ISSN 2563-7711

CANADIAN ALLERGY & IMMUNOLOGY TODAY

CAIT
VOLUME 2 | ISSUE 1

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Ronald Olivenstein, MD, FRCPC

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EDITOR'S WELCOME



Dear Canadian Allergy & Immunology Community,

Welcome to our first issue of *Canadian Allergy & Immunology Today* in 2022! We are delighted to be back for Year 2 of this publication and equally delighted to have received so much positive feedback about its content from the medical community.

In our newest issue, we discuss a dermatologist's approach to patch testing, asthma and pregnancy, the role of monoclonal antibody therapy in the treatment of chronic rhinosinusitis with nasal polyposis and component driven oral food challenges in the community.

As always, we hope you find these articles informative and helpful. We are grateful to our sponsors for their ongoing support in 2022, to our authors for their commitment to sharing best practices and to our readers for their continued readership!

Best wishes,

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

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COMPONENT DRIVEN ORAL FOOD CHALLENGES IN THE COMMUNITY

The diagnosis of immunoglobulin E (IgE) mediated food allergy is based on the clinical evaluation of a patient's history, physical examination, and specific test results.[1] These tests may include skin prick testing, serum IgE testing, and/or oral food challenge (OFC).[1] Component-resolved diagnosis (CRD) targeting specific allergenic proteins in a food has the potential for improved diagnostic accuracy compared to serum IgE testing to whole allergens.[1-3] An overview of the clinical considerations of how and when to proceed with an OFC will be outlined in this review, with special consideration given to the utility of component testing in making this determination.

Oral food challenges "OFCs" are indicated when the diagnosis of a food allergy is unclear or to assess the resolution to a specific food allergy.[1, 4, 5] Careful consideration of multiple factors is involved when deciding to proceed with an OFC. For instance, the importance of the food in the diet and whether it is likely to be integrated in the diet, are considerations that influence if and/or when a food challenge may occur.[5] Guidance from an individual's history of clinical reactivity, test results, and shared decision making between the patient and provider are needed.[1, 4, 5] A risk-benefit assessment of the possibility of allergic reaction versus the benefit of potentially adding the food into the diet should be discussed between the patient/family and physician.[5] Being familiar with indications for when to offer an OFC is the foundation for allergists to facilitate safe, relevant, and targeted food introduction.[4, 5]

Component testing is a recent and innovative approach that offers additional insights into food allergy diagnosis and management.[1-3] CRD uses recombinant allergens to assess for serum IgE (sIgE) binding to individual proteins within an allergenic food, rather than to a mixture of proteins in an allergen extract, thus distinguishing between sensitization to relevant allergens versus other cross-reactive proteins.[1, 2] CRD testing for plant-derived and animal-derived food allergies are available and can help further guide OFC selections.[6, 7]

For plant-derived food allergies, pollen cross-reactivity should be considered when deciding if an OFC should be offered. In individuals with pollen sensitization, ingestion of plant-derived foods may result in localized symptoms of the oropharyngeal area (i.e., oral allergy syndrome/pollen-food allergy syndrome). This occurs when individuals are sensitized to pollen allergens that cross-react with food allergens including profilins or pathogenesis-related class 10 (PR-10) proteins which are homologous to white birch pollen antigen (*Betula verrucosa* 1 or Bet v 1).[8, 9] These proteins are heat-labile so fruits or vegetables in the raw form trigger symptoms.[10] Without pollen sensitization, allergies to plant-derived foods are due to primary sensitization to more stable proteins, including nonspecific lipid transfer or seed storage proteins, which are more often implicated in systemic allergic reactions and/or anaphylaxis.[11]

In peanut allergy, several studies support the use of CRD.[1, 12] Persistent peanut allergy is associated with detectable IgE levels to specific

seed storage proteins; IgE to Ara h (*Arachis hypogaea*) 2, has been found to be the most predictive component of clinical allergy, outperforming that of whole peanut extract alone.[12-17] Ara h 2 IgE has the greatest specificity in confirming the diagnosis of peanut allergy, and is considered cost-effective.[12] Although an Ara h 2 IgE value of >0.35 kU/L is considered significant, there is no established cutoff level for Ara h 2 IgE, or any peanut component, that seamlessly differentiates between allergy and sensitization at this time.[12] Severe reactions to peanut have been associated with an Ara h 2 IgE level of 2 kU/L or higher, but these cutoffs are limited by low sensitivity (0.78) and specificity (0.45).[12] A recent prospective multicenter study from Germany in which 210 children were challenged orally with peanut estimated a 90% probability for a positive peanut challenge with an Ara h 2 IgE value at 14.4 kU/L, and a 95% probability of reactivity at 42.2 kU/L.[18] Hemmings et al. found that IgE to Ara h 2 and Ara h 6 in isolation were most predictive of peanut allergy, but that a IgE to a combination of allergen components (Ara h 1, 2, 3, and 6) was superior to individual peanut components.[19] Thus, the overall mosaic of specific component proteins may be useful in determining which individuals may have increased risk of allergic reaction, especially when considering IgE binding to Ara h 2.[13, 19] In contrast, sensitization to Ara h 8, which is homologous to Bet v 1, is associated with low risk of clinical reactivity to peanut, and may be considered an indicator for favorable OFC outcome in select individuals without significant sensitization to Ara h 2.[20] Component testing can be helpful for individuals with minimal or no prior reaction history, birch sensitization, older age, and for those with low peanut IgE levels (0.35-15 kU/L).[21] Component testing is less informative with a clear history of recent reaction, lack of birch sensitization, younger children, and/or a remote history of reaction with peanut IgE level ≥15 or levels >25 and <0.35 kU/L.21 While CRD for peanut, especially Ara h 2, has improved the diagnostic accuracy beyond the use of peanut extract alone, it should not replace clinical history and OFC, as there are no universal cutoffs for clinical reactivity.[1, 12, 22]

Component testing is also available for many tree nuts, including cashew, hazelnut, walnut, and Brazil nut. IgE to Ana o 3 (2S albumin protein) is predictive of cashew allergy, and better than cashew-IgE alone.[23, 24] Previous studies have identified the optimum cutoff for the 2S albumin protein, Ana o 3, between 0.16-0.70 kU/L when considering OFC.[25, 26] For hazelnut, sensitization to Cor a 9, an 11S globulin, and Cor a 14, a 2S albumin, are specific for severe food challenge reactions.[27, 28] IgE cutoffs in children for severe hazelnut allergy have been suggested as ≥1 kU/L for Cor a 9 and ≥5 kU/L for Cor a 14.[28] In a German cohort, a 90% probability for a positive hazelnut challenge was estimated for Cor a 14 IgE at 47.8 kU/L.[18] However, Cor a 1 is a heat-labile protein similar to birch pollen that is usually associated with localized oropharyngeal symptoms or hazelnut tolerance, and thus sensitization may indicate a favorable OFC when elevated in isolation.[29] Major walnut (*Juglans regia*, Jug r) allergens include Jug r 1, 2, 3, 4, and 6 and Jug r 5 and 7 are pollen-related. IgE to Jug r 1 and/or Jug r 4 are most predictive of clinical allergy.[30, 31] A prospective cohort study of adults with suspected walnut allergy in the Netherlands found that Jug r 1 had the best discriminative ability to separate between walnut-tolerant and walnut-allergic individuals, compared to Jug r 2 or 3, among a series of double-blind placebo-controlled food challenges to walnut.[32] In this cohort, a cutoff of 1.49 kUA/L (ImmunoCAP Jug r 1) or 2.85 kUA/L (ImmunoCAP ISAC Jug r 1) had a 100% positive predictive value and specificity.[32] A cutoff of 0.1 kU/L (ImmunoCAP Jug r 1) had 91% positive predictive value and specificity (**Table 1**).[32] For Brazil nut, Ber e 1 has been identified as the major allergen, with an optimum cut off as 0.25 kU/L in one UK study of 36 patients with suspected nut allergy.[33] While the role of CRD in tree nuts allergy diagnosis is still being investigated, these studies, many from Europe, illustrate the predictive values of IgE to Ana o 3 (cashew), Cor a 9 and 14 (hazelnut), Jug r 1-4 and 6 (walnut), and Ber e 1 (Brazil nut) in assessing clinical allergy.

Additional plant-derived food allergies with identified component proteins include wheat and soy, however sensitization to these allergens is not consistently associated with clinical allergy or reaction severity.[30, 34] An exception is wheat-dependent exercise-induced anaphylaxis, where IgE to omega-5-gliadin (Tri a 19) has been implicated in clinical reactivity.[35, 36] An optimal cutoff of 0.53 kU/L for omega-5-gliadin IgE has been suggested with an 88% positive predictive value for reactivity, but only 65% specificity.[37] Soy allergens include Gly m 4, Gly m 5, Gly m 6, and Gly m 8.[38] Among these, an optimal IgE cutoff for clinical reactivity has been suggested for Gly m 8 at 3.55 kU/L, however this component has equal sensitivity as soy skin prick test (SPT) or soy IgE.[38] In addition, cross-reactivity of legumes is rare, so legumes (peanut, soybean, green bean,

FOOD	CUTOFF sIgE LEVEL (kU/L) FOR CONSIDERING OFC	STUDY
Milk	BAKED MILK: **Casein IgE:** 4.95 kU/L Milk IgE: 9.97 kU/L	Caubet et al. 2013 [43]
Egg	BAKED EGG: **Ovomucoid IgE:** 1.16-50 kU/L	Bird et al. 2020 [5] Ando et al. 2008 [50] Lemon-Mulé et al. 2008 [51] Caubet et al. 2012 [52] Bartnikas et al. 2013 [53] Saifi et al. 2016 [54]
Wheat	**Omega-5-gliadin (Tri a 19):** 0.53 kU/L	Shibata et al. 2011 [37]
Soy	**Gly m 8:** 3.55 kU/L	Kattan et al. 2015 [38]
Peanut	**Ara h 2:** 2 kU/L – associated with severe reaction 14.4 kU/L – 90% probability of positive OFC 42.2 kU/L – 95% probability of positive OFC	Greenhawt et al. 2020 [12] Beyer et al. 2015 [18]
Cashew	**Ana o 3:** 0.16-0.70 kU/L	Savvatianos et al. 2015 [25] Sato et al. 2019 [26]
Hazelnut	**Cor a 9:** ≥1 kU/L **Cor a 14:** ≥5-47.8 kU/L	Masthoff et al. 2013 [28] Beyer et al. 2015 [18]
Walnut	**Jug r 1** (ImmunoCAP): 1.49 kU/L – 100% positive predictive value and specificity **Jug r 1** (ImmunoCAP ISAC): 2.85 kU/L – 100% positive predictive value and specificity **Jug r 1** (ImmunoCAP): 0.1 kU/L– 91% positive predictive value and specificity	Blankestijn et al. 2017 [32]
Brazil nut	**Ber e 1:** 0.25 kU/L	Rayes et al. 2016 [33]

