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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Artificial Intelligence as an ally in the approach to Inborn Errors of Immunity: a pioneering experience in Brazil

Inteligência Artificial como aliada para abordagem de Erros Inatos da Imunidade: uma experiência pioneira no Brasil

Marina Mayumi Vendrame Takao[1], Marta Duran Fernandez[1,2,3], Marcos Tadeu Nolasco da-Silva[1], Adriana Gut Lopes Riccetto[1]

The use of Artificial Intelligence (AI) in the medical field has expanded remarkably over the past decade, contributing to improvements in clinical practice and patient outcomes, particularly in the specialties of oncology, neurology, and cardiology.[1] In allergy and immunology, a similar trend has been observed, with a growing number of scientific publications addressing the use of AI in the specialty since 2010. However, studies primarily focused on inborn errors of immunity (IEIs) remain scarce: a systematic review conducted in August 2025 identified only 23 studies using AI for the identification and management of patients with IEIs.[2]

The development of AI tools targeted at IEIs is both a fertile area and a field filled with challenges. The rarity of most disorders, their heterogeneous clinical presentation, and the difficulty of establishing a genetic diagnosis, combined with the massive volume of data—generally fragmented across multiple sources and lacking standardization—pose significant challenges to the development of generalizable AI models.[1,3,4] Added to this is the need for careful data processing, including curation, cleaning, integration, and anonymization, to ensure quality, consistency, and ethical compliance without compromising the clinical representativeness of the phenomenon under investigation.

Conversely, these same characteristics are what make AI models so valuable in the approach to IEIs, since traditional diagnostic approaches are increasingly limited in achieving early diagnosis of disorders within this group as knowledge continues to advance. This complexity also provides several opportunities for AI applications, including phenotype and genotype classification, biomarker identification, risk prediction, outcome analysis, and individualized therapeutic support, among others.[1-3]

Against this background, in 2019, our group initiated a project to develop an AI-based system for detecting the risk of IEIs in children with suspected disease, with the aim of providing a tool for the early identification of IEIs in the Brazilian context, targeted at nonimmunologist physicians. In 2022, an initial study was published evaluating the performance of machine learning models—a branch of AI—in predicting the risk of IEIs in children with clinical suspicion of IEIs based on the assessment of clinical and laboratory

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data from 128 children; the study demonstrated high performance of the AI models, particularly the Random Forest model.5 Since then, additional studies have been conducted, culminating in the launch of the TAMIS-AI platform (approved by the institutional ethics committee – CAAE 22418919.6.0000.5404, opinion no. 3.660.580, October 24, 2019, and CAAE 46454821.6.0000.5404, opinion no. 4.881.50, August 3, 2021).

The development of TAMIS-AI initially involved expanding the sample to 369 children followed at the Pediatric Allergy and Immunology Outpatient Clinic of a tertiary teaching hospital between 2018 and 2024, with or without IEIs. Clinical and laboratory data serving as markers of IEIs were compiled from medical history, physical examination, and laboratory tests included in basic immunological screening. The data were used to develop an AI algorithm using three robust techniques (ie, Random Forest, Grid Search, and CatBoost), selected because, in combination, they are capable of identifying complex patterns among symptoms, test results, and infection history; optimizing the model's hyperparameters, ensuring good performance in terms of accuracy, sensitivity, and specificity; efficiently handling categorical data (for example, type of infection, previous antibiotic use), reducing biases and improving model explainability; and justifying its decisions in an interpretable manner for physicians by showing the factors that contributed most to the risk alert. The system was developed according to the principles of "secure by design," in which security layers are applied at each stage of development, as well as the principles of the Brazilian Data Protection Law, particularly considering that it is a system that works with sensitive data.

Preliminary results demonstrated that the model achieved an accuracy of 88.6%, a sensitivity of 88.6%, and a precision and recall of 88.5%. These indices allow for an objective and comparable assessment of performance, increasing transparency and confidence in the results. Without well-defined performance metrics, it becomes impossible to determine whether the model adds clinical value or whether its decisions are merely random. In settings such as the diagnosis of rare diseases, in which there is marked imbalance between categories (affected and unaffected), simple overall accuracy may be insufficient, reinforcing the need for a multidimensional assessment of performance. Thus, such metrics help prevent misinterpretations and reduce the risk of adopting models that appear to perform well but have limited clinical utility. After the algorithm development stage, a platform was created for use on desktops (web version) and smartphones and was then made available free of charge in mobile application stores.

It is essential to emphasize that, despite the model's high performance and the availability of the platform, it was trained on a small sample (as is already expected for rare diseases in general); therefore, expanding the model's generalizability is particularly important in a large and geographically diverse country such as Brazil. We recognize that we are at an unprecedented historical moment and that promoting broad use of the tool across the country, feeding the algorithm with new data from different regions, will contribute significantly to population representativeness and diversity.

Finally, the support that AI can provide to allergists and immunologists, as well as the growing role this technology has assumed, is so significant that, in 2022, the AAAAI Health Informatics, Technology and Education Committee published a work group report[6] recommending that specialists become actively involved in the development, validation, and implementation of AI within the specialty. In this context, TAMIS-AI is a tool created by pediatric immunologists and computer scientists whose development phase was successfully completed. Acting as a digital sentinel by integrating complex clinical data, specialized knowledge, and advanced analytical techniques, TAMIS-AI has the potential to reduce diagnostic delays, support medical decision-making, and promote earlier and more accurate interventions. The experience reported here highlights the importance of pioneering initiatives that pave the way for scalable, ethical, and clinically relevant solutions for addressing rare diseases.

Acknowledgments

We would like to thank all collaborators who contributed to the development of the application, including students, residents, physicians, professors, and computer scientists.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Case reports in Allergy and Immunology: relevance and structure

Relatos de casos em Alergia e Imunologia: relevância e estruturação

Ekaterini Simões Goudouris[1]

ABSTRACT

Although they are at the bottom of the scientific evidence hierarchy, case reports remain a classic format in medical literature and play a key role in advancing knowledge and health education. This article reviews the importance and limitations of case reports, presents guidelines for their structure, and proposes practical recommendations for the specialty of allergy and immunology. This is a narrative review developed with the support of artificial intelligence tools and human curation. Although they have methodological limitations and are subject to publication bias toward positive data, case reports are vital for medical education, both during training and in continuing education. They also play a crucial role in pharmacovigilance, the study of rare conditions, the discovery of new diseases and treatments, and the generation of hypotheses to be tested using more rigorous study methods. Inconsistent reporting quality led to the development of the CARE guidelines in 2013, which are fundamental for ensuring the accuracy, completeness, and transparency of case reports. In allergy and immunology, case reports are essential for describing inborn errors of immunity, novel allergens, and immunotherapy outcomes, among others. When conducted and reported with methodological rigor and adherence to structured guidelines, case reports in allergy and immunology have high scientific and educational value, serving as an indispensable source of innovation and improvement in clinical practice.

Keywords: Case reports, guideline, methods, allergy and immunology, inborn errors of immunity.

RESUMO

Os relatos de caso, embora estejam na base da pirâmide de evidências científicas, constituem um formato clássico da literatura médica, fundamentais para o avanço do conhecimento e para a educação em saúde. Este artigo revisa a importância e as limitações dos relatos de caso, apresenta diretrizes de estruturação e propõe recomendações práticas para a especialidade de Alergia e Imunologia. Trata-se de uma revisão narrativa apoiada em ferramentas de inteligência artificial e com curadoria humana. Embora apresente limitações metodológicas e haja um viés de publicação de dados positivos, os relatos de casos são vitais para a educação médica, tanto no processo de formação quanto na educação continuada. São importantes também na farmacovigilância, no estudo de condições raras, na descoberta de novas doenças e de novos tratamentos, bem como na geração de hipóteses a serem testadas por meio de métodos de estudo mais rigorosos. A inconsistência na qualidade levou ao desenvolvimento das diretrizes CARE, em 2013, cujo uso é crucial para garantir a precisão, a completude e a transparência dos relatos de casos. Na Alergia e na Imunologia, os relatos são essenciais para descrever erros inatos da imunidade, novos alérgenos e desfechos da imunoterapia, entre outros. Quando conduzidos e relatados com rigor metodológico, seguindo diretrizes estruturadas, os relatos de caso em Alergia e Imunologia mantêm elevado valor científico e educacional, sendo uma fonte indispensável de inovação e aprimoramento da prática clínica.

Descritores: Relatos de casos, guia, metodologia, alergia e imunologia, síndromes de imunodeficiências.

Introduction

Case reports represent one of most traditional forms of medical literature, having played a historical role in the identification of new diseases, adverse events, and pathophysiological mechanisms.[1] While occupying the lowest level in the hierarchy of evidence-based medicine, they remain an essential strategy for advancing medical knowledge.[2]

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Often overshadowed by the statistical power of large randomized controlled trials (RCTs) and meta-analyses, case reports and case series are sometimes mistakenly regarded as "anecdotal evidence" or as having limited scientific value. However, this perspective is simplistic, as it overlooks both the nature and history of medical discoveries.

Nevertheless, the lack of methodological standardization may compromise the usefulness and reproducibility of published reports. Variability in quality and insufficient transparency among case reports published in scientific journals prompted the development of reporting guidelines, such as the 2013 CAse REport (CARE) Statement, which established a standardized framework to improve completeness and methodological rigor.[3]

The number of journals that publish case reports has steadily increased and now exceeds 200 indexed journals worldwide.[4] A demonstration of the growing recognition of this study design is the recent publication of a proposal outlining steps to conduct a systematic review of case reports.[5]

This study aimed to review the importance and limitations of case reports in health care, present recognized guidelines for their preparation, and propose practical recommendations for authors to promote their rigorous and methodologically sound use in the field of allergy and immunology.

Methods

This article is a narrative review supported by artificial intelligence (AI) tools.

The author used AI-based literature search platforms (OpenEvidence, Undermind, Consensus, AnswerThis, and SciSpace) to identify publications addressing methodological guidelines for case reports and the available evidence regarding their educational and scientific impact. Unlike conventional database searches, which rely on keywords and Boolean operators, AI-assisted literature retrieval is driven by natural-language queries. The following question was used: "How should a case report be prepared for scientific publication, and what is its relevance?" The bibliographic databases accessed by these AI tools included PubMed and Semantic Scholar.

Data synthesis and curation were performed by the author with the assistance of a natural-language processing tool (NotebookLM), ensuring that the final interpretation of the evidence and the practical recommendations proposed for the field of allergy and immunology reflected clinical experience and critical human judgment.

Definitions and historical perspective

A case report in health care is a detailed narrative describing a clinical problem experienced by one or more patients for professional, scientific, or educational purposes.[3,6] It typically documents an unusual or novel clinical occurrence, providing a detailed account of the findings, clinical course, and prognosis of one or more patients.

Although most case reports are retrospective, they may also be designed prospectively; for example, to evaluate the implementation of a novel diagnostic or therapeutic approach.[1]

Clinical case reports have been an integral part of medical literature throughout history. The oldest known preserved example dates to an Egyptian papyrus from approximately 1600 BC addressing the management of a dislocated mandible. From the Hippocratic case histories recorded in the Epidemics (400 BC) to the Galenic case reports in the second century AD and the extensive collection compiled by the Persian physician Al-Razi (865–929 AD), case reports have served as the principal means of communicating clinical observations.[1] Sir William Osler, widely regarded as the father of modern medicine, valued and encouraged physicians to observe, document, and publish "the unusual." [7]

Some examples can illustrate how well-documented case reports can lead to major changes in clinical practice. The association between thalidomide use during pregnancy for the treatment of nausea and phocomelia was first described in a 1962 case report. A 1961 letter to the editor published in The Lancet also played a pivotal role in bringing the tragedy to attention. Likewise, the recognition of the efficacy of systemic propranolol for infantile hemangiomas originated from a case series published in a high-impact journal, subsequently prompting RCTs.[8]

With the emergence of evidence-based medicine during the second half of the twentieth century, clinical case reports came to occupy a paradoxical position in the hierarchy of evidence.[2,9] Although case reports are considered to have the lowest level of methodological rigor, they continue to be published in leading medical journals and remain highly relevant to contemporary clinical practice.[9]

Relevance

Although RCTs and systematic reviews occupy the highest level in the hierarchy of evidence, case reports play a crucial and complementary role in advancing science and health care education.[10,11]

Detection of novel findings and hypothesis generation

The greatest strength of case reports lies in their ability to identify novel findings. They are often the only means of documenting unusual or unexpected findings, including new symptoms, clinical manifestations, disease courses, disease associations, and responses to interventions. They can serve as the "first line of evidence," where everything begins.[1,12]

Individual case reports or case series frequently generate new hypotheses that can subsequently be tested using more rigorous research designs. An analysis of case reports published in The Lancet showed that, among 103 published reports, 24 were subsequently followed by RCTs.[1]

Pharmacovigilance: identification of adverse drug reactions

Case reports are indispensable to pharmacovigilance and remain one of the primary sources for detecting rare adverse drug reactions.[9,12] It has been estimated that approximately 40% of all adverse drug reactions are first identified through case reports.[8]

Most recent drug withdrawals from the market, ranging from weight-loss agents to nonsteroidal anti-inflammatory drugs, were prompted by case reports.

Research on rare diseases

For rare diseases, conducting RCTs is often impractical because of the limited number of eligible patients. In these settings, case reports and case series represent the highest level of available evidence to inform clinical practice and guide future research.[2,9]

Medical education

Case reports are a valuable resource in medical education.[11,13] Clinical learning is fundamentally case-based — cases that are multifaceted, as described below.

– *Diagnostic reasoning:* well-prepared case reports that clearly describe the diagnostic approach, differential diagnosis, and therapeutic approach are essential in medical training and continuing education. Moreover, the practice of identifying potentially publishable cases encourages "critical and intentional" clinical observation, fostering broader and clearer diagnostic thinking and strengthening pattern-recognition skills.[14]

– *Skills development:* for medical students, residents, and fellows, writing a case report is often their first experience with scientific writing. The process develops critical thinking, literature appraisal, and collaborative skills. Case reports may also enhance understanding of patient-centered care by incorporating the perspectives of patients and their caregivers.[15]

– *Active learning:* case reports provide early-career authors with an opportunity to participate in the preparation of a manuscript by applying the steps of evidence-based medicine: formulating a clinical question, identifying the best available evidence, critically appraising that evidence, and applying it to patient care.[1,16]

Limitations and challenges

The scientific value of a case report is directly proportional to its methodological quality and the clarity of its presentation.

Incomplete reports that fail to document excluded differential diagnoses (negative results) or lack objective data on the intervention contribute little to scientific knowledge and face increasing barriers to publication. A common error in submitted manuscripts is the omission of normal test results.[17]

Nevertheless, even when rigorously prepared, case reports have inherent methodological limitations.

Publication bias and the risk of overinterpretation

Scientific journals tend to favor reports with positive outcomes. One study found that 90% of published case reports and case series described successful outcomes, whereas only 10% reported failures.[18]

Case reports are also susceptible to over-interpretation, that is, a tendency to generalize when there is no justification for it.[12] The emotional appeal of an individual story may lead readers to conclude prematurely that there is a causal connection.[9]

Generalization and causal inference not possible

The major methodological limitations of case reports include:

– *Generalization not possible:* because patients are not selected from representative population samples, the findings cannot be generalized.[2,11]

– *Causal inference not possible:* causality cannot be inferred from an uncontrolled observation. An observed association could be a mere coincidence.[2,17]

– *No denominator:* case reports provide a numerator without a denominator, precluding the calculation of epidemiological rates, such as incidence and prevalence.[2,9,11]

Impact factor and editorial policies

Case reports are cited less frequently than other types of research articles, which may negatively affect a journal's impact factor.[19] Consequently, many editors are reluctant to publish them or have eliminated this article type from their journals. In response, numerous open-access journals dedicated exclusively to case reports have emerged.

Studies evaluating the completeness of published case reports have shown inconsistent adherence to the CARE guidelines. An analysis of 114 case reports published in high-impact journals found an overall median completeness score of 81%. Reports published in journals endorsing the CARE guidelines demonstrated greater completeness than those published in journals without such endorsement (77% vs. 65%).[17]

Case reports may also generate false alarms. For example, a medication marketed for morning sickness, containing dicyclomine, doxylamine, and pyridoxine, was withdrawn from the United States market after case reports suggested an association with fetal malformations. However, subsequent, more rigorous investigations failed to confirm this risk.[12]

Relevance of case reports in allergy and immunology

Examples of case reports with particular relevance to allergy and immunology include: (a) an atypical presentation of a well-recognized allergic disease, such as atopic dermatitis; (b) identification of a novel allergen or a previously unrecognized cross-reactivity; (c) a previously undescribed adverse effect of a medication widely used in the specialty; (d) rare hypersensitivity reactions to drugs, biologic agents, vaccines, or immunotherapy; (e) clinical outcomes associated with innovative therapeutic approaches; (f) a distinct clinical or genetic phenotype of an inborn error of immunity (IEI) or secondary immunodeficiency; (g) unexpected therapeutic efficacy of a commonly used medication in an unconventional clinical setting; and (h) an interaction between allergy and another clinical condition that substantially modifies its clinical presentation.[2,9,11,12,14]

Pharmacovigilance relies heavily on sentinel reports to identify rare or paradoxical hypersensitivity reactions to immunotherapies, biologic agents, and small molecules, often long before such events can be detected in cohort studies.[10]

The identification of new IEIs invariably begins with the detailed description of a single patient or family, whose molecular investigation reveals previously unrecognized cell signaling pathways.[2] Case reports have also been instrumental in describing novel phenotypes of IEIs and secondary immunodeficiencies, as well as diagnostic and therapeutic approaches to rare cases.

Recommended structure based on the CARE guidelines

To address inconsistencies in quality and lack of methodological rigor in published case reports, an international panel of experts developed the CARE guidelines in 2013. Created through a formal consensus process, these guidelines provide a standardized framework to ensure accuracy, completeness, and transparency in the reporting of clinical cases.[3,20] Subsequently, the CARE guidelines were endorsed by the EQUATOR Network and by multiple medical journals, including several high-impact journals in allergy and immunology, aiming to improve the reliability and value of health research.

Essential structural components[3,21]

Title page

The title should be concise and descriptive, highlighting the phenomenon of greatest clinical interest (symptom, diagnostic finding, specific diagnosis and/or differential diagnosis, intervention, outcome). Generic titles that may hinder indexing and

retrieval in bibliographic databases should be avoided. The title should also include the words “case report.”

Abstract

The abstract should contain 150–250 words and may be either structured or unstructured, depending on the requirements of the target journal. It should not include references or nonstandard abbreviations.

Background or introduction: provide a brief overview of the relevant literature and explain why the case warrants publication, emphasizing its novelty or relative rarity.

Case presentation: summarize the clinical scenario, including essential demographic information, clinical and laboratory findings, diagnosis, intervention, and outcome.

Conclusions: highlight the main “take-away” lessons and implications for clinical practice or future research.

Keywords: include 2 to 5 keywords that identify the diagnosis and intervention, as well as the term “case reports.” The Health Sciences Descriptors (DeCS) and the Medical Subject Headings (MeSH) databases should always be consulted when selecting keywords.

Introduction

This section should place the case in the context of current knowledge. It should include: (a) a brief overview of the clinical problem addressed by the case; (b) relevant references establishing the current state of knowledge; and (c) an explanation of why the case deserves to be reported. The introduction often concludes with a single sentence describing the patient and their primary condition.

In allergy and immunology, the introduction should clearly establish the rarity or educational significance of the case: Does it describe an atypical presentation of a known disease? A previously unreported allergen? A previously unreported adverse effect associated with an established or emerging therapy? A new IEI or a novel pathogenic variant in a known gene? An atypical phenotype of a recognized IEI?

Case presentation

This is the core section of the report and comprises most of its content. The clinical episode should be presented systematically and in chronological order, reflecting the actual sequence of clinical events and data acquisition, as described below.

Relevant demographic information: include age, sex, geographic origin, occupation (when relevant), and significant family history. Sex and race or ethnicity should be reported when clinically pertinent to the topic under discussion.

Clinical history: describe the initial presentation, main and associated symptoms, symptom duration before medical evaluation, and any recognized precipitating factors.

Past medical history: include previous allergic diseases, other relevant medical conditions, current medications, and documented drug or food allergies.

Physical examination: report the findings relevant to the case, quantifying them whenever possible. Clinically meaningful negative findings should be documented in addition to abnormal findings.

Diagnostic workup: present laboratory and imaging studies, including testing methods when appropriate. Diagnostic workup should follow a logical sequence, with specific results reported. For allergy cases, include the results of skin testing (skin prick and intradermal), specific IgE measurements, basophil activation tests, and provocation tests, when performed. For IEIs, report T- and B-cell counts, immunoglobulin levels, specific functional testing, and genetic sequencing results. All values should be quantified and interpreted against the appropriate reference ranges.

Differential diagnosis: rather than providing a simple list of possible diagnoses, explain why alternative hypotheses were considered and how they were subsequently excluded.

Therapeutic approach: describe the treatment strategy implemented, including nonpharmacologic interventions, dosage regimens, and duration of treatment. Any changes in the treatment plan should be explained.

Clinical course and follow-up: describe patient monitoring and clinical and laboratory outcomes. Adverse or unexpected events, treatment adherence, and tolerability should also be reported. Whenever available, physician-reported severity assessment tools should be included.

Patient perspective: whenever feasible, incorporate the perspectives of the patient and/or caregivers using validated patient-centered outcome measures, such as Patient-Reported Experience Measures (PREMs) and Patient-Reported Outcome Measures (PROMs).

Visual timeline: a table or figure summarizing the chronological sequence of the major clinical events is recommended to facilitate an integrated understanding of the case.

Discussion

The discussion section should place the clinical significance of the case within the context of existing knowledge and include the following elements.

Case summary: briefly recapitulate the most important clinical features.

Review of the relevant literature: compare the case with previously reported similar cases and with the established characteristics of the condition, highlighting similarities and differences. Rather than providing an exhaustive literature review, the discussion should present a critical synthesis explaining how the reported case contributes new knowledge.

Discussion of mechanisms: when appropriate, discuss the potential underlying pathophysiological mechanisms, particularly if the case suggests new insights into known mechanisms.

Implications for clinical practice: clearly explain how the findings may influence current diagnostic or therapeutic approaches or identify important questions for future investigation.

Limitations: acknowledge the inherent limitations of an individual case report in generating generalizable evidence.

Conclusions

Provide a concise summary of the key findings, reaffirming the relevance of the case to the scientific community.

Informed consent and ethical considerations

This essential component is frequently underreported or insufficiently emphasized. Written informed consent must be obtained from the patient (or from a parent or legal guardian in the case of minors) before manuscript submission. The consent should specifically authorize publication. Complete patient anonymization is mandatory. Identifying information, including names, initials, medical record numbers, and exact dates of birth or clinical encounters, should be omitted (use age or month/year alone if necessary). Clinical photographs should be carefully edited to prevent patient identification; ideally, they should not include the patient's face.

References

There is no ideal number, but the references should be sufficient to support the discussion appropriately. For case reports of moderate complexity, 15 to 25 references are generally adequate. Preference should be given to primary sources and articles published in reputable peer-reviewed journals. References should be formatted strictly according to the requirements of the target journal.

Required declarations

Most journals require a dedicated Declarations section addressing the following items: institutional ethics committee approval (as applicable), informed consent (mandatory), data availability, conflicts of interest, funding sources, and author contributions.

Figure 1 presents a summary of the CARE checklist.

Considerations specific to case reports in allergy and immunology

Journals specializing in allergy and immunology often establish specific criteria for the acceptance of case reports. Authors should carefully review the journal's instructions for authors before manuscript submission. In general, case reports are expected to make a meaningful contribution to medical knowledge by providing clear educational value or by demonstrating findings that may influence current diagnostic, therapeutic, or prognostic approaches.

Several elements deserve particular attention to ensure that essential information is not omitted: the comprehensive reporting of immunological data, such as total and specific IgE levels, skin test results, and other relevant biomarkers; a chronological presentation of exposure, symptoms, and interventions (preferably using a visual timeline) is especially important in reports of food or drug allergies; a detailed description of the patient's response to immunotherapy, immunosuppressive therapy, or biologic therapy in the various clinical conditions of the specialty; and ethical considerations and appropriate informed consent for rare conditions, such as IEIs.

Practical recommendations for authors

– Use the CARE checklist as a guide – a free online tool, available at https://care-writer.com/, can help authors systematically organize information

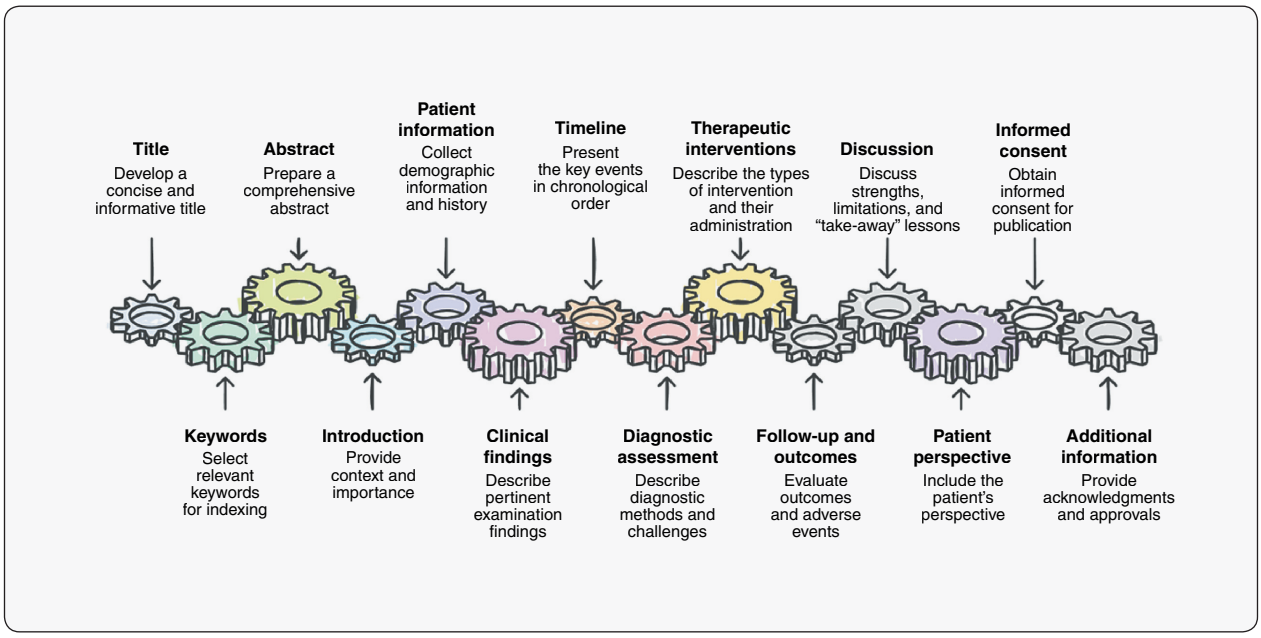

Figure 1
Infographic summary of the key steps in preparing a case report. Created by the author using Napkin, based on the CARE guidelines.

in accordance with the CARE guidelines and facilitate compliance with international reporting standards.

- Avoid speculative language.
- Include supplementary data, high-quality images, and laboratory findings.
- Ensure anonymization and obtain explicit consent.
- To strengthen the quality of the report, include a visual timeline, objective outcome measures, a repository of supplementary materials (such as protocols, scales, and chronologies), and the patient's perspective.
- Before submission, the manuscript should undergo rigorous self-assessment based on the following criteria:

  clarity: can the reader easily understand the clinical sequence?;

  completeness: have all relevant clinical data been included?;

  novelty: what does this case add to existing knowledge?;

  transparency: have the limitations been adequately acknowledged?;

  anonymization: is the patient's identity fully protected?
- Do not be discouraged by rejection. Use reviewers' feedback to improve the manuscript and consider submission to another journal.

Adherence to the CARE guidelines is particularly low for items intended to enhance transparency and incorporate the patient's perspective.[17] These elements should therefore receive special attention.

Figures 2 and 3 present items that authors should consider carefully, including recommendations on what to do and what not to do.[4]

Conclusion

Despite occupying the lowest level in the hierarchy of evidence, case reports remain an indispensable source of information, discovery, and health care education. They offer a narrative perspective that complements quantitative data, enriching the evidence base and enhancing patient care.

The adoption of reporting standards such as the CARE guidelines is essential to maximize the value of case reports by ensuring that clinical observations are

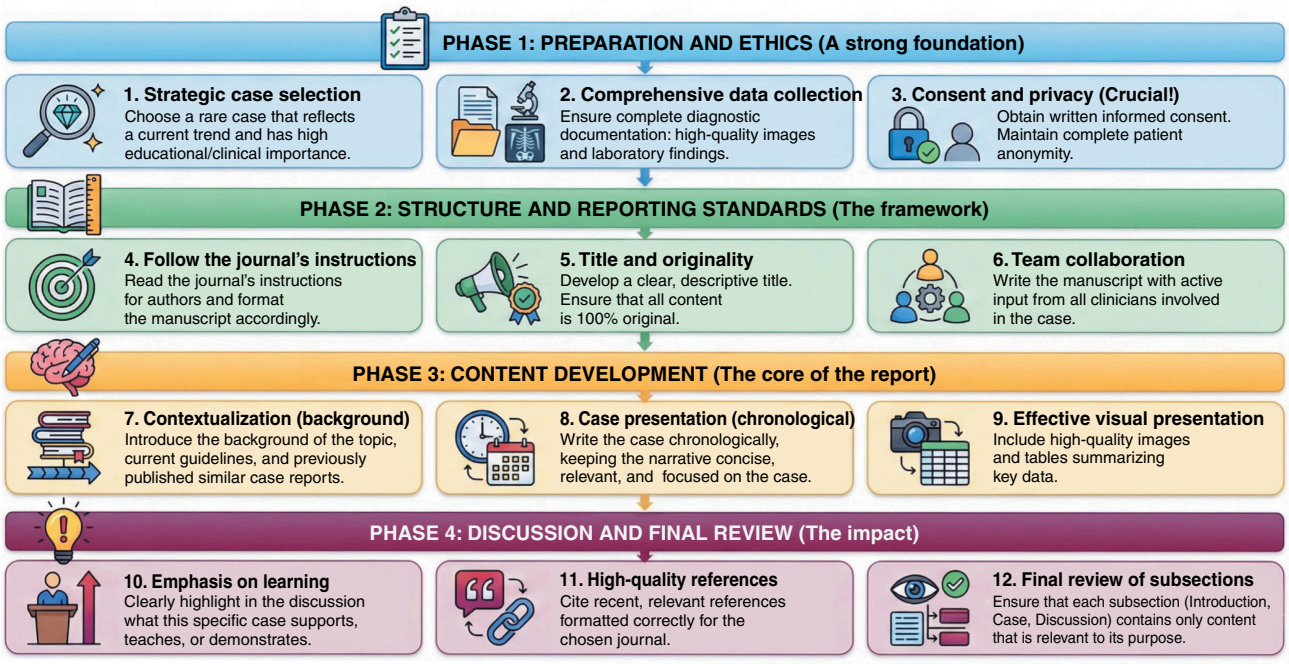

Figure 2
Practical recommendations on what to do. Created by the author using the NotebookLM infographic generation tool, based on information from Parums DV[4]

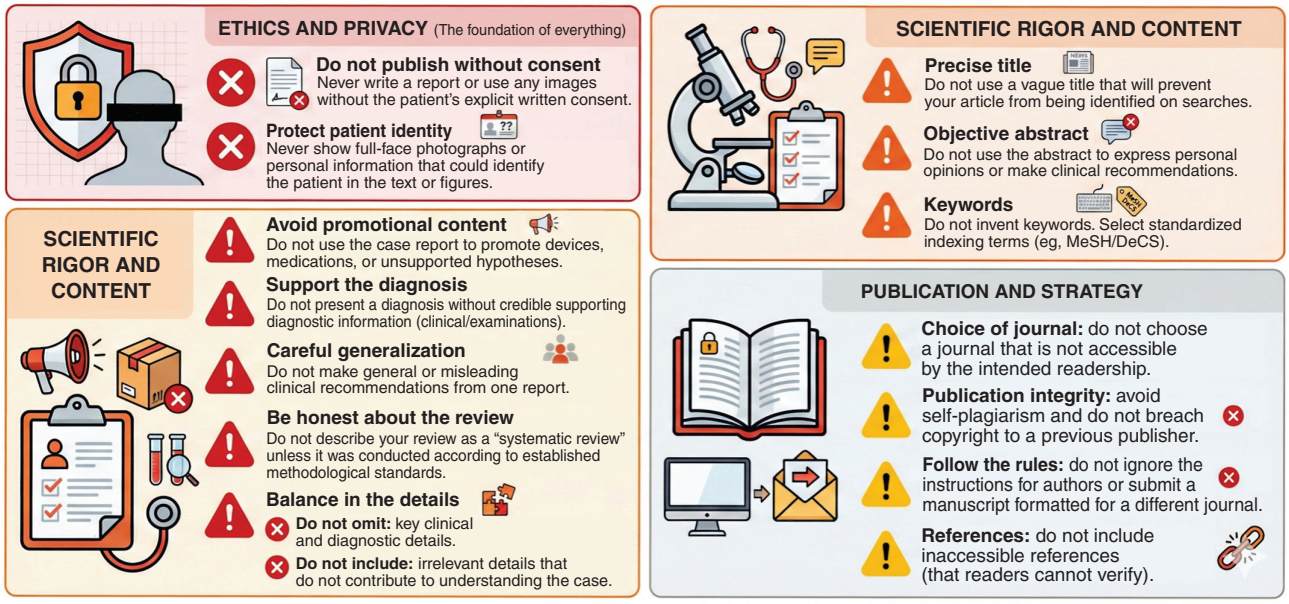

Figure 3
Practical recommendations on what not to do. Created by the author using the NotebookLM infographic generation tool, based on information from Parums DV[4]

communicated with the necessary rigor, transparency, and completeness. By recognizing both their strengths and their inherent limitations, the medical community can continue to use case reports effectively to advance knowledge and improve clinical practice in allergy and immunology.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Immunotherapy in Autism Spectrum Disorder: a critical view from Clinical Immunology experts

Imunoterapia no Transtorno do Espectro Autista: uma visão crítica de especialistas em Imunologia Clínica

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ABSTRACT

Research suggests that immune dysfunction may play a central role in the development of autism spectrum disorder (ASD), at least in a subset of individuals. Several treatments have been proposed based on these findings. Our objective was to critically analyze the evidence regarding immune system-based interventions proposed for the treatment of ASD. An artificial intelligence-assisted scoping review was conducted using five different tools, followed by a critical review by experts from the Scientific Department of Inborn Errors of Immunity of the Brazilian Association of Allergy and Immunology, using a human-in-the-loop approach, a strategy that combines innovation with the required academic rigor. Several approaches were reviewed, including intravenous immunoglobulin, low-dose IL-2, cell therapies, and microbiome modulation. Although case reports and open-label trials suggest potential behavioral benefits, the few randomized clinical trials available have yielded mixed and inconclusive results. Most studies identified have significant methodological

RESUMO

Pesquisas têm sugerido que a disfunção imune possa desempenhar um papel central no desenvolvimento, ao menos em um subgrupo de indivíduos com Transtorno do Espectro Autista (TEA). Diversos tratamentos têm sido propostos com base nessas pesquisas. Nosso objetivo foi analisar criticamente as evidências sobre intervenções baseadas no sistema imune propostas para o tratamento do TEA. Foi realizada uma revisão de escopo assistida por inteligência artificial, utilizando cinco ferramentas diferentes, submetida posteriormente à leitura crítica por especialistas do Departamento Científico de Erros Inatos da Imunidade da Associação Brasileira de Alergia e Imunologia (*human-in-the-loop*). Uma estratégia inovadora que conta com o rigor acadêmico necessário. Diversas abordagens foram revisadas, incluindo imunoglobulina intravenosa, IL-2 em baixa dose, terapias celulares e modulação do microbioma. Embora relatos de casos e estudos abertos sugiram benefícios comportamentais, os poucos ensaios clínicos randomizados disponíveis apresentaram resultados

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limitations, including small sample sizes, predominantly pediatric populations, short follow-up periods, lack of specification in diagnostic criteria or stratification of ASD severity, and lack of standardization of clinical outcomes. Immunotherapies for ASD should be considered experimental and are not recommended for routine use—their application should be restricted to clinical trials approved by research ethics committees. The future of immune-based interventions for ASD treatment depends on precision medicine and the validation of predictive biomarkers. Currently, behavioral and educational interventions remain the gold standard of care.

Keywords: Case reports, guideline, methods, allergy and immunology, immunologic deficiency syndromes.

mistos e inconclusivos. A grande maioria das publicações identificadas apresenta limitações metodológicas importantes, como amostras pequenas, prioritariamente de população pediátrica, acompanhamento de curto prazo, sem especificação de critérios diagnósticos e de estratificação da gravidade do TEA, e falta de padronização de desfechos clínicos. As imunoterapias para TEA são consideradas experimentais e não recomendadas para uso rotineiro, devendo limitar-se a ensaios clínicos aprovados por comitês de ética em pesquisa. O futuro do tratamento do TEA, baseado em intervenções que envolvem o sistema imune, depende da medicina de precisão e da validação de biomarcadores preditivos. Atualmente, as intervenções comportamentais e educacionais permanecem como o padrão-ouro de cuidado.

Descritores: Relatos de casos, guia, metodologia como assunto, alergia e imunologia, síndromes de imunodeficiência.

Introduction

The etiology of autism spectrum disorder (ASD) is complex and involves an interaction between genetic predisposition and environmental factors. Research has suggested that immune dysfunction may play a key role in this interaction during both prenatal and postnatal development, at least in a subgroup of individuals with ASD.

The intrauterine immune environment could have a profound influence on fetal neurodevelopment to increase the risk of ASD. Studies on prenatal immune abnormalities have identified the mechanisms listed below as possibly implicated:

– *Maternal immune activation (MIA).* The MIA model posits that maternal infections during pregnancy (e.g., rubella, influenza) could increase the risk of ASD in the fetus. The central mechanism is not the pathogen itself, but rather the maternal inflammatory response. Animal studies have shown that immune activation by agents such as poly(I:C) can induce autism-like phenotypes in offspring, including social deficits and repetitive behaviors[1,2];
– *Role of maternal cytokines.* Pro-inflammatory cytokines, especially interleukin (IL)-6 and IL-17a, are key mediators in the MIA model. Elevated maternal levels of these cytokines can cross the placental barrier and alter processes critical to fetal brain development, such as neuronal proliferation, migration, and synaptic pruning[1,3];
– *Maternal autoantibodies specific for fetal brain proteins.* A distinct subphenotype of ASD, described as "maternal autoantibody-related autism" (MAR-ASD), has been identified in 20–23% of cases. Mothers of children with MAR-ASD have circulating IgG autoantibodies that react to a specific set of proteins crucial for fetal brain development (LDH, STIP1, CRMP1, etc.). Passive exposure to these autoantibodies during pregnancy has been shown to cause cerebral and behavioral changes in animal models.[1]

After birth, some individuals with ASD may exhibit a profile of immune dysregulation, both systemic and central. The main changes proposed to take place in the postnatal period are described below:

– *Chronic pro-inflammatory state.* There is evidence of a low-grade chronic inflammatory state, with elevated peripheral and central levels of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and IFN-γ, and of chemokines such as MCP-1, as well as reduced levels of the anti-inflammatory cytokine TGF-β[4-6];
– *T-cell imbalance.* Another finding is an imbalance among CD4+ T-lymphocyte subpopulations. A decrease in the proportion or function of regulatory T cells (Tregs), which are crucial for suppressing excessive immune responses, has been observed, alongside a relative increase in pro-inflammatory effector T cells, such as Th1 and Th17 cells[7,8];
– *Dysfunction of innate immune cells.* In the central nervous system, microglia (the brain's resident

immune cells) are frequently found in an active state in postmortem brain tissue obtained from individuals with ASD. Peripherally, natural killer (NK) cells may exhibit elevated baseline cytolytic activity but a blunted response to stimulation, indicating a state of functional exhaustion[1];

– *Gut–brain axis.* Gut microbiome dysbiosis is common in individuals with ASD and is frequently associated with gastrointestinal symptoms. Such changes in the microbiota could lead to increased intestinal permeability, allowing microbial metabolites and inflammatory molecules such as lipopolysaccharide (LPS) to enter the systemic circulation, promoting low-grade inflammation and affecting brain function.[3,9]

Several treatments have been proposed based on these and many other studies on immune-system changes in individuals diagnosed with ASD.

