE showed to be a well-tolerated, safe, and effective treatment for uncontrolled moderate/severe AR, which was revealed by a significant improvement not only of nasal symptoms but also of ocular symptoms.

References

1. Bousquet J, Schünemann HJ, Togias A, Bachert C, Erhola M, Hellings PW, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol. 2020;145(1):70-80.
2. Solé D, Wandalsen GF, Camelo-Nunes IC, Naspitz CK; ISAAC – Brazilian Group. Prevalence of symptoms of asthma, rhinitis, and atopic eczema among Brazilian children and adolescents identified by the International Study of Asthma and Allergies in Childhood (ISAAC) - Phase 3. J Pediatr (Rio J).2006;82:341-6.
3. Bousquet JJ, Schünemann HJ, Togias A, Erhola M, Hellings PW, Zuberbier T, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy. 2019;9:44.
4. Papadopoulos N, Bernstein J, Demoly P, Dykewicz M, Fokkens W, Hellings P, et al. Phenotypes and endotypes of rinithis and their impact on management: a PRACTALL report. Allergy. 2015;70:474-94.
5. EMC [Internet]. Dymista 137 micrograms/50 micrograms per actuation nasal spray. Summary of product characteristics. 2019. Available at: www.medicines.org.uk/emc/product/9450/smpc. Acessado em junho de 2022.
6. Wallace DV, Dykewicz MS, Oppenheimer J, Portnoy JM, Lang DM. Pharmacologic treatment of seasonal allergic rhinitis: synopsis of guidance from the 2017 joint task force on practice parameters. Ann Intern Med. 2017;167(12):876-81.
7. Dykewicz MS, Wallace DV, Baroody F, Bernstein J, Craig T, Finegold I, et al. Treatment of seasonal allergic rhinitis: an evidence-based focused 2017 guideline update. Ann Allergy Asthma Immunol. 2017;119(6):489-511.
8. Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica G, et al. Clinically relevant effect of a new intranasal therapy (MP 29-02) in allergic rhinitis assessed by responder analysis. Int Arch Allergy Immunol. 2013;161:369-77.
9. Derendorf H, Meltzer E, Hermann R, Canonica G. Clinical development of an advanced intranasal delivery system of azelastine hydrochloride and fluticasone propionate. Drugs Today (Barc). 2014;50:15-31.
10. Pepys J. Skin testing. Br J Hosp Med. 1975;14:412.
11. Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica G, et al. Clinically relevant effect of a new intranasal therapy (MP 29-02) in allergic rhinitis assessed by responder analysis. Int Arch Allergy Immunol. 2013;161:369-77.
12. Fernandes PH, Matsumoto F, Solé D, Wandalsen GF. Translation into Portuguese and validation of the Rhinitis Control Assessment Test (RCAT) questionnaire. Braz J Otorhinolaryngol. 2016;333:1-6.
13. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. Clin Exp Allergy. 2013;43:881-8.
14. Nathan RA, Eccles R, Howarth PH, Steinsvåg SK, Togias A. Objective monitoring of nasal patency and nasal physiology in rhinitis. J Allergy Clin Immunol. 2005;115(3 Suppl 1):S442-59.
15. Meltzer E, Wallace D, Dykewicz M, Shneyer L. Minimal Clinically Important Difference (MCID) in Allergic Rhinitis: Agency for Healthcare Research and Quality or Anchor-Based Thresholds? J Allergy Clin Immunol Pract. 2016;4:682-8.
16. Barnes M, Vaidyanathan S, Williamson P, Lipworth B. The minimal clinically important difference in allergic rhinitis. Clin Exp Allergy. 2010;40:242-50.
17. Kaulsay R, Nguyen DT, Kuhl HC. Real-life effectiveness of MP-AzeFlu in Irish patients with persistent allergic rhinitis, assessed by visual analogue scale and endoscopy. Immun Inflamm Dis. 2018;6(4):456-64.
18. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010;105(2):168-73.
19. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012;129(5):1282-9.
20. Price D, Shah S, Bhatia S, Bachert C, Berger W, Bousquet J, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. J Investig Allergol Clin Immunol. 2013;23(7):495-503.
21. Berger WE, Shah S, Lieberman P, Hadley J, Price D, Munzel U, et al. Long-term, randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) in subjects with chronic rhinitis. J Allergy Clin Immunol Pract. 2014;2(2):179-85.
22. Klimek L, Bachert C, Mosges R, Munzel U, Price D, Virchow JC, et al. Effectiveness of MP29-02 for the treatment of allergic rhinitis in real-life: results from a noninterventional study. Allergy Asthma Proc. 2015;36(1):40-7.
23. Berger W, Bousquet J, Fox AT, Just J, Muraro A, Nieto A, et al. MP-AzeFlu is more effective than fluticasone propionate for the treatment of allergic rhinitis in children. Allergy. 2016; 71(8):1219-22.
24. Berger W, Meltzer EO, Amar N, Fox AT, Just J, Muraro A, et al. Efficacy of MP-AzeFlu in children with seasonal allergic rhinitis: importance of paediatric symptom assessment. Pediatr Allergy Immunol. 2016;27(2):126-33.
25. Klimek L, Bachert C, Stjarne P, Dollner R, Larsen P, Haahr P, et al. MP-AzeFlu provides rapid and effective allergic rhinitis control in real life: a pan-European study. Allergy Asthma Proc. 2016;37(5):376-86.
26. Berger W, Sher E, Gawchik S, Fineman S. Safety of a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in children: a randomized clinical trial. Allergy Asthma Proc. 2018;39(2):110-6.
27. Patel P, Salapatek AM, Tantry SK. Effect of olopatadine-mometasone combination nasal spray on seasonal allergic rhinitis symptoms in an environmental exposure chamber study. Ann Allergy Asthma Immunol. 2019;122(2):160-6.
28. Debbaneh PM, Bareiss AK, Wise SK, McCoul ED. Intranasal azelastine and fluticasone as combination therapy for allergic rhinitis: systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2019;161(3):412-8.

29. Klimek L, Berger WE, Bousquet J, Smith P, Sole D, Scadding G, et al. MP-AzeFlu in Moderate-to-Severe Allergic Rhinitis: A Literature Review. Int Arch Allergy Immunol. 2021;182:1026-35.

30. Neffen H, Mello J Jr, Sole D, Naspitz C, Dodero A, Garza H, et al. Nasal allergies in the Latin American population: results from the Allergies in Latin America survey. Allergy Asthma Proc. 2010;31(Suppl 1):S9-27.

31. Seresirikachorn K, Chitsuhipakorn W, Kanjanawasee D, Khattiyawittyakun L, Snidvongs K. Effects of anti-histamine addition to intranasal corticosteroid for allergic rhiniits: a systematic and meta-analysis. Int Forum Allergy Rhinol. 2018;8(10):1083-92.

32. Maltenfort MG. The minimally important clinical difference. Clin Spine Surg. 2016;29(9):383.

33. Embry TW, Piccirillo JF. Minimal clinically important difference reporting in randomized clinical trials. JAMA Otolaryngol Head Neck Surg. 2020;146(9):862-3.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Immediate adverse events to the yellow fever vaccine in egg-allergic children

Eventos adversos imediatos à vacina febre amarela em crianças alérgicas ao ovo

Bianca Noleto Ayres Guimarães[1], Tânia Cristina de Mattos Barros Petraglia[1], Ana Karolina Barreto Berselli Marinho[2], Adauto Dutra Moraes Barbosa[3]

ABSTRACT

Introduction: The yellow fever vaccine is grown in embryonated chicken eggs and may be contraindicated for egg-allergic individuals. When indicated, it should be applied with caution, after testing and desensitization. Its safety in egg-allergic patients is still poorly studied. **Objective:** To describe a pediatric population referred for egg allergy, with or without a confirmed diagnosis, and cases of immediate-type adverse events to the yellow fever vaccine at a reference center for special immunobiologicals. **Material and methods:** This cross-sectional study collected retrospective data from children between 9 months and 12 years of age who were vaccinated for yellow fever between 2018 and 2019 and had a history of egg allergy. **Results:** In the 829 children diagnosed with presumed egg allergy, a higher prevalence of symptoms was identified after egg exposure, with detectable specific IgE for egg, egg white, and/or egg albumin. Yellow fever vaccine tests were performed in 25 children suspected of severe allergy or anaphylaxis to eggs, and 15 (60%) tested positive to the vaccine after desensitization. Only 11 (1.3%) cases of immediate adverse events to the vaccine occurred, all classified as non-serious events that especially involved the skin (local reaction and rash or urticaria). Most events occurred in children under 2 years of age, those symptomatic after egg ingestion, and those with high levels of specific IgE to egg white. **Conclusion:** This study demonstrated that the yellow fever vaccine can be safely administered to egg-allergic children, including those with a history of anaphylaxis, in an appropriate environment and with specialized professionals.

Keywords: Yellow fever vaccine, egg hypersensitivity, anaphylaxis, desensitization, drug-related side effects and adverse reactions.

RESUMO

Introdução: A vacina contra a febre amarela é cultivada em ovos embrionados de galinha e por isso pode estar contraindicada em indivíduos alérgicos ao ovo. Quando indicada, deve ser aplicada com cautela, após atendimento especializado para avaliação de testes e necessidade de dessensibilização. Sua segurança nos alérgicos ao ovo ainda é pouco estudada. **Objetivo:** Descrever uma população pediátrica encaminhada por alergia ao ovo, com ou sem diagnóstico comprovado, e os casos de eventos adversos do tipo imediata à vacina contra a febre amarela em um centro de referência para imunobiológicos especiais (CRIE). **Material e métodos:** Estudo transversal realizado com coleta de dados retrospectivos de crianças entre 9 meses e 12 anos de idade, vacinadas contra a febre amarela com história de alergia ao ovo, no período de 2018 a 2019. **Resultados:** Dentre as 829 crianças, com diagnóstico presumido de alergia ao ovo, foi identificada uma maior prevalência de sintomáticos após exposição ao ovo, com IgE específica detectável para ovo, clara de ovo e/ou ovoalbumina. Testes para vacina febre amarela foram realizados em 25 crianças com suspeita de alergia grave ou anafilaxia ao ovo, sendo 15 (60%) positivos com a vacina aplicada após dessensibilização. Foram evidenciados apenas 11 (1,3%) casos de evento adverso imediato à vacina, todos classificados como evento adverso não grave e com acometimento especial da pele (reação local e exantema ou urticária). A maioria dos eventos ocorreu em menores de 2 anos, nos sintomáticos após ingesta de ovo e naqueles com altos valores de IgE específica para clara de ovo. **Conclusão:** Este estudo evidencia que a vacina contra a febre amarela pode ser aplicada em crianças alérgicas ao ovo, de forma segura, inclusive naquelas com história de anafilaxia, desde que em ambiente adequado e com profissionais especializados.

Descritores: Vacina contra febre amarela, anafilaxia, dessensibilização imunológica, hipersensibilidade a ovo, efeitos colaterais e reações adversas relacionados a medicamentos.

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Introduction

Yellow fever (is a potentially serious viral disease transmitted by mosquitoes to humans and other primates. The most significant outbreak of yellow fever in Brazilian history occurred between 2017 and 2018 (1,376 cases; 35% lethality rate), and the risk of its re-urbanization again became a concern when the outbreak reached the most populous region of the country. Since 2019, the National Immunization Program's vaccination recommendation has been extended nationwide.[1]

Egg protein allergy (EPA), which is prevalent among children[2], may contraindicate the use of yellow fever vaccine due to the risk of adverse reactions, as this vaccine contains egg protein.[3] However, further research is needed to confirm the safety of the yellow fever vaccine in patients with EPA.[4-7] The objective of the present study was to determine the relationship between EPA and allergic reactions to the yellow fever vaccine in children.

Material and methods

This cross-sectional study collected retrospective data from a pediatric population with a history of EPA who were vaccinated for yellow fever at the Reference Center for Special Immunobiologicals (CRIE), Rocha Maia Municipal Hospital, Rio de Janeiro, RJ. We included boys and girls aged from 9 months to 12 years, 11 months, and 29 days who were vaccinated between January 2018 and December 2019. This period was selected due to the ongoing yellow fever outbreak in the city and the high demand for the vaccine.

Children diagnosed with EPA who were referred for yellow fever vaccination received prior care by the service's pediatrician, who performed an anamnesis to assess EPA severity and the risk of immediate adverse events to the vaccine. After an initial medical assessment, children with a history of mild/moderate EPA were given the yellow fever vaccine under 30 to 60 minutes of on-site observation. Those with a severe allergy or anaphylaxis to egg were referred for evaluation by the service's allergist and immediate skin testing for yellow fever vaccine was performed.

The immediate skin test to assess type I hypersensitivity consists of a prick test with the pure vaccine (1:1 dilution), followed by an intradermal test with the diluted vaccine (1:100) if the initial prick test is negative. Children with positive results at any stage of the immediate skin testing received the yellow fever vaccine after desensitization in a safe environment and under continuous monitoring, according to Brazilian Society of Allergy and Immunology (ASBAI) protocol.[4] Immediate reactions considered vaccine adverse events (VAE) were reported to the health surveillance team by the attending physician. According to the Ministry of Health's VAE manual, any events that resulted in hospitalization, significant dysfunction and/or permanent disability, or death or risk of death with immediate clinical intervention to prevent death, were considered severe VAE.[8] An event can be considered mild, moderate, or intense, regardless of its severity, such as intense local hyperemia.[8]

The yellow fever vaccine, manufactured by Bio-Manguinhos® during the national vaccination campaign of 2018, was applied in either the standard dose (0.5 mL) in individuals < 2 years of age and travelers or in the campaign dose (0.1 mL) in those > 2 years of age and non-travelers. Vaccinations were excluded if they were not referred through formal documentation to CRIE due to EPA, if they were revaccinations, or if the patient was not kept under observation after application for the period indicated by the doctor according to protocol.

Data were collected through the Ministry of Health's National Immunization Program Information System and anamneses, including the data used by attending physicians to define EPA severity and report VAE. The following variables were analyzed: age at vaccination, sex, clinical and laboratory information from the anamnesis (on which the referral based), comorbidities and other allergic diseases associated with EPA, immediate skin test results for yellow fever vaccine, vaccine dose and form of application of (with or without desensitization), and VAE during the observation period. The clinical information used to diagnose EPA was stratified into signs and symptoms of EPA prior to vaccination.

When reported, the results of the *in vivo* sensitization test (prick test for egg and/or egg components), which were carried out by the patient's physician prior to evaluation at CRIE, were classified as negative or positive. The oral challenge test was not evaluated in this study due to its limited use in non-specialized services.

The *in vitro* sensitization test, involving specific dosages of serum IgE for egg, egg white, ovalbumin, and/or ovomucoid, was mainly performed using the fluoroenzyme immunoassay method (ImmunoCAP,

Thermo Fisher Scientific, Waltham , MA, USA).[9] When reported, the results were classified as undetectable/detectable. Detectable results (low, moderate, or high) were classified according to the reference values of the clinical analysis laboratories where they were performed. The examination date, when reported, was also collected.

This study was approved by the Research Ethics Committee of the Rio de Janeiro Municipal Secretary of Health (CAAE: 33512620.9.0000.5279).

Results

The sample included a total of 829 children with probable EPA who were vaccinated for yellow fever (Table 1).

Table 1
Sex and age of 829 children vaccinated for yellow fever at the Rocha Maia Municipal Hospital Reference Center for Special Immunobiologicals

Variable	
Sex	**n (%)**
Male	460 (55)
Female	369 (45)
	Total: 829 (100)
Age	
Minimum – Maximum	9 months – 12 years
Median	1 year, 11 months
Mean (years ± SD)	3 ± 2
Age	**n (%)**
9 months	64 (8)
9 months to < 2 years	359 (43)
2 to 5 years	235 (28)
6 to 12 years	171 (21)
	Total: 829 (100)

SD = standard deviation.

Diagnostic criteria for egg protein allergy

The following criteria were used to evaluate a presumed diagnosis of EPA: the presence or absence of signs and symptoms after egg exposure (n = 688[83%]), prick test results for egg and/or its components (n = 190[23%]), and specific serum IgE for egg, egg white, and/or ovalbumin (n = 563[68%]).

