CANADIAN ALLERGY & IMMUNOLOGY TODAY

ISSN 2563-7711 (PRINT)
ISSN 2563-772X (ONLINE)

VOLUME 4
ISSUE 3
FALL 2024

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A Practical Approach to NSAID Allergy

Andrew Wong-Pack, MD
David Fahmy, MD

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for pain management and inflammation.[1] Acetylsalicylic acid (ASA) is a commonly used treatment for cardiovascular diseases including acute coronary syndromes.[2] Reactions to NSAIDs can vary widely, ranging from exacerbation of underlying cutaneous and respiratory conditions to anaphylaxis and delayed hypersensitivity reactions (DHRs).[3,4] A thorough clinical history is essential for diagnosing NSAID hypersensitivity, with a focus on the systems involved, reaction timing, and the presence and control of comorbid allergic conditions. Although commonly referred to as an allergy, the mechanisms behind these reactions are not solely IgE-mediated. As such, the authors will primarily use the term "hypersensitivity reactions" in concordance with the latest American Academy of Allergy, Asthma and Immunology (AAAAI) drug allergy practice parameter.[5] While NSAID hypersensitivity reactions may cross-react among cyclooxygenase-1 (COX-1) inhibitors, reactions to selective cyclooxygenase-2 (COX-2) inhibitors are rare and they are typically well tolerated as alternative agents.[5]

Classification

NSAID hypersensitivity reactions can be classified into acute and delayed presentations. Acute hypersensitivity reactions can be further divided into four major phenotypes, while DHRs are often described as distinct entities **(Table 1)**.[6]

Phenotype	Symptoms	COX-1 Mediated	Comorbidities	Desensitization	Notes
Aspirin or NSAID-exacerbated respiratory disease (N-ERD or AERD)	Sneezing, congestion, bronchospasm, laryngospasm. Rare: gastrointestinal pain, flushing	Yes	Asthma, Chronic rhinosinusitis with nasal polyposis (CRSwNP)	Yes	After desensitization to 325 mg of ASA, tolerance is achieved to other COX-1 inhibitors
NSAID-exacerbated cutaneous disease	Urticaria, angioedema	Yes	Chronic Spontaneous Urticaria (CSU), 10-40% of patients	No, may exacerbate underlying CSU	COX-2 inhibitors are generally well tolerated. Single dose challenge can be considered once CSU is controlled.
NSAID-induced urticaria and angioedema	Urticaria, angioedema	Yes	None	Can be considered	8-11% may react to COX-2 inhibitors so in-office challenge can be considered.
Single NSAID-induced reactions	Urticaria, angioedema. Rare: anaphylaxis.	No	None	Typically not recommended but possible	Challenge to structurally dissimilar NSAID for diagnostic clarification.
Delayed hypersensitivity reactions	Meningitis, pneumonitis, nephritis, fixed drug eruption, DRESS, SJS, AGEP,	No	Varies	Not for severe reactions	Challenge not recommended for severe reactions

Table 1. Phenotypes of NSAID Hypersensitivity; *adapted from Table XVI. Khan DA, et al.*[5]
Abbreviations: AERD: Aspirin-exacerbated respiratory disease; **AGEP:** acute generalized exanthematous pustulosis; **ASA:** acetylsalicylic acid; **COX 1:** cyclooxygenase-1; **COX 2:** cyclooxygenase 2; **CRSwNP:** chronic rhinosinusitis with nasal polyps; **DRESS:** drug-related eosinophilia with systemic symptoms (DRESS); **CSU:** chronic spontaneous urticaria; **NSAID:** nonsteroidal anti-inflammatory drug; **SJS:** Steven Johnson Syndrome

Generic name	Brand names
Ibuprofen	Advil, Motrin
Naproxen	Aleve
Acetylsalicylic Acid	Aspirin

Table 2. Examples of commonly used oral COX-1 NSAIDs available over-the-counter in Canada; *courtesy of Andrew Wong-Pack, MD, David Fahmy, MD,*

Acute NSAID hypersensitivity

NSAID-exacerbated respiratory disease (N-ERD/AERD)

Aspirin-exacerbated respiratory disease (AERD) is specific to Aspirin and has been previously described as "Aspirin induced asthma" and "Aspirin sensitivity".[3] It is most famously described in the context of "Samter's Triad" as a combination of bronchial asthma, nasal polyposis, and life-threatening reactions to ASA.[7,8] These reactions occur in patients with underlying chronic rhinosinusitis and/or asthma. However, they are not unique to ASA, and cross-reactivity is common. Therefore, the term has been expanded to NSAID-*exacerbated respiratory disease* to highlight this.[5] Characteristic symptoms include an acute development of congestion, rhinorrhea, bronchospasm, and less commonly gastrointestinal and skin involvement, which can be clinically difficult to differentiate from anaphylaxis.[1] The onset is typically within 30-180 minutes after drug ingestion.[8]

The causative mechanism is thought to be secondary to the inhibition of COX-1, leading to a decrease of prostaglandin E2 and a shift toward leukotriene production.[3,10,11] Weak COX-1 inhibitors can cause reactions in particularly sensitive individuals, and, though rare, COX-2 inhibitors can cause reactions.[5] For a list of commonly used oral COX-1 NSAIDs availabe over-the-counter in Canada, please see **Table 2**.

NSAID-exacerbated cutaneous disease (NECD)

NSAID-exacerbated cutaneous disease (NECD) refers to patients with underlying chronic spontaneous urticaria (CSU) who experience worsening of their symptoms after exposure to an NSAID.[5] NSAIDs have been described as co-factors for the worsening of urticaria, which can affect approximately 10-40% of patients with an underlying CSU.[4,5] In addition, the initial presentation of cutaneous NSAID hypersensitivity has been described as a precursor to the development of CSU.[12] The mechanism is also thought to be secondary to COX-1 inhibition. Given the fluctuating nature of CSU, predicting who may react to NSAIDs is challenging.[12]

Multiple NSAID-induced urticaria and angioedema (NIUA)

Patients who develop isolated cutaneous manifestations without an underlying history or current diagnosis of CSU are thought to have multiple NSAID-induced urticaria and angioedema (NIUA), which is the most common type of NSAID hypersensitivity reaction.[5] The onset of symptoms varies and typically occurs 1-6 hours after drug ingestion.[13],These reactions are most commonly observed with potent COX-1 inhibitors, however, symptoms have also been reported with weak COX-1 inhibitors such as acetaminophen as well as with COX-2 inhibitors such as celecoxib.[3,5]

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

Cutaneous reactions to individual NSAIDs, including anaphylaxis, may involve an IgE-mediated mechanism, although the exact mechanism is not completely understood.[5] Patients can typically tolerate other NSAIDs without symptoms. However, when patients choose to avoid other NSAIDs prior to presentation, the diagnosis of a single NSAID-induced reaction can be challenging. There are few reports of anaphylaxis or isolated cutaneous symptoms with ASA, and reports of serum-specific IGE to NSAIDs are limited.[5]

Delayed NSAID hypersensitivity

NSAID-induced delayed hypersensitivity reactions

Delayed reactions typically occur >6 hours after drug ingestion. However, many delayed reactions may take days to weeks of exposure before clinical manifestations develop.

Fixed drug eruptions (FDE) are cutaneous reactions where lesions recur at the same anatomical region with each re-exposure. Contact and photocontact dermatitis have been reported with topical formulations of NSAIDs as well. In addition, maculopapular or morbilliform eruptions have been documented with various forms of NSAIDs.[14]

Severe cutaneous adverse reactions (SCARs) such as Steven Johnson Syndrome (SJS), Toxic-Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), and Drug related eosinophilia with systemic symptoms (DRESS) are rare but may occur with NSAIDs. The pathophysiology of these reactions is thought to be T-cell-mediated.[5,14]

Other uncommon manifestations of NSAID reactions include pneumonitis, meningitis, interstitial nephritis, and drug-induced liver injury,

which are considered other forms of type B reactions.[5,13]

Diagnosis and management of NSAID hypersensitivity

The recent publication of the 2022 AAAAI drug allergy practice parameter has revised and consolidated the approach to diagnosing and treating NSAID hypersensitivity.[9] Although the specific recommendations vary depending on the phenotype, a selective COX-2 inhibitor can generally be used for analgesia in any patient with acute NSAID hypersensitivity for intermittent use.[5] For multiple NIUA, an initial dose challenge in the clinic can be considered.[5] Immediate single NSAID-induced reactions are rarely caused by Aspirin. As a result, Aspirin becomes a useful diagnostic tool, as tolerance suggests that the culprit is a single non-ASA NSAID, whereas a reaction suggests that the patient is susceptible to the entire class of COX-1 inhibitors. The authors recommend a total challenge dose of 162mg of ASA as this would be the expected dose used acutely for cardiovascular emergencies. We recommend for COX-2 challenges, a total challenge dose of 200mg of celecoxib. We recommend challenges be completed in a two-step fashion with at least 30 minutes between doses and monitoring for at least two hours after the final dose. By removing the drug allergy labels to ASA and celecoxib, this opens therapeutic options for most patients. Subsequent challenges to alternatives would be up to the discretion of the allergist depending on the clinical history and patient preference or needs.

