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EDITOR'S WELCOME

Dear Canadian Allergy and Immunology Community,

As we reach the midway point of 2021, we all continue to be affected by the COVID-19 pandemic. On behalf of our editorial board, we hope that you and your families are coping and managing well during these difficult times.

Our readership continues to grow, and we are immensely thankful to all of those who have expressed such positive feedback about the journal. We continue to welcome ideas about new topics and issues that are germane to your practices.

We have also created a central hub where all our articles are now archived and accessible for all subscribers. Please take a look by visiting www.canadianallergyandimmunologytoday.ca

In this issue we have many fascinating topics ranging from the changing concepts in the treatment and management of amoxicillin allergy to the treatment of anaphylaxis during COVID-19 to thoughts on overcoming barriers to successful management of atopic dermatitis. We also have two wonderful articles on insect sting hypersensitivity and an overview of mast cell disorders.

As always, we hope you find these articles informative and helpful. Please feel free to share our registration link at canadianallergyandimmunologytoday.com with your peers so that, they too, can subscribe to future issues and access all archived articles!

Best wishes,

Vipul Jain, MD Nikhil Joshi, MD Jason Ohayon, MD Susan Waserman, MD

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MAST CELL DISORDERS: OVERVIEW, CLINICAL PEARLS AND PERSPECTIVES

It has been almost 145 years since the discovery of mast cells (MC) and we continue to learn about their function and the consequences of their dysregulation. The focus of this article is to provide an overview on the current, yet evolving, classification of mast cell disorders (MCD) and provide clinical pearls and perspectives for their management for the allergist/immunologist (A/I).

THE SENTINELS OF THE IMMUNE SYSTEM

MC, first identified in 1878 by Paul Ehrlich, have mainly been viewed as effectors of allergic processes.[1] In recent decades research has revealed many other processes where these cells play essential roles, particularly as sentinels of the immune system and in the maintenance and restoration of homeostasis.[2]

MC are predominantly present at the interface between the host and the external environment, not in circulation, and, in contrast with other hematopoietic cells, they do not mature in the bone marrow but rather in the tissues where they are extensively distributed. These include the skin, conjunctiva, respiratory mucosa, gastrointestinal tract, genitourinary tract, myocardium, connective tissue surrounding blood vessels, lymphatics, nerves, smooth muscle cells, mucus glands, and hair follicles.[3] Of note, they are also present in the brain (choroid plexus, thalamus, hypothalamus, basal ganglia, vascular bed of the meninges) where they appear to act as sensors of environmental and psychological stress and first responders at sites of injury.[4]

As innate immune cells, MC can rapidly sense invading microorganisms, antigens, and toxins (venoms); recruit eosinophils, neutrophils and others to sites of inflammation; amplify complement activation; phagocyte bacteria or immobilize them by ejecting extracellular DNA traps or mast cell extracellular traps (MCETs).[2,5,6] For the adaptive immunity, MC act as antigen-presenting cells, help in the defense against parasitic infections, and lead to the activation of Th2 responses. They are also immunomodulatory by limiting the duration and magnitude of immune responses and contributing to tissue repair and angiogenesis.[1] Their role in IgE-mediated allergic/anaphylactic reactions is the most widely known and studied.[7]

Knowing the MC mediators (close to 100 biologically active mediators described to date[8])and their physiological targets and effects is key to understanding the varied symptomatology of MCD. For the purposes of this article, **Table 1** provides a non-exhaustive overview of the most relevant mediators, their physiological effects, associated signs and symptoms, and the therapies currently used to target them.[1,6,9,10,11,12]

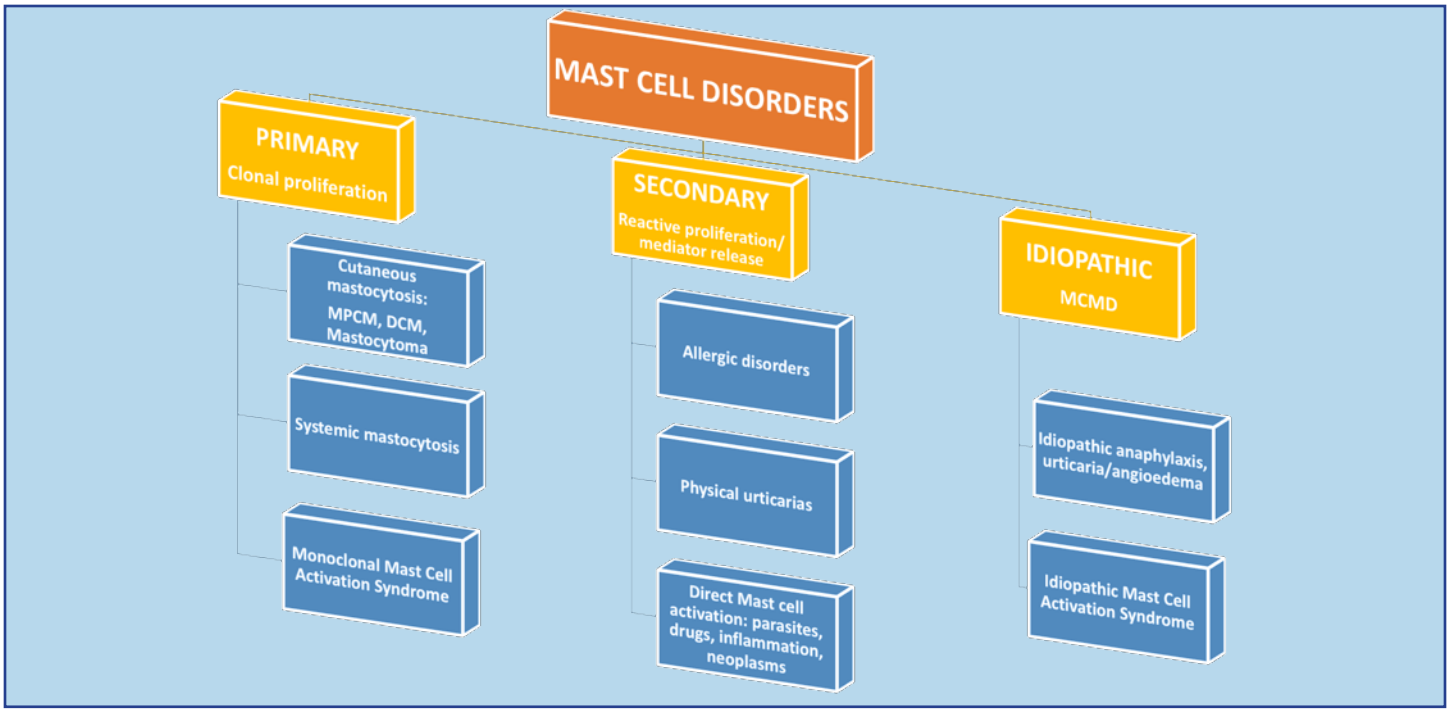

Figure 1. Classification of Mast Cell Disorders; (Adapted from Theoharides TC et al. 2019[9], Valent P et al. 2012[13], and Valent P et al. 2013[14])
Abbreviations. MPCM: maculopapular cutaneous mastocytosis, DCM: diffuse cutaneous mastocytosis, MCMD: mast cell mediator disorders.

MC are stimulated by an array of triggers including allergens, physical conditions (cold, heat, pressure, vibration); microorganisms, foods, drugs, heavy metals, neuropeptides, antibodies, and cytokines. Exercise and psychological stress are also well-recognized triggers, that often act as co-factors in amplification of histamine release. Some of these triggers cause degranulation but, contrary to the classical notion, others do not and instead cause the selective release of mediators.[9]

MAST CELL DISORDERS

Classification of MCD commonly causes confusion and it continues to evolve as the understanding of these conditions deepens. **Figure 1** shows the current proposed classification of MCD into primary, secondary, and idiopathic conditions. Primary disorders are those with abnormal clonal proliferation of MC, secondary disorders cause reactive MC proliferation and/or mediator release, and idiopathic or MC mediator disorders (MCMD) are those in which there is no evidence of proliferation yet mediator release from unknown trigger leads to the clinical picture.[9,13,14]

PRIMARY MAST CELL DISORDERS

Also referred simply as "Mastocytosis", these disorders are characterized by the clonal expansion and activation of MCs primarily in the skin (cutaneous) or the bone marrow and other tissues (systemic), mostly caused by gain-of-function mutations in the *KIT* gene.

Cutaneous mastocytosis (CM)

CM is the abnormal clonal proliferation of MC in the skin and most commonly seen in children; however, adult patients with systemic mastocytosis (SM) also frequently have cutaneous manifestations of the disease. It presents in 3 forms: 1) maculopapular cutaneous mastocytosis (MPCM) or urticaria pigmentosa ("UP") as shown in **Figure 2**, with two variants (monomorphic and polymorphic), 2) diffuse cutaneous mastocytosis (DCM), and 3) mastocytoma of the skin. The lesions can be highly heterogeneous (macular, nodular, plaques, and sometimes blistering) and also differ between children (polymorphic) and adults (monomorphic).[15] The term often described for mastocytoma is "peau d'orange" or skin that looks like the "peel of an orange".

The diagnosis of CM is mainly clinical, but it may be helpful to have histological confirmation of MC infiltration and, in 35% (children) to 80% (adult) of patients, the finding of an

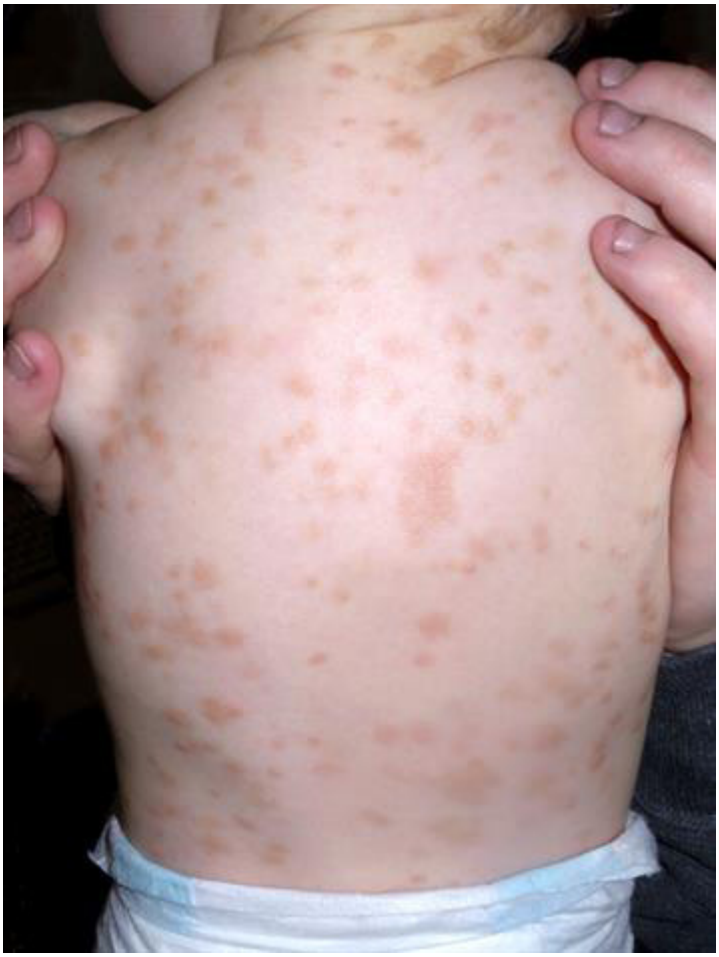

Figure 2. Urticaria pigmentosa in a pediatric patient; from aboutkidshealth.ca

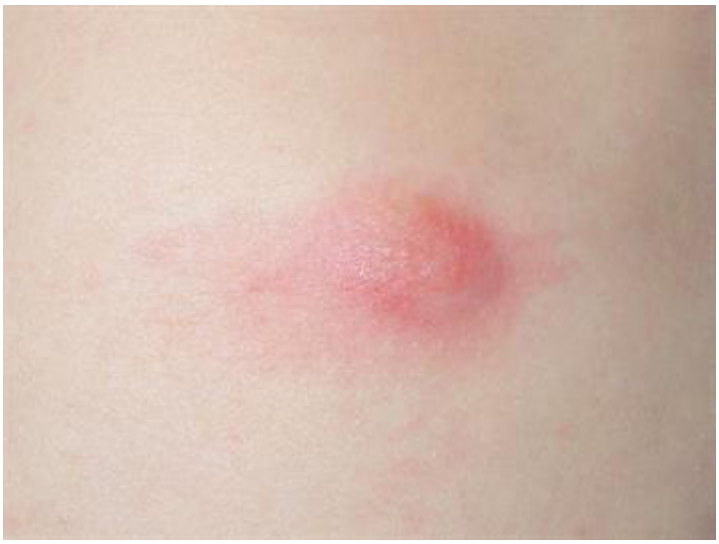

Figure 3. Positive Darier's sign; from aboutkidshealth.ca

activating *KIT* mutation (D816V in adults and others in children) is present.[15,16] A highly specific diagnostic clinical tool is Darier's sign (**Figure 3**), which manifests as wheals and erythema of the lesions after rubbing them.[17]

