International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn25S206

Basophils in allergy: immunological mechanisms, diagnostic innovations, and clinical implications in the context of meat allergy

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DOI: https://doi.org/10.54448/ijn25S206
Received: 01-14-2025; Revised: 03-28-2025; Accepted: 04-30-2025; Published: 05-06-2025; IJN-id: e25S206

Editor: Dr. Idiberto José Zotarelli-Filho, MSc, Ph.D., Post-Doctoral.

Abstract

Introduction: Allergic diseases remain a widespread clinical problem, affecting diverse populations and placing increasing demands on healthcare resources. **Objective**: This review set out to assess the modern research about the immunological functions of basophils in the context of allergic disorders and to evaluate their diagnostic and therapeutic relevance. **Methods**: A thorough literature review, which adhered to PRISMA 2020 guidelines, was performed utilising the PubMed, Scopus, and Web of Science databases. Research published from 2019 to 2024 was chosen according to certain keywords pertaining to basophil activation, α-gal syndrome, and the diagnostic uses of the basophil activation test (BAT). **Results and Conclusion**: The evidence compiled here demonstrates the pivotal contribution of basophils to both IgE-dependent and IgE-independent allergic processes. These cells release potent mediators such as histamine and interleukin-4 (IL-4), influencing T-helper 2 (Th2) cell differentiation and amplifying inflammatory cascades. Recent research highlights the usefulness of the BAT in detecting IgE-mediated hypersensitivities to foods, medications, and insect venoms, owing to its notable sensitivity and specificity. Studies further suggest that monitoring basophil responsiveness during allergen-specific immunotherapy or biological interventions may guide therapeutic decisions, as declining basophil reactivity correlates with improved allergen tolerance. Notably, emerging research on meat allergies, particularly α-gal syndrome, reveals that basophils are critical mediators in IgE-mediated reactions to mammalian meat allergens. BAT is proving instrumental in diagnosing meat allergies, helping to distinguish sensitized individuals from those with clinical manifestations. Despite promising developments, several obstacles hinder the wider integration of BAT into clinical protocols, including variations in basophil responsiveness, lack of standardized testing procedures, and insufficient large-scale population studies. These gaps underscore the importance of ongoing research aimed at refining diagnostic accuracy, developing targeted therapeutics, and clarifying the multifaceted interplay between basophils and other immune components.

Keywords: Immunology. Sensitization. Laboratory Diagnostics. Immunoglobulin E. α-gal syndrome. Leucocytes.

Introduction

Allergic illnesses impact more than 30% of the worldwide population, with an increasing prevalence noted in both developed and developing countries **[1]**. The prevalence of allergic disorders, such as asthma, atopic dermatitis, allergic rhinitis, and food allergies, has consistently risen over the past twenty years, imposing a significant strain on global healthcare systems **[2]**. Traditional allergens, including peanuts, milk, and shellfish, have historically been the primary focus of food-related hypersensitivities; nevertheless, increasing epidemiological evidence suggests a significant rise in atypical allergies, particularly hypersensitivity to

mammalian meat products [3,4]. This novel category of food allergy is frequently linked to α-gal syndrome, an IgE-mediated condition initiated by sensitization to Galactose-α-1,3-galactose (α-gal), a carbohydrate epitope present in red meat and transferred to humans mostly by tick bites.

The growing acknowledgement of α-gal syndrome highlights the necessity for a deeper comprehension of the immunological mechanisms underlying these unusual allergic reactions. In this context, basophils have attracted heightened scientific interest. Despite constituting less than 1% of circulating leukocytes, basophils exert a disproportionate impact on allergic inflammation [5]. By rapidly releasing histamine and interleukin-4 (IL-4), these granulocytes facilitate type I hypersensitivity and the development of T-helper 2 (Th2) cells.

Furthermore, recent research indicates that basophils may function as supplementary antigen-presenting cells (APCs), augmenting allergen-specific immune responses even in IgE-independent scenarios. Historically eclipsed by mast cells because of their overlapping roles, basophils are now recognized as essential immunological effectors in both traditional and emerging allergy disorders [6]. In instances of meat allergy, the reactivity to α-gal-containing epitopes provides diagnostic and prognostic information that has practical relevance for clinical allergy assessment and therapy categorization [7,8]. Therefore, enhancing our comprehension of basophil biology is crucial for addressing the diagnostic intricacies and treatment obstacles presented by developing allergy disorders like α-gal syndrome.