In total, 720 (87%) children had symptoms after egg exposure, and/or specific serum IgE, and/or positive prick test results for egg or egg components. For in 12% (n = 97) of the children, no information was found about EPA symptoms or diagnostic tests.

Of the 623 children (91%) with signs and symptoms after egg exposure, 490 (79%) had cutaneous manifestations, 219 (35%) had gastrointestinal manifestations, 67 (11%) had respiratory manifestations, and 48 (8%) had neurological manifestations. Signs and symptoms in more than 1 organ or system occurred in 172 (28%) children. Anaphylaxis or suspected anaphylaxis was described in 22 (4%) children. The most commonly reported signs and symptoms of EPA were: urticaria (58%), dermatitis (29%), vomiting (26%), diarrhea (14%), angioedema (10%), cough (8%), irritability (7%), abdominal pain (6 %), rhinitis (4%), and anaphylaxis (4%). Although information about the range of EPA symptoms and the date of yellow fever vaccination were not reported in most records, in the symptomatic group, 356 (57%) were nursing infants when they received the vaccine.

Among the analyzed egg components, serum IgE levels for egg white (92%), ovalbumin (20%), and egg (17%) were the most frequent. Ovomucoid-specific IgE results were reported in < 1% of the sample. In total, 499 (89%) children had detectable specific serum IgE levels indicative of sensitization to eggs, egg whites, and/or ovalbumin, with 170 (30%) having specific serum IgE levels > 3.50 kU/l, which is considered high. The test date was reported for 176 (31%) children, of whom 95% were aged < 12 months and 81% were aged < 6 months when vaccinated.

Comorbidities, such as other allergic diseases associated with EPA prior to vaccination, were reported in 221 (27%) of the children, distributed as follows: atopic dermatitis (35%), cow's milk protein allergy (28%), other food allergies (8%), rhinitis (26%), and asthma or bronchitis (17%). None of the children were positive for gelatin allergy.

To assess sensitivity to yellow fever vaccine, immediate skin tests were performed in 25 (3%) of the children by the CRIE allergist: 20 who had a history of or suspected anaphylaxis to egg and 5 who had a

clinical history of severe EPA (urticaria and/or intense angioedema). High specific serum IgE values for egg, egg white, and/or ovalbumin were found in 21 of the 22 children with reported results. The prick test was positive in 10 of the 11 reported applications. Of the 22 children with anaphylaxis to egg, only 2 (5 and 6 years old), who had episodes in infancy, did not undergo an immediate skin test for yellow fever vaccine due to subsequent improvement.

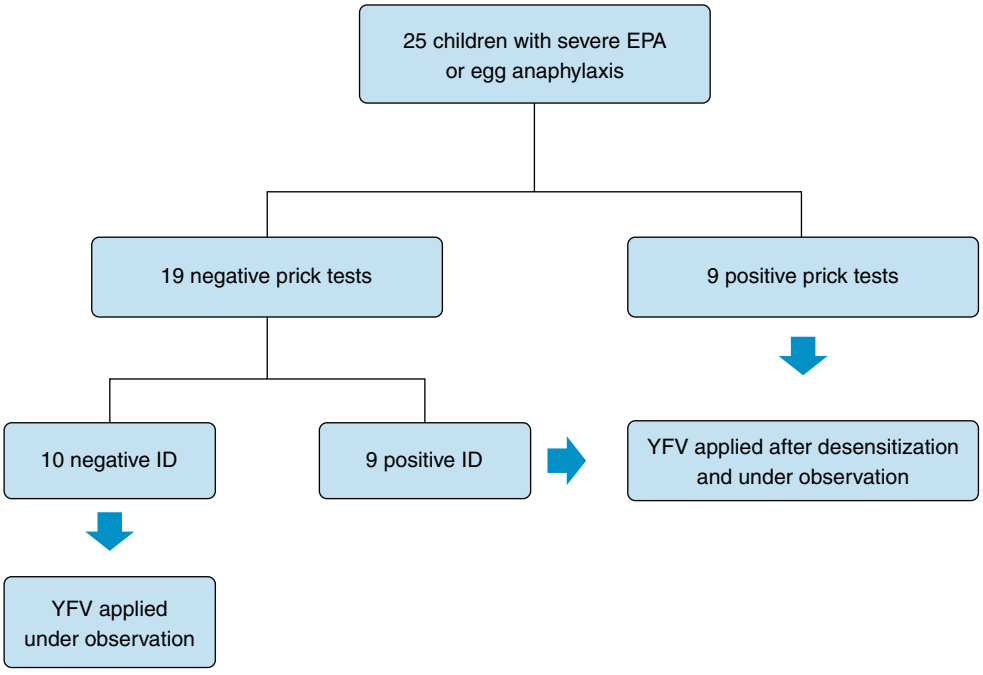
To assess sensitivity to the yellow fever vaccine, a prick test with the pure vaccine was performed, followed by an intradermal test with diluted vaccine (1:100) if the initial results were negative. Of the 25 prick tests performed for yellow fever vaccine, 6 were positive. The 19 children with negative results underwent intradermal testing with the diluted vaccine, of whom 9 were positive. Following the dose escalation (or desensitization) protocol, the 15 (60%) children with a positive test result (prick or intradermal) received the vaccine (Figure 1).

The standard vaccine dose (0.5 mL) was administered to 568 (69%) children. A dose of 0.1 mL (2018 campaign) was applied to 261 (31%) children > 2 years of age. Of the 15 children who received the vaccine after desensitization, 3 received it during the campaign (0.1 mL dose).

Adverse events to yellow fever vaccine

Of the 829 children presumed to have EPA, only 11 (1.3%) had immediate VAE (Table 2). All of these cases were reported as non-serious. No anaphylactic reactions to vaccination were reported.

An 8-year-old child reported mild "shortness of breath", although there were no changes in vital signs and the condition improved during the observation period (case 3). Four (36%) children had an immediate wheal reaction and hyperemia at the application site: 3 of the cases were mild (cases 7, 10 and 11) and 1 was severe (case 8).



EPA = egg protein allergy, ID = intradermal test, YFV = yellow fever vaccine.

Figure 1
Flowchart of immediate skin testing for yellow fever vaccine sensitivity in children with a history of severe egg protein allergy or anaphylaxis at the Rocha Maia Municipal Hospital Reference Center for Special Immunobiologicals

Seven (64%) children had cutaneous manifestations away from the vaccination site: 1 with angioedema (case 9), 4 with urticaria (cases 1, 2, 4, and 6), and 2 with exanthema (cases 5 and 11). Case 5 (an infant) had mild conjunctival hyperemia associated with urticaria. Case 11 (nursing infant) had a mild local reaction within a few minutes that evolved to urticaria 2 hours after vaccination.

Of those who had immediate VAE, 7 (64%) were nursing infants, 8 (73%) had a history of cutaneous manifestations after egg exposure, 1 (9%) was suspected of egg anaphylaxis, 4 (36%) had a history of multiple organ/system manifestations after egg exposure (but no anaphylaxis or simultaneous symptoms), and 7 (64%) had high egg white-specific IgE values (> 3.50 kU/L).

Table 2
Immediate adverse events following yellow fever vaccination at the Rocha Maia Municipal Hospital Reference Center for Special Immunobiologicals

Case	Age, sex	Clinical condition of EPA	IgE [a] (kU/l)	Prick test for egg	Comor-bidities	IST for YFV	Dose (mL)	Reaction to YFV
1	3 y, F	NI	Egg white: 4.5	NI	NI	No	0.5	Mild rash
2	5 y, M	Urticaria, abdominal pain, cough and bronchospasm	NI	Pos.	NI	No	0.1	Mild urticaria
3	8 y, F	Angioedema	Egg white: 4.94	Pos.	NI	No	0.1	"Shortness of breath"
4	1 y, M	Anaphylaxis	Egg white: 23.5	NI	NI	Yes [b]	0.5	Mild urticaria
5	10 m, M	Urticaria	Egg white: 1.4	NI	CMPA	No	0.5	Mild rash
6	1 y, M	Urticaria and vomiting	Egg white: 12	NI	NI	No	0.5	Urticaria and conjunctival hyperemia
7	10 m, F	Urticaria and dermatitis	Egg white: 14	Pos.	DA	No	0.5	Mild local reaction
8	2 y, M	Urticaria and rhinitis	Egg white: 85.1	Pos.	CMPA, rhinitis and asthma	No	0.5	Intense local reaction
9	10 m, F	Irritability	Egg white: 0.22	NI	Denied	No	0.5	Angioedema
10	1 y, F	Asymptomatic (no direct egg exposure)	Egg white: 3.75	Pos.	CMPA	No	0.5	Mild local reaction
11	1 y, F	Urticaria and vomiting	NI	NI	Denied	No	0.5	Mild local reaction and urticaria after 2 hours

CMPA = cow's milk protein allergy, IST = immediate skin test, NI = not informed, Pos. = positive, YFV = yellow fever vaccine.
[a] IgE for egg, egg white, and/or ovalbumin; [b] Positive prick test for yellow fever vaccine.

Of the 15 children with positive immediate skin test (prick/intradermal) results for yellow fever vaccine, only 1, who had a previous history of anaphylaxis to egg, had a reaction (urticaria) during the desensitization process (case 4). No children with negative immediate skin test results had a reaction to the vaccine.

Children who reacted to the vaccine were discharged under medical supervision. None of the children required intravenous medication, oxygen therapy, or adrenaline. According to the VAE notifications, 4 other children who received the yellow fever vaccine at CRIE were reported as having late and non-severe exanthema reactions 6 hours after application; these were not considered immediate-type reactions.

Discussion

The present study evaluated a population of 829 patients with probable EPA, a significant sample compared to other published studies.[5,10-17] Among the demographic factors, age proved to be relevant, since most of the children were < 5 years of age, in whom EPA is more common, especially at < 2 years of age, when EPA is even more prevalent.[2,7]

In the CRIE risk assessment, the symptomatology criteria (specific serum IgE values or immediate response test results) were the most commonly used types in routine diagnosis and classification of allergy severity and in clinical practice.[7,9] In 87% of the children, at least 1 diagnostic criterion was present, and no information was found on asymptomatic children with negative test results, which suggests that the majority of this population did have EPA.

Egg sensitization, detected by specific serum IgE to egg, egg white, and/or ovalbumin, was identified in the majority of the children, of whom 170 had high values (> 3.5 kU/L). Ovomucoid-specific IgE was rarely reported by the referring physicians, and it was not found in isolation in any child. It is unclear why so few were tested for this specific IgE, and it was not possible to investigate this issue in detail. The detection of specific IgEs has been considered indicative of food sensitization, although this generally only points to the need for a double-blind placebo-controlled oral challenge test to diagnose EPA. However, the oral challenge test, considered the gold standard for diagnosing EPA, was not reported in the children's records, probably because it requires a supervised environment, is seldom available in clinical practice[9], and most children are clinically diagnosed without it.[7]

Other IgE-mediated allergic diseases (cow's milk protein allergy, atopic dermatitis, rhinitis, and asthma) were prevalent in the group with reported comorbidities. It is known that a history of allergic diseases can be a risk factor for hypersensitivity reactions to vaccines.[5,12,13]

Most delays in yellow fever vaccination are due to EPA, because it requires prior guidance from a health professional and referral to a specialized center for application.[4,8,18]

Although anaphylactic and hypersensitivity reactions to yellow fever vaccine have been reported[19-22], few studies have evaluated adverse events to the vaccine in patients with EPA. Four studies that performed desensitization protocols for yellow fever vaccine in patients with anaphylaxis to egg found no serious VAE.[5,12,13,16] The present study found a history or suspicion of egg anaphylaxis in 4% (n = 22) of the vaccinated children. This number is probably an underestimate, since 28% of the children had signs and symptoms of EPA in more than one organ or system, but no information on anaphylaxis or the time between symptoms was provided. Anaphylaxis is often underdiagnosed, particularly in children.[23]

Immediate skin tests for yellow fever vaccine (prick tests, followed by intradermal tests if negative) were performed in 25 children suspected of severe allergy or anaphylaxis to egg, of which 15 (60%) were positive (6 prick tests and 9 intradermal tests). This percentage is high compared to other studies of children with EPA. Sharma et al. (2020) evaluated 11 children with EPA and performed prick tests on 7 (2 anaphylactic), all of which were negative. Only 1 underwent an intradermal test, which was also negative.[13] Gerhardt et al. (2019) tested yellow fever vaccine in 43 children with proven egg allergy (7 anaphylactic), finding negative prick test results in all cases and positive intradermal tests in 6 (14%).[12] Likewise, Julião et al. (2018) performed prick tests for yellow fever vaccine in 5 children with EPA (2 anaphylactic), finding negative results in all cases and positive intradermal results in 2 cases.[16] The higher number of positive immediate skin test results in the present study could be explained by the fact that the sample was selected for greater EPA severity, with 19 (76%) considered anaphylactic to egg. Following negative prick test results for the yellow fever vaccine with intradermal tests resulted in a higher number of positive results, as occurred in in other studies.[12,16]

Gerhadt et al. found an immediate reaction in 3 of the 6 children with positive intradermal test results who were desensitized to yellow fever vaccine, concluding that intradermal tests can help predict a higher risk of vaccine reaction.[12] In the present study, the 9 desensitized patients with positive intradermal test results had no VAE, and only 1 infant with positive test results reacted with immediate urticaria to the yellow fever vaccine. Intradermal tests can be more painful and difficult to perform in infants, presenting a greater possibility of skin irritation and false-positive results.[13] Larger studies are needed to determine the sensitivity and specificity of immediate skin tests for yellow fever vaccine.

Egg is one of the most frequently associated vaccine components with immediate hypersensitivity reactions.[24-26] Eleven (1.3%) cases of immediate VAE occurred in our sample, all defined as non-serious, which was suggestive of severe EPA and a likely risk of immediate reaction to yellow fever vaccine.

Studies of large populations who received the yellow fever vaccine have shown low rates of immediate reaction suggestive of hypersensitivity.[19,22,27] However, in studies on patients with EPA, the actual frequency of VAE has not been defined due to population variability and the small number of affected individuals.[5,10-17]

Most VAE in our sample occurred in infants who were symptomatic after egg exposure and had high egg white-specific IgE values. This suggests that VAE are likely related to age and EPA severity. However, these results are not comparable due to a lack of studies with large samples of EPA patients.[5,10-17]

Urticaria was the most commonly reported symptom in EPA diagnostic criteria, as well as in immediate reactions to the yellow fever vaccine. This corroborates large population studies, which do not specifically assess EPA, but frequently report urticaria in hypersensitivity events and immediate reactions to the yellow fever vaccine.[19,22]

We were unable to associate vaccine dosage with the occurrence of adverse events. Most VAE in this study were occurred after a dose of 0.5 mL (91%). However, the 0.1 mL dose (2018 campaign) was applied to 32% of the sample, all > 2 years of age, when EPA prevalence/severity usually decreases.[2,7]

Although we studied a significant population of children with presumed EPA, there were no anaphylactic reactions to the yellow fever vaccine. The few observed VAE were classified as non-serious, although immediate reactions did occur in children without a history of severe EPA.

The yellow fever vaccine testing protocol, followed by desensitization for patients with positive results, made yellow fever vaccination safer in children with severe EPA. Based on these results, we conclude that the yellow fever vaccine can be safely applied to children with EPA after evaluation by a specialist and in an appropriate and supervised environment.