Even when the abnormal accumulation of MC is limited to the skin, DCM and MPCM can be associated with systemic symptoms from the release of MC mediators into the bloodstream (see **Box 1**). It is very important not to confuse this with SM, which is extraordinarily rare in the pediatric population, with only two case reports cited in the literature.[18]

Children with CM usually have spontaneous resolution by puberty and, in contrast to adults, less than 10% experience anaphylaxis, therefore the prescription of an adrenaline auto-injector in children is left to individual clinician preference rather than being a requirement.[15,16,18] (See **Box 2**)

Systemic mastocytosis (SM)

SM refers to the oligoclonal and neoplastic extra-cutaneous proliferation of MC.[19] The diagnosis of SM requires the fulfillment of one major and one minor criterion, or three minor criteria, as established by the World Health Organization's classification of myeloid neoplasms and acute leukemia . The one major criterion is the finding of multifocal, dense infiltrates of MC (≥15 cells and in aggregates) in bone marrow and/or other organs. The minor criteria are: 1) finding by biopsy of bone marrow and/or other organs of > 25% of MC to be spindle shaped or with other atypical morphology; or when > 25% of MC in a bone marrow aspirate smear are shown to be immature or atypical, 2) finding of *KIT* D816V mutation in bone marrow, blood, or other extracutaneous organ, 3) CD2 and/or CD25 expression in MC in the bone marrow, blood or other extracutaneous organ, and 4) persistently elevated baseline serum total tryptase of >20 ng/ml.[20]

The classification and risk stratification of SM is based on the correlation between clinical and laboratory evaluations. It includes indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis

- **Skin**: pruritus, urticaria, angioedema, flushing, dermatographism
- **Cardiovascular**: hypotension, tachycardia, syncope
- **Respiratory**: cough, wheezing, stridor, hoarseness, nasal congestion, rhinorrhea
- **Gastrointestinal**: nausea/vomiting, abdominal pain/cramping, bloating, diarrhea
- **Musculoskeletal**: bone/muscle pain, osteoporosis/osteopenia
- **Neurologic**: headache, memory and concentration difficulties ("brain fog"), irritability
- **Systemic**: fatigue, malaise

Box 1. Systemic symptoms associated with mast cell mediator release

-associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), and mast cell sarcoma (MCS).[19,20] Details of each are beyond the scope of this review.

The treatment of SM is highly individualized and involves the use of kinase inhibitors (imatinib for SM without D816V, and midostaurin and avapritinib for those with the mutation) and symptom-directed treatment for other causes of mast cell mediator release.[19] (See **Box 1, Box 2, and Table 1**)

Collaboration with hematologists who specialize in MCD is essential in the proper investigation and treatment of patients with SM. For systemic mastocytosis, all adult medicine tertiary centers with a Hematology service will generally see these patients. For cutaneous mastocytosis, there is great variability in regard to diagnosis and treatment of these patients. Some are seen exclusively by dermatologists, some by community allergists, and some (usually the ones with diffuse cutaneous mastocytosis) are seen by immunologists in tertiary centers.

Monoclonal mast cell activation syndrome (MMCAS)

MMCAS is characterized by intermittent episodes of the release of MC mediators without an identified trigger. Patients with MMCAS are usually identified through systemic reactions to Hymenoptera stings or unexplained episodes of anaphylaxis.[18,21] Patients, mostly adults, do not have cutaneous lesions nor MC aggregates in the bone marrow and they manifest clinically with the signs and symptoms of MC mediator release.[22] (see **Box 1**)

- **Non-sedating, second generation anti-H1 antihistamines**: cetirizine, rupatadine, bilastine, fexofenadine, desloratadine
- **Anti-H1 antihistamine with anti-PAF and anti-eosinophil actions**: rupatadine, ketotifen
- **Anti-H1 antihistamine with anti-serotonin action**: cyproheptadine
- **Anti-H1 antihistamine with tricyclic antidepressant action**: doxepin
- **Anti-H2 antihistamines**: famotidine, cimetidine, ranitidine
- **Mast cell stabilizers**: ketotifen, cromolyn sodium (sodium cromoglycate), rupatadine, flavonoids (quercetin, luteolin)
- **Leukotriene antagonist**: montelukast
- **Antispasmodics (overactive bladder)**: oxybutynin, fesoterodine

Box 2. Symptomatic treatment agents for mast cell mediator release

MAST CELL MEDIATOR	PHYSIOLOGIC EFFECT	SIGNS/SYMPTOMS	THERAPY
Histamine	**H1 receptors** Blood vessels and sensory nerves of: • Skin: increased vascular permeability • Bronchial, intestinal, and cardiac smooth muscle: contraction Brain: cerebral cortex and infralimbic structures in regions concerned with neuroendocrine, behavioral, and nutritional state control.	• Urticaria, flushing, pruritus • Cough, wheezing • Diarrhea • Increased heart rate and cardiac output • Headaches, memory and attention deficit ("brain fog"), fatigue, malaise, weight loss	• Non-sedating, second generation anti-H1 antihistamines: cetirizine, bilastine, fexofenadine, loratadine, desloratadine • Anti-H1 with anti-platelet-activating factor effect: rupatadine • Anti-H1 mast stabilizing antihistamine: ketotifen • Anti-H1 tricyclic antidepressant: doxepin
	H2 receptors • Gastric mucosa: increased acid secretion • Airway mucous glands: increased production • Brain: basal ganglia, hippocampus, amygdala • Chondrocytes	• Gastritis, gastric or duodenal ulcers, abdominal pain • Congestion • Potentiation of synapsis excitation	For gastric effects*: Famotidine, cimetidine, ranitidine
	H3 receptors • Brain (cortex, thalamus, basal ganglia, hypothalamus): regulates serotonergic, noradrenergic, cholinergic, and dopaminergic release • Presynaptic nerves in the peripheral sympathetic adrenergic system: suppression of norepinephrine release	• Sleep disturbances • "brain fog": memory, concentration, and attention deficits • Fatigue/lethargy • Sleep disturbances	None available for this clinical use* (Pitolisant is the first available anti-H3 but only authorized for narcolepsy in adults in U.S.A)
	H4 receptors • Eosinophils, mast cells, basophils, neutrophils, and dendritic cells: potent chemotaxis and cytokine release	• Inflammatory responses	None available for clinical use

MAST CELL MEDIATOR	PHYSIOLOGIC EFFECT	SIGNS/SYMPTOMS	THERAPY
Tryptase	• Bronchial smooth muscle contraction • Proliferation of fibroblasts and degradation of collagen • Chemotaxis for eosinophils • anticoagulation	• Cough, wheezing • fibrosis and tissue remodeling • osteopenia/ osteoporosis • Bleeding	None available for clinical use*
Serotonin	• Gastrointestinal tract: regulates intestinal movements • CNS: regulation of mood, appetite, and sleep	• Diarrhea • Flushing • Sleep and appetite disturbances	Cyproheptadine
Prostaglandins (D2 and E2)	• Vasodilation and increased vasopermeability • Airway smooth muscle bronchoconstriction • Nerve cell activation	• Angioedema, flushing • Cough, wheezing, mucus secretion • Sleep-inducing	None available for this clinical use. NSAIDs are known triggers of mediator release and should be avoided, if possible.
Leukotrienes (B4 and C4)	• Increased microvascular permeability • Smooth muscle constriction	• Angioedema, flushing • Long lasting wheal-flare responses • bronchoconstriction	Montelukast
Platelet-activating factor (PAF)	• Vasopermeability • Bronchoconstriction • Neutrophil attachment and transmigration	• Pruritus • Urticaria • bronchoconstriction	Rupatadine Ketotifen
Heparin	• Anticoagulation • Others not well defined	• Bleeding (reported in severe SM)	Protamine
Th1 (IL-6, TNFα) and Th2 cytokines (IL-4, IL-5, IL-9, IL-31), chemokines	• Multiple cellular targets and functions	• Allergic and non-allergic inflammation • IL-31: particularly pruritogenic	Specific anti-cytokine treatments have only seldomly been used for mast cell disorders

Table 1. Mast cell mediators, physiologic effects, signs and symptoms, and targeted therapy.[1,6,9,10,11,12]

Abbreviations. PAF: platelet-activating factor, CNS: central nervous system, NSAID: non-steroidal anti-inflammatory drugs, SM: systemic mastocytosis.

** Complementary agents include: mast cell stabilizers preventing the release of most mediators; topical cromolyn sodium preparations for skin manifestations; oral cromolyn sodium for gastrointestinal symptoms; flavonoids for CNS and gastrointestinal symptoms; calcium and vitamin D supplementation for osteopenia/osteoporosis; antispasmodics for overactive bladder.*

To be considered MMCAS, the *KIT* D816V mutation and the abnormal expression of CD25 and CD2 should be present in at least a few clonal MC in the bone marrow.[21,22] If these features are not found, then idiopathic mast cell activation syndrome (IMCAS) may be considered. In MMCAS patients, baseline serum tryptase is typically not elevated but may occur during acute exacerbations between 30 minutes to 2 hours after symptom onset. In order to establish clinical significance and support the diagnosis of MMCAS, **the tryptase elevation from baseline should be ≥ 1.2 times plus 2 ng/ml.**[22] Ordering a c-kit D816V test can be done through one of two methods.

1. In bone marrow aspirate/biopsy in the setting of systemic mastocytosis: it is requested directly by hematology through the hemopathology department assessing the sample.
2. In peripheral blood for all mast cell disorders, when indicated: it is ordered, with prior approval by the local Genetic Resource Center, through any of the genetic testing companies as a single gene test.

SECONDARY (REACTIVE) MAST CELL DISORDERS

These are disorders in which external stimuli cause the reactive polyclonal proliferation, hyperplasia, and/or mediator release of MC. Included among these secondary mast cell disorders are the classic IgE-mediated hypersensitivity reactions induced by allergens (foods, drugs, insect venoms, and other environmental factors); physical urticarias (heat, cold, vibration, stress); and direct MC activation from infections (parasites, tuberculosis, syphilis), drugs (vancomycin, opioids, NSAIDs, muscle relaxants, contrast media), inflammation (psoriasis, rheumatoid arthritis), and neoplasms (melanoma, gastrointestinal neoplasms).[1,16]

IDIOPATHIC MAST CELL MEDIATOR DISORDERS (MCMD)

In these disorders, the cause of abnormal MC activation is unknown. Importantly, the mediator release is thought to happen without proliferation or even degranulation of MC. One way of describing MC status is as "unstable" and exhibiting aberrant stimulation.[9] Included in this group are idiopathic anaphylaxis (not explained by MMCAS), idiopathic urticaria/angioedema, and IMCAS (see next section).