Within this context, our objective is to briefly present the main immune-based therapeutic interventions (immunotherapies) proposed for the treatment of ASD, as well as the currently available scientific evidence, followed by a critical review by members of the Scientific Department on Inborn Errors of Immunity of the Brazilian Association of Allergy and Immunology (ASBAI).

Methods

This text was conceived as a critical review of the literature, conducted by a specialized ASBAI working group, combining an artificial intelligence (AI)-assisted scoping review design with a human-in-the-loop approach. Briefly, AI tools were used to accelerate and support the search, screening, extraction, and synthesis steps of the review while still relying on human critical judgment as a core element, a methodological strategy that leverages innovation while preserving the necessary scientific rigor.

The search strategy, conducted in October 2025 using the term "immunotherapy for autism spectrum disorder," adopted a multimodal, AI-assisted approach. An ecosystem of AI tools geared toward academic research (AnswerThis, Consensus, OpenEvidence, SciSpace, and Undermind) was employed, enabling a comprehensive semantic scan of the PubMed and Semantic Scholar databases, as well as preprint repositories.

The five AI tools used to conduct this review played complementary roles in discovery and semantic analysis: Undermind and AnswerThis were used for deep research and to identify relevant articles that might escape conventional indexing; Consensus and OpenEvidence were employed to assess the current scientific consensus and extract evidence-based answers, with a focus on reducing hallucinations; and SciSpace was used for structured data extraction and comparative analysis of the identified publications.

After the publication retrieval phase, a triangulation of results was performed, i.e., the references identified by one tool were cross-checked with those identified by the other tools.

Studies were included if they involved individuals of any age diagnosed with ASD; proposed immunological or immunomodulatory interventions; were conducted in any clinical or research setting; and were published within the last 10 years. Original articles (clinical trials, observational studies, case series, or case reports), systematic reviews, scoping reviews, and guidelines/consensus documents addressing immunotherapy for ASD were considered eligible. We excluded editorials, letters not reporting primary data, conference abstracts for which no full text was available, opinions not based on data, and studies focusing on other forms of ASD treatment.

Next, the working group conducted a comprehensive critical review of the selected articles, following the established tenets of evidence-based medicine. Therefore, the results presented herein reflect the searches conducted using AI tools and the experts' critical interpretation of the identified articles pertaining to the main proposed treatment modalities.

Results

Immunomodulatory approaches: evidence and mechanisms

The possibility of an immune basis for ASD has led to the investigation of various therapies aimed at modulating or suppressing immune dysregulation.

Intravenous immunoglobulin (IVIG)

IVIG is a human plasma-derived product that contains a wide range of antibodies and has complex immunoregulatory effects, including neutralization of autoantibodies, modulation of cytokine and immune-cell function, and inhibition of complement activation. The clinical evidence for IVIG in ASD is described below.

A case series by Connery et al. (2018) evaluated 82 children with ASD for autoimmune encephalopathy and treated 31 with IVIG. Most parents (90%) reported some improvement, with 71% observing improvements in two or more symptoms.[10]

Statistically significant improvements were found on the Aberrant Behavior Checklist (ABC) and Social Responsiveness Scale (SRS). Treatment response was significantly associated with specific biomarkers from the Cunningham panel in cerebrospinal fluid (CSF), such as anti-dopamine D2L receptor and anti-tubulin antibodies. However, smaller randomized placebo-controlled studies have reported mixed results or failed to demonstrate clear benefits, highlighting the importance of patient selection.[11]

Regarding safety, adverse effects were common (62% in the Connery study), but generally mild and transient, such as headache, vomiting, and fever during infusion.

Low-dose interleukin-2 (Ld-IL-2) therapy

Ld-IL-2 is an emerging therapy that aims to correct immune imbalances through selective expansion of the Treg cell population, which is essential for maintaining immune tolerance.

The sole clinical evidence found comes from a case report published by Chen et al. (2025), who administered Ld-IL-2 to four autistic children with immune dysfunction. Improvements were observed in Childhood Autism Rating Scale (CARS), ABC, Autism Treatment Evaluation Checklist (ATEC), and Krug's Autism Behavior Scale (CABS) scores. The behavioral improvements were associated with immune modulation; three of the four patients showed an increase in the proportion of Treg cells and a reduction in type 1 cytotoxic T cells (Tc1).[7]

Preclinical evidence was presented in a study by Li et al. (2025) using BTBR mice (an animal model of autism), which demonstrated that treatment with Ld-IL-2 significantly improved core symptoms, including social and repetitive behaviors. The mechanism was directly associated with an increase in peripheral and central Treg cells, restoration of the Th17/Treg and Tfh/Treg balance, and a decrease in neuroinflammation (reduction of pro-inflammatory cytokines and stabilization of M1/M2 microglial polarization). Experimental depletion of Treg cells abolished the therapeutic effects of Ld-IL-2, confirming their central role.[8]

Regarding safety, this therapy has been considered safe and well-tolerated in the available studies.

Cell therapies (stem cells)

Cell therapies, including those based on autologous and allogeneic umbilical cord blood, mesenchymal stem cells (MSCs), and bone marrow mononuclear cells (BMMNCs), are being investigated for their immunomodulatory and neuroprotective properties. These cells are believed to act by secreting anti-inflammatory (IL-10, TGF-β) and neurotrophic factors (BDNF, GDNF), thereby modulating the immune response and promoting neural repair.

Clinical evidence obtained from meta-analyses of studies—most of which were open-label—has shown improvements on scales such as the ABC and CARS. However, the high heterogeneity among the included studies constitutes a major limitation.[12-14]

A phase 2 RCT found that BMMNCs combined with educational intervention resulted in a greater reduction in ASD severity and improved adaptive skills compared to education alone, although the lack of blinding limits confidence in the results.[15]

In contrast, a phase 2 trial using autologous umbilical cord blood conducted at Duke University (NCT01638819), one of the most rigorous studies to date, did not demonstrate any significant benefit in the primary outcome in the full cohort.[16]

Clinical response appears to correlate with changes in biomarkers, such as cytokine profiles in CSF.

The short-term safety profile of cell therapies has generally been acceptable, with the most common adverse events including fever, hyperactivity, and headache. More serious risks, although rare, include seizures (especially in patients with pre-existing risk) and alloimmunization (development of antibodies against allogeneic cells). Long-term safety is unknown and requires ongoing monitoring.

Microbiome modulation

Interventions targeting the gut microbiome, such as fecal microbiota transplantation (FMT) and the use of probiotics, aim to correct dysbiosis and modulate the gut–brain axis. Restoring a healthy microbiota may reduce bowel inflammation, improve intestinal barrier integrity, increase the production of beneficial metabolites such as short-chain fatty acids (SCFAs), and, ultimately, possibly modulate neuroinflammation.

Clinical evidence regarding FMT is based on meta-analyses of open-label studies reporting significant improvements in ABC and CARS scores, as well as in gastrointestinal symptoms.[17-20] RCTs are currently underway (NCT04706611, NCT04014413) to confirm these findings.

As for probiotics, RCTs have demonstrated significant improvements in social functioning in children with ASD given *Lactobacillus reuteri*. The mechanism is believed to involve modulation of the vagus nerve pathway and the release of oxytocin. The results of studies with other probiotics, prebiotics, and synbiotics have been mixed and inconclusive.[3]

Probiotics are considered very safe. FMT, on the other hand, carries potential risks of pathogen transmission and long-term metabolic effects; rigorous and regulated donor screening is required.

Other anti-inflammatory and immunomodulatory agents

Table 1 summarizes other therapies with anti-inflammatory mechanisms that have been investigated in ASD.

Other proposed strategies that still lacking data on long-term efficacy, effectiveness, and safety from large, high-quality clinical studies include anti-inflammatory diets, folinic acid, JAK inhibitors, resveratrol, palmitoylethanolamide, agmatine, mTOR inhibitors, vitamin D, modulation of the tryptophan pathway, and chimeric antigen receptor (CAR)-T cell therapy.

Discussion

A critical review of the evidence

Despite an optimistic outlook, the field of immunotherapy for ASD faces significant challenges that must be addressed for these strategies to translate into effective and safe clinical treatments. Criticism of studies on immunotherapy for ASD is largely based on methodological limitations, the main points of which are outlined below:

– *Lack of robust studies.* The literature is still in its early stages and is dominated by case reports, case series, and open-label (non-blinded) studies. There is a dearth of randomized, double-blind, placebo-controlled clinical trials. Currently, there are no RCT protocols registered in databases such as ClinicalTrials.gov designed to evaluate the use of Ld-IL-2 or IVIG specifically in patients with ASD.

– *Small sample sizes.* Most studies, including RCTs, have been conducted with small samples (many with fewer than 100 participants), which significantly limits statistical power to confirm findings or generalize results.

– *Inconsistent results and bias.* Although open-label studies often report substantial behavioral gains, when controls and blinding are introduced, these effects are generally smaller, inconsistent, or absent. Additionally, conflicting results between different studies on the same therapy are common.

– *Short follow-up periods.* The duration of follow-up is often brief, with a median of less than 6 months across studies, which precludes assessment of long-term efficacy and safety. The durability of benefits and potential long-term adverse effects remain largely unknown.

– *Lack of diagnostic criteria and severity stratification for ASD. T*he highly heterogeneous nature of ASD—with its multifactorial etiology, wide range of clinical manifestations, and varying levels of severity—poses the greatest challenge, as it hinders comparisons between studies, identification of specific immune-system targets, and prediction of treatment response.

– *Lack of standardization of interventions.* There is substantial variability in treatment protocols (cell types, doses, routes of administration) and in outcome assessment tools, which hinders comparisons between studies and makes robust meta-analyses impossible.

– *Inconsistent outcome measures.* There is heterogeneity in outcome measures (variable use of scales such as ABC, CARS, CGI, etc.) and disparity in psychometric instruments, which makes it difficult to compare findings across different studies.

– *Lack of stratification by biomarkers.* Most clinical trials have included heterogeneous populations without prior immunophenotyping. The absence of validated biomarkers for diagnosis, stratification, and prediction of treatment response is a major obstacle.

– *Focus on limited subgroups.* Results may be applicable only to a small subset of individuals with ASD.

– *Limited age range.* Almost all trials have been conducted in children and adolescents, and their findings may not be applicable to adults with ASD.

Table 1
Selected anti-inflammatory strategies investigated in autism spectrum disorder (ASD)

Therapy	Main mechanism	Summary of the evidence
Corticosteroids	Broad-spectrum immunosuppression	Case reports and open-label studies suggest benefits in language and behavior, especially in children under 5 years of age with a history of regression and elevated inflammatory markers
Celecoxib	COX-2 inhibition	A double-blind RCT (n=40) showed significant improvement in irritability, social withdrawal, and stereotyped behavior (when used as an adjunct to risperidone)
Thioperamide (and others)	Histamine H3 receptor antagonism	Studies of H3 receptor antagonists are linked to broader research on microglia and neuroinflammatory diseases. There have been no RCTs in ASD
N-Acetylcysteine (NAC)	A synthetic N-acetyl derivative of the endogenous amino acid L-cysteine. An antioxidant and anti-inflammatory agent, it can modulate signaling pathways such as PI-3K/Akt/mTOR	A few RCTs with small numbers of patients have investigated the efficacy of (complementary) treatment with NAC in improving core and associated symptoms in individuals with ASD
Omega-3 Fatty Acids	Immunomodulatory and anti-inflammatory	Systematic reviews and meta-analyses of RCTs have yielded mixed or inconclusive findings regarding their efficacy
Pioglitazone	Antidiabetic medication of the thiazolidinedione class	A double-blind RCT (n=44) showed significant improvement in hyperactivity, irritability, and lethargy (when used as an adjunct to risperidone)
Luteolin	A natural flavonoid with antioxidant and anti-inflammatory properties	An open-label study (n=50) showed benefits in adaptive functioning (VABS) and overall behavior (ABC)
Suramin	Purinergic receptor antagonism, mitochondrial restoration	A proof-of-concept RCT showed improvement in Clinical Global Impression (CGI-I) score at a dose of 10 mg/kg
Sulforaphane	Activation of the Nrf2 antioxidant pathway, anti-inflammatory	An RCT showed improvement on the ABC scale as reported by caregivers and changes in biomarkers. Mixed results for the primary outcome
Minocycline	Tetracycline antibiotic with anti-inflammatory and neuroprotective effects (inhibits microglial activation)	RCTs have yielded mixed results, with no consistent benefits for core ASD symptoms
Rituximab	Monoclonal antibody that depletes CD20+ B cells	Used successfully in a very specific subgroup of ASD associated with hereditary folate malabsorption and antineuronal autoantibodies
Tocilizumab	Anti-IL-6R monoclonal antibody	Has been studied in other neuropsychiatric conditions, such as schizophrenia and depression. There are no controlled clinical trials to indicate its use in ASD

RCT: Randomized Controlled Trial; ASD: Autism Spectrum Disorder; PPARγ: Peroxisome Proliferator Activated Receptor Gamma Agonist.
Sources: references 2, 3, 4, 5, 9, 21, 22, and 23.

– *Presence of confounding factors.* The use of psychiatric medications and/or concomitant behavioral treatments, as permitted in several studies, may have influenced results, making it difficult to attribute any benefit to immunotherapy.
– *Efficacy for core symptoms not always identified.* Many interventions primarily target symptoms associated with ASD (such as irritability, hyperactivity, or lethargy), demonstrating limited efficacy for the core manifestations of the autism spectrum (such as deficits in social communication or repetitive behaviors).
– *Risk of adverse events.* Immunotherapies, especially more invasive ones, carry risks and frequent adverse effects that must be taken into account. For example, IVIG is very commonly associated with adverse effects, although these are generally limited to the infusion period. Some therapies, such as the intrathecal administration of BMMNCs, involve procedural risks and the potential for neurological reactions (such as seizures in subgroups with pre-existing risk), and the use of allogeneic (donor) cell products can lead to alloimmunization.
– *Preclinical-to-clinical translation failure.* Many treatments that showed promise in preclinical animal models failed to translate these benefits to human clinical trials, highlighting the need for more predictive animal models and a better understanding of the mechanisms which underpin ASD.

Implications for clinical practice

Based on the current evidence, we propose the following guidelines.

– Immunotherapies for ASD should be considered experimental. Therefore, they should not be recommended for routine use and should be conducted only within the context of clinical trials subject to ethical approval.
– A comprehensive evaluation of immunity should be considered for patients with ASD who present with: actual developmental regression (loss of previously demonstrated language or social skills), not merely a delay in diagnosis; severe or recurrent infections; a personal or family history of autoimmune comorbidities; or seizures refractory to standard treatment.
– It is essential that families receive balanced information about the experimental nature of such therapies, their known and unknown risks, their costs, and the lack of coverage by the Unified Health System and private health insurance. Treating physicians should discourage the pursuit of unregulated treatments that promise a cure.
– Evidence-based behavioral and educational interventions (e.g., ABA, speech-language therapy, occupational therapy) should remain the cornerstone of treatment for all individuals with ASD.

Precision medicine perspectives and future research

The future of ASD treatment lies in precision medicine, moving away from a one-size-fits-all approach in favor of targeted therapies designed to act on specific pathophysiological mechanisms.

Research priorities in this field are listed below.

– Biomarker validation: identify and validate biomarkers capable of predicting response to specific treatments (e.g., cytokine profiles, autoantibodies, microbiome signatures).
– Stratified RCTs: conduct randomized, double-blind, placebo-controlled clinical trials, preferably based on biomarkers, in clinically well-defined subgroups of ASD.
– Long-term registries: establish mandatory registries for all participants of immunotherapy trials to monitor the safety and durability of effects over 1 to 5 years.
– Harmonization of endpoints: Develop and adopt a set of core endpoints for clinical trials in ASD, including objective measures, to enable data comparison and synthesis.

The limitations of the methodology adopted for this review must be noted. The use of AI in this context is recent, with models and approaches changing on a near-daily basis. The algorithms of AI tools are subject to biases, while searches conducted with their aid are subject to reproducibility issues: the tools themselves may change over time, and the same search, performed using the same tool at different times, may yield different results. Additionally, neither the literature search nor our analysis of the material was systematic.

Conclusion

Several immunotherapy strategies have been attempted in ASD, with improvements reported in ASD-associated behavioral symptoms (such as irritability and hyperactivity) and, in some cases, in core symptoms (such as social interaction and communication). However, effects have been markedly heterogeneous, with more robust results in open-label studies than in randomized placebo-controlled trials. Emerging evidence suggests that treatment response is associated with specific immune biomarkers, such as autoantibodies and cytokine profiles in CSF, indicating that patient stratification is crucial for evaluating any such therapies. Furthermore, although most of the treatments investigated have acceptable short-term safety profiles, data on the duration of their effects and on long-term safety remain limited.

The field is still in its infancy. The low quality of studies and the heterogeneity of results highlight the critical need to move away from empirical approaches and advance toward an era of precision medicine. Future success will depend on the ability to stratify patients based on biomarkers, allowing the appropriate therapy to be administered to the right patient.

Until rigorous, large-scale, biomarker-stratified clinical trials confirm long-term efficacy and safety, immunotherapies for ASD should remain restricted to the realm of research. In other words, immunotherapies for ASD should currently be considered experimental treatments.

Behavioral and educational interventions remain—and should be emphasized as—the gold standard of care and the cornerstone of ASD management.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Adverse events associated with dupilumab in the treatment of chronic type 2 inflammatory diseases

Eventos adversos associados ao dupilumabe no tratamento de doenças inflamatórias crônicas tipo 2

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ABSTRACT

Biologic agents have revolutionized the management of chronic type 2 (T2) inflammatory diseases. As of September 2025, omalizumab, mepolizumab, benralizumab, dupilumab, tezepelumab, and lebrikizumab had been approved in Brazil for the treatment of one or more allergic conditions associated with T2 inflammation. Although these therapies are generally very safe, adverse events may occur. The members of the Scientific Department of Biologic Agents of the Brazilian Association of Allergy and Immunology (ASBAI) for the 2025–2026 term proposed compiling data from the scientific literature regarding these adverse events and, over the coming issues of this journal, will publish articles on this topic. In this first review, we present and discuss the potential adverse events associated with dupilumab therapy.

Keywords: Dupilumab, monoclonal antibodies, biologic agents, adverse drug reactions, safety, type 2 inflammation

RESUMO

Os imunobiológicos revolucionaram o manejo das doenças inflamatórias crônicas do tipo 2 (T2). Até setembro de 2025, estão aprovados no Brasil o uso do omalizumabe, mepolizumabe, benralizumabe, dupilumabe, tezepelumabe e lebrikizumabe para tratamento de uma ou mais dessas condições alérgicas que envolvem a inflamação T2. Embora muito seguros, eventos adversos associados ao uso dessas terapias podem ocorrer. Os membros do Departamento Científico de Imunobiológicos da Associação Brasileira de Alergia e Imunologia (ASBAI) no biênio 2025-2026 consideraram compilar dados da literatura científica acerca desses eventos adversos, e ao longo dos próximos números escreverão artigos sobre esse tópico. Nessa primeira revisão, apresentamos e discutimos os possíveis eventos adversos associados ao uso do dupilumabe.

Descritores: Anticorpos monoclonais, produtos biológicos, efeitos colaterais e reações adversas a medicamentos, segurança.

Biologics targeting type 2 inflammation and their safety profile

Immunobiologic agents, or biologics, constitute a diverse group of medications that include growth factors, immunomodulators, monoclonal antibodies (mAbs), and vaccines. In general, they are high-molecular-weight molecules, predominantly proteins, synthesized by living organisms, which interact with the immune system by binding to specific targets.[1,2]

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The World Health Organization (WHO) defines an adverse drug reaction (ADR) as any "response to a drug that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease." ADRs can be classified as predictable (type A), i.e., those related to the direct effects of the drug, or unpredictable or idiosyncratic (type B), which depend on individual susceptibility and are not directly related to the effects of the drug.[3]

At the time of writing, there are six biologics licensed in Brazil for use in type 2 (T2) chronic inflammatory diseases: dupilumab, omalizumab, benralizumab, mepolizumab, tezepelumab, and lebrikizumab. Although all of these therapies are considered very safe and effective, their use has been associated with adverse events, including both type A and type B reactions. The Scientific Department on Biologic Agents of the Brazilian Association of Allergy and Immunology (ASBAI) has been conducting an extensive review of the literature on adverse events possibly associated with biologics used to treat T2 diseases and will publish a series of narrative reviews on the topic.

In this first manuscript, we present and discuss the potential adverse events of dupilumab. To this end, we conducted literature searches in the MEDLINE (via PubMed), SciELO, and LILACS databases, covering articles published in English and Portuguese, using the terms "dupilumab" (or "dupilumabe"), "type 2 inflammation" (or "inflamação do tipo 2 (ou T2)"), "adverse effects" (or "efeitos adversos"), and "adverse events" (or "eventos adversos"). We selected original articles, clinical trials, systematic reviews, narrative reviews, and case series. Those considered most relevant by the authors were included and are presented in sections 3 through 6 of this manuscript.

Adverse events related to other biologics that target T2 inflammation will be covered in other articles yet to be published in the Archives of Asthma, Allergy, and Immunology.

Dupilumab

First approved in 2017 by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD), over the years its use has been expanded to include patients with AD older than 6 months as well as to other indications, such as asthma (in patients > 6 years of age), chronic rhinosinusitis with nasal polyps (CRSwNP, in patients ≥ 18 years of age), eosinophilic esophagitis (EoE, in patients ≥ 1 year of age), chronic spontaneous urticaria (CSU, in patients ≥ 12 years of age), prurigo nodularis, chronic obstructive pulmonary disease (COPD), and bullous pemphigoid. Dupilumab has reached the milestone of 1 million patients in use worldwide, across its various indications and age groups.

Dupilumab is a human monoclonal antibody that acts by blocking the interleukin (IL)-4 receptor alpha subunit (IL-4Rα),4 a shared component of the IL-4 and IL-13 signaling pathways. These cytokines are key mediators of T2 inflammation, which drives the pathogenesis of various inflammatory diseases, both allergic and non-allergic—i.e., mediated or not mediated by immunoglobulin E (IgE). The main adverse events reported in clinical trials were injection-site reactions, conjunctivitis, and rhinopharyngitis.[4-8]

As dupilumab has become more widely used in clinical practice, new evidence has emerged regarding potential adverse events associated with its use. This article aims to compile the most recent data on the subject.

Major adverse events associated with dupilumab

Injection-site reactions

Injection-site reactions are the most common adverse events.[1] Generally mild and transient, they include pain, redness, edema, and pruritus. The frequency of these reactions tends to decrease with continued treatment. Treatment is typically symptomatic, involving cold compresses or topical or oral analgesics.

Ocular manifestations

Conjunctivitis is the most commonly reported ocular adverse effect in patients with AD receiving dupilumab, ranging from mild to severe.[2] It may be associated with pruritus, tearing, and, in rare cases, inflammation of the cornea (keratitis) and of the eyelids (blepharitis).[2] The mechanisms underlying these reactions are not fully understood, but hypotheses suggest that IL-4 and IL-13 blockade may alter ocular surface homeostasis, affecting mucus production and local immunity. A recent review highlighted that the blockade of IL-13 by dupilumab drastically reduces the density of conjunctival goblet cells and

mucin (MUC5AC) production, leading to tear film instability, ocular surface dryness, and epithelial barrier dysfunction.[9]

Several case series of patients with AD receiving dupilumab have described ocular involvement at frequencies ranging from 7.4% to 15.8%.[10,11] A recent publication based on FDA Adverse Event Reporting System (FAERS) data described a reporting odds ratio (ROR) of 18.9 and a proportional reporting ratio (PRR) of 18.8.[12]

The management of dupilumab-associated conjunctivitis generally involves the use of lubricating eye drops, antihistamines, and, in more severe cases, topical corticosteroids or topical calcineurin inhibitors. Referral to an ophthalmologist is recommended in the most severe cases.[13]

Eosinophilia

Dupilumab may cause a transient increase in eosinophil levels, which often stabilize or return to baseline with continued treatment. Eosinophilia, defined as an increase in the number of eosinophils in the peripheral blood to > 500 cells/mm^3, is a common adverse effect but is generally not clinically significant.[1] Clinically relevant eosinophilia (hypereosinophilia) is rare, but may be associated with conditions such as eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg–Strauss syndrome.[1,5]

In the pivotal study published on the efficacy of dupilumab in asthma, an increase in absolute eosinophil count was observed in 4.1% of participants in the treatment group vs 0.6% in the placebo group.[14] Recently, in a multicenter real-world study evaluating patients with severe asthma who received dupilumab for 5 years, the mean blood eosinophil count increased significantly from 332/mm^3 to 1309/mm^3 during the first year of treatment and then decreased progressively, although it remained above baseline levels over the course of 5 years.[15]

More recent studies show that some degree of eosinophilia may occur in up to 55% of patients with respiratory disease (asthma or CRSwNP), with up to 14.9% experiencing hypereosinophilia.[16,17] Therefore, monitoring of eosinophil levels is recommended, especially in patients with a history of pre-treatment eosinophilia or in those who develop systemic symptoms during treatment.

Paradoxical cutaneous manifestations

Some patients, especially those with AD, may develop paradoxical erythema of the face and neck, referred to in the literature as “dupilumab facial redness” (DFR). This reaction, although rare, can be persistent and unrelated to sun exposure. Other less common cutaneous manifestations include exacerbations of psoriasis, seborrheic dermatitis, or the onset of pemphigus. The pathogenesis of these reactions is still under investigation, but may involve an increase in the Th1/Th17-mediated immune response due to inhibition of T2 inflammatory pathways.

A systematic review investigated the occurrence of face and/or neck dermatitis in patients with AD treated with dupilumab, compiling data from 16 studies. Most of the studies included were case reports and case series. Among these was a registry of 1000 patients in which the incidence of face and/or neck dermatitis was 4.2%. Across all evaluated studies, 101 patients were identified who developed such dermatitis. A total of 52 (52%) had rosacea involving the face or neck at baseline, and 45 (45%) reported cutaneous symptoms different from their preexisting rosacea, possibly suggesting a different etiology. Suggested etiologies included rosacea, allergic contact dermatitis, and facial and neck dermatitis. The most commonly used treatments included topical corticosteroids, topical calcineurin inhibitors, and antifungal agents.[1,18]

Suggested mechanisms for the development of this dermatitis include T helper 1 (Th1)-mediated hypersensitivity to commensal microorganisms, such as *Malassezia furfur* or *Demodex*, which are concentrated primarily on the head region, due to suppression of T helper 2 (Th2)-mediated inflammation, resulting in rosacea- or seborrheic dermatitis-like reactions, respectively.

Some patients with DFR respond to antifungal agents.[19] Treatment options include topical agents, such as calcineurin inhibitors, corticosteroids, ivermectin, antibiotics (metronidazole, mupirocin), and antifungals (oxiconazole, terbinafine, ketoconazole); and oral agents, including antibiotics (doxycycline, azithromycin), corticosteroids, and antifungals (fluconazole, itraconazole).[18]

Psoriasiform lesions have been reported in 3 to 4.25% of patients. These reactions resemble psoriasis both clinically and histologically and tend to be temporally related to the initiation of dupilumab therapy. It is believed that these lesions result from IL-4 inhibition leading to Th1- and IL-17/IL-23-

mediated inflammation and, ultimately, to psoriasiform plaques.[19] An interval of 4 to 6 months has been reported between the start of dupilumab therapy and the onset of these lesions, depending on the patient's age and whether there is a history of psoriasis. A personal or family history of psoriasis appears to be a risk factor.[20,21]

Treatment depends on severity. Topical therapies commonly used in psoriasis (topical corticosteroids, vitamin D analogs, and calcineurin inhibitors) may suffice for milder disease, but more severe cases may require escalation of therapy (narrowband UVB [NBUVB] therapy, ciclosporin, methotrexate, or topical delgocitinib) and discontinuation of dupilumab; in such instances, tralokinumab (a selective IL-13 inhibitor), ustekinumab (an IL-12/23 inhibitor), upadacitinib (a JAK-1 inhibitor), and baricitinib (a JAK-1/2 inhibitor) have all been successfully used to treat the psoriasiform eruption.[19]

Other adverse events

Infections

The risk of infections is generally low, with upper respiratory tract infections and oral herpes being most common. Dupilumab, unlike biologics that suppress Th1 or Th17 populations, does not appear to increase the risk of severe opportunistic infections. Pooled data from clinical trials suggest that, although dupilumab is associated with slightly higher rates of herpesvirus infections, rates of clinically significant eczema herpeticum are significantly lower with dupilumab than with placebo.[22]

Pivotal clinical trials documented a lower incidence of non-herpetic skin infections in adults and children treated with dupilumab compared to placebo groups. In addition, a significant reduction in *Staphylococcus aureus* skin colonization has been reported in adult patients treated with dupilumab as early as 2 weeks into treatment.[23] This body of data corroborates the safety of dupilumab regarding the risk of serious infections.

Arthritis and joint pain

Some case reports and real-world studies have described the onset of joint pain or inflammatory arthritis in patients receiving dupilumab. The causal relationship is still under investigation. Symptoms generally appear within the first four months of treatment.[19] Although most patients develop generalized symptoms, oligoarticular and focal presentations involving the hands, ankles, and knees have been reported. Ultrasonography may reveal enthesitis, most commonly in the lateral epicondyles, Achilles tendons, or patellar tendons.[24,25] The frequency of this event is not well defined, nor is it known with certainty whether it is more strongly associated with the use of dupilumab in any particular indication. A study of patients with chronic rhinosinusitis reported development of arthralgia in 14% of patients treated with dupilumab.[26] Another survey, in patients with AD, showed that only 3.8% sought medical care for joint pain.[27] A recent study attempted to compare the risk of this adverse event across indications for dupilumab and found a higher prevalence in patients with chronic rhinosinusitis (11.2%) compared with asthma (8.7%) and AD (4.7%).[28]

In mild to moderate cases, treatment with nonsteroidal anti-inflammatory drugs is indicated. In moderate cases, there are also reports in the literature of a reduction in the frequency of dupilumab administration. In severe cases, discontinuation of dupilumab, a short course of oral corticosteroids, and referral to a rheumatologist are recommended.[29]

Hypersensitivity reactions

Anaphylactic reactions and angioedema are rare but serious events that require immediate discontinuation of dupilumab.

Adverse events under investigation

An association between dupilumab and T-cell lymphoma, particularly cutaneous T-cell lymphoma (CTCL)[2,4] in patients with AD, has been the subject of study and debate within the medical community. It is crucial to understand that most of the available data on this subject come from case reports and retrospective observational studies, rather than from controlled, prospective clinical trials, which would be the gold standard for establishing a causal relationship. Therefore, although an association has been observed, direct causality has not yet been definitively proven.

Severe AD is per se already associated with a slight increase in the risk of developing lymphoma, particularly CTCL. This is because chronic skin inflammation can lead to changes in T cells. Often, early-stage CTCL can be mistaken for AD, and the true diagnosis is not made until years later.

Cases of CTCL diagnosed after initiation of dupilumab treatment have been reported in patients previously classified as having AD. In these cases, the hypothesis has been raised that dupilumab may have contributed to the clinical detection of a preexisting cutaneous lymphoma, which may have been masked until then by clinical manifestations mimicking AD. Another hypothesis is that dupilumab may have accelerated the progression of a neoplasm that was already present but had not yet been clinically recognized.[2,4]

The risk or odds of reporting CTCL/mycosis fungoides (MF) in individuals who received dupilumab (181,575 unique reports of dupilumab-related adverse events) was analyzed comparatively to that of other medications in the FAERS database, in accordance with the standard U.S. pharmacovigilance protocol. When medications were grouped by therapeutic class, dupilumab, ustekinumab, IL-23 inhibitors, and IL-17 inhibitors showed the strongest signals for CTCL based on PRR and ROR.[30] An unexpectedly robust signal for disproportionality of CTCL was present with dupilumab compared to other biologics and small molecules commonly used for inflammatory skin diseases. This pharmacovigilance and transcriptomics study suggests that dupilumab may be associated with unmasking or progression of CTCL. If an adult patient's AD worsens while on dupilumab, this should raise suspicion of CTCL.[30]

Inflammation in AD is driven by the IL-4 and IL-13 signaling pathways, which dupilumab blocks. However, in some subtypes of T-cell lymphoma, these pathways may play a tumor-suppressive role. Blocking these pathways with dupilumab could thus facilitate lymphoma proliferation. In some case reports, patients with suspected AD showed initial improvement with dupilumab followed by a worsening of skin symptoms and emergence of other signs of lymphoma, such as enlarged lymph nodes.

T-cell lymphoma is a rare event; whether there is a real increase in its incidence among dupilumab recipients remains unknown. We found only two studies, based on large multicenter cohort databases, and the prevalence of this outcome ranged from 0.18% to 0.36% of users.[31,32] On the other hand, in a study that included asthmatics treated with or without dupilumab, the drug was associated with a lower all-cause mortality rate, confirming its safety.[32]

Most long-term surveillance studies in large groups of patients treated with dupilumab in clinical trials and in real-world practice generally found no significant increase in the risk of malignancies, including lymphomas. Thus, given that incident T-cell lymphoma remains a rare event possibly unrelated to use of this drug, clinical and laboratory monitoring is mandatory.

The major adverse events possibly associated with the use of dupilumab, as well as their frequency and management, are summarized in Table 1.

Pregnancy

Dupilumab is in FDA pregnancy category B. A multicenter retrospective cohort study suggested that exposure to dupilumab between the 2nd and 24th gestational weeks might be associated with an increased risk of adverse pregnancy outcomes, including miscarriage or embryonic anomalies, although no statistically significant effects were found. Conversely, Avallone et al. observed that the use of dupilumab during pregnancy was associated with improvement of AD and a very low risk of adverse outcomes.[33] A review published in 2024 on the use of T2 biologics during pregnancy summarized the studies available at that time, including those on dupilumab. Although most studies reported discontinuation of the drug during pregnancy due to a lack of safety data, in case series where patients continued to take it, primarily for skin condition, dupilumab proved safe.[34]

Vaccinations in children

FDA-endorsed guidelines advise against the use of live-attenuated vaccines in dupilumab-treated children, due to limited safety data.[35-37] A recent retrospective study, which included children between 6 months and 10 years of age diagnosed with AD and receiving dupilumab, observed a minimal risk of adverse reactions in those who received live-attenuated vaccines (MMR and varicella), including one serious adverse event, but which was supposedly not attributable to the immunization in question (hospitalization for bronchiolitis).[38] These data are consistent with a recently published guideline from the American College of Allergy, Asthma, and Immunology, which states that vaccines (including attenuated vaccines) may be administered to patients receiving dupilumab through shared decision-making, reinforcing its safety.[39]

Table 1
Adverse events described as possibly associated with dupilumab therapy

Adverse event	Indication associated with increased risk	Frequency (%)	Management
Conjunctivitis	AD	8.4	Artificial tears, topical H1 antagonists, TCS
Eosinophilia	Asthma, CRSwNP	22 to 55	Ranges from watchful waiting to drug discontinuation
Facial redness	AD	4.2	Calcineurin inhibitors, TCS, antiparasitic agents, antibiotics, antifungals
Arthralgia	CRSwNP (?[a])	3.8 to 14	NSAIDs, OCS, drug discontinuation (if required)
Cutaneous lymphoma[b]	AD (?)	0.18 to 0.36	Drug discontinuation; referral to oncologist/ hematologist for appropriate treatment

[a] Limited data available; one study suggested a higher incidence in CRSwNP compared to asthma and AD.
[b] The actual association between dupilumab and new onset of T-cell lymphoma has not yet been established, but most reported cases occurred in individuals with AD.
AD: atopic dermatitis; CRSwNP: chronic rhinosinusitis with nasal polyps; NSAID: nonsteroidal anti-inflammatory drug; OCS: oral corticosteroid; TCS: topical corticosteroid.

Limitations

This review has some limitations which must be considered. First, it is purely narrative, with no comprehensive systematization of search methods or even a quantitative meta-analysis. This may have resulted in the loss of relevant data or overestimation of irrelevant data. Furthermore, since dupilumab is a relatively new medication and its use in clinical practice is growing exponentially, new, significant adverse events that have not yet been recognized in the literature may still emerge. Nevertheless, unpublished data from the manufacturer indicates that, as of 2025, more than one million patients had already been treated with dupilumab, suggesting that most of the actual adverse events that may not have been detected in studies up to phase III have likely already been described to date.

Concluding remarks

Dupilumab is a safe, effective therapy for the treatment of various chronic T2 inflammatory diseases, widely used and with documented efficacy in real-world studies, which has provided significant improvements in quality of life for thousands of patients with severe immune-mediated diseases. Its most common adverse events are injection-site reactions and conjunctivitis; most cases are mild to moderate and do not require discontinuation of therapy.

Although dupilumab-associated hypereosinophilia with clinical manifestations is rare, laboratory monitoring is important during therapy with this biologic. In patients with a baseline blood eosinophil count > 1,500 cells/mm^3 and who have conditions for which other therapeutic options are available, such as asthma and CRSwNP, dupilumab should not be the first-line treatment of choice.

Less frequent adverse events which nonetheless compromise patient quality of life, such as paradoxical skin reactions and enthesitis, must be detected and treated appropriately to allow continued biologic therapy. In severe cases that are refractory to specific treatment, dupilumab should be discontinued.

A possible association between dupilumab and T-cell lymphoma has been described in case reports; however, there is currently no scientific evidence to establish a causal relationship. It is most likely that, in such cases, dupilumab unmasked a preexisting lymphoma that was behaving as an AD mimic. In any case, heightened clinical suspicion is important, and it is essential that a diagnosis of severe AD be carefully established before initiating dupilumab therapy. Periodic clinical and laboratory follow-up of all patients receiving biologic therapy is crucial to monitor safety and allow better management.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Considerations on chronic rhinosinusitis with nasal polyps in pediatrics

Considerações sobre rinossinusite crônica com pólipos nasais em pediatria

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ABSTRACT

Chronic rhinosinusitis with nasal polyps in the pediatric population is a rare but clinically significant inflammatory condition, often associated with substantial impairment in quality of life. Diagnosis is challenging due to symptom overlap with other common childhood conditions, such as adenoid hypertrophy, allergic rhinitis, and recurrent respiratory infections. The presence of nasal polyps should prompt investigation for underlying comorbidities, such as cystic fibrosis, primary ciliary dyskinesia, and inborn errors of immunity. The current classification of chronic rhinosinusitis into phenotypes and endotypes enables a more individualized approach to management. Treatment remains primarily clinical, with intranasal corticosteroids and nasal saline irrigation as the mainstays. Biologic agents such as dupilumab are emerging as therapeutic options for refractory cases in patients aged 12 years and older, although pediatric-specific data remain limited. This article reviews the main differential diagnoses and therapeutic considerations related to chronic rhinosinusitis with nasal polyps in children, emphasizing the importance of a multidisciplinary approach.

