Drug-induced anaphylaxis visits: temporal trends, triggers and management in four Emergency Departments across Canada

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Abstract

Data is sparse on drug-induced anaphylaxis (DIA). We aimed to assess the percentage, diagnosis and management of DIA among all visits due to anaphylaxis in 3 pediatric Emergency Departments (ED)s and 1 adult ED across Canada. Children presenting to the Montreal Children's Hospital (MCH), British Columbia Children's Hospital (BCCH) and London Health Sciences Centre Children's Hospital (LHSC) and adults presenting to Hôpital du Sacré-Coeur de Montréal (HSC) with anaphylaxis were recruited as part of the Cross-Canada Anaphylaxis Registry (C-CARE). A standardized data form documenting the reaction and management was completed and patients were followed annually to determine if they were assessed by an allergist. From June 2012 to May 2016, 40 children presented to the MCH and 64 adults to HSC with DIA. From June 2014 to May 2016, 7 children and 4 children presented with DIA to the BCCH and the LHSC, respectively. More than half the cases were prospectively recruited. The percentage of DIA among all cases of anaphylaxis was similar in all three pediatric centres but was higher in the adult centre in Montreal. Most reactions in children were triggered by non-antibiotic drugs, and in adults, by antibiotics. The majority of adults and a third of children did not see an allergist after the initial reaction. In those that did see an allergist, diagnosis was established by either a skin test or an oral challenge in less than 20% of cases. Our results reveal high levels of DIA in adults compared to children and that most cases of suspected drug allergy are not appropriately established. It is crucial to develop guidelines for better assessment and diagnosis of DIA in order to appropriately manage these patients.

Résumé

Les données sur le choc anaphylactique (CA) médicamenteux sont clairsemées. Notre objectif est d'évaluer le pourcentage, diagnostique et traitements de CA médicamenteux parmi les visites dû à l'anaphylaxie dans 3 département d'urgences de pédiatrie et 1 département d'urgence d'adulte à travers le Canada. Les enfants qui se présentent à l'Hôpital de Montréal pour enfants (HME), British Columbia Children's Hospital (BCCH), London Health Sciences Centre Children's Hospital (LHSC) et les adultes qui se présentent à l'Hôpital du Sacré-Cœur (HSC) avec anaphylaxie sont recrutés dans le cadre d'un registre transcanadien d'anaphylaxie nommé C-CARE. Un formulaire normalisé documentant les réactions et traitements a été complété et les patients ont été suivis annuellement pour déterminer s'ils étaient évalués par un allergologue. Chez ceux qui ont vu un allergologue, le diagnostic a été établi soit par un test cutané ou une provocation orale dans moins de 20% des cas. De Juin 2012 à Mai 2016, 40 enfants se sont présentés au HME et 64 adultes au HSC avec CA médicamenteux. De Juin 2014 à Mai 2016, 7 enfants se sont présentés avec CA médicamenteux au BCCH et 4 enfants au LHSC. Plus que la moitié des cas ont été recrutés prospectivement. Le pourcentage de CA médicamenteux parmi tous les cas d'anaphylaxie était semblable dans les trois centres pédiatriques, mais était plus élevé dans le centre pour adultes de Montréal. La plupart des réactions chez les enfants ont été déclenchées par des médicaments non-antibiotiques, et chez les adultes, par des antibiotiques. La majorité des adultes et un tiers des enfants n'ont pas vu un allergologue après la réaction initiale. Nos résultats nous révèlent un taux élevé de CA médicamenteux chez les adultes comparativement aux enfants et que la majeure partie des cas suspects d'allergie aux médicaments n'étaient pas correctement établis. Il est crucial de développer des lignes directrices

pour une meilleure évaluation et diagnostique de la CA médicamenteux afin de correctement traiter ces patients.

Preface

This thesis discusses the percentage, management, and diagnosis of DIA between 3 pediatric centres and 1 adult centre across Canada. First, an introduction is presented highlighting the important role of drugs in anaphylaxis, the increasing prevalence of DIA, and the burden of misdiagnosis of drug allergy in Section 1.0. In order to assess the disparities in management and diagnosis of DIA in adults and children, it is crucial to understand how the diagnosis of DIA is established through clinical symptoms and confirmatory tests. Sections 2.1, 2.2, and 2.3 provide detailed description of the classification, clinical presentation, and diagnosis of DIA. A literature review of the current knowledge regarding DIA is given in Section 2.0. The study objectives are then presented in Section 3.0, followed by the study methodology and results in Sections 4.0 and 5.0, respectively. Finally, the Sections 6.0 and 7.0 discuss interpretation of results and concluding remarks.

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Contribution of Authors

The idea for the thesis was developed by Dr. Moshe Ben-Shoshan. The study design and protocol for C-CARE were developed by Dr. Ben-Shoshan and Dr. Ann Clarke. Data collection, which involved recruiting patients in the EDs and contacting patients annually for follow-up, was conducted by Sofianne Gabrielli and Dr. Harley Eisman at the Montreal Children's Hospital, Dr. Judy Morris at Hôpital du Sacré-Coeur de Montréal, Dr. Paul Enarson and Christopher Mill at the British Columbia Children's Hospital, and Dr. Rod Lim at the Children's Hospital at London Health Science Centre. The data was analyzed and prepared by Sofianne Gabrielli, Dr. Lawrence Joseph, Dr. Ben-Shoshan, and Dr. Ann Clarke.

Abbreviations

DIA – Drug-induced anaphylaxis
ED – Emergency department
NSAIDs – Non-steroidal anti-inflammatory drugs
OC – Oral challenge
SPT – Skin prick test
IDT – Intradermal skin test
PPV – Positive predictive value
NPV – Negative predictive value

CI – Confidence interval
OR – Odds ratio
IQT – Interquartile range

MCH – Montreal's Children Hospital
HSC – Hôpital du Sacré-Coeur de Montréal
BCCH – British Columbia Children's Hospital
LHSC – Children's Hospital at London Health Science Centre

1.0 Introduction

Drug-induced anaphylaxis (DIA) is a life-threatening allergic reaction involving at least two organ systems and/or hypotension triggered by a drug exposure[1, 2]. Drugs are a common yet under-recognized cause of anaphylaxis that can affect people of all ages[3]. Studies report that the prevalence of anaphylaxis ranges from 8 to 50 people per 100 000 per year[4], however the true prevalence of DIA is unknown, with estimates of 1 case per 4000 Emergency Department (ED) visits due to DIA[5]. A recent study conducted in Australia found that hospital admission rates due to DIA have increased by 6.8% per year over 16 years and that DIA was the leading cause of fatal anaphylaxis[6]. In the United States, drugs were also found to be the most common cause of fatal anaphylaxis with fatalities significantly increasing from 1999 to 2010[7]. Appropriate follow-up by an allergist is recommended for confirmation of the allergen and proper education for avoidance or desensitization. Yet, it is reported that patients who have experienced DIA are

more likely to consult an allergist only if the individual has a concomitant allergic condition, such as asthma, and has already seen an allergist prior to the ED visit[3].

Studies suggest an increased prevalence of self-reported antibiotic allergy over the past decade, mainly in children[8, 9]. Almost 10% of the Canadian population report having an allergy to an antibiotic, of which the majority are labelled as allergic and are not properly evaluated by confirmatory tests[10]. Direct costs as a result of the increase in use of alternative broad-spectrum antibiotics instead of first-line drugs are estimated to be as high as 30 million CAD annually[11]. Indirect costs, due to possible antimicrobial resistance leading to increased ICU admissions and length of hospital stays, have been reported to be as high as 30 billion CAD annually[12]. In order to avoid the misdiagnosis of children and adults who are not truly allergic, assessment by an allergist is needed to either establish or rule out the diagnosis of drug allergy.