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References

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Imunização e Doenças Transmissíveis. Plano de contingência para resposta às emergências em Saúde Pública: febre amarela [recurso eletrônico]. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Imunização e Doenças Transmissíveis. 2ª ed. Brasília: Ministério da Saúde; 2021. Available at: https://bvsms.saude.gov.br/bvs/publicacoes/plano_contingencia_emergencias_febre_amarela.pdf.
2. Solé D, Silva LR, Cocco RR, Ferreira CT, Sarni RO, Oliveira LC, et al. Consenso Brasileiro sobre Alergia Alimentar: 2018 - Parte 1 - Etiopatogenia, clínica e diagnóstico. Documento conjunto elaborado pela Sociedade Brasileira de Pediatria e Associação Brasileira de Alergia e Imunologia. Arq Asma Alerg Imunol. 2018;2(1):7-38.
3. Bula VFA Bio-Manguinhos [Internet]. Available at: https://www.bio.fiocruz.br/en/images/stories/pdfs/bulas/fa/BMBUL04500V190702FA10Nacional.pdf. Accessed on: 08/25/2021.
4. Marinho AKB, Ouricuri AL, Valente CFC, Fernandes FR, Saciloto G, de Castro Diniz L, et al. Vacina contra a febre amarela: reações adversas e populações de risco. Arq Asma Alergia Imunol. 2017;3:245-56.
5. Rutkowski K, Ewan PW, Nasser SM. Administration of yellow fever vaccine in patients with egg allergy. Int Arc h Allergy Immunol. 2013;161:274-8.
6. Nilsson L, Brockow K, Alm J, Cardona V, Caubet JC, Gomes E, et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr Allergy Immunol. 2017;28:628-40.
7. Clark AT, Skypala I, Leech SC, Ewan PW, Dugué P, Brathwaite N, et al; British society for Allergy and Clinical Immunology. British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. Clin Exp Allergy. 2010;40:1116-29.
8. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Imunizações e Doenças Transmissíveis. Manual de vigilância epidemiológica de eventos adversos pós-vacinação [recurso eletrônico] / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Imunizações e Doenças Transmissíveis. 4ª ed. Brasília: Ministério da Saúde, 2020. Available at: https://bvsms.saude.gov.br/bvs/publicacoes/manual_vigilancia_epidemiologica_eventos_vacinacao_4ed.pdf.

9. Solé D, Silva LR, Cocco RR, Ferreira CT, Sarni RO, Oliveira LC, et al. Consenso Brasileiro sobre Alergia Alimentar: 2018 - Parte 2 – Diagnóstico, tratamento e prevenção. Documento conjunto elaborado pela Sociedade Brasileira de Pediatria e Associação Brasileira de Alergia e Imunologia. Arq Asma Alerg Imunol. 2018;2(1):39-82.
10. Ruiz G, Sanchis-Merino E, Monsalve B, Perez I, Allue M, Berbel C. Yellow fever vaccination in egg-allergic patients. J Epidemiol Res. 2016;2:22.
11. Muñoz-Cano R, Sanchez-Lopez J, Bartra J, Valero A. Yellow fever vaccine and egg allergy: really a problem? Allergy. 2010;65:533-4.
12. Gerhardt CMB, Feitosa GDSJ, Aquilante BP, de Barros Dorna M, dos Santos CDJN, Pastorino AC, et al. Segurança da vacina de febre amarela em pacientes comprovadamente alérgicos à proteína do ovo. Arq Asma Alerg Imunol. 2019;3:143-50.
13. Sharma K, Perrett KP, Wood N. Yellow Fever Vaccination in EGG-Allergic Children. Pediatr Infect Dis J. 2020;39:e76-e78.
14. Catelain A, Cousin F, Piperno D, Pacheco Y, Nicolas JF. Vaccination anti-amarile et allergie à l oeuf. Rev Fr Allergol Immunol Clin. 2002;42:163-4.
15. Mosimann B, Stoll B, Francillon C, Pécoud A. Yellow fever vaccine and egg allergy. J Allergy Clin Immunol. 1995;95:1064.
16. Juliao GS, Barbosa PA, Silva PF, Cunha MA, Formigari CF, Pastorino AC, et al. Yellow fever vaccine in egg-allergic patients: safety of a vaccination protocol. J Allergy Clin Immunol. 2018;141:AB256.
17. Charpin J, Vervloet D, Birnbaum J, Tafforeau M, Sentissi S. Yellow fever: desensitization to an anti-amaril 17D vaccine performed on a patient with anaphylaxis to eggs. Bull Acad Natl Med. 1987;171:1001-5.
18. Guia de Imunização SBIm/ASBAI – Asma, Alergia e Imunodeficiências 2020-2021 [Internet]. Available at: https://sbim.org.br/images/guias/guia-sbim-asbai-miolo-201013b-web.pdf. Accessed on: 08/24/2021.
19. Lindsey NP, Rabe IB, Miller ER, Fischer M, Staples JE. Adverse event reports following yellow fever vaccination, 2007-2013. J Travel Med. 2016;23:1-6.
20. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018;141:463-72.
21. Porudominsky R, Gotuzzo EH. Yellow fever vaccine and risk of developing serious adverse events: a systematic review. Rev Panam Salud Publica. 2018;42:e75.
22. Breugelmans JG, Lewis RF, Agbenu E, Veit O, Jackson D, Domingo C, et al. Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010. Vaccine. 2013;31:1819-29.
23. Bernd LAG, Sá AB, Watanabe AS, Castro APM, Solé D, Castro FM, et al. Guia Prático para o manejo da anafilaxia – 2012. Rev bras alerg imunopatol. 2012;35:53-70.
24. Stone CA Jr, Rukasin CRF, Beachkofsky TM, Phillips EJ. Immunemediated adverse reactions to vaccines. Br J Clin Pharmacol. 2019;85:2694-706.
25. Staples JE, Gershman M, Fischer M; Centers for Disease Control and Prevention (CDC). Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010;59:1-27.
26. Caubet JC, Ponvert C. Vaccine allergy. Immunol Allergy Clin North Am. 2014;34:597-613.
27. Franceschini F, Bottau P, Caimmi S, Crisafulli G, Lucia L, Peroni D, et al. Vaccination in children with allergy to non-active vaccine components. Clin Transl Med. 2015;4:3.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Anaphylaxis to sunflower seed

Anafilaxia à semente de girassol

Cristiana Sofia Ferreira[1], Bartolomé Borja[2]

ABSTRACT

Sunflower seed (*Helianthus annuus*) is an uncommon allergenic source frequently consumed in snacks, as component of some types of bread, as condiment in some dishes, and also used in animal feeding. Occasional cases of anaphylaxis to this seed have been reported in the current literature, mainly in workers occupationally exposed to sunflower allergens and bird breeders. The allergenic nature of the storage protein albumin 2S and the non-specific lipid transfer protein (nsLTP) of this seed has been described. The authors report the case and diagnostic approach of a seed anaphylaxis.

Keywords: Anaphylaxis, food hypersensitivity, food allergy, *helianthus*.

RESUMO

A semente de girassol (*Helianthus annuus*) é uma fonte alergênica incomum frequentemente consumida em lanches, como componente de alguns tipos de pães, como condimento em alguns pratos, e também utilizada na alimentação animal. Casos eventuais de anafilaxia a esta semente têm sido relatados na literatura atual, principalmente em trabalhadores com exposição ocupacional a alérgenos de girassol e criadores de aves. A natureza alergênica da proteína de armazenamento albumina 2S e da proteína não específica de transferência de lipídios (nsLTP) dessa semente foi descrita. Os autores relatam o caso e a abordagem diagnóstica de uma anafilaxia por sementes.

Descritores: Anafilaxia, hipersensibilidade alimentar, alergia alimentar, *helianthus*.

Introduction

Sunflower seed (*Helianthus annuus*) is an uncommon allergenic source frequently consumed in snacks, as component of some types of bread, as condiment in some dishes, and also used in animal feeding. Occasional cases of anaphylaxis to this seed have been reported in the current literature, mainly in workers occupationally exposed to sunflower allergens and bird breeders. The allergenic nature of the storage protein albumin 2S and the non-specific lipid transfer protein (nsLTP) of this seed has been described. The authors report the case and diagnostic approach of a sunflower seed anaphylaxis.

Case report

A 47-year-old man, with no personal history of atopy, experienced generalized hives, vocal change, dyspnea, wheezing, and repetitive vomiting few minutes after eating a snack with sunflower seeds. He referred previous symptoms like sneezing, itching, and a runny nose while feeding his birds with sunflower seeds.

In the allergology and clinical immunology appointment, skin prick tests (using extracts from Roxall®, Spain) were performed. The tests were positive for sunflower seed (24 mm) and negative for common inhalant allergens, sesame seed, peanut,

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and other nuts such as almond, hazelnut, pistachio, cashew, and walnut. Total serum immunoglobulin E (IgE) was 34 IU/mL and specific IgE to sunflower seed extract was 3.44 kU/L (Thermo Fisher Scientific®, Sweden). Specific IgE against Pru p 3 (peach nsLTP) analyzed by ImmunoCAP was negative.

To determine the molecular mass of IgE-reactive proteins, a sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) using an immunoblot assay under reducing conditions (with 2-mercaptoethanol) was performed as described by Laemmli,1 with raw and roasted sunflower seed extracts. The immunoblot assay revealed an intense IgE-binding band with an apparent molecular mass lower than 14 kDa in the two samples. No bands were detected in control serum (pool of sera from non-atopic subjects). SDS-PAGE immunoblotting was performed as described by Schagger and Jagow,[2] with raw sunflower seed extract to better assess the molecular mass of the IgE-reactive band, obtaining a value of 11 kDa (Figure 1).

The patient is currently under strict avoidance of sunflower seed, including eating food cooked in sunflower seed oil. An epinephrine autoinjector device was prescribed.

Conclusion

Sunflower seed (*Helianthus annuus*) is frequently consumed but rarely induces anaphylaxis.[3-6] The first case of sunflower seed allergy was described in 1979.[7] Allergy to sunflower seed has been reported mainly in bird breeders, but cases as the one described here with severe IgE-mediated food allergy are rare.[8] In our report, the patient had symptoms of allergic rhinitis on exposure to sunflower seed prior to food allergy, which led us to consider a sensitization by inhalation while feeding birds with sunflower seeds.

Sunflower allergens have so far been relatively poorly described. To date, the following have been reported: Hel a 1 (a 34-kDa major allergen); Hel a 2 (a 14.7-kDa profilin); Hel a 3 (a 9-kDa LTP); and

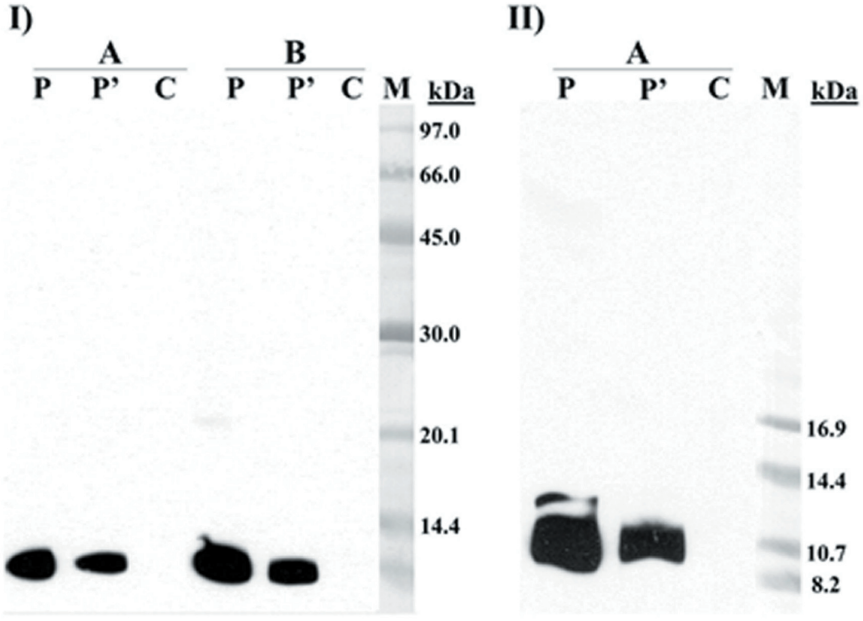

Figure 1
I) SDS-PAGE immunoblotting (Lowry). II) SDS-PAGE immunoblotting (Schagger). A) Raw sunflower seed extract. B) Roasted sunflower seed extract. Lane P, P': Patient serum, two dilutions; Lane C: Control serum (pool of sera from non-atopic subjects); Lane M: Molecular mass standard

Hel a 6 (a 42-kDa pectate lyase).[9] Others have also been described as potential allergens, such as Hel a 2S albumin, a 12-kDa storage protein that appears as a 16-kDa protein in immature form, and a 13-kDa nsLTP. Furthermore, various 2S albumins have been described in sunflower seed with molecular mass of 18-10 kDa.[10-14]

Our study confirmed the diagnosis of anaphylaxis to sunflower seed. In our patient, the diagnosis of IgE-mediated sensitization to sunflower seed was demonstrated by a positive skin prick test for sunflower seed extract and detection of sunflower-seed IgE-reactive proteins. The *in vitro* SDS-PAGE immunoblot assay revealed a protein band with molecular mass of 11 kDa. Although in our case the IgE-binding protein was not identified, its molecular mass suggests that the methionine-rich 2S albumin is involved in this case.[10-11]

To our knowledge, this is the fourth report of a monoallergic patient experiencing an anaphylactic reaction after the consumption of sunflower seeds. In addition, the severity of the clinical reaction reported here and the high likelihood of consumption of sunflower seed as a hidden allergen in snacks justifies the publication of this case: this allergy should be considered during the diagnostic workup of patients when the foodstuff causing the allergic reaction is not clear. A prompt and definite diagnosis allows a timely recommendation of strict avoidance, minimizing the possibility of recurrence of severe anaphylactic reactions.

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References

1. Laemmli U. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature. 1970;227(5259):680-5.
2. Schagger H, von Jagow G. Tricine-sodium dodecyl sulfate-polyacrylamide gel electrophoresis for the separation of proteins in the range from 1 to 100 kDa. Anal Biochem. 1987 Nov 1;166(2):368-79.
3. Labella Álvarez M, De Aramburu Mera T, Baynova K, Bartolomé Zavala B, Prados Castaño M. Anaphylaxis due to roasted sunflower seeds with tolerance to raw sunflower seeds. Ann Allergy Asthma Immunol. 2018;120:330-1.
4. Barbarroja-Escudero J, Sánchez-González MJ, Pineda F, Rodríguez-Rodríguez M, Antolín-Amérigo D, Castillo M, et al. Identification of lipoproteins from sunflower seeds in 2 monosensitized anaphylaxis patients. J Investig Allergol Clin Immunol. 2018;28(5):334-6.
5. Ukleja-Sokołowska N, Gawrolska-Ukleja E, Zbikowska-Gotz M, Bartuzi Z, Sokołowski L. Sunflower seed allergy. Int J Immunopathol Pharmacol. 2016;29(3):498-503.
6. Axelsson IG, Ihre E, Zetterstrom O. Anaphylactic reactions to sunflower seed. Allergy. 1994;49:517-20.
7. Noyes JH, Boyd GK, Settipane GA. Anaphylaxis to sunflower seed. Journal of Allergy and Clinical Immunology. 1979;63:242-4.
8. Asero R, Mistrello G, Roncarolo D, Amato S. Airborne allergy to sunflower seed. J Investig Allergol Clin Immunol. 2004;14:244-6.
9. The WHO/IUIS Allergen Nomenclature Sub-committee (2015) [Internet]. Available at: http://www.allergen.org.
10. Kelly JD, Hefle SL. 2S methionine -rich protein (SSA) from sunflower seed is an IgE -binding protein. Allergy. 2000;55:556-9.
11. Berecz B, Clare Mills EN, Tamas L, Lang F, Shewry PR, Mackie AR. Structural stability and surface activity of sunflower 2s albumins and nonspecific lipid transfer protein. J Agric Food Chem. 2010,58,6490-7.
12. Labella Álvarez M, De Aramburu Mera T, Baynova K, Bartolomé Zavala B, Prados Castaño M. Anaphylaxis due to roasted sunflower seeds with tolerance to raw sunflower seeds. Ann Allergy Asthma Immunol. 2018;120:330-1.
13. Yagami A. Anaphylaxis to lipid transfer protein from sunflower seeds. Allergy. 2010;65:1340-9.
14. Patel A, Bahna SL. Hypersensitivities to sesame and other common edible seeds. Allergy. 2016;71:1405-13.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Is pollinosis in Rio de Janeiro possible? Case report

Polinose no Rio de Janeiro é possível? Relato de caso

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ABSTRACT

Pollinosis is a common disease in temperate countries, which have well-defined seasons. It presents clinically as rhinoconjunctivitis and/or seasonal or perennial asthma that is exacerbated in spring. In Brazil, cases of pollinosis due to grass pollens have been reported, especially in the south, despite its subtropical climate. The expansion of the population and deforestation, including increasing urbanization of forest areas, are contributing to the rise in cases in various regions of the country. This case report describes a case of pollinosis due to grass pollens in a military patient who lived in Europe and currently resides in a region of native forest in Rio de Janeiro metropolitan area. Although pollinosis is not found in the state of Rio de Janeiro, this diagnosis should not be excluded in patients with seasonal conjunctivitis/rhinoconjunctivitis, especially when they have lived outside the country for several years.

