

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

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de Alergia e Imunologia

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de Alergia, Asma e Inmunología

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Case reports are welcome, following the recommended guidelines

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July-September 2025

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Case reports are welcome, following the recommended guidelines

Relatos de casos são bem-vindos, seguindo o padrão recomendado

Ekaterini Simões Goudouris¹

Case reports hold invaluable importance across all medical specialties, including Allergy and Immunology, a field that encompasses conditions ranging from highly prevalent disorders to rare diseases.¹ While evidence-based medicine places strong emphasis on randomized, double-blind, placebo-controlled trials, case reports and case series remain essential sources of clinical knowledge, particularly in the context of inborn errors of immunity (IEIs) and unusual manifestations of allergic diseases.

In IEIs, recruiting a large number of individuals is often challenging. In this setting, case reports frequently represent the first documentation of newly recognized diseases, syndromes, and genetic defects. Such publications have been instrumental in the identification and classification of several IEIs over recent decades.²

In common allergic conditions, including asthma and rhinitis, as described in many other medical conditions, case reports may document atypical presentations, unexpected treatment responses, and innovative diagnostic or treatment approaches.^{3,4}

Moreover, these publications serve as valuable tools in the teaching-learning process in the health field.^{3,4}

Case reports should therefore not be underestimated. They help bridge gaps in knowledge and

support continuing medical education, both of which are essential for advancing the specialty of Allergy and Immunology.

In an upcoming issue, our journal will publish an article addressing the relevance of case reports and the currently available reporting guidelines. Our aim is to encourage the submission of high-quality case reports that meet established standards and provide meaningful contributions to professionals in our field, as well as to those seeking to engage more deeply with it. Case reports are welcome, provided they adhere to recommended guidelines.

We invite you to contribute to the success of our journal!

References

1. Warner JO. Case reports – What is their value? *Pediatric Allergy and Immunology*. 2005;16(2):93-4. doi 10.1111/J.1399-3038.2005.00266.X.
2. Poli MC, Aksentijevich I, Bousfiha AA, Cunningham-Rundles C, Hambleton S, Klein C, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. *J Hum Immun*. 2025;1(1):e20250003. doi: 10.70962/jhi.20250003.
3. Kienle GS. Why Medical Case Reports? *Global Advances in Health and Medicine*. 2012;1(1):8-9. doi: 10.7453/gahmj.2012.1.1.002.
4. Vu M & Weinberg GL. Making the Case for Case Reports. *Anesthesia & Analgesia*. 2018;127(5):1278-9. doi 10.1213/ANE.0000000000003541.

1. Editor-in-chief, Arquivos de Asma, Alergia e Imunologia (AAAI) - São Paulo, SP, Brazil.

Belém Charter – COP30. The Belém Health Action Plan for the adaptation of the health sector to climate change – A joint document of the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics

Carta de Belém – COP30. Plano de Ação de Saúde de Belém para a adaptação do setor de saúde às mudanças climáticas – Documento conjunto da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria

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ABSTRACT

During the United Nations Climate Change Conference (COP30), held from November 10 to 21 in the city of Belém, northern Brazil, the Brazilian Ministry of Health released a document outlining the Belém Health Action Plan for the adaptation of the health sector to climate change. This special article, jointly authored by the Brazilian Association of Allergy and Immunology and the Brazilian Society of Pediatrics, summarizes the main elements of the plan published by the Brazilian Ministry of Health/Unified Health System (SUS).

Keywords: Climate change, United Nations, Belém, health.

RESUMO

Durante a Conferência das Nações Unidas sobre Mudanças Climáticas (COP30), realizada entre 10 e 21 de novembro na cidade de Belém, o Ministério da Saúde do Brasil publicou um documento em que apresenta o Plano de Ação de Saúde de Belém para a adaptação do setor de saúde às mudanças climáticas: *The Belém Health Action Plan for the adaptation of the health sector to climate change*. Este é um artigo especial, redigido em conjunto pela Associação Brasileira de Alergia e Imunologia e pela Sociedade Brasileira de Pediatria, que reúne os pontos principais do plano publicado pelo Ministério da Saúde/SUS.

Descritores: Mudanças climáticas, Nações Unidas, Belém, saúde.

Introduction

Climate change is one of the most pressing global health challenges of the 21st century, as demonstrated by a growing body of scientific evidence.

Its effects, which already place significant pressure on health systems worldwide, disproportionately affect developing countries and vulnerable populations.

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Extreme weather events, rising sea levels, changes in precipitation patterns, and resource scarcity are intensifying inequality, negatively affecting quality of life, and exacerbating the social determinants of health. These changes have increased the burden of climate-sensitive diseases, increased mortality from extreme heat, deteriorated air quality, and caused disruptions to food and water security.

Article 7 of the 2015 Paris Agreement established a worldwide goal of enhancing adaptive capacity, strengthening resilience, and reducing vulnerability to climate change, in an effort to foster sustainable development and ensure an adequate response regarding the temperature target set in Article 2.¹

Thus, there is an urgent need to foster collective action and strengthen governance mechanisms so that health systems are equipped to prevent, detect, and respond to the growing challenges of climate change. It is equally essential to mobilize resources for initiatives dedicated to safeguarding and promoting human health. Achieving this will require a committed and coordinated approach to climate and health adaptation, one that is guided by detailed priority measures, such as those incorporated in this document: the Belém Health Action Plan (BHAP).²

BHAP provides a framework for advancing the Action Agenda of the 2025 United Nations Climate Change Conference (COP30), particularly Key Goal 16 (promoting resilient health systems), as well as for supporting the Parties to this document (hereafter referred to as the “Endorsing Parties”) in implementing the second Global Stocktake process, which will conclude at COP33 in 2028.

BHAP is based on international policies and commitments that increasingly recognize the link between climate change and health, including those of the World Health Organization (WHO), its Member States, the United Nations Framework Convention on Climate Change (UNFCCC), and its COP processes.³ BHAP seeks to consolidate and promote these initiatives, based on World Health Assembly Resolutions WHA61.19, WHA77.14, and WHA77.2, which address climate change, health, and social participation in health governance.

BHAP is also aligned with the WHO Global Action Plan on Climate Change and Health, which was approved in May 2025 (Decision WHA78[27]). While the WHO Global Action Plan has a broader scope and covers all climate change and health priorities, BHAP is more specific to the adaptation priorities included

in the Global Action Plan, and it provides actionable items to be implemented for each priority.

BHAP is also consistent with the Global Adaptation Goal and the United Arab Emirates-Belém Work Programme, building on the progress achieved in the UNFCCC, especially initiatives launched since COP26: I) COP26: Health Programme and the subsequent creation of the Alliance for Transformative Action on Climate and Health (ATACH); II) COP27: Initiative on Climate Action and Nutrition; III) COP28: Declaration on Climate and Health and Guiding Principles for Financing Climate and Health Solutions; and IV) COP29: Baku COP Presidencies Continuity Coalition for Climate and Health and the Baku Initiative on Human Development for Climate Resilience.⁴

BHAP is organized around 3 interrelated lines of action, each supported by specific measures designed to address priority areas and promote health system adaptation and resilience to climate challenges. These lines of action comprise: (1) surveillance and monitoring; (2) evidence-based policies, strategies, and capacity building; and (3) innovation, production, and digital health. In addition to these 3 lines of action, BHAP is underpinned by 2 cross-cutting principles that guide the design and implementation of all actions: (1) to advance health equity and the concept of “climate justice”; and (2) social participation in climate and health leadership and governance.

These principles are essential for addressing the effects of climate change on health, as they recognize that different population groups are affected in different ways and acknowledge that leadership, governance, and broad social participation are crucial for achieving meaningful and lasting progress.

I - United Nations Framework Convention for Climate Change - Decision

Main Objective

The main objective of the UNFCCC is to strengthen the health sector's adaptation and resilience to climate change by advancing integrated surveillance and monitoring systems, accelerating capacity building, promoting the implementation of evidence-based policies, and fostering innovation and sustainable production. BHAP considers the diverse needs and national contexts of health systems worldwide and recognizes the importance of intersectoral collaboration to accelerate mitigation efforts that lead to collateral health benefits.

Global Goal

The overall objective is to integrate BHAP into UNFCCC progress reports within the framework of the Global Stocktake and other relevant mechanisms. By COP33 (2028), during the next Global Stocktake, all Endorsing Parties will be invited to report on their progress in implementing the actions outlined in BHAP, which is aligned with the Global Stocktake indicators and any other nationally appropriate indicators.

Cross-Cutting Principles

- i. Advancements in health equity and the concept of ‘climate justice’: adaptation measures must address health inequalities, which are exacerbated by climate change, as well as to consider the importance of ‘climate justice’ when taking measures to address climate change;
- ii. Social participation in climate and health leadership and governance: adaptation policies should be guided by the principles of accountability, transparency, and oversight, adapted to each country’s circumstances and structures.

BHAP advocates for comprehensive, equitable, and bottom-up approaches that ensure the active participation of civil society, particularly representatives of the most affected peoples and communities, in all stages of policy formulation, implementation, and evaluation, through consultative and deliberative mechanisms. These processes should involve the voices of those in vulnerable situations who face structural, environmental, or health-related disadvantages.

Lines of Action and Proposed Measures for Adapting to and Developing Climate-Resilient Health Systems

First Line of Action – Surveillance and Monitoring

Objectives: To implement and strengthen health-related climate services that are integrated, interoperable, inclusive, and participatory, considering the needs of vulnerable populations; to establish continuous evaluation and improvement mechanisms to ensure that these systems can detect both extreme events and the gradual effects of climate change, while providing real-time data to support early warning and response actions; and to enhance epidemiological and environmental monitoring capacities through evidence-based measures that can prevent or reduce

climate-related health effects, in line with global health adaptation commitments.

1.1. Enhancing Climate-Informed Health Surveillance:

- 1.1.1. Invest in data infrastructure and establish partnerships between health institutions, meteorological agencies, emergency agencies, cities, and research centers for climate and health surveillance;
- 1.1.2. Implement integrated methodologies that link environmental, meteorological, social, climate, and health monitoring data to develop effective health surveillance systems that can improve early detection, assess risk, and anticipate climate-related public health threats. These systems should incorporate effective and inclusive risk communication strategies to ensure that early warnings and health alerts are communicated clearly, accessibly, and immediately to all relevant stakeholders;
- 1.1.3. Create early warning systems, which may require the development of predictive models adapted to local climates, health profiles, and other relevant characteristics. Improve data recording, reporting, and digitization processes to promote the timely generation and dissemination of actionable information for these systems, including the use of disaggregated data;
- 1.1.4. Promote data collection and analysis on the health effects of climate change, disaggregated by vulnerable groups, including morbidity and mortality associated with climate-sensitive risks. These efforts will strengthen climate and health surveillance, improve responses for at-risk populations, and promote equity in health outcomes in the context of climate change;
- 1.1.5. Establish and/or strengthen institutional decision-making mechanisms to respond to early warning systems and to risks that are identified through surveillance;
- 1.1.6. Promote early warning systems and public health campaigns that are accessible, culturally appropriate, and provide continuous feedback to communities in formats that preserve their right to information, for example, through: (a) digital and visual platforms, such as risk

dashboards, heat maps, and seasonal alerts to anticipate climate-related risks and extreme events (eg, heat waves, floods, and droughts); (b) health-specific climate bulletins addressing topics such as climate-sensitive pathogens, extreme heat, and air pollution;

1.1.7. Integrate climate adaptation and resilience measures at all levels of health care and in specific health programs, including immunization, disease elimination initiatives, and the expansion of prevention, diagnosis, treatment, and rehabilitation services, promoting coordinated, effective, and equitable responses to climate-related events;

1.1.8. Accelerate inter-regional and cross-border collaboration for shared learning, funding coordination, and joint investment, with the support of WHO and ATACH, where appropriate. Cross-border information sharing should be promoted by interoperable and privacy-respecting data standards, in line with international obligations.

1.2. Identifying a Priority List of Climate-Related Risks and Diseases:

1.2.1. Develop a national list of health threats associated with potential climate change scenarios, encompassing current and projected effects. This list may include climate threats, diseases, vulnerabilities, and health risks, among others, considering national and international scientific evidence, methodologies, and references. The list should be updated periodically to inform and guide surveillance and monitoring efforts and, where appropriate, request technical guidance and strategic advice from the WHO to support country-led climate prioritization;

1.2.2. Promote inter- and transdisciplinary research and technology development, facilitate the transfer of knowledge and experience between countries. Support health promotion, prevention, early detection, and the treatment of high priority climate-sensitive diseases, including risk assessment;

1.2.3. Integrate local and community knowledge as a legitimate source of evidence and strengthen grassroots health surveillance mechanisms as essential components in the assessment

of and response to climate-sensitive risks and diseases, as appropriate.

1.3. Improving Health Risk Management for Climate Events and Emergencies:

1.3.1. Strengthen institutional health capacity for emergency response using established coordination mechanisms with formal protocols for real-time communication and action within and between sectors, including planning, capacity building, and simulation exercises with relevant stakeholders;

1.3.2. Develop contingency plans adapted to address different climate risks, prioritizing areas of greatest vulnerability and populations in vulnerable situations, promoting the continuity of integrated health care and preventing overload in health systems and services;

1.3.3. Promote flexibility in administrative, regulatory, and procurement processes to enable rapid and effective emergency response actions, guided by ethical protocols that uphold transparency and strengthen social responsibility, following legal and regulatory frameworks;

1.3.4. Develop operational response protocols based on climate forecasts, especially in areas and periods of greater vulnerability, incorporating Indigenous, local, and traditional knowledge, when appropriate;

1.3.5. Promote equitable workforce distribution and retention policies, supported by mechanisms to address the shortage of health professionals, seeking continuous service provision during climate-related emergencies, with special attention to vulnerable regions, when appropriate;

1.3.6. Develop and implement climate adaptation and contingency plans for health services in Indigenous territories to promote infrastructure, logistics, and supply chains resilient to extreme events such as floods, droughts, and forest fires.

Second Line of Action – Evidence-based Policies, Strategies, and Capacity Building

Objectives: To strengthen national and local capacities and accelerate the implementation of

evidence-based policies and solutions through multidisciplinary, intersectoral, and participatory approaches, taking into account health equity, the concept of ‘climate justice,’ and inclusive governance with the active involvement of relevant groups, such as Indigenous peoples, traditional and local communities, and civil society, at all stages of policy formulation and decision-making.

2.1. Harmonizing the Concepts of Climate Adaptation and Health:

2.1.1. Adopt a standardized, consensus-based classification of terms, concepts, and categories related to climate and health, including health equity, health system adaptation, climate and health financing, and resilience. Align adaptation terminology with established references, such as WHO definitions (eg, climate-resilient health systems) and the Intergovernmental Panel on Climate Change (IPCC) glossary, integrating sociocultural perspectives from diverse contexts, including those of Indigenous peoples, traditional communities, and other sectors;

2.1.2. Promote linguistic accessibility in policy formulation and project cycles (formulation, implementation, monitoring, and evaluation) and strengthen climate and health governance through greater clarity and conceptual coherence.

2.2. Promoting Multisectoral Policies with Collateral Benefits for Health:

2.2.1. Promote and implement intersectoral policies and strategies that maximize collateral benefits for health and climate. Prioritize strategic intersectoral interventions, such as sustainable mobility and quality public transport; green cities; transform food systems through agroecology and the regulation of products that are harmful to health or have a high carbon footprint; invest in universal water, soil, sanitation, and waste management systems; and reduce exposure to chemicals;

2.2.2. Strengthen national and international cooperation toward unified health systems; enhance collaboration regarding food security systems, antimicrobial resistance, zoonotic and climate-sensitive disease control, and pandemic preparedness and response;

2.2.3. Integrate climate and health education into school curricula and community programs, promoting, from childhood, diversity, inclusion, psychosocial well-being and awareness raising about the effects of climate change on health and health equity;

2.2.4. Establish and operationalize prevention and response strategies to protect the health, nutrition, hydration, and psychosocial well-being of children and adolescents in educational settings and in the context of extreme climate-related events, ensuring the continuity of learning through safe, inclusive, and climate-resilient educational systems;

2.2.5. Promote policies and investments that address climate change’s effects on health access in historically marginalized territories, fostering the formal integration of traditional knowledge into public policies and creating funding lines for community-based adaptation initiatives, as appropriate.

2.3. Integrating Mental Health into Climate Adaptation in the Health Sector:

2.3.1. Integrate Mental Health and Psychosocial Support into national climate and health policies and strengthen multidisciplinary teams to assist communities affected by climate change. Promote coordinated intersectoral actions with shared leadership and responsibility, considering community-based approaches. When relevant, expand Mental Health and Psychosocial Support initiatives grounded in traditional and Indigenous knowledge to promote participatory and context-appropriate responses;

2.3.2. Strengthen mental health systems to anticipate, absorb, and respond to climate-related stressors and disasters, ensuring continuity of care, uninterrupted access to essential medicines, and the resilience of community facilities and services;

2.3.3. Promote research, monitoring systems, and indicators to track the effects on climate-related mental health, both globally and nationally, using intersectional and equity-based approaches to inform policies and guide targeted interventions, where appropriate;

2.3.4. Prepare health, social, and community professionals, educators, and first responders with structured training, supervision, and peer support to provide effective and inclusive psychosocial support at all stages of climate-related emergencies.

2.4. Promoting Adaptation Policies to Support Vulnerable Populations:

2.4.1. Strengthen multi-sectoral and multi-level capacities to address the disproportionate impacts of climate change on vulnerable populations, particularly those facing intersectional forms of discrimination;

2.4.2. Integrate the social determinants of health into climate-health vulnerability assessments and adaptation strategies in coordination with relevant sectors and systematically collect and analyze disaggregated health and vulnerability data, including social status, race, ethnicity, and other relevant factors;

2.4.3. Promote evidence-based health policies and programs that integrate gender-sensitive approaches and the needs of children and adolescents into all climate adaptation and health efforts. This may include protection protocols to prevent and respond to violence, promote safe and inclusive shelters, maintain the continuity of sexual and reproductive health and rights and pediatric and psychosocial care during and after climate-related emergencies, in coordination with relevant sectors;

2.4.4. Promote the effective participation of vulnerable populations and their representative organizations in national and regional climate and health governance mechanisms, including monitoring committees and decision-making bodies;

2.4.5. Strengthen adaptation measures that safeguard food security, access to water, and the territorial rights of Indigenous peoples and traditional communities, recognizing them as fundamental determinants of health in the face of climate change;

2.4.6. Promote access to and continuity of care for people with disabilities in the context of climate adaptation and emergency response efforts, including access to medications,

assistive devices, and support for caregivers. This includes adapting urban and health infrastructure to climate change to promote full physical, communicational, digital, and attitudinal accessibility, as well as inclusive warning systems and evacuation routes based on universal design principles⁴, in collaboration with people with disabilities where appropriate.

2.5. Protecting and Promoting Worker Health in the Context of Climate Change:

2.5.1. Promote evidence-based regulations and policy interventions to address the impact of climate change on work environments, processes, and relationships, focusing on its direct and indirect effects on the physical and mental health of workers in the formal and informal sectors, in line with local circumstances;

2.5.2. Promote worker health surveillance systems, including periodic examinations, transparent monitoring, and the expansion of local and regional health teams and surveillance centers to encompass formal and informal workers and Indigenous and traditional communities;

2.5.3. Enhance multi-sectoral engagement and coordination among organizations in the public and private sectors and civil society to safeguard worker health through climate adaptation policies, in accordance with safety standards and just transition frameworks and strategies.

2.6. Strengthening the Health Workforce to Address Climate Change:

Challenges:

2.6.1. Provide customized technical training to the health workforce and health managers to address the effects of climate change on the health sector, from gradual manifestations to extreme events. Develop accessible and regularly updated training programs that utilize case studies and simulations to strengthen health workforce capacity;

2.6.2. Integrate environmental- and climate change-related content into health education. Promote knowledge exchange through peer learning and mentoring and establish intercultural and

interdisciplinary programs that incorporate Indigenous and traditional knowledge, multilingual resources, and continuous professional development to strengthen climate-resilient health and disaster preparedness.

2.7. Promoting Community Resilience to Climate Change:

2.7.1. Develop and support public education initiatives and campaigns about climate change and health adaptation on local, regional, and national levels that are tailored to diverse audiences (including in-person and digital formats) and are sensitive to cultural and territorial specificities, as appropriate;

2.7.2. Encourage community-led climate and health initiatives and programs, especially those led by women and young people, to strengthen local adaptation and health systems;

2.7.3. Support community health strategies through accessible funding and ongoing engagement with primary health care to ensure continuous participation in program planning, implementation, and evaluation.

Third Line of Action – Innovation, Production and Digital Health

Objectives: To promote research, development, application, and equitable access to innovative technologies and approaches that effectively meet the health needs of diverse populations; to enhance the resilience and sustainability of the supply chain and manufacturing of essential health products by adapting infrastructure, equipment, supplies, and services to climate change, including digital solutions and climate-adapted health innovations.

3.1. Strengthening Climate-Resilient Infrastructure and Services:

3.1.1. Promote investment in sustainable innovation and technology to ensure the uninterrupted operation of health services during extreme weather events (eg, droughts, floods, heat waves, cold waves, hurricanes, wildfires, storms) and outbreaks of climate-related diseases;

3.1.2. Ensure that health facilities are prepared for extreme weather events (eg, droughts, floods,

heat waves, cold waves, hurricanes, wildfires, and storms) by assessing the risk of areas and periods of greatest exposure, adopting measures to prevent damage to infrastructure and ensure the continuity and adequacy of care;

3.1.3. Implement energy efficiency solutions, renewable energy sources, potable water and sanitation systems, and logistics systems in health units to strengthen their operational resilience;

3.1.4. Expand and provide equitable access to health services through telehealth, strengthening public digital infrastructure, connectivity, and digital inclusion, while also promoting territory-adapted care for remote and underserved communities.

3.2. Evaluating and Innovating Adaptation Policies in the Health Sector:

3.2.1. Conduct, with intersectoral participation, systematic analyses of the effects of public policies, programs, and interventions related to climate change and health, considering the entire life cycle of the implemented actions, using existing monitoring and evaluation structures to ensure global comparability and national accountability, as appropriate;

3.2.2. Strengthen institutional capacity to assess and integrate evidence on the risks, vulnerabilities, and effects of climate change on health into decision-making processes, based on quantitative and qualitative data, as well as economic evaluations, including cost-effectiveness and return on investment, guided by the Health in All Policies approach;

3.2.3. Identify and promote a set of cost-effective, evidence-based adaptation measures for the health sector, which are especially relevant in contexts of fiscal constraint, to guide prioritization and international funding at national and international levels, considering both efficiency and equity;

3.2.4. Promote the production and use of data in open and interoperable formats, with safeguards for privacy, data integrity, and data security, ensuring their reuse in different phases of the development and implementation of evidence-based policies.

3.3. Promoting Just Transition in Health Sector Adaptation:

3.3.1. Incorporate measures into the energy transition process to address the unequal health effects experienced by vulnerable populations. Where appropriate, sectoral policies supporting a just transition should integrate collateral health benefits, including those linked to equitable access to decent work, clean energy, and healthy environments, among others;

3.3.2. Enhance community involvement when assessing the potential health effects of energy transition projects on local populations, developing joint strategies to ensure that interventions are culturally appropriate, inclusive, and sustainable.

3.4. Enhancing the Resilience of Health Care Supply Chains:

3.4.1. Expand the material and technological base of the health care supply chain, creating regulatory and financial conditions to strengthen it while increasing purchasing power for strategic supplies, thus promoting local, regional, diversified, reliable, and sustainable production;

3.4.2. Promote sustainable supply chains, prioritizing short, economical, and resilient infrastructures, supporting local and regional industries, while promoting research on sustainable manufacturing, packaging, product design, and logistics to ensure equitable production and reduce the health care sector's carbon footprint;

3.4.3. Integrate digital technologies, information systems, online health services, and telehealth tools as structural components for continuity of care, real-time surveillance, and climate risk management, promoting the inclusion of remote and vulnerable populations and universal digital access;

3.4.4. Integrate climate data into demand forecasting and health supply chain planning and establish regional platforms for essential health products to strengthen information sharing, foster regulatory harmonization, and enable rapid and coordinated responses.

3.5. Strengthening Strategic Stockpiles and Equitable Access to Essential Health Products:

3.5.1. Promote innovation in the development and adaptation of health care products, including advances in thermal stability, long-lasting technologies, and resilient supplies and equipment that remain effective without specialized conservation infrastructure, as well as strategies to reduce required doses and extend the shelf life of medical countermeasures;

3.5.2. Establish strategically located regional stockpiles, conduct simulation exercises in border areas, and strengthen international cooperation and solidarity among countries in times of crisis;

3.5.3. Maintain and monitor stockpiles of essential health products, including vaccines, diagnostics, and medicines adapted to climate-adapted health systems, services, and programs, prioritizing areas of greater vulnerability;

3.5.4. Develop public mechanisms and climate-adapted care models to promote availability and equitable access to essential health products, particularly in remote and hard-to-reach areas and among vulnerable populations.

Reporting and Coordination Mechanisms

BHAP reporting, monitoring, and follow-up will be performed through voluntary reports to the WHO by the Endorsing Parties during upcoming UNFCCC climate change conferences, thereby strengthening continuity, accountability, and institutional coherence in climate and health actions.

This process will be based on health-related indicators developed within the framework of the United Arab Emirates-Belém Work Programme, and Endorsing Parties will be encouraged to monitor and report their progress in line with these indicators. Through regular and voluntary reports to the WHO, national updates can be integrated into the organization's broader climate adaptation and health monitoring.

As mentioned above, by COP33 (2028), all Endorsing Parties will be invited to report their progress toward implementing the actions set out in BHAP, in line with the Global Goal on Adaptation (GGA) indicators and any other appropriate national

indicators, and through the Global Stocktake they will be invited to report their progress toward implementing the actions set out in BHAP, in line with GGA indicators and any other appropriate national indicators as well as other relevant UNFCCC mechanisms. This will promote greater transparency, comparability, and alignment with global climate frameworks.

Social Participation and Transparency

To conduct public online consultations for updates to metrics, indicators, and technical guidelines, as the Endorsing Parties deem appropriate.

References

1. International Institute for Sustainable Development - IISD. The Paris Agreement: Built to last. Available from: https://www.iisd.org/articles/insight/paris-agreement-built-last?gad_source=1&gad_campaignid=22208053183&gbraid=0AAAAADQ3eTB0WwDSKV-h7BFVEs0JxdP-3&gclid=CjwKCAiA24XJBhBXEiwAXEIO30o1NB4UNy8jeOnDHTiTqDc3j8uloMbSnDtcuhGOx5J6pf92AVnrshoC-cEQAvD_BwE. Accessed on: Nov 2025.
2. Brasil. Ministério da Saúde/SUS. Saúde COP 30 – The Belém health action plan for the adaptation of the health sector to climate change. Available from: <https://cdn.who.int/media/docs/default-source/climate-change/en---belem-action-plan.pdf>. Accessed on: Nov 2025.
3. UNFCCC. Decision 2/CMA.5: Global Goal on Adaptation. 2023. Available from: <https://unfccc.int/documents/637073>. Accessed on: Oct 2025.
4. United Nations Framework Convention on Climate Change (UNFCCC). Decision 1/CMA.5. Outcome of the first global stocktake. FCCC/PA/CMA/2023/16/Add.1. Dubai: UNFCCC, 2023. Available from: https://unfccc.int/sites/default/files/resource/1_CMA.5.pdf. Accessed on: Nov 2025.

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Sleep and immunity: a vital connection for human health

Sono e imunidade: uma conexão vital para a saúde humana

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ABSTRACT

This literature review examines the relationship between sleep, immunity, and allergic diseases, emphasizing the impacts of sleep deprivation across different age groups and its clinical implications. The search included original articles, narrative and systematic reviews, and meta-analyses published between 2005 and 2024, retrieved from databases such as PubMed, SciELO, Bireme, and Google Scholar. Inclusion criteria comprised studies addressing the effects of sleep on the immune system and allergic diseases. This review was conducted in light of the timeliness and relevance of the topic. The findings indicate that chronic sleep deprivation negatively affects immunity by increasing pro-inflammatory markers, such as C-reactive protein and interleukin-6, and impairing immune responses. Studies highlight that circadian cycles regulate immune functions, with innate immunity predominating during daytime and adaptive immunity being more active at night. Sleeping fewer than 7 hours per night has been associated with a range of health problems, including cardiovascular, respiratory, cognitive, gastrointestinal, immunological, dermatological, and musculoskeletal disorders, as well as obesity, kidney disease, reproductive disorders, and increased stress. Atopic dermatitis, allergic rhinitis, and asthma affect sleep quality, with sleep disruption correlating with disease severity. In conclusion, sleep plays a crucial role in immune regulation, underscoring the need for clinical interventions that prioritize sleep quality and circadian rhythm alignment to promote balanced immune health and reduce the risk of chronic diseases.

Keywords: Sleep, immunity, health.

RESUMO

A revisão literária apresentada aborda a relação entre sono, imunidade e doenças alérgicas, enfatizando os impactos da privação de sono em diferentes faixas etárias e suas implicações clínicas. A pesquisa incluiu artigos originais, revisões narrativas e sistemáticas, e metanálises publicadas entre 2005 e 2024, encontrados em bases como PubMed, SciELO, Bireme e Google Scholar. Os critérios de inclusão englobaram estudos sobre os efeitos do sono no sistema imunológico e nas doenças alérgicas. Essa revisão foi feita dada a atualidade e importância do tema. Os resultados indicam que a privação crônica de sono afeta negativamente a imunidade, aumentando marcadores pró-inflamatórios, como proteína C-reativa e interleucina-6, e prejudicando a resposta imunológica. Estudos destacam que ciclos circadianos regulam funções imunológicas, sendo que a imunidade inata predomina durante o dia, enquanto a adaptativa é mais ativa à noite. Dormir menos de sete horas por noite tem sido associado a uma série de problemas de saúde, como doenças cardiovasculares, respiratórias, cognitivas, gastrointestinais, imunológicas, dermatológicas, musculoesqueléticas, obesidade, doenças renais, distúrbios reprodutivos e aumento do estresse. A dermatite atópica, rinite alérgica e asma afetam a qualidade do sono, com interrupções relacionadas à gravidade das doenças. Conclui-se que o sono desempenha um papel essencial na regulação imunológica, evidenciando a necessidade de intervenções clínicas que valorizem a qualidade do sono e o alinhamento dos ritmos circadianos, com o objetivo de promover uma saúde imunológica equilibrada e minimizar o risco de doenças crônicas.

Descritores: Sono, imunidade, saúde.

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Introduction

Sleep is widely recognized as an essential physiological requirement for survival, and a vast body of scientific evidence underscores its importance for overall health. In recent years, experimental research on sleep restriction has focused on a key question: how much sleep do individuals need to preserve their health? Chronic sleep restriction, often caused by medical conditions such as allergies and sleep disorders, as well as occupational demands, social and domestic responsibilities, and lifestyle patterns, has become an increasing concern. In modern societies, there is an alarming trend toward shorter sleep duration, with many individuals sleeping below the recommended ranges for optimal health. Epidemiological and laboratory studies have demonstrated the harmful effects of sleep deprivation on multiple aspects of health, and several systematic reviews have shown that short sleep duration is associated with important health outcomes, including not only mortality but also hypertension, cardiovascular disease, stroke, diabetes mellitus, and obesity.¹

The link between sleep and immunity goes both ways. Activation of the immune system alters sleep, which in turn influences both innate and adaptive immune responses. Stimulation of the immune system by microbial challenges triggers an inflammatory response that, depending on its magnitude and duration, may induce increased sleep duration and intensity, but may also disrupt sleep. Enhancement of sleep during an infection is assumed to feedback to the immune system to promote host defense. Indeed, sleep affects various immune parameters, is associated with a reduced infection risk, and can improve infection outcome and vaccination responses. The induction of a hormonal constellation that supports immune functions is one likely mechanism underlying the immune-supporting effects of sleep. In the absence of an infectious challenge, sleep appears to promote inflammatory homeostasis through effects on several inflammatory mediators, such as cytokines. This notion is supported by findings that prolonged sleep deficiency (eg, short sleep duration, sleep disturbance) can lead to chronic, systemic low-grade inflammation.²

Although the assumption that sleep plays an important role in immune functions has existed for a long time, the systematic investigation of the interactions between sleep and the immune system is a relatively new research area. Therefore,

several questions remain open for future studies to provide a deeper understanding. The mechanisms underlying these complex interactions are still not well understood. It is likely that multiple factors act in concert to mediate the influence of sleep on the immune system and vice versa. Importantly, studies in humans relating sleep-induced alterations in immune parameters, such as changes in immune cell numbers, to actual infection risk and outcome remain limited. The causal involvement of sleep-related immune changes in the development or progression of chronic inflammatory or infectious diseases still requires further investigation. In clinical settings, it is essential to monitor sleep during conditions of acute and chronic immune activation and to assess the effects of specific immunomodulatory therapies. These approaches may contribute to a more comprehensive understanding of the relationship between sleep and immunity, enabling the development of more effective strategies to mitigate the impact of sleep deprivation on immune health.²

Charles Dickens (1812–1870), one of the most celebrated writers in English literature, reflected on the importance of sleep in his novel *Barnaby Rudge* (1841), describing it as “sleep, heaven’s gift to all its creatures.”³

This study aimed to review the relationship between sleep, immunity, and allergic diseases, as well as to address the comorbidities associated with sleep deprivation.

Methods

The aim of this literature review was to examine the relationship between sleep, the immune system, allergies, and diseases associated with sleep deprivation. Scientific articles published in English were identified through searches conducted in the PubMed, SciELO, BIREME, and Google Scholar databases.

Original articles, narrative reviews, systematic reviews, and meta-analyses were included in order to provide a comprehensive and up-to-date analysis of the subject. The search strategy used combinations of the following descriptors and free-text terms: sleep and immunity, sleep and sleep deprivation, sleep and inflammation, sleep deprivation and immunity, sleep and immune response, sleep and allergies, sleep disorders and allergic diseases.

Inclusion criteria comprised studies that directly addressed the association between sleep and the

topics of immunity, inflammation, or allergic diseases, according to the search terms used. In an effort to broaden the scope of the review and capture the diversity of approaches available in the scientific literature, no specific exclusion criteria were applied.

Results

According to Schoenborn and Adams,⁴ sleep duration has declined substantially over time. Early in the 20th century, adults slept, on average, about 9 hours per night. By the 1980s, this average had decreased to 7 hours, and by 2010, approximately 30% of adults reported sleeping fewer than 7 hours per night.⁴ Currently, sleep deprivation is widely recognized as a public health problem, and its prevalence is estimated to range from 9% to 24%, making it one of the leading reasons for consultation in sleep clinics.^{5,6}

The National Institutes of Health (NIH), the leading health research agency in the United States, recommends that preschool children sleep an average of 10 to 12 hours per day, school-age children and adolescents approximately 9 hours per day, and adults between 7 and 8 hours per day.⁷

With the increasing dissemination of screen time among children, several studies have investigated the impact of this behavior on pediatric sleep, highlighting the need to counsel patients' parents. One such example is the study by Qiu-Ye Lan et al., which analyzed 2,903 preschoolers to investigate the relationship of screen time and use of different electronic media devices with sleep duration. The results showed that 40% of the children did not achieve the recommended sleep duration for their age group, and that portable electronic device use was associated with reduced sleep duration, with each additional hour of use corresponding to a reduction of 11 minutes of daily sleep in boys and 6 minutes in girls.⁸

Definition, importance, and stages of sleep

Sleep is an active physiological state that is essential for life, characterized by reversible unconsciousness, during which the brain becomes less responsive to external stimuli. Occupying approximately one-third of human existence, sleep plays a key role in maintaining physical, mental, and emotional health. During sleep, the body undergoes a series of changes that are essential for biological and physiological functioning, such as the regulation

of blood pressure, heart rate, hormone secretion, immune functions, cellular repair, body temperature control, and the restoration of memory and cognitive abilities.⁹

Sleep needs and patterns are influenced by a complex interaction of factors, including age, developmental stage, genetic predispositions, individual behaviors, and environmental and social aspects.⁹

In humans, sleep is traditionally divided into 2 main phases: Rapid Eye Movement (REM) sleep and non-REM sleep. Non-REM sleep is subdivided into 4 stages: stages 1 and 2, and stages 3 and 4, the latter collectively known as delta sleep. Throughout the night, sleep follows alternating cycles between non-REM and REM phases, with an approximate duration of 90 minutes per cycle. During the first half of the night, delta sleep predominates, whereas the second half is characterized by more frequent episodes of REM sleep. Each phase performs specific functions. For example, growth hormone is released predominantly during delta sleep, while hypothalamic-pituitary-adrenal axis activity is reduced. These cyclical oscillations and associated physiological events are essential for maintaining homeostasis.⁹

Sleep is also fundamental for immune balance. According to Irwin,¹⁰ sleep contributes to the modulation of inflammation and the adaptive immune response. Sleep deprivation or poor sleep may lead to immune dysfunctions that increase the risk of chronic diseases, such as hypertension, diabetes, and cardiovascular diseases. In addition, Grandner and Drummond¹¹ emphasize that insufficient sleep is associated with risk behaviors, such as unhealthy food choices and lower adherence to healthy practices, intensifying the negative impacts on overall health.

In the cognitive and emotional context, Walker¹² highlights that sleep promotes memory consolidation, emotional regulation, and information processing, and is crucial for learning and psychological well-being. Sleep disruption may result in significant cognitive deficits and increased susceptibility to mood disorders, such as anxiety and depression.¹²

Therefore, sleep is much more than a period of rest; it is an active state of physiological and neurological recovery that sustains mental and body balance. Understanding its importance and adopting healthy sleep habits are key strategies for promoting quality of life and preventing disease, establishing sleep as a cornerstone of human health.⁹

Sleep deprivation and related comorbidities

Chronic sleep deprivation is a complex problem influenced by various medical and behavioral factors that affect both sleep quality and duration. In addition to disorders such as obstructive sleep apnea and insomnia, aspects of modern society such as long working hours, excessive smartphone use, and unhealthy eating habits play an important role in this scenario. Sleep deprivation may be classified as *acute*, when there is a temporary reduction in sleep time, usually lasting 1 or 2 days, with waking time extending beyond the typical 16 to 18 hours, or *chronic*, characterized by excessive daytime sleepiness caused by routinely sleeping less than enough for at least 3 months.¹³

Sleeping fewer than 7 hours per night has been associated with a range of health problems, including cardiovascular, respiratory, cognitive, gastrointestinal, immunological, dermatological, and musculoskeletal diseases, as well as obesity, kidney disease, reproductive disorders, and increased stress.¹⁴

Itani et al.¹ conducted the first systematic review to investigate the association between short sleep duration and multiple major health outcomes. A distinguishing feature of the study was the use of a standardized methodology for meta-analyses, including dose-response analyses through meta-regression. The authors found that individuals with short sleep duration likely have higher mortality compared with those with normal sleep duration, with a relative risk (RR) of approximately 1.12, ie, an absolute increase of approximately 12%. For other outcomes, individuals with short sleep duration showed an estimated absolute increase of 37% for diabetes mellitus, 17% for hypertension, 16% for cardiovascular disease, 26% for coronary artery disease, and 38% for obesity. Regarding depression and dyslipidemia, there is no sufficient evidence from meta-analyses to conclude whether short sleep duration is associated with an increased incidence of these outcomes. The results reported by the authors were similar to those of previous systematic reviews, such as an RR of 1.12 for mortality and 1.23 for hypertension. Subgroup analyses in the study also showed that short sleep defined as a duration less than 6 hours was associated with a significant increase in mortality, diabetes, cardiovascular disease, and obesity. In the meta-regression analysis, shorter duration of sleep definition was linearly associated with increased mortality. A significant association in the opposite direction was observed for obesity, and no significant linear

association was observed for the other outcomes; however, the authors were unable to conclude whether the association existed or not due to the small number of studies included for each outcome. They also emphasized that, although the study confirmed that short sleep duration is associated with increased rates for major health outcomes, the mechanisms do not appear to be straightforward. Previous studies cited in the review showed that sleep deprivation reduces energy expenditure in healthy men, induces a state of insulin resistance in human adipocytes, and results in inadequate pancreatic insulin secretion and increased plasma glucose concentrations after a meal. Thus, chronic sleep restriction may lead to outcomes related to metabolic systems. In addition, short sleep duration has been associated with increased ghrelin and decreased leptin levels, which tend to increase appetite, possibly explaining the rise in obesity and diabetes mellitus. Alterations in these hormones, hyperactivity of the sympathetic nervous system, and changes in circadian rhythm may also play an important role in the development of hypertension. Cardiovascular diseases may be caused by complex combinations of these metabolic and circulatory abnormalities. Although these endocrine and cardiovascular diseases are adjusted for in statistical models in most studies investigating mortality, such conditions may have developed or worsened over time among participants, contributing to subsequent deaths. Despite the apparently compelling findings, the authors cautioned against overinterpreting the implications of the results for the general community. First, although short sleep duration is associated with increased mortality and other health outcomes, there is no rigorous evidence that increasing sleep duration reduces the frequency of these outcomes. They reported that they do not intend to recommend the use of hypnotics for individuals who sleep fewer than 6 hours per night and that, regarding psychoeducation, psychotherapy, and psychosocial interventions, many studies have focused on insomnia and on the effectiveness of these interventions for improving sleep quality, as reported in recent systematic reviews. Based on their observations, there is no evidence to recommend these interventions to the community with the goal of reducing mortality and other health outcomes.¹

Population-based studies reveal a growing prevalence of individuals sleeping fewer than 6 hours per night, a problem that affects not only adults but also children and adolescents. A notable example is the

study conducted by Kocevskaja et al.,¹⁵ who assessed 1,081,734 individuals and found that a quarter of all adults and half of all adolescents sleep less than the recommended duration for adequate health.

Sleep and immunity

The interactions between sleep and the immune system can be observed in everyday life. Sleep duration increases during infection as part of the body's physiological response to promote recovery from viral illness. Adequate sleep is essential for strengthening immunity and overall health. The body's daily needs are modulated by time perception, a fundamental aspect of how biological mechanisms work. To meet these needs, various cycles regulate hormones (as in the neuroendocrine system), temperature, and the sleep-wake cycle, as observed in circadian rhythms. When these biological cycles are disrupted, health problems may arise. Disruption of the sleep-wake cycle, for example, is a potential risk factor for metabolic diseases such as diabetes, cancer, and cardiovascular abnormalities.¹⁶

During sleep, the withdrawal of afferent stimuli results in the functional activation of specific brain regions. Sleep, therefore, is not a simple process; it modulates memory consolidation, mood, concentration, and temperature, in addition to influencing immune response. Thus, lack of sleep affects immunity, increasing the likelihood of contracting an illness. Field studies indicate changes in sleep patterns due to chronic activation of the immune system.²

In immune processes, maintaining sleep cycle patterns and the circadian rhythm plays a key role. The circadian rhythm is essential for the two-way communication between the immune system and the central nervous system through shared signals (such as neurotransmitters, hormones, and cytokines) and through direct interventions of the autonomic nervous system. Many immune functions operate in tandem with the 24-hour circadian rhythm and sleep, underscoring the relationship between the sleep-wake cycle and the immune system. Effector cells of the innate immune system, such as cytotoxic NK cells and effector cytotoxic T lymphocytes, are more active during the wake phase of the circadian rhythm, allowing an immediate response to pathogens or other antigens. This also favors faster repair of damaged tissue during the waking cycle. Adaptive immunity, in turn, is generally more active at night, when less differentiated cells, such as naive T cells and

memory T cells, reach peak activity. During nocturnal sleep, especially in the slow-wave phase, the anti-inflammatory action of cortisol and catecholamines is minimized. In contrast, nocturnal sleep promotes growth hormone (GH) and prolactin release. The endocrine environment at sleep onset favors increased production of IL-12 and enhances the interaction between antigen-presenting cells and T cells. The cytokine balance shifts toward Th1 cytokines, with increased proliferation of Th1 cells. This environment also facilitates the migration of naive T cells to lymph nodes. Thus, the endocrine environment supports durable immune memory responses during the early phases of sleep, favoring the formation of long-lasting immunological memory. Chronic sleep deprivation leads to stress, promoting the release of persistent, nonspecific pro-inflammatory substances, resulting in chronic low-grade inflammation that impairs immune function and harms health. Although the exact relationship between the activation of adaptive and innate immunity and the circadian rhythm is not yet fully understood, innate immunity is known to be more active during the day, while adaptive immunity predominates at night. Understanding the precise mechanisms underlying the interaction among the immune system, the endocrine system, and the central nervous system is essential for developing more effective therapies that take the circadian rhythm into account.¹

Sleep deprivation has been associated with increases in both pro-inflammatory and anti-inflammatory markers. Elevated inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been observed in sleep disorders and sleep deprivation. The decrease in mature neutrophil levels observed in sleep deprivation suggests the need to further investigate the relationship between sleep deprivation and susceptibility to infection. Sleep deprivation has been associated with the induction of cellular inflammation in young adults, whereas in older adults it results in decreased toll-like receptor 4 expression, contributing to the development of infectious diseases. In addition, increased interaction of autoantibodies has been linked to the development of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. In animal models, it has been observed that mice subjected to prolonged sleep deprivation continued to exhibit signs of neuroinflammation, apoptosis, and microglial activation even 3 months after recovery. There is substantial evidence in the literature documenting the

effects of chronic sleep deprivation on inflammatory cells; however, data on the effects of fragmented sleep on acute inflammation remain limited.¹⁴ Dumaine and Ashley¹⁷ studied the effects of varying durations of intermittent or fragmented sleep on levels of pro-inflammatory cytokines (IL-1 β , TNF- α), anti-inflammatory cytokines (TGF- β 1), and corticosterone in mice. The study concluded that 24 hours of sleep fragmentation caused a significant increase in peripheral pro-inflammatory cytokine and stress hormone levels. Ironically, the study also reported that sleep fragmentation induced the production of anti-inflammatory cytokines in the brain.¹⁷

The discovery of muramyl peptide, a bacterial cell wall component that activates the immune system and regulates sleep, established a direct connection between immunity and sleep. Other factors, such as cytokines (IL-1, TNF- α), prostaglandins, and lipopolysaccharides, influence sleep, particularly non-REM sleep. Moderate doses of these substances increase non-REM sleep, whereas high doses inhibit it. Anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13, reduce non-REM sleep. These substances signal the brain through humoral, neural, and cellular pathways, interacting with neurotransmitters, neuropeptides, melatonin, and the hypothalamic-pituitary-adrenal axis. In the central nervous system, cytokines regulate functions such as neurogenesis, plasticity, and complex behaviors, including sleep and memory. Sleep is also an adaptive response that promotes recovery during infection and inflammation by optimizing energy allocation to the immune system.¹³

Table 1 summarizes key findings regarding sleep, sleep deprivation, and immunity. Table 2 presents the effects of sleep on various immune parameters. The left column shows the acute effects of sleep, defined as the impact of one night of adequate sleep (in duration and quality) compared with one night of total or partial sleep deprivation. This approach seeks to understand the active role of sleep in immune regulation. The right column shows the effects of prolonged sleep loss—ie, the impact of several consecutive nights of total or partial sleep deprivation—allowing an assessment of the cumulative consequences of sleep restriction on immune parameters. The table provides a broad overview of findings from different studies and indicates how frequently each result has been replicated. A visual icon system represents the number of studies supporting each finding. It should be noted that the studies included in the review have

diverse methodologies, which is not reflected in the simplicity of the graphical representation. Most samples were collected during the day (after a night of normal sleep or sleep deprivation), rather than at night, which may generate apparently contradictory results between parameters measured at different times. For this reason, some findings should be interpreted with caution.

Sleep and allergic diseases

Shorter sleep duration or poor sleep quality is associated with decreased antibody production and increased generation of inflammatory cytokines, which has implications for the pathophysiology of allergic diseases such as atopic dermatitis (AD), allergic rhinitis (AR), and asthma.^{2,18-21}

Several epidemiological studies have found a correlation between sleep and allergic diseases. Results from the National Health and Nutrition Examination Survey (NHANES), a research program conducted in the United States by the Centers for Disease Control and Prevention (CDC), specifically by the National Center for Health Statistics (NCHS), showed that sleep impairment due to obstructive sleep apnea was associated with higher odds of hay fever and eczema, while a sleep duration of 6 hours or less was correlated with higher odds of allergic sensitization.²²

Studies specifically focusing on sleep and AD-related outcomes have consistently found a significant association between AD and sleep quality, but not with sleep duration.²³⁻²⁵ Interestingly, although increased AD severity was also significantly associated with more sleep interruptions, individuals with mild or inactive AD had a higher likelihood of sleep disturbance.²³ Moreover, sleep interruptions in individuals with AD in remission were not accompanied by episodes of nocturnal itching.²⁶

Investigations on AR and sleep have shown that increased upper airway resistance and nasal discharge, both characteristic symptoms of AR, cause microarousals during sleep.²⁷ Furthermore, increased upper airway resistance associated with AR has been accompanied by obstructive sleep apnea and sleep-related respiratory disorders, which also negatively impact sleep quality.^{28,29} On the other hand, a recent systematic review found that sleep duration was not significantly associated with AR, whereas sleep quality, sleep disturbance, and sleep latency scores

Table 1

Summary of key findings on the relationship between sleep, sleep deprivation, and immunity

- Sleep is essential for immune health, and adequate sleep duration and quality improve infection outcomes and reduce infectious disease risk.
- Chronic sleep deficiency disturbs immune homeostasis, thereby increasing the risk of diseases in which immune dysregulation is common, such as cardiovascular, metabolic, autoimmune, and neurodegenerative diseases.
- Maintenance of sleep and the circadian rhythm is crucial for two-way communication between the immune system and the central nervous system, mediated by neurotransmitters, hormones, cytokines, and the autonomic nervous system.
- During the circadian rhythm, effector cells of the innate immune system, such as NK cells and cytotoxic T lymphocytes, are more active during wakefulness, favoring rapid responses to pathogens and the repair of damaged tissue.
- Adaptive immunity is more active at night, with naive and memory T cells reaching peak activity.
- At the onset of sleep, the endocrine environment favors IL-12 production and the interaction between antigen-presenting cells and T cells, increasing Th1 cell proliferation and facilitating the migration of naive T cells to lymph nodes, thereby promoting immunological memory.
- Chronic sleep deprivation induces stress and the release of pro-inflammatory substances, resulting in low-grade chronic inflammation and impaired immune function.
- Inflammatory markers such as CRP and IL-6 are elevated in sleep disorders and sleep deprivation.
- Sleep deprivation induces cellular inflammation in young adults and, in older individuals, reduces toll-like receptor 4 expression, favoring the development of infectious diseases.
- Cytokines such as IL-1 and TNF- α influence non-REM sleep, with moderate doses increasing sleep, whereas high doses inhibit it. Anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 reduce non-REM sleep.

Adapted from Besedovsky L et al.².

were higher among patients with AR; sleep efficiency, however, was lower in these patients.³⁰

Inadequate sleep patterns have been identified as risk factors for asthma.³¹ Although asthma has been associated with poor sleep quality, this probably results from asthma symptoms affecting sleep or from comorbid AR causing AR-related sleep disturbances in individuals with asthma.^{32,33}

Despite evidence suggesting that sleep influences the risk of allergic diseases, the consensus that allergic diseases may disrupt sleep and that sleep disturbances can be used as indicators of allergic disease severity introduces an element of uncertainty regarding the directionality of this relationship.³⁴

Indeed, higher prevalence and greater severity of sleep disturbances have been associated with increased AD severity, as determined by the SCORing Atopic Dermatitis (SCORAD) index.³⁵ In AR, Allergic Rhinitis and its Impact on Asthma (ARIA) classifies moderate-to-severe AR as that which negatively affects any aspect of quality of life, including sleep disturbances.³⁶ In addition, systematically reviewed evidence indicates that AR is associated with decreased sleep duration and quality, sleep disturbances, and daytime dysfunction resulting from impaired sleep.³⁰ Finally, nocturnal awakenings due to asthma are essential for assessing disease severity, control, and remission.³⁷⁻⁴¹

Conclusion

Sleep plays an essential role in maintaining immune function, and sleep deprivation is associated with a significantly increased risk of chronic diseases. Scientific evidence suggests that inadequate

sleep alters immune response, promoting chronic inflammation and impairing defense mechanisms. Understanding the molecular mechanisms involved and identifying specific biomarkers are essential for the development of effective preventive interventions.

Table 2

Sleep effects on immune parameters. The number of icons represents the number of studies supporting the respective finding (3 icons = 3 studies; 2 icons = 2–3 studies; 1 icon = 1 study)

Immune parameter	Acute effect of sleep	Effect of prolonged wakefulness
Leukocyte numbers in blood		
White cells	↓↓↓ = = =	↑↑↑ =
Lymphocytes	↓↓ = = = ↑ (evening after normal sleep)	↑ = = =
Monocytes	↓↓↓ = = = ↑ (evening after normal sleep)	↑↑↑ = =
T cells, CD4 T cells, CD8 T cells	↓↓↓ = = = ↑↑ (mainly evening after sleep)	= = =
B cells	↓ = = =	↑ = =
NK cells	↓↓↓ = = ↑↑↑	↑↓
NK cells	↓↓↓ = = = ↑	↑↑↑ =
Basophils and eosinophils	= = =	= =
Cytokines and cytokine receptors		
IL-6 (plasma/saliva levels)	↓↓ = = = ↑↑	↑↑↑ = = =
TNF (plasma levels)	↓↓ = = = ↑ (daytime after normal sleep)	↑↑↑ = = =
IL-1 (plasma levels)	↓↓ =	= = ↑↑
IL-2 (plasma levels)	=	= =
IL-12 (intracellular production)	↓↑↑	
IL-4, IL-10 (plasma levels)	=	= = =
Antibodies, complement and other immune parameters		
Total IgG, IgM, or IgA antibody levels	↓↓ = = ↑	↓ = = = ↑↑
Complement	↓ = = ↑	= = ↑
Adhesion molecules	↓↓ = =	
Inflammatory gene expression		↑↑
Atividade e proliferação de células imunológicas		
Immune cell activity and proliferation		
NK-cell activity	= ↑↑	↑ = ↓
Lymphocyte proliferation	= = ↑↑	↑ = = ↓
Neutrophil function	↓ = = ↑	= =
Natural regulatory T cell function (nTreg)	↑	

Adapted from Besedovsky L et al.²

(↑) increase, (↓) decrease, (=) no change.