Currently there are no prospective studies assessing the clinical characteristics and management of DIA. Furthermore, no studies so far have assessed differences in clinical characteristics and management of DIA between pediatric centres across Canada, nor between pediatric and adult EDs. We assessed the percentage, demographics, clinical characteristics and management of DIA cases treated in 3 pediatric EDs and 1 adult ED across Canada.

2.0 Literature Review

2.1 Classification

Hypersensitivity reaction to drugs can be classified as four types. Type I hypersensitivity reaction is an IgE-mediated reaction that is immediate[13], occurring in less than 1 hour from exposure to the drug[14]. Symptoms include urticaria, angioedema, wheezing, hypotension, abdominal pain, and diarrhea[14]. Type II hypersensitivity reaction is a cytotoxic reaction that is non-immediate[13]. The symptoms include hemolytic anemia, granulocytopenia, and

thrombocytopenia[14]. Type III hypersensitivity is a non-immediate immune complex reaction[13]. Symptoms of the reaction include fever, urticaria, arthralgia, nephritis, and hepatitis[14]. Type IV hypersensitivity is the most common non-immediate reaction that usually develops 6 hours to 10 days after drug exposure[14]. The reaction is T-cell mediated and usually manifests itself as a delayed cutaneous reaction but may have various types of clinical presentations[14].

Anaphylaxis is a life threatening type I hypersensitivity reaction and will be the focus of this thesis.

2.2 Clinical Picture

Anaphylaxis is a serious, life-threatening allergic reaction that has a rapid onset[2]. The most common manifestation of anaphylaxis is cutaneous, with over 80% of cases experiencing skin symptoms[15], followed by respiratory, cardiovascular and gastrointestinal symptoms[1]. To appropriately identify cases of anaphylaxis, criteria were developed which define anaphylaxis as the involvement of 2 or more organ systems after exposure to a possible allergen or hypotension after exposure to a known allergen[15].

Mild anaphylactic reactions include the symptoms urticaria, erythema, angioedema, oral pruritus, nausea, nasal congestion, sneezing, rhinorrhea, or throat tightness[16]. Symptoms of moderate reactions include crampy abdominal pain, diarrhea, recurrent vomiting, dyspnea, stridor, cough, wheeze, or "light-headedness"[16]. Finally, severe reactions include symptoms of cyanosis, hypoxia, respiratory arrest, hypotension, dysrhythmia, confusion, or loss of consciousness[16].

2.3 Diagnosis

2.3.1 Skin Tests

Standardized skin tests for allergy testing include skin prick test (SPT), intradermal skin test (IDT) for immediate reactions, and patch test for non-immediate reactions. An SPT is done by pricking the surface of the skin, usually the forearm, with a needle. This method is safe and easy, but has low to moderate sensitivity[17]. An IDT test is done by injecting 0.02 to 0.05 mL of an allergen intradermally. This method is more sensitive that an SPT but carries the risk of irritation leading to false positive results[17]. For both the SPT and IDT, the patients are observed for 15 to 20 minutes after application for any skin reaction. If no wheals or erythema are present after the allotted time, the test is negative. If wheals appear, the mean diameter of the wheal is measured, along with the wheal of the negative control. The skin test is considered positive when the size of the wheal is 3 mm greater than the diameter of the negative control for an SPT or 5 mm for an IDT[17]. A patch test is usually placed on the upper back of patients and is read 1 day and another 2-3 days after. The results between the 2 days are compared to determine if the patch test is positive[17].

Skin testing for certain drugs can help in identifying the cause of the reaction, however diagnosis of immediate reactions can be difficult. Standardized skin tests are only available for penicillin[17]. The positive predictive value (PPV) for penicillin skin testing is over 95%[18], while the negative predictive value (NPV) is about 50%[19, 20], indicating a high number of false positives. In a study conducted by our team, Mill et al. were able to demonstrate that penicillin skin tests were not useful in diagnosing children who had previously reacted to amoxicillin. In patients who had reacted immediately, skin tests were negative in 95% of cases[21]. However, SPT for penicillin can be important tool used to de-label patients who report a penicillin allergy,

since 90% of these patients are not truly allergic and can tolerate subsequent treatment with β-lactam antibiotics[10, 22]. De-labeling of these patients reduces the use of other broad-spectrum antibiotics, thus reducing antibiotic resistance[22, 23].

For many other antibiotics, such as cephalosporins, macrolides, and fluoroquinolones, skin testing is not ideal since the tests are not standardized and may cause skin irritation leading to a high rate of false positive tests[20, 24, 25]. The PPV of cephalosporin and macrolide antibiotics are unclear, with multiple single studies reporting vastly different results[26-28]. Diagnosis of fluoroquinolone allergy can be especially challenging because fluoroquinolones induce direct histamine release[29]. Skin tests for NSAIDs are not useful since there have not been studies documenting their sensitivity, specificity or PPV[1, 30].

A negative skin test result is not sufficient to rule out a drug allergy. In most cases, the patient may need to proceed with a graded oral challenge in order to establish or exclude drug allergy[17]. However, a positive skin test is considered sufficient for the diagnosis of a drug allergy. When interpreted together with the clinical history of the initial reaction, the patient is advised to avoid the drug and alternative drugs should be used[17].

Along with skin tests, laboratory tests such as specific IgE assays, basophil activation test, and leukocyte histamine release test can be performed to diagnose drug allergy. However, these tests have not been validated for many drugs and are not widely available[20, 31].

2.3.2 Graded Oral Challenges

A graded oral challenge (OC), is considered the gold standard to establish drug allergy since it reproduces allergic symptoms. An OC should be performed with dose-controlled administration under strict medical surveillance[32]. Since these challenges are not without risk, the risk-benefit ratio must be weighed for each individual patient[20]. In patients with non-

immediate reactions, OCs are usually safe. OCs are contraindicated for pregnant women, patients with uncontrolled asthma, patients with acute infections, and patients with underlying diseases. They should also not be performed in those who have had severe, life-threatening reactions to drugs such as Steve Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms[32]. The drug is usually administrated through the oral route, but can also be given parenterally or nasally to replicate the initial reaction[32]. An OC is started with a low dose, ranging from 1:100000 to 1:10 of the therapeutic dose, and is increased gradually with a time interval of at least a half hour between doses[1, 32]. Drug OCs should be done in 2 to 3 incremental doses maximum as to not inadvertently induce drug desensitization. Patients should be observed for at least 1 hour after the therapeutic dose is reached or for the length of time a severe reaction can be expected depending on the drug[32]. An OC is positive if an objective symptom is reproduced. False positive tests can also occur during an OC due to anxiety causing throat tightness or dyspnea. The risk of a false positive OC can be reduced through a placebo-blind procedure. An OC is negative in the absence of symptoms; however, a false negative result is still possible due to lack of co-factors (ie. medication, viral infection, exercise), incorrect dosing, or inadvertent desensitization[32]. If an OC establishes a positive drug allergy, the treatment is usually avoidance of the drug.