Keywords: Biologic agents, nasal polyps, rhinosinusitis, pediatrics.

RESUMO

A rinossinusite crônica com pólipos nasais em pediatria é uma condição inflamatória rara, porém clinicamente relevante, associada a comprometimento significativo da qualidade de vida. Seu diagnóstico é desafiador devido à sobreposição de sintomas com outras doenças comuns na infância, como hipertrofia adenoideana, rinite alérgica e infecções respiratórias recorrentes. A presença de pólipos nasais deve sempre levantar suspeita de comorbidades como fibrose cística, discinesia ciliar primária e imunodeficiências. A classificação atual da rinossinusite crônica baseada em fenótipos e endótipos permite uma abordagem mais individualizada. O tratamento ainda é predominantemente clínico, com uso criterioso de corticosteroides tópicos e lavagem nasal. Imunobiológicos como o dupilumabe emergem como alternativa terapêutica para casos refratários a partir dos 12 anos, embora ainda haja escassez de evidências em pediatria. Esse artigo revisa os principais diagnósticos diferenciais e considerações terapêuticas da rinossinusite crônica com pólipos nasais na população pediátrica, destacando a importância de uma abordagem multidisciplinar.

Descritores: Produtos biológicos, pólipos nasais, rinossinusite, pediatria.

Introduction

Chronic rhinosinusitis (CRS) is described by the Academy of Otolaryngology – Head and Neck Surgery Foundation as a persistent inflammation of the sinonasal mucosa lasting 12 weeks or more.[1] It is generally defined as the presence of two or more sinonasal symptoms during this time, including nasal obstruction, purulent rhinorrhea, coughing, or facial pressure or pain, with nasal endoscopy or computed

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tomography of the paranasal sinuses confirming the suggestive findings.[1]

Knowledge of the disease's true prevalence among children remains limited because of specific difficulties related to performing nasal endoscopy in pediatric patients and concerns about the need for sedation for diagnostic imaging.[2] While widely studied, there are barriers to precise diagnosis of CRS in the pediatric age group, primarily related to the difficulty of differentiating CRS from other conditions, such as pharyngeal tonsil hypertrophy, adenoiditis, and allergic rhinitis.[3]

The prevalence of CRS is around 2.1% to 4% in children, with predilection for children aged 10 to 15 years.[4] According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, the 1996 United States National Health Interview Survey found a CRS rate of 63.9 per 1,000 individuals under the age of 18.[5,6]

Possible predisposing factors include anatomic differences in relation to adults or anatomic variations from normality, adenoid hypertrophy, viral infections, allergic rhinitis, asthma, passive smoking, gastroesophageal reflux disease, immunodeficiencies, cystic fibrosis, and primary ciliary dyskinesia.[7] Regardless of whether these factors are systemic, local, or triggered by environmental conditions, doubts remain about their roles as predisposing or common factors in the pathogenesis of CRS in children.[6]

Pediatric patients with a CRS diagnosis may have significantly impaired quality of life.[8] A study of data from ambulatory care surveys for a 7-year period in the United States found that patients from 0 to 20 years of age made around 5.6 million visits annually because of CRS, primarily concentrated in the age groups from 5 to 10 years and 10 to 15 years.[4] The most common impacts were absence from lessons, and impairment of concentration at school, sleep quality, and physical and emotional health.[9]

A study published by the Massachusetts Eye and Ear Infirmary in 2000 administered the Child Health Questionnaire to children aged 4-18 years and their parents, finding that children with CRS were perceived by their parents to have significant impairment of the following functions: physical (activities such as walking, bathing, and strenuous sports); psychosocial, socioemotional, and behavioral (schoolwork or activities with friends).[10]

In addition to impacting these functions, CRS was also detrimental to general health (self-reported health and disease), including bodily pain (intensity and frequency of bodily pain or discomfort) and the emotional health of parents or guardians, with restricted personal time because of their children's condition. The children's self-assessments reported lower scores for psychosocial functions and bodily pain, even when CRS was compared to other chronic pediatric diseases such as asthma, epilepsy, hyperactivity-attention deficit disorder, and rheumatoid arthritis.[10]

It is uncommon for CRS to occur in isolation in children and in the majority of cases, particularly those refractory to appropriate medical treatment, the possibility of comorbidities should be investigated, including allergy, cystic fibrosis, primary ciliary dyskinesia, and immunodeficiency (inborn errors of immunity).[6,7]

The objective of this article is to conduct a review of CRS differential diagnoses in pediatric patients, with emphasis on chronic rhinosinusitis with nasal polyps.

Methods

This is a narrative, descriptive, and exploratory review of the literature. Searches were conducted of databases including PubMed, Embase, SciELO, and Scopus, with no publication date limits, using the pertinent keywords for each section. Only publications in English or Portuguese were included. Examples of the terms employed and the databases searched are shown in Table 1.

Classification of CRS

In addition to the CRS classification proposed for adults, which categorizes patients phenotypically as having chronic rhinosinusitis with nasal polyps or chronic rhinosinusitis without with nasal polyps, current concepts are not restricted to phenotypes (based on clinical characteristics, such as presence of nasal polyps, comorbidities, and radiographic findings), but also include endotypes (the distinct biological or immunological pathway involved in disease genesis and progression) allowing classifications that include factors of physiopathogenesis, improving and speeding patient treatment and also enabling better analysis of the results of the treatments used.[11,12]

Ten different endotypes have been described and subdivided according to biomarkers and T helper cells

Table 1
Literature databases and search terms employed, by article section

Section	Databases/Sources	MeSH keywords used
Introduction	PubMed, SciELO, Embase, Books in physical or digital formats	"Rhinosinusitis", "Sinusitis", "Chronic Disease", "Child", "Pediatrics", "Quality of Life"
Classification of CRS	PubMed, SciELO, Embase	"Rhinosinusitis", "Sinusitis", "Chronic Disease", "Child", "Pediatrics", "Nasal Polyps", "Th1 Cells", "Th2 Cells", "Th17 Cells", "Allergic Fungal Sinusitis"
Differential diagnoses	PubMed, Embase, Scopus, Books in digital format	"Rhinosinusitis", "Sinusitis", "Chronic Disease", "Child", "Pediatrics", "Cystic Fibrosis", "Ciliary Motility Disorders", "Primary ciliary dyskinesia", "Kartagener Syndrome", "Nasal Polyps", "Paranasal Sinuses"
Clinical treatments and use of immunobiologicals	PubMed, Embase, SciELO, Books in physical or digital formats, ANVISA Content Center	"Immunologic Deficiency Syndromes", "Common Variable Immunodeficiency", "Primary Immunodeficiency Diseases", "Dupilumab"

(Th) found when analyzing tissues and mucus from the nasal cavities of patients into type 1, type 2, and type 3, for Th1, Th2, and Th17 inflammatory patterns, respectively.[13]

The type 1 inflammatory pattern targets intracellular pathogens and is characterized by a predominance of IFN-γ and TNF-α. Type 2 targets extracellular parasites and is characterized by predominant production of IL-4, IL-5, and IL-13. Finally, the type 3 inflammatory pattern targets extracellular bacteria and fungi and exhibits predominance of IL-22 and IL-17. In vivo, immune responses are generally mixed, but CRS cases can be defined histologically on the basis of the predominant pattern.

CRS cases with type 1 and 3 inflammatory responses are characterized by neutrophilic inflammatory infiltrate, whereas type 2 inflammatory responses are characterized by eosinophilic inflammatory infiltrate.[14] Eosinophils, CD4-positive lymphocytes, and neutrophils all play important roles, with lymphocytes and neutrophils being more abundant in the facial sinuses of younger children.[14-19] In general, characteristic findings in children include less tissue damage, reduced basal membrane thickening, and greater hypertrophy and hyperplasia of the submucosal glands.[20]

The CRS classification currently most widely accepted divides the pathology into two major groups, primary and secondary (Table 2). Primary CRS is the result of a primary inflammatory disorder, is not caused by immunodeficiencies, autoimmune diseases, genetic abnormalities, odontogenic sinusitis, or localized tumors, exclusively involves the airway or respiratory system, and is subdivided into localized (involves the sinonasal mucosa without affecting the lower airway or the contralateral paranasal sinuses) and diffuse (a more comprehensive inflammatory disorder that may involve upper and lower airways) and also into type 2 and non-type 2 endotypes.[12]

Primary CRS that is classified as localized and type 2 is characteristic of Allergic fungal rhinosinusitis and when it is non-type 2, the phenotype is Sinusitis in isolation. Diffuse, type 2 classifications encompass Rhinosinusitis with nasal polyps (CRSwNP) [Eosinophilic rhinosinusitis], Central compartment atopic disease, and Allergic fungal rhinosinusitis, while

Table 2
Classification of Chronic Rhinosinusitis

Group	Extent	Inflammatory pattern/ Endotype	Phenotype
Primary	Localized	Type 1 or Type 3	Isolated sinusitis
		Type 2	Allergic fungal rhinosinusitis
	Diffuse	Type 1 or Type 3	Non-eosinophilic rhinosinusitis
		Type 2	Rhinosinusitis with nasal polyps (CRSwNP) [Eosinophilic rhinosinusitis], central compartment atopic disease, and allergic fungal rhinosinusitis
Secondary		Localized disease	Odontogenic sinusitis, fungal ball, and tumors
	Diffuse	Mechanical	Cystic fibrosis and primary ciliary dyskinesia
		Inflammatory	Granulomatosis with polyangiitis and Eosinophilic granulomatosis with polyangiitis
		Immunity	Selective immunodeficiencies

diffuse non- type 2 characterizes Non-eosinophilic rhinosinusitis.

Secondary CRS is caused by an established systemic disease or a localized pathology, such as sinonasal tumors or odontogenic sinusitis. Secondary CRS is also subdivided into local and diffuse. When localized, the endotype is local disease, encompassing Odontogenic sinusitis, Fungal ball, and Tumors. When diffuse, there are three predominant endotypes. The mechanical endotype includes Cystic fibrosis and Primary ciliary dyskinesia; the inflammatory endotype covers Granulomatosis with polyangiitis and Eosinophilic granulomatosis with polyangiitis; and, finally, when the endotype is immunity, the phenotype is Selective immunodeficiencies.

The CRSwNP phenotype occurs in around 0.1% of CRS cases in the pediatric age group,[14] and, as described, the diagnostic possibilities include primary and secondary CRS. Regardless, when present, it should raise a clinical suspicion of a possible congenital genetic disease, the most prevalent of which are cystic fibrosis and primary ciliary dyskinesia.[2,14] In the absence of genetic disorders, children with refractory CRS should be assessed for presence of humoral immunodeficiencies[6,15] and vasculitis.[14]

There are few studies demonstrating pathophysiology or reporting evidence of the potential relevance of classification into endotypes and phenotypes of CRS in the pediatric population. The majority of studies report lower prevalence of CRSwNP in children compared with adults,[19] with the exception of cases in which Cystic fibrosis, Allergic fungal rhinosinusitis, or Aspirin-Exacerbated Respiratory Disease (AERD) is diagnosed.[21-25]

Differential diagnoses

Cystic fibrosis

Cystic fibrosis (CF) is caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene that cause formation of dysfunctional CFTR chloride channels or absence of these

transporters, in respiratory epithelium, resulting in thick, viscous secretions that promote respiratory tract infections.[26] This is an autosomal recessive disorder that is diagnosed by high levels of chlorine in sweat and/or genetic testing.[6]

Persistent secretions and tissue inflammation block the sinus ostia, resulting in hypoxia, mucosa edema, and additional compromise of mucociliary function.[27] Consequently, patients with CF have CRS, with or without sinonasal polyposis, in 90-100% of cases.[28] Nasal obstruction is present in around 80%, anosmia in 25%, and rhinorrhea and headaches are present in more than 50% of cases.[29] Some studies have shown that sinonasal polyposis secondary to the chronic localized inflammatory process occurs in up to 86% of patients with CF, with prevalence increasing with age.[29,30] Despite the high incidence of CRS in patients with CF, only 10-15% report sinonasal symptoms.[31]

Computed tomography of the facial sinuses of people with CF typically shows enlargement of the paranasal sinuses, most often seen as pseudomucocele of the maxillary sinuses, and also underdevelopment of the frontal and sphenoid sinuses, with no associated bone erosion.[32] In children, tomographic studies are only indicated for surgical planning, since findings will not change clinical management.[33] Currently, there are no well-defined criteria for choosing between clinical management and endoscopic sinonasal surgery, so decisions are made on the basis of the physician's experience and the patient's complaints. In these cases, the low incidence of self-reported symptoms, despite radiological and endoscopic signs of sinus involvement, demonstrate the difficulty of indicating surgery.[34]

Analyses involving exclusively pediatric populations report a 5-15.2% prevalence of sinonasal polyposis in patients with CF.[35,36] From the point of view of diagnosis, a high degree of suspicion of CF should be aroused by children with nasal polyposis and sinusitis, especially when accompanies by failure to thrive, gastrointestinal changes, and respiratory diseases, particularly allergic rhinitis and asthma.[6] Tests include neonatal screening (the "Guthrie test"), genetic panels, and the chloride sweat test.[6]

Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a group of disorders that involve compromised mucociliary clearance due to dysmotility and/or reduced numbers of cilia in the respiratory epithelium, caused by autosomal recessive mutations.[6] Clinically, PCD predominantly manifests in childhood, with chronic symptoms such as productive coughing and nasal obstruction, in addition to chronic rhinitis, recurrent otitis media, and neonatal respiratory distress syndrome of the newborn.[37,38] A clinical form known as Kartagener Syndrome is characterized by PCD, situs inversus, and bronchiectasis.[39]

The prevalence of continuous sinonasal symptoms is estimated at 35% in infants, children, and adolescents up to 15 years of age with PCD, which is similar to the prevalence of endoscopic evidence of nasal obstruction, in particular changes involving the mucosa and hypertrophy of the inferior turbinates.[40] The occurrence of CRS in adult patients with documented PCD was 59-100% in recent series and was linked to SNOT-22 scores (22-item Sinonasal Outcome Test) in the 'moderate' range.[40-44] CRS is part of the typical Kartagener Syndrome triad, with prevalence closer to 100% in this form.[45-47] Nasal polyposis is less prevalent in the pediatric population, present in less than 10%, although PCD has been associated with CRSwNP at higher frequencies (15-33%) in patients of all age groups.[6,40,43,48] It is estimated that the incidence of severe otitis media with effusion in children with PCD is close to 85%, with reports of rates exceeding 92%.[49,50] Recurrent otological involvement leads to a higher frequency of hearing loss, particularly conductive forms, in this group of patients.[50]

A diagnostic hypothesis of PCD should be considered in CRS presentations refractory to clinical treatment combined with recurrent otitis media.[39] Once suspected, investigation includes histopathological tests, in particular biopsy followed by electronic microscopy; genetic tests, of which whole exome sequencing offers 97% accuracy; and nasal nitric oxide measurement, which is a sensitive and specific test for PCD offering similar diagnostic precision to the previous two methods if palate closure maneuvers are employed.[6,51,52] The most common tomographic sinonasal findings in children with PCD are hypoplasia or aplasia of the sphenoid, frontal, maxillary, and/or ethmoidal paranasal sinuses, with rates of involvement generally following this order.[53,54]

Primary immunodeficiencies (Inborn errors of immunity)

Syndromes related to primary immunodeficiency, especially those related to humoral immunity, should

be considered in pediatric patients with frequent and persistent acute rhinosinusitis, in cases of chronic rhinosinusitis, or in cases of rhinosinusitis in conjunction with otitis media, bronchiectasis, or pneumonia.[7,55-57] Due to dysfunction or deficiency of antibodies, these patients are also at increased risk of invasive infections, such as meningitis, osteomyelitis, and septicemia.[58]

Studies attempting to assess the prevalence of humoral immunity in children, as manifest by low levels of immunoglobulin or hyporesponsiveness to pneumococcal vaccine, report results varying from 21.8 to 34%.[55,56] However, in a study with 4,044 children diagnosed with chronic rhinosinusitis, 12.3% had a diagnosis consistent with an immunological disorder.[57] When pediatric patients with different types of primary humoral immunodeficiency were analyzed, it was found that CRS was most prevalent among those diagnosed with agammaglobulinemia (85.96%), followed by those diagnosed with dysgammaglobulinemia (81.81%), and other antibody deficiencies (72.72%).[59] The true incidence of primary immunodeficiencies in pediatric patients with chronic rhinosinusitis is unknown.[39]

Humoral immune dysfunctions in pediatric patients may be associated with low total IgG and IgG subclasses, low IgA, and insufficient immune response to antipneumococcal vaccine, since the most common immunodeficiencies in this age group include common variable immunodeficiency, IgG subclass deficiency, selective IgA deficiency, and specific antibody deficiency.[7,32,39] The possibility of primary immunodeficiency should be investigated in children in whom allergic sensitization is suspected if total IgE is low or absent.[60]

Common variable immunodeficiency is characterized by hypogammaglobulinemia, with low levels of IgG and IgA or IgM, accompanied by variable clinical symptomology, primarily involving recurrent upper and lower airway infections, with possible development of bronchiectasis as the disease progresses.[57] Possible concomitant symptoms include gastrointestinal infections, chronic diarrhea, splenomegaly, liver disease, portal hypertension, and autoimmune conditions such as thrombocytopenia, hemolytic anemia, and pernicious anemia.[57,61] There is a greater risk of development of malignity, predominantly B cell lymphoma.[61,62] Treatment depends on immunoglobulin replacement, which is accompanied by reductions in the incidence of pneumonias and hospitalizations.[63]

Selective IgA deficiency is associated with reduced serum IgA levels, but normal IgG and IgM levels. This is the most common primary immunodeficiency and its symptoms include recurrent sinus and pulmonary infections, gastrointestinal infections, and inflammatory disorders, predisposition to asthma and atopic disease, and anaphylactic shock in the presence of anti-IgA antibodies. Treatment involves management of associated conditions and antibiotic prophylaxis should be considered.[57]

IgG subclass deficiency is caused by a deficiency of one of the four IgG isotypes, with normal serum total IgG levels. Clinically, it can predispose to repeated sinus and pulmonary infections, atopic disease, associated IgA deficiency, and insufficient response to vaccination.[64] Since IgG1 accounts for 60% of total IgG, deficiencies involving this subclass can cause reductions in total IgG. IgG2 deficiencies are more prevalent in children than in adults and can be associated with recurrent infections because of their role in the immune response against capsular polysaccharide antigens. IgG3 deficiency is more common in adults, and IgG4 deficiency is the most common in the general population, and is associated with pulmonary infections, bronchiectasis, and autoimmune conditions.[57,65,66] Treatment involves pneumococcal conjugate vaccination in cases with poor response to non-conjugate vaccine, antibiotic prophylaxis, and, controversially, intravenous Ig replacement.[67,68]

Specific polysaccharide antibody deficiency is characterized by normal serum concentrations of IgG, IgM, and IgA, but inadequate response to polysaccharide antigens, and is clinically associated with allergic rhinitis and recurrent infections, such as otitis media, sinusitis, and bronchitis.[57,69-71] The incidence of specific antibody deficiency in children with recurrent infections is 14.9%.[70] Pneumococcal conjugate vaccine 13 is recommended and 80-90% of children who do not respond to pneumococcal polysaccharide vaccination will respond to conjugate vaccination.[72] Antibiotic prophylaxis may be indicated, while intravenous immunoglobulin replacement remains controversial.[57]

A diagnosis of agammaglobulinemia should also be considered in these patients. This immunodeficiency is caused by sporadic or X-linked genetic mutations, resulting in cell signaling deficiency and changes to B cell survival. Clinical manifestations are described in the first year of life, and infections by encapsulated germs are normally reported, in addition to episodes

of sinusitis and otitis media due to IgA deficiency.[57] Treatment involves intravenous Ig replacement.[77]

Other differential diagnoses include Wiskott-Aldrich syndrome, Chronic granulomatous disease, Chédiak-Higashi syndrome, Severe combined immunodeficiency, DiGeorge Syndrome, complement deficiencies, and ataxia telangiectasia.

According to EPOS 2020, it appears prudent to assess immunological function in children with chronic or recurrent rhinosinusitis with quantitative immunoglobulin assays (total IgG and subclasses, IgA, IgM, and IgE) and serology for tetanus and diphtheria, in addition to assaying antipneumococcal vaccine 23 antibody serotypes (before and 6-8 weeks after immunization with the Pneumo23 vaccine).[6]

Clinical treatments and use of immunobiologicals

Although there are no studies reporting high level scientific evidence for treatment of chronic rhinosinusitis in the pediatric age group, it is believed that nasal topical corticosteroids can be used in view of their potential anti-inflammatory effect and safety profile. As with intranasal corticosteroids, studies on use of nasal saline solution for childhood CRS are rare and the evidence level is low. However, their use is generally indicated on the basis of the benefits that have been demonstrated in the adult population.[7]

Addition of short courses of systemic corticosteroids has proven effective in selected patients. These courses are usually used to treat inflammatory sinus disorders unresponsive to topical corticosteroids.[39] It should be noted that the potential for adverse effects from use of systemic corticosteroids justifies limiting their use to cases refractory to conservative treatment.[74,75] The Brazilian Academy of Rhinology states that use of systemic corticosteroids in gradually decreasing doses in combination with antibiotics appears to be more effective for CRS in children than placebo but maintains the position that systemic corticosteroids are not recommended for treatment of CRS in children.[7]

There are studies demonstrating that use of oral antibiotics, for short periods of time (up to 4 weeks) or longer (12-15 weeks), or use of injectable or topical antibiotics is not justifiable for the pediatric age group.[1,76] Use of antibiotic prophylaxis in patients with recurrent symptoms is controversial. It may be beneficial for patients with cystic fibrosis or primary ciliary dyskinesia or for patients with primary immunodeficiency.[76]

Surgical treatment is considered when conservative treatment fails.[39] The Brazilian Academy of Rhinology recommends that initial surgical interventions should focus on simpler procedures, such as adenoidectomy and sinus lavage, with good success rates. Endonasal surgery is preferably reserved for presence of comorbidities such as cystic fibrosis, primary ciliary dyskinesia, and immunodeficiencies, using techniques and extent of intervention as appropriate to the underlying disease.[7]

Immunobiologicals are an emerging treatment modality for chronic eosinophilic rhinosinusitis in adults, targeting several mediators associated with type 2 inflammation, including IL-5, IL-4, and IgE.[11] Only one immunobiological is currently approved for CRS in the pediatric age group—dupilumab—which is indicated for supplementary maintenance treatment in patients 12 years or older with inadequately controlled chronic rhinosinusitis with nasal polyps.[77] Safety was demonstrated in children over the age of 6 months for other indications, such as moderate to severe atopic dermatitis.[11]

There is still little scientific evidence for the use of immunobiologicals for chronic rhinosinusitis in the pediatric population. There is just one published study on use of dupilumab in the pediatric population with CRS with nasal polyps, conducted with the AERD phenotype, and just one robust clinical trial is ongoing, using dupilumab in a compassionate use program.[2]

In Brazil, dupilumab was approved by Anvisa for patients 12 years of age or older in January of 2025. This approval was supported by evidence from two positive pivotal clinical trials (SINUS-24, SINUS-52) conducted in adults with inadequately controlled CRS with nasal polyps, by pharmacokinetic data from adult and adolescent patients over the age of 12 with moderate to severe asthma, and by safety data for dupilumab in adolescents over the age of 12 with moderate to severe asthma. The results of an extrapolation analysis of data from pediatric populations with asthma, atopic dermatitis, and eosinophilic esophagitis and efficacy data from adults with CRS with nasal polyps were also presented in support.[78]

Conclusions

CRS in pediatric patients imposes a considerable burden on patients and their families. While many of

the phenotypes and endotypes of adult CRS are also observed in childhood and adolescence, particularly in cases of CRS with nasal polyps, we must be alert to the differential diagnoses.

In the era of approval of immunobiologicals for treatment of CRS with nasal polyps in patients aged 12 years and over, investigation of secondary causes is essential to guarantee that treatment is safe and effective for the patient's profile.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Pathogenic processes related to IgA deposition

Processos patogênicos relacionados ao depósito de IgA

Victoria Luisa Pereira Aguiar[1], Maria Helena Sampaio Favarato[1]

ABSTRACT

Immunoglobulin A (IgA) antibodies play an important role in immunity owing to their structure, glycosylation, location, receptor interactions, and multiple functions. Dysregulation of IgA-mediated immune responses can result in diseases associated with IgA deficiency or inflammation, including diseases characterized by tissue deposition of IgA, such as IgA nephropathy (IgAN), IgA vasculitis (IgAV), and linear IgA bullous dermatosis (LABD). A systematic literature review was conducted to describe the pathogenic mechanisms underlying IgA deposition in IgAN, IgAV, and LABD. Searches were performed in the PubMed, BVS, and LILACS databases, including articles published from 2018 to 2023 in English, Portuguese, Spanish, and French. Results were summarized to correlate key pathogenic mechanisms with relevant clinical findings. A total of 461 articles were identified, of which 46 were included for IgAV, 122 for IgAN, and 3 for LABD. In IgA-V, galactose-deficient IgA1 (Gd-IgA1) produced by activated B cells forms immune complexes that activate neutrophils and trigger vascular inflammation. In IgAN, pathogenesis involves the aberrant production of Gd-IgA1, formation of autoantibodies, glomerular and mesangial deposition, and complement activation. In LABD, genetic susceptibility appears to play an important role, particularly through associations with specific human leukocyte antigen (HLA) alleles. Several HLA alleles have also been associated with disease susceptibility. In addition, elevated levels of pro-inflammatory cytokines, including interleukin (IL)-17, IL-8, and IL-6, as well as dysregulation of immune cells, such as T helper 1 (Th1), Th2, Th17, and regulatory T cells, contribute to disease pathogenesis. This review integrates current knowledge of the pathogenic mechanisms of IgA deposition and dysfunction, correlating them with diverse clinical manifestations observed across IgA-mediated diseases.

Keywords: Immunoglobulin A, IGA glomerulonephritis, IgA vasculitis, immune system diseases, linear IgA bullous dermatosis.

RESUMO

Os anticorpos do isotipo imunoglobulina A (IgA) desempenham um papel importante na imunidade devido à sua estrutura, glicosilação, localização e interações com receptores, bem como às suas múltiplas funções. Disfunções nesse sistema podem levar a doenças associadas à deficiência de IgA ou à inflamação, como doenças relacionadas à deposição tecidual de IgA: nefropatia por IgA (NIgA), vasculite por IgA (VAIgA) e dermatose autoimune bolhosa mediada por IgA (DIgA). Foi realizada revisão sistemática nos bancos de dados PubMed, BVSalud e LILACS com o objetivo de descrever os processos patogênicos que explicam a deposição de IgA na NIgA, VAIgA e DAIgA. A busca por artigos incluiu artigos do período 2018 a 2023 nos idiomas português, inglês, francês e espanhol. Os resultados foram resumidos de forma a correlacionar os pontos-chave da patogênese e os achados clínicos relevantes. Foram encontrados 461 artigos, sendo incluídos 46 para VIgA, 122 para IgAN e 3 para DIgA. A NIgA envolve produção aberrante de IgA1, formação de autoanticorpos, deposição glomerular e mesangial e ativação do complemento. Na DIgA, destaca-se a influência genética em doenças dermatológicas, como a associação com alguns alelos HLA. Na IgA-V, a Gd-IgA1 produzida por células B ativadas e imunocomplexos ativa neutrófilos, desencadeando inflamação vascular. Os alelos HLA estão associados à suscetibilidade. Citocinas pró-inflamatórias, como IL-17, IL-8, IL-6, estão elevadas, enquanto células imunes (Th1, Th2, Th17 e Treg), estão desreguladas. Esta revisão de literatura unifica o conhecimento atual sobre a fisiopatologia das doenças relacionadas à deposição e disfunção de IgA, correlacionando-a com as diferentes manifestações clínicas.

Descritores: Imunoglobulina A, glomerulonefrite por IGA, vasculite por IgA, doenças do sistema imunitário, dermatose linear bolhosa por IgA.

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Introduction

Immunoglobulin A (IgA) plays a critical role in the immune response, especially at mucosal surfaces. IgA exists in 2 main forms, commonly classified as monomeric IgA and dimeric IgA. Its structure enables interactions with immune cells and molecules of the complement system through the Fc region of its heavy chains, while the Fab region, composed of light chains, is responsible for recognizing and binding specific antigens. The production of IgA depends on the activation of B cells within mucosa-associated lymphoid tissue (MALT).

B-cell activation is initiated by antigens present on mucosal surfaces, many of which are derived from pathogens.[1] Activated B cells subsequently proliferate and differentiate into IgA-producing plasma cells. Two major pathways are involved in IgA production: the T cell-dependent pathway and the T cell-independent pathway. In the T cell-dependent pathway, interactions between activated B cells and CD4+ T helper (Th) cells are essential for IgA production. Th cells secrete cytokines, such as interleukin (IL)-4 and IL-5, which promote the differentiation of B cells into IgA-producing plasma cells.[2] In contrast, the T cell-independent pathway occurs without the direct involvement of Th cells. In this mechanism, specific antigens directly activate B cells, leading to IgA production.[3] After differentiation, IgA-producing plasma cells secrete IgA, which is subsequently transported across the epithelium to mucosal surfaces.[4]

Although IgA production is a physiological process essential for mucosal immunity, abnormal immune responses involving IgA can contribute to the development of several pathological conditions. These disorders arise from aberrant IgA-mediated mechanisms and include linear IgA bullous dermatosis (LABD), dermatitis herpetiformis, IgA vasculitis (IgAV; formerly known as Henoch-Schönlein purpura), and IgA nephropathy (IgAN; formerly known as Berger's disease).

Several studies have highlighted the importance of understanding the mechanisms underlying IgA deposition in tissues to improve patient care and support the development of targeted therapeutic strategies. Therefore, investigating the formation of IgA deposits and their role in disease pathophysiology is essential for advancing current knowledge of these conditions. The primary objective of this review was to examine the pathogenic mechanisms associated with IgA deposition in different tissues, with a particular focus on IgAV, IgAN, and LABD. In addition, a practical diagram was developed for health care professionals to summarize the key pathogenic mechanisms and correlate them with their most relevant clinical manifestations.

Methods

A systematic literature review was conducted to describe the pathogenic mechanisms underlying IgA deposition in IgAV, IgAN, and LABD. Literature searches were performed in the PubMed, Biblioteca Virtual em Saúde (BVS), and LILACS databases.

For IgAV, the search strategy used was: (("IgA vasculitis" OR "Henoch-Schönlein purpura") AND ("pathogenesis")). For IgAN, the following descriptors were applied: (("IgA nephropathy" OR "Berger's disease") AND ("pathogenesis")). For LABD, the search strategy used was: ("IgA dermatosis" AND ("pathogenesis")). Searches were limited to articles published between 2018 and 2023 and written in English, Portuguese, Spanish, or French.

The retrieved studies were screened to identify the publications most relevant to the research question. Article selection was based on study design and eligibility according to the predefined inclusion and exclusion criteria described below.

After study selection and analysis, a diagram summarizing the main findings was developed as a practical resource for readers. All studies were independently and blindly reviewed by 2 authors based on their original citations. Publications were classified as "relevant," "partially relevant," and "not relevant." Studies categorized as "relevant" underwent full-text review by the same authors. Any disagreements regarding study eligibility or evaluation were resolved through discussion between the authors until consensus was reached.

Studies addressing the main pathogenic mechanisms associated with IgA deposition were considered eligible for inclusion. Case reports, clinical case series, or systematic reviews were excluded, as were articles published before 2018 or in languages other than English, Portuguese, Spanish, and French. Selected studies were grouped according to the disease investigated —IgAV, IgAN, or LABD — to facilitate the analysis of disease-specific pathogenic mechanisms.

Data extracted from the included studies were used to develop a practical diagram integrating the major pathogenic pathways and the main clinical

manifestations of each disease. The methodology used to construct this visual synthesis was based on the propositions described by Rohwer et al.[5]

IgA vasculitis

The literature search using the selected descriptors identified 108 articles, 46 of which met the inclusion criteria. The study selection process is presented in a PRISMA flow diagram (Figure 1).[6] The diagram summarizing the main findings is shown in Figure 2.

IgAV and IgAN share morphological similarities regarding IgA deposition. However, histopathologically, crescents are more frequently observed in renal biopsies from patients with IgAV than in those with IgAN.[7,8] Therefore, the frequent presence of crescents is expected in the histological description of IgAV. According to Pillebout,[9] immunofluorescence in IgAV shows deposition of IgA, IgG, IgM, C3, and fibrin in the mesangium. Light microscopy may reveal mesangial hypercellularity with increased mesangial matrix, endocapillary hypercellularity, segmental glomerulosclerosis, and cellular crescents.

The pathogenesis of IgAV is still unclear; however, several mechanisms have been proposed to explain disease development. The formation of galactose-deficient IgA1 (Gd-IgA1) and related immune complexes appears to play a key role in IgAV. In addition, IgA binding to the Fc alpha I receptor stimulates neutrophil activation, leading to systemic vascular inflammation and tissue damage.[10] Mucosal antigens can activate B cells in MALT through T cell-dependent or T cell-independent pathways, including activation through Toll-like receptor (TLR) signaling.[11] In association with genetic factors, activated B cells differentiate into plasma cells and produce Gd-IgA1. Gd-IgA1 and anti-Gd-IgA1 autoantibodies form circulating immune complexes together with other components. These immune complexes subsequently deposit in target organs and activate inflammatory responses, providing a pathogenic basis for IgAV.[12] Immune complexes also increase the production of C3 and C5 in endothelial cells and induce the expression of IL-8, E-selectin, and intercellular adhesion molecule-1 (ICAM-1).

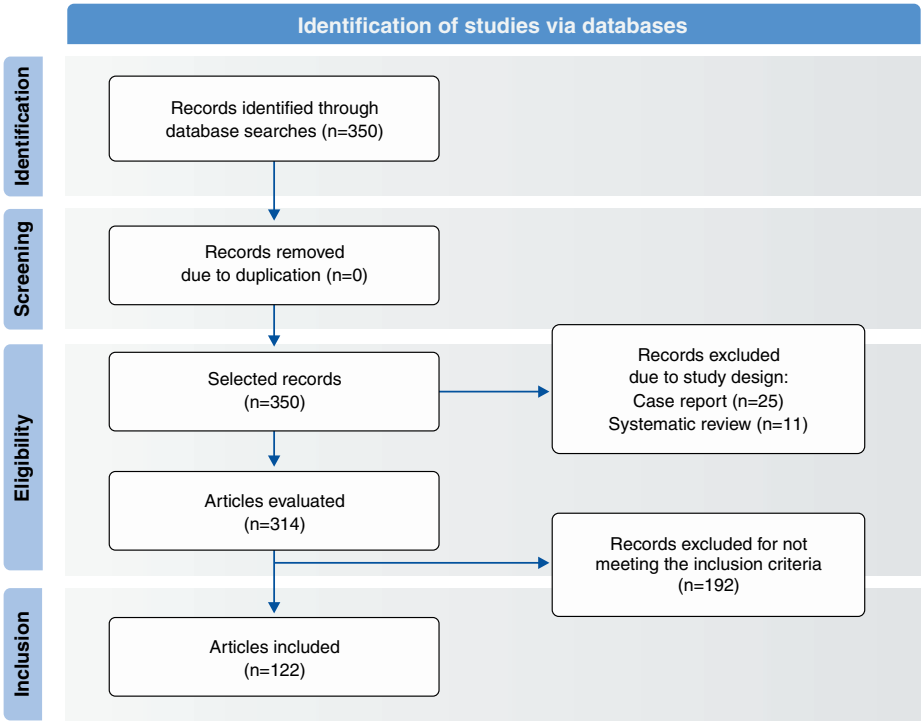

Figure 1
PRISMA flow diagram[6] of records identified for IgA vasculitis

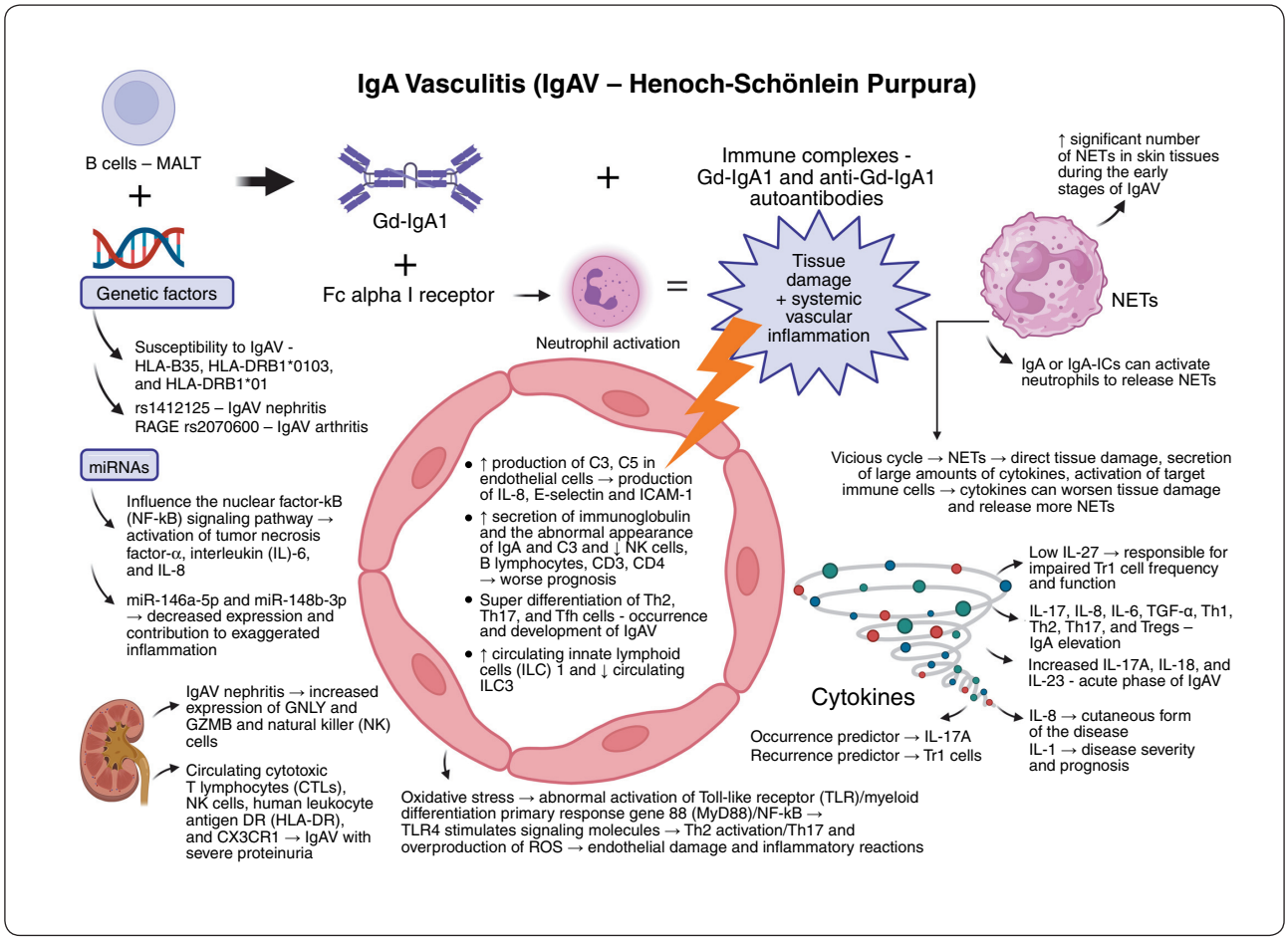

Figure 2

Practical diagram for IgA vasculitis

MALT: mucosa-associated lymphoid tissue; HLA: human leukocyte antigen; miRNA: microRNA; Gd-IgA1: galactose-deficient IgA1; ICAM-1: intercellular adhesion molecule-1; Th: T helper; Tfh: T follicular helper; ROS: reactive oxygen species; NETs: neutrophil extracellular traps; IgA-ICs: IgA-containing immune complexes; TGF-α: transforming growth factor alpha; Tregs: regulatory T cells.