Despite noteworthy advancements, there remain critical knowledge gaps in basophil-driven immunological pathways. Although the BAT holds promise as a powerful diagnostic modality, uncertainties persist regarding the consistency of BAT results across varied patient cohorts, how to establish standardized reference values, and how reliably it predicts long-term treatment outcomes. The precise mechanisms that govern basophil interactions with dendritic cells and Th2 lymphocytes also require further study to clarify their roles in regulating allergic memory and ongoing inflammation. These open questions underscore the necessity for expanded research aimed at refining diagnostic methods and identifying new therapeutic strategies that target basophils in allergic disorders.

Multiple critical deficiencies persist in our comprehension of basophil-mediated immune mechanisms and their diagnostic uses. The therapeutic use of the Basophil Activation Test (BAT) encounters persistent obstacles related to standardization, reproducibility across cohorts, and long-term prognostic significance. Spiewak et al. [9] established the elevated diagnostic sensitivity and specificity of BAT in children allergic to home dust mites while also recognizing the diversity of basophil responsiveness, which complicates the interpretation of test thresholds among different populations. Krupka Olek et al. [10] similarly discovered that BAT performance in patients with skin illnesses, including atopic dermatitis and hand eczema, can exceed established approaches such as skin prick testing. However, they also identified discrepancies that highlight the absence of standardised diagnostic criteria. In addition to these findings, Urbańska et al. [11] discovered other basophil-related indices, including eosinophil-basophil ratios, as possible biomarkers for the severity of venom allergies; however, their clinical use is constrained by a lack of standardized validation techniques.

Aside from these technological aspects, many mechanistic concerns remain. Pałgan [12] has shown that basophils are involved in IgE-independent anaphylactic pathways, which are mediated by complement-derived anaphylatoxins and MRGPRX2 activation—pathways that standard IgE-centric tests, including BAT, do not detect. Furthermore, Gomułka et al. [13] observed increased basophil activation in asthma patients exhibiting irreversible bronchoconstriction, suggesting a function for vascular endothelial growth factor (VEGF) in regulating CD203c expression. This discovery underscores the extensive role of basophils in chronic inflammatory remodeling, an area that is yet under investigated. Chakrapani et al. [14] enhanced our comprehension of meat allergy by demonstrating that α-gal, a glycan found on mammalian glycoproteins and glycolipids, induces basophil-mediated reactions in sensitized individuals. Their research also highlighted the necessity for improved diagnostic stratification, as existing methods may inadequately differentiate between clinical reactivity and asymptomatic sensitization.

The present investigation aimed to address certain aspects of these unresolved issues by examining the modern researches about immunological processes underpinning basophil activation and their diagnostic implications, thereby contributing to an improved understanding of basophil functions in allergy and enhancing the clinical decision-making process.

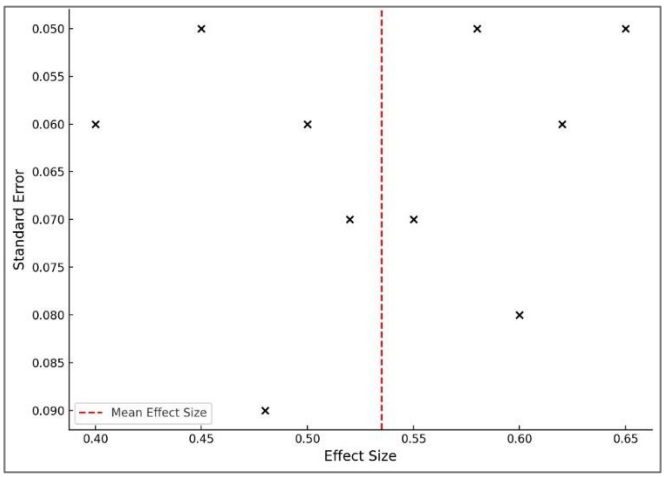
Methods

This review was conducted using a systematic literature search to explore the role of basophils in allergic diseases, with a specific focus on their involvement in meat allergies such as α-gal syndrome.

Relevant studies were identified through comprehensive searches of electronic databases, including PubMed, Scopus, and Web of Science, using predefined keywords such as "basophil activation," "meat allergy," "α-gal syndrome," and "Basophil Activation Test (BAT)." The search was limited to publications from 2019 to 2024, although foundational studies from earlier years were also included to provide context. Included studies were selected based on their relevance to basophil activation, immune mechanisms in allergies, and the diagnostic and therapeutic applications of BAT. Data extracted from the studies were analyzed to identify key findings on the role of basophils in allergic reactions, particularly in meat allergies, and to assess the utility of BAT as a diagnostic and monitoring tool.

The PRISMA 2020 principles guided this review, ensuring transparency and reproducibility **[15]**. A systematic review process was developed using PRISMA's 27-item checklist, encompassing research selection, bias risk evaluation, and data synthesis phases. Data extraction and quality evaluation were confirmed utilizing established templates. A visual evaluation based on a funnel plot was performed to assess potential publication bias among the papers included (Figure 1). The distribution of effect estimates appeared symmetrical, indicating low risk of publication bias.