NSAID-exacerbated respiratory disease (N-ERD/AERD)

For patients with a clinical history strongly suggestive of N-ERD such as experiencing two or more respiratory reactions to different NSAIDs, or a respiratory reaction requiring hospitalization, an oral challenge is not recommended. Instead, Aspirin desensitization can be considered if indicated.[5] Skin testing to ASA or in vitro tests are not recommended for diagnosis.[15] When there is diagnostic uncertainty, such as in the setting of atypical or minor symptoms or to only a single NSAID, an oral challenge to Aspirin is suggested for diagnosis.[5]

Desensitization is recommended for patients who require daily therapy, such as for secondary cardiovascular prevention or to reduce polyp regrowth.[16] Protocols can vary, including multi-day protocols, and the AAAAI practice parameter can be referenced for these.[5] Should a patient develop a reaction during desensitization, this serves as a positive challenge. Doses should be repeated and increased until the patient tolerates a minimum daily dose of either 81 mg or 325 mg of ASA.[5,16] Higher doses, such as 650 mg twice daily, may be needed for polyp control.[16] After 5 days without therapy, repeat desensitization is required for all patients and sometimes if >48 hours occur between doses.[5]

Desensitization therapy has been shown to be cost effective.[16,17] However, with the increasing use of dupilumab for chronic rhinosinusitis with nasal polyposis (CRSwNP), using desensitization for N-ERD may be shifting.[5]

NSAID-exacerbated cutaneous disease (NECD)

The diagnosis of NSAID-exacerbated cutaneous disease (NECD) relies on the presence of active CSU combined with the worsening of cutaneous symptoms.[12] The mainstay of treatment is to control the underlying urticaria, and a single-dose challenge can be considered once control is achieved.[18] Desensitization is not typically recommended as this may trigger a flare of the urticaria.[5]

Multiple NSAID-induced urticaria and angioedema (NIUA)

Diagnosing NIUA can be challenging in patients who avoid all NSAIDs after a reaction to a single NSAID. As such, a challenge with a structurally dissimilar NSAID, typically Aspirin as the initial choice, is recommended.[5] Although COX-2 inhibitors are generally well tolerated in all NSAID hypersensitivity cases, an in clinic challenge can be considered given the low rate of reactions in this phenotype (8-11%).[19] Patients who pre-medicate with high dose non-sedating antihistamines may be able to tolerate occasional NSAIDs.[5]

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

After identifying the culprit NSAID, it is recommended to challenge with a structurally dissimilar NSAID for the initial evaluation, preferentially with Aspirin when possible. Single NSAID-induced reactions to Aspirin are rare, and most challenges to Aspirin in this setting are negative, allowing future use. While desensitization is theoretically possible given the concerns about an IgE-mediated mechanism, it is typically not

recommended given the high rate of negative challenges to Aspirin.[5]

NSAID-induced delayed hypersensitivity reactions

In the setting of severe cutaneous reactions or other severe idiosyncratic NSAID reactions, challenging the culprit NSAID or its class is not recommended. Patch testing has been evaluated for FDE, and patients may tolerate a structurally dissimilar NSAID. Additional diagnostic tools are needed in this phenotype.[5]

Acute desensitization for acute coronary syndromes

For all non-AERD NSAID immediate hypersensitivity reactions, a modified rapid two-step protocol has been reported. This consists of an initial dose of 40.5 mg of Aspirin and a second dose of 40.5 mg 90 minutes later.[20] The dose can be repeated as a single dose or a dose of 325 mg later for further clarification. The benefit of successfully tolerating a challenge rather than desensitization is the removal of the Aspirin allergy label and eliminating the need for desensitization if doses are missed.[20] Desensitization remains a safe option for unstable patients or those with AERD.[5]

Summary

NSAIDs are widely used medications with multiple indications and are common triggers of hypersensitivity reactions. A thorough clinical history and a systematic approach to diagnostic evaluation and management is essential for distinguishing between the various phenotypes of NSAID hypersensitivity. Proactive evaluation of individuals labelled with an NSAID allergy is recommended due to their role of these drugs in cardiovascular diseases and non-opioid analgesia.

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Financial Disclosures

None declared.

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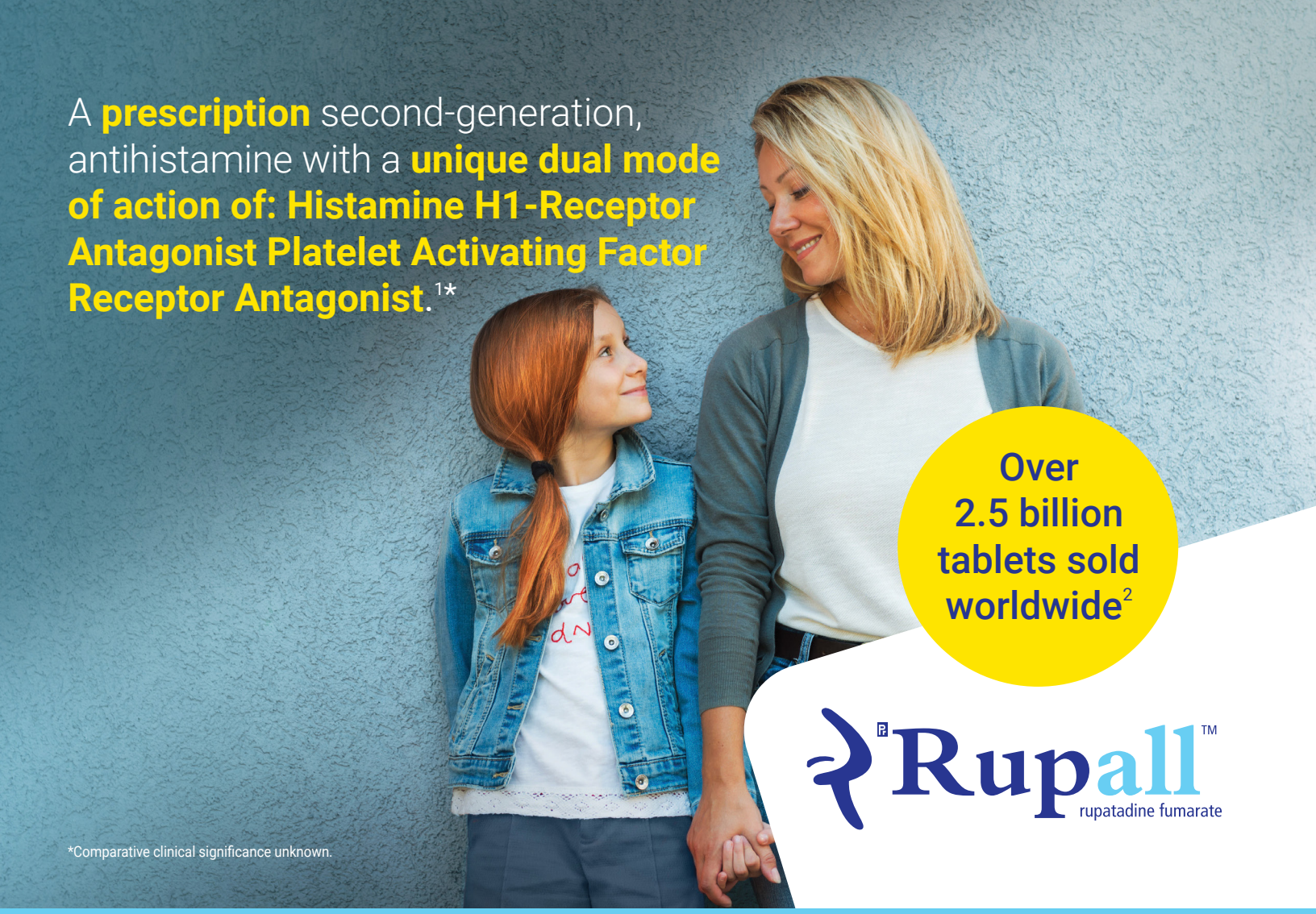

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Occupational Asthma Management

Susan M. Tarlo, MD, BS, FRCPC

Introduction

Occupational asthma is defined as asthma that is caused by work exposures, accounting for approximately 10-15% of all new-onset adult asthma.[1] Typically, this is a new-onset of asthma in workers with no previous history of asthma. However, the diagnosis may also be made in individuals who had previous childhood asthma that cleared, then recurred as an adult due to work exposure. In contrast, work-exacerbated asthma is defined as asthma that is exacerbated but not caused by work exposures.

Occupational asthma can be caused by different mechanisms **(Figure 1)**.[2] It is most often due to a workplace sensitizer, which is a high- or low-molecular weight agent that causes asthma from an immunologic response. Asthma symptoms do not occur on the first exposure. Instead, they require a period ranging from days to years for sensitization. Once sensitized, subsequent exposures, even to very low levels of exposure, will trigger asthma. When this response is due to high-molecular weight sensitizers, which are typically proteins or glycoproteins, it is associated with specific IgE antibodies. In addition, specific IgE-antibodies are also associated with the response to some low molecular-weight sensitizers (chemical sensitizers) such as complex platinum salts and other metal salts. However, for most low-molecular weight sensitizers, the immune mechanism is unclear.

In most case series, irritant exposures are also recognized to cause occupational asthma,[3,4] although this is less common than sensitizer-induced occupational asthma. The diagnosis is most clear when asthma onset occurs within 24 hours of a very high level of exposure to a respiratory irritant (also termed reactive airways dysfunction syndrome, [RADS]). However, lower-level exposures to respiratory irritants, especially if prolonged, have also been associated with irritant-induced asthma. This is often seen in occupations such as cleaning or working in paper mills with bleaching agents.