Idiopathic mast cell activation syndrome (IMCAS)

The diagnostic criteria for IMCAS (requires all three) are: 1) episodic, objective signs and symptoms of MC activation in at least two organ systems. Clinicians should note that subjective symptoms (e.g., fatigue, brain fog) in the absence of the signs and symptoms in two other organs systems **do not count**, 2) evidence of systemic MC mediator release corresponding temporally to the presence of symptoms, and 3) clinical response to medications that inhibit MC mediators.[14]

Other conditions that can be frequently reported by patients with IMCAS include postural orthostatic tachycardia syndrome and other dysautonomia[23], hypermobile Ehlers-Danlos syndrome and other hypermobility conditions[23,24], psoriasis[25], fibromyalgia and chronic fatigue syndromes[23], interstitial cystitis/overactive bladder syndrome[26], irritable bowel syndrome[27], post-traumatic stress disorder, and neuropsychiatric disorders[4,28], to name the most relevant. More studies are needed to clarify these associations and the specific role of MC. Given the type of symptoms and, very often, the lack of objective evidence of systemic MC mediator release, the diagnosis of IMCAS is prone to be misused by parents/patients (online self-diagnosing and other motives), physicians (in the presence of a challenging diagnosis and often challenging patients/families), and more concerningly by non-physicians who profit from the often long journey that many of these patients endure and that greatly affects their quality of life.[29]

Clinical pearls and perspectives

- Knowledge about the effects of MC mediators is key in understanding the clinical presentation of patients with MCD and in tailoring their therapy.
- The classification, nomenclature, and diagnostic criteria of MCD causes confusion. It is relevant for the A/I to stay informed on this topic.
- The distinction between SM and CM with systemic symptoms is very important; often the cause of referral to an A/I.
- Patients with CM, especially DCM, can sometimes have tryptase levels >20 ng/ml at presentation. In children, and in the absence of cytopenia and/or other infiltrative features such as lymphadenopathy, hepatomegaly, or abnormal liver function, a referral to hematology for a bone marrow aspirate/biopsy is **not required**. Follow up of these levels with age and adequate symptomatic treatment usually reveals normalization.
- SM is extremely rare in children. As per above, the same rules would apply for referral to hematology.
- MMCAS and IMCAS are diagnoses of exclusion, after ruling out other serious diagnoses such as SM, carcinoid, pheochromocytoma, vipoma, gastrinoma, and medullary carcinoma of the thyroid, when applicable
- The most objective, yet challenging way to assess for MCD is the proper measurement of mediators in blood and urine.
- Currently, there are no drugs that solely and selectively target MC.
- It is important, for both the patient and treating clinician to accept that limiting triggers and targeting the patient's specific symptoms of mediator release are currently the best available therapeutic approaches
- The recommended therapy is a combined approach of at least anti-H1 + H2 antihistamine(s) + mast cell stabilizer(s), with the addition of other agents based on specific symptoms. Doses should be maximized as indicated/tolerated aiming for full symptomatic control to then progressively taper to lower doses that are able to achieve symptom control.
- More targeted therapies are needed (e.g. anti-H3 and -H4 antihistamines, anti-tryptase agents, non-NSAID prostaglandins inhibitors, anti-IL-31), and more effective MC stabilizers
- Prophylactic precautions may be warranted for some patients before and during surgical procedures.
- The ideal care for patients with/suspicion of a MCD may include and involve A/I, dermatology, hematology and, clinical psychology and social work.
- When assessing for MCD especially MMCAS and IMCAS, explore alternative or concomitant mental health conditions.

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ITCHING TO KNOW MORE: OVERCOMING BARRIERS TO SUCCESSFUL MANAGEMENT OF ATOPIC DERMATITIS

Case A.R.

You're seeing a 5-year-old girl along with her mother, referred for hard-to- control eczema. Mom reports this has been "life-long". She moisturizes her daughter's skin regularly but doesn't think it makes much difference. She finds the topical steroids that have been provided work "a bit" but never really seem to clear the eczema and she's quite reluctant to use them as many people have told her she shouldn't use them if not needed. She'll use them when the eczema is really bad. Sometimes the eczema is "okay" and she'll only be up at night a few times a week but when it's really bad she can be awoken two times a night with pruritus. Mom and dad work in shifts and their schedules change frequently. Mom feels she is constantly "chasing" the eczema. What she hopes to get from the consultation with you is a way to stop the eczema "once and for all". You note on exam that the daughter has moderate eczema over 70% of her body though her face is clear; the girl is also fidgety and restless.

BACKGROUND

Patients suffering from atopic dermatitis ("eczema") are frequently referred to specialists for management advice. Different published guidelines and management recommendations for eczema typically share a common goal of helping health care practitioners (HCPs) provide patients with strategies to control their eczema and include 1) trigger reduction, 2) emollient use, 3) topical anti-inflammatory medications, 4) treatments for complications and 5) ancillary treatments.[1]

While it is encouraging that emerging systemic therapies may change eczema management in the future, currently, for many patients, topical treatments remain the mainstay of therapy.

Many patients remain **sub-optimally** controlled--not because of a lack of good strategies—rather, due to barriers in executing these strategies successfully. The focus of this article will be to help identify and overcome some of these common barriers that might impede treatment management success.

BARRIERS TO SUCCESSFUL TREATMENT MANAGEMENT

Table 1 provides a framework of questions to identify barriers to optimal eczema control.

1. Does the patient (or patient's parent) **understand** the treatment management plan?
2. Does the patient (or patient's parent) **accept** the treatment management plan?
3. Is the patient (or patient's parent) able to **implement** the treatment management plan?

Table 1 Questions to identify barriers to optimal eczema control; courtesy of Miriam Weinstein, MD

1. DOES THE PATIENT UNDERSTAND THE TREATMENT MANAGEMENT PLAN?

Increasingly it is recognized that education about eczema and therapy significantly enhances the efficacy of disease management. The literature on therapeutic patient education (TPE) in eczema has grown considerably in the last decade and the education is itself considered part of therapy.[2] However, there are many potential barriers to patients increasing their health literacy around eczema.

Confusion for the patient as new information is added

Patients often have misinformation, conflicting information, gaps in information and too much information that can be overwhelming. This can create confusion if not addressed by the clinician who is able to better guide patients to reliable sources of information that will avoid such situations.

Unique learning needs

Patients vary in the amount and type of information they need to effectively put management strategies in place. Furthermore, patients differ in learning styles, for example, auditory versus visual leaners. Differences in cognitive skills, memory and processing information will also impact information acquisition and understanding. These individual needs preclude a "one size fits all" approach to educating patients.

Cultural and language variations

Non-verbal communication may have different meanings culturally and could impact comprehension. Spoken language can be filled with nuance, idioms and jargon and can be confusing. Modern day access to online translation software such as Google Translate can help in situations where English is not the first language for patients and their caregivers.

Situational impacts

Patients can experience fatigue, distraction and difficulty concentrating which may impact how information is received.

2. DOES THE PATIENT ACCEPT THE PLAN?

Even when information is successfully understood, there can be significant potential barriers to gaining patient acceptance to the proposed plan.

Trust not yet established

Patients bring information with them from their own trusted sources and established relationships. The specialist may have to earn the patient's trust before advice will be accepted. This is a challenge in a time-limited consultation. Some sources of information that are important to patients may include primary care physicians, pharmacists and other specialists. Many patients seek advice and treatments from complementary healthcare practitioners and have different beliefs about health and health care practices.

Family, friends, coworkers, and peers are common sources of information, with advice sometimes being provided in an unsolicited fashion. Different media sources and the internet are also frequent sources of medical information.[3] Despite the lack of accuracy, utility, and relevance of much of the accessible internet information, many consumers are unable to appropriately distinguish between high-value and low-value online health information.

Steroidphobia

Fear of topical corticosteroids is extremely prevalent among patients, families and also health care practitioners. Fear of steroid side effects has been proven to **negatively** impact adherence to therapy and, thus, outcomes.[4]

Focus on food allergies

Often thought to be the cause of the disease itself or the cause of flares, food allergies are best thought of as a co-morbidity rather than a directly provocative cause of a flare. Certain foods, as a source of health issues, and the withdrawal of certain foods as a remedy for health problems are often strongly held beliefs by many and supported strongly in the lay media. It may be confusing as many patients have both conditions and both food allergies and eczema cause pruritic rashes—urticaria and dermatitis, respectively. Further complicating the interpretation of food reactions is that certain foods - usually acidic foods such as citrus-based foods - act as an irritant, not allergic trigger for a flare of eczema.

Patient's perception of value in eczema management

Often patients hear messages that trivialize their experience of eczema. Phrases such as "just eczema" or advice to use treatment only when "really needed" or a focus on the eventual improvement with time may cause patients themselves to minimize their disease and undermine the value of therapy.

3. IS THE PATIENT ABLE TO IMPLEMENT THE PLAN?

Even with patient understanding and acceptance of a treatment management plan, hurdles may remain in the implementation of a successful treatment plan.

Components of management plan

Complex plans with multiple steps or actions such as different medications for different stages of a flare and complicated plans with tasks that may be difficult to complete such as bleach baths and wet wraps can be barriers to successful management. While "straightforward" to those of us who suggest such strategies daily, this may not be the case for patients. Patients may find it easier to avoid tasks that are too complicated or complex. Therefore multi-step strategies such as bleach baths –particularly when the evidence for its utility is equivocal --may best be reserved for select patients in whom optimal first-line management is insufficient for control.

Costs

There are important non-financial costs to consider as patients expend significant time, energy and effort on management plans and failure to consider these burdens in selecting treatment management strategies can pose barriers to achieving desired outcomes. Some patients truly desire to see their skin improve and understand how to get there but feel that the tradeoffs may not be worth it. They ultimately accept living with suboptimal control as the "price" to pay. However, treatment management plans can be altered to lower these burdens and improve outcomes.

Application of topical therapy

A common assumption dictates that patients will know where, when and how to use their medications. This false assumption is an under-appreciated barrier and one of the easiest to address. Like any "tool", patients need to know where, when and how to use topical therapy. A starting point is to be able to identify where there is active eczema, and this can be challenging for patients (**Table 2**).

CHALLENGE	FEATURES
Eczema can present with many morphologies	e.g., classic dermatitis, lichenification, excoriations etc.
Associated skin finding may be hard to distinguish from eczema	e.g., keratosis pilaris, follicular prominence etc.
Variation in prominence of eczema	range from visibly obvious to very subtle rough patches only appreciated on palpation
Some perceive mild-moderate eczema as "normal" and only a worsening is called a "flare"	chronic patches/plaques of active eczema thought to be normal
Eczema may present only as pruritus	skin looks and feels normal but is itchy

Table 2. Challenges to identifying active eczema; courtesy of Miriam Weinstein, MD

Patients often don't know when to use medications and thus will use them with less-than-ideal frequency and duration resulting in mild-to-moderate improvements in symptoms such as rash and itch but never the clearing of a flare completely (**Figure 1**). The patient may not connect the sub-optimal use of medications with sub-optimal outcome and control. The patient's perception is often that the medication simply doesn't work, and they seek a different medication. Prescribing a different medication—without knowing where, when and how they used the "failed" medication—may beget the same problem. In patients with predictable areas of flare-ups, an additional preventive strategy to daily moisturization, could be 2-3 times weekly application of a topical steroid or topical calcineurin inhibitor to suppress new flares from developing.

How patients apply medications can impact outcomes. Sparing use of medications rather than adequate use or the mixing of medications with moisturizers to save time---which dilutes the intended potency of the medication—are common strategies that undertreat the eczema.

Strategies to overcome barriers

Challenges impacting health literacy—the ability to access, understand, accept and utilize information to manage health—can be overt or hidden and thus all patients should be provided with treatment management plans that ensure barriers are identified and minimized.[5]

1. PROMOTE UNDERSTANDING OF THE MANAGEMENT PLAN

Just the facts. Keep information simple and recommendations based on evidence. Some aspects of dermatologic dogma are often suggested but not well substantiated in the literature. For example, despite many firmly held opinions on bathing techniques, the literature lacks evidence supporting specific advice regarding bathing.[6] Similarly, there is a paucity of data supporting many of the laundry practices often suggested.