Thus, promoting healthy sleep, together with healthy lifestyle habits, is fundamental not only for optimizing immune response but also for preventing the adverse effects of sleep deprivation. These strategies may substantially contribute to improvements in both public and individual health, providing a solid foundation for disease prevention and the promotion of general well-being.

References

- Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. *Sleep Med.* 2017;32:246-56.
- Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. *Physiol Rev.* 2019;99(3):1325-80.
- Dickens C. Barnaby Rudge. London: Chapman and Hall; 1841.
- Schoenborn CA, Adams PE. Health behaviors of adults: United States, 2005-2007. *Vital Health Stat* 10. 2010 Mar;(245):1-132.
- Kolla BP, He JP, Mansukhani MP, Frye MA, Merikangas K. Excessive sleepiness and associated symptoms in the U.S. adult population: prevalence, correlates, and comorbidity. *Sleep Health.* 2020 Feb;6(1):79-87. doi: 10.1016/j.sleh.2019.09.004.
- Ng TP, Tan WC. Prevalence and determinants of excessive daytime sleepiness in an Asian multi-ethnic population. *Sleep Med.* 2005;6:523-9.
- Luyster FS, Strollo PJ Jr, Zee PC, Walsh JK; Boards of Directors of the American Academy of Sleep Medicine and the Sleep Research Society. Sleep: a health imperative. *Sleep.* 2012 Jun 1;35(6):727-34. doi: 10.5665/sleep.1846.
- Lan QY, Chan KC, Yu KN, Chan NY, Wing YK, Li AM, et al. Sleep duration in preschool children and impact of screen time. *Sleep Med.* 2020;76:48-54.
- Palma BD, Tiba PA, Machado RB, Tufik S, Suchecki D. Immune outcomes of sleep disorders: the hypothalamic-pituitary-adrenal axis as a modulatory factor. *Rev Bras Psiquiatr.* 2007;29(Suppl 1):S33-8.
- Irwin MR. Why Sleep Is Important for Health: A Psychoneuroimmunology Perspective. *Annual Review of Psychology.* 2015;66(1):143-72.
- Grandner MA, Drummond SPA. Who are the long sleepers? Towards an understanding of the mortality relationship. *Sleep Medicine Reviews.* 2007 Oct;11(5):341-60.
- Walker MP. The role of sleep in cognition and emotion. *Ann N Y Acad Sci.* 2009 Mar;1156:168-97. doi: 10.1111/j.1749-6632.2009.04416.x.
- Garbarino S, Lanteri P, Bragazzi NL, Magnavita N, Scoditti E. Role of sleep deprivation in immune-related disease risk and outcomes. *Commun Biol.* 2021 Nov 18;4(1):1304. doi: 10.1038/s42003-021-02825-4.
- Liew SC, Aung T. Sleep deprivation and its association with diseases – a review. *Sleep Med.* 2021;77:192-204. doi: 10.1016/j.sleep.2020.07.048.
- Kocevska D, Lysen TS, Dotinga A, Koopman-Verhoeff ME, Luijk MP, Antypa N, et al. Sleep characteristics across the lifespan in 1.1 million people from the Netherlands, United Kingdom and United States: a systematic review and meta-analysis. *Nat Hum Behav.* 2021;5(1):113-22. doi: 10.1038/s41562-020-00965-x.
- Farhud D, Aryan Z. Circadian rhythm, lifestyle and health: a narrative review. *Iran J Public Health.* 2018;47(8):1068-76.
- Dumaine JE, Ashley NT. Acute sleep fragmentation induces tissue-specific changes in cytokine gene expression and increases serum corticosterone concentration. *Am J Physiol Regul Integr Comp Physiol.* 2015;308(12):R1062-9.
- Singh KK, Ghosh S, Bhola A, Verma P, Amist AD, Sharma H, et al. Sleep and immune system crosstalk: implications for inflammatory homeostasis and disease pathogenesis. *Ann Neurosci.* 2024;31:1-11.
- Baranwal N, Yu PK, Siegel NS. Sleep physiology, pathophysiology, and sleep hygiene. *Prog Cardiovasc Dis.* 2023;77:59-69.
- Paganelli R, Petrarca C, Di Gioacchino M. Biological clocks: their relevance to immune-allergic diseases. *Clin Mol Allergy.* 2018;16(1):1.
- Nakao A. Circadian regulation of the biology of allergic disease: clock disruption can promote allergy. *Front Immunol.* 2020;11:1237.
- Xi Y, Deng YQ, Chen SM, Kong YG, Xu Y, Li F, et al. Allergy-related outcomes and sleep-related disorders in adults: a cross-sectional study based on NHANES 2005-2006. *Allergy Asthma Clin Immunol.* 2022;18(1):27.
- Fishbein AB, Mueller K, Kruse L, Boor P, Sheldon S, Zee P, et al. Sleep disturbance in children with moderate/severe atopic dermatitis: a case-control study. *J Am Acad Dermatol.* 2018;78(2):336-41.
- Ramirez FD, Chen S, Langan SM, Prather AA, McCulloch CE, Kidd SA, et al. Association of atopic dermatitis with sleep quality in children. *JAMA Pediatr.* 2019;173(5):e190025.
- Camfferman D, Kennedy JD, Gold M, Simpson C, Lushington K. Sleep and neurocognitive functioning in children with eczema. *Int J Psychophysiol.* 2013;89(2):265-72.
- Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med.* 1999;153(3):249-53.
- Lavie P, Gertner R, Zomer J, Podoshin L. Breathing disorders in sleep associated with "microarousals" in patients with allergic rhinitis. *Acta Otolaryngol.* 1981;92(5-6):529-33.
- McNicholas WT, Tarlo S, Cole P, Zamel N, Rutherford R, Griffin D, et al. Obstructive apneas during sleep in patients with seasonal allergic rhinitis. *Am Rev Respir Dis.* 1982;126(4):625-8.
- Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol.* 1997;99(2):757-62.
- Liu J, Zhang X, Zhao Y, Wang Y. The association between allergic rhinitis and sleep: a systematic review and meta-analysis of observational studies. *PLoS One.* 2020;15(2):e0228533.
- Xiang B, Hu M, Yu H, Zhang Y, Wang Q, Xue F. Highlighting the importance of healthy sleep patterns in the risk of adult asthma under the combined effects of genetic susceptibility: a large-scale prospective cohort study of 455,405 participants. *BMJ Open Respir Res.* 2023;10(1):e001535.
- Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktaş H. Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. *Respir Med.* 2005;99(5):529-34.
- Cukic V, Lovre V, Dragisic D. Sleep disorders in patients with bronchial asthma. *Mater Sociomed.* 2011;23(4):235-7.
- Koinis-Mitchell D, Craig T, Esteban CA, Klein RB. Sleep and allergic disease: a summary of the literature and future directions for research. *J Allergy Clin Immunol.* 2012;130(6):1275-8.
- Bawany F, Northcott CA, Beck LA, Pigeon WR. Sleep disturbances and atopic dermatitis: relationships, methods for assessment, and therapies. *J Allergy Clin Immunol Pract.* 2021;9(4):1488-500.
- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update. *Allergy.* 2008;63(Suppl 86):8-160.
- Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. *Eur Respir J.* 2008;32(3):545-54.
- Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009;180(1):59-99.

39. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020;145(3):757-65.
40. Global Initiative for Asthma. Global strategy for asthma management and prevention [Internet]. 2022. Available from: <https://ginasthma.org/>.
41. Ambrose Y, Lim JJ, Ng JY, Ying Y, Sio YY, Chew FT. Sleep and allergic diseases among young Chinese adults from the Singapore/Malaysia Cross-Sectional Genetic Epidemiology Study cohort. *J Physiol Anthropol*. 2024;43(1):1-10.

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Efficacy and safety of IL-6 inhibitors for polymyalgia rheumatica: a meta-analysis of randomized controlled trials

Eficácia e segurança dos inibidores de IL-6 para polimialgia reumática: uma metanálise de estudos clínicos randomizados

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ABSTRACT

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease, common in older adults, characterized by fatigue, morning stiffness, and pain in the neck, shoulders, and hip girdle. Its pathophysiology is believed to involve abnormal interleukin (IL)-6 activity. Although glucocorticoids are the standard treatment, frequent relapses and long-term adverse effects pose challenges. IL-6 inhibitors may offer an alternative, but their efficacy in isolated PMR, unlike in giant cell arteritis, remains unclear. The present review sought to evaluate the efficacy and safety of IL-6 inhibitors (tocilizumab, sarilumab) combined with glucocorticoids versus glucocorticoids alone in PMR. A systematic review was conducted in the PubMed, Embase, and Cochrane databases to identify randomized controlled trials (RCTs). The primary outcome was the SF-36 Physical Component Score. Secondary outcomes included adverse events, treatment discontinuation, and evaluator global assessment via visual analogue scale (VAS). Analyses were performed in R 4.3.1, with odds ratios (OR) for binary and mean differences (MD) for continuous outcomes, all with 95% confidence intervals (CI). Heterogeneity was assessed using I^2 . Four RCTs ($n=358$; IL-6 inhibitors=188; placebo=170) were included. IL-6 inhibitors significantly improved SF-36 scores (MD 4.75; CI 0.67 to 8.83; $p=0.02$). No significant differences were found in adverse events (OR 1.69; $p=0.16$), discontinuation rates (OR

RESUMO

A polimialgia reumática (PMR) é uma doença reumática inflamatória comum em idosos, caracterizada por fadiga, rigidez matinal e dor em região cervical, cintura escapular e pélvica. Sua fisiopatologia parece envolver atividade anormal da interleucina-6 (IL-6). Embora os glicocorticoides sejam o tratamento padrão, recaídas frequentes e efeitos adversos em longo prazo representam desafios. Inibidores de IL-6 podem oferecer uma alternativa, mas sua eficácia em casos isolados de PMR, diferentemente da arterite de células gigantes, ainda é incerta. Este trabalho teve por objetivo avaliar a eficácia e segurança dos inibidores de IL-6 (tocilizumabe, sarilumabe) associados a glicocorticoides, em comparação ao uso isolado de glicocorticoides na PMR. Realizou-se uma revisão sistemática nas bases PubMed, Embase e Cochrane para identificar ensaios clínicos randomizados (ECRs). O desfecho primário foi o escore físico do SF-36. Desfechos secundários incluíram taxa de eventos adversos, descontinuação do tratamento e avaliação global do investigador por escala visual analógica (EVA). As análises foram realizadas no R 4.3.1, utilizando razão de chances (OR) para desfechos binários e diferença média (DM) para contínuos, com intervalos de confiança (IC) de 95%. A heterogeneidade foi avaliada com estatística I^2 . Foram incluídos quatro ECRs ($n = 358$; IL-6i = 188; placebo = 170). Os inibidores de IL-6 melhoraram significativamente o escore físico do SF-36 (DM 4,75; IC 0,67-8,83;

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0.80; $p=0.723$), or VAS scores (MD -6.51; CI -12.92 to -0.09). IL-6 inhibitors improved physical function without increasing adverse events, supporting their potential use as adjunctive therapy in PMR.

Keywords: Polymyalgia rheumatica, immunology, drug therapy.

$p = 0,02$). Não houve diferenças significativas nos eventos adversos (OR 1,69; $p = 0,16$), descontinuações (OR 0,80; $p = 0,723$) ou EVA (DM -6,51; IC -12,92 a -0,09). Os inibidores de IL-6 melhoraram a função física sem aumento nos eventos adversos, sugerindo seu potencial como terapia adjuvante na PMR.

Descritores: Polimialgia reumática, imunologia, tratamento farmacológico.

Introduction

Polymyalgia rheumatica (PMR) is a rheumatic disorder of inflammatory origin, characterized by pain and stiffness in the neck, shoulders, and hips. It is the second most common inflammatory systemic rheumatic disease after rheumatoid arthritis (RA).¹ Evidence suggests a genetic susceptibility to PMR, with shared genetic risk factors such as the HLA-DRB1*01 and HLA-DRB1*04 alleles.^{2,3} PMR also shares pathophysiological mechanisms with other systemic inflammatory disorders, including elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6).^{4,5}

The mainstay of PMR management is long-term glucocorticoid (GC) therapy, with a mean duration of 1.8 years of therapy in PMR.⁶ The starting daily prednisone equivalent dose is recommended to range between 12.5 and 25 mg; the minimum effective dose should be used.⁷ The response to GCs in PMR is usually rapid and the GC tapering regimen should be individualized. Despite the striking initial response to GCs in most cases, disease relapses are common, and the burden of long-term GC therapy has an impact on the development of comorbidities in patients with PMR.⁸ A systematic review and meta-analysis has shown that 77%, 51%, and 25% of PMR patients remain on GC therapy at 1, 2, and 5 years, respectively.⁹

Since the 1990s, IL-6 has been recognized as a key driver of inflammation in PMR.^{6,7} Elevated IL-6 levels are strongly associated with disease activity, underscoring its critical role in the pathogenesis of this condition. IL-6 inhibitors (IL6i), initially developed for the treatment of RA, block the interaction between IL-6 and its receptors and effectively suppress IL-6-mediated inflammation. Given the aforementioned central role of IL-6 in PMR pathophysiology, targeting this pathway holds promise for reducing disease activity.⁹⁻¹²

Within this context, we carried out a systematic literature review and meta-analysis to assess the efficacy and safety of IL6i compared with placebo in patients with PMR already receiving GC therapy.

Methods

This systematic review and meta-analysis followed the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.^{13,14} This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in December 2024 (ID CRD42024629302).¹⁵

Outcomes of interest and eligibility criteria

The primary outcome was disease remission. The secondary efficacy outcome was cumulative GC dose. Secondary safety outcomes included (i) overall adverse event rate, (ii) occurrence of neutropenia, and (iii) occurrence of infections (Table 1). Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: randomized controlled trials (RCT), inclusion of patients with an established clinical diagnosis of PMR, and comparison of adjunctive IL6i therapy with placebo. Studies without a control group that did not report at least one outcome of interest were also excluded. No language restrictions were applied. Abstracts, editorials, letters to the editor, reviews, systematic reviews, and meta-analyses were excluded from the sample.

Search strategy and data extraction

we systematically searched PubMed, Embase, and the Cochrane Library in November 2024 using the following search strategy: ("IL-6 inhibitors" OR Tocilizumab OR Sarilumab OR Satralizumab OR Siltuximab) AND ("Polymyalgia rheumatica" OR PMR

OR “Giant Cell arteritis” OR GCA). We also conducted a hand search of references from the included studies, previous systematic reviews, and meta-analyses for

additional studies that might warrant inclusion. Our search strategy encompassed studies on giant cell arteritis (GCA) due to the significant clinical overlap

Table 1

Details of the included randomized controlled trials

Study and Type of Infection	Intervention (n)	Control (n)
Bonelli- Common cold	6	4
Bonelli- Conjunctivitis	3	0
Bonelli- Respiratory Infection	2	1
Bonelli- Abscess/suppurative focus teeth	1	1
Bonelli- Fever blister	1	0
Bonelli- Erysipela	1	0
Spiera- Opportunistic infections	2	2
Spiera- Bacterial cystitis	1	0
Spiera- Intervertebral discitis	1	0
Spiera- COVID-19	0	1
Spiera- Erysipela	0	1
Spiera- Bacterial Urinary tract infection	1	0
Spiera- Pneumonia	1	0
Devauchelle-Pensec- Abscess limb	1	0
Devauchelle-Pensec- Bronchitis	5	4
Devauchelle-Pensec- Conjunctivitis	1	0
Devauchelle-Pensec- Cystitis Klebsiella	1	0
Devauchelle-Pensec- Gastroenteritis	3	0
Devauchelle-Pensec- Herpes	6	2
Devauchelle-Pensec- Dermatophytosis of nails	0	1
Devauchelle-Pensec- Fungal infection	0	4
Devauchelle-Pensec- Hordeolum	0	1
Devauchelle-Pensec- Laryngitis	0	1
Devauchelle-Pensec- Site of injection abscess	1	0
Devauchelle-Pensec- Influenza	0	1
Devauchelle-Pensec- Nasopharyngitis	1	3
Devauchelle-Pensec- Pharyngitis	1	0
Devauchelle-Pensec- Pyelonephritis	0	1
Devauchelle-Pensec- Rhinitis	2	2
Devauchelle-Pensec- Sinusitis	3	1
Devauchelle-Pensec- Tonsillitis	1	0
Devauchelle-Pensec- Abscess/suppurative focus teeth	2	1
Devauchelle-Pensec- Teeth infection	2	1
Devauchelle-Pensec- Tracheitis	1	1
Devauchelle-Pensec- Urinary tract infection	0	4
Devauchelle-Pensec- Viral infection	2	0
Devauchelle-Pensec- Bacterial wound infection	1	1

between PMR and GCA, as well as to the inclusion of individuals with symptoms of both conditions in some trials, which were later excluded.

Two authors (O.C.M. and B.A.A.H.M.) independently conducted the search, imported the results into Zotero software (version 6.0.26),¹⁶ and performed study screening. In cases of disagreement, a third author (M.M.S.) adjudicated. Data extraction was also performed independently by the same two authors. When the included studies did not report means and standard deviations, these values were estimated from the reported medians and ranges based on Luo et al. and Wan et al.^{17,18}

Risk of bias and evidence quality assessment

Risk of bias assessment was performed by two independent authors (B.A. A. H. M. and M. L. R. D.), using the second version of the Cochrane Risk of Bias Assessment Tool (RoB 2).¹⁹ Five domains were evaluated for each outcome of the selected studies: (1) bias in the randomization process, (2) bias due to deviations from the intended interventions, (3) bias due to missing data, (4) bias in outcome measurement, and (5) bias in the selection of the reported results.

The overall risk-of-bias assessment for each trial outcome was based on individual domain judgments, with any disagreements resolved through consensus after a critical debate on the reasons for unconformity.

Statistical analysis

The risk ratio (RR) was used to compare the treatment effects for dichotomous endpoints, whereas the mean difference (MD) with 95% confidence intervals (95% CI) was used for continuous outcomes. Statistical significance was accepted at p -values < 0.05 . We assessed heterogeneity using the I^2 statistic and Cochran's Q test; a p -value < 0.10 or $I^2 > 25\%$ were regarded as significant for heterogeneity. Sensitivity analyses were conducted using a leave-one-out plot in the presence of significant heterogeneity ($I^2 > 25\%$). DerSimonian and Laird random effects models were used for all outcomes. R software version 4.3.2 was used for statistical analysis.²⁰

Results

Study selection and characteristics

The initial search yielded 2079 results, as shown in Figure 1. After removing duplicate records and

ineligible studies, 31 remained and were reviewed in full. Of these, 3 RCTs with 254 patients (128 on IL6i vs. 126 on placebo) were included. Initially, the search strategy also included GCA, as both PMR and GCA are related conditions and a substantial proportion of PMR patients present with subclinical GCA or progress to overt GCA after some time of disease.²¹

Tocilizumab and sarilumab were administered to 136 and 118 participants, respectively. The dose regimen and route of administration differed between trials for the former: one RCT evaluated tocilizumab given intravenously at a monthly dose of 8 mg/kg, whereas the other RCT assessed tocilizumab given via the subcutaneous route at a dose of 162 mg weekly. Details of the included RCTs are shown in Table 2.

The mean age of the patients was 69 years at baseline, and 168 (66%) were women. The total treatment duration also differed between the RCTs, ranging from 24 weeks in both RCTs assessing tocilizumab to 52 weeks in the RCT evaluating sarilumab.

Pooled analysis of all studies

Primary outcome

The definition of disease remission in PMR remains heterogeneous across studies, reflecting the ongoing challenge of establishing standardized outcome measures. Devauchelle-Pensec et al.²² defined remission based on inflammatory markers, specifically a C-Reactive Protein Polymyalgia Rheumatica Activity Score (CRP-PMR-AS) below 1.5. In contrast, Bonelli et al.²³ adopted a strictly clinical approach, defining remission as the absence of shoulder and/or hip girdle stiffness attributable to active PMR as determined by a blinded investigator. Although CRP levels were measured at each visit, Bonelli's criteria excluded inflammatory markers from remission assessments, instead relying on clinical parameters such as patient and assessor global scores, patient pain score, morning stiffness (all assessed via 100 mm visual analog scales [VAS]), 'Elevation of the Upper Limb Score' (a semiquantitative scale), the Health Assessment Questionnaire Disability Index (HAQ), and the Short Form-36 (SF-36). Spiera et al.²⁴ integrated both clinical and laboratory findings, defining remission as the resolution of PMR symptoms accompanied by CRP normalization (<10 mg/L). Recognizing these discrepancies, an international Delphi survey was conducted among PMR experts

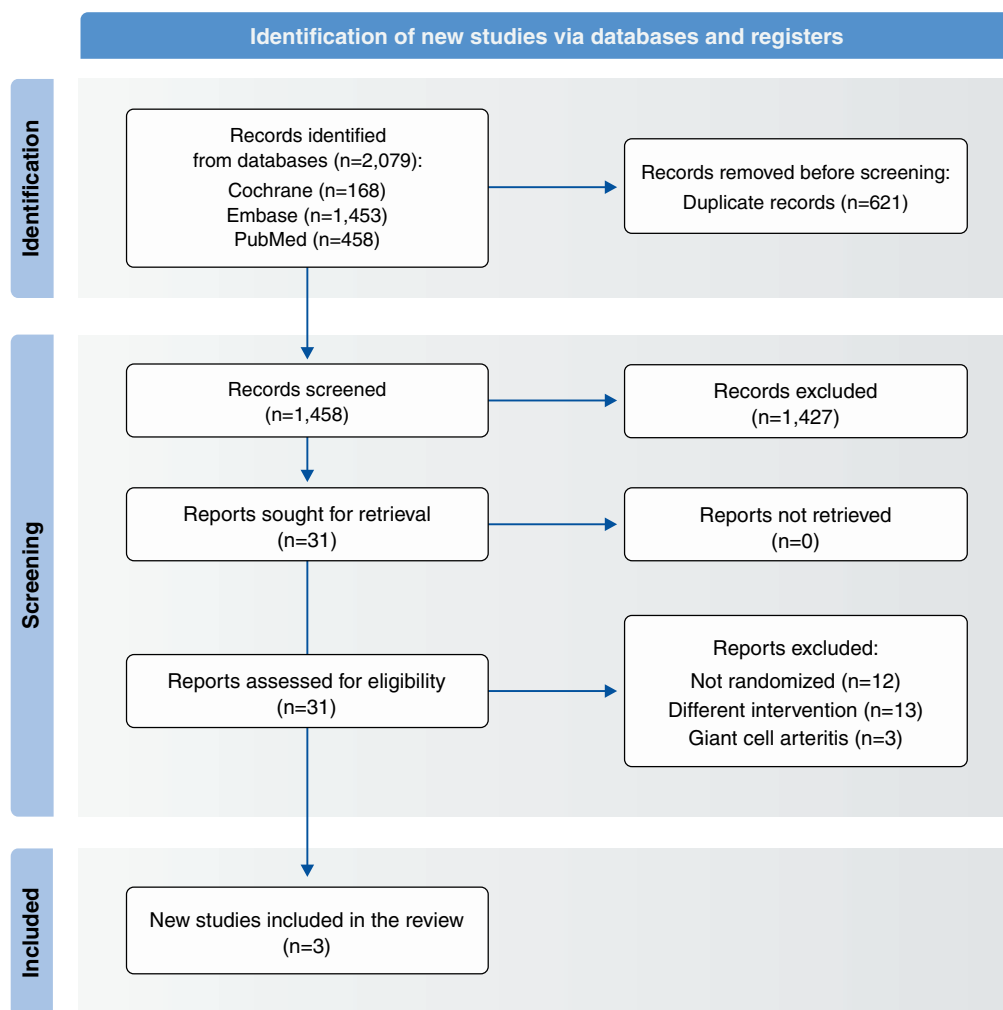


Figure 1
PRISMA flow diagram of study selection

Table 2
Baseline characteristics of included studies

Study	IL6i	IL6i Dose	Groups	Sample size	Age, years ^a	Female, n (%)	Total treatment time (weeks)
Devauhelle-Pensec et al., 2022	Tocilizumab	8 mg/kg every 4 weeks	IL6i + GC	49	68	34 (69.4)	24 weeks
			Placebo + GC	51	67	33 (64.7)	
Spiera et al., 2023	Sarilumab	200 mg every other week	IL6i + GC	60	69	45 (75)	52 weeks
			Placebo + GC	58	70	37 (64)	
Bonelli et al., 2021	Tocilizumab	162 mg weekly	IL6i + GC	19	68.8	10 (52.6)	24 weeks
			Placebo + GC	17	71.1	9 (52.9)	

^a: Mean or median.

IL6i: IL-6 inhibitors; GC: Glucocorticoid; NA: Not available.

to establish consensus criteria for remission and disease flare and highlighted a key limitation of CRP and ESR: up to 20% of PMR patients exhibit normal inflammatory markers at diagnosis, underscoring the critical role of clinical assessment in defining true disease remission.²⁵⁻²⁸

In the RCTs included in this review disease remission was significantly higher in the 52-week IL6i group than in the placebo group (RR: 2.81; 95% CI: 1.52–5.20; $p < 0.01$; $I^2 = 0\%$) (Figure 2). In the subgroup analyzed at 24 weeks, disease remission was also significantly higher in the IL6i group (RR: 2.96; 95% CI: 1.03–8.55; $p = 0.04$; $I^2 = 30.2\%$) (Figure 3). No individual study influenced the overall results regarding induction of disease remission (Figure 4).

Secondary efficacy outcome

The cumulative GC dose for the 52-week treatment group (ie, sarilumab vs. placebo RCTs) showed no statistically significant difference between groups

(MD: -741.19 mg; 95% CI: -1562 to -80.28; $p = 0.08$; $I^2 = 98.3\%$) (Figure 5). In the 24-week subgroup (ie, both RCTs assessing tocilizumab vs. placebo), the cumulative GC dose was significantly lower in the IL6i group (MD: -374.65 mg; 95% CI: -736.47 to -12.82; $p = 0.04$; $I^2 = 81.4\%$) (Figure 6). Leave-one-out analysis showed that Spiera et al.²⁴ contributed the most to heterogeneity in these outcomes (Figure 7).

Secondary safety outcomes

There was no significant difference in the overall adverse event rate between all IL6i groups and placebo (RR: 1.17; 95% CI: 0.89; 1.54; $p = 0.26$; $I^2 = 72.7\%$) (Figure 8C), nor in the rate of infections (RR: 1.32; 95% CI: 0.91–1.93; $p = 0.15$; $I^2 = 0$; Figure 8A). However, the incidence of neutropenia was significantly higher in the IL6i group than in the placebo group (RR: 14.56; 95% CI: 1.95–108.80; $p < 0.01$; $I^2 = 0\%$) (Figure 8B). Leave-one-out analysis revealed that, again, Spiera et al.²⁴ contributed the most to heterogeneity in the overall adverse event rate (Figure 9).

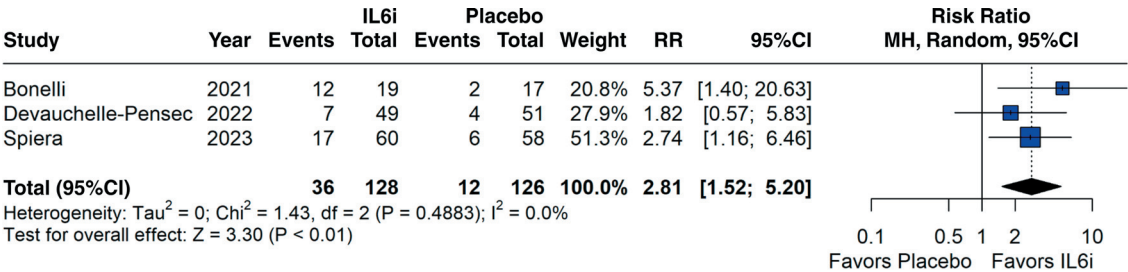


Figure 2
Disease remission was significantly more frequent in the IL6i group

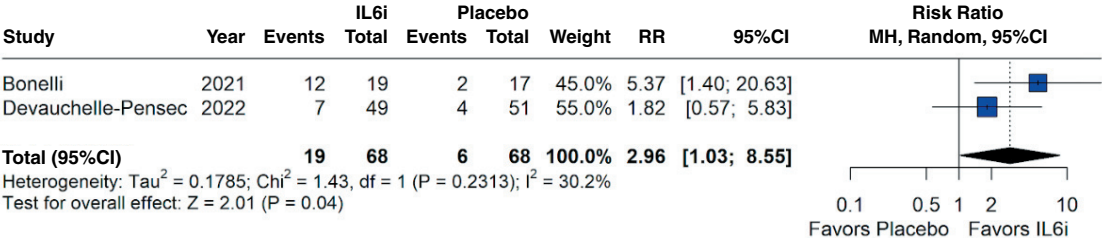
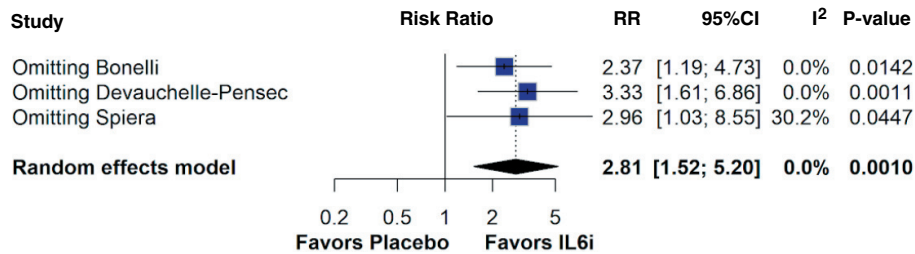
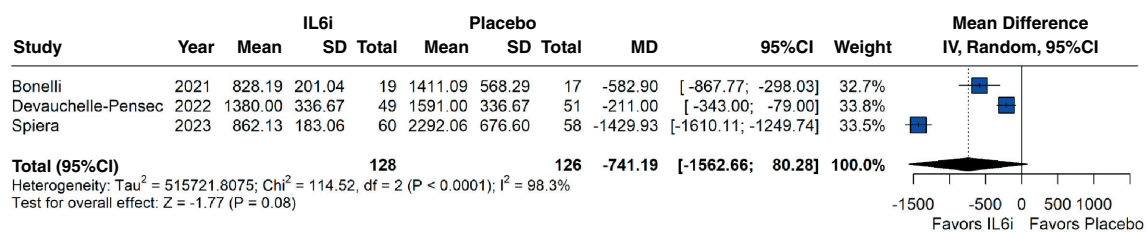


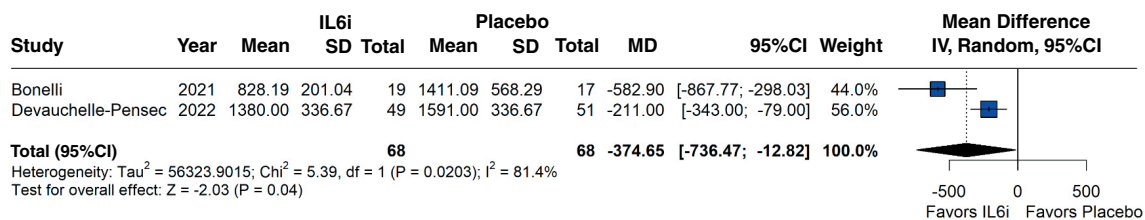
Figure 3
Disease remission was significantly more frequent with IL6i in the 24-week subgroup

**Figure 4**

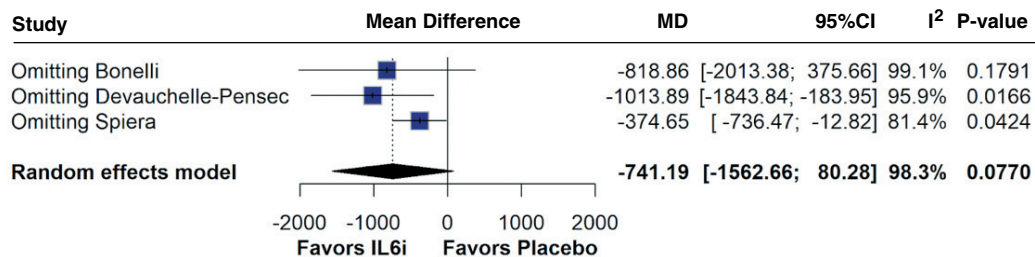
Leave-one-out plot of disease remission

**Figure 5**

The cumulative glucocorticoid dose was significantly lower in the IL6i group

**Figure 6**

The cumulative glucocorticoid dose was not significantly different in the 24-week subgroup

**Figure 7**

Leave-one-out plot of cumulative glucocorticoid dose

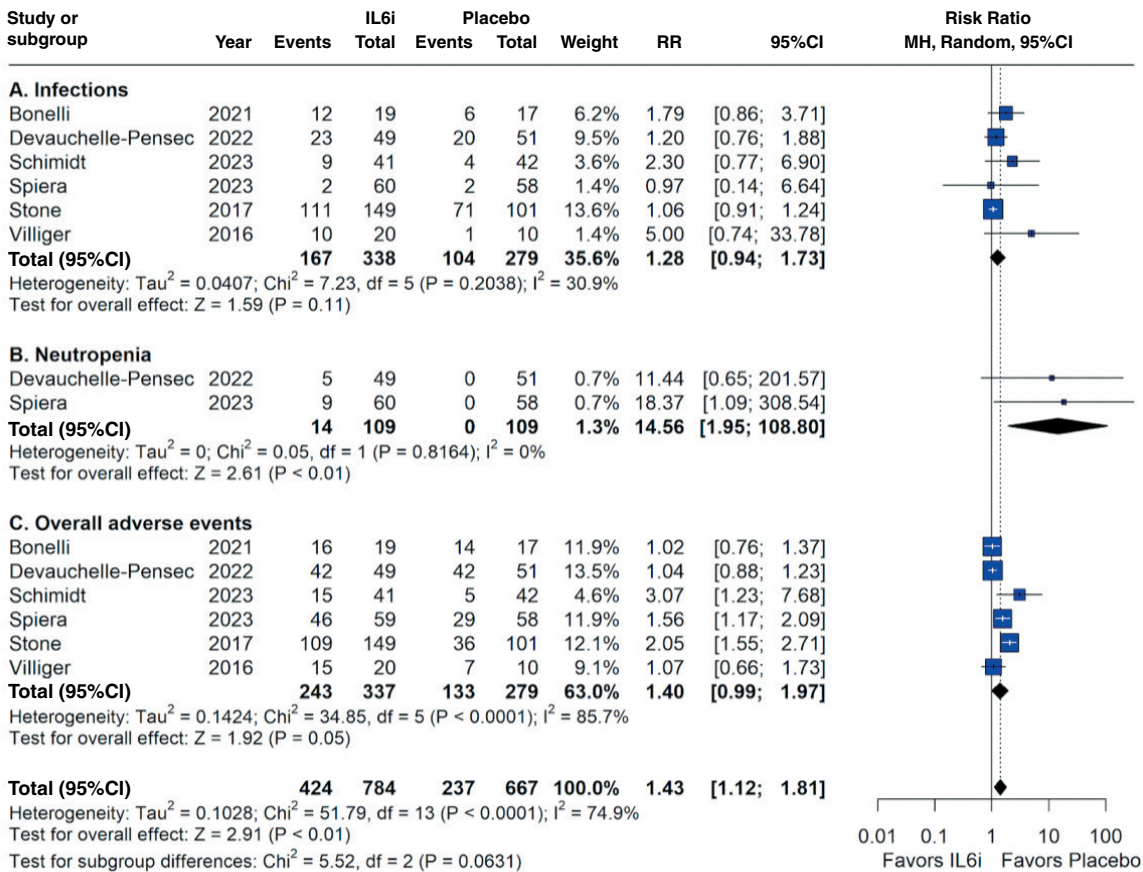


Figure 8
No significant between-group differences were found in infections (A) or overall adverse events (B); however, neutropenia (C) was significantly higher in the IL6i group compared with placebo

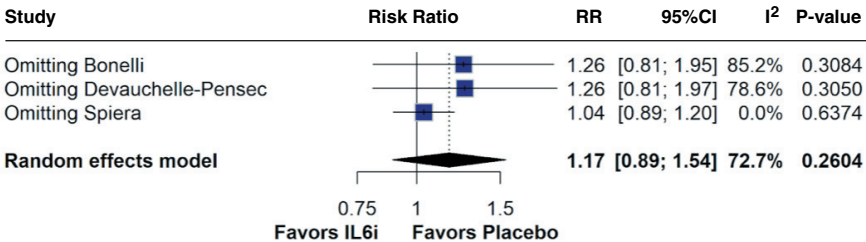


Figure 9
Leave-one-out plot of overall adverse events

Quality assessment

Figure 10 shows the quality assessment of each RCT included in this meta-analysis. All 3 RCTs were classified as having a low risk of bias.

Discussion

In this systematic review and meta-analysis of 3 RCTs²²⁻²⁴ encompassing 254 patients, we conducted a comparative analysis of the efficacy of adjunctive use of IL6i as a steroid-sparing strategy in patients with PMR. The main findings were as follows: (1) IL6i therapy was associated with a higher disease remission rate, (2) the use of IL6i was associated with a reduced cumulative GC dose at 24 weeks, and (3) there was no difference in overall adverse events between IL6i and placebo; however, the incidence of neutropenia was higher in patients receiving IL6i therapy.

A recent meta-analysis conducted by Floris et al.²⁹ demonstrated that GCs are effective in managing PMR, with a significant number of patients achieving remission. However, long-term therapy is necessary and relapse rates remain substantial, making the wide-ranging side-effect profile that comes with long-term GC exposure a concern.

Oral GCs are a well-proven therapy that is widely used for autoimmune and rheumatic diseases; however, the optimal initial dose and tapering regimens are unknown.³⁰ The European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) recommendations advocate the use of the minimum effective daily dose, ranging from 12.5 to 25 mg of prednisone, as initial treatment.

GCs inhibit B and T cells and phagocytes, thereby affecting the innate and adaptive immune systems through genomic and nongenomic mechanisms. Their use is associated with various side effects (including cumulative dose-related effects), such as weight gain, dyspepsia, osteoporosis, hyperglycemia, cardiovascular diseases, and infections.³¹

In a previously published meta-analysis evaluating the relationship between long-term GC therapy and relapse rates in individuals with PMR, a relapse rate of 40% was observed in the first year, with rates increasing to 67% over a 6-year follow-up period. This contributes to prolonged GC use and increased exposure to the severe side effects associated with such treatment in these patients.^{29,32}

The EULAR/ACR recommendations for PMR treatment suggest methotrexate be added to GCs for patients with a high risk of relapse, those under prolonged GC therapy, or those at high risk of developing adverse effects to GCs.^{31,33}

Although IL-6 inhibition represents the use of a biologic therapy in a predominantly older PMR population, its clinical appeal lies in its glucocorticoid-sparing effect. IL-6 inhibitors are associated with a higher incidence of neutropenia, although there is no clear evidence that they increase the rate of infection.

A prospective study by Lally proved IL6i to be safe, effective, and well tolerated for patients newly diagnosed with PMR, with a significant steroid-sparing effect.³⁴ Another retrospective study suggested that IL6i were safer and more effective than other biologic disease-modifying antirheumatic drugs (bDMARDs) in reducing GC exposure in PMR.^{35,36}

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Bonelli et al., 2021						
Devauhelle-Pensec et al., 2022						
Spiera et al., 2023						

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
 **Low**

Figure 10

The Cochrane collaboration's tool for assessing the risk of bias in randomized trials (RoB 2)

Our meta-analysis is subject to limitations, including the small number of published RCTs and the relatively modest sample sizes of these studies. Additionally, substantial heterogeneity was observed in outcomes related to cumulative GC doses and overall adverse events, likely due to variations in study design and treatment protocols. These findings emphasize the need for a harmonized, evidence-based definition that balances both clinical and biochemical parameters to improve disease monitoring and treatment outcomes in PMR.

Conclusion

IL6i can be safely added to steroid tapering regimens to increase the disease remission rate in patients with PMR under GC therapy.

References

- González-Gay MA, Matteson EL, Castañeda S. Polymyalgia rheumatica. *Lancet*. 2017 Oct 07;390(10103):1700-12.
- Carmona FD, Mackie SL, Martín JE, Taylor JC, Vaglio A, Eyre S, et al. A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility. *Am J Hum Genet*. 2015 Apr 2;96(4):565-80. doi: 10.1016/j.ajhg.2015.02.009.
- Liozon E, Ouattara B, Rhaïem K, Ly K, Bezanahary H, Loustaud V, et al. Familial aggregation in giant cell arteritis and polymyalgia rheumatica: a comprehensive literature review including 4 new families. *Clin Exp Rheumatol*. 2009 Jan-Feb;27(1 Suppl 52):S89-94.
- Salvarani C, Cantini F, Niccoli L, Macchioni P, Consonni D, Bajocchi G, et al. Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: a prospective follow-up study. *Arthritis Rheum*. 2005 Feb 15;53(1):33-8.
- Gazitt T, Zisman D, Gardner G. Polymyalgia Rheumatica: a Common Disease in Seniors. *Curr Rheumatol Rep*. 2020 Jun 19;22(8):40. doi: 10.1007/s11926-020-00919-2.
- Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al.; European League Against Rheumatism; American College of Rheumatology. 2015 recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Arthritis Rheumatol*. 2015 Oct;67(10):2569-80. doi: 10.1002/art.39333.
- Partington R, Muller S, Mallen CD, Abdul Sultan A, Helliwell T. Comorbidities in patients with polymyalgia rheumatica prior to and following diagnosis: A case control and cohort study. *Semin Arthritis Rheum*. 2020 Aug;50(4):663-72. doi: 10.1016/j.semarthrit.2020.05.003.
- Floris A, Piga M, Chessa E, Congia M, Erre GL, Angioni MM, et al. Long-term glucocorticoid treatment and high relapse rate remain unresolved issues in the real-life management of polymyalgia rheumatica: a systematic literature review and meta-analysis. *Clin Rheumatol*. 2022 Jan;41(1):19-31. doi: 10.1007/s10067-021-05819-z.
- Schwabe M, Allaire J. Interleukin-6 receptor inhibition with tocilizumab in rheumatoid arthritis: an evidence-based review of its place in therapy. *Core Evidence*. 2007;2(3):133-48.
- Tanaka T, Narazaki M, Kishimoto T. IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harbor Perspectives in Biology*. 2014;6(10):a016295.
- Mihara M, Kasutani K, Okazaki M, Nakamura A, Kawai S, Sugimoto, et al. Tocilizumab (a humanized anti-IL-6 receptor antibody) improved clinical symptoms, the disability index, and quality of life in patients with rheumatoid arthritis. *International Immunopharmacology*. 2005;5(12):1807-13.
- Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. *Nature Reviews Rheumatology*. 2020;16(6):335-45. doi: 10.1038/s41584-020-0419-z.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71.
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023. Available from: www.training.cochrane.org/handbook.
- PROSPERO: International Prospective Register of Systematic Reviews. University of York, Centre for Reviews and Dissemination. 2025. Available from: <https://www.crd.york.ac.uk/prospero/>.
- Takats S, Stillman D, Cheslack-Postava F, Bagdonas M, Jellinek A, Najdek T, et al. Zotero [software] Windows 10, versão 6.0.26. Corporation for Digital Scholarship; 2023. Available from: <https://www.zotero.org/>.
- D Luo, X Wan, J Liu, T Tong. Optimally estimating the sample mean from the sample size, median, mid-range and/or mid-quartile range. *Statistical Methods in Medical Research*. 2018;27:1785-805.
- X Wan, W Wang, J Liu, T Tong. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology*. 2014;14:135.
- Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing the risk of bias in randomized trials. *BMJ*. 2019;366:14898.
- R Core Team. R: A language and environment for statistical computing [software]. Vienna: R Foundation for Statistical Computing; 2012. Available from: <https://www.R-project.org/>.
- De Miguel E, Karalilova R, Macchioni P, Ponte C, Conticini E, Cowley S, et al. Subclinical giant cell arteritis increases the risk of relapse in polymyalgia rheumatica. *Ann Rheum Dis*. 2024 Feb 15;83(3):335-41. doi: 10.1136/ard-2023-224768.
- Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, Richez C, Truchetet ME, Wendling D, et al. Effect of tocilizumab on disease activity in patients with active polymyalgia rheumatica receiving glucocorticoid therapy: A randomized clinical trial. *JAMA*. 2022;328(11):1053-62. doi: 10.1001/jama.2022.15459.
- Bonelli M, Radner H, Kerschbaumer A, Mrak D, Durechova M, Stieger J, et al. Tocilizumab in patients with new onset polymyalgia rheumatica (PMR-SPARE): a phase 2/3 randomized controlled trial. *Ann Rheum Dis*. 2022 Jun;81(6):838-44. doi: 10.1136/annrheumdis-2021-221126.
- Spiera RF, Unizony S, Warrington KJ, Sloane J, Giannelou A, Nivens MC, et al.; SAPHYR Investigators. Sarilumab for Relapse of Polymyalgia Rheumatica during Glucocorticoid Taper. *N Engl J Med*. 2023 Oct 5;389(14):1263-72. doi: 10.1056/NEJMoa2303452.
- D'Agostino J, Souki A, Lohse A, Carvajal Alegria G, Dernis E, Richez C, et al. Concordance and agreement between different activity scores in polymyalgia rheumatica. *RMD Open*. 2024 Mar 15;10(1):e003741. doi: 10.1136/rmdopen-2023-003741.
- Dejaco C, Duftner C, Cimmino MA, Dasgupta B, Salvarani C, Crowson CS, et al.; International Work Group for PMR and GCA. Definition of remission and relapse in polymyalgia rheumatica: data from a literature search compared with a Delphi-based expert consensus. *Ann Rheum Dis*. 2011 Mar;70(3):447-53. doi: 10.1136/ard.2010.133850.

27. Leeb BF, Bird HA. A Disease Activity Score for Polymyalgia Rheumatica. *Annals of the Rheumatic Disease*. 2004;63(10):1279-83.
28. Brito-Zerón P, Acar-Denizli N, Bosch X, et al. Long-term glucocorticoid treatment and high relapse rate remain problematic in polymyalgia rheumatica. *Clin Rheumatol*. 2021;40(8):3333-3344. doi:10.1007/s10067-021-05819-z.
29. Floris A, Piga M, Chessa E, Congia M, Erre GL, Angioni MM, et al. Long-term glucocorticoid treatment and high relapse rate remain unresolved issues in the real-life management of polymyalgia rheumatica: a systematic literature review and meta-analysis. *Clin Rheumatol*. 2022 Jan;41(1):19-31. doi: 10.1007/s10067-021-05819-z.
30. Buttgeriet F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis. *JAMA*. 2016;315(22):2442. doi: 10.1001/jama.2016.5444
31. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al.; European League Against Rheumatism; American College of Rheumatology. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis*. 2015 Oct;74(10):1799-807. doi:10.1136/annrheumdis-2015-207492.
32. Gensler LS. Glucocorticoids: complications to anticipate and prevent. *Neurohospitalist*. 2013;3(2):92-7. doi: 10.1177/1941874412458678.
33. Caporali R, Cimmino MA, Ferraccioli G, Gerli R, Klersy C, Salvarani C, et al. Prednisone plus methotrexate for polymyalgia rheumatica. *Annals of Internal Medicine*. 2004;141(7):493. doi: 10.7326/0003-4819-141-7-200410050-00005.
34. Ferraccioli G, Salaffi F, De Vita S, Casatta L, Bartoli E. Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. *J Rheumatol*. 1996 Apr;23(4):624-8.
35. Lally L, Forbess L, Hatzis C, Spiera R. A prospective open-label phase IIa trial of tocilizumab in the treatment of polymyalgia rheumatica. *Arthritis Rheumatol*. 2016;68(10):2550-4. doi:10.1002/art.39740.
36. Ohkubo N, Miyazaki Y, Nakayamada S, Fukuyo S, Inoue Y, Satoh-Kanda Y, et al. Efficacy and Safety of Biologics in Polymyalgia Rheumatica: A Retrospective Study. *Rheumatol Ther*. 2024 Oct;11(5):1303-19. doi: 10.1007/s40744-024-00707-9.

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Ciguatera from fish consumption: a differential diagnosis of food allergy and an emerging alert for Brazilian coastal regions

Ciguatera por consumo de pescados: diagnóstico diferencial de alergia alimentar e alerta emergente para regiões costeiras brasileiras

Bruno Emanuel Carvalho Oliveira¹

ABSTRACT

Ciguatera is a foodborne intoxication caused by the ingestion of reef fish contaminated with ciguatoxins, potent lipophilic toxins produced by dinoflagellates of the genera *Gambierdiscus* and *Fukuyoa*. These toxins bioaccumulate along the food chain, reaching higher concentrations in large carnivorous fish. Ciguatoxins are thermostable, colorless, and tasteless, and are not degraded by freezing or human digestion, rendering them resistant to inactivation by cooking. Their structure favors binding to voltage-gated sodium channels, leading to sustained depolarization of cell membranes and explaining the gastrointestinal and neurological symptoms observed. Although endemic in tropical regions of the South Pacific and the Caribbean, ciguatera has emerged in new areas such as Brazil. Between 2022 and 2025, approximately 190 suspected cases were reported in Fernando de Noronha, in addition to cases described in Natal, Rio Grande do Norte, northeastern Brazil. Clinically, it presents with acute gastrointestinal symptoms followed by paresthesias, cold allodynia, temperature reversal, and persistent fatigue. Severe cases may progress to bradycardia, hypotension, and cardiac rhythm disturbances. Diagnosis is essentially clinical, based on recent consumption of reef fish and characteristic neurological signs. There is no specific antidote, and treatment is symptomatic. Given its similarity to food-related allergic reactions, particularly during the acute phase, ciguatera should be considered in the differential diagnosis of such conditions, especially in individuals living in or visiting coastal regions. Recognition of ciguatera as an emerging issue is crucial for epidemiological surveillance, early diagnosis, and appropriate clinical management.

Keywords: Ciguatera, fish, marine toxins.

RESUMO

A ciguatera é uma intoxicação alimentar causada pela ingestão de peixes recifais contaminados por ciguatoxinas, potentes toxinas lipofílicas produzidas por dinoflagelados dos gêneros *Gambierdiscus* e *Fukuyoa*. Essas toxinas se bioacumulam ao longo da cadeia trófica, atingindo maiores concentrações em peixes carnívoros de grande porte. A ciguatoxina é termoestável, incolor, insípida, não degradada por congelamento ou digestão humana, o que inviabiliza sua inativação por métodos culinários. Sua estrutura favorece a ligação a canais de sódio voltagem-dependentes, promovendo despolarização sustentada das membranas celulares e explicando os sintomas gastrointestinais e neurológicos observados. A doença é endêmica em regiões tropicais do Pacífico Sul e Caribe, mas tem emergido em novas áreas, como o Brasil. Entre 2022 e 2025, cerca de 190 casos suspeitos foram registrados em Fernando de Noronha, além de relatos em Natal (RN). Clinicamente, manifesta-se com sintomas gastrointestinais agudos seguidos de parestesias, alodinia ao frio, inversão térmica e fadiga persistente. Casos graves podem evoluir com bradicardia, hipotensão e distúrbios cardíacos. O diagnóstico é essencialmente clínico, baseado na ingestão recente de peixe recifal e sinais neurológicos característicos. Não há antídoto específico, e o tratamento é sintomático. Diante da semelhança com quadros alérgicos relacionados à ingestão de alimentos, especialmente nas manifestações agudas, a ciguatera deve ser considerada no diagnóstico diferencial dessas condições, sobretudo em populações que habitam ou frequentam regiões costeiras. Seu reconhecimento como problema emergente é crucial para a vigilância epidemiológica, o diagnóstico precoce e o manejo clínico adequado.

Descritores: Ciguatera, peixes, toxinas marinhas.

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Introduction

Ciguatera is a foodborne toxicological syndrome caused by the ingestion of tropical or subtropical marine fish contaminated with ciguatoxins, potent lipophilic toxins produced by dinoflagellates of the genera *Gambierdiscus* and *Fukuyoa*, especially *Gambierdiscus toxicus*.¹ These microalgae, which proliferate on substrates such as marine macrophytes, dead corals, and sandy sediments, are ingested by herbivorous (phytophagous) fish, in which the toxins accumulate.

Transmission of ciguatoxins occurs through the marine food chain: larger carnivorous fish that prey on herbivores become even more contaminated, exhibiting high concentrations of these toxins, which are not inactivated by freezing, cooking, or other preparation methods.² When consumed by humans, these contaminated fish may trigger a clinical condition known as ciguatera (Figure 1).