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Inflammatory cell Infiltration further increases ICAM-1 expression.[12,13] IgA1 has also been identified as an autoantibody in host immunity. IgA1 promotes immune-complex deposition in blood vessels, leading to complement activation, inflammation exacerbation, and vascular injury.[14] During disease progression, a reduction in natural killer (NK) cells, B lymphocytes, CD3+ cells, and CD4+ cells may occur, along with increased immunoglobulin secretion and abnormal IgA and C3 expression. These alterations may indicate a worse prognosis and increased risk of dedifferentiation.[15] Furthermore, circulating cytotoxic T lymphocytes and NK cells are activated in patients with IgAV and severe proteinuria, with increased surface expression of human leukocyte antigen DR (HLA-DR) and CX3CR1.

Several cell populations are involved in IgAV pathogenesis. Among the inflammatory mediators involved, IL-17, IL-8, IL-6, and transforming growth factor alpha (TGF-α) are particularly relevant,[16] as they are directly associated with increased IgA levels in affected patients. Jiang et al.[17] concluded that p300 plays a crucial role in IgAV pathogenesis. By binding to glucocorticoid receptor alpha (GRα), p300 may negatively regulate the expression of resistance genes, including AP-1 and TGF-β1, thus helping to prevent further renal injury and glucocorticoid resistance. Other immune cells, such as Th1, Th2, Th17, and regulatory T cells, also contribute to IgAV progression. However, the role of NK cells in disease pathogenesis remains poorly defined, although these cells appear to be closely associated with the

renal complications of IgAV.[18,19] Prieto-Peña et al.[20] suggested that the IL-33/IL-1RL1 signaling pathway does not contribute to the activation network underlying vasculitis. Although serum levels of IL-17A, IL-18, and IL-23 increase significantly during the acute phase of IgAV, they do not appear to predict disease course. Conversely, IL-17A may be a useful predictor of IgAV occurrence.[21]

Regarding genetic factors associated with susceptibility and pathophysiology, HLA-B35, HLA-DRB1*0103, and HLA-DRB1*01 have been linked to IgAV susceptibility.[22,23] Certain polymorphisms have also been associated with the cutaneous form of the disease,[24] such as IL-8 polymorphisms, and with disease severity and prognosis, such as IL-1 polymorphisms. The expression of microRNAs (miRNAs) and their relationship with IgAV have also been investigated.

According to Jurcic et al.,[16] most aberrantly expressed miRNAs in IgAV-affected skin influence the nuclear factor kappa B (NF-κB) signaling pathway,[25] which is crucial for the activation of key pro-inflammatory genes, including those encoding tumor necrosis factor-α (TNF-α), IL-6, and IL-8. In addition, miR-146a-5p and miR-148b-3p, which negatively regulate inflammatory gene expression, show decreased expression and may contribute to exaggerated inflammation.[26,27] Levin et al.[28] reported that dendrin messenger RNA levels and relative nuclear protein concentrations are increased and associated with a more benign phenotype and disease progression in patients with IgAV.

Neutrophil extracellular traps (NETs) have increasingly been implicated in IgAV pathogenesis. Chen et al.[29] concluded that NETs are released into the circulation of patients with IgAV and are associated with disease activity, suggesting their potential use as biomarkers of disease activity. In a more recent study by Chen et al.,[30] consistent with the findings of Takeuchi et al.,[31] a significant increase in NETs was observed in skin tissues during the early stages of vasculitis. This study also provided the first confirmation that NETs are involved in IgAV pathogenesis in mice. Another study by Chen et al.[32] concluded that IgA or IgA-containing immune complexes can activate neutrophils and induce NET release. NET-related components may directly damage tissues or stimulate the secretion of large amounts of cytokines, thus activating downstream target immune cells. In a vicious cycle, cytokine production may further exacerbate tissue injury and promote neutrophil aggregation. However, the mechanism by which neutrophils mediate tissue damage in IgAV is not completely understood, nor is the specific IgA/FcαR signaling pathway involved in regulating NET formation.

IgA nephropathy

The literature search using the selected descriptors identified 350 articles, 122 of which met the inclusion criteria. The study selection process is presented in a PRISMA flow diagram (Figure 3).[6] The diagram summarizing the main findings is shown in Figure 4.

IgAN is an immune-mediated kidney disease characterized by the deposition of IgA in the mesangial matrix of the renal glomeruli. Its pathogenesis is complex and multifactorial, involving interactions among genetic, environmental, and immunological factors. Suzuki et al.[33] demonstrated that activation of both innate and adaptive immune responses contributes to disease development. Deposition of IgA-containing immune complexes in the mesangium activates complement pathways and inflammatory responses, leading to renal injury and fibrosis. Perse et al.[34] identified several inflammatory mediators and cytokines involved in IgAN pathogenesis, including TNF-α, IL-6, IL-17, and TGF-β.

The pathogenesis of IgAN also involves multiple epigenetic mechanisms, including DNA methylation, histone modification, miRNA regulation, and other epigenetic alterations.[35-38] The widely accepted "four-hit hypothesis" proposes 4 sequential pathogenic events: (1) production of Gd-IgA1; (2) formation of IgG or IgA1 anti-Gd-IgA1 autoantibodies and immune complexes; (3) mesangial deposition of these complexes; and (4) inflammation and injury.[39,40] Aberrantly glycosylated IgA1, produced through reduced activity of β-1,3 galactosyltransferase, triggers the formation of IgG autoantibodies that bind to Gd-IgA1. These immune complexes circulate in the bloodstream via monocytes and are deposited in glomerular mesangial cells via CD71 receptors expressed locally. Subsequent activation of inflammatory pathways involves the alternative complement pathway, T lymphocytes, TLRs, cytokines, and chemokines, ultimately recruiting phagocytic cells to eliminate the deposited immune complexes.[41-43] Si et al.[44] further highlighted that anomalous kinetics of renal Gd-IgA1 deposition contribute to IgAN pathogenesis.

Current evidence suggests that aberrant glycosylation of IgA1 represents the initiating event

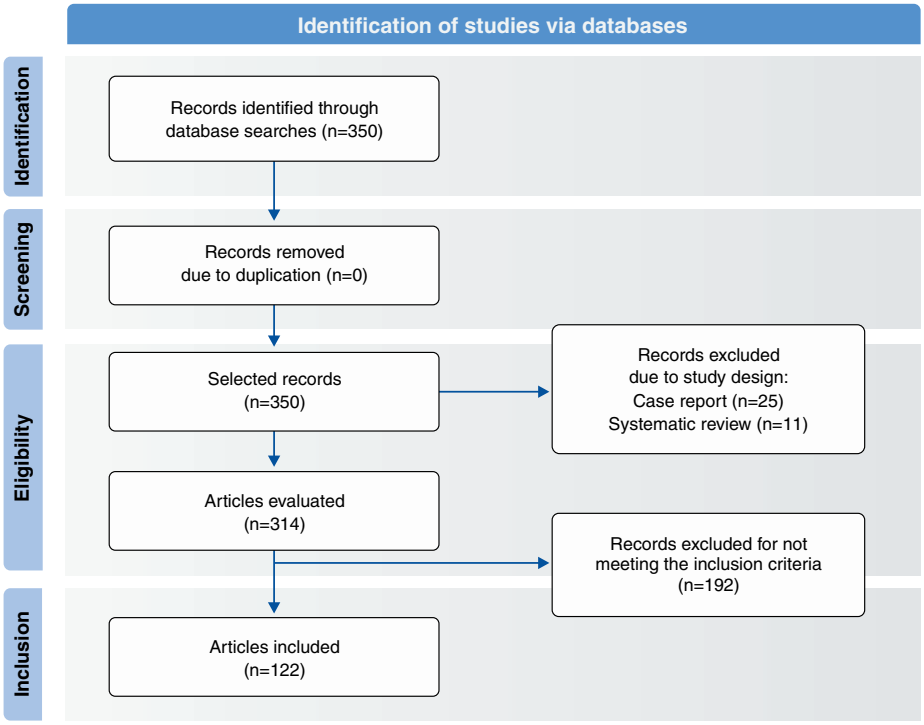

Figure 3
PRISMA flow diagram6 of records identified for IgA nephropathy

in IgAN. Multiple structural features of IgA1 and IgA2 N-glycosylation have been associated with disease susceptibility and glomerular dysfunction, including alterations in galactosylation, sialylation, bisection, fucosylation, and N-glycan complexity. In particular, IgA1 O-glycan sialylation has been associated with both disease development and glomerular function.[45]

Glomerular immune deposits are believed to originate from circulating immune complexes containing aberrantly O-glycosylated IgA1, the major autoantigen of IgAN, bound to IgG autoantibodies. This observation suggests a connection between disease pathogenesis, activation of the mucosal immune system in the upper respiratory and gastrointestinal tracts, and altered IgA1 glycosylation. Certain cytokines can increase the production of aberrantly O-glycosylated IgA1 through dysregulated signaling pathways in IgA1-producing cells of patients with IgAN.[46]

Several immune cells, including dendritic cells, NK cells, macrophages, and T- and B-lymphocyte subsets, as well as immune mediators, such as IgA receptors, TLRs, and complement components, are involved in the pathogenesis of IgAN.[47] Furthermore, abnormal regulation of the mucosal immune system is considered the core of the immunopathogenesis of IgAN.[48-50]

The role of TNF-α in IgAN remains under investigation. According to Chronopoulou et al.,[51] TNF-α does not appear to be a major determinant of the genetic architecture of the disease, although additional evidence is needed to clarify its precise contribution. Zhang et al.[52] demonstrated that mesangial cells cultured in the presence of IgA exhibit increased expression of TLR4, enhanced secretion of TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1), and increased expression of myeloid differentiation primary response gene 88 (MyD88)/NF-κB. TLR4 shRNA silencing and NF-κB inhibition

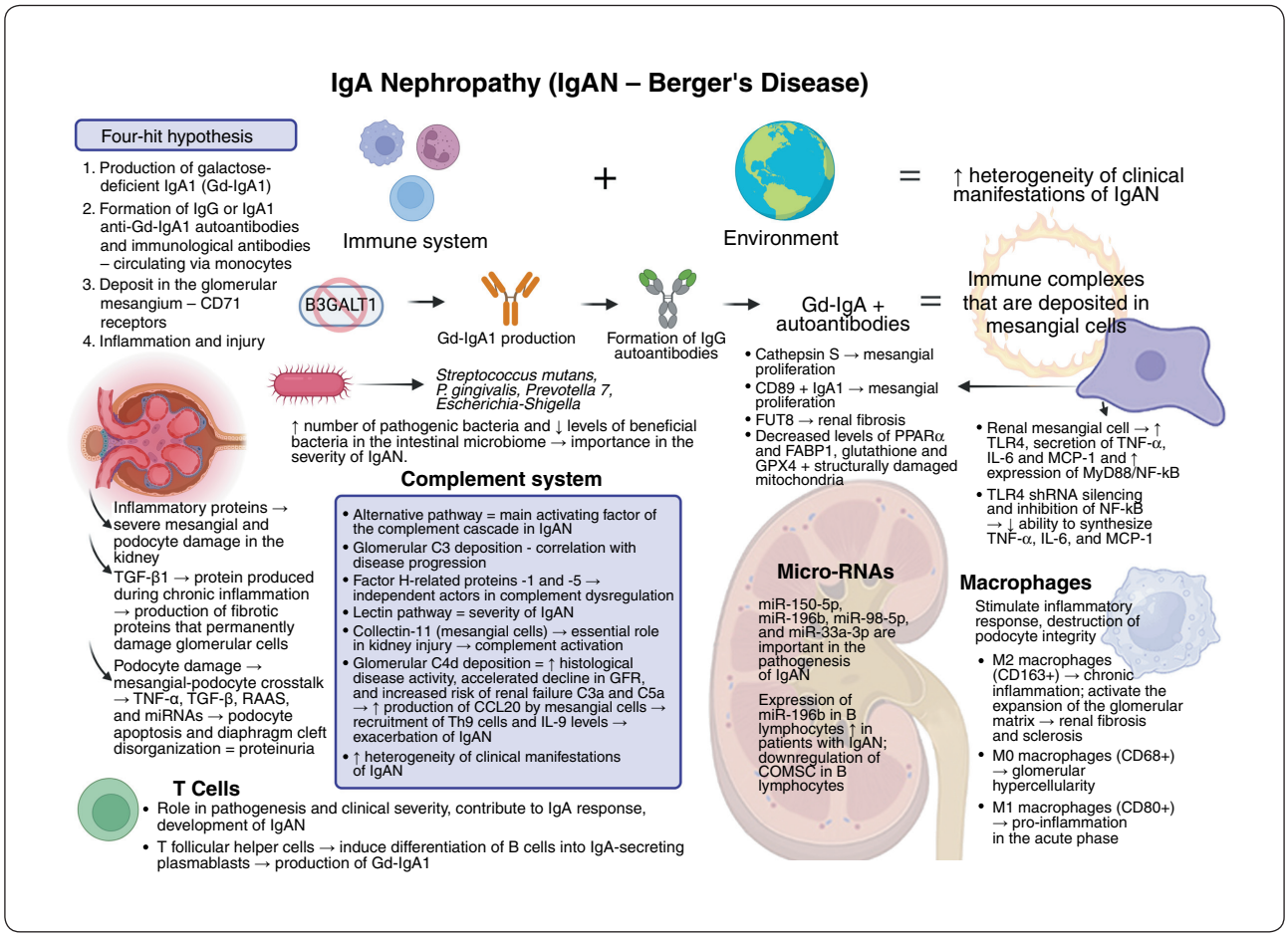

Figure 4

Practical diagram for IgA nephropathy

TGF-β1: transforming growth factor beta 1; TNF-α: tumor necrosis factor-α; RAAS: renin-angiotensin-aldosterone system; miRNA: microRNA; GFR: glomerular filtration rate; Th: T helper; IL: interleukin; MCP-1: monocyte chemoattractant protein-1; TLR: Toll-like receptor; MyD88: myeloid differentiation primary response gene 88.

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reduce the ability of mesangial cells to synthesize TNF-α, IL-6, and MCP-1. These findings suggest that IgA induces high TLR4 expression in mesangial cells, activating downstream signaling pathways that promote cytokine secretion and contribute to renal injury in patients with IgAN. Similarly, Tang et al.[10] reported increased expression of several novel genes in mesangial cells affected by IgAN, including MALAT1, GADD45B, SOX4, and EDIL3, which were associated with cell proliferation and matrix accumulation. In tubular cells, overexpressed genes were mainly enriched in inflammatory pathways, including TNF signaling, IL-17 signaling, and nucleotide-binding oligomerization domain (NOD)-like receptor signaling pathways.

Complement activation has also been implicated in IgAN pathogenesis.[53,54] The alternative complement pathway is the main activator of the complement cascade, and glomerular C3 deposition has been associated with disease progression. In addition, activation of the lectin pathway contributes to disease severity. Glomerular C4d deposition has been associated with increased histological disease activity, accelerated decline in estimated glomerular filtration rate, and increased risk of renal failure.[55]

Several genes associated with susceptibility to renal injury in IgAN have been identified. Chen et al.[32] reported that ATF3, FOSB, and CXCL6 may serve as potential biomarkers of IgAN. CXCL6 appears particularly relevant, as it may contribute to disease

pathogenesis through the recruitment and enrichment of immune cells.

Gholaminejad et al.[56] and Hu et al.[57] identified 11 genes as potentially important contributors to IgAN pathogenesis, including transmembrane proteins such as CD44, TLR1, TLR2, GNG11, CSF1R, TYROBP, ITGB2, and PECAM1, as well as DNMT1, CYBB, and PSMB9. Furthermore, Zhai et al.[58] demonstrated that HMGB2, a target gene of hsa-miR-590-3p, is associated with IgAN pathogenesis and severity.

Infections are considered important contributors to IgAN pathogenesis, because synpharyngitic hematuria is a characteristic clinical feature of the disease. More recent evidence has also shown that alterations in the intestinal microbiome have a profound effect on host immune responses and may contribute to the development and progression of IgAN.[59-61] Additionally, specific strains of *Streptococcus mutants*, a pathogen associated with dental caries, have been associated with IgAN when present in the tonsils.[63]

Overall, consistent with the conclusions of Xia et al.,[23] interactions among genetic factors, immune dysregulation, and environmental influences appear to lead to the heterogeneity of clinical manifestations observed in patients with IgAN.

Linear IgA bullous dermatosis

The literature search using the selected descriptors identified 3 articles, all of which met the inclusion criteria. The study selection process is presented in a PRISMA flow diagram (Figure 5).[6] Although relatively few studies specifically addressed the pathogenic mechanisms of IgA deposition in LABD, limiting the availability of preliminary evidence, the importance of this topic and the need for further research remain evident. The diagram summarizing the main findings is shown in Figure 6.

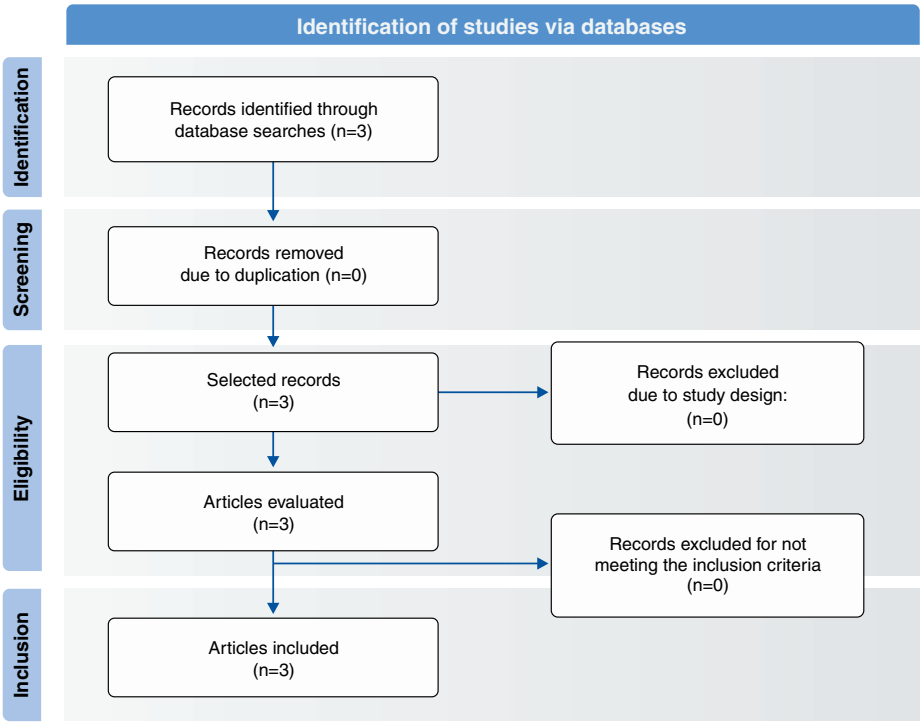

Figure 5
PRISMA flow diagram[6] of records identified for IgA dermatosis

According to Bernett et al.,[64] genetic predisposition may contribute to the development of chronic bullous disease of childhood, and several types of HLA alleles have been implicated as harbingers of an increased risk of developing the disease. HLA-B8, HLA-DR3, HLA-DQ2, and HLA-cw7 are well known for their association with both pediatric and adult forms of LABD.

Perkovic et al.[65] demonstrated that epidermolysis bullosa acquisita is induced by autoantibodies against type VII collagen, an important component of the anchoring fibrils located at the dermal-epidermal junction (DEJ). Binding of these autoantibodies to type VII collagen results in the detachment of the epidermis and the formation of mucocutaneous blisters.

Costan et al.[66] described pemphigus as a group of chronic inflammatory diseases characterized by the production of autoantibodies against components of desmosomes. This process disrupts intercellular adhesion between keratinocytes, resulting in the formation of intraepithelial blisters. The pemphigus group consists of 4 major clinical forms: (1) pemphigus vulgaris, including the variants pemphigus vegetans and pemphigus herpetiformis; (2) pemphigus foliaceus; (3) paraneoplastic pemphigus; and (4) IgA pemphigus, which includes 2 clinical variants: intraepidermal neutrophilic IgA dermatosis and subcorneal pustular dermatosis.

Genetic susceptibility appears to play an important role in the pathogenesis of these autoimmune blistering disorders. HLA-DR4 (DRB1*0402) and HLA-DRw6 (DQB1*0503) are more frequently observed in patients with pemphigus vulgaris. In paraneoplastic pemphigus, associations have been reported with HLA class II DRB1*0344 and HLA Cw*1445, whereas HLA-DRB1*04:01, HLA-DRB1*04:06,

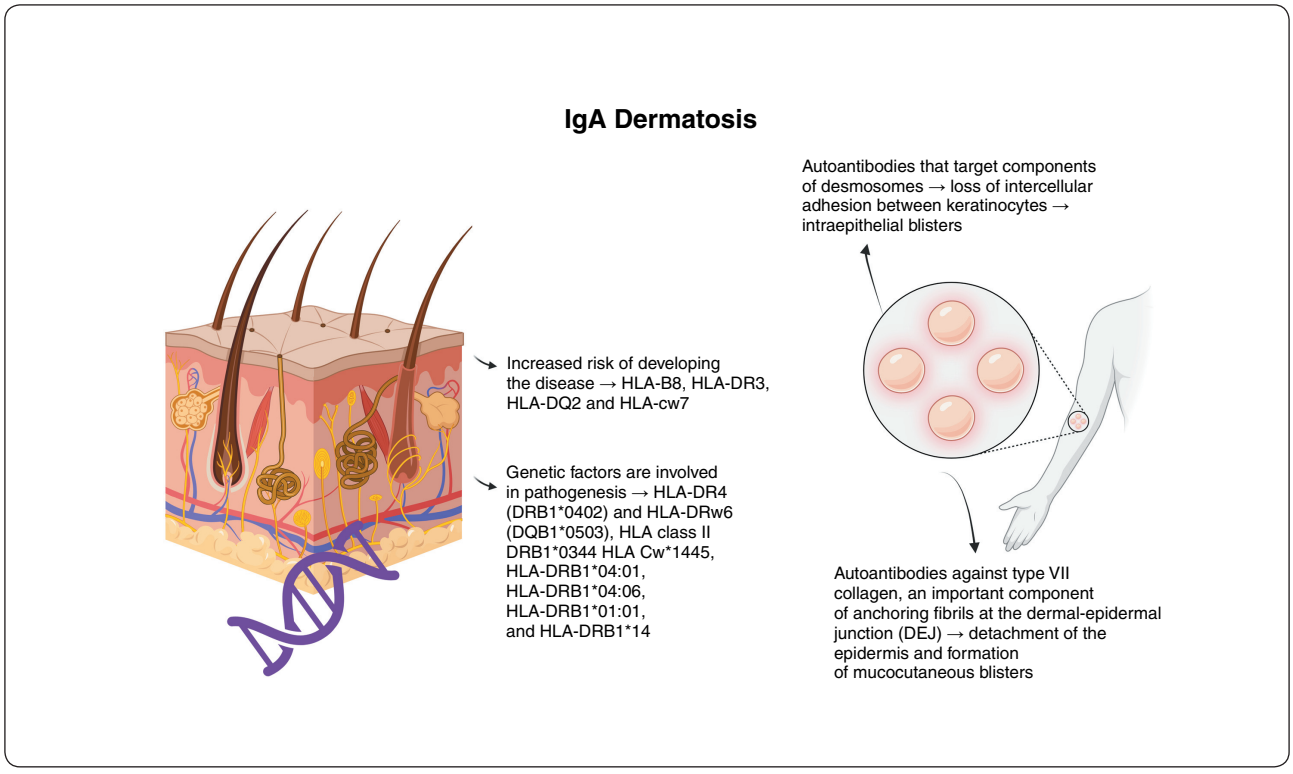

Figure 6
Practical diagram for IgA dermatosis
HLA: human leukocyte antigen.
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HLA-DRB1*01:01, and HLA-DRB1*14 have been associated with an increased risk of developing pemphigus foliaceus.[65-67]

Another bullous dermatosis related to IgA deposition is dermatitis herpetiformis, that is closely related to celiac disease (gluten intolerance).[65] Granular deposits of IgA in the papillary dermis, detected by direct immunofluorescence in perilesional skin, characterize dermatitis herpetiformis. This granular IgA pattern differentiates dermatitis herpetiformis from linear bullous IgA dermatosis, which presents with linear deposits. There is a genetic predisposition associated with certain alleles such as HLA-DR3 and- particularly- HLA-DQW2. Through a mechanism of exposure to gluten, a production of specific IgA autoantibodies (anti-tissue transglutaminase) is triggered, which are also present in the skin.[68] There are two main hypotheses for the pathogenic process, namely the possibility of circulating immune complexes that end up depositing in the skin or the IgA in the skin acting against epidermal transglutaminase.[24] The deposition of IgA in the skin causes an inflammatory reaction involving the activation of neutrophils and T cells, with consequent release of cytokines and chemokines that can explain the dermatological picture of pruritic and vesicular lesions on an erythematous base. Furthermore, it has been shown that granular IgA deposits can occur in the skin of patients with celiac disease without dermatitis herpetiformis. A prospective multicenter study found IgA deposits in 64.4% of newly diagnosed celiac patients without DH, with 100% specificity.[69]

Conclusion

Diseases associated with IgA deposition present distinct clinical phenotypes but share complex pathogenic mechanisms that remain incompletely understood. These mechanisms involve genetic susceptibility, aberrant IgA1 production, complement activation, and tissue inflammation. Therefore, reviewing and understanding the principal pathogenic processes related to IgA deposition is highly relevant for health care professionals involved in direct patient care, particularly because the multifactorial and complex nature of these diseases can make their pathophysiology challenging to interpret. This theoretical synthesis may also help identify potential prognostic biomarkers and future therapeutic targets for further investigation.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Exercise-induced bronchoconstriction

Broncoconstrição induzida pelo exercício

João Cardoso Lopes[1], Álvaro Nogueira[2], Helena Pereira[1], Pedro Botelho Alves[1]

ABSTRACT

Exercise-induced bronchoconstriction (EIB) is defined as a transient, reversible narrowing of the airways that occurs during or after physical exercise and is frequent in children, adults, and athletes. It results primarily from airway inflammation, cooling of inhaled air, and/or dehydration of the respiratory mucosa caused by hyperventilation. Typical symptoms include coughing, wheezing, dyspnea, and chest tightness, which may also manifest as early fatigue and reduced exercise performance. Diagnosis relies on a detailed clinical history, physical examination, and pulmonary function tests, using specific bronchoprovocation protocols to document a reduction in post-exercise forced expiratory volume in one second (FEV_1) or after indirect stimuli. Management combines non-pharmacological strategies – including optimization of pre-exercise warm-up routines and reduction of environmental triggers – with pharmacological measures such as short-acting β2-agonists, inhaled corticosteroids, and leukotriene receptor antagonists, tailored to the clinical context and the presence of underlying asthma. Structured follow-up, ideally involving specialists in sports medicine and allergy, is essential to ensure adequate symptom control, patient safety, and maintenance of regular physical activity.

Keywords: Exercise-induced bronchoconstriction, asthma, athletes, pulmonary function tests, beta-agonists, corticosteroids.

RESUMO

A broncoconstrição induzida pelo exercício (BIE) é caracterizada pelo estreitamento transitório e reversível das vias aéreas durante ou após o exercício físico, sendo uma condição frequente em crianças, adultos e, em particular, em atletas. Resulta sobretudo da inflamação das vias aéreas, do arrefecimento do ar inalado e/ou da desidratação da mucosa respiratória induzida pela hiperventilação. Os sintomas mais comuns incluem tosse, sibilância, dispneia e opressão torácica, podendo traduzir-se em fadiga precoce e limitação do desempenho físico. O diagnóstico baseia-se na história clínica, exame objetivo e provas de função respiratória, recorrendo a testes de broncoprovocação específicos para documentar uma diminuição do FEV_1 (volume expiratório forçado no 1° segundo) após o esforço ou após estímulos indiretos. A abordagem terapêutica combina medidas não farmacológicas – como otimização do aquecimento pré-exercício e modificação de fatores ambientais – com medidas farmacológicas, incluindo agonistas beta-2 de curta duração, corticosteroides inalados e antagonistas dos receptores dos leucotrienos, selecionados e ajustados de acordo com o contexto clínico e a presença de asma subjacente. Um seguimento estruturado, idealmente em articulação com equipes de Medicina Desportiva e Imunoalergologia, é fundamental para garantir o controlo dos sintomas, a segurança e a manutenção da prática de atividade física.

Descritores: Broncoconstrição induzida pelo exercício, asma, atletas, provas de função respiratória, beta-agonistas, corticosteroides.

Introduction

Regular physical exercise is one of the most effective means of maintaining good physical and mental health. A substantial proportion of the world's population, including patients with asthma, practices sports at both recreational and competitive levels.[1-4] On the other hand, physical exercise is one of the

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most important triggers of asthma exacerbations, and the concept of exercise-induced asthma (EIA) was introduced nearly 60 years ago.[2,5,6]

Initially, EIA broadly encompassed exercise-related respiratory conditions, including transient bronchoconstriction. Exercise was often interpreted as the "cause" of exacerbations, since most patients with asthma also exhibited exercise-induced bronchoconstriction (EIB).[5,6] Later, the concept of EIB was refined and came to designate the acute, transient, and reversible narrowing of the airways that typically occurs between 2 and 5 minutes after the onset of physical activity, reaches its peak at approximately 10 minutes, and may resolve spontaneously within 30 to 60 minutes.[7,8] EIB may occur in individuals with or without underlying asthma and is particularly frequent among athletes without a prior diagnosis of asthma.[3,4]

EIB is a distinct entity from bronchial hyper-responsiveness, which refers to the propensity of the airways to constrict in response to various bronchoconstrictive stimuli. To distinguish EIB from EIA, EIB refers specifically to acute exercise-induced bronchospasm, whereas EIA primarily reflects the inflammatory component and the overall clinical condition associated with preexisting asthma.[7,9,10]

Although international reference documents on asthma and exercise are available, practical and up-to-date syntheses on EIB—particularly for athletes and physically active individuals, with a focus on diagnosis and therapeutic strategies—remain relatively dispersed.[11,12] Therefore, the aim of this evidence-based narrative review is to consolidate the definition of EIB and to provide an integrated review of its pathophysiology, diagnostic approach, and therapeutic options, with particular emphasis on their application in clinical practice.

Methods

A non-systematic narrative review of the literature was conducted in accordance with methodological recommendations for narrative reviews (including the PRISMA - Narrative Review principles), with the aim of synthesizing the available evidence on EIB.

The literature search was conducted in two electronic databases: MEDLINE (via PubMed) and Elsevier (via ScienceDirect). Different combinations of the English search terms "exercise-induced bronchoconstriction," "asthma," "athletes," "respiratory function tests," "beta-agonists," and "corticosteroids" were used.

Original articles and case reports published between January 2010 and January 2024 were considered. Literature reviews were consulted whenever useful to provide context for the evidence. Studies published before 2010 were included when considered particularly relevant, especially publications in high-impact journals that introduced key clinical concepts or were frequently cited in more recent studies.

Duplicate articles, studies unavailable in English or Portuguese, and investigations conducted exclusively in vitro, ex vivo, or in animal models were excluded.

A total of 125 studies were identified at first. The corresponding abstracts were screened according to the inclusion criteria, taking into account originality of research, relevance to the topic, and contribution to the understanding and critical discussion of EIB. Studies that did not directly address the topic or its treatment were excluded. Following this screening process, 60 original articles and case reports were selected for the present review.

The process of study identification, screening, and inclusion is summarized in a study selection flowchart following a PRISMA framework adapted for narrative reviews (Figure 1).

Evidence-based review and discussion

This section presents and discusses the main findings available in the literature on EIB, integrating the epidemiological, pathophysiological, clinical, diagnostic, and therapeutic aspects of the condition.

Prevalence

The prevalence of EIB ranges from 5% to 20% in the general population and is higher among athletes, with an estimated prevalence of 11% to 50%.[2,3,13] The condition may develop at any age but is more frequent during childhood, with a prevalence ranging from 3% to 35% in individuals younger than 16 years. This prevalence is probably associated with the higher levels of physical activity characteristic of this age group.[14-16]

It is estimated that up to 90% of patients diagnosed with asthma exhibit some degree of EIB.[3,5] However, not all individuals with EIB necessarily have asthma.[2,3,13] On the other hand, patients with

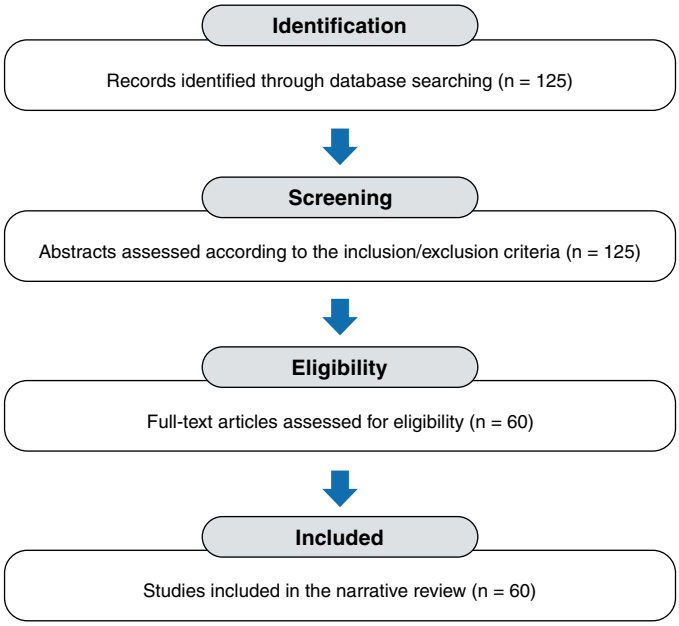

Figure 1
Study selection flowchart (PRISMA - narrative review)

mild intermittent asthma, characterized by mild bronchial inflammation and slightly increased airway hyperresponsiveness, may not develop clinically significant bronchoconstriction, even during vigorous physical exercise.[10,12]

EIB is particularly frequent among athletes and is most prevalent in endurance sports, in which the ventilatory load is high and sustained over time.[4,11,17] A systematic review reported that the prevalence of EIB among adolescent athletes with asthma ranges from 2.1% to 61%.[13] This heterogeneity may be attributable, for example, to differences in sample size, ethnic or environmental factors, and the nature of study designs.[14,16]

EIB may occur in any athlete and in any environment. However, athletes who compete in endurance sports involving prolonged periods of intense aerobic activity appear to be at higher risk. In particular, Mountjoy et al. observed that the competitive sports most commonly associated with the need for a Therapeutic Use Exemption (TUE) among athletes diagnosed with asthma were swimming, cycling, triathlon, pentathlon, and rowing, with reported prevalence rates ranging from 7% to 18%.[4,18] In contrast, the prevalence of asthma among athletes participating in sports such as gymnastics, fencing, and sailing was below 5%.[4]

Nevertheless, EIB in athletes remains underdiagnosed, both because symptoms may be underreported and because self-reported exercise-induced dyspnea is a poor predictor of EIB when regarded as an isolated symptom.[11,13]

Pathophysiology

Pathophysiological theories

The pathophysiology of EIB is multifactorial and still not fully understood.

Several distinct mechanisms have been proposed. Initially, it was speculated that cold, dry air played an important role: during exercise, increased inhalation of large volumes of air was thought to exceed the capacity of the upper airways to adequately warm it, allowing colder and drier air to reach the distal lower airways.[7,8] Based on this rationale, the thermal

hypothesis was proposed—airway cooling followed by rapid rewarming would cause reactive hyperemia of the bronchial microvasculature and edema of the airway wall, ultimately resulting in their narrowing.[7,8] However, neither airway cooling nor rewarming appears to be necessary factors for the development of EIB. Some studies have shown that severe EIB may occur under conditions of warm, dry air, challenging the role of cold air in its pathophysiology.

More recently, airway dehydration resulting from the high respiratory rate has been proposed as the primary trigger of bronchoconstriction, producing substantial osmotic changes (Figure 2).[19] Known as the osmotic hypothesis, this concept proposes that the increase in minute ventilation promotes mouth breathing, leading to cooling and dehydration of the mucosa throughout the airways. As water evaporates from the airway surface, the airway surface liquid becomes hyperosmolar, providing an osmotic stimulus for extracellular water movement that results in cell shrinkage. As a consequence of this dehydration, the cell-volume regulatory mechanisms promote the release of inflammatory mediators from mast cells (such as prostaglandins, leukotrienes, and histamine), ultimately leading to smooth muscle contraction and increased vascular permeability.[8,10] Airway cooling itself also triggers activation of cholinergic receptors in the airways, resulting in increased smooth muscle tone in the airway and enhanced mucus secretion.[8,20] In addition, during physical effort, water supply to the central airways is insufficient to meet the increased demand for humidification. This requires recruitment of the small airways, which, despite having a substantially greater volume of airway surface liquid, are also more susceptible to dehydration-induced injury because their diameter is less than 1 mm.[21]

In addition to the pathophysiological hypotheses described above, the literature also implicates other factors in the pathophysiology of EIB.