Management of occupational asthma consists of diagnosis and treatment.[5] The diagnosis should be suspected in all adult workers with new-onset asthma, and they should be asked specifically about a possible association with their work.[6] Helpful screening questions to ask include: a) whether the onset occurred shortly after an accidental exposure at work to irritating smoke, dusts, fumes, vapors, or gases, b) whether there was improvement in their asthma symptoms on days off or during holidays, and any worsening on

returning to work. If the answer is "yes" to either question, further details should be identified. This includes details of the work exposures, any associated work-related upper respiratory symptoms (which often precede sensitizer-induced occupational asthma symptoms), and the timing of temporal associations of symptoms. Published questionnaires may also help in raising suspicion of the diagnosis among those with asthma.[7] Although the history of occupational asthma is key and sensitive, it is not sufficiently specific, and objective tests are needed for the diagnosis.

Since there are over 300 known workplace sensitizers that have been associated with occupational asthma, with new agents reported each year, and numerous potential workplace respiratory irritating exposures, information about the exposures at work is helpful but not sufficient to exclude a diagnosis of occupational asthma. Details of work exposure may increase suspicion of the diagnosis when the patient works in high-risk occupations such as bakeries, animal handling, and spray painting (with exposures to wheat or other grains, animal proteins, and diisocyanates, respectively). In addition, details of any accidental exposure to high levels of respiratory irritants, shortly before the onset of asthma, are important in the diagnosis of irritant-induced asthma.

Patients can provide some details of the work exposure, including exposures that may result from adjacent workers in the same environment, e.g., who may be welding or using adhesives containing diisocyanates. Additional details can be obtained by asking the patient to request copies of safety data sheets from their workplace for review. Workers are entitled to copies of these documents, and it can be helpful to give the patient a note to request these, which they can present to the appropriate person at work.

The value of objective investigations for occupational asthma has been well detailed in several previous consensus documents and reviews.[1,5,8,9] After asthma is objectively confirmed by spirometry or methacholine challenge, skin prick tests when feasible, or serologic tests for specific IgE antibodies are helpful in identifying potential sensitization to a workplace sensitizer. Demonstration of specific IgE, especially in combination with other diagnostic tests, has a high predictive value for identifying sensitization to agents such as wheat or rye in bakers,[10] or animal allergens in laboratory animal workers.[11]

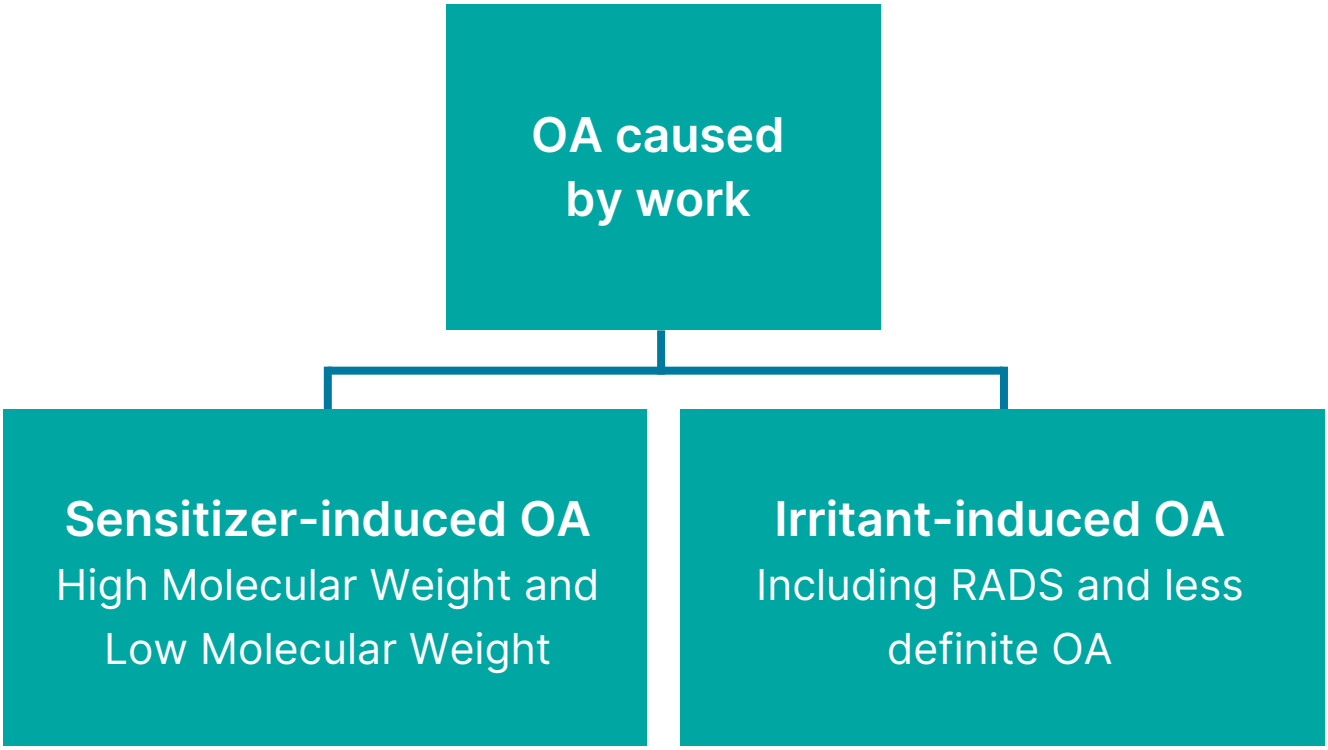

Table 1. Potential mechanisms involved in occupational asthma; *courtesy of Susan M. Tarlo, MD, BS, FRCPC*
Abbreviations: OA: occupational asthma; **RADS:** reactive airways dysfunction syndrome.

Objectively investigating possible sensitizer-induced occupational asthma, and assessing the association of asthma with work, includes recording serial peak flow readings four times a day in triplicate, with symptom scores and bronchodilator use during periods while both working and off work. Conducting methacholine challenges both at the end of a typical work period and after several days off work (as during a holiday) can add to diagnostic certainty. In addition, induced sputum cytology and/or exhaled nitric oxide if available can support the diagnosis. Specific inhalation challenges are considered the gold standard for diagnosis and are particularly helpful if other tests are inconclusive.[5]

In patients suspected of having irritant-induced occupational asthma, the most helpful information for the diagnosis is from the history of the implicated irritant exposure(s), the timing of asthma onset after the exposure, confirmation that asthma did not precede the exposure, and objective confirmation of the diagnosis of asthma. In some patients, the development of irritant-induced asthma may be followed by exacerbation of asthma at work. These can then be assessed further by monitoring of serial peak flow readings, symptoms, and bronchodilator use, as described above.

Management of the patient starts during the investigation period, including the appropriate management of asthma, and any associated rhinoconjunctivitis. This includes controlling non-occupational relevant environmental triggers, and using pharmacotherapy, similar to the approach for other patients with asthma and rhinoconjunctivitis. Good communication with the patient is essential to explain the purpose for further investigation of possible occupational asthma and the possible outcomes, since a confirmed diagnosis may lead to recommendations for work modifications and, in many cases, a claim for workers' compensation support. When occupational asthma is suspected, it is important to initiate investigations early, while the patient is still employed and working, since these investigations cannot be performed if the worker leaves their job, resulting in an uncertain diagnosis.

In Canada, work-related injury or disease is potentially compensable by Workers Compensation Systems, which operate independently in each province. Most workers in Canada are eligible to submit a claim for support through their provincial system, though the details vary somewhat between provinces. Each system's website provides information and access to the necessary application forms.

In the example of the Ontario Workplace Safety and Insurance Board (WSIB), applications can be initiated by the patient, a physician (with the patient's permission), or the employer. Each party uses a slightly different form, but all forms indicate the contact details for the worker and employer. After an initial form is submitted to WSIB by one of these three parties, the other two are sent a form from WSIB to complete. The physician's form in Ontario (Form 8) also asks for the date and site "of the work-attributed injury" and the work-related diagnosis. With the patient's permission, the physician's consultation notes can also be included. Other information requested includes the results of investigations, medications prescribed, work ability, and any work modifications needed. The patient (claimant) is also asked to provide a signed release for WSIB to obtain their medical reports and investigations.

Each compensation claim generates a claim number that is sent to the patient. The physician should obtain this number from the patient to include it on all subsequent communications with the compensation board for that claim.

Decisions on claims are made by the compensation system, with claims accepted if the work-related condition is deemed to be more probable than not, or at least 50% likely. The physician reports are considered in the process, though the claim decision is made by the compensation board. In Ontario, an additional medical assessment may be requested, and additional medical investigations may be needed. If a claim is denied, an appeal process is available for the patient with submission of additional supporting information. If the claim is again denied, further appeals can be made in Ontario to the Ontario Workplace Safety and Insurance Appeals Tribunal. Additional advice may be provided to the patient via occupational medicine clinics.

If a workers' compensation claim is initiated but has not yet been decided, a decision needs to be reached with the patient about whether to continue their current work, pending their claim decision. If the patient has clear and objective medical evidence of sensitizer-induced asthma, and there is a potential work area in the same company without exposure to that sensitizer, this alternative could be a better option. A written note (without specific medical information, and with the patient's permission) may then be given to the patient by the physician to request modified work

if feasible. Employers are responsible for providing accommodations for their workers if possible. If that is not an option, a decision on whether the patient continues working in the same area with the sensitizer until the compensation claim decision is reached (if possible with enhanced respiratory protective equipment and optimized asthma medications), or stops work and applies for short-term or long-term disability, and/or looks for a different job, will depend on discussions with the patient and the severity and control of their asthma. Factors that may influence work decisions include the possibility that the modified work might be paid at a lower rate, the compensation claim may be denied, and even if a claim is accepted, leaving the workplace may result in loss of other benefits (e.g., dental plans, or non-respiratory medication coverage).