Keywords: Pollinosis, grasses, Brazil.

RESUMO

A polinose é uma doença comum dos países de clima temperado, onde as estações do ano são bem definidas. Apresenta-se clinicamente como rinoconjuntivite e/ou asma sazonal ou perene com exacerbação na primavera. No Brasil, há relatos de casos de polinose por polens de gramíneas que são os principais causadores dessa patologia, principalmente na Região Sul, apesar do clima subtropical. A expansão da população e desmatamento com crescente urbanização de áreas florestais são alguns dos responsáveis pelo aumento de casos em vários locais do país. Neste relato de caso, descrevemos um caso de polinose por polens de gramínea em um paciente militar que morou em países da Europa e que atualmente reside em uma zona de mata nativa no Rio de Janeiro, RJ, Brasil. Apesar de a polinose não ser uma doença encontrada no RJ, este diagnóstico não deve ser excluído em pacientes com conjuntivite/rinoconjuntivite sazonal, principalmente quando têm uma história pregressa de morar vários anos fora país.

Descritores: Polinose, gramíneas, Brasil.

Introduction

Pollinosis (also known as hay fever or seasonal conjunctivitis/rhinoconjunctivitis) is a disease caused by sensitization to plant pollen (flowers, grasses, or trees).[1] Not all pollens are allergenic, but anemophilous pollens (carried by the wind) are more closely related to pollinosis.[2,3]

Pollinosis commonly occurs in temperate climate regions, where the seasons are well defined, but in Brazil, where a large area of the territory has a tropical or subtropical climate with poorly defined seasons, cases of pollinosis have been mostly described in the southern region.[4,5]

Grass pollens are a common cause of pollinosis because they are distributed worldwide and because they have a great capacity to produce allergenic pollens.[5-8]

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Several factors, including population growth, travel, climate change, and the introduction of grasses in agricultural activities, have increased the exposure to pollens and, consequently, favored the increase in cases of pollinosis in several regions of Brazil.[9]

The diagnosis of pollinosis is based on a clinical history of rhinoconjunctivitis/conjunctivitis/asthma, with onset or exacerbation between September and December, and *in vivo* and/or *in vitro* tests that identify the presence of specific immunoglobulin E (IgE) to proteins of allergenic pollen grains.[10,11]

Treatment includes prophylactic measures against the allergens involved, preventive medications (nasal or ophthalmic corticosteroids or nasal corticosteroids/antihistamines) and, in certain cases, specific immunotherapy.[7]

Case report

A 73-year-old male patient retired from the military complained of nasal, ocular, and oral pruritus for 2 years. Symptoms were intermittent but worsened in September. He denied associated cough, dyspnea, wheezing, or angioedema. The patient reported improvement of symptoms with mometasone nasal spray despite irregular use.

The patient reported symptom onset in 2008 while he lived in Europe (Brussels, Belgium), which persisted until 2011, when he returned to Brazil. In Brazil, the patient remained asymptomatic until 2 years ago, when he moved to Recreio dos Bandeirantes, and symptoms further intensified 6 months ago, when he moved to Vargem Grande (both neighborhoods in the western region of Rio de Janeiro). There was no family history of allergic rhinitis/conjunctivitis or asthma, but there was a current pathological history of hypertension and hyperthyroidism.

On physical examination, the patient had inferior turbinate hypertrophy with pale mucosa, hyaline post-nasal drip, and bilateral conjunctival hyperemia. There were no changes on pulmonary auscultation.

Skin prick testing for inhalant allergens was performed on the volar forearm using antigens from Alergolatina – Produtos Alergênicos Ltda. Results with papules 3 mm greater than the negative control were considered positive12 and are described in Table 1 and Figure 1.

Total and specific IgE dosages for inhalants, including grass and tree pollen, were requested and obtained using the fluoroenzyme immunoassay (ImmunoCAP, Phadia®) method. Results showed a total IgE of 43.3 (laboratory reference value: ≥15 years old – up to 160 kU/L). Specific IgE values for other inhalants are described in Table 2.

These results, in combination with the patient's clinical history, confirmed the diagnosis of grass pollen allergy (pollinosis).

Table 1
Results of skin prick test for inhalants

Tested inhalants	Results
Dermatophagoides pteronyssinus	< 3 mm
Dermatophagoides farinae	< 3 mm
Blomia tropicalis	< 3 mm
Dog epithelium	< 3 mm
Cat epithelium	< 3 mm
Grass mix (*Lolium multiflorum* [Italian ryegrass] + *Paspalum notatum* [bahiagrass] + *Cynodon dactylon* [common grass])	10 mm
Positive control (histamine) 10 mg/mL	7 mm

Discussion

In this case report, the patient was diagnosed with pollinosis after presenting symptoms of seasonal rhinoconjunctivitis and positive *in vivo* and *in vitro* tests for specific IgE to grass pollen.

Pollen consists of a set of grains that carry male gametes, which fertilize the ovules (female) of certain plants. Some plants have both female and male parts, whereas others only have a female or male part. In these cases, pollen needs to be transferred to the female part, and this movement is called pollination. Pollen can be carried by insects, water, or the wind.[2,3]

Rhinoconjunctivitis and/or asthma caused by a specific IgE-mediated hypersensitivity reaction to proteins in the pollen grains of flowers, trees, and/or grass is called pollinosis.[9]

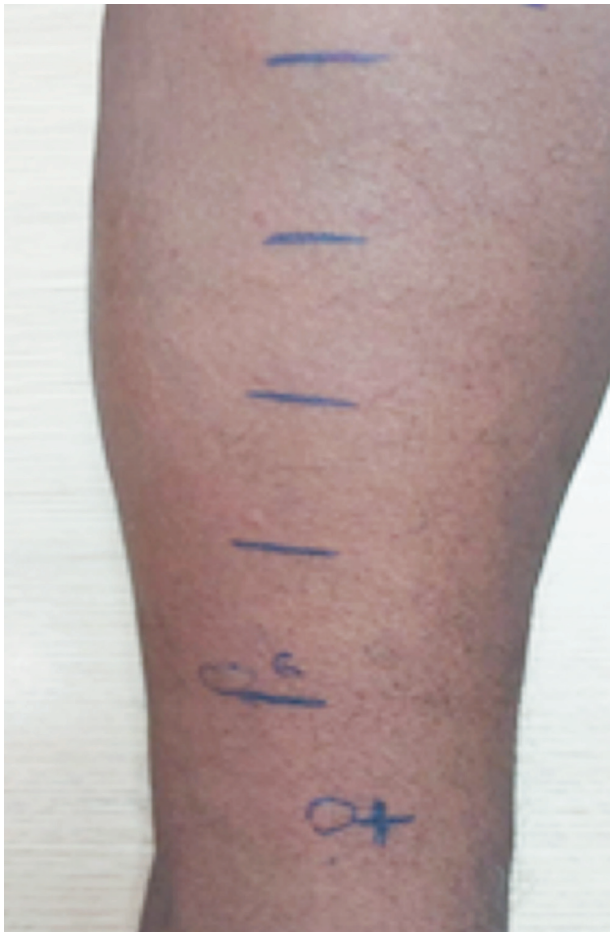

Figure 1
Skin prick test for grasses

When pollen grain proteins get in contact with the conjunctival, nasal, or bronchial mucosa, they bind to specific IgE on mast cells and basophils, triggering degranulation and release of inflammatory mediators that cause symptoms such as ocular pruritus and conjunctival hyperemia in association or not with coryza, sneezing, nasal pruritus and congestion, and eventually bronchospasm. The periodicity of symptoms is of note, as they normally occur in the spring.[7]

Not all pollens are allergenic, but anemophilous pollens (those carried by the wind) are more closely related to pollinosis.[13] Pollinosis often occurs in temperate climate regions, where seasons are well defined.[4] In Brazil, where a large area of the territory has a tropical or subtropical climate with poorly defined seasons, cases of pollinosis have been mostly described in the southern region.[8,14-18]

This happens because in the south, winter has lower temperatures and is followed by spring, which has higher temperatures, favoring the growth of certain species that need pollination for their development.[6,19]

Most patients report that ophthalmologic and nasal symptoms occur in October and subside in December, coinciding with the pollen season. However, symptoms may last from August to March and, therefore, clinical manifestations may persist during this period, depending on the patient's degree of awareness.[6,19]

Grass pollens are a common cause of pollinosis[5,6] because they are distributed worldwide and because they have a great capacity to produce allergenic proteins.[8]

Grasses belong to the large *Poaceae* family, and the subfamilies *Pooideae* (*Phleum pratense*, *Lolium multiflorum*), *Chloridoideae* (*Cynodon dactylon*), and *Panicoideae* (*Paspalum notatum*) are associated with most cases of pollinosis.[8]

Several factors, such as deforestation, land exploitation, population growth, and the introduction of grasses with highly allergenic pollen in areas of agricultural activity, are responsible for the increase in cases of pollinosis in Brazil not only in the southern region, but in other regions as well.[9,20]

In addition, climate changes due to global warming are happening all over the world and are associated with rapid and early blossoming, making the pollen season start earlier and last longer, thus increasing the possibility of sensitization to pollen.[5,7]

Another important factor is globalization, as people travel to diverse and remote parts of the world,

exposing themselves to a variety of allergens and even carrying allergens to non-native environments, promoting sensitization to new components.[5]

The Recreio dos Bandeirantes and Vargem Grande neighborhoods are located in the western region of the city of Rio de Janeiro, in the Pedra Branca State Park, which is considered the largest urban forest in Brazil. These neighborhoods have undergone a progressive urbanization process over the years, but the forest on the hillside has been preserved.[21] The possible proximity between the patient and the native flora of that region promoted by this urbanization process may have exposed him to anemophilous species and, consequently, to pollens to which he became sensitized when he lived in Europe, where he probably developed pollinosis.

The grass pollens most often related to pollinosis are *P. pratense*, *L. multiflorum*, *C. dactylon*, and *P. notatum*.[8]

Among grasses that cause pollinosis in Brazil, the subfamily Pooideae is the most common, with *L. multiflorum* (ryegrass or Italian ryegrass), *Anthoxanthum odoratum* (sweet vernal grass), and *Holcus lanatus* (meadow soft grass) being the main representative species. It is important to note that there is cross-reactivity between these species. Although *P. pratense* is not found in Brazil, it cross-reacts with *L. multiflorum*, which can be found in several regions of the country.[8]

C. dactylon (Bermuda grass or common grass), from the *Chloridoideae* subfamily, and *P. notatum* (bahiagrass), from the *Panicoideae* subfamily, are also

Table 2
Specific IgE dosage results

Specific IgE	Result (kUA/L)
Dermatophagoides pteronyssinus	0.1
Dermatophagoides farinae	0.2
Blomia tropicalis	0.1
Dog epithelium	0.1
Cat epithelium	2.1
Grass mix 2 (GX2)	
(*Cynodon dactylon* [G2] + *Lolium perenne* [G5] + *Phleum pratense* [G6] + *Poa pratensis* [G8] + *Sorghum halepense* [G10] + *Paspalum notatum* [G17])	6.4
Grass mix 1 (GX1)	
(*Dactylis glomerata* [G3] + *Festuca elatior* [G4] + *Lolium perenne* [G5] + *Phleum pratense* [G6] + *Poa pratensis* [G8])	7.0
Cynodon dactylon	0.9
Lolium perenne	4.7
Phleum pratense	4.9
Poa pratensis	5.9
Festuca elatior	4.9

Reference laboratory values: 0.10 to 0.70 KU/L = low; 0.70 to 3.50 KU/L = moderate; > 3.50 KU/L = high.

found in Brazil, but have lower cross-reactivity with the *Pooideae* subfamily.[22]

This case report shows that the patient had a clinical history and symptoms compatible with seasonal allergic rhinoconjunctivitis, in addition to the presence of specific IgE to various grass pollens. However, the ImmunoCAP and prick tests were positive for specific IgE to grass pollens that are not found in Brazil (*P. pratense*) but that cross-react with *L. multiflorum*, the main grass pollen in the country. In addition, specific IgE to pollens that have low cross-reactivity with each other and with *L. multiflorum*, such as *C. dactylon*, *Poa pratensis*, and *Festuca elatior*, were also identified. These facts suggest that the patient developed pollinosis in Europe and that the condition recurred when he moved to Rio de Janeiro.

Another important fact is the small amount of specific IgE to dust mites (*Dermatophagoides farinae*, *D. pteronyssinus, Blomia tropicalis*), which are the main agents responsible for cases of rhinoconjunctivitis and/or perennial asthma in Brazil.

This study has some limitations, including the impossibility of collecting and classifying grass pollen samples from the region where the patient lived (Recreio dos Bandeirantes and Vargem Grande) to confirm the presence of these pollens in that region and the fact that conjunctival and nasal provocation tests were not performed to determine the cause-and-effect relationship of these pollens on the patient's clinical presentation.

However, the association between *in vivo* and *in vitro* allergic test results and the patient's seasonal symptoms was strongly suggestive of pollinosis or seasonal rhinoconjunctivitis.

These results suggest that patients with symptoms of allergic rhinoconjunctivitis who live in close proximity to native vegetation in Rio de Janeiro should also be tested for grass pollen allergy. These agents may be among the antigens responsible for the symptoms experienced by these patients.

Although pollinosis is not commonly found in Rio de Janeiro, it should not be ruled out when treating a patient with seasonal conjunctivitis/rhinoconjunctivitis, especially when the patient has a previous history of living abroad.

References

1. Taketomi EA, Sopelete MC, de Sousa Moreira PF, de Assis Machado Vieira F. Pollen allergic disease: pollens and its major allergens. Braz J Otorhinolaryngol. 2006;72(4):562-7.
2. Knox RB. Pollen and Allergy (Studies in Biology no 107). London: Hodder & Stoughton Ltd; 1979.
3. Stanley RG, Linskens HF. Pollen: Biology Biochemistry and Management [online version]. Berlin, New York: Springer-Verlag; 1974.
4. Vieira FM. Polinose: estudos epidemiológicos, estações de aerobiologia e qualidade de vida [carta ao editor]. Rev bras alerg imunopatol. 2010;33(2):73-4.
5. Vieira FM. Diagnóstico molecular por componentes e polinose por gramíneas no trópico brasileiro: "uma nova mira no alvo" [carta ao editor]. Braz J Allergy Immunol 2014;2(6):248-9.
6. Vieira FAM. Novas práticas agropastoris estão influenciando a relação meio ambiente/polinose no Sul do Brasil? [carta ao editor]. Rev bras alerg imunopatol. 2003;26(1):37.
7. Brasil. Associação Brasileira de Alergia e Imunologia - ASBAI [Internet]. Primavera traz com ela a alergia ao pólen, e a região Sul é a mais atingida. Available at: https://asbai.org.br/primavera-traz-com-ela-a-alergia-ao-polen-e-a-regiao-sul-e-a-mais-atingida. Acessado em 05/06/2022.
8. Vieira FM, de Braga GL, Ferreira EN. Cynodon dactylon e Paspalum notatum: revisar conceitos de sensibilização polínica por gramíneas no Sul do Brasil? [carta ao editor]. Rev Bras Alerg imunopatol. 2011;34(5):219.
9. Vieira FM. Sensibilização polínica associada à polinose no trópico brasileiro: um desafio atual para o diagnóstico clínico. Braz J Allergy Immunol. 2014;2(2):81-2.
10. Vieira FAM. Polinose no Brasil. In: Negreiros EB, Ungier C. Alergologia Clínica. São Paulo: Atheneu; 1995. p.106-11.
11. Pierotti FF, Aranda CS, Cocco RR, Mallozi MC, Solé, D. Testes laboratoriais de triagem para doenças alérgicas: ainda têm espaço na prática clínica? Braz J Allergy Immunol. 2018;2(4):399-404.
12. Dreborg S, et al. Skin tests used in type 1 allergy testing. Position paper prepared by the subcommittee on skin tests of the European Academy of Allergology and Clinical Immunology. Allergy. 1989;44(10):31-7.
13. Vieira FAM. Existe polinose no Brasil tropical? [carta ao editor]. Rev bras alerg imunopatol. 2002;25(2):71-2.
14. Esteves PC, Trippia SG, Rosário Filho N, Caleffe LG. Validação do Questionário do ISAAC para Rinite Alérgica Perene e Sazonal (Polinose) em Curitiba. Rev bras alerg imunopatol. 1999;22:106-13.
15. Lorscheitter ML, Vieira FM, Oliveira F. Conteúdo polínico atmosférico na cidade de Caxias do Sul, Rio Grande do Sul (Brasil), e sua correlação alergógena. Boletim IG-USP. Série Científica. 1986;17:131-9.
16. Bernardes CT, Moreira PF, Sopelete MC, Vieira FA, Sung SS, Silva DA, et al. IgE cross-reactivity between Lolium multiflorum and commercial grass pollen allergen extracts in Brazilian patients with pollinosis. Braz J Med Biol Res. 2010;43:166-75.
17. Vieira FM. Polinose com síndrome de alergia oral: uma raridade no Brasil? Vamos visitá-la. Braz J Allergy Immunol. 2013;1(6):345-6.
18. Vieira FM, Braga GL, Oliveira Filho PF. Prevalência de polinose em soldados do exército no Sul do Brasil. Rev Bras Alergia Imunopatol. 2009;32(6):221-6.
19. Vergamini SMN, Zoppas BCDA, Valencia-Barrera RM, Fernandéz González D. Dinâmica aeropalinológica de Gramineae na Cidade de Caxias do Sul, RS. Rev bras alerg imunopatol. 2006;29(1):14-7.

