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- When switching from IV treatment, begin HyQvia 1 to 2 weeks after the last IV dose. If patients were previously on a 3-week dosing regimen, increasing the interval to 4 weeks can be accomplished by administering the same weekly equivalents.

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†Please see the Product Monograph for complete dosing and administration instructions.

‡Please see the Product Monograph for full information on adverse events.

Reference: Takeda Canada Inc. HYQVIA (Normal Immunoglobulin [Human] 10% and Recombinant Human Hyaluronidase) Product Monograph. Revised December 9, 2022.

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HyQvia
Human Normal Immunoglobulin (10%)
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PRMCDA/CA/HYQ/0004 APRIL 2023

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THE USE OF IVIG FOR ALLERGY CONSULTANTS

Introduction

IgG plays multiple roles in the immune system. Best known as an effector molecule in host defence, infusions of polyclonal IgG have been employed as the mainstay of treatment for patients with immunodeficiency diseases affecting the humoral immune system. IgG preparations are fractionated from pools of several hundred to several thousand donors or more[1] and therefore contain a broad spectrum of antibodies, capable of providing protection against many bacterial and viral diseases. Preparations of human IgG are available for intravenous (IVIG) or subcutaneous (SCIG) administration, allowing individuals with both primary and secondary immune defects to have significantly fewer infections, decreased hospitalizations and overall improved quality of life (QOL)[2]. Moreover, IVIG has been employed as a regulator of a large number of autoimmune and inflammatory conditions since the 1980s.[3]

IgG Replacement for Immune Deficiency

How do you choose who should receive immunoglobulin therapy? Is it simply a history of recurrent infections, such as frequent ear infections or pneumonia? Should all individuals with risk factors such as immune suppressive therapies, cancer treatments or hematologic malignancies be considered for immunoglobulin replacement? The scarcity of plasma for fractionation, exacerbated by the recent COVID-19 pandemic, led to shortages of raw materials for IVIG. This demands that practitioners carefully scrutinize the use of immunoglobulin replacement, and employ

caution not only in prescribing, but in over-rationing this essential therapy, to the detriment of patients with primary antibody immune deficiency.[4]

Physicians evaluating individuals who may potentially benefit from IVIG replacement therapy should take a systematic approach to their assessment **(Figure 1**). The patient's history is commonly that of an unusual number of sinopulmonary infections, but can also include unexplained severe infections including sepsis, meningitis, osteomyelitis, and unusual abscesses in the upper or lower respiratory tract. All suspected patients should have a complete blood count (CBC) performed, looking for deficiencies in total lymphocytes, as well as measurements of IgG, IgA, IgM and IgE. The key to this evaluation is the demonstration of poor production of IgG (<4.0 g/L), as well as impaired production of specific antibodies. This is most easily performed by measuring antibody levels against common vaccines, such as diphtheria, tetanus, pneumococcus, measles, mumps, rubella, or hepatitis A or B. If the initial vaccine antibody levels are low, a booster vaccine followed by a repeat blood sample drawn 28 days later will demonstrate if the subject has responded appropriately.[5] In addition to antibody levels, evaluation of total T and B lymphocytes can illuminate deficiencies in the antibody producing B-cells or defects in T-cells which contribute to combined immune deficiencies. Indeed, the evaluation can also include additional studies of B and T-cell memory, T-cell function, complement studies, and neutrophil studies as appropriate. It is important to remember two important caveats: first, if IgG is low, but response to booster vaccination is normal, the benefit of IgG replacement is very suspect and other causes of IgG loss should be evaluated; second, IgA deficiency alone is not an indication for IgG replacement.[2]

Secondary immune deficiencies are an increasingly important group of conditions that may require long-term IgG replacement therapy. Although there are numerous conditions that lead to secondary hypogammaglobulinemia, broad indications are hematologic malignancies including chronic lymphocytic leukemia (CLL) or multiple myeloma (MM), diseases that lead to protein or immunoglobulin loss, or medications that decrease antibody production. Recent practice guidelines have reviewed the approach to the diagnosis and treatment of secondary hypogammaglobulinemia.[6] In particular, it is important for practitioners to be aware of the long-term effects of anti-CD20 B-cell ablation therapies including rituximab and ocrelizumab.[7] Used extensively for rheumatologic, hematologic and neurologic conditions, the increased use of these highly effective therapies has led to long-term decreases in B lymphocytes, impaired antibody production and increased susceptibility to infections. This has been identified in 3%-15% of individuals treated with anti-CD20 therapies. It has been postulated that secondary immune deficiency following anti-CD20 therapies may be a sign that the autoimmune or inflammatory process was due to an underlying primary humoral immune defect that was completely unmasked by the anti-CD20 therapy. Therefore, guidelines from multiple societies have recommended at minimum to evaluate serum immunoglobulins prior to initiating anti-CD20 therapy. However, a strong argument can be made for evaluating B-cell numbers as well, prior to initiating therapy, to document pre-existing B-cell lymphopenia. Follow-up should include IgG, IgA and IgM levels 3-6 months and one year post-therapy to ensure they are at normal levels, with more frequent measurements if the patient is suffering from recurrent or severe infections. A summary of guidelines suggests IgG replacement therapy for IgG levels below 3 or 4g/L in the context of severe or recurrent infections[6] **(Figure 1).**

Antibody replacement therapy can be achieved with either IVIG or SCIG IgG therapy. These are both very effective and can be administered at home, in an infusion centre or in hospital. SCIG is generally prescribed at 100-150 mg/kg SC weekly, with the dose titrated based on IgG levels, the patient's clinical status and provincial guidelines. As replacement therapy in primary immunodeficient patients, IVIG is dosed at 400-800 mg/kg.[2] IVIG is generally prescribed every 3-4 weeks and is similarly adjusted based on the patient's clinical parameters (infection frequency, general status , etc.) and IgG trough levels obtained at 3-6-month intervals. As IVIG contains antibodies to diverse pathogens, the primary objective of low-dose replacement therapy is to prevent recurrent infections in primary immunodeficient patients or in patients with recurrent infections with secondary immunoglobulin deficiencies.

IgG Replacement for Autoimmune disorders

IVIG is employed as an effective treatment for many autoimmune and inflammatory disorders. This commonly entails doses 3-5-fold higher than those employed for immune deficiency, ranging from 1-2gm/kg. IVIG has been consistently and successfully used for numerous conditions, including immune thrombocytopenic purpura (ITP), Kawasaki Disease (KD), Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), systemic lupus erythematosus, dermatomyositis, and other autoimmune and neurologic disorders.[8] Indeed, the number of conditions for which IVIG is used "off label" outnumbers that of the conditions with regulatory approval.[9,10] This is due to the wide-ranging interaction of various components of IgG molecules with multiple targets in the immune system, including immune cells, epithelial cells, cytokines, and other soluble molecules including complement. Studies on IVIG in these conditions have uncovered naturally occurring regulatory molecules that represent a small percentage of pooled IVIG, such as anti-idiotype antibodies, fractions that have specific glycosylation, and other components.[3] A more complete discussion of the

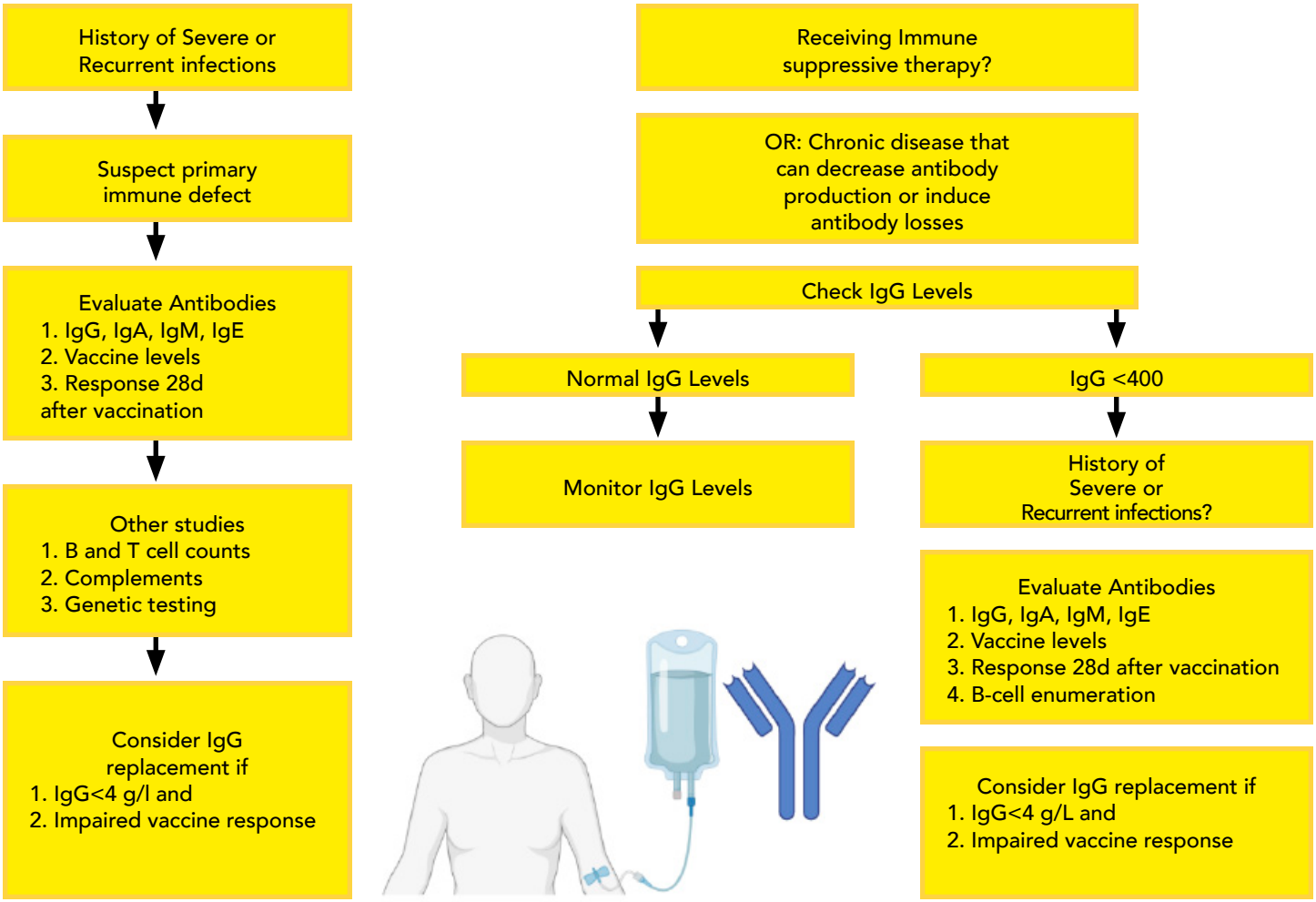

Figure 1: *Evaluation of primary and secondary antibody deficiencies; courtesy of Bruce Mazer, MD*

mechanism of action of IVIG in autoimmunity has recently been published.[11]

In individuals with inflammatory disorders on high-dose IVIG therapy, there is no clear IgG level that correlates with success; therefore, clinical scoring systems for patients with chronic diseases such as dermatomyositis[12] or neurological conditions are essential tools for monitoring therapy.