Figure 1. Funnel plot for publication bias assessment.



Source: Own authorship.

During the review process, multiple layers of analysis were carried out. The first step involved identifying recurring themes and findings, particularly those related to non-IgE-driven mechanisms of mediator release and basophil involvement in chronic allergic disorders such as asthma and urticaria. The second step concentrated on the BAT, critically appraising published data on test sensitivity, specificity, and positive and negative predictive values across diverse allergic presentations. Sample size considerations, research design rigor, and the strength of statistical analyses were also evaluated.

Additionally, the review investigated basophil responses in a range of therapeutic scenarios. These included allergen-specific immunotherapy and newer biological treatments targeting immune regulation. Special attention was given to how molecular mechanisms were tested, particularly the consistency of experimental protocols, the thoroughness of control conditions, and the reproducibility of reported outcomes.

Finally, the review process employed a thematic organization of findings to highlight established concepts, points of scientific agreement, unresolved research questions, and emerging directions. Throughout this endeavor, systematic records of inclusion and exclusion decisions were maintained, along with precise documentation of data extraction and synthesis approaches. Moreover, the marked variation in methodologies, patient demographics, and clinical endpoints encountered across the selected studies underscores the necessity for standardized research protocols and rigorous peer review, ultimately facilitating more robust comparisons, reproducibility, and deeper insight into basophil-mediated processes in allergic pathophysiology. This transparent methodology supported the reliability and replicability of the overall literature review, ensuring that both foundational studies and contemporary investigations were appropriately represented.

Results and Discussion

Fundamental basophil researches

The elucidation of basophilic granulocytes immunological significance represents a paradigmatic shift in contemporary immunobiology, transcending their historically circumscribed characterization as mere effector cells within the immunological milieu. These remarkably scarce hematopoietic elements, constituting a mere half-percentage of the leukocytic repertoire in peripheral circulation, have emerged from relative obscurity to assume a position of paramount importance in immunological orchestration, particularly within the context of hypersensitivity responses and allergic pathophysiology **[16-17]**. The contemporary understanding of basophilic functionality has undergone substantial reconceptualization, with mounting empirical evidence substantiating their multifaceted role as both initiators and modulators of immunological cascades, specifically in the context of allergic manifestations. The revolutionary revelation of basophils' capacity for antigen presentation, empirically validated through

rigorous immunological investigations published in preeminent scientific periodicals has fundamentally revolutionized the comprehension of their physiological significance **[18,19]**. This paradigm shift is particularly evidenced by the observation of significant basophilic accumulation within lymphoid tissues during the preliminary phases of allergen sensitization, notably preceding the characteristic expansion of Th2 lymphocytes and the concomitant elevation in IL-4 concentrations **[20]**.

The demonstration of direct cellular interactions between basophils and T-lymphocytes has further corroborated their integral role in immune response initiation. Revealing basophils' noteworthy ability to internalize antigens, illustrated by their engagement with ovalbumin and their surface display of key costimulatory molecules such as CD80, CD86, and CD40 has provided mechanistic insight into how they modulate immune functions **[21]**.

The observation that basophil stimulation via immunoglobulin E-mediated antigen recognition precipitates substantial IL-4 secretion has illuminated their central role in Th2 cell differentiation, notably occurring independently of exogenous IL-4 supplementation **[22]**. The physiological significance of basophilic function has been definitively demonstrated through experimental manipulations in murine models of allergic pathologies, wherein the selective depletion of circulating basophils resulted in marked attenuation of Th2 responses, diminished specific immunoglobulin E production, and reduced allergic inflammatory manifestations thus offering undeniable proof of their key role in allergic pathogenesis **[23]**.

The complex role of basophils in immunological processes continues to generate vigorous scientific discourse **[24]**. Such debate becomes especially pronounced when examining their possible status as APCs. Certain investigators contest their designation as "professional" APCs because they are unable to handle and display insoluble antigens a functional shortcoming that sets them apart from conventional APCs like dendritic cells and macrophages **[25]**.

Furthermore, this perspective is reinforced by the observation that basophils exhibit either negligible or undetectable messenger RNA expression related to major histocompatibility complex (MHC) class II molecules, despite the presence of these molecules on their cellular surface. This intriguing phenomenon has led to the discovery that basophils can acquire MHC class II-peptide complexes from dendritic cells through the process of trogocytosis. As a result, a sophisticated model has emerged, describing the initiation of Th2 responses by basophils through three distinct but potentially complementary mechanisms. First, basophils can directly present antigens while secreting IL-4 at early stages, thereby facilitating Th2 cell differentiation. Second, they can enhance dendritic cell activation and the subsequent release of cytokines supporting the Th2 response. Third, they can acquire MHC class II-peptide complexes from dendritic cells, enabling basophils to function as surrogate APCs **[26,27]**.