Patients with acute irritant-induced asthma can often continue their current work with pharmacologic management of their asthma, if the high-level irritant exposure is not repeated, and if lower exposures do not exacerbate their asthma. Those with presumed subacute or chronic irritant-induced asthma, similarly, may be able to continue their current work preferably with some modifications to reduce work irritant exposures.

The best outcome for those with sensitizer-induced occupational asthma is to completely avoid the exposures that caused their asthma.[12] The outcomes are best with an early diagnosis, early removal from further exposure, and milder asthma at the time of removal from exposure. A majority of patients experience improvement after removal from exposure, although complete clearing of asthma occurs only in a minority, approximately 20% in some series.[13] Recent studies suggest the outcome is worse for irritant induced asthma.[14,15]

Support for patients with an accepted claim for occupational asthma includes: partial compensation for loss of earnings due to occupational asthma, coverage for the costs of medications needed to treat their asthma, and compensation for non-economic loss (disability) due to their asthma (usually determined once maximal medical recovery is achieved). If a job change is necessary to avoid exposure to the causative work agent, workers might receive support for retraining.

Prevention and identification of occupational asthma in other workers should also be considered once the diagnosis is reached in a patient. In Ontario, the Ministry of Labour has a surveillance program for diisocyanates in the workplace, which includes monitoring diisocyanate levels in the air, regular respiratory questionnaires, and spirometry for workers with potential exposure, with further assessments if abnormalities are detected. This program has been associated with a temporal reduction in rates of occupational asthma from isocyanates in Ontario.[16] Similar programs are not mandated for other causes of occupational asthma, however, an Ontario Ministry of Labour work visit can be requested by the worker or physician, especially if the patient is aware of co-workers with similar symptoms. This may lead to changes in the workplace to protect the workers.

Summary

In summary, occupational asthma should be suspected in all cases of adult-onset asthma among workers and should be promptly and thoroughly investigated. Upon diagnosis, patients should receive appropriate medical treatment for asthma and any necessary work modifications. In addition, patients should be assisted in pursuing potential workers' compensation when appropriate.

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Financial Disclosures

Susan Tarlo has received grant support from Ontario Workplace Safety and Insurance Board (WSIB) and has performed clinical consultations for Ontario WSIB and WSIB Appeals Tribunal.

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10.58931/cait.2024.4373

Treatment and Management of Chronic Cough in Children

Tristan Henry, MBBS
Anya McLaren, MD, MSc, FRCPC

Background

Chronic cough (CC) in children is common and most often post-viral in nature. CC in children should be comprehensively evaluated and the underlying etiology treated to prevent irreversible lung damage. Refractory chronic cough (RCC) is proposed as a distinct clinical entity in children, which is defined by a persistent cough that does not resolve after comprehensive evaluation and adherence to systematic, guideline-based treatments. RCC may involve a heightened cough reflex sensitivity or altered neural regulation influenced by genetic, environmental, or immunologic factors. This review focuses on the definition, diagnostic approach, and evidence-based management of pediatric RCC, emphasizing the need for a multidisciplinary approach and highlighting research gaps for future targeted therapies.

Definition

Chronic cough (CC) in children is a distinct clinical entity that is defined by most expert panels as a daily cough that persists for more than 4 weeks in children 14 years or younger.[1-3] This 4-week cut-off aims to ensure that all children are universally and comprehensively assessed in a timely manner, minimizing the risk of progression to serious conditions while preventing respiratory morbidity.[4] *For the purposes of this review, chronic cough will be defined as a daily cough that lasts for longer than 4 weeks.*

CC is categorized into specific and non-specific types. Specific CC is cough accompanied by additional symptoms or signs indicative of an associated or underlying condition.[1] Non-specific CC describes a dry cough that occurs in children who otherwise appear well and do not seem to have a serious underlying disorder.[5] A non-specific CC is more likely to resolve without medications.[6]

Refractory chronic cough (RCC) is defined in adults as a persistent cough that does not resolve despite comprehensive evaluation and systematic, guideline-based trials of empiric treatments for causes of cough-associated conditions or traits.[2] In children, however, RCC has not been formally defined as a clinical entity. However, we propose that RCC in children is similarly defined as a persistent CC that does not resolve after a comprehensive evaluation and systematic, guideline-based trials of empiric treatment for cough-associated conditions or traits. RCC can be considered an overlapping entity with both specific CC and non-specific CC.

Epidemiology

The global prevalence of CC in children, particularly RCC, is not clearly defined. The estimated prevalence rates range from 1.1% to 21.9%. The methods of data collection, definition of chronic cough used, socio-economic status, culture and country of origin, under- and over- reporting age of the child, and the study setting are factors impacting the observed differences.[7] CC presents a significant burden not only to children but also to their families, causing significant distress to parents.[8] CC impacts children's daily activities, sleep, school performance, and social participation, and causes feelings of annoyance, discomfort, frustration, and embarrassment in children. CC imparts a high toll on health service utilization because of increased visits to primary care providers and specialist care providers. Furthermore, CC is associated with multiple clinic visits and inappropriate antibiotic use,[9] as well as overuse of over the counter (OTC) medications,[10] which can lead to toxicity.[11]

Etiology

Understanding the underlying causes of CC in children is essential for guiding appropriate management and treatment, especially because the causes of CC in children differ significantly from those in adults due to the unique respiratory physiology of prepubertal children compared to adults.[12] The child's age, country, and region must also be considered.[12] The etiology of CC also varies depending on whether the child is evaluated in a primary care setting, by a specialist, the type of specialist, or a team of specialists **(Table 1)**. In family practice and primary care settings in Westernized countries, the most common causes of CC include post-viral, respiratory tract infections, asthma, and pertussis.[13] These causes differ from those frequently identified in subspecialty clinics (e.g., pediatrics, pulmonology, allergy, and otolaryngology), where asthma or asthma-like conditions, protracted bacterial bronchitis (PBB), and natural resolution (no specific diagnosis) predominate.[12] In this setting, post-nasal drip and gastroesophageal reflux disease (GERD) are not commonly reported. This is in stark contrast to an exclusive pediatric otolaryngology setting where GERD is one of the common causes of CC in children. Children with CC presenting to a pediatric respirologist in a tertiary care centre will most likely have PBB.[14]

In children with refractory CC, the underlying cause may be more elusive and require comprehensive evaluation and targeted investigations to identify and address it effectively. This may include advanced imaging studies, specialized laboratory tests, or referrals to subspecialists for interdisciplinary assessment. Furthermore, there is data on the role of triple endoscopy in diagnosing the reason for CC in children.[15] Among 240 children (median age of 2 years), some of the diagnoses include laryngeal clefts, tracheoesophageal fistula (congenital or acquired), eosinophilic esophagitis, GERD, chronic aspiration in children with neuromuscular disorders, and congenital syndromes or genetic abnormalities (e.g., Trisomy 21, cystic fibrosis, immunodeficiencies).[15] It is also probable that a subset of children with chronic wet cough, including those with chronic suppurative lung disease of unknown etiology, remain unrecognized in the literature as having RCC, resulting in limited available data.

Pathophysiology

Cough is typically triggered by an irritant stimulus in the airway leading to activation of the airway mucosal sensory fibres. A signal is then transmitted to the brainstem circuitry, which modifies the normal breathing cycle into a cough specific pattern.[7] The maturation of the neuronal circuits is demonstrated as age-related alterations in the sensitivity of the cough reflex in infants and young children, as well as sex-related differences that become apparent in adolescence.[17] In essence, children may have a more sensitive cough reflex that is more easily activated due to ongoing neural development and heightened activity of neuromodulators such as substance P and neuropeptides, resulting in an exaggerated response.[17]

Different stimuli such as viral infections or inflammatory mediators can increase the physiologic cough reflex, possibly inducing plasticity in the neural pathways associated with coughing, leading to the persistence of cough even after the pathogenic trigger has been resolved.[18] However, there is limited data on the pathophysiology or natural history of post-viral cough, which is the most common cause of CC in children in the community beyond 25 days.[19] Possibly, children with RCC represent a subset of individuals with heightened cough reflex sensitivity or altered neural pathway regulation, making them more prone to persistent cough even after the resolution of the initial trigger. Understanding these mechanisms may help identify children at risk for recurrent or CC and guide targeted therapeutic approaches to improve outcomes. Further research is needed to elucidate the pathophysiology and natural history of post-viral and recurrent CC in children, especially to differentiate those with self-limiting conditions from those requiring medical intervention.