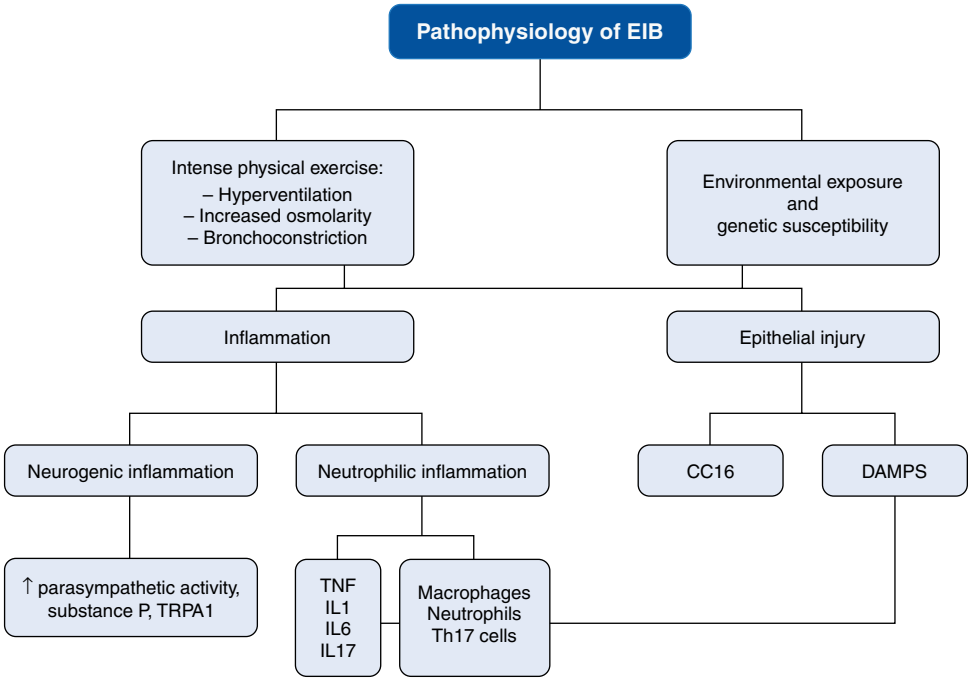

Figure 2

Pathophysiology of exercise-induced bronchoconstriction (EIB)

CC16: Clara Cell 16, DAMPS: Danger-Associated Molecular Patterns, IL: interleukin, Th17: T helper 17, TNF: tumor necrosis factor, TRPA1: transient receptor potential ankyrin 1.

Pro-inflammatory phenomena are particularly evident in individuals exposed to irritants associated with certain sports, such as chlorine in swimmers, air pollution in runners and cyclists, and cold, dry air in ice hockey players.[13,22]

Furthermore, intense and prolonged physical activity may induce some degree of autonomic dysfunction, and neurogenic inflammation may also play an important role in the pathogenesis of EIB. Endurance athletes are known to have increased parasympathetic activity, which promotes bronchoconstriction. Increased levels of substance P, an important factor in neurogenic inflammation, have also been observed following intense exercise.[8,20,21]

Finally, several genetic alterations have been proposed in the pathogenesis of EIB. These include the PPT-1 gene, which is involved in substance P production; the aquaporin channel (AQP5) gene, which may contribute to protecting airway reactivity against nonspecific stimuli; and the gene encoding protein CC16, a biomarker of respiratory epithelial injury. However, an association between these genetic alterations and the development of EIB has yet to be demonstrated.[8,23]

Aggravating factors

Environmental factors

The environment, including exposure to temperature, humidity, aeroallergens, irritants, and air pollution, may influence the pathophysiology of EIB.

Depending on the sport, hyperosmolarity of the upper and lower airways may be caused by hyperventilation (in runners), leading to bronchoconstriction, nasal congestion, rhinorrhea, and impaired mucociliary function, as well as by exposure to irritants, allergens, and atmospheric pollutants, as previously described.[11,13,17]

Similarly, swimmers may develop nasal congestion, rhinorrhea, and bronchospasm secondary to inhalation of chloramines derived from hypochlorite, found in swimming pool disinfectants. Studies indicate that chlorination by-products present in chlorinated pools may adversely affect swimmers' respiratory health, particularly in indoor facilities, due to the higher concentration of volatile compounds. Pools using alternative disinfection methods (eg, UV irradiation) seem to reduce these risks.[22]

Divers may develop nasal congestion and rhinosinusitis secondary to barotrauma, while boxers may experience increased nasal resistance, impaired mucus clearance, and anosmia/hyposmia as a result of repeated nasal trauma. Finally, skiers and skaters may develop bronchospasm and rhinitis secondary to the irritant effects of cold, dry air or ultrafine particles and nitrogen dioxide generated by ice resurfacers. In addition, adverse weather conditions, such as low temperatures, are frequently identified as aggravating factors for EIB, with this condition reported in 24% of winter sports athletes.

Urban and high vehicular traffic areas may also be considered risk factors. Indeed, air quality has increasingly been recognized as having a significant impact on lung health, although most studies have focused on competitive athletes. This association between air quality and athletes' respiratory health raises the possibility of an association between airway epithelial injury and subsequent development of airway hyperresponsiveness.

However, further studies are required to determine the contribution of environmental factors to the bronchial modulatory effects observed in EIB.

Atopy

Atopy and training styles are independent risk factors for EIA/EIB. Atopy has been shown to contribute significantly to and amplify the inflammatory phenomena described above.[14,16]

Following exposure to aeroallergens such as pollens, house mites, and dander, the respiratory epithelium releases alarmins, pro-inflammatory signaling proteins that initiate a cascade culminating in epithelial injury. This mechanism is particularly relevant in patients with asthma, in whom the immune response to alarmins may result in chronic airway inflammation. Collectively, these processes contribute to impaired mucociliary clearance and airway remodeling. For example, atopic athletes have a 25-fold higher risk of EIB compared to non-atopic individuals. Deep-sea divers have a 42-fold higher risk, and elite swimmers have a 92-fold higher risk of developing EIB.[11]

In patients with asthma, in whom persistent bronchial inflammation is the primary underlying mechanism, acute intense exercise may further exacerbate airway inflammation—hyperpnea induces epithelial injury and increases the production of leukotrienes and inflammatory cytokines (IL-1, TNF-α, and IL-6), findings that have been demonstrated in bronchoalveolar lavage fluid from athletes with EIB.[8,13,20,21]

In addition, increased numbers of eosinophils have been detected in the blood and sputum of patients with EIB, together with elevated levels of exhaled nitric oxide, histamine, tryptase, and leukotrienes, as well as evidence of subsequent epithelial injury.[24-26]

Clinical manifestations

The most frequent clinical manifestations include dyspnea, wheezing, and cough; however, chest tightness/discomfort may also occur (particularly in children). More subtle symptoms, such as early fatigue and decreased performance, may also be present, especially in athletes.[11]

Atypical symptoms include muscle cramps and chest pain, and, in some cases, dysphonia or stridor.

The clinical spectrum is highly variable in terms of severity, ranging from mild chest tightness with subsequent reduction in pulmonary function to severe bronchospasm with marked reduction in FEV_1, which may even progress to respiratory failure.[12,13]

EIB typically develops 2 to 5 minutes after the onset of exercise, reaches its peak at approximately 10 minutes, and resolves spontaneously within about 30-60 minutes if appropriate treatment is not provided.[2,3] However, more recent international guidelines, including the Guía Española para el Manejo del Asma 5.4 (Spanish Guideline on the Management of Asthma — GEMA 5.4), state that symptoms may occur during or after exercise and may be followed by a refractory period lasting 2 to 3 hours.

Diagnostic approach

The diagnostic approach to EIB should begin with a detailed clinical history followed by a thorough physical examination. However, symptoms are not pathognomonic, and a diagnosis of EIB based solely on symptoms lacks both sensitivity and specificity for predicting a positive exercise challenge test result in either adults or children. Moreover, physical examination does not reveal abnormalities in most cases.[2,3]

Therefore, diagnostic confirmation requires complementary testing, including assessment of pulmonary function and airway inflammation.

Pulmonary function testing is fundamental to the diagnosis of EIB, and the initial assessment should always include spirometry with bronchodilator testing. In most individuals with EIB, baseline pulmonary function is normal, leading to a diagnosis of isolated EIB. Spirometry with bronchodilator testing is therefore useful for distinguishing EIB from bronchial asthma.[12,27,28]

According to the Global Initiative for Asthma 2023 (GINA) and GEMA 5.4, the result of a bronchodilator test is considered positive when FEV_1 increases by 12% or more and 200 mL or more from baseline, or by more than 10% of predicted value in FEV_1 or FVC.[12,27,28] This finding confirms airway reversibility and supports the diagnosis of asthma.

If spirometry with bronchodilator testing is normal, bronchial provocation testing is recommended. Bronchial provocation testing may use direct stimuli (acting directly on effector cells), such as methacholine or histamine, or indirect stimuli (which mediate secondary activation of effector cells), such as exercise, mannitol, hypertonic solutions, or eucapnic voluntary hyperventilation. A positive test result, defined as a reduction in FEV_1 of at least 10% to 15% from baseline (depending on the stimulus used), establishes the diagnosis.[9,10,13,29]

The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) consider exercise bronchial provocation testing to be the most useful for diagnosing EIB in individuals without a history of asthma who have normal spirometry and no response to bronchodilator testing.[13,29]

Exercise bronchial provocation testing, performed on a treadmill or cycle ergometer, requires 6 to 8 minutes of exercise at an intensity sufficient to achieve 40%-60% of the maximum voluntary ventilation (MVV), where $MVV = 35 \times FEV_1$. This level of intensity should be maintained for 4 minutes. Heart rate should be monitored, and in individuals aged 40 years and older, continuous electrocardiographic monitoring should be performed throughout exercise and for 5 minutes after its completion.[22,24]

A decrease of 10% or more in FEV_1 compared with the pre-exercise value is diagnostic of EIB.

It is not always possible to ensure that all individuals achieve the required level of ventilation or maintain treadmill or cycle ergometer exercise at sufficient intensity and duration to induce bronchoconstriction. To overcome this limitation, an alternative test based on achieving high levels of ventilation was developed.[13]

Eucapnic voluntary hyperventilation, a technique with 82% sensitivity and 70% specificity, consists of hyperventilating a gaseous mixture containing

5% CO_2 and 21% O_2 at 85% of the maximum voluntary ventilation for 6 minutes. FEV_1 is measured at predetermined intervals after hyperventilation, applying the same diagnostic criterion of a decrease of 10% or more in FEV_1 compared with baseline.[22,29]

When the objective is to assess EIB in patients with known asthma, it is preferable to begin with an incremental challenge test, such as the mannitol challenge. If the result is negative but clinical suspicion remains high, an additional challenge using a different stimulus should be considered. For elite athletes, bronchial provocation tests accepted for diagnosis of EIB include exercise challenge, eucapnic voluntary hyperventilation, hypertonic saline, mannitol, and methacholine challenge tests.[3,11-13,18,29]

When assessing airway inflammation, measurement of fractional exhaled nitric oxide (FeNO) is a reliable, noninvasive method.

Interpretation of FeNO results is generally based on fixed cutoff values (measured in parts per billion [ppb]), as recommended by the American Thoracic Society[26]: low (< 25 ppb in adults and < 20 ppb in children), intermediate (25-50 ppb in adults and 20-35 ppb in children), and high (> 50 ppb in adults and > 35 ppb in children). However, reference equations that account for individual factors such as sex, age, height, and smoking have recently been developed.[26]

Elevated FeNO levels have been linked to EIB in children with atopic asthma, regardless of other indicators of asthma severity or medication dosage. FeNO has been proposed as a screening tool for EIB in this age group.[8,16]

EIB has also been shown to correlate with FeNO levels and with mannitol bronchial provocation testing. Because FeNO measurement is faster and safer than mannitol bronchial provocation testing, its use is also recommended as a diagnostic assessment tool.[13,29]

Another potentially useful complementary test is induced sputum analysis. Although not part of routine clinical practice, it may be used to determine the etiopathogenesis of EIB.[9,10]

Differential diagnosis

Other causes of exercise-induced dyspnea should be considered in the differential diagnosis of EIB, particularly in individuals without other asthma symptoms, with normal baseline spirometry, and in the absence of a response to bronchodilator therapy.[2,3,13]

Potential differential diagnoses include central airway obstruction, paradoxical vocal fold motion, laryngomalacia, exercise-induced anaphylaxis, interstitial lung disease, gastroesophageal reflux disease, physical deconditioning, dysfunctional breathing, coronary artery disease, and exercise-induced arrhythmias in patients presenting with atypical exercise-induced dyspnea.[11]

Diagnosis often requires a high degree of clinical suspicion.

The following conditions in particular should be considered:

– Exercise-induced laryngeal obstruction, previously known as paradoxical vocal fold motion or vocal cord dysfunction, presents as inspiratory stridor accompanied by respiratory distress during exercise.[30]
– Exercise-induced anaphylaxis, characterized by the abrupt onset of multisystem symptoms, with dyspnea accompanied by other symptoms, ranging from generalized pruritus and urticaria to hypotension and/or cardiovascular collapse.[11,13]
– Dysfunctional breathing, such as hyperventilation, deep sighing, thoracic-dominant breathing, predominantly mouth breathing, use of accessory muscles at rest, and thoracoabdominal asynchrony, may contribute to persistent dyspnea during exercise and may be present in association with EIB or as an independent diagnosis.[25,31]

Therapeutic approach

The combination of general measures and pharmacological intervention can prevent EIB in almost all patients (Table 1).[3,11,13] One of the primary goals of treatment is to ensure that physical activity is not avoided.[12,28]

Nonpharmacological measures

A better understanding of the pathophysiology of EIB has resulted in general recommendations that may help reduce its impact. These measures are based on the strict relationship between the severity of bronchoconstriction and the magnitude of minute ventilation, as well as the temperature and humidity of inhaled air.[7,8]

One proposed measure is to incorporate an appropriate warm-up before exercise and a gradual return to baseline afterward—a pre-exercise warm-up at submaximal intensity for approximately 15 minutes is recommended.

In addition, better cardiovascular fitness reduces the minute ventilation required for a given exercise level, thereby decreasing the stimulus for bronchoconstriction. Some studies suggest that high-intensity and variable-intensity warm-up protocols mitigate the decline in FEV_1, although the data remain inconsistent.[11,13,32]

For individuals with EIB who participate in sports in cold climates, the use of devices that warm and humidify air during exercise—such as a face mask or scarf—is recommended.[3,22]

Other nonpharmacological measures include education on avoiding or minimizing exposure to environmental factors and instruction in proper inhaler technique when bronchodilator therapy is prescribed.[11,12,33]

Pharmacological measures

Selection of pharmacotherapy

The treatment of EIB has been studied primarily in patients with EIB and underlying asthma. Therapeutic options for isolated EIB have not been investigated extensively.[3,11-13]

EIB frequently occurs in patients with poorly controlled asthma, and in these cases, the main therapeutic strategy is to optimize treatment of the underlying asthma.[12,22,28]

For isolated EIB, there is no specific consensus on its management, and treatment should therefore be individualized.[10]

The therapy regimen should depend on the patient's age, the type of exercise they practice, patient preference, and the concomitant presence of asthma.

In any case, combination therapy seems to be more effective than monotherapy, and inhaled corticosteroids (ICSs) and leukotriene receptor antagonists (LTRAs) are the therapies most frequently used in combination.[10,13,34]

In addition, pre-exercise prophylactic treatment with an inhaled short-acting beta-2-agonist (SABA) should be considered for all patients.

The following sections briefly describe the main pharmacological agents available in Portugal for the management of patients with EIB.[12,22,35]

Table 1 lists several therapeutic approaches based on different clinical scenarios of EIB.

Short-acting beta-2-agonists

SABAs are the most effective medications for EIB. They are the most frequently recommended pre-exercise prophylactic therapy to minimize or prevent EIB symptoms. A regimen of 2 to 4 inhalations of a SABA 15 to 30 minutes before exercise appears to provide peak bronchodilation within 15 to 60 minutes and airway protection for at least 3 hours in most individuals.[10,12,13]

On the other hand, regular SABA use may lead to the development of tachyphylaxis. Reduced duration of beta-2-agonist protection may result in increased use and, consequently, a higher risk of adverse effects, such as tremor, palpitations, and other dose-dependent effects. In such cases, maintenance therapy, particularly with ICSs, should be added, especially with recurrent SABA use.[3,11]

The addition of a corticosteroid may also be warranted in patients with persistent concomitant asthma. This may be achieved with combination therapy, such as budesonide/formoterol (160 µg/4.5 µg), administered as one inhalation approximately 5 to 20 minutes before exercise.[12,22,28]

Long-acting beta-2-agonists

Pharmacologically, long-acting beta-2-agonists (LABAs) act similarly to SABAs. However, their bronchodilator effect may last up to 12 hours, making them more suitable for prolonged-duration sports (eg, deep-sea diving).

Although considered effective in preventing EIB, concerns regarding tachyphylaxis have led to recommendations against their use as monotherapy.[10,13]

The recommended dose is one inhalation 30 minutes before exercise for salmeterol or 15 minutes before exercise for formoterol.

In patients with asthma, LABAs should not be used as monotherapy, given the potential risk of morbidity and mortality during exacerbations; they should always be prescribed in combination with ICSs.[12,28]

Inhaled corticosteroids

Although ICSs do not provide immediate protection against bronchoconstriction, they reduce airway hyperresponsiveness over time, thereby decreasing the extent of bronchoconstriction induced by the same level of physical exertion.[12,13]

Table 1
Therapeutic approach to EIB in different clinical settings

Problem	Intervention	Comments
In **all** patients with **EIB**	Inform about exercise characteristics that may trigger EIB (effects of temperature, dry air, exercise intensity, allergens, and air pollution) and attenuation strategies	–
	Inform about the use of SABA to relieve EIB symptoms	–
	Provide instructions on the use of SABA or other agents to prevent EIB	–
	Advise caution regarding vigorous exercise when underlying asthma is poorly controlled	–
Patients **intolerant to SABA**	Try a lower dose of salbutamol	May not provide adequate symptom prevention
	Review inhalation technique and consider using a spacer	–
	Improve overall control of the underlying asthma (eg, with ICSs) to reduce the need for prophylaxis	If asthma is not well controlled, add an ICS. If asthma is well controlled, try alternative preventive agents
	Try an alternative SABA	–
	Try regular LTRA use	LTRAs may be more effective in children than in adults
	Try SAMA (ipratropium bromide): 2 inhalations, 20-30 minutes before exercise	–
SABA-refractory EIB	Add regular LTRA use	–
	Improve overall control of the underlying asthma if possible (eg, with ICSs)	
	Reassess diagnosis	
Patients **exercising** for **more than 3 hours per day or more than once daily**	Avoid LABA monotherapy or daily SABA use	Daily SABA or LABA use may lead to tachyphylaxis
	Try LTRA	May be more effective in preventing EIB in children than in adults
	Improve overall control of the underlying asthma (eg, with ICSs)	–
Patients **exercising** under **extreme conditions** (eg, high-intensity exercise or cold, dry air)	Try mitigation methods (eg, warm-up, scarf, or face mask), depending on the context	–
	Empirical trial of salbutamol plus ipratropium bromide 20-30 minutes before exercise	–

EIB: exercise-induced bronchoconstriction; ICS: inhaled corticosteroids; LABA: long-acting beta-2-agonists; SABA: short-acting beta-2-agonists; LTRA: leukotriene receptor antagonists; SAMA: short-acting muscarinic receptor antagonists; LAMA: long-acting muscarinic receptor antagonists.

ICSs are the first-line controller therapy for patients with diagnosed asthma and concomitant EIB and should be used daily.

Most guidelines recommend the use of low-dose ICS, even for isolated EIB. These include fluticasone, budesonide, mometasone, and beclomethasone, among others.[18,22]

Although studies have shown the benefit of a single-dose ICS regimen in EIB, therapeutic efficacy increases when treatment is continued for 7 to 14 days, with maximal effects expected after approximately 8 weeks of treatment.

It should be stressed that ICS does not require a TUE from the World Anti-Doping Agency (WADA), unlike oral or intravenous corticosteroid therapy.[18,22]

Leukotriene receptor antagonists

LTRAs exert anti-inflammatory effects and may prevent bronchoconstriction when used continuously. These medications do not have short-acting bronchodilator effects and therefore do not reverse acute bronchoconstriction. However, they contribute to faster recovery and help reduce bronchospasm, although they are comparatively less effective than beta-2-agonists or ICSs.

Indeed, compared with salbutamol, montelukast (the only LTRA available in Portugal) was less effective when taken immediately before exercise as well as less effective than low-dose ICS.[34]

Accordingly, combining LTRAs with either a LABA or a SABA (with greater synergistic benefit observed with the latter) seems to be more effective than monotherapy.

LTRAs should be administered orally once per day, approximately 2 hours before exercise, and there appears to be no risk of developing tolerance. On the other hand, 30% to 40% of patients treated with LTRAs are unresponsive.[3,11]

These medications may be useful in patients who have difficulty with inhalation technique and may be a feasible monotherapy option for individuals with EIB who exercise only a few times per week. However, their effect is heterogeneous, with considerable variability in efficacy across individuals.

Anticholinergic agents or short- and long-acting muscarinic receptor antagonists (SAMAs and LAMAs)

Anticholinergic agents such as ipratropium bromide (SAMA) and tiotropium (LAMA) have also been shown to be effective in the treatment of EIB, although they appear to be less effective than the more commonly used agents discussed above.[10,13]

Ipratropium bromide is generally not used for rapid symptom relief because its bronchodilator effect is slower (onset in approximately 15 minutes, peak effect at 1-2 hours) than that of SABAs.[10]

Studies in competitive cross-country skiers have shown that inhaled ipratropium bromide (SAMA) was associated with a greater increase in FEV_1 than inhaled salbutamol. Furthermore, improvement in FEV_1 correlated with lower airway hyperresponsiveness on methacholine bronchoprovocation testing. Nevertheless, it remains unclear whether this response translates into greater protection against EIB during intense exercise in cold air.[35]

Monitoring

Response to treatment may be assessed subjectively in terms of symptom control and exercise tolerance. Measurement of peak expiratory flow (PEF) before and after exercise may be useful, although FEV_1 measurements are more reliable.[13,27,30]

Although monitoring PEF at home or during sports or exercise has not been shown to prevent EIB, sports medicine specialists and some athletic programs have used PEF monitoring to detect subclinical or previously undiagnosed EIB in athletes.[10,22,24]

When an objective assessment of therapeutic response is required, an exercise bronchoprovocation test should be performed as an alternative to the more widely available methacholine bronchoprovocation test.[22,29]

Conclusion

EIB, which affects up to 20% of the population, corresponds to episodic bronchoconstriction occurring during and/or after exercise as a result of acute, transient, and reversible airway narrowing.

The pathophysiological mechanisms of EIB have yet to be fully explained, but several models support the combined roles of inflammation and cell damage, osmotic changes, neurogenic phenomena, and epithelial stress as the most likely hypotheses.

Diagnosis requires complementary testing, to wit, pulmonary function testing with bronchoconstrictive stimuli. No single currently available test can identify all individuals with EIB; therefore, the choice of diagnostic protocol should be tailored to the clinical context

and, in elite athletes, to regulatory requirements. In patients with known asthma, the mannitol challenge test may be particularly useful, whereas in elite athletes, exercise bronchoprovocation test, eucapnic voluntary hyperventilation, hyperosmolar solutions, mannitol, or methacholine bronchoprovocation tests are recommended.

Pharmacologic treatment of EIB varies according to clinical setting and should be individualized. Overall, it includes beta-2-adrenergic receptor agonists administered 15-30 minutes before exercise, and long-acting beta-2-agonists may be beneficial for prolonged-duration activities. In patients with concomitant asthma, asthma controller therapy with ICSs is key, often in combination with other medications.

In conclusion, this review addresses various aspects of EIB, highlighting its mechanisms, clinical impact, and therapeutic options. Further studies are needed to clarify its pathophysiological mechanisms and responses to different treatment strategies in order to support more precise and personalized approaches. It should be emphasized that, with appropriate assessment and proper treatment, EIB should not represent a barrier to participation in recreational or competitive sports.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Anaphylaxis and hidden allergens

Anafilaxia e os alérgenos ocultos

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ABSTRACT

Allergic immediate hypersensitivity reactions may be triggered by high-molecular-weight agents, such as food proteins, seeds, grains, spices, and insects, or by low-molecular-weight agents, such as chemicals and industrial additives. These allergens can induce respiratory and cutaneous manifestations, and may cause severe systemic reactions such as anaphylaxis. When not properly identified on product labels, when present as unexpected contaminants, or when introduced as novel ingredients in previously safe products, they are known as hidden allergens. These components may go unnoticed during clinical investigation, contributing to misdiagnosis, particularly in cases classified as idiopathic anaphylaxis. The goal of this review is to provide a comprehensive understanding of rare causes of anaphylaxis triggered by hidden allergens, emphasizing the importance of recognizing them as potential triggers for accurate diagnosis and appropriate preventive measures. The methods employed included a narrative review of the MEDLINE, LILACS, and SciELO databases covering the period from April 2024 to April 2025. Original open-access studies published in English or Portuguese were selected without date restrictions. Incomplete articles, conference proceedings, opinion papers, review articles, and studies not directly addressing the topic were excluded. The findings reinforce that the identification of hidden allergens remains a significant challenge in clinical practice. Although not intended to be exhaustive, this review highlights the need to routinely consider these agents in the etiological investigation of allergic reactions,

RESUMO

As reações de hipersensibilidade imediata alérgicas podem ser desencadeadas por agentes de alto peso molecular, como proteínas alimentares, sementes, grãos, especiarias e insetos, ou por agentes de baixo peso molecular, como produtos químicos e aditivos industriais. Esses alérgenos são capazes de induzir manifestações respiratórias, cutâneas e até quadros sistêmicos graves, como anafilaxia. Quando não estão devidamente identificados nos rótulos de produtos, são contaminantes inesperados ou representam novos ingredientes adicionados a itens previamente seguros, recebem a denominação de alérgenos ocultos. Esses componentes podem passar despercebidos durante a investigação clínica, contribuindo para diagnósticos equivocados, especialmente nos casos classificados como anafilaxia idiopática. Esta revisão tem como objetivo a compreensão ampla das causas raras de anafilaxia provocadas por alérgenos ocultos, reforçando a importância de reconhecê-los como possíveis gatilhos, essencial para o diagnóstico correto e orientação de medidas preventivas eficazes. Os métodos empregados incluíram uma revisão narrativa nas bases MEDLINE, LILACS e SciELO, no período de abril de 2024 a abril de 2025. Foram selecionados estudos originais, de acesso aberto, nos idiomas inglês ou português, sem restrições de data. Excluíram-se artigos incompletos, anais de congressos, opiniões, resenhas e trabalhos que não abordassem diretamente o tema. Os achados reforçam que a identificação de alérgenos ocultos permanece um desafio significativo na prática clínica. Embora não esgote o tema, esta revisão destaca a necessidade

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especially in cases of idiopathic anaphylaxis, as well as the importance of developing investigation guidelines and algorithms to facilitate diagnosis.

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de considerar rotineiramente esses agentes na investigação etiológica de reações alérgicas, sobretudo nos quadros de anafilaxia idiopática, além de criar algoritmos e diretrizes de investigação, visando facilitar o diagnóstico.

Descritores: Anafilaxia, alérgenos, cosméticos, excipientes, alimentos.

Introduction

The agents involved in allergic immediate hypersensitivity reactions (IHRs) are commonly classified as high molecular weight (HMW) and low molecular weight (LMW).[1] These allergens may trigger respiratory diseases such as rhinitis and asthma; skin allergies; as well as severe systemic reactions, such as anaphylaxis.

When they are not identified on labels, either in finished products or their sources, or when they are present as contaminants or new ingredients in products that previously did not contain them, they are known as hidden allergens.[2] Examples of high-molecular-weight allergens include seeds, grains, foods, spices, and insects, whereas low-molecular-weight allergens include chemicals and additives.

This review provides a comprehensive overview of rare causes of anaphylaxis related to hidden allergens, which are often overlooked and may lead to misdiagnoses of idiopathic anaphylaxis. Understanding these uncommon triggers is essential for the accurate diagnosis of anaphylactic reactions.

Below, we review the most important hidden allergens involved in anaphylactic reactions.

The goal of this review is to increase awareness among health care professionals regarding hidden allergens so that etiological investigation can become increasingly accurate, thereby directly improving quality of life for patients at risk of anaphylaxis.

Methods

In this narrative review, we searched the MEDLINE, LILACS, and SciELO databases from April 2024 to April 2025. Electronic bulletins published by ANVISA (Brazil's National Health Surveillance Agency) were also included. The inclusion criteria were original studies available in full text and free of charge, with no restrictions on publication date, published in English or Portuguese. The exclusion criteria comprised articles unavailable in full text, book reviews, conference proceedings, opinion articles, review studies, and other studies that did not directly address the subject of this review. A total of 93 articles were included. The following keywords were used: allergens, hidden, children, adults, allergy, anaphylaxis, foods, medications, excipients, latex, perioperative, pancake syndrome, oral mite anaphylaxis, cosmetics, occupational, antiseptic.

Hidden allergens

Latex

The discovery and widespread use of latex predate the arrival of Europeans in the Americas, demonstrating the long history of use of this natural material. Over the years, latex came to be used in a wide variety of products and may therefore represent a “hidden” cause of anaphylaxis, as its presence may not be identified in certain objects or may not be suspected.[4,5] Natural rubber is secreted by the Amazonian tree Hevea brasiliensis (Hev b), commonly known as the rubber tree, and consists of a long-chain unsaturated aliphatic hydrocarbon polymer.[5,6] Frequent and prolonged exposure to products containing latex proteins appears to be the main cause of sensitization. Latex allergies may be IgE-mediated (type I) or, less commonly, mediated by a type IV hypersensitivity mechanism.[5,7,8]

Exposure to hidden latex allergens may trigger reactions even without direct contact with conventional latex products such as gloves or catheters.[9,10] It is estimated that more than 40,000 products contain latex,[1] and some may release proteins or contain powdered lubricants that carry airborne latex proteins, which may cause reactions, including anaphylaxis, via inhalation[10,11] (Table 1).

Beginning in the late 1990s, preventive measures against latex allergy were implemented, such as the production of low-allergen latex gloves, restrictions or bans on powdered latex gloves in some countries,

Table 1
Potential sources of latex[11]

Environment	Products that may contain latex
Home	Gloves, toys, shower curtains, garden hoses, bath mats, sponges, balloons, condoms, fabrics containing elastane, hair glue, pacifiers and baby bottle nipples, elastic bands, resistance bands, physical therapy bands, rubber bands, footwear, inflatable mattresses, sports equipment (swim masks, goggles, fins)
Office	Adhesive tape, erasers, telephone cords, mouse pads, rubber bands
Medical	Gloves, cervical dilators, tourniquets, probes, electrodes, drains, catheters, surgical masks, hemodialyzers, infusion sets, anesthesia masks, vial stoppers
Dental	Gloves, adhesives, dressings and packaging, orthodontic elastics, root canal sealers, dental polishing rubber, others

and public health campaigns.[12] The prevalence of latex sensitization in the general population ranges from < 1% to 7.6%, but may reach 64% in specific high-risk groups.[13] The main risk groups are health care workers and patients undergoing multiple surgical procedures, particularly those with myelomeningocele.[14,15] To date, 15 latex allergens have been identified and characterized (Table 2), and the sensitization profile is likely influenced by genetic factors, underlying disease, onset of exposure, and route of exposure.

Between 21% and 58% of patients with latex allergy exhibit cross-reactivity with plant foods, particularly fruits, resulting in latex-fruit syndrome.[10] Class I chitinases (Hev b 6), which have defensive functions, play an important role in this syndrome because of their high homology with chitinases present in other plant species (banana, avocado, and chestnut).[4,10,15] Health care professionals are the group most frequently and severely affected by latex-fruit syndrome and may present food-induced anaphylaxis as the initial manifestation,[5] whereas the syndrome appears to be rare and associated with mild reactions in patients with myelomeningocele.[16]

Diagnosis should be based on a suggestive clinical history together with confirmation of sensitization by epicutaneous testing (skin prick testing), serum testing, and/or challenge testing.[4,17] Latex-induced anaphylaxis usually occurs during surgical procedures and dental interventions[7]; therefore, latex should always be investigated as a possible cause in anaphylactic reactions in these settings.[18] Measurement of serum-specific IgE allows an assessment of latex components (Hev b 1, 3, 5, 6.01, 6.02, 8, 9, and 11) and may be useful when sensitization has not been confirmed by other methods, as well as for establishing sensitization profiles in specific patient groups.[19] Challenge testing is considered the gold standard for the diagnosis of latex allergy, and its indication should be considered in three situations: sensitized but asymptomatic patients, to rule out an allergy diagnosis; patients with a highly suggestive clinical history; and patients with negative or inconclusive results from other methods.[20]

Mites

Oral mite anaphylaxis (OMA), also known as pancake syndrome, is an underdiagnosed allergic condition. It is an acute, potentially fatal allergic reaction that occurs shortly after ingestion of foods contaminated with mites, even after cooking. These are IgE-mediated reactions, with respiratory, cutaneous, gastrointestinal, and/or cardiovascular symptoms. OMA may also present as food-dependent exercise-induced anaphylaxis following ingestion of foods containing mites.[21]

It may affect individuals of any sex or age group but is more prevalent in tropical and subtropical regions because mites proliferate more easily in warm, humid environments. Both dust mites and storage mites may be involved, and any flour may become contaminated, although OMA is most frequently associated with wheat and corn flours used in the preparation of pancakes.[21]

The allergens involved are resistant to heat, explaining why reactions occur even after food has been cooked at high temperatures. For reasons still

Table 2
Characteristics of the primary allergenic components of latex

Allergen	Allergenicity	Name	Population at risk	Cross-reactivity
Hev b 1	32%-81%	Rubber elongation factor	SB	
Hev b 2	40%	1,3-glucanase	HCW	Banana and tomato
Hev b 3	32%-100%	SRPP	SB	
Hev b 4	39%-77%	Microhelix component		
Hev b 5	83%	Acidic latex protein	HCW	Kiwi
Hev b 6	63%-88.9%	Pro-hevein (Hev b 6.01) Hevein (Hev b 6.02) C-domain (Hev b 6.03)	HCW	Avocado, chestnut, and banana
Hev b 7	45%	Patatin-like protein	SB	Banana and tomato
Hev b 8	39%-100%	Latex profilin		Banana and pollens
Hev b 9	14.5%	Latex enolase		Tomato and fungi
Hev b 10	10%	Superoxide dismutase		Fungi
Hev b 11		Class I chitinase		Avocado, chestnut, and tomato
Hev b 12	24%	Latex LTP		Panallergen
Hev b 13	63%	Latex esterase	HCW	Fruits of the Rosaceae family
Hev b 14		Hevamine		
Hev b 15		Serine protease inhibitor	HCW	PR-6

SRPP: small rubber particle protein, LTP: lipid transfer protein.

unknown, prevalence is higher among patients with hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), suggesting a possible role of cyclooxygenase inhibition in its pathogenesis. OMA is often associated with respiratory allergy (mite-induced asthma and/or allergic rhinitis).[21-23]

Dust mites are found in virtually all homes and are considered one of the major sources of indoor allergens. Cross-antigenicity has been demonstrated among the different mite species. Although underreported in the literature, OMA has been documented in several countries and should always be considered in the differential diagnosis of idiopathic anaphylaxis.[22,23]

The first case of OMA in Brazil was reported after ingestion of a cheese pastry prepared with wheat flour contaminated by the mite *Aleuroglyphus ovatus* (300 mites per gram of wheat flour).[24] Italian pasta, crêpes, breaded foods, and oats are also potentially vulnerable. The enzymatic activity of mite antigens contributes to pathogenesis by injuring the gastrointestinal mucosa, thereby facilitating allergen absorption.

Prophylaxis requires that all flours be stored under refrigeration rather than in conventional cupboards or pantries, as low temperatures inhibit the proliferation of mites that may contaminate these foodstuffs. All patients should carry an epinephrine autoinjector.[25]

Vaccines

Although vaccine reactions are common, anaphylaxis is extremely rare.[26]

Vaccines contain an active component (the antigen) and additional components. Vaccine antigens can comprise whole organisms or parts of organisms, inactivated toxins (toxoids), or both that induce protective immune responses. Vaccine antigens themselves are rarely the cause of IHRs, unlike the other vaccine components. Thus, egg protein, gelatin, bovine casein used as a stabilizing agent, and antimicrobials (streptomycin, neomycin, and polymyxin B) are more commonly involved in these reactions. Some preservatives may be hidden, such as latex and polyethylene glycol (PEG).[27] The package inserts for vaccines administered in the United States are available on the Food and Drug Administration (FDA) website. In Brazil, the ANVISA electronic package insert database provides specific information on each vaccine, including a description of all its components. The database is available at https://consultas.anvisa.gov.br/#/bulario/.

The guidelines of the British Society for Allergy and Clinical Immunology (BSACI) recommend that children with egg allergy receive routine measles-mumps-rubella (MMR) vaccination under appropriate medical supervision.[27-31] Although the vaccine may contain other egg proteins, ovalbumin has been the most frequently found in most vaccines.[27,30] However, reactions to gelatin have also been reported.[29]

Gelatin is used as a stabilizing agent in vaccines containing live or attenuated agents. An animal protein widely used in foods and medications (see the section on excipients), it may be of porcine or bovine origin. However, it is not always explicitly identified in the package insert.[31]

Residual amounts of culture media used to grow organisms may also be present both in live vaccines and in viruses cultured in cell lines. Vaccines expressed in *Saccharomyces cerevisiae* (baker's yeast) include hepatitis B, human papillomavirus, and meningococcal conjugate vaccines. Accordingly, these vaccines may contain residual yeast proteins.[32]

Tetanus, diphtheria, and acellular pertussis vaccines may contain bovine casein, a milk protein used as a stabilizing agent, although only in nanogram quantities and therefore rarely associated with anaphylaxis. Nevertheless, caution is recommended when administering booster doses to children with high sensitization to cow's milk protein, and the vaccine ingredients should be reviewed in these cases.[30,32]

Previously, a high rate of IHR was detected among children vaccinated with an Indian MMR vaccine, in which hydrolyzed lactalbumin was identified as a contaminant. The Brazilian Ministry of Health recommended the use of vaccines from other manufacturers in patients with a history of cow's milk allergy.[31]

Immediate hypersensitivity reactions attributed specifically to aluminum salts are exceptional and their causal relationship is difficult to establish. However, they may cause type IV hypersensitivity reactions and the formation of granulomas or nodules following administration of vaccines containing aluminum adjuvants.[27,32]

Preservatives such as thimerosal, 2-phenoxyethanol, and phenol are present in multidose vials to prevent bacterial growth. Thimerosal may cause contact dermatitis (CD) and is only rarely associated with anaphylaxis. Patients with CD and positive patch tests to thimerosal generally do not develop reactions to

vaccines and have no contraindication to receiving vaccines containing thimerosal.[27]

Reports of anaphylaxis in Japan between 2011 and 2012 were associated with an influenza vaccine containing 2-phenoxyethanol produced by a single manufacturer, raising the possibility that this preservative may have had a role in IgE-mediated reactions.[32] Phenol, in turn, is widely used in mouthwashes, lozenges, and throat sprays, but there have been no reports of IHR.[32] Formaldehyde is still used in vaccine preparation, but no IgE-mediated reactions have been described in recent years. As previously discussed, latex may be present in rubber stoppers used to seal vaccine vials and in the plungers of some prefilled syringes. PEG is present in messenger RNA COVID-19 vaccines and will be discussed in the section on excipients.