Less is more. Disease state and treatment information can be built "in layers" beginning with the basic concepts and adding information if that patient needs/wants more. If the volume of information provided causes confusion, mental fatigue or overwhelms the patient then successful disease management may be hindered. Use simple, clear, lay language. Use diagrams and photos to represent concepts or to reinforce discussion points (e.g., models of the barrier defect; photos showing different morphologies of eczema, etc.). Written action plans as a take home reminder of the patient's plan have demonstrated utility in eczema management.[7]

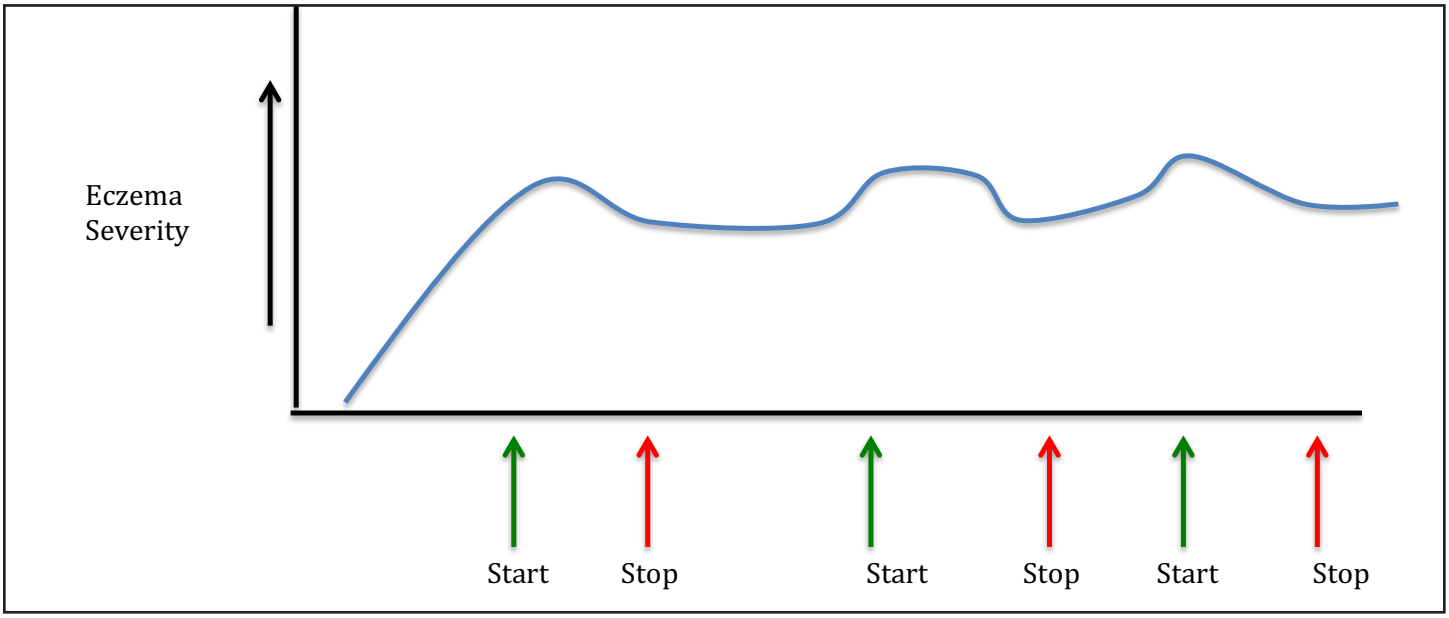

Figure 1. Common treatment pattern: treat only as flare gets "really bad"; eczema in chronic flare; never clear.

Check in and Follow up. It is important to be mindful that cultural and language differences may impact perspective, interpretation and understanding. Therefore, periodically "checking in" to ensure comprehension is important. It is also critical to provide opportunities for patients to ask questions or clarifications as some patients do not feel comfortable interrupting a physician even if needed. It may also be of value to offer interpreters when indicated.

Read the room. Distractions, fatigue, and trouble concentrating will greatly impact information uptake. Physicians should observe for loss of eye contact and attention; patients looking at their phones, parents turning attention to children's needs or patient disinterest. Physicians may also consider providing information over several sessions if it is too much for one session. It is imperative to repeat key information multiple times.

2. ENHANCING ACCEPTANCE OF THE PLAN

New kid on the block. A new specialist won't yet be a part of the patient's cadre of trusted sources of information. A specialist may be well-intentioned and armed with an excellent care plan but without "buy in", it won't be used. Trust can be a challenge to build in a short time, but some strategies can help. Avoid a paternalistic tone in favour of a collaborative approach. While it is critical to offer corrections to mis-information, it is important to do so without being dismissive of their valued sources. If there are concerns about their particular practices, state why there is a concern and help them put safeguards in place if they plan to continue these practices. For example, if a patient is going to use dietary restrictions as a strategy, though you haven't advised this, suggest they see a nutritionist to ensure their plan won't negatively impact their health. If a patient relies on the internet, identify sites that use vetted, reliable information; advise patients to check the sponsors of the site and to be wary of sites with ads or those that sell products along with providing information.

The elephant in the room. "Steroidphobia" exists for many patients even if they don't voice the concern and thus should be assessed in all patients. A useful validated tool to assess steroid fears is TOPICOP©.[8] While side effects such as atrophy and absorption are real side effects of topical steroid use, their risk of occurring with optimal usage is rarer than many appreciate.[9] Risk can be a challenging concept for patients to understand. Analogies from everyday life where risk exists but is low may be helpful in providing context and appropriate frames of reference for patients. There is a widely-held belief that if steroids are used too much they will lose their efficacy. Tachyphylaxis has not been well-established with topical steroids for eczema and failure to respond may represent under-use, not overuse.[10] Living with untreated or under-treated eczema often produces more frequent and more profound side effects than those from medications (**Table 3**).

Sleep disruption for patient and family
School/work negatively impacted (attendance and/or performance)
Self-esteem negatively impacted
Socialization negatively impacted
Sexual/intimate relationships negatively impacted
Sports/activities disrupted
Staph aureus/Streptococcus/HSV infections

Table 3. Potential side effects from untreated or under-treated eczema; courtesy of Miriam Weinstein, MD

"People don't care how much you know until they know how much you care" Patients need their experience with eczema and its impact on their lives acknowledged and validated as being worthy of treatment. It is not a trivial disease for many. Data abounds on the negative impact that poorly controlled eczema

can have on quality of life.[11] Patients may need "permission" to treat their disease and be empowered with knowledge and strategies to control their disease as would be offered with other chronic illnesses, but which may be provided reluctantly or with reservation in the treatment and management of eczema.

3. SUPPORTING IMPLEMENTATION OF THE PLAN

If you build it, they will come. Clinicians should strive to build plans that are as simple and basic as possible so that patients can easily adopt them. Could one medication be used instead of two different ones? Is every step in the plan necessary? Every single action being asked of a patient should have a value-added benefit. If a step may not have significant impact on outcomes, then clinicians should reconsider if it is needed. For example, antihistamines are often advised but with little support in the literature for their utility.[12]

Sedating antihistamines have been used in the past to help reduce nighttime sleep disruption from pruritus, but a more effective strategy is to adequately and completely treat all active areas of disease, and thus the source of the pruritus

Teamwork makes the cream work. It's important to work collaboratively with patients when developing plans so that we know what costs they are willing to incur. Management plans require patients to expend their time, money and effort and clinicians cannot effectively choose treatment plans without knowing what patients value. A desired outcome may be achievable with a milder medication dosed more frequently or a stronger one dosed less often. An ointment might be a better choice in a given situation but if a patient won't use it, could a cream work instead?

Add a demo to the memo. In addition to a written action plan, try demonstrating where and how to apply topical therapy—which may not be intuitive for many. In order to know when to treat, one must first know what constitutes active disease—i.e., where to treat. Clinicians should take care to point out active eczema, different morphologies, different severities and unaffected skin. It is important to ensure that patients understand that itchy skin-even in the absence of the rash- is active eczema and should be treated. Have some jars/tubes of un-medicated creams and ointments to demonstrate how much to use and how to apply. The Finger-Tip Unit can be a useful strategy for medications dispensed in tubes.[13] Ensuring that patients know when to treat—ideally from the start of a flare until clear skin --can be demonstrated and shown with a graph (**Figure 2**).

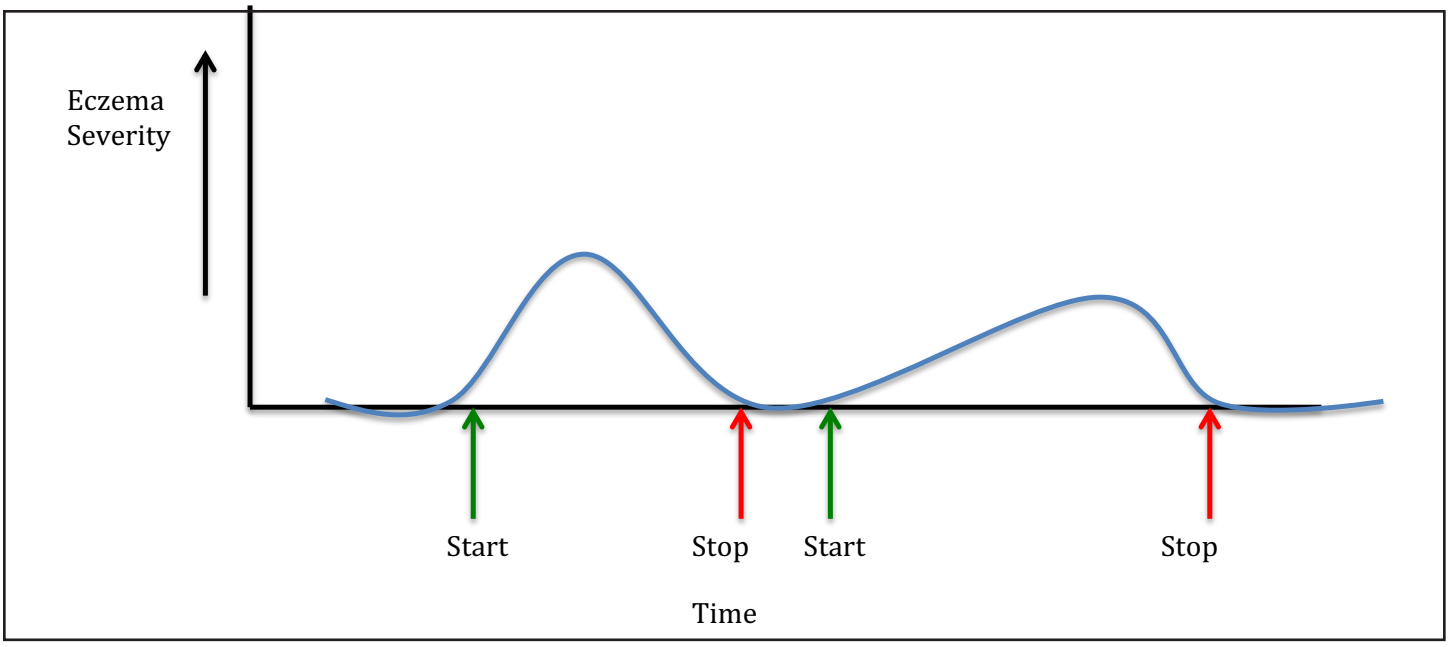

Figure 2. Optimal treatment pattern: treat as soon as a flare starts until it has resolved; eczema clears between flares

For patients unable to achieve adequate control with proper use of first line therapies or for those unable to implement such strategies successfully, consideration should be given to systemic agents. Currently, this includes phototherapy; the off-label use of such agents as cyclosporine and methotrexate or dupilumab which is a biologic agent targeting IL-4/IL-13 and is approved in Canada for patients age 6 and above.

Let's now turn our attention back to patient A.R. who is suffering from chronic, significant eczema. Assessing for potential barriers while developing a management plan and employing strategies to mitigate these barriers should increase the plan's efficacy (**Table 4**).

CONCLUSION

Eczema is not curable but there are established, effective management strategies that can bring about excellent control. Many patients can be managed successfully with topical therapy. Ensuring patient understanding and acceptance of treatment plans with support from their healthcare team will best overcome the many barriers impeding control to lead to improved quality of life in these patients.