OCs can be used to diagnose both patients who have had non-immediate or immediate reaction to antibiotics, with the benefit of de-labeling them as being allergic[23]. Mill et al. demonstrate, based on an OC, that of the population suspected to have amoxicillin allergy, 2% have immediate reactions to the challenge, 4% will have non-immediate reactions, and almost 10% reactions will occur only during full treatment. The amoxicillin OC was shown to have a

specificity of 100%, a NPV of 89.1%, and a PPV of 100%. The OC proved to be useful and safe in both non-immediate and immediate reactors[21].

OCs can be used to diagnose allergy to fluoroquinolones, however this carries some risk since reactions to fluoroquinolones can be severe[29]. A study by Venturini et al. performed quinolone challenges in patients with either positive or negative skin tests to the same quinolone, which revealed that in patients with positive skin tests, 50% had a negative OC, further establishing the need for OC to diagnose drug allergy[33].

Due to the lack of standardized skin tests available for NSAIDs, an OC with the culprit drug is necessary to confirm drug allergy[20, 34]. If positive, an OC with an alternative NSAID with a chemically different structure should be considered to determine tolerance and provide alternative treatment [30].

The OC has potential risks, which can mostly be avoided with a detailed clinical history and by carrying out the challenge in an appropriate hospital setting in the presence of an allergy specialist and experienced nurse. There is no consensus on the use of OCs to confirm drug allergy[20], however they are often necessary[1, 21, 24]. Usually a stepwise approach, beginning with an SPT, followed by an OC if the SPT is negative, is carried out by most centres.

2.4 Prevalence

The prevalence of anaphylaxis in developed countries such as Australia, United States and Canada has increased over the past decade[6, 35-37]. A nationwide study previously reported that 1.6% of the general population will experience anaphylaxis in their lifetime[38], with food and drugs as the primary causes[39]. A study done in a Montreal ED by our group revealed that the percentage of anaphylaxis cases among all ED visits over a 4-year period in a pediatric hospital, from 2011 to 2015, doubled from 0.2% to 0.41%[36]. Hospital admissions due to

anaphylaxis have also increased over time; an Australian study showed total admission rates of anaphylaxis increased by 10.2% per year over a period of 15 years[6]. Similarly, in the United States, there was a 4-fold increase in hospital admissions for anaphylaxis[40]. In Europe, while the percentage may not be as high, multiple countries report increasing rate of anaphylaxis[41, 42]. From 1999 to 2011, the rate of hospitalization for anaphylaxis increased approximately 3-fold in both Finland and Sweden[41]. Generally, anaphylaxis is reported most in children in the 0- to 4-year-old range than any other age group[37], accounting for an increasing percentage of visits in pediatric EDs[36]. Most studies concluded that anaphylaxis, as a disease, was underdiagnosed and undertreated.

Recently, multiple studies report that the rate of DIA is also increasing[1, 6, 39], however this remains unclear. Mullins et al. reported that DIA hospital admissions in Australia increased by 6.8% per year from 2000 to 2015[6]. In the United States, DIA is responsible for over 230,000 hospital admissions annually, with over 80% of reactions occurring in an ambulatory setting[1]. Higher rates of DIA were reported in adults in middle and older age groups[37, 39, 43] and in African-Americans[37]. The prevalence of fatal anaphylaxis is rare, having been reported as 0.69 people per million[37]. In a Canadian study, the province of Ontario experienced a decline in deaths caused by anaphylaxis, however fatalities related to medications increased from 1986 to 2011[44]. In Australia, the leading cause of fatalities due to anaphylaxis was caused by medications[6], accounting for 57% of deaths[39]. Similarly, the U.S., the U.K. and New Zealand also all report that deaths caused by medication-related anaphylaxis is about 50% among all deaths due to anaphylaxis[1, 37, 39].

2.5 Main Drug Types Involved in Allergic Reactions

2.5.1 Antibiotics

The rate of anaphylaxis induced by various drugs is not well known[2]. In some cases, the drug culprit involved in anaphylaxis is not identified[37]. Multiple studies report that the majority of DIA cases are caused by antibiotic drugs[20, 27, 39, 45], with β-lactam antibiotics being the most common[46, 47]. Antibiotics have also been reported as the main cause of fatal DIA, among which penicillin was the most common[6, 44].

2.5.1.i Beta-Lactams

The prevalence of self-reported β-lactam antibiotic allergy is one of the highest among all antibiotics due to considerable patterns of prescribing and consumption of the drug[39, 46]. β-lactams have diverse chemical structures which can spontaneously bind to proteins, forming hapten-carrier complexes that are recognized by the immune system[46-48].

Penicillin is a common β-lactam used as first-choice treatment for numerous gram-negative and gram-positive bacterial infections[49]. The general structure of penicillins include a thiazolidine ring attached to a 5-membered β-lactam ring and a differing side chain[48]. When the β-lactam ring is cleaved, benzyl penicilloyl (BPO) is formed, which is the major determinant in penicillin allergy[48]. The prevalence of suspected allergy to penicillin in the general population ranges from 2 to 10%[49, 50], however less than 5% will have a positive confirmatory test to confirm an IgE-mediated reaction[51]. The prevalence of anaphylaxis to penicillin is estimated to occur in 0.01% to 0.05% of the population[22]. It is reported that allergy to penicillin is associated with history of atopy, history of adverse reactions to other drugs, and a history of penicillin allergy in a first-degree relative[52]. Since the late 1980s, there has been an increase in the use of amoxicillin, a type of penicillin antibiotic, which is now being reported as the most commonly

consumed β-lactam antibiotic in countries such as Spain, France and the U.S.[53, 54]. Establishing the diagnosis of amoxicillin allergy is especially challenging given high rates of suspected adverse reactions, mainly cutaneous, reported to occur during amoxicillin treatment and given that recent studies suggest that conducting an OC is crucial for the diagnosis of amoxicillin allergy[21].

Cephalosporin antibiotics also consist of a β-lactam ring, which differes from that of penicillins since it is 6-membered. The other difference is the existence of a functional group (R) at position 3 of the fused ring system. Cephalosporins are classified into 4 generations, which have similar antibacterial properties to that of penicillin[22, 48]. Similarly, the major determinant for allergy to cephalosporin is formed when the β-lactam ring is opened[55]. With the increasing consumption of cephalosporins, there is a rising concern for the cause of allergy[48, 54]. It is reported that only 1% of the population has a cephalosporins allergy[50]. A study by Johannes et al. estimated the prevalence of anaphylaxis to cephalosporins as 0.002%[56]. Cephalosporins are reported to be the second most common cause of fatal DIA, after penicillins[37]. In patients who report having a penicillin allergy, cephalosporins are often the prescribed drug of choice [23]. There is concern regarding use of first and second generation cephalosporins in patients with penicillin allergy due to the potential for cross-reactivity and increased risk for reaction due to their shared β-lactam ring in their structure[22]. However, studies report that there is little evidence to support this[45], and that the risk of cross-reactivity is less than 10%[22, 49].

2.5.1.ii Quinolones

Quinolone antibiotics are synthetic antimicrobial agents used to treat infections of both gram-negative and gram-positive bacteria[57]. At the core, all quinolones are composed of 2 aromatic rings[58]. Quinolones are categorized into 4 groups, from first to fourth generation[25, 58].

While hypersensitivity reactions to quinolones are rare, immediate type reactions are more common, occurring in 0.4% to 2% of the general population[25, 29]. Due to potential toxicity and cartilage damage of weight-bearing joints, quinolones are restricted for use in pediatric patients[57].