Administration of the live-attenuated dengue vaccine (QDENGA®) began in Brazil in February 2024. Although no cases of anaphylaxis were reported during phase I–III clinical trials, post-marketing pharmacovigilance (phase IV) identified a safety signal for hypersensitivity reactions, including anaphylaxis, which, although rare, seemed to occur more at higher rates than observed in other vaccines. A total of 124 cases of anaphylaxis (3.6 per 100,000 administered doses) had been reported through September 2024, with no associated deaths. Most individuals (66.2%) developed symptoms within 30 minutes of vaccination. To date, no published scientific evidence has identified the vaccine components that may be responsible for IHRs, although investigations are ongoing, and the presence of endotoxins in vaccine samples has been ruled out. In Brazil, ANVISA stresses the importance of pre-vaccination assessment and post-vaccination monitoring while continuing to recommend vaccination and emphasize that benefits outweigh risks. These findings were reported in a recent ANVISA technical bulletin. (Available at: https://sbim.org.br/images/SEI_MS%20-%20 0046213575%20-%20Nota%20Te%CC%81cnica%20 ATUALIZAC%CC%A7O%CC%83ES%20VACINA%20 DENGUE.pdf_2025-03-01.pdf).

Substances present in cosmetics

Cosmetics are substances intended for application to the skin, mucous membranes, or teeth and may induce allergic reactions. Examples include soaps, lotions, makeup, perfumes, and others. The Food and Drug Administration (FDA) has identified 5 major classes of allergens commonly found in cosmetics: natural rubber (latex), fragrances (which may consist of various ingredients), preservatives, dyes and color additives, and metals.[33]

Although CD is the most common adverse reaction to cosmetics, atopic dermatitis may promote percutaneous sensitization and IgE-mediated reactions.[33] Only a few cases of hair dye inducing IHR (anaphylaxis or respiratory symptoms) have been reported, attributed to paraphenylenediamine (PPD) and its derivatives, including p-aminophenol, p-methylaminophenol, and toluene-2,5-diamine.[34] The reaction appears to occur only after hydrogen peroxide (H_2O_2) oxidation and is usually milder when the antioxidant sodium sulfite is added to the mixture.[34,35] Permanent natural henna hair dye, derived from the leaves of *Lawsonia alba* or *Lawsonia inermis*, may also cause respiratory symptoms or urticaria on rare occasions, and sensitization appears to occur primarily through inhalation of airborne henna powder.[36] Temporary tattoos, particularly those containing black pigments, may contain PPD, and delayed reactions to this compound may cause substantial facial edema, mimicking an immediate type I reaction.[37] Persulfate salts are potent oxidizing agents that accelerate the bleaching of dyed hair. Potassium persulfate, due to having one of the least unpleasant odors, is among the most commonly used. These salts may induce urticaria, rhinitis, and asthma, with respiratory symptoms occurring through inhalation, primarily in occupational settings.[38] Individuals with asthma appear to be more susceptible to these reactions.

Disinfectants are widely used in everyday life, and sodium benzoate, at concentrations of 1% to 4%, is used in toothpaste to reduce tartar formation. It may cause contact urticaria (CU) and anaphylaxis, as may p-chloro-m-cresol, present in many topical preparations. There have been reports of CU as well as more severe reactions to triclosan, an ingredient found in several cosmetics.[39]

Benzophenone, present in sunscreens that filter UVA and UVB radiation, is used in textiles and plastics to prevent discoloration of cosmetics potentially exposed to sunlight.[40] It must be listed separately on cosmetic labels and may cause CU and even anaphylaxis. The severity of the reaction depends in part on the area exposed, making immediate patch testing less likely to trigger anaphylaxis.[40] Mathias et al. reported a case of lip edema following use of cinnamic aldehyde in a mouthwash in a patient with allergic rhinitis and asthma.[41] The compound may also

be found in toothpaste and cinnamon-flavored candy. Geraniol, a component of Fragrance Mix I, may cause facial edema,[42] and IgE-mediated reactions may also occur with mint-flavored toothpaste.[43] IgE-mediated allergy to mint and menthol may manifest as urticaria, rhinitis, asthma, and/or anaphylaxis. R-carvone, the major component of spearmint oil, is also present in toothpaste and may cause delayed allergic reactions, resulting in cheilitis, or immediate reactions, such as lip angioedema, with onset within minutes.

The use of hair extensions and the application of artificial eyelashes have become increasingly common, and consequently, so has the use of adhesives with high concentrations of soluble latex (natural rubber) antigens. Repeated exposure to these adhesives may lead to sensitization to this agent.[44]

Widely used in the treatment of atopic dermatitis, emollients and moisturizers often contain plant protein derivatives (e.g., from soy, wheat, oats, or sesame). Oat protein, popular because of its anti-inflammatory, antioxidant, and antipruritic properties, may trigger CU and oral allergy syndrome.[45] Sensitization to these proteins may occur through the gastrointestinal, respiratory, or percutaneous route, and although protein penetration through the stratum corneum is more limited, it may occur when the skin is inflamed. Most cases present as latex-fruit syndrome in patients sensitized to natural rubber latex, due to cross-reactivity between class I chitinases containing a hevein-like domain and those found in fruits and tree nuts. However, tree nut allergy may occur independently, with recognition of Cas s 8, a lipid transfer protein. Unfortunately, with the increasing number of food proteins incorporated into so-called "natural cosmetics," new cases may emerge in the literature, such as anaphylaxis induced by facial peeling products containing chestnut.[46] There are reports of immediate allergy and anaphylaxis caused by the ingestion of sesame seeds or sesame oil found in pharmaceutical products and topical cosmetics.[47] Hydrolysates of collagen, keratin, elastin, milk, wheat, almonds, and silk added to hair conditioners are also causes of CU. Hydrolyzed wheat proteins are widely used in other cosmetics, with several reported cases of IHR, including wheat-dependent exercise-induced anaphylaxis from a protein in a soap.[48] Wheat contains salt-soluble proteins (albumins and globulins) and salt-insoluble proteins, such as gluten (gliadins and glutenins). Its widespread use in foods and non-food products increases the risk of sensitization, and hydrolysis may generate new epitopes, as may additives, which can also act as allergens. Hydrolyzed wheat proteins, composed of large polypeptide aggregates, may induce greater sensitization than compounds of lower molecular weight.[48]

In addition to plants, animal protein allergens present in cosmetics may also represent hidden allergens. There is one report of IHR to a cosmetic cream containing elastin derived from fish in a patient with a history of respiratory symptoms after inhaling the odor of grilled fish[49]; and another of anaphylaxis after egg ingestion in a patient who had used a homemade egg-white based hair mask weekly.[50] One study showed that hydroxypropyltrimonium hydrolyzed collagen (steartrimonium hydrolyzed collagen: Protein Q) is a particularly potent cause of immediate cutaneous reactions.[51]

There are also reports of IHR to chamomile, very popular in teas and infusions as well as in cosmetics such as creams, depilatory waxes, and facial masks. CU localized to the area of application of a glycolic acid peel has also been described.[33]

Permanent makeup and tattoos used in cosmetic procedures are growing increasingly popular; however, although cases of anaphylaxis associated with purple and blue inks have been reported, manufacturers are not legally required to declare all ingredients on product labels, hindering the investigation of the causative agents.[33]

Angioedema after alcohol ingestion may be caused by various agents found in alcoholic beverages, such as yeast. It remains a rarely reported and poorly understood syndrome that may be triggered by primary alcohols or alcohol metabolites (aldehydes and acetic acid) and appears to be more common among individuals of East Asian ancestry with aldehyde dehydrogenase deficiency, leading to increased serum aldehyde levels during alcohol metabolism.[53] Reports of CU caused by topical alcohol application are very rare, although cases involving ethanol and isopropyl alcohol have been described.[52,53]

Quaternary and tertiary ammonium ions are often present in medications, foods, cosmetics, disinfectants, and industrial residues. There is evidence of IgE antibodies against quaternary ammonium neuromuscular blocking agents (widely used in procedures requiring general anesthesia), with cross-reactivity to other compounds containing quaternary or tertiary ammonium ions in their molecular structure.[54] Contact with these compounds may lead to sensitization and explain why anaphylaxis may occur upon first exposure in some cases.

A literature review showed that anaphylaxis to neuromuscular blocking agents is more common in women, suggesting that cosmetics may be the route through which sensitization occurs.[54]

It is necessary to investigate the components involved in reactions to cosmetics and to properly educate patients regarding possible exposures, cross-reactivity, and appropriate treatment through an action plan.

Disinfectants

Disinfectants are important in medical and dental procedures and may trigger anaphylaxis of varying severity. Chlorhexidine is the primary agent implicated in this type of reaction. This antiseptic is ubiquitous in hospital settings and widely used in surgical and perioperative procedures but has significant allergenic potential. The lack of adequate documentation about its use means it is often overlooked,[55] which may lead to recurrent episodes of anaphylaxis, making it a hidden allergen.[55] Refractoriness during the treatment of an acute episode of anaphylaxis may also be caused by continued exposure to chlorhexidine during the procedure.[55] Although its true prevalence is unknown, chlorhexidine accounts for 5% to 10% of perioperative anaphylaxis cases in some series,[56] and these reactions are believed to be increasing because of its widespread use in household and industrial products.[57] Exposure may occur through skin disinfection, eyewash solutions, chlorhexidine-coated central venous catheters, mouthwashes containing chlorhexidine, lubricating gels used in urologic and gynecologic procedures or on urethral catheters, among other sources.[56] The symptoms of chlorhexidine-induced IHR may range from mild skin reactions to severe, life-threatening manifestations. The onset and severity of symptoms vary according to the type of exposure. The risk appears to increase when the integrity of the skin barrier is compromised or after vascular exposure, with contact involving blood vessels and mucous membranes considered the route most likely to trigger faster and more severe reactions.[56] Mild reactions with skin rash and pruritus or urticaria have been reported as initial manifestations, preceding more severe and potentially fatal reactions.[56,57] Furthermore, up to one-third of patients with confirmed chlorhexidine allergy are re-exposed to this agent, highlighting the need to increase awareness among health care professionals regarding its use and allergenic potential.[56,57]

The investigation combines skin tests, specific IgE measurement, and in vitro tests, when available (such as the basophil activation test [BAT] and the mast cell activation test), while challenge testing is not recommended.[56,58] Specific IgE measurement and chlorhexidine skin prick and intradermal tests should be considered in all patients with suspected perioperative anaphylaxis.[56] The sensitivities of specific IgE measurement and BAT are generally lower than those of skin tests, but their specificity is high.[56,58]

There are still few case reports of reactions to other disinfectants, such as ortho-phthalaldehyde, a 0.55% solution of which is used to disinfect heat-sensitive medical equipment. The product information recommends that it should not be used in patients requiring repeated cystoscopy, as it has been associated with hypersensitivity reactions. However, it continues to be used for the disinfection of endoscopic equipment in many centers.[59] Skin testing with ortho-phthalaldehyde and the BAT appear to be useful for the diagnosis of hypersensitivity.[59]

Ethylene oxide, a reactive gas used as a sterilizing and disinfecting agent for dialyzers, was implicated as a cause of anaphylactic reactions in the 1980s. As an alkylating agent, ethylene oxide is capable of modifying proteins, such as serum albumin, rendering them immunogenic. Reactions typically occur during the first use of the dialyzer due to the presence of residual ethylene oxide and are more frequent when dialyzers are not thoroughly rinsed. Reactions are generally observed within the first few minutes after the start of dialysis, although they may be delayed for up to 30 minutes. With the transition to alternative sterilization techniques, these reactions have become rare.[60] Specific IgE measurement and BAT are used to demonstrate hypersensitivity in recent cases reported in the literature.[60,61] However, ethylene oxide is not routinely tested, and although sensitization rates are low, cases may still be underdiagnosed because of limited awareness of its allergenic potential.[60]

Povidone-iodine is an extremely rare cause of anaphylaxis, despite its wide use as an antiseptic in surgery, but it should be considered in the investigation of perioperative anaphylaxis.[61] Other possible hidden allergens, such as excipients, may be present in disinfectant products as solutions, gels, and dressings, and are discussed below.[61]

Excipients

From a pharmaceutical standpoint, an excipient is an inert substance added to a medication to modify its solubility or absorption kinetics, improve stability, influence palatability, or provide a distinctive appearance; in other words, it is any constituent of a medication other than the active substance. Thus, adjuvants, stabilizers, antimicrobial preservatives, flavoring agents, solubilizing agents, diluents, and antioxidants are examples of excipients, as are the constituents of the outer coating of medications, such as gelatin capsules. Excipients must be fully characterized by manufacturers because several of them can cause IHR and lead to a false diagnosis of drug allergy[62] (Table 3).

Mannitol

Intravenous mannitol is known to cause non-immunologic reactions attributed to its hyperosmolarity, resulting in nonspecific mast cell and basophil degranulation. However, there are also reports of reactions after oral ingestion of preparations containing mannitol, such as analgesics, sweeteners, and dyspepsia medications. Skin prick and intradermal tests with mannitol may be performed when IgE-mediated reactions are suspected (although they lack standardization), as may an oral challenge test using an oral laxative containing mannitol.[63]

Povidone/Polyvinylpyrrolidone (PVP)

Anaphylaxis has been reported within minutes of oral ingestion of paracetamol containing povidone. Skin tests with povidone were positive, and laboratory assays demonstrated PVP-specific IgE. Cases have also been described following vaginal application of PVP-iodine, and there are reports of anaphylaxis associated with the use of PVP as an intraoperative antiseptic, in eye drops, and in contrast media.[64]

Polyethylene glycol (macrogol)

Polyethylene glycol (PEG), also known as macrogol, has been reported as an important

Table 3
Primary excipients found in medications involved in immediate hypersensitivity reactions (IHRs)

Medication type	Primary excipients
Analgesics	Mannitol, PVP
Antibiotics	Macrogol, PS80
Chemotherapy agents	Cremophor, PS80
Contrast media	CMC, macrogol, PVP, trometamol
Corticosteroids	Macrogol, CMC, lactose, PVP, PS80, propylene glycol
Dyspepsia medications	Macrogol, mannitol
Insulin	Metacresol, protamine, nickel
Laxatives	Macrogol
Supplements	Casein, macrogol
Monoclonal antibodies	PS20, PS80
NSAIDs	Macrogol
Eye drops	CMC, benzalkonium chloride, PVP
Parenteral medications	Benzyl alcohol
Perioperative environment	Gelatin, mannitol, macrogol, PVP
Radiopharmaceuticals	Poloxamer
Ultrasound gels	PEG
Vaccines	Aluminum, PEG, PS80, gelatin

PVP: polyvinylpyrrolidone; PS: polysorbate; CMC: carboxymethylcellulose; NSAIDs: nonsteroidal anti-inflammatory drugs; PEG: polyethylene glycol.

cause of IHR, including anaphylaxis. Formed by the polymerization of ethylene oxide, PEG may be identified by number that, in the cosmetic industry, refers to the average number of ethylene oxide units in each molecule, whereas in the pharmaceutical industry it indicates the rounded average molecular weight. Therefore, the same compound may be designated PEG-75 or PEG-33[49], depending on the type of product. PEGs are used as excipients but are also the active ingredients of bowel preparation laxatives and have emulsifying properties (allowing the combination of two substances that do not naturally mix, such as water and oil). They are also used in the production of medications to prevent recognition by the immune system (a process known as pegylation or PEGylation). IHRs are primarily associated with higher molecular weight PEGs.[65] There are several reports of anaphylaxis caused by pharmacologically unrelated medications that do contain PEG, particularly high-molecular-weight PEG.

These reactions are primarily associated with injectable corticosteroids, laxatives, mRNA vaccines, and parenteral nutrition.[65,66] Although true corticosteroid allergy is uncommon, there is growing evidence of IHR caused by the excipients contained in corticosteroids.[67]

Although there is no standardized protocol, testing is suggested with the medications containing the PEG implicated in the reaction, with other medications containing PEGs of different molecular weights, and with PEG alone. In our setting, pure PEG is only available as an oral formulation, precluding intradermal testing; therefore, only skin prick testing is recommended (or at 1:10 in cases of severe reactions). Challenge testing should be considered with caution.[68]

Polysorbate (PS)

There are reports of IHR after intramuscular injection of medications, with positive intradermal tests for PS80; however, negative oral challenge test results suggest that it is probably not absorbed orally. Reactions to adalimumab and later ustekinumab (both containing PS80 as a common excipient) were investigated, with positive skin tests for PS80. IHR caused by omalizumab injections and eye drops was investigated with positive test results for PS20. Reports of cross-reactivity between polysorbate and macrogol have been described, but are controversial, since patients allergic to PEG tolerate vaccines containing PS80 in case series.[68,69] Table 4 shows the procedures for skin testing with PEG and PS.

Cremophor

There is a report of IHR following chemotherapy with paclitaxel and etoposide, as well as after administration of a multivitamin supplement. The list of components of paclitaxel and the multivitamin identified cremophor as the common excipient. The etoposide contained polysorbate. Skin tests with cremophor and polysorbate were positive, suggesting potential cross-reactivity between these structurally related polymers.[61]

Carboxymethylcellulose (CMC)

Cases of anaphylaxis associated with barium sulfate suspension and intra-articular corticosteroids containing CMC have been reported, with positive test results for barium, corticosteroids, and CMC, and negative results with alternative preparations lacking this excipient. No cross-reactivity with hydroxypropyl cellulose has been demonstrated. Because it is not absorbed through the gastrointestinal tract, it may be tolerated when ingested.[62,63]

Polyvinylpyrrolidone (PVP)

Bronchospasm induced by an ioxitalamate preparation, an iodinated contrast medium containing PVP, was investigated, with positive intradermal testing, BAT, and leukocyte histamine release testing for PVP. Another case of bronchospasm associated with an oral prednisolone solution showed a positive oral challenge and positive skin test for PVP. Reports of IHR following intra-articular administration of mepivacaine hydrochloride and paramethasone acetate (containing PVP) showed positive test results only after intramuscular administration of pure PVP (1 mL). Cases of anaphylaxis to eye drops containing PVP have also been confirmed by skin testing.[64]

Tromethamine or trometamol

An IHR to gadoteridol, a gadolinium-based contrast agent, was investigated using gadoteridol, gadobutrol, and gadoterate meglumine, resulting in negative skin prick tests and positive intradermal tests for the first two (which contained trometamol) and a negative result for gadoterate. The intradermal test for trometamol was positive. With the introduction of COVID-19 vaccines containing trometamol as one

Table 4
Skin tests for the investigation of immediate hypersensitivity reactions to PEG and PS

Step		Drug tested	Dilution
1	Positive control	Histamine	1:1
	Negative control	Glycerin	1:1
	Skin prick test	PEG 3350	1:100
	Skin prick test	Polysorbate 80	1:100
2	Skin prick test	PEG 3350	1:10
	Skin prick test	Polysorbate 80	1:10
3	Skin prick test	PEG 3350	1:1
4	ID	Methylprednisolone acetate 40 mg/mL	1:100
	ID	Triamcinolone acetate 40 mg/mL	1:100
5	ID	Methylprednisolone acetate 40 mg/mL	1:10
		Triamcinolone acetate 40 mg/mL	1:10

PEG: polyethylene glycol; PS: polysorbate; ID: intradermal test.

of their excipients, it has also been suspected to be responsible for some cases of vaccine reactions.[69]

Hexylene glycol

Anaphylaxis has been described after the topical application of mometasone furoate cream, with positive challenge tests to both mometasone furoate cream and ointment. Reactions to pure hexylene glycol, a common ingredient in both mometasone formulations, at concentrations of 1% and 10% on skin testing, have also been reported.[70]

Lactose

Lactose was responsible for reactions in 10 patients with cow's milk allergy who received intravenous methylprednisolone. Subsequent analysis showed that the lactose was contaminated with β-lactoglobulin as a result of imperfect purification.[64] Another patient, who had previously tolerated inhaled fluticasone and salmeterol, developed anaphylaxis with a different batch of the same medication containing lactose. The dry powder budesonide inhaler (which contains lactose) was also responsible for anaphylaxis in a patient allergic to milk.[64] Anaphylaxis in a patient allergic to milk after the use of an iron succinylate preparation occurred because of casein, the presence of which in the medication was confirmed by the manufacturer.[64]

Insulin excipients

The prevalence of IHRs to insulin products is approximately 2%, with less than one third of cases related to insulin itself and most caused by excipients (metacresol, protamine, and zinc).[71] Metacresol is present in several insulin formulations, including aspart, NPH, glargine, and detemir. NPH insulin contains protamine to prolong its metabolism, resulting in a longer therapeutic effect than regular insulin. Several reports of IHRs to protamine, confirmed by testing, have been described. Zinc is used together with protamine to promote slow insulin release.

Testing with zinc chloride may be performed when reactions are suspected. In addition to switching the type of insulin used, desensitization is also possible in patients with IHRs.[71]

Benzalkonium chloride

Two episodes of anaphylaxis have been reported after use of benzalkonium chloride in nebulized salbutamol solution, eye drops, and nasal decongestant, with positive skin tests and a report of anaphylactic shock during intradermal testing with the agent.[72]

Gelatin and alpha-gal

Anaphylaxis after the application of Gelfoam and Floseal (which contain bovine gelatin) was associated with positive IgE to porcine gelatin but negative IgE to bovine gelatin. Skin testing was positive for a mixture of bovine and porcine gelatins. This diagnosis should be suspected in patients who experience reactions to meat. Gelatin is a bovine or porcine protein produced by partial hydrolysis and processing of collagen, used as a stabilizing agent in medications and vaccines containing attenuated viruses. The oligosaccharide galactose-α-1,3-galactose (α-Gal) is the cause of reactions after exposure to medications containing this molecule, either as part of the active ingredient, such as the monoclonal antibody cetuximab, polyvalent antivenom (*Crotalidae*), and bovine gelatin colloids, or in medications and vaccines containing gelatin as an excipient.[69]

Others

Benzyl alcohol, used as a bacteriostatic preservative in intravenous and topical medications, may cause sensitization through both contact and systemic exposure. Anaphylaxis to lysozyme present in tablets, aged cheese, and raw egg has been described, with tolerance to cheeses without the agent and positive tests with commercial egg white and lysozyme extracts. Anaphylaxis after administration of a tetanus vaccine containing aluminum, as well as urticaria after switching colchicine treatment to a pharmaceutical formulation containing aluminum, has been reported. Aluminum test results were positive, and challenge with the aluminum-free medication was negative. Excipients should be considered in reactions to medications from different drug classes and in reactions to unrelated medications and products, especially in cases of anaphylaxis.[62,69]

Foods

Hidden allergens comprise a diverse group of substances in food products that often go undetected by consumers. Cross-contamination during processing, incorrect labeling, and the unintentional inclusion of allergenic ingredients represent substantial risks, especially for individuals with severe allergies. The eliciting dose for a severe allergic reaction varies from one individual to another, and cumulative exposures within a given period may trigger reactions that were not initially elicited by those levels of exposure.[73] The most common food allergens include milk, eggs, peanuts, nuts, soy, wheat, fish, and shellfish, but less common foods, often used in seasoning blends, can also trigger reactions as hidden allergens. These include honey, cinnamon, lupin, peas, paprika, mustard, ginger, oregano, garlic, and others.[74] Another factor to consider is that orally ingested allergens may be influenced by food processing, meaning that not only the food itself but also its method of preparation may determine whether or not an allergic reaction occurs. Their molecular properties, such as disulfide bonds that contribute to protein folding and the formation of conformational IgE epitopes, post-translational protein modifications, or interactions within the food protein matrix, may affect the enzymatic and thermal stability of allergens.[75] Cross-reactivity between aeroallergens and foods may induce food allergy, with symptoms ranging from oral allergy syndrome to severe anaphylaxis. This phenomenon has been described for many plant proteins and gives rise to pollen-food syndromes, including birch-apple, cypress-peach, celery-mugwort-spice, mugwort-peach, mugwort-chamomile, mugwort-mustard, ragweed-melon-banana, and melon-goosefoot (a plant of the *Chenopodium* family, which includes quinoa). Other respiratory allergens may also exhibit cross-reactivity, such as fungi (Alternaria-spinach syndrome) and allergens from invertebrates, mammals, or birds (mite-shrimp, cat-pork, bird-egg). Allergic reactions following the ingestion of products containing pollen grains from specific plants have also been reported in patients with respiratory allergy to Asteraceae pollen, especially mugwort and ragweed, present in dietary supplements containing honey, royal jelly, and bee pollen. Likewise, IHRs may occur after ingestion of foods contaminated with mites or fungi in patients with respiratory allergy to these aeroallergens (oral mite anaphylaxis).[76]

Celery is a seasoning widely used in cooking and may act as a hidden allergen, especially in individuals allergic to birch and/or mugwort. In addition to celery, mustard and other spices may exhibit cross-reactivity with these pollens. It is important to remember that celery contains both relatively heat-stable allergens, including LTPs, and heat-labile allergens, such as profilins. In addition, cofactors such as exercise, NSAIDs or alcohol may be required in some patients or may increase the severity of the reaction.[74] Lupin has also been identified as a potential hidden allergen in various foods. Its popularity has increased in recent years as a means of improving the protein content of breads, cookies, pasta, salads, hamburgers, and processed meats, and it may replace soy and milk proteins in bakery, meat, and dairy products. Cross-sensitization may occur in individuals sensitized to lupin and other legumes, especially peanuts, lentils, chickpeas, and peas. Inhalation of flours containing lupin may sensitize workers in the baking industry, making it an occupational allergen in these cases.[77] Mustard is an uncommon allergen that may be involved in reactions that are difficult to recognize and diagnose. Cross-reactivity has been described with mugwort, nuts, legumes (including peanuts), fruits of the *Rosaceae* family, and even other vegetables such as Brussels sprouts, cauliflower, and broccoli.[78]

Seasonings such as pepper, coriander, thyme, and others less commonly used in Brazil, such as sumac and fenugreek, have also been cited as hidden allergens capable of triggering anaphylactic reactions. Guar gum, pectin, and gelatin, often used as thickeners, may also be implicated.[74] The online promotion of gluten-free diets has contributed to increased wheat restriction and the use of substitutes such as oats, quinoa, buckwheat, corn, and amaranth, with a corresponding increase in reported cases of anaphylaxis to these foods.[79] Amaranth seed is a staple food in some countries, but is used as a grain substitute for wheat in others.[80] Although quinoa is not a cereal, it is a very popular wheat substitute and has been reported as a cause of anaphylaxis.[81] A Spanish group published case reports of two children with celiac disease who developed allergic reactions immediately after accidental exposure to wheat, with the allergen Tri a 14 (wheat LTP) causing the reaction.[82]

There are few documented case reports of milk substitutes causing anaphylaxis, but Gly m 4, the soy milk allergen, exhibits cross-reactivity with the primary birch pollen allergen, Bet v 1, and is capable of causing severe reactions.[83] Approximately 10% of patients with cow's milk anaphylaxis also exhibit cross-reactivity with soy allergens, particularly Gly m 5, Gly m Bd 28k, and Gly m Bd 30k.[84] Meat substitutes used to be primarily soy-based products, but over the past 20 years, a fungus called *Fusarium venenatum* has increasingly been used for this purpose. This mycoprotein, which readily absorbs the flavor of herbs and spices, has been associated with reported cases of IHR, many involving anaphylaxis. Two case reports published in 2002 and 2003 also highlighted a possible link between fungal sensitization and allergic reactions following ingestion of mycoproteins.[86] As discussed, the most common allergy involving fruits and vegetables is pollen-food allergy syndrome, usually presenting with mild to moderate oropharyngeal symptoms and therefore not associated with severe reactions or anaphylaxis. However, more severe reactions may occur when patients with this syndrome consume these foods in concentrated forms, such as fresh fruit smoothies, juices, or soy milk.

Goji fruit has the potential to cause severe reactions due to its LTP-type allergens.[87] Medicinal products containing plants of the *Asteraceae* family, such as *Echinacea*, dandelion, ragweed, mugwort, goldenrod, and sunflower, bee products, *Ginkgo biloba*, *ginseng*, *psyllium*, or *ispaghula* (a natural hydrophilic mucilloid of the genus *Plantago*, traditionally used as a laxative and lipid-lowering agent) have also been described as causes of anaphylaxis.[88,89] Contamination of various medications with milk protein or lactose may also be responsible for allergic reactions in individuals sensitized to them.[90]

Anisakis simplex, a parasite that infects fish such as cod and salmon, has also been implicated in allergic reactions.[91]

Insects may be consumed as food in some communities, or as contaminants. Beetles, silkworms, caterpillars, grasshoppers, bees, and *Dactylopius coccus* (the insect associated with cochineal allergy) are some examples. Allergens such as tropomyosin, arginine kinase, and others, commonly implicated in allergy to crustaceans, mollusks, mites, and cockroaches, may explain anaphylaxis due to cross-reactivity in sensitized patients.[92]

Conclusion

This review shows the challenge of identifying hidden allergens in underdiagnosed cases of anaphylaxis. Although it does not exhaust the topic, this study highlights the need to routinely consider

hidden allergens as potential triggers of allergic symptoms, particularly anaphylaxis.

Undeclared food components, environmental contaminants, and substances that are unfamiliar to health care professionals contribute to diagnostic delays, recurrent severe episodes, inadequate management, and difficulties in establishing the etiological diagnosis of anaphylaxis.

A comprehensive investigation that includes a detailed dietary and medication history, label review, specific IgE testing, and expanded allergen panels may help identify hidden allergens. We believe that systematically incorporating these procedures may reduce the number of cases of anaphylaxis currently classified as idiopathic.

Despite recent advances, many gaps remain in the literature. Much of the available information is based on case reports, and there are no robust epidemiological studies and no standardized guidelines for the investigation of these cases. Future research should prioritize the development of more sensitive laboratory methods, as well as studies assessing the impact of hidden allergens in triggering anaphylaxis. Furthermore, education of health care workers, the food industry, the pharmaceutical industry, and consumers about hidden allergens is essential to improve early identification and prevent future exposures.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Desensitization to human albumin in a patient with hepatic cirrhosis: a case report

Dessensibilização com albumina humana em paciente com cirrose hepática: relato de caso

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ABSTRACT

Liver cirrhosis may lead to severe complications such as ascites and hepatorenal syndrome (HRS), requiring human albumin infusion as an essential therapy. Hypersensitivity reactions to albumin, although rare, may be severe and pose a challenge in the management of these patients. We report the case of a 55-year-old man with alcoholic liver cirrhosis who developed anaphylaxis during albumin replacement following large-volume paracentesis. During the diagnostic workup, an intradermal skin test for immediate hypersensitivity to albumin yielded a positive result. A rapid 8-step desensitization protocol was successfully performed, allowing the patient to be re-exposed to the full albumin dose without adverse reactions. Desensitization may represent a safe procedure for managing albumin hypersensitivity in patients with decompensated cirrhosis.

Keywords: Drug hypersensitivity, immediate hypersensitivity, liver cirrhosis, human serum albumin, immunologic desensitization.

RESUMO

A cirrose hepática pode apresentar complicações graves como ascite e síndrome hepatorrenal (SHR), cujo manejo exige a infusão de albumina humana como terapia essencial. Reações de hipersensibilidade à albumina, embora raras, podem ser graves e representarem um desafio no manejo destes pacientes. Relatamos o caso de um homem de 55 anos, com cirrose hepática de etiologia alcoólica, que desenvolveu anafilaxia durante a reposição de albumina pós-paracentese de grande volume. Na investigação diagnóstica, o teste cutâneo intradérmico de hipersensibilidade imediata à albumina foi positivo. A dessensibilização rápida com protocolo em 8 etapas foi realizada com sucesso, e permitiu a reexposição do paciente à dose plena de albumina sem reações adversas. A dessensibilização pode ser utilizada como um procedimento seguro no manejo da hipersensibilidade à albumina em pacientes com cirrose descompensada.

Descritores: Hipersensibilidade a drogas, hipersensibilidade imediata, cirrose hepática, albumina sérica humana, dessensibilização imunológica.

Introduction

Liver cirrhosis constitutes a global public health problem, one that was responsible for more than 1.32 million deaths in 2017, which equates to 2.4% of all global deaths.[1] The most common etiologies are excessive alcohol consumption, viral hepatitis, and Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD).[1,2] Disease progression often leads to development of serious complications such as ascites, digestive variceal hemorrhage, spontaneous bacterial peritonitis (PBE), and hepatorenal syndrome

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(HRS), all conditions that increase morbidity and mortality.[2]

In these situations, infusion of human albumin plays a central therapeutic role. Its oncotic and non-oncotic properties are essential for plasma volume expansion, systemic hemodynamic improvement, and inflammatory response modulation.[4] Albumin is indicated as first line treatment for prevention of large volume paracentesis-induced circulatory dysfunction, for treatment of PBE, which reduces the incidence of HRS and improves survival, and as a pillar of HRS, in combination with vasoconstrictors.[4,5]

Although albumin has a good safety profile, hypersensitivity reactions can occur, with an estimated 0.011% incidence of anaphylactic shock reactions, which can be severe, and potentially fatal.[6,7] Pathogenesis has not been entirely explained and diagnosis is a clinical challenge.[6,8] When faced with such reactions, systematic diagnostic investigation should be conducted using immediate hypersensitivity skin tests (prick tests and intradermal tests), according to the algorithm recently proposed by Basu et al.[9] (Figure 1).

Desensitization is a procedure that can enable continuation of treatment in patients with confirmed hypersensitivity to albumin. This method induces a temporary state of immunological hyporesponsiveness by scaled administration of suboptimal doses of the medication.[10] Desensitization should be considered in patients who develop hypersensitivity to albumin and for whom there is no equally effective alternative treatment.[11] The present report describes the case of a patient with liver cirrhosis who underwent anaphylactic shock in response to albumin infusion and who, after diagnostic investigation and implementation of a rapid desensitization protocol, was able to continue to receive his essential treatment.

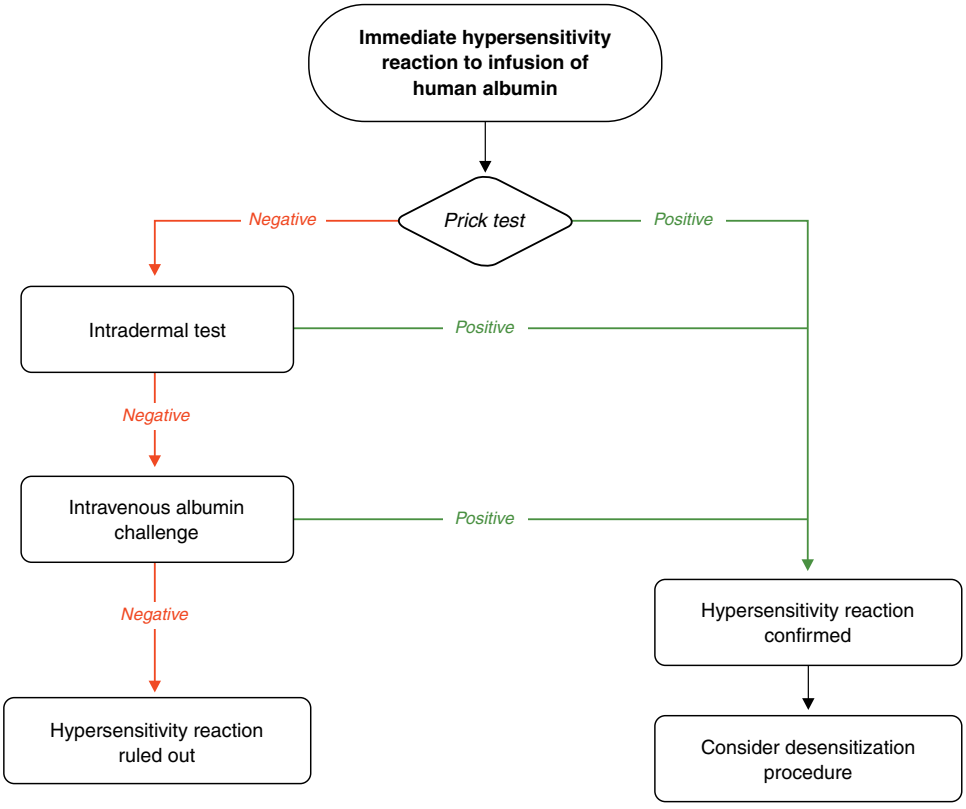

Figure 1
Adapted algorithm for management of immediate hypersensitivity reaction to human albumin

Case report

The patient was a 55-year-old male with a diagnosis of alcoholic liver cirrhosis (MELD-Na 25, Child-Pugh C11), complicated by refractory ascites. He had no known history of allergies and had received human albumin infusions on two prior occasions, during episodes of acute kidney injury, with no complications.

He was admitted for therapeutic large volume paracentesis, with drainage of 6.5 liters. As set out in the protocol for prevention of post-paracentesis circulatory dysfunction, he was administered albumin replacement with 50 g of 20% human albumin, calculated at a dosage of 6-8 g per liter of ascitic fluid removed. Immediately after initiation of the infusion, he complained of itching involving the lower limbs and began dry coughing. Soon after administration was complete, he exhibited dyspnea, low oxygen saturation and rapid breathing, sialorrhea and facial angioedema, constituting grade 3 anaphylactic shock according to the Ring and Messmer classification.[12]

Emergency treatment was initiated with administration of intramuscular adrenaline, intravenous hydrocortisone, and intramuscular promethazine, followed by clinical stabilization in the intensive care unit (ICU). Serum tryptase was not assayed during the acute event because it is not available as an urgent test at the institution.

Systematic investigation was started with a skin prick test using human albumin at a concentration of 200 mg/mL, with a negative result. Next, an intradermal test was performed at a concentration of 2 mg/mL (1:100), with an initial wheal of 7 × 6 mm and final wheal of 10 × 9 mm, with no hyperemia; a result considered negative. Next, an intradermal test was conducted at a concentration of 20 mg/mL (1:10), observing an initial wheal size of 7 × 7 mm and a final wheal size of 10 × 22 mm, accompanied by hyperemia, characterizing a positive result. The negative control, conducted with saline, provoked initial and final wheals of 7 × 6 mm, with no evidence of hyperemia (Figure 2).

Desensitization was performed using two albumin solutions at the following concentrations: solution 1 contained 20 mg/mL and solution 2 contained 200 mg/mL. The 8-step protocol, adapted from Cristallo M et al.,[6] was conducted without pre-medication (Table 1). The target dose of 40 g was reached after 325 minutes. This procedure was successful and well tolerated.

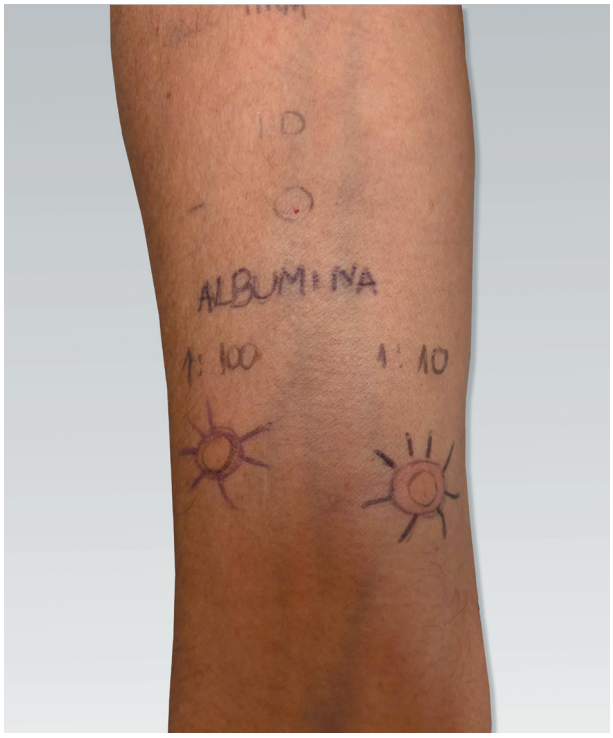

Figure 2
Negative intradermal test with 2 mg/mL albumin and positive intradermal test with 20 mg/mL albumin. At the 20 mg/mL concentration the wheal spread from 7x7 mm (initial) to 10x22 mm (final reading)

Fourteen days after the first albumin desensitization treatment, the patient underwent paracentesis again, removing 7.7 liters. Considering that the interval elapsed was shorter than the half-life of exogenous albumin (approximately 20 days), it was decided to infuse the full 50 g dose of albumin following routine practice, without repeating the desensitization protocol. The infusion was well-tolerated, with no adverse reactions.