Safety of IVIG

The safety of IgG therapy is frequently questioned. It is, after all, a blood product derived from human plasma sources. How then can IgG products be made secure with relation to infectious viruses such as hepatitis and human immunodeficiency virus (HIV)? The procedure varies depending on the plasma fractionation facility or manufacturer; however, there are currently several very common steps that ensure product and patient safety.[13] Donors are screened and blood samples taken to ensure that signs of diseases such as transaminase levels are not elevated. All plasma is fractionated using cold ethanol in a process known as Cohn-Oncley fractionation. This step disrupts enveloped viruses such as HIV. However, a hepatitis outbreak in the 1990s led to important steps taken to ensure that non-enveloped viruses were deactivated or eliminated. Currently, virtually all plasma products undergo steps in which solvent-detergent is added, followed by other viral inhibitors, and finally nanofiltration.[14] These steps are highly effective in eliminating pathogens of concern and can even completely eliminate SARS-CoV-2 if it is present in the plasma of a donor.[14]

IVIG for the COVID-19 Virus

During the recent SARS-CoV-2 pandemic, clinicians showed extreme interest in antibody therapies that could mitigate the severity of acute COVID-19-related disease, particularly during the first waves of the pandemic when hospitalization was very common, particularly in the elderly. These treatments were shown to be highly instructive and provided insights into what antibodies can and cannot do in the setting of acute infections. Trials of hyperimmune plasma therapy (IgG infusions of plasma from patients recovering from severe SARS-CoV-2infection) were unsuccessful and, at times, worsened outcomes.[15] Similarly, IVIG infusions in hospitalized patients with severe COVID-19[16,17] were

not successful at altering the clinical course of the virus. Even Multi-systemic Inflammatory Syndrome of Children (MIS-C), which is highly analogous to Kawasaki Disease, was initially treated with IVIG; however, therapy has migrated to a combination of IVIG and corticosteroids or other biologic anti-inflammatory treatments.[18] Even monoclonal antibody agentsagainst SARS-CoV-2, while initially showing some promise, were unable to maintain pace with the changing landscape of COVID-19 variants and therefore had a very narrow window of usefulness.

The experience with COVID-19 has underscored some valuable teaching points regarding harnessing the power of IgG replacement therapy. First, although antibodies are an excellent first line of defence against bacterial and viral invaders, they have demonstrated greater efficacy in prevention than in treatment. As a result, vaccination or prophylactic infusion of an appropriate monoclonal antibody is generally more effective than antibody treatment in established disease. Second, IVIG therapy can only prevent COVID-19-related disease in individuals who require antibody supplementation when there was a high level of population immunity through vaccination and/or infection. This means there was a lag time between the acquisition of donor plasma and the appearance of relevant antibodies against SARS-CoV-2. IVIG varies in effectiveness depending on the variants in the community. Third, antibody levels to coronaviruses wane significantly within a short period of time vs other vaccine-preventable diseases.[19] This suggests that IVIG will have variable effectiveness for protection against SARS-CoV-2 and its variants, unless tailored COVID-19 vaccination becomes a regular feature of adult immunization programs.

Conclusion

IVIG remains an extremely useful tool and is the mainstay of treatment for individuals with impaired antibody production. It is essential for allergy and immunology clinicians to ensure that they thoroughly evaluate patients with frequent infections and initiate IVIG therapy for those patients with primary immune defects and the increasing population with secondary immune deficiencies. Moreover, while IVIG has had an excellent track record of both safety and efficacy, the COVID-19 pandemic has underscored several limitations of antibody therapy.

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Financial Disclosures:

None declared

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ALLERGIC CONJUNCTIVITIS: TREATMENT UPDATES AND LONG-TERM MONITORING

Introduction

Allergic conjunctival diseases have a significant impact on the ocular surface, affecting the conjunctiva, cornea, and eyelids. Estimates indicate that approximately 35% of North Americans are affected by these diseases.[1-5] Seasonal and perennial allergic conjunctivitis are the most common and mildest forms of ocular allergic disease, affecting 15–20% of the population.[4] lMore severe conditions of ocular allergenic diseases include atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis (GPC). This article will review allergic conjunctivitis classifications, ocular sequelae, and a simplified treatment algorithm.

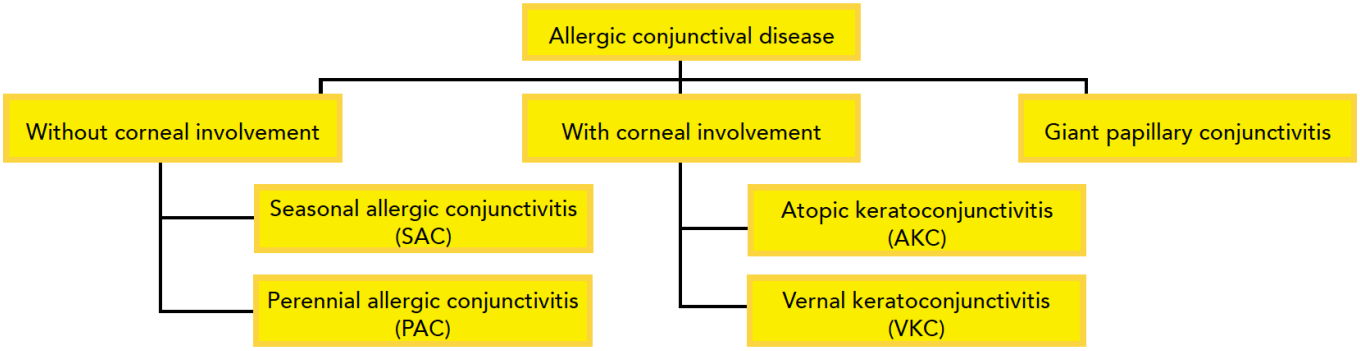


Figure 1. *Top Classification of allergic conjunctival diseases; courtesy of Clara C. Chan, MD and Caberry Yu, MD*

Classification

Seasonal allergic conjunctivitis (SAC), also known as hay fever conjunctivitis, is triggered by allergens from trees, grass, pollen, and weeds. Patients commonly have comorbid conditions such as asthma and allergic rhinitis.[5] Perennial allergic conjunctivitis (PAC) persists year-round, with animal dander, dust mites, and mould as typical allergens. Patients with SAC and PAC commonly present with symptoms such as tearing, clear discharge, and itching without corneal involvement **(Figure 1)**.

In contrast, patients with AKC, VKC and GPC experience more severe symptoms, which include pain, blurry vision, and foreign body sensation. Patients with AKC and VKC often have a history of other atopic diseases and are more likely to be male.[5] AKC affects older individuals, spanning young adulthood to the fifth decade of life, with relapses and remissions showing minimal seasonal patterns. In fact, atopic dermatitis is present in 95% of patients with AKC, and 87% of patients have asthma.[5] VKC often peaks in the teenage years and occurs in warm, dry climates.[5] Patients report seasonal fluctuations, with symptoms worse in spring and often include intensified ocular pruritus. GPC is considered a non-immune reaction that is related to repeated mechanical irritation to an ocular foreign body (e.g. contact lenses, a prosthesis, or sutures from surgery).

Pathophysiology

SAC and PAC are classified as type I hypersensitivity reactions. Allergens bind to immunoglobulin E (IgE) antibodies at the mast cell surface, triggering mast cell degranulation, whereby mast cells release histamines and proinflammatory mediators including prostaglandins and leukotrienes.[1,6] Patients manifest with symptoms of allergic conjunctivitis (redness, itching, swelling, and tearing). Hours later, inflammatory cell infiltration (e.g. eosinophils, neutrophils) sustains the inflammation.[1,6]

VKC, AKC, and GPC are characterized by chronic inflammation, and might involve combined type I and IV (delayed) hypersensitivity reactions; however, the underlying mechanisms of these conditions are poorly understood.[7] In type IV hypersensitivity reactions, CD4+ T-helper 2 (Th2) lymphocytes interact with antigens, become activated, and release chemotactic factors. VKC involves Th2 lymphocytes and type 2 innate lymphoid cells, while AKC is hypothesized to include a combination of T-helper 1 (Th1) and Th2 inflammation with Th1 predominance.[7]AKC and VKC show sustained mast cell, eosinophil, and lymphocyte infiltration, which can lead to remodelling of the ocular surface with the potential for serious vision impairment.[2]