Basophils play a role beyond initial immune responses, extending into the critical domain of immunological memory. Evidence obtained from both animal and clinical investigations confirms their instrumental function in maintaining and activating memory immune responses **[28-29]**. Specifically, experimental studies in murine models have shown that introducing basophils into sensitized subjects significantly augments memory responses driven by Th2 cells, whereas their selective depletion results in a marked attenuation of this response **[30]**. Moreover, basophils enhance the longevity of effector T cells while increasing their per-cell cytokine production capacity. These findings are further corroborated by *in vitro* studies utilizing human basophils, which demonstrate their ability to boost IL-4 secretion by Th2 memory cells.

Notably, the immunomodulatory capabilities of basophils extend beyond the Th2 axis to include support for the T-helper 17 (Th17) response, even in contexts where dendritic cells are absent. This observation carries particular significance given the established role of Th17 cells in the pathogenesis of allergic airway inflammation, suggesting that basophils may constitute a previously unrecognized therapeutic target in the management of allergic respiratory diseases **[31]**. Thus, these findings collectively underscore the remarkable versatility and importance of basophils in both the initiation and maintenance of diverse immunological responses. They challenge traditional perspectives on the role of basophils in immune system function and open new avenues for therapeutic intervention in allergic and inflammatory conditions.

Clinical applications in allergic diseases

The persistent escalation in the prevalence of allergic pathologies, particularly bronchial asthma and allergic rhinitis among pediatric populations, represents a significant contemporary challenge in clinical immunology and allergology. This trend necessitates increasingly sophisticated diagnostic and therapeutic approaches to address the fundamental questions routinely confronting clinicians in their management of allergic conditions: the definitive establishment of allergic etiology, the precise identification of specific allergens, and the prognostication of potential disease recurrence following therapeutic intervention.

These clinical requirements emphasize the urgent

need for the development and integration of robust diagnostic techniques and precise biomarkers to enhance the accuracy of assessments and ensure comprehensive, ongoing monitoring of patients **[32]**. Within this context, the BAT has emerged as an exceptionally valuable clinical tool, supported by extensive research demonstrating its utility in both the diagnosis and monitoring of allergic diseases. The mechanistic underpinning of allergic responses involves the coordinated activity of basophils and mast cells, which function as primary effector cells in type I hypersensitivity reactions **[33]**. These cells are characterized by their expression of high-affinity immunoglobulin E receptors (FcεRI) on their cellular surfaces **[34]**.

In individuals who have undergone allergic sensitization, these receptors serve as binding sites for specific immunoglobulin E. Subsequent exposure to relevant allergens triggers receptor crosslinking **[35,36]**, culminating in cellular degranulation and the rapid upregulation of specific activation markers – most notably CD63 and CD203c – on the basophil membrane. These and other specific activators are mentioned in Table 1.

Table 1. Basophil activation markers and their expression profiles.

Marker	Main expressing cells	Key points
CD63	Basophils, mast cells, platelets, macrophages	Often used as a primary indicator of cell degranulation in basophils
CD107a, CD107b	Activated basophils, mast cells, T cells, NK cells	Expression increases in parallel with CD63; pattern may overlap with other markers such as CD203c
CD13	Basophils, myeloid-lineage cells	Detected in various granulocytic populations; sometimes compared to CD203c in terms of expression dynamic
CD164	Basophils, CD34+ progenitor cells	Shares expression traits with CD203c; provides information on cell lineage and activation
CD69	Basophils, lymphocytes, neutrophils, monocytes, eosinophils	Can be upregulated by interleukin-3; shows weaker expression in certain IgE-mediated settings
p38 MAPK, STAT5	Multiple cell types, including basophils	Intracellular phosphorylation events can be measured as an alternative way to assess basophil activation

Source: Own authorship.

The BAT represents an innovative *in vitro* diagnostic methodology that recapitulates the fundamental mechanisms of type I hypersensitivity reactions by quantifying the degree of basophil degranulation in response to controlled allergen exposure. This sophisticated analytical approach evaluates two critical parameters. The first is basophil reactivity, which quantifies the proportion of basophils undergoing degranulation in response to specific allergen challenge **[37]**.

The second is the threshold of allergen sensitivity, designated as CD-sens, which determines the precise allergen concentration required to induce degranulation in fifty percent of the basophil population **[38]**. These complementary parameters serve distinct diagnostic purposes. Basophil reactivity facilitates the definitive confirmation of allergy, while CD-sens enables both therapeutic monitoring and the assessment of allergen tolerance.