Fluoroquinolones are the most common, non-β-lactam drugs involved in IgE-mediated hypersensitivity reactions[59]. Fluoroquinolone antibiotics contain a fluorine atom attached to the carbon rings at the center of the molecule[58]. The use of fluoroquinolones has been found to be increasing in adults since the early 2000s[24, 25]. A study led by Blanca-Lopez et al. found that while the number of patients being evaluated for fluoroquinolone hypersensitivity was increasing, the number of patients with confirmed hypersensitivity were also increasing[24]. The reason could be due to the increased prescribing of the drug from physicians over the years and the introduction of moxifloxacin, a new fluoroquinolone, onto the market as first line antibiotic for respiratory infections[60]. Immediate reactions to fluoroquinolone have the potential to be severe, with moxifloxacin reported as causing the most severe type of reactions[24]. In a cohort study conducted in the U.S., the incidence of anaphylaxis to moxifloxacin was estimated to be 0.3 per 10,000 dispensings of the antibiotic[56]. Reactions to fluoroquinolones have been found to be associated with being diagnosed as allergic to β-lactams[24].

2.5.1.iii Macrolides

Macrolides are a class of antibiotics that are active against gram-negative and gram-positive bacteria implicated in respiratory tract infections and skin infections[61]. The structure of macrolides is composed of a large lactone ring with either 12, 14, 15, or 16 carbon atoms making up the structure. Macrolides are classified in 4 groups, according to the number of carbons in the cycle[61]. Macrolides are claimed to be one of the safest antibiotics on the market with only 0.4 to

3% of treatments reporting a hypersensitivity reaction. The mechanism of macrolide hypersensitivity is IgE-dependent and is unknown[61].

Azithromycin, a type of macrolide antibiotic, is implicated in the majority of hypersensitivity cases[28], however immediate reactions are mostly reported with erythromycin treatment[61]. While values in the literature for prevalence of anaphylaxis to macrolides are limited, the incidence of anaphylaxis to clarithromycin was reported as 1 case per 1 million[62].

2.5.2 Non-antibiotic drugs

2.5.2.i NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs used to treat pain and fever by relieving inflammation through the inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) thus impeding the synthesis of prostaglandins[63, 64]. NSAIDs are available over the counter in many countries[64], of which the most common include aspirin and ibuprofen[2, 65]. NSAIDs are the second most reported cause of drug hypersensitivity reactions after β-lactam antibiotics[20, 30, 43, 66], with ibuprofen accounting for more than half of reported reactions[67]. Other studies report that NSAIDs are implicated in the majority of reactions among children and adolescents[2, 65], which may be due to the increased use in this population[66]. The reported prevalence of hypersensitivity reactions to NSAIDs in the general population ranges from 1 to 3%[30, 64]. As per DIA, NSAIDs play a major role in anaphylactic reactions, especially in children, accounting for more cases than antibiotics[34, 68]. However, anaphylactic reactions to NSAIDs have been reported to be less severe than reactions to antibiotics and other drugs which have higher rates of hospitalization, ICU admission, and intubation[2, 39].

Due to the variety of mechanisms involved, NSAIDs reactions are complex. The two main types of reactions that exist are cross-intolerance and selective reactions[63]. Cross-

intolerance refers to patients that react to multiple chemically unrelated NSAIDs, while patients with selective reactivity react to only one type of NSAID and tolerate other unrelated types[69]. Within these main types, there are various subtypes with specific criteria for diagnosis. Cross-intolerance reactions include NSAIDs exacerbated respiratory disease (NERD), NSAIDs exacerbated cutaneous disease (NECD), and NSAID-induced urticaria/ angioedema (NIUA), of which all involve non-allergic mechanisms and are related to the inhibition of COX-1[66]. Selective type hypersensitivity reactions include single NSAIDs-induced urticaria/ angioedema/ anaphylaxis (SNIUAA), which is an IgE-mediated immunological-type reaction with a typically immediate manifestation[66]. The second type of selective reactions is NSAIDs-induced delayed hypersensitivity reactions (NIDHR), which is also an allergic-type reaction with a delayed cutaneous manifestation that is T-cell mediated[66].

Patients who react to a single NSAID have a higher prevalence of atopic disease[2, 70], indicative of an IgE-mediated reaction[71]. In younger children, allergic disease such as asthma and rhinitis have been reported as significant risk factors for hypersensitivity reactions to NSAIDs[67]. A family history of atopic disease was associated with increased risk of cross-intolerance reactions only[63].

2.6 Pathophysiology

Drugs typically are reported to induce IgE-mediated anaphylaxis, however non-IgE-mediated anaphylaxis can also occur in response to certain drug triggers[2]. IgE-mediated DIA occurs immediately after contact is made between the drug and the immune system[1]. The drug, or allergen, interacts with allergen-specific IgE bound on the FcεRI receptor, present on the surface of mast cells and basophils[72]. Cross-linking occurs when the allergen interacts with IgE on 2 or more receptors on the cell surface, causing activation of the mast cells and/or basophils[1,

[15, 22]. Upon activation, mast cells and basophils undergo rapid degranulation, releasing stored inflammatory agents such as vasoactive mediators, enzymes, histamine, tryptase, and TNF (tumor necrosis factor)[1, 22, 72]. The pro-inflammatory mediators induce a severe systemic response by acting directly on tissue and, simultaneously, recruit and activate other inflammatory cells to the site which amplify the reaction[72]. Histamine and other vasoactive mediators are responsible for the manifestation of symptoms such as flushing, swelling, urticaria, angioedema, wheezing and upper airway involvement, decrease in blood pressure and blood volume, and cardiac arrhythmia[1, 22]. The pathophysiology of alternative pathways which include IgG-mediated and complement activation anaphylaxis are not well understood[72]. In the case of non-allergic DIA, histamine and vasoactive mediators are also released by mast cells and basophils by direct drug action[1, 22].

2.7 Risk Factors

2.7.1 Demographic determinants

Age: While the incidence of all-cause anaphylaxis is highest in children aged 0 to 4 years old[39], DIA is the most frequent in middle- to older-aged adults[43]. The potential of greater exposure and sensitization over a longer lifespan and underlying cardiovascular and respiratory comorbidities may explain why the incidence of DIA increases with age[6]. A study in Australia reported that over an 8-year period, in the 55- to 84-year age group, the hospitalization rates for DIA were highest at 3.8 per 100 000 persons[73]. Variables such as older age and the presence of pre-existing comorbidities have been found to be predictors of serious outcomes in various studies[1, 65, 74].

Studies report higher risk of fatality in older individuals due to DIA[39]. A study conducted in the U.S. found that DIA fatalities among those aged 19 years old and younger was estimated at 0.05 per million versus 1.28 per million among people over the age of 80 [37].

Gender: In adults, anaphylaxis is more common in females[75] likely due to the effects of estrogens, leading to enhanced mast cell activation[39, 72]. A study done by Hox et al. demonstrated that in mouse models, female mice had more severe reactions that were dependent on estrogens[76]. There are no reported differences in the severity or mortality of DIA cases between sexes in population studies[2, 43].

Race/Ethnicity: Higher rates of fatalities due to DIA and all-cause anaphylaxis were observed in African-American race[37]. In the U.S., Jerschow et al. demonstrated significant differences between the prevalence of DIA deaths in African-Americans, estimated at 0.54 per million, compared with Caucasians, 0.45 per million, and Hispanics, 0.19 per million. The higher prevalence may reflect increased comorbidities, greater use of medication, genetic effects, and less access to healthcare among African-Americans[37, 77].