Associated Ocular Sequelae

Allergic conjunctivitis can harm vision and quality-of-life. Dry eye can exacerbate allergic conjunctivitis because these patients lack the normal quantity or quality of tears that are essential for diluting and washing away allergens, thereby increasing allergen exposure. Approximately 50% of patients with allergic conjunctivitis have dry eye, and approximately 20% of patients with dry eye have allergic conjunctivitis.[2] In addition, chronic conjunctival inflammation and membrane formation over the punctum cause eyelid issues such as punctal stenosis.[5] Keratinized lid margins lead to lid malposition (e.g. ectropion) and eyelash abnormalities (e.g. trichiasis, madarosis).[8] Severe cases of ocular surface diseases can lead to thickened, lichenified eyelids with conjunctival scarring, shortening, and adhesions (e.g. symblepharon).[9]

Vision can be affected by other causes. For example, pruritus prompts habitual eye rubbing, which elevates the risk of developing a condition termed keratoconus, in which the cornea becomes irreversibly warped, and thinned, resulting in vision loss.[10] Patients should stop rubbing their eyes, especially if they have risk factors associated with keratoconus, such as floppy eyelids or sleep apnea. Of note, inflammatory changes such as shield corneal ulcers can occur in VKC and corneal scarring and neovascularization can occur in AKC.[5] Chronic severe VKC and AKC can lead to limbal stem cell deficiency and an increased risk of contracting corneal infections, especially from *Staphylococcus aureus* bacteria and herpes simplex virus.[11] It is important to keep in mind that these complications are

Generic (Trade) Name	Class	Drug Availability (Over-the-counter, Prescription)	Canadian Age Guidelines: Dosage
VASOCONSTRICTOR			
Antazoline phosphate 0.51% (Refresh Eye Allergy Relief)	Vasoconstrictor	OTC	1–2 drops up to every 3–4 hours
Naphazoline hydrochloride 0.01–0.1% (Many, including Albalon, Clear Eyes, Collyre Bleu Laiter, Refresh Eye Allergy Relief, Opti-Tears Red Eye)	Vasoconstrictor	OTC	1 drop up to 4 times daily
Tetrahydrozoline hydrochloride 0.05% (Many, including a few Visine varieties, and Clear Eyes Triple Action)	Vasoconstrictor	OTC	≥6 years: 1–2 drops up to 4 times a day
COMBINED VASOCONSTRICTOR AND ANTIHISTAMINE			
Pheniramine maleate/naphazoline 0.3%/0.025% (Many, including Naphcon-A, Opti-Tears Allergy, Sooth Allergy previously Opcon-A, Visine for Allergy with Antihistamine, Reactine Eye Drops)	Combination first generation H1 receptor antagonist and vasoconstrictor	OTC	≥6 years: 1–2 drops up to 4 times a day
Antazoline phosphate 0.5%,/naphazoline HCl 0.05% (Refresh Eye Allergy Relief)	Combination first generation H1 receptor antagonist and vasoconstrictor	OTC	1–2 drops up to 4 times daily
MAST CELL STABILIZER			
Cromolyn sodium 2% (Cromolyn)	Mast cell stabilizer	OTC	≥5 years: 1–2 drops up to 4 times daily
Lodoxamide tromethamine 0.1% (Alomide)	Mast cell stabilizer	Rx	≥4 years: 1–2 drops up to 4 times daily
COMBINED ANTIHISTAMINE AND MAST CELL STABILIZER			
Bepotastine besilate 1.5% (Bepreve)	Selective H1 receptor antagonist and mast cell stabilizer	Rx	≥3 years: 1 drop twice daily
Ketotifen fumarate 0.035% (Zaditor, Alaway - not yet approved in Canada)	Noncompetitive H1 receptor antagonist and mast cell stabilizer	Rx (Zaditor)	≥3 years: 1 drop up to 3 times daily (Zaditor)
Olopatadine hydrochloride 0.1% (Pataday twice daily relief, previously Patanol), 0.2% (Pataday once daily relief), 0.7% (Pataday once daily relief extra strength, previously Pazeo)	Selective H1 receptor antagonist and mast cell stabilizer	Rx, OTC	≥3 years: 1–2 drops twice daily (Patanol), once daily (Pataday, Pazeo)

Table 1: *Topical pharmacotherapy for allergic conjunctivitis currently marketed in Canada[12,13] Continues on next page.*
Abbreviations: H1, histamine type 1 receptor; NSAID, nonsteroidal anti-inflammatory drug; OTC, over the counter; Rx, prescription

Generic (Trade) Name	Class	Drug Availability (Over-the-counter, Prescription)	Canadian Age Guidelines: Dosage
LOW-POTENCY CORTICOSTEROID			
Loteprednol etabonate 0.2% (Alrex), 0.5% (Lotemax, Lotemax Gel, Lotemax Ointment	Ester-based corticosteroid	Rx	≥18 years: 1–2 drops up to 4 times daily
Fluorometholone 0.1% (FML), Fluorometholone acetate 0.1% (Flarex)	Ketone-based corticosteroid	Rx	≥3 years: 1–2 drops 2 to 4 times daily, 18–65 years, (Flarex)
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS			
Ketorolac tromethamine 0.4% (Acular LS), 0.45% (Acuvail), 0.5% (Acular)	NSAID	Rx	≥3 years: 1 drop up to 4 times daily (Acular LS) ≥18 years: 1–2 drops 3 to 4 times daily (Acular, Acuvail)
Bromfenac sodium 0.07% (Prolensa)	NSAID	Rx	≥18 years: 1 drop once daily
Diclofenac sodium 0.1% (Voltaren)	NSAID	Rx	≥18 years: 1 drop up to 4 times daily
Nepafenac 0.1% (Nevanac)	NSAID	Rx	≥10 years: 1 drop 3 times daily
IMMUNOMODULATOR			
Cyclosporine 0.05% (Restasis), 0.09% (Cequa), 0.1% (Verkazia)	Calcineurin inhibitor	Rx	≥18 years: 1 drop twice daily (Restasis, Cequa) ≥4 years: 1 drop 4 times daily (Verkazia)
Tacrolimus 0.03% and 0.1% ointment (Protopic)	Calcineurin inhibitor	Rx	≥2 years: apply to eyelid or conjunctival sac twice daily (0.03%), ≥16 years (0.1%)

Table 1 (Cont.): *Topical pharmacotherapy for allergic conjunctivitis currently marketed in Canada[12,13] ; courtesy of Clara C. Chan, MD and Caberry Yu, MDAbbreviations: H1, histamine type 1 receptor; NSAID, nonsteroidal anti-inflammatory drug; OTC, over the counter; Rx, prescription*

associated with guarded outcomes.[9]

Stepwise Therapeutic Approach

Treatment of allergic conjunctivitis aims to minimize symptoms and prevent inflammation. Stepwise therapy begins with non-pharmaceutical cold compresses and progresses to different topical and oral medications **(Figure 2)**.[2] Patients should avoid known allergens if possible and stop eye rubbing, which worsens symptoms by triggering mast cell degranulation. Cool compresses provide relief, and preservative-free artificial tears dilute allergens that may be on the surface of the eye.

For SAC and PAC, common therapeutic agents include antihistamines, mast-cell stabilizers, and dual-action agents. Treatment of VKC and AKC may require topical corticosteroids and immunomodulators such as cyclosporine to suppress severe conjunctival inflammation and prevent corneal disease. For GPC, removing the causative agent (e.g. sutures with exposed knots, contact lens) is crucial. **Table 1** outlines the topical pharmacotherapies available in Canada for the treatment of allergic conjunctivitis diseases.[12,13]

Topical Antihistamine

Topical antihistamines reversibly block the H1 receptor and provide relief from redness and itching. They have limited ability to prevent the allergic reaction from occurring because they do not target mast cells, and only provide short-lasting relief.[2,4,5] Selective

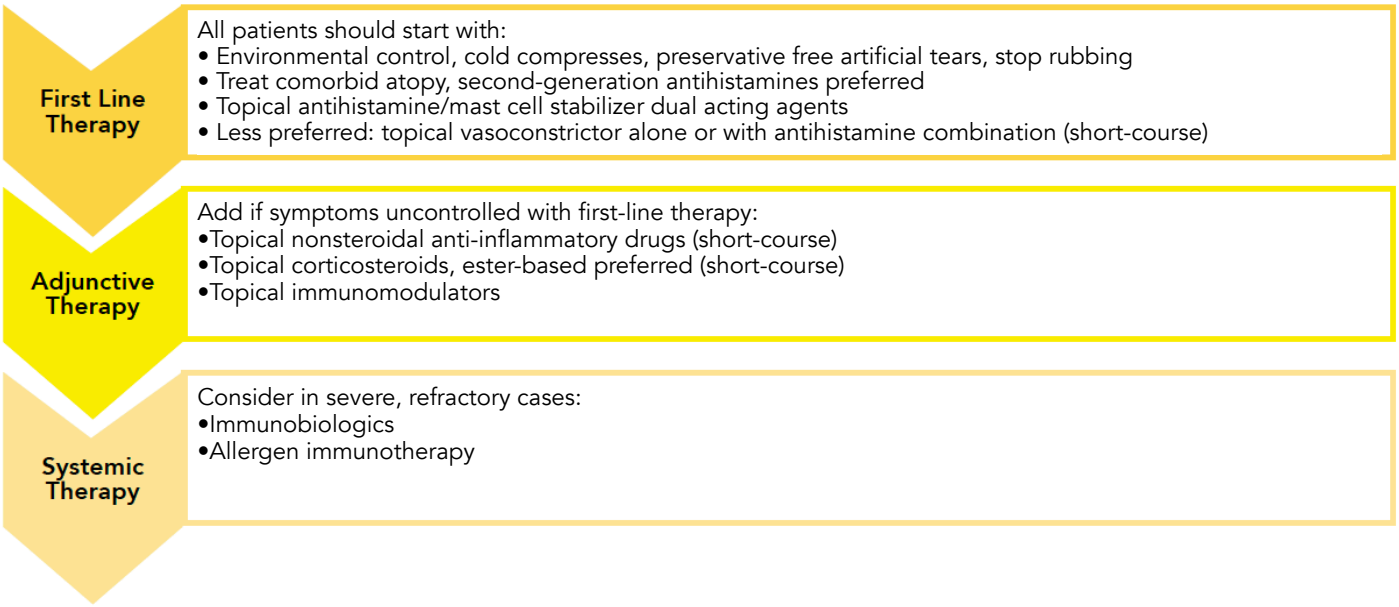


Figure 2. *Stepwise approach to management of allergic conjunctivitis; courtesy of Clara C. Chan, MD and Caberry Yu, MD*

H1 receptor targeting reduces adverse effects such as drowsiness and dryness.[14] Second-generation antihistamines such as emadastine are better tolerated due to their selectivity for H1 receptors and longer duration of effect.[5] Cetirizine ophthalmic solution 0.24% (Zerviate) has recently received FDA approval as a topical antihistamine, and has been shown to alleviate both ocular and nasal signs and symptoms associated with allergic conjunctivitis (not available in Canada).[15] Other second-generation antihistamines such as bilastine are currently being developed into a formulation that can be used as eye drops.[16]

Topical Mast Cell Stabilizers

Mast cell stabilizers inhibit mast cell degranulation, which reduces inflammation associated with late-phase allergic response inflammation.[2,4] While some patients experience symptom relief within 2 days if mast cell stabilizers are used after allergen exposure, they are rarely prescribed as a monotherapy for acute ocular allergies. This is because mast cell stabilizers are more effective as a preventive measure and are administered 3 days to 2 weeks before allergen exposure to target impending histamine release.