20. Sopelete MC, Vaz LAJ, Taketomi EA. Sensitization to Cynodon dactylon and Paspalum Notatum Grass Pollens in Pollinosis Patients in Uberlândia, Minas Gerais. Brasil. [Abstracts of WAO International Scientific Conference; 2014 December 6-9; Rio de Janeiro, Brazil].
21. Oliveira CMR. A apropriação da natureza enquanto mercadoria: um olhar sobre o bairro de Vargem Grande (Rio de Janeiro). Anais do XV Seminário de Iniciação Científica da PUC - Rio, 2007.
22. Davies JM, Bright ML, Rolland JM, O Hehir RE. Bahia Grass pollen specific IgE is common in seasonal rhinitis patients but has limited cross-reactivity with ryegrass. Allergy. 2005;60(2):251-5.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Persistent allergic rhinitis with high sensitization to grass pollen: personalized medicine can identify immunotherapy patients who are truly allergic to pollen

Rinite alérgica persistente com elevada sensibilização a pólen de gramíneas: a medicina personalizada pode identificar os verdadeiros alérgicos a polens na imunoterapia

Francisco Machado Vieira[1]

ABSTRACT

This study aimed to evaluate patients with persistent allergic rhinitis who are sensitized to house mites and have high sensitization to grass pollen without seasonal symptoms. Molecular diagnosis was used to determine patients truly allergic to grass pollen. This retrospective study analyzed the medical records of patients from areas of Caxias do Sul and nearby municipalities (all with the same climatic characteristics) in the state of Rio Grande do Sul, Brazil between 2016 and 2017. Fifty patients allergic to dust mites were selected through a prick test (papule ≥ 5 mm) and grass pollen (papule ≥ 7 mm), but were asymptomatic in the spring. A total of 52% were female, and their ages ranged from 4 to 56 (mean 26.6) years. Specific serum IgE levels for grass pollen antigens, such as Phl p1, Phl p5, and Cyn d1, were investigated in all patients. Thirteen patients (26%) were diagnosed with at least one studied molecular antigen. The restricted sample included 5 (10%) patients with Phl p5 > Phl p1, ie, truly allergic to the *Pooideae* subfamily, while 2 (4%) had Cyn d1 (*Chloridoideae* subfamily) > Phl p1. The results indicate that among patients with persistent allergic rhinitis polysensitized to mites and grass pollen but without characteristic seasonal symptoms, molecular tests can diagnose those who are truly allergic to pollen.

Keywords: Mites, pollen, allergic rhinitis, diagnosis, immunotherapy.

RESUMO

Este trabalho teve como objetivo avaliar pacientes com rinite alérgica persistente, sensibilizados a ácaros domésticos, associado à elevada sensibilização por pólen de gramíneas, sem sintomatologia estacional. Usou-se como método o diagnóstico molecular por componentes para selecionar os verdadeiramente alérgicos ao pólen de gramíneas. Foi realizado um estudo retrospectivo com análise de prontuários de pacientes em áreas de Caxias do Sul e municípios próximos no estado do RS, nos anos de 2016 e 2017, com as mesmas características climáticas. Foram selecionados 50 pacientes com alergia a ácaros, através de teste de punctura (pápula ≥ 5 mm) associado ao pólen de gramíneas (pápula de ≥ 7 mm) sem sintomatologia na primavera. Um total de 52% era do sexo feminino, a idade variou entre 4 e 56 anos, com uma média de 26,6 anos. Pesquisou-se a dosagem de IgE específica no soro para antígenos moleculares de pólen de gramíneas como estes: Phl p1, Phl p5, Cyn d1, em todos os pacientes. Houve 13 pacientes (26%) com diagnóstico, pelo menos, a um dos antígenos moleculares estudados. A amostra restringida apresentou 5 (10%) deles que possuíam Phl p5 > Phl p1, ou seja, eram verdadeiramente alérgicos à subfamília *Poideae*, enquanto 2 (4%) apresentaram Cyn d1 (subfamília *Chloridoideae*) > Phl p1. O estudo mostra que, em pacientes com rinite alérgica persistente, polissensibilizados a ácaros associados a pólen de gramíneas, sem sintomas estacionais característicos, os testes moleculares podem diagnosticar os verdadeiros alérgicos ao pólen.

Descritores: Ácaros, pólen, rinite alérgica, diagnóstico, imunoterapia.

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The occurrence of symptoms of allergic rhinitis can be persistent or seasonal, the latter being particularly related to exposure to allergenic pollens during the pollen season. In southern Brazil, grass pollen triggers symptoms in previously sensitized individuals during spring (September to December).[1,2] The presence of rhinitis and/or bronchial asthma for two or more consecutive years is relatively easy to diagnose, especially when accompanied by conjunctivitis and a positive skin prick test.

House dust mites are the main etiological agents of rhinitis, especially *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis.*[3] When associated with grass pollen, it can be difficult to diagnose a true pollen allergy. Patients may not be able to explain or identify the reflex symptoms that occur in their environment during the pollen season (spring). This would be a bias for indicating pollen-specific immunotherapy.

Skin prick tests to aeroallergens are the main resources for the diagnosis of respiratory allergy and can identify IgE-mediated allergic reactions. However, the diagnosis of allergy should not be based solely on skin prick test responses but also on the correlation between symptoms, clinical history, and test results.[3,4]

Component-resolved molecular diagnosis, with a large number of recombinant or purified antigens, is a novel tool that uses biomarkers to achieve a clinical diagnosis of excellence in allergic diseases and to guide specific immunotherapy.[5]

The ImmunoCAP-Solid phase Allergen Chip (ISAC) is an *in vitro* molecular allergy test used to detect IgE antibodies specific for 103 to 112 different recombinant or purified natural allergens from serum or plasma samples. Results are expressed in a range of 0.3 to 100 ISAC standardized units (ISU). The method includes the grass *Phleum pratense* (subfamily: *Pooideae*), which is not found in Brazil but shows extensive cross-reactivity with *Lolium multiflorum* (ryegrass), the main pollen antigen in southern Brazil.[5,6]

IgE antibodies to Phl p1, Phl p2, Phl p5, and Phl p6 recombinant antigens are biomarkers of true sensitization to the *Poaceae* family.[7] Group 5 allergens are restricted to the *Pooideae* subfamily, such as *Lolium multiflorum*, with limited cross-reactivity with components of the *Chloridoideae* and *Panicoideae* subfamilies, which mainly contain group 1 allergens.[5-7]

Combined positivity for Phl p1 and Phl p5 characterizes a true pollen allergy to the *Pooideae* subfamily. This suggests that recombinant *Phleum pratense* allergens could also be used for diagnosis and specific immunotherapy in the population living in southern Brazil.[5]

Molecular allergy diagnosis represents a major contribution to personalized medicine by assisting in the assessment of risk prediction, disease severity, and genuine sensitization/cross-reactivity and in the application of treatment strategies.[8,9]

Component-resolved molecular diagnosis is used to guide the prescription of grass pollen immunotherapy in regions of the world where grass pollen seasons overlap with other types of pollen.[8] However, differently, there are no associated studies in polysensitized individuals that have included house dust mites. The following databases were searched: PubMed and Elsevier, using keywords such as grass pollen, sensitization, perennial symptoms, house dust mites, allergy, molecular diagnosis, and immunotherapy.

The main objective was to evaluate patients with persistent allergic rhinitis caused by house dust mites associated with high sensitization to grass pollen, without characteristic seasonal symptoms or with symptoms difficult to characterize, in a region of pollinosis. Component-resolved molecular diagnosis was used to determine patients with true allergy and screen them for possible pollen-specific immunotherapy.

Methods

A retrospective study was conducted with a review of the medical records of patients seen at an allergy and immunology clinic in Caxias do Sul, southern Brazil, between 2016 and 2017, who lived in the municipality or nearby regions (all with similar climate and vegetation characteristics).

Fifty patients with persistent allergic rhinitis for two or more consecutive years were included in the study, and the characteristic symptoms (sneezing, itching, rhinorrhea, nasal obstruction) occurred for consecutive days, for more than one hour, in most participants.

Patients had immediate skin prick test results with papules ≥ 5 mm in diameter for the following house dust mites: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis*.

Papules were ≥ 7 mm for mixed grass pollen and *Lolium multiflorum*. Saline solution and histamine (10 mg/mL) served as controls. Papule size was determined by the average of their perpendicular diameters, in relation to the negative control (extracts provided by FDA Allergenic/Immunotech, RJ, Brazil).

We adopted the random cutoff of papule size for the mites (≥ 5 mm), confirming the clinical diagnosis of persistent allergic rhinitis, associated with symptoms. However, we adopted papule ≥ 7 mm for grass pollen, which characterizes high sensitization (without seasonal symptoms) capable of causing confusion, requiring the diagnosis of a true allergy.

All patients (or their legal representatives) were informed of the procedures and provided written consent, including laboratory tests, which would define a true pollen allergy and accurate treatment indication.

None of the participants had or reported seasonal symptoms during the grass pollen season (September to December), were taking medication that could affect the test results, or had previously undergone specific immunotherapy with the allergens under study.

We performed a component-resolved analysis of sera from 100% of patients for the presence of IgE antibodies specific for Phl p1, Phl p5, and Cyn d1 antigens using the ImmunoCAP-ISAC (ThermoFischer Scientific®).

Results

Of the 50 patients included in the study, 52% were female, with a mean age of 26.6 years (median, 25 years; range, 4 to 56 years).

The duration of symptoms was greater than or equal to two consecutive years, with or without associated conjunctivitis.

Thirteen patients (26%) had a positive diagnosis for at least one of the antigens under investigation (Phl p1, Phl p5, and Cyn d1). However, the restricted sample showed a significant change: only 5 patients (10%) were truly allergic to the *Pooideae* subfamily with Phl p5 > Phl p1, whereas 2 (4%) were allergic to the *Chloridoideae* subfamily with Cyn d1 > Phl p1 (Table 1).

Discussion

Aerobiology studies have identified a grass pollen season in southern Brazil, during spring.[1,10,11] This coincides with the characteristic symptom complex of pollinosis reported in previously sensitized patients, which repeats annually.

In Brazil, there is no succession of other important allergenic pollens in nature, as observed in other countries, mainly in the Northern Hemisphere. However, there are potent indoor allergens such as dust mites, which, in real life, can act as a diagnostic confounder when associated with grass pollens not only in southern Brazil but also in some regions of the Brazilian tropics.[12] Here, it is possible to identify potential candidates for personalized medicine, also known as precision medicine.

In our environment, a continuous air monitoring system has been used for more than a decade with a Burkard volumetric pollen and spore trap, located on the main campus of the University of Caxias do Sul, in southern Brazil. Grass pollens are the main allergenic pollens and can reach high concentrations in November (spring), ranging from 512 to 949 grains/m³ of air in that specific area.[10]

It is estimated that most grass pollen-allergic patients show symptoms with daily levels between 30 and 50 grains/m³ of air. This estimate may be lower in the presence of a preexisting mite-induced inflammatory process, similarly to what occurs in successive pollen seasons.

Patients sensitized to grass pollen, when exposed to the external environment, will have symptoms of rhinitis associated with a high frequency of conjunctivitis characterized mainly by severe ocular itching.[13]

Immediate skin prick testing allows us to confirm, or not, sensitization and atopy when associated with clinical history and physical examination, which altogether enable a diagnosis to be made.

The presence of a mean papule diameter ≥ 3 mm, compared with the negative control, associated with a well-circumscribed erythematous plaque > 10 mm, characterizes sensitized patients.[4] Patients selected for inclusion in this study had papules ≥ 7 mm in mean diameter for grass pollen, associated with papules ≥ 5 mm for dust mites. We acknowledge that high sensitization to grass pollen can make the diagnosis difficult, even for the most experienced physicians, since there is associated persistent allergic rhinitis.

In real life, high pollen sensitization may be included in the pollens associated with perennial antigens in a potential immunotherapy, without a true diagnosis.

The reflex symptoms obtained via patient symptoms could be altered by the use of masks during the period of the COVID-19 pandemic, a fact that did not occur at the time of the study.

Nasal or conjunctival provocation tests with grass allergens would be indicated if there was doubt about the diagnosis.[14] In polysensitized patients, it can be complemented with the measurement of specific IgE levels (ImmunoCAP-ISAC), using components such as Phl p1, Phl p5, and Cyn d1.[5,12]

Cyn d1 (*Cynodon dactylon* - Bermuda grass) is the main pollen allergen of the *Chloridoideae* subfamily, widely distributed in Brazil and with high allergenic potential.[12]

Monosensitization to Phl p1 is related to the detection of low IgE levels for *Lolium multiflorum*, when tests are performed with pollen extracts. However, specific IgE anti-Phl p5 antibody would be a true allergy biomarker for the Pooideae subfamily, rarely found as the only sensitizer.[5,6] In summary, when there is IgE positivity for the association of Phl p5 > Phl p1, defined by their potencies and frequencies, the Pooideae subfamily can be considered the cause of pollen allergy.[5] The same is true for the *Chloridoideae* subfamily when Cyn d1 > Phl p1.

Component-resolved molecular diagnosis has been suggested to facilitate the identification of true disease-causing allergens and the prescription of allergen-specific immunotherapy.[9] This information could be extended to the patient.

The discrepancies between the results obtained from the extracts used in the skin prick tests and those from the molecular diagnosis are possibly due to cross-reactivity between allergens from unrelated plant species, such as profilins and other cross-reactive allergens.[9]

Table 1
Sample restricted to patients with true allergy: potential candidates for specific immunotherapy, within a group of 50 patients

Age	Sex	Phl p5	Phl p1	Cyn d1	Eosinophils	Total IgE*
26	M	3.37	4.53	26.8	2.5/129	393
41	F	27.3	21.1	3.46	0.5/46	198
37	F	0.1	0.1	2.16	1.4/155	1020
12	F	9.18	3.28	0.14	ND	582.7
26	F	33.8	19.8	3.74	7.4/438.82	108
4	M	45.1	34.8	10.6	10.4/1280	534
32	F	11.4	4.77	2.23	ND	144

Group of patients with grass pollen allergy: n = 7 (14% of the total).

Monosensitization to Cynodon (Cyn d1).

ISAC Standardized Units (ISU)	Class
< 0.3	Not detectable
> 0.3 to ≤ 1	Low
> 1 to ≤ 15	Moderado
> 15	High

* Degree of sensitization (kU/L) - ImmunoCAP.

Conclusion

Molecular tests for grass pollen, restricted to Phl p1, Phl p5, and Cyn d1, can be included in cases of doubtful diagnosis. This would make the indication for immunotherapy more accurate and reduce costs in polysensitized patients with a difficult diagnosis, not only in the southern region but also in other specific regions of Brazil.