Geography: Geography has been reported to play an important role in anaphylaxis, suggesting increased rates of anaphylaxis in the north compared to the south. Higher latitudes and lower amounts of solar radiation have been associated with increased admissions for anaphylaxis and greater sales of epinephrine auto-injectors[78-80]. It is hypothesized that the differences in north-south gradient may be due to varying levels or deficiency of vitamin D[80], however data remains limited. In a study conducted in the U.S., the rate of DIA was significantly lower in the Northeast region, however the cause of lower risk in this region is not clear [37].

2.7.2 Concomitant disease

Atopy: Atopy is defined by the presence of one or more atopic diseases such as asthma, atopic dermatitis, food allergy, and allergic rhinitis[81]. There is no general consensus if atopy is a risk factor for most drug allergies[1, 77]. However, in studies evaluating different populations with DIA, asthma and eczema are usually represented in over 20% of the reactors[35, 44, 82]. In the cases of NSAIDs, atopy has been described as a risk factor for severe anaphylactic reactions[65, 67, 69-71]. In patients with chronic rhinosinusitis, asthma, or chronic urticaria, the prevalence of NSAIDs hypersensitivity might be as high as 20 to 30%[30, 83].

Cardiovascular disease: Diabetes and cardiovascular disease are considered risk factors for DIA[1, 72]. Older patients with these comorbidities may experience more severe reactions and increased mortality[39]. Such diseases may alter metabolic pathways and immunologic responses to certain allergens, causing a predisposition to develop an allergic reaction[77]. In healthy individuals, mast cells are present around coronary arteries and intramural vessels. In patients with ischemic heart disease, the number and density of cardiac mast cells is increased in these areas[84]. During anaphylaxis, the release of histamine and other inflammatory mediators from the cardiac mast cells contribute to vasoconstriction and coronary artery spasms[85].

Allergy to other drugs: A previous history of anaphylaxis to a drug is a risk factor and predictor of a reoccurring severe reaction. Patients with a confirmed penicillin allergy are more likely to develop allergies to other antibiotics[1]. In patients with confirmed hypersensitivity to fluoroquinolone antibiotics, having a confirmed allergy to β-lactam antibiotics was an associating factor[24]. This may in part be explained by the fact that patients who report being allergic to penicillin are prescribed other alternative antibiotics, such as quinolones and vancomycin, compared to patients who tolerate penicillin[23] . In the case of NSAIDs, patients

with DIA often report having had previous reactions to the same or different NSAID from the same class[2].

2.7.3 Co-factors

The presence of co-factors may explain why certain conditions lead to anaphylaxis while in other cases the allergen elicits a milder response or is even tolerated. Co-factors either lower the reaction threshold or make the allergic symptoms more severe by directly influencing the immunological mechanism of type I reactions[86]. The prevalence of reactions occurring due to co-factors have been reported in up to 30% of cases of anaphylaxis[87].

Exercise: Exercise is the best known co-factor, however the mechanism is poorly understood. Most reported cases of exercise-induced anaphylaxis have been caused by food, with wheat being the most frequent[88]. There are three proposed mechanisms on how exercise affects anaphylaxis. The first is through the activation of tissue transglutaminase during exercise which creates complexes able to elicit anaphylaxis[89]. Another potential mechanism is the increase of blood circulation during exercise, which leads to an increase in intestinal absorption, absorbing the allergen from the gastrointestinal tract[90]. Lastly, exercise may lower the threshold for IgE-mediated mast cell degranulation due to changes in plasma osmolarity during exercise[91, 92].

Menstruation: Estrogen and progesterone may increase the risk of anaphylaxis as recurrent episodes have been reported around the time of menstruation[93]. Hox et al. demonstrated that female mice experienced more severe anaphylaxis than their male counterparts due to increased vascular permeability promoted by estrogens[94].

Alcohol: Alcohol has been reported as a co-factor in up to 15% of cases of anaphylaxis[95]. While there is little evidence on its mechanism of action, it has been hypothesized that alcohol

increases absorption of the intestine by increasing the permeability of the intestinal epithelial barrier[96].

NSAIDs: NSAIDs have mostly been shown to enhance anaphylaxis in association with food allergies[72]. The mechanism is complex and not fully understood, therefore two hypotheses have been proposed. The first is that NSAIDs increase the permeability of the intestinal barrier increasing the absorption of allergens and accelerating the development of symptoms[97, 98]. The second is that NSAIDs may directly affect mast cells and basophils, amplifying their degranulation[99].

Drugs: Multiple drugs from various classes have been found to be associated with increased risk for allergic reactions. Lipid-lowering drugs, which lower the amount of low-density lipoproteins in circulation in the body, also lower levels of platelet-activating factor-acetylhydrolase[100]. Platelet-activating factor is a phospholipid activator secreted by mast cells and basophils during degranulation[101]. The binding of platelet-activating factor to its receptors on platelets, monocytes, macrophages, and neutrophils is responsible for the life-threating manifestations of anaphylaxis[102]. Platelet-activating factor in circulation is controlled through degradation by the activity of platelet-activating factor-acetylhydrolase[103]. It is reported that in patients with decreased amounts of circulating platelet-activating factor-acetylhydrolase, there is a diminished ability to inactivate circulating platelet-activating factor, leading to a more severe manifestation of anaphylaxis[102, 104].

There have been conflicting findings in the association of angiotensin-converting enzyme inhibitors and β-blockers as co-factors of anaphylaxis[16, 105], however they have recently been shown to directly target mast cells, enhancing degranulation[106]. The same study demonstrated that the combined use of these two medications was associated with an increased risk of severe

anaphylaxis in a German population[106]. Angiotensin-converting enzyme inhibitors or β-blockers used to manage cardiovascular disease may be associated with resistance to effective treatment of DIA with epinephrine[107] which may complicate management, howevere there is no contraindication for the use of epinephrine [108].

The use of proton-pump inhibitors has also been reported to be implicated in augmenting anaphylaxis. These medications lower acidity and hence may restrict digestion, allowing larger and intact allergens to reach lower parts of the gastrointestinal tract[86].

2.7.4 Genetic determinants

Genetics have been shown to be increasingly important in driving the predisposition of certain types of drug allergy[74]. The identification of a person's specific genetic HLA markers may allow the prediction of future immune-mediated reactions[109]. Data is scarce, however there have been some associations made in the literature.

The best known examples are the association between the presence of HLA-B*5701 to abacavir in Caucasians and HLA-B*1502 to phenytoin or carbamazepine in Chinese[110-112]. A Chinese study suggested that alleles in the HLA-DRB region may be involved in penicillin allergy through the modulation of specific serum IgE[113]. A recent genome-wide association study of 387 patients with immediate reactions to β-lactams reported that HLA-DRA rs7192 and rs8084 were significantly associated with allergy to penicillins and amoxicillin[114]. However, this study had major limitations since the presence of drug allergy was not established through the use of graded OC, only immediate reactions were included, and the population studied was Spanish and Italian only. Aspirin-exacerbated respiratory disease has also been associated with the class-II HLA allele HLA-DPB1*0301 in European and Asian populations through genome-wide association studies[115, 116].