Table 1: Food Allergen Components and Proposed Cutoff Levels for Clinical Reactivity from Selected Studies

pea, and lima bean) should be considered individually.[39]

CRD has also been used for animal-derived food allergies including milk, egg, shrimp, and red meat. For milk, casein (*Bos domesticus* or Bos d 8) is the major cow milk allergen accounting for up to 80 percent of protein and more severe reactions.[40, 41] Beta-lactoglobulin and alpha-lactalbumin are less clinically relevant. Most milk-allergic children are able to tolerate baked or extensively heated milk.[42] OFC to baked milk should be considered in individuals with favorable history and testing, especially those with favorable casein IgE levels, ideally below 4.95 kU/L when considering both sensitivity and specificity (74% sensitivity, 77% specificity), and with favorable milk IgE levels below 9.97 kU/L (62% sensitivity, 85% specificity).[43] In a small retrospective study, SPT to milk commercial extract was more helpful than a casein SPT and milk IgE levels in determining OFC outcomes.[44] Another retrospective study showed that IgE to milk (p=.011) outperformed a SPT to milk extract (p=.031) and a SPT to fresh milk (p=.473) as the best predictor of baked milk tolerance, suggesting that CRD may not be helpful.[45] Overall, additional data is needed to assess the role of CRD in milk allergy. Other studies that explored the use of boiled milk-specific IgE, cow milk IgE, casein IgE, SPT, and the ratio of specific IgE to total IgE for milk in predicting baked milk OFC outcome have not confirmed their superiority to CRD in diagnostic accuracy.[46-48]

For egg, IgE to ovomucoid (*Gallus domesticus* or Gal d 1) is the best predictor of egg allergy and baked egg tolerance.[49, 50] Similar to milk, most egg-allergic individuals tolerate baked egg.[51] Cutoffs for ovomucoid sIgE that are predictive

of baked egg reactivity range from 1.16-50 kU/L.[5, 50-54] Ovomucoid IgE levels appear to have the greatest predictive value in assessing clinical reactivity to baked egg, and undetectable levels are associated with less than a 10% chance of reactivity to extensively heated (baked) egg.[51]

For shrimp, tropomyosin (*Penaeus monodon* or Pen m 1 and *Penaeus aztecus* or Pen a 1) is the major allergen, and cross-reactivity exists between shrimp and environmental allergens such as cockroach and dust mite.[55] Currently, there is not enough data to suggest that IgE to tropomyosin is predictive of shrimp OFC outcome.[56]

Alpha-gal allergy is a delayed, IgE-mediated, allergy in response to a carbohydrate moiety found in most mammals. Commercial tests for IgE to alpha-gal or galactose-alpha-1,3-galactose are available but have poor sensitivity and specificity, thus favoring fresh meat testing and/or food challenge instead.[57]

In summary, many advances in predicting clinical reactivity have emerged with CRD for both plant and animal-derived food allergies, especially with peanut allergy. **Table 1** summarizes proposed cutoff levels for offering OFC based on existing studies of food allergen components. Consideration of pollen sensitization, cross-reactivity of allergens, and overall trends of skin prick tests and/or serum IgE levels to whole allergen extracts with relevant component proteins are important factors in guiding OFC in practice. CRD is meant to supplement, not replace, a detailed clinical history. It is important to continue to focus on risk of reaction, patient/family preferences, and the nutritional value of a specific food when considering OFC. Staffing and adequate medical supplies in case of allergic reaction should be available for OFC. Ultimately, it is a multifactorial decision to offer and undergo an OFC that involves shared decision making between patient and provider.

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A NEW ERA: EXPLORING THE ROLE OF MONOCLONAL ANTIBODY THERAPY IN THE TREATMENT OF CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS

INTRODUCTION

Chronic rhinosinusitis (CRS), in its simplest form, is inflammation of the paranasal sinuses that has been present for more than three months. The clinical diagnosis is characterized by nasal obstruction/congestion/discharge, facial pain and decreased/absent smell with signs of inflammation in the sinonasal mucosa on endoscopy or computed tomography. An impaired sense of smell and olfactory loss is a cardinal feature of patients with nasal polyps.[1]

CRS affects about 5-12% of the population according to recent epidemiological studies, with a peak prevalence of 16% between the ages of 50-59.[2,3] While the symptoms are often downplayed by patients themselves, the impact on quality of life has been shown to be on par with congestive heart failure, moderate chronic obstructive pulmonary disorder and Parkinson's disease.[4] The most common extra-nasal sequelae are fatigue and depression, with approximately half of patients surveyed reporting fatigue and one-quarter reporting depression.[6] The societal impact is significant with annual rates of absenteeism estimated at 24.6 days a year, and at an overall productivity cost estimated at $10,077 per patient.[6]

A CRS patient's phenotype has generally been classified by the presence or absence of nasal polyps as CRSwNP and CRSsNP, respectively. This phenotyping is also reflected in therapeutic choice for disease management; CRSwNP is generally treated with topical and or oral corticosteroids, and CRSsNP with intranasal corticosteroids and antibiotics. However, as our understanding of the underlying pathophysiology evolves, the treatment strategy is shifting to a more tailored approach. Many different factors have been implicated in the development of CRS including superantigens, microbiome disturbance, biofilm formation, epithelial barrier disturbance, allergy, vitamin D deficiency and genetic predisposition.

Today, most studies concentrate on endotype-driven inflammation in the sinus mucosa. In recent years, Type 2 inflammation has been the most studied, characterized by the presence of interleukins [4,5,9,13] and eosinophils in peripheral blood or nasal mucosal biopsies.[7] Other inflammatory pathways such as Th-17/Th-22, Th1, and neutrophilic inflammation have also been implicated and appear to be more common in the CRSsNP patient population. Other type 2 inflammatory conditions, such as allergic rhinitis, atopic dermatitis and asthma, are highly prevalent among CRS patients, with up to 66% of CRS patients suffering from comorbid allergic asthma.[8] The severity of clinical symptoms and radiographical findings of CRS has been shown to corelate well with the severity of asthma.[9,10] Perhaps the most recalcitrant and severe form of CRS is NSAID-exacerbated respiratory disease (NERD), a clinical syndrome combining CRSwNP, asthma and non-IgE mediated allergy to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) that is also associated with type 2 inflammation.[11]

Management of CRS

It is important for both the physician and the patient to understand that CRSwNP is a chronic disease. The main goal of management is to achieve and maintain clinical symptomatic control of the disease, using appropriate medical therapy, with minimal side effects and the requirement for surgical intervention only when needed. The mainstay of medical therapy is the

use of saline irrigation and intranasal corticosteroid therapy typically dosed b.i.d. but may vary depending on the spray used, both of which are supported by high levels of evidence.[5] High volume nasal corticosteroid delivery by adding corticosteroid to the saline irrigation appears to provide incremental benefit without additional risk. Systemic corticosteroid therapy can provide immediate transient relief of many CRS symptoms, but regular use is associated with significant side-effects and risk, and escalation of therapy should be considered if it is required more than one to two times per year.[12]

In general, endoscopic sinus surgery (ESS) is indicated in CRSwNP patients that fail to achieve symptomatic control with pharmacologic therapy (**Figure 1**). It is important to emphasize that surgery is not curative but rather performed to remove inflammatory polypoid tissue, improve sinus drainage and, most importantly, to allow for effective delivery of topical corticosteroid to the inflamed sino-nasal mucosa.

The majority of CRSwNP patients benefit from surgery, the success of which is largely dictated by the underlying severity of disease and the extent of surgery. Most patients undergoing surgical treatment are able to obtain good control of (most) symptoms with post-operative medical therapy. One retrospective review of 29,934 patients with CRSwNP found that 15.9% required 1 repeat surgery over a mean follow-up of 9.7 years.[13] Performing a "complete/full house FESS" surgery versus "targeted surgery" has been shown to confer a greater improvement in quality of life scores (SNOT-22), smell and endoscopic scores.[14] Targeted surgery vs. complete/full house endoscopic sinus surgery does not confer different risk. The risk to skull base or orbital injury is largely the same in experienced hands, especially with the use of navigation.

CRSwNP patients suffering from co-morbidities such as asthma and N-ERD have a more severe phenotype of CRSwNP, and often need multiple treatments and recurrent surgeries for symptom control.[15,16] It is within this patient population that targeted therapy with monoclonal antibodies appear to offer the most utility.