Topical Combined Antihistamine and Mast Cell Stabilizers

Preferred as a first line treatment, these agents combine both antihistamine properties and mast cell stabilization, providing relief within 30 minutes.[4] Side effects are mild and include cold-like symptoms, headache, and ocular stinging.[2]

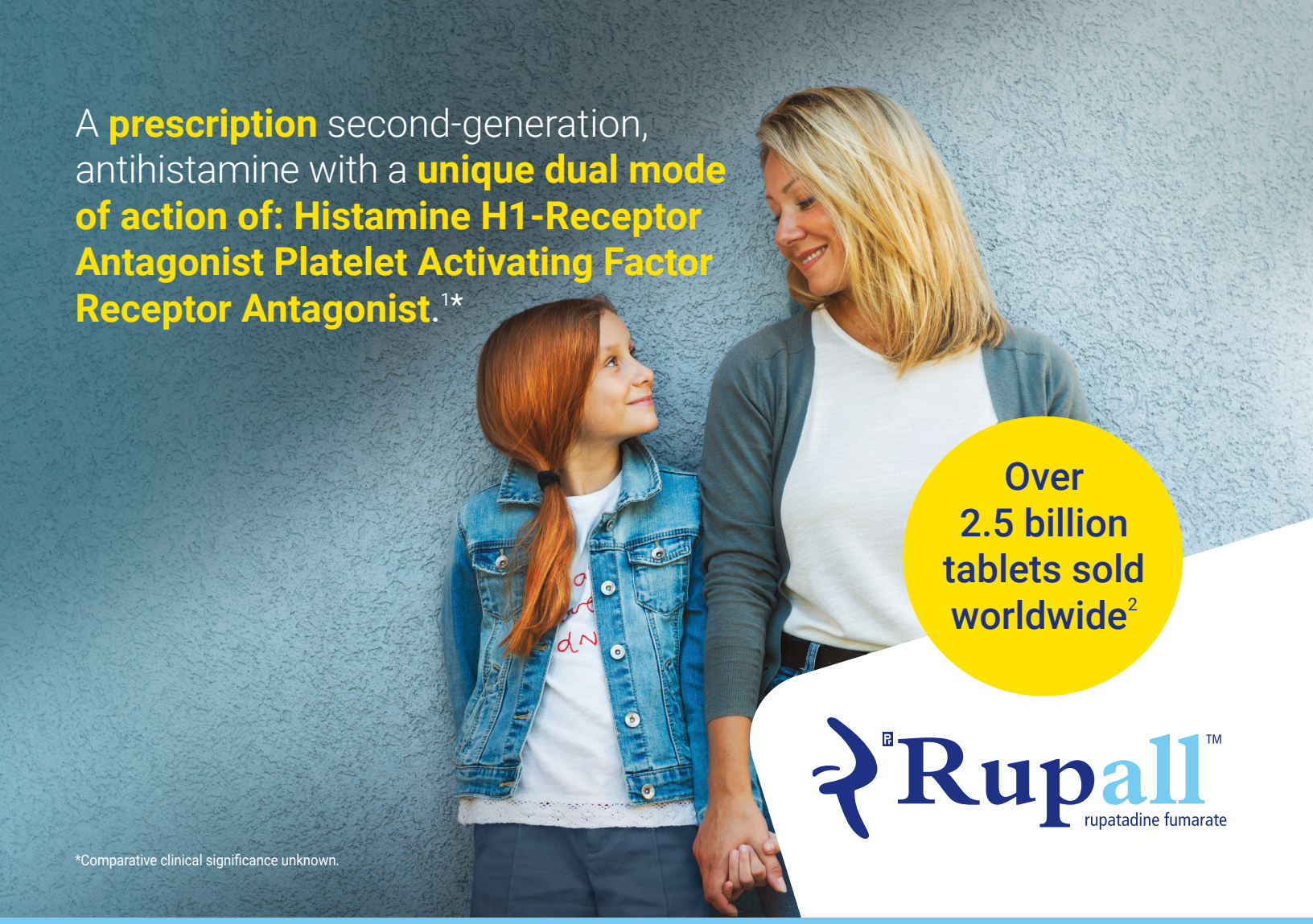
Olopatadine is a commonly chosen treatment for allergic conjunctivitis, offering better relief than that of nedocromil and ketotifen. Olopatadine is only available with a prescription in Canada.[14] Bepotastine is a selective H1-antagonist that has a rapid onset of action of 3 minutes and a duration of action of up to 8 hours. Alcaftadine (not available in Canada) is a unique antihistamine that antagonizes H1, H2, and H4 receptors, which prevents recruitment of eosinophils and reduces ocular itching within 15 minutes, and this effect lasts up to 16 hours after administration.

Topical Corticosteroids

Topical corticosteroids target inflammation in both early and late stages of the allergic response, and are prescribed when the patient reports excessive and persistent signs and symptoms that interfere with quality-of-life.[2] Corticosteroids are prescribed in short courses (e.g. 2 weeks) owing to risks of associated ocular effects, including intraocular pressure (IOP) elevation, cataract formation, and opportunistic infections. Patients using topical corticosteroids for longer periods should have an ophthalmologic consultation for monitoring of side effects. Older ocular corticosteroids with a ketone group at carbon-20, (e.g., prednisolone, dexamethasone, fluorometholone) have been prescribed for severe cases of allergic conjunctivitis.[2] Recently, loteprednol etabonate (0.2% Alrex, 0.5% Lotemax), which is a newer carbon-20 ester-based corticosteroid, has become the preferred agent because it is rapidly metabolized, leading to fewer steroid-induced side effects.[17]

Topical Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs work by inhibiting the cyclooxygenase pathway, which blocks prostaglandin production from arachidonic acid.[2] NSAIDs result in reduced cellular infiltration and can improve symptoms of itching, redness, and chemosis. In addition, they pose no risk of infections, IOP increase, or cataract formation. Monitoring is essential owing to rare complications such as corneal melt and perforation.[18] Multiple NSAIDs have been



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

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prescribed for ocular allergies, including ketorolac, diclofenac, bromfenac, and nepafenac. Only ketorolac is has received FDA approval for SAC. Topical NSAIDs are typically used as adjunctive therapy.

Topical Vasoconstrictors

Topical vasoconstrictors are adrenergic agonists that constrict blood vessels.[2,4,5] They do not reduce the underlying allergic response and are less effective for symptoms other than redness. Overuse of topical vasoconstrictors leads to rebound hyperemia due to α-1 receptor downregulation.[16] They are contraindicated for angle-closure glaucoma and in pregnancy, and are used cautiously in patients with cardiovascular disease, hyperthyroidism, and diabetes.[5,19] Combination therapy with topical antihistamines and vasoconstrictors is more efficacious than individual agents alone; however, its use can be limited due to side effects including rebound hyperemia, epiphora, and mydriasis.[2] In 2017, brimonidine 0.025%, a selective α-2 receptor agonist approved for glaucoma, received FDA approval for ocular redness. Brimonidine has a rapid onset of action, a duration effect up to 8 hours, along with a few reports of rebound hyperemia.[16]

Topical Immunomodulators

Immunomodulators such as topical cyclosporine A and tacrolimus are calcineurin inhibitors that inhibit interleukin-2 (IL-2) activation and the proliferation of lymphocytes.[2,16] Both agents are steroid-sparing alternatives and are safer for long-term use than corticosteroids for more severe allergic conjunctivitis. These agents inhibit mast cell and eosinophil activation and mediators. Cyclosporine has traditionally been approved to treat moderate-to-severe dry eye and was recently approved for treatment of VKC.[20] While not yet approved for other forms of allergic conjunctivitis, topical cyclosporine is effective for AKC and can reduce steroid dependency.[9]

Tacrolimus is a macrolide derivative that blocks T lymphocyte activity with a higher immunosuppressive potential than that of cyclosporine. Tacrolimus has been used off-label with success for treating AKC, VKC, and severe atopic dermatitis of the eyelids.[7,9] Studies have shown similar efficacy and safety profiles for tacrolimus and cyclosporine in the treatment of VKC. However, both calcineurin inhibitors have been associated with a risk of local viral or molluscum infections.[5]

Lifitegrast 5% (Xiidra) is a novel topical immunomodulator used in patients with severe dry eye. It works by inhibiting T-cell inflammation by preventing the binding of cell surface lymphocyte function-associated antigen-1 and intercellular adhesion molecule-1. Lifitegrast has high water solubility and rapid ocular tissue absorption. After promising animal studies, a phase II trial is underway to evaluate lifitegrast for allergic conjunctivitis in humans.[21]