A particular strength of the BAT lies in its capacity to provide comprehensive immunological information by simultaneously evaluating multiple parameters: the quantity of specific immunoglobulin E, its binding affinity, and the presence of potentially competing antibodies such as immunoglobulin G4 **[39]**. This multifaceted evaluation offers a more nuanced and complete assessment of the allergic response than traditional diagnostic methodologies.

The pervasive nature of food allergies among pediatric populations manifests through an extensive spectrum of clinical presentations. These include oral allergy syndrome, diverse gastrointestinal symptoms, cutaneous reactions such as urticaria and eczematous conditions, allergic rhinitis, and bronchial hyperreactivity. Modern diagnostic strategies for food allergies employ a combination of methods, such as detailed clinical history analysis, measurement of specific immunoglobulin E levels, and SPT to assess cutaneous reactivity. Nevertheless, the oral food challenge remains the gold standard due to its superior diagnostic precision, despite notable drawbacks, including considerable time consumption and the risk of triggering severe allergic reactions. In this context, the BAT has proven to be an especially effective diagnostic method for assessing immunoglobulin E-mediated food allergies **[40-41]**.

It demonstrates remarkable diagnostic performance characteristics, with sensitivity rates ranging from 77% to 98% and specificity values extending from 75% to 100%. One of the most significant advantages of BAT lies in its unique ability to differentiate between patients who exhibit clinical allergy and those who, despite demonstrating allergic sensitization, maintain tolerance to specific allergens **[42]**. This sophisticated diagnostic methodology can identify patients capable of tolerating thermally processed allergenic foods such as milk and egg products, a determination of considerable clinical significance. The *in vitro* nature of the BAT completely eliminates the risk of inducing severe allergic reactions during diagnostic evaluation, thereby offering a substantial safety advantage over traditional challenge-based approaches.

In the equally challenging domain of drug allergy

diagnosis – where diagnostic inaccuracies can have profound clinical implications – BAT has also demonstrated remarkable utility. False positive results can lead to unnecessary therapeutic restrictions, while false negative outcomes risk severe allergic reactions **[43]**. The BAT accurately identifies allergic responses to a diverse array of pharmaceutical agents, including neuromuscular blocking drugs, beta-lactam antibiotics, quinolone antimicrobials, radiocontrast media, and various nonsteroidal anti-inflammatory medications **[44]**. Consequently, BAT significantly enhances both the precision and safety of drug allergy diagnosis. Representative BAT cutoff values, sensitivity, and specificity for selected allergens presented in Table 2.

Table 2. Representative BAT cutoff values, sensitivity, and specificity for selected allergens.

Allergy category	Example of allergen(s)	Typical allergen range	Proposed CD63+ cutoff	Approx. sensitivity	Approx. specificity	Notes
Food Allergy	Peanut extract	0.1–10,000 ng/mL	~8% CD63+ basophils	~98%	~96%	Often used for peanut allergy diagnosis
	Ovalbumin (egg)	0.1–100 µg/mL	~5% CD63+ basophils	~77%	~100%	Common threshold for detecting egg allergy
Drug Allergy	Beta-lactam antibiotics	Various	~5% CD63+ basophils	~55%	~80%	Values vary by specific beta-lactam
	Neuromuscular blocking agents (e.g., rocuronium)	Varies by agent	~4% CD63+ basophils	~80%	~96%	Applies to different blocking agents
Insect Venom Allergy	Wasp venom	0.0001–1 µg/mL	~10% CD63+ basophils	~85%	~83%	Reflects typical wasp venom testing thresholds
	Bee venom	0.0001–1 µg/mL	~10% CD63+ basophils	~91%	~93%	Similar range to wasp venom testing

Source: Compiled by the author based on references 41 to 44.

The diagnostic precision of the BAT in the context of neuromuscular blocking agent hypersensitivity is evidenced by its impressive performance characteristics. Sensitivity values range from 50% to 100%, while specificity measurements lie between 85% and 90%. Positive predictive values extend from 85% to 100%, and negative predictive values span from 55% to 80% **[45]**. The particular utility of the BAT is further highlighted by its capacity to identify drug allergies in patients who demonstrate negative cutaneous reactivity. Additionally, its ability to detect cross-reactive drug allergies represents a significant advantage over conventional diagnostic approaches, such as skin testing and specific immunoglobulin E quantification, both of which are inherently limited by the restricted availability of standardized test reagents for specific pharmaceutical agents.