Biologic agents

OMALIZUMAB
(Anti-IgE antibodies):
The interest in monoclonal antibodies for

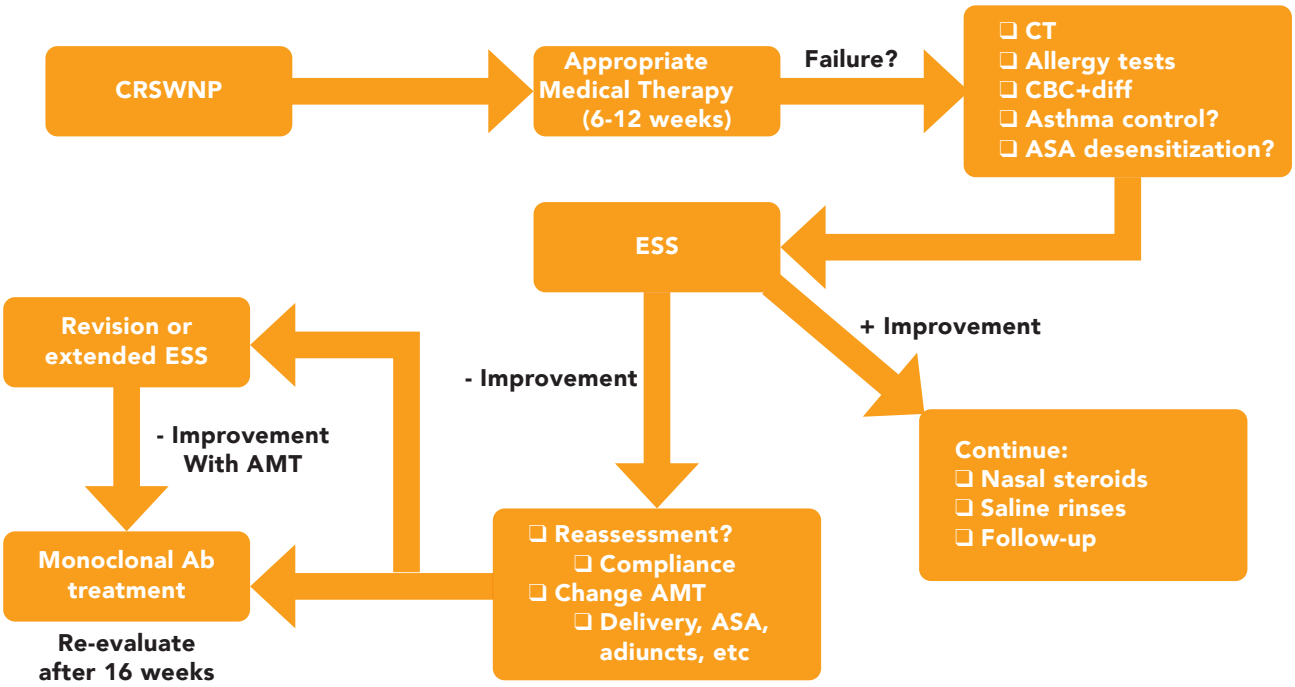


Figure 1. CRSwNP treatment recommendations; adapted from EPOS guidelines,

CRSwNP started when improvements in CRS symptoms were seen with the use of omalizumab for the treatment of asthma. In December 2020, the U.S. Food and Drug Administration (FDA) approved omalizumab for use in CRSwNP patients. This was followed by Health Canada approval in the summer of 2021.

Two randomized, multi-center, phase 3 trials – POLYP 1 and POLYP 2 – evaluated the efficacy and safety of omalizumab in CRSwNP across 82 centers in the U.S and Europe.[17] Patients with CRSwNP and an inadequate response to intranasal corticosteroids were randomized to receive weight and IgE-based dosing of s.c. omalizumab (75-600 mg every 2-4 weeks) or placebo with mometasone nasal spray for 24 weeks. At week 24, the mean changes from baseline for omalizumab versus placebo for POLYP 1 and POLYP 2 were as follows: Nasal polyp score (maximum score 8), -1.08 versus 0.06 and -0.90 versus -0.31; Nasal Congestion Score (maximum score 3), -0.89 versus -0.35 and -0.70 versus -0.20; and SNOT-22 score (patient reported symptoms, maximum score 110), -24.7 versus -8.6 and –21.6 versus -6.6. Clinical improvements were observed as early as 4 weeks for most endpoints, and at 8 weeks for olfaction. An improvement in the objective measurement of olfaction was seen at the end of the trial in comparison to both placebo and baseline (3.8 and 3.4 points, maximum score 40). In smaller studies, omalizumab also exhibited improvement in patient-reported outcome scores.[18,19]

DUPILUMAB
(Anti-IL-4/IL-13 Antibodies) :
Dupilumab is a monoclonal antibody that targets the ∝ subunit of the IL-4 receptor resulting in interruption of IL-4 and IL-13 binding. IL-4 promotes Th2 differentiation, activation of B cell lymphocytes, induces IgE B-cell class switching, trafficking of eosinophils, and M2 macrophage polarization. The function and differentiation of macrophages are controlled by multiple factors. M1 macrophages (classically activated macrophages) are induced by INF-gamma, and M2 macrophages (alternatively activated macrophages) are induced by either IL-4, IL-13, IL-10, or glucocorticoid. Both IL-4 and IL-13 generate their effects on the inflammatory cascade via this receptor pathway, thus, blocking the IL-4 receptor has an effect on both cytokines. In August 2020, Health Canada approved dupilumab as add on therapy for the treatment of CRSwNP in adults. A small study with 60 patients demonstrated an improvement in polyp score, SNOT-22 scores and radiological findings in patients treated with dupilumab versus placebo over 16 weeks.[18] This led to two larger multicenter, randomized controlled phase 3 trials (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52).[19]

In SINUS-24, 276 CRSwNP patients were randomized to receive dupilumab 300 mg s.c. or placebo with mometasone spray every 2 weeks for 24 weeks and then followed for an additional 24 weeks. At the end of the treatment period, a significant decrease in polyp score (-1.89 versus 0.17, maximum score 8) and in nasal congestion score (-1.34 versus -0.45, maximum score 3) were seen. However, after discontinuing dupilumab injections at 24 weeks, a worsening in nasal polyp score and nasal congestion score trending back to baseline was seen.

In SINUS-52, 448 patients were randomized into 3 arms, all of whom received mometasone spray concurrently; the first arm received dupilumab every 2 weeks for 52 weeks, the second arm received dupilumab every 2 weeks for 24 weeks and then every 4 weeks until 52 weeks, and the third arm received placebo. A pooled analysis of the treatment groups demonstrated improvement in nasal polyp score (-1.71 versus 0.10, maximum score 8) and nasal congestion score (-1.25 versus –0.38, maximum score 3). An incremental improvement was seen in nasal polyp score and CT grading in the q2 weekly versus the q4 weekly groups; nasal congestion and other secondary endpoints were similar between groups. The q2 weekly group was also found to have fewer treatment-emergent events of sinusitis and asthma exacerbations.

Both studies demonstrated a significant improvement in measured olfaction with an improvement of 11.3 points on the University of Pennsylvania Smell Identification Test (UPSIT) in SINUS-24 and 9.8 points (maximum score 40) in SINUS-52. Improvement in the primary endpoints were seen as early as 4 weeks in both studies.

MEPOLIZUMAB
(anti IL-5 antibody):
Mepolizumab , an anti-IL-5 antibody was approved for the treatment of CRSwNP in Canada in November 2021. IL-5 is considered to be a primary cytokine in eosinophil activation, and as such, monoclonal therapy targeting IL-5 was felt to hold great promise.[20]

In 2017, researchers reported the results of a randomized double blind placebo-controlled trial assessing the efficacy of 750 mg of mepolizumab in the treatment of CRSwNP.[21] In this study from 2017, 105 patients received 750 mg of

IV mepolizumab or placebo every 4 weeks for a total of 24 weeks (6 doses) in addition to daily topical corticosteroid treatment. In the mepolizumab group, a significantly greater proportion of patients no longer required surgery at Week 25 (16 [30%] vs 5 [10%], respectively; P = .006) A significant improvement in nasal polyposis severity VAS score was also observed in the mepolizumab group (-4.2 versus -2.4, maximum score 10).[21]

That initial study led to SYNAPSE, a randomized, double-blind, placebo-controlled study with 414 patients of whom 407 patients were included in the final analysis.[21] Patients received either 100 mg mepolizumab subcutaneously or placebo, every 4 weeks for 52 weeks, in addition to mometasone nasal spray. During the 52-week treatment period, the risk of nasal surgery was significantly lower with mepolizumab versus placebo (9% versus 23% of patients underwent surgery respectively). The change in nasal obstruction VAS score was -4.4 versus -2.5 in the placebo group (maximum score 10). The improvement in total endoscopic nasal polyp score was significantly higher with mepolizumab (-0.9 versus -0.1, maximum score 8). In the mepolizumab group, 73% of patients had a clinically significant improvement from baseline in SNOT-22 score versus 54% in the placebo group – a numerical improvement of -29 versus -16 respectively (maximum score 110). Objective measures of olfaction were not statistically significant but subjective measures of olfaction improved from baseline by 2.8 in the mepolizumab group versus 1.4 in the placebo group (out of 10).

BENRALIZUMAB
(anti IL-5 receptor antibody):
Benralizumab is a monoclonal antibody that targets the IL-5R ∝ chain. It reduces the blood eosinophil count in peripheral blood and airway mucosa, and may have greater eosinophilic effects than mepolizumab.[23] In the OSTRO study, patients were randomized to benralizumab 30 mg sq or placebo every 4 weeks for the first 3 doses and every 8 weeks for 48 weeks with concurrent mometasone spray.[24] A significant improvement in the total mean nasal polyp score was seen in the benralizumab group compared to placebo at week 40 (-0.42 versus 0.15, maximum score 8). Nasal blockage scores were also improved with benralizumab (-0.71 versus –0.44, maximum score 3) by week 40. Improvement in SNOT-22 scores was seen in both groups (-16 versus –11, maximum score 110), however, the difference between groups did not achieve statistical significance. The time to first surgery was similar between groups and there was no difference between groups in objective measures of olfaction.

Emerging therapeutic agents:

IL-33 and thymic stromal lymphopoietin (TSLP) are mediators of type 2 inflammation. TSLP triggers dendritic cell-mediated Th2 inflammatory responses, and IL-33 targets Th2 cells (i.e., eosinophils, mast and dendritic cells) via the IL-1 receptor. These two innate cytokines can drive Th2 cytokine production and induce and maintain the type 2 inflammation cascade. In recently published data, tezepelumab (anti-TSLP) reduced the number of asthma exacerbations, blood eosinophil count, and IL-5 and IL-13 levels.[25] Etokimab (anti-IL-33) has also demonstrated good results in the treatment of eosinophilic asthma.[25] A clinical trial for etokimab has been completed for CRSwNP but results are not yet published[26], and there is an active phase 3 trial underway for tezepelumab. Thus, these new medications may serve as future therapies for CRSwNP.

No head-to-head studies have yet been completed comparing monoclonal antibodies with each other. A recent meta-analysis[27] examined 29 RCTs evaluating 8 treatments (n=3,461) and compared the outcomes of monoclonal antibodies and aspirin desensitization for treatment of CRSwNP. All biologic agents had a better outcome than placebo, however, dupilumab had superior results in patient-reported outcomes, polyp score, olfactory testing, endoscopic and radiographic scores when compared to other biologics and aspirin desensitization (**Figure 2**). It is also important to note that the placebo group in the majority of trials demonstrated clinical improvement in outcome measures. This may be reflective of the importance and efficacy of stringent adherence to medical therapy with nasal corticosteroid as it is seen in both subjective and objective measures.