Diagnostic Approach

The evaluation of CC in children begins with a thorough history and physical exam with the goal of characterizing the cough as either specific or non-specific.[1] Initial investigations include a chest radiograph and spirometry (where age-appropriate).[4] Although both investigations lack sensitivity, their specificity is high, as abnormal findings strongly indicate underlying pathology.[20] Advanced diagnostic techniques such as CT imaging or bronchoscopy

Specialist/Clinical Setting	Etiology of Chronic Cough	Comments
Family practice and primary care[13]	Respiratory tract infections Asthma Pertussis	Systematic review; low methodological quality of individual articles
Pediatrics, Pulmonology, Allergy, Otolaryngology[12]	Asthma/Asthma-like conditions Protracted bacterial bronchitis Natural resolution without specific cause	Systematic review; significant difference in quality of studies used (e.g., rural vs urban)
Otolaryngology[16]	Upper respiratory infection Airway hyperreactivity GERD	Retrospective study; small sample size; limited to otolaryngology settings
Pediatric Pulmonology[14]	Post-acute respiratory illness Protracted bacterial bronchitis	Prospective; focused on post-acute illness; limited generalizability to non-acute settings

Table 1. Etiology of Chronic Cough is dependent on the clinical care setting; *courtesy of Tristan Henry, MBBS and Anya McLaren, MD, MSc, FRCPC*
Abbreviations: GERD: gastroesophageal reflux disease

are reserved for cases where initial evaluations are incomplete.[4] Triple endoscopy performed by an aerodigestive team can identify structural or functional abnormalities in RCC cases, reducing the need for multiple sedations. Routine tests such as the skin prick test, Mantoux test, Bordetella pertussis testing, or GERD studies should only be performed if clinically indicated.[4] The use of CC management protocols/algorithms improves outcomes in children under 15 years of age and is recommended despite the severity of the cough.[4] As the CHEST guideline provides the highest level of evidence for the optimal pathway, it is the approach discussed here.[1] Furthermore, the protocol algorithm can eliminate the inappropriate use of OTC medications, antibiotics, proton pump inhibitors, corticosteroid metered-dose inhalers, and unnecessary investigations for children with chronic non-specific cough.[4]

Management

General principles

For all CC cases, environmental factors that could exacerbate cough, such as tobacco smoke exposure, should be taken into consideration. Testing such as the skin prick test, Mantoux test, Bordetella pertussis testing, bronchoscopy, and chest CT should not be routinely performed. Instead, testing should be individualized based on the clinical setting.[4] An empiric approach to treating post-nasal drip, GERD, and/or asthma is not recommended unless other features consistent with these conditions are present.

Oftentimes, the primary concern of families may not be the cough itself, but rather the associated consequences, such as sleep disturbances, daytime drowsiness, and the impact on school, work, and overall quality of life. Adopting a shared decision-making approach and collaboratively defining goals can enhance the patient-caregiver relationship and improve outcomes.[4]

In children who present with a wet or productive CC in the absence of an underlying disease and without any cough specific pointers, a 2-week course of antibiotics targeting common respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) should be trialled. If there is resolution with the antibiotic course, a diagnosis of PBB is appropriate.[4] Treatment of CC in children should be targeted to the underlying etiology. As most non-specific CC is post-viral, a watchful waiting period with re-evaluation in a few weeks is acceptable.[12] Beyond a period of 2-4 weeks, the child should be re-evaluated for the emergence of specific etiological pointers.[4] If asthma is suspected, an assessment of airway hyper-responsiveness should be undertaken. If there are risk factors for asthma in a child with CC, a

short (2-4 weeks) trial of inhaled corticosteroid may be considered. A defined trial of therapy is often attempted for non-specific CC such as a 2–4-week period with the plan to evaluate for the emergence of specific pointers to an underlying cause.[4]

Empirically treating conditions such as upper airway syndrome, GERD, and/or asthma without the presence of signs and symptoms consistent with these conditions is not recommended.[4] Antihistamines have not shown significant benefit, and while cetirizine showed benefit over placebo in a relatively small randomized controlled trial, this benefit was only observed in patients with seasonal allergies.[21] Honey has been shown to be of more benefit in relieving symptoms of cough compared to no intervention, diphenhydramine, or placebo, making it a better alternative than antihistamines that do not include dextromethorphan.[21] Further research is needed to understand if there is a role for dextromethorphan and other neuromodulators in the treatment of CC.

A detailed review of the treatment of specific CC based on underlying etiology is outlined in the CHEST guidelines.[4] For the other specific cough syndromes, their investigation and management should be tailored to the specific etiologies which are beyond the scope of this review.

Refractory Chronic Cough (RCC)

Mukerji et al recommend triple endoscopy conducted by an aerodigestive team for patients with problematic and persistent CC after the appropriate management.[15] This triple endoscopy includes direct laryngoscopy conducted by ENT, flexible bronchoscopy conducted by a pulmonologist, and upper gastrointestinal endoscopy conducted by a gastroenterologist, all completed at one sitting, which may lead to an earlier diagnosis without the need for multiple sedations for different procedures and a possible cost-saving benefit. In one study that employed triple endoscopy for RCC, 83.5% of the cohort had at least one abnormal finding, while 42% had abnormalities that involved at least 2 of the 3 subspecialities of the aerodigestive team.[15]

Invariably, there remains a subset of patients with CC who, after a thorough history and appropriate extensive investigations, remain symptomatic with an undefined etiology. These patients are classified as having unexplained CC. These patients will require having pointed conversations with specialist providers that consider how the cough is affecting their quality of life. If there is no significant impact on quality of life, a watch and wait approach may be appropriate. Two European-wide studies conducted in adults reported unsatisfactory or limited satisfaction with the care of RCC, with rates of 57% and 32% respectively.[22] This has led to several studies in adults to assess interventions including cough-directed physiotherapy and speech and language interventions, the use of neuromodulators, older drugs such as opioids and gabapentin/pregabalin,[2] as well as newer drugs including P2X3 and P2X2/3 receptor antagonists (e.g., gefapixant, eliapixant, among others).[22] While these interventions have shown promise in adults, their external validity is limited, and there are no trials involving children for any of these interventions. These, along with other applicable interventions, will form the basis for further inquiry and evaluation for managing RCC in children.

Emerging Therapies and Future Directions

While long-term azithromycin is commonly used for chronic wet cough owing to its anti-inflammatory properties, the role of this therapy in other types of RCC is unclear.[23] Neuromodulators and targeted therapies such as P2X3 inhibitors (e.g., gefapixant) are promising but lack pediatric-specific data.[24] Research into biomarkers, genetic predispositions, and neural plasticity could refine diagnostic criteria and guide personalized treatments. Global or multicenter studies are needed to establish standardized definitions and management strategies for RCC in children.

Summary

Pediatric CC is a common condition that affects both the child and their family. Extensive research on this subject has resulted in expert panel guidelines for its management. The population of children with RCC is less well-defined, and there remains much to be understood about its underlying mechanisms and optimal management strategies. In most cases, the etiology of CC in children can be identified through thorough investigations and appropriate treatments. A comprehensive understanding of the diverse etiologies of CC in children, tailored to their unique physiology, age, clinical setting, and regional context, is essential for guiding effective diagnoses and management strategies. The above

review may assist community MDs to investigate and treat pediatric CC to minimize morbidity and improve quality of life for child and family. Further research is needed to define the population of children with RCC and to develop approaches to care, to optimize outcomes and improve care for this complex and heterogeneous population.

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Financial Disclosures

T.H.: None declared.
A.M.: None declared.

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Manali Mukherjee, PhD

Dr. Mukherjee is an Assistant Professor in the Division of Respirology, Department of Medicine, and a translational scientist affiliated with the Research Institute of St. Joe's, Hamilton. She has demonstrated expertise in investigating inflammatory mechanisms of chronic respiratory diseases, in particular autoimmunity, response to treatment and development/validation of clinical biomarkers. Her research has identified the presence of localized autoimmune responses in the airways of patients with complex airways disease and determined their pathogenic role in driving disease severity. Recently, she has identified autoimmune responses in acute-severe COVID and linked autoimmunity with post-acute COVID-19 sequelae (or Long COVID). In the field of respiratory medicine, she published ~65 manuscripts, and in the past 5 years these have accumulated >2500 citations (*Google Scholar h-index 24, i10-index 40*). Dr. Mukherjee's research program focuses on "Lung autoimmunity and biomarkers". She is the past recipient of the Emerging Researcher Award in Allergic Asthma awarded conjointly by the Canadian Institutes of Health Research (CIHR) and the Canadian Asthma, Allergy and Immunology Foundation (CAAIF). Her lab is funded by federal and non-federal sources including CIHR-ICRH and industry. Dr. Mukherjee was recently named the AstraZeneca Chair in Respiratory Diseases (2023-2028).

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Pearls from the 2024 European Respiratory Congress

Manali Mukherjee, PhD

Introduction

The European Respiratory Congress 2024, held from September 7th to 11th, 2024, in Vienna, Austria, featured several presentations on airway diseases, interstitial lung diseases, bronchiectasis, and critical care, with a focus on emerging therapies, particularly on asthma and chronic obstructive pulmonary disease (COPD).

I. "*Treating eosinophilic exacerbations of asthma and COPD with benralizumab: The Acute exacerbations treated with BenRAlizumab trial (ABRA) study*" was presented in the Abstracts Leading to Evolution in Respiratory Medicine Trials (ALERT:2) session titled "*Fighting the burden of asthma and respiratory symptoms.*" The session was chaired by Drs Richard Costello and Kristin Walter. The study was presented by its senior author **Dr. Mona Bafadhel**.