The Research Ethics Committee approved the study (CAAE 90198825.0.0000.5440, Plataforma Brazil) and the patient signed a free and informed consent form.

Discussion

Hypersensitivity reactions (HSR) to drugs and blood products are a challenge in clinical practice. Albumin treatments are essential for patients with decompensated cirrhosis, but the occurrence of HSR complicates management of these patients.[3] The pathogenesis of these reactions can involve multiple mechanisms.[9] Classic IgE-mediated reactions

Table 1
Description of the eight steps in the process of desensitization to human albumin

Step	Solution	Velocity (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered per step (g)	Accumulated dosage (g)
1	1	30	20	10	0.2	0.2
2	1	60	20	20	0.4	0.6
3	1	90	20	30	0.6	1.2
4	1	120	20	40	0.8	2
5	2	30	20	10	2	4
6	2	40	30	20	4	8
7	2	45	30	22.5	4.5	12.5
8	2	50	165	137.5	27.5	40
Total duration of infusion = 325 minutes						

were confirmed in some cases using immediate hypersensitivity skin tests, basophil activation tests, and immunoblotting, which identified a 67 kDa albumin monomer as the allergen.[13] However, other pathways, related to the manufacturing process of the commercial product have also been proposed. Pasteurization can lead to formation of protein aggregates or alter the molecular structure, creating neoantigens.[14,15] Some patients with HSR to commercial albumin have shown tolerance to human plasma, which contains albumin in its native form.[13] Moreover, stabilizers such as caprylate, added to prevent thermal degradation, can change albumin and induce specific immune responses.[7,15] Another mechanism described is contamination with prekallikrein activator (PKA), potentially associated with anaphylactic reactions.[14]

Intradermal testing is an essential tool because of its greater sensitivity.[7-9,13] However, intradermal testing with albumin is not risk free and can trigger systemic symptoms.[10] The non-irritant concentration for skin tests with human albumin is yet to be standardized. In the case reported herein, the intradermal investigation was initiated with a dilution of 1:100 (2 mg/mL), prioritizing the patient's safety in view of his history of severe anaphylactic shock (grade 3). Confirmation of positivity at the 1:10 dilution (20 mg/mL), as confirmed in recent published data that suggest this concentration is not irritant,[9] supports the hypothesis of an IgE-mediated mechanism, even in the absence of tests with healthy controls at the time the patient was receiving care.

There are few cases of albumin desensitization described in the literature, which confirms the relevance of each documented case.[6] The success of the 8-step protocol adapted from Cristallo et al.,[6] combined with the subsequent tolerance of a standard infusion at full dosage, demonstrates that the procedure was capable of inducing a temporary state of tolerance. This enabled the patient to continue receiving essential treatment. Regarding therapeutic management, desensitization was the only option for safe reintroduction. While the 12-step protocol proposed by Castells et al.[10,11] is the gold standard for chemotherapy and biological drugs, adaptations are often necessary for agents with large volume or specific colloidal properties, such as albumin. The 8-step protocol used in the present case was designed to enable gradual increments of volume

and velocity, ensuring tolerance without the need for rigid dose duplication at each step, which could provoke reactions in patients with high sensitivity or fluid overload in liver disease patients, and proved safe and effective in terms of the final outcome.

In conclusion, this report demonstrates the importance of systematic investigation, including clinical history, skin tests, and the choice of desensitization procedure. Moreover, it also demonstrates that rapid desensitization is a feasible, safe, and effective strategy, enabling this essential treatment to be continued in patients with decompensated liver cirrhosis and confirmed allergy to the blood product in question.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Desensitization to ocrelizumab: a case report

Dessensibilização com ocrelizumabe: relato de caso

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system characterized by progressive functional impairment. Ocrelizumab, an anti-CD20 monoclonal antibody, is used to treat both the relapsing-remitting and primary progressive forms of MS, but may trigger infusion-related reactions, including type I hypersensitivity. This report describes the case of a 34-year-old woman with MS and no prior history of allergy who developed urticaria during her first ocrelizumab infusion. A rapid desensitization protocol consisting of 12 steps and 3 infusion bags was performed. During the administration of the third bag, the patient developed facial erythema, which was successfully managed with bilastine, allowing the protocol to resume without further complications. Subsequent infusions followed the same protocol and were completed successfully. Reactions to ocrelizumab may range from cytokine release-related phenomena to immediate or delayed hypersensitivity, and distinguishing between these reaction types is essential for appropriate management. Although the allergic nature of the reaction could not be confirmed by skin testing, desensitization was both safe and effective. This case supports the feasibility of desensitization as a strategy to maintain first-line therapy in patients with MS who develop infusion-related reactions. Case reports such as this are important for expanding current knowledge regarding the management of hypersensitivity reactions to ocrelizumab, which remain sparsely documented, and help ensure continuity of treatment in complex clinical scenarios.

Keywords: Immunologic desensitization, immediate hypersensitivity, drug hypersensitivity, ocrelizumab.

RESUMO

A esclerose múltipla (EM) é uma doença inflamatória e neurodegenerativa do sistema nervoso central, com impacto funcional progressivo. Ocrelizumabe, um anticorpo monoclonal anti-CD20, é utilizado para tratamento de formas recorrente-remitente e primária progressiva da EM, podendo causar reações infusionais, incluindo hipersensibilidade do tipo 1. Este relato descreve o caso de uma paciente de 34 anos com EM, sem história prévia de alergia, que apresentou urticária durante a primeira infusão de ocrelizumabe. Optou-se por realizar dessensibilização rápida com protocolo em 12 etapas e 3 bolsas. Durante a terceira bolsa, a paciente apresentou eritema facial, tratada com sucesso com bilastina, e o protocolo foi retomado sem intercorrências. As infusões subsequentes seguiram o mesmo esquema com sucesso. As reações ao ocrelizumabe podem incluir desde liberação de citocinas até hipersensibilidade imediata ou tardia, sendo fundamental distinguir os tipos de reação para manejo adequado. Apesar de não ter sido possível confirmar a natureza alérgica da reação por meio de testes cutâneos, a dessensibilização foi segura e eficaz. Esse caso reforça a viabilidade da dessensibilização como estratégia para manter a terapia de primeira linha em pacientes com EM que desenvolvem reações infusionais. Relatos como esse são importantes para ampliar o conhecimento sobre o manejo de reações de hipersensibilidade ao ocrelizumabe, ainda pouco descritas na literatura, e garantir continuidade terapêutica em casos clínicos complexos.

Descritores: Dessensibilização imunológica, hipersensibilidade imediata, hipersensibilidade a drogas.

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Introduction

Multiple sclerosis (MS) is a disease of the central nervous system characterized by a chronic inflammatory process and progressive neurodegeneration, resulting in functional impairment and incapacity in adolescents, young adults, and, rarely, children.[1] Monoclonal antibodies have often been used to treat inflammatory, neurodegenerative, and malignant diseases. Ocrelizumab is a humanized monoclonal antibody that promotes selective depletion of B cell CD20+ and has been approved for treatment of recurrent-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS), based on its safety and efficacy demonstrated in clinical trials.[2] However, use of these biological agents can cause varying phenotypes: cytokine release reactions; IgE or non-IgE mediated mast cell activation reactions (type I hypersensitivity); and delayed reactions (type III and type IV hypersensitivity).[3,4] It is important to note that reactions to monoclonal antibodies may also be mixed, simultaneously manifesting characteristics of cytokine release syndrome and hypersensitivity reactions.

Reactions caused by cytokine release are generally self-limiting and provoke symptoms such as fever, tachycardia, rubor, shivering, dyspnea, nausea, and vomiting, and are common in response to a first infusion of the medication. Reactions caused by mast cell activation result in clinical findings typical of immediate reactions: urticaria, angioedema, itching, hypotension, and cardiorespiratory arrest. Type III and type IV reactions are rare and account for less than 5% of reactions to monoclonal antibodies.[5] According to the Brown classification, reactions limited to the skin and subcutaneous tissue are considered mild (such as urticaria and angioedema), while moderate and severe reactions provoke systemic involvement.[6] Mild reactions associated with ocrelizumab infusion, such as urticaria and angioedema, occur in approximately one third of patients. In cases with mild reactions, clinical risk stratification and systematic investigation using immediate reading skin tests and challenge test may clear the way for an attempt to infuse the medication before prescribing desensitization. In the absence of an effective alternative treatment, rapid drug desensitization (RDD) can enable continuation of the first-choice treatment in patients with type 1 hypersensitivity reactions. This procedure consists of gradual reintroduction of the drug, starting with subtherapeutic doses and increasing doses progressively, thereby inducing a temporary state of tolerance that allows the patient to be given the total dose needed safely.[7,8]

We describe a successful case of desensitization to ocrelizumab in a female patient with MS who had urticaria during infusion.

Case report

The patient was a previously healthy, 34-year-old woman with no history of allergy who began to develop paresthesia of the left hemiface. Magnetic resonance of the encephalon showed plaques of demyelination. After extensive investigation, the patient was diagnosed with MS. Treatment was initiated with 40 mg of glatiramer acetate (an immunomodulating amino acid polymer similar to myelin) three times per week. After 1 year of treatment, the patient presented with disproportionate right-side hemiparesis and new areas of demyelination were seen on magnetic resonance. The decision was taken to scale treatment up to 300 mg natalizumab once a month. During treatment with natalizumab, the patient had elevated polymerase chain reaction (PCR) in blood for John Cunningham virus (JCV), which indicates an increased risk of development of progressive multifocal leukoencephalopathy (PML), making continuation of treatment with natalizumab potentially unsafe. Treatment with natalizumab was therefore suspended and ocrelizumab was prescribed. The first cycle was administered with 300 mg, followed by the same dose again after 14 days. Maintenance was prescribed at 600 mg per week, without premedication. During the first infusion of ocrelizumab, the patient developed diffuse urticaria all over the body in 20 minutes, with no systemic manifestations. The medication was suspended and 50 mg intravenous diphenhydramine was administered, with a good response. Since no alternative drug was available, treatment with rapid desensitization to ocrelizumab was prescribed, using a protocol described by Aun et al.,[8] adapted from the standard 12-step desensitization protocol for monoclonal antibodies proposed by Castells et al.[9] The ocrelizumab desensitization protocol was conducted in the ward of a University Hospital, with clinical monitoring and without premedication, over 12 steps and using 3 bags[8,9] (Tables 1 and 2). During infusion of the third bag, at a velocity of 80 mL/h, the patient developed facial erythema, without itching or urticaria. The infusion was immediately suspended and the patient was treated with 20 mg of oral bilastine. After 30 minutes, her clinical status had improved and the procedure was resumed at

the same infusion velocity, with no complications. All subsequent infusions were successfully completed in accordance with the desensitization protocol. The study was approved by the Ethics Committee (CAAE 88737225.5.0000.5440, Plataforma Brazil) and the patient signed a consent form.

Discussion

We describe the case of a female patient with MS who was successfully desensitized to ocrelizumab after developing generalized urticaria during the first infusion. In this clinical scenario, with mild reactions and low risk, strategies such as challenge testing

Table 1
Solutions used during desensitization to ocrelizumab 300 mg

Solution	Total volume (mL)	Concentration (mg/mL)	Total mg per bag	Cumulative total infused per bag (mL)
Solution 1	250	0.012	3.000	9.25
Solution 2	250	0.120	30.000	18.75
Solution 3	250	1.191	297.639	250

Table 2
Description of the 12 stages of desensitization to ocrelizumab 300 mg

Step	Solution	Velocity (mL/h)	Time (min)	Volume infused per step(mL)	Dose administered per step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0060	0.0060
2	1	5.0	15	1.25	0.0150	0.2100
3	1	10.0	15	2.50	0.0300	0.0510
4	1	20.0	15	5.00	0.0600	0.1110
5	2	5.0	15	1.25	0.1500	0.2610
6	2	10.0	15	2.50	0.3000	0.5610
7	2	20.0	15	5.00	0.6000	1.1610
8	2	40.0	15	10.00	1.2000	2.3610
9	3	10.0	15	2.50	2.9764	5.3374
10	3	20.0	15	5.00	5.9528	11.2902
11	3	40.0	15	10.00	11.9056	23.1957
12	3	80.0	147,375	232.50	276.8043	300.0000

Total infusion time = 339.375 minutes = 5.66 hours

and use of premedication could be considered as alternatives to desensitization.[5] Immediate reading skin testing and serum tryptase assay are also valuable tools for risk stratification.[10] However, given the lack of standardization of skin tests for biological drugs[11] and technical inability to assay tryptase, neither test was used. Considering the high risk of disease progression (JCV positive), the clinical urgency of treatment, and the absence of effective alternative treatment options, RDD was chosen.

There are few case reports in the literature describing desensitization to ocrelizumab. In 2019, reports of 2 cases were presented at scientific congresses.[7] In 2022, Aun M et al.[8] reported the case of patient with MS who developed urticaria and angioedema during a first ocrelizumab infusion and was successfully desensitized using a 12-step protocol with 3 dilution bags. In the ORATORIO study, analyzed by Mayer et al.,[12] severe reactions were observed in two patients related to infusion of ocrelizumab, although they were not identified as type 1 reactions.

Although there are few studies investigating the safety of desensitization to ocrelizumab, less than 30% of patients in studies involving chemotherapy and biological agents exhibited reactions during desensitization and less than 10% were severe.[10,13] In this patient with MS, RDD was performed safely, using a 12-step, 3 bag protocol, enabling treatment with ocrelizumab to be continued. Reports of cases of desensitization to biological agents contribute to the sharing of clinical experience, showing that RDD is a safe and effective tool for management of patients with reactions to biological agents.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Peristomal psoriasis secondary to the Koebner phenomenon: a diagnostic challenge

Psoríase periestomal secundária ao fenômeno de Koebner: um desafio diagnóstico

Cristina Coelho[1], Maria Lages[2], Joana Matos[3], Arminda Guilherme[1], Susana Cadinha[1], Inês Machado Cunha[1]

ABSTRACT

Peristomal skin complications are prevalent in ostomy patients, substantially impacting quality of life and contributing to increased health care costs. Contact dermatitis is one of the most common conditions affecting this population. Atypical cases can mimic this condition, making diagnosis challenging, especially when the clinical course deviates from expectations. We present the case of a 61-year-old man with psoriasis who underwent an ileostomy in 2023. In 2024, he developed a persistent peristomal lesion unresponsive to hydrocortisone. A negative allergological study and favorable response to psoriasis treatment supported the diagnosis of Koebner phenomenon-induced psoriatic lesions. This case highlights the need to consider the Koebner phenomenon in peristomal skin complications, particularly in patients with pre-existing dermatological conditions. The Koebner phenomenon occurs in psoriasis when trauma or external stimuli induce secondary lesions in previously unaffected skin. Early recognition and interdisciplinary management improve outcomes and quality of life for ostomy patients.

Keywords: Contact dermatitis, psoriasis, ileostomy.

RESUMO

As complicações cutâneas periestomais são prevalentes em doentes com ostomia, tendo um impacto significativo na sua qualidade de vida e contribuindo para o aumento dos custos de cuidados de saúde. A dermatite de contacto é uma das condições mais comuns. Casos atípicos podem mimetizar esta condição, tornando o diagnóstico desafiante, especialmente quando a progressão clínica se desvia das expectativas. Apresentamos o caso de um homem de 61 anos com psoríase, submetido a uma ileostomia em 2023. Em 2024, desenvolveu uma lesão *de novo*, periestoma, persistente, que não respondeu à hidrocortisona tópica. O estudo alergológico negativo e a boa resposta ao tratamento usado na psoríase contribuíram para apoiar a hipótese de se tratarem de lesões psoriáticas induzidas pelo fenômeno de Koebner. Este caso destaca a necessidade de considerar o fenômeno de Koebner nas complicações cutâneas periestomais, principalmente naqueles doentes com patologia dermatológica prévia. Este fenômeno ocorre na psoríase quando o trauma ou estímulos externos induzem lesões secundárias em pele previamente não afetada. O reconhecimento precoce e o cuidado interdisciplinar melhoram os resultados e a qualidade de vida dos pacientes com ostomia.

Descritores: Dermatite de contacto, psoríase, ileostomia.

Introduction

Peristomal skin complications (PSCs) represent a frequent and clinically significant problem among patients with ostomies. The surgical creation of a stoma – commonly performed to manage both benign and malignant gastrointestinal diseases – is associated with a wide range of postoperative complications, with reported incidence rates between 20% and 70%.[1] These complications may develop either early or late in the postoperative period and can include necrosis, leakage, granuloma formation, retraction, stenosis, prolapse, parastomal hernia, and peristomal skin disorders.

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The prevalence of PSCs following stoma creation has been reported to range from 36.3% to 73.4%.[2] Their etiology is multifactorial, involving surgical technique, patient-related factors, and postoperative care practices. Although PSCs may occur at any time after surgery, they are most commonly observed within the first 5 years. Several risk factors have been associated with their development. A case-control study from Denmark demonstrated that ostomy type, leakage, and obesity (body mass index > 30) were significantly correlated with PSCs.[2] Patients with ileostomies are particularly predisposed compared to those with colostomies or urostomies.[3]

The clinical severity of PSCs ranges from mild erythema to extensive ulceration. Patients may present with irritant or allergic contact dermatitis (ACD), mechanical trauma, folliculitis, psoriatic lesions, or rare entities such as peristomal pyoderma gangrenosum.[4] Contact dermatitis is especially common and has been reported in up to 91.7% of cases.[5] PSCs substantially impair quality of life and contribute to increased health care costs.[6,7] Effective prevention and timely management are therefore essential in ostomy care.

In patients with psoriasis, new skin lesions may appear on previously unaffected areas after trauma, a response known as the Koebner phenomenon.[8] A study of 1,665 patients with stomas found that 4.7% had psoriasis affecting their stoma. In many cases, the lesions resolved with thicker hydrocolloid barriers alone, while others required topical corticosteroids or systemic treatments such as cyclosporine, methotrexate, UVB phototherapy, infliximab, or adalimumab.[9]

The pathogenesis of the Koebner phenomenon appears to associated with the nature, location, extent, and severity of the skin lesion.[8] Proposed mechanisms include epidermal trauma, increased dermal blood flow, release of nerve growth factor, activation of resident memory T cells, and production of type I interferons, all of which can promote the development of psoriatic lesions at previously unaffected sites.[10,11]

This report describes a case of peristomal psoriasis secondary to the Koebner phenomenon, highlighting its diagnostic challenges.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Case report

A 61-year-old Caucasian male (Fitzpatrick phototype III) with a 20-year history of psoriasis vulgaris, managed with topical betamethasone/calcipotriol (0.5 mg/g + 0.05 mg/g, Enstilar®), underwent an ileostomy in May 2023 due to ileal perforation secondary to gastric heterotopia. In early 2024, he developed a well-demarcated, pruritic, erythematous plaque around the ileostomy site (Figure 1). The lesion remained unchanged for several months despite twice-daily application of hydrocortisone 10 mg/g cream over 4 months, prompting further investigation.

To evaluate the possibility of ACD, patch testing was performed in accordance with the European Society of Contact Dermatitis (ESCD) guidelines. Testing included standardized allergens and the patient's personal ostomy products, applied with IQ Ultimate™ chambers and evaluated at 48 hours, 96 hours, and 1 week.

The Portuguese baseline series (Chemotechnique Diagnostics®), consistent with national guidelines from the Portuguese Contact Dermatitis Research Group, was negative. Additional testing with rubber additives and patient-specific ostomy care products, including adhesive pastes, barrier rings, sprays, powders, and bags, was also negative (Table 1).

In collaboration with the Dermatology Service, topical therapy was changed to betamethasone/calcipotriol (Katriomet®, same dosage), applied to the peristomal region, and systemic acitretin 25 mg daily was initiated. This regimen led to marked improvement (Figure 2), with complete resolution of lesions over 3 months. Given the absence of allergic sensitization and the favorable response to psoriasis-directed therapy, the lesions were attributed to Koebner phenomenon-induced psoriasis.

Discussion

PSCs are common in gastrointestinal surgical practice, particularly after ileostomy. While contact dermatitis, either irritant or allergic, is often suspected, clinicians must also consider less common differential diagnoses. This case highlights the Koebner phenomenon as a potential mimic of PSCs, complicating both diagnosis and management.

The Koebner phenomenon, also known as the isomorphic response, is characterized by the

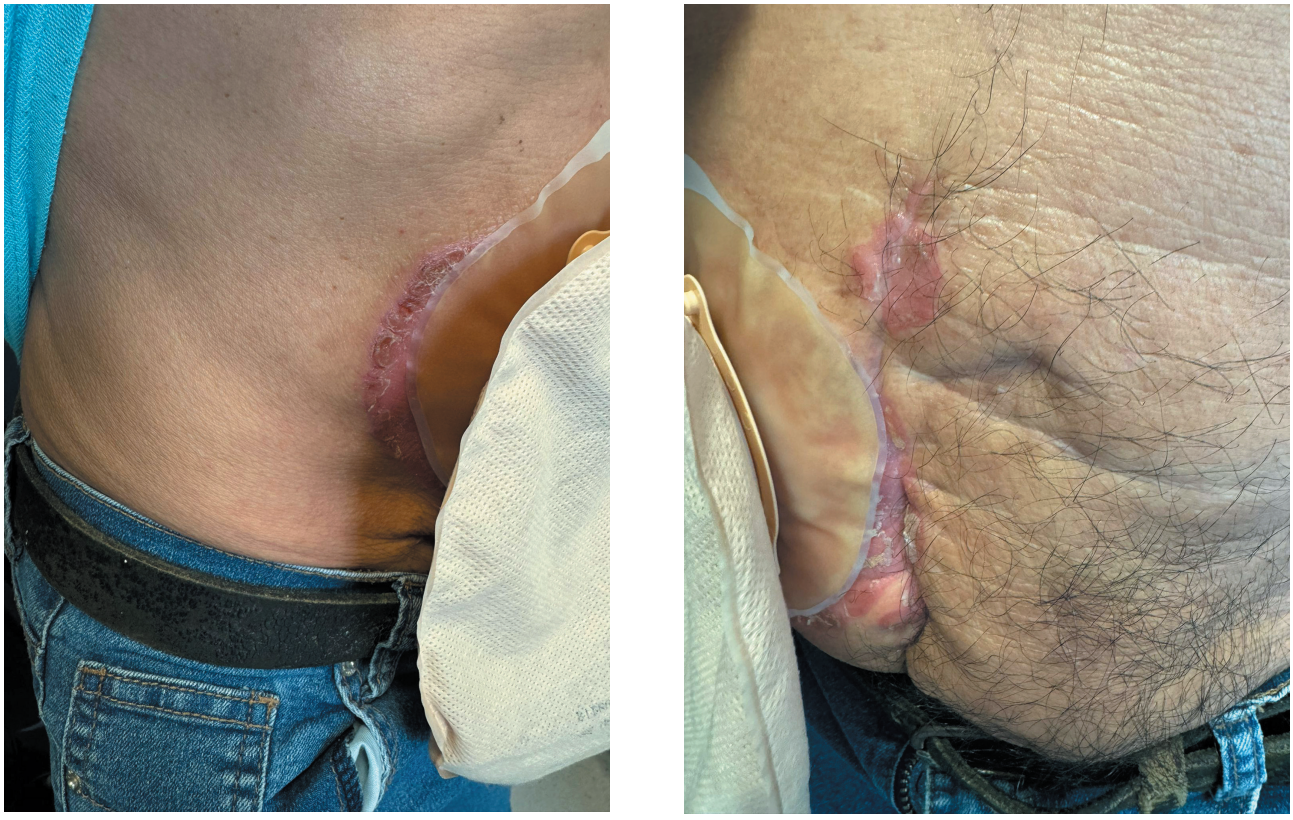

Figure 1
Peristomal skin complications

Table 1
Products and substances used for patch testing

Product	Vehicle	Concentration
Hydroquinone (Chemotechnique®)	Pet	1%
Phenyl salicylate (Chemotechnique®)	Pet	1%
Butylhydroxytoluene (Chemotechnique®)	Pet	1%
Drometrizole (Chemotechnique®)	Pet	1%
2-tert-Butyl-4-methoxyphenol (Chemotechnique®)	Pet	2%
Hydroabietyl alcohol (Chemotechnique®)	Pet	10%
ConvaTec® spray	As is	As is
Oxmed® Protective Powder	As is	As is
Braun® Ostomy bag	As is	As is
Healthcare® Ostomy bag	As is	As is
Zensiv® Ostomy bag	As is	As is

Pet: petrolatum.

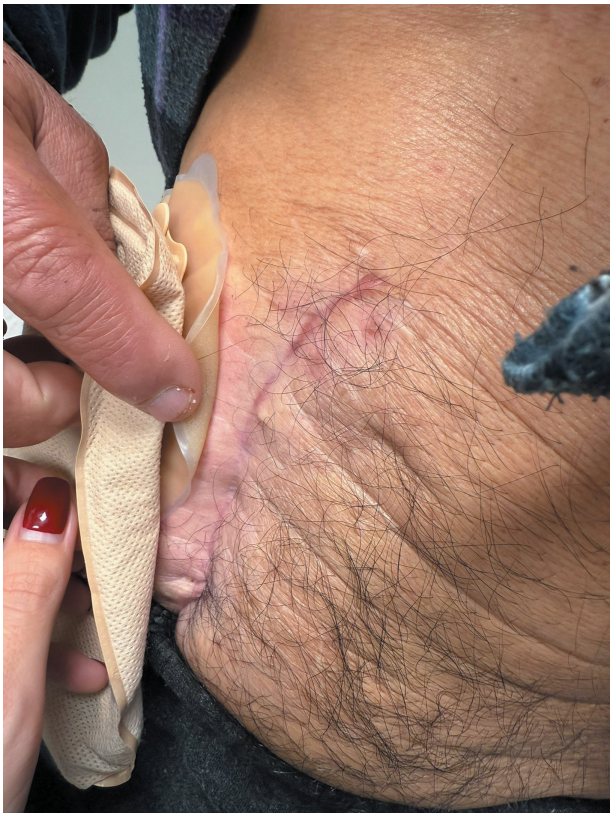

Figure 2
Improvement of skin lesions

development of new lesions at sites of skin trauma that mimic the underlying dermatosis in morphology and histopathology. In psoriasis, mechanical trauma, chemical irritation, infections, or procedural injury can trigger inflammatory cascades leading to lesion formation on previously unaffected skin.[12] Approximately 25%-30% of patients with psoriasis develop new lesions after trauma or experimentally induced stimuli, such as acupuncture or tape stripping.[13]

In the present case, the ileostomy site likely acted as a persistent source of mechanical and chemical irritation due to repeated appliance use and skin barrier disruption, thereby initiating lesion development via the Koebner response.[14] Misdiagnosis as ACD or irritant dermatitis could have resulted in delayed or inappropriate therapy, prolonged discomfort, and higher treatment costs. Comprehensive allergological evaluation, including patch testing with both baseline allergens and patient-specific products, was crucial for excluding ACD. The subsequent improvement with psoriasis-specific therapy confirmed the diagnosis.

Koebnerization in psoriasis typically manifests within 10-14 days after skin trauma, but latency can range from 3 days to 2 years. In this patient, the latency was approximately 7 months, longer than commonly reported.[15]

Currently, no standardized diagnostic criteria exist for the Koebner phenomenon. Most published evidence consists of case reports, though some epidemiological studies are available.[12]

Conclusion

This case underscores the importance of considering the Koebner phenomenon when evaluating PSCs, particularly in patients with psoriasis. Early recognition is vital to avoid mismanagement, improve patient comfort, and reduce costs. Multidisciplinary collaboration between dermatology, gastroenterology, and allergology was key to diagnostic accuracy and treatment success. A limitation of this report is that no skin biopsy was performed, which could have provided histopathological confirmation of the Koebner phenomenon and further strengthened the diagnosis. Raising awareness of such atypical presentations and incorporating them into clinical education and guidelines may improve outcomes and support the development of evidence-based protocols for ostomy care.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Good syndrome: a case report of an atypical presentation and the challenges of diagnosis

Síndrome de Good: um relato de caso de uma apresentação atípica e os desafios diagnósticos

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ABSTRACT

Good syndrome (GS) is a rare immunodeficiency disorder with a broad clinical and immunological spectrum. Although the classic triad of thymoma, hypogammaglobulinemia, and susceptibility to infections remains the diagnostic cornerstone, the lack of consensus and the existence of atypical presentations make diagnosis challenging. This study reports the case of a 59-year-old woman with prior thymoma and recurrent infections, including refractory esophageal candidiasis and pyelonephritis caused by unusual pathogens. Immunological evaluation found near-absent peripheral B lymphocytes (CD19 <1%) and an inverted CD4+/CD8+ ratio. Notably, the patient did not present persistent hypogammaglobulinemia, an uncommon finding that may suggest the existence of subtypes, such as Good-like syndrome. This case underscores the broad phenotypic spectrum of GS and the need for more flexible diagnostic criteria capable of encompassing atypical presentations.

Keywords: Good's syndrome, thymoma, immunodeficiency, atypical cases, immunophenotyping.

RESUMO

A Síndrome de Good (SG) é uma imunodeficiência rara, com apresentação clínica e imunológica heterogênea. Embora a tríade clássica de timoma, hipogamaglobulinemia e suscetibilidade a infecções seja fundamental, a ausência de consenso e a existência de apresentações atípicas tornam o diagnóstico desafiador. Relatamos o caso de uma paciente de 59 anos com timoma prévio e infecções recorrentes, incluindo candidíase esofágica refratária e pielonefrite por patógenos incomuns. Os achados imunológicos incluíram uma ausência quase total de linfócitos B periféricos (CD19 < 1%) e inversão da relação CD4+/CD8+. Notavelmente, a paciente não apresentou hipogamaglobulinemia persistente, um achado raro que sugere a possibilidade de subtipos, como a síndrome Good-like. Este caso destaca a amplitude fenotípica da SG e a necessidade de critérios diagnósticos mais flexíveis para abarcar apresentações atípicas.

Descritores: Síndrome de Good, timoma, imunodeficiência, casos atípicos, imunofenotipagem.

Introduction

Good syndrome (GS) was first described by Robert Good in 1954.[1-3] This rare syndrome was initially considered a humoral deficiency, a variant of common variable immunodeficiency associated with thymoma and characterized by a triad comprising thymoma (Figure 1), hypogammaglobulinemia, and increased susceptibility to bacterial, viral, and fungal infections, in addition to several autoimmune manifestations. Reduced immunoglobulin levels are linked to reduction or absence of mature B cells in peripheral blood and inversion of the expected ratio of CD4+/CD8+ T cells. Several populations of innate immune cells can also be affected. Good syndrome primarily emerges in people aged from 50 to 60 years,

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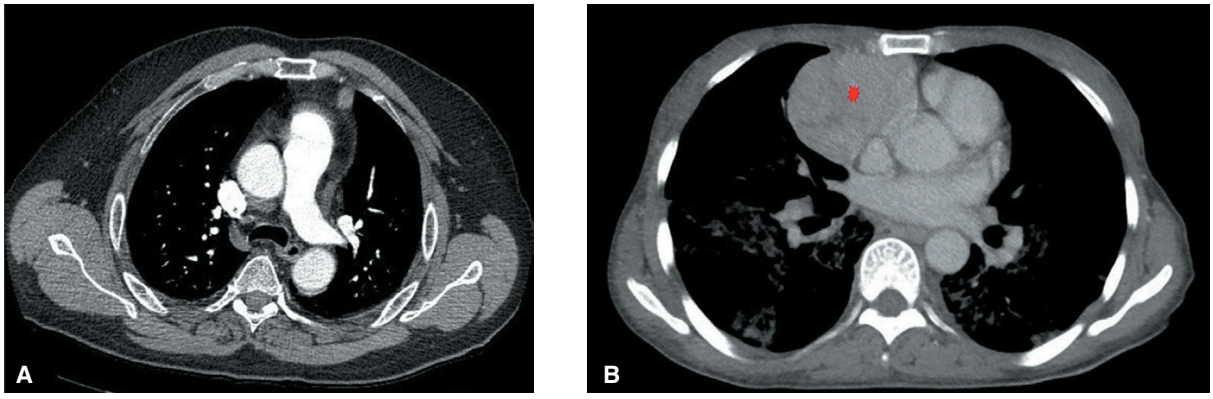

Figure 1
Computed tomography images showing evidence of thymoma. (A) mediastinal nodule with diameter of 1.6 cm;[8] (B) anterior mediastinal soft tissue mass (red star) measuring 6.5 cm x 5.5 cm x 9.5 cm with a hypodense component and multiple enlarged mediastinal lymph nodes, the largest measuring 1.2 cm, in the left hilar region[3]

with a discrete predominance among females. Type AB thymomas are responsible for more than 50% of GS cases whereas thymic carcinomas are found in less than 10% of cases.[4,5]

Clinical status is variable. Since the syndrome is characterized by humoral and cellular immunodeficiency (Late Onset Combined Immunodeficiency) in conjunction with thymoma, the most common symptoms are caused by these changes. Of these, the most important include airway infections and bronchiectasis, symptoms caused by compression by the thymoma, such as postprandial vomiting, dysphagia and weight loss, and paraneoplastic syndromes, including superior vena cava syndrome, myasthenia gravis, and Horner syndrome.[5]

Chronic diarrhea is observed in 30-50% of patients, often associated with absorptive disorders, possibly caused by damage to mucosa and rapid bacterial growth, although the cause has not been fully explained. Other findings include complications secondary to infections, such as pulmonary fibrosis and pleural effusion.[6] Tables 1 and 2 list the frequencies of infections and infectious agents in a group of 42 Chinese patients with GS.[7]

Typical laboratory findings include an absence or significant reduction of B lymphocytes, T cell dysfunction, hypogammaglobulinemia, and inversion of the CD4/CD8 ratio, in addition to reports of increases in the population of gamma delta T lymphocytes.[9]

The pathogenesis of GS is not entirely understood (Figure 2). One theory suggests that autoreactive CD8+ T cells may inhibit maturation of B cells from pro-B precursor cells, with a negative impact on immunoglobulin production. Another hypothesis involves production by bone marrow stromal cells of cytokines such as limitin and type I interferon, which

Table 1
Types of infections described in 42 Chinese patients with Good syndrome[7]

Infection	Number of patients
Sinopulmonary infection	31
Skin infection	4
Intestinal infection	4
Eye infection	2
Encephalitis	2
Urinary tract infection	1
Spontaneous peritonitis	1
Joint infection	1
Intra-abdominal infection	1
Carbuncle	1
Cellulitis	1
Viremia	1

may influence growth and differentiation of thymic precursors and B cells. However, neither of these theories has been proven unequivocally, or accepted widely.[7]

The thymoma provokes structural changes in the thymic microenvironment, such as deficient expression of the AIRE gene in thymic epithelial cells, leading to loss of central self-tolerance. As a consequence, autoreactive T lymphocytes are released into the circulation, causing the frequent coexistence of autoimmune manifestations in patients with GS. There is also experimental evidence showing that these mechanisms may act in synergy.[2,5]

Diagnostic criteria for GS are not yet well-defined because of a lack of consensus.[10] While there is therefore no formal diagnosis, a recent systematic review defined the presence of thymoma and hypogammaglobulinemia as the minimal essential criteria for diagnosis. Absence or significant reduction of peripheral B lymphocytes, inverted CD4+/CD8+ ratio, and T cell dysfunction reinforce the diagnosis.[5,9,11] Good syndrome was previously classified as a subset of common variable immunodeficiency, but GS has

Table 2
Pathogens identified in patients with Good syndrome[7]

Pathogens	Number of patients
Cytomegalovirus	7
Pseudomonas aeruginosa	5
Pneumocystis carinii pneumonia	4
Klebsiella pneumoniae	3
Herpes zoster	2
Staphylococcus aureus	2
Clostridium difficile	2
Herpes simplex	1
Mucor	1
Tuberculosis	1
Toxoplasma gondii	1
Staphylococcus	1
Escherichia coli	1
Haemophilus influenzae	1

Note: some patients had more than one site of infection.

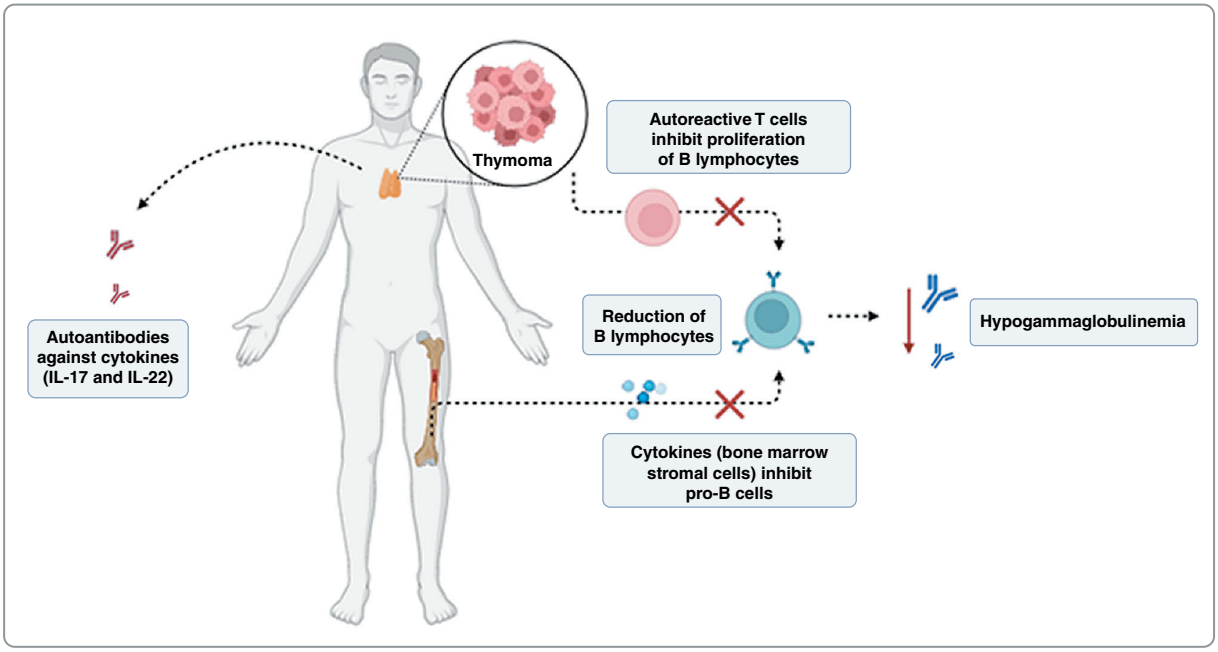

Figure 2
The major mechanisms related to immunodeficiency in Good syndrome. The hypogammaglobulinemia may be attributable to inhibition of proliferation of B lymphocytes by T lymphocytes, in addition to the regulatory effect of cytokines produced by bone marrow stromal cells, such as IFN-γ, on the growth and differentiation of pro-B lymphocytes. In turn, autoimmunity may be associated with presence of antibodies against cytokines involved in Th17 response, such as IL-17 and IL-22[2,5]

a reduced number or absence of peripheral B cells and no change to B cell maturation, which is seen in common variable immunodeficiency. It is thus important to distinguish GS from other immunodeficiencies, especially common variable immunodeficiency, with which it may be confused clinically.[6] Finally, the World Health Organization and the International Union of Immunological Societies both define GS as a separate condition to common variable immunodeficiency and define it as an immunodeficiency with thymoma.[12]

Management of Good syndrome requires a multifaceted approach, with both therapeutic and preventative strategies. Studies emphasize that surgical resection of the thymoma is considered the standard treatment, although it does not result in remission of the autoimmune diseases or the immunodeficiency. Plasmapheresis and splenectomy were associated with modest results in terms of recovery of immunological function in patients with GS.[13]

To treat the hypogammaglobulinemia in patients with GS, intravenous or subcutaneous immunoglobulin replacement therapy is indicated to promote a reduction in the frequency of infections. Monitoring of pulmonary, renal, and hepatic function and surveillance for signs suggestive of additional autoimmune diseases are also part of adequate management of the syndrome.[14]

Retrospective studies have shown that respiratory and intestinal infections are common among patients with GS, with pathogens such as cytomegalovirus and *Pneumocystis jirovecii* identified with frequency.[15] Moreover, use of macro- genomic next-generation sequencing is suggested to detect pathogens in cases in which empirical antimicrobial treatment fails, enabling more targeted treatment in individual cases.[16]

Prevention of infections is a critical aspect of management of Good syndrome, using antibiotic agents that target particularly recurrent etiologic agents, in addition to immunoglobulin replacement therapy. Vaccines based on live agents should be avoided.[16]

Case report

The patient was a 59-year-old woman, with a history of thymectomy in 2016 and hiatus hernia repair in 2021, who sought medical care in July 2022 because of complaints of weakness, lack of appetite and dysphagia, with considerable weight loss of ~24 kg over the previous 6 years; reaching a current weight of 38 kg. Prior to thymectomy, she had not had any history of recurrent or serious infections, or of hospital admissions.