During this process, some toxin analogues may undergo structural modifications, resulting in different regional variants. In the Pacific, poisoning is primarily associated with 2 structural families of ciguatoxins:

analogues of Pacific-ciguatoxin-1 (P-CTX-1, also called CTX1B) and P-CTX3C (CTX3C).³ In the Atlantic and Indian Oceans, the predominant variants are Caribbean-CTX (C-CTX) and Indian Ocean-CTX (I-CTX).⁴

The risk increases significantly with the consumption of visceral tissues, where toxin concentrations are higher.⁵ Due to their high potency, even small amounts of ciguatoxins may cause clinical symptoms. The U.S. Food and Drug Administration (FDA) recommends a safety limit of 0.01 µg/kg of P-CTX-1 equivalents in fish flesh, whereas Japan adopts a less restrictive limit of 0.175 µg/kg.^{6,7}

Traditionally, ciguatera has been considered endemic in tropical areas of the South Pacific and the Caribbean, with increasing reports in the Indian Ocean as well.⁴ However, climate change, globalization of food supply chains, and increased health surveillance have contributed to the identification of cases in previously non-endemic regions, such as the Brazilian coast.² It is estimated that ciguatera accounts for 50,000 to 500,000 cases annually worldwide, although this is likely an underestimate due to underreporting

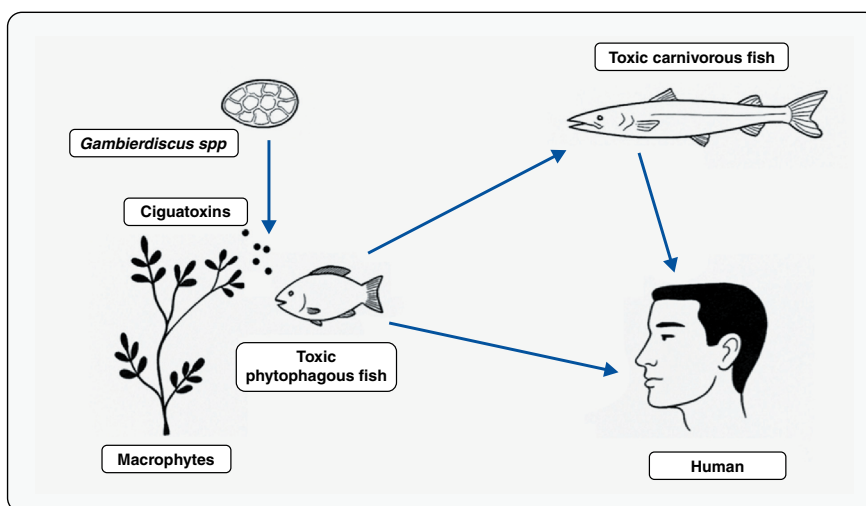


Figure 1

Schematic representation of the food chain involved in ciguatera poisoning. Epiphytic dinoflagellates of the genus *Gambierdiscus*, which colonize marine macrophytes, produce ciguatoxins—potent lipophilic and heat-stable toxins. These microalgae are ingested by herbivorous (phytophagous) fish, which accumulate the toxins in their tissues. As the food chain progresses, carnivorous fish that prey on herbivores become increasingly contaminated, exhibiting high concentrations of ciguatoxins. When consumed by humans, these contaminated fish may trigger a syndrome known as ciguatera

Adapted from Ubaldi et al.²

and limited familiarity of health care professionals with the clinical condition.¹ In this context, ciguatera represents a neglected yet emerging condition that requires greater attention from public health systems, particularly in tropical and subtropical coastal regions.

More than 400 species have been implicated in ciguatera, notably *Lutjanus spp.*, *Gymnothorax spp.*, *Epinephelus spp.*, *Balistes vetula*, *Sphyrna barracuda*, and *Seriola fasciata*, as well as invertebrates such as *Tridacna maxima*, *Octopus cyanea*, and *Tripneustes esculentus*. The disease is associated with the consumption of fish caught between latitudes 35° north and 36° south, although cases outside this geographic range have been reported, such as in the Canary Islands, Madeira, and the Azores in 2008. Experimental studies show that large fish, due to their greater capacity to bioaccumulate toxins, may remain hazardous for years.⁸

Methods

A narrative literature review with a descriptive and analytical approach was conducted on ciguatera fish poisoning, with emphasis on the epidemiological situation in Brazil. The literature search was conducted in May 2025 in the PubMed, SciELO, Web of Science, ScienceDirect, and Google Scholar databases, using the descriptors “ciguatera,” “ciguatoxin,” “fish poisoning,” “dinoflagellates,” “Gambierdiscus,” “Fukuyoa,” “ciguatoxina,” and “intoxicação alimentar por peixe recifal,” in Portuguese and English. Scientific articles, case reports, guidelines, and technical and public health documents published between 2000 and 2025 in Portuguese, English, French, and Spanish were included. Source selection and critical data analysis were performed by the author, prioritizing studies providing information on the pathophysiology, clinical manifestations, diagnosis, treatment, and epidemiological surveillance of ciguatera, focusing on cases reported in Brazil, especially in the Northeast and Southeast regions. Complementary information on recent outbreaks and control measures was obtained from technical reports issued by official bodies, such as the State Health Departments of Pernambuco and Rio Grande do Norte.

Discussion

Ciguatoxin

Ciguatoxin is a marine toxin with a highly complex chemical structure and remarkable stability, belonging

to the class of lipophilic polyethers.⁹ Its molecule consists of a sequence of linearly fused and rigid ether rings, generally totaling 13 to 14 units, with multiple chiral centers and functional groups such as hydroxyls and epoxides that modulate its biological activity¹⁰ (Figure 2). It is a colorless, tasteless, and odorless substance with high molecular weight and marked affinity for cellular membranes, facilitating its incorporation into the lipid bilayer of cells.¹¹

This structural configuration enables ciguatoxin to act effectively on voltage-gated sodium channels, promoting their prolonged opening and resulting in persistent membrane depolarization.¹² The effect is particularly intense in excitable cells, such as those of the nervous system, causing continuous sodium ion influx that leads to excitotoxicity and to the typical clinical manifestations of ciguatera, including paresthesias, thermosensory reversal, muscle weakness, and gastrointestinal disturbances.³

Different regional variants of ciguatoxin exist, such as CTX1B, predominant in the Pacific and considered one of the most potent, as well as Caribbean and Indian Ocean variants, which share the same structural core with subtle chemical modifications.¹³ Ciguatoxin is heat-stable and resistant to freezing and is not degraded by conventional food preparation processes or by human digestion.¹ Its structure was elucidated through advanced methods such as nuclear magnetic resonance and mass spectrometry, revealing an extremely potent toxin active at nanogram concentrations, making it one of the most toxic natural substances known to man.¹⁴

The pathophysiology of ciguatoxin involves multiple mechanisms affecting excitable cells, particularly through its action on membrane ion channels. Ciguatoxin is a potent sodium channel poison in mammals. The toxin causes sustained sodium channel activation and blocks potassium channels. These combined alterations lead to membrane depolarization and spontaneous, repetitive action potential firing. Increased sodium influx damages excitable cells, particularly the neurons and cardiac myocytes. Swelling of the axons, nerve terminals, and perisynaptic Schwann cells occurs in the neurons. In the cardiac myocytes, animal studies demonstrate that sodium channel-mediated ciguatoxin action influences cardiac contractility. Moderate ciguatoxin concentrations have indirect and direct positive inotropic actions, while high toxin levels produce negative inotropic effects. Ciguatoxin's activation of calcium as a secondary messenger contributes to the

cardiovascular, musculoskeletal, and gastrointestinal manifestations of the illness. Intracellular calcium increases due to inositol triphosphate-mediated stored calcium release, terminal calcium channel activation, and sodium-calcium exchanger stimulation. As a result, spontaneous and tetanic contractions occur in the heart, skeletal, and smooth muscles. Intestinal smooth muscle contraction disturbances lead to intestinal fluid stimulation and diarrhea without mucosal injury. The toxin also impairs synaptic vesicle recycling, exhausting neurotransmitter reserves. In addition, ciguatoxin causes pruritus owing to deranged low-frequency discharge in C-polymodal nociceptive fibers (cutaneous afferent unmyelinated fibers), which are not normally active in undamaged skin at normal physiological conditions. Cold allodynia or cold temperature inversion is due to increased nerve depolarization of type A δ and C5 fibers.

Epidemiological data on ciguatera in Brazil

In Brazil, the consumption of fish and seafood is a deeply rooted dietary habit, especially in coastal communities, where it represents not only a culinary preference but also a central element of local cultural identity and socioeconomic dynamics. This practice is supported by artisanal fishing activities and regional trade and is reflected in the everyday life of coastal populations. During specific periods of the religious calendar, such as Holy Week, there is a significant increase in demand for fish to replace red meat

in accordance with Catholic traditions historically widespread in the country. In the state of Rio Grande do Norte, where the population is predominantly concentrated in coastal areas, this consumption pattern contributes to continuous exposure to marine products, including species with potential risk for foodborne illnesses.

A literature review on foodborne illnesses associated with fish consumption in Brazil, covering the period from 2012 to 2022, identified that ciguatera poisoning accounted for 1.37% of reported cases. Although this percentage may appear modest, the authors underscore the scarcity of epidemiological data and limited communication regarding outbreaks, factors that hinder accurate estimation of the true magnitude of the problem and suggest a likely scenario of substantial underreporting.¹⁶

In recent years, however, ciguatera has emerged as a relevant issue in Brazil. According to a technical report issued by the Pernambuco State Department of Health, between 2022 and 2025 approximately 190 suspected cases were recorded in the Fernando de Noronha archipelago, affecting both residents and visitors, both in isolated episodes and outbreaks still under investigation. Initially, cases were attributed to the consumption of fish such as yellow jack and barracuda; more recently, however, reports have involved other species, including Atlantic horse mackerel, lane snapper, and mutton snapper, whose association with the toxin remains under investigation.¹⁷

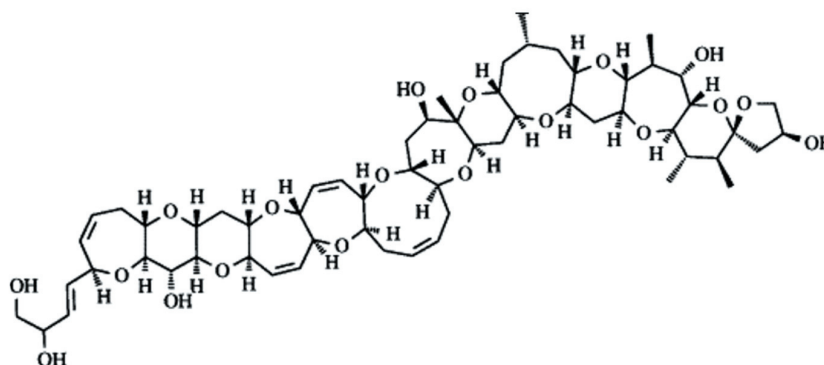


Figure 2
Ciguatoxin molecule

Source: Novel Nanomaterials for Biomedical, Environmental and Energy Applications, 2019¹⁵

Previous evidence also corroborates the presence of ciguatera in the country. In 2012, a study conducted in the state of Espírito Santo documented 12 cases associated with the consumption of fish such as greater amberjack, barracuda, moray eel, snapper, dogfish, and triggerfish, with predominantly gastrointestinal and neurological manifestations beginning 3 to 6 hours after ingestion.¹⁸

In 2022, a high density of the microalga *Gambierdiscus*, a producer of ciguatoxins, was detected in the waters of Fernando de Noronha, coinciding with the increase in cases in the region.¹⁷ The following year, in August 2023, a major outbreak affected approximately 30 individuals after the consumption of contaminated fish at a restaurant on the island, with characteristic symptoms such as vomiting, diarrhea, myalgia, intense fatigue, pruritus, and thermal paresthesia (reversal of hot and cold sensations).¹⁹

In May 2025, 2 severe cases of ciguatera poisoning were recorded in Natal (Rio Grande do Norte), involving 2 physicians who developed severe neurological manifestations and required admission to an intensive care unit after consuming golden dorado. In addition, laboratory tests had previously confirmed 2 other episodes in the city, one in 2022 and another in 2023.²⁰

These recent episodes reinforce the warning regarding the geographic expansion of ciguatera in Brazil, particularly in coastal regions of the Northeast, and highlight the urgent need to strengthen epidemiological surveillance systems, improve reporting mechanisms, and promote educational initiatives directed at both the general population and health care professionals. Such measures are essential to ensure early diagnosis, appropriate clinical management, and effective prevention of a foodborne illness that remains underdiagnosed and neglected in the country.

Clinical manifestations of ciguatera

Ciguatera is characterized by a complex set of polymorphic and nonspecific symptoms, resulting from the wide range of biological targets of ciguatoxins, such as voltage-gated sodium and potassium channels, and from the negative effects of these toxins on nerve impulse transmission.²¹ These symptoms vary among individuals and depend both on the amount of toxin ingested and on the geographic origin of the fish they consumed. It is estimated that the

literature has described more than 175 symptoms, making diagnosis particularly challenging, especially in non-endemic regions. Importantly, ciguatera does not appear to confer lasting immunity, often resulting in increased sensitization to seafood.²²

In the absence of confirmatory laboratory tests, the diagnosis of ciguatera is based on the patient's clinical history, the occurrence of outbreaks, suggestive clinical manifestations, and the exclusion of other conditions with similar presentations (Table 1). Ciguatera should be considered in afebrile patients presenting with a combination of gastrointestinal, neurological, and cardiovascular symptoms, in the absence of signs of allergic reaction, with onset within 48 hours of consumption of seafood from endemic tropical or subtropical regions.⁸

In some cases, such as poisoning caused by toxic marine invertebrates, atypical symptoms may occur, including extremely rapid onset (within minutes) and severe paralysis, requiring hospitalization. There are also rare reports of progression to Guillain-Barré syndrome and related neurological disorders.²³⁻²⁵

Initial symptoms generally resolve within a few days and are followed by a persistent neurological condition that may include paresthesias in the extremities and around the mouth, dysesthesias (particularly cold allodynia), muscle weakness, dizziness, headaches, visual disturbances, balance impairment, difficulty focusing, and sleep disturbances. These are frequently associated with pruritus without visible skin lesions, asthenia, myalgia, arthralgia, oropharyngeal burning, dysgeusia, orofacial pain, and occasionally urogenital discomfort. In up to 20% of patients, these symptoms may progress to chronic forms with neurosensory sequelae, such as dysesthesias, paresthesias, fatigue, general malaise, mood disorders, and chronic fatigue syndrome. These manifestations may occur continuously or episodically and may be reactivated by foods and beverages (especially seafood, meats, histamine-rich and protein-rich foods, and nuts), alcoholic or energy drinks, as well as by intense thermal stimuli, physical activity, and stress. Although symptoms resolve spontaneously in most cases, adoption of an exclusion diet may accelerate recovery.^{8,26,27}

In 2023, Haddad Junior et al.²⁸ reported the case of a 61-year-old woman who developed a clinical condition compatible with ciguatera poisoning after consuming unidentified white fish at a restaurant in the Fernando de Noronha archipelago. Approximately 30 minutes after the meal, the patient experienced about

Table 1

Examples of some illnesses with clinical presentations similar to ciguatera fish poisoning

Illness	Cause	Symptom presentation
Paralytic shellfish poisoning	Caused by ingestion of marine bivalve mollusks such as mussels, clams, and oysters, contaminated with saxitoxins	Within minutes of ingestion, there is onset of intraoral and perioral paresthesia, particularly of the tongue and gums similar to ciguatera but slower in onset. Paresthesias are rapidly followed by weakness, dysarthria, dysphagia, and other symptoms. The mortality rate is estimated at 25%, or higher in children
Pufferfish (fugu) poisoning	Caused by ingestion of pufferfish contaminated with tetrodotoxins	Paresthesia of the face and extremities, nausea, dizziness, loss of reflexes, weakness and paralysis. The marked weakness and paralysis of pufferfish poisoning is not seen in ciguatera
Neurotoxic shellfish poisoning	Caused by ingestion of molluscan shellfish contaminated with brevetoxins	Nausea and vomiting, paresthesias of the mouth, lips, tongue, and extremities, ataxia, slurred speech, and dizziness. Neurologic symptoms can progress to partial paralysis; respiratory distress may occur
Scombrototoxin fish poisoning	Caused by ingestion of fresh, canned or smoked fish with high histamine levels due to improper processing or storage	Flushing, rash, hives, palpitations, headache, dizziness, sweating, and burning of the mouth and throat; abdominal cramps, nausea, vomiting and diarrhea; bronchospasm, respiratory distress and vasodilatory shock may occur
Botulism	Caused by ingestion of canned foods contaminated with botulinum toxin	Vomiting, diarrhea, abdominal pain, extraocular muscle weakness, dysphagia, and respiratory paralysis. Unless promptly treated in the intensive care setting, it may result in death. Unlike in ciguatera, there are no sensory symptoms
Guillain-Barré syndrome	Unknown cause. Believed to be an autoimmune reaction in response to a viral or bacterial infection	Acute inflammatory demyelinating polyradiculoneuropathy, which may present with paresthesia followed by weakness of the extremities, loss of reflexes, and, in severe cases, dysphagia and respiratory failure. The early onset paresthesia may resemble ciguatera, especially if there is a history of gastrointestinal symptoms prior to the onset of paresthesia and history of having eaten fish associated with ciguatera
Acute arsenic poisoning	Caused by the intentional or unintentional ingestion of arsenic	Gastrointestinal symptoms and subsequent peripheral neuropathy may be the initial presentation. Unless there is suspicion of arsenic ingestion, the diagnosis may be overlooked, and ciguatera may be wrongly diagnosed
Organophosphate poisoning	Caused by dermal, inhalational or oral exposure to organophosphate compounds, usually pesticides	Initial symptoms of vomiting, diarrhea, and abdominal pain may resemble ciguatera. It may cause delayed sensory and motor peripheral neuropathy. Unlike ciguatera, it has cholinergic symptoms of salivation, bronchorrhea, and bronchospasm
Acute bacterial or viral gastroenteritis	Caused by ingestion of contaminated food or exposure to infectious individuals	Nausea, vomiting and diarrhea alone or combined, with or without neurologic symptoms (enterotoxigenic <i>E. coli</i> , <i>Shigella</i>) in patients with a history of exposure

20 episodes of vomiting, followed by similar symptoms in her daughter and her daughter's boyfriend, who had also ingested the fish. All were hospitalized and treated with intravenous hydration, symptomatic therapy, and oral azithromycin, although medication administration was hindered by repeated vomiting and diarrhea. The daughter developed intense muscle pain and thermosensory reversal, burning sensation upon contact with cold water, and abdominal pruritus. Even 1 week later, the daughter's boyfriend still reported intense fatigue, leg pain, and a "burned tongue" sensation. The patient remained symptomatic with fatigue, diarrhea, abdominal pain, intense pruritus on the palms, soles, and lower abdomen, and cold allodynia. Ten days after the poisoning, all individuals were still symptomatic. Improvement in pruritus was observed with the use of amitriptyline, but neurosensory symptoms persisted. The outbreak involved approximately 30 individuals who consumed fish at the same restaurant, reinforcing the clinical diagnosis of ciguatera.²⁸

Clinical course

The clinical course is often self-limited; however, symptoms such as paresthesias, fatigue, and pruritus may persist for weeks or months. Patients are advised to avoid fish, shellfish, nuts, caffeine, alcohol, fish sauces, and intense physical activity for up to 6 months after the episode, due to the risk of symptom reactivation. Treatment of ciguatera poisoning is primarily supportive, as there is no specific antidote for the toxin. Nausea and vomiting should be controlled with ondansetron or another antiemetic. Antidiarrheal medication may also be used to manage episodes of diarrhea. Because dehydration is common due to gastrointestinal symptoms, fluid replacement should be administered orally or intravenously if the patient is unable to tolerate oral intake. For relief of pruritus, antihistamines and amitriptyline may be considered. Cold baths may also provide temporary relief from the burning sensation of the skin. For musculoskeletal pain, nonsteroidal anti-inflammatory drugs are recommended. Medications such as gabapentin and amitriptyline may also be useful in the treatment of associated neuropathies. Seizures should be treated with benzodiazepines and, if refractory, barbiturates or propofol may be used. Patients should be instructed to avoid alcohol and intense physical activity for several months, as these factors may worsen neuropathic symptoms. Foods such as fresh or preserved fish, fish sauces, shellfish and their derivatives, nuts, and nut

oils should also be avoided. Symptomatic bradycardia may be treated with intravenous atropine, and in cases of postural hypotension, alpha-adrenergic agonists such as phenylephrine may be administered. If medical care is provided within the first hours of ingestion, and before the onset of vomiting, activated charcoal may be administered to reduce intestinal absorption of ciguatoxin. However, there is risk of aspiration and pneumonitis if the patient begins vomiting after charcoal administration. The use of intravenous mannitol remains controversial. Although it is an osmotic diuretic that potentially reduces neuronal swelling and relieves neurological symptoms, clinical studies have not confirmed its superiority over normal saline. Nevertheless, some experts consider that the potential benefits of mannitol may justify its use in selected cases of acute ciguatera poisoning.^{2,29,30}

Conclusion

Ciguatera represents a neglected yet emerging foodborne illness, with increasing impact in tropical and subtropical regions such as the Brazilian coastline. Its association with the consumption of reef fish contaminated by ciguatoxins, highly stable and potent lipophilic toxins, gives it a broad and challenging clinical profile, which may include gastrointestinal, neurological, and cardiovascular manifestations, often persistent. In Brazil, the recent identification of outbreaks in Fernando de Noronha, Espírito Santo, and Rio Grande do Norte highlights the geographic expansion of the disease and underscores the need for greater epidemiological surveillance and preparedness of health care professionals. Particularly relevant is that ciguatera may mimic allergic reactions, neurosensory disorders, and immune-mediated diseases, complicating the differential diagnosis. In this context, allergists and immunologists—professionals used to managing multisystem syndromes, atypical phenotypes, and cutaneous and mucosal manifestations—play a strategic role in early case identification. Their involvement is essential not only for accurate clinical diagnosis, but also for proper notification, preventive dietary counseling, and symptomatic management of both acute and chronic forms of ciguatera poisoning. Including ciguatera within the diagnostic scope of these specialists is crucial to improve case detection in Brazil, enhance clinical response, and strengthen prevention and control strategies in the face of a foodborne condition that remains underdiagnosed yet highly relevant to coastal public health.

References

- Lehane L, Lewis RJ. Ciguatera: recent advances but the risk remains. *Int J Food Microbiol*. 2000 Nov;61(2-3):91-125.
- Ubaldi P, Galli P, Belingeri M, Maggioni D, Montalbetti E, Saliu F. Overview of the state of the art of ciguatera fish poisoning. *Acta Sci Vet Sci*. 2021;Special Issue 1:20-6.
- Friedman MA, Fleming LE, Fernandez M, Bienfang P, Schrank K, Dickey R, et al. Ciguatera fish poisoning: treatment, prevention and management. *Mar Drugs*. 2008 Mar;6(3):456-79.
- Chinain M, Gatti CM, Roué M, Darius HT. Ciguatera poisoning in French Polynesia: insights into the novel trends of an ancient disease. *New Microbes New Infect*. 2019 Sep;31:100565.
- Dechraoui Bottein MY, Wang Z, Ramsdell JS. Toxicokinetics of the ciguatoxin P-CTX-1 in rats after intraperitoneal or oral administration. *Toxicology*. 2011 Jun;284(1-3):1-6.
- FAO/WHO. Report of the Expert Meeting on Ciguatera Poisoning. Rome: Food and Agriculture Organization of the United Nations; 2020.
- U.S. Food and Drug Administration (FDA). Fish and Fishery Products Hazards and Controls Guidance. 4th ed. Washington, DC: FDA; 2021.
- Friedman MA, Fernandez M, Backer LC, Dickey RW, Bernstein J, Schrank K, et al. An updated review of ciguatera fish poisoning: clinical, epidemiological, environmental, and public health management. *Mar Drugs*. 2017 Mar 14;15(3):72. doi:10.3390/md15030072.
- Lewis RJ. Ciguatoxins: chemical structure and mechanism of action. In: Hall S, Strichartz G, editors. *Marine Toxins: Origins, Structures, and Molecular Pharmacology*. Washington DC: American Chemical Society; 1990. p.191-206.
- Murata M, Yasumoto T. Chemistry and toxicology of marine toxins. *J Nat Toxins*. 2000;9(3):391-409.
- Bottein Dechraoui MY, Wang Z, Ramsdell JS. Toxicokinetics of the ciguatoxin P-CTX-1 in rats after intraperitoneal or oral administration. *Toxicology*. 2011 Jun;284(1-3):1-6.
- Catterall WA, Cestèle S, Yarov-Yarovoy V, Yu FH, Konoki K, Scheuer T. Voltage-gated ion channels and gating modifier toxins. *Toxicon*. 2007 Feb;49(2):124-41. doi: 10.1016/j.toxicon.2006.09.022.
- Dickey RW, Plakas SM. Ciguatera: a public health perspective. *Toxicon*. 2010 Oct;56(5):618-28.
- Murata M, Legrand AM, Ishibashi Y, Yasumoto T. Structures of ciguatoxin and its congener. *J Am Chem Soc*. 1989;111(24):8929-31.
- Wang X, Chen X, editors. *Novel nanomaterials for biomedical, environmental and energy applications*. Amsterdam: Elsevier; 2019.
- Soares MMP, Costa GR, Neto JS. Revisão de literatura sobre doenças transmitidas por alimentos relacionadas ao consumo de pescados no Brasil: 2012 a 2022. *Rev Pan Amaz Saude*. 2022;13:e202300367.
- Brasil, Pernambuco, Secretaria Estadual de Saúde. Nota Técnica Conjunta nº 06/2025 – Ciguatera em Fernando de Noronha. Recife: SES/PE; 2025.
- Torres MC, Leão RNQ, Matias MFS. Intoxicação alimentar por ciguatera no Espírito Santo, Brasil, 2012. *Rev Inst Adolfo Lutz*. 2014;73(1):98-104.
- Junior VH, Xavier JL, Fernandes LMC. Intoxicação por ciguatera em turistas em Fernando de Noronha: relato de caso. *Braz J Infect Dis*. 2024;28(Supl. 1):S94.
- Rio Grande do Norte. Secretaria de Estado da Saúde Pública. Nota Informativa nº 1/2025 - SESAP - CVS - SUVIGE - AGUDAS. Natal (RN): SESAP; 2025.
- Mattei C, Benoit E, Molgó J. An overview of the ion channel modulation and neurocellular disorders induced by ciguatoxins. In: *Toxins and Ion Transfers*. SFET Publications; 2011. p. 39-42. (Collection Rencontres en Toxinologie).
- Chinain M, Gatti CMI, Darius HT, Quod JP, Tester PA. Ciguatera poisonings: A global review of occurrences and trends. *Harmful Algae*. 2021 Feb;102:101873.
- Laurent D, Chinain M, Deixonne T, Maestrini S. Ciguatera shellfish poisoning (CSP), a new ecotoxicological phenomenon. From cyanobacteria to humans via giant clams. In: *Food Chain: New Research*. Chapter 1. New York: Nova Science; 2012.
- Gatti CMI, Lonati D, Darius HT, Zancan A, Roué M, Schicchi A, et al. *Tectus niloticus* (Tegulidae, Gastropod) as a Novel Vector of Ciguatera Poisoning: Clinical Characterization and Follow-Up of a Mass Poisoning Event in Nuku Hiva Island (French Polynesia). *Toxins* (Basel). 2018 Feb 28;10(3):102. doi: 10.3390/toxins10030102.
- Oehler E, Gatti C, Legrand AM, Ghawche F. Ciguatera and acute polyradiculoneuritis. Description of two cases in French Polynesia: immunoallergic hypothesis? *Med Trop (Mars)*. 2009 Feb;69(1):75-7.
- Baumann F, Bourrat MB, Pauillac S. Prevalence, symptoms and chronicity of ciguatera in New Caledonia: Results from an adult population survey conducted in Noumea during 2005. *Toxicon*. 2010 Oct;56(5):662-7.
- Pearn J. Chronic ciguatera: One organic cause of the chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome*. 1996;(2-3):29-34.
- Haddad Junior V, Reis SLCD. Ciguatera on the coast of Northeastern Brazil: report of an outbreak in Fernando de Noronha Archipelago. *Rev Soc Bras Med Trop*. 2023 Nov 27;56:e04042023. doi: 10.1590/0037-8682-0404-2023.
- Boada LD, Zumbado M, Luzardo OP, Almeida-González M, Plakas SM, Granade HR, et al. Ciguatera fish poisoning on the West Africa Coast: An emerging risk in the Canary Islands (Spain). *Toxicon*. 2010 Dec;56(8):1516-9.
- Katz AR, Terrell-Perica S, Sasaki DM. Ciguatera on Kauai: investigation of factors associated with severity of illness. *Am J Trop Med Hyg*. 1993 Oct;49(4):448-54.

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Granulomatous Lymphocytic Interstitial Lung Disease (GLILD)

Doença Pulmonar Intersticial Linfocítica Granulomatosa (GLILD)

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ABSTRACT

Granulomatous lymphocytic interstitial lung disease (GLILD) is a serious complication of inborn errors of immunity and is associated with immune dysregulation and autoimmune phenomena. Diagnosis requires the integration of clinical manifestations with functional, tomographic, and histological findings. Immunosuppressive therapy, with corticosteroids or cytotoxic agents, is the first-line approach aimed at controlling inflammation. However, response to therapy is variable, and many patients experience disease progression with the development of pulmonary fibrosis. This review highlights the most relevant aspects of GLILD pathogenesis and diagnosis and discusses treatment options, based on publications from the past 10 years.

Keywords: Immune system diseases, interstitial lung diseases, common variable immunodeficiency, primary immunodeficiency diseases.

RESUMO

A Doença Pulmonar Intersticial Linfocítica Granulomatosa (GLILD) é uma das complicações graves dos erros inatos da imunidade e está relacionada à desregulação imunológica e a fenômenos autoimunes. O diagnóstico requer associação das manifestações clínicas aos achados funcionais, tomográficos e histológicos. O tratamento imunossupressor, com corticosteroides ou agentes citotóxicos, é a primeira linha de abordagem, visando controlar a inflamação. No entanto, a resposta à terapia é variável e muitos pacientes apresentam progressão da doença e desenvolvimento de fibrose pulmonar. Nesta revisão destacamos os aspectos mais relevantes sobre a patogênese e diagnóstico, discutindo-se as opções terapêuticas, com base nas publicações dos últimos 10 anos.

Descritores: Doenças da imunodeficiência primária, doenças pulmonares intersticiais, imunodeficiência de variável comum, doenças do sistema imunitário.

Introduction

Granulomatous-lymphocytic interstitial lung disease (GLILD), which is associated with lymphocytic infiltrate and/or granulomatous inflammation,¹ is a non-infectious complication of patients with inborn errors of immunity. It occurs especially in patients with common variable immunodeficiency (CVID), but also in people with mutations in the following genes: N-methyltransferase 2D (*KMT2D*), recombination-activation gene 1 (*RAG1*), cytotoxic T-lymphocyte associated protein 4 (*CTLA4*), LPS-responsive beige-

like anchor protein (*LRBA*), nuclear factor kappa B subunit 1 (*NFKB1*), tumor necrosis factor superfamily member 13b (*TNFRSF13B*), and signal transducer and activator of transcription (*STAT1* & *STAT3*), as well as in those with 22q11.2 deletion syndrome.^{2,3} It most frequently affects patients between 20 and 50 years of age, although it also occurs in the pediatric age group.^{4,5} Women are more affected than men, and approximately 70% of patients have a history of autoimmune cytopenias.⁶

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Pathogenesis

Although the pathogenesis of GLILD is not yet fully understood, it is a serious non-infectious complication of inborn errors of immunity, in which phenomena related to immune dysregulation predominate. These include an increased number of activated T cells and memory T cells and increased production of B cell-activating factor, which leads to activation of the anti-apoptotic factor Bcl-2, promoting greater B cell survival. The expansion of CD21^{low} and self-reactive B cells has been postulated as responsible for the aberrant interaction between T and B cells.⁷

Additionally, follicular CD4 T cells with a Th1 phenotype (CXCR3⁺CCR6⁻) are present in greater numbers in both the peripheral blood and lymph nodes of patients with CVID and non-infectious complications. This expansion has been associated with increased IFN- γ production and T-bet+CD21^{low} B cell accumulation in peripheral blood and lymph nodes. T-bet B cells are a subset of B cells that express the myeloid markers CD11c and CD11b, whose

expression increases with age.⁸ Figure 1 illustrates the cycle of expansion and migration of age-related B cells at inflammation sites.

Interestingly, in patients with CVID, viral infections, such as human herpesvirus 8 and an oropharyngeal microbiome with a relative abundance of *Streptococcus*, have also been linked to GLILD, but further evidence is needed.^{9,10}

Diagnosis

Clinical manifestations

Cough and dyspnea, which intensify slowly and progressively over months to years, are the most common symptoms of GLILD. Their nonspecificity can lead to confusion with other pulmonary diseases that have an interstitial or granulomatous pattern, especially sarcoidosis, particularly if inborn errors of immunity have not yet been diagnosed or in cases where GLILD is the initial manifestation of inborn errors of immunity.

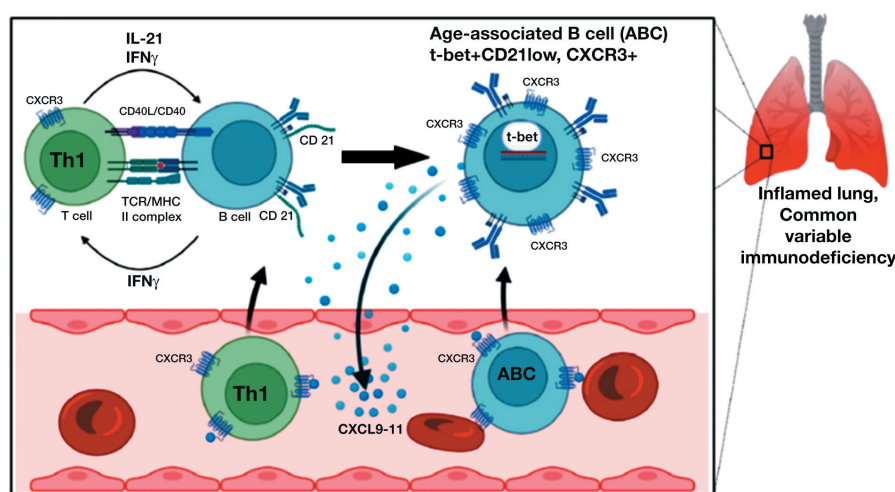


Figure 1

Th1 cells expressing CXCR3 interact with B cells during antigen presentation via CD40L/CD40, secreting IL-21 and IFN- γ . This leads to the induction of age-associated B cells (ABC), which are characterized by decreased CD21 expression and upregulation of T-bet transcription factor and CXCR3 chemokine receptor. ABCs then secrete IFN- γ , further promoting Th1 cell formation. Cells in inflamed tissues, including ABCs, express the chemokines CXCL9, CXCL10, and CXCL11, which bind to the CXCR3 receptor and further promote ABC migration and CXCR3 Th1 cell expression in the target tissue

Adapted from Long et al.⁸

Table 1 shows the differences and similarities between GLILD and sarcoidosis. Other differential diagnoses include lymphoproliferative disorders, granulomatous infections (by mycobacteria and fungi), and other causes of granulomatous lung disease, such as drug reactions, occupational exposure (berylliosis), hypersensitivity pneumonitis, and vasculitis.¹¹

Other findings, such as splenomegaly and lymphadenopathy, are common findings in physical examinations. Nodular regenerative hyperplasia of the liver occurs in approximately 20% of patients with GLILD, and autoimmune enteropathy and cytopenias can also occur. Thus, GLILD is the pulmonary component of a multisystem granulomatous

Table 1

Differences between granulomatous lymphocytic interstitial lung disease and sarcoidosis

	GLILD (%)	Sarcoidosis (%)
Affected organ		
Lung	51	95
Lymph nodes/spleen	46	15/7
Liver	41	11
Digestive tract	15	rare
Bone marrow	8	4
Skin	7	16
Clinical and laboratory characteristics		
Recurrent infections	++++	+/-
Autoimmunity	+++	+
Immunoglobulin levels	Low	Normal or high. May be low in patients on prolonged use of SC
Lymphocytic interstitial pneumonia	++++	++
Follicular bronchiolitis	++++	++
CD4/CD8 ratio	Usually normal	High (> 3.5)
Spontaneous remission	+/-	+++
Radiological characteristics (HRCT)		
Parenchymal involvement	Lower lung zones	Upper lung zones
Nodules surrounded by ground-glass opacity	+++	+
Hilar lymphadenopathy	+	+++
Nodules	Prominent, wide, distributed randomly or perilymphatic	Micronodular, perilymphatic in bronchovascular distribution
Bronchiectasis	+++	+

GLILD: granulomatous lymphocytic interstitial lung disease; HRCT: high-resolution computed tomography; SC: systemic corticosteroid.

Adapted from Verbsky & Routes¹⁶ and Perlman et al.³⁵

lymphoproliferative disease, resulting from immune dysregulation in patients with various types of inborn errors of immunity.⁶

Because patients with CVID and GLILD are often asymptomatic, a screening chest computed tomography (CT) scan should be performed initially and at follow-up for all diagnosed patients.¹² For patients who show no evidence of interstitial lung disease in their initial screening, a repeat examination is recommended every 4-5 years, or less frequently if the patient experiences a decline in annual pulmonary function test values or develops symptoms of dyspnea on exertion, cough or changes in cough pattern, excessive fatigue, or night sweats.¹

Pulmonary function

In patients with GLILD, pulmonary function assessment is more useful for monitoring than for diagnosis, being important for analyzing disease progression and treatment response. Plethysmography is the preferred examination because it allows for a more comprehensive analysis. Positive findings will show restrictive disorders and interstitial dysfunction, with lower total lung capacity values and low carbon monoxide diffusing capacity (DL_{CO}) values.^{13,14} It should be noted, however, that some patients may present with normal pulmonary function, especially in cases with less extensive lung involvement.¹⁵ During follow-up, a $\geq 20\%$ increase in DL_{CO} has been considered a significant response among patients who respond to treatment.¹

Tomographic findings

High-resolution CT (HRCT) chest scan findings include generalized centrilobular micronodular and macronodular changes, predominantly in the lower lung zones.¹⁶ Thickening of the interlobular septum, ground-glass opacities, hilar and/or mediastinal lymphadenopathy, and bronchiectasis have also been described.^{1,14,17} Fibrosis and honeycombing have been observed in more advanced cases.¹¹ Thin-walled cysts with bronchovascular distribution, as frequently seen in lymphocytic interstitial pneumonia, are neither a frequent nor a dominant pattern in GLILD, although they may be useful in differentiating GLILD from follicular bronchiolitis or diffuse lymphoma.¹¹

Increased or decreased pulmonary opacities are a common finding in GLILD, and the differential diagnosis includes organizing pneumonia, eosinophilic pneumonia, infectious and non-infectious

granulomatous disorders, and lymphoproliferative diseases. The often migratory nature of the nodules in serial HRCT often excludes granuloma, infection, and lymphoma and suggests organizing pneumonia.¹¹ Figure 2 illustrates some of these findings. However, clinical, radiological, and functional findings are often nonspecific, and lung biopsy may be necessary to confirm the diagnosis.

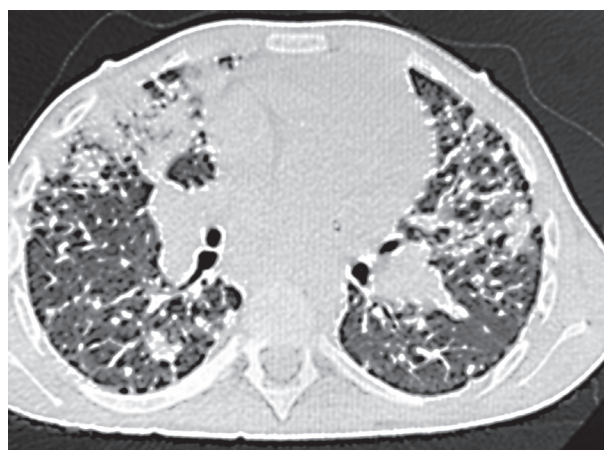


Figure 2

Changes found in a high-resolution computed tomography scan of an adolescent with GLILD. Diffuse interstitial thickening. Coalescing consolidations in the left midclavicular lymph node, lingula, and bilaterally in the lower lobe. Defined bilateral perivascular nodules

Lung biopsy findings

In addition to being very important for diagnostic confirmation, lung biopsy helps exclude differential diagnoses, especially infections and neoplasia. Typical pathological findings include peribronchiolar/interstitial lymphocytic infiltration (lymphocytic interstitial pneumonia), granulomas, and organizing pneumonia.¹⁸

Lymphoid proliferation is an important finding, and different patterns have been described, including follicular bronchiolitis, lymphocytic interstitial pneumonitis, lymphocytic infiltrate, and nodular lymphoid hyperplasia. In a case series of patients with CVID, in which a correlation was sought between clinical and laboratory findings and pulmonary changes, nodular lymphoid hyperplasia appeared to be a predictor of a more severe spectrum of CVID¹⁹ and follicular bronchiolitis and/or lymphocytic

interstitial pneumonitis were found in about half of the GLILD cases.²⁰

Granulomas can be found throughout the lung parenchyma and tend to be well-circumscribed, but it is important to note that they are not always present.¹⁸ Furthermore, GLILD involves some histological characteristics similar to sarcoidosis and hypersensitivity pneumonitis. Thus, clinical and radiological correlation is important in distinguishing these conditions.

Organizing pneumonia, a histological pattern characterized by granulation tissue polyps within alveolar ducts and alveoli, including chronic inflammation of the adjacent lung parenchyma, is frequently reported in patients with GLILD.¹⁸ Pulmonary fibrosis is described in a quarter of GLILD patients, but studies have indicated that most patients may have some degree of impairment, which is associated with poor prognosis.²¹

Immunohistochemistry of lymphocytic infiltrate reveals a predominance of CD4 T lymphocytes and a variable number of CD8 T and B cells, as well as an absence of FOXP3-positive regulatory T cells.^{22,23} Tertiary lymphoid structures with evidence of germinal centers have been described.^{19,23} Table 2 shows the distribution of histopathological findings from lung biopsies of patients with CVID and interstitial lung disease, and Table 3 summarizes the main tomographic and biopsy changes.

Treatment

A multidisciplinary team involving immunologists, pulmonologists, radiologists, and pathologists is needed to treat patients with GLILD, including

respiratory physical therapy and psychological support when necessary. Pharmacological treatment consists mainly of immunosuppressive medication, in addition to immunoglobulin replacement. Serum IgG levels should be optimized before starting immunosuppressive therapy; a serum level of at least 1000 mg/dL has been proposed.⁴

Immunosuppressive therapy is not necessary for everyone and should be reserved for cases in which pulmonary function is deteriorated, generally characterized as a $\geq 20\%$ reduction in carbon monoxide diffusion. Thus, it is mainly indicated for symptomatic or asymptomatic patients with deteriorated or altered pulmonary function and symptomatic patients with normal but deteriorating pulmonary function.^{1,7}

Although systemic corticosteroid therapy is considered the first-line treatment,¹ half of patients do not respond to corticosteroids, making second-line therapy necessary.^{7,24} The most commonly used second-line agents are azathioprine, rituximab, and mycophenolate mofetil. An combination of azathioprine and rituximab has been used in several case series due to its combined effects on T and B cells.^{6,7,24}

Systemic corticosteroids

Corticosteroids have been proposed as a first-line treatment for GLILD.¹ The initial dose of prednisone/prednisolone used in the literature varies. Based on clinical experience, some authors advocate an initial dose of 1 mg/kg/day until significant improvement in radiological abnormalities and pulmonary function is observed, followed by a gradual reduction.¹ The total treatment time has not been well established.

Table 2

Variations in histological findings reported in different literature studies of patients with common variable immunodeficiency (IDCV) and granulomatous-lymphocytic interstitial lung disease (GLILD)

Granulomas	Pulmonary lymphoid hyperplasia				Organizing pneumonia	Pulmonary fibrosis	
	Interstitial inflammation	Peribronchial inflammation	Lymphocytic inflammation	Lymphoid hyperplasia		Fibrosis	Remodeling

5-93%	33-100%	33-100%	17-97%	29-33%	32-87%	3-75%	16-37%
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Table 3

Summary of key chest high-resolution computed tomography and lung biopsy findings in patients with GLILD

HRCT pattern	Distribution	Features	Other findings
Typical GLILD	Axial: predominantly peribronchovascular Craniocaudal: predominantly in the lung bases	Presence of all of the following findings: – Nodularity – Opacity in frosted glass – Consolidation	– Hilar and mediastinal lymphadenopathy – Splenomegaly
Compatible with GLILD	Heterogeneous or diffuse	Presence of some , but not all of the following findings: – Nodularity – Opacity in frosted glass – Consolidation – Splenomegaly	– Hilar and mediastinal lymphadenopathy – Splenomegaly
Favors alternative diagnosis	Predominantly in the upper lobe , as in hypersensitivity pneumonitis or sarcoidosis. Asymmetrical distribution unilateral or bilateral , as in aspiration or infection	Presence of: – Focal nodule or growing mass progressively over 3-6 months despite the treatment (such as lymphoma)	Absence of: – Lymphadenopathy – Splenomegaly

Histopathological pattern	Criteria
Typical GLILD	Presence of 2 main criteria in at least 1 lung lobe on surgical biopsy: 1. Pulmonary lymphoid hyperplasia with reactive germinal centers in the form of: – Follicular bronchiolitis and/or – Nodular lymphoid hyperplasia and/or – Any interstitial lymphocytic infiltrate 2. Granulomas (well-formed, moderate, or malformed)
LIP associated with CVID without granulomas	Presence of 2 main criteria in ≥ 1 lung lobe on surgical biopsy: – Follicular bronchiolitis and/or – Nodular lymphoid hyperplasia and/or – Any interstitial lymphocytic infiltrate and the absence of granulomas and findings suggestive of alternative diagnoses.
Favors alternative diagnosis	Histopathological findings indicative of other diseases: – Infection: well-formed granulomas, often with necrosis, positive results for infection. – Lymphoproliferative diseases: atypical lymphocytic proliferation with a diagnosis of lymphoma confirmed by immunohistochemistry, immunophenotyping by flow cytometry, and monoclonality confirmed by positive gene rearrangement. – Hypersensitivity pneumonitis: bronchiocentric distribution/accentuation with poorly formed granulomas and prominent peribronchiolar metaplasia – Sarcoidosis: well-formed coalescing granulomas associated with hyaline fibrosis; lymphatic distribution, and absence of significant interstitial inflammation. – Berylliosis: histology similar to sarcoidosis; history of exposure and positive lymphocyte proliferation test for beryllium, when available. – Nonspecific interstitial pneumonia: idiopathic or secondary to other causes (eg, drug toxicity, connective tissue diseases), absence of granulomas. – IgG4-related disease: marked infiltrate of plasma cells with an increased proportion of IgG4+ cells; absence of granulomas.

A retrospective and prospective multicenter observational study found that corticosteroid treatment resulted in clinical and/or radiological improvement in 67% of patients, with no increase in respiratory tract infections. CT response was achieved in 76% of cases, while improved pulmonary function was achieved in 37% of cases and long-term remission was achieved in 42% of cases.²⁵ However, maintenance therapy with low doses of corticosteroids provided no benefit, and the effectiveness of a new course of treatment in patients with relapsing disease was low. Regarding side effects, this study found no increased risk of infection.²⁵ However, other side effects, such as Cushing's syndrome and osteopenia, must be considered and prevented, since treatment is long term.^{2,25}

Immunosuppressive agents

The most commonly used immunosuppressive agents after corticosteroid failure are azathioprine, mycophenolate mofetil, and rituximab, which are administered in combination or as monotherapy; there is no consensus on a preferred therapy.^{1,26-28} Several studies have found clinical improvement with a combination of rituximab and azathioprine (or mycophenolate), including a 92% response rate for lung parenchymal abnormalities. Treatment duration ranged from 16 to 18 months.^{6,7,27} Sustained disease remission occurred in 75% of treated patients, with a median follow-up of 4 years.⁶ Case studies have also reported improved pulmonary function tests.²⁸⁻³⁰ Monotherapy with rituximab has also shown good results, including clinical, functional, and radiological improvement.²⁶ Although most of rituximab's immunomodulatory effect is due to B cell depletion, there is evidence that it may also interfere with the action of CD4+ and CD8+ T cells.³¹ It is possible that the effect on the T cell compartment consists of indirectly reducing T cell activation,²⁶ in addition to promoting an increase in regulatory T cells and normalization of the Th1/Th2 ratio.³¹ Experimental data have shown that lung B cells play a role in the generation of CD4 memory cells.³² Figure 3 illustrates proposed mechanisms for rituximab's immunosuppressive effect.

The suggested treatment regimens are as follows^{6,7}:

- Rituximab: 375 mg/m² by infusion, every 7 days, for 4 weeks, repeating the infusion every 6 months, for a total of 3-4 courses of medication (12-16 infusions);

- Azathioprine: 1-2 mg/kg/day;
- Mycophenolate mofetil: 250 to 1000 mg, twice/day.

Other therapeutic options

Other medications reported as potentially useful for treating GLILD are anti-TNF agents, cyclosporine, hydroxychloroquine, methotrexate, tacrolimus, abatacept, and sirolimus.^{1,7,33} However, these alternatives require further study. Sirolimus, a mammalian TOR inhibitor that affects effector T cells and can cause decreased lymphocyte survival, has proven effective in monogenic immune disorders, such as PI3K δ syndrome, CTLA4 deficiency, and autoimmune lymphoproliferative disorders. Increased expression of CTLA-4 by regulatory T cells after sirolimus administration suggests improved T cell function.³³ Abatacept has also been proposed for patients with CTLA-4 haploinsufficiency and LRBA defects due to significant improvement in pulmonary function and radiological findings.⁷

Monitoring

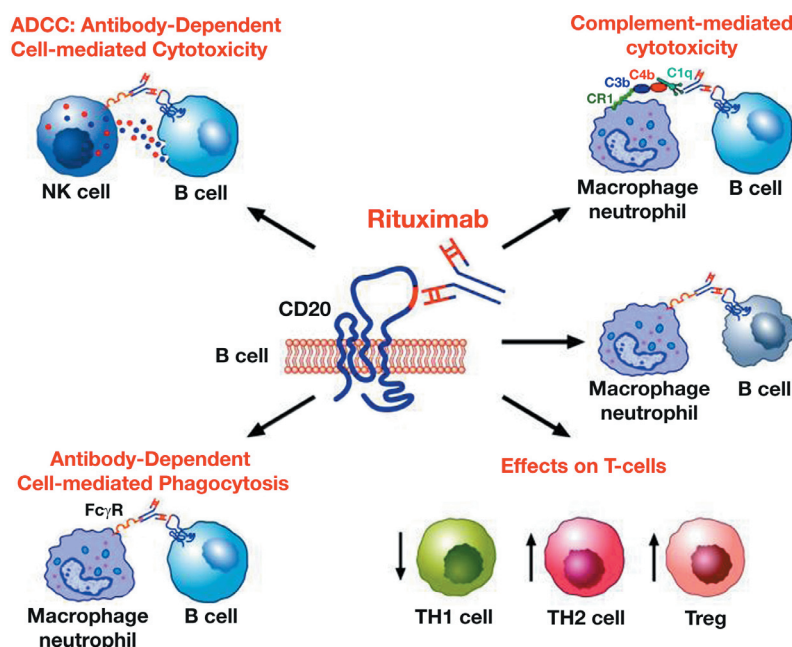
Treatment response or progression should be evaluated according to clinical, radiological, and pulmonary function parameters. Functional assessment can be repeated 3 months after treatment initiation, preferably by plethysmography, in which a 20% increase in DL_{CO} is already considered significant. Repeating the HRCT scan 4 to 6 months later is suggested.¹ Chest radiography can also be used for disease monitoring if changes are initially visible.

Prognosis

GLILD diagnosis is associated with poor outcomes in patients with CVID. A retrospective study of 69 patients found that median survival was 50% (13.7 years) lower in patients with CVID and GLILD than in patients without the disease.³⁴

Conclusions

GLILD, the most common cause of diffuse lung disease to affect patients with inborn errors of immunity, especially patients with CVID, is a manifestation of systemic granulomatous lymphoproliferative disease. Treatment studies have involved small samples and are often of low quality and have a high risk of bias,

**Figure 3**

Schematic representation of the mechanisms that have been proposed to explain the immunosuppressive effects of rituximab. Rituximab is a chimeric monoclonal antibody (IgG1) that targets the CD20 protein in human B cells. It depletes B cells primarily through antibody-dependent cell-mediated cytotoxicity and complement-mediated cytotoxicity. There is evidence that rituximab can decrease Th1 cells and increase Th2 and Treg cells

Adapted from Pecoraro, et al.³¹

making it impossible to define which therapeutic option is ideal for treatment. The effectiveness of different therapies can also be influenced by the heterogeneity of the disease etiology and manifestations. Further studies are needed on the pathogenesis, natural history, and optimal treatment of GLILD in larger multicenter cohorts. Future studies should compare immunosuppressive regimens, as well as the timing and safety of drug discontinuation.

References

- Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. *J Allergy Clin Immunol Pract.* 2017 Jul-Aug;5(4):938-45.
- Rodina Y, Deripapa E, Shvets O, Mukhina A, Roppelt A, Yuhacheva D, et al. Rituximab and Abatacept Are Effective in Differential Treatment of Interstitial Lymphocytic Lung Disease in Children With Primary Immunodeficiencies. *Front Immunol.* 2021;12:704261. doi: 10.3389/fimmu.2021.704261.
- Matson EM, Abyazi ML, Bell KA, Hayes KM, Maglione PJ. B Cell Dysregulation in Common Variable Immunodeficiency Interstitial Lung Disease. *Front Immunol.* 2021;11:622114.
- Galant-Swofford J, Catanzaro J, Achcar RD, Cool C, Koelsch T, Bang TJ, et al. Approach to diagnosing and managing granulomatous-lymphocytic interstitial lung disease. *EClinicalMedicine.* 2024;75:102749. doi: 10.1016/j.eclinm.2024.102749.
- Pac M, Bielecka T, Grzela K, Komarnicka J, Langfort R, Koltan S, et al. Interstitial Lung Disease in Children With Selected Primary Immunodeficiency Disorders-A Multicenter Observational Study. *Front Immunol.* 2020;11:1950. doi: 10.3389/fimmu.2020.01950.
- Verbsky JW, Hintermeyer MK, Simpson PM, Feng M, Barbeau J, Rao N, et al. Rituximab and antimetabolite treatment of granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency. *J Allergy Clin Immunol.* 2021;147(2):704-12.e17. doi: 10.1016/j.jaci.2020.07.021.