More than 4 million people die of acute exacerbations of asthma and COPD worldwide every year. For the past 60 years the standard of care for acute exacerbations has remained unchanged, i.e., prednisolone, despite its well-known severe long-lasting side effects. Since eosinophilic infiltration plays a significant role in acute exacerbations of asthma and COPD, blocking the key T2 inflammatory pathway would be beneficial.[1,2] Benralizumab, a humanized monoclonal antibody against interleukin (IL)-5 receptor-α, is approved at a 30 mg subcutaneous dose. It has been shown to deplete eosinophils in blood and sputum, as well as reduce T2 cytokines.[3-6] Therefore, in the multi-centre, double-blind, double-dummy, active-comparator, placebo-controlled randomized controlled ABRA trial, the authors tested the hypothesis that a single injection of benralizumab administered during an acute eosinophilic exacerbation, either alone or in combination with prednisolone, will improve clinical outcomes compared with prednisolone, the standard of care.

Adults diagnosed with COPD/asthma at the time of acute exacerbations, with blood eosinophil counts of ≥300 cells per µL, were randomly assigned in a 1:1:1 ratio to receive acute treatment with:

Arm 1: prednisolone 30 mg once daily for 5 days and a single 100 mg benralizumab subcutaneous injection (BENRA plus PRED group)

Arm 2: placebo tablets once daily for 5 days, and a single 100 mg benralizumab subcutaneous injection (BENRA group), or

Arm 3: prednisolone 30 mg once daily for 5 days, and placebo subcutaneous injection (PRED group).

Co-primary outcomes:

Total visual analogue scale (VAS) symptoms at Day 28 and treatment failure rates (deaths, hospitalizations and retreatment) over 90 Days

Results:

A total of 158 patients were recruited, of whom 55% were diagnosed with asthma, 32% with COPD, and 12% with both. Blood eosinophil counts and fractional exhaled nitric oxide (FeNO) were raised in all 3 arms and comparable at baseline. At 90 days, treatment failures occurred in 39 (74%) of 53 participants in the PRED group (Arm 3), and 47 (45%) of 105 participants in the pooled-BENRA (Arms 1 and 2) group (OR 0.26; p=0.0005). The 28-day total VAS (mean difference of 49 mm; p=0.0065) favoured the pooled-BENRA group. Benralizumab, administered at a higher one-time administration dose of 100 mg (subcutaneous), was well tolerated, with no fatal adverse events reported, and an overall improvement in quality of life questionnaires.

Main takeaway message

1. By depleting eosinophils (and other IL-5R+ cells), benralizumab is more effective than the current standard treatment (oral corticosteroids, such as prednisolone) in the event of an exacerbation.

2. Patients receiving benralizumab had fewer treatment failures and required less additional treatment compared to those on standard steroid therapy. The number needed to treat (NNT) for benralizumab was 4. The NNT for prednisolone to prevent treatment failure in COPD is 9, and to prevent hospitalizations in asthma is approximately 8.7.

3. Potential game-changer: benralizumab could revolutionize the management of asthma and COPD exacerbations, offering a more effective and safer alternative to steroids.

The study has now been published in *The Lancet Respiratory Medicine*,[8] accompanied by an editorial from Drs Donald Sin and Clarus Leung.[9] It has received significant press and media attention given its potential impact on the clinical management of asthma and COPD exacerbations.

II. *"Depemokimab efficacy/safety in patients with asthma on medium/high-dose ICS: The Phase IIIA randomized SWIFT-1/2 studies"* was presented in the Abstracts Leading to Evolution in Respiratory Medicine Trials (ALERT:2) session titled "*Fighting the burden of asthma and respiratory symptoms.*" The session was chaired by Drs Richard Costello and Kristin Walter. The study was presented by its senior author **Dr. David Jackson.**

Type 2 inflammation is pivotal to asthma pathophysiology, supporting the current pipeline of 6 monoclonal antibodies approved for treating eosinophilic asthma. Notably, these treatments have been shown to reduce blood eosinophils, symptoms, and exacerbations.[10] IL-5 remains central to eosinophil biology. Depemokimab (GSK3511294) is a novel humanized IgG_1 anti-IL-5 monoclonal antibody, similar to its predecessor mepolizumab, which neutralizes free IL-5. However, compared to mepolizumab (monthly dosing), depemokimab has an amino acid modification (YTE modification) in its Fc region that extends its half-life, allowing for biannual dosing.[11] Dr. Jackson presented the results from the 2 parallel Phase III randomized, placebo-controlled studies, SWIFT1 and SWIFT2, which reported the efficacy of depemokimab.

Results:

In the 2 trials, 732 patients with severe eosinophilic asthma (physician diagnosis of ≥2 years) received 100 mg of depemokimab subcutaneously every 6 months over a 52-week period. Both trials met their primary endpoint, showing a statistically significant reduction in the annualized exacerbation rate by 58% in SWIFT-1 and 48% in SWIFT-2 compared to placebo (in total 54%; rate ratio 0.46; P < <0.0001) over 52 weeks. Blood eosinophil counts rapidly normalized by approximately 80% and remained suppressed for the remainder of the study, despite biannual dosing. Yet, the effect on asthma symptoms (Asthma Control Questionnaire 5 [ACQ-5], St. George's Respiratory Questionnaire [SGRQ]) or lung function (pre-bronchodilator forced expiratory volume in 1 second [FEV1]) remained unremarkable throughout the study period in both trials. The incidence and severity of treatment-emergent adverse events were similar between the depemokimab and placebo groups.

Main takeaway message

1. Depemokimab, offered a sustained inhibition of the IL-5 pathway indicated by normalized blood eosinophil counts with a convenient 6-month dosing schedule.

2. This could simplify treatment for patients with severe asthma, potentially requiring only 2 injections per year, thereby improving compliance and adherence.

3. The study is attractive to patients who are hesitant to start biologics due to a fear of needles.

The study is now published in the *New England Journal of Medicine*.[12]

The mechanistic basis for understanding the clinical effects of depemokimab was presented in another oral abstract session, titled *"Recent advances in biological treatments for asthma and chronic obstructive pulmonary disease"* chaired by Dr. Florence Schleich and me. In this session, Dr. David Jackson presented "Enhanced in vitro potency of depemokimab for interleukin-5 inhibition versus mepolizumab." This study showed that depemokimab is significantly more potent than mepolizumab in: (i) reducing IL-5-mediated proliferation of a human eosinophil cell line (TF-1) by 24.9 fold, and (ii) achieving a 31.0-fold (range

7.5–76.7) higher inhibition of IL-5-enhanced IgE-R-mediated basophil degranulation.

III. ***"Efficacy of high and low dose rilzabrutinib from a Phase II study"*** was presented in the late breaking oral presentation session titled "Airway diseases therapeutics: novel research studies." The session was chaired by Dr. Alex Mathioudakis and me. The study was presented by its senior author, **Dr. Ian Douglas Pavord.**

Rilzabrutinib (SAR444671) is an oral, reversible covalent inhibitor of Bruton's tyrosine kinase (BTK) that has shown excellent clinical benefits in treating chronic urticaria. BTK plays a key role in immune cell signalling across multiple cellular types relevant in orchestrating chronic airway inflammation, including B cells, mast cells, eosinophils, and neutrophils. It is therefore being investigated in the severe asthma domain for its clinical efficacy.[13] This was the first Phase II study in an asthma population.

The study's objective was to report the efficacy of rilzabrutinib at doses of 800 mg and 1200 mg in patients with poorly controlled moderate-to-severe asthma who were on inhaled corticosteroids (ICS)/long-acting beta-agonist (LABA) therapy (NCT05104892). In this placebo-controlled Phase II study, 196 patients were randomized 1:1 (drug and placebo) into 2 cohorts to assess the low and high doses of the drug. The study design included an initial stabilization phase (week 0 – week 4), followed by a step-wise withdrawal phase of background therapy (week 4 – week 9) and no background therapy from week 9 – week 12 (end of study). The primary endpoint was the proportion of patients who experienced level of asthma control (LOAC) events during the treatment periods. A LOAC event was defined by any one of the following: (i) ≥30% reduction in morning peak expiratory flow on 2 consecutive days; (ii) ≥6 additional reliever puffs within a 24-hour period on 2 consecutive days; (iii) an increase in ICS to ≥4 times the last prescribed dose or ≥50% of the prescribed dose if background therapy is completely withdrawn; or, (iv) an exacerbation requiring systemic steroid treatment, hospitalization or an ER visit. The secondary endpoint evaluated was a change in the ACQ-5 score from baseline.

Results:

In 32 patients on rilzabrutinib 800 mg and 32 patients on placebo over 12 weeks, LOAC events occurred in 37.5% of patients in the drug arm compared to 50% in the placebo arm (OR:0.570; 95% CI: 0.202-1.608), with a relative risk reduction (RRR) of 25%. In the high dose group (1200 mg rilzabrutinib, n=64) there was an RRR of 36.1% compared to placebo (n=68). Significant improvements in ACQ-5 scores were observed as early as week 2 with rilzabrutinib compared to placebo that were sustained up to week 12 (LS mean difference vs placebo: rilzabrutinib 800 mg: -0.59, p=0.0184; rilzabrutinib 1200 mg: -0.54, p=0.0013) despite complete ICS/LABA withdrawal. The investigational drug was safe and well-tolerated over the 12-week treatment period.

Main takeaway message

1. In a heterogenous, unselected asthma population, rilzabrutinib was associated with a reduction in LOAC events, showing clinically meaningful improvement over 12 weeks.

2. The improvement in the asthma symptoms was rapid and was observed despite the complete removal of background-controlled therapy.

3. These positive results demonstrate the potential of rilzabrutinib as a novel first-in-class oral BTK inhibitor for poorly controlled asthma, warranting further investigation in Phase 3 studies.