References

1. Lorsheitter ML, Vieira FM, Oliveira F. Conteúdo polínico atmosférico na cidade de Caxias do Sul, Rio Grande do Sul – Brasil e sua correlação alergógena. Bol IG-USP. 1986;17:131-9.
2. Rosário Filho NA. Reflexões sobre polinose: 20 anos de experiência. Rev bras alergia imunopatol. 1997;20:210-3.
3. Sakano E, Sarinho ES, Cruz AA, Pastorino AC, Tamashiro E, Kuschnir F, et al. IV Brazilian Consensus on Rhinitis – an update on allergic rhinitis. Braz J Otorhinolaryngol. 2018;84:3-14.
4. Anca MC, Bousquet J, Demoly P. Principles of Allergy Diagnosis. In: O'Hehir RE, Holgate ST, Sheikh A, eds. Middleton's Allergy Essentials. Elsevier; 2017. p.117-31.
5. Moreira PF, Gangl K, Vieira FA, Ynoue LH, Linhart B, Flicker S, et al. Allergen Microarray Indicates Pooideae Sensitization in Brazilian Grass Pollen Allergic Patients. PloS One. 2015;10(6):e0128402.
6. Bernardes CT, Moreira PF, Sopelete MC, Vieira FA, Sung SS, Silva DA, et al. IgE cross-reactivity between Lolium multiflorum and commercial grass pollen allergen extracts in Brazilian patients with pollinosis. Braz J Med Biol Res. 2010;43:166-75.
7. Popescu FD. Molecular biomarkers to grass pollen immunotherapy. World J Methodol. 2014;4:26-45.
8. Sastre J, Landivar ME, Ruiz-Garcia M, Andregnette-Rosigno MV, Mahillo I. How molecular diagnosis can change allergen-specific immunoterapy prescrition in a complex pollen area. Allergy. 2012:709-11.
9. Saltabayeva U, Garib V, Morenko M, Rosenson R, Ispayeva Z, Gatauova M, et al. Greater Real – life diagnostics efficacy of allergen molecule-based diagnosis for prescription of immunotherapy in area with multiple pollen exposure. Int Arch Allergy Immunol. 2017;173:93-8.
10. Vergamini SM, Zoppas BCDA, Valencia-Barrera RM, Fernandéz González D. Dinâmica aeropalinológica de Gramineae na cidade de Caxias do Sul, RS. Rev bras alerg imunopatol. 2006;29:14-7.
11. Rosário Filho NA. Contagem de polens aéreos na cidade de Curitiba. Rev bras alerg imunopatol. 1983;6:12-5.
12. Vieira FM. Diagnóstico molecular por componentes e polinose por gramíneas no trópico brasileiro: uma nova mira no alvo. Rev bras alerg imunopatol. 2014:2(6):248-9.
13. Vieira FAM, Motta VT. Conjuntivite alérgica polínica em Caxias do Sul, Brasil. Rev. bras alerg imunopatol. 2008;31:56-9.
14. Vieira FAM, Wandalsen GF, Matsumoto FY. Teste de provocação nasal com alérgenos. In: Solé D, Rosário Filho NA, Rubini NPM. Compêndio de alergia e imunologia clínica. Editora dos Editores; 2021. p.595-601.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Mastocytosis: the safety of different COVID-19 vaccines

Mastocitose: segurança de diferentes vacinas contra a COVID-19

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ABSTRACT

The COVID-19 pandemic has forced the development of vaccines to fight SARS-CoV-2. After vaccination began, reports of adverse reactions, including anaphylaxis, emerged. This raised concerns about the safety of COVID-19 vaccines in patients diagnosed with mastocytosis. The authors share their experience in administering different COVID-19 vaccines to patients diagnosed with mastocytosis.

Keywords: COVID-19, COVID-19 vaccines, mastocytosis, vaccine hypersensitivity, premedication.

RESUMO

A pandemia por COVID-19 obrigou ao rápido desenvolvimento de vacinas para combate ao SARS-CoV-2. Após o início da vacinação começaram a surgir relatos de reações adversas às vacinas, incluindo reações anafiláticas, surgindo dúvidas sobre a segurança das vacinas em doentes com mastocitose. Os autores apresentam a sua experiência em relação à administração de diferentes vacinas contra a COVID-19 em doentes com diagnóstico de mastocitose.

Descritores: COVID-19, vacinas contra COVID-19, mastocitose, hipersensibilidade a vacinas, pré-medicação.

Introduction

The COVID-19 pandemic emerged intensely worldwide and forced the scientific community to develop vaccines. After the start of vaccination campaigns, reports of vaccine reactions began to appear, including anaphylaxis. Vaccine safety has been called into question, especially regarding the possibility of triggering allergic reactions.[1,2]

Mastocytosis, a disease characterized by proliferation and accumulation of mast cells,[3] can increase the frequency and severity of immediate hypersensitivity reactions, with anaphylaxis occurring in 22%-49% of these adults.[3] There is no evidence of an increased number of vaccine reactions in adults with mastocytosis,[4] with only a few reports of adverse reactions to vaccines.[5] However, the exposure of these patients to drugs or procedures capable of triggering adverse reactions raises a degree of concern as well as some questions about whether patients with mastocytosis could safely tolerate COVID-19 vaccines. The aim of this study was to evaluate the safety of COVID-19 vaccines in a series of patients with mastocytosis.

Methods

We performed a retrospective and descriptive review of patients with a diagnosis of mastocytosis referred to our Allergy and Clinical Immunology

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department to assess the risk of allergic reaction to COVID-19 vaccines. Patients were characterized according to demographic data, mast cell disorder classification and basal tryptase levels, daily medication, and comorbidities. Data were recorded on the vaccination process, premedication, vaccine type, and complications. The anonymity of all the participants of this study was guaranteed.

Results

To date, 14 adult patients diagnosed with mastocytosis have been referred to our department. All patients were stable with no uncontrolled mast cell-mediated symptoms and were selected to be vaccinated in our department. A total of 11 patients received a COVID-19 vaccine under hospital-based supervision, whereas three refused vaccination. Of the 11 vaccinated patients, 73% (n=8) were female. Regarding mastocytosis classification, 55% (n=6) of the patients had systemic mastocytosis and 45% (n=5) had cutaneous mastocytosis. Basal tryptase levels were within the reference range (<11.4 ng/mL) in 36% (n=4) of the patients and ranged from 26.8 to 51.3 ng/mL in the remaining patients (64%, n=7). Regarding allergic comorbidities, three patients had Hymenoptera venom allergy, two patients had respiratory allergy, and one patient had idiopathic hypereosinophilic syndrome. Data on the type of vaccine and the number of doses received are summarized in Table 1. A total of 25 vaccines were administered. Only 36% (n=4) of the patients has not received a booster shot yet. The type of vaccine to be administered was randomly selected according to availability and included Comirnaty® (Pfizer-BioNtech), Vaxzevria® (AstraZeneca), or Janssen® (Johnson & Johnson). Most patients received premedication with H1-antihistamine and montelukast, once daily on the 3 days before and about 1 hour before administration, combined with H2-antihistamine administration (Table 1). All patients completed a 1-hour post-vaccination observation period. There were no adverse reactions, even in cases in which the vaccination schedule was completed with different vaccines.

Table 1
Demographic data, mast cell disorder classification, type of vaccine administered, and premedication

Age (years)	Mastocytosis	Vaccines administered	Premedication
60	CM	1st, 2nd, and booster shot: Comirnaty®	Ebastine [ab], Montelukast [ab], Famotidine [b]
67	SM	1st, 2nd, and booster shot: Comirnaty®	Ebastine [ab], Montelukast [ab]
65	SM	1st and 2nd doses: Vaxzevria®	Ebastine [ab], Montelukast [ab]
42	CM	1st and 2nd doses: Comirnaty®	None
60	SM	1st dose: Janssen®; Booster shot: Comirnaty®	Hydroxyzine [ab], Montelukast [ab], Famotidine [b]
53	SM	1st dose: Janssen®	Cetirizine [ab], Montelukast [ab], Famotidine [b]
63	SM	1st dose: Janssen®; Booster shot: Comirnaty®	Ebastine [ab], Montelukast [ab], Famotidine [b]
42	CM	1st dose: Janssen®; Booster shot: Comirnaty®	Ebastine [ab], Montelukast [ab], Famotidine [b]
36	CM	1st, 2nd, and booster shot: Comirnaty®	Ebastine [ab], Montelukast [ab], Famotidine [b]
57	CM	1st, 2nd, and booster shot: Comirnaty®	Ebastine [ab], Montelukast [ab], Famotidine [b]
68	SM	1st and 2nd doses: Comirnaty®	Ebastine [ab], Montelukast [ab], Famotidine [b]

CM: cutaneous mastocytosis, SM: systemic mastocytosis. [(a)] on the 3 days before vaccine administration, [(b)] 1 hour before vaccine administration.

Discussion

COVID-19 vaccination is recommended for all patients with mastocytosis.[5] The European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Diseases (AIM) have recently recommended, based on the opinion of experts, the administration of H1-antihistamines 30 to 60 minutes before vaccination; H1-antihistamines, montelukast, and corticosteroids can be considered on a case-by-case basis.[6] According to these recommendations, patients should be vaccinated in a health care facility equipped and experienced with the treatment of anaphylaxis, and should be observed for a period of at least 30 minutes after vaccination.[6] In this study, we report the experience of our department in administering different COVID-19 vaccines in an adult population with mastocytosis. All vaccination procedures were performed safely and without complications, regardless of patient-dependent factors or vaccine-dependent factors. There already are some reports of patients with mastocytosis who have safely received the COVID-19 vaccine.[7-12] Further studies and reports are needed to settle on the best approach to vaccinate these patients.

References

1. Banerji A, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract. 2021;9(4):1423-37. doi: 10.1016/j.jaip.2020.12.047.
2. Klimek L, Jutel M, Akdis CA, Bousquet J, Akdis M, Torres MJ, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines – An EAACI-ARIA Position Paper. Allergy Eur J Allergy Clin Immunol. 2021;76(6):1624-8. doi: 10.1111/all.14726.
3. Bonadonna P, Pagani M, Aberer W, Bilò MB, Brockow K, Oude Elberink H, et al. Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper. Allergy Eur J Allergy Clin Immunol. 2015;70(7):755-63. doi: 10.1111/all.12617.
4. Zanoni G, Zanotti R, Schena D, Sabbadini C, Opri R, Bonadonna P. Vaccination management in children and adults with mastocytosis. Clin Exp Allergy. 2017;47:593-6. doi: 10.1111/cea.12882.
5. Valent P, Akin C, Bonadonna P, Brockow K, Niedoszytko M, Nedoszytko B, et al. Risk and management of patients with mastocytosis and MCAS in the SARS-CoV-2 (COVID-19) pandemic: Expert opinions. J Allergy Clin Immunol. 2020;146(2):300-6. doi: 10.1016/j.jaci.2020.06.009.
6. Bonadonna P, Brockow K, Niedoszytko M, Elberink HO, Akin C, Nedoszytko B, et al. COVID-19 Vaccination in Mastocytosis: Recommendations of the European Competence Network on Mastocytosis (ECNM) and American Initiative in Mast Cell Diseases (AIM). J Allergy Clin Immunol Pract. 2021;9(6):2139-44. doi: 10.1016/j.jaip.2021.03.041.
7. Rama TA, Moreira A, Castells M. mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis. J Allergy Clin Immunol. 2021 Mar;147(3):877-8. doi: 10.1016/j.jaci.2021.01.004.
8. Kaakati R, Khokhar D, Akin C. Safety of COVID-19 vaccination in patients with mastocytosis and monoclonal mast cell activation syndrome. J Allergy Clin Immunol Pract. 2021;9(8):3198-9. doi: 10.1016/j.jaip.2021.05.010.
9. Ruano-Zaragoza M, Carpio-Escalona LV, Diaz-Beya M, Piris-Villaespesa M, Castaño-Diez S, Muñoz-Cano R, et al. Safety of COVID-19 vaccination in patients with clonal mast cell disorders. J Allergy Clin Immunol Pract. 2022 May;10(5):1374-6.e3. doi: 10.1016/j.jaip.2022.01.030.
10. Lazarinis N, Bossios A, Gülen T. COVID-19 vaccination in the setting of mastocytosis-Pfizer-BioNTech mRNA vaccine is safe and well tolerated. J Allergy Clin Immunol Pract. 2022 May;10(5):1377-9. doi: 10.1016/j.jaip.2022.01.037.
11. Tuncay G, Bostan OC, Damadoglu E, Karakaya G, Kalyoncu AF. SARS-CoV-2 vaccines are well tolerated in patients with mastocytosis. Ann Allergy Asthma Immunol. 2022 Mar 4:S1081-1206(22)00172-7. doi: 10.1016/j.anai.2022.02.026.
12. Rama TA, Álvarez-Twose I. Delving into covid-19 vaccination – induced anaphylaxis: Are mRNA vaccines safe in mast cell disorders? J Investig Allergol Clin Immunol. 2021;31(2):193-5. doi: 10.18176/jiaci.0680.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Use of belimumab in a patient with systemic lupus erythematosus refractory to conventional treatment: case report

Uso de belimumabe em paciente com lúpus eritematoso sistêmico refratário ao tratamento convencional: relato de caso

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ABSTRACT

Systemic lupus erythematosus is an immune-mediated disease caused by hormonal, environmental and genetic factors. It is characterized by the presence of reactive autoantibodies to different cells and tissues, with diverse clinical manifestations and periods of exacerbation and remission, which complicates treatment. This case report highlights progress with the use of a human monoclonal antibody in a woman diagnosed with systemic lupus erythematosus in May 2019 (at age 30). Since she was refractory to conventional drugs, belimumab treatment was begun in September 2019. Belimumab is a human monoclonal antibody that binds to soluble B lymphocyte-stimulating proteins, including self-reactive ones, and reduces the differentiation of B lymphocytes into plasma cells, decreasing the serum IgG and anti-dsDNA antibody levels, in addition to improving patient clinical status. Despite being a high-cost biological drug, it drastically reduces the clinical symptoms of systemic lupus erythematosus, enabling reduced used of corticosteroids and their effects, in addition to reestablishing laboratory parameters altered by the disease, without changing liver and kidney indicators. Since systemic lupus erythematosus has no cure, the goal of treatment is to reduce symptoms and the active phases of the disease.

Keywords: Immunotherapy, systemic lupus erythematosus, monoclonal antibodies, belimumab.

RESUMO

O lúpus eritematoso sistêmico (LES) é uma doença de caráter imunomediado, ocasionada por fatores hormonais, ambientais e genéticos. Caracteriza-se pela presença de autoanticorpos reativos para diferentes células e tecidos, apresentando manifestações clínicas diversificadas, períodos de exacerbação e remissão, o que dificulta o tratamento desses pacientes. Este relato de caso destaca o progresso do uso de anticorpo monoclonal humano em uma paciente do gênero feminino, diagnosticada com LES em maio de 2019, aos 30 anos, e, por ser refratária ao tratamento medicamentoso convencional, utilizou o tratamento com anticorpo monoclonal humano belimumabe, com início em setembro de 2019. O belimumabe é um anticorpo monoclonal humano que se liga à proteína estimuladora de linfócito B (BLyS) solúvel, inclusive dos autorreativos, e desta maneira, reduz a diferenciação de linfócitos B em plasmócitos, diminuindo os níveis de IgG sérica e dos anticorpos anti-dsDNA, além de melhorar o quadro clínico dos pacientes. Apesar de ser um medicamento biológico de alto custo, diminui drasticamente os sintomas clínicos do LES, possibilitando a redução do uso do corticoide e os efeitos consequentes de seu uso, além de reestabelecer os parâmetros laboratoriais alterados pela doença, sem alteração de indicadores hepáticos e renais. O LES não tem cura, logo, o objetivo do tratamento é diminuir os sintomas e conter as fases ativas da doença.