Her first admission was because of white plaques on the oral mucosa and swollen cervical lymph glands. An upper digestive endoscopy showed esophageal candidiasis, hiatus hernia, pangastritis, and atrophic gastric mucosa. Serology for HIV, and hepatitis B and C was negative. During this prolonged hospital stay she also needed treatment for pyelonephritis, with blood and urine cultures positive for multisensitive *Escherichia coli*, *Phytobacter ursingii*, and *Citrobacter koseri*. A culture from her oral mucosa was positive for *Candida albicans* resistant to fluconazole and voriconazol.

The oral and esophageal candidiasis was resistant to usual antifungals, requiring therapeutic upscaling. The patient had been admitted several times over the previous 6 years, for administration of intravenous antifungals to treat the recurrent and refractory candidiasis. An upper digestive endoscopy showed esophageal stasis and esophageal manometry confirmed a diagnosis of type I achalasia and she underwent Heller-Pinotti cardiomyotomy via laparotomy.

Currently, the patient is using a nasogastric probe because of esophageal stenosis caused by the candidiasis. She is taking nystatin solution, 5 mL twice a day; 20 mg Omeprazole twice a day; and 150 mg fluconazole, 3 capsules once a day.

Tables 3 and 4 list the results of serum immunoglobulin assays and white blood cell counts. Immunophenotyping showed peripheral B lymphocytes were almost absent (CD19 < 1%), an inverted CD4/CD8 ratio, and elevated gamma delta TCR.

The patient had no sign of protein loss and serum albumin was 3.68 g/dL (RR 3.65 – 5.2) in a serum protein electrophoresis study from 2023, with gamma globulins at 0.99 g/dL (RR 0.9 – 2.1) with no monoclonal pattern. Hepatosplenomegaly was absent. Serology: anti-HIV non-reactive (NR); HBsAg NR; Anti-HBc NR; hepatitis C NR; HIV viral load not detected; rubella IgG reactive and IgM NR; Epstein-Barr virus (EBV) IgG reactive and IgM NR; cytomegalovirus (CMV) IgG reactive and IgM NR.

Discussion

Good syndrome (GS) is classified as a phenocopy of inborn error of immunity, with acquired combined

Table 3
Serum immunoglobulin levels

Date	IgG (mg/dL) (RR: 952–1538)*	IgA (mg/dL) (RR: 153–359)	IgM (mg/dL) (RR: 73–171)	IgE (UI/mL) (RR: 2–214)
07/2022	795	194	62	< 1
09/2022	1086	247	112	< 1
05/2023	1051	221	101	< 1
02/2024	1327	242	107	< 1
08/2024	1396	290	112	< 1

*RR, laboratory reference range, for age.

immunodeficiency associated with the presence of thymoma, hypogammaglobulinemia, and absence of peripheral B lymphocytes.[5,17] However, the case reported herein exhibited immunological and infectious findings that partially challenge this traditional definition.

The patient had near-total absence of B lymphocytes (CD19 <1%), inverted CD4+/CD8+ ratio, and growth of the gamma delta TCR population. These findings reflect a profound immunological imbalance, compatible with the pathophysiology of GS, the origin of which may involve inhibition of B cell maturation by autoreactive T lymphocytes, or dysfunction of the hematopoietic microenvironment, mediated by cytokines such as limitin and type I interferon.[7] The increase in gamma delta T cells, which is described less frequently, may suggest a compensatory innate mechanism in response to the adaptive deficiency, especially considering the presence of persistent fungal infections.[9]

One singular feature of this case is the absence of persistent hypogammaglobulinemia. Serum IgG levels remained within normal limits every time they were measured, contrasting with the majority of reports of GS. While rare, this finding has been described before, and some authors propose classifying these cases as Good-like syndrome, emphasizing the need for more flexible diagnostic criteria to encompass atypical presentations.[10]

Another factor that diverges from the classic phenotype is the pattern of infections: whereas bacterial sinopulmonary infections and infections by pathogens such as cytomegalovirus and *Pneumocystis jirovecii* are most frequently described in GS, in the present case there was difficult to manage esophageal candidiasis and pyelonephritis caused by unusual agents. These infections, which were recurrent and refractory to treatment, indicate a functional deficit of Th17 response, as has been proposed in recent pathophysiologic models of GS, involving autoantibodies against IL-17 and IL-22 and failures to maintain mucosal immunity.[5]

Considering the immunological and infectious findings in conjunction, the case is phenotypically similar to Good syndrome, although lacking one of its central diagnostic criteria, hypogammaglobulinemia, indicating that the clinical spectrum may be broader than previously described. This observation has been raised by Nabavi et al.,[18] who reported cases with compatible clinical manifestations, but with partial immunophenotypes. Therefore, discussing the existence of subgroups within GS, such as the Good-like syndrome, may be relevant to both clinical practice and to formulation of future diagnostic guidelines.[8]

Conclusions

Good syndrome is a complex and rare immunodeficiency with heterogeneous clinical and

Table 4
Immunophenotyping of lymphocytes in peripheral blood

	07/2022	06/2023	05/2025
CD3 RR*: 849.1-1963.3 cells/mm³	1,066 cells/mm³	810 cells/mm³	1,221 cells/mm³
CD3 (%) RR: 55.5-75.2	75.1	73.0	76.3
CD4 RR: 477.5-1140.8 cells/mm³	408 cells/mm³	309 cells/mm³	535 cells/mm³
CD4 (%) RR: 30.7-49	40.6	38.2	43.8
CD8 RR: 211.7-724.6 cells/mm³	505 cells/mm³	382 cells/mm³	552 cells/mm³
CD8 (%) RR: 13.8-27.4	50.2	47.1	45.2
CD4/CD8	0.8	0.81	0.96
CD19 RR: 124.2-415.9 cells/mm³	27 cells/mm³	8 cells/mm³	14 cells/mm³
CD19 (%) RR: 6.1-17.1	2.0	0.7	0.9
CD56 RR: 137-567.8 cells/mm³	304 cells/mm³	291 cells/mm³	362 cells/mm³
CD56 (%) RR: 7-22.8	22.7	26.2	22.6
CD3/CD56	46 cells/mm³	79 cells/mm³	62 cells/mm³
CD3/CD56 (%)	4.6	9.7	5.1
TCR α/β	923 cells/mm³	730 cells/mm³	1,099 cells/mm³
TCR α/β (%)	91.7	90.1	90
TCR γ/δ	37 cells/mm³	49 cells/mm³	61 cells/mm³
TCR γ/δ (%)	3.7	6.0	5

*RR, laboratory reference range, for age; a/b = alpha/beta, g/d = gamma/delta.

immunological presentations. The present case demonstrates the importance of considering the possibility of GS even in the absence of persistent hypogammaglobulinemia, a classic criterion. The findings of B lymphocytopenia and inverted CD4+/CD8+ ratio are consistent with GS, while the peculiar infectious pattern of this patient suggests specific deficits of mucosal immunity. Discussion of subtypes, such as the Good-like syndrome, is crucial to achieve better understanding and management of GS. This case report underscores the need for more comprehensive diagnostic guidelines that reflect the disease's phenotypical diversity and contribute to refinement of patient recognition and prognosis.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

The role of mid- and terminal-expiratory flows in the assessment of small-airway function

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Dear Editor,

This communication synthesizes recent evidence on the clinical value of mid and end-expiratory flows for the early detection of small-airway obstruction. In chronic obstructive pulmonary disease (COPD), one of the earliest functional abnormalities is a reduction in flows such as $FEF_{25–75\%}$ and $FEF_{75\%}$.[1] Although these parameters do not constitute standalone diagnostic criteria, they may reveal subclinical abnormalities and act as early markers in both asthma and early-stage COPD. Small-airway obstruction may precede a decline in the FEV_1/FVC ratio, manifesting during the terminal phase of expiration and indicating a risk of disease progression, even in asymptomatic individuals, particularly smokers and former smokers.[2]

Evidence in COPD

In the SPIROMICS study, which included 2,771 current and former smokers, Ronish et al. (2022) showed that reduced $FEF_{25–75\%}$ was associated with greater COPD severity, including increased emphysema burden (particularly homogeneous emphysema), more pronounced small-airway involvement, increased total lung capacity (TLC) and residual volume (RV), airway wall thickening, more severe symptoms, poorer performance on the 6-minute walk test, and greater bronchodilator responsiveness. These associations persisted after adjustment for FEV_1 and FVC, reinforcing that $FEF_{25-75\%}$ provides additional information on structural and functional changes related to loss of elastic recoil and air trapping.[3]

In a multinational study including 3,957 participants with a mean follow-up of 8.3 years, Knox-Brown et al. (2023) demonstrated that isolated small-airway obstruction, defined by $FEF_{25–75\%}$ or FEV_3/FVC below the lower limit of normal with preserved FEV_1/FVC, significantly increased the risk of chronic airflow obstruction, with $FEF_{25–75\%}$ emerging as the strongest predictor (OR 2.95; AUC 0.764). These findings, replicated in the UK Biobank cohort, reinforce the role of these parameters as early markers of COPD.[2]

Gelb et al. (2021) demonstrated that symptomatic smokers may exhibit small-airway obstruction or early emphysema despite normal conventional spirometry. In a cohort of 16 patients, all exhibited reduced $FEF_{75\%}$, which proved to be more sensitive for early abnormalities than $FEF_{50\%}$, $FEF_{25–75\%}$, RV, or the RV/TLC ratio. Correlations were observed between computed-tomography and pathological findings, suggesting that analysis of terminal expiratory flows, particularly $FEF_{75\%}$, may facilitate earlier diagnosis and help guide treatment.[4]

In restrictive lung diseases, despite reduced lung volumes, increased elastic recoil tends to keep the airways open, such that the $FEF_{25–75\%}$/FVC ratio is usually normal or elevated. Therefore, a reduced ratio suggests obstruction, whereas preserved or elevated values may indicate a restrictive pattern.[5]

Evidence in asthma

A study by Ciprandi et al. evaluated 439 outpatients with asthma and found reduced $FEF_{25–75\%}$ (<65% predicted) in 31% of the sample. Among patients with normal FEV_1 and FEV_1/FVC, 19.6% still showed reduced $FEF_{25–75\%}$, which was associated with lower FEV_1 and FEV_1/FVC values and the presence of symptoms. The authors emphasized that this index deserves attention in asthmatic patients with normal conventional spirometric parameters, as its reduction may indicate the need for a more targeted therapeutic approach.[6]

The asthma phenotype characterized by small-airway dysfunction (SAD) involves narrowing of airways with a diameter <2 mm and is associated with poorer disease control and a higher risk of exacerbations. SAD can be assessed using $FEF_{25–75\%}$, oscillometry, or multiple-breath nitrogen washout. Its prevalence increases with asthma severity and, given the limited penetration of inhaled therapies into the distal airways, systemically administered biologic agents targeting distal inflammatory mediators have emerged as a promising alternative.

Limitations and interpretation

$FEF_{25–75\%}$ shows substantial variability, limiting its sensitivity and specificity. Therefore, isolated values neither confirm nor exclude airflow obstruction, and this parameter is recommended only as a complementary measure to FEV_1, the FEV_1/FVC ratio, and bronchodilator response, in accordance with the 2024 Brazilian Thoracic Association (SBPT) guidelines.[1]

Interpretation of $FEF_{25–75\%}$ in spirometry

Forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25–75\%}$) represents the average flow during the mid portion of forced expiration. It has traditionally been considered more sensitive to early changes in the small airways, despite significant limitations to its interpretation.

Methodological limitations

Interpretation of $FEF_{25–75\%}$ requires high-quality spirometry, as submaximal effort, variability between maneuvers, or inadequate expiratory time compromise reproducibility. This index is effort-dependent and declines physiologically with aging, increasing uncertainty in older individuals. In addition, inappropriate reference equations may distort the relationship between lung function, age, and height; in this regard, Brazilian reference equations are more appropriate because they are based on robust population data. These limitations may generate false-positive or false-negative results, which is why the SBPT recommends strict quality control, population-validated reference equations, and, ideally, multicenter studies.[1]

Clinical relevance

Despite these limitations, reduced $FEF_{25–75\%}$ values have been associated with greater extent of emphysema, airway hyperresponsiveness, and hyperinflation, even in the presence of normal FEV_1.[2,5] In smokers, reduced $FEF_{25–75\%}$ with preserved FEV_1/FVC increases the risk of developing COPD, reinforcing its role as an early marker.[3] Although mid-expiratory flows may also decrease in proximal obstruction or in the presence of reduced FVC, in some cases of mild asthma or early COPD, $FEF_{25–75\%}$ may be the only abnormal parameter, supporting its clinical relevance.[1,4,6]

Interpretative approach

A low $FEF_{25–75\%}$/FVC ratio may indicate dysanapsis, i.e., a mismatch between airway caliber and lung volume. Imaging studies have shown that individuals with dysanapsis are at increased risk of COPD.[2] Therefore, $FEF_{25–75\%}$ should always be interpreted in conjunction with other spirometric parameters. In pulmonary function reports, direct attribution of "small airways disease" should be avoided, favoring neutral descriptions such as "Reduced flows at mid lung volumes ($FEF_{25–75\%}$)" instead.[1]

Supplemental analytical strategies

In clinical practice, $FEF_{75\%}$ may allow early detection of abnormalities in patients with suspected obstruction despite normal conventional indices. Its isolated interpretation is valid only when FVC is normal; otherwise, the $FEF_{25–75\%}$/FVC ratio helps distinguish true obstruction from proportional reductions related to lower lung volumes, particularly in children with preserved FEV_1/FVC.[1] Other indices, such as FEV_3/FVC and FEV_3/FEV_6, may also increase sensitivity for terminal airflow limitation, but their use in Brazil remains limited by the lack of validated reference values.[1]

Conclusion

Although $FEF_{25–75\%}$ provides additional information on small-airway function, its isolated interpretation is not recommended. Technical limitations of the test and a lack of reference equations may compromise its accuracy; therefore, this parameter should be interpreted in a contextual manner, alongside clinical findings and conventional spirometric indices.

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The need for official recognition of Inborn Errors of Immunity as a clinical subspecialty in Brazil

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Dear Editor,

Inborn Errors of Immunity (IEIs) encompass more than 575 monogenic diseases and 17 phenocopies associated with recurrent infections, autoimmunity, inflammation, lymphoproliferation, and malignancies. Their estimated prevalence ranges from 1 in 1,000 to 1 in 5,000 individuals and may reach up to 1 in 500 in the general population.[1] Advances in techniques such as next-generation sequencing (NGS) and multiparametric flow cytometry have significantly improved diagnosis of these conditions, enabling personalized therapies including immunoglobulin replacement, biologics, immunosuppressive drugs, hematopoietic stem cell transplantation, and gene therapy.[2]

Current situation in Brazil

In Brazil, the diagnosis and management of IEIs are still largely performed by allergists, whose training has traditionally focused on asthma, rhinitis, and other allergic diseases. Consequently, their background is often insufficient for the complexity of IEI diagnosis and treatment. It is estimated that about 80% of severe combined immunodeficiency cases remain undiagnosed, leading to increased morbidity and mortality, treatment delays, and higher costs for the public health system. This is largely due to a shortage of specialists and referral centers.[3]

The diagnostic triad of IEIs

The diagnosis of IEIs is complex and depends on integrating three complementary dimensions:

- ***Clinical diagnosis:*** recognition of syndromic patterns, recurrent or severe infections, and autoimmune, inflammatory, or lymphoproliferative phenotypes;
- ***Functional diagnosis:*** use of laboratory tests that characterize and quantify immune disturbances, including flow cytometry, lymphocyte proliferation assays, cytokine production, phagocytic function, and immunoglobulin quantification;
- ***Genetic diagnosis:*** identification and interpretation of pathogenic variants in immunity-related genes through NGS, gene panels, or exome/genome sequencing.

Therefore, it is essential that specialists master both the clinical manifestations and the interpretation of functional and genetic tests, integrating these dimensions into a single, personalized diagnostic approach.[4,5]

Rationale for establishing a recognized subspecialty

Given this scenario, it is crucial to establish Inborn Errors of Immunity as a recognized area of practice within the field of Allergy and Immunology, acknowledging an internationally consolidated subspecialty that requires integrated clinical and laboratory competencies.[6] The IEI specialist must operate across multiple domains of knowledge. Beyond basic training in Allergy and Immunology, the specialist must acquire expertise in:

Hematology, to evaluate cytopenias, lympho-proliferative disorders, and manage hematopoietic stem cell transplantation;

Clinical genetics, for the interpretation of genetic variants and family counseling;

Immunopathology, to connect pathophysiologic mechanisms with clinical manifestations;

Infectious diseases, due to the high frequency of recurrent and opportunistic infections in patients with these conditions;

Flow cytometry and laboratory medicine, to characterize cell populations and functional defects;

Molecular biology, essential for understanding genetic mutations, interpreting NGS reports, and correlating laboratory findings with clinical phenotypes;

Gastroenterology, given the frequent enteric manifestations such as protein-losing enteropathy, malabsorption, and chronic diarrhea;

Dermatology, indispensable for diagnosing infectious or autoimmune skin lesions that are frequent and may guide early recognition of IEIs;

Pulmonology, due to the risk of recurrent pneumonias, bronchiectasis, and chronic respiratory complications;

Otorhinolaryngology, to identify recurrent upper airway infections and prevent structural complications;

Rheumatology, to recognize and distinguish autoimmune and autoinflammatory manifestations, allowing for safe immunomodulatory therapy.

This multidisciplinary profile demonstrates that the management of IEIs requires comprehensive and structured training, integrating clinical assessment, advanced laboratory investigation, and genetic interpretation.[4,6]

Advantages of establishing a recognized subspecialty

The primary advantage of recognizing IEIs as a clinical subspecialty would be improving the quality of patient care. Formal recognition would promote the creation of referral centers and structured training programs, enabling the development of specialists with expertise in molecular investigation, flow cytometry, immunopathology, and advanced therapies. Another benefit would be the positive impact on public health. Early diagnosis reduces recurrent hospitalizations, antibiotic overuse, and irreversible complications such as bronchiectasis and organ failure, which would not only improve patient survival and quality of life but also enhance cost-effectiveness within the Brazilian Unified Health System (SUS). From a scientific perspective, recognition would strengthen national research in immunogenetics, expanding Brazil's participation in collaborative networks and clinical trials. For the specialty, it would consolidate the role of the allergist/immunologist in managing complex immune disorders, preventing fragmentation of care and fostering precision medicine.[6]

Challenges and potential drawbacks

The main counterargument concerns the risk of fragmenting the specialty. However, the "area of practice" model recognized by the Brazilian Medical Association (AMB) and Federal Council of Medicine (CFM) has been successfully implemented in other specialties without causing fragmentation. The current shortage of professionals with robust training in IEIs, stemming from the lack of specific education in residency programs, further reinforces the need for formal recognition, which would encourage the development of fellowships and international collaborations. Additionally, logistic and economic barriers remain significant: access to molecular testing and NGS is extremely limited in the public sector, and advanced therapies are costly and scarce. Nevertheless, official recognition could facilitate the creation of national protocols and the incorporation of these technologies into the SUS.

It should be emphasized that early diagnosis of IEIs often depends on initial recognition by non-specialist physicians. Formal recognition of this area of practice would facilitate the dissemination of warning signs and referral pathways, enabling primary care and other services to promptly refer these patients to specialized centers.

International precedent

International experience supports the feasibility of this proposal. In the United States and Europe, dedicated fellowship programs in IEIs are already recognized by organizations such as the Federation of Clinical Immunology Societies (FOCIS) and the European Society for Immunodeficiencies (ESID). These programs have structured curricula encompassing advanced laboratory diagnosis, transplantation management, and gene therapy. Recognizing the subspecialty in Brazil would foster the establishment of centers of excellence, benefiting both patients and researchers while increasing the country's high-impact scientific output.

Conclusion

Inborn errors of immunity represent one of the most advanced areas of clinical immunology, with significant infectious, autoimmune, and oncologic implications. In Brazil, the absence of an officially recognized subspecialty limits professional training and contributes to underdiagnosis. Formal recognition would bring tangible benefits to patients, the public health system, and scientific advancement. Despite current limitations in workforce, cost, and infrastructure, only official recognition can ensure standardization, organization, and sustained investment. To advocate for the creation of this subspecialty is to advocate for a fairer, more efficient, and internationally aligned healthcare system.

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Recurrent vulvovaginal candidiasis: emerging pathogenic, immunological, and genetic determinants

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Dear Editor,

Vulvovaginal candidiasis (VVC) is a fungal infection caused by species of the *Candida* genus and characterized by inflammation of the vulvar and vaginal epithelium. It is a highly prevalent condition that affects up to 75% of women at some point in life, primarily during the reproductive phase. The recurrent form is called recurrent vulvovaginal candidiasis (RVVC) and is defined as the occurrence of three or more episodes within a 12-month period, accounting for approximately 5-8% of cases and constituting an important public health problem. The most common etiologic agent is *Candida albicans*, responsible for the majority of sporadic and recurrent episodes. However, species other than albicans, such as *Nakaseomyces glabratus* (previously known as *Candida glabrata*), have progressively been associated with recurrent cases.[1]

Candida albicans is an opportunistic and commensal human fungus and its name refers to the white color. It has a genome with approximately 28 Mb in the diploid state, which exhibits peculiar CTG codon coding, and it has notable morphological plasticity, altering between yeast, hyphae and pseudohyphae forms. This combination of genomic and morphological characteristics facilitates environmental adaptation and drives its considerable virulence. It has dynamic cell walls, made up of β-glucan, chitin and several proteins (such as ALS and Hwp1), conferring protection against environmental stressors and immunological attacks. Its main virulence factors include: production of hydrolytic enzymes (proteases, lipases), ALS adhesins, morphological transition between yeast and hyphae forms, production of Candidalysin toxin and formation of biofilms. Biofilms pass through adhesion, maturation, and dispersion stages that involve polysaccharide matrices and changes in gene expression, especially in pathways related to metabolism of sulfur amino acids, glycolysis, and ergosterol synthesis. This arsenal of adaptive and virulent mechanisms enables *Candida albicans* to invade epithelium, evade phagocytosis, adhere to medical devices (catheters, prostheses, heart valves), and cause infections ranging from superficial mucocutaneous presentations to severe systemic forms, which are frequently resistant to antifungal agents.[2]

Candida albicans is part of the local microbiota of healthy individuals. In this context it is not a threat, unless the immune system is weakened, which can lead to fungal proliferation and, potentially, to initiation of an infectious process. Immunodeficiency can be caused by bacterial or viral infections, stress, and many diseases, such as cancer affecting organs or burns, in addition to treatments such as use of antimicrobials, hemodialysis, immunosuppressive agents, or major surgery. Other medical risk factors include prolonged hospitalization and admission to an intensive care unit. Infections range from mild and superficial forms, such as mucosal and cutaneous infections — oral candidiasis, diaper rash and vaginal candidiasis — to severe, highly lethal blood-borne infections. Subsets of immunocompromised patients at particular risk include patients with acquired immunodeficiency syndrome or on cancer treatments. Severe invasive diseases caused by *Candida albicans* include candidemia, candidiasis of the central nervous system, urinary candidiasis, endophthalmitis and chorioretinitis, *Candida* endocarditis, bone and joint candidiasis (spondylodiskitis, osteomyelitis, arthritis, and infection of prosthetic joints), and *Candida* pneumonia.[3-7]

Patients with VVC frequently report dysuria, vulvar pruritus, dyspareunia, and pain, while signs of VVC include vulvar edema and erythema, vaginal fissures, abrasions, and secretion, in addition to introital and vaginal erythema. While these signs and symptoms are characteristic, they are not exclusive to candidiasis. As such, diagnosis should not be made on the basis of clinical assessment alone. Workup must include preparation of fresh samples of vaginal discharge to identify budding yeast, hyphae, or pseudohyphae (using saline solution and microscopy with 10% KOH) or cultures, confirming the presence of a yeast species. In RVVC cases, culture of vaginal discharge or polymerase chain reaction (PCR) testing is essential to identify the *Candida* species involved.[8]

Studies of RVVC have concentrated on three main axes: factors intrinsic to the pathogen, changes related to host immunological dysregulation, and genetic predispositions.[1]

(1) Factors intrinsic to the pathogen: Gai Ge et al. conducted a 1-year prospective study at a local hospital with 98 patients diagnosed with *Candida* gynecological infections. Of the total sample, 20.41% had RVVC and 79.59% had VVC. *Candida albicans* was responsible for the majority of the pathogens isolated from both groups (90%

of RVVC, and 96.1% of VVC), with no significant differences in antifungal susceptibility. However, it was observed that patients with RVVC had lower serum IFN-γ, TNF-α, and IL-17F levels and higher levels of IL-4, IL-6, and IL-10 compared with patients with VVC. These findings suggest that immune responses, especially those related to Th1/Th2 equilibrium, play a central role in disease prognosis.[9] A study by Ji-Yun Tian et al. investigated recurrence of VVC, distinguishing between relapse (same pathogen) and reinfection (different isolate). To achieve this, they extracted the genomic DNA of *Candida albicans* and amplified and sequenced seven genes (AAT1a, ACC1, ADP1, MPIb, SYA1, VPS13, and ZWF1b). Multilocus Sequence Typing (MLST) was used to attribute a specific Diploid Sequence Type (DST) to each strain. The results showed that 59.1% (26/44) of the patients exhibited relapse, with predominance of the DST 79 genotype (65.4%). The etiology was reinfection in the remaining 40.9% (18/44), primarily involving the genotypes DST 79 (33.3%), DST 124 (8.6%), and DST 1895 (8.6%).[10]

Xinzheng Li et al. investigated whether RVVC recurrence was more associated with antifungal resistance or with increased *Candida albicans* virulence. To do so, they assessed two classic markers of virulence: formation of germ tubes, the initial stage in transition from yeast to hyphae that is essential for tissue invasion, and biofilm formation capacity, since this structure confers protection against the host immune response and reduces the efficacy of antifungals. The results revealed that *Candida albicans* strains isolated from patients with RVVC had significantly higher rates of formation of germ tubes and biofilms compared to strains from patients with sporadic VVC and from healthy women ($p < 0.001$). This finding indicates that the greater virulence of strains associated with RVVC may be determinant for infection persistence and recurrence, irrespective of the antifungal susceptibility profile. Interestingly, susceptibility analysis showed that strains from the sporadic VVC group were less sensitive to antifungals than those from patients with RVVC and healthy women. As such, while antifungal resistance appears to be more related to sporadic infections, the critical factor for recurrence in RVVC appears to be increased fungal virulence.[11]

(2) Factors related to immunological dysregulation: RVVC is associated with significant immunological dysregulation compared with patients with sporadic VVC and healthy women. In a study already cited above, by Gai G et al., a reduction in serum IFN-γ, TNF-α, and IL-17F levels was observed in conjunction with increased IL-4, IL-6, and IL-10 levels, indicating reduced Th1/Th17 response and a predominance of Th2 response.[9] Similarly, in a study by Consuegra-Asprilla JM et al., in situ analysis of vaginal mucosa showed reduced expression of T-bet, RORγ-T, IL-1β, and IL-17 and increased expression of FOXP3, IL-4, IL-8, IL-10, and IL-18, emphasizing the Th1/Th17 imbalance in favor of Th2/Treg.[12] Results for the influence of mannose bonding lectin (MBL) were divergent: levels were reduced in patients with RVVC in one study,[12] there was no significant difference in another,[13] and a third found elevated levels compared with healthy women (0.330 ng/mL vs. 0.253 ng/mL; $p = 0.001$).[14] With regard to innate immunity, patients with RVVC exhibited lower neutrophil fungicide capacity and reduced proliferation of mononuclear cells in peripheral blood after stimulation with *Candida albicans*, compared with healthy controls ($p < 0.05$ and $p < 0.01$, respectively).[15] Additionally, biopsies of vaginal mucosa revealed overexpression of CD163+ macrophages and of NLRP3 inflammasome in patients with RVVC compared with women with VVC and healthy women ($p < 0.01$).[16] In conjunction, these findings suggest that RVVC results from a complex interaction between reduced protective immune responses, changed innate cell function, and local inflammatory activation, contributing to disease persistence and recurrence.

(3) Genetic factors: recent studies have demonstrated that genetic factors play an important role in susceptibility to RVVC. Polymorphism of codon 54 of exon 1 of the MBL2 gene showed a significant association with the disease: the variant "B" allele was more frequent among patients with RVVC (16.1%) than in healthy controls (6%), increasing the risk of recurrence by 3.04 times. Moreover, patients with mutant genotypes (AB and BB) exhibited significantly lower serum MBL levels than those with the wild genotype (AA).[17] In the case of IL-12, there was greater mRNA expression in patients with RVVC (twice that of healthy women; $p = 0.0013$) and a significant difference in genotypic distribution of the single nucleotide polymorphism (SNP) rs568408 on gene IL-12A. The GG genotype was more prevalent among patients (29.47%) compared with controls (6.94%), suggesting that overexpression of IL-12 can increase susceptibility to the disease.[18] With regard to the NLRP3gene, Jaeger M et al.[19] found that the VNTR polymorphism on intron 4, especially genotype 12/9, was significantly more frequent in patients with RVVC ($p = 0.02$) and was associated with elevated IL-1β levels in vaginal fluid, indicating that inflammasome-mediated hyperinflammation may be involved in pathogenesis. Among the innate receptors, the TLR2 Pro631His polymorphism was associated with a 2.7 times increase in risk of RVVC ($p = 0.046$), with harmful effects on protein function and reduced IL-17 and IFN-γ production after stimulation by *Candida albicans*.[20]

In contrast, there were no significant differences in the Dectin-1 Y238X polymorphism when patients and controls were compared.[21] Taken together, this evidence suggests that variants of the MBL2, IL-12, NLRP3, and TLR2 genes contribute to predisposition to RVVC, supporting the conclusion that the disease results from a complex interaction between immunological and genetic factors. A case-control study conducted in Nairobi (Kenya) with 174 women with RVVC, 157 with acute VVC and 347 controls, found genome variants associated with susceptibility to RVVC. The main findings were SNPs rs8181503 (MS4A12) and rs58936172 (TMEM39A). Pathway analysis revealed involvement of genes linked to energy metabolism, cell signaling, and adhesion, including gluconeogenesis, fatty acid and linoleic acid metabolism, pentose phosphate pathways, chemotaxis, and growth factor signaling. These results suggest that genetic factors contribute to VVC recurrence and could guide care strategies for African populations.[22]

For management of these patients, the choice of antifungal treatment should take account of the *Candida* species identified, its susceptibility profile, and individual metabolic conditions. In women with type 2 diabetes (DM2), even uncomplicated acute episodes demand rigorous monitoring. Traditional regimes, including 150 mg oral fluconazole in a single dose or topical azoles for 3 to 7 days remain effective in the majority of cases. However, recently published Mexican clinical guidelines stressed the need to control the underlying metabolic disorder, avoid short duration treatments, and include nystatin as a safe option. For complicated cases of VVC or RVVC, more intensive regimens are recommended: 150 mg fluconazole every 72 hours for two or three doses, or alternative treatments, such as voriconazol, boric acid, or nystatin ovules. Rigorous metabolic control is essential, because improved immune function and reduced glycosuria directly reduce the fungal load and risk of recurrence. For management of RVVC, a maintenance treatment with 150 mg fluconazole weekly for 6 months remains the most widely adopted strategy, reducing risk of recurrence by up to 95% during the treatment period. However, around half of the patients relapse after withdrawal, demonstrating a need for longer lasting or more innovative treatments. Prolonged fluconazole use is not free from adverse effects, including hepatotoxicity, gastrointestinal intolerance, drug interactions, and teratogenic risk. In response to these limitations, new antifungals such as oteseconazole were developed. This new generation azole acts on fungal lanosterol-14α-demethylase with greater specificity, minimizing off-target effects. Significantly lower relapse rates (5% in 48 weeks) compared with fluconazole (42%) were demonstrated in women with RVVC. Additionally, immunotherapeutic approaches, such as NDV-3A, which is a recombinant vaccine based on *Candida albicans* Als3p adhesin, and PEV7, based on Sap2 antigens, are under clinical assessment in phase II trials. The objective of these vaccines is to stimulate robust Th1 and Th17 responses, boosting mucosa immunity and reducing the risk of recurrence. While not yet approved for clinical use, they exhibit great potential, especially in immunocompromised or metabolically vulnerable populations, such as women with DM2, because of their capacity to overcome local immunological dysfunction.[23]

In view of these findings, it is evident that RVVC should be recognized, not merely as a recurrent infection, but as a multifactorial condition with great clinical and immunological relevance. It is thus essential that allergists and immunologists remain alert to the subject, since in-depth understanding of its determinants enables more complete, individualized, and effective management, amplifying the strategies for diagnosis, prevention, and treatment.

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Skincare in childhood: it's important to be aware

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Dear Editor,

While reading Folha de São Paulo (July 2, 2025 edition), we came across a report addressing an issue that has long concerned health care professionals and been the subject of ongoing discussions among experts: the indiscriminate use of cosmetic products by children and adolescents.[1] The article, "Kids' skin care TikToks are costly and counterproductive" (Ian McMahan, The Washington Post), highlights a growing and alarming phenomenon — the popularization of complex skin care routines among preadolescents, driven by social media and pseudo-influencers who promote products without any scientific basis and are motivated solely by commercial interests.[1]

In this context of intense media exposure and aspirational consumerism, it is imperative to discuss the risks and consequences of this trend. The study cited by McMahan analyzed videos targeting 13-year-old adolescents that prescribed skin care regimens costing an average of US$168 and involving the application of up to 6 products per day — yet only 25% included sunscreen.[2] Even more concerning, most routines contained combinations of approximately 11 potentially irritating or allergenic active ingredients and excipients.[2]

The pursuit of "perfect skin," fueled by content that exploits the insecurities typical of adolescence, has accelerated the onset of cosmetic consumption among increasingly younger age groups. Recent data indicate that 70% of children aged ≤12 years have already used children's makeup or body care products, excluding hygiene and moisturizing items, and more than half of these users (57%) are between 0 and 3 years of age.[3] These findings are alarming because they not only expose children to potentially unnecessary chemical substances but also reflect the imposition of unrealistic beauty standards beginning in early childhood.

Children's skin, particularly that of neonates and infants, is physiologically fragile and immature. It is characterized by a thinner epidermis and immature skin barrier, resulting in increased absorption of topically applied substances.[4] Repeated exposure to fragrances, preservatives, and surfactants with sensitizing potential increases the risk of allergic contact dermatitis, the incidence of which has risen significantly in recent decades, especially in pediatric populations.[5] In addition to immediate skin reactions, chronic sensitization may occur, potentially compromising skin tolerance and predisposing individuals to future allergic diseases.

Products labeled as "hypoallergenic" or "safe for children" frequently contain haptens such as propylene glycol, fragrances (eg, limonene and linalool), and surfactants (eg, cocamidopropyl betaine and glucosides).[4,6] Even cosmetics marketed as "clean" by major U.S. retailers have been shown to contain a high prevalence of pediatric contact allergens, underscoring the substantial gap between fragrance-free marketing claims and the reality of product formulations.[6]

Even more concerning, however, is the sociocultural dimension of this phenomenon. Influencers with no technical training have transformed skin care into a multibillion-dollar market driven by emotional persuasion, encouraging comparisons and insecurities among typically boys and girls in their formative years. The promise of "instant self-esteem" through consumption creates a form of "symbolic dependence" on products, distorts healthy relationships with one's own body, and places health concerns in a secondary position. This represents a modern form of exploitation of child and adolescent vulnerability.

Social media platforms have become spaces of visibility and self-promotion, where the pursuit of recognition is mediated by algorithms that function as invisible engines driving consumption. On X (formerly Twitter), engagement-based dynamics favor content capable of generating intense emotional reactions, thus amplifying self-promotional discourse and symbolic status consumption. Instagram, in turn, is structured around carefully curated imagery and aesthetics as markers of distinction, transforming appearance into social capital and linking digital prestige to adherence to specific beauty standards. TikTok further reinforces a culture of immediate gratification in which visibility becomes synonymous with value, and success is tied to virality. These digital architectures are designed to maximize user exposure and encourage continuous consumption, fostering the internalization of the notion that personal worth depends on the acquisition and display of goods. Consequently, algorithms do more than recommend content — they shape desires, behaviors, and self-perceptions. Within the broader framework of influencer capitalism, these platforms transform consumption into performance and identity into a commodity. The result is

a system of emotional reinforcement that fuels aesthetic and financial dependence among increasingly younger audiences, especially children and adolescents whose identities are being formed under digitally mediated systems of validation.

Parents, schools, health care professionals, and opinion leaders must work together to reverse this trend. For most children and preadolescents, the ideal skin care routine should be limited to 3 basic pillars: gentle cleansing, simple moisturization, and daily sun protection. Nothing more is necessary — and anything beyond this may be harmful.

In an era in which social media increasingly dictates behavior, the debate surrounding pediatric skin care extends far beyond the fields of pediatrics, allergy, and dermatology: it is a matter of public health, digital education, and social responsibility that demands attention and intervention. Medical societies must recognize their civic responsibility to repeatedly inform the public of the risks associated with these practices. Health care professionals have a duty to remind families that beauty cannot be measured in bottles and that children's skin should never

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