Honorary mentions:

Multiple interesting short abstracts were presented at the 2024 European Respiratory Society Congress, and a few are highlighted:

1. *Dupilumab reduces mucus plugging and volume*: phase 4 VESTIGE trial – presented by Dr. Celeste Porsbjerg: The VESTIGE study (NCT04400318) assessed the impact of dupilumab (anti-IL-4/IL-13 blocking monoclonal antibody) on airway mucus plugging and volume, inflammation, and lung function. The dupilumab group had reduced mucus scores and mucus volumes (voxels/mucus plugs) and were 9.8 times more likely to achieve FeNO <25 ppb and improvements in pre-bronchodilator FEV_1.

2. *Time to first moderate or severe COPD exacerbation with tezepelumab (COURSE)*- presented by Dr. Dave Singh: COURSE was a phase 2a, randomized, double-blind, placebo-controlled study that included 333 moderate-to-severe COPD patients who were randomized 1:1 to receive either tezepelumab 420 mg or placebo subcutaneously every 4 weeks for up to 52 weeks. Tezepelumab delayed the time to the first moderate or severe exacerbation compared

to placebo in the overall population (HR, 0.80 [95% CI: 0.61–1.06; median days: 253 in the tezepelumab group vs 214 in the placebo group]) irrespective of subgroups stratified by blood eosinophil counts.

3. *Safety and PK of KN-002 in subjects with moderate to severe asthma using ICS/LABA* - presented by Dave Singh: A novel lung selective potent pan-Janus kinase (JAK) inhibitor formulated as a dry powder for inhalation was well tolerated by moderate-to-severe asthma patients on ICS/LABA therapies in a Phase I study.

4. *KN-002 reduces fractional exhaled nitric oxide in moderate-to-severe asthma* - presented by Dave Singh: KN-002, an inhaled small molecule pan-JAK inhibitor. Since JAK/STAT signalling is implicated in multiple pro-inflammatory pathways of airway inflammation, its potential to reduce FeNO was evaluated. The study showed that KN-002 caused a clinically relevant FeNO reduction over 10 days, independent of baseline FeNO/blood eosinophils.

Summary

Many sessions at this year's annual congress organized by the European Respiratory Society in Vienna, Austria, highlighted promising new therapies for severe asthma and COPD, with a vision to reduce exacerbations.

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Financial Disclosures

MM: Grants: Canadian Institute for Health Research and COVID-19 Immunity Task Force, Canadian Asthma, Allergy and Immunology Foundation (CAAIF), Mirimus, Methapharm Specialty Pharmaceuticals, Sanofi; **Speaking Engagement Fees (personal):** AstraZeneca, Sanofi, GSK, EAACI Knowledge Hub, and Resiplus.

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Malignancies: lymphoma and other malignancies were observed in patients taking JAK inhibitors to treat inflammatory conditions and were more frequently observed in patients with rheumatoid arthritis (RA) during a clinical trial with another JAK inhibitor versus TNF inhibitors.

Thrombosis: including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients taking JAK inhibitors to treat inflammatory conditions. Many of these events were serious; some resulted in death. Consider risks and benefits prior to treating patients who may be at increased risk. In a clinical trial in patients ≥50 years of age with RA, a higher rate of all-cause mortality and thrombosis occurred in patients treated with another JAK inhibitor versus TNF inhibitors. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Major adverse cardiovascular events (MACE): including non-fatal myocardial infarction, were observed more frequently in patients ≥50 years of age with RA during a clinical trial comparing another JAK inhibitor versus TNF inhibitors.

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AD=atopic dermatitis; JAK1=Janus kinase 1.
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At-home Management of Food-induced Anaphylaxis

Anne K. Ellis, MD, MSc, FRCPC

Introduction: Anaphylaxis

Anaphylaxis is an acute, potentially life-threatening, systemic reaction characterized by the involvement of two or more body systems.[1] The National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (NIAID/FAAN) have well-established criteria for the clinical definition of anaphylaxis.[2] Anaphylaxis is a severe allergic reaction that occurs suddenly after contact with an allergy-causing substance (e.g., peanuts), insect venom or medications (e.g., antibiotics). Anaphylaxis criteria include an acute onset of symptoms (within minutes to several hours) involving the skin, mucosal tissue, or both, which may present with generalized hives, pruritus or flushing, or swollen lips, tongue, and uvula. In addition, one or more of the following must be present: respiratory compromise, reduced blood pressure, or associated symptoms of end-organ dysfunction. Anaphylaxis results in a sudden release of mediators, including, but not limited to, histamine from activated mast cells and basophils following the cross-linking of specific immunoglobulin E. Together with downstream mediators, such as prostaglandin D2, platelet activating factor, and leukotrienes, this reaction manifests clinically through peripheral vasodilation, bronchoconstriction, and increased vascular permeability, presenting as a multi-organ emergency requiring immediate intervention.[3]

It is estimated that up to 5% of the population has experienced anaphylaxis, although fatality rates are very low at approximately 0.3% and occur most commonly with drug-induced anaphylaxis.[4,5] Older age, often consistent with pre-existing comorbidities, and delayed epinephrine administration, pose the most significant risk factors for anaphylaxis fatality. While the global rates of anaphylaxis appear to be on the rise, case fatalities fortunately do not seem to follow this trend.[6]

Anaphylaxis is uniphasic in the majority of cases, whereby symptoms peak within 60 minutes and resolve within the next hour without any symptom recurrence.[7] Less commonly, anaphylaxis may be persistent (symptoms lasting for at least 4 hours), refractory (the initial reaction is treated with 3 or more doses of epinephrine in addition to other management strategies and remains unresolved), or biphasic (symptoms recur between 1 and 48 hours following the complete

resolution of the initial reaction.[8] Biphasic reactions are estimated to occur in between 4% and 20% of cases and are often associated with initial reactions of greater severity.[9-12]

Epinephrine in Anaphylaxis Management

The role of epinephrine in the management paradigm for anaphylaxis cannot be over-emphasized – it is essential first-line treatment. In addition to being fast-acting, it is the only treatment that stabilizes mast cell membranes halting the release of more mediators and can reverse the life-threatening respiratory and cardiac symptoms.[13,14] The timely administration of epinephrine is paramount to the reduction of anaphylaxis mortality and morbidity, including biphasic reactions.[15] There are no substitutes or contraindications for the use of epinephrine. Recent evidence updates support the repeated administration of intramuscular epinephrine if symptoms do not improve within 5 minutes of the previous dose.[16]

Autoinjectors administer epinephrine intramuscularly usually into the anterior lateral thigh, with a recommended dosage based on weight. This is the fastest route of administration, achieving a peak plasma epinephrine concentration in 6 to 10 minutes, compared to subcutaneous administration, which may take 20 to 48 minutes.[13] More recently, a novel intranasal epinephrine preparation was found to be safe, well-tolerated and fast-acting (median time to peak plasma concentration was 2.5 minutes).[17] This needle-free design has received approval from the European Union's European Medicines Agency and the United States Food and Drug Administration.[18,19]

Adjunct symptom management therapies, including intravenous bolus, supplemental oxygen and beta-2 agonists, may be considered following stabilization with epinephrine to mediate hypotension and persisting respiratory symptoms. The use of antihistamines in the management paradigm is limited to providing relief for persisting cutaneous symptoms.[16]

Shifting the Paradigm of Anaphylaxis Management

In some situations, it may be appropriate to manage food-induced anaphylaxis at home using epinephrine without having to call emergency medical services (EMS). In 2020, during the COVID-19 pandemic, Casale et al published an updated anaphylaxis management algorithm intended to reduce the burden on healthcare services and lower the risk of infection. The revised algorithm included the important note that for severe cases of anaphylaxis, the usual procedure of immediately contacting EMS after using epinephrine should still be adhered to.[20] In 2022, Casale et al published a follow-up article examining the possibility of managing anaphylactic events at home, even outside of a pandemic. The authors argued that with proper selection, education and access to the right medications, patients can safely manage an anaphylactic event using a home management algorithm. Furthermore, they argued that this approach should reduce the need for a hospital Emergency Department (ED) visit and is likely to improve outcomes due to quicker administration of epinephrine.[21]

Following this, a notable shift occurred in the field, prompting widespread debate and reassessment of this long-established algorithm for anaphylaxis management **(Figure 1)**. In 2023, Dribin et al published an article in *Journal of Allergy and Clinical Immunology: In Practice* discussing the epinephrine auto-injector prescription; use for optimal clinical care of individuals at risk of anaphylaxis; proposing an alternative treatment algorithm.[22] Greenhawt et al also advocated retiring routine EMS activation after epinephrine use in their perspective article in *Annals of Allergy, Asthma and Immunology*.[23] The Canadian Society of Allergy and Clinical Immunology (CSACI) published their considerations for at-home management of food-induced anaphylaxis.[24] The rationale for implementing the updated guidance for home management has been discussed at length in each of these articles and is summarized in **Table 1.** In considering this guidance, at-home anaphylaxis management could occur under certain circumstances that begin with the patient and caregiver's comfort level and preference, access to at least two in-date, weight-appropriate doses of epinephrine autoinjectors, absence of risk factors for a biphasic reaction or severe anaphylaxis outcomes,[26-28] and symptoms resolution with one dose of epinephrine administration.[24] However, at-home management of anaphylaxis may not be appropriate under certain considerations, as outlined in **Table 2.**[25]