Descritores: Imunoterapia, lúpus eritematoso sistêmico, anticorpos monoclonais, belimumabe.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease of unknown etiology related to genetic, environmental, and hormonal factors. It predominantly affects females of fertile age, because of the regulatory role that estrogens play in the immune system.[1] Since it is a multisystemic disease, its clinical manifestations are heterogeneous, with periods of exacerbation and remission triggered by exposure to the sun and physical or emotional stress.[2]

The clinical manifestations are caused by auto-antibodies that interact with the body's own genetic material, present in apoptotic cells, forming immune complexes (antibodies bound to antigens) which build up in tissues, causing lesions.[2] These auto-antibodies may also attack the body's own proteins, found in cells such as red blood cells, lymphocytes, and platelets, activating a reaction in cascade in the complement system, causing lysis of the target cells. Reductions in these cells can be used as a parameter for diagnosis of SLE and for classification of disease activity.[3]

SLE has no cure, but with pharmacological treatment the immunological changes can be regulated, attenuating its consequences. Medications used to modulate the immune system in SLE include glucocorticoids, anti malaria drugs, and immunosuppressants.[4] However, the human monoclonal antibody belimumab is indicated for patients refractory to conventional drug treatment who are over the age of 18 years.[5]

Belimumab is a human monoclonal antibody that binds to a soluble B-lymphocyte stimulator (BLyS) protein, also known as B cell activating factor, part of the tumor necrosis factor (TNF) family, and a type II transmembrane protein that can exist both in a membrane-bound form or in a soluble form.[6] Use of belimumab causes reduction of B lymphocyte differentiation into immunoglobulin-producing plasmacytes, thus achieving the objective of treatment, which is to reduce serum IgG and anti double-stranded DNA (anti-dsDNA) antibodies, improving patients' clinical status.[7]

The objective of this paper is to present the progress achieved using human monoclonal antibodies in a patient with SLE refractory to treatment with conventional medications.

Methods

This is a case report with the objective of presenting the progress achieved using human monoclonal antibodies in a patient with SLE refractory to treatment with conventional medications. Data were collected from medical reports and laboratory tests provided by the patient and personal accounts reported orally to the authors of the patient's main experiences with the disease since her first symptoms in mid-September of 2018, until the most recent laboratory tests on June 7, 2021.

Case report

A female patient was diagnosed with SLE in March 2019, at 30 years of age, after having noticed enlarged lymph nodes in her cervical region in mid-September of 2018. After consultation with a head and neck surgeon, cervical ultrasonography with Doppler was ordered to attempt to understand the palpable enlargement, suspected of being Hodgkin's lymphoma.

The cervical Doppler ultrasonography report described unusual cervical lymphadenomegaly in the left cervical region, with rounded, hypoechogenic lymph nodes, some with no obvious central hilum, others with the hilum extruded, with no areas of cystic permeation and no internal microcalcifications. Cervical lymph nodes with a normal elongated appearance and preserved hilum were also noted. There was intense hilar and subcapsular vascularization with vascular structures with normal path and caliber. The remaining cervical structures assessed, such as thyroid and salivary glands, were normal.

In view of the Doppler ultrasonographic analysis of the cervical region, in conjunction with the lymphadenomegaly of the cervical region observed during the medical consultation, the physician responsible for the case ordered another ultrasonography examination with Doppler, but at level III of the cervical region, with the intention of analyzing the abnormal area in greater detail. This confirmed the enlargement and abnormality of the left supraclavicular lymph nodes. Therefore, combined with puncture examination and biopsy results, the primary hypothesis of Hodgkin's lymphoma was ruled out, but no definitive diagnosis was achieved.

The patient complained of severe joint pain, fatigue, and hives, and was therefore referred to a rheumatologist, in March of 2019, who ordered

laboratory tests to attempt to make a conclusive diagnosis. An antinuclear factor (ANF) assay and a full blood test were conducted (Table 1).

The patient was diagnosed with SLE on the basis of the rheumatologist's clinical assessment in conjunction with the positive ANF result, with a thick speckled nucleus and titers of 1/640, and analysis of the blood test results, which showed leukopenia, neutropenia, and low serum C3 concentration. Initially, conventional drug treatment for SLE was employed (Table 2), in addition to vitamin supplements to control hair loss, a third-generation hormonal contraceptive, desogestrel 75 mg, to avoid a risk of pregnancy during active disease periods, and factor 50 sun protection on the body and factor 70 on the face, because of the risks of exposure to sunlight.

This treatment was maintained until the start of July 2019, but without results, when the rheumatologist substituted methotrexate 2.5 mg with azathioprine 50 mg, 1-3 mg/kg/day. However, the substitute was only maintained for approximately 1 month, because of worsening fatigue, urticaria, and joint pain and onset of depressive symptoms. For these reasons, the patient was instructed to withdraw azathioprine and

Table 1
Analytes at abnormal levels in the blood test performed before diagnosis of SLE

Analytes	Normal reference values for women	Results 03/20/2019
Leukocytes	5,000 to 10,000/mm^3	2,930
Neutrophils	1,700 to 7,000/mm^3	1,440
C3	Age 31 to 49 years: 84 to 160 mg/dL	56

Abnormal results of blood test on March 20, 2019, showing leukopenia, neutropenia, and low serum C3 concentration, characteristic of autoimmune diseases. Other analytes were normal according to the reference values.

Table 2
Medications and dosages used in conventional treatment for SLE

Medication		Administration		
Name	Concentration	Quantity	Route	Frequency
Methotrexate	2.5 mg	6 pills	Oral	1x/week
Folic acid	5 mg	1 pill	Oral	6x/week, except on day methotrexate taken
Prednisone	5 mg	2 pills	Oral	1x/day
Hydroxychloroquine	400 mg	1 pill	Oral	5x/week

resume methotrexate 2.5 mg, 6 pills 1x/week, with the addition of venlafaxine 150 mg, a selective serotonin reuptake inhibitor antidepressant, and noradrenaline, at a dosage of 1 pill 1x/day.

However, even continuing this treatment for 6 months (March 2019 to September 2019), the patient did not improve, proving refractory to the medications employed. The rheumatologist therefore suggested adding the monoclonal antibody belimumab to the treatment regimen.

The monoclonal antibody belimumab was administered for the first time on September 23, 2019, 10 mg/kg via intravenous infusion, for 1 hour, allowing a 2 week interval between administrations to elapse for the first three doses, and then administering doses every 4 weeks. The patient described a gradual improvement in symptoms from the third administration onwards. The last administration was on August 29, 2020.

Treatment with belimumab resulted in more rapid and significant improvements than the conventional drug treatment, as shown by the laboratory tests summarized in Table 3.

In January of 2020, while still on belimumab, the rheumatologist adjusted the drug treatment, increasing the frequency of hydroxychloroquine 400 mg to 1 pill 6x/week, to help contain the disease.

After treatment with belimumab, while the laboratory test result values were still not within normal reference ranges, they revealed little variation, which is evidence of a reduction in disease activity. In the last urine test, conducted on June 7, 2021, microscopy of sediments revealed numerous epithelial cells, sparse crystals of calcium oxalate, sparse amorphous urate crystals, and abundant mucus filaments, which had not been present in previous samples, and there was a significant increase in erythrocyte levels, which had been absent in the previous test, on April 5, 2021.

Discussion

SLE is diagnosed on the basis of many different clinical and laboratory parameters proposed by the American College of Rheumatology (ACR) in 1997,[8] and universally accepted, which can be used at any time of life. At least 4 of the 11 classification criteria are needed for a positive diagnosis, as follows: malar rash, discoid rash, photosensitivity, mouth sores, arthritis, serositis, renal changes, neurological changes, hematological changes, immunological changes, and positive antinuclear factor (ANF) titers.[9]

The assay to detect ANF is most often used in suspected SLE cases. ANF constitutes a group of autoreactive antibodies that attack nuclear structures such as ribonucleoproteins, histones, and the double-strand of DNA. The test is based on staining a sample with immunofluorescence, so that the autoreactive antibodies in the sample become fluorescent and can be seen with microscopy. The result is positive if fluorescence is still present after 40 or more dilutions of the stained sample (result 1/40 or 1:40). The greater the number of dilutions needed to eliminate fluorescence from the sample, the more severe the disease state.[2]

Pharmacological treatment should be individualized, paying attention to which organs or systems are being comprised during the current phase of the disease and its severity. The Brazilian Unified Health System (SUS) national technology commission recommendations[10] adopt the following drugs for treatment of SLE: chloroquine or hydroxychloroquine, dexamethasone and betamethasone, methylprednisolone and prednisone, azathioprine, cyclosporine, cyclophosphamide, danazol, methotrexate and thalidomide, all of which are distributed by the SUS. Notwithstanding, treatment with the human monoclonal antibody belimumab is indicated for patients over the age of 18 who are refractory to these medications and are taking corticosteroids, non-steroidal anti-inflammatories, anti malaria drugs, or immunosuppressants.[5]

Belimumab is the first biological drug for patients with SLE. It was developed by Human Genome Sciences Inc., (HGS, Rockville, MD) in conjunction with GlaxoSmithKline (Research Triangle Park, NC) and was only approved in 2011 by the US Food and Drug Administration (FDA) and the European Medications Agency.[11] Belimumab is a human monoclonal IgG1λ antibody that binds to the human B-lymphocyte stimulator (BLyS), also known as the B cell activating factor of the TNF family (BAFF), inhibiting its biological activity. BLyS is a type II transmembrane protein that exists both in a form bound to the surface membranes of a wide variety of cell types, such as monocytes, activated neutrophils, T cells, and dendritic cells, when in the soluble form after cleavage.[6] When soluble, it becomes a ligand for three receptors on B lymphocytes: BLyS receptor 3 (BR3), transmembrane activator and calcium-modulator and cyclophilin ligand interactor 1 (TACI), and B-cell

maturation antigen (BCMA).[11] Belimumab blocks soluble BLyS, causing a reduction in lymphocyte B differentiation into plasmacytes, reducing serum IgG and anti-dsDNA antibodies, improving patients' clinical status. BLyS is overexpressed in patients with SLE, so there is a robust association between SLE activity and plasma BLyS concentrations.[7]

The hematological abnormalities generally present for diagnosis of SLE are: hemolytic anemia with reticulocytosis; leukopenia with values below 4,000/mm^3 on two or more occasions; lymphopenia less than 1,500/mm^3 on two or more occasions; thrombocytopenia less than 100,000/mm^3 in the absence of drugs responsible for this.[8] In the current case, the patient had sufficient hemolytic anemia, leukopenia, and lymphopenia for a diagnosis of SLE, but never had thrombocytopenia during the entire period analyzed.

Table 3
Progression of results of laboratory tests during the period analyzed, from September 23, 2019 to August 29, 2020

Analytes	Normal reference for women	Results					
		Before*			During*	After*	
		April 25, 2019	July 4, 2019	July 7, 2019	January 25, 2020	April 5, 2021	June 7, 2021
Erythrocytes	4.0 to 5.40 milh./mm^3	4.01	3.88	3.47	4.09	4.03	3.96
Hemoglobin	11.50 to 16.30 g/dL	12.1	12.1	11.0	13.1	12.40	12.10
VCM	82.0 to 98.0 fL	89.5	94.3	101.4	96.8	–	–
Leukocytes	5,000 to 10,000/mm^3	4,050	2,710	2,400	4,700	5,330	4,760
Neutrophils	1,700 to 7,000/mm^3	2,090	1,320	1,330	3,160	–	–
Eosinophils	100 to 400/mm^3	60	40	100	40	59	52
Lymphocytes	1,000 to 4,000/mm^3	1,410	1,030	610	860	981	1,309
VHS	Up to 15 mm/1st hour	19	21	30	16	–	18
Total complement	72 to 140 units	–	60	–	35	–	–
C3	Age 31 to 49 years: 84 to 160 mg/dL	56	60	49	74	–	96
Platelets	150,000 to 450,000/mm^3	238,000	284,000	221,000	261,000	234,000	266,000
Quantitative erythrocyte assay, urine	Up to 5,000/mL	< 10,000	< 10,000	< 10,000	22,000	Absent	< 26,000

* Before, during and after treatment with belimumab.

In this case, the clinical and laboratory improvement exhibited by the patient after the third dose of belimumab was in line with the reduction in disease activity, as demonstrated by the significant reduction in VHS levels, which is a test often used to screen for inflammatory conditions, such as infections, autoimmune diseases, and cancers.[12] Despite frequent use of VHS as a nonspecific marker of diseases in clinical practice, VHS tends to accompany disease activity in chronic inflammatory diseases and levels generally fall when there is a clinical response to treatment, as seen in the laboratory results in this report, in which VHS increased exponentially until treatment with belimumab was initiated.[13]

Urine analysis should be ordered in SLE cases to detect inflammatory processes in the initial stages, since renal inflammation only causes symptoms in severe and advanced states. The elevated erythrocyte counts in urine after treatment with belimumab seen in this case reveal the renal inflammation described in the drug leaflet.[14]

A case similar to this one was described by Bazílio AP,[15] in which a female patient diagnosed with SLE in 2004 was treated successfully with the conventional drug regimen until 2011, when renal function worsened significantly and joint involvement set in, with arthritis of the hands and knees. Despite changes to the drugs used, in 2014 the patient still had intense disease activity and was refractory to treatment. At this point, belimumab 10 mg/kg was indicated in combination with the treatment. After 6 months' treatment the drug dosages were reduced significantly because of clinical and laboratory improvement, manifest as absence of fatigue, increased lymphocytes, leukocytes, hemoglobin, platelets, C3, and C4 and reduced VHS levels. These factors are all evidence of reduced disease activity and successful treatment. In September 2014, it proved possible to completely withdraw corticoid therapy.

Conclusions

SLE is an autoimmune inflammatory disease that can be controlled with drug treatments. However, as analyzed in this paper, some patients are refractory to these treatments, in which case monoclonal antibodies such as belimumab can be used. While this is an expensive drug, it yields rapid improvement in clinical symptoms, enabling corticoids to be reduced, along with the effects consequent to them, in addition to reestablishing the laboratory parameters affected by the disease, without changing hepatic or renal indicators. Considering the progress in terms of laboratory results seen in the patient described, in conjunction with the efforts of the treating physician, and also the patient's own testimony, it can be concluded that treatment with belimumab was successful.

References

1. Enderle D, Machado D, Mendes K, Costa F, Carvalho A. Manifestações clínicas do Lúpus Eritematoso Sistêmico (LES). FACIDER - Revista Científica. 2019;12(12). Available at: http://revista.sei-cesucol.edu.br/index.php/facider/article/view/182/210. Accessed on: 07/24/2021.
2. Barasuol LL, Figueiredo MO. Análise comparativa dos aspectos clínicos e sorológicos de pacientes com Lúpus Eritematoso Sistêmico com e sem anticorpo Anti-RNP. Curitiba, PR. Trabalho de conclusão de curso [Graduação em Medicina]. Faculdade Evangélica Mackenzie do Paraná; 2019.
3. Abbas AK, Lichtman AK, Pillai S. Imunologia Celular e Molecular. 9ª ed. Guanabara Koogan; 2019. p. 576.
4. Wallace DJ, Gladman DD. Clinical manifestations and diagnosis of systemic lupus erythematosus in adults. UpTotDate. 2020. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-systemic-lupus-erythematosus-in-adults. Accessed on: 07/24/2021.
5. Nakata KCF, Riveros BS. Uso de belimumab em pacientes lúpicos refratários ao tratamento convencional: avaliação de impacto orçamentário. Rev. Gestão & Saúde (Brasília) Vol. 09, nº 01, Jan. 2018.
6. Moore PA, Belvedere O, Orr A, Pieri K, LaFleur DW, Feng P, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. Science. 1999 Jul 9;285(5425):260-3.
7. Frieri M, Heuser W, Bliss J. Efficacy of novel monoclonal antibody belimumab in the treatment of lupus nephritis. J Pharmacol Pharmacother. 2015 Apr-Jun;6(2):71-6.
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997 Sep;40(9):1725.
9. BRASIL. Ministério da saúde. Protocolo Clínico e Diretrizes Terapêuticas do Lúpus Eritematoso Sistêmico. Portaria nº 100. 2013. Available at: http://conitec.gov.br/images/Protocolos/LupusEritematoso_Sistemico.pdf. Accessed on: 08/10/2021.
10. BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Protocolos clínicos e diretrizes terapêuticas: volume 3. Brasília;2014. p.604.
11. Chiche L, Jourde N, Thomas G, Bardin N, Bornet C, Darque A, et al. New treatment options for lupus - a focus on belimumab. Ther Clin Risk Manag. 2012;8:33-43.
12. Santos VM, Cunha SFC, Cunha DF. Velocidade de sedimentação das hemácias: utilidade e limitações. Rev Assoc Med Bras. 2000;6(3):232-6.
13. Oliveira JFC. Relação da atividade clínica do lúpus eritematoso b sistêmico medida pelo VHS, PCR E SLEDAI. Rev Med Paraná, Curitiba. 2017;75(1):67-72.