Immunobiologics

Historically, immunobiological interventions in allergic disorders have focused on asthma, atopic dermatitis, and chronic spontaneous urticaria. Omalizumab is an anti-IgE antibody that inhibits mast cell degranulation and has shown efficacy in treating allergic rhinoconjunctivitis and treatment-resistant VKC and AKC in trials,[7] although use in rhinoconjunctivitis is off-label. Other immunobiologics targeting IL-5 are being investigated for their potential to reduce eosinophilic activity in VKC.[16]

Dupilumab, an IL-4 and IL-13 pathway inhibitor, is approved in Canada for severe, refractory atopic dermatitis, asthma, and rhinosinusitis with nasal polyps, eosinophilic esophagitis and prurigo nodularis. However, dupilumab treatment can lead to mild or moderate conjunctivitis as an ocular surface side effect, particularly in patients with preexisting allergic conjunctivitis and atopic dermatitis.[22] Most cases of conjunctivitis respond well to topical corticosteroid treatment or off-label treatment with tacrolimus 0.03%–0.1% eye drop or ointment.[7] Case reports have shown that dupilumab has been used to successfully treat patients with refractory AKC and VKC, and an ongoing clinical trial is being conducted for AKC treatment.[7]

Immunotherapy

Allergen immunotherapy includes sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT).[23] Immunotherapy is a treatment approach that can provide long-term relief from symptoms even after treatment completion. Immunotherapy has demonstrated improvement in exposure to ten- to one-hundred-fold allergen concentrations in conjunctival provocation studies. While there is more evidence for SCIT and SLIT in allergic rhinitis, their effectiveness in allergic conjunctivitis is less clear.[2] Patients may experience symptomatic improvement, but it is unclear if treatment reduces the need for topical eye drops. SCIT and SLIT are reserved for patients with IgE sensitization to aeroallergens or comorbid allergic rhinitis, especially when pharmacotherapy has failed.[23]

Oral Antihistamines

Oral antihistamines offer initial relief from allergy symptoms. First-generation antihistamines may worsen dry eye symptoms, while second- and third-generation H1 receptor antagonists have fewer sedative or anticholinergic effects and are less likely to reduce tear flow.[5] However, of the novel antihistamines, none have demonstrated superiority over the others in treating ocular allergies.[2] Second-generation oral antihistamines are often used as adjunctive therapy to topical treatment or in severe exacerbations with corneal involvement in AKC or VKC.[5]

Intranasal Corticosteroids

Intranasal corticosteroids such as fluticasone and mometasone may reduce symptoms of allergic conjunctivitis, although they are mainly prescribed for allergic rhinitis owing to concerns about IOP elevation.[16] A recent study has shown an increase of 0.8% in the incidence of elevated IOP compared to placebo, with no increase in glaucoma rates.[24]

Future Therapeutic Targets

Reproxalap 0.25% is an investigational reactive aldehyde species modulator that has shown reduced ocular itching, tearing, and redness in a phase III clinical trial.[25] The FDA has accepted the New Drug Application for Reproxalap for treating dry eye disease. Other medications under investigation have limited evidence for treating ocular allergies. These include glucocorticoid receptor agonists, various immune receptor antagonists (e.g. C-C chemokine receptor type 3, C-C chemokine receptor type 2, IL-1, integrin), Janus Kinase inhibitors, tyrosine kinase inhibitors, and resolvins.[16]

Several novel devices are under study that include drug delivery systems, such as ketotifen-eluting contact lenses for antiallergic and vision-correction purposes, epinastine-hydrochloride-releasing soft contact lenses, and solid lipid nanoparticles to increase bioavailability.[16] The FDA has approved dexamethasone ophthalmic insert at a dose of 0.4 mg (Dextenza), which is a physician-administered intracanalicular device for treating ocular itching in allergic conjunctivitis.[26]

Conclusion

Allergic conjunctival diseases require safe and effective treatment to reduce symptoms and improve quality-of-life. Topical dual-acting antihistamines and mast cell stabilizers are the mainstay of pharmacotherapy for patients with allergic conjunctivitis. During severe exacerbations, short courses of topical corticosteroids are recommended. For severe and chronic forms of ocular allergies, such as VKC and AKC, topical immunomodulators are effective steroid-sparing alternatives. Proper diagnosis and treatment with a collaborative approach involving the allergist, dermatologist, and eye-care specialist is essential to prevent vision-threatening complications.

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None declared

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HYDROGEN AND METHANE BREATH TESTING FOR ABDOMINAL BLOATING OF SMALL INTESTINAL ORIGIN

Introduction

Abdominal bloating with or without excessive gas production and with or without abdominal distention is common, very bothersome for patients, and is poorly understood. Bloating can be associated with gastrointestinal disorders, nutrient malabsorption, and systemic illnesses. The origin of abdominal bloating is often unclear, though it is usually associated with food intake and bowel motility dysfunction. Often, food allergies, food intolerance, or food poisoning are considered by the patient or physician as potential causes for bloating. A common concern in the patient's mind is that healthcare professionals will dismiss or misdiagnose their complaint. The limited understanding of the pathophysiology of bloating leads to current empirical management, and bloating is often characterized as a "functional" disorder. Bloating carries a heavy clinical, psychological, and economic burden. Proper diagnosis will provide the patient with peace of mind and lead to effective treatment. This review focuses on the mechanisms and management of abdominal bloating associated with different small intestinal disorders identified by non-invasive hydrogen and methane breath tests.

The pathophysiology of bloating

Bloating is a heterogeneous condition produced by a combination of pathophysiological mechanisms that differ among individual patients and, in most cases, are subtle and undetectable by conventional methods.[1,2] Gas transit studies have provided evidence that patients with bloating have impaired reflex control of gut handling of content leading to ineffective motility [3]. The build-up of liquid or gas in a section of the intestine may induce bloating, particularly in patients with altered gut perception.[3]

The small intestine is richly innervated by vagal sensory nerves. These nerves are associated with various types of receptors, including mechanoreceptors, chemoreceptors, thermoreceptors, and osmoreceptors. These receptors transmit information to the nucleus tractus solitarius, an important control center for autonomic regulation. The response to this sensory information is influenced by many nuclei in the central autonomic network, including the amygdala, such that various factors, including stress, can influence perception and the experience of bloating. To avoid bloating, intestinal distention needs to evoke proper motor patterns. During fasting, the migrating motor complex (MMC), which is a cyclical wave of neural excitation that generates motor activity in the stomach and proximal intestine, moves slowly across the intestine, approximately every 130 minutes, to remove waste, including bacteria. In fact, the MMC serves as a natural protection against bacterial overgrowth[4-6]; hence, a sufficient period of fasting is needed for its development.

In response to food intake while awake, stomach distention triggers vagal sensation that will evoke peristaltic activity in the stomach and in the small intestine. In addition, the intrinsic enteric nervous system is, independent of the central nervous system, capable of initiating distention-induced peristalsis.[7] These neural activities trigger excitation in the pacemaker cells of the gut, termed the interstitial cells of Cajal, which orchestrate peristaltic and segmental contractile activity.[8,9] A reduction of intestinal pacemaker cells can lead to bacterial overgrowth.[10]
When any of the factors involved in contraction generation to move gas in the anal direction are weakened, bloating may develop. In addition, medications, such as anticholinergics, can potentially influence motility, and therefore, medication intake may have to be adjusted. The activity of the sympathetic nervous system normally inhibits motility but this can become excessive due to stress, anxiety, spinal injury, and general autonomic dysfunction.[11-13] Hence, in concert with testing for bacterial overgrowth, motility disorders need to be evaluated and incorporated into the treatment strategy.

A diet rich in fermentable products can exacerbate bacterial overgrowth, thus, a discussion with the patient about diet should also be included in the treatment strategy.[14] Patients taking proton pump inhibitors (PPIs) have a 3-fold higher risk of developing bacterial overgrowth.[15] Since PPIs are massively oversubscribed,[16] speaking with the patients about their use is warranted.

Clinical features of small intestine bacteria and methanogen overgrowth

Excessive gas content in the small intestine can induce uncomfortable sensations and symptoms such as bloating, fullness, belching, flatulence, increased abdominal girth, and associated difficulty of breathing. In a healthy person, normal gas formation in the intestine is removed by motility-induced transit. Excessive gas may be caused by swallowing air associated with gulping food or liquids, anxiety, gum chewing, smoking, products of fermentation such as