7. Lamers OAC, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm VASH, et al. Treatment Strategies for GLILD in Common Variable Immunodeficiency: A Systematic Review. *Front Immunol.* 2021;12:606099. doi: 10.3389/fimmu.2021.606099.
8. Long A, Kleiner A, Looney RJ. Immune dysregulation. *J Allergy Clin Immunol.* 2023;151(1):70-80. doi: 10.1016/j.jaci.2022.11.001.
9. Berbers RM, Mohamed Hoessein FAA, Ellerbroek PM, van Montfrans JM, Dalm VASH, van Hagen PM, et al. Low IgA Associated With Oropharyngeal Microbiota Changes and Lung Disease in Primary Antibody Deficiency. *Front Immunol.* 2020;11:1245. doi: 10.3389/fimmu.2020.01245.
10. Wheat WH, Cool CD, Morimoto Y, Rai PR, Kirkpatrick CH, Lindenbaum BA, et al. Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. *J Exp Med.* 2005;202(4):479-84. doi: 10.1084/jem.20050381.
11. Fernández Pérez ER. Granulomatous lymphocytic interstitial lung disease. *Immunol Allergy Clin North Am.* 2012;32(4):621-32. doi: 10.1016/j.iac.2012.08.003.
12. Maarschalk-Ellebroek LJ, de Jong PA, van Montfrans JM, Lammers JW, Bloem AC, Hoepelman AI, et al. CT screening for pulmonary pathology in common variable immunodeficiency disorders and the correlation with clinical and immunological parameters. *J Clin Immunol.* 2014;34(6):642-54. doi: 10.1007/s10875-014-0068-6.
13. Buso H, Firinu D, Gambier RF, Scarpa R, Garzi G, Soccodato V, et al. Lung function trajectories in common variable immunodeficiencies: An observational retrospective multicenter study. *J Allergy Clin Immunol.* 2024 Nov 19:S0091-6749(24)01230-2. doi: 10.1016/j.jaci.2024.10.037.
14. Cabanero-Navalon MD, Garcia-Bustos V, Forero-Naranjo LF, Baettig-Arriagada EJ, Núñez-Beltrán M, Cañada-Martínez AJ, et al. Integrating Clinics, Laboratory, and Imaging for the Diagnosis of Common Variable Immunodeficiency-Related Granulomatous-Lymphocytic Interstitial Lung Disease. *Front Immunol.* 2022;13:813491. doi: 10.3389/fimmu.2022.813491.
15. Bouvry D, Mouthon L, Brillet PY, Kambouchner M, Ducroix JP, Cottin V, et al. Granulomatosis-associated common variable immunodeficiency disorder: a case-control study versus sarcoidosis. *Eur Respir J.* 2013;41(1):115-22. doi: 10.1183/09031936.00189011.
16. Verbsky JW, Routes JM. Sarcoidosis and common variable immunodeficiency: Similarities and differences. *Semin Respir Crit Care Med.* 2014;35(3):330-5.
17. Cinetto F, Scarpa R, Carrabba M, Firinu D, Lougaris V, Buso H, et al. Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) in Common Variable Immunodeficiency (CVID): A Multicenter Retrospective Study of Patients From Italian PID Referral Centers. *Front Immunol.* 2021;12:627423. doi: 10.3389/fimmu.2021.627423.
18. Dhalla F, Lochlainn DJM, Chapel H, Patel SY. Histology of Interstitial Lung Disease in Common Variable Immune Deficiency. *Front Immunol.* 2020;11:605187. doi: 10.3389/fimmu.2020.605187.
19. Maglione PJ, Ko HM, Beasley MB, Strauchen JA, Cunningham-Rundles C. Tertiary lymphoid neogenesis is a component of pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency. *J Allergy Clin Immunol.* 2014;133(2):535-42. doi: 10.1016/j.jaci.2013.08.022.
20. Ho HE, Cunningham-Rundles C. Non-infectious Complications of Common Variable Immunodeficiency: Updated Clinical Spectrum, Sequelae, and Insights to Pathogenesis. *Front Immunol.* 2020;11:149. doi: 10.3389/fimmu.2020.00149.
21. Patel S, Anzilotti C, Lucas M, Moore N, Chapel H. Interstitial lung disease in patients with common variable immunodeficiency disorders: several different pathologies? *Clin Exp Immunol.* 2019;198(2):212-23. doi: 10.1111/cei.13343.
22. Rao N, Mackinnon AC, Routes JM. Granulomatous and lymphocytic interstitial lung disease: a spectrum of pulmonary histopathologic lesions in common variable immunodeficiency-histologic and immunohistochemical analyses of 16 cases. *Hum Pathol.* 2015 Sep;46(9):1306-14. doi: 10.1016/j.humpath.2015.05.011.
23. Friedmann D, Unger S, Keller B, Rakhmanov M, Goldacker S, Zissel G, et al. Bronchoalveolar Lavage Fluid Reflects a TH1-CD21low B-Cell Interaction in CVID-Related Interstitial Lung Disease. *Front Immunol.* 2021;11:616832. doi: 10.3389/fimmu.2020.616832.
24. Van de Ven AAJM, Alfaro TM, Robinson A, Baumann U, Bergeron A, Burns SO, et al. Managing Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders: e-GLILDnet International Clinicians Survey. *Front Immunol.* 2020;11:606333. doi: 10.3389/fimmu.2020.606333.
25. Smits B, Goldacker S, Seneviratne S, Malphettes M, Longhurst H, Mohamed OE, et al. The efficacy and safety of systemic corticosteroids as first line treatment for granulomatous lymphocytic interstitial lung disease. *J Allergy Clin Immunol.* 2023;152(2):528-37.
26. Tessarin G, Baronio M, Gazzurelli L, Rossi S, Chiarini M, Moratto D, et al. Rituximab Monotherapy Is Effective as First-Line Treatment for Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) in CVID Patients. *J Clin Immunol.* 2023;43(8):2091-103.
27. Tillman R, Guillermin RP, Trojan T, Silva-Carmona M, Chinn IK. Treatment-Responsive Granulomatous-Lymphocytic Interstitial Lung Disease in a Pediatric Case of Common Variable Immunodeficiency. *Front Pediatr.* 2019 Mar 29;7:105. doi: 10.3389/fped.2019.00105.
28. Motezuma SI, Panizo CM, Landecho MF. Common variable immunodeficiency-associated granulomatous and lymphocytic interstitial lung disease successfully treated with a combination regimen of rituximab and azathioprine. *Med Clin (Barc).* 2017;149(7):312-3. English, Spanish. doi: 10.1016/j.medcli.2017.05.041.
29. Jolles S, Carne E, Brouns M, El-Shanawany T, Williams P, Marshall C, et al. FDG PET-CT imaging of therapeutic response in granulomatous lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin Exp Immunol.* 2017;187(1):138-45. doi: 10.1111/cei.12856.
30. Limsuwat C, Daroca PJ, Lasky JA. A 56-Year-Old-Man With Common Variable Immunodeficiency and Worsening Dyspnea. *Chest.* 2018;154(1):e27-e30. doi: 10.1016/j.chest.2017.11.034.
31. Pecoraro A, Crescenzi L, Galdiero MR, Marone G, Rivellese F, Rossi FW, et al. Immunosuppressive therapy with rituximab in common variable immunodeficiency. *Clin Mol Allergy.* 2019;17:9. doi: 10.1186/s12948-019-0113-3.
32. Cereser L, De Carli R, Girometti R, De Pellegrin A, Reccardini F, Frossi B, et al. Efficacy of rituximab as a single-agent therapy for the treatment of granulomatous and lymphocytic interstitial lung disease in patients with common variable immunodeficiency. *J Allergy Clin Immunol Pract.* 2019;7(3):1055-1057.e2. doi: 10.1016/j.jaip.2018.10.041.
33. Deyà-Martínez A, Esteve-Solé A, Vélez-Tirado N, Celis V, Costa J, Cols M, et al. Sirolimus as an alternative treatment in patients with granulomatous-lymphocytic lung disease and humoral immunodeficiency with impaired regulatory T cells. *Pediatr Allergy Immunol.* 2018;29(4):425-32. doi: 10.1111/pai.12890.
34. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. *J Allergy Clin Immunol.* 2004;114(2):415-21. doi: 10.1016/j.jaci.2004.05.057.
35. Perlman DM, Sudheendra MT, Racilla E, Allen TL, Joshi A, Bhargava M. Granulomatous-Lymphocytic Interstitial Lung Disease Mimicking Sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2021;38(3):e2021025. doi: 10.36141/svld.v38i3.11114.

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Immunosenescence in older adults with pulmonary tuberculosis

Imunossenescência em idosos portadores de tuberculose pulmonar

Ana Laura Pereira¹, Andrea Gobetti Coelho Bombonatte¹

ABSTRACT

Immunosenescence refers to age-related alterations in the immune system, which may lead to a less effective response to tuberculosis, making its understanding essential in the context of global population aging. This study aimed to describe the immune response to pulmonary tuberculosis, the immunosenescence changes associated with aging, and their influence on disease susceptibility in older adults. A literature review was conducted using major databases, selecting articles published over the past 20 years that addressed the topic of the study; studies focusing on extrapulmonary tuberculosis or immunosenescence associated with other diseases were excluded. The analysis identified key immunological mechanisms involved in the response to tuberculosis infection, the role of cells, the importance of cytokines, and granuloma formation. It also highlighted the main factors underlying immunosenescence, such as cellular senescence and the phenomenon of inflammaging, and their influence on the response to infection and the maintenance of granuloma in older adults. The study also underscores the diagnostic challenges in this population due to senescence, comorbidities, and differences in clinical manifestations, showing that management of tuberculosis in older adults requires special attention and continuous updating of health care professionals. In conclusion, older adults with tuberculosis deserve a differentiated approach to diagnosis and treatment; immunosenescence should be the focus of further in-depth investigation to clarify ambiguities in the literature; health care professionals should improve their understanding of age-related immune changes; and greater investment in public health policies targeting the older population is needed.

Keywords: Cellular senescence, aging, *Mycobacterium tuberculosis*, immunologic factors.

RESUMO

A imunossenescência representa a alteração do sistema imunológico associada ao envelhecimento, favorecendo uma menor eficácia na resposta à tuberculose, sendo essencial compreender essa alteração diante do envelhecimento mundial. O presente estudo teve como objetivo descrever a resposta imune à tuberculose pulmonar, as alterações imunossenescentes relacionadas ao envelhecimento e sua influência na suscetibilidade frente à doença em idosos. Para tanto, realizou-se uma revisão bibliográfica utilizando como fonte as principais bases de dados, sendo selecionados artigos dos últimos 20 anos voltados ao tema de estudo, e desconsiderados aqueles que abordaram sobre tuberculose extrapulmonar e imunossenescência associada a outras doenças. A análise permitiu identificar os principais mecanismos imunológicos na resposta à infecção por tuberculose, a atuação das células, a importância das citocinas e a formação do granuloma. Além disso, evidenciaram-se os fatores que compõem a imunossenescência, como senescência celular e o fenômeno do *inflammaging*, e sua influência na resposta à infecção e na manutenção do granuloma em idosos. O estudo ressalta as dificuldades de diagnóstico que podem ocorrer devido à senilidade, comorbidades e diferenças de manifestação clínica, evidenciando que o tratamento nesta população requer cuidado especial e constante atualização dos profissionais da saúde. Conclui-se que o idoso com tuberculose merece um olhar diferenciado em seu diagnóstico e tratamento, a imunossenescência deve ser objeto de estudos mais aprofundados para elucidar as ambiguidades presentes na literatura, os profissionais da saúde devem aprimorar a compreensão das mudanças imunológicas decorrentes da imunossenescência, e que deve ser investido em políticas públicas voltadas à população idosa.

Descritores: Senescência celular, envelhecimento, *Mycobacterium tuberculosis*, fatores Imunológicos.

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Introduction

Immunosenescence, defined as a set of aging-induced changes in immune response, is synonymous with immunodegeneration.^{1,2} Aging leads to changes in the innate and adaptive immune systems and, according to some researchers, can also be defined as immune system remodeling, as it becomes the 'normal' body function past a certain age.¹⁻³

A bacterial infectious disease that primarily affects the lungs, tuberculosis is caused by the bacillus *Mycobacterium tuberculosis* (Mtb).^{4,5} Transmission occurs through the air, by inhaling aerosols expelled by patients with active tuberculosis (pulmonary or laryngeal) when they cough, sneeze, or speak.⁵

It has been argued that tuberculosis infection in older adults is distinct from that in younger individuals due to differences in clinical presentation and laboratory tests, and these distinctions may be associated with immunosenescence.^{1,4} Immunological protection against the disease is obtained primarily through immunity mediated by phagocytic cells and adaptive T cells, which act to eliminate or contain bacteria; thus, alterations in immune response increase susceptibility to infection.^{1,2}

According to World Health Organization (WHO) estimates, approximately 10.6 million people developed tuberculosis in 2022, and the disease caused 1.3 million deaths. In 2022, tuberculosis was the second leading cause of death worldwide from a single infectious agent, surpassed only by COVID-19.^{6,7} In Brazil, 80,012 new cases were identified in 2023, corresponding to an incidence of 37.0 cases per 100,000 population.⁷

The world's population is aging due to increased life expectancy and declining birth rates. While a large portion of the older adult population lives in developed countries, this population is also growing rapidly in less developed regions. By 2050, nearly 80% of the world's older adult population is projected to live in less developed countries.¹

In the Western Pacific, Eastern Mediterranean, and Southeast Asia, tuberculosis notifications have become progressively more prevalent among older individuals, peaking in those aged ≥ 65 years.¹ In this century, the older adult population has increased noticeably in Brazil. According to the WHO, Brazil had the world's sixth largest older adult population in 2025.^{2,8}

With increasing life expectancy and increasing susceptibility to respiratory infections with advanced age, understanding the relationship between immunosenescence and tuberculosis cure in older adults is essential for preventing complications and improving quality of life in this population.¹ Thus, the aim of this study was to explain immune response to tuberculosis, describe age-related immunosenescence changes, and identify the influence of these changes on susceptibility to pulmonary tuberculosis infection in older adults.

Methods

This study was based on a literature review conducted on SciELO, MEDLINE, BVS, CAPES Journals, and Google Scholar databases. The following keywords were used to search for articles published in Portuguese or English: 'Tuberculose', 'Tuberculosis', 'Tuberculose pulmonar', 'Tuberculose idoso', 'Tuberculosis immunosenescence', 'Cells tuberculosis', 'Immunosenescence', 'Tratamento tuberculose'; using the Boolean operator "AND" between keywords. According to WHO guidelines and Brazilian legislation, older adults are defined as individuals aged ≥ 60 years and can be divided into 2 subgroups: those between 60 and 79 years of age, and the oldest old (≥ 80 years).⁹

The search for articles was limited to a 20-year period, and articles addressing concepts and epidemiology of pulmonary tuberculosis, treatment for older adults with tuberculosis, cells involved in the response to mycobacteria, immunosenescence, and comparative studies between the immune systems of young adults and older adults were included. Epidemiological bulletins and guidelines were also selected to provide a better understanding of the disease.

Cases of extrapulmonary tuberculosis were excluded, since pulmonary tuberculosis is more frequent and relevant to public health.⁵ Furthermore, extrapulmonary manifestations are heterogeneous, as signs and symptoms can vary depending on the affected organs and/or systems, making standardization and comparison between studies difficult.⁵ The following publications were excluded: abstracts, theses, texts addressing cases and aggravating factors of extrapulmonary tuberculosis, studies focusing on disease or treatment in young individuals, and immunosenescence involving other diseases.

Results and discussion

Immune response to tuberculosis

Not everyone exposed to Mtb becomes ill; the risk of developing the disease is associated with endogenous factors, including immune system integrity.^{5,10} It is estimated that 10% of infected individuals become ill, of whom 5% are unable to prevent the initial multiplication of the mycobacterium, thus progressing to active disease. The other 5% become ill later due to bacillus reactivation, which can occur in immunosuppressed individuals, resulting in the rupture of the granuloma. Reactivation can also occur due to exposure to a new source of infection, especially in areas of high prevalence.^{5,10,11}

The disease can be controlled in most infected individuals but not eliminated completely, remaining asymptomatic and non-transmissible, given that the immune system can contain the bacilli, preventing them from developing and causing illness.^{5,10,12} This clinically silent infection is called latent tuberculosis infection, in which the bacteria can remain dormant for many years until reactivation.^{10,12}

Immune response plays an important role in controlling initial infection and preventing the reactivation of latent infection, especially innate immune response, which plays a role in controlling the bacterial load and determining the intensity of adaptive response.^{12,13} After transmission, alveolar macrophages are the first cells to fight the antigen, engulfing it in a phagocyte. However, the bacillus possesses escape mechanisms that prevent the phagosome maturation process and fusion with the lysosome, favoring its survival and replication inside the phagocyte.¹²⁻¹⁵

Following phagocytosis, the bacilli captured by antigen-presenting cells are transported to the lymph nodes and presented to T cells, stimulating an adaptive response. Nevertheless, this can take weeks to migrate to the infected lung.^{12-14,16} Antigen-presenting cells are also responsible for the production of inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α) and interleukin (IL)-1, which recruit neutrophils and monocytes to the site of infection.^{14,15}

These cytokines are important agents in disease response, and the literature reports that treatments involving anti-TNF- α and IL-1 blockers are associated with a higher risk of disease reactivation. However, excess TNF- α can promote hyperinflammation

and host death. Similarly, excess IL-1 is related to increased neutrophil influx and pulmonary inflammation, leading to a high bacterial load and mortality.¹⁵ Hence, excessive production of protective factors can be harmful.¹⁵

Over time, the bacillus' reach is expanded, infecting neutrophils, dendritic cells, and recruited macrophages. Although neutrophils can respond effectively to various microorganisms, Mtb manages to evade these defenses, creating a favorable environment for proliferation.^{13,15,16} It induces neutrophil necrosis, which promotes its growth when phagocytosed by macrophages, thus leading to further neutrophil recruitment and perpetuation of the infection cycle.¹⁶ Necrosis, which results in the uncontrolled release of cellular content, assists the pathogen by promoting inflammation and facilitating bacterial dissemination, whereas apoptosis benefits the host because it occurs in a controlled manner, limiting inflammation and the release of infectious material.^{16,17}

Adaptive response is mediated by CD4+ and CD8+ Th1 T lymphocytes, which are both critical for infection control, acting synergistically by producing pro-inflammatory cytokines (interferon [IFN]- γ and TNF), or through cytotoxic mechanisms in the case of CD8+ T cells.^{12,14,16,18} Animal studies have determined that bacterial population growth is unlimited in macrophages until the arrival of CD4 T cells in the lungs, which is likely due to their IFN- γ production, since this cytokine activates macrophage antimicrobial capacity.^{12,14,15} Although IFN- γ plays an important role in infection, it is ineffective on its own; synergy with vitamin D is important for effective antimicrobial action.¹³⁻¹⁵ When associated with TNF- α , IFN- γ induces the production of the enzyme nitric oxide synthase, which generates high levels of nitric oxide and other nitrogenous intermediate radicals, which play a bactericidal role and participate in Mtb infection resistance.¹⁴

Granulomas, the main histopathological feature of tuberculosis, consist of macrophages, lymphocytes, and neutrophils.^{12,16} When adaptive immune response is effective, granulomas can control or even eliminate the infection, becoming sclerotic and calcified, while in cases of active disease they are necrotic and have a caseous appearance.^{12,16} This structure is the result of the host's attempt to contain and limit the infection, creating a site for the response interaction between lymphocytes and macrophages activated by IFN- γ .^{12,14} CD4 T cells and TNF play an essential

role in granuloma formation and host protection. People with compromised CD4 T cells (eg, HIV-positive individuals) or those treated with anti-TNF have difficulty forming structured granulomas, which puts them at high risk of active tuberculosis and disseminated infection.^{11,16}

An essential immunosuppressive function of regulatory T cells is to maintain immune homeostasis, preventing excessive inflammatory response to infection, acting in conjunction with anti-inflammatory cytokines such as IL-10 and transforming growth factor β .^{15,18,19} There is debate about the role of regulatory T cells in tuberculosis infection, because, in cases of an excessive inflammatory response, they may benefit the host by preventing hyperinflammation. Nevertheless, their immunosuppressive role may benefit the bacillus by causing a slower immune response.^{15,19} However, it must be remembered that many individuals infected with *Mtb* succumb to the disease due to exacerbated immunopathology rather than bacterial overgrowth.¹⁸

Immunosenescence

Aging encompasses several characteristics, including genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, dysregulated nutrient sensing, cellular senescence, stem cell exhaustion, altered intercellular communication, loss of proteostasis, impaired autophagy, dysbiosis (microbiome disorder), and inflammation.^{3,20} Together, these factors contribute to the development of immunosenescence.^{3,20} In this study, we do not provide a detailed discussion of each of these factors; instead, we highlight selected aspects, with particular emphasis on the impact of aging on immune responses.

First, it is important to emphasize that although cellular senescence and immunosenescence are complementary, they describe different phenomena.^{3,21,22} Cellular senescence is cellular aging, defined as the arrest of the cell cycle in response to stress, which occurs in both younger and older individuals. The role of the immune system is to remove these cells and prevent their buildup in tissue.^{3,21,22} However, as the immune system ages and its functions are rearranged, these cells tend to build up due to inefficient elimination and resistance to apoptosis.^{21,22} Cellular senescence can occur in fibroblasts, solid organ cells, and immune cells, and their accumulation leads to age-related

tissue degeneration.²¹ When accumulated, they secrete senescence-associated pro-inflammatory mediators, which can attract immune cells toward the senescent cell for elimination. However, chronic exposure to inflammatory mediators can be detrimental to circulating cells, which can also become senescent.^{3,21,22} In the long term, cellular senescence induces chronic inflammation, another characteristic of immunosenescence, which drives loss of resilience and susceptibility to many diseases.^{3,21} Some studies refer to this characteristic as inflammaging, due to the unbalanced increase in systemic pro-inflammatory cytokines (TNF, IL-6, and IL-1) and reduced levels of anti-inflammatory cytokines during aging.^{3,23,24}

One study presented the theory that immunosenescence, associated with “inflammaging,” decreases adaptive immune response due to inflammatory mediators but increases innate response as an attempt to protect the organism.³ However, several other factors besides inflammation can influence the innate and adaptive immune systems, such as senescent cells, splenic deterioration, thymic involution, and bone marrow aging.^{3,22}

The thymus is a central lymphoid organ that gradually degenerates with age, shrinking and replacing its specialized tissue with adipose tissue, a process known as thymic involution.^{22,25} Thymic involution has a major impact on adaptive response, since its functional decline reduces the production of naive T cells.^{24,26} Low production of naive T cells in the thymus leads to a gradual increase in effector memory cells, resulting in fewer nonspecific cells and more cells at an advanced stage of differentiation.^{2,3,22,27} Studies in animal models have shown that naive T cells have reduced activation, differentiation, and cytokine production after antigen presentation, while memory cells produce fewer cytokines.^{2,25}

Although regulatory T cells are less affected by thymic atrophy due to their possible origin from CD4 T cell differentiation, in specific populations they can still be reduced in certain tissues.^{24,25} The results of the literature have been ambiguous about the function of regulatory T cells, with some authors reporting that their function decreases in older adults, while others have reported that their functioning remains unchanged or even increases.²⁵

The spleen and the lymph nodes are peripheral lymphoid organs in which immune cells proliferate,

mature, differentiate, and interact with antigen-presenting cells.²⁵ Increased fibrosis, caused by cellular senescence, leads to a progressive reduction in the number and size of lymph nodes. This, combined with altered permeability and inflammation, impairs the migration and recruitment of immune cells, resulting in decreased humoral immunity and a greater susceptibility to infections in older adults.^{3,25} The spleen maintains white blood cell and platelet populations, which, when mobilized, support protective immune response.³ With aging, the spleen increases the expression of the pro-inflammatory cytokine IL-6, which can impair T cell recruitment and inhibit macrophage phagocytosis, contributing to inflammaging.²⁵

Bone marrow produces myeloid progenitors, which differentiate into dendritic cells, macrophages, and neutrophils.^{2,27} These cells, which are associated with natural killer cells of lymphoid origin, are part of the innate immune system, and aging can reduce their function, despite increased production.^{2,27}

Dendritic cells, the bridge between the innate and adaptive immune responses, can also originate from lymphoid (plasmacytoid) cells.^{3,21,28} Cellular senescence can impair some dendritic cell functions, such as antigen uptake, chemotaxis and migration, phagocytic activity, and cytokine secretion.^{25,26} A reduction in circulating plasmacytoid dendritic cells and impaired signaling can lead to reduced/delayed production of type I IFN. This group of cytokines is responsible for the recruitment and activation of innate cells, such as macrophages and natural killer cells.²¹

Macrophages and neutrophils are phagocytic cells that remove pathogens from the body.²¹ With aging, phagocytosis may become compromised in tissue-derived macrophages, affecting local homeostasis.^{3,21} Moreover, their ability to secrete TNF in response to infections is reduced, which can affect innate immune response.²⁶ In aged bone marrow, macrophages and neutrophils have shown inflammatory and senescent patterns in gene expression.²¹ An inflammatory state can lead neutrophils to have abnormal adhesion and chemotaxis, altered metabolism, impaired microbicidal function, increased apoptosis, and reduced phagocytic capacity.^{3,25,26} Furthermore, the production of certain chemokines can cause irregular neutrophil trafficking to remote organs, such as the lungs, rather than to local injured tissues, resulting in organ damage.²¹

Natural killer cells tend to decrease due to their reduced proliferative capacity, resulting from a lack of activating cytokines (IL-2, IFN- α , and IFN- γ), especially in the 75-85-year age group.^{3,25,26} However, increased specialized natural killer subpopulations, along with preserved telomere length, result in maintained or even increased function, compensating for the reduced number of cells.^{3,25,26}

As discussed previously, aging leads to changes in innate and adaptive immune responses, which can increase the risk of developing diseases such as tuberculosis. Thymic involution can compromise the availability of CD4 T lymphocytes to maintain the granuloma and, along with immune cell senescence and reduced production of certain cytokines, Mtb reactivation may occur.^{1,11,16} An unbalanced pattern of pro- and anti-inflammatory factors, associated with alterations in IL-2 and TNF- α production in the lung, may be beneficial to the bacillus.^{1,3} This is because inflammaging associated with an inflammatory response to tuberculosis further contributes to the pathogenesis of the bacteria and to lung tissue damage.²³ Understanding the nature of these changes in the immune system and how they occur can help improve diagnosis and treatment.

Diagnosing and treating tuberculosis in older adults

Diagnosing the disease can be more difficult in older adults than younger people, which may be related to several factors.^{4,29} Deafness, blindness or partial vision, verbalization difficulties, memory deficits, and senility negatively affect accurate diagnosis among older adults since they can hinder symptom reporting.^{4,29} The second category involves comorbidities that can increase the risk of developing active tuberculosis or mask its symptoms, such as diabetes mellitus, kidney failure, cancer, HIV, chronic obstructive pulmonary disease, other respiratory diseases (eg, asthma, pulmonary fibrosis), and cardiovascular diseases.^{1,4,18,29,30}

It is important to recognize the clinical manifestations of the disease, as radiological findings and symptoms may differ in older adults.^{1,4,29} For example, decreased lung elasticity, impaired respiratory neural mechanisms, and weakened respiratory muscles can impair the expulsion of infectious agents through coughing, sneezing, or breathing, eliminating prolonged cough.^{10,23,31} It is important to note that the results of

some immunological tests that detect past exposure to infection may also show altered results due to age, such as the tuberculin skin test or IFN- γ release assays.^{1,29}

Although death can be prevented in older adults with tuberculosis, this age group does experience a higher mortality rate.^{4,32-35} Studies suggest that this may be associated with age-related immunosuppression, co-infections, malnutrition, comorbidities, and/or late diagnosis.^{4,32} A Taiwanese study conducted between 2004 and 2009 in patients with pulmonary tuberculosis aged ≥ 20 years³² observed treatment delays in all patients, but greater delays and worse outcomes among older patients, concluding that older adults required more hospitalizations (65-79 years 55.9%, ≥ 80 years 66.7%), intensive care unit admissions (65-79 years 12.5%, ≥ 80 years 20.3%), and invasive ventilatory support (65-79 years 11.4%, ≥ 80 years 20.1%) than younger patients.³² Older adults also had the highest mortality rates (65-79 years 18.5%, ≥ 80 years 34.7%),³² leading to the conclusion that aging is associated with unfavorable outcomes, especially in patients with comorbidities.³² Delays in diagnosis, and hence treatment, may be related to difficulty accessing health care services, inadequate reception, ignorance of symptoms, and even incorrect diagnosis.^{4,32}

Additionally, a study at the Lishui Hospital of Traditional Chinese Medicine³⁶ identified malnutrition as a risk factor for infection, attributing an estimated 2.3 million cases to it, making it a more common cause than HIV or diabetes mellitus. Malnutrition results in a lack of energy, which can lead to alterations in body composition, metabolism, and immune status. Previous studies have demonstrated that a lack of vitamins (A, E, and D) and trace elements (zinc and magnesium) interferes with immune system function.^{20,26,36-38}

A study in eastern Pacific countries³⁹ reported that an annual screening program for older adults was an effective tactic for diagnosing the disease. According to this study, mobile chest X-ray screening for active cases was added to a previously established older adult health surveillance program in China, resulting in fewer cases and outbreaks in older adult care facilities.³⁹ In Japan, in addition to mobile radiography, people aged ≥ 65 years undergo annual tuberculosis screening to prevent outbreaks, and admission tests are conducted for care facility

staff to increase early detection.³⁹ All of the countries involved in the study have specific tuberculosis treatment facilities and programs.³⁹

In Brazil, the main objective of the National Health Policy for Older Adults (*Política Nacional de Saúde da Pessoa Idosa*) is to recover, maintain, and promote the autonomy and independence of older adults through collective and individual health initiatives for all citizens aged ≥ 60 years.⁴⁰ The National Week of Mobilization and Fight Against Tuberculosis (*Semana Nacional de Mobilização e Luta Contra a Tuberculose*) sought to mobilize society and provide guidance on prevention, symptoms, and treatment.^{7,41} Furthermore, active searches for individuals with persistent cough can result in the early detection of cases and more rapid treatment initiation, being part of the Programmatic Strategies of the National Tuberculosis Control Program (*Estratégias Programáticas do Programa Nacional de Controle da Tuberculose*).⁴² Together, these initiatives can help monitor older adults with tuberculosis.³⁹

Following diagnosis, treatment should be carefully considered, as older adults may be more susceptible to adverse effects due to polypharmacy, comorbidities, and physiological changes.^{1,29,35,43} Adverse reactions are divided into minor and major, with major reactions generally requiring treatment discontinuation.^{5,10,44} In the general population, risk factors for major reactions include age (≥ 40 years), alcohol consumption, malnutrition, a history of liver disease, and HIV co-infection.¹⁰ These immunosenescence-related factors can further compromise the body's ability to metabolize medications, increasing the risk of toxicity and reduced therapeutic efficacy.

Polypharmacy is defined as the simultaneous use of ≥ 5 medications, often due to comorbidities and self-medication.⁴⁵ Excessive medication use can cause adverse reactions, drug interactions, and poisoning.⁴⁵ Antituberculosis drugs, despite being effective against the bacillus, can cause adverse reactions, such as hepatotoxicity.⁴⁴ In combination with other medications, the effects of antituberculosis drugs may be potentiated or reduced; similarly, antituberculosis drugs may influence the effectiveness of the medications with which they interact (eg, corticosteroids, diuretics, antacids).^{10,29,44}

Health care professionals, especially nurses and pharmacists, can play an important role in ensuring

proper treatment adherence and self-care.^{10,46,47} Greater understanding of the disease among older adults may improve the effectiveness of interventions, including medication administration, monitoring of adverse effects, and treatment adherence strategies.^{4,46} Directly observed treatment (DOT) represents a humanized strategy for treatment support and monitoring to achieve treatment success.^{10,32,39} A group of researchers³⁹ reported that the implementation of a series of changes, including DOT, reduced infection rates in China. Similarly, a Taiwanese study³² reported that completion rates of tuberculosis treatment increased among older adults after DOT was implemented. In Brazil, DOT has been in use since 1998. However, in addition to this strategy, other initiatives, such as individualized therapy for more complex situations, and patient care support groups and discussion circles should be implemented.^{10,48}

Conclusions

In view of the foregoing, we can conclude that older adults with tuberculosis require a differentiated approach to diagnosis and treatment, since immunosenescence changes immune system functioning, making these patients more susceptible to infections and morbidity. More humanized therapeutic measures are necessary, as these are the primary method for understanding this population's complaints.

Immunosenescence must be studied and discussed in greater detail to clarify the ambiguities in the literature. With increasing older adult populations worldwide, a better understanding of these characteristics is crucial to ensure healthy aging. Age-related morbidity can be reduced through drugs and biological products, such as vaccines, which are less aggressive to the aging immune system.

Investment in training and development for health care professionals regarding immunosenescence and its consequences are fundamental for better tuberculosis care. Furthermore, health initiatives such as “Senior Citizen Week” and the “National Week of Mobilization Against Tuberculosis” should be encouraged and publicized, because they can serve as strategies for the promotion and prevention of tuberculosis among older adults.

References

1. Byng-Maddick R, Noursadeghi M. Does tuberculosis threaten our ageing populations? *BMC Infect Dis*. 2016 Mar 11;16:119. doi: 10.1186/s12879-016-1451-0.
2. Alves AS, Bueno V. Immunosenescence: participation of T lymphocytes and myeloid-derived suppressor cells in aging-related immune response changes. *Einstein (Sao Paulo)*. 2019 May 2;17(2):eRB4733. doi: 10.31744/einstein_journal/2019RB4733.
3. Quiros-Roldan E, Sottini A, Natali PG, Imberti L. The Impact of Immune System Aging on Infectious Diseases. *Microorganisms*. 2024 Apr 11;12(4):775. doi: 10.3390/microorganisms12040775.
4. Chaves EC, Carneiro ICRS, Santos MIPO, Sarges NDA, Guimarães DSO. Diagnóstico da tuberculose pulmonar em idosos de um hospital universitário no período 2009-2013, Belém, Pará. *Rev Bras Ciênc Envelhec Hum*. 2016;13(3):299-308. doi: 10.5335/rbceh.v13i3.6558.
5. Brasil. Ministério da Saúde. Guia de Vigilância em Saúde [Internet]. Brasília; 2017. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/guia_vigilancia_saude_3ed.pdf. Accessed on: Jun 18 2024.
6. World Health Organization. Global tuberculosis report 2023 [Internet]. Geneva:WHO;2023. Available from: <https://www.who.int/publications/item/9789240083851>. Accessed on: Jun 18 2024.
7. Brasil. Ministério da Saúde. Boletim Epidemiológico Tuberculose 2024 [Internet]. Brasília; 2024. Available from: <https://www.gov.br/aids/pt-br/central-de-conteudo/boletins-epidemiologicos/2024/boletim-epidemiologico-tuberculose-2024/view>. Accessed on: Jul 17 2024.
8. Felix JS. Economia da longevidade: uma revisão da bibliografia brasileira sobre o envelhecimento populacional. In: *Anais 8th Encontro da Associação Brasileira de Economia da Saúde* [Internet]; São Paulo, SP; 2007. Available from: http://www.observatorionacionaldoidoso.fiocruz.br/biblioteca/_artigos/45.pdf. Accessed on: Aug 20 2024.
9. Brasil. Ministério do Desenvolvimento e Assistência Social, Família e Combate à Fome, Brasil. Secretaria Nacional da Política de Cuidados e Família. Nota Informativa nº 5/2023: Envelhecimento e Direito ao Cuidado [internet]. Brasília; 2023. Available from: https://www.gov.br/mds/pt-br/noticias-e-conteudos/desenvolvimento-social/noticias-desenvolvimento-social/mds-lanca-diagnostico-sobre-envelhecimento-e-direito-ao-cuidado/Nota_Informativa_N_5.pdf. Accessed on: Feb 19 2025.
10. Brasil. Ministério da Saúde. Manual de recomendações para o controle da tuberculose no Brasil [internet]. 2ª ed. Brasília; 2019. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/manual_recomendacoes_controle_tuberculose_brasil_2_ed.pdf. Accessed on: Sep 09 2024.
11. Alves ACFPB, Prado AIF, Takenami I. Imunologia da tuberculose: uma revisão narrativa da literatura. *Arq Asma Alerg Imunol*. 2022;6(2):239-50. doi: 10.5935/2526-5393.20220024.
12. Lin PL, Flynn JL. CD8 T cells and Mycobacterium tuberculosis infection. *Semin Immunopathol*. 2015 May;37(3):239-49. doi: 10.1007/s00281-015-0490-8.
13. Sia JK, Georgieva M, Rengarajan J. Innate Immune Defenses in Human Tuberculosis: An Overview of the Interactions between Mycobacterium tuberculosis and Innate Immune Cells. *J Immunol Res*. 2015;2015:747543. doi: 10.1155/2015/747543.
14. Moutinho ILD. Tuberculose: aspectos imunológicos na infecção e na doença. *Rev Méd Minas Gerais*. 2011;21(1):42-8. Available from: <https://www.rmmg.org/artigo/detalhes/289>.

15. Ravesloot-Chávez MM, Van Dis E, Stanley SA. The Innate Immune Response to Mycobacterium tuberculosis Infection. *Annu Rev Immunol.* 2021 Apr 26;39:611-37. doi: 10.1146/annurev-immunol-093019-010426.
16. Chandra P, Grigsby SJ, Philips JA. Immune evasion and provocation by Mycobacterium tuberculosis. *Nat Rev Microbiol.* 2022 Dec;20(12):750-66. doi: 10.1038/s41579-022-00763-4.
17. Iba T, Hashiguchi N, Nagaoka I, Tabe Y, Murai M. Neutrophil cell death in response to infection and its relation to coagulation. *J Intensive Care.* 2013 Dec 4;1(1):13. doi: 10.1186/2052-0492-1-13.
18. Chai Q, Lu Z, Liu CH. Host defense mechanisms against Mycobacterium tuberculosis. *Cell Mol Life Sci.* 2020 May;77(10):1859-78. doi: 10.1007/s00018-019-03353-5.
19. Cardona P, Cardona PJ. Regulatory T Cells in Mycobacterium tuberculosis Infection. *Front Immunol.* 2019 Sep 11;10:2139. doi: 10.3389/fimmu.2019.02139.
20. Dominguez LJ, Veronese N, Barbagallo M. Magnesium and the hallmarks of aging. *Nutrients.* 2024;16(4):496. doi: 10.3390/nu16040496.
21. Lee K-A, Flores RR, Jang IH, Saathoff A, Robbins PD. Immune Senescence, Immunosenescence and Aging. *Front. Aging.* 2022;3:900028. doi: 10.3389/fragi.2022.900028.
22. Slaets H, Veeningen N, de Keizer PLJ, Hellings N, Hendrix S. Are immunosenescent T cells really senescent? *Aging Cell.* 2024 Oct;23(10):e14300. doi: 10.1111/ace1.14300.
23. Piergallini TJ, Turner J. Tuberculosis in the elderly: Why inflammation matters. *Exp Gerontol.* 2018 May;105:32-39. doi: 10.1016/j.exger.2017.12.021.
24. Thomas R, Wang W, Su DM. Contributions of Age-Related Thymic Involution to Immunosenescence and Inflammation. *Immun Ageing.* 2020 Jan 20;17:2. doi: 10.1186/s12979-020-0173-8.
25. Wang Y, Dong C, Han Y, Gu Z, Sun C. Immunosenescence, aging and successful aging. *Front Immunol.* 2022 Aug 2;13:942796. doi: 10.3389/fimmu.2022.942796.
26. Ongrádi J, Kövesdi V. Factors that may impact on immunosenescence: an appraisal. *Immun Ageing.* 2010 Jun 14;7:7. doi: 10.1186/1742-4933-7-7.
27. Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence and human vaccine immune responses. *Immun Ageing.* 2019;16(1):25. doi: 10.1186/s12979-019-0164-9.
28. Ewers I, Rizzo LV, Kalil Filho J. Imunologia e envelhecimento. *Einstein.* 2008;6:13-20.
29. Caraux-Paz P, Diamantis S, de Wazières B, Gallien S. Tuberculosis in the Elderly. *J Clin Med.* 2021 Dec 15;10(24):5888. doi: 10.3390/jcm10245888.
30. Abbara A, Collin SM, Kon OM, Buell K, Sullivan A, Barrett J, Corrah T, McGregor A, Hansel T, John L, Davidson RN. Time to diagnosis of tuberculosis is greater in older patients: a retrospective cohort review. *ERJ Open Res.* 2019 Nov 4;5(4):00228-2018. doi: 10.1183/23120541.00228-2018.
31. Lalley PM. The aging respiratory system--pulmonary structure, function and neural control. *Respir Physiol Neurobiol.* 2013 Jul 1;187(3):199-210. doi: 10.1016/j.resp.2013.03.012.
32. Lee CH, Wang JY, Lin HC, Lin PY, Chang JH, Suk CW, et al. Treatment delay and fatal outcomes of pulmonary tuberculosis in advanced age: a retrospective nationwide cohort study. *BMC Infect Dis.* 2017 Jun 24;17(1):449. doi: 10.1186/s12879-017-2554-y.
33. Hussein MT, Yousef LM, Abusedera MA. Pattern of pulmonary tuberculosis in elderly patients in Sohag Governorate: Hospital based study. *Egypt J Chest Dis Tuberc.* 2013;62(2):269-74. doi: 10.1016/j.ejcdt.2013.05.001.
34. GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *Lancet Infect Dis.* 2018;18(3):261-84. doi: 10.1016/S1473-3099(17)30703-X.
35. Chaves EC, Carneiro ICRS, Santos MIPO, Sarges NA, Neves EOS. Epidemiological, clinical and evolutionary aspects of tuberculosis among elderly patients of a university hospital in Belém, Pará. *Rev Bras Geriatr Gerontol.* 2017;20(1):45-55. doi: 10.1590/1981-22562017020.160069.
36. He M, Yang X, Zhang Z, Liu Z. Impaired pulmonary function and associated factors in the elderly with tuberculosis on admission: a preliminary report. *BMC Infect Dis.* 2023;23(1):251. doi: 10.1186/s12879-023-08183-2.
37. Haase H, Rink L. The immune system and the impact of zinc during aging. *Immun Ageing.* 2009;6(1):9. doi: 10.1186/1742-4933-6-9.
38. Fantini C, Corinaldesi C, Lenzi A, Migliaccio S, Crescioli C. Vitamin D as a shield against aging. *Int J Mol Sci.* 2023;24(5). doi: 10.3390/ijms24054546.
39. Teo AKJ, Rahevar K, Morishita F, Ang A, Yoshiyama T, Ohkado A, et al. Tuberculosis in older adults: case studies from four countries with rapidly ageing populations in the western pacific region. *BMC Public Health.* 2023;23(1):370. doi: 10.1186/s12889-023-15197-7.
40. Brasil. Ministério da Saúde. Portaria de Consolidação nº 2/2017. Consolidação das normas sobre as políticas nacionais de saúde do Sistema Único de Saúde [internet]. Brasília, Brasil; 2017. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prc0002_03_10_2017_comp.html. Accessed on: Oct 09 2024.
41. Brasil. Ministério da Saúde. Departamento de HIV, Aids, Tuberculose, Hepatites Virais e Infecções Sexualmente Transmissíveis. Semana Nacional de Mobilização e Luta Contra a Tuberculose contou com mais de 1900 acessos [internet]. Brasília, DF: Ministério da Saúde; 2022. Available from: <https://www.gov.br/aids/pt-br/assuntos/noticias/2022/maio/semana-nacional-de-mobilizacao-e-luta-contra-a-tuberculose-contou-com-mais-de-1900-acessos>. Accessed on: Oct 17 2024.
42. Prefeitura do Município de São Paulo, Brasil. Secretaria Municipal da Saúde. Nota Informativa 04PMCT/2022: Busca ativa de sintomático respiratório – SR [Internet]. São Paulo; 2022. Available from: https://www.prefeitura.sp.gov.br/cidade/secretarias/upload/Nota_Informativa_Sint%20Resp%20PMCT%202022.pdf. Accessed on: Sep 02 2025.
43. Cantalice Filho JP, Bóia MN, Sant Anna CC. Análise do tratamento da tuberculose pulmonar em idosos de um hospital universitário do Rio de Janeiro, RJ, Brasil. *J Bras Pneumol.* 2007;33(6):691-8. doi: 10.1590/s1806-37132007000600013.
44. Vieira DEO, Gomes M. Efeitos adversos no tratamento da tuberculose: experiência em serviço ambulatorial de um hospital-escola na cidade de São Paulo. *J Bras Pneumol.* 2008;34(12):1049-55. doi: 10.1590/s1806-37132008001200010.
45. de Oliveira BS, Ribeiro AMVB, Araújo PS, Ponce JT, Novaes HPO. Polifarmácia entre idosos de uma unidade de saúde da família: um relato de experiência multiprofissional. *Saúde.com.* 2021;17(3). doi: 10.22481/rsc.v17i3.8213.
46. Maciel DO, Rupf JMO, Oliveira EM, Jacinto RRS, Almeida MSL, Cordeiro JPP. Assistência de enfermagem em pacientes com tuberculose multirresistente. *Doenças Infec Parasit.* 2024;12:34-41.

47. Shuhama BV, Silva LMC, Andrade RLP, Palha PF, Hino P, Souza KMJ. Avaliação do tratamento diretamente observado da tuberculose segundo dimensões da transferência de políticas. *Rev Esc Enferm USP*. 2017;51:e03275. doi 10.1590/S1980-220X2016050703275.
48. Nicoletti GP, Antunes ADA, Gurgel JAR, Costa SS, Brandão GHA. A importância do profissional farmacêutico no processo de cura da tuberculose/the importance of pharmaceutical professionals in the tuberculosis healing process. *Braz J Dev*. 2020;6(11):85213-38. doi 10.34117/bjdv6n11-078.

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Specific substances in a new cosmetic patch test series: a narrative review

Substâncias específicas de nova série de cosméticos para teste de contato: uma revisão narrativa

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ABSTRACT

Contact dermatitis lesions are a frequent cause of consultation in the daily practice of allergists, particularly those induced by substances present in cosmetic products. Accurate diagnosis of these eczematous conditions requires patch testing using updated series with clinical relevance. In Brazil, the currently available cosmetic patch test series is outdated, originating from the period in which the Brazilian standard series was established. Recently, a new cosmetic series comprising 20 elements has been proposed, following the specific numbering of each hapten. Based on this proposal, a literature search was conducted in PubMed and ClinicalKey databases, focusing on publications from the past 10 years that addressed allergens in the context of contact dermatitis. Within this scenario, the present review aimed to discuss the selected allergens involved in cosmetic-related contact dermatitis, highlight their current scientific relevance, and reaffirm the need for the development of a new, specific cosmetic patch test series.

Keywords: Patch testing, cosmetics, contact dermatitis, allergy.

RESUMO

As lesões de dermatite de contato constituem uma causa frequente de consulta na prática diária do alergista, entre elas, as induzidas por substâncias presentes em cosméticos. O diagnóstico adequado desses eczemas requer a realização de testes de contato por séries atualizadas com relevância clínica. No Brasil existe uma bateria de cosméticos antiga proveniente do período da composição da bateria padrão brasileira. Recentemente foi proposta uma nova série de cosméticos, com 20 elementos, seguindo-se o número específico de cada hapteno. Partindo-se desta sugestão, foi realizada busca nas bases de dados PubMed e ClinicalKey, considerando as publicações dos últimos 10 anos que conectavam os alérgenos no contexto da dermatite de contato. Neste cenário, esta revisão tem como objetivo explicar sobre os alérgenos selecionados envolvidos na dermatite de contato associada a cosméticos, destacando a importância científica atual destas substâncias e reafirmar a necessidade da criação de uma nova série específica.

Descritores: Teste de contato, cosméticos, dermatite de contato, alergia.

Introduction

According to the Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA), cosmetics are preparations made from natural or synthetic substances, intended for application in various external parts of the human

body, including skin, hair, nails, lips, external genitals, teeth, and the mucous membranes of the oral cavity, with the sole or principal purpose of cleaning them, perfuming them, changing their appearance, and/or correcting bodily odors, and/or protecting them

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or keeping them in good condition.¹ Based on this definition, one can assume suspected hypersensitivity to ingredients in personal care products, particularly cosmetics, is the most common reason for referring individuals for patch testing. Centers performing these examinations must have an extensive cosmetic patch test series available to supplement the baseline series when clinically indicated.²

In Brazil, there is an outdated cosmetic patch test series consisting of only 10 haptens, created when the Brazilian standard baseline series was first established. This cosmetic series has never been revised. Testing patients' own products and their ingredients is essential not only to avoid missing clinically relevant allergens but also to monitor fluctuations in hypersensitivity incidence, given that the composition of cosmetics and personal care products is always changing.² The beauty industry is continuously evolving and constantly reinventing itself.

A recent study proposed a new cosmetic patch test series.³ Initially, data from the European Surveillance System on Contact Allergies (ESSCA) were used to identify allergens commonly used in different centers to test contact allergy to cosmetics. Subsequently, major studies reporting large patch test case series were reviewed to identify substances that showed a prevalence above 0.3%. Next, commercial product databases were searched to confirm whether the selected allergens were present in cosmetics available on the retail market. Ultimately, 20 substances were selected, each identified by its individual Chemical Abstracts Service (CAS) number.³ This number is a unique numerical identifier assigned to every chemical substance by the CAS, regardless of their commercial name.

It is important to note that many haptens present in cosmetics have a prevalence high enough to justify their inclusion in a baseline series (positivity rates exceeding 0.5%–1% of tested individuals). Therefore, when patch testing individuals with suspected allergic contact dermatitis (ACD) to cosmetics, both an adequate baseline series and a specific cosmetic series should be used. The following substances should be included in the baseline series: formaldehyde, bronopol, diazolidinyl urea, quaternium-15, methylchloroisothiazolinone/methylisothiazolinone, methylisothiazolinone, sodium metabisulfite, paraben mix, propyl gallate, lanolin alcohol, Amerchol L-101, propolis, cocamidopropyl betaine, decyl glucoside, propylene glycol, colophony, tosylamide/formaldehyde

resin, and 2-hydroxyethyl methacrylate. These substances (already included in the baseline series) fall outside the scope of the present review.

Thus, the objective of this study was to present the selected allergens involved in ACD to cosmetics, highlighting the current scientific relevance of these substances and the need to establish a new specific cosmetic series.

Methods

This narrative literature review compiled and analyzed data on allergens proposed for inclusion in a new cosmetic patch test series. The PubMed and ClinicalKey databases were searched, from November 2024 to February 2025, for articles published in English in the past 10 years. Descriptors corresponding to the name of each hapten were used in combination with the term "contact dermatitis," connected by the Boolean operator "AND." After screening of titles and abstracts, publications containing information relevant to the topic were included in the review to illustrate the clinical relevance of the investigated substances. Articles published in the journal *Arquivos de Asma, Alergia e Imunologia* were included as references when relevant. In addition to scientific articles, case reports were included whenever available to illustrate cases highlighting the importance of testing the respective substances.

The evaluated haptens, along with their respective concentrations, vehicles, and specific CAS numbers, are presented in Table 1.

Results

Below, each of the investigated substances is discussed according to the respective references and reported findings.

Butylated hydroxyanisole

Butylated hydroxyanisole (BHA) is an antioxidant used in foods and pharmaceuticals. Its use in cosmetics has been increasing progressively.⁴ An investigation of chemical substances in cosmetic products identified BHA in 1.6% of the analyzed items, particularly in rinse-off products (shampoo) and makeup (lip balms); the substance was not identified in leave-on products.⁵ The North American Contact Dermatitis Group (NACDG), using a supplemental

patch test series designed to identify additional allergens, reported a 1% positivity rate for BHA.⁶ BHA exhibits cross-reactivity with butylated hydroxytoluene (BHT) and tert-butylhydroquinone (TBHQ).⁴

Cocamide diethanolamine

Cocamide diethanolamine is a nonionic emulsifier or surfactant, also known as cocamide DEA, that functions as a foaming agent and viscosity enhancer. It is used in cosmetic products such as liquid soaps and shampoos, as well as in industrial and household

products.⁷ Other sources include hair dyes, shaving creams, deodorants, topical antifungals, and antiseptic solutions.⁸ In a retrospective study involving more than 1700 patients, 1% showed a clear positive allergic response to this substance. All affected individuals presented with hand eczema, although many also had involvement of other body areas. Importantly, all patients had a previous history of impaired skin barrier due to atopic/contact dermatitis.⁷ It should be noted that cocamide diethanolamine may also cause irritant dermatitis.⁹ Cross-reactivity has been described with lauramide DEA and cocamide monoethanolamine.¹⁰

Table 1

Proposed cosmetic patch test series

No.	Substance	Concentration (%)	Vehicle	CAS ^a
1	Tocopheryl acetate	10	Petroleum jelly	7695-91-2
2	Benzyl alcohol	10	Softisan	100-51-6
3	Cetearyl alcohol	20	Petroleum jelly	67762-27-0
4	Sodium benzoate	5	Petroleum jelly	532-32-1
5	Benzophenone-3	10	Petroleum jelly	131-57-7
6	Benzophenone-4	10	Petroleum jelly	4065-45-6
7	Butylated hydroxyanisole	2	Petroleum jelly	121-00-6
8	Benzalkonium chloride	0.1	Aqueous	63449-41-2
9	Coco glucoside	5	Petroleum jelly	68424-94-2
10	Cocamide diethanolamine	0.5	Petroleum jelly	68603-42-9
11	Chlorhexidine digluconate	1	Aqueous	18472-51-0
12	DMDM hydantoin	2	Aqueous	6440-58-0
13	Dodecyl gallate/lauryl gallate	0.25	Petroleum jelly	1166-52-5
14	Shellac	20	Alcohol	9000-59-3
15	Imidazolidinyl urea	2	Petroleum jelly	39236-46-9
16	Iodopropynyl butylcarbamate	0.2	Petroleum jelly	55406-53-6
17	Lauryl glucoside	3	Petroleum jelly	110615-47-9
18	<i>Mentha piperita</i>	2	Petroleum jelly	8006-90-4
19	Sorbitan sesquioleate	20	Petroleum jelly	8007-43-0
20	Tert-butylhydroquinone	1	Petroleum jelly	1948-33-0

^a Numerical identifier of the substance.