Cost of biologic therapy:

The cost of monoclonal antibody therapy is significant in comparison to traditional therapy. The treatment cost per year is between $20,000-$33,000, in contrast to the estimated annual cost of functional endoscopic sinus surgery (FESS) of $3,510 in Canada.[28] A recent Markov analysis compared the cost effectiveness of ESS treatment versus dupilumab in CRSwNP patients; FESS was more cost-effective than dupilumab regardless of the frequency of revision surgery and at any yearly cost of dupilumab above $855. More studies are needed to isolate potential phenotypes or endotypes that will benefit most from dupilumab in a cost-effective manner.[29]

Figure 2. Summary of meta-analysis findings.

	Patient-Important Outcomes						Surrogate Outcomes	
	HRQoL SNOT-22 (0-110)†	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue Polyp Surgery	Adverse events	Nasal Polyp Size (0-8)	CT Score LMK (0-24)
Standard Care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	-19.91 (-22.50, -17.32)	-3.25 (-4.31, -2.18)	10.96 (9.75, 12.17)	-21.73 (-24.61, -18.22) RR 0.32 (0.23, 0.43)	-16.35 (-18.13, -13.48) RR 0.22 (0.14, 0.36)	0.13 (-8.12, 9.88) RR 1.00 (0.88, 1.13)	-2.04 (-2.73, -1.35)	-7.51 (-10.13, -4.89)
Omalizumab	-16.09 (-19.88, -12.30)	-2.09 (-3.15, -1.03)	3.75 (2.14, 5.35)	-12.46 (-23.65, 12.78) RR 0.61 (0.26, 1.40)	-7.40 (-11.04, -2.43) RR 0.65 (0.48, 0.88)	-2.60 (-15.58, 13.28) RR 0.96 (0.79, 1.18)	-1.09 (-1.70, -0.49)	-2.66 (-5.70, 0.37)
Mepolizumab	-12.89 (-16.58, -9.19)	-1.82 (-3.13, -0.50)	6.13 (4.07, 8.19)	-10.23 (-15.98, -2.88) RR 0.68 (0.50, 0.91)	-12.33 (-15.56, -7.22) RR 0.41 (0.26, 0.66)	-3.07 (-13.44, 9.07) RR 0.96 (0.82, 1.12)	-1.06 (-1.79, -0.34)	
Benralizumab	-7.68 (-12.09, -3.27)	-1.15 (-2.47, 0.17)	2.95 (1.02, 4.88)	-9.91 (-16.30, -0.96) RR 0.69 (0.49, 0.97)	-2.53 (-9.05, 7.16) RR 0.88 (0.57, 1.34)	-1.48 (-13.28, 12.54) RR 0.98 (0.82, 1.17)	-0.64 (-1.39, 0.12)	-1.00 (-3.83, 1.83)
Reslizumab					-18.82 (-20.93, 20.56) RR 0.11 (0.01, 1.98)	-2.55 (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						2.54 (-27.11, 51.03) RR 1.03 (0.63, 1.69)	-0.20 (-1.61, 1.21)	
Etokimab	-1.30 (-8.99, 6.40)					188.14 (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	-0.33 (-1.58, 0.92)	
ASA desensitization	-10.61 (-14.51, -6.71)	-2.74 (-3.92, -1.57)	2.72 (-1.17, 6.61)		-16.00 (-19.79, 0.21) RR 0.24 (0.06, 1.01)	209.21 (8.30, 901.87) RR 3.84 (1.11, 13.22)	-0.95 (-2.44, 0.55)	-0.31 (-3.50, 2.88)

Classification of intervention (colour)			Certainty (shading)	
Among most beneficial	Among intermediate beneficial	Among least beneficial/ not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (dotted line)

HRQoL, health-related quality of life; SNOT-22, sino-nasal outcome test 22; VAS, visual analog score; UPSIT, University of Pennsylvania Smell Identification Test; OCS, oral corticosteroids; CT, computed tomography; LMK, Lund-Mackay

**The expected risk of each outcome with standard care is reported in the grey row*

Numbers in the colored cells are the estimated mean differences (95%CI) for HRQoL, symptoms, smell, nasal polyp size and CT score and absolute risk differences (95%CI) per 100 patients (with accompanying relative risks [95% CI]) for rescue OCS, rescue nasal polyp surgery and adverse events versus standard care.

tThe only scale presented where higher is better. Higher scores indicate worse outcome for all other scales shown. GRADE certainty24• 29

High certainty - Further research is very unlikely to change our confidence in the estimate of effect

Moderate certainty - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low certainty - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low certainty - Any estimate of effect is very uncertain

Conclusion:

Monoclonal therapy in treatment of CRSwNP is truly life-changing for patients with severe disease., Most CRSwNP cases can be effectively managed with intranasal corticosteroids and complete surgery. Biologic therapy should be discussed with the patient as part of a potential treatment algorithm and offered when surgical therapy is either contraindicated or already complete in extent. The extent of surgery performed for CRSwNP is subject to wide variability. Patients can undergo multiple polypectomies without complete or adequate response, thus necessitating the important role of CT and review with an experienced surgeon in determining appropriate next steps. The presence of co-morbidities may also help with appropriate patient selection, such as patients with AERD.

Authors from different countries continue to attempt to define a clear protocol for treatment of CRSwNP with biologic agents.[30-32] These consensus statements and published guidelines universally conclude that biologic agents should be considered in patients with recalcitrant disease after appropriate medical and surgical therapy, as well as those with significant co-morbidities.

A Canadian rhinology consensus was published with 11 statements intended to provide guidance on biologic therapy for CRSwNP.[33] In these statements, a key consideration prior to initiation of therapy is whether adequate sinus surgery was performed. This same Canadian rhinology consensus group note that biologics in Canada indicated for asthma can range between $600 to $4000 per vial/ syringe. A recent econometric evaluation demonstrated that upfront surgery for CRSwNP is a more cost-effective option than dupilumab, However, it is clearly evident from the published guidelines that patients who may require revision surgery more than once will likely require it repeatedly and that the time interval between surgeries will diminish with each surgery. Therefore, a cost utility analysis in this clinical scenario is required to address the question of whether biologics or surgery are the most cost-effective approach and in which specific patient populations the benefit may be greatest,[33] Additionally, patients' response to biologic therapy should be evaluated objectively by endonasal endoscopy or CT scan 16 weeks after the onset of the treatment. This clinical assessment can be done with fiber-optic nasal endoscopy or CT scan. In asymptomatic patients with improved subjective scores using questionnaires and improved objective endonasal scores, a CT scan is not needed. In general, endoscopic assessment is recommended as it is easier, less costly and has no radiation associated with it (although the radiation associated with a CT sinus is minimal, and equivalent to approximately 6 chest x-rays). If there is a loss of response, comparing pre vs. post-CT scans would allow for those without access to endoscopy to evaluate if continuing on biologics is warranted.

In summary, CRSwNP is a complex chronic disease that afflicts about 10% of the population. The understanding of the pathophysiology of this disease continues to evolve while the current treatment landscape encompasses the use of therapeutic agents and surgical interventions. Advanced surgical techniques and good adherence to topical therapy can achieve excellent control of symptoms in the vast majority of CRSwNP patients. As newer monoclonal antibodies emerge, it will be important to ensure that appropriate risk-benefit calculations are taken into account for biologic therapy in a targeted CRSwNP patient in addition to an appreciation of the direct and indirect costs to the health system as clinicians strive to achieve optimal outcomes for their CRSwNP patients.

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A DERMATOLOGIST'S APPROACH TO PATCH TESTING: INDICATIONS, PITFALLS AND BENEFITS

INTRODUCTION:

Allergic contact dermatitis (ACD) is a T-cell mediated delayed type IV hypersensitivity reaction that occurs after topical or systemic exposure to an allergen. Patch testing is the gold standard in diagnosing ACD. Acquiring a detailed history from the patient including their medical history, occupational history, hobbies, topical and oral exposures, and site(s) of involvement while having knowledge of the common allergens allows the clinician to create a targeted and personalized approach thus increasing the diagnostic yield of patch testing for each patient.

Indications and approach:

Important indications for patch testing include: a) an acute onset of new dermatitis b) an acute flare of chronic dermatitis and c) dermatitis that is unresponsive to standard topical or systemic therapies. There are key common sites of ACD including eyelids, lips, hands, feet and a widespread distribution that drive most referrals. These particular sites are also commonly associated with specific allergens (**Table 1**) which underscores the rationale for taking a regional approach to patch testing. Although these sites are more common, it is important to remember that ACD can affect any site on the body. Most patients suffering from chronic hand dermatitis should be patch tested as the etiology is often multifactorial including endogenous atopic dermatitis, irritant contact dermatitis (e.g. wet work, hand washing) and superimposed ACD all potentially playing a role.

Some clinicians may benefit from providing the patient with a comprehensive questionnaire prior to their assessment. Although questionnaires can be helpful they can also gather information that is not relevant to the patient's complaint. Questioning should be targeted with a regional approach and requires familiarity with key allergen sources that cause ACD at specific sites. Pertinent details to obtain include: the patient's age, sex, co-morbidities (with special attention to history of atopy including eczema, asthma and seasonal allergies), medications (including over the counter preparations, medical devices, and herbal remedies), underlying medical conditions including previously diagnosed ACD, occupation, and hobbies (including use of sports equipment, specialized gear, cosmetics, grooming practices etc.).

The initial flare of ACD is often described as a pruritic erythematous papulo-vesicular spreading eruption which resolves with scaling. The morphology of ACD varies depending on the site of involvement (**Table 2**) and the stage of the dermatitis (i.e. acute vs chronic). The clinician should ask the patient to specify which sites of the body are affected. It is helpful if the patient has photographs of their dermatitis especially if it has resolved by the time they are seen. It is also important to establish the clinical course of their eruption. ACD typically has a delayed onset after exposure (6-48 hrs) to the allergen and may last for days to weeks, whereas an urticarial reaction will usually occur within minutes to hours of exposure and individual lesions resolve within 24 hours. Other dermatoses such as urticaria, irritant contact dermatitis, scabies, rosacea, seborrheic dermatitis, psoriasis, and lichen planus can be mistaken for ACD and generate unnecessary referrals for patch testing. Performing a pre-assessment

of cases referred by non-dermatologists may help screen these patients, avoid unnecessary patch testing and allow for proper management.

When considering potential allergens that are linked to occupational exposures the patient should be asked if they flare at work and whether improvement is seen during weekends and holidays.

A hairstylist and a mechanic for example will have very different work environments and exposures and therefore it is important for the clinician to recognize key potential allergens that are relevant to each occupational group.