2.8 Treatment

Prompt intramuscular epinephrine administration is the first-line treatment of all cases of anaphylaxis regardless of the trigger[15]. While intramuscular is the usual accepted route[117], in the case of severe reactions, epinephrine may be administered via IV in patients with severe hypotension or cardiac arrest[15]. Epinephrine binds to both the alpha and beta adrenergic receptors of body tissue and counteracts the effects of anaphylaxis by the constriction of blood vessels to increase blood pressure and circulation[117]. Epinephrine also acts by dilating smooth muscle around the lungs and airways, reducing bronchoconstriction[117]. Additionally, epinephrine prevents further degranulation of mast cells and basophils stopping the progression of the reaction[117].

Multiple studies report the underuse of epinephrine in the treatment of anaphylaxis in the ED. For adult patients presenting with anaphylaxis, epinephrine is administered in less than 50% of cases[2, 3, 35, 118-120]. Instead, a substantially larger percentage of adults are treated with antihistamines and corticosteroids[35, 120]. Antihistamines should only be considered for second-line treatment for anaphylaxis due to a slow onset of action and insignificant effect in the treatment of immediate reactions[15, 121]. Antihistamines are useful for the symptomatic treatment of urticaria, angioedema, and pruritus[15]. While steroids are listed in the treatment guidelines for anaphylaxis, they have a slow onset of action and are not useful in the treatment of acute anaphylaxis[15]. The use of corticosteroids might prevent a biphasic reaction from occurring by counteracting the effect of inflammatory mediators[15, 22], however there is no evidence surrounding their use and steroids should not replace the use of epinephrine in anaphylaxis[35]. A study conducted by Asai et al. in a Canadian ED demonstrated that the underuse of epinephrine was associated with older age. The persistent underuse of epinephrine in adults could be

attributed to the fear of adverse cardiovascular events in adults treated with epinephrine[35]. However, there is a lack of large-scale studies to support this premise [118]. Compared to adults, a considerably larger percentage of pediatric patients presenting to the ED with anaphylaxis are treated with epinephrine. However, it is reported that only 70 to 80% of moderate to severe cases of pediatric anaphylaxis are administered epinephrine with a similar percentage of children receiving antihistamine treatment[35, 82]. The low use of epinephrine in children may be due to improper physician training to appropriately diagnose anaphylaxis in the absence of cutaneous symptoms[2].

It is recommended to observe anaphylaxis cases for 4 to 6 hours due to the risk of a biphasic reaction, which is a second reaction occurring 1 to 72 hours after initial recovery[122], which can occur in 1 to 20% of anaphylactic reactions[15].

2.9 Desensitization

Upon confirmation of the diagnosis of type I hypersensitivity to a drug, the treatment is usually avoidance. In some instances, desensitization with the culprit drug can be used for patients requiring essential medication[74, 123]. Desensitization refers to the process of administering suboptimal doses of the medication until the therapeutic dose is reached and is tolerated by the patient. Desensitization has been shown to be successful and rapid with most penicillins and β-lactams, however desensitization should not be attempted in patients who experienced severe symptoms such as internal organ involvement or mucosal involvement[123]. In cardiac patients requiring the use of aspirin, which is an NSAID, desensitization has been shown to be safe and achievable[123]. In a multicenter study conducted over 2 years in Europe, 138 patients with acute coronary syndrome were evaluated, of which 101 underwent desensitization to aspirin. Results revealed that desensitization was a safe choice in patients with acute coronary

syndrome that experienced a hypersensitivity reaction, including anaphylaxis[124]. Since up to 30% of cases undergoing desensitization are reported to develop adverse events, mainly allergic reactions, this procedure should be conducted under medical supervision in a hospital setting [74]. Drug desensitization is temporary, therefore this procedure much be repeated each time the patient requires treatment. In some cases, prolonged treatment can be achieved by taking a daily dose of the drug[74].

2.10 Socioeconomic Burden of Misdiagnosis of Drug Allergy

The majority of common bacterial infections in adults and children are treated with β-lactam antibiotics, of which the most prescribed is amoxicillin[9]. Up to 10% of patients on treatment will develop a reaction and consequently will chose to avoid the suspect drug instead of being evaluated by an allergy specialist[10]. These patients are mislabeled as being truly allergic and will be prescribed alternative antibiotics that are less effective, more toxic, and more expensive[125]. An OC is considered the gold standard in the diagnosis of drug allergy[50], since SPT and specific IgE assays are misleading[126]. However, due to the fact that OCs are expensive, time-consuming, contain some risk, and there is a lack of data regarding their safety and accuracy, children and adults with suspected drug allergy are misdiagnosed. It was reported in a meta-analysis study done by our group that in adult and pediatric patients with a suspected immediate allergy to penicillin, less than 5% were confirmed with a skin test or oral challenge[127].

There are direct and indirect costs associated with being labelled with an antibiotic allergy. The acquisition cost of antibiotics in a penicillin-allergic patient compared to a non-allergic patient is estimated as being 2.3 times higher with a mean extra cost per patient of 20 to 147.32 CAD[11, 128-131]. Other factors such as administrating of the drug, monitoring for side

effects, treating side effects, nursing costs, and medical care costs can lead to a cost of 8 times the acquisition cost, averaging 668 CAD per patient[132]. Among the 10% of Canadians reporting an antibiotic allergy, at least 30% will be prescribed antibiotics annually[8]. The total direct cost savings by using amoxicillin in those that are not truly allergic is therefore estimated to be 561,120,000 CAD annually.

With the increased use of broad-spectrum antibiotics, such as vancomycin, cephalosporins, and fluoroquinolones[23], there has been an increase in the rate of antimicrobial resistance[45, 133, 134]. The use of fluoroquinolone and second-generation cephalosporin antibiotics have been found to be associated with an increased risk of acquiring *C. difficile*[135], with an increasing hazard ratio over a longer duration of treatment[136]. The use alternative broad-spectrum antibiotics, such as vancomycin, fluoroquinolones, and cephalosporins, have also been associated with an increased risk of vancomycin-resistant enterococci[137] and methicillin-resistant Staphylococcus aureus[138]. The use of penicillin-based antibiotics was not found as having a significant increased risk of developing antimicrobial resistance[137]. The total savings of the indirect costs associated with antimicrobial resistance such as longer hospital stays, increased ICU admissions and need for surgery are estimated to be 7,501,098 CAD annually[139-145].

3.0 Study Objectives

3.1 Overall Objectives

Currently there are no prospective studies that have assessed differences in clinical characteristics and management of DIA between pediatric centres across Canada, nor between pediatric and adult EDs. Therefore, we aimed to assess the percentage, demographic and clinical

characteristics, management, and assessment of DIA cases treated in 3 pediatric centres and 1 adult centre across Canada.

3.1 Primary Objective

To determine if cases of DIA were appropriately assessed for the diagnosis of drug allergy in 3 pediatric centres and 1 adult centre across Canada.

3.2 Secondary Objectives

To determine the percentage of cases of DIA among all cases of anaphylaxis over time at the 3 pediatric centres and 1 adult centres across Canada.

To determine differences in the management and demographic and clinical characteristics between the 3 pediatric centres, and between the pediatric centres and adult centre, across Canada.

4.0 Study Methodology

4.1 Study Design

From June 2012 to May 2016, children presenting to the Montreal Children's Hospital (MCH) ED and adults presenting to the Hôpital du Sacré-Coeur de Montréal (HSC) EDs with anaphylaxis were recruited as part of the Cross-Canada Anaphylaxis Registry (C-CARE). Over a 2-year period, from June 2014 to May 2016, children presenting to the British Columbia Children's Hospital (BCCH) and Children's Hospital at London Health Sciences Centre (LHSC) EDs with anaphylaxis were recruited for C-CARE. The MCH and HSC are tertiary hospitals located in Montreal, Quebec that treat approximately 80,000 and 60,000 patients annually in their EDs, respectively. The BCCH is a tertiary pediatric centre located in Vancouver, British

Columbia that treats approximately 45,000 patients annually in their ED. The LHSC is a teaching hospital located in London, Ontario, treating 36,000 patients annually in their ED.