POTENTIAL BARRIERS	POSSIBLE SOLUTIONS
Incorrect information about expectations of management	Provide info about remitting/relapsing nature; stopping eczema "once and for all" not a realistic goal; treating flares is realistic
Child is fidgety and restless	Keep information simple; watch for distraction; provide information over multiple sessions
Steroidphobia	Explain when used properly, risk of side effects are rare; impacts of disease are a greater risk
Minimizing impact of disease	Sleep disruption is significant; acknowledge this is a significant impact on quality of life and a disease worth treating
Underusing medication	Explain that using medications to all active areas until clear will promote remissions between flares rather than treating just when "really bad"
Potential time factor in application of medication	Shift work for parents may make multi-step plan complicated; consider 1 medication of adequate strength b.i.d. at times that work for family

Table 4. Management plan for A.R.: Potential barriers and possible solutions; courtesy of Miriam Weinstein, MD

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References: 1. Rupall Product Monograph, Pediapharm Inc. January 3, 2017. 2. Data on file.

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TREATMENT OF ANAPHYLAXIS AND MODIFICATIONS DURING COVID-19

BACKGROUND

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and is potentially life-threatening.[1,2] The lifetime prevalence of anaphylaxis is between 1.6 to 5.1% with the largest number of incident cases among children and adolescents.[3–5] Most episodes of anaphylaxis are immunoglobulin- E (IgE) mediated with foods, medications and stinging insects being the most common triggers.[6] While various definitions of anaphylaxis exist,[2,7–9] most rely on two body systems being affected, with some combination of cutaneous, respiratory, gastrointestinal and/or cardiac symptoms. Cutaneous symptoms are by far the most common, reported in over 80% of anaphylaxis, followed by respiratory then gastrointestinal involvement.[1]

Food allergy is one of the most common chronic conditions of childhood, directly impacting up to 10% of children and indirectly up to 50% of the population.[10–12] It is the most common cause of anaphylaxis in children.[6] Anaphylaxis is less common in infants than it is in children.[13] While anaphylaxis can be life-threatening, the risk of fatal anaphylaxis is about 1 in 10 million (this is equivalent to being struck by lightning).[14] While it is essential that anaphylaxis be recognized and managed, the risk of fatality is very low. Factors that increase the risk of anaphylaxis severity and/or fatality include comorbidities, such as asthma, mastocytosis, hyperdynamic states including exercise and infection, concurrent medication use (i.e. ACE inhibitors), and age where increased risk taking behavior is common (i.e. in adolescents).[1,15]

Investigations at the time of an anaphylactic reaction include plasma histamine and/or serum tryptase levels, although neither is specific for anaphylaxis.[1] If food allergy is suspected as a trigger of anaphylaxis, subsequent skin prick testing (SPT) and/or food-specific IgE (sIgE) can be measured. However, while SPT and food-specific IgE testing are highly sensitive (from 70-90%), the specificity of testing remains low (less than 50%).[1,2] The rate of false positive tests is up to 40%.[16] As a result, food allergy testing is diagnostic within the context of the presenting anaphylactic history. An allergy skin test (AST) should be performed when a convincing clinical history of allergen induced anaphylaxis is present.[17]

Biphasic anaphylaxis is defined as recurrent symptoms occurring 1 to 72 hours after resolution of the initial reaction (although often within 8 hours) and occurs in 1-20% of patients.[1,15,18,19] Risk factors for biphasic anaphylaxis include more severe initial symptoms, the requirement of more than one dose of epinephrine for recovery, unknown trigger for anaphylaxis, and medication-induced anaphylaxis in the pediatric population.[15]

MANAGEMENT OF ANAPHYLAXIS

Guidelines uniformly recommend epinephrine as first-line therapy in anaphylaxis.[1] Beneficial and life-saving mechanisms of epinephrine include reduction in laryngeal angioedema, cardiac inotropic and chronotropic effects, bronchodilation, and vasoconstriction.[1,16,20] Delay in the use of epinephrine has been associated with increased morbidity and mortality.[21] Despite this, epinephrine autoinjectors are often underutilized both in incidence and within ideal timing of anaphylaxis.[22]

Anyone with a history of anaphylaxis should receive education that includes allergen avoidance, early and appropriate recognition of the signs and symptoms of anaphylactic reaction with appropriate referral to a consulting allergist.[1,15] An epinephrine autoinjector should always be prescribed with education around its proper use and technique. A possible exception to the prescription of an epinephrine autoinjector is if the known trigger was a medication, in which case deferral of this prescription may be possible pending allergy evaluation.[15] A medical alert band is strongly advised in medication-induced anaphylaxis.

Antihistamines (AH1) are often erroneously used in place of epinephrine in the treatment of anaphylaxis. Their role remains as second or third-line therapeutic options in anaphylaxis guidelines.[23] Antihistamines do not relieve upper or lower airway obstruction, shock or hypotension and their onset of action ranges from 1-3 hours.[1] Early AH1 use often delays the use of epinephrine, which is associated with increased risk of anaphylaxis fatality.[24] In addition, there are significant safety concerns with the use of first-generation sedating antihistamines (such as diphenhydramine) which can be associated with somnolence, sedation, or a paradoxical stimulatory response in children.[25] This effect may actually mask worsening anaphylaxis, which can be associated with central nervous system effects.[1] In adolescents and adults, first generation antihistamines have been associated with poor sleep quality, decreased school and work performance, automobile and boat accidents, cardiac toxicity, and are known drugs of abuse.[26] In contrast, second and third generation H1-antihistamines have much fewer adverse effects and a faster onset of action than first generation antihistamines.[26]

Antihistamines should never be used in place of epinephrine; if used as an adjunct therapy, non-sedating antihistamines are preferred to first-generation antihistamines. The Canadian Society of Allergy and Clinical Immunology notes that first-generation antihistamines should only be used if absolutely necessary in the treatment of allergic disease and have advocated to have them available only behind the counter in pharmacies.[26]

While oral corticosteroids are often prescribed, there is no evidence that their use prevents a biphasic reaction.[27,28] In fact, some studies suggest that oral steroids can actually increase risk. The Cross-Canada Anaphylaxis Registry found that pre-hospital corticosteroid treatment was associated with an increased risk of intensive care unit/hospital ward admission after adjusting for reaction severity, treatment with epinephrine, sex, age and comorbidities.[29] In this study, a total of 3498 cases of anaphylaxis, of which 80.3% were children, presented to 9 EDs across Canada. Pre-hospital treatment with epinephrine was administered in 31% of cases, whereas antihistamines and corticosteroids were used in 46% and 2% of cases, respectively. Admission to the intensive care unit/hospital ward was associated with pre-hospital treatment with corticosteroids (adjusted odds ratio, 2.84; 95% confidence interval [CI], 1.55, 6.97). In addition, even short-term use of oral steroids can have detrimental effects in children including vomiting, sleep disturbances and behavioral changes as evidenced by a systematic review involving thirty-eight studies of which 22 randomised controlled trials (RCTs) met the inclusion criteria. The studies involved a total of 3,200 children in whom 850 ADRs were reported.[30] Recent 2020 guidance from the Joint Task Force on anaphylaxis management recommend against the use of corticosteroids to prevent biphasic anaphylaxis.[15]

MANAGEMENT OF ANAPHYLAXIS DURING COVID-19

COVID-19 and its impact on healthcare resources, as well as the reallocation of medical services has resulted in changes to care across medicine as a whole, including the management of allergy care such as anaphylaxis.[31] Prior to COVID-19, if an epinephrine autoinjector was used for treatment of anaphylaxis, it was commonly recommended that emergency medical services (EMS) be activated, with the patient transported to the hospital to be monitored in the case of a biphasic reaction.[32,33] During COVID-19, an alternative approach has been outlined which involves at-home monitoring (instead of reflex EMS activation) with epinephrine use.[34] Based on this approach, epinephrine would be administered in the case of a severe allergic reaction, with patients then monitored at home for treatment response.[34] If symptoms resolve, their healthcare provider would be notified non-urgently for routine follow-up. If symptoms either persist or worsen a second dose of epinephrine should be injected and EMS activated. At-home monitoring would only be recommended in those who have a clear understanding of anaphylaxis monitoring, who have at least 2 epinephrine autoinjectors available with good control of comorbidities such as asthma.[34] A review of this alternative approach will be needed to assess outcomes and any adverse reactions and/or delayed access to further anaphylactic care. The decision to monitor at home should only be made in the context of shared decision making, between the healthcare team, patients and their families with agreement of the risks and benefits of this approach.[35] Immediate EMS activation would remain available if there is concern of any further allergy symptoms or lack of familial comfort.[35] A revised anaphylaxis algorithm has been developed that incorporates this at-home monitoring approach during COVID-19 (**Figure 1**).[34]

It has been posited that while this recommendation was designed specifically in the context of COVID-19, and the need to reduce risk of contracting COVID-19 in the ED as well as to reduce the burden on healthcare resources, there may be reason to consider this approach after the pandemic.[35] The rationale for this is multifactorial. Firstly, the requirement for EMS activation has been shown to be a barrier to using an epinephrine autoinjector among families of children with food allergy.[36] Second of all, the practice of automatic EMS activation has not been shown to reduce fatality due to anaphylaxis (only early use of epinephrine has been shown to do that).[35] Finally, the practice of automatic EMS activation has not been shown to be cost-effective (unless there was a very high risk of fatality with the majority of children requiring other additional care while in the ED).[37]

CONCLUSION

While anaphylaxis is relatively common, fatality due to anaphylaxis is exceptionally rare. Epinephrine is uniformly recommended as first-line therapy for the treatment of anaphylaxis. While antihistamines are often used in place of epinephrine they have a secondary or tertiary role in the acute management of anaphylaxis. Antihistamines used as adjunct therapy for cutaneous symptoms, should be from second- or third-generation non-sedating antihistamine categories over first generation antihistamines due to safety profile. While oral steroids are often prescribed to prevent biphasic anaphylaxis evidence is lacking for this approach. Finally, with the impact of the COVID-19 pandemic, recommendations for anaphylaxis management suggest at home epinephrine auto-injector use, and monitoring without reflex EMS activation unless poor response to epinephrine is encountered. The practice of EMS activation has not proven to be cost-effective and may serve as a barrier to epinephrine use. Analysis and data capture of this "at home" modified anaphylaxis treatment plan may result in the long-term reassessment of the management of anaphylaxis in the post-pandemic era as well.

Revised Anaphylaxis Management Algorithm During COVID Pandemic

To be implemented based on the local risk / benefit assessment

Patients with history of severe anaphylaxis such as those who have been intubated and ventilated, or had reactions treated with more than two doses of epinephrine should follow their routine anaphylaxis plan and activate emergency services immediately when anaphylaxis is recognized.

IMPORTANT REMINDER: Anaphylaxis is a potentially life-threatening, severe allergic reaction.
If in doubt, give epinephrine.

SEVERE SYMPTOMS: any of the following

LUNG
Shortness of breath
Wheezing, repetitive cough

HEART
Pale or bluish skin, faintness, weak pulse, dizziness

GUT
Repetitive vomiting, severe diarrhea

THROAT
Tight or hoarse throat, trouble breathing or swallowing

SKIN
Many hives over body, widespread redness

MOUTH
Significant swelling of the tongue or lips

OTHER
Feeling something bad is about to happen, anxiety, confusion

Mild symptoms from <u>more than one</u> system area:
Itchy runny nose, sneezing and/or Itchy mouth and/or few hives, mild itch and /or mild nausea or discomfort

1. INJECT EPINEPHRINE IMMEDIATELY
while seated; have telephone within reach

2. **Notify a housemate or neighbor to help you**
3. **Lay down with legs elevated near the doorway, which should be unlocked or open to allow others to enter and help. Keep children in a position of comfort, to minimize respiratory distress and agitation and risk of aspiration in case of vomiting.**
4. **Administer oral antihistamine, preferably non-sedating (e.g. cetirizine)**
5. **Administer albuterol for respiratory symptoms if prescribed and available**
6. **Monitor symptoms and blood pressure/pulse if possible**

SYMPTOMS DON'T IMPROVE OR WORSEN

Repeat epinephrine injection in 5 minutes or sooner if symptoms escalate rapidly

SEVERE SYMPTOMS DON'T IMPROVE OR WORSEN

Activate Emergency Services *(Call 911)*

SEVERE SYMPTOMS RESOLVE

Continue to monitor for 4-6 hours for the recurrence of symptoms

Be ready to administer treatment if symptoms reappear (biphasic anaphylaxis)

Notify your physician on a non-urgent basis

Replenish emergency medications

Figure 1. Revised anaphylaxis algorithm replacing the standard management protocol during the COVID-19 pandemic ; adapted from Casale et al, 2020

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INSECT STING HYPERSENSITIVITY

As spring and summer approach and people look to spend more time engaged in outdoor activities, it is timely that we discuss insect sting hypersensitivity. Patients with previous allergic reactions to insect stings are especially nervous. Most importantly, patients with mast cell disorder are at risk of future life-threatening reactions from insect stings. It is critical that clinicians are able to provide information about available treatment options. This review will discuss the approach to the diagnosis and treatment of insect sting hypersensitivity.