Further inquiries should be targeted to understand the patient's

SITE	COMMON ALLERGENS	COMMON SOURCES
Eyelids	MCI/MI, MI fragrance, balsam of peru, nickel, neomycin, , Quaternium-15, cobalt, DMDM hydantoin, amidoamine, CAPB, thiuram mix, bacitracin, cinnamic aldehyde, tocoperol acetate, tosylamide formaldehyde, propylene glycol, ethyl acrylate, MMA, colophony, ylang ylang, lanolin, gold, hyperoxides of linalool and lemonene[4] Ophthalmic medications such as antibiotics (especially aminoglycosides), neomycin, tobramycin, corticosteroids, tixocortol-21-pivalate, Budesonide, hydrocortisone butyrate, HEMA, Benzalkonium chloride[5]	Shampoos, conditioners, makeup, moisturizers, cleansers, eye cream, wet wipes, jewelry, topical medicaments, artificial nails, glues/adhesives, perfumes[4] eyelash curler, glasses, tweezers, makeup applicators, contact lenses (HEMA), medicated eyedrops[5]
Lips	MCI/MI, rosin, propolis, fragrance mix, balsam of peru, nickel, neomycin, cobalt, propylene glycol, lanolin, gallates, peppermint, cinnamic aldehyde, bacitracin, benzophenone-3, tea tree oil, budesonide, formaldehyde, potassium dichromate, tosylamide formaldehyde[6]	Lip balms, lipstick, makeup, cosmetic products, moisturizers, sunscreens, oral hygiene products, dentistry products, artificial nails, topical medications[6]
Hands	Nickel, MCI/MI, formaldehyde, Quaternium-15, fragrance, neomycin, bacitracin, balsam of peru, cobalt, carba mix, thiuram mix, PPD, potassium dichromate, diphenyl guanidine, HEMA, benzalkonium chloride, propylene glycol, lanolin[7]	Gloves, soaps/cleansers, jewelry, electronic devices, coins, tools[7], moisturizer, personal care products, topical medicaments, acrylic nails.
Feet	Potassium dichromate, PTBFR, thiuram mix, dialkylthioureas, carba mix, colophony, mercaptobenzothiazole, PPD, IPBC, black rubber mix[8]	Rubber shoe linings/insoles, shoe adhesive, leather tanning agent, fabric dyes in footwear, socks and hosiery[9]
Other	**Vulva** Fragrances, preservatives (eg. Quaternium-15, paraben mix, MCI/MI, ethylenediamine dihydrochloride), medicaments (eg. neomycin, bacitracin, clotrimazole, tixocortal-21-pivalate, benzocaine), metals (nickel, cobalt), plant extracts, flavours (eg. peppermint), emollients/vehicles (eg. propylene glycol, lanolin, glycerin), acrylates, rubber accelerators[10]	Topical medicaments, cleansers, condoms, douches, personal hygiene products, sanitary napkins, wipes, cosmetic products[10]
	Occupational contact dermatitis (commonly hands/face) Carba mix, thiuram mix, MI, bisphenol A epoxy resin, formaldehyde, nickel, PPD[11] *Occupations:* Service workers, machine operators/assemblers/inspectors, precision production workers, mechanics/repairers, health professionals, hair dressers[11]	Gloves, safety equipment (masks, respirators), adhesives, glues, bonding agents, paint, metalworking fluid, cutting oils, tools, cement, hair dye, soaps, moisturizers[11]
	Pediatric Nickel, cobalt, neomycin, bacitracin, balsam of peru, fragrances, formaldehyde, MCI/MI, lanolin, propylene glycol, CAPB[12]	Jewelry, toys, electronics, topical antibiotics, sports equipment, personal care products, perfume, cleaning products, toys, glue, slime, moisturizer, lip balm, packaged foods[12]
	Diabetic devices IBOA, MMA, DMAA, cyanoacrylates, epoxy resin, colophonium[13]	Insulin pump and glucose monitor devices specifically the adhesives, circuit boards, plastics, and tubing[13]
	Scalp PPD, fragrance, nickel, balsam of peru, cinnamic aldehyde, MCI/MI, IPBC, oleamidopropyl dimethylamine, MDBGN/PE[14]	Shampoos/conditioners, hair dyes, hair styling products, hair appliances, jewelry, glasses[14]
	Photoallergic contact dermatitis Oxybenzone, ketoprofen, avobenzone, fragrance (sandalwood), benzophenone-4, padimate O, oxtyl methoxycinnamate, PABA, triclosan, chlorhexidine, SQL, thiourea[15]	Sunscreen, medications, anti-microbials, plant extracts, fragranced products

**MI: methylisothiazindone, PPD: paraphenylenediamine, NSAID: non-steroidal anti-inflammatory drug, HEMA: 2-hydroxyethyl-methacrylate, PTBPFR: Para tertiary butylphenol formaldehyde resin, CAPB: cocamidopropyl betaine, MCI/MI: methylchloroisothiazolinone/methylisothiazolinone, IPBC: 3-iodo-2-propynyl-butylcarbamate, SQL: sesquiterpene lactone, MMA: methyl methacrylate, IBOA: isobornyl acrylate, DMAA: dimethylacrylamide, PABA: para-aminobenzoic acid*

Table 1. Examples of common allergens based on site of involvement; courtesy of Veillet-Lemay and Pratt

SITE	CLINICAL PRESENTATION
Hands	Papulovesicular eruption of palmar surface of hand and fingers spreading onto dorsal and lateral fingers as well as dorsal hand. There is often extension of dermatitis onto the ventral and dorsal forearms
Eyelids	Papulovesicular and/or edematous eruption +/- scale affecting both the upper and lower eyelids
Lips	Papulovesicular and/or scaly dermatitis affecting both the upper and lower lips extending onto the perioral region
Feet	Papulovesicular eruption and/or scaly dermatitis affecting the dorsal forefoot as well as dorsal great toe in addition to plantar surface
Widespread	Episodic and vesicular and/or scaly dermatiti explosive episodes that last weeks to months. Some variants include: photo distributed, airborne contact dermatitis, systemic contact dermatitis, symmetric erythema of gluteal and inguinal area and other flexural sites[16]

Table 2. Clinical presentation of allergic contact dermatitis based on site; courtesy of Veillet-Lemay and Pratt

potential allergen exposures and some examples of questions might include: Does the patient use or diffuse essential oils at home? Has the patient tried to treat their dermatitis with an over-the-counter antimicrobial cream or herbal remedy? What exposures does the patient have in the workplace? Do their hobbies require special equipment (gloves, goggles, sports equipment, paints, etc.)?

Patients should be encouraged to bring their personal care products to their appointment (or a photograph of the product including the ingredients) or provide a printed list. These include shampoos, conditioners, soaps, moisturizers, dish and laundry detergents, cosmetics, topical medicaments, etc. The clinician should review the ingredients of each product to identify potential allergens. This process will help target the approach to patch testing and help to better counsel and educate the patient once the final test results have been received. With experience, this process can become very efficient. In some cases it may also be appropriate to patch test the patient to their own products. Leave on products (e.g. moisturizers and topical medicaments) are applied to the skin as is, whereas rinse off products (eg. shampoo, conditioner, soaps) are applied with a semi-open technique. The "semi-open" technique is performed by using a cotton swab to apply a thin layer of the product to a small, marked area on the skin then allowing the product to air dry and then covering with Scanpor tape. Occupational allergens (such as epoxy resins, acrylates, isocyanates etc.) must be appropriately diluted prior to application. A comprehensive textbook written by De Groot can be referenced to find the appropriate dilution concentration and vehicle of various chemicals for patch testing[1]. Finally, testing solid products such as sports equipment, gloves, glucose monitors, stoma devices, dressings, textiles or shoes is performed by cutting a small piece of the material into an approximately 1 inch square, placing it on the patient's skin and covering it with Scanpor tape. After four to five days the product can be removed and the patch test results can be interpreted. After patch testing is completed and a patient is diagnosed with ACD a confirmatory "usage test" or ROAT (repeated open application test can be performed. The "usage test" is performed by applying a product that is known to contain the patient's allergen to a small circular area (approximately 1 inch in diameter) on the volar forearm twice daily for 2 weeks in an attempt to reproduce the initial ACD eruption.

In order to proceed with patch testing, the patient must be advised to stop using all products that are potential sources of their ACD. This includes essential oils (scented candles, massage oils, diffusers), hair dyes, cosmetic products, fragrances etc. Patients are provided with a list of products (shampoo, conditioner, moisturizer, laundry detergent, dish soap etc) that are free of major allergens. If the ACD is thought to be related to their occupation, a medical letter can be provided to exempt them from work or to request the patient be placed in an alternate work environment until patch testing is done. If the patient requires topical treatment of their dermatitis as they await patch testing, we prefer to use ointments that are free of propylene glycol such as betamethasone valerate 0.1% ointment for the body (a group III steroid with lower risk of ACD) and tacrolimus 0.1% ointment for the face and skin folds.

Patch testing is a very valuable tool for both the adult and pediatric population. Patch testing in the pediatric population can be done at any age however is more practical for patients who are five years and older from a compliance perspective. A study examining the patch test results of 1,871 children and 41,699 adults revealed that the prevalence of ACD among children referred for patch testing is similar to adults (55.2% and 57.3% respectively). The most common allergens seen in children included nickel, hyperoxides of linalool, methylisothiazolinone, cobalt, and fragrance mix I. Approximately

20% of children were allergic to products that were not part of the North American Contact Dermatitis Group (NACDG) standard series, emphasizing the need for supplementary testing in some cases[2]. The risk of primary sensitization of children secondary to patch testing to the NACDG standard series is low and should not deter the clinician from proceeding with testing.

There are over 4,000 recognized allergens but a small subset of these are repeatedly seen in the clinic and have emerged as the most common allergens. The NACDG collect data from patch testing and compile the incidence of allergies to various compounds annually. We have summarized the twenty most common allergens from 2017-18 in **Table 3**[3]**.**

Pitfalls:

Although patch testing is a safe and non-invasive procedure, there are factors related to the test and to the patient that must be considered prior to proceeding.

Patient factors:

In order for patch testing to be successful the patient must be motivated and willing to follow instructions which can be difficult especially in the pediatric population. After the patches are applied, the patient is instructed to avoid vigorous activity and should only sponge bathe until after the final reading. Patches are removed after 48 hours, and a first reading is complete. The final reading is done at 96-168 hours (day 4 or 7) after patch test application. Failure to follow these instructions can lead to poor patch adherence and/or false negative results.