This study followed the RECORD guideline for observational studies[146]. Data on patients were collected either prospectively or retrospectively. Prospective data was collected at the time of patient presentation. The treating physician identified cases of anaphylaxis and with the help of a trained research member obtained consent and completed a standardized data entry form documenting symptoms, triggers, and management of anaphylaxis. Data on missed cases that were not recruited at the time of presentation to the ED was collected retrospectively. In brief, all cases presenting to the ED were reviewed according to ICD-10 codes related to allergic reactions/anaphylaxis based on a previously validated algorithm[36, 147]. Anaphylaxis was defined as the involvement of 2 or more organ systems after exposure to a possible allergen or hypotension after exposure to a known allergen[15]. Only prospective and retrospective cases meeting the definition of anaphylaxis as determined by two independent reviewers (SG and MBS) were included. Consenting prospective patients or families (in the case of children) were contacted annually to determine if they had been seen by an allergist and if the culprit drug was confirmed through the use of skin tests or an oral challenge. Treating allergists were contacted and asked to provide documented results of skin tests and challenges. Data regarding the use of confirmatory tests for retrospective cases was obtained through chart review for patients who had been seen at the study centres.

4.2 Ethics Approval

All appropriate ethics reviews and approvals were obtained before beginning this study. The study was approved by the McGill University Ethics Committee, the Research Ethics Board of the Hôpital du Sacré-Coeur, the University of British Columbia/Children's and Women's

Health Centre of British Columbia Research Ethics Board and Health Science Research Ethics Board at Western University.

4.3 Statistical Analysis

All statistical analyses were done using R version 3.2.2. (R Core Team [2013]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Percentages with a 95% confidence intervals (CI, binomial or multinomial for variables with more than two categories) were used to assess patient demographics, symptoms, culprit drugs, reaction severity, management, and percentage of DIA cases. Linear regression models were fit to estimate the relationship between the study year and percentage of cases of all anaphylaxis visits and DIA anaphylaxis cases. Univariate and multivariate logistic regression models were compared to estimate factors associated with reaction severity, assessment by an allergist, and established drug allergy for the pediatric and adult EDs. All variables, excluding age and follow-up time, were dichotomized. Given the difference in catchment population between sites and that previous studies suggest differences regarding the risk of drug allergy as well as the culprit between adults and children[127], separate regression models for each site were fit.

5.0 Results

5.1 Temporal Trends in the Percentage of DIA Among All Anaphylaxis Cases

Over 4 years at the MCH, the percentage of DIA among all cases of anaphylaxis and among all ED visits showed no conclusive change (0.8% [95%CI, -2.4%, 4.0%] and 0.0036% [95%CI, -0.083%, 0.016%], respectively) (Table I). Over the 2-year period at BCCH, the percentage of DIA among all cases of anaphylaxis and among all ED visits showed no conclusive change (-0.94% [95%CI, -4.6%, 2.7%] and -0.0023% [95%CI, -0.016%, 0.011%],

respectively) (Table I). Over the same time, the percentage of DIA among all cases of anaphylaxis and among all ED visits at the LHSC showed no conclusive change (0.70% [95%CI, -16.2%, 8.3%] and 0.0055% [95%CI, -0.0085%, 0.020%], respectively) (Table I).

At HSC, the percentage of DIA among all anaphylaxis visits and among all ED visits also showed no change from 2012 to 2016 (2.1% [95%CI, -13.3%, 17.4%] and 0.0023% [95%CI, -0.017%, 0.022%], respectively) (Table I).

There was no conclusive difference in the percentage of DIA among all cases of anaphylaxis between the 3 pediatric EDs over 2 years (Table I). The percentage of DIA among all cases of anaphylaxis was substantially higher in the adult centre versus the pediatric centres (Table I).

At the MCH, the rate of DIA visits in the ED over 4 years increased with a slope of 1.2 (95% CI, 0.16, 2.2), while the rates of anaphylaxis and all ED visits showed no conclusive change (13.9 [95%CI, -14.7, 42.5] and 77.6 [95%CI, -2053.3, 2208.5], respectively) (Table II, Figure 1).

At the HSC, the rate of all ED visits over 4 years increased with a slope of 846.7 (95%CI, 575.0, 1118.4), while the rate of anaphylaxis and DIA visits showed no conclusive change (0.6 [95%CI, -15.0, 16.2] and 0.8 [95%CI, -1.7, 3.3], respectively) (Table II, Figure 1).

Due to the study length at BCCH and LHSC being over a 2-year period, linear regression was conducted with only 2 data points, therefore no conclusive findings could be drawn (Table II, Figure 2).

Table I. Percentage and Percent Difference of Anaphylaxis and Drug-Induced Anaphylaxis Cases

Variable (%, 95% CI)	Montreal Children's Hospital	Hôpital Sacré-Coeur	British Columbia Children's Hospital	Children's Hospital at London Health Science Centre
Percentage of anaphylaxis among all ED cases				
2012 – 2013	0.35% (0.31%, 0.40%)	0.11% (0.089%, 0.15%)	-	-
2013 – 2014	0.33% (0.29%, 0.37%)	0.16% (0.13%, 0.20%)	-	-
2014 – 2015	0.42% (0.38%, 0.47%)	0.15% (0.13%, 0.19%)	0.34% (0.29%, 0.40%)	0.097% (0.068%, 0.14%)
2015 – 2016	0.38% (0.34%, 0.42%)	0.11% (0.089%, 0.15%)	0.40% (0.34%, 0.46%)	0.12% (0.089%, 0.17%)
Differences				
Year 1 to Year 2	-0.024% (-0.082%, 0.034%)	0.047% (0.019%, 0.091%)	-	-
Year 2 to Year 3	0.094% (0.034%, 0.15%)	-0.0061% (-0.053%, 0.041%)	-	-
Year 3 to Year 4	-0.046% (-0.11%, 0.017%)	-0.041% (-0.084%, -0.0030%)	-	-
Total (Year 1 to Year 4)	0.024% (-0.036%, 0.085%)	-0.00016% (-0.039%, 0.039%)	0.055% (-0.024%, 0.14%)	0.024% (-0.028%, 0.077%)
Percentage of DIA among all cases of anaphylaxis				
2012 – 2013	2.8% (1.3%, 5.7%)	20.0% (11.5%, 32.1%)	-	-
2013 – 2014	3.2% (1.6%, 6.3%)	18.3% (11.3%, 27.9%)	-	-
2014 – 2015	3.5% (1.9%, 6.1%)	21.1% (13.5%, 31.2%)	2.5% (0.8%, 6.8%)	3.0% (0.16%, 17.5%)
2015 – 2016	3.6% (1.9%, 6.6%)	22.1% (13.3%, 34.1%)	1.6% (0.41%, 5.0%)	7.0% (1.8%, 20.1%)
Differences				
Year 1 to Year 2	0.4% (-2.8%, 3.6%)	-1.7% (-15.5%, 12.1%)	-	
Year 2 to Year 3	0.2% (-2.8%, 3.3%)	2.8% (-9.8%, 15.4%)	-	
Year 3 to Year 4	0.2% (-2.8%, 3.2%)	0.9% (-13.0%, 14.9%)	-	
Total (Year 1 to Year 4)	0.8% (-2.4%, 4.0%)	2.1% (-13.3%, 17.4%)	-0.94% (-4.6%, 2.7%)	0.70% (-16.2%, 8.3%)
Percentage of DIA among all ED visits				
2012 – 2013	0.010% (0.0047%, 0.021%)	0.023% (0.013%, 0.040%)	-	-
2013 – 2014	0.011% (0.0052%, 0.021%)	0.029% (0.018%, 0.048%)	-	-
2014 – 2015	0.015% (0.0079%, 0.026%)	0.033% (0.020%, 0.052%)	0.0086% (0.0028%, 0.024%)	0.0029% (0.0002%, 0.019%)
2015 – 2016	0.014% (0.0072%, 0.025%)	0.025% (0.015%, 0.043%)	0.0063% (0.0063%, 0.020%)	0.0085% (0.0022%, 0.027%)
Differences				
Year 1 – Year 2	0.00064% (-0.0099%, 0.011%)	0.0065% (-0.014%, 0.027%)	-	-
Year 2 – Year 3	0.0039% (-0.0081%, 0.016%)	0.0033% (-0.019%, 0.025%)	-	-
Year 3 – Year 4	-0.00097% (-0.014%, 0.012%)	-0.0075% (-0.029%, 0.014%)	-	-
Total (Year 1 – Year 4)	0.0036% (-0.083%, 0.016%)	0.0023% (-0.017%, 0.022%)	-0.0023% (-0.016%, 0.011%)	0.0055% (-0.0085%, 0.020%)