The clinical relevance of testing this allergen is illustrated by the case of a 50-year-old nonatopic woman who developed genital, pruritic eczema for 2 months. She had started using an intimate hygiene gel 1 month before the onset of dermatitis. Application of topical corticosteroids did not lead to improvement, but discontinuation of the gel resulted in clinical resolution. A repeated open application test (ROAT) with the gel was positive after 3 days. Subsequent patch testing showed positive reactions both to the product diluted at 1% and to cocamide diethanolamine, one of its ingredients.⁸

Chlorhexidine digluconate

Chlorhexidine, in the form of digluconate, is used in aqueous solutions as an antiseptic and disinfectant. It has broad-spectrum action against Gram-positive and Gram-negative bacteria, as well as some viruses and fungi.¹¹ In healthcare settings, it is used for oral hygiene, hand cleansing, preoperative antiseptic baths, intraoperative disinfection, and sterilization of medical instruments. Outside the hospital environment, it is used as a preservative in personal care products such as hair care products, sunscreens, contact lens solutions, antiwrinkle creams, and moisturizers, among others.¹¹ It may also be tested in the form of diacetate, as cross-reactivity with this compound is expected. In addition to ACD, chlorhexidine may also cause irritant and photoallergic dermatitis.¹¹ It has also been associated with reactions such as contact urticaria and even anaphylaxis. For patients with positive patch test results, prick testing for immediate allergic reactions and measurement of specific IgE are recommended.¹² The same extract can be used for prick testing.

An analysis of antiseptic chemicals used by healthcare professionals and in surgical preparation of patients found that approximately one quarter (25.8%) of them contained chlorhexidine digluconate. These antiseptics are used for surgical hand scrubbing and patient surgical cleansing.¹³ A study conducted by the NACDG found positive reactions in 0.7% of cases, with 52.3% of these reactions demonstrating current clinical relevance.¹¹ In a Danish study, a positivity rate of 1% was observed.¹² Hands and face are the most frequently affected areas.¹¹ Another study, however, reported that chlorhexidine allergy was significantly associated with lesions on the lower extremities and with individuals older than 40 years.¹⁴ Authors have highlighted that some patients who test positive are re-

exposed to the allergen after diagnosis, emphasizing the need for better patient education regarding potential sources of exposure to the substance.¹²

Numerous cases of reactivity to this allergen have been reported in the literature. One example involves a nurse who developed bilateral hand dermatitis for 6 months. She suspected the antiseptic hand wash she was using was the causative agent and sought assistance from the occupational health team, who advised her to avoid the chlorhexidine hand wash and to use an emollient soap as a substitute. Despite these measures, her dermatitis persisted. Patch testing was then performed and showed a strong positive response to chlorhexidine (++) . Notably, chlorhexidine was listed as an ingredient in the substitute soap she had been using. After she was advised to avoid the implicated product and to use a povidone-iodine-based hand wash instead, clinical remission occurred within 3 weeks.¹⁵

Benzophenone-3 and benzophenone-4

Benzophenones are chemical UV light absorbers. They primarily absorb light in the UVB range, but benzophenone-3 and benzophenone-4 also absorb light in the UVA range.¹⁶ Six types of benzophenones are known, but types 3 and 4 account for most of those found in personal care products. Nevertheless, cross-reactivity between benzophenone-3 and benzophenone-4 has been considered low.¹⁷ This group of chemicals is found not only in sunscreens but is also widely used in other cosmetics (such as shampoos and moisturizers) and industrial products (including paints and varnishes) to prevent photodegradation.¹⁸ The expansion of their use, driven by growing concern about the harmful effects of sun exposure, has contributed to an increased prevalence of sensitization to benzophenones. These allergens can cause contact and photoallergic dermatitis, as well as contact urticaria and, in some cases, anaphylaxis.¹⁶ Some authors estimate that approximately one third of lip ACD cases are due to sunscreen agents, which justifies their investigation in all patients presenting with lip dermatitis.¹⁸ A study by the NACDG revealed that, compared with patients with negative patch tests, those with positive reactions to the two main benzophenones had a significantly higher history of atopic dermatitis and facial involvement. Most reactions were currently clinically relevant.¹⁷

Benzophenone-3, also known as oxybenzone, is the most common sunscreen component associated

with allergic reactions and is also the compound most frequently implicated in cases of photoallergy.¹⁶ In the NACD study, 0.5% of tested patients showed a positive reaction to benzophenone-3.¹⁷ There is significant cross-reactivity between benzophenone-3 and octocrylene (another sunscreen agent), as well as ketoprofen (a topical anti-inflammatory medication).¹⁶

Benzophenone-4, also known as sulisobenzone, is considered an emerging allergen, as reports of sensitization have continued to appear following its progressive incorporation into cosmetics and personal hygiene products.¹⁶ A study reported a positivity rate of 1.6% among more than 19,000 tested patients.¹⁷ However, benzophenone-4 may cause irritant reactions, and results should therefore be interpreted with caution. It has also been implicated in ACD to printing ink, highlighting the importance of considering this compound in occupational settings.¹⁶

The clinical relevance of these allergens is illustrated by the case of a 25-year-old man who developed pruritic erythema at the site of a lower-limb tattoo performed 7 days earlier. An additional erythematous plaque was observed in the popliteal fossa of the tattooed leg. Skin biopsy findings were suggestive of dermatitis. Patch testing showed a ++ reaction to benzophenone-4 and a + reaction to the tattoo pigment. Chromatographic analysis confirmed the presence of benzophenone in the tattoo ink.¹⁹

Sorbitan sesquioleate

Sorbitan sesquioleate is a nonionic surfactant derived from sorbitol that functions as an emulsifying agent.²⁰ It is used in cosmetics and topical medications, including corticosteroids. It has been shown to cause ACD mainly in patients with leg ulcers.²¹ A study reported a prevalence of ACD to sorbitan sesquioleate of 0.48%, with 1.3% of patients having a doubtful reaction. In another investigation, the positivity rate was 0.6%. Sorbitol and its derivatives, such as sorbitan trioleate, sorbitan monolaurate, and sorbitan monopalmitate, may exhibit cross-reactivity.²⁰

Fragrance mix I and balsam of Peru frequently yield positive results in patch testing. However, these extracts, particularly those produced by major international manufacturers, contain sorbitan sesquioleate to ensure solution stability. The issue arises because sorbitan sesquioleate itself may cause contact allergy. Consequently, patients sensitized to this allergen may present positive reactions to

fragrance preparations without being sensitized to fragrances, potentially leading to an incorrect diagnosis.²² Thus, diagnosing ACD becomes particularly challenging when patients show positive reactions to sorbitan sesquioleate simultaneously with other allergens containing sorbitan sesquioleate in their formulation.²¹ It is not known whether this substance is present in the extracts commercially available in Brazil.

An illustrative case involves a 27-year-old patient who developed pruritic eruptions on the neck lasting 3 weeks. He had been applying topical medication A, a product he had used in the past, as well as topical medication B, which he was using for the first time. Both were over-the-counter medications. Patch testing revealed a positive reaction only to medication B (+) on day 7, sorbitan stearate, and sorbitan sesquioleate. These two allergens were ingredients of product B and share similar chemical structures.²³

Benzyl alcohol

Benzyl alcohol is used in many products primarily as a bactericidal agent.²⁴ It is also used as a preservative, solvent, and component of fragrance materials.²⁵ It is commonly found in topical and injectable medications as well as in cosmetic products.^{26,27} When comparing patients sensitized to this substance with those who are not, individuals reacting to benzyl alcohol tend to be polysensitized. They are frequently sensitized to fragrance allergens, balsam of Peru, and propolis. Reactions to balsam of Peru and propolis are expected because benzyl alcohol is present in both of these natural extracts. Regarding fragrances, the association is believed to result from co-exposure in topical medications and personal care products. Sensitization to benzyl alcohol is uncommon, occurring mainly in patients with stasis dermatitis.²⁵ The prevalence of sensitivity to this allergen is low, estimated at 0.3% by a North American study.²⁸ However, benzyl alcohol is widely present as a preservative in products (14.7%) included in the Contact Allergen Management Program (CAMP) database.²⁹ Due to the increasing use of this substance, it was added to the NACDG patch test series.²⁸ The currently employed test concentration was increased to 10%, using Softisan as the vehicle. Softisan, derived from essential fatty acids, is considered non-sensitizing and well tolerated by the skin.³⁰

The clinical relevance of this allergen is illustrated by the case of a 78-year-old woman with recurrent

cheilitis for several years. Her condition improved with oral prednisone but recurred after discontinuation. She had been using hydrocortisone and ketoconazole creams. Patch testing revealed positive reactions to several substances, including benzyl alcohol (++) . Assessment of clinical relevance identified benzyl alcohol as an excipient in the topical corticosteroid she had been using (tixocortol tested negative). Discontinuation of the medication resulted in significant improvement within 4 weeks.²⁷

Tert-butylhydroquinone

Tert-butylhydroquinone (TBHQ) is a synthetic phenolic compound used as a preservative.³¹ It prevents oxidation of lipid components in cosmetics, such as skin oils, lipsticks, and hair dyes.³² It is also a common food additive because it does not alter color or flavor.³¹ CAMP data reveal the presence of this allergen in a wide variety of products, including hair care products; all-purpose cleaners, bleaches, and fabric softeners; mascara and eyeshadows; anti-aging creams, moisturizers, and soaps.² TBHQ is a common allergen among individuals with leg ulcers. It shows cross-reactivity with other synthetic phenolic compounds, such as BHA and BHT.³¹ The prevalence of sensitivity to TBHQ is approximately 0.7%.²

Interestingly, identifying sensitivity to this allergen may assist in the diagnosis of reactions associated with alternative medicine compounds. An illustrative case involved a 46-year-old woman who presented with eczema of the face, scalp, and shoulders for 2 weeks. She had been applying *Nigella sativa* (black cumin) oil daily to treat alopecia for 2 months. Topical corticosteroid treatment and discontinuation of the oil resolved the eczema. An open application test with the suspected allergen was positive, and patch testing also showed a positive reaction to TBHQ (++) .³³ It has been hypothesized that thymoquinone is the primary sensitizing agent; however, it is not commercially available for patch testing. Although TBHQ is not present in *N. sativa*, its chemical structure is similar to that of thymoquinone. The authors emphasize that when positivity to TBHQ is identified, patients should be questioned about the use of this vegetable oil.³²

Dodecyl gallate

Oxidation in cosmetic products is undesirable because it leads to changes in color and odor, in addition to deterioration of active ingredients.³⁴

Gallates are antioxidants used as preservatives in processed foods and cosmetic products.³⁵ The three main compounds are propyl gallate, octyl gallate, and dodecyl gallate (also known as lauryl gallate). Propyl gallate is the most widely used and, consequently, the gallate most frequently reported in the literature as a cause of ACD. However, cross-reactivity among gallates has been documented. In foods, gallates are classically found in products such as margarine and peanut butter.³⁵ Their presence in cosmetics occurs mainly in various types of lip products.³⁴ Accordingly, allergy to these compounds most commonly presents as cheilitis.³⁶

A Canadian center consecutively patch tested patients with a cosmetic series and found positive reactions to dodecyl gallate in 1.53% of patch tests.² Another study assessing contact sensitization specifically in patients with rosacea reported a positivity rate of 8.74% for dodecyl gallate.³⁷ Published cases of eczema related to gallates are relatively recent in the literature. One hypothesis is that oral exposure to these substances previously induced immunological tolerance, which could explain the historically low rates of allergy to these compounds. Currently, the increasing use of gallates in the cosmetic industry, together with regulatory measures and reduced use of these substances in foods, may explain the rising incidence of gallate-induced ACD.³⁵

DMDM hydantoin and imidazolidinyl urea

Dimethyloldimethyl hydantoin, commonly referred to as DMDM hydantoin, and imidazolidinyl urea, also known as Germall 115, are formaldehyde-releasing preservatives. Formaldehyde and its releasers are ubiquitous preservatives, with numerous sources of exposure, both occupational and nonoccupational, including cosmetics, household cleaning products, personal hygiene items, and a wide range of industrial applications.³⁸ In personal care products, formaldehyde has largely been replaced by formaldehyde-releasing preservatives, which provide similar broad-spectrum action against bacteria and fungi. It is important to note that formaldehyde is not always declared on product labels and has been identified as a hidden compound in many cosmetic formulations.³⁹

A prospective multicenter study reported a sensitization rate of 0.34% for imidazolidinyl urea.⁴⁰ Data from the European Surveillance System on Contact Allergies (ESSCA) showed comparable rates of sensitization to DMDM hydantoin and

imidazolidinyl urea (0.42%).³⁸ These values may be related to the low prevalence of these preservatives in cosmetic products. In the United States, however, the use of imidazolidinyl urea is more common, and the prevalence of sensitization is correspondingly higher, ranging from 2% to 3%.^{38,39} Regarding DMDM hydantoin, sensitization rates in U.S. studies have reached up to 4.7%.³⁹

The clinical presentation associated with these allergens is broad, including localized dermatitis, airborne dermatitis, and even erythroderma. When dermatitis is related to the presence of formaldehyde or formaldehyde-releasing preservatives in cosmetics, it typically affects middle-aged women who present with eczema of the face and/or hands triggered by rinse-off or leave-on products containing these preservatives. Facial cosmetics may also cause “low-grade” eczema, characterized by mild but persistent erythema and/or scaling, which can resemble seborrheic dermatitis.³⁹

When individuals demonstrate ACD to formaldehyde and one or more of its releasers, it is generally assumed that the reaction is due to the formaldehyde released by these compounds. However, it has been demonstrated that sensitization to a formaldehyde releaser may occur independently of contact allergy to formaldehyde itself. This finding suggests that other components of formaldehyde-releasing preservatives may also induce sensitization.³⁸ Thus, in clinical practice, if sensitization to formaldehyde is identified, both formaldehyde and its releasers should be avoided. Conversely, if an individual is sensitized to a specific formaldehyde releaser but not to formaldehyde itself, only that particular releaser should be avoided.³⁹

Iodopropynyl butylcarbamate

Iodopropynyl butylcarbamate is a broad-spectrum preservative with bactericide and fungicide properties.⁴¹ It is used in cosmetics such as moisturizers, shampoos, and infant care products.⁴² In household settings, it is also present in detergents. An Australian survey reported positive patch test reactions in 2.3% of tested patients, with 31% of these reactions considered clinically relevant.⁴³ It has been suggested that, with the replacement of methylisothiazolinone in leave-on products, an increase in sensitization to iodopropynyl butylcarbamate may occur.⁴² There is some controversy regarding whether reactions to this preservative in iodine-allergic individuals are due to iodine released from the compound.⁴¹

An illustrative case involved a 28-year-old woman with a 12-month history of facial erythema and hand eczema. She had a history of atopic dermatitis and rhinitis. Patch testing revealed a strong positive reaction (++) to iodopropynyl butylcarbamate. Investigation of clinical relevance showed that she had been using a daily moisturizer for more than 1 year that was labeled as hypoallergenic and recommended for atopic dermatitis. This product, which appeared to be harmless, contained the preservative iodopropynyl butylcarbamate.⁴⁴

Lauryl and coco glucosides

Lauryl and coco glucosides are nonionic, biodegradable surfactants belonging to the alkyl glucoside family, widely used in cleansing products. They are broadly available in rinse-off products such as shampoos and soaps, as well as in leave-on formulations such as sunscreens and moisturizers.⁴⁵ Women are more frequently affected, likely because they use personal care products more regularly.⁴⁶ Interestingly, these compounds are generally considered safe even for sensitive skin. However, one study demonstrated notable positivity rates in patch testing for lauryl glucoside (1.5%) and coco glucoside (1.4%).⁴⁷

Lauryl and decyl glucosides are the members of the alkyl glucoside family most commonly implicated in ACD. Concomitant positive reactions to both substances were observed in 37% of patch tests.⁴⁸ This rate was not considered sufficiently high to justify using only one of them as a screening allergen for the entire family. Therefore, it has been suggested that another alkyl glucoside, such as coco glucoside, should also be tested when ACD dermatitis is suspected.⁴⁸ This consideration is particularly relevant in cases related to cosmetics, since reactions to alkyl glucosides are not uncommon and their clinical relevance is high.⁴⁹

The prevalence of allergy to these compounds may be underestimated due to their absence from many patch test series.⁵⁰ The importance of testing these substances is illustrated by the case of a 72-year-old man who developed eczema on the back and forearms 7 days after using a sunscreen. Similar episodes had previously occurred with other sunscreen brands. Photopatch testing demonstrated a ++ reaction to the implicated sunscreen both in irradiated and nonirradiated areas. Patch testing with the individual components of the commercial product revealed a ++

reaction to lauryl glucoside, while testing with decyl glucoside was negative.⁵¹

Mentha piperita

Peppermint oil is the essential oil obtained by distillation of the flowers and leaves of *Mentha × piperita* L., a plant widely used in herbal medicine. The main allergen appears to be menthol. It has cooling properties and is used for topical application in conditions such as muscle spasms, neuralgia, headache, and toothache. Orally, it is used for relieving dyspepsia, nausea, and other intestinal disorders. It is also commonly used for flavoring chewing gum, cough drops, and mouthwashes and for cosmetics, among other products.⁵² A recent study analyzing over 28 000 patch tests performed over a 12-year period found a positivity rate of 0.6% for this substance.⁵³ The most frequently affected anatomical sites were the face (specifically the lips), hands, and generalized, with 80.1% of cases being considered currently relevant. The most common sources of exposure were oral hygiene products, lip cosmetics, and foods. Notably, 40.4% of sensitizations to *Mentha piperita* would have been missed if only the standard patch test series with three fragrance screening markers (balsam of Peru, fragrance mix I, and fragrance mix II) had been used.⁵³

This type of sensitization was reported in a woman who presented with recurrent cheilitis for several years. She experienced partial improvement with lip moisturizers and topical tacrolimus. Patch testing revealed a strong positive reaction to *Mentha piperita* (++). The patient reported using toothpaste containing this flavor. Avoidance of mint-flavored toothpaste and similar products, combined with topical treatment, led to complete resolution of symptoms.⁵⁴ Another similar case of prolonged cheilitis has been reported. Testing was also performed with the implicated personal care products (toothpaste and throat spray), both of which tested positive, as did the extracts containing the substance and menthol.⁵⁵

Shellac

Shellac, also known as lac resin, is a purified form obtained through alcoholic extraction of a resin secreted by an Asian insect known as *Laccifer lacca*.⁵⁶⁻⁵⁸ It is used in a wide range of applications, including as an emollient in lipsticks, a hair fixative, and a thickener in cosmetics such as mascara and

eyeliners.⁵⁶ A Spanish group evaluating patients with suspected cosmetic ACD reported a positivity rate of 3.7% for shellac.⁵⁹ Similarly, a German study analyzing consecutively patch-tested patients identified a prevalence of 3.5%.⁵⁶ The NACDG found that patients with isolated eyelid dermatitis or eyelid involvement associated with head and neck dermatitis were more likely to react to shellac compared with patients without eyelid involvement.⁶⁰

The clinical relevance of this allergen is illustrated by the case of a 66-year-old woman who sought medical attention for progressive hair loss along the frontotemporal hairline (frontal fibrosing alopecia) associated with pruritic eczema in the same area. She reported daily use of an ecological hair spray. Patch testing demonstrated a strong reaction (++) to shellac contained in the product recommended by her hairdresser. A ROAT with the spray produced an eczematous reaction after 3 days. Discontinuation of the product led to complete remission of the eczema, although the alopecia remained unchanged during follow-up.⁶¹

Tocopheryl acetate

Vitamin E, also known as tocopherol, is a plant-derived mixture of lipid-soluble antioxidants. Because tocopherol is an unstable molecule, it is commonly esterified into a more stable form, usually tocopheryl acetate.⁶² Vitamin E and its derivatives are frequently found in cosmetics, sunscreens, and other skin care products, as their antioxidant properties are believed to promote wound healing.⁶³ In addition, they have photoprotective and antiphotoreaging effects. More than one third (37.2%) of products in the CAMP database contain tocopherol, and it is present in approximately 50% of makeup products. Tocopherol has been associated with ACD and contact urticaria.⁶² Conversely, vitamin E has also been proposed as an adjuvant treatment for atopic dermatitis, since oxidative stress and inflammation are among the mechanisms involved in the pathogenesis of this condition.⁶⁴ In a survey involving more than 38,000 patients patch tested to tocopherol, 0.9% had a positive reaction, of which 87.6% were currently relevant. Compared with tocopherol-negative patients, those with positive reactions were more frequently female and exhibited a more generalized pattern of dermatitis.⁶²

The clinical significance of tocopherol sensitization is illustrated by the case of a 13-year-old adolescent with a history of atopic dermatitis since childhood

involving the face, neck, back, and scalp. For many years, treatment consisted of “hypoallergenic” emollients and topical corticosteroid ointments, with minimal relief. Due to the lack of improvement, patch testing was performed and revealed a ++ reaction to tocopherol, along with weaker reactions to cobalt and limonene hydroperoxide. Avoidance of tocopherol (both dietary sources and topical products) led to dramatic clinical improvement. Reintroduction of the allergen resulted in recurrence of eczema, and its subsequent removal again led to clinical resolution.⁶³

Sodium benzoate

Sodium benzoate and benzoic acid are related chemicals that function both as preservatives and fragrance ingredients. Sodium benzoate is synthetically produced by the addition of benzoic acid, which occurs naturally, to sodium hydroxide.⁶⁵ These compounds are commonly added to acidified foods and beverages, such as pickles and soft drinks. They are also used in cosmetics (eg, facial creams and sunscreens) and medications (eg, topical antifungals and anesthetics).⁶⁶ Sodium benzoate has been associated with ACD, particularly affecting the perioral region and lips. In addition to ACD, it may also induce nonimmunologic contact urticaria.⁶⁵ An evaluation of labels from 283 cosmetic products found sodium benzoate in 35.6% of them. It was the most common preservative in rinse-off products (57.6%) and was also the most frequently identified preservative in products labeled as organic (50%).⁵

Benzalkonium chloride

Benzalkonium chloride is a quaternary ammonium compound used as both a preservative and an antiseptic.⁶⁷ It is commonly found in personal care products, with the main sources including ophthalmic solutions, nasal sprays, mouthwashes, and cosmetics.⁶⁸ Benzalkonium chloride was identified in 2.3% of products in the CAMP database and is the most prevalent surfactant found in ophthalmic solutions (27.7%).⁶⁹ This substance is well recognized as an irritant; however, it may also be associated with ACD. For this reason, the interpretation of a positive patch test reaction to benzalkonium chloride should be made with caution.⁶⁷ Health care professionals are particularly exposed to this allergen, placing them at higher risk of developing sensitization.⁶⁸ A study reported a positivity rate of 1.5%, with a progressive increase in the number of cases over time. It has

been suggested that, following the epidemic of ACD caused by methylisothiazolinone, preservatives have increasingly been replaced by benzalkonium chloride in several products, such as wet wipes.⁶⁷ It should also be noted that this allergen may exhibit cross-reactivity with other compounds, including benzethonium chloride, cetrimide, cetrimonium chloride, and related substances.⁶⁸

An illustrative case involved a patient presenting with recurrent pruritic erythematous plaques for 9 months. The lesions progressively spread throughout the body, sparing only the face and scalp. Initially diagnosed with atopic dermatitis, the patient was treated with methylprednisolone and baricitinib without sustained improvement. There were no lesions in areas of contact with underwear, which initially suggested textile contact dermatitis. However, the patient reported having started using a new disinfectant detergent shortly before the onset of symptoms (undergarments were hand-washed). Testing revealed several positive reactions. When the manufacturer was contacted, it was confirmed that the identified allergens were not ingredients in the product. However, the detergent did contain benzalkonium chloride. A subsequent test with benzalkonium chloride was positive, and after discontinuation of the product, no recurrence of the disease was observed.⁷⁰

Cetearyl alcohol

Cetearyl alcohol is a combination of stearyl alcohol and cetyl alcohol and is found in many topical medications and cosmetic products. It functions as a stabilizer and emulsifier.⁷¹ A study evaluating facial cleansing wipes confirmed that approximately one quarter of these products (25.8%) contained cetearyl alcohol.⁷² In another investigation focusing specifically on products labeled as “hypoallergenic,” cetearyl alcohol was identified as the most frequently detected allergen among leave-on products.⁷³ Despite its widespread use, the relatively low frequency of allergy to this substance is associated with its limited ability to penetrate the skin. Therefore, it is generally well tolerated by sensitized individuals when the skin barrier is intact. Consequently, allergic manifestations usually occur in individuals with a preexisting impairment of the skin barrier, such as leg ulcers.⁷¹ In fact, patch testing performed in patients with dermatitis affecting the lower extremities, particularly those with chronic venous insufficiency or leg ulcers, showed positive reactions to cetearyl alcohol in 4.4% of cases.⁷⁴

Conclusion

The scientific studies included in this review clearly demonstrate the importance of the selected substances proposed for inclusion in a new cosmetic patch test series, with the aim of further improving the diagnosis of patients with ACD. Therefore, it is believed that this review will promote discussion and contribute to the development and proposal of new and updated patch test series.

References

1. Brasil. Agência Nacional de Vigilância Sanitária (ANVISA). Resolução da Diretoria Colegiada – RDC N° 530, de 04 de Agosto de 2021. Dispõe sobre os requisitos técnicos para a regularização de produtos de higiene pessoal, cosméticos e perfumes [Internet]. Brasília: ANVISA; 2021.
2. Morin CB, Sasseville D. Expanding Patch Testing Beyond the Baseline Series: Usefulness of Customized Antimicrobials, Vehicles, and Cosmetics Series. *Dermatitis*. 2020;31(6):367-72. doi:10.1097/DER.0000000000000674.
3. Belluco PES, Uber M, Silva F de P, Belluco JEF, Abagge KT, Belluco RZF, et al. New cosmetics patch test series : A proposal. *Rev Alerg México*. 2025;72(2):107-18. doi:10.29262/ram.v72i2.1437.
4. Karels S, Weber B, Neeley A. Demonstration of Cross-Reactivity Between trans-Anethole and Butylhydroxyanisole. *Dermatitis*. 2025 Jul-Aug;36(4):e397-e399. doi: 10.1089/derm.2024.0322.
5. Panico A, Serio F, Bagordo F, Grassi T, Idolo A, DE Giorgi M, et al. Skin safety and health prevention: an overview of chemicals in cosmetic products. *J Prev Med Hyg*. 2019;60(1):E50-E57. doi:10.15167/2421-4248/jpmh2019.60.1.1080.
6. Atwater AR, Liu B, Walsh R, Bemby R, Ward JM, Green CL. Supplemental Patch Testing Identifies Allergens Missed by Standard Screening Series. *Dermatitis*. 2024;35(4):366-72. doi:10.1089/derm.2023.0310.
7. Mertens S, Gilissen L, Goossens A. Allergic contact dermatitis caused by cocamide diethanolamine. *Contact Dermatitis*. 2016;75(1):20-4. doi:10.1111/cod.12580.
8. Navarro-Triviño FJ, Ruiz-Villaverde R. Genital allergic contact dermatitis caused by cocamide DEA. *Contact Dermatitis*. 2021;85(6):701-3. doi:10.1111/cod.13934.
9. Presley CL, Militello M, Barber C, Ladd R, Laughter M, Ferguson H, et al. The History of Surfactants and Review of Their Allergic and Irritant Properties. *Dermatitis*. 2021;32(5):289-97. doi:10.1097/DER.0000000000000730.
10. Scheman A, Te R. Contact Allergy to Cocamide Diethanolamine and Cross-reactions. *Dermatitis*. 2018;29(2):91-2. doi:10.1097/DER.0000000000000350.
11. Warshaw EM, Han J, Kullberg SA, DeKoven JG, Adler BL, Silverberg JL, et al. Patch Testing to Chlorhexidine Digluconate, 1% Aqueous: North American Contact Dermatitis Group Experience, 2015-2020. *Dermatitis*. 2023;34(6):501-8. doi:10.1089/derm.2023.0077.
12. Opstrup MS, Johansen JD, Zachariae C, Garvey LH. Contact allergy to chlorhexidine in a tertiary dermatology clinic in Denmark. *Contact Dermatitis*. 2016;74(1):29-36. doi:10.1111/cod.12487.
13. Schlarbaum JP, Hylwa SA. Allergic Contact Dermatitis to Operating Room Scrubs and Disinfectants. *Dermatitis*. 2019;30(6):363-70. doi:10.1097/DER.0000000000000525.
14. Calado R, Calvão da Silva J, Gomes T, Gonçalves M. Is there a place for chlorhexidine in the European baseline series? *Contact Dermatitis*. 2021;85(3):372-3. doi:10.1111/cod.13861.
15. Watts TJ, Li PH, Ue KL, Haque R. Chronic Allergic Contact Dermatitis Due to Chlorhexidine. *J Allergy Clin Immunol Pract*. 2018;6(1):254-5. doi:10.1016/j.jaip.2017.08.002.
16. Heurung AR, Raju SI, Warshaw EM. Benzophenones. *Dermatitis*. 2014;25(1):3-10. doi:10.1097/DER.0000000000000025.
17. Warshaw EM, Xiong M, Belsito DV, Adler BL, Atwater AR, DeKoven JG, et al. Patch Testing With Benzophenone-3 and -4: The North American Contact Dermatitis Group Experience, 2013–2020. *Dermatitis*. 2023;34(2):105-12. doi:10.1089/derm.2022.29013.ewa.
18. Hanson JL, Warshaw EM. Sensitivity to Multiple Benzophenone Sunscreen Agents. *Dermatitis*. 2015;26(4):192-4. doi:10.1097/DER.0000000000000131.
19. Tsiogka A, Liopyris K, Gregoriou S. Allergic contact dermatitis associated with benzophenone sensitization after a recent black ink tattoo. *Contact Dermatitis*. 2022;86(6):549-51. doi:10.1111/cod.14071.
20. Özkaya E, Pehlivan G, Babuna Kobaner G. Sorbitan sesquioleate: a rare contact allergen that is also an important indicator of allergic contact dermatitis from crossreacting compounds as well as for false-positive fragrance allergy. *Clin Exp Dermatol*. 2022;47(7):1291-7. doi:10.1111/ced.15158.
21. Sukakul T, Bruze M, Mowitz M, Svedman C. Use of sorbitan sesquioleate in patch test preparations and patch testing with the substance—What do our results mean? *Contact Dermatitis*. 2023;88(2):134-8. doi:10.1111/cod.14239.
22. de Groot A, Gilissen L, Geier J, Orton D, Goossens A. Adding sorbitan sesquioleate to the European baseline series: Necessary, reasonable, or unavoidable? *Contact Dermatitis*. 2019;81(3):221-5. doi:10.1111/cod.13332.
23. Yokoi A, Suzuki K, Takahashi M, Yagami A, Matsunaga K. Case of allergic contact dermatitis caused by sorbitan derivatives included in an over-the-counter topical medicament. *J Dermatol*. 2017;44(6):e113-e114. doi:10.1111/1346-8138.13731.
24. Tripp M, Ribeiro M, Kmiecik S, Go R. A "Rash" Decision in Anesthetic Management: Benzyl Alcohol Allergy in the Perioperative Period. *Case Rep Anesthesiol*. 2021 Jun 24;2021:8859823. doi:10.1155/2021/8859823.
25. Geier J, Ballmer-Weber B, Buhl T, Rieker-Schwiebächer J, Mahler V, Dickel H, et al. Is benzyl alcohol a significant contact sensitizer? *J Eur Acad Dermatol Venerol*. 2022;36(6):866-72.
26. Kubin ME, Rieki R. Benzyl alcohol allergy mimicking corticosteroid allergy. *Contact Dermatitis*. 2016;75(1):58-9. doi:10.1111/cod.12562.
27. Xiong M, Peterson MY, Hylwa S. Allergic contact dermatitis from benzyl alcohol in hydrocortisone cream. *Contact Dermatitis*. 2022;86(5):424-5. doi:10.1111/cod.14042.
28. Atwater AR, Petty AJ, Liu B, Green CL, Silverberg JL, DeKoven JG, et al. Contact dermatitis associated with preservatives: Retrospective analysis of North American Contact Dermatitis Group data, 1994 through 2016. *J Am Acad Dermatol*. 2021;84(4):965-76. doi:10.1016/j.jaad.2020.07.059.
29. Beene KM, Scheman A, Severson D, Reeder MJ. Prevalence of Preservatives Across All Product Types in the Contact Allergen Management Program. *Dermatitis*. 2017;28(1):81-7. doi:10.1097/DER.0000000000000259.
30. Väänänen A, Hannuksela M. Softisan – a new vehicle for patch testing. *Contact Dermatitis*. 1986;14(4):215-6. doi:10.1111/j.1600-0536.1986.tb01227.x.
31. Sherson DL, Jacobsen IB, Thomsen GF. The antioxidant, tert-butylhydroquinone: a new cause of asthma. *Occup Med (Chic Ill)*. 2023;73(2):109-11. doi:10.1093/occmed/kqac093.
32. Seiller H, Kurihara F, Chasset F, Soria A, Barbaud A. Tert-butylhydroquinone is a marker for sensitivity to Nigella sativa oil allergy: Five new cases. *Contact Dermatitis*. 2021;84(6):447-9. doi:10.1111/cod.13750.
33. Kurihara F, Soria A, Lepoittevin J, Chasset F, Barbaud A, Pecquet C. Thymoquinone as a causative allergen in Nigella sativa oil contact dermatitis with cross-reactivity to tert-butylhydroquinone. *Contact Dermatitis*. 2020;83(2):132-4. doi:10.1111/cod.13542.
34. Pal B, Kumari S, Kumari A, Singh SK, Babbar H. Allergic contact dermatitis to lip care cosmetic products – a systematic review. *Cutan Ocul Toxicol*. 2024;43(1):13-21.
35. Holcomb ZE, Van Noord MG, Atwater AR. Gallate Contact Dermatitis: Product Update and Systematic Review. *Dermatitis*. 2017;28(2):115-27. doi:10.1097/DER.0000000000000263.
36. O’Gorman SM, Torgerson RR. Contact allergy in cheilitis. *Int J Dermatol*. 2016;55(7):e386-e391. doi:10.1111/ijd.13044.

- 37 Ozbagicvan O, Akarsu S, Dolas N, Fetil E. Contact sensitization to cosmetic series of allergens in patients with rosacea: A prospective controlled study. *J Cosmet Dermatol*. 2020;19(1):173-9. doi:10.1111/jocd.12989.
- 38 Whitehouse H, Uter W, Geier J, Ballmer-Weber B, Bauer A, Cooper S, et al. Formaldehyde 2% is not a useful means of detecting allergy to formaldehyde releasers- results of the ESSCA network, 2015-2018. *Contact Dermatitis*. 2021;84(2):95-102. doi:10.1111/cod.13691.
- 39 Goossens A, Aerts O. Contact allergy to and allergic contact dermatitis from formaldehyde and formaldehyde releasers: A clinical review and update. *Contact Dermatitis*. 2022;87(1):20-7. doi:10.1111/cod.14089.
- 40 Sanz-Sánchez T, García PM, Silvestre Salvador JF, Mendaza FH, Guijarro SC, Pérez RG, et al. Contact allergy to formaldehyde releasers. Prospective multicenter study. *Contact Dermatitis*. 2020;82(3):173-5. doi:10.1111/cod.13417.
- 41 Vanhoutte C, Goossens A, Gilissen L, Huygens S, Vital-Durand D, Dendooven E, et al. Concomitant contact-allergic reactions to iodopropynyl butylcarbamate and iodine. *Contact Dermatitis*. 2019;81(1):17-23. doi:10.1111/cod.13224.
- 42 Batista M, Morgado F, Gonçalves M. Patch test reactivity to iodopropynyl butylcarbamate in consecutive patients during a period of 7 years. *Contact Dermatitis*. 2019;81(1):54-5. doi:10.1111/cod.13213.
- 43 Mizutani H, Nguyen J, Tam MM, Tate B, Cahill J, Nixon R. Patch test reactivity to iodopropynyl butylcarbamate between 2011 and 2018 in Melbourne, Australia. *Contact Dermatitis*. 2021;85(5):604-6. doi:10.1111/cod.13930.
- 44 Kwon HJ, Kim JM, Oh WJ, Park KY, Kim MN, Seo SJ. Allergic contact dermatitis caused by a moisturizer containing iodopropynyl butylcarbamate. *Clin Exp Dermatol*. 2018;43(1):62-3.
- 45 Belluco PES, De-Alcántara CTDA, Belluco JEF, Ferreira MD, Belluco RZF, Azevedo F da SM. Dermatite de contato aos alquil glicosídeos: estamos cientes da importância? *Arq Asmas Alerg e Imunol*. 2024;8(4):371-6. doi:10.5935/2526-5393.20240050.
- 46 Warshaw EM, Xiong M, Atwater AR, DeKoven JG, Pratt MD, Maibach HI, et al. Patch testing with glucosides: The North American Contact Dermatitis Group experience, 2009-2018. *J Am Acad Dermatol*. 2022;87(5):1033-41. doi:10.1016/j.jaad.2022.04.058.
- 47 Warshaw EM, Xiong M, DeKoven JG, Taylor JS, Belsito DV, Reeder MJ, et al. Co-reactivity of glucosides: Retrospective analysis of North American Contact Dermatitis Group Data 2019–2020. *Contact Dermatitis*. 2023;88(2):153-6. doi:10.1111/cod.14237.
- 48 Soriano LF, Bertram CG, Chowdhury MMU, Cousen P, Divekar P, Ghaffar SA, et al. Prevalence of allergic contact dermatitis to decyl and lauryl glucoside in the UK and Ireland. *Br J Dermatol*. 2021;184(3):571-3. doi:10.1111/bjd.19603.
- 49 Severin RK, Belsito DV. Patch Testing with Decyl and Lauryl Glucoside: How Well Does One Screen for Contact Allergic Reactions to the Other? *Dermatitis*. 2017;28(6):342-5. doi:10.1097/DER.0000000000000327.
- 50 Alfalah M, Loranger C, Sasseville D. Alkyl Glucosides. *Dermatitis*. 2017;28(1):3-4. doi:10.1097/DER.0000000000000234.
- 51 Martínez-González MI, González-Pérez R, García-Río I, Heras-González S. Allergic contact dermatitis caused by benzoic acid and lauryl glucoside in a sunscreen. *Contact Dermatitis*. 2017;77(3):186-7. doi:10.1111/cod.12810.
- 52 de Groot A, Schmidt E. Essential Oils, Part V: Peppermint Oil, Lavender Oil, and Lemongrass Oil. *Dermatitis*. 2016;27(6):325-32. doi:10.1097/DER.0000000000000218.
- 53 Warshaw EM, Peterson MY, DeKoven JG, Adler BL, Pratt MD, Belsito DV, et al. Patch Testing to Mentha piperita (Peppermint) Oil: The North American Contact Dermatitis Group Experience (2009–2020). *Dermatitis*. 2024;1-7. doi:10.1089/derm.2024.0118.
- 54 Griggs J, Almohanna H, Ahmed A, Ren S, Tosti A. "Fresh Breath" on Toothpaste: Peppermint as Cause of Cheilitis. *Dermatitis*. 2019;30(1):74-5. doi:10.1097/DER.0000000000000433.
- 55 Bourgeois P, Goossens A. Allergic contact cheilitis caused by menthol in toothpaste and throat medication: a case report. *Contact Dermatitis*. 2016;75(2):113-5. doi:10.1111/cod.12571.
- 56 Schubert S, Worm M, Dickel H, Wagner N, Brans R, Schröder-Kraft C, et al. Patch testing shellac in consecutive patients-Data of the Information Network of Departments of Dermatology (IVDK) 2021. *Contact Dermatitis*. 2023;88(1):77-80. doi:10.1111/cod.14227.
- 57 Mercader-García P, Ruiz-Gonzalez I, Gonzalez-Perez R, Sanz-Sanchez T, Sanchez-Pérez J, Borrego L. Alergia de contacto a shellac. Estudio transversal retrospectivo con datos del Registro Español de Investigación en Dermatitis de Contacto y Alergia Cutánea (REIDAC). *Actas Dermosifiliogr*. 2023;114(5):T377-T381. doi:10.1016/j.ad.2023.04.010.
- 58 Veverka KK, Killian JM, Yiannias JA, Hall MR, Drage LA, Davis MDP. Shellac: A Tertiary Care Center Experience. *Dermatitis*. 2018;29(4):226-7. doi:10.1097/DER.0000000000000394.
- 59 Mercader-García P, Ruiz-Gonzalez I, Gonzalez-Perez R, Sanz-Sanchez T, Sanchez-Pérez J, Borrego L. Contact Allergy to Shellac. Retrospective Cross-Sectional Study With Data From the Spanish Registry of Research in Contact Dermatitis and Cutaneous Allergy (REIDAC). *Actas Dermosifiliogr*. 2023;114(5):377-81.
- 60 Warshaw EM, Voller LM, Maibach HI, Zug KA, DeKoven JG, Atwater AR, et al. Eyelid dermatitis in patients referred for patch testing: Retrospective analysis of North American Contact Dermatitis Group data, 1994-2016. *J Am Acad Dermatol*. 2021;84(4):953-64. doi:10.1016/j.jaad.2020.07.020.
- 61 Navarro-Triviño FJ. Allergic contact dermatitis from shellac in an ecological hair spray occurring in a patient with frontal fibrosing alopecia. *Contact Dermatitis*. 2022;86(6):544-5.
- 62 Warshaw EM, Ruggiero JL, DeKoven JG, Silverberg JL, Maibach HI, Taylor JS, et al. Patch Testing With Tocopherol and Tocopherol Acetate: The North American Contact Dermatitis Group Experience, 2001 to 2016. *Dermatitis*. 2021;32(5):308-18.
- 63 Chen R, Raffi J, Murase JE. Tocopherol Allergic Dermatitis Masquerading as Lifelong Atopic Dermatitis. *Dermatitis*. 2020;31(1):e3-e4. doi:10.1097/DER.0000000000000543.
- 64 Teo CWL, Tay SHY, Tey HL, Ung YW, Yap WN. Vitamin E in Atopic Dermatitis: From Preclinical to Clinical Studies. *Dermatology*. 2021;237(4):553-64. doi:10.1159/000510653.
- 65 Schalock PC, Dunnick CA, Nedorost S, Brod B, Warshaw E, Mowad C. American Contact Dermatitis Society Core Allergen Series: 2017 Update. *Dermatitis*. 2017;28(2):141-3. doi:10.1097/DER.0000000000000261.
- 66 Aerts O, Goossens A. Contact Allergy to Preservatives. In: *Contact Dermatitis*. Springer International Publishing; 2021:835-76. doi:10.1007/978-3-030-36335-2_85.
- 67 Dear K, Palmer A, Nixon R. Contact allergy and allergic contact dermatitis from benzalkonium chloride in a tertiary dermatology center in Melbourne, Australia. *Contact Dermatitis*. 2021;85(2):146-53. doi:10.1111/cod.13826.
- 68 Okeke CAV, Khanna R, Ehrlich A. Quaternary Ammonium Compounds and Contact Dermatitis: A Review and Considerations During the COVID-19 Pandemic. *Clin Cosmet Investig Dermatol*. 2023;Volume 16(June):1721-8. doi:10.2147/CCID.S410910.
- 69 Weinhammer AP, Scheman A, Reeder MJ. Prevalence of Surfactant in the Contact Allergen Management Program. *Dermatitis*. 2019;30(6):358-62. doi:10.1097/DER.0000000000000511.
- 70 Chen J, Yin M, Wu R, Dou X. Allergic contact dermatitis caused by benzalkonium chloride from laundry disinfectant. *Int J Dermatol*. 2024;63(1):119-20. doi:10.1111/ijd.16909.
- 71 Armengot-Carbo MAC, Rodríguez-Serna M, Taberner-Bonastre P, Miquel-Miquel J. Allergic contact dermatitis from cetearyl alcohol in Thrombocid® ointment. *Dermatol Online J*. 2016;22(7).
- 72 Aschenbeck KA, Warshaw EM. Allergenic Ingredients in Facial Wet Wipes. *Dermatitis*. 2017;28(6):353-9.
- 73 Hiranput S, McAllister L, Hill G, Yesudian PD. Do hypoallergenic skincare products contain fewer potential contact allergens? *Clin Exp Dermatol*. 2024;49(4):386-7. doi:10.1093/ced/llad436.
- 74 Erfurt-Berge C, Geier J, Mahler V. The current spectrum of contact sensitization in patients with chronic leg ulcers or stasis dermatitis – new data from the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis*. 2017;77(3):151-8.

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Impact of urbanization, rurality, and contact with nature on hospitalizations for asthma and pneumonia in children and adolescents in Santa Catarina, southern Brazil

Impacto da urbanização, ruralidade e contato com a natureza nas hospitalizações por asma e pneumonia em crianças e adolescentes de Santa Catarina

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ABSTRACT

Introduction: Children's respiratory health is closely related to environmental conditions. For this reason, understanding how urbanization, rurality, and contact with nature affect this aspect of child and adolescent health may inform public health strategies and support improved clinical practices. **Objective:** To analyze the relationship between urbanization, rurality, contact with nature, and hospitalizations for asthma and pneumonia in children and adolescents (aged 0-19 years) in Santa Catarina, southern Brazil, in 2023. **Methods:** This ecological study used data from the Hospital Information System of the Brazilian Unified Health System, characterized by age-adjusted hospital morbidity rates for asthma and pneumonia. Spatial classifications from the Brazilian Institute of Geography and Statistics were also used, including municipal percentages of urban area (%urban), rural area (%rural), and contact with nature (%contact with nature) across Santa Catarina. **Results:** Urbanization and rurality were associated with the occurrence of asthma and pneumonia in children, especially in early childhood. Municipalities with lower levels of urbanization and higher levels of rurality showed higher hospitalization rates for both conditions. However, contact with nature did not significantly influence hospitalizations for asthma or pneumonia. **Conclusion:** This study highlights the multifactorial complexity of children's respiratory health and underscores the need for public policies that account for environmental and socioeconomic factors, such as air pollution, access to health care services, use of biomass fuels, and exposure to pesticides.

Keywords: Asthma, pneumonia, child, rural population, urban population.

RESUMO

Introdução: A saúde respiratória infantil possui uma estreita relação com as condições ambientais. Por esse motivo, compreender como os efeitos da urbanização, ruralidade e contato com a natureza afetam esse aspecto da saúde infantil pode orientar estratégias de saúde pública e fomentar melhores práticas clínicas. **Objetivo:** Analisar a relação entre urbanização, ruralidade, contato com a natureza e hospitalizações por asma e pneumonia em crianças e adolescentes (0-19 anos) em Santa Catarina no ano de 2023. **Métodos:** Estudo ecológico, utilizando a base de dados do Sistema de Informação Hospitalar (SIH) do Sistema Único de Saúde (SUS), caracterizada pelas taxas de morbidade hospitalar por asma e pneumonia ajustadas por faixa etária. Também foram utilizadas as classificações espaciais do Instituto Brasileiro de Geografia e Estatística (IBGE), descritas por % urbano, % rural e % contato com a natureza dos municípios de Santa Catarina. **Resultados:** A urbanização e a ruralidade estiveram associadas à ocorrência de asma e pneumonia em crianças, especialmente nos primeiros anos de vida. Municípios com menor grau de urbanização e maior grau de ruralidade apresentaram maiores taxas de hospitalização por ambas as doenças. No entanto, o contato com a natureza não influenciou significativamente a hospitalização por asma e pneumonia. **Conclusão:** O estudo destaca a complexidade multifatorial da saúde respiratória infantil e reforça a necessidade de políticas públicas que considerem as especificidades ambientais e socioeconômicas como a poluição do ar, acesso a serviços de saúde, uso de combustíveis de biomassa e exposição a agrotóxicos.

Descritores: Asma, pneumonia, criança, população rural, população urbana.

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Introduction

Healthy child development is influenced by multiple factors, including physical, social, familial, individual, and environmental elements. However, the contemporary world, which is characterized by globalization, demanding daily routines, widespread use of electronic devices, and the predominance of urbanized living environments, has led to a significant reduction in children's contact with nature. Limited exposure to natural environments in large urban centers has become increasingly common, raising concerns about potential long-term impacts on children's respiratory health.^{1,2}

Understanding how environmental conditions affect children is essential for informing public policies and interventions aimed at promoting healthy child development. Moreover, given the growing interest in preventing respiratory diseases, clarifying how exposure to environmental pollutants influences children's respiratory health may help guide public health strategies and clinical practices.³

Regarding children's respiratory health, exposure to air pollution is associated with several conditions, including asthma, bronchiolitis, and respiratory infections. Both prenatal exposure and short- and long-term exposure to air pollutants are linked to a range of adverse outcomes, including reduced lung function, increased risk of respiratory infections, and exacerbation of asthma. For this reason, air quality policies play a crucial role in preventing respiratory morbidity in children, particularly in low-income settings.^{4,5}

This study aims to address an important gap in current literature by providing scientific evidence on the effects of urban, rural, and natural environments on children's respiratory health. The findings may help support improvements in urban planning, child education, and health promotion strategies, with the goal of fostering environments that support healthy child development in modern cities. In this context, the objective of this study was to analyze the association between the percentage of urban, rural, and natural areas in cities of Santa Catarina, southern Brazil, and hospitalizations for asthma and pneumonia among children and adolescents in 2023.

Methods

An ecological study was conducted including hospitalizations for pneumonia and asthma recorded

in the Brazilian Unified Health System (SUS) across cities in the state of Santa Catarina from January to December 2023.

Cases of hospital morbidity due to pneumonia (ICD-10 codes J12-J18) and asthma (ICD-10 codes J45-J46) were included for both sexes among individuals aged 0-19 years. Data were obtained from SUS Hospital Information System.⁶ Records incomplete or not relevant to the study objectives were excluded.

To assess environmental exposure in each city, spatial classifications described by the Brazilian Institute of Geography and Statistics (IBGE) were used. These classifications follow the methodological proposal for defining rural, urban, and natural spaces in Brazil. In this framework, each city is characterized by the percentage of urban area (% urban), rural area (% rural), and natural area (% nature).^{7,8}

Age-adjusted hospital morbidity rates for asthma and pneumonia were calculated as follows:

Hospital morbidity rate = number of hospitalizations in 2023 by city and age group / estimated population in 2023 for each city and age group.

Age groups were categorized as 0-4 years, 5-9 years, 10-14 years, 15-19 years, and 0-19 years (total).

The dataset used in this study is publicly available and contains no information that could be used to identify individual participants. As data are anonymous and publicly accessible, the study complies with the Brazilian National Health Council Resolution No. 510/2016 (Article 1, Sole Paragraph, Items II, III, and V) and requires no review by a human research ethics committee under Resolution No. 466/2012.

Data were organized and stored using Microsoft Excel and analyzed using SPSS, version 20.0 (IBM Corp., Armonk, N.Y., USA). Quantitative variables were described using measures of central tendency and dispersion. Qualitative variables were summarized using absolute and relative frequencies. Data analysis included analysis of variance and Pearson correlation to evaluate the relationship of % urban, % rural, and % nature with hospital morbidity due to asthma and pneumonia. The level of statistical significance was set at 5% ($p < 0.05$).

Results

This study evaluated hospital morbidity due to pneumonia and asthma among children and

adolescents in the state of Santa Catarina in 2023. For pneumonia, 6182 cases were recorded among children aged 0-4 years, 1198 among those aged 5-9 years, 364 among those aged 10-14 years, and 271 among those aged 15-19 years, totaling 8015 cases. For asthma, 888 cases were recorded among children aged 0-4 years, 954 among those aged 5-9 years, 239 among those aged 10-14 years, and 54 among those aged 15-19 years, totaling 2135 cases.

Figure 1 shows the distribution of % urban, % rural, and % nature across the state of Santa Catarina. The eastern region is more urbanized, with smaller rural and natural areas, particularly along the largest coastal cities. The western and central-western regions are predominantly rural, with lower levels of urbanization and extensive natural and agricultural areas. The mountainous and southeastern regions contain larger natural areas, lower urban density, and a moderate presence of rural areas.

Regarding hospitalizations for asthma, rurality was associated with higher hospitalization rates, particularly among younger children. Cities with a higher degree

of rurality (> 75%) showed higher hospitalization rates for asthma among children aged 0-4 years ($p = 0.071$, close to the significance threshold) and 5-9 years ($p = 0.031$). When all age groups were considered together, rurality remained significantly associated with higher asthma hospitalization rates ($p = 0.011$).

Urbanization also showed a trend toward significance. Cities with lower levels of urbanization (< 25%) presented higher asthma hospitalization rates among children aged 5-9 years ($p = 0.094$). When all age groups were analyzed together, lower levels of urbanization also showed a trend toward association with asthma hospitalization ($p = 0.070$) (Table 1).

For pneumonia hospitalizations, rurality was the factor most strongly associated with higher hospitalization rates. Cities with a higher degree of rurality (> 75%) showed significantly higher hospitalization rates among children aged 0-4 years ($p < 0.001$) and 10-14 years ($p = 0.042$). When all age groups were considered together, rurality remained significantly associated with higher pneumonia hospitalization rates ($p = 0.001$).

