

at $P < .05$, and the analyses were performed using GraphPad Prism software (GraphPad Software Inc, CA).

The most relevant outcomes are reported in Table 1. We stratified children with asthma, using 2 rhinitis classifications: the traditional method based on the symptom seasonality (such as perennial, seasonal, or mixed) and that proposed by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.^{2,3} Allergic rhinitis (AR) and asthma were diagnosed according to validated criteria defined by guidelines.^{3,4} In addition, we evaluated concordance between the 2 rhinitis classifications.

The findings showed that 88% of children with asthma had rhinitis as a comorbidity. The ARIA classification presented significant differences among subgroups concerning age, asthma duration, asthma control, asthma severity, oral corticosteroid use in the past year, and dosage of inhaled corticosteroids (ICS; Table 1).

Conventional AR classification shows that some variables were also significantly different, consistently with stratification, such as age, BMI, asthma duration, forced expiratory flow at 25% to 75% of the pulmonary volume (FEF₂₅₋₇₅), and c-ACT.

Finally, no concordance was found between the 2 classifications, because there was no overlapping between them without any significant difference.

Rhinitis, particularly allergic rhinitis, is associated with asthma very frequently. The ARIA and conventional classifications are not interchangeable and represent 2 different ways of characterizing AR, as previously reported.⁵ In other words, the information obtained from the classifications is in both cases relevant but may not be consistent.

The ARIA classification was found to be more suitable for characterizing some parameters associated with asthma control and asthma severity. Significant differences were seen among the rhinitis phenotypes in features such as age, asthma duration, use of oral corticosteroids, asthma exacerbations, and ICS dosage. In short, the ARIA classification provides clear indications about the impact of rhinitis phenotyping on asthma severity.

Conventional classification identified parameters that differentiate the rhinitis phenotypes. Significant differences among groups were found for age, BMI, asthma duration, c-ACT score, and FEF₂₅₋₇₅ value, the last of which may be considered an early predictor of bronchial airflow limitation.⁶ These results show that children without rhinitis (NoR) were younger, had lower BMI and FEF₂₅₋₇₅, and had shorter asthma duration than did the other subjects. More interestingly, children with mixed allergic rhinitis (MAR) had longer asthma duration (consistent with poly-allergy), whereas children with seasonal allergic rhinitis (SAR) had higher FEF₂₅₋₇₅ than children with perennial allergic rhinitis (PAR) (consistent with shorter allergen exposure). Therefore, the conventional classification of rhinitis may be useful for providing indications about the impact of rhinitis phenotypes on clinical and functional variables in these children with asthma.

Comparing the findings obtained from the 2 rhinitis classifications, consistent results were obtained only for age and asthma duration: younger children and those with shorter asthma duration more frequently did not present rhinitis comorbidity. The ARIA classification better identified significant differences

among rhinitis phenotypes concerning asthma control and severity scoring. On the contrary, conventional classification better identified notable differences among rhinitis phenotypes regarding the subjective perception of asthma control (c-ACT) and the functional parameter FEF₂₅₋₇₅.

The results of this study suggest that the 2 rhinitis classifications provide different information about children with asthma, and that both information sets can generate clinically relevant data that may be useful in asthma management. In clinical practice, using both rhinitis classifications would seem to be more helpful than considering only 1. In particular, rhinitis is well known to have a profound impact on asthma, mainly concerning the upper airways treatment. Therefore, phenotyping rhinitis in children with asthma could drive therapeutic strategies directed toward nasal inflammation dampening. The current study suggests that poly-allergy and severe rhinitis are factors associated with poorly controlled and severe asthma.

The main limitation of this study is its cross-sectional design, but follow-up is ongoing.

In conclusion, rhinitis is frequently associated with asthma in children; rhinitis phenotyping should be performed using both conventional and ARIA classification; and rhinitis phenotyping allows clinicians to diagnose and treat the asthma properly.