ALLERGEN (CONCENTRATION %)	POSITIVE PATCH TEST RESULT (%)
Nickel sulfate (2.5)	16.2
Methylisothiazolinone (0.2)	15.3
Methylchloroisothiazolinone/methylisothiazolinone (0.02)	11.0
Fragrance mix (8.0)	9.2
Hydroperoxide of linalool (1.0)	8.9
Formaldehyde (2.0)	7.4
Formaldehyde (1.0)	5.4
Benzisothiazolinone (0.10)	7.3
Balsam of Peru (25.0)	7.1
Cobalt chloride hexahydrate (1.0)	6.7
Phenylenediamine (1.0)	5.6
Bacitracin (20.0)	5.5
Neomycin sulfate (20.0)	5.4
Propolis (10.0)	4.7
Fragrance mix II (14.0)	4.4
Lanolin alcohol (50.0)	4.4
Propylene glycol (100)	3.8
Oleamidopropyl dimethylamine (0.1)	3.7
Carba mix (3.0)	3.4
Quaternium-15 (2.0)	3.4
Thiuram mix (1.0)	3.4

Table 3. Twenty most common positive patch test rates adapted from North American Contact Dermatitis Group Patch test results from 2017-2018 by DeKoven et al[3]; courtesy of Veillet-Lemay and Pratt

In most adult patients, the patches containing the allergens are applied to their back, however, there are some circumstances when this is not possible (for example if the patient has a large tattoo over their back) and an alternate location such as the upper outer arms are used. If the patient has active dermatitis on their back, due to atopic dermatitis, ACD, or a combination of both, they must be treated prior to patch testing as interpretation of results on already inflamed skin is both difficult and inaccurate.

Many patients that are referred for patch testing have already been prescribed topical or systemic immunomodulating therapies to control their dermatitis which could potentially cause false negative results. Ideally, patients would be patch tested while not utilizing any immunomodulating drugs however this is not always possible. The NACDG released their expert opinion regarding effects of various agents (both topical and systemic) on patch testing which is summarized in **Table 4**[17]. A more recent review article also found that patch testing generally benefits patients receiving dupilumab, low dose prednisone (<10 mg/day) and cyclosporine for the treatment of dermatitis and TNF-$\propto$ inhibitors, ustekinumab and methotrexate for the treatment of psoriasis[18]. Patient's on these medications can still develop positive patch test results therefore it can still be beneficial to investigate if discontinuation of systemic therapies is warranted prior to patch testing. Newer systemic agents for the treatment of atopic dermatitis such as tralokinumab (IL-13 inhibitor), abrocitinib (JAK inhibitor) and upadacitinib (JAK inhibitor) are on the market in North America however we do not yet have data on their impact on patch testing; hopefully over time this data will become available.

Finally, while patch testing during pregnancy and lactation is not known to cause harm it is generally avoided as a precaution[19].

Patch testing specific factors:

An important drawback of patch testing is that it is not readily available in some centers and access can be associated with long wait times. When patch testing is available, there are some circumstances where testing must be delayed. As discussed above, if the patient has active dermatitis on the back, the patient should be treated prior to patch testing to ensure accuracy of results. If the patient does not bring their belongings/products to the initial consult and it is felt to be relevant to their disease manifestation, testing may be delayed (ex: shoes, textiles, dressings, equipment, etc.). There are some circumstances, especially occupational cases, when the suspected allergen is not part of a standard series and must be prepared in advance which may also delay testing.

After many years of experience performing patch testing, the clinician will become familiar with which allergens cause irritant reactions or false positive results. Real-world experience has shown that this can be seen with gallates, formaldehyde, linalool, chromium, methyldibromo glutaronitrile, benzalkonium chloride as well as gold, to name a few. The clinician will also come across equivocal reactions. Interpreting these results in the context of the clinical history requires experience and expertise. **Table 5** summaries how patch test results are interpreted as per the NACDG morphology codes and **Figures 1-4** provides examples.

Lastly, patch testing is a multiple day commitment for the patient

Agent	Consensus opinion
Topical corticosteroids on test site	Avoid between 3-7 days
Ultraviolet exposure at test site	Avoid for one week
Oral prednisone	Can test at 10 mg or less however best to discontinue completely prior to patch testing, by 2 weeks
Intramuscular triamcinolone (40 mg)	Delay patch testing until 4 weeks after injection
Methotrexate	Has little to no effect on patch test results
TNF-a inhibitors	Has little to no effect on patch test results
Ustekinumab	Has little to no effect on patch test results
Azathioprine	Dose dependent inhibition of results
Cyclosporine	Dose dependent inhibition of results
Mycophenolate mofetil	Dose dependent inhibition of results

Table 4. Summary of NACDG expert opinion on effects of various agents on patch test results adapted from Fowler et al.17; courtesy of Veillet-Lemay and Pratt

PATCH TEST RESULT	MORPHOLOGY
1 (+)	Weak (non-vesicular) reaction. Erythema, infiltration, possibly papules
2 (++)	Strong (edematous or vesicular) reaction
3 (+++)	Extreme (spreading, bullous, ulcerative) reaction
4	Macular erythema only
5	Irritant morphology
6 (-)	Negative reaction

Table 5. Interpretation of patch test results

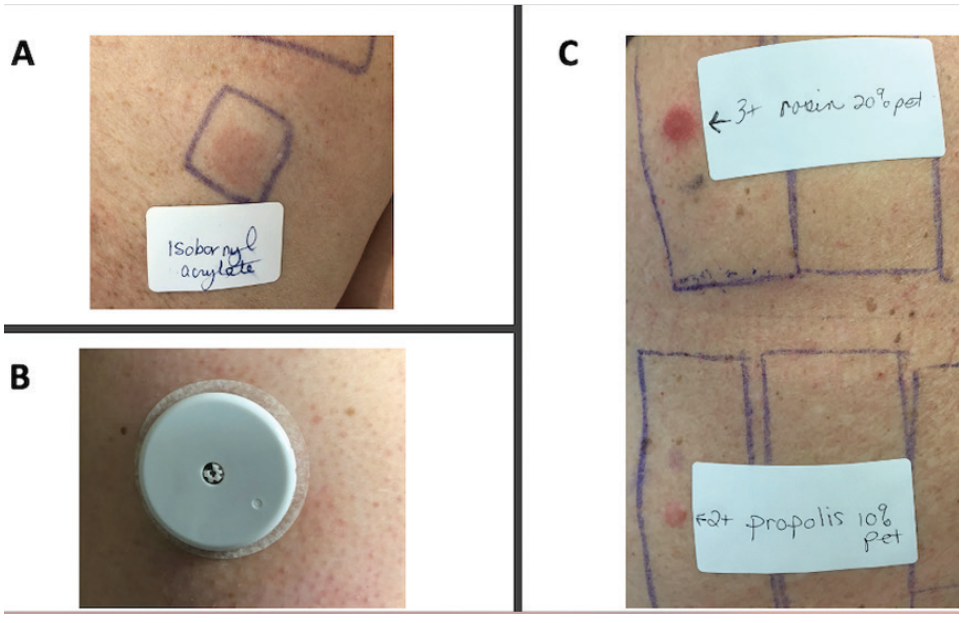


Figure 1. A) and B) An example of a 2+ reaction to isobornyl acrylate found in the adhesive of a glucose monitor. C) Example of a 3+ reaction to rosin in 20% petrolatum and 2+ reaction to propolis 10% in petrolatum.

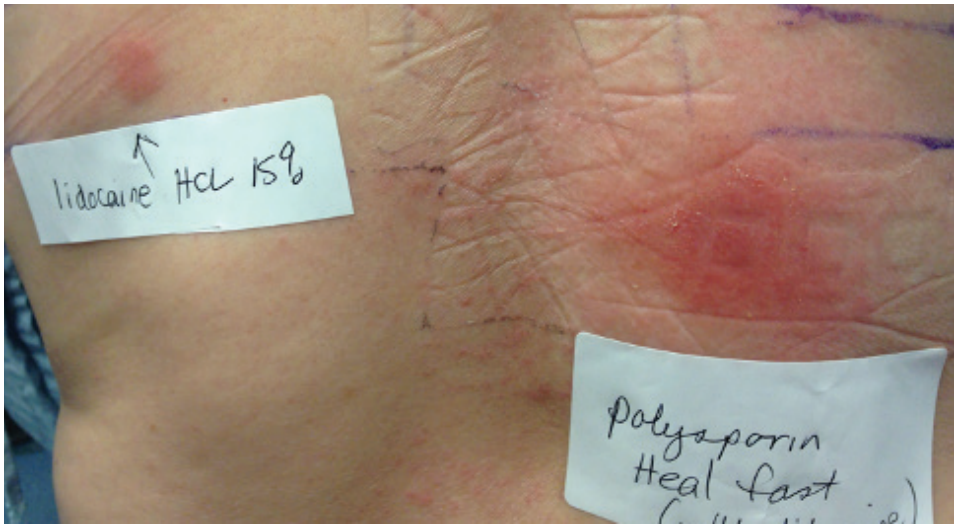


Figure 2. An example of a 2+ reaction to lidocaine hcl 15% and a 3+ reaction to Polysporin ∝ containing lidocaine