In the critically important domain of transfusion medicine, allergic transfusion reactions represent a potentially life-threatening complication. Established preventive strategies and early identification methods remain inadequate Recent scientific investigations have explored the application of a novel passive BAT methodology for predicting allergic transfusion reactions. Compelling research demonstrates the presence of specific immunoglobulin E directed against donor blood components in patients who experienced such reactions. Particularly noteworthy is the observation that the passive BAT yielded positive results in 9 out of 10 patients who experienced severe allergic transfusion reactions, while maintaining complete specificity (no false positives) in the control population **[46]**. Collectively, these findings suggest that the BAT represents an extraordinarily promising diagnostic tool for the prediction and prevention of transfusion-related complications. Its adoption in clinical practice could potentially revolutionize transfusion safety through enhanced risk stratification and preventive intervention.

Recent research has increasingly highlighted the significant role of basophils in mediating hypersensitivity reactions to meat, particularly in patients diagnosed with α-gal syndrome, a condition induced by tick bites that results in an IgE-mediated allergy to the Galactose-α-1,3-galactose (α-gal) molecule present in mammalian meat **[47,48]**. Basophils in individuals with α-gal syndrome exhibit heightened reactivity when exposed to meat allergens, with a rapid release of pro-inflammatory mediators such as histamine and interleukin-4 (IL-4). This increased basophil activation underscores their pivotal role in the inflammatory cascade associated with meat allergies, particularly following exposure to red meat. Notably, recent studies have shown that the severity of allergic reactions in these patients correlates with basophil activation, further emphasizing their critical contribution to the allergic response.

The growing body of evidence indicates that basophils, which were once thought to play a limited role in allergic reactions compared to mast cells, are now recognized as essential players in the pathophysiology of α-gal syndrome. This is particularly relevant in the context of diagnostic strategies, where the Basophil Activation Test (BAT) has emerged as a key tool. BAT can effectively measure basophil reactivity to α-gal and other meat-derived allergens, distinguishing individuals who are sensitized from those who are clinically allergic. As research into the immunological mechanisms of meat allergies continues to evolve, the role of basophils in these processes becomes increasingly clear, highlighting their importance not only as mediators of the allergic

response but also as targets for more precise diagnostic and therapeutic approaches.

Monitoring allergic diseases and evaluating therapy effectiveness

The utilization of basophil sensitivity as a stable and reproducible metric for evaluating therapeutic efficacy in both allergen-specific immunotherapy and biological therapeutic interventions represents a significant advancement in clinical allergology. The demonstrated correlation between increasing allergen tolerance during allergen-specific immunotherapy and the concurrent reduction in basophil sensitivity to target allergens provides a valuable objective parameter for therapeutic monitoring **[49]**. This immunological modification is mechanistically linked to elevated concentrations of specific immunoglobulin G (particularly immunoglobulin G4), which functions as a competitive inhibitor of allergen binding to specific immunoglobulin E. As a result, basophil activation responses are attenuated. In the specific context of food allergy immunotherapy, the observed reduction in basophil reactivity to target allergens serves as a reliable indicator of therapeutic success **[50]**. A similar principle applies in venom-specific immunotherapy, where diminished basophil sensitivity to insect toxins represents a positive prognostic indicator. Conversely, the persistence of elevated basophil sensitivity following therapeutic intervention identifies patients at increased risk for allergic reactions upon treatment discontinuation, thereby informing clinical decision-making regarding therapy duration and modification **[51]**.

The emergence of biological therapeutic agents as a cornerstone in the management of allergic diseases has further expanded the utility of the BAT in therapeutic monitoring **[52]**. For instance, omalizumab therapy typically induces a marked reduction in basophil sensitivity as quantified by the CD-sens index, with subsequent return to baseline values following treatment cessation **[53]**. Particularly noteworthy is the predictive value of improved BAT parameters during omalizumab therapy in pediatric patients with milk allergy, where favorable changes correlate with successful development of allergen tolerance. In the management of asthmatic disease, basophil sensitivity assessment facilitates the identification of therapeutic responders and enables objective evaluation of treatment efficacy. Consequently, basophil-based monitoring optimizes the clinical application of biological therapies through enhanced patient stratification and response tracking **[54]**.

BAT offers a range of substantial advantages that underscore its growing importance in contemporary allergy diagnostics **[55]**. First and foremost, this technique requires only a relatively small volume of blood from the patient, which simplifies sample collection and eases the logistical demands of follow-up assessments. By using minimal blood volumes, clinicians can more readily perform repeated measurements, thereby enabling dynamic monitoring of a patient's immunological status over the course of treatment or during periods of suspected allergen exposure **[56]**. Furthermore, BAT is generally faster to perform than certain other *in vitro* immunological assays, which allows for the rapid generation of results that can inform prompt clinical decision-making.