ADVERSE REACTION TO STING INSECTS

There are fundamentally two types of IgE-mediated reactions to insect stings. The first type is the large local reaction (LLR) which is defined by swelling contiguous to the site of the sting. This swelling increases in size over the following 24 to 48 hour period and resolves 3 to 10 days later.[1] There is no universal definition of a LLR, however, the swelling can be larger than 10 cm in diameter around the sting site and can affect the entire extremity. This local reaction may lead to lymphangitis, often confused with cellulitis. It can be differentiated from cellulitis by its early onset (after 1-2 days) and also by the absence of fever or other markers of infections, such as an increase in WBC or neutrophilia. The risk of a systemic reaction in patients who experience a large local reaction is less than 10%.[1] In general, a LLR is not dangerous but may lead to significant impact to local tissue from local swelling. The exception to this is an unfortunate sting occurring accidentally in the oropharynx. A 30-year-old female who had a sting in her upper palate after drinking from a soda can where an insect was hidden ended up in the emergency room two hours later with significant swelling of the oropharynx with airway compromise from progressive swelling that extended to the oropharyngeal region.

Systemic reactions (SR) are characterized by any signs and symptoms distant from the initial sting site. These reactions can be further divided into cutaneous (CSR) and anaphylactic reactions. CSR usually present with generalized pruritus, flushing, urticaria and angioedema. These are commonly seen in children but uncommon in the adult population. Anaphylaxis involves different systems including the skin (urticaria, angioedema, flushing, and pruritis), gastrointestinal system (difficult or painful swallowing, nausea, vomiting, diarrhea, and abdominal cramps), respiratory system (bronchospasm, coughing, respiratory distress, upper and lower obstruction), cardiovascular system (hypotension) and sometimes neurological symptoms (loss of consciousness, etc.). The cardiovascular and respiratory symptoms constitute both a serious and potentially life threatening event for the patient. The onset of SR is usually seen within 20 minutes in 75% of patients and within 40 minutes in 87% of insect sting anaphylaxis. Laryngeal edema and circulatory failure are the most common causes of death from an insect sting anaphylaxis reaction and half of the fatal reactions occur in people with no prior history of systemic reaction to a stinging insect.[1,2]

CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE[1]

Recommendation Rating Scale

Category of Evidence

- Ia Evidence from meta-analysis of randomized controlled trials
- Ib Evidence from at least one randomized controlled trial
- IIa Evidence from at least one controlled study without randomization
- IIb Evidence from at least one other type of quasi-experimental study
- III Evidence from non-experimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of Recommendation

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- LB Laboratory Based
- NR Not rated

NATURAL HISTORY

The importance of defining the type of allergic reaction is paramount in insect sting reactions. The history of the reaction will allow for a proper diagnosis and clear approach to patient counselling about their risk of future reactions.

There are people in the community who have asymptomatic sensitization and their risk of future SR is low (estimated at 5-15%). Unfortunately, there is no diagnostic test that can predict future reactions in this population other than baseline serum tryptase. It should be noted that high serum tryptase levels have prognostic implications, with higher risk for SR to stinging insects in future and failure to respond to venom immunotherapy (VIT).[1] As a result, it is not recommended to perform any investigation in those patients without a history of reaction.[3]

Patients with a history of LLR have a risk of systemic reaction of approximately 4-15% if re-stung and some of these reactions can be severe.[4]

In patients with a history of SRs, the risk of future anaphylaxis to stings is 40-60%. The severity of the reaction will depend on the severity of the previous reaction. Among those who have had a severe reaction, the risk of having a future severe reaction is increased.[5] Among patients with a history of CSR, there is an approximate 10% risk of future SR and a 3% chance of a more severe reaction.[5]

The risk of future SR is associated with elevated tryptase levels, use of antihypertensive medications (i.e. ACE inhibitors), increased age, beekeeper occupation, and multiple stings or sequential stings (within weeks or months of each other). One other issue that clinicians may encounter in clinical practice is the degree of sensitivity (skin test or specific serum IgE) which correlates with the frequency of reaction rather than severity. This is important as many patients believe that the larger the skin test size, the greater the likelihood of a more severe reaction.[3]

PREVENTION OF INSECT STING REACTION/ALLERGIC REACTION

There are effective measures that have been recommended for patients with a history of SR (**recommendation: D evidence**):

1. Measures to avoid insect stings[2]
   a. Minimize preparing, grilling or eating outdoors
   b. Minimize flowering plants
   c. Minimize drinking from straws, cans or bottles when outdoors
   d. Remove fallen fruits near lounging areas
   e. Cover trashcans
   f. Watch for nests in bushes or in the ground when mowing
   g. Avoid walking barefoot (**recommendation: D evidence**)

2. Discuss the need to have access to an epinephrine autoinjector with education on its indication and its use (**strong recommendation: C evidence**)

3. Referral for evaluation by an allergist/immunologist for diagnosis and long-term therapy. (**strong evidence: D evidence**)

One of the important discussions to have with patients is the use of an epinephrine autoinjector. When counselling patients, it is important to focus on why and when the autoinjector should be available. Although this is prudent in high-risk patients for future reactions, there is also a burden to the patient such as inconvenience, cost and fear of use that accompany the epinephrine prescription.[6] From anecdotal experience, patients with a history of insect sting anaphylaxis who are undergoing VIT have a better quality of life in comparison to those who carry an epinephrine autoinjector. For patients with a history of large local reactions or CSR, the risk of a systemic/anaphylactic reaction is low, and it is important to discuss their low risk of anaphylaxis with them so that they can make an informed decision about whether carrying an epinephrine autoinjector is needed for personal security.

WHO NEEDS VENOM IMMUNOTHERAPY?

One of the only types of anaphylaxis for which VIT has been proven highly effective is insect sting anaphylaxis. The indication for VIT is a history of insect sting anaphylaxis plus evidence of an allergy by way of either positive intradermal venom test or the presence of venom-specific IgE. Clinicians are reminded that positive intradermal testing does not predict severity of future sting reactions. The consulting allergist is often asked to investigate patients who have family members with serious or fatal reactions to stings. There is no current evidence of increased risk of insect sting allergy (ISA) in first degree family members of these patients. Moreover, testing family members without history of insect stings may lead to increased anxiety and negative impact on their quality of life. For patients with CSR and LLRs, venom immunotherapy is not indicated as the risk of a more severe anaphylactic reaction remains low. However, among those with frequent exposures and reactions leading to poorer quality of life, VIT may result in a decrease in local swelling yielding benefit for the affected patient.

Among those patients who have a remote history of severe SR, the relative risk of these patients does not decline over time. In children who did not receive VIT, systemic reactions can occur within 20 years if re-stung.[7] This important point suggests that a re-assessment of venom allergy status is needed with the possibility of VIT.

The detection of specific IgE antibodies in serum is less sensitive than skin testing. However, in situations where venom skin testing is not an option i.e., severe atopic dermatitis or due to chronic concurrent medication usage (antihistamines), serum specific IgE-testing may be the only way of assessing allergy status. Ultimately, the patient's clinical history remains the basis for guiding and informing the best treatment practice. Alternatively, there are many factors that may lead to a person having a negative skin test despite a positive history. These factors include systemic diseases such as mastocytosis. Mastocytosis presents with severe systemic allergic reactions and increased serum tryptase levels. Patients with mastocytosis have demonstrated an increased risk of future severe anaphylactic reactions, including during desensitization to VIT injection. As a result, these patients are at risk of treatment failure, and/or increased relapse rate if VIT is stopped. Mastocytosis may present in up to 2% of patients with insect sting anaphylaxis.[1] Clinicians should consider measuring serum tryptase levels in patients who have had a severe life-threatening reaction, hypotension as well as those with a negative allergy skin test (positive history).[1]

VENOM IMMUNOTHERAPY AND EPINEPHRINE AUTOINJECTOR

VIT significantly reduces the risk of future SR by greater than 95% among those individuals sensitized. After diagnostic confirmation of ISA, VIT should be recommended. VIT to the honeybee, yellow jacket, hornet, and wasp is an extremely effective approach for those patients with SR to a sting. It reduces the risk of subsequent sting anaphylaxis from 60%

in the untreated population to less than 5% in treated patients.[1] These patients should naturally be informed of the goal of the treatment which is to prevent a severe anaphylactic reaction. Secondary goals of reduction of anxiety around insect sting reactions is also achieved.[1] These patients should continue to have an epinephrine autoinjector available.

Among individuals who have a low risk of systemic anaphylactic reaction, such as those with a LLR or CSR where the risk of anaphylaxis remains less than 5% with re-stings, the clinical conundrum centers on whether these patients need VIT. Sometimes this decision can be confusing for patients in whom venom immunotherapy is not recommended but to whom access to an epinephrine autoinjector is provided. Prescribing an epinephrine autoinjector can cause impairment in the patient's quality of life[7] and this situation may be better addressed with discussion using a shared decision making model which involves both the patient and their family.

The current recommendation for the duration of the VIT is 3-5 years (**strong recommendation; B evidence**). However, there are risk factors that may necessitate the need for VIT to be considered lifelong therapy such as in those patients with a severe reaction before VIT (severe respiratory distress, hypotension, or syncope, etc.), systemic reaction during the VIT, honeybee allergy and increased serum tryptase level (**strong recommendation; C evidence**).[1]

Allergic reactions to insect stings can be life-threatening and negatively impact the lives of those individuals affected. It is crucial that we remember the importance of shared decision making with patients and their families and offer VIT in those individuals found to be at high risk of systemic allergic reactions. VIT is an effective treatment to reduce the future risk of having a severe life-threatening anaphylactic reaction. Helping patients venture outside their homes is an important quality of life improvement that allergists can offer to their patients. Insect sting hypersensitivity causes a great deal of anxiety and helping patients overcome it can be tremendously rewarding.

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AMOXICILLIN ALLERGY: OLD CONCEPTS, NEW CONCEPTS AND CHANGE OF CONCEPTS

BACKGROUND

More than one million Canadian children are treated annually with antibiotics, mainly amoxicillin.[1-4] Up to 10% of children develop rashes while treated with amoxicillin.[1-5] The majority of children presenting with rashes during amoxicillin treatment are diagnosed with amoxicillin hypersensitivity without further evaluation and often carry this diagnosis into adulthood .[1]

There remains controversy in the medical literature regarding the most accurate and safe strategy for diagnosing amoxicillin hypersensitivity.[1,5,10-13] As a result, most children continue to avoid amoxicillin and other penicillin derivatives throughout life in favor of alternatives that are reported to be less effective, more toxic, and more expensive.[12-16]

There is much we do not know about the pathogenesis of amoxicillin hypersensitivity. Consequently, the appropriate diagnostic strategy required to establish the presence of true amoxicillin hypersensitivity is unclear. In order to develop an appropriate diagnostic approach, it is important to understand the pathogenic mechanisms accounting for amoxicillin hypersensitivity and the validity of the available confirmatory tests. This review will discuss the pathogenic mechanisms underlying amoxicillin allergy, describe the challenges in the diagnosis of amoxicillin allergy, critically assess the role of skin testing and IgE levels and discuss the appropriate diagnostic strategy in individuals presenting with suspected amoxicillin allergy.