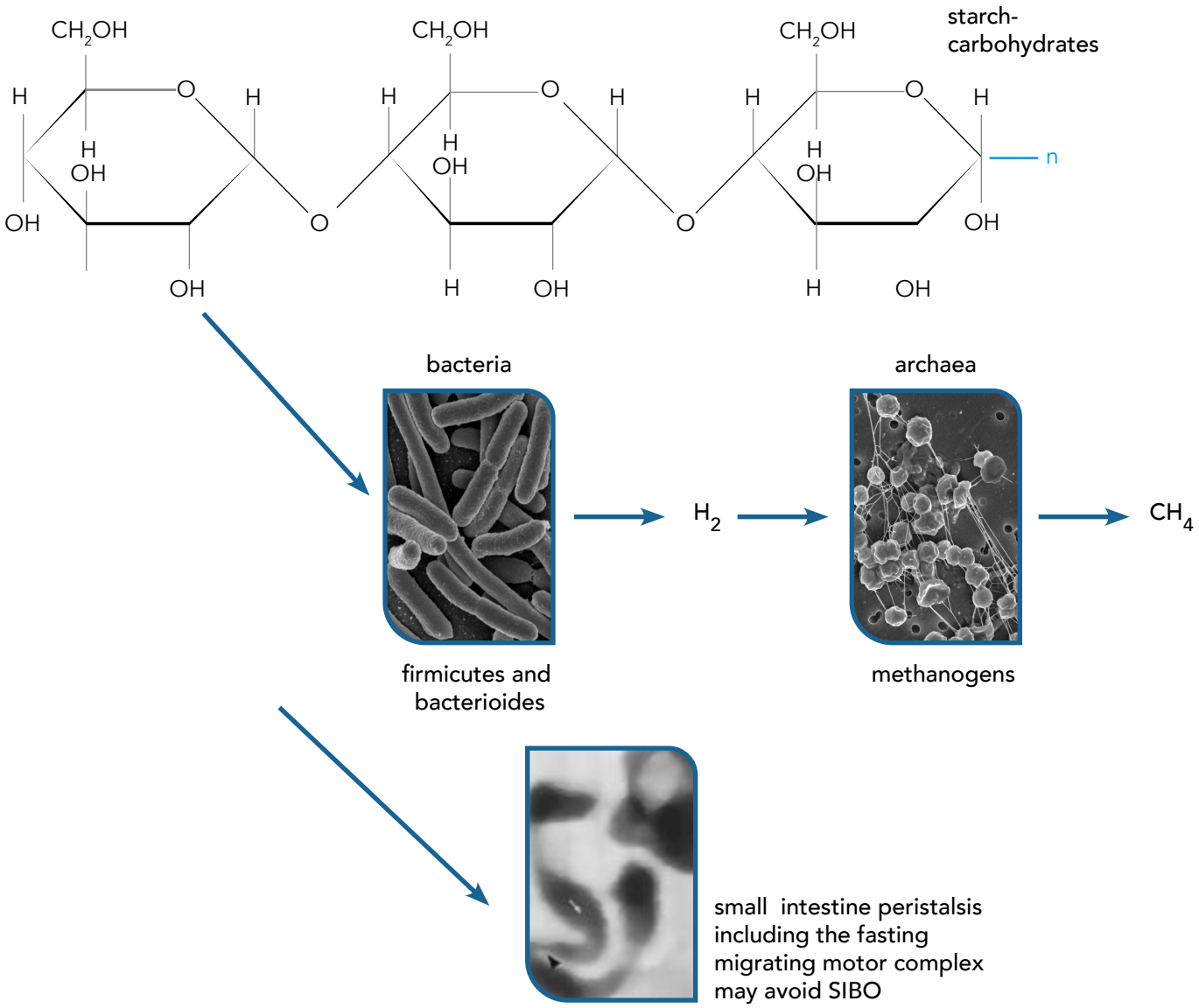

Figure 1: *Gas production in the small intestine Bacterial overgrowth can lead to excessive hydrogen (H2) production, hydrogen, which may feed methanogens to produce methane (CH4). Excessive gas production may be a result of poor small intestinal peristalsis, including a diminished fasting motility pattern, known as the migrating motor complex,[42] that may hinder bacterial removal. Adpated from Der-Silaphet T. et al, 1998*

carbon dioxide from the digestion of fat and protein, hydrogen from bacteria, or methane from archaea, such as *Methanobrevibacter smithii*.[17]

Small intestine bacterial overgrowth (SIBO) is defined by the presence of excessive bacterial growth in the small intestine, which often causes diarrhea and may cause weight loss and malnutrition. Intestinal methanogenic overgrowth (IMO) is defined as methanogen overgrowth in the small intestine and/or in the colon.[14,18,19] Elevated methane levels induce slow intestinal transit through the small intestine, leading to constipation that may be irresponsive to laxatives.[20] A patient may experience up to two weeks without bowel movements despite laxatives and prokinetics. When IMO is demonstrated by breath tests, patients are five times as likely to have constipation compared to hydrogen-dominant SIBO.[14]

In addition, the degree of breath methane production in irritable bowel syndrome (IBS) correlates with the severity of constipation.[21]

Methanogens primarily metabolize hydrogen and carbon dioxide to produce methane. Therefore, the overgrowth of hydrogen-producing bacteria will coexist with IMO **(Figure 1)**. Abdominal pain is often present in SIBO and IMO.[22] Hence, SIBO and IMO often meet the diagnostic criteria for IBS. Therefore, patients with SIBO or IMO might be incorrectly treated for IBS for many years. Conversely, IBS may not be associated with bacterial overgrowth and should not be treated with antibiotics without carrying out the appropriate testing. Poor response to treatment and dietary confusion have a significant impact on a patient's daily life. Delayed diagnosis and treatment of severe SIBO can lead to

abnormal bacterial colonization and micronutrient deficiency of vitamin B12, fat-soluble vitamins, iron, thiamine and niacin.[23]

Etiology and risk factors

Intestinal motility disorders, together with chronic pancreatitis, account for about 90% of cases of SIBO.[24] Pancreatic insufficiency predisposes SIBO by diminishing the quantity and composition of digestive enzymes and reducing the synthesis of antimicrobial enzymes.[24] SIBO may also contribute to pancreatic insufficiency: excess bacteria in the small intestine deconjugate bile acids, which impairs micelle formation and thereby reduces the efficacy of pancreatic lipases.[25] Immune disorders affect immunoglobulins in intestinal secretions, which are important in maintaining microbial homeostasis.[26] Our own experience suggests that previous food poisoning and occupational exposure to wild animals or toxins can be risk factors. D-lactic acidosis is a rare neurologic syndrome in patients with SIBO that is associated with short bowel syndrome or a prior jejunoileal bypass.[27]

Given that both diet and bacterial metabolites influence immune responses, the influence of gut microbiota on the increasing incidence of allergies and asthma has been considered.[28] In a study that included 70 children with chronic abdominal pain, 35 tested positive for SIBO, and 71% of those with SIBO were found to have an allergic disease, in contrast to 29% of children without SIBO.[29] The association between SIBO and allergic diseases included allergic rhinitis, cow's milk protein allergy, and asthma. SIBO is also common in mast cell activation syndrome.[30]

Hydrogen and methane breath test

Hydrogen and methane breath tests are non-invasive diagnostic procedures used to identify specific conditions related to the digestion of carbohydrates (starchy foods, sugars) in the small intestine. Notably, these tests can detect SIBO and IMO. Patients with frequent abdominal bloating, cramping, increased gas production, irregular bowel function, and those whose symptoms appear to be related to prior infection[31,32] or triggered by food containing lactose or fructose may benefit from these tests. Hydrogen and methane are exclusively produced by microbial fermentation in the gut, which is the principle behind clinical breath testing. Gut microbes readily digest carbohydrates, producing these gases as byproducts, which diffuse into the abdominal venous circulation and are transported to the lungs, where they can be detected in the exhaled breath.[33] In healthy individuals, carbohydrates are hydrolyzed into glucose, fructose and galactose which

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Not a real patient, for illustrative purposes only.

In the MEASURE UP 1 study:‡

RINVOQ 15 mg demonstrated significant improvement in skin clearance (as measured by proportion of patients with EASI 75; co-primary endpoint & EASI 90; secondary endpoint) **vs.** placebo at Week 16[1,2]

- **EASI 75**: **69.6%** (n/N=196/281) **vs. 16.3%** (n/N=46/281) of patients achieved EASI 75 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).
- **EASI 90**: **53.1%** (n/N=149/281) **vs. 8.1%** (n/N=23/281) of patients achieved EASI 90 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

A rapid improvement in skin clearance was achieved for RINVOQ 15 mg compared to placebo (defined as EASI 75 by Week 2; secondary endpoint)[1,2]

- **EASI 75**: **38.1%** (n/N=107/281) **vs. 3.6%** (n/N=10/281) of patients achieved EASI 75 at Week 2 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

A greater proportion of patients treated with RINVOQ 15 mg achieved clinically meaningful itch reduction (≥4-point reduction in Worst Pruritus NRS; secondary endpoint) compared to placebo treatment group at Week 16

- **≥4-point reduction in Worst Pruritus NRS**: **52.2%** (n/N=143/274) **vs. 11.8%** (n/N=32/272) of patients achieved a ≥4-point reduction in Worst Pruritus NRS with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

At Week 16, a greater proportion of patients treated with RINVOQ 15 mg achieved clinically meaningful improvement in emotional state (ADerm-IS emotional state domain score improvement from baseline; secondary endpoint) vs. placebo group (RINVOQ 15 mg [n/N=142/227]: 62.6%; placebo [n/N=42/212]: 19.8%; p<0.0001, RINVOQ vs. placebo, multiplicity-controlled).

RINVOQ is only indicated in patients not adequately controlled with a systemic treatment or when it's inadvisable; majority of the study subjects were treated with systemic therapy or phototherapy before starting RINVOQ.

* Comparative clinical significance has not been established.
† Please see Product Monograph for additional dosing and administration information.
‡ MEASURE UP 1 was a 16-week, randomized, double-blind, multicentre, placebo-controlled study that included adolescent and adult patients with refractory moderate to severe atopic dermatitis not adequately controlled by topical medication(s). At baseline, patients had an vIGA-AD score ≥3 in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) on an increasing severity scale of 0 to 4, an EASI score ≥16 (composite score assessing extent and severity of erythema, edema/papulation, scratches and lichenification across 4 different body sites), a minimum BSA involvement of ≥10%, and weekly average Worst Pruritus NRS ≥4. Patients received RINVOQ 15 mg or RINVOQ 30 mg once daily, or placebo.

ADerm-IS: Atopic Dermatitis Impact Scale; BSA: body surface area; EASI: Eczema Area and Severity Index; JAK: Janus kinase; NRS: Numerical Rating Scale; vIGA-AD: validated Investigator's Global Assessment for Atopic Dermatitis.

References: 1. RINVOQ Product Monograph. AbbVie Corporation. **2.** Guttman-Yassky E, Teixeira HD, Simpson EL, *et al.* Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet* 2021;397(10290):2151-68.

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are quickly absorbed in the small intestine so that little hydrogen production will be measured in the breath. Of note, hydrogen is produced by bacteria, but archaea produce methane. Archaea are similar to bacteria in that they are single-cell microbes without nuclei; however, their membrane composition is different from that of bacteria, and they do not react to most antibiotics. When methane is detected by a breath test, the hydrogen levels in a breath test become unreliable. This is because most of the methanogenic archaea in the human gut utilize hydrogen in the generation of methane, which then impacts hydrogen measurements in the breath test. The methanogens in the gut consume 4 molecules of hydrogen and 1 molecule of carbon dioxide to produce each molecule of methane. Hence, in a situation of excess methane producers, the detection rate of an early rise in hydrogen production can significantly decrease.