Maria Angela Tosca, PhD*
Marzia Duse, MD†

Gianluigi Marseglia, MD‡

Giorgio Ciprandi, MD§ “Control’Asma” Study Group

*Pediatric Allergy Center

Istituto Giannina Gaslini

Genoa, Italy

†Pediatrics Department

Umberto I Hospital

Roma

Sapienza University

Roma, Italy

‡Pediatrics Clinic, Pediatrics Department, Policlinico San Matteo,

University of Pavia, Pavia, Italy

§Allergy Clinic

Casa di Cura Villa Montalegno

Genoa, Italy

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The many flavors of pineapple reactions

Hypersensitivity reactions to fruit, particularly apples, stone fruits, and bananas, are commonly reported.¹ One fruit less frequently

described in the literature causes adverse reactions in many patients: pineapple (*Ananas comosus*). Pineapple is best known in developed countries for its sweet and tangy coalesced berries, but its anti-inflammatory properties and enzymatic activity have been used for centuries.² Despite its pleasant taste and putative salutary

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Table 1
Types of Adverse Reactions to Pineapple

Type of reaction	Proposed mechanism(s)	Signs/symptoms	Management strategies
Mucosal irritation	1) Bromelain-induced proteolytic degradation of oral mucosa 2) Acid-induced mucosal injury	Burning, soreness of oral mucosa and tongue	1) Ingest with dairy product or sprinkle fruit with salt 2) Avoidance
Oral allergy syndrome	Profilin (<i>Ana c 1</i>)-mediated though pollen cross-reactivity unclear	Itching and swelling of lips, tongue, and oropharynx	1) Heating the fruit 2) Avoidance
Anaphylaxis	Pineapple-specific or bromelain-specific IgE-mediated mast cell degranulation	Urticaria, angioedema, wheezing, coughing, vomiting, diarrhea, hypotension	1) Strict avoidance 2) Food allergy action plan 3) Epinephrine auto injector prescription and training

effects, pineapple has been implicated in an array of adverse reactions, including uncomfortable mucosal irritation due to acidic pH and bromelain, oral allergy syndrome, and anaphylaxis (Table 1). We present a case illustrating a commonly encountered pineapple reaction.

A 35-year-old woman with a history of aspirin-exacerbated respiratory disease and allergic rhinitis presented to the outpatient allergy/immunology clinic for follow-up of asthma, rhinosinusitis, and complaints of a reaction to pineapple. On prior skin testing she was positive to cat, rabbit, maple tree, birch tree, and *Cladosporium*. She reported symptoms of tongue swelling and irritation after consumption of raw pineapple. She denied diffuse urticaria, wheezing, dyspnea, vomiting, or diarrhea. These symptoms were reproduced on subsequent ingestion of pineapple, so she began to avoid eating the fruit. Percutaneous testing to pineapple extract was negative with adequate histamine control. Serum specific immunoglobulin E (IgE) to pineapple was less than 0.35 kU/L. Weeks later, she underwent fresh prick testing to pineapple, which was negative. She consumed a small amount of pineapple in the clinic under physician supervision. Fifteen minutes after ingestion, she reported a sensation of irritation and “bumps” on her tongue. Examination revealed erythema and papules on the tongue centrally, with erythema distally on the left and right sides, but no lip, tongue, or pharyngeal edema. She denied cutaneous pruritus or respiratory symptoms. She was monitored for 20 minutes and given a second dose of fresh pineapple. She reported similar tongue symptoms 15 minutes after the second dose. She did not experience any systemic symptoms during the challenge.

This patient exhibits symptoms of mucosal irritation, most likely induced by the acidic pH of the fruit as well as the proteolytic activity of bromelain. Bromelain, a combination of multiple proteolytic enzymes in the papain family of cysteine proteases, has been most commonly used as a meat tenderizer and a wound debridement agent. It is naturally found in pineapple, concentrated most highly in the pineapple stem.² In fresh pineapple, bromelain as well as the fruit's acidity can cause mouth soreness and pain, particularly when eaten in large amounts. Because the localized discomfort is enzyme-driven rather than mast cell–driven, symptoms include oropharyngeal pain rather than pruritus. Bromelain denatures when heated, which explains symptoms occurring with fresh but not heated pineapple products.² Symptoms often can be mitigated by pairing pineapple with dairy or a small amount of salt.