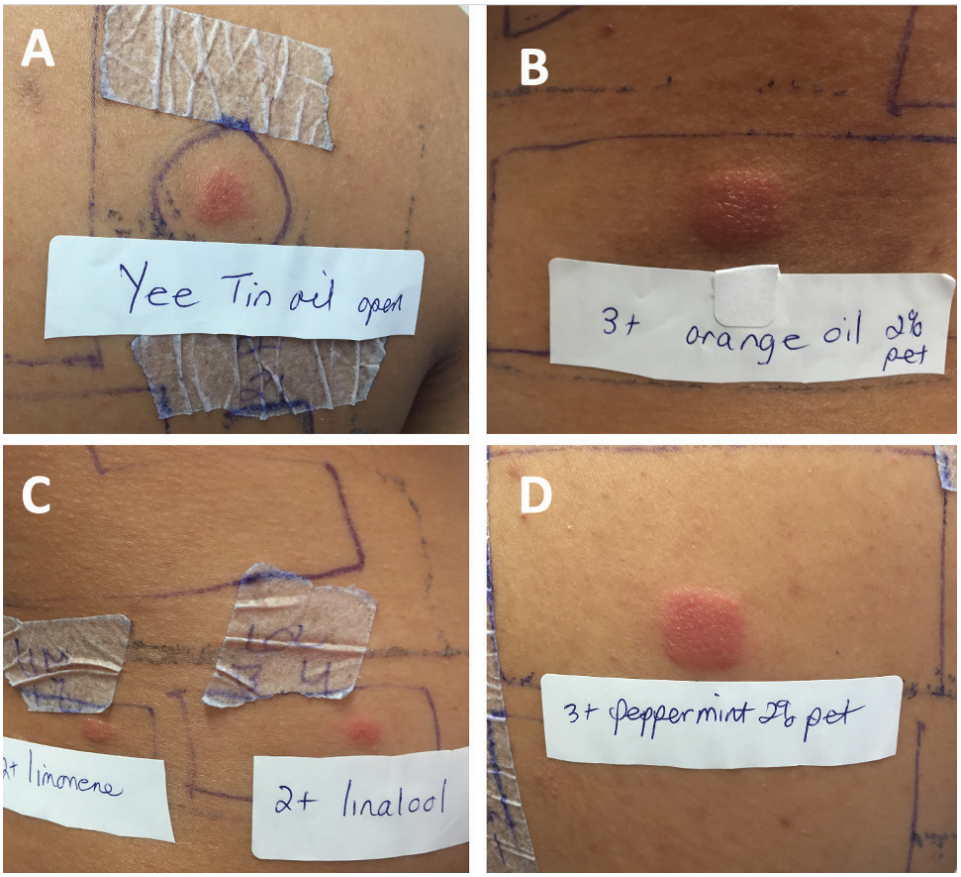


Figure 3. a) An example of an "open patch test" 3+ reaction to Yee Tin oil which is known to contain orange oil, peppermint oil, and limonene and linalool. b) Same patient with a 3+ reaction to orange peel oil 2% in petrolatum. c) Same patient with a 2+ reaction to both hydroperoxide of limonene and hydroperoxide of linalool. d) Same patient with a 3+ reaction to peppermint oil 2% in petrolatum.

which often requires time away from work and recreational activities. Furthermore, patch testing has been associated with reports of itch, sleep difficulty, pain and worsening of rash[20] which is often observed as a recall dermatitis. The patient must understand the level of involvement and be motivated to proceed in order for patch testing to be successful.

Benefits:

Many patients who suffer from allergic contact dermatitis experience a significant improvement in their quality of life after patch testing[21]. There is also value in patch testing patients, both adult and pediatric, with atopic dermatitis. A study looking at 36,834 patch test results from 2001-2016 revealed that most adults (56%) and children (52.8%) with a history of atopic dermatitis that were referred for patch testing had a final diagnosis of ACD. Patch testing and allergen avoidance in these cases can help clarify the etiology of the patient's dermatitis and allow for proper management[22].

In order to reap the benefits of patch testing, the patient must be educated regarding the disease and the sources of their allergens so that they can be avoided in the future. A common misconception among patients and some physicians is that if a product has been used for many months or years, it is unlikely for it to be the cause of the patient's ACD. It is therefore imperative that the patient understand that contact allergies are acquired and can occur even after using a product for years. Once sensitization occurs, future exposures to the allergen will trigger ACD at the site of exposure which, if severe, can become widespread. Patients can be provided with comprehensive handouts detailing their positive allergens and clinicians should consider revisiting the patient's own products to identify any that contain their allergens so that they can be replaced with safer alternatives.

At the initial assessment, patients may be provided with a short list

of products that are low in irritants and allergens and that are safe to use while waiting for the patch testing procedure. For patients who have many allergens or use a wide variety of products, the CAMP database (Contact Allergy Management Program), which is a free resource for members of the American Contact Dermatitis Society (ACDS), may be used. The CAMP database allows users to enter all relevant allergens and generate a list of products free of these same ingredients. Patients are also encouraged to read product ingredient labels or to research ingredients online prior to finalizing a purchase.

Conclusion:

Patch testing is a safe and beneficial procedure when applied to the appropriate patient population. When ACD is suspected, even the most skilled and knowledgeable dermatologist cannot guess what specific allergen is causing the dermatitis as there are hundreds of possibilities. For this reason, patch testing with an informed and systematic regional approach is imperative to the diagnosis and management of ACD. The more familiar a dermatologist becomes with common allergen exposures as well as occupational allergens, the higher the likelihood of successful outcomes in the management of ACD.



Figure 4. This patient is a wood shop worker and was found to be allergic to numerous exotic woods which were all diluted to 10% in petrolatum except Blackwood which was diluted to 5% in petrolatum. They had a 3+ reaction to Cocobolo, Santos Rosewood, East Indian Rosewood, Blackwood, Pau ferro and Bocole. They had a 2+ reaction to Pau Amarello and Bloodwood and a 1+ reaction to Canary Wood. The common allergen found in all of these woods is quinone.

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ASTHMA AND PREGNANCY: WHEN YOU HAVE TO THINK OF TWO (OR MORE) INSTEAD OF ONE

BACKGROUND

Asthma is the most common chronic disease in pregnancy affecting 3 to 12% of women.[1] Poor asthma control is associated with adverse outcomes for both the mother and child.[1] Unfortunately, nearly half of asthmatics[2] discontinue or alter their asthma medication during pregnancy leading to diminished asthma control, and increased risks for mother and fetus from asthma exacerbation, manifesting most often in the middle-to-latter third of gestation. The triggers for asthma exacerbation are the same with or without pregnancy, mainly non-adherence to medications and viral infections. A significant association exists between severe asthma exacerbations in the first trimester and congenital malformations in the fetus as demonstrated in a 2015 publication in which the prevalence of any congenital malformation was 19.1%, 11.7% and 12.0% among women with severe, moderate and no such exacerbations during the first trimester, respectively. The adjusted OR for all malformations in this retrospective cohort study was 1.64 (95% CI 1.02 to 2.64) including cleft lip or palate, heart malformations and spina bifida when women with severe exacerbations were compared with those in the reference group, while no association was seen for moderate exacerbations. Asthma exacerbation can lead to maternal hypoxia which in turn affects fetal development and has been linked to congenital malformations.[3] Accordingly, appropriate treatment in this patient population is essential (**Table 1**).[4]

Pulmonary physiology during pregnancy

Functional residual capacity decreases significantly due to changes in chest wall compliance, but total lung capacity decreases only 5%. Best clinical practice suggests obtaining spirometry at each clinical visit as in non-pregnant women. FEV1 and forced vital capacity (FVC) are not affected by pregnancy leaving the FEV1/FVC ratio unchanged and so FEV1, FVC and the FEV1/FVC ratio remain reliable measurements to monitor asthma. Declines in spirometry reflect real changes in airway patency[5] and therefore in pregnant women with asthma any such decrease in spirometric measurement should be of concern. Hormonal influences on the respiratory center increase minute ventilation 30-50% due to increased tidal volume rather than respiratory rate.[6] Increased abdominal girth contributes to dyspnea in late pregnancy.

Fetal-maternal risks during asthma and pregnancy

Adverse outcomes may include preeclampsia, placental abruption, placenta previa and increased caesarian delivery.[7] In a cohort of asthmatic and non-asthmatic women linking [3] administrative data bases from Quebec, the

	Hospitalisation for asthma (n=110)	ED* visit and no hospitalisation for asthma (n=1413)	No hospitalisation and no ED* visit for asthma (n=35 064)
Any congenital malformation, n (%)	21 (19.1)	166 (11.7)	4196 (12.0)
Major congenitalmalformation, n (%)	13 (11.8)	107 (7.6)	2384 (6.8)

**ED, emergency department.*
Table 1. Prevalence of congenital malformations according to the level of asthma exacerbation in the first trimester of pregnancy: severe (hospitalization), moderate (ED visit and no hospitalization) and reference group (neither ED visit nor hospitalization).

prevalence of spontaneous abortions was 15.9%. Maternal asthma was associated with an increased risk of spontaneous abortion (OR= 1.41) and uncontrolled asthma increased the risk of spontaneous abortion by 26%.[8] Poor asthma control may even affect fertility.[9] Comorbid maternal conditions such as an increased risk of gestational diabetes may normalize with good asthma management.[10]

Poor asthma control can lead to numerous pediatric complications including low birth weight and small-for-gestational-age (SGA) infants. Uncontrolled asthma on two or more occasions during pregnancy may worsen perinatal outcomes even more so than exacerbations. Interestingly, female fetuses are at increased risk for SGA infants while male fetuses tend more towards preterm birth suggesting that fetuses may adjust to pregnancy stresses in a sex-specific manner. [11] Pregnant asthmatics have an increased risk of respiratory viral infections including the common cold[12] and influenza[13] and co-morbid conditions such as rhinitis[14] GERD[15] and sleep apnea may worsen during pregnancy.[16]

Management of Asthma in Pregnancy

Asthma management in pregnancy follows the usual general principles emphasizing symptom control, prevention of exacerbations and preservation of lung function. Discussion with the patient on therapeutics should emphasize the minimal risks and highlight the benefits of appropriate therapy and to develop an independent treatment plan with which the patient is comfortable. Monthly assessments are recommended by GINA (Global Initiative for Asthma).[17] A written asthma control plan should be developed for each patient.

Nonpharmacologic measures

Smoking cessation should be discussed prior to pregnancy. Data from the UK has demonstrated that the few documented tragic deaths in pregnant asthmatics have occurred in smokers.[18] Sensible allergen avoidance measures should be encouraged. Allergen immunotherapy (AIT), subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) should not be initiated during pregnancy due to the potential risk of anaphylaxis. Patients who have tolerated AIT and are maintained on their AIT with clinical benefits may continue their AIT.[19]

Pharmacological Therapy

INHALED AND ORAL CORTICOSTEROIDS (ICS AND OCS)

ICS are the mainstay of drug therapy in asthma. ICS suppress eosinophilic inflammation resulting in improved symptom control, fewer exacerbations and lower mortality. Pregnant patients, concerned about the potential teratogenic effects of any medication including ICS, will often stop inhalers but the deleterious effects of uncontrolled asthma for both mother and fetus are well documented.[20]

WHAT ARE THE FACTS ABOUT RISK VERSUS BENEFIT FOR ICS?