A second key advantage of BAT is its high sensitivity and specificity in detecting immunoglobulin E (IgE)-mediated hypersensitivity reactions. Through the measurement of basophil degranulation or the expression of activation markers – most commonly CD63 or CD203c – upon controlled allergen exposure, BAT captures the essential mechanism of a type I hypersensitivity reaction *in vitro*. By restricting the allergic reaction to a laboratory environment, the test prevents the potential for severe or life-threatening responses that can arise with *in vivo* procedures such as oral food challenges or SPTs **[57]**.

This laboratory-based approach thus provides an additional layer of safety, making BAT especially valuable in cases where significant clinical suspicion of anaphylaxis exists or where traditional methods might present considerable risk. Although BAT offers significant advantages, its application in routine clinical practice is limited by challenges such as the high costs of specialized reagents, advanced equipment, and the technical expertise needed to guarantee reliable results **[58]**. BAT is considered relatively complex from a technical standpoint, necessitating strict adherence to standardized laboratory protocols and controlling numerous variables – such as temperature, sample handling, and timing – to maintain basophil viability and responsiveness. Basophils themselves are exquisitely sensitive cells that can be easily compromised by suboptimal conditions, leading to possible false-negative or inconclusive outcomes **[59]**. Consequently, the need for skilled laboratory personnel and well-established operating procedures can present logistical barriers, particularly for smaller clinics or healthcare systems operating with limited resources **[60]**.

Another noteworthy drawback is that BAT cannot efficiently accommodate large-scale screening for numerous allergens in a single run. In contrast to SPT, where multiple allergens can often be evaluated simultaneously on a patient's skin, each BAT typically focuses on a narrower set of suspect allergens **[61]**. This limitation may slow down the diagnostic process when clinicians aim to evaluate a broad range of allergens or when the clinical history suggests multiple

potential triggers. Furthermore, there remains a relative scarcity of comprehensive data regarding normal BAT reference values for various demographic groups and across different geographic regions, making it challenging for clinicians to interpret intermediate or borderline results and to distinguish between truly elevated basophil responses and variations within normal limits.

From a practical standpoint, an estimated 5-10% of individuals appear to possess basophils that do not respond reliably to allergenic stimuli *in vitro*. In such cases, the test becomes entirely uninformative, as the lack of detectable basophil response prevents clinicians from drawing valid conclusions about the patient's sensitivity profile **[62]**. The underlying reasons for this lack of basophil responsiveness are still being investigated, yet it underscores the necessity of a multifaceted diagnostic approach that may include additional tests – such as specific IgE quantification, skin testing, or controlled provocation tests – to confirm or rule out allergy in patients where BAT yields no clear result **[63]**.

Given both its strengths and its constraints, BAT is particularly recommended under several clinically significant circumstances. One key scenario arises when conventional skin testing yields results suspected to be false positive, prompting the need for further, more specific confirmation via a laboratory-based method **[64]**. Another frequent indication is the unavailability of the required reagents for performing skin testing or for measuring specific IgE to certain allergens, as some specialized or novel allergens may not be supported by widely available diagnostic kits. In addition, BAT is advisable when clinical findings conflict with skin test outcomes – a situation that can occur in complex or atypical allergy cases, or where patients exhibit cross-reactivity to multiple allergens that complicates standard testing protocols **[65]**.

An equally important consideration is patient safety in contexts where skin tests carry a significant risk of eliciting severe allergic reactions. For individuals with a history of life-threatening anaphylaxis or those deemed at high risk due to comorbid conditions, it may be prudent to forego direct allergen exposure through skin testing. Instead, BAT can be conducted in a carefully controlled laboratory environment, eliminating the possibility of anaphylaxis *in vivo* **[66]**. Moreover, in situations where clinicians are considering a provocation challenge with a potentially dangerous allergen, it is often wise to perform BAT in advance to assess the likelihood of a severe reaction and to refine the decision-making process regarding whether or how to proceed with *in vivo* testing.

Monitoring allergic diseases and evaluating therapy effectiveness are crucial for tailoring individualized treatment plans, especially in cases of food allergies, including meat allergies like α-gal syndrome **[67]**. Basophil reactivity, assessed through the BAT, has proven to be a valuable tool in this process. In patients with meat allergies, particularly those sensitive to the Galactose-α-1,3-galactose (α-gal) molecule, monitoring basophil activation levels can help track the progression of the allergy and assess the effectiveness of therapeutic interventions **[68]**. By evaluating changes in basophil reactivity over time, clinicians can gain insights into the patient's immune response, helping to adjust treatment strategies accordingly.