Her oral symptoms could be interpreted by some physicians as oral allergy syndrome (OAS). However, typical OAS symptoms include oropharyngeal pruritus, occasionally with lip angioedema, rather than oropharyngeal pain or gross mucosal irritation on examination.¹ Two German studies described pineapple-induced OAS symptoms.^{3,4} One of the studies described 380 patients with known birch-related OAS, of which 18 patients also reported OAS symptoms with pineapple consumption. On investigation of recombinant pineapple profilins, they found that the amino acid sequence was largely homologous with birch tree (*Bet v 2*) and natural rubber latex (*Hev b 8*) and partially homologous with apple, cherry, peanut, celery, pear, and timothy grass. Only 8 of the 18

patients had positive specific IgE to this pineapple profilin. Thus they could not rule out concomitant acidic or bromelain-induced mucosal irritation.³

Although this patient certainly did not exhibit symptoms of anaphylaxis, studies have reported anaphylaxis to pineapple, whether by patient/parent self-report or case studies.^{5–8} The 2018 Australian SchoolNuts study outlined 5 of 372 children who reported pineapple allergy: 4 subjects had “likely IgE-mediated” reactions, and 1 subject had “unrecognized anaphylaxis.”⁵ A case series from Bangladesh described 32 pediatric and adult patients with symptoms of intense pruritus, urticaria, abdominal pain, vomiting, and diarrhea within 30 minutes of pineapple ingestion. Twenty of 32 patients had shock; all patients were treated with intravenous fluids and antihistamines; and 8 received epinephrine. Only 4 of 32 patients had elevated levels of pineapple-specific IgE; thus, patients without detectable pineapple-specific IgE were labeled as “anaphylactoid.”⁶

Bromelain has also been implicated in systemic reactions, particularly after occupational exposure. A German case study described a pharmaceutical plant worker intermittently exposed to bromelain who developed rhinitis, dyspnea, and wheezing on exposure to the enzyme. Percutaneous, specific IgE, and bronchoprovocation testing to bromelain were all positive. An oral pineapple challenge produced rapid development of abdominal pain, bloating, and dyspnea, with findings of rhonchi on examination and obstruction on spirometry.⁷ This suggests that exposure to bromelain, particularly through the respiratory tract, may induce sensitization, thus permitting mast cell degranulation on ingestion of bromelain.

Percutaneous and in vitro testing can guide allergists when the history is inconclusive. Although commercial extracts and in vitro tests are helpful with such foods as milk, egg, and peanut, they are less accurate with fruits, particularly in cases of OAS.¹ Decades ago, Ortolani et al⁹ demonstrated that fresh food prick testing was more sensitive than commercial extracts for fruits and vegetables when compared with peanut, pea, and walnut.⁹ Pineapple percutaneous and in vitro testing are available; however, in addition to extrapolation of the finding from Ortolani et al, relevant proteins possibly can be broken down by proteases found in pineapple extracts, permitting false-negative testing.³ Furthermore, fresh food percutaneous testing with pineapple could theoretically cause a false positive from bromelain or acid-induced irritation. Sensitivity, specificity, and positive and negative likelihood ratios have not been specifically demonstrated for pineapple. Thus, we rely on our knowledge of the various types of reactions caused by pineapple and a detailed clinical history—which remains the best predictor for establishing or ruling out a diagnosis of clinical allergy.

Samantha Knox, MD

David Lang, MD

Alice Hoyt, MD

Department of Allergy and Immunology

Respiratory Institute

Cleveland Clinic

Cleveland, Ohio

samantha.knox85@gmail.com

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Superficial allergic lymphangitis with a cutaneous recall reaction to a mosquito bite



Although the major morbidity from mosquito bites is from transmission of infections, several types of clinical hypersensitivity reactions have been described, mediated through both nonimmune and a variety of immune mechanisms, including IgE, IgG, immune complex, and T cell.¹ The most common reactions are local cutaneous, including minor immediate reactions and more disturbing large local reactions. Delayed local reactions may persist for days to weeks and include large, firm, painful induration or even vesicles or bullae. Systemic reactions are less common and include the so-called skeeter syndrome, which typically consists of large local reactions that develop within hours of a bite, accompanied by fever. Serum sickness-like reactions have also been reported. Anaphylaxis to mosquito bites is exceedingly rare but has been reported. Perhaps the most severe systemic reaction is chronic, active Epstein-Barr virus-associated T cell or natural killer cell lymphoproliferative disease associated with mosquito bite hypersensitivity, which can lead to malignant tumors and has a high mortality rate. This case report describes a child with superficial lymphangitis to a mosquito bite, including what appears to be a cutaneous recall reaction.