14. Belimumabe: Pó liofilizado para solução para infusão intravenosa. Responsável técnico Monique Lellis de Freitas. Rio de Janeiro: Glaxo Operations UK Ltd, 2012. Bula - Profissional de saúde. Available at: https://consultas.anvisa.gov.br/#/medicamentos/25351699419201015/?nomeProduto=BenlysTa. Accessed on: 08/01/2021.

15. Bazílio AP. Caso clínico uma experiência real com Benlysta®. 2015. Available at: https://gskpro.com/content/dam/global/hcpportal/pt_BR/Areas%20Terapeuticas/Imunologia%20-%20LES/PDF/Caso%20Ana%20Paula.pdf. Accessed on: 08/11/2021.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Baseline series update

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Dear Editor,

A wide variety of substances may be involved in the genesis of allergic contact dermatitis (ACD), thus recommending treatment according to the culprit allergen is difficult . For this reason, all patients with suspected ACD should preferably undergo patch testing for a standard baseline series,[1] which consists of a series of allergens that are commonly associated with ACD in a certain population.[2] The allergen should cause a positive and significant reaction in 0.5% to 1% of patients tested to be included in a baseline series.[3] Thus, the baseline series should be constantly updated by adding new allergens and removing those that have become irrelevant.[2] The issues in question are: what standard baseline series is available today? How and when was it created? How may we improve it?

A historical survey shows that the desire to create a regional baseline series is old. With this purpose, Brazilian specialists gathered at the Brazilian Congress of Dermatology in Curitiba, state of Paraná, in 1993 and created the Contact Dermatitis Brazilian Studying Group (Grupo Brasileiro de Estudos em Dermatite de Contato, GBEDC). The aim was to create a standard patch test series for the Brazilian population using a standardized method that would be published later, which was a novelty at the time. Thus, in 1995/1996, 967 patch tests were performed with the proposed baseline series, and the study was published in 2000.[4] Tests were positive in 62% of participants, with nickel being the most common hapten, followed by thimerosal, a substance currently of little relevance. In addition to standardizing tested antigens, the order of testing was considered an important factor in the prevention of false-positive results. Substances with similar chemical structures may cross-react and should not be tested in close proximity to each other.[5,6] However, the standard Brazilian baseline series has never been updated in the sense of adding new substances and removing those whose sensitization prevalence is sufficiently low or not sufficiently relevant.

In 2013, the Colegio Ibero-Latinoamericano de Dermatología proposed the creation of a more comprehensive baseline series that included relevant substances and updated concentrations. The new series comprised 40 allergens and was published as a consensus in 2015 by the Dermatitis de Contacto de la Sociedad Argentina de Dermatología group.[7] The aim was to create a unified patch test series for all countries in Latin America with the goal of standardizing ACD conducts and practices.[8] In addition, the use of a "multinational" baseline series could allow comparative studies between countries, increasing the knowledge of geographic variations related to sensitizations.[9] A study conducted in Argentina with the Latin American baseline series found that nickel was the most common allergen, followed by palladium and methylisothiazolinone. Tests were positive in 82.4% of patients.[10]

There are several differences between the Brazilian and Latin American baseline series. The Brazilian series does not include any markers of allergy to corticosteroids.[11] The Latin American series includes as markers of fragrance sensitivity fragrance mix I and II, similarly to international series, and Lyral®. It also includes other formaldehyde releasers, such as diazolidinyl urea and imidazolidinyl urea.[8] Benzocaine was replaced by caine mix, the most comprehensive marker of local anesthetics, following the European baseline series.[12] Other important additional allergens were included to facilitate the diagnosis of specific allergies, such as cocamidopropyl betaine (surfactant), propyl gallate (antioxidant), sesquiterpene lactone (plants), disperse blue (textile dyes), dialkyl thiourea (neoprene), and tosylamide/formaldehyde resin (enamel).[8] The inclusion of methylisothiazolinone in the Latin American baseline series lead to the identification of an important allergy epidemic, which was previously undiagnosed.[13]

The Latin American baseline series was finally commercialized in Brazil at the end of 2020, following requests from the expert community. It was adapted to

include hydrocortisone acetate instead of tixocortol, as the latter is not sold in Brazil. In addition, propolis replaced primin, which currently lacks relevance, according to the European baseline series.[14] A prospective study using the adapted baseline series reported that tests were positive in 67.9% of patients and found significant sensitivity to methylisothiazolinone, as expected, which was positive in 13.5% of patients.[15]

However, we believe the issues surrounding patch testing are not resolved. How often does a patient with clinical symptoms suggestive of ACD test negative for the disease? Several hypotheses may explain this, but could it be due to an outdated baseline series? Nonetheless, due to Brazil's continental dimensions, a baseline series supported by new and recent international research that is relevant to the country's reality should be created. Haptens such as thimerosal and others that are no longer allowed in personal care products should be removed, and acrylates, which are no longer exclusive to artificial nail products, should be included.[16] We understand that special attention should be given to substance concentrations to prevent patch test sensitization, but concentrations should not be low enough to cause false-negative results. All substances should be identified by their CAS Registry Number, and manufacturing companies should be required to provide substances with a degree of purity as close to 100% as possible. These measures would help standardize the quality of supplies, allowing patch tests to reach a level of excellence.

Considering the aforementioned, the Board of Directors of the Brazilian Association of Allergy and Immunology (Associação Brasileira de Alergia e Imunologia, ASBAI), chaired by Dr. Emanuel Sarinho, understood the issues and took action. First, the Board created the Department of Contact Dermatitis and supported educational activities aimed at informing allergists of the novelties in the field. Second, the structure of lectures at national congresses was changed to allow for more specific classes, avoiding commonplace topics on the subject. Finally, the Board also promoted the launch of a book exclusively on the topic of ACD. In summary, the Board understood that it was time to create a group focused on learning about new scientific evidence on the field to elaborate a new baseline series, which will decisively improve patch testing quality in the country.

It is time to update.

References

1. Cortés Pinto C, Sanmartín Novell V, Giménez-Arnau AM. Practical Advice to Correctly Perform Patch Test. Curr Treat Options Allergy. 2019 Mar 14;6(1):71-91.
2. Veverka KK, Hall MR, Yiannias JA, Drage LA, El-Azhary RA, Killian JM, et al. Trends in Patch Testing With the Mayo Clinic Standard Series, 2011-2015. Dermatitis. 2018 Nov;29(6):310-5.
3. Whitehouse H, Wilkinson M. Updated Criteria to Include Contact Allergens in the European Baseline Series With Suggested Additions. Curr Treat Options Allergy. 2022 Jun 1;9(2):52-66.
4. Belliboni N, De Avelar Alchorne ADO, Luiz A, Maruta CW, Costa EB, et al. Multicentric study for the development of a standard Brazilian patch test series. An Bras Dermatol. 2000;75(2):147-56.
5. Duarte IAG, Tanaka GM, Suzuki NM, Lazzarini R, Lopes AS de A, Volpini BMF, et al. Patch test standard series recommended by the Brazilian Contact Dermatitis Study Group during the 2006-2011 period. An Bras Dermatol. 2013;88(6):1015-8.
6. Duarte I, Lazzarini R, Buense R. Interference of the position of substances in an epicutaneous patch test battery with the occurrence of false-positive results. Am J Contact Dermat. 2002 Sep;13(3):125-32.
7. La Forgia M, Cannavo A, Fortunato L, Infante L, Kvitko E, Russo J. Dermatitis por contacto. 2015;1-30.
8. Aerts O, Rustemeyer T, Wilkinson M. Comments on Various Baseline Series for Patch Testing. In: Johansen JD, Mahler V, Lepoittevin JP, Frosch PJ (eds). Contact Dermatitis. Springer, Cham. https://doi.org/10.1007/978-3-030-36335-2_95.
9. Lachapelle J-M. Baseline series of patch tests. In: Lachapelle J-M, Maibach HI, editors. Patch Testing and Prick Testing [Internet]. Cham: Springer International Publishing; 2020. p. 85-103.
10. Chessé CD, Abaca MC, Senarega A, Innocenti C, Bassoti A, Parra V. Epidemiología de la dermatitis alérgica de contacto en Mendoza: prevalencia de sensibilización a diferentes alérgenos y factores asociados. Dermatología Argentina. 2019;25(2):58-63.
11. Belluco PES, Milhomem OS, Belluco JEF, Azevedo FDSM, Belluco RZF, Novaes MRCG, et al. O que a bateria padrão latino-americana de teste de contato acrescenta? In: Junior FF de C, editor. Alergia e Imunologia: abordagens clínicas e prevenções - Volume 2 [Internet]. 1ª ed. Editora Científica Digital; 2022. p. 50-64.
12. Wilkinson M, Gallo R, Goossens A, Johansen JD, Rustemeyer T, Sánchez-Pérez J, et al. A proposal to create an extension to the European baseline series. Contact Dermatitis. 2018 Feb;78(2):101-8.
13. Belluco PES, Giavina-Bianchi P. Dermatite de contato à metilisotiazolinona - estamos atentos a essa epidemia? Brazilian J Allergy Immunol. 2019;3(2):139-42.
14. Wilkinson M, Gonçalo M, Aerts O, Badulici S, Bennike NH, Bruynzeel D, et al. The European baseline series and recommended additions: 2019. Contact Dermatitis. 2019 Jan;80(1):1-4.
15. Belluco PES, Giavina-Bianchi P, Belluco RZF, Novaes MRCG, Reis CMS. Prospective study of consecutive patch testing in patients with contact dermatitis using an adapted Latin American baseline series. Eur Ann Allergy Clin Immunol. 2022 (ahead to print).
16. Vandaele V, Bossuyt L, Lapeere H, Stockman A. Case report: A veterinarian with a contact allergy to acrylates. Contact Dermatitis. 2022 Apr 27;86(4):312-3.

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Are type-2 biomarkers of any help in distinguishing chronic rhinosinusitis with nasal polyps from chronic rhinosinusitis without nasal polyps?

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Dear Editor,

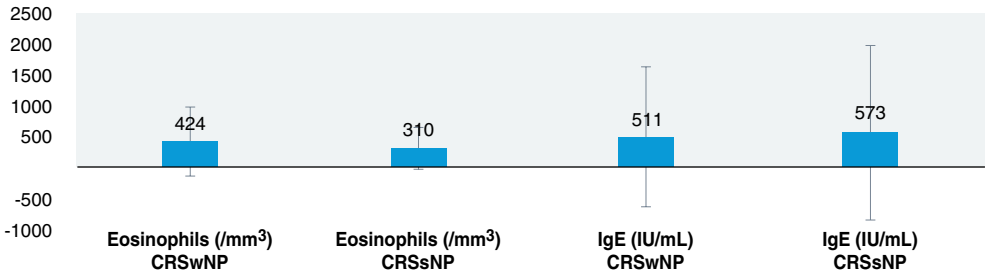
Chronic rhinosinusitis with nasal polyps (CSwNP) is a common chronic airway disease. Knowledge of CSwNP has progressed from an era where physicians collected information together with the patient using tools such as the endoscope, X-ray, and computed tomography (CT) scanner to the incorporation of methods of genotyping, phenotyping, and endotyping.[1] Genotypic classification is used to identify related monogenic conditions such as cystic fibrosis and ciliary dysmotility.[2,3] Phenotypic classifications use clinically observable characteristics such as endoscopic findings, the presence of comorbid or systemic illness, and timing of disease onset.[4] Endotypic classifications subdivide chronic rhinosinusitis (CRS) based on pathobiologic mechanisms, and for CRS this was based on histologic features such as the presence of neutrophilia, eosinophilia, fibrosis, glandular hypertrophy, and epithelial dysmorphosis.[1]

In western countries, approximately 80% of patients with CRSwNP exhibit a type 2 (T2) inflammatory endotype, which is characterized by increased levels of interleukin (IL) 4, IL-5, IL-13, and immunoglobulin E (IgE). Conversely, most patients with CRS without nasal polyps (CRSsNP) do not exhibit a T2 inflammatory endotype.[5,6] T2 inflammation is derived from the activation of antigen-specific T helper 2 (Th2) cells or group 2 innate lymphoid cells, and cytokines (IL-4, IL-5, and IL-13) likely act in concert with one another to drive the pathology of CRSwNP. In response to IL-4, B cells differentiate into IgE-producing plasma cells, which bind to the surface of mast cells and basophils via the high-affinity IgE receptor. IgE class switching is also caused by local mucosal inflammation induced by the presence of *Staphylococcus aureus* enterotoxins in the middle nasal meatus, a key region at the entrance to the sinuses.[5,7] IL-5 promotes the differentiation, migration, activation, and survival of eosinophils.[5] Current guidelines on the management of CRS recommend assessment of total immunoglobulin E levels and serum eosinophilia as biomarkers of T2 inflammation.[8,9]

We investigated the utility of T2 biomarkers in distiguising CRSwNP from CRSsNP. To this end, we conducted a retrospective study of patients with CRSwNP (n=137) and CRSsNP (n=23) on our database. Clinical data such as sex, age, serum eosinophilia, and total IgE levels were analyzed. Data were included after informed consent was obtained.

Ninety (56%) patients were women. Mean patient age was 63 years (18-89) in the CRSwNP group and 56 years (20-81) in the CRSsNP group. Serum eosinophilia ranged from 0 to 3.510 /mm^3 (mean = 423,5) in patients with CRSwNP and from 0 to 1.408 /mm^3 (mean = 310) in those with CRSsNP. In the CRSwNP group, mean total IgE level was 511 IU/mL (6-7.200); in the CRSsNP group, mean total IgE level was 573 IU/mL (4,5-5.190) (Figure 1).

Our data indicate that the use of T2 inflammation biomarkers as index tests is not effective in distinguishing



CSwNP: Chronic rhinosinusitis with nasal polyps.
CRSsNP: Chronic rhinosinusitis without nasal polyps.

Figure 1
Number of eosinophils and IgE levels (standard deviation)

patients with and without nasal polyps. However, it does not negate the clinical value of measuring T2 biomarkers in CRS phenotyping in times of precision medicine and availability of T2-driven biologics.

In conclusion, using T2 biomarkers to assess the presence or absence of nasal polyps lacks accuracy. Therefore, performing imaging tests such as nasal endoscopy and/or CT scan is extremely important.

References

1. Kato A, Peters AT, Stevens WW, Schleimer RP, Tan BK, Kern RC. Endotypes of chronic rhinosinusitis: Relationships to disease phenotypes, pathogenesis, clinical findings, and treatment approaches. Allergy. 2022 Mar;77(3):812-26. doi: 10.1111/all.15074.
2. Stevens WW, Lee RJ, Schleimer RP, Cohen NA. Chronic rhinosinusitis pathogenesis. J Allergy Clin Immunol. 2015 Dec;136(6):1442-53. doi: 10.1016/j.jaci.2015.10.009.
3. Gudis D, Zhao KQ, Cohen NA. Acquired cilia dysfunction in chronic rhinosinusitis. Am J Rhinol Allergy. 2012 Jan-Feb;26(1):1-6. doi: 10.2500/ajra.2012.26.3716.
4. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600.
5. Schneider AL, Schleimer RP, Tan BK. Targetable pathogenic mechanisms in nasal polyposis. Int Forum Allergy Rhinol. 2021 Aug;11(8):1220-34. doi: 10.1002/alr.22787.
6. Bachert C, Akdis CA. Phenotypes and Emerging Endotypes of Chronic Rhinosinusitis. J Allergy Clin Immunol Pract. 2016 Jul-Aug;4(4):621-8. doi: 10.1016/j.jaip.2016.05.004.
7. Bachert C, Zhang N. Chronic rhinosinusitis and asthma: novel understanding of the role of IgE 'above atopy'. J Intern Med. 2012 Aug;272(2):133-43. doi: 10.1111/j.1365-2796.2012.02559.x.
8. Fokkens WJ, Lund V, Luong AU, Orlandi RR. A Comparison of International Guidelines for Rhinosinusitis. J Allergy Clin Immunol Pract. 2022 Jun;10(6):1418-22. doi: 10.1016/j.jaip.2022.01.013.
9. Bachert C, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. J Allergy Clin Immunol. 2021 Jan;147(1):29-36. doi: 10.1016/j.jaci.2020.11.013.

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