In the context of allergen-specific immunotherapy (AIT), which is commonly used to desensitize patients to specific allergens, including food allergens like α-gal, BAT has demonstrated its ability to monitor treatment progress. Studies have shown that as patients undergo AIT for meat allergies, there is a gradual reduction in basophil sensitivity to meat allergens, which correlates with an improvement in clinical symptoms and reduced risk of severe allergic reactions **[69,70]**. This dynamic monitoring of basophil activation provides a more objective measure of therapeutic efficacy compared to traditional clinical assessments, allowing healthcare providers to make informed decisions about the continuation or modification of treatment. Additionally, in the case of biological therapies that modulate the immune system, such as omalizumab, BAT can help track the reduction in basophil reactivity and gauge the patient's responsiveness to treatment.

Evaluating therapy effectiveness using BAT can also identify patients at risk of treatment failure. If basophil activation levels remain elevated despite treatment, it may indicate inadequate response to the therapy, prompting adjustments in the management plan. This ability to measure and track basophil responses offers a more personalized approach to managing meat allergies and other allergic diseases, enhancing both diagnostic accuracy and therapeutic outcomes. By providing realtime data on immune responses, BAT serves as an invaluable tool in optimizing the clinical management of allergic disorders.

While the BAT does exhibit certain limitations – in terms of cost, complexity, and the proportion of non-responsive basophils in some individuals – it nonetheless provides a uniquely detailed glimpse into the cellular events that drive IgE-mediated hypersensitivity. Its ability to model the allergic response *in vitro* offers a safer alternative to direct allergen challenges, and the test's robust sensitivity and specificity can facilitate the accurate diagnosis of even subtle or ambiguous allergic conditions. As clinical practice continues to evolve and

standardization initiatives expand the availability of validated reagents and reference values, BAT is poised to play an increasingly integral role in both routine allergy diagnostics and more specialized investigational settings, ensuring that patients at risk of severe allergic reactions receive the most precise and safest possible evaluation.

Limitations

The variable demographic representation in the included research partly constrains generalizability. The limited availability of reference standards for the Basophil Activation Test limits cross-study comparability.

Conclusion

Basophils, despite making up a small percentage of circulating leukocytes, play a critical role in both the initial and subsequent stages of allergic and inflammatory reactions. They were once considered exclusively effector cells but are now recognized for their functions in antigen presentation, polarization of T helper cells, and maintenance of immunological memory. Basophils influence type I hypersensitivity reactions by secreting IL-4 and directly interacting with T cells, and in some cases, they contribute to Th17-mediated inflammation. Their role goes beyond standard allergic reactions, making them essential mediators in a number of diseases, including food allergy, drug hypersensitivity, and allergic respiratory diseases. The basophil activation test is the main direct basophil assay that assesses basophil reactivity in vitro by monitoring degranulation markers, such as CD63 or CD203c, after controlled allergen exposure. Basophil activation test has increased sensitivity and specificity for IgE-mediated allergy, allowing differentiation between simple sensitization and clinical allergy. It also allows real-time monitoring of patients receiving allergen-specific immunotherapy or biologic therapy. In addition, basophil activation test has demonstrated efficacy in detecting drug allergy, which eliminates diagnostic ambiguity and minimizes unwarranted therapeutic restrictions.

Despite its efficacy, implementation of basophil activation test requires strict standardization of protocols due to the susceptibility of basophils to exogenous influences. Challenges remain, including high costs, technical complexity, and non-response in a small proportion of patients. The lack of broad reference ranges has hindered wider adoption of basophil activation test, especially in the interpretation of borderline reactions. Increasing attention is being paid to the role of basophils in meat allergy, especially in patients with α-gal syndrome. This tick bite-induced disorder associated with hypersensitivity to the galactose-α-1,3-galactose (α-gal) molecule found in red meat emphasizes the growing importance of basophils in allergic disorders beyond common food allergens. Studies suggest that basophils play a key role in facilitating IgE-mediated reactions in α-gal syndrome because their activation leads to the release of histamine and interleukin-4, which exacerbate the clinical manifestations of meat allergy.

As α-gal syndrome becomes increasingly recognized, basophil activation test functions as an essential tool for detecting meat allergy, distinguishing sensitized individuals from those with clinical symptoms. Monitoring basophil activation may aid in making therapy decisions and evaluating treatment efficacy in the management of meat allergy. Future research should focus on developing universal reference standards for basophil activation test, improving its cost-effectiveness, and discovering additional biomarkers to expand its diagnostic applicability. Studying the molecular biology of basophils and their interactions with other immune cells will elucidate the mechanisms underlying allergies, especially those induced by meat allergens, allowing for improved diagnostic methods and treatment strategies.

CRediT

Author contributions: **Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, writing - original draft, and writing-review & editing-** Maria Zofia Lisiecka.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

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Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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