A.THE PATHOGENESIS OF AMOXICILLIN ALLERGY

Until recently, it was believed that all immediate reactions to amoxicillin were IgE mediated. However, recent studies suggest that other mechanisms related to allotype interactions between the drug and specific HLA molecules play a major role in both immediate (occurring within one hour of exposure) and non-immediate reactions (occurring more than one hour after exposure)[10] to amoxicillin.

The term "drug allergy" refers to a specific immune response to a drug acting as hapten, and is directed against a hapten-carrier complex, which functions as an

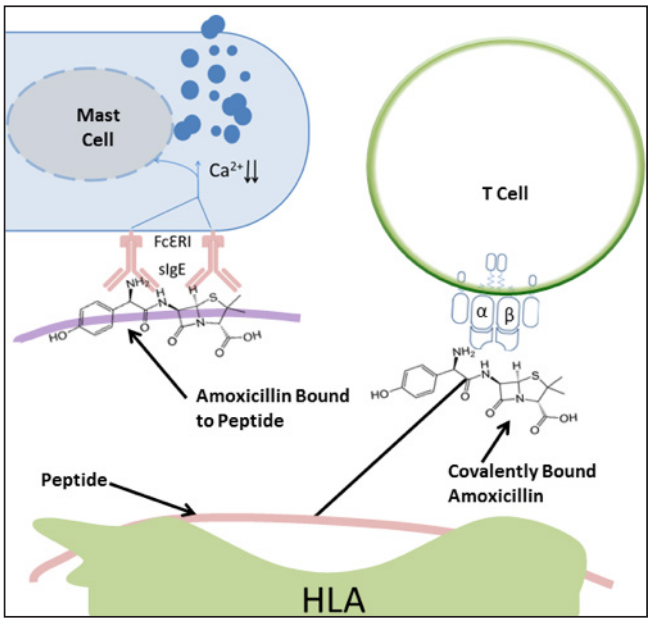

Figure 1. Drug hypersensitivity as a result of covalent binding of drugs to proteins ; courtesy of Moshe Ben-Shoshan, MD

allergen. In contrast, the term drug hypersensitivity (DH) goes beyond drug allergy. It includes, in addition to the aforementioned allergy definition, reactions of immune or inflammatory cells, which are not due to a hapten-protein antigen. Studies suggest three main forms of DH:[17]

The first form of hypersensitivity relies on the covalent binding of drugs to proteins, which then form new antigens, to which a humoral and/or cellular immune response can develop that will cause DH in subsequent exposure (**Figure 1**). This pathogenic mechanism has led to a reliance on skin tests with major and minor penicillin allergens for the diagnosis of amoxicillin allergy. However, given that at least 50% of DH to amoxicillin is reported to occur with the first exposure[5] and given that tests relying on the detection of specific humoral and/or cellular immune responses to amoxicillin are negative in most cases of amoxicillin associated DH, this mechanism is unlikely to play a major role in the majority of cases with amoxicillin DH.[5]

The second form of DH ("pseudo-allergy") is represented by drug interactions with receptors of inflammatory cells, which may lead to their direct activation or enhanced levels of inflammatory products (**Figure 2**).[20] Specific IgE or T cells are not involved.[10] Given that these reactions usually involve drugs containing tertiary and quaternary ammonium structures (present in quinolones e.g. but not in amoxicillin) binding to the G-protein-coupled receptor X2 (MRGPRX2),[20] amoxicillin hypersensitivity reactions are unlikely mediated by this pathway.

Finally, the p-i (pharmacological interaction with immune receptor) concept represents an off-target activity of drugs with immune receptors (HLA or TCR), which can result in unorthodox, alloimmune-like stimulations of T cells that will lead to immediate/ non-immediate DH reactions even upon first exposure. Some of these p-i stimulations occur only in carriers of certain HLA alleles and can result in clinically severe reactions (**Figure 3**).

Recent studies suggest that amoxicillin related hypersensitivity reactions are mainly related to the third form of DH reactions.[17] In these cases drug-dependent but not necessarily antigen-dependent stimulation of immune competent cells like T cells and/or inflammatory cells by drugs occurs.[18] This premise, although not well established yet for amoxicillin, is supported by several studies for beta lactam antibiotics in adults as well as for other drugs.[17] Drug-naïve patients (almost 50% of children reacting in some cohorts[5]) often react with hypersensitivity reactions to amoxicillin, an unlikely phenomena according to the Gell and Coombs classification (form 1).[5] In addition, limited data reported for drugs including beta lactams in adults, suggest that it is possible to predict drug hypersensitivity through the identification of a patient's specific genetic HLA markers.[17,19,20]

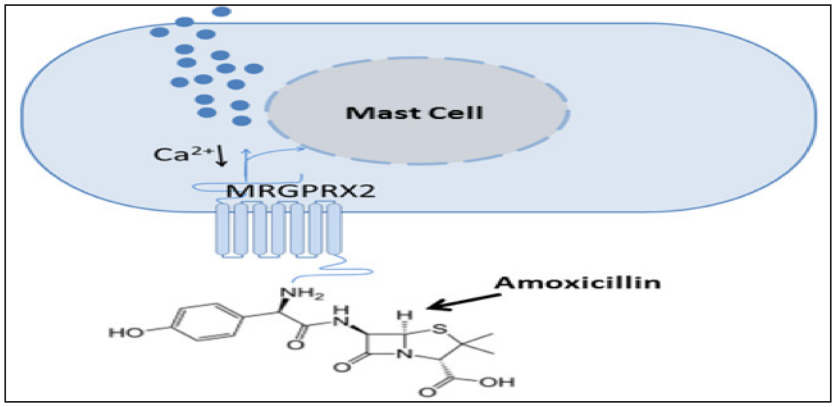

Figure 2. Drug hypersensitivity as a result of drug interactions with receptors of inflammatory cells; courtesy of Moshe Ben-Shoshan, MD

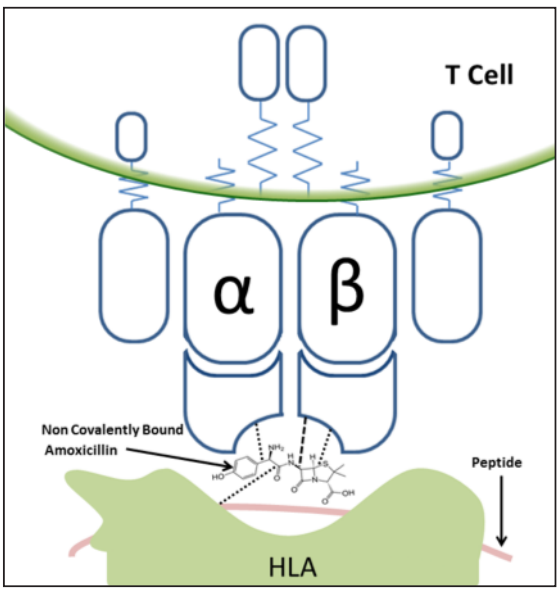

Figure 3. Drug hypersensitivity as a result of pharmacological interaction with immune receptors; courtesy of Moshe Ben-Shoshan, MD

B. CLINICAL FEATURES OF AMOXICILLIN ALLERGY

Studies reveal that immediate reactions to amoxicillin – defined most often as reactions occurring within the first hour after exposure-- as well as non-immediate reactions usually present with cutaneous symptoms only. These symptoms may include hives, macular / papular rashes as well as serum sickness-like reactions (SSLRs) (**Figures 1A, B and C**).[5,22] It is noteworthy that studies suggest that patients' self-reported history has low accuracy and concordance with an actual diagnosis of penicillin allergy.[23]

Benign reactions are limited to the skin, present often as maculopapular exanthemas/ urticaria and do not involve mucosal surfaces, or blisters. SSLR is characterized by large erythematous urticarial plaques with dusky to ecchymotic centers, often associated with hand and foot swelling that develop 7 to 21 days after medication exposure.[24] In addition to the characteristic cutaneous manifestations, patients with SSLRs are reported to have fever, malaise, lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, myalgias, headaches and self-limiting symmetric arthritis.[24] Similarly, in rare cases, viral infections can be associated with a similar rash called urticaria multiforme.[25] Although SSLRs have the important property of benignity, until recently it has been recommended to avoid amoxicillin in any suspected

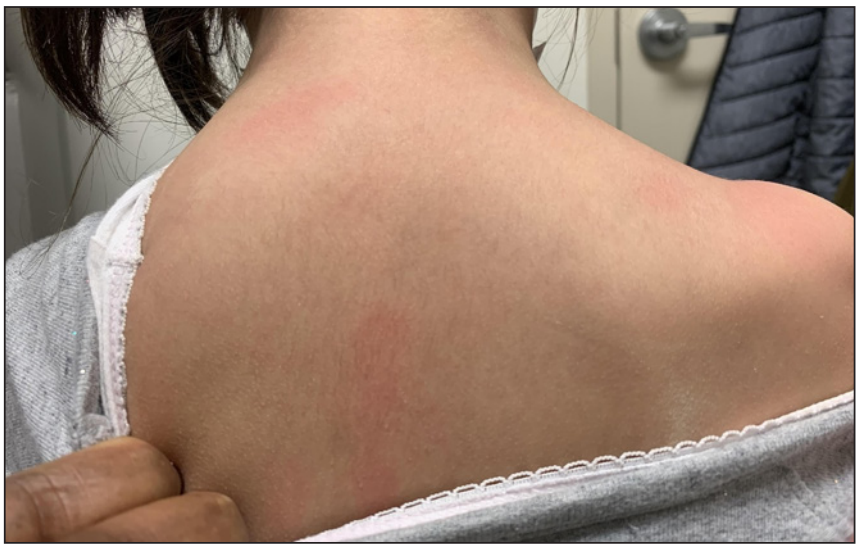

Figure 1A. Immediate reaction to amoxicillin in a 6-year-old girl within 15 minutes of amoxicillin challenge; photo courtesy of Moshe Ben-Shoshan, MD

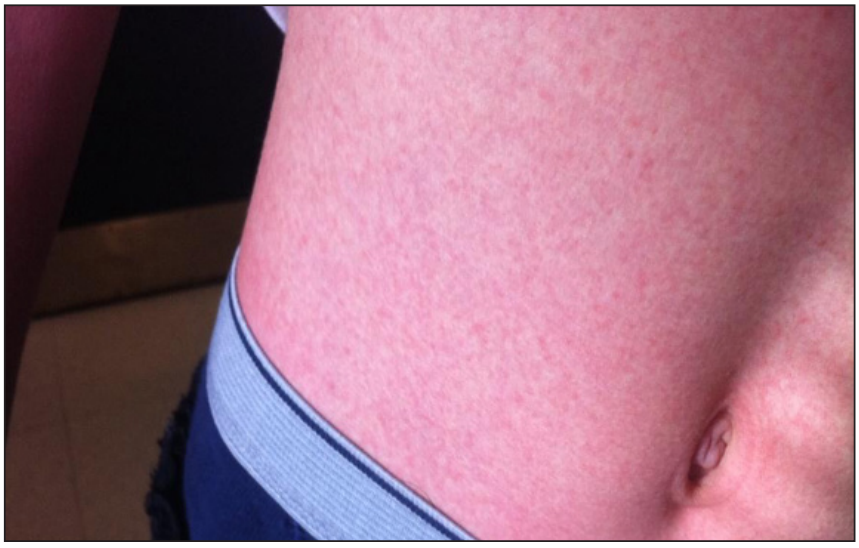

Figure 1B. Non-immediate reaction to amoxicillin in a 17-year-old boy 8 hours after amoxicillin challenge; photo courtesy of Moshe Ben-Shoshan, MD