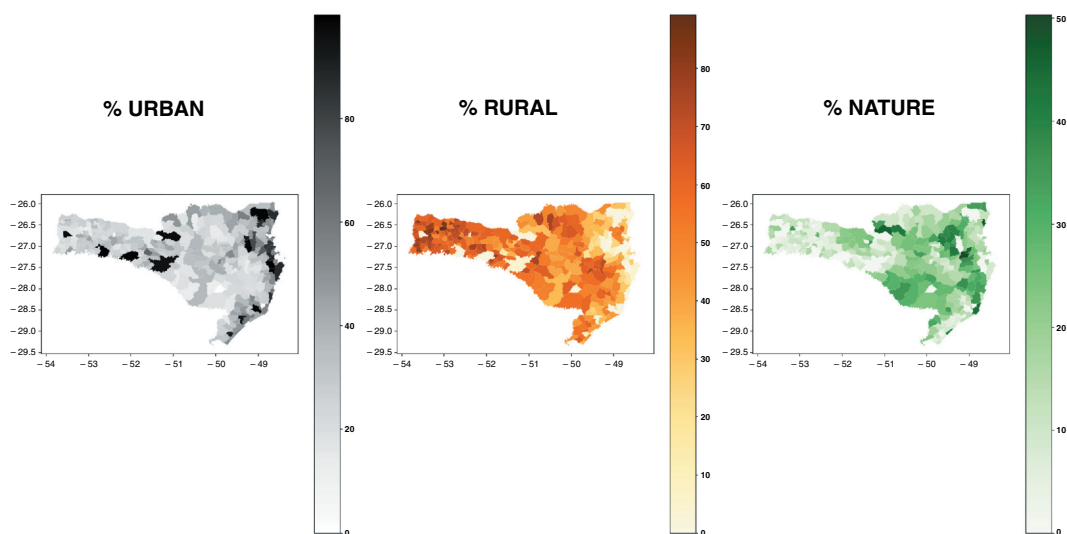


Figure 1

Distribution of % urban, % rural, and % nature in municipalities across the state of Santa Catarina, southern Brazil, in 2023

Urbanization also showed significant associations, although less consistently. Cities with lower levels of urbanization (< 25%) presented significantly higher hospitalization rates for pneumonia among children aged 0-4 years ($p = 0.037$) and when all age groups were analyzed together ($p = 0.024$) (Table 2).

No significant differences were found in hospitalization rates for asthma or pneumonia according to the degree of contact with nature.

Figure 2 illustrates a weak negative correlation between asthma hospitalization rates and the degree of urbanization. Conversely, a weak positive correlation was observed between asthma hospitalization rates and the percentage of rurality, particularly among younger children.

Figure 3 illustrates a weak negative correlation between pneumonia hospitalization rates and both urbanization and contact with nature. In contrast,

Table 1

Age-adjusted asthma hospitalization rate (/10,000 population) in relation to % urban and % rural in municipalities across the state of Santa Catarina, southern Brazil, in 2023

Age group	% urban	N	Mean	SD	p	% rural	N	Mean	SD	p
0-4 years	< 25%	48	35.3	39.5	0.172	< 25%	40	18.6	22.7	0.071
	25%-50%	102	27.8	47.2	25%-50%	67	22.8	25.4		
	50%-75%	26	17.7	14.7	50%-75%	81	32.1	53		
	> 75%	21	16.2	16.2	> 75%	9	51.1	48.3		
5-9 years	< 25%	48	34.8	47.2	0.094	< 25%	40	17.5	14.2	0.031
	25%-50%	102	21.1	32.9	25%-50%	67	19.7	20.4		
	50%-75%	26	19.1	19.8	50%-75%	81	27.6	46.5		
	> 75%	21	18.9	12.9	> 75%	9	51	43.7		
10-14 years	< 25%	48	9	20.6	0.509	< 25%	40	5.2	6	0.379
	25%-50%	102	9.5	27.6	25%-50%	67	5.5	12.6		
	50%-75%	26	2.9	4.7	50%-75%	81	11.2	31.4		
	> 75%	21	4.5	3.6	> 75%	9	9.7	29.2		
15-19 years	< 25%	48	4.2	13.2	0.710	< 25%	40	0.7	1.7	0.143
	25%-50%	102	4.4	18.4	25%-50%	67	2.5	8.6		
	50%-75%	26	1.7	5.8	50%-75%	81	6.5	21.6		
	> 75%	21	1.1	2.1	> 75%	9	0	0		
Total asthma	< 25%	48	22.1	15.2	0.07	< 25%	40	10.5	8	0.011
	25%-50%	102	16	26.8	25%-50%	67	13	11.7		
	50%-75%	26	10.7	9	50%-75%	81	20.1	29.9		
	> 75%	21	10.2	8	> 75%	9	30.1	13.6		

a weak positive correlation was observed between pneumonia hospitalization rates and the percentage of rurality. This association was more pronounced among younger children.

Discussion

The findings indicate that urbanization and rurality may be associated with the occurrence of asthma and

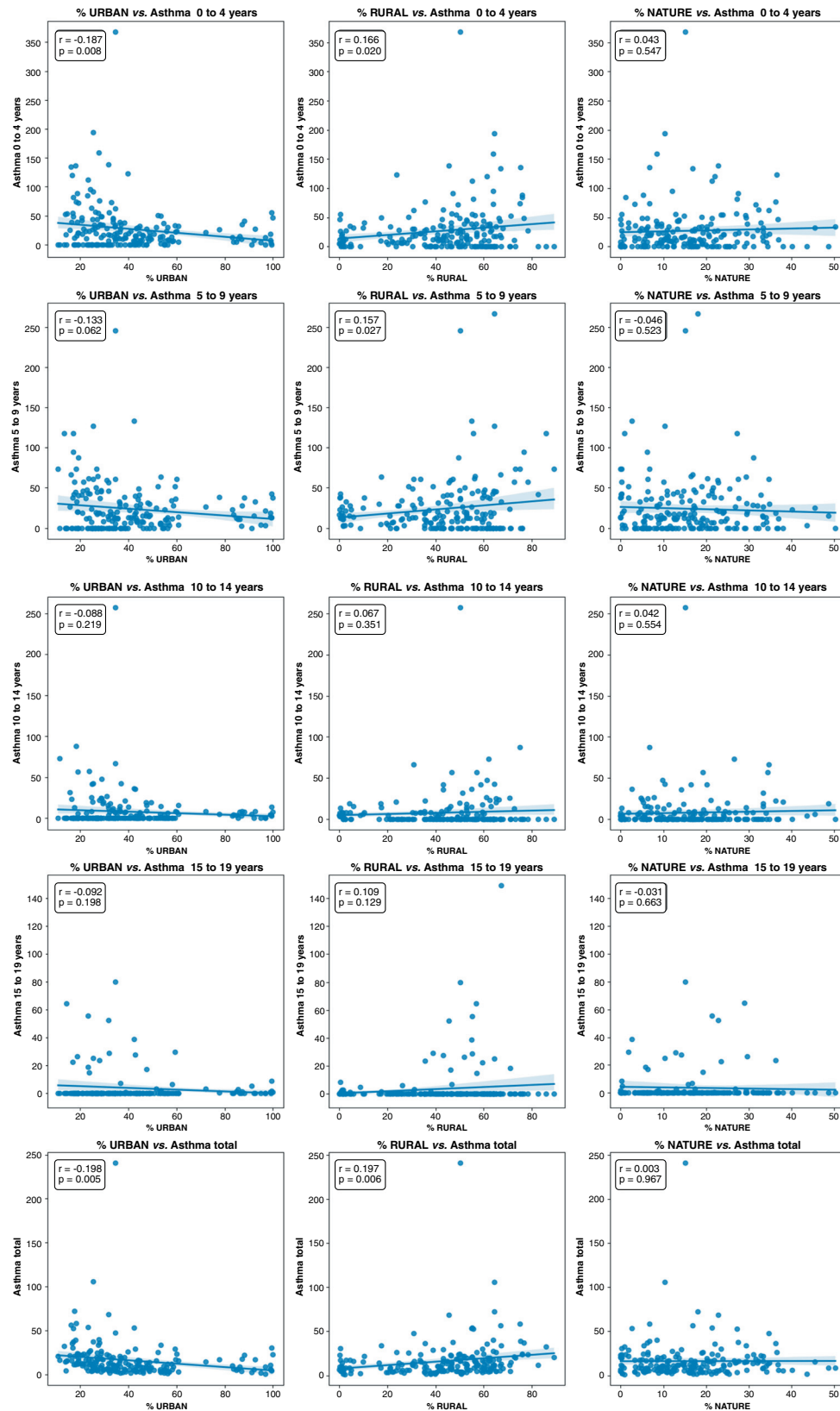
pneumonia in children, particularly during the first years of life. Cities with lower levels of urbanization and higher levels of rurality showed higher hospitalization rates for both conditions. However, contact with nature did not appear to significantly influence hospitalizations for asthma or pneumonia.

Areas with a higher percentage of natural environments are concentrated in the eastern region of Santa Catarina, which is also the most urbanized

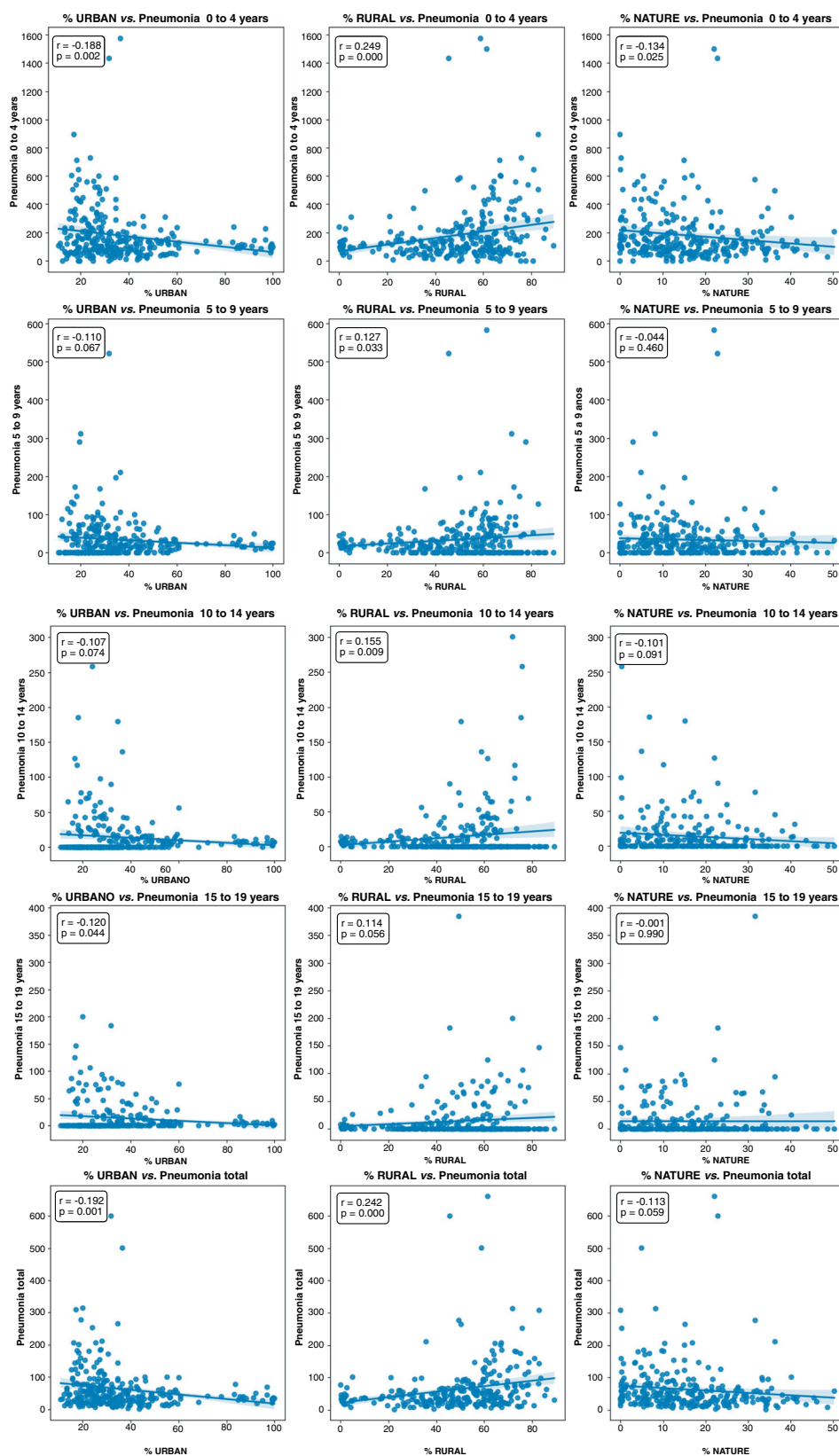
Table 2

Age-adjusted pneumonia hospitalization rate (/10,000 population) in relation to % urban and % rural in municipalities across the state of Santa Catarina, southern Brazil, in 2023

Age group	% urban	N	Mean	SD	p	% rural	N	Mean	SD	p
0-4 years	< 25%	93	220.4	228	0.037	< 25%	42	119.1	64.5	< 0.001
	25%-50%	140	171.6	208		25%-50%	83	133.2	172	
	50%-75%	26	121.7	67.9		50%-75%	135	206.2	224	
	> 75%	22	115.7	44.5		> 75%	21	301.8	249	
5-9 years	< 25%	93	39.1	79.6	0.445	< 25%	42	22.1	13.3	0.204
	25%-50%	140	34.3	56.4		25%-50%	83	26.8	61	
	50%-75%	26	20.7	16.4		50%-75%	135	41.1	67.5	
	> 75%	22	22.2	10.1		> 75%	21	36	72.1	
10-14 years	< 25%	93	20.3	49.9	0.138	< 25%	42	7.2	5.6	0.042
	25%-50%	140	11.7	24.8		25%-50%	83	7.9	16.3	
	50%-75%	26	8.2	11		50%-75%	135	17.9	38.5	
	> 75%	22	6.9	3.6		> 75%	21	24.4	68.4	
15-19 years	< 25%	93	19.3	52.7	0.211	< 25%	42	5.1	7.6	0.298
	25%-50%	140	12.1	25.8		25%-50%	83	15.7	48.8	
	50%-75%	26	9.1	17.3		50%-75%	135	13.7	30.1	
	> 75%	22	4.3	3.8		> 75%	21	21.7	43.1	
Total pneumonia	< 25%	93	79.9	90	0.024	< 25%	42	39.3	20.7	0.001
	25%-50%	140	59.8	74.8		25%-50%	83	48.1	72.5	
	50%-75%	26	41.8	23.7		50%-75%	135	73.6	83.7	
	> 75%	22	38.2	13.7		> 75%	21	101.9	76.3	

**Figure 2**

Correlation between % urban, % rural, and % nature vs age-adjusted asthma hospitalization rate (/10,000 population)

**Figure 3**

Correlation between % urban, % rural, and % nature vs age-adjusted pneumonia hospitalization rate (/10,000 population)

part of the state. This spatial overlap may introduce bias in the results, as urban areas with greater contact with nature may differ substantially from rural areas with lower levels of natural coverage. For example, urban areas with more green spaces may benefit from improved air quality, which may reduce hospitalizations for respiratory diseases. In contrast, rural areas with lower percentages of natural environments may be associated with intensive agricultural activities, such as pastures or monocultures, which may increase exposure to pollutants and pesticides and contribute to higher hospitalization rates.

In comparison, a cross-sectional study conducted in Canada involving 3509 children aged 5-14 years found that asthma prevalence was lower among children living in rural areas than among those living in urban areas (15.1% vs. 21.5%). However, the study identified an inverse association between respiratory symptoms, such as wheezing, and more than 3 asthma episodes per year among rural patients during the previous 12 months. A modest association was also observed between rural asthma patients and the need for at least one medical consultation during the previous year.⁹ Nevertheless, comparisons between the Canadian study and the present analysis should consider methodological differences in the classification of urban and rural areas. IBGE uses specific criteria to define these areas in Brazil, which may not be directly comparable with those used in Canada. For instance, rural areas in Canada may have better infrastructure and access to health services than rural areas in Brazil, which may partly explain the differences in findings.

Similarly, a study conducted with an initial sample of 1038 adults, 516 living in rural areas and 522 in urban areas, found that 15% (n = 78) and 11% (n = 59) of participants were patients with asthma, respectively. The study also reported that patients with asthma living in urban areas experienced more symptoms, exacerbations, and required more treatment than those living in rural areas, which contrasts with the findings reported in the previous study.¹⁰

Regarding pneumonia, a study conducted in 2 districts of Maharashtra, India, evaluated 3671 children younger than 5 years through questionnaires administered to their mothers and reported a higher annual incidence of pneumonia in rural populations compared with children living in urban areas.¹¹ Another analysis conducted in the southern Netherlands between 2009 and 2013 examined the association between proximity to livestock farms and the risk of

pneumonia. Individuals living within approximately 1 km of poultry farms showed an increased risk of pneumonia. In addition, a higher risk was observed among individuals living 1.5-2 km from goat farms, although the study did not account for differences related to sex, age, or occupational exposure.¹² A similar cross-sectional study examined pneumonia in a sample of 5640 children aged 3-6 years living near highways in a Chinese province and found a positive association between childhood pneumonia and residential proximity to major traffic roads, automobile shops within a 200 m radius, and residential areas with ground-level parking facilities.¹³

The differences in hospitalization rates for respiratory diseases observed between more rural and less rural cities in Santa Catarina reinforce the multifactorial nature of these conditions, particularly in pediatric populations. Asthma is influenced by both genetic and environmental factors, with environmental exposures playing a key role in geographic disparities. In rural areas, biomass fuels such as wood, charcoal, and crop residues are commonly used to meet household energy needs, particularly in rudimentary stoves and ovens. These practices often occur under inadequate ventilation conditions, exposing children to harmful particles that may exacerbate airway inflammation. Although the adoption of modern energy sources has increased, progress in rural regions remains limited, which may partly explain the greater vulnerability of children to asthma in these settings. In addition, lifestyle factors and environmental exposures specific to rural communities, such as proximity to agricultural areas and exposure to allergens, may contribute to differences in hospitalization rates.¹⁴

Scientific evidence also links pesticide exposure and tobacco cultivation to negative respiratory health outcomes, including among children, although most studies focus on agricultural workers and their families. Studies conducted in southern Brazil, a region known for tobacco farming, have documented respiratory diseases exacerbated by exposure to dust from dried tobacco leaves and the intensive use of pesticides. Pesticide intoxication may lead to acute and chronic respiratory problems as well as other health conditions, including dermatological diseases and neuropsychiatric disorders.¹⁵ This evidence is consistent with the findings of the present study, which identified a significant association between rurality and higher hospitalization rates for asthma and pneumonia.

Although most research has focused on direct occupational exposures, these environmental factors may also affect children living in rural communities where tobacco cultivation and pesticide use are common. Children exposed to such environments may be more susceptible to respiratory diseases due to environmental contamination of air, soil, and water as well as indirect exposure to agricultural chemicals. Although studies specifically addressing children's respiratory outcomes remain limited, existing evidence suggests that tobacco farming may represent a risk factor not only for workers but also for rural communities more broadly.¹⁶

In urban environments, substantial evidence documents the harmful effects of air pollution on children's respiratory health. In densely populated urban areas, particularly in developing countries, air pollution remains a major public health concern.¹⁷ These environments are characterized by higher emissions of pollutants and multiple sources of contamination, including motor vehicles, biomass burning, waste combustion, cigarette smoke, and other pollutants. Such exposures represent an important risk to children's respiratory health.

However, in the present study, cities with higher levels of urbanization (> 50% urban area) in Santa Catarina showed an inverse relationship with hospitalization rates for asthma and pneumonia. This finding may reflect socioeconomic conditions commonly observed in more urbanized regions, including greater access to health services, earlier diagnosis, improved disease management, and more effective preventive care.

The relationship between urbanization, rurality, and children's respiratory health is therefore complex and multifactorial. While research extensively documents the harmful effects of urban air pollution, studies also highlight the impact of pesticides, allergens, and biomass burning in rural environments. Consistent with these considerations, the present study found a negative correlation between the degree of urbanization and hospitalization rates for asthma and pneumonia as well as a positive correlation with rural environments, particularly among younger children. These findings suggest that risk factors for children's respiratory diseases vary substantially between urban and rural contexts and underscore the importance of public health strategies tailored to each setting. Access to health services, geographic proximity, and availability of health care resources are

important determinants that should be considered when planning interventions aimed at preventing and managing these conditions, particularly among vulnerable populations such as young children living in rural areas.

With respect to contact with nature, the present study did not identify a significant association. Nevertheless, several studies¹⁸⁻²¹ suggest that exposure to natural environments may provide health benefits. Practices such as forest bathing and access to green spaces have been associated with improved lung function, reduced stress levels, enhanced immune responses, and the filtration of airborne pollutants. One possible explanation for the absence of an observed association in this study may be the increasing amount of time children spend in daycare centers and full-time schools, which may limit actual contact with natural environments even in cities with higher proportions of natural areas.

Santa Catarina has a human development index of 0.840, one of the highest in Brazil, reflecting favorable conditions in education, income, and longevity. However, regional disparities remain. The eastern region, which is more urbanized, has higher development indicators, whereas the western region, characterized by rural areas and strong agricultural activity, presents lower socioeconomic indicators. Such differences may influence the study findings as rural areas with lower development levels may have reduced access to health care services, which may contribute to higher hospitalization rates for respiratory diseases.²²

Several limitations should be considered when interpreting the results. First, the ecological design limits the ability to establish direct causal relationships because analyses are conducted at the population level rather than at the individual level, which may introduce ecological bias. Second, the overlap between urban areas and areas with higher percentages of natural environments complicates the interpretation of the independent effects of these environmental factors. Urban areas may benefit from greater access to health care services, potentially reducing hospitalization rates, whereas rural areas with lower proportions of natural environments may experience higher exposure to biomass burning and pesticides. Another potential limitation is the influence of the return to in-person activities in daycare centers and schools following the COVID-19 pandemic. In Brazil, the Public Health Emergency of National

Importance ended on May 22, 2022, while the World Health Organization declared the end of the Public Health Emergency of International Concern on May 5, 2023. This transition period may have influenced the transmission dynamics of respiratory infections among children and may have affected hospitalization patterns observed in 2023.

Conclusion

This study contributes to the understanding of the relationship between urbanization, rurality, and children's respiratory health, highlighting the multifactorial complexity of these conditions. The findings suggest that less urbanized areas show higher hospitalization rates for asthma and pneumonia, possibly influenced by factors such as reduced access to health care services, greater use of biomass fuels, and increased exposure to environmental hazards such as pesticides. Conversely, the negative association between urbanization and hospitalizations may reflect better socioeconomic conditions and greater access to diagnosis and treatment in urban settings. Although contact with nature did not show a significant association in this study, prior research indicates potential benefits for respiratory health. Limitations inherent to ecological studies, particularly the difficulty in establishing causal relationships, highlight the need for future research using more specific methodological approaches. These results emphasize the importance of public health policies aimed at improving respiratory health by addressing environmental risk factors in both urban and rural settings.

References

- Li D, Menotti T, Ding Y, Wells NM. Life Course Nature Exposure and Mental Health Outcomes: A Systematic Review and Future Directions. *Int J Environ Res Public Health*. 2021 May 12;18(10):5146. doi: 10.3390/ijerph18105146.
- Jimenez MP, DeVille NV, Elliott EG, Schiff JE, Wilt GE, Hart JE, et al. Associations between Nature Exposure and Health: A Review of the Evidence. *Int J Environ Res Public Health*. 2021 Apr 30;18(9):4790. doi: 10.3390/ijerph18094790.
- Oswald TK, Rumbold AR, Kedzior SGE, Moore VM. Psychological impacts of "screen time" and "green time" for children and adolescents: A systematic scoping review. *PLoS One*. 2020 Sep 4;15(9):e0237725. doi: 10.1371/journal.pone.0237725.
- Dondi A, Carbone C, Manieri E, Zama D, Del Bono C, Betti L, et al. Outdoor Air Pollution and Childhood Respiratory Disease: The Role of Oxidative Stress. *Int J Mol Sci*. 2023 Feb 22;24(5):4345. doi: 10.3390/ijms24054345.
- Aithal SS, Sachdeva I, Kurmi OP. Air quality and respiratory health in children. *Breathe (Sheff)*. 2023;19(2):230040. doi:10.1183/20734735.0040-2023.
- Brasil, Ministério da Saúde. DATASUS. Sistema de Informações Hospitalares do SUS (SIH/SUS) [Internet]. Available from: <http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/nisc.def>. Accessed on: Feb 16 2024.
- Instituto Brasileiro de Geografia e Estatística. Proposta Metodológica para Classificação dos Espaços do Rural, do Urbano e da Natureza no Brasil [Internet]. Available from: <https://biblioteca.ibge.gov.br/visualizacao/livros/liv102019.pdf>. Accessed on: Feb 16 2024.
- Instituto Brasileiro de Geografia e Estatística. Classificação Rural e Urbana [Internet]. Available from: <https://www.ibge.gov.br/geociencias/organizacao-do-territorio/tipologias-do-territorio/15790-classificacao-rural-e-urbana.html?edicao=37670&t=downloads>. Accessed on: Feb 16 2024.
- Lawson JA, Rennie DC, Cockcroft DW, Dyck R, Afanasieva A, Oluwole O, et al. Childhood asthma, asthma severity indicators, and related conditions along an urban-rural gradient: a cross-sectional study. *BMC Pulm Med*. 2017;17(4). doi: 10.1186/s12890-016-0355-5.
- Romero-Mesones C, Ojanguren I, Espejo D, Granados G, González-Barcala FJ, Cruz MJ, et al. Influence of the environment on the characteristics of asthma. *Sci Rep*. 2022 Nov 28;12(1):20522. doi: 10.1038/s41598-022-25028-1.
- Gothankar J, Doke P, Dhumble G, Pore P, Lalwani S, Quraishi S, et al. Reported incidence and risk factors of childhood pneumonia in India: a community-based cross-sectional study. *BMC Public Health*. 2018 Sep 11;18(1):1111. doi: 10.1186/s12889-018-5996-2.
- Kalkowska DA, Boender GJ, Smit LAM, Baliatsas C, Yzermans J, Heederik DJJ, et al. Associations between pneumonia and residential distance to livestock farms over a five-year period in a large population-based study. *PLoS One*. 2018 Jul 17;13(7):e0200813. doi: 10.1371/journal.pone.0200813.
- Chang J, Liu W, Huang C. Residential Ambient Traffic in Relation to Childhood Pneumonia among Urban Children in Shandong, China: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2018;15(6):1076. doi:10.3390/ijerph15061076.
- Jie Y, Isa ZM, Jie X, Ju ZL, Ismail NH. Urban vs. rural factors that affect adult asthma. *Rev Environ Contam Toxicol*. 2013;226:33-63. doi: 10.1007/978-1-4614-6898-1_2.
- Santos LB, Soares MR, Caló RS, Costa AAS, Souza BSN, Santana BEF, et al. 2023. Doenças respiratórias em menores de cinco anos relacionadas ao uso de agrotóxicos em Mato Grosso. *Revista Eletrônica Acervo Saúde*. 2023;23(7):e13449. doi: 10.25248/reas.e13449.2023.
- Riquinho DL, Hennington ÉA. Sistema integrado de produção do tabaco: saúde, trabalho e condições de vida de trabalhadores rurais no Sul do Brasil. *Cadernos de Saúde Pública*. 2016;32(12). doi:10.1590/0102-311x00072415.
- Madani NA, Carpenter DO. Patterns of Emergency Room Visits for Respiratory Diseases in New York State in Relation to Air Pollution, Poverty and Smoking. *International journal of environmental research and public health*. 2023;20(4):3267. doi:10.3390/ijerph20043267.
- Zhang J, Wang Y, Feng L, Hou C, Gu Q. Effects of air pollution and green spaces on impaired lung function in children: a case-control study. *Environ Sci Pollut Res Int*. 2022 Feb;29(8):11907-19. doi: 10.1007/s11356-021-16554-y.
- Lambrecht BN, Hammad H. The immunology of the allergy epidemic and the hygiene hypothesis. *Nat Immunol*. 2017 Sep 19;18(10):1076-83. doi: 10.1038/ni.3829.

20. Li Q. Effect of forest bathing trips on human immune function. *Environ Health Prev Med*. 2010 Jan;15(1):9-17. doi: 10.1007/s12199-008-0068-3.
21. Chawla L. Benefits of Nature Contact for Children. *Journal of Planning Literature*. 2015;30(4):433-52. doi 10.1177/0885412215595441.
22. Programa das Nações Unidas para o Desenvolvimento (PNUD). Atlas do Desenvolvimento Humano no Brasil [Internet]. 2023. Available from: <http://www.atlasbrasil.org.br>.

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Translation, Cultural Adaptation, and Validation of the Allergy Questionnaire for Athletes (AQUA) for Brazilian Portuguese

Tradução, adaptação cultural e validação do Questionário de Alergia para Atletas (AQUA) para o português brasileiro

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ABSTRACT

Introduction: Exercise-induced bronchospasm is characterized by temporary airway obstruction, causing breathlessness, dry cough, and wheezing during or after exercise. In athletes, exercise-induced bronchospasm may be linked to pre-existing allergies, affecting health, quality of life, and performance. **Methods:** This cross-sectional study included athletes who had been on university sports teams for ≥ 6 months and was conducted in 2 phases: (1) translation and cultural adaptation following international guidelines for semantic and conceptual equivalence; (2) validation and reproducibility by assessing inter- and intraobserver reliability. Exercise capacity and lung function were evaluated using incremental leg exercise testing and spirometry. Fifteen athletes (mean age 21.6 [SD, 2.3] years; 66.7% male) participated, whose most common sport was volleyball (33.3%). All participants had normal lung function. **Results:** Total scores were consistent between initial and repeated applications by the same examiner (6.6 [SD, 2.5] vs. 6.6 [SD, 2.6]; $p = 1.0$) and different examiners (6.6 [SD, 2.5] vs. 7 [SD, 3]; $p = 0.4$). The Cronbach's alpha of 0.94 ($p < 0.001$) indicated excellent reliability. Bland-Altman analysis confirmed good agreement between applications, supporting the instrument's reproducibility. **Conclusions:** The Brazilian version of the Allergy Questionnaire for Athletes is a reliable and reproducible instrument for assessing allergies in athletes. It also demonstrates validity in associating allergy status with exercise testing to detect exercise-induced bronchospasm.

Keywords: Bronchospasm, exercise, athletes, exercise-induced bronchospasm.

RESUMO

Introdução: O broncoespasmo induzido pelo exercício (BIE) é caracterizado por uma obstrução temporária das vias aéreas, causando falta de ar, tosse seca e chiado no peito durante ou após o exercício. Em atletas, o BIE pode estar relacionado a alergias pré-existentes, afetando a saúde, a qualidade de vida e o desempenho. **Método:** Foi realizado um estudo transversal com atletas que participavam de equipes esportivas há pelo menos seis meses. O estudo foi dividido em duas fases: (1) tradução e adaptação cultural seguindo diretrizes internacionais para equivalência semântica e conceitual; e (2) validação e reprodutibilidade, avaliando a confiabilidade interobservador e intraobservador. A capacidade de exercício e a função pulmonar foram avaliadas por meio de um teste incremental com os membros inferiores e espirometria. Participaram 15 atletas (média de idade 21,6 $\pm$ 2,3 anos), sendo a maioria do sexo masculino (66,7%), com o vôlei como esporte mais comum (33,3%). Todos apresentaram função pulmonar normal. **Resultados:** Os escores totais do AQUA foram consistentes entre a aplicação inicial e a reaplicação pelo mesmo avaliador (6,6 $\pm$ 2,5 vs. 6,6 $\pm$ 2,6; $p = 1,0$) e entre avaliadores diferentes (6,6 $\pm$ 2,5 vs. 7 $\pm$ 3; $p = 0,4$). O alfa de Cronbach de 0,94 ($p < 0,001$) indicou excelente confiabilidade. A análise de Bland-Altman confirmou boa concordância entre as aplicações, apoiando a reprodutibilidade do instrumento. **Conclusão:** A versão brasileira do AQUA é confiável e reprodutível para avaliar alergias em atletas. Também demonstra validade ao associar o status alérgico com os testes de exercício para detectar broncoespasmo induzido pelo exercício.

Descritores: Broncoespasmo, exercício, atletas, broncoespasmo induzido pelo exercício.

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Introduction

Exercise-induced bronchospasm (EIB) is a temporary airway obstruction caused by exercise that leads to dyspnea, dry cough, and wheezing.¹ It results from hyperventilation-induced dehydration of the lower airways, altering the osmotic gradient and triggering bronchospasm. Environmental factors, such as exercise intensity, air quality, temperature, and humidity, influence its onset.² EIB in athletes may also be linked to pre-existing allergic diseases, which involve abnormal immune responses. Thus, diagnosing allergies is crucial in the clinical assessment of athletes, given that allergic diseases can significantly affect health, quality of life, and performance.³

The Allergy Questionnaire for Athletes (AQUA) is a reliable allergy screening tool.^{3,4} Despite its practicality and accessibility, no validation study has been conducted for the Portuguese language. Thus, we translated, validated, and culturally adapted the AQUA questionnaire into Brazilian Portuguese.

Methods

This cross-sectional study was conducted at the University of Fortaleza's Human Movement Analysis Laboratory with athletes 18–30 years of age who had been on university sports teams for ≥ 6 months. The exclusion criteria included recent respiratory infections (≤ 6 weeks) and asthma requiring continuous medication.

The study was conducted in 2 phases: 1) translation and cultural adaptation of AQUA to Portuguese and 2) validation and reproducibility testing. The process followed best practices from the literature.⁵ The ethical guidelines of National Health Council Resolution 466/12 were observed, including informed consent from all participants and approval from the University of Fortaleza Ethics Committee (decision 5,959,262).

AQUA consists of 25 questions on allergic symptoms, family history, suspected allergies, and medication use, which are scored based on a positive likelihood ratio. The total score determines the questionnaire's sensitivity, specificity, and predictive value. In this study, questions 4 to 16 were scored, classifying athletes as AQUA (+) (≥ 5) or AQUA (–) (< 5). The final Portuguese version is provided in the Supplementary Material. For validation and reproducibility, 15 athletes completed the questionnaire

twice with different examiners (30 minutes apart) and once more with the initial examiner to assessment intraobserver agreement.

The exercise test assessed EIB and its correlation with AQUA. Participants avoided intense exercise, stimulants, and corticosteroids on test day. They wore light clothing and sneakers, with the lab temperature set at 24 °C–26 °C, as per guidelines.⁶ Athletes performed an incremental leg test on a load-bearing ergometer, starting at 25 W for 3 minutes and increasing by 25 W per minute until exhaustion.

Pulmonary function was assessed using spirometry, measuring forced expiratory volume in the first second (FEV₁) and forced vital capacity. Four measurements were taken: before, immediately after, 5 minutes after, and 10 minutes after the incremental leg test. FEV₁ decreases $> 10\%$ were considered indicative of EIB. This criterion followed established recommendations from the Brazilian Thoracic Society and the American Thoracic Society.⁶

Statistical Analysis

The data were analyzed using IBM SPSS Statistics 20.0 and GraphPad Prism 6.0. The Shapiro-Wilk test was used to assess data distribution, and descriptive analysis included mean (SD), frequencies, and delta variations. The instrument's reproducibility was assessed via the intraclass correlation coefficient, the Wilcoxon test, and Bland-Altman plots, while Cronbach's alpha was used to assess internal consistency. Spearman's correlation was used to validate AQUA against spirometry (FEV₁) and the incremental leg test (maximum load), with a significance level of 5%.

Results

Fifteen athletes participated in the study, with a mean age of 21.6 [SD, 2.3] years and normal pulmonary function (Table 1). The reproducibility analysis showed no significant differences in AQUA scores between initial and repeated applications by the same examiner (6.6 [SD, 2.5] vs. 6.6 [SD, 2.6]; $p = 1.0$) or between applications by different examiners (6.6 [SD, 2.5] vs. 7 [SD, 3]; $p = 0.4$).

The intra-observer intraclass correlation coefficient was 0.93 (95% CI: 0.80–0.97), while the inter-observer intraclass correlation coefficient was 0.91 (95% CI: 0.75–0.97). Cronbach's alpha (0.94, $p < 0.001$) confirmed excellent reliability. Bland-Altman analysis

Table 1

Personal and clinical characteristics of the study participants

n = 15	
Age (years)^a	21.6±2.3
Sex^b	
Male	10/66.6
Female	5/33.7
Weight (kg)^a	77±19.6
Height (cm)^a	1.79±0.1
BMI (kg.cm²)^a	23.8±4.9
Sport^b	
Volleyball	5/33
Athletics	3/20
Tennis	3/20
Basketball	2/13.3
Martial arts	2/13.3
Pulmonary function^a	
FEV ₁ (L)	3.7±0.8
FEV ₁ (%)	87.3±10.5
FVC (L)	4.4±0.9
FVC (%)	91.6±10.6

^a Data expressed as mean ± standard deviation; ^b Data expressed as relative and absolute frequency; BMI = body mass index; cm = centimeters; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; kg = kilograms; L = liters.

demonstrated strong intra- and interobserver agreement (Figure 1).

Regarding validity, AQUA scores showed moderate, significant correlations with $\Delta\%$ FEV₁ immediately after vs. 5 minutes post-exercise ($r = -0.6$; $p=0.04$) and maximum load in the exercise test ($r = -0.6$; $p = 0.04$) (Table 2), supporting its reliability for identifying EIB in athletes.

Discussion

The Portuguese version of AQUA demonstrated excellent reliability and reproducibility when administered by different observers and the same observer. This consistency suggests that the Portuguese version of AQUA reliably reproduces results when administered to athletes under similar conditions. These findings align with previous studies, reinforcing the instrument's reliability in assessing allergic predisposition in athletes.^{3,7} Regarding sex

and sports modality, the results were consistent with existing literature, showing a predominance of male athletes and a high proportion of AQUA (+) individuals.⁸

AQUA scores showed a moderate inverse correlation with pulmonary function ($\Delta\%$ FEV₁) immediately after vs. 5 minutes post-exercise and maximum exercise load. While AQUA identifies allergy predisposition, its predictive capacity for EIB may be limited due to the small sample size and its design as a screening tool rather than a diagnostic test. This observation is consistent with a Swedish study that used a similar incremental test under more extreme temperatures (18 °C and -15 °C) and found no significant changes in FEV₁ or FEV₁/forced vital capacity post-exercise, suggesting that high-intensity exercise may not always induce EIB.⁹ Similarly, a study in Lithuania with recreational runners using a stair test at approximately 20 °C found no significant differences in FEV₁ decrease at 1, 2, 5,

and 10 minutes post-exercise, with only 42.3% of the participants experiencing a decrease > 10%.¹⁰

One limitation of this study is its single-center design, as data were collected exclusively from athletes at one university, potentially limiting generalizability. Additionally, the small sample size may limit the external validity and generalizability of the findings, especially for broader populations of athletes. Moreover, as a cross-sectional study, it was not possible to evaluate the responsiveness of the Portuguese version of AQUA to interventions, such as bronchodilator therapy or behavioral and environmental changes.

As a reliable screening tool, AQUA enables early identification of allergic predisposition, which

is crucial in sports, given that allergies impact performance, health, and well-being. Identifying at-risk athletes allows for preventive measures and early interventions, minimizing effects on performance while improving overall health and quality of life. AQUA also facilitates a multidisciplinary approach to athlete care, encouraging collaboration between sports medicine professionals, allergists, pulmonologists, and coaches. This integrated care model enhances decision-making and supports the development of comprehensive management plans that address each athlete's needs.

In conclusion, the Brazilian Portuguese version of AQUA is a reliable, reproducible, and valid tool for assessing allergic predisposition in athletes.

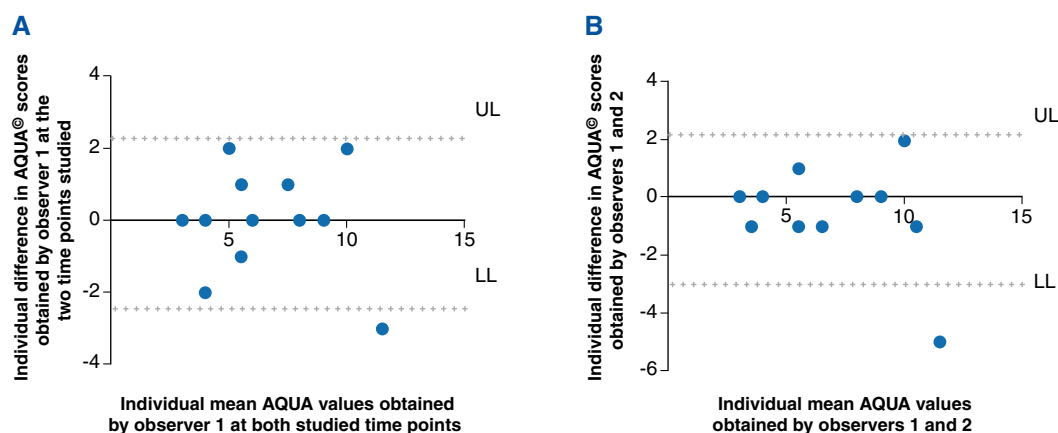


Figure 1

Bland-Altman graphs of intra- and interobserver analysis. In **A**, intraobserver analysis: mean = 0.1; upper limit (UL) = 2.56 and lower limit (LL) = -2.56. In **B**, interobserver analysis: mean = -0.33; UL = 2.69 and LL = -3.35

Table 2

Correlation between AQUA scores and spirometric data and incremental leg test results

	AQUA (-)		AQUA (+)	
	r	p	r	p
$\Delta\%FEV_1$ pre-test vs immediately post-test	0.9	0.5	0.3	0.30
$\Delta\%FEV_1$ pre-test vs 5 min post-test	-0.4	0.6	-0.5	0.05
$\Delta\%FEV_1$ immediately post-test vs 5 min post-test	-0.4	0.6	-0.6	0.04*
Maximum workload in exercise test (watts)	-0.3	0.6	-0.6	0.04*

AQUA (+) = score ≥ 5 ; AQUA (-) = score < 5; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

Supplement

Brazilian version of the Allergy Questionnaire for Athletes (AQUA)

Brazilian Version of the Allergy Questionnaire for Athletes (AQUA)
Versão Brasileira do Questionário de Alergia para Atletas

Iniciais do nome _____
Local de Nascimento _____
Data de Nascimento _____
Cidade _____ Telefone (opcional) _____
Peso (kg) _____ Altura (m) _____
Modalidade Esportiva _____
Instituição de Ensino/Time _____
Matrícula _____

1) Quantas vezes na semana você treina?

- ☐ Até 3 vezes
☐ Mais de 3 vezes

2) Qual a duração média de cada treino?

- ☐ De 1–2 horas
☐ De 2–3 horas
☐ Mais de 3 horas

3) Você treina normalmente em:

- ☐ Locais abertos
☐ Locais fechados

4) Você já foi diagnosticado com alguma doença alérgica?

- ☐ Não
☐ Sim

Se sim, quais?

- ☐ Asma
☐ Rinite
☐ Conjuntivite
☐ Urticária
☐ Eczema
☐ Alergia a medicamentos
☐ Alergia a alimentos
☐ Alergia a picada de insetos (abelhas, mosquitos)
☐ Anafilaxia

Outras: _____

5) Você suspeita ter algum tipo de alergia mesmo sem nenhum diagnóstico médico?

- ☐ Não
☐ Sim

6) Você já usou medicamentos antialérgicos (“anti-histamínicos”, “esteroides tópicos”, “vacinas de alergias”)?

- ☐ Não
☐ Sim

7) Existe alguém alérgico na sua família?

- ☐ Não
☐ Sim, mãe e pai
☐ Sim, mãe ou pai
☐ Sim, outros parentes

Supplement (continuation)

Brazilian version of the Allergy Questionnaire for Athletes (AQUA)

8) Você fica frequentemente com os olhos vermelhos, lacrimejando e coçando?

() Não

() Sim

9) Você frequentemente espirra, tem coriza ou coceira no nariz (independente de estar resfriado)?

() Não

() Sim

10) Você já sentiu aperto no peito e/ou chiado?

() Não

() Sim

11) Você já teve coceira com erupções cutâneas?

() Não

() Sim

12) Você já teve alergias graves ou reações anafiláticas?

() Não

() Sim

13) Você já teve falta de ar, tosse e/ou coceira na garganta após um exercício?

() Não

() Sim

Se sim, teve mais dificuldades:

() No início do treino

() No final do treino

() Durante todo o treino

14) Se você sofreu alguns dos sintomas acima, eles ocorreram:

() Principalmente em ambientes abertos

() Principalmente em ambientes fechados

() Principalmente em dias quentes

() Principalmente em locais úmidos ou frios

() Independente de qualquer condição ambiental

15) Você já teve alguma reação alérgica a alimentos?

() Não

() Sim

Se sim, lembra qual alimento? _____

16) Você já teve alguma reação alérgica a medicamentos?

() Não

() Sim

Se sim, lembra qual medicamento? _____

17) Você sabia que alguns medicamentos para alergia e doenças respiratórias estão proibidos ou sob restrições da Agência Mundial Antidoping (WADA)?

() Não

() Sim

Se sim, marque quais substâncias você acha que estão incluídas nessa categoria:

() Anti-histamínicos

() Broncodilatadores

() Vasoconstritores

Supplement (continuation)

Brazilian version of the Allergy Questionnaire for Athletes (AQUA)

- () Corticoides inalatórios (em doses ou em pó)
 () Esteroides dermatológicos
 () Esteroides injetáveis ou orais

18) Você tem receio que medicamentos respiratórios e/ou antialérgicos possam prejudicar sua performance ou infringir alguma regulamentação antidoping?

- () Não
 () Sim

19) Você usa algum suplemento alimentar (vitaminas, aminoácidos, creatina)?

- () Não
 () Ocasionalmente
 () Regularmente

20) Você fuma?

- () Não
 () Sim

Se sim, quantos cigarros você fuma por dia?

- () Menos que 5
 () Entre 5–20
 () Mais que 20

21) Com qual frequência você usou esses medicamentos no último ano?

Medicamentos	Nunca	1–3 vezes	3–5 vezes	5–10 vezes	Mais de 10 vezes
Antibióticos					
Anti-inflamatórios					
Analgésicos					
Antitérmicos					
Outros:					

22) Você fez uso de algum medicamento na semana passada?

- () Não
 () Sim

Se sim, qual? _____

23) Você sofre frequentemente de alguma infecção respiratória (faringite, bronquite, resfriados) ou febre?

- () Não
 () Sim

Se sim, essas infecções são mais frequentes em períodos de treinamentos intensos?

- () Não
 () Sim

24) Você tem crises recorrentes de herpes labial?

- () Nunca
 () De 1-3 vezes por ano
 () Mais de 3 vezes por ano

25) No último ano, quantas vezes você não pôde treinar devido a alguma infecção?

- () Nenhuma
 () De 1-3 vezes
 () Mais de 3 vezes

References

1. Silva LOE, Silva PLD, Silva MB, Cheik N. Avaliação dos fatores de risco associados ao broncoespasmo induzido pelo exercício em crianças e adolescentes sem diagnóstico prévio de asma. *Arq Asma Alerg Imunol*. 2017;1(4):387-94. doi: 10.5935/2526-5393.20170057.
2. Rizzo JÂ, Souza-Machado A, Sano F, Cruz Filho ÁASD, Serpa FS, Wandalsen GF, et al. Broncoespasmo induzido por exercício no atleta. *Brazilian Journal of Allergy and Immunology (BJAI)*. 2015;3(2):47-55. doi: 10.5935/2318-5015.20150011.
3. Bonini M, Braidó F, Baiardini I, Del Giacco S, Gramiccioni C, Manara M, et al. AQUA: Allergy Questionnaire for Athletes. Development and validation. *Med Sci Sports Exerc*. 2009;41:1034-41. doi: 10.1249/MSS.0b013e318193c663.
4. Teixeira RN, Mendes FA, Martins MA, Mickleborough TD, Carvalho CR. AQUA© as predictor of allergy in elite marathon runners. *World Allergy Organ J*. 2014;7:7. doi: 10.1186/1939-4551-7-7.
5. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health*. 2005;8:94-104. doi: 10.1111/j.1524-4733.2005.04054.x
6. Neder JA, Nery LE. Teste de Exercício Cardiopulmonar. *Jornal Brasileiro de Pneumologia*. 2002;28:166-206.
7. Allen H, Hull JH, Backhouse SH, De Carné T, Dimitriou L, Price OJ. The Allergy Questionnaire for Athletes provides value in ruling-out exercise-induced bronchoconstriction. *Allergy*. 2019;74:1794-6. doi: 10.1111/all.13778.
8. Robson-Ansley P, Howatson G, Tallent J, Mitcheson K, Walshe I, Toms C, et al. Prevalence of allergy and upper respiratory tract symptoms in runners of the London marathon. *Med Sci Sports Exerc*. 2012;44:999-1004. doi: 10.1249/MSS.0b013e318243253d.
9. Gavrielatos A, Ratkevica I, Stenfors N, Hanstock HG. Influence of exercise duration on respiratory function and systemic immunity among healthy, endurance-trained participants exercising in sub-zero conditions. *Respir Res*. 2022;23. doi: 10.1186/s12931-022-02029-2.
10. Venckunas T, Balsys D. High Incidence of Bronchospastic Response to a Stair Climbing Exercise. *Cureus*. Published online May 4, 2021. doi: 10.7759/cureus.14843.

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Study on the prevalence of sleep disorders in atopic dermatitis

Estudo da prevalência de distúrbios de sono na dermatite atópica

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ABSTRACT

Introduction: Atopic dermatitis is a chronic inflammatory skin disease that affects a large number of individuals. Patients with this condition often experience sleep disturbances secondary to intense pruritus. **Objective:** To investigate the prevalence of sleep disturbances in patients with atopic dermatitis and to examine aggravating factors, demographic characteristics, and the implications of these disorders. **Methods:** This analytical observational study included 60 participants treated at a specialized service in Santo André, southeastern Brazil. Data were collected using a questionnaire that incorporated screening tools such as the Global Sleep Assessment Questionnaire (GSAQ), the Patient-Oriented Eczema Measure (POEM), the Atopic Dermatitis Control Tool (ADCT), the Dermatology Life Quality Index (DLQI), and the Peak Pruritus Numerical Rating Scale (NRS). **Results:** A high prevalence of sleep disorders was detected in the study group, with 96.6% presenting some degree of sleep disturbance. Statistically significant associations were observed between sleep deterioration and disease severity ($p=0.001$), pruritus intensity ($p=0.026$), and inadequate disease control ($p=0.009$). Greater sleep disturbances were also associated with poorer quality of life ($p=0.003$). No statistically significant differences were found between men and women ($p=0.333$) or among patients with multiple atopic diseases ($p=0.445$). **Conclusion:** The results of this study demonstrate a high prevalence of sleep disorders in patients with atopic dermatitis, with substantial negative implications for their overall quality of life. Additionally, a strong association was observed between these disorders and disease severity.

Keywords: Atopic dermatitis, circadian rhythm sleep disorders, pruritus.

RESUMO

Introdução: A dermatite atópica é uma doença inflamatória crônica da pele que afeta um grande número de pessoas. Portadores desta doença muitas vezes apresentam alterações de sono secundárias ao prurido intenso. **Objetivo:** Esta pesquisa tem como objetivo investigar a prevalência de perturbações de sono em pacientes com dermatite atópica, além de examinar fatores de agravamento, fatores demográficos, e as implicações destes distúrbios. **Método:** Este é um estudo observacional analítico que envolveu 60 participantes em um serviço especializado em Santo André. A pesquisa utilizou um questionário, que inclui ferramentas de triagem como o Questionário de Avaliação Global do Sono (GSAQ), a Medida Orientada ao Paciente com Eczema (POEM), a Ferramenta de Controle de Dermatite Atópica (ADCT), o Índice de Qualidade de Vida em Dermatologia (DLQI) e a Escala de Avaliação Numérica de Pico de Prurido (NRS). **Resultados:** Foi detectada uma alta prevalência de distúrbios de sono no grupo estudado, com 96,6% apresentando algum grau de alteração. Obteve-se significância estatística ao comparar a deterioração do sono com a gravidade da doença ($p = 0,001$), intensidade da coceira ($p = 0,026$) e controle inadequado da doença ($p = 0,009$). Maiores alterações no sono mostraram-se relacionadas com uma pior qualidade de vida ($p = 0,003$). Não houveram diferenças estatísticas entre homens e mulheres ($p = 0,333$), ou em casos de doenças atópicas múltiplas ($p = 0,445$). **Conclusão:** Os resultados deste estudo demonstram uma alta prevalência de distúrbios de sono em pacientes com dermatite atópica, bem como grandes implicações negativas na sua qualidade de vida geral. Também, observa-se a forte associação destes distúrbios com a gravidade da doença.

Descritores: Dermatite atópica, transtornos do sono do ritmo circadiano, prurido.