In a meta-analysis of aggregated data from three cohort studies of more than 500,000 pregnancies in Norway (2004-2010), Wales (2000-2010) and Funen, Denmark (2000-2010) a small increased risk of congenital anomalies for women taking asthma ICS medication was observed.[21] Studies based on medical registries in Denmark and Quebec looking at thousands of mother-child pairs showed that ICS treatment during pregnancy is not associated with fetal risk of congenital malformations particularly at doses of less than 1000 µg/d of beclomethasone. Corticosteroid -regulated pathways in the fetus are not affected by ICS use, reassuring the safety of ICS on fetal development. Doses greater than 1000 µg/d of ICS confirm a minimally increased risk of congenital malformation[22] but this requires cautious interpretation as the role of residual confounders such as uncontrolled or severe asthma have not been fully elucidated.

Budesonide (Class B) has long been considered the safest ICS during pregnancy. Recent data confirm fluticasone and beclomethasone are equally safe.[23] Newer ICS such as ciclesonide, mometasone and fluticasone furoate lack long-term safety data but are likely equally safe. A switch of ICS to budesonide during pregnancy is rarely warranted but may be preferred by some patients interested in ICS with the longest safety profile.[24]

The underuse of ICS increases the likelihood of asthma exacerbations thereby requiring the use of OCS. Prednisone is the most commonly-used OCS but about 90% of the blood concentration is inactivated by placental 11ß-HSD-2. Nevertheless, evidence suggests an increased risk of fetal cleft lip and palate with OCS use in the first trimester highlighting the need to maximize asthma control prior to conception. Overall, the benefits of OCS, when warranted clinically, outweigh the risks of sub-optimal asthma therapy.[25]

Bronchodilators

BETA-2-AGONISTS

Beta-2-agonists are known to inhibit airway contractility. Short-acting beta-2-agonists (SABA) such as salbutamol and terbutaline are safe in pregnancy. Long-acting beta-2-agonists (LABA) include the slower onset of action salmeterol, fast-

acting formoterol, and longer (24h) acting vilanterol and indacaterol. Salmeterol has the longest track record of clinical use and formoterol has not been associated with teratogenic effects. Both are safe for use in pregnancy[26] and should always be used in combination with an ICS. Once-a-day ICS-LABA combinations lack adequate safety data in pregnancy and should not be first-line therapy unless adherence is a significant issue.

SABA alone is no longer recommended by GINA. Canadian guidelines now recommend SABA alone only for very mild asthma at low risk for exacerbation.[27] SABA alone should not be used in pregnancy and should always be accompanied by a dose of ICS even for exercise induced symptoms. Budesonide-formoterol use p.r.n. is an alternative. Although not specifically studied in pregnancy, the individual components are safe, and the strategy has been confirmed in mild asthma.[28]

ANTIMUSCARINICS, LEUKOTRIENE MODIFIERS AND THEOPHYLLINES

Short-acting antimuscarinics (ipratropium) are sometimes used in asthma exacerbation and are considered safe in pregnancy.[29] Long-acting anti-muscarinic antagonists (LAMAs) are recommended as adjunctive therapy for more severe asthma that is not optimally controlled by combination therapy with an ICS-LABA combination.[17,27] Perinatal outcome data is lacking but usually LAMAs are continued during pregnancy.

Leukotriene modifiers are used mainly in mild asthma or as adjunctive therapy to ICS-LABA combinations.[17] Their clinical benefit is modest, and a leukotriene modifier should not, in general, replace an ICS in pregnancy. However leukotriene modifiers are generally considered to be safe in pregnancy[30] and so can be continued during pregnancy if effective and well tolerated prior to pregnancy.

Theophyllines are rarely used to treat asthma but are considered safe in pregnancy.

Biologics

Biologics are monoclonal antibodies (mAb) used to treat moderate to severe asthma, mediated by IgE and/or eosinophils. Biologic treatments are IgG-based and as a result they do cross the placenta,[31] but no evidence of teratogenicity has been observed to date.[32] Biologic agents can maximize asthma control in appropriate candidates prior to conception. Successful therapy with biologics prior to conception is usually continued but would rarely be instituted during pregnancy itself due to lack of specific data and the small risk of anaphylaxis.[32] Omalizumab is an anti-IgE mAb with two decades of clinical experience in patients with severe atopic asthma. Omalizumab significantly improves asthma control, prevents exacerbations and decreases the overall use of corticosteroids. A recent analysis of a cohort of pregnant asthmatics using omalizumab (EXPECT)[32] showed that proportions of major congenital anomalies, prematurity, low birth weight, and small size for gestational age observed in the EXPECT registry are consistent with findings from other studies in this asthma population and therefore do not suggest higher incidence from use in pregnancy.

Mepolizumab and reslizumab, biological agents that directly inhibit IL-5 (interleukin-5) and benralizumab which binds to the IL-5 receptor, have been successfully used in patients with severe eosinophilic asthma. Primate studies have not shown any adverse fetal effects.[34] Specific data in pregnancy and lactation is lacking, but no evidence of harm has been noted.

Dupilumab inhibits IL-4 and IL-13 by binding to the IL-4 receptor alpha and is indicated for severe asthma and with other Type 2 diseases such as nasal polyposis and atopic dermatitis. Clinical response is predicted by higher levels of FeNO and serum eosinophilia. Dupilumab use in pregnancy has limited data and should be reserved in pregnancy when other agents with registry data have failed or cannot be used.

KEY CLINICAL TAKE AWAYS

Asthma is the most common chronic disease during pregnancy.

Asthma exacerbation is most common between weeks 24 and 36 of pregnancy.

Uncontrolled asthma before and during pregnancy is harmful to mother and fetus and good asthma control prevents complications such as pre-eclampsia, premature birth and small for gestational age infants.

Current asthma medications and in particular inhaled corticosteroids, bronchodilators and biologics are safe to use during pregnancy and promote asthma control.[33]

Asthma care for pregnancy should begin before conception.

Can biomarkers be useful in asthma management in pregnancy?

A FeNO-based algorithm to adjust ICS and LABA in pregnant asthmatics showed an important reduction in asthma exacerbations as well as improvements in quality of life and reduced neonatal hospitalizations.[35] ICS doses were increased earlier in eosinophilic

asthma and, for asthmatics with low inflammatory markers, the doses of ICS were decreased and LABA introduced earlier leading to better asthma control. Further study of this interesting phenotypical approach to treat asthma in pregnancy is needed.

Considerations during labour

During labour, usual inhalers should be continued and induction therapy such as oxytocin and prostaglandin E2 are considered safe.[36] Prostaglandin F2 alpha derivatives should be avoided in cases of obstetric bleeding, if possible, as they can cause bronchoconstriction. Stress protocol hydrocortisone can be considered for the patient who is cortico-dependent or after an OCS boost prior to delivery.

Conclusions

Uncontrolled asthma in pregnancy is harmful to mother and fetus. The clinical benefit and innocuity of current asthma medications in pregnancy is well established. Most of the anti-inflammatory medications available for asthma whether alone or in combination with long-acting bronchodilators can be safely used in pregnancy and the choice should depend on factors such as ease of use and likelihood to promote adherence.

The establishment of a therapeutic relationship between patient and health care professional and regular follow-up during pregnancy is essential.[37] Asthma care for pregnancy should begin well before conception for any asthmatic considering having a child to ensure optimal asthma care, encourage discussion of the risk-benefit profile of different medications and to facilitate coordination of care with the obstetrics or family medicine team.

Algorithm for asthma management in the MAP (Managing Asthma in Pregnancy) trial*

	FeNO concentration (ppb)	Symptoms (ACQ score)	IS dose change	B2-agonist dose change
Level 1	>29	NA	ICS x 1 step	No change
Level 2	16-29	<1.5	No change	No change
Level 3	16-29	>1.5	No change	LABA x 1 step
Level 4	<16	< 1.5	ICS x1 step	No change
Level 5	<16	>1.5	ICS x1 step	LABA x 1 step

FeNO=fraction of exhaled nitric oxide. ACQ=asthma control questionnaire. ICS=-inhaled corticosteroid. NA=not part of the assessment at this FeNO level. LABA=longacting B2 agonist.

Table 2: Dose changes based on FeNO and ACQ results for the FeNO intervention algorithm

	ICS step	B2 step
Step 1	0	Salbutamol as required
Step 2	Budesonide 100 ug twice per day	Formoterol 6 ug twice per day
Step 3	Budesonide 200 ug twice per day	Formoterol 12 ug twice per day
Step 4	Budesonide 400 ug twice per day	Formoterol 2 x 12 ug twice per day
Step 5	Budesonide 800 ug twice per day	Formoterol 2 x 12 ug twice per day

FeNO=fraction of exhaled nitric oxide. IS=inhaled corticosteroid.

Table 3: FeNO algorithm treatment steps

The treatment algorithm used a two step process. First the level of ICS was adjusted using the FeNO concentration; then the ß2-agonist dose was adjusted using the Asthma Control Questionnaire (ACQ) score. A significant reduction in asthma exacerbations during pregnancy was demonstrated using this methodology. The mean daily dose of ICS was decreased and more LABA was used during the pregnancy.
**Powell et al Lancet 2011.*

Asthma Control Questionnaire[16] : a clinical tool to measure how well asthma is controlled

The total score is divided by 7. An ACQ score of < 0.75 denotes good asthma control; 0.75-1.50 denotes partial asthma control; >1.5 denotes poor asthma control; Juniper et al Eur Respir J 1999; 14: 902-7[38]

ASTHMA CONTROL QUESTIONNAIRE **Please answer questions 1-6** **Circle the number of the response that best describes how you have been during the past week**	
1. On average, during the past week, how often were you woken by your asthma during the night?	0 Never 1 Hardly Ever 2 A few minutes 3 Several times. 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning.	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3. In general, during the past week, how limited were you in your activities because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited"
4. In general, during the past week, how much shortness of breath did you experience because of you asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5. In general, during the past week, how much of the time did you wheeze?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6. On average, during the past week, how many puffs of short-acting bronchodilator (eg. Ventolin) have you used each day?	0 None 1 1-2 puffs most days 2 4 puffs most days 3 8 puffs is most days 4 9-12 puffs most days 5 13 -16 puffs most days 6 More than 16 puffs most days"
To be completed by a member of the clinic staff 7. FEV1pre-bronchodilator: ..... FEV1 predicted ..... FEV1 % precicted ..... (Record actual values on the dotted lines and score the FEV1 % predicted in the next column)	0 >95% predicted 1 95-90% 2 89-80% 3 79-70% 4 69-60% 5 59-50% 6 <50% predicted

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