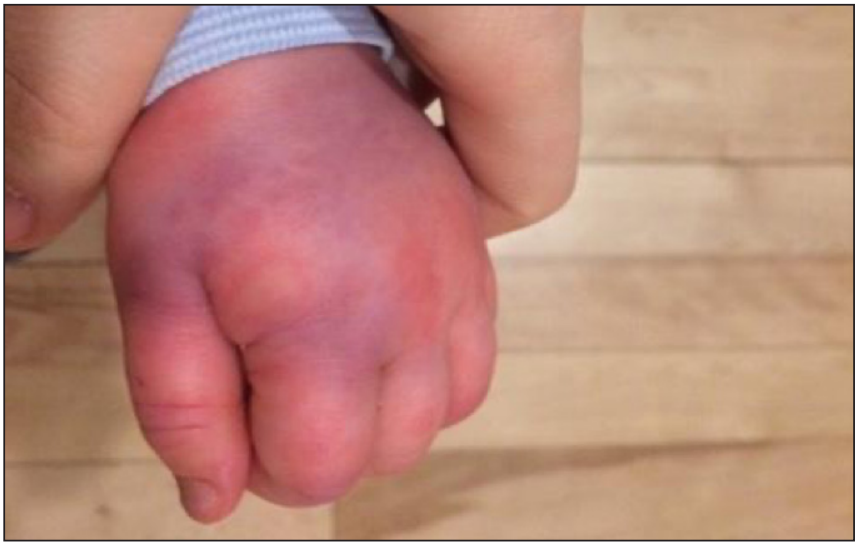

Figure 1C. SSLR in an 8-month-old baby after 7 days of amoxicillin treatment (photo exemplifies hemorrhagic lesions and swelling of wrist); photo courtesy of Moshe Ben-Shoshan, MD

case of SSLR without further investigation. More recently, however, the literature has shown that a dose provocation test (DPT) can be safely used in children (n=75, median age= 2.0 years) presenting with suspected SSLR. Investigators were able to demonstrate that positive immediate reaction to the DPT occurred in 2.67% of subjects, a positive non-immediate reaction to the DPT occurred in 4%, and of the 43 patients successfully contacted, 20 reported subsequent culprit antibiotic with 25% of these subjects experiencing reactions that were mild and limited to the skin.[22]

More rarely, reactions to amoxicillin may present as anaphylaxis when at least two organ systems or hypotension are involved in the hypersensitivity reaction.[26] Although these cases represent an important entity, they are rarely appropriately diagnosed. In a study conducted by our group, we reported that the majority of adult and pediatric cases presenting to the emergency room with suspected antibiotic-associated anaphylaxis, were not appropriately diagnosed. Of the 18 (40%) children that presented to the emergency room, only 10 (55.5%) patients had seen an allergist for assessment. Of these ten children, seven underwent skin testing, of which one was positive to ceftriaxone by intradermal skin testing. Among the six with a negative skin test, two proceeded to a graded oral challenge, which was positive in one case to amoxicillin (mild cutaneous reaction). For adults with suspected antibiotic associated anaphylaxis, only 33.3% had been assessed by an allergist. Of these patients only one patient underwent skin testing which was negative, and that same patient underwent a graded oral challenge which was positive to cefadroxil (mild cutaneous reaction).[27] Other rare presentations include Stevens-Johnson syndrome, and toxic epidermal necrolysis.[28] In these cases, the future use of amoxicillin should be **avoided**, and a diagnosis should be made based on the clinical presentation. Some studies suggest that the use of a skin biopsy can confirm the clinical diagnosis and delayed hypersensitivity tests, especially the patch test and the lymphoblastic transformation test (LTT)[29] may be important in validating the etiological diagnosis, although their validity is not well established.

Fatality related to amoxicillin allergy is extremely rare. The risk of fatal anaphylaxis with penicillin has previously been estimated to be about 1 in 100,000 and is greater in those receiving penicillin parenterally than orally.

Various risk factors have been hypothesized to increase the risk of amoxicillin hypersensitivity. Limited data in adults suggest that beta lactam allergy is more common in females.[31,32] Certain co-morbid conditions including immunosuppression and cystic fibrosis are reported to increase the risk of true amoxicillin hypersensitivity.[12] Other factors include previous exposure to the implicated medication, prolonged dose and duration of the implicated medication, route of administration (with parenteral and cutaneous routes more sensitizing),[33] and concurrent viral infection (up to 100% of children and adolescents with Epstein-Barr virus with rash if on amoxicillin).[34] However, the effect of these factors has not yet been established in children to date.

C. LIMITATIONS OF CURRENTLY USED STRATEGIES TO DIAGNOSE AMOXICILLIN HYPERSENSITIVITY

The diagnosis of amoxicillin hypersensitivity is challenging. The traditional approach relies on intradermal skin tests and, if negative, a drug challenge is recommended. The validity of a test is defined as its ability to distinguish between those who have a disease and those who do not.[35] Thus, the validity of such an approach is best judged based on studies assessing the sensitivity and specificity of the skin test compared to the gold standard test (i.e. drug challenge). A critical appraisal of the few studies challenging all cases with suspected drug allergy reveals that the validity of available skin tests is, at best, questionable.[5,36] Recent studies[5,36,37] underscore that available standardized skin tests (skin prick and intra-dermal tests with Pre-Pen, or penicillin G) for children have a limited role

in the diagnosis of immediate reactions to penicillin derivatives with a sensitivity of less than 10% and positive predictive value of 30%.[5,36,37] Moreover, it was concluded that skin tests may result in a false positive rate in up to 80% of pediatric cases who tolerate the culprit beta lactam antibiotic when challenged.[36] In addition, skin tests have no role in the diagnosis of non-immediate reactions[38,39] and for non-penicillin beta-lactam antibiotics where there are no standardized skin tests.[40]

Recently a new kit for penicillin evaluation containing the major allergenic determinant (penicilloyl polylysine), a minor determinant mixture (penicillin G, penicilloate, penilloate), and amoxicillin was reported to have a negative predictive value of 98%.[41] The interesting aspect about positive and negative predictive values is that they change when the prevalence of the disease changes. In fact, for any diagnostic test, the positive predictive value will fall as the prevalence of the disease falls while the negative predictive value will rise.[42]

A low prevalence simply means that the person we are testing is unlikely to have the disease and therefore, based on this fact alone, a negative test result is likely to be correct.[42] Two recent systematic reviews report a positive predictive value of skin tests in children of 33%,[43,44] leading to a high rate of inaccurate diagnosis and the risk of mislabelling.

D.USE OF DIRECT DRUG PROVOCATION TEST

Although a DPT is considered the gold standard for diagnosis,[39] it has been rarely used in practice, owing to a lack of data regarding its safety and accuracy in children. Prior to 2016 it was considered unethical to challenge children with a suspected antibiotic allergy in the absence of skin tests. However, recent studies[5,22,36,40] reveal that in children this approach is safe and ethically acceptable in cases of non-severe reactions limited to the skin[45] including SSLRs.[22] Moreover, given that skin tests are negative in more than 95% of cases, an oral challenge is ultimately needed to confirm tolerance in most of these children.[5,22,36,40] Positive challenges are rare, and even where children have reproducible signs on challenge, they rarely constitute immediate or serious symptoms.[5,22,36,40]

A DPT may be conducted in one or two-step doses (10% of the therapeutic dose, then 20 minutes later 90% of the therapeutic dose). We have shown that among children with immediate reactions undergoing a two-step challenge, almost one third reacted within 20 minutes after the first dose and that among those who had a non-immediate reaction (defined as more than one hour after the challenge), almost a third reacted more than 24 hours after the challenge (up to five days). All reactions were classified as mild.[5] Hence, it is recommended to follow patients one week after a negative DPT to document potential late reactions. Challenges should be conducted only in the allergy clinic in the presence of an allergist and/or health care providers that are trained and have the required equipment to treat adverse reactions. Following a DPT, observation time should be at least one hour with DPT over a longer time interval, such as five to seven days having also been suggested.[46] However, a lengthier challenge also exposes patients to the risk of bacterial antibiotic resistance development, making subsequent use of antibiotics ineffective.[47] Furthermore, recent studies suggest a lack of value for prolonged challenge in cases with suspected antibiotic allergy[48] and indicate that the vast majority of cases of nonimmediate reactions may be captured by a one-day challenge.[49] It is also possible that in some cases the diagnosis of an antibiotic allergy in the context of infection could be related to the interaction between a viral infection and the antibiotic.[50-52] It should be noted that the negative predictive value of a DPT is reported to be 89% (49 out of 55) and 10% of cases (6 out of 55) with a negative DPT were reported to have developed mild skin reactions on subsequent future use.[5]

Most data regarding the use of DPT to diagnose amoxicillin/penicillin allergy are based on pediatric studies,[5,22,36] More

recently, a limited number of studies suggest that this approach may be used in adults presenting with benign skin rashes. In one study of 156 adults, 2.6% of subjects reacted to a DPT. Interestingly, almost 10% also reacted to placebo.[53] Similarly, in a small retrospective study of twenty adults with a history of benign rash, benign somatic symptoms, or unknown history associated with the last penicillin exposure of more than one year prior to assessment, none of the subjects developed immediate, or delayed hypersensitivity reactions.[54]

E. DEFINING LOW RISK PATIENTS

It is crucial to define low-risk patients for true amoxicillin sensitivity as these patients are more likely to benefit from a direct drug challenge approach. A multicenter study in Australia found that the optimal definition for low-risk penicillin allergy history in patients 16 years or older is a benign rash, either immediate or delayed, occurring at least one year prior to evaluation.[55] In another U.S. study, patients five years or older with a cutaneous-only or unknown reaction (>1 year for those aged 5-17 years; >10 years for those 18 years or older) were randomized 1:1 to skin tests or a 2-step direct challenge. All children younger than five years of age (n=13) underwent direct challenge, and patients with extra-cutaneous reaction histories underwent skin tests. This study concluded that in those subjects aged 5 to 17 years old, low-risk patients included those with cutaneous reactions only that occurred at least one year prior to evaluation, while in those that were 18 years and older, low-risk patients were those reporting with cutaneous reactions only that occurred at least ten years prior to assessment.[56] Finally, another Australian study developed a statistical model to help define low-risk criteria for direct amoxicillin challenges.[57] This study defined patients with a total score less than 3 as low-risk with a negative predictive value of 96%. The major criteria comprising this risk score included an allergy event occurring five or fewer years ago (2 points) and anaphylaxis/angioedema or SCAR (2 points); the minor criterion (1 point), included whether treatment was required for an allergy episode.[57]

F. CROSS-REACTIVITY

Beta lactam antibiotics belonging to the penicillin-class have an R1 side chain only. This R1 side chain is shared between penicillin and cephalosporin, as well as among cephalosporins and is thought to account for cross-reactivity based on a study demonstrating that structurally similar penicillins share IgE specificity.[58]

It has been reported that 2% of patients with positive reactions to multiple penicillin skin test reagents have sensitization to cephalosporins.[59] It has also been shown that patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, and cefatrizine) or receive them via rapid induction of drug tolerance.[60] It is noteworthy that cefazolin has a unique side chain and very low cross-reactivity with penicillin. There is no immunological or clinical cross-reactivity between penicillin and the monobactam aztreonam.[61]

There is evidence that allows for the safe use of all but a few early generation cephalosporins in patients with penicillin or amoxicillin allergy. Patients with a history of penicillin allergy generally have an elevated risk of allergic reaction and may develop an allergic response to cephalosporins by coincidence, but the risk is comparable to that of receiving a sulfonamide antibiotic.[61] Thus, the attributable risk of allergic cross-reactivity between penicillin and cephalosporins, for all but a few cephalosporins with similar side-chain structures to penicillin, is essentially nil.[61]

F. CONCLUSION

Improving the diagnosis of amoxicillin hypersensitivity in children and reducing the risk of mislabeling is crucial. Until recently, the recommended allergy work-up to explore suspected allergic reactions to amoxicillin in children was based on data from adults and included skin tests and, if negative, a DPT.[4] However, given that pediatric studies have demonstrated the sensitivity of skin tests to be poor, false positive rates to be high, the positive predictive value low, and given that most reactions occurring during DPTs are mild, there has been

a recent paradigm shift in the diagnostic algorithm for benign skin reactions in favor of a direct DPT. The situation may differ in adults who are at higher risk for reactions, although some studies report favorable results in adults as well with the use of DPT.[53] Based on the published evidence to date, a DPT can be used in pediatric cases presenting with cutaneous non-vesicular lesions while more studies are required to establish the best diagnostic strategy in adults.

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