Percent differences of DIA among anaphylaxis cases between HSC and MCH	
2012 – 2013	17.2% (6.3%, 28.0%)
2013 – 2014	15.0% (6.2%, 23.9%)
2014 – 2015	17.7% (8.3%, 27.0%)
2015 – 2016	18.4% (7.5%, 29.4%)
Percent differences of DIA among anaphylaxis cases between HSC and BCCH	
2014 – 2015	18.6% (8.9%, 28.2%)
2015 - 2016	20.5% (9.4%, 31.5%)
Percent differences of DIA among anaphylaxis cases between HSC and LHSC	
2014 – 2015	18.1% (5.7%, 30.4%)
2015 - 2016	15.1% (0.7%, 29.4%)
Percent differences of DIA among anaphylaxis cases between MCH and BCCH	
2014 – 2015	0.9% (-2.6%, 4.5%)
2015 – 2016	2.0% (-1.2%, 5.2%)
Percent differences of DIA among anaphylaxis cases between MCH and LHSC	
2014 – 2015	0.4% (-6.2%, 7.0%)
2015 – 2016	-3.4% (-12.6%, 5.9%)
Percent differences of DIA among anaphylaxis cases between BCCH and LHSC	
2014 – 2015	-0.5% (-7.3%, 6.3%)
2015 - 2016	-5.4% (-14.6%, 3.9%)

Table II. Linear Regression of Anaphylaxis and Drug-Induced Anaphylaxis Cases

Variable	Slope (95% CI)	R^2 Value	P value
Montreal Children's Hospital			
All ED Visits	77.6 (-2053.3, 2208.5)	0.0025	0.95
All Anaphylaxis visits	13.9 (-14.7, 42.5)	0.31	0.44
DIA visits	1.2 (0.16, 2.2)	0.72	0.15
Hôpital du Sacré-Coeur			
All ED visits	846.7 (575.0, 1118.4)	0.95	0.026
All Anaphylaxis visits	0.6 (-15.0, 16.2)	0.0028	0.95
DIA visits	0.8 (-1.7, 3.3)	0.16	0.60
British Columbia Children's Hospital			
Al ED visits	1097[a]	1	-[b]
All Anaphylaxis visits	30 [a]	1	-[b]
DIA visits	-1 [a]	1	-[b]
Children's Hospital at London Health Science Centre			
All ED visits	1410 [a]	1	-[b]
All Anaphylaxis visits	10 [a]	1	-[b]
DIA visits	2 [a]	1	-[b]

[a]Regression for two data points therefore CI could not be computed
[b]Regression for two data points therefore p-value could not be computed

Figure 1. Rate of Anaphylaxis and Drug-Induced Anaphylaxis at Montreal Children's Hospital over 4 years

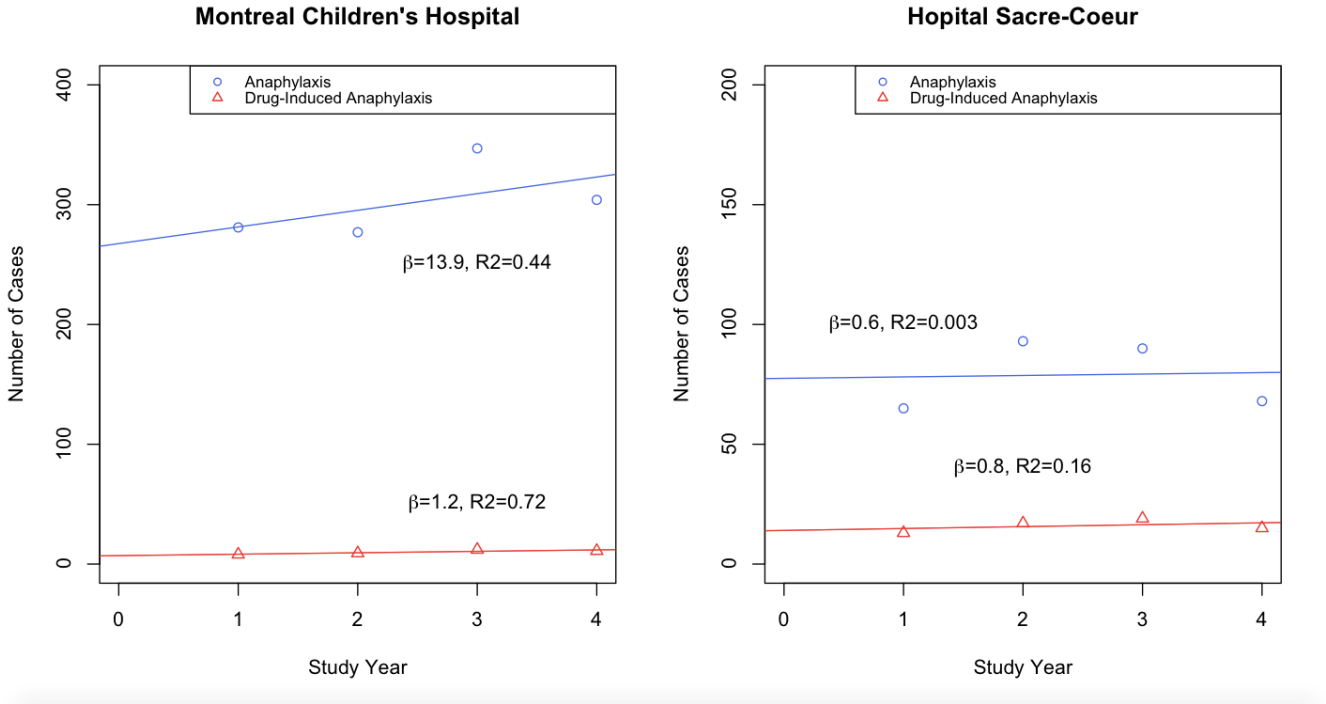