A previously healthy, 13-year-old girl with a family history of atopy but no significant personal history of allergic diseases or other medical history began to receive frequent mosquito bites during the spring 2018. The family attributed this to recent construction in their backyard with long periods of standing water. Her initial reactions were described as normal, meaning immediate onset of minor local erythema, swelling, and itching that typically resolved in a few days with no specific interventions. She presented to her primary physician after what started out as a routine-appearing mosquito bite on the volar aspect of her left wrist. Within a day, she developed an erythematous streak up her arm nearly to her axilla. She also had temperatures to 102°F for less than 24 hours that self-resolved, with no systemic symptoms and specifically no pain along the streak and no local lymphadenopathy. She was initially prescribed oral amoxicillin clavulanate but did not improve. The next day she developed a similar streak, this time starting from the volar aspect of her right wrist and extending up nearly to her antecubital fossae (Fig 1). Of note, before this second streak, she had no known mosquito bite on the right wrist, only the initial bite on the left. She was taken to a local emergency department (ED), where oral clindamycin was prescribed, and within 24 hours the streaking started to resolve. The skin cleared up entirely with no additional systemic symptoms and no sequelae. Approximately 2 months later, she received another mosquito bite on her ankle and developed a red streak up to her midcalf within hours of the bite. This episode was not associated with any fever,

pain, or systemic symptoms. She was given oral clindamycin in her local ED, and the streaking improved within a couple days. Of note, she continued to receive a few more mosquito bites subsequent to this episode of leg streaking but described the bites as normal reactions similar to those she used to experience before the initial streaking reaction.

Superficial lymphangitis reactions to mosquito bites^{2–4} and to the bites of other arthropods have been described.^{5,6} This condition is underrecognized because it is likely that many of these reactions are incorrectly diagnosed and treated as infections, which is understandable given the prominent cutaneous streaking. However, it is unlikely that this patient had infectious lymphangitis. The onset of her streaking was sooner than would be expected if it was attributable to a secondary infection. Although she did have a fever, it was brief (<24 hours) and resolved before starting antibiotics, and it would be unlikely that a few doses of oral antibiotics would treat such an extensive infection so quickly. The streaking was not tender, and she had no local adenopathy or any systemic signs that would be expected in an infection of that degree. The fact that she developed a similar immediate-onset lymphangitic streak from an ankle bite, with no fever and or systemic symptoms, supports the contention that this was a hypersensitivity reaction and not an infection.

The pathophysiologic mechanisms responsible for superficial lymphangitis are unknown but are often attributed to a hypersensitivity reaction based on rapid onset of symptoms and rapid response to glucocorticoids without antibiotics and also to limited reports of biopsy specimens showing typical allergic inflammation, including increased eosinophils and mast cell infiltrates.⁷ Although both IgE and IgG antibodies to mosquito saliva have been demonstrated in skeeter syndrome, no reports have examined mosquito saliva antibodies in patients with superficial lymphangitis. It is unclear whether her brief fever was related to the bite or just coincidental but suggests perhaps a shared mechanism with skeeter syndrome. There is no physiologic basis for infectious lymphangitis to jump to the arm contralateral to the bite. Although she typically developed an obvious local reaction that consisted of redness and induration with every bite, she had no such reaction on her right wrist and believes she did not receive a bite on her right wrist with this acute episode. However, she had been bitten on that arm earlier in the season. The streaking that developed on the arm contralateral to her bite suggests an immune memory response similar to what has been described with systemic contact dermatitis⁷ or antigen-specific recall urticaria.⁸

Autodesensitization with a decremental decrease in reactivity after several sequential bites has been described and may explain why the reactions to some of her bites were more mild.¹ The area of Los Angeles in which this child lives recently had a marked