This proposed algorithm has challenges. Many patients don't carry more than one dose of epinephrine; reports show that fewer than half of people always have more than one epinephrine

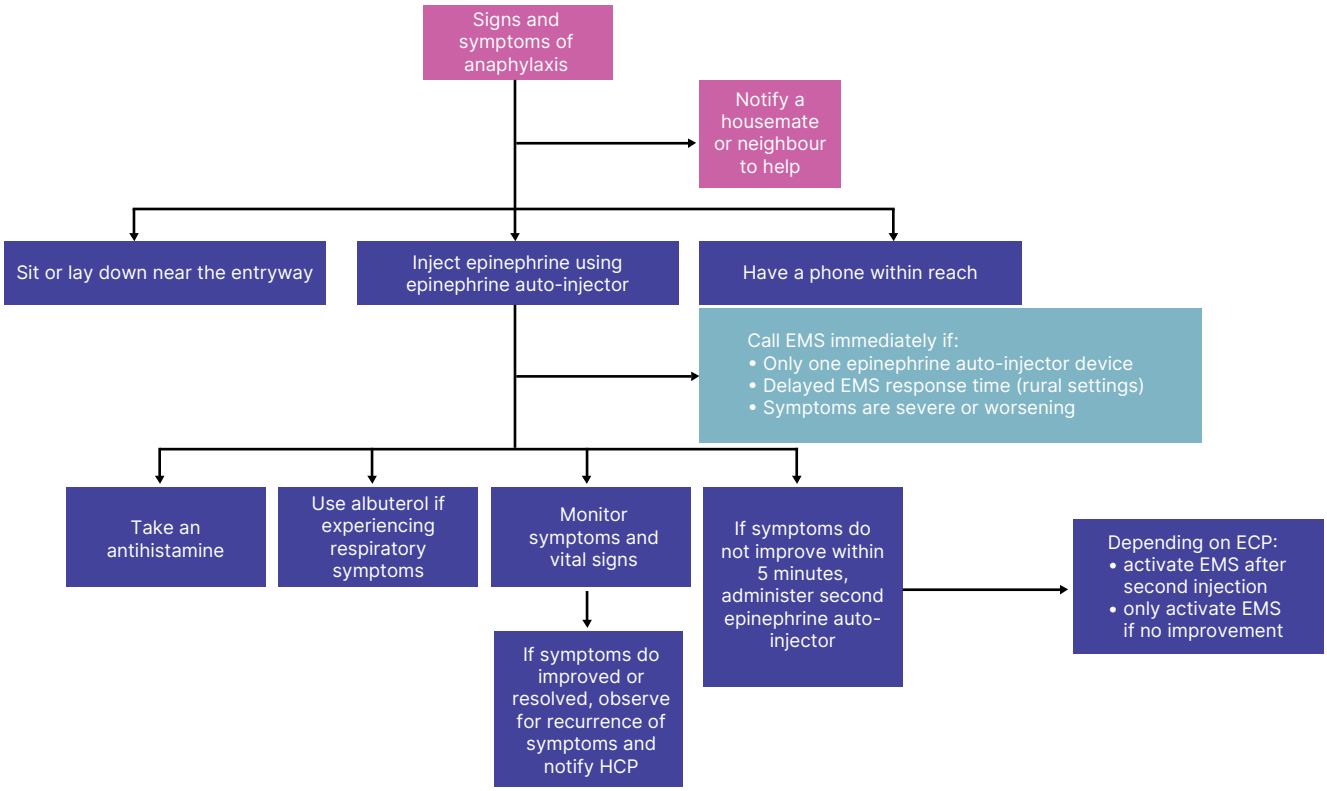

Figure 1. Proposed algorithm for at-home management of food-induced anaphylaxis. Adapted from Casale et al and Dibrin et al.
Abbreviations: EMS: Emergency medical services; **ECP:** Emergency care plan

1. Requiring EMS activation might lead to associating the use of epinephrine with needing EMS, which could result in delaying or avoiding the use of intramuscular epinephrine.
2. Fatalities from anaphylaxis are extremely rare.
3. Severe biphasic anaphylaxis and deaths from biphasic anaphylaxis are extremely rare.
4. Early administration of epinephrine is the most effective way to prevent biphasic and other severe anaphylaxis reactions, including those requiring intensive care unit or hospital admission.
5. Intramuscular epinephrine is very safe and does not require monitoring in the hospital ED; it can be managed safely at home.
6. Additional treatments given in the ED, like antihistamines and corticosteroids, have not been shown to reduce the risk of biphasic reactions or fatalities.
7. Routine EMS activation for anaphylaxis that has resolved after epinephrine treatment is not very beneficial and incurs high healthcare costs ($142 million per life-year saved and $1.4 billion to prevent one death).
8. There are significant issues with healthcare resource use in hospital EDs and increased risks of infection transmission, including COVID-19 and other respiratory viruses.

Table 1. Rationale for at-home management of anaphylaxis with epinephrine use.[20-25]

1. Patient and caregiver are not comfortable with managing anaphylaxis without contacting EMS or visiting the ED.
2. Epinephrine autoinjectors are not available or only one autoinjector is available.
3. Being alone, without immediate access to a caregiver for assistance if needed.
4. Being unaware of the allergic symptoms that necessitate using an epinephrine autoinjector.
5. Lack of technical skills for using an epinephrine autoinjector.
6. Hesitancy about the intramuscular injection due to needle phobia.

Table 2. Factors to consider against managing anaphylaxis at home.[25]
Abbreviations: EMS: Emergency medical services; **ED:** Emergency department

auto-injector on hand.[29] Additionally, some patients and caregivers may not know how to use epinephrine or monitor symptoms properly. Assessing whether patients or caregivers are "capable and compliant" is often subjective and can be influenced by personal biases.[22]

Importantly, these discussions have highlighted gaps in our understanding of anaphylaxis treatment. Variations in the use of epinephrine may arise from inconsistencies in how anaphylaxis is defined. One of the most significant evidence gaps in allergy care is our inability to predict the risk of severe future reactions or biphasic reactions.[30] While our understanding of the risk factors and co-factors that may worsen reactions is improving, further research is needed to determine if emergency care plans enhance anaphylaxis care and outcomes.[31] Additionally, research should focus on improving these plans to better address the needs of patients and caregivers. Reliable strategies are necessary to assess how well patients and caregivers can recognize and manage reactions and enhance their performance through targeted educational interventions.[22] In conclusion, until an algorithm for home management can be verified to be safe and effective, it will face barriers to widespread adoption by relevant stakeholders.

Summary

Anaphylaxis is a severe, potentially life-threatening allergic reaction involving multiple organ systems, typically triggered by foods, insect stings, or medications. It results from rapidly releasing histamine and other inflammatory mediators, leading to peripheral vasodilation and bronchoconstriction, among other manifestations. Prompt administration of epinephrine is crucial, as it is the only treatment that effectively counteracts these severe reactions. The management of anaphylaxis, particularly at home, has been evolving. Recent discussions suggest that some cases could be managed at home with proper education and resources to reduce hospital ED visits, and hopefully encourage epinephrine auto-injector use given reluctance to present to the ED. However, this approach faces challenges such as ensuring patients have multiple doses of epinephrine on hand and are appropriately trained. There is a call for further research to refine treatment guidelines for at-home management of anaphylaxis, and to improve patient outcomes.

The author wishes to acknowledge the help of Lubnaa Hossenbaccus, MSc and Sophia Linton, BSc in preparing this manuscript.

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Financial Disclosures

A.K.E.: Advisory boards: AstraZeneca, Bausch Health, GSK, Miravo, Merck, Novartis; **Speaker:** ALK Abello, AstraZeneca, Bausch, Miravo, Medexus, Novartis, Pfizer, Sanofi, StallergenesGreer and Regeneron. **Institutional grant funding:** ALK Abello, Aralez, AstraZeneca, Bayer LLC, Medexus, Novartis, Sanofi and Regeneron. **Independent consultancy:** Bayer LLC, Pharming, and Regeneron.

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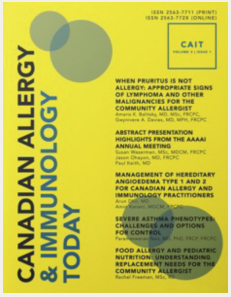

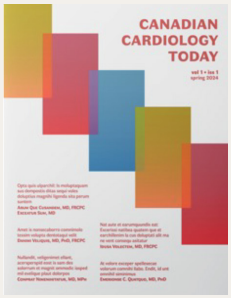

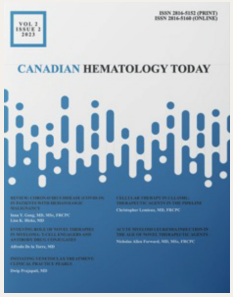

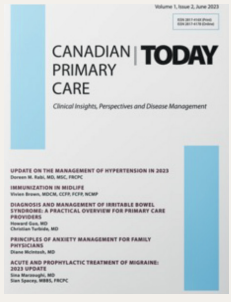

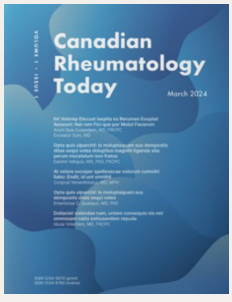

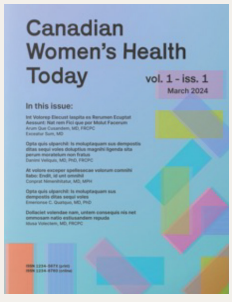

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