Hydrogen breath test using glucose for the diagnosis of small intestinal bacterial overgrowth

Under normal conditions, glucose is absorbed in the proximal and mid small intestine and does not reach the colon. During the short time glucose is in the small intestine, there is little bacterial fermentation and little hydrogen production. However, if bacterial overgrowth occurs in the small intestine, a 75 g dose of oral glucose will be metabolized,[14] and hydrogen can be measured in the breath.

Methane breath test to assess the presence of excessive methane-producing microbes

The methane breath test will assess the presence of microbes that produce methane, termed methanogens, in response to a dose of 75 g of oral glucose.[14] These microbes are primarily archaea, such as *Methanobrevibacter smithii*. In addition, when executing a hydrogen breath test, it is critical to measure methane levels as well to rule out a compromised hydrogen breath test that may be caused by the consumption of hydrogen by methanogens.

Hydrogen breath testing for the diagnosis of fructose or lactose maldigestion/intolerance

If fructose or lactose are not absorbed in the small intestine, bloating can occur. Fructose is absorbed by intestinal epithelial cells via the membrane transporter GLUT 5. If this transporter is not present, fructose cannot be absorbed. Lactose, exclusively found in dairy products, cannot be absorbed by intestinal epithelial cells; the enzyme lactase, present along the brush border membrane of the intestinal epithelial cells, is responsible for breaking lactose down into glucose and galactose, which can be absorbed. Normally, fructose and the metabolic products of lactose are absorbed in the small intestine, and are therefore not significantly metabolized by bacteria, resulting in a negative hydrogen breath test. If, during the test, fructose or lactose are not absorbed in the small intestine because of maldigestion or intolerance, they will enter the colon where they are fermented by bacteria that produce hydrogen. Thus, hydrogen will appear in the breath test. These breath tests should be conducted for up to 180 minutes, with the timing of the peak hydrogen level depending on small intestine transit time. Importantly, before testing for lactose or fructose intolerance, intestinal bacterial overgrowth needs to be excluded.

Hydrogen breath test using lactulose for orocecal transit time

Lactulose is metabolized in the colon by colonic bacteria, and it does not normally undergo fermentation in the small intestine. Hence, the time it takes for hydrogen to be detected in the breath after lactulose intake is considered the time that lactulose has entered the colon. Rapid transit would show a peak in the hydrogen level from ~ 30–90 minutes, and normal transit from ~ 90–180 minutes.[33] Considering that SIBO may cause an early peak in the hydrogen level, the presence of SIBO should be excluded prior to the test to interpret the transit time correctly. This test is helpful in some patients for a correct breath test interpretation, although it should not be used as a routine transit test.[14,33]

Treatment strategies for small intestine bacterial overgrowth, intestinal methanogenic overgrowth and fructose intolerance

The treatment strategy for SIBO is to control bacterial overgrowth, and for IMO, it is to control both hydrogen and methane producers in the small intestine. Approximately 40% of patients with SIBO have persistent symptoms after initial antibiotic treatment.[34] IMO is more refractory than SIBO, because methanogens are not sensitive to antibiotics.[35] SIBO recurrence is more likely to occur in older adults, those who have undergone an appendectomy, and those with long-term PPI use.[19] For patients in these circumstances, further courses of treatment need to be considered. In our clinic, one or two courses of oral amoxicillin-clavulanate 875 mg twice daily for 10 days have achieved successful control of both gastrointestinal symptoms and hydrogen/methane levels. Other antibiotic options include metronidazole and ciprofloxacin. Rifaximin, a non-absorbable rifamycin derivative, is effective in the treatment of SIBO.[36] For the treatment of IMO, neither rifaximin or neomycin are able to specifically target archaea or methanogens. Rifaximin alone and a combination of rifaximin and neomycin have shown some effectiveness in reducing methane production in the gut.[37] Owing to the high cost of rifaximin and the adverse effects of neomycin, such as neurotoxicity, this combination treatment is rarely used in clinical practice.

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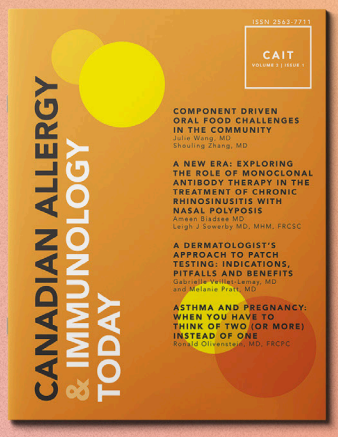

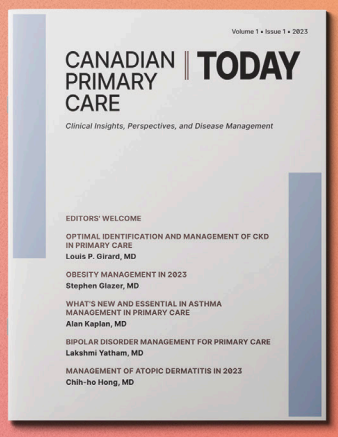

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Recently, statins have been considered as a treatment for methane production in humans.[37,38] Lipid-soluble statins are fungal metabolites that enter *Methanobervibacter smithii* inhibiting their growth and activity.[39] Clinical trials have not yet been successful, likely because of the difficulty of maintaining levostatin in the small intestine for a sufficient amount of time.[M. Pimentel, personal communication, October 2023]

Fructose is a carbohydrate that is naturally found in fruits, fruit juices, some vegetables, and honey.[40] Patients with fructose intolerance should limit high-fructose foods, such as juices, apples, grapes, watermelon, asparagus, peas, zucchini, and large servings of tomato. Patients can experiment to determine if they can tolerate lower fructose foods, which include bananas, blueberries, strawberries, carrots, avocados, green beans, and lettuce. Patients should be aware that sweeteners in many processed foods and beverages are high in fructose, such as table sugar, corn syrup, honey, and molasses.[41]

Conclusion

Hydrogen and methane breath tests help to identify a variety of diseases of the small intestine that have bloating as the dominant symptom. These tests can be a useful addition to a diagnostic strategy to reveal anatomic (small intestine and colon), metabolic (lactose/fructose digestion), motility (transit), and infectious origins of the symptoms. Breath testing guides the optimization of clinical management. Eradicating overgrowth of bacteria and methanogens may not be sufficient to combat symptoms of bloating. Abnormal small intestinal motility plays an important role in the pathogenesis of SIBO and IMO and this issue should be addressed in concert with dietary advice and a thorough evaluation of medication use.

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

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EPINEPHRINE AUTO-INJECTORS IN CANADA: A REVIEW OF AVAILABLE PRODUCTS AND CLINICAL PROPOSALS

Background

Anaphylaxis is a severe reaction with significant associated morbidity and mortality that necessitates prompt on-demand management for patients. Epinephrine administered intramuscularly at a dose of 0.01 mg/kg of body weight, up to a maximum single dose of 0.5 mg at one time, is the first-line treatment for anaphylaxis.[1,2] Epinephrine auto-injectors (EAIs) are devices designed to deliver a predetermined dose of epinephrine rapidly and reliably into the vastus lateralis muscle of the mid-anterolateral thigh for treatment of anaphylaxis.[3,4] All commercially available auto-injectors in Canada are fixed-dose delivery systems, therefore titration of epinephrine dose based on patient weight is not possible.[5-7]

In Canada, there are several manufacturers of EAIs, providing treating physicians and patients with a variety of options to treat anaphylaxis in the community. However, as these devices all contain the same medication, physicians may not realize that specific EAIs may be of greater utility in certain clinical circumstances. This scientific review aims to describe all currently available EAIs in Canada, with detailed discussion on the differences between products and the nuances of a patient-centred approach to prescription in a market filled with seemingly "one size fits all" devices.

Epinephrine Dosing and Needle Length

Canadian Society of Allergy and Clinical Immunology (CSACI) Recommendations

The CSACI recommends the use of a 0.15 mg EAI for children weighing 15 kg-25 kg, a 0.3 mg EAI for adults and children weighing 25-45kg, and a 0.5 mg EAI for adults and adolescents weighing 45 kg or greater.[8,9]

Although recommendations are not explicitly made regarding needle length, the recommendation for a 0.5 mg EIA in patients greater than 45 kg acts as a de facto recommendation, as there is only one 0.5 mg EIA on the market in Canada, and it is manufactured with a 24 mm needle.[8] The longer needle length when compared to competitors was largely developed based on data demonstrating differences in anterolateral thigh subcutaneous adipose tissue depth and skin-to-muscle distance (STMD) in patients with higher body mass indices.[10]

Conversely, care should be taken when counselling regarding pediatric patients under 15 kg body weight, as the 0.15 mg EIAs available may have needle lengths exceeding the STMD, potentially resulting in inadvertent intraosseous administration.[11]

Other Society Recommendations

ecommendations from other societies, including the American Academy of Allergy, Asthma, & Immunology (AAAAI), the American College of Allergy, Asthma, & Immunology (ACAAI), and the European Academy of Allergy & Clinical Immunology (EAACI) are largely the same as the Canadian recommendations, with major differences in recommendations based upon commercial availability of various EIA products, needle lengths and dosages.[9]

Epinephrine Auto-injectors Commercially Available in Canada

EpiPen®

EpiPen® is a widely recognized epinephrine auto-injector on the Canadian market. It is available in two different needle lengths and dosages: EpiPen Jr® and EpiPen. The Product Monograph for EpiPen Jr and EpiPen **(Figure 1)** recommends the use of EpiPen Jr for pediatric patients weighing 15-30 kg and EpiPen for pediatric and adult patients weighing 30 kg or more. The EpiPen Jr delivers a single dose of 0.15 mg epinephrine[5] with a needle length of approximately 12.7 mm, whereas EpiPen delivers a single fixed dose of 0.3 mg epinephrine with a needle length of approximately 16 mm **(Table 1)**.[3]

Although the product monograph for EpiPen Jr limits its use to those pediatric patients weighing <15 kg, as discussed above, most experts agree that off-label prescription of this product for patients weighing <15 kg is appropriate in areas where the 0.1 mg version of this auto-injector is not available (including in Canada).[3,9] Further to this, it should be noted that the 30 kg Product Monograph weight cut-off is different from the 25 kg cut-off suggested by North American allergy societies.[8] This discrepancy reflects the notion that patients weighing 25-30 kg should be administered 0.3 mg instead of 0.15 mg of epinephrine as this higher dose is closer to the internationally accepted dosing at 0.01 mg/kg.[9,12,13]

Practically speaking, therefore, if clinicians prescribe the EpiPen or EpiPen Jr products, the CSACI recommendations are for EpiPen Jr in patients weighing 0-25 kg (vs 30 kg listed by the product monograph), and the regular EpiPen product for those weighing 25-45 kg.[8] Once a patient exceeds this weight, consideration should be made to switch to a product available in 0.5 mg dosing.