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Introduction

Atopic dermatitis (AD), also known as eczema, is one of the most common chronic inflammatory skin diseases. It affects up to 20% of children and adolescents and 10% of adults.¹ Disease severity is classified as moderate in 20%–37% of cases and severe in 10%–34% of patients.²

AD results from a complex interplay of various factors, including skin barrier dysfunction, cutaneous dysbiosis, and immune dysregulation. The skin barrier has key functions which are impaired in AD, primarily to prevent water loss and to stop the entry of external foreign substances.¹

Environmental factors also play an important role in skin barrier dysfunction, such as environmental pollution, diet, and antibiotic exposure.¹

AD presents with symptoms such as dry skin, erythema, eczema, lichenification, crusts, and papules, in addition to intense pruritus, especially at night. In addition to these characteristic symptoms, AD may be associated with many known comorbidities, including airway disease (asthma, allergic rhinitis, and obstructive sleep apnea), food allergies, atopic eye diseases, and autoimmune conditions.¹

Patients with AD often experience sleep disturbances secondary to intense nocturnal pruritus. Published data from studies of patients with AD suggest that 33%–90% of adults with the disease experience sleep disturbances.³ In addition to their high prevalence rates, sleep disorders represent one of the main factors causing loss of quality of life and are associated with health problems, impaired functioning and well-being, work-related injuries, health care expenditures, and neurocognitive deficits.⁴ Despite these implications, sleep disorders are not widely detected or treated during medical appointments.

This study aimed to investigate the prevalence of sleep disturbances in patients with AD, as well as to examine aggravating factors, demographic characteristics, and the implications of these disturbances.

Methods

This analytical observational study was conducted at a specialized service in Santo André, São Paulo, Brazil. Inclusion criteria comprised patients aged 18 years or older with a diagnosis of AD.

After signing the informed consent form, participants completed a questionnaire, either in paper or digital format, including the following validated assessment tools: the Global Sleep Assessment Questionnaire (GSAQ)⁵; the Patient-Oriented Eczema Measure (POEM)⁶; the Atopic Dermatitis Control Tool (ADCT)⁷; the Numerical Rating Scale (NRS) for peak pruritus in the past 24 hours⁶; the Dermatology Life Quality Index (DLQI)⁸; in addition to questions regarding sex and associated atopic diseases. The results of each questionnaire were compared with GSAQ results to assess the relationship between different aspects of the disease and sleep disturbances (Table 1).

Absolute and relative frequencies were used for qualitative variables, and mean (SD) for quantitative variables, after normality was assessed using the Shapiro-Wilk test. The chi-square test, the Pearson correlation coefficient, and analysis of variance (ANOVA) were used to assess relationships between variables. The significance level was set at 5%, and analyses were performed using Stata® version 16.0.

Results

The study included 60 individuals diagnosed with AD. The GSAQ was used to classify sleep disturbances, POEM to classify disease severity, ADCT to determine disease control, DLQI to assess impact on quality of life, and NRS to indicate pruritus level (Table 2).

A high prevalence of sleep disturbances was observed among participants, with 96.6% presenting some degree of disturbance in their sleep patterns. Statistical analysis showed significant associations between worsening sleep quality and clinical severity of AD ($p = 0.001$), as well as with pruritus intensity ($p = 0.026$) and inadequate disease control ($p = 0.009$).

In addition, greater sleep impairment was strongly associated with poorer quality of life; that association was statistically significant ($p = 0.003$). On the other hand, no statistically significant differences in sleep quality were found between sexes ($p = 0.333$) or between individuals with and without multiple atopic comorbidities ($p = 0.445$) (Table 2).

Discussion

Using the assessment tools analyzed in this study, a high prevalence of sleep disturbances was

observed among the participants, which included only patients diagnosed with AD. Only 2 patients (3.33%) had no sleep disturbances, whereas the vast majority (96.67%) reported some degree of disturbance of varying intensity. These findings are consistent

with the literature, as major studies on the subject estimate that between 33% and 90% of adults with AD experience sleep disturbances.³

In the study by Perez et al.,⁹ involving 180 adults and adolescents with AD from Brazil, Mexico, and Argentina,

Table 1

Characteristics of the sample

Variable	Mean	Minimum - maximum
Pruritus	5.11	1 - 10
GSAQ classification	n	%
No change	2	3.33
Mild/Intermediate	38	63.33
Intense	20	33.33
POEM classification	n	%
Clear/almost clear	1	1.67
Mild	14	23.33
Moderate	28	46.67
Severe	14	23.33
Very severe	3	5
ADCT classification	n	%
Controlled	18	30
Uncontrolled	42	70
DLQI classification	n	%
No impact	3	5
Low impact	14	23.33
Moderate impact	21	35
High impact	19	31.67
Very high impact	3	5
Sex	n	%
Female	30	50
Male	30	50
Atopic diseases	n	%
Only atopic dermatitis	26	43.33
Allergic rhinitis or asthma	18	30
Allergic rhinitis + asthma	16	26.67

sleep-related characteristics were assessed, and 53% of participants reported major sleep problems, frequently accompanied by functional impairment.

These disturbances are often associated with intense nocturnal pruritus. One explanation involves

nocturnal variation in skin barrier function, particularly regarding transepidermal water loss (TEWL). As peripheral skin temperature increases at night as part of the mechanism to regulate core temperature, TEWL may increase, therefore increasing pruritus.¹

Table 2

Comparison of clinical variables with GSAQ classification

GSAQ classification	Mild	Intermediate	Severe	p-value
Pruritus (mean [min–max])	2 [1–3]	4.55 [1–9]	6.5 [2–10]	0.026
POEM classification - n (%)				0.001
Clear/almost clear	1 (50)	0	0	
Mild	0	12 (31.58)	2 (10)	
Moderate	1 (50)	20 (52.63)	7 (35)	
Severe	0	6 (15.79)	8 (40)	
Very severe	0	0	3 (15)	
ADCT classification - n (%)				0.009
Controlled	2 (100)	14 (36.84)	2 (10)	
Uncontrolled	0	24 (63.16)	18 (90)	
DLQI classification - n (%)				0.003
No impact	1 (50)	2 (5.26)	0	
Low impact	1 (50)	11 (28.95)	2 (10)	
Moderate impact	0	16 (42.11)	5 (25)	
High impact	0	9 (23.68)	10 (50)	
Very high impact	0	0	3 (15)	
Sex				0.333
Female	0	19 (63.33)	11 (36.67)	
Male	2 (6.67)	19 (63.33)	9 (30)	
Atopic diseases				0.445
Only atopic dermatitis	2 (7.69)	16 (61.54)	8 (30.77)	
Rhinitis or asthma	0	13 (72.22)	5 (27.78)	
Rhinitis + asthma	0	9 (56.25)	7 (43.75)	

In addition, nocturnal pruritus may be intensified by circadian fluctuations in hormone secretion, particularly cortisol, and subsequent variations in immunological activity, such as fluctuating expression of pruritogenic cytokines.¹

A direct relationship between disease severity and poorer sleep quality was also observed. When comparing POEM and GSAQ results and classifications, there was positive statistical significance ($p = 0.001$) and moderate correlation ($\rho = 0.61$) (Figure 1). These findings are supported by the literature, which indicates that sleep disturbances tend to worsen with increasing AD severity.³ The study by Mann et al.,¹⁰ which used the EASI instrument to classify AD severity, demonstrated that higher disease activity was associated with increased sleep interruption.

In the present study, a direct relationship was observed between poorer AD control and greater sleep deterioration when comparing ADCT and GSAQ results ($p = 0.009$). This association has also been reported in the literature.² Wei et al.² conducted a cross-sectional study to characterize disease control in patients with moderate-to-severe AD, involving 202 physicians and 1064 of their patients. The results showed that adequate AD control led to better sleep

outcomes: only 8.5% of patients with well-controlled AD had sleep disturbances, compared with 23.8% of those with inadequate control.

In this study, a direct association was observed between patient-reported pruritus level and sleep quality when comparing NRS and GSAQ results ($p = 0.026$). This finding is consistent with the literature.¹⁰

The present study found a direct relationship between more severe sleep disturbances and poorer overall quality of life when comparing GSAQ and DLQI results ($p = 0.003$). These findings are consistent with the literature, which indicates that sleep disturbances substantially impact quality of life and other health outcomes in adults with AD.¹¹⁻¹³ In a study by Silverberg et al.¹² which used a cross-sectional survey of 34,613 adults to investigate the relationship between AD, sleep disturbances, and their impacts on overall health, more frequent and severe sleep disturbances were associated with higher DLQI scores. In addition, a substantial share of U.S. adults with AD reported fatigue (32.8%), regular daytime sleepiness (26.0%), and regular insomnia (34.4%).¹²

In the analysis by Coghi et al.,¹³ which included 75 Brazilian adults with AD, the use of self-administered DLQI and SF-36 quality-of-life questionnaires also

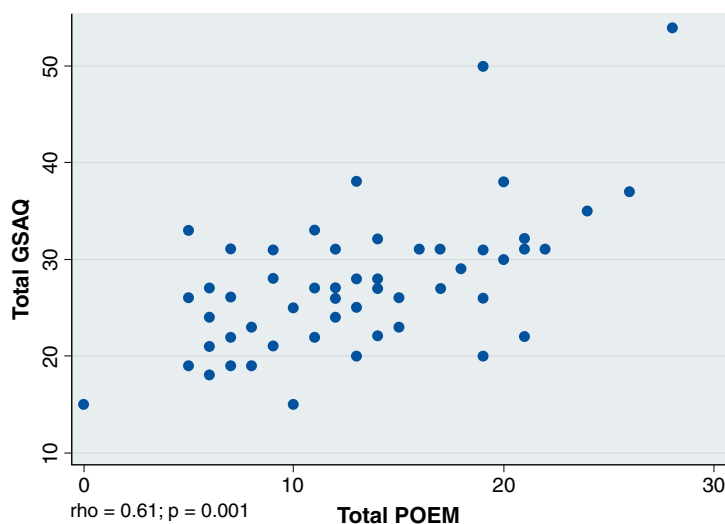


Figure 1

Comparison between Global Sleep Assessment Questionnaire (GSAQ) and Patient-Oriented Eczema Measure (POEM)

found substantial quality-of-life impairment, associated both with disease severity and psychological factors.

Furthermore, sleep disturbances caused by AD are directly associated with numerous health problems, impaired functioning and well-being, work-related injuries, health care expenditures, and neurocognitive deficits.⁴ Sleep disturbances have also been associated with increased hypertension, obesity, cardiovascular disease, coronary events, and depression.¹⁰

In this study, atopic diseases associated with AD were not found to be aggravating factors for sleep disturbances ($p = 0.445$). However, the literature has demonstrated a relationship between atopic diseases, such as asthma and allergic rhinitis, and sleep disturbances, both independently and in association with AD.¹⁴ A longitudinal cohort study of 13,988 children diagnosed with AD, conducted by Ramirez et al.,¹⁴ found that sleep impairment was more common in cases of AD with comorbid asthma or allergic rhinitis. Children with active AD alone were nearly 50% more likely to report sleep disturbances compared with those who had never had the disease. Children with active AD associated with asthma or allergic rhinitis were nearly 80% more likely to report these disturbances. These results suggest that children with multiple atopic conditions are a high-risk group for sleep disturbances.

The present study found no statistical differences in sleep quality between men and women ($p = 0.333$). However, the literature has demonstrated differences in the prevalence of specific sleep indicators between them. Overall, women report shorter sleep duration, more sleep symptoms, and greater rates of insomnia than men.¹⁵ Across all age groups, women report more sleep disturbances and daytime tiredness, even though men have higher rates of specific disturbance, such as obstructive sleep apnea.¹⁵

Interventions primarily focus on reducing pruritus through improved disease control. AD management follows a multi-step approach, beginning with basic skin care, use of moisturizers, topical anti-inflammatory agents such as corticosteroids and calcineurin inhibitors, and light therapy, progressing to systemic immunomodulatory agents if necessary.³ Sleep hygiene advice is also an important first-line treatment. Patients are advised to have a regular bedtime, eat a balanced diet, and avoid caffeine consumption and screen exposure immediately before bedtime. It is also advisable to maintain a cool bedroom environment and wear light sleepwear.¹

Study limitations include the relatively small number of participants, due to recruitment at a single treatment center.

Based on the analyses performed in the present study, we can conclude that there is a high prevalence of sleep disturbances among patients with AD and substantial negative consequences for their overall quality of life. Direct relationships were also observed between sleep disturbances and disease severity, pruritus intensity, and inadequate disease control. Therefore, appropriate attention to the diagnosis and management of sleep disorders is essential in the management of patients with AD.

References

1. Cameron S, Donnelly A, Broderick C, Arichi T, Bartsch U, Dazzan P, et al. Mind and skin: Exploring the links between inflammation, sleep disturbance and neurocognitive function in patients with atopic dermatitis. *Allergy*. 2024 Jan;79(1):26-36.
2. Wei W, Anderson P, Gadkari A, Blackburn S, Moon R, Piercy J, et al. Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. *J Dermatol*. 2018 Feb;45(2):150-7.
3. Bawany F, Northcott CA, Beck LA, Pigeon WR. Sleep Disturbances and Atopic Dermatitis: Relationships, Methods for Assessment, and Therapies. *J Allergy Clin Immunol Pract*. 2021 Apr;9(4):1488-500.
4. Hillman DR, Lack LC. Public health implications of sleep loss: the community burden. *Med J Aust*. 2013 Oct;199(8):S7-10.
5. Roth T, Zammit G, Kushida C, Doghramji K, Mathias SD, Wong JM, et al. A new questionnaire to detect sleep disorders. *Sleep Med*. 2002 Mar;3(2):99-108.
6. Silverberg J, Margolis D, Boguniewicz M, Fonacier L, Grayson M, Ong P. Validation of five patient-reported outcomes for atopic dermatitis severity in adults. *BR J Dermatol*. 2022 Jan;182(1):104-11.
7. Zhang J, Miltner L, Loman L, Ragamin A, Oosterhaven J, Schuttelaar M. Validation of the Atopic Dermatitis Control Tool (ADCT) and a Comparison with the Recap of Atopic Eczema Questionnaire (RECAP). *Acta Derm Venereol*. 2025 Feb;18:105:adv42364.
8. Finlay AY, Khan G. Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994 May;19(3):210-6.
9. Perez C, Aoki V, Criado R, Antila M, Angles M, Cestari T. The real-world burden of atopic dermatitis: MEASURE-AD results from Brazil, Mexico, and Argentina. *An Bras Dermatol*. 2025 Jun;100(3):470-86.
10. Mann C, Dreher M, Wess HG, Staubach P. Sleep Disturbance in Patients with Urticaria and Atopic Dermatitis: An Underestimated Burden. *Acta Derm Venereol*. 2020 Mar;100(6):5678.
11. Ali F, Vyas J, Finlay AY. Counting the Burden: Atopic Dermatitis and Health-related Quality of Life. *Acta Derm Venereol*. 2020 Jun;100(12):5766.
12. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol*. 2015 Jan;135(1):56-66.

13. Coghi S, Bortoletto M, Sampaio S, Andrade H, Aoki V. Quality of life is severely compromised in adult patients with atopic dermatitis in Brazil, especially due to mental components. Clinics. 2007 Jun;62(3):235-42.
14. Ramirez FD, Chen S, Langan SM, Prather AA, McCulloch CE, Kidd SA, et al. Association of Atopic Dermatitis With Sleep Quality in Children. JAMA Pediatr. 2019 May;173(5):e190025.
15. Grandner MA. Sleep, Health, and Society. Sleep Med Clin. 2017 Mar;12(1):1-22.

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The impact of gut microbiota on thyroid immune response: bioinformatics analysis

O impacto da microbiota intestinal na resposta imunológica da tireoide – avaliação com ferramentas de bioinformática

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ABSTRACT

Introduction: Perturbations in the composition and functionality of gut microbiota have been implicated in various autoimmune diseases, including those affecting the thyroid gland, but the exact mechanisms are still unclear, despite recent progress in research. **Objective:** To investigate the influence of gut microbiota on thyroid immune response through bioinformatics analysis. **Methods:** The study used genomic and proteomic sequence data from the National Center for Biotechnology Information database to examine the influence of gut microbiota on thyroid immune response. Taxonomic analysis and metagenomic analysis were performed, and functional annotation tools were used to identify sequences and pathways involved in immune response. Biological networks were constructed to understand the complex biological interactions. **Results:** Sequences of 944 microorganisms specific to thyroid immune response were obtained from the National Center for Biotechnology Information. The taxonomic composition consisted of *Bacteroides stercoris* (35%), *Agathobacter rectalis* (25%), *Prevotella jejuni* (15%), and *Roseburia* (10%), and smaller percentages of *Bifidobacterium faecale*, *Clostridium coccoides*, *Clostridium leptum*, and *Lactobacillus iners*. The taxonomic diversity index was high (0.85). Biological networks were constructed, revealing 8 significant modules. The NF- κ B and MAPK signaling pathway was identified as specifically influencing gut microbiota, playing a critical role in modulating

RESUMO

Introdução: Perturbações na composição e funcionalidade da microbiota intestinal têm sido implicadas em diversas doenças autoimunes, incluindo aquelas que afetam a glândula tireoide, mas os mecanismos exatos ainda não estão claros, apesar dos avanços recentes na pesquisa. **Objetivo:** Investigar a influência da microbiota intestinal nas respostas imunes da tireoide usando ferramentas bioinformáticas. **Métodos:** O estudo utilizou dados de sequências genômicas e proteômicas do banco de dados NCBI para avaliar a influência da microbiota intestinal nas respostas imunes da tireoide. Foram realizadas análises taxonômicas e metagenômicas, e ferramentas de anotação funcional foram usadas para identificar sequências e vias envolvidas na resposta imune. Redes biológicas foram construídas para entender as interações biológicas complexas. **Resultados:** Um total de 944 sequências de microrganismos específicos para a resposta imune da tireoide foi obtido do NCBI. A composição taxonômica consistiu em *Agathobacter rectalis*, *Bacteroides stercoris*, *Bifidobacterium faecale*, *Clostridium coccoides*, *Clostridium leptum*, *Lactobacillus iners*, *Prevotella jejuni* e *Roseburia*. *Bacteroides stercoris* representou 35% da composição, *Agathobacter rectalis* representou 25%, *Prevotella jejuni* representou 15% e *Roseburia* representou 10%. O índice de diversidade taxonômica foi de 0,85, indicando alta diversidade. Redes biológicas foram construídas, revelando 8 módulos significativos. A via de sinalização NF- κ B e MAPK foi

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thyroid immune response. **Conclusions:** We identified a diverse set of microorganisms specific to thyroid immune response, and through biological network analysis we identified a critical signaling pathway in modulating thyroid immune response.

Keywords: Gastrointestinal microbiome, thyroid gland, autoimmune diseases, computational biology.

identificada como a via específica que influencia a microbiota intestinal nas respostas imunes da tireoide, desempenhando um papel crítico na modulação da resposta imune da tireoide.

Conclusão: Identificamos um conjunto diversificado de microorganismos específicos para a resposta imune da tireoide e, por meio da análise de redes biológicas, identificamos a via de sinalização como sendo essencial na modulação da resposta imune da tireoide.

Descritores: Microbioma gastrointestinal, glândula tireoide, autoimunidade, biologia computacional.

Introduction

In recent years, an increasing body of evidence has highlighted the intricate interplay between gut microbiota and host immune systems. The gut microbiota, a complex ecosystem of microorganisms residing in the intestinal tract, actively influences immune response and plays a crucial role in maintaining overall health and homeostasis.^{1,2} Perturbations in the composition and functionality of the gut microbiota have been implicated in various autoimmune diseases, including those affecting the thyroid gland.³

Autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, are characterized by dysregulated immune responses targeting self-antigens in the thyroid gland.^{4,5} While genetic predisposition and environmental factors contribute to the development of autoimmune thyroid diseases, emerging evidence suggests that gut microbiota may exert a significant influence on the initiation and progression of these disorders.⁶ Alterations in the composition and metabolic activities of gut microbiota can affect immune tolerance, leading to a breakdown of self-tolerance mechanisms and subsequent autoimmunity.⁷

Bioinformatics has revolutionized our ability to decipher complex biological systems by integrating and analyzing vast amounts of multi-omics data.⁸ In the context of investigating the relationship between microorganisms and their hosts, bioinformatics allows for the comprehensive analysis of microbiome data, the identification of microbial taxa, and the prediction of functional pathways involved in disease pathogenesis.⁹ By harnessing the power of bioinformatics, we can unravel the intricate network of interactions between gut microbiota and thyroid immune response.

Despite advancements in our understanding of the gut microbiota's role in health and disease, there remains a notable research gap in the specific relationship between gut microbiota and thyroid-related autoimmune conditions, particularly through bioinformatics analysis. Existing studies have primarily focused on clinical and experimental investigations, often lacking the integrative analysis necessary to comprehensively characterize the intricate interplay between gut microbes and immune response. This gap must be bridged to unlock the potential for personalized treatment strategies targeting the gut microbiota-immune axis in autoimmune thyroid diseases.

This study evaluated the relationship between gut microbiota and thyroid immune response by employing bioinformatics tools and approaches.

Methods

Publicly available genomic and proteomic sequence data from the National Center for Biotechnology Information (NCBI) database were used in this study. Sequences related to microorganisms associated with thyroid immune response were collected. Pre-processing steps, including the removal of redundant and low-quality sequences, were performed to ensure data quality. We used the NCBI Taxonomy browser, a powerful tool for identifying the taxonomic origin of sequences, which allowed taxonomic composition to be compared between conditions and groups.

Metagenomic analysis was conducted to investigate the functional aspects of immune response. Proteomic sequences were again collected from the NCBI database and underwent pre-processing. The MG-RAST and MetaPhlAn tools were used to assess taxonomic diversity. Functional annotation tools, such

as KEGG and GO, were used to identify genes and pathways involved in immune response.

To understand the complex biological interactions underlying thyroid immune response, biological networks were constructed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) and the NCBI Gene databases. Significant modules within these networks were identified utilizing algorithms such as Louvain and Walktrap.

By using these techniques and tools, we aimed to gain insight into the influence of gut microbiota on thyroid immune response, contributing to our understanding of the intricate interplay between the microbiome and the immune system.

According to the Brazilian National Research Ethics Committee (CONEP), this study did not require submission to an ethics committee as it relied on

publicly available databases, without involving human or animal subjects.

Results

Taxonomic composition

- A total of 944 sequences of microorganisms specific to thyroid immune response were obtained from the NCBI Taxonomy Browser: *Agathobacter rectalis* (260 Genomes), *Bacteroides stercoris* (164 Genomes), *Bifidobacterium faecale* (1 Genome), *Clostridium coccoides* (25 Genomes), *Clostridium leptum* (31 Genomes), *Lactobacillus iners* (381 Genomes), *Prevotella jejuni* (22 Genomes), and *Roseburia* (59 Genomes) (Table 1).
- The taxonomic variation in microorganism genera specific to thyroid immune response was: *Bacteroides stercoris* (35%), *Agathobacter rectalis*

Table 1

National Center for Biotechnology Information taxonomy browser results for specific microorganisms

Species	<i>Agathobacter rectalis</i>	<i>Bacteroides stercoris</i>	<i>Bifidobacterium faecale</i>	<i>Clostridium coccoides</i>
Domain	Bacteria	Bacteria	Bacteria	Bacteria
Phylum	Firmicutes	Bacteroidetes	Actinobacteria	Firmicutes
Class	Clostridia	Bacteroidia	Actinobacteria	Clostridia
Order	Clostridiales	Bacteroidales	Bifidobacteriales	Clostridiales
Family	Lachnospiraceae	Bacteroidaceae	Bifidobacteriaceae	Clostridiaceae
Genus	Agathobacter	Bacteroides	Bifidobacterium	Clostridium

Species	<i>Clostridium leptum</i>	<i>Lactobacillus iners</i>	<i>Prevotella jejuni</i>	<i>Roseburia</i>
Domain	Bacteria	Bacteria	Bacteria	Bacteria
Phylum	Firmicutes	Firmicutes	Bacteroidetes	Firmicutes
Class	Clostridia	Bacilli	Bacteroidia	Clostridia
Order	Clostridiales	Lactobacillales	Bacteroidales	Clostridiales
Family	Ruminococcaceae	Lactobacillaceae	Prevotellaceae	Lachnospiraceae
Genus	Clostridium	Lactobacillus	Prevotella	Roseburia

(25%), *Prevotella jejuni* (15%), *Roseburia* (10%), and other (15%).

Taxonomic Diversity

- Metagenomic analysis revealed significant taxonomic diversity.
- To calculate the taxonomic diversity index, the Shannon-Wiener index formula was used: $H' = - \sum (p_i * \ln(p_i))$, and the proportions of each species relative to the total species count were as follows: *Agathobacter rectalis*: 260/1,768,139 $\approx$ 0.000147, *Bacteroides stercoris*: 164/1,768,139 $\approx$ 0.000093, *Bifidobacterium faecale*: 1/1,768,139 $\approx$ 0.000001, *Clostridium coccoides*: 25/1,768,139 $\approx$ 0.000014, *Clostridium leptum*: 31/1,768,139 $\approx$ 0.000018, *Lactobacillus iners*: 381/1,768,139 $\approx$ 0.000215, *Prevotella jejuni*: 22/1,768,139 $\approx$ 0.000012, and *Roseburia*: 59/1,768,139 $\approx$ 0.000033.
- The taxonomic diversity index was high (0.85).

Construction of biological networks

- Integration of databases (STRING) allowed the construction of biological networks.
- Result: A total of 8 significant modules were identified in the networks.

Signaling pathway obtained from the study

- The NF- κ B and MAPK signaling pathway was identified as specifically influencing gut microbiota (Figure 1).
- Activation of the NF- κ B and MAPK pathway regulates immune response by triggering inflammation and adaptive immune genes.
- The NF- κ B and MAPK signaling pathway plays a critical role in modulating thyroid immune response, highlighting the importance of the interaction between the microbiome and the immune system in thyroid function.

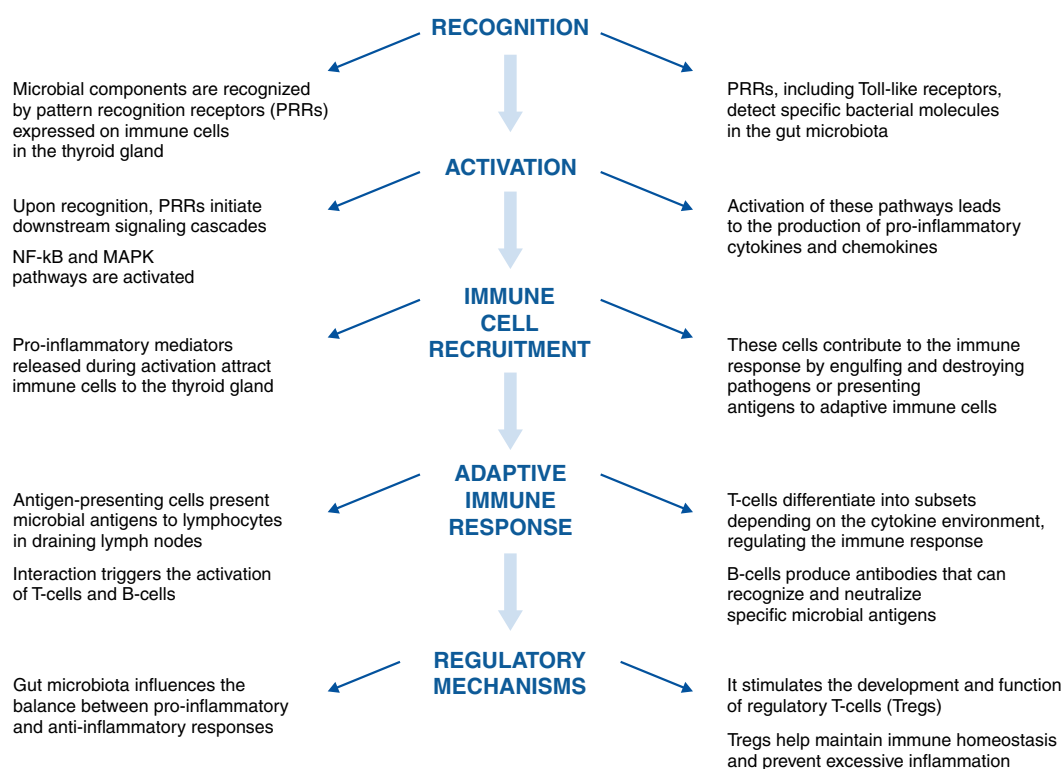


Figure 1

Signaling pathway for thyroid immune response

Discussion

Our results provide insight into the taxonomic composition, diversity, and functional aspects of microorganisms associated with thyroid immune response.

The taxonomic composition analysis demonstrated that various microorganisms are specific to thyroid immune response. The dominant microorganisms in the database evaluated in this study were *Agathobacter rectalis*, *Bacteroides stercoris*, *Lactobacillus iners*, and *Roseburia*. Our findings are consistent with previous studies reporting the presence of these microbiota genera in the gut.^{10,11} However, the proportions of each microorganism differed among these studies, indicating potential variations influenced by factors such as geographical location, diet, and health status. It is worth noting that *Bifidobacterium faecale* and *Prevotella jejuni* were also identified, which have not been extensively studied in the context of thyroid immune response.

The taxonomic diversity of microorganisms associated with thyroid immune response was also investigated, indicating a high level of diversity among the microorganisms present in thyroid immune response. This is in line with previous studies that have reported gut microbiota diversity.^{12,13} The Shannon-Wiener index, which accounts for both the richness and evenness of species, is used to quantify taxonomic diversity.¹⁴ Our results indicated a high level of diversity among the studied microorganisms. This suggests that the gut microbiota could affect thyroid immune response through a complex network of interactions. This finding is consistent with previous studies that have reported diverse microbial communities in various body sites and their correlation with immune response.¹⁵ The high taxonomic diversity suggests that multiple microorganisms contribute to the regulation of thyroid immune response, potentially influencing overall immune system functionality.

Our understanding of the interactions between microorganisms involved in thyroid immune response was deepened by integrating databases, constructing biological networks that provided insight into the potential interactions between the identified microorganisms. The significant modules found in the networks indicate the presence of interconnected microorganisms that may work together to influence thyroid immune response. The identification of significant modules within these networks highlight the complex and interconnected nature of microorganism

function.¹⁶ This finding is in line with previous research that has emphasized the importance of studying microbial interactions and community dynamics in various biological systems.¹⁷ Thus, biological network construction can be a valuable tool for further investigating the specific roles of individual microorganisms and their interactions in thyroid immune response.

We also found that the NF-κB and MAPK signaling pathway influences gut microbiota in thyroid immune response. Activation of these pathways plays a critical role in the immune system by triggering inflammation and adaptive immune response.¹⁸ This finding supports previous literature that has demonstrated the impact of microbial-host interactions in immune signaling pathways.^{19,20} The identification of this signaling pathway further emphasizes the importance of the interaction between the gut microbiome and the immune system in thyroid regulation.

The analysis of taxonomic composition and diversity provided valuable insight into the microorganisms associated with thyroid immune response. The identification of specific microorganisms, the assessment of taxonomic diversity, the construction of biological networks, and the identification of key signaling pathways contribute to our understanding of the complex interactions between microorganisms and the immune system in thyroid regulation.²¹ Thus, by comparing our findings with the literature, we can better comprehend the significance of the microbial-host interactions in the context of thyroid immune response.

Conclusions

We identified a diverse set of microorganisms specific to thyroid immune response, and through biological network analysis we identified a critical signaling pathway in thyroid immune response modulation.

References

1. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157(1):121-41.
2. Hand T, Belkaid Y. Microbial control of regulatory and effector T cell responses in the gut. *Curr Opin Immunol*. 2010;22(1):63-72.
3. Virili C, Fallahi P, Antonelli A, Benvenga S, Centanni M. Gut microbiota and Hashimoto's thyroiditis. *Rev Endocr Metab Disord*. 2018;19(4):293-300.

4. Weetman AP. An update on the pathogenesis of Hashimoto's thyroiditis. *J Endocrinol Invest.* 2021;44(5):883-90.
5. Kahaly GJ. Management of Graves Thyroidal and Extrathyroidal Disease: An Update. *J Clin Endocrinol Metab.* 2020;105(12):3704-20.
6. Zhao H, Yuan L, Zhu D, Sun B, Du J, Wang J. Alterations and Mechanism of Gut Microbiota in Graves' Disease and Hashimoto's Thyroiditis. *Pol J Microbiol.* 2022;71(2):173-89.
7. Kriegel MA. Self or non-self? The multifaceted role of the microbiota in immune-mediated diseases. *Clin Immunol.* 2015;159(2):119-21.
8. Nobile MS, Cazzaniga P, Tangherloni A, Besozzi D. Graphics processing units in bioinformatics, computational biology and systems biology. *Brief Bioinform.* 2017;18(5):870-85.
9. Pallen MJ. Microbial bioinformatics 2020. *Microb Biotechnol.* 2016;9(5):681-6.
10. Sittipo P, Lobionda S, Lee YK, Maynard CL. Intestinal microbiota and the immune system in metabolic diseases. *J Microbiol.* 2018;56(3):154-62.
11. Gul L, Modos D, Fonseca S, Madgwick M, Thomas JP, Sudhakar P, et al. Extracellular vesicles produced by the human commensal gut bacterium *Bacteroides thetaiotaomicron* affect host immune pathways in a cell-type specific manner that are altered in inflammatory bowel disease. *J Extracell Vesicles.* 2022;11(1):e12189.
12. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol.* 2016;14(8):e1002533.
13. Zhao F, Feng J, Li J, Zhao L, Liu Y, Chen H, et al. Alterations of the Gut Microbiota in Hashimoto's Thyroiditis Patients. *Thyroid.* 2018;28(2):175-86.
14. Shannon CE. A mathematical theory of communication. *Bell System Technical Journal.* 1948;27:379-423.
15. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol.* 2016;16(6):341-52.
16. Guven-Maiorov E, Tsai CJ, Nussinov R. Structural host-microbiota interaction networks. *PLoS Comput Biol.* 2017;13(10):e1005579.
17. Cordero OX, Datta MS. Microbial interactions and community assembly at microscale. *Curr Opin Microbiol.* 2016;31:227-34.
18. Peng C, Ouyang Y, Lu N, Li N. The NF- κ B Signaling Pathway, the Microbiota, and Gastrointestinal Tumorigenesis: Recent Advances. *Front Immunol.* 2020;11:1387.
19. Tripodi D, Conti F, Rosati M, Maccauro G, Saggini A, Cianchetti E, et al. IL-36 a new member of the IL-1 family cytokines. *J Biol Regul Homeost Agents.* 2012;26(1):7-14.
20. Yang M, Sun B, Li J, Yang B, Xu J, Zhou X, et al. Alteration of the intestinal flora may participate in the development of Graves' disease: a study conducted among the Han population in southwest China. *Endocr Connect.* 2019;8(7):822-8.
21. Cuan-Baltazar Y, Soto-Vega E. Microorganisms associated to thyroid autoimmunity. *Autoimmun Rev.* 2020;19(9):102614.

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Solar urticaria refractory to standard therapy: a case report and brief literature review

Urticária solar refratária ao tratamento padrão: relato de caso e breve revisão da literatura

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ABSTRACT

Solar urticaria is a rare, physically induced chronic urticaria that causes skin lesions and a sensation of itching, burning, or both within minutes of sun exposure, greatly interfering with patients' quality of life. The probable pathophysiological mechanism involves mast cell activation and degranulation by the binding of specific IgE to a photoallergen activated by a particular wavelength of the light spectrum. Clinical manifestations persist as long as exposure continues and may range from mild, localized reactions to severe, generalized presentations, such as anaphylaxis, depending on the intensity and duration of exposure. The treatment of solar urticaria is based on avoidance of sun exposure (protective clothing and sunscreen use), administration of second-generation H1 antihistamines, and, in selected cases, phototherapy, immunosuppressant agents, or biologic therapies. The anti-IgE monoclonal antibody omalizumab, approved for the treatment of chronic spontaneous urticaria, has been indicated in cases of inducible urticaria, such as solar urticaria, refractory to first- and second-line treatments. We report the case of a patient with solar urticaria who did not respond to quadruple-dosed H1 antihistamines and showed a favorable clinical response to omalizumab, followed by a brief review of the literature.

Keywords: Solar urticaria, chronic inducible urticaria, omalizumab.

RESUMO

A urticária solar é uma urticária crônica induzida, física e rara, que causa lesões cutâneas e sensação de prurido, ardência ou ambos, minutos após a exposição solar, interferindo sobremaneira na qualidade de vida dos pacientes. O mecanismo fisiopatológico provável é a ativação e degranulação de mastócitos por ligação de IgE específica a um fotoalérgeno ativado por um determinado comprimento de onda do espectro luminoso. O quadro clínico persiste enquanto a exposição for mantida, e, na dependência da intensidade e duração da exposição, ele pode ser leve e localizado, ou grave e generalizado, como anafilaxia. O tratamento da urticária solar baseia-se na prevenção à exposição à luz solar, (roupas protetoras e uso de fotoprotetores), anti-histamínicos H1 de segunda geração e, em determinados casos, fototerapia, imunossupressores ou imunobiológicos. O anticorpo monoclonal anti-IgE omalizumabe, aprovado para tratamento da urticária crônica espontânea, tem sido indicado para o tratamento de urticárias induzidas, como a urticária solar, refratárias às terapias de primeira e segunda linhas. Relatamos o caso de uma paciente com urticária solar que não respondeu ao uso de anti-histamínicos H1 em doses quadruplicadas e a evolução favorável com o uso de omalizumabe, assim como uma breve revisão da literatura.

Descritores: Urticária solar, urticária crônica induzida, omalizumab.

Introduction

Solar urticaria is a rare form of chronic inducible urticaria (CIndU), characterized by the onset of hives upon exposure to sunlight or to artificial sources of UV radiation.¹

Clinical manifestations develop within minutes of exposure to sunlight, including UV radiation (UVA and UVB) and visible light. Lesions are usually rapidly evanescent, disappearing 1-2 hours after exposure

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ceases. Symptom severity depends on how potent the exposure was and how long the skin was exposed. Reactions may be localized or, in more serious cases, involve systemic manifestations.²

The diagnosis is usually suggested by the clinical history and confirmed by physical examination and photoprovocation testing (controlled exposure to light of different wavelengths). The underlying pathophysiologic mechanism probably involves IgE production in response to a photoallergen.³

Most cases of solar urticaria are adequately controlled with second-generation antihistamines at usual doses, and these are considered the first-line treatment of choice. If control is not achieved with this measure, the treatment algorithm suggested for chronic spontaneous urticaria (CSU) should be followed: 4-fold up-dosing of antihistamines as the second line and omalizumab as the third line of therapy.⁴

Omalizumab is a humanized anti-IgE monoclonal antibody which has been approved for the treatment of CSU. Several studies have demonstrated its efficacy in cases of induced urticaria, including solar urticaria,⁵⁻⁷ not adequately controlled with 4-fold up-dosing of second-generation H1 antihistamines.

Case report

A 29-year-old woman sought care at our Skin Allergy clinic complaining of a “sun allergy”. The patient reported a clinical picture of 18 years’ duration characterized by onset of hives, itching, and a burning sensation 10 to 15 minutes after sun exposure. The lesions appeared on areas of uncovered skin exposed to sunlight, resolving completely within 40 minutes once covered. She also reported that the severity of the clinical manifestations was proportional to the duration and intensity of sun exposure and that, on one occasion while at the beach, she developed a systemic reaction with vomiting, hypotension, tachycardia, and lightheadedness following the onset of hives.

Symptoms occurred daily due to the patient’s inability to avoid exposure to sunlight, which greatly impaired her quality of life.

Previous trials of therapy included various first- and second-generation antihistamines at the usual dose for 3 months, at double doses for 1 month, and hydroxychloroquine for 2 months, in addition to several courses of oral corticosteroids, all of which failed to control her symptoms.

At the time of her first visits, the patient was irregularly taking a second-generation antihistamine at its standard dose, reported as one tablet daily. Her Urticaria Control Test (UCT) score was 1, and her Urticaria Quality of Life Questionnaire (CUQ2oL) score was 66 points.

As an initial course of action, we recommended 2-fold up-dosing of her current antihistamine for 4 weeks. The patient returned to the clinic complaining of hives which developed during activities of daily living, with no improvement in her condition and a UCT score of 0. During that visit, we performed photoprovocation testing, which consisted of direct exposure to natural sunlight, a mini-UVA lamp, and visible light (from a slide projector) onto a 2-cm² skin area on the volar aspect of her forearm, for 10 minutes, at a 10-cm distance from the light source (when possible). Readings were taken at 10, 20, and 30 minutes. After exposure to the light source, the patient reported itching and burning at the exposed site right away, with onset of itchy wheal-and-flare lesions expanding beyond the test area within the first 10 minutes, both for sunlight and visible light (Figures 1 and 2). These symptoms persisted throughout the patient’s 2-hour stay at the clinic. There was no reaction to UVA light (315-400 nm). Thus, we concluded that the patient reacts to longer wavelengths, namely visible light (400-700 nm) and sunlight.

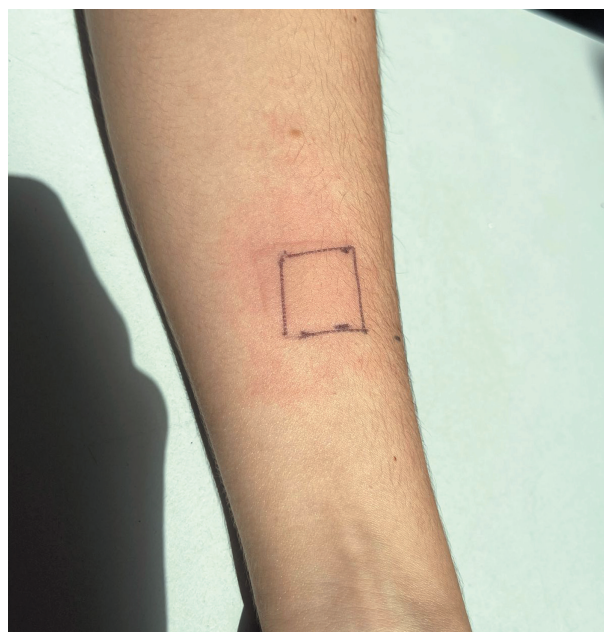


Figure 1
Photoprovocation test (sunlight)

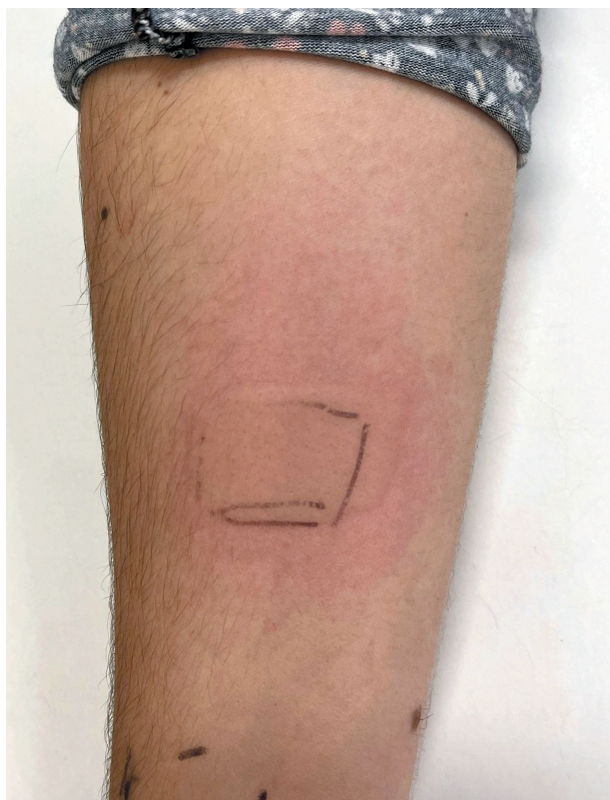


Figure 2
Photoprovocation test (visible light)

As symptom control had not been achieved, we decided to quadruple her dosage of antihistamine for a further 4 weeks. Still, there was no clinical improvement.

Over the course of the patient's follow-up, other diseases and photodermatoses were ruled out through a comprehensive diagnostic workup.

Given the persistent absence of disease control (UCT score of 0), we decided to add omalizumab at a dose of 300 mg subcutaneously every 4 weeks, while continuing her regimen of 4-fold-dose antihistamines.

Two weeks after the first dose of omalizumab, the patient reported improvement, with reduced frequency and severity of flare-ups, despite daily exposure to sunlight, and a UCT score of 10. The treatment plan was maintained.

Further photoprovocation testing with visible light was performed after the second dose of omalizumab and yielded encouraging results, with presence of well-defined erythema in the exposed area and an almost imperceptible urticarial reaction 20 minutes

after exposure (Figure 3). The patient remained asymptomatic throughout the test and specifically denied any pruritus.

After 3 months of omalizumab therapy, disease control was achieved, with a UCT score of 12, demonstrating a positive and promising milestone in the condition.

However, therapy was then temporarily suspended for 3 months due to a shortage of omalizumab in the health care system. During her third month off treatment, the patient had an anaphylactic episode, and her UCT score returned to 0.

Discussion

Solar urticaria is a photodermatosis defined by the rapid onset of hives and/or angioedema, with itching and/or burning of the skin, after exposure to sunlight. It is classified as a form of CIndU. It is a rare condition, representing less than 0.5% of all chronic urticaria cases. It mainly affects women in the third decade of life,^{2,8} although cases have been reported in the pediatric population.^{9,10} Solar urticaria accounts for 3.2% of all photodermatoses in white patients, making this the most affected ethnicity.¹¹

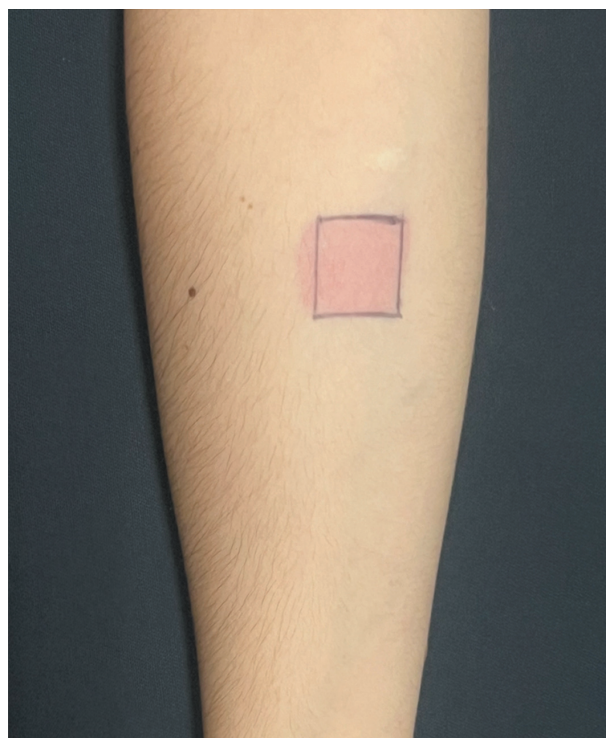


Figure 3
Photoprovocation test (sunlight) while on omalizumab

The clinical picture is quite characteristic, with onset of symptoms 5 to 15 minutes after exposure to different specific wavelengths of solar radiation, including UV and/or visible light. However, there are reports of a delayed reaction onset for up to 1 hour.^{9,12,13} Symptoms persist as long as exposure continues; once exposure ceases, lesions resolve rapidly (within approximately 1 hour in 75% of cases), although they may persist for up to 24 hours.^{14,15}

Skin lesions characteristically appear in areas exposed to the stimulus. In 10% of cases, there may be systemic symptoms such as tachycardia, nausea, dyspnea, and presyncope, with severity depending on the intensity, duration, and extent of exposure.^{2,15} In our patient, manifestations appeared approximately 10 minutes after exposure and, in cases of intense sunlight, she developed clinical signs and symptoms of anaphylaxis.

Although the diagnosis of solar urticaria can be made from the very first history and physical examination, the average time to diagnostic confirmation has been reported as 2 years.¹⁶ Our patient's diagnosis was established definitively only 18 years after first onset of symptoms, despite her classic clinical presentation.

Key differential diagnoses that must be ruled out include other inducible urticarias, such as heat urticaria and cholinergic urticaria, as well as polymorphic light eruption and secondary photodermatoses, including porphyrias, cutaneous lupus erythematosus, and contact photodermatitis.¹⁷

The pathophysiology of solar urticaria continues to be extensively investigated. It unquestionably involves mast-cell activation and degranulation, with subsequent release of inflammatory mediators. Patients with CIndU, regardless of subtype, exhibit increased expression of the high-affinity IgE receptor (FcεRI) in mast cells and basophils, as do patients with CSU, suggesting a significant role for mast cells and IgE in the pathophysiology of these conditions.¹⁸ IgE-mediated autoallergy remains the most widely accepted hypothesis, based on the positive results observed after passive serum transfer from patients with solar urticaria to healthy recipients, confirming the transfer of causative IgE antibodies. Solar urticaria is characterized by mast-cell activation induced by chromophores modulated by solar radiation. It has been classified into 6 subtypes by Harber et al., based on the wavelength spectrum to which the patient reacts, and into 2 subtypes by Leenutaphong et al. Nevertheless, the pathophysiology of solar urticaria appears to be

multifactorial, which means these theories do not fully explain the phenomenon.¹⁹

Physiologically, constant exposure to UV radiation causes immunosuppression of cutaneous mast cells, resulting in a reduction in IgE levels which varies with the physiological doses of UVA or UVB to which these cells are exposed. This tolerance mechanism, known as hardening, is often observed in cases of solar urticaria and has served as the basis for the development of phototherapy regimens for desensitization.^{20,21} This phenomenon can be explained by the nature of the interaction between the antigen and IgE present in patients with solar urticaria, which show signs of intracellular activation resulting from exposure to an adequate dose of antigen in the context of high-affinity IgE and electromagnetic solar radiation.¹⁹

The possibility that cutaneous mast cells are directly activated by sunlight cannot be ruled out, since *in vitro* studies have shown that cutaneous mast cells from healthy individuals, in the absence of IgE cross-linking, can exhibit increased baseline histamine levels.²²

Considering that UVA wavelengths are responsible for reactions in many cases of solar urticaria, one hypothesis suggests that intracellular generation of reactive oxygen species by UVA radiation could modulate mast cell activation in some patients.⁹

Finally, there is suspicion that mast cells in patients with solar urticaria may overcome UV-mediated immunosuppression due to a pro-inflammatory cutaneous microenvironment, a concept already established in cases of CSU. Evidence supporting this suspicion comes from histological studies performed on patients with solar urticaria, which showed perivascular infiltrates with neutrophils and eosinophils soon after the onset of symptoms, with continued presence of eosinophils and monocytes 24 hours later.^{23,24}

Solar urticaria appears to be a rare phenotype associated with genetic variants involving various defects, which is supported by the frequent presence of comorbid atopic diseases in patients with this condition.²

Following a thorough clinical history, the diagnosis should be confirmed by photoprovocation testing, consisting of exposure of a 2 cm² area of skin to specific different wavelengths of light, obtained with a monochromator. Exposure should last 10 minutes, and the light source should be placed 10 cm away

from the test site.^{3,5} The test is considered positive when a wheal-and-flare reaction with localized pruritus develops within 10 minutes of exposure.¹⁴ Our patient's phototest was positive only at longer wavelengths (visible light [400–700 nm] and sunlight), with no reaction to UVA light (315–400 nm).

Up to 26% of patients with clinical presentations characteristic of solar urticaria may have a negative photoprovocation test, since theoretically there is a need for different wavelengths to interact with their respective chromophores to induce a reaction.^{25,26}

At the time of writing, there is no approved curative treatment for solar urticaria; therefore, the goal should be prevention and symptom control until a possible spontaneous remission occurs.¹⁴

Non-pharmacological interventions consist of avoiding sun exposure by both physical (parasols, hats, sun-protective clothing) and chemical (sunscreens) photoprotection methods.²⁷ However, in our patient's case, maintaining a normal lifestyle would be essentially impossible, since she lives in Rio de Janeiro, a city known for its almost year-round summer climate.

Other treatments, such as desensitization by phototherapy, have been trialed, but responses were only temporary.²⁸

Regarding pharmacological treatment, second-generation non-sedating antihistamines are considered the first line of therapy, following the same algorithm as for CSU, ie, starting at the usual daily dosage and up-dosing every 2–4 weeks, until disease control is achieved or a 4-fold dose is reached (second line of therapy).⁴ The international literature suggests that off-label omalizumab at a starting dose of 300 mg every 4 weeks can be tried as a third line of therapy. Patients should not be considered nonresponders until they have had at least 6 months of omalizumab.²⁹ In the case reported here, our patient only experienced significant improvement in her solar urticaria after starting omalizumab therapy.

Omalizumab, approved since 2014 for patients aged 12 years and older with chronic urticaria unresponsive to second-generation antihistamines, prevents the interaction between FcεRI in mast cells and circulating IgE, thus impeding degranulation and, consequently, preventing the onset of symptoms.³⁰ Several studies have demonstrated its effectiveness in controlling solar urticaria.^{6,7}

A recent Spanish study demonstrated improved symptom control with omalizumab, as defined by an

increase in UCT scores, but no curative potential.¹⁶ This was evident in our patient, as her symptoms recurred after omalizumab was discontinued.

The present case report illustrates several aspects of solar urticaria. This rare form of CIndU has a significant impact on patient quality of life, especially in tropical countries. Treatment should follow established guidelines for CSU. Good outcomes can be achieved across all lines of therapy, including omalizumab, although this indication is still off-label. Unlike in CSU, biologic therapy should be continued until disease remission is achieved.

References

- Goetze S, Elsner P. Solar urticaria. *J Dtsch Dermatol Ges*. 2015;13:1250-3.
- 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;108(2):132-9.
- 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):780-2.
- 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.
- Junior SDD, 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.
- Arasi S, Crisafulli G, Caminiti L, Guarneri F, Aversa T, Porcaro F, et al. Treatment with omalizumab in a 16-year-old Caucasian girl with refractory solar urticaria. *Pediatr Allergy Immunol*. 2015 Sep;26(6):583-5. doi: 10.1111/pai.12413.
- Baliu-Piqué C, Aguilera Peiró P. Three cases of solar urticaria successfully treated with omalizumab. *J Eur Acad Dermatol Venereol*. 2016;30(4):704-6.
- 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;159:192-7.
- Beattie PE, Dawe RS, Ibbotson SH, Ferguson J. Characteristics and prognosis of Idiopathic solar urticaria: a cohort of 87 cases. *Arch Dermatol*. 2003;139(9):1149-54.
- Fityan A, McGibbon D, Fassini H, Sarkany R. Paediatric solar urticaria: a case series. *Brit J Dermatol*. 2018;178(6):1453-4.
- Muñoz M, Kiefer LA, Pereira MP, Bizjak M, Maurer M. New insights into chronic inducible urticaria. *Current allergy and asthma reports*. 2024;24(8):457-69.
- Du-Thanh A, Debu A, Lalheve P, Guillot B, Dereure O, Pevron JL. Solar urticaria: a time-extended retrospective series of 61 patients and review of literature. *Eur J Dermatol*. 2013;23(2):202-7.
- Monfrecola G, Masturzo E, Riccardo AM, Balato F, Avala F, Di Costanzo MP. Solar urticaria: a report on S/ cases. *Am J Contact Dermatitis*. 2000;11(2):89-94.
- Ritzel D, Altrichter S. Chronic Inducible Urticaria. *Immunology and allergy clinics of North America*. 2024;44(3):439-52.

15. Photiou L, Foley P, Ross G. Solar urticaria - An Australian case series of 83 patients. *Australas J Dermatol*. 2019 May;60(2):110-117. doi: 10.1111/ajd.12975.
16. Pesqué D, Ciudad A, Andrades E, Soto D, Gimeno R, Pujol RM, et al. Solar Urticaria: An Ambispective Study in a Long-term Follow-up Cohort with Emphasis on Therapeutic Predictors and Outcomes. *Acta Derm Venereol*. 2024 Jan 8;104:adv25576. doi: 10.2340/actadv.v104.25576.
17. Dinardo CL, Fonseca GHH, Suganuma LM, Gualandro SFM, Chamone DAF. Porfirias: quadro clínico, diagnóstico e tratamento. *Rev Med (São Paulo)*. 2010;89(2):106-14.
18. Giménez-Arnau AM, Ribas-Llauradó C, Mohammad-Porras N, Deza G, Pujol RM, Gimeno R. IgE and high-affinity IgE receptor in chronic inducible urticaria, pathogenic, and management relevance. *Clin Transl Allergy*. 2022 Feb 1;12(2):e12117. doi: 10.1002/ctt2.12117.
19. McSweeney SM, Sarkany R, Fassihi H, Tziotziou C, McGrath JA. Pathogenesis of solar urticaria: Classic perspectives and emerging concepts. *Exp Dermatol*. 2022 Apr;31(4):586-93. doi: 10.1111/exd.14493.
20. Botto NC, Warsnaw EM. Solar urticaria. *J Am Acad Dermatol*. 2008;59(6):909-20.
21. Dawe RS, Ferguson J. Prolonged benefit following ultraviolet A phototherapy for solar urticaria. *Brit J Dermatol*. 1997;137(1):144-8.
22. Guhl S, Stefaniak R, Strathmann M, Babina M, Piazena H, Henz BM, et al. Bivalent effect of UV light on human skin mast cells-low-level mediator release at baseline but potent suppression upon mast cell triggering. *J Invest Dermatol*. 2005 Feb;124(2):453-6. doi: 10.1111/j.0022-202X.2004.23523.x.
23. Norris PG, Murphy GM, Hawk JL, Winkelmann RK. A histological study of the evolution of solar urticaria. *Arch Dermatol*. 1988;124(1):80-3.
24. Leiferman KM, Norris PG, Murphy GM, Hawk JL, Winkelmann RK. Evidence for eosinophil degranulation with deposition of granule major basic protein in solar urticaria. *J Am Acad Dermatol*. 1989;21(1):75-80.
25. Uetsu N, Nomura Y, Matsuvama Y, Okamoto H. Characteristics and clinical significance or augmentation spectra in solar urticaria. *J Dermatol*. 2020;47(4):369-77.
26. Uetsu N, Mivauchi-Hashimoto H, Okamoto H, Horio T. The clinical and photobiological characteristics of solar urticaria in 40 patients. *Br J Dermatol*. 2000;142(1):32-8.
27. Kieselova K, Santiago F, Henrique M. Incapacitating solar urticaria: successful treatment with omalizumab. *Anais brasileiros de dermatologia*. 2019;94(3):331-3.
28. Beissert S, Ständer H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. *J Am Acad Dermatol*. 2000 Jun;42(6):1030-2. doi: 10.1016/s0190-9622(00)90299-8.
29. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, et al. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. *J Allergy Clin Immunol*. 2018 Feb;141(2):638-49.
30. Okayama Y, Matsumoto H, Odajima H, Takahagi S, Hide M, Okubo K. Roles of omalizumab in various allergic diseases. *Allergol Int*. 2020 Apr;69(2):167-77. doi: 10.1016/j.alit.2020.01.004.

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Desensitization to alglucosidase alfa in a patient with Pompe disease: a case report

Dessensibilização à alglucosidase alfa em paciente com Doença de Pompe: relato de caso

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ABSTRACT

Pompe disease (PD), also known as glycogen storage disease type II, is an autosomal recessive inherited metabolic disorder caused by variants in the *GAA* gene, which encodes the production of lysosomal enzyme acid alpha-1,4-glucosidase. Enzyme replacement therapy (ERT) with acid alpha-glucosidase is the most effective treatment for reducing disease-related morbidity and mortality. However, hypersensitivity reactions may occur during ERT, requiring desensitization to the enzyme. We report the case of a child with PD who developed an immediate-type hypersensitivity reaction to ERT and was successfully treated using a desensitization protocol.

Keywords: Alglucosidase alfa, Pompe disease, drug hypersensitivity, immunologic desensitization.

RESUMO

A Doença de Pompe (DP), ou glicogenose tipo II, é uma doença metabólica hereditária autossômica recessiva causada por variantes no gene *GAA*, que codifica a produção da enzima lisossomal alfa-glucosidase ácida (acidalpha-1,4-glucosidase). A terapia de reposição enzimática (TRE) com alfa glucosidase ácida é a forma de tratamento mais eficaz para a redução da morbidade e mortalidade desta doença. Reações de hipersensibilidade podem ocorrer durante a TRE, sendo necessária a dessensibilização a esta enzima. Relatamos aqui o caso de uma criança com DP que apresentou reação do tipo imediata à TRE e foi tratada com sucesso através de um protocolo de dessensibilização.

Descritores: Alglucosidase alfa, doença de Pompe, hipersensibilidade a drogas, dessensibilização imunológica.

Introduction

Pompe disease (PD), also known as glycogen storage disease type II, is an autosomal recessive inherited metabolic disorder caused by pathogenic variants in the *GAA* gene, located on the long arm of chromosome 17. The *GAA* gene encodes the production of lysosomal enzyme acid alpha-glucosidase, which hydrolyzes glycogen to glucose. Deficiency of this enzyme leads to glycogen accumulation in cell lysosomes, resulting in progressive damage particularly to skeletal and cardiac muscle.¹ The classic infantile PD presents in the first months of

life and is characterized by skeletal muscle weakness, delayed neuromotor development, macroglossia, hepatomegaly, and severe cardiomyopathy, typically with a progressive and fatal outcome. The non-classic infantile PD often presents at 2 years of age, with slower progression and less severe cardiomyopathy. Late-onset PD develops during adolescence, characterized by slow progression, with skeletal muscle weakness, central nervous system vasculopathy, and respiratory failure associated with significant morbidity.^{2,3} The overall PD incidence is

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estimated at approximately 1 in 40,000 live births and varies according to ethnic factors and the screening methods used for detection.³

Enzyme replacement therapy (ERT) with alglucosidase alfa is currently the only disease-specific treatment available and has demonstrated efficacy in improving muscle and respiratory function, as well as prolonging survival, particularly in infantile PD. Mortality and morbidity have declined after the introduction of ERT with alglucosidase alfa.⁴ Although rare, hypersensitivity reactions to the medication may occur during ERT with alglucosidase alfa. Rapid desensitization to alglucosidase alfa can induce temporary tolerance to the enzyme and represents an effective and safe strategy in the management of PD, allowing disease-specific treatment and improving prognosis.⁵

Case report

A 1-year-old girl had a family history suggestive of PD, including a sibling who died at 2 months of age with a postmortem diagnosis of the disease. Genetic testing performed at 1 month of age identified 2 pathogenic variants in the *GAA* gene: c.2560C>T (Arg854*) and c.1978C>T (Arg660Cys). Enzyme assay demonstrated acid alpha-glucosidase activity of 0.24 (reference value for newborns up to 30 days of life: ≥ 2.58). After diagnosis, at 2 months of age, ERT with alglucosidase alfa was initiated at a dose of 20 mg/kg administered at intervals of 7 to 14 days. Premedication consisted of montelukast (4 mg), diphenhydramine (1 mg/kg), and hydrocortisone (10 mg/kg).

During infusion 24, approximately 30 minutes after initiation, the patient developed facial angioedema and a skin rash involving the face and neck, without systemic manifestations. The infusion was discontinued, and intravenous hydrocortisone and diphenhydramine were administered, with symptom resolution within 1 hour. Subsequent infusion attempts with premedication were performed; however, the patient again developed angioedema. Because ERT is the only effective treatment for PD and no effective alternative therapy was available, rapid desensitization to alglucosidase alfa was indicated, as previously described in the literature.⁵⁻⁷ Immediate-reading skin testing with alglucosidase alfa could not be performed. Written informed consent was obtained from the patient's parents.

Rapid desensitization to alglucosidase alfa was performed using a specific 12-step protocol adapted from previously published studies (Table 1).⁶⁻⁸ The administered dose was 20 mg/kg, totaling 200 mg. The medication was prepared for infusion and diluted in 3 bags with 0.9% saline solution at an initial concentration of 1:1000 (Table 2). The patient experienced no reactions during the infusion and has since continued ERT with desensitization every 2 weeks without complications. The study was approved by the institutional ethics committee (CAAE 88377625.0.0000.5440, Plataforma Brasil), and written informed consent was obtained from the patient's parents.

Discussion

Adverse and hypersensitivity reactions to different classes of medications have increased substantially in recent years, particularly with antibiotics, chemotherapeutic agents, and biologic therapies.⁹ New medications have been introduced for specific treatment of several diseases across different age groups, including PD, with reports of hypersensitivity reactions to ERT with alglucosidase alfa.¹⁰ Both IgE-mediated reactions and reactions mediated by nonimmunologic mechanisms may occur during ERT. However, most infusion-related reactions can be successfully managed by reducing the infusion rate and/or administering antihistamines, antipyretics, or corticosteroids.¹¹ When these measures fail to prevent reactions and no equally effective alternative medications are available, desensitization is indicated.^{5,6,12} Few cases of desensitization to alglucosidase alfa have been reported in adults and children. We reported the case of a child with PD who developed an immediate hypersensitivity reaction (angioedema and skin erythema) to ERT with alglucosidase alfa despite premedication and reduced infusion rate. Rapid desensitization was successfully performed without adverse reactions. The patient has since continued ERT with desensitization without complications. The protocol used followed practical recommendations for the management of patients undergoing desensitization with an initial dose of 1:1000 of the total treatment dose, as described in previous studies.¹³⁻¹⁵ Because the patient had developed angioedema during ERT, desloratadine and prednisolone were used as premedication. Multicenter studies have shown that the frequency of reactions to ERT in patients with PD ranges from

Table 1

Specific 12-step protocol for desensitization to alglucosidase alfa

Step	Infusion bag	Rate (mL/h)	Time (min)	Volume (mL)	Dose (mg)	Cumulative dose (mg)
1	1	2	15	0.500	0.004	
2	1	5	15	1.250	0.010	0.010
3	1	10	15	2.500	0.020	0.030
4	1	20	15	5.000	0.040	0.070
5	2	5	15	1.250	0.100	0.170
6	2	10	15	2.500	0.200	0.370
7	2	20	15	5.000	0.400	0.770
8	2	40	15	10.000	0.800	1.570
9	3	10	15	2.500	1.980	3.560
10	3	20	15	5.000	3.690	7.530
11	3	40	15	10.000	7.930	15.460
12	3	80	147.375	232.500	184.530	200.000

Total infusion time: 339.375 minutes (5.66 hours).

Table 2

Preparation and dilution of infusion bags

Infusion bag	Components	Concentration (mg/mL)
1	250 mL of 0.9% saline solution + 0.4 mL of reconstituted medication	0.008
2	250 mL of 0.9% saline solution + 4.0 mL of reconstituted medication	0.08
3	250 mL of 0.9% saline solution + 35.6 mL of reconstituted medication	0.712

Medication: alglucosidase alfa.

Reconstitution procedure: each vial of the medication was reconstituted with 10.3 mL of distilled water, as described in the package insert.

28.5% to 39.7%.¹⁶ Other studies indicate that the prevalence of severe reactions to ERT in infantile PD is low or even absent. In one study involving 10 patients who received ERT for 52 weeks, no severe reactions were reported.¹⁷ Ertoy Karagol et al.⁶ prospectively evaluated 13 patients with infantile PD receiving ERT for 12 years and found that 4 patients (30.8%) developed moderate to severe anaphylaxis, suggesting that anaphylaxis during ERT is not uncommon. A report of 390 desensitization procedures without severe reactions further demonstrated that rapid desensitization was an effective and safe strategy in these patients.⁶ Turgay Yagmur et al.¹⁸ evaluated 9 patients who developed urticaria during ERT; 3 patients underwent rapid desensitization, and 2 experienced moderate to severe anaphylaxis during the procedure.¹⁸ Studies also suggest that higher ERT doses and shorter intervals between administrations may predispose patients to reactions during ERT. Reactions during desensitization procedures may occur more frequently when protocols employ higher initial infusion doses. Management of reactions consists of temporarily discontinuing the infusion and administering medications according to symptoms. Once the reaction has resolved, the protocol may be resumed at the same step at which it was discontinued. For subsequent desensitization procedures, additional prophylactic measures should be implemented before the step at which the reaction previously occurred, such as using premedication and increasing the number of steps in the protocol.

Discontinuation of ERT in patients with PD who experience adverse reactions to *α*-glucosidase alfa may negatively affect prognosis. Careful evaluation of these patients and implementation of rapid desensitization using standardized protocols allow continuation of treatment, reducing morbidity and mortality. The present case report illustrates that desensitization can be an effective and safe strategy in the management of these patients.

References

1. Taverna S, Cammarata G, Colomba P, Sciarrino S, Zizzo C, Francofonte D, et al. Pompe disease: pathogenesis, molecular genetics and diagnosis. *Aging (Albany NY)*. 2020;12(15):15856-74.
2. Bay LB, Denzler I, Durand C, Eiroa H, Frabasil J, Fainboim A, et al. Infantile-onset Pompe disease: Diagnosis and management. *Arch Argent Pediatr*. 2019;117(4):271-8.
3. Labella B, Cotti Piccinelli S, Risi B, Caria F, Damioli S, Bertella E, et al. A Comprehensive Update on Late-Onset Pompe Disease. *Biomolecules*. 2023;13(9):1279.

4. Davison JE. Advances in diagnosis and management of Pompe disease. *J Mother Child*. 2020;24(2):3-8.
5. Capanoglu M, Dibek Misirlioglu E, Azkur D, Vezir E, Guvenir H, Gunduz M, et al. IgE-Mediated Hypersensitivity and Desensitization with Recombinant Enzymes in Pompe Disease and Type I and Type VI Mucopolysaccharidosis. *Int Arch Allergy Immunol*. 2016;169(3):198-202.
6. Ertoy Karagol HI, Inci A, Terece SP, Kilic A, Demir F, Yapar D, et al. Long-Term Experience with Anaphylaxis and Desensitization to *α*-glucosidase Alfa in Pompe Disease. *Int Arch Allergy Immunol*. 2023;184(4):370-5.
7. Toh TSW, Chong KW, Goh AEN, Goh JCY, Ting TW, Tan ES, et al. Enzyme replacement therapy desensitization in a child with infantile onset Pompe disease. *Asian Pac J Allergy Immunol*. 2022;40(4):414-7.
8. Hong DI, Dioun AF. Indications, protocols, and outcomes of drug desensitizations for chemotherapy and monoclonal antibodies in adults and children. *J Allergy Clin Immunol Pract*. 2014;2(1):13-9; quiz 20.
9. Madrigal-Burgaleta R, Castells M. Diagnosis and management of allergy to chemotherapy and biologics [editorial]. *Front Allergy*. 2023;4:1205345.
10. Gragnaniello V, Fecarotta S, Pecoraro A, Tarallo A, Catzola A, Spadaro G, et al. Desensitization of two young patients with infantile-onset Pompe disease and severe reactions to *α*-glucosidase alfa. *Neurol Sci*. 2019;40(7):1453-5.
11. El-Gharbawy AH, Mackey J, DeArme S, Westby G, Grinnell SG, Malovrh P, et al. An individually modified approach to desensitize infants and young children with Pompe disease, and significant reactions to *α*-glucosidase alfa infusions. *Mol Genet Metab*. 2011;104(1-2):118-22.
12. Castells M. Rapid desensitization for hypersensitivity reactions to medications. *Immunol Allergy Clin North Am*. 2009;29(3):585-606.
13. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, et al. European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. *Allergy*. 2010;65(11):1357-66.
14. Yang BC, Castells MC. The Who, What, Where, When, Why, and How of Drug Desensitization. *Immunol Allergy Clin North Am*. 2022;42(2):403-20.
15. Alvarez-Cuesta E, Madrigal-Burgaleta R, Broyles AD, Cuesta-Herranz J, Guzman-Melendez MA, Maciag MC, et al. Standards for practical intravenous rapid drug desensitization & delabeling: A WAO committee statement. *World Allergy Organ J*. 2022;15(6):100640.
16. Nagura H, Hokugo J, Ueda K. Long-Term Observation of the Safety and Effectiveness of Enzyme Replacement Therapy in Japanese Patients with Pompe Disease: Results From the Post-marketing Surveillance. *Neurol Ther*. 2019;8(2):397-409.
17. Zhu D, Zhu J, Qiu W, Wang B, Liu L, Yu X, et al. A Multi-Centre Prospective Study of the Efficacy and Safety of *α*-glucosidase Alfa in Chinese Patients with Infantile-Onset Pompe Disease. *Front Pharmacol*. 2022;13:903488.
18. Turgay Yagmur I, Unal Uzun O, Kucukcongar Yavas A, Kulhas Celik I, Toyran M, Gunduz M, et al. Management of hypersensitivity reactions to enzyme replacement therapy in children with lysosomal storage diseases. *Ann Allergy Asthma Immunol*. 2020 Oct;125(4):460-7. doi: 10.1016/j.anai.2020.07.010.

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Paraneoplastic eosinophilic dermatosis mimicking prurigo nodularis as the initial manifestation of B-cell lymphoma in an older adult

Dermatose eosinofílica paraneoplásica simulando prurigo nodular como manifestação inicial de linfoma de células B em idoso

Bruno Emanuel Carvalho Oliveira¹, Mirella Dantas Fulco², Máira Medeiros Pacheco de-Andrade³

ABSTRACT

Chronic pruritus is a common complaint among older adults and, when refractory to treatment, may indicate underlying systemic diseases, including hematologic neoplasms. This article presents the case of an 81-year-old patient with intense pruritus lasting 6 months, accompanied by disseminated nodular lesions and peripheral eosinophilia. The initial skin biopsy was consistent with prurigo nodularis; however, the absence of clinical improvement prompted a repeat biopsy with immunophenotyping, which revealed a dermal infiltrate predominantly composed of eosinophils and a clonal population of B lymphocytes with strong CD20 expression, confirming mature B-cell lymphoma. The final diagnosis was eosinophilic dermatosis as a paraneoplastic manifestation of lymphoma. The discussion addresses the multifactorial pathophysiology of senile pruritus, including impairment of the skin barrier, immune dysregulation with Th2 polarization, and the inflammatory role of eosinophils, which may act as unconventional antigen-presenting cells and tissue mediators. Paraneoplastic eosinophilic dermatoses, although rare and often underdiagnosed, are important clinical manifestations of malignant hematologic disorders and may mimic benign dermatoses such as prurigo nodularis. Recognition of these atypical presentations is essential for early diagnosis. It can be concluded that cases of chronic refractory pruritus in older adults should prompt a high index of clinical suspicion and a comprehensive diagnostic workup. Multidisciplinary collaboration among allergists, dermatologists, and hematologists was crucial for diagnostic clarification and treatment decision-making. Early diagnosis of paraneoplastic syndromes may alter the clinical course and improve patient prognosis.

Keywords: Pruritus, B-cell lymphoma, eosinophilia.

RESUMO

O prurido crônico é uma queixa prevalente entre idosos e, quando refratário ao tratamento, pode indicar doenças sistêmicas subjacentes, incluindo neoplasias hematológicas. Este artigo descreve o caso de um paciente de 81 anos com prurido intenso de seis meses de duração, acompanhado de lesões nodulares disseminadas e eosinofilia periférica. A biópsia cutânea inicial foi compatível com prurigo nodular, mas a ausência de melhora clínica levou à realização de nova biópsia associada à imunofenotipagem, que revelou infiltrado dérmico com predomínio de eosinófilos e presença de população clonal de linfócitos B com forte expressão de CD20, confirmando linfoma de células B maduras. O diagnóstico final foi de dermatose eosinofílica como manifestação paraneoplásica do linfoma. A discussão aborda a fisiopatologia multifatorial do prurido senil, incluindo alterações na barreira cutânea, disfunções imunológicas com polarização Th2 e papel inflamatório dos eosinófilos, que podem atuar como células apresentadoras de antígenos não convencionais e mediadores teciduais. As dermatoses eosinofílicas paraneoplásicas, embora raras e frequentemente subdiagnosticadas, são manifestações clínicas importantes em hematopatias malignas e podem simular dermatoses benignas como o prurigo nodular. O reconhecimento dessas apresentações atípicas é essencial para o diagnóstico precoce. Conclui-se que quadros de prurido crônico refratário em idosos devem ser abordados com alta suspeição clínica e investigação ampliada. A atuação conjunta de especialistas em alergologia, dermatologia e hematologia foi decisiva para a elucidação diagnóstica e definição terapêutica. O diagnóstico precoce de síndromes paraneoplásicas pode modificar o curso clínico e melhorar o prognóstico do paciente.

Descritores: Prurido, linfoma de células B, eosinofilia.

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Introduction

Pruritus is an unpleasant cutaneous sensation that provokes the desire to scratch. Prurigo, in contrast, is a hyperplastic and reactive skin condition characterized by intensely pruritic papules, plaques, or nodules. Both may be classified as acute or chronic, with chronic conditions defined as those with symptoms persisting for more than 6 weeks.

Chronic pruritus is a common complaint among older adults, with an estimated prevalence ranging from 11% to 78%, and it may significantly impair quality of life, leading to sleep disturbances, irritability, anxiety, and even depression. Despite its impact, pruritus is frequently overlooked in clinical practice, particularly when no visible lesions are present or when a clear diagnosis is lacking.

The causes are broad and include skin conditions such as xerosis and inflammatory dermatoses, as well as systemic disorders, including renal and hepatic dysfunction, drug reactions, and hematologic malignancies. In cases refractory to conventional treatment, comprehensive assessment addressing both dermatologic and systemic causes is essential. Certain features should prompt further investigation, such as recent-onset symptoms in patients without a history of atopy, atypical skin lesions, and laboratory abnormalities, including peripheral eosinophilia. In such cases, dermatologic findings may be indicative of an underlying undiagnosed condition.¹⁻³

Table 1, adapted from Criado et al.,⁴ summarizes selected dermatologic diseases associated with chronic pruritus and prurigo, as well as chronic pruritus/prurigo without skin lesions from other dermatoses.

Table 1
Dermatologic diseases associated with chronic pruritus and prurigo, and chronic pruritus/prurigo without skin lesions from other dermatoses

Dermatologic diseases associated with chronic prurigo	
Inflammatory or parasitic skin diseases	Atopic dermatitis, lichen planus, scabies, lichen simplex chronicus
Drug-related prurigo	Contact eczema, adverse drug reactions
Autoimmune diseases	Autoimmune bullous dermatoses (dermatitis herpetiformis, bullous pemphigoid, linear IgA dermatosis, pemphigus vegetans)
Genodermatoses	Transient acantholytic dermatosis (Grover's disease), Darier's disease
Neoplastic diseases	Cutaneous T- or B-cell lymphoma, leukaemia cutis
Psychiatric diseases	Pruritus associated with anxiety, depression, or other psychiatric conditions

Chronic prurigo without skin lesions from other dermatoses	
Infectious/parasitic conditions	Gastrointestinal parasitoses, chronic hepatitis, HIV infection
Metabolic diseases or endocrinopathies	Acquired perforating dermatoses, chronic renal failure, cholestatic liver diseases, hyper/hypothyroidism, nodular amyloidosis
Drugs	Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, morphine, amiodarone, hydrochlorothiazide, and allopurinol, among others
Psychiatric	Psychotic or neurotic conditions
Neuropathic causes	Brachioradial pruritus, postherpetic neuralgia, polyneuropathy or mononeuritis
Venous stasis	Prurigo nodularis due to the pruritus and scratching of varicose veins

Adapted from Criado PR⁴.

This case report describes the clinical approach to an older patient with persistent, treatment-refractory chronic pruritus, underscoring the importance of maintaining a high index of suspicion in atypical presentations.

Case report

An 81-year-old man from Rio Grande do Norte, northeastern Brazil, retired, was referred to an allergy and clinical immunology service for evaluation of intense pruritus lasting 6 months, associated with the development of disseminated nodular lesions. He denied any personal history of atopy. His medical history was significant for type 2 diabetes mellitus, non-dialysis-dependent chronic kidney disease, and nonmelanoma skin cancer. His regular medications included olmesartan/hydrochlorothiazide (40/25 mg), dutasteride/tamsulosin (0.5/0.4 mg), linagliptin (5 mg), metformin (850 mg), mirtazapine (15 mg), and high-dose bilastine (20 mg every 6 hours).

Physical examination revealed erythematous papules, plaques, and nodules, some excoriated, distributed over the back, chest, abdomen, and upper extremities (Figures 1 and 2). There was no palpable lymphadenopathy. Laboratory tests showed leukocytosis ($17,740/\text{mm}^3$), lymphocytosis ($7,932/\text{mm}^3$), and absolute eosinophilia ($2,377/\text{mm}^3$). Stool examination for ova and parasites (O&P-MIF) was negative.

The first skin biopsy demonstrated epidermal hyperplasia with ulceration and an inflammatory infiltrate containing eosinophils. The histopathologic findings were interpreted as consistent with prurigo nodularis, possibly representing a reactive manifestation secondary to intense pruritus. However, given the lack of clinical response, recurrence of symptoms, and persistent peripheral eosinophilia, a second skin biopsy was performed in conjunction with peripheral blood immunophenotyping. The second biopsy revealed mild epidermal spongiosis, focal lymphocytic exocytosis, parakeratosis, and a moderate dermal infiltrate rich in eosinophils arranged in a superficial perivascular pattern, findings indicative of eosinophilic dermatosis (Figure 3).

Immunophenotyping identified a clonal B-lymphocyte population (86%) expressing CD19, CD22, CD20 (strong), CD45 (strong), CD200, FMC7, and CD79b, with absence of CD5, CD10, and CD23 expression, compatible with a mature B-cell lymphoproliferative disorder.



Figure 1

Presence of erythematous and excoriated papules, plaques, and nodules on the back and arms



Figure 2

Presence of erythematous and excoriated papules, plaques, and nodules on the chest, abdomen, and arms

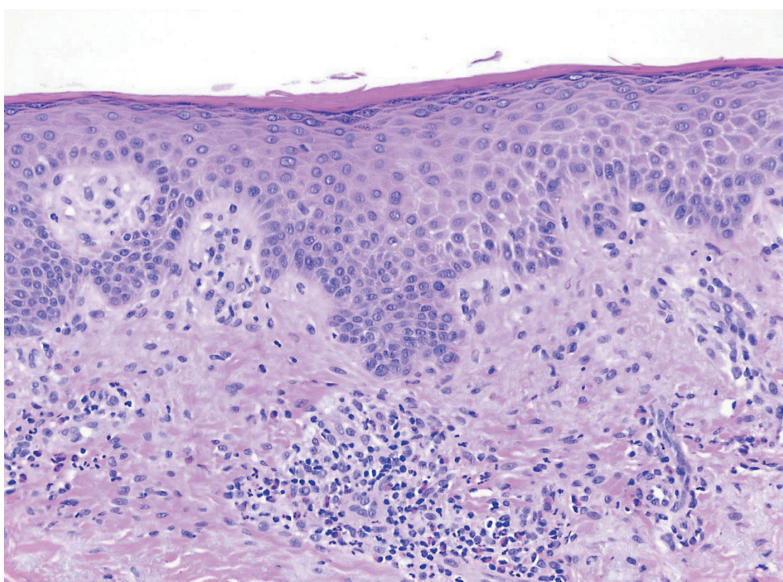


Figure 3

Hematoxylin and eosin-stained skin biopsy showing mild epidermal spongiosis, focal lymphocytic exocytosis, and foci of parakeratosis. The dermis reveals a moderate inflammatory infiltrate, predominantly lymphocytic, with several eosinophils interspersed, in a superficial perivascular location

Although the clinical presentation initially suggested prurigo secondary to scratching, subsequent findings demonstrated that the skin lesions were part of a primary paraneoplastic manifestation characterized by a predominantly eosinophilic inflammatory pattern.

Based on the clinical, laboratory, histopathologic, and immunophenotypic findings, a diagnosis of eosinophilic dermatosis as a paraneoplastic manifestation associated with mature B-cell lymphoma was established. The patient was referred to the hematology-oncology unit for specialized management, where treatment with the CVP regimen (cyclophosphamide, vincristine, and prednisone) was initiated. After the second treatment cycle, improvement in pruritus and reduction in the number of skin lesions were observed.

Discussion

The pathophysiology of pruritus in older adults is complex and multifactorial, involving changes in the skin barrier, immune dysfunctions, and peripheral or central neuropathies. Among dermatologic factors, xerosis is particularly prominent and represents

one of the most common causes in this population, with an estimated prevalence ranging from 38% to 85%. Skin aging compromises the integrity of the stratum corneum, reducing the effectiveness of the barrier against transepidermal water loss and the penetration of external agents. This process is associated with slower cell turnover, decreased production of essential lipids, such as ceramides, cholesterol, and free fatty acids, and progressive alkalization of the skin surface pH. Increased pH inhibits enzymes involved in ceramide synthesis, reduces the production of natural moisturizing factors, and promotes activation of serine proteases that stimulate protease-activated receptor 2 (PAR-2), implicated in pruritus mediation. In addition, reduced activity of sebaceous and sweat glands, combined with age-related hormonal changes, particularly decreased estrogen levels in women, further disrupts lipid homeostasis. As the skin barrier weakens, susceptibility to allergen and irritant penetration increases, predisposing to contact dermatitis. Aging skin is also more vulnerable to adverse reactions to topical medications, which should be prescribed with caution.¹

Paraneoplastic diseases are defined as hormonal, neurologic, or hematologic disturbances, as well as clinical and biochemical abnormalities associated with the presence of neoplasms, without a direct relationship to primary tumor invasion or metastasis.^{5,6} The skin may provide clinical clues suggestive of systemic disease, thus contributing to early cancer diagnosis. In 1868, Hebra was the first to suggest that skin pigmentation could indicate visceral malignancy.⁷ Since then, more than 50 dermatoses have been described as potential markers of malignancy.⁸ Skin involvement can be direct, when there is tumor infiltration, or indirect, resulting from inflammatory, metabolic, or immunologic mechanisms mediated by substances such as cytokines, antibodies, or hormones, without the presence of tumor cells in the skin. In these cases, the condition is classified as a paraneoplastic cutaneous syndrome.^{9,10}

Eosinophilic dermatoses fall within this spectrum, especially in patients with hematologic malignancies. Clinically, they are characterized by pruritic and painful papules, vesicles, bullae, or nodules resembling insect-bite reactions on an erythematous-edematous base.⁷ They are most frequently associated with B-cell chronic lymphocytic leukemia, mantle cell lymphoma, diffuse large B-cell lymphoma, and acute leukemias, including T-cell lineage.^{10,11} The pathophysiology involves increased production of interleukin (IL)-4 and IL-5 after stimulation by allergens, medications, or viral agents, leading to an eosinophil-predominant immune response.¹² Another hypothesis links the treatment or the neoplasm itself to a Th2 immune profile, favoring cutaneous eosinophil activation. Blood eosinophilia may be present but is not mandatory. Eosinophilic skin infiltrates are not associated with infectious or allergic processes.¹¹

Eosinophils are granular leukocytes traditionally associated with allergic and parasitic responses but also exert complex immunomodulatory functions. They produce toxic cationic proteins, such as major basic protein and eosinophil peroxidase, as well as cytokines, chemokines, and lipid mediators that modulate local inflammation. In chronic inflammatory states, including paraneoplastic eosinophilic dermatoses, eosinophils may express major histocompatibility complex (MHC) class II molecules and costimulatory markers (CD80, CD86), functioning as nonconventional antigen-presenting cells. Their maturation occurs in the bone marrow under IL-5 stimulation, and tissue migration depends on chemokines, such as eotaxin-3, and the expression of adhesion molecules, such as

VLA-4. In the skin, eosinophil degranulation leads to the formation of flame figures, reflecting collagen damage, although without diagnostic specificity. In paraneoplastic syndromes, eosinophil activation appears to be mediated by a Th2 environment with a predominance of IL-4 and IL-5, even in the absence of overt allergic or infectious processes.¹³

Three principal clinical forms of eosinophilic dermatoses have been described: a bullous form, resembling bullous pemphigoid; an insect bite-like form; and a cellulitis-like form, with plaques or nodules similar to those of Wells syndrome.¹¹ Skin lesions may precede or follow the diagnosis of hematologic malignancy.¹⁴ The diagnosis of paraneoplastic eosinophilic dermatosis is based on treatment-refractory lesions, histologic evidence of eosinophilic infiltration, exclusion of alternative causes of eosinophilia, and confirmation of hematologic malignancy. Treatment options include topical or systemic corticosteroids, phototherapy, dapsone, immunosuppressive agents such as methotrexate and azathioprine, lenalidomide, and more recently dupilumab. Control of the underlying disease is essential for improvement of cutaneous manifestations.^{10,15-17}

Finally, lymphoma is a malignant neoplasm resulting from the proliferation of lymphoid cells, with variable aggressiveness and organ involvement. Different neoplasms derive from the lymphoid lineage, such as lymphocytic leukemias, plasmacytomas, Hodgkin lymphoma, and non-Hodgkin lymphomas. Non-Hodgkin lymphomas comprise a heterogeneous group of neoplasms arising from clonal lymphocytes at different stages of maturation. They originate primarily in the lymph nodes (nodal lymphomas) or in mucosa-associated lymphoid tissue, skin, or other organs (extranodal lymphomas). Among extranodal lymphomas, cutaneous lymphomas stand out, which are classified according to their cellular origin into T-cell lymphomas and B-cell lymphomas. The mean incidence of cutaneous lymphomas is approximately 0.3 cases per 100,000 patient-years, of which nearly 65% are T-cell lymphomas, 25% are B-cell lymphomas, and 10% are composed of true histiocytic lymphomas or rare cell types.¹⁸ From a clinical and dermatologic point of view, cutaneous B-cell lymphomas typically manifest as few lesions, presenting as nodules or infiltrations with relatively rapid growth. In contrast to T-cell lymphomas, these lesions are usually not associated with pruritus. Histopathologically, B-cell lymphomas are characterized by monomorphic infiltrates (composed of small or large cells) separated

from the epidermis by a band of collagen known as the Grenz zone (Unna band). T-cell lymphomas, in contrast, characteristically exhibit epidermotropism. Immunohistochemical differentiation between the two subtypes relies on monoclonal antibody expression. The presence of CD3, CD4, CD8, CD43, or CD45 indicates T-cell lineage, whereas the expression of CD20 (principal marker), CD19, CD23, CD79, CD5, CD10, CD32, or CD38 confirms B-cell origin.¹⁹⁻²¹ In the present case, immunophenotyping demonstrated CD20 expression, confirming the diagnosis of B-cell lymphoma.

This case underscores the importance of considering unusual cutaneous manifestations, such as treatment-refractory chronic pruritus, as potential paraneoplastic markers, especially in older patients. Integration of clinical, laboratory, and histopathologic findings was crucial for reaching a diagnosis. A multidisciplinary approach involving allergy and immunology, dermatology, and hematology proved essential for both early diagnosis and appropriate treatment referral. Timely recognition of these atypical presentations may facilitate earlier detection of occult hematologic malignancies, reduce delays in treatment, and potentially improve patient prognosis.

References

- Chung BY, Um JY, Kim JC, Kang SY, Park CW, Kim HO. Pathophysiology and treatment of pruritus in elderly. *Int J Mol Sci*. 2020;22(1):174.
- Silva JA, Mesquita KC, Igreja AC, Lucas ICRN, Freitas AF, Oliveira SM, et al. Paraneoplastic cutaneous manifestations: concepts and updates. *An Bras Dermatol*. 2013;88(1):9-22.
- Dalgard F, Dawn A, Yosipovich G. Are itch and chronic pain associated in adults? Results of a large population survey in Norway. *Dermatology*. 2007;214:305-9.
- Criado PR, Ianhez M, Criado RFJ, Nakano J, Lorenzini D, Miot HA. Prurigo: review of its pathogenesis, diagnosis, and treatment. *An Bras Dermatol*. 2024;99:706-20.
- Ramos-E-Silva M, Carvalho JC, Carneiro SC. Cutaneous paraneoplasia. *Clin Dermatol*. 2011;29:541-7.
- Pipkin CA, Lio PA. Cutaneous manifestations of internal malignancies: an overview. *Dermatol Clin*. 2008;26:1-15.
- Sneddon IB. Cutaneous manifestations of visceral malignancy. *Postgrad Med J*. 1970;46:678-85.
- Poole S, Fenske NA. Cutaneous markers of internal malignancy. I. Malignant involvement of the skin and the genodermatoses. *J Am Acad Dermatol*. 1993;28:1-13.
- Ortega-Loayza AG, Ramos W, Gutierrez EL, Paz PC, Bobbio L, Galarza C. Cutaneous manifestations of internal malignancies in a tertiary health care hospital of a developing country. *An Bras Dermatol*. 2010;85:736-42.
- Sato-Sano M, Teixeira SP, Vargas JC, Baiocchi OCCG, Enokihara MMSES, Gomes EE, et al. Lenalidomide in the management of eosinophilic dermatosis of hematological malignancy. *J Dermatol*. 2019;46(7):618-21.
- Maglie R, Genovese G, Solimani F, Guglielmo A, Pileri A, Portelli F, et al. Immune-mediated dermatoses in patients with haematological malignancies: a comprehensive review. *Am J Clin Dermatol*. 2020;21:833-54.
- Rodríguez-Lojo R, Almagro M, Piñeyro F, Pérez-Varela L, Fernández-Jorge B, Del Pozo J, et al. Eosinophilic panniculitis and insect bite-like eruption in a patient with chronic lymphocytic leukaemia: a spectrum of the same entity. *Dermatol Res Pract*. 2010;2010:263827.
- Peckruhn M, Elsner P, Tittelbach J. Eosinophilic dermatoses. *J Dtsch Dermatol Ges*. 2019;17(10):1039-51.
- Farber MJ, La Forgia S, Sahu J, Lee JB. Eosinophilic dermatosis of hematologic malignancy. *J Cutan Pathol*. 2012;39(7):690-5.
- Lucas-Truyols S, Rodrigo-Nicolás B, Lloret-Ruiz C, Quecedo-Estébanez E. Dermatoses eosinofílicas asociadas a procesos hematológicos. *Actas Dermosifiliogr*. 2017;108:e39-44.
- Jin A, Pousti BT, Savage KT, Mollanazar NK, Lee JB, Hsu S. Eosinophilic dermatosis of hematologic malignancy responding to dupilumab in a patient with chronic lymphocytic leukemia. *JAAD Case Rep*. 2019;5(9):815-7.
- de Souza PK, Amorim RO, Sousa LS, Batista MD. Dermatological manifestations of hematologic neoplasms. Part II: nonspecific skin lesions/paraneoplastic diseases. *An Bras Dermatol*. 2023;98(2):141-58.
- Nunes M de G, Pierro APS de M, Coutinho MFV, Morais JCO de, Carneiro SC da S, Azulay DR. Linfoma cutâneo de células B: relato de caso. *Anais Brasileiros de Dermatologia*. 2004 Dec;79(6):715-20.
- Sampaio SAP, Rivitti EA. Leucemias, Linfomas e Pseudolinfomas. In: *Dermatologia*. 2ª ed. São Paulo: Artes Médicas; 2000. p.887-913.
- Odom RB, James WD, Berger TG. Cutaneous Lymphoid Hyperplasia, Cutaneous T-Cell Lymphoma, Other Malignant Lymphomas, and Allied Diseases. In: *Andrews Diseases of the Skin, Clinical Dermatology*. 9ª ed. Philadelphia: W.B. Saunders Company; 2000. p.918-42.
- Burg G, Kempf W, Haeflner AC. Cutaneous lymphomas. *Curr Probl Dermatol*. 1997; 9:137-204.

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Allergy and Immunology subspecialties: a necessary step toward precision medicine?

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Dear Editor,

Contemporary medicine has been reshaped by rapid scientific expansion, technological advances, and increasing clinical complexity. In this scenario, specialties and subspecialties have become essential strategies to ensure accurate diagnosis, effective treatment, and individualized care. Although Allergy and Immunology is recognized as a unified specialty in Brazil, its scope is inherently cross-sectional, encompassing pathophysiological and clinical aspects across multiple organ systems.¹

With the sophistication of knowledge in immunology, biotechnology, and targeted therapies, it has become increasingly challenging for the general allergist to master all fields with the necessary depth. This has led, in clinical and academic practice, to the consolidation of “functional subspecialties” within the specialty, including food allergy, inborn errors of immunity, severe asthma, drug allergy, and allergic dermatoses. These subfields already operate with dedicated clinical pathways, requiring specific expertise and specialized infrastructure. The presence of outpatient clinics devoted to these “subspecialties” at institutions such as the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), Universidade Estadual de Campinas (Unicamp), and Universidade do Estado do Rio de Janeiro (UERJ) – as well as internationally at Mount Sinai, the National Institutes of Health (NIH), Guy’s and St Thomas’, and Elliot and Roslyn Jaffe Food Allergy Institute – demonstrates that these fronts are not merely emerging but are already well established in clinical practice.^{2,3}

However, these subfields do not yet have formal recognition as official areas of expertise by the Brazilian Federal Board of Medicine or the Brazilian Medical

Association, creating a gap between practice and regulation.¹ According to Resolution No. 2,330/2023 of the Brazilian Federal Board of Medicine, the official designation of “area of expertise” applies to clinical fields requiring additional expertise beyond that of the primary specialty.¹ The absence of formal regulation hinders professional certification, the development of structured training programs, the organization of care pathways, and the integration of education, research, and clinical practice.

The formal recognition of areas of expertise in Allergy and Immunology represents a fundamental step toward precision medicine. The diagnosis and management of complex allergic diseases increasingly incorporate technologies such as molecular diagnostics, biomarkers, immunologic and genetic profiling, all of which require specific expertise that extends beyond generalist training.⁴⁻⁶ Subfields such as food allergy, inborn errors of immunity, and allergen-specific immunotherapy illustrate this evolution, demanding not only scientific precision but also sensitivity to interpret the social, emotional, and biological context of each patient, particularly in pediatric populations, rare diseases, and highly complex conditions.

The impact on patient care is substantial. Advanced training in subfields enables faster diagnoses, more effective protocols, and individualized clinical follow-up, reducing risks and improving quality of life. International experience suggests that formal recognition of subfields strengthens, rather than fragments, specialties, as observed in Pediatric Oncology, Pediatric Allergy, and Sleep Medicine.⁷ Likewise, Allergy and Immunology may advance by formally recognizing its subfields while preserving its integrative perspective and enhancing clinical excellence.

By acknowledging these subfields, the specialty aligns with precision medicine,⁵ reinforces clinical safety and effectiveness, and reaffirms its commitment to humane, equitable, and evidence-based care. Formal recognition would facilitate the organization of care pathways, foster centers of excellence, integrate health care networks, and reduce disparities in access to advanced therapies. Furthermore, it would stimulate research and innovation for the benefit of society.

However, the creation of new areas of expertise requires careful planning and a commitment to equity. Despite its advantages, this process entails risks that should be thoughtfully addressed to preserve the integrity of the specialty. Major challenges include excessive fragmentation, which may compromise comprehensive care for allergic patients⁷; regulatory bureaucratization, which may delay innovation; and the exclusion of experienced clinicians who lack formal certification despite recognized expertise.

Another potential adverse effect would be a future shortage of general allergists. The training of overly segmented specialists may discourage generalist practice, which remains essential for initial assessment, broad diagnostic reasoning, and integrated management of allergic manifestations.^{4,7} The general allergist plays an irreplaceable role in triage, longitudinal follow-up, and care delivery in low complexity settings or resource-limited regions. Preserving this professional is also a strategic priority.

To mitigate these risks, the creation of new areas of expertise should be planned, progressive, and inclusive. Feasible strategies include competency-based certification organized by medical societies, definition of minimum curricula, accreditation of centers of excellence, and recognition of professionals with established expertise in specific subfields.

The careful preparation of a Justification Memorandum is essential to support the proposal for formal recognition. Such a document should address:

- Demonstrated health care demand, based on epidemiologic data and impact on morbidity and mortality;
- An established technical workforce, with a substantial number of specialists in centers of excellence;
- A consolidated scientific foundation, including guidelines, consensus statements, and relevant literature;
- Educational impact, with potential for residency programs, fellowships, and continuing education;
- International trends, including recognition of these subfields in global centers;
- Patient benefits, such as increased diagnostic accuracy, improved access to specific therapies, and reduced hospitalizations.

The formal recognition of areas of expertise in Allergy and Immunology represents a necessary and strategic advancement in response to the growing complexity of clinical practice. It offers an opportunity to align the specialty with the principles of personalized medicine, strengthen specialist training, organize care pathways, and expand equitable access to cutting-edge therapies. With progressive planning, inclusion of experienced professionals, and a commitment to integrated care, this formal recognition will not fragment the specialty; rather, it will enhance its effectiveness, social relevance, and ethical commitment to patients.

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References

1. Conselho Federal de Medicina. Resolução CFM nº 2.330/2023 [Internet]. Available from: https://sistemas.cfm.org.br/normas/arquivos/resolucoes/BR/2023/2330_2023.pdf.
2. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. *J Allergy Clin Immunol*. 2018;141(1):11-9.
3. Elliot and Roslyn Jaffe Food Allergy Institute [Internet]. Available from: <https://icahn.mssm.edu/research/jaffe>.
4. Popov TA, Passalacqua G, González-Díaz SN, Plavec D, Braidó F, García-Abujeta JL, et al. Medical devices in allergy practice. *World Allergy Organ J*. 2020 Sep 30;13(10):100466. doi: 10.1016/j.waojou.2020.100466.
5. Ferrando M, Bagnasco D, Varricchi G, Bernardi S, Bragantini A, Passalacqua G, et al. Personalized Medicine in Allergy. *Allergy Asthma Immunol Res*. 2017 Jan;9(1):15-24. doi: 10.4168/aa.2017.9.1.15.
6. Incorvaia C, Ridolo E, Bagnasco D, Scurati S, Canonica GW. Personalized medicine and allergen immunotherapy: the beginning of a new era? *Clin Mol Allergy*. 2021 Jul 7;19(1):10. doi: 10.1186/s12948-021-00150-z.
7. Ehrlich JH, Kerbl R, Pettoello-Mantovani M, Lenton S. Opening the Debate on Pediatric Subspecialties and Specialist Centers: Opportunities for Better Care or Risks of Care Fragmentation? *J Pediatr*. 2015;167(5):1177-8.e2. doi: 10.1016/j.jpeds.2015.07.060.

Advances in olive tree cultivation in Rio Grande do Sul, southern Brazil: Is a future regional pollinosis likely?

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Dear Editor,

Within the Oleaceae family, the most allergenic pollen is produced by *Olea europaea*, the olive tree which in the Mediterranean region has long been recognized as one of the most important causes of seasonal respiratory allergy.¹

The olive tree is an ancient species adapted to temperate climates, requiring at least 300 hours per year at temperatures below 12 °C. It has adapted well to certain regions of Rio Grande do Sul, the southernmost state of Brazil, particularly the Western Frontier and the Southern Half of the state. In Brazil, olive cultivation is also found in other elevated areas, such as the Serra da Mantiqueira, among others.²

Traditional olive groves contain approximately 100 trees per hectare (100×100 m spacing), and the trees are of medium size, reaching up to 15 m in height. Olive tree cultivation in Rio Grande do Sul accounts for 75% of national production, covering 4,300 hectares across 110 municipalities. Estimates suggest that within the next 4-5 years this area may expand to 100,000 hectares, given that 6.8 million hectares in the state have “recommended” edaphoclimatic suitability for olive production.^{2,3} For spatial reference, one hectare is approximately the size of a soccer field.

The airborne dispersion of olive pollen depends not only on intrinsic factors but also on extrinsic variables, particularly meteorologic conditions. Heat and sunlight generally increase airborne pollen concentrations by promoting dehydration and anther dehiscence, as well as facilitating dispersion through thermal currents.⁴

Olive pollen is typically distributed within 300 to 1,000 meters of the trees; however, it may travel several kilometers. A noteworthy characteristic is its strong aerobiologic capacity, that is, its ability to be easily transported by air.¹

Among multiple molecular allergen categories involved in *Olea europaea* pollinosis, Ole e 1 is the

principal allergen, exhibiting homology with allergens from other members of the Oleaceae family, such as *Ligustrum*, which is commonly used in urban landscaping in some cities.⁵

Although belonging to different families, grass pollen may increase the risk of sensitization to olive pollen, as observed with *Ligustrum*.⁶ We must remember that the grass pollen season in southern Brazil (September to December) overlaps with the olive pollination period (October to November), producing a potential and predictable priming effect, that is, with an increased risk of sensitization and symptoms.^{3,6}

The diagnosis of pollen allergy should always be based on symptoms that demonstrate a close relationship between pollen concentrations. For olive pollen, an initial threshold of approximately 150 grains/m³ of air has been proposed, potentially decreasing to 30 grains/m³ with repeated exposure. *Olea europaea* pollen may also induce subclinical sensitization depending on the individual's place of residence.⁷ However, the development of sensitization or pollinosis requires genetic predisposition, which may occur only in a subset of the population.

A practical question of interest to physicians, agronomists, biologists, environmental scientists, rural producers, and society at large concerns the appropriate minimum distance between large olive plantations and urban centers to reduce the risk of sensitization and pollinosis in the population. A suggested average distance ranges from 15 to 20 km to minimize airborne transport of pollen (personal communication⁸).

Currently, the number of olive trees in Rio Grande do Sul remains modest compared with countries such as Spain, Italy, Portugal, and Greece. Brazil is the world's second-largest importer of olive oil, according to the International Olive Council (IOC). However, as the population of *Olea* trees expands, systematic pollen monitoring (measuring grains per cubic meter of air) may become necessary, as is routinely performed in countries where pollen-related disease is prevalent in the population: a collaboration among medicine, agricultural sciences, and environmental sciences.

A predictable source of confusion for clinicians may arise from patients with pollinosis who might simultaneously have dual sensitization to both grasses and *Olea*, since both pollinate during the spring.

In regions with olive groves, skin prick testing to both allergens or measurement of specific IgE levels should therefore be considered. Monosensitization to *Olea* pollen appears uncommon among allergic patients, similar to other members of the Oleaceae family.^{6,7}

Taking into account all variables, environmental changes, exposure to allergenic olive pollen, and the economy, there would be a future sign of prosperity in this context.

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References

1. Liccardi G, D'Amato M, D'Amato G. Oleaceae Pollinosis: A Review. *Int Arch Allergy Immunol*. 1996;111(3):210-7.
2. Filoda PF, Chaves FC, Hoffmann JF, Rombaldi CV. Olive oil: A Review on the identify and quality of olive oils produced in Brazil. *Rev Bras Frutic*. 2021;3:43.
3. Filipini A, Flores CA, Wrege MS, Coutinho EF, Jorge RO. Zoneamento edafoclimática da Olivicultura para o Rio Grande do Sul [Internet]. *Anais do XXIII Congresso Brasileiro de Fruticultura*; 2014; Cuiabá-MT, Brasília, DF: Embrapa;204. Available from: <https://www.embrapa.br/busca-de-publicacoes/-/publicacao/995817/zoneamento-edafoclimatico-da-olivicultura-para-o-rio-grande-do-sul>. Accessed on: Nov 2023.
4. La Guardia CD, Alba F, Trigo MD, Galán LR, Sabariego S. Aerobiological analysis of *Olea Europea* L. pollen in different localities of Southern Spain. *Grana*. 2003;42:234-43.
5. Vara A, Fernández-González M, Aira MJ, Rodríguez-Rajo FJ. Oleaceae cross-reactions as potential pollinosis cause in urban areas. *Sci Total Environ*. 2016 Jan 15;542(Pt A):435-40. doi: 10.1016/j.scitotenv.2015.10.107.
6. Vieira FAM, Ferreira EM, Cruz AA. Grass Allergy increases the risk of tree pollen sensitization: A Warning to urban planners. *J Allergy Clin Immunol*. 1998;102:700-1.
7. Feo Brito F, Galindo Bonilla PA, García Rodríguez R, Gómez Torrijos E, Fernández Martínez F, Fernández-Pacheco R, et al. Pólenes alergénicos en Ciudad Real: Aerobiología e incidència clínica. *Rev Esp Alergol Inmunol Clin*. 1998;13:75-95.
8. Francisco Feo Brito. Sección de Alergia, Hospital General, Ciudad Real, Spain. *Comunicação Pessoal*.

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