As EpiPen has been available on the Canadian market for the longest period of time (and had been the sole EAI on the market on multiple occasions), it likely benefits from both provider and patient name recognition. Further to this, the EpiPen name has also become somewhat of a proprietary eponym, perhaps further driving prescribing practices. From a strictly scientific perspective, other benefits of EpiPen include a moderate-length needle and lower dosing for smaller-sized adults and children.[9] Drawbacks of this device include limited dosing options for patients >45 kg, and short needle length, which may be an issue in patients with a greater degree of subcutaneous tissue.

Based on a growing body of clinical evidence, there is a clear need for the 0.1 mg EpiPen Jr auto-injector in Canada, as well as a higher dose of 0.5 mg, similar to that available with other devices.[9,13,14]

*Emerade™**

Emerade™ **(Figure 1)** is a relatively novel EAI available in Canada.* Each auto-injector delivers a fixed dose of epinephrine into the anterolateral muscle of the thigh, similar to EpiPen. However, Emerade is unique as it is available in both 0.3 mg and 0.5 mg doses, as well as in a longer needle length of approximately 24 mm (23-25 mm listed depending on the resource).[3,6] The Product Monograph suggests the 0.3 mg dose for patients weighing 30-60 kg, with either the 0.3 mg or 0.5 mg dose recommended for those weighing over 60 kg, depending on "clinical judgement" which is not further defined **(Table 1)**.[6]

Figure 1: *Commercially available epinephrine auto-injectors in Canada[17-19] ; courtesy of Harold Kim, MD and Graham Walter, MD*

CSACI recommendations regarding Emerade suggest the use of the 0.3 mg device in patients weighing 25-45 kg, with an increase to the 0.5 mg dose in all patients >45 kg.[8] This implies a switch from a 0.3 mg EAI (of any manufacturer) to the 0.5 mg Emerade EAI in all patients weighing more than 45 kg.

As mentioned above, the major benefits of the Emerade EAI lie in its dosing and needle length. Emerade 0.5 mg EAI is also the only product with a 24 mm needle length, which theoretically ensures more appropriate intramuscular dosing of epinephrine in patients with relatively more adipose tissue.[10] Further to this, the increase in epinephrine dosing available from the Emerade 0.5 mg auto-injector is likely more evidence-based in the majority of patients weighing >45 kg (and certainly in those weighing ≥ 60 kg as recommended by the product monograph).[9,13,14]

The drawbacks of this device are actually rooted in these same features, namely the concern for epinephrine overdose and accidental intraosseous injection due to a needle length that exceeds skin-to-bone distance (STBD).[3,15] These risks can be mitigated by proper patient phenotyping and discussion regarding which patients might benefit from this longer needle length and higher dosing. This patient population typically consists of patients weighing

>45-60 kg with an STMD similar to said needle length, which can be determined by point-of-care (POC) ultrasound in clinics equipped with such technology.[15] Further drawbacks include the lack of a 0.15 mg product on the Canadian market. In addition, this may affect patient comfort with said EAI, as patients and parents anecdotally seem to feel more comfortable continuing use of the same product when increasing dose for weight (i.e., transitioning from the 0.15 mg EpiPen Jr to the 0.3 mg EpiPen when their child reaches 25 kg, rather than altering both the dose and the device).

Allerject®
Allerject® **(Figure 1)** is an additional brand of EAI on the Canadian market. These EAIs have the identical intended use as EpiPen and Emerade, with several unique features. Allerject is available in two different doses and needle lengths: 0.15 mg (12.7 mm) and 0.3 mg (16 mm).[7] Its product monograph suggests identical dosing to that of EpiPen/ EpiPen Jr, with the 0.15 mg EAI recommended in children weighing 15 kg-30 kg, and the 0.3 mg EAI used in those weighing ≥ 30 kg **(Table 1)**.

The recommendations by the CSACI are therefore identical to those for EpiPen/ EpiPen Jr, i.e.; Allerject 0.15 mg is recommended in patients weighing 0-25 kg, and Allerject 0.3 mg is recommended in patients 25-45 kg. Again, once a patient exceeds this weight, consideration should be made to switch to a product available in 0.5 mg dosing (Emerade 0.5 mg EAI).

Allerject auto-injectors offer a unique, compact design, likely making this product easier to carry in a pocket when compared to other available products on the Canadian market. Another distinguishing feature of this device is its voice assistance, with real-time instructions provided aloud when the auto-injector is removed from its sheath to assist patients with epinephrine administration. Not only can this be helpful for pediatric patients, but it may theoretically also hold an advantage in patients with disabilities.

The drawbacks of this product are the same as those for the EpiPen given the similarity in available needle lengths and dosages. They include limited evidence-based dosing options for patients >45 kg, and short needle length, which may be an issue in patients with a greater amount of subcutaneous tissue.

Recommendations

Patients Weighing <25 kg
Based on available EAIs and local recommendations, we would suggest the use of either the EpiPen Jr or Allerject 0.15 mg product in all patients weighing less than 25 kg in the absence of a 0.1 mg product in any device currently on the market. There exist no head-to-head clinical trials to assist in deciding which product might be best for your patient. As both these EAIs contain the identical medication and dose, prescribers should consider their respective product-specific benefits such as unique features, product dimension and patient comfort when deciding between them. Patients may also have a personal preference for one product over another based on prior experience

Patients Weighing 25-45 kg
Recommendations in this weight class are for the EpiPen, Allerject 0.3 mg or Emerade 0.3 mg* device. When deciding between these EAIs, we offer similar guidance to that provided above regarding the 0.15 mg devices.

Patients Weighing >45 kg
In agreement with the CSACI recommendations, we propose use of the Emerade 0.5 mg product*. Given that the product monograph does not recommend this product until patient weight reaches 60 kg, we also suggest some caution in the 45-60 kg patient population with small body habitus and less adipose tissue.

Special Populations

All of the above proposals are weight-based, rather than based on metrics that may encompass more relevant patient attributes such as body mass index (BMI). Therefore, we recommend gross assessment of adiposity by all clinicians prescribing EAIs for patients who meet the weight criteria suggested but have a lower BMI or less adipose tissue. Further to this, POC ultrasonographic assessment of the STMD in centres equipped with this technology adds a greater degree of specificity to this assessment and is recommended.[15]

Conversely, some patients may not meet the weight criteria, but have a higher degree of adiposity which may necessitate a longer needle length. Additionally, we recommend these patients undergo assessment of adiposity either clinically or, more optimally, by ultrasound. It is unlikely that many patients have an STMD that would necessitate the 24 mm needle while weighing <45 kg.

In the pediatric population <15, kg, care should be taken to review EAI use with caregivers, in particular that the anterolateral thigh muscle may need to be laterally compressed between the caregiver's hand before the EAI is deployed, in order to prevent intraosseous administration.

***As of May 5, 2023, Bausch Health has recalled all lots of Emerade auto-injectors in Canada due to possible device failure. Our recommendations have been left unchanged to emphasize the need for a device with more adequate needle length and dosing for many patients.**

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Reference: 1. DUPIXENT® Product Monograph, sanofi-aventis Canada Inc., March 25, 2022. **2.** Data on file, sanofi-aventis Canada Inc., August 1, 2022. **3.** IQVIA. Geographic Prescription Monitor Total Prescription Share. May 2022. **4.** Data on file, sanofi-aventis Canada Inc., July 13, 2022.

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Pr DUPIXENT® (dupilumab) Injection

Device	Manufacturer	Approximate Cost in Canadian Dollars per device (ON)[16]	Doses Available	Needle-length	Weight Indication (monograph)	Weight Indication (CSACI) (monograpgh)	Approximate Product Dimensions In(Out) of Package (cm)	Other Features
EpiPen / EpiPen Jr	Pfizer	$94.44-$108.61	0.15 mg	12.7 mm	15-30 kg	<25 kg	16 (14) x 3.5 (2.9)	
			0.3 mg	16.0 mm	>30 kg	25-45 kg		
Emerade	Bausch Health	$85.54-$98.37	0.3 mg	16.0 mm	30-60 kg	25-45 kg	18 (17) x 2.9 (2.1)	
			0.5 mg	24.0 mm	>60 kg**	>45 kg		
Allerject	Valeo Pharma	$93.35-$108.50	0.15 mg	12.7 mm	>30 kg	>25 kg	5.2 (5) x 8.5 (8.5)	Voice-assisted instructions on administration
			0.3 mg	16.0 mm	>30 kg	25-45 kg		

Table 1: *Comparison of epinephrine auto-injector features and recommendations ; courtesy of Harold Kim, MD and Graham Walter, MD mg = milligrams, mm = millimetres, cm = centimetres, kg = kilograms*
***Recommendation in monograph applies to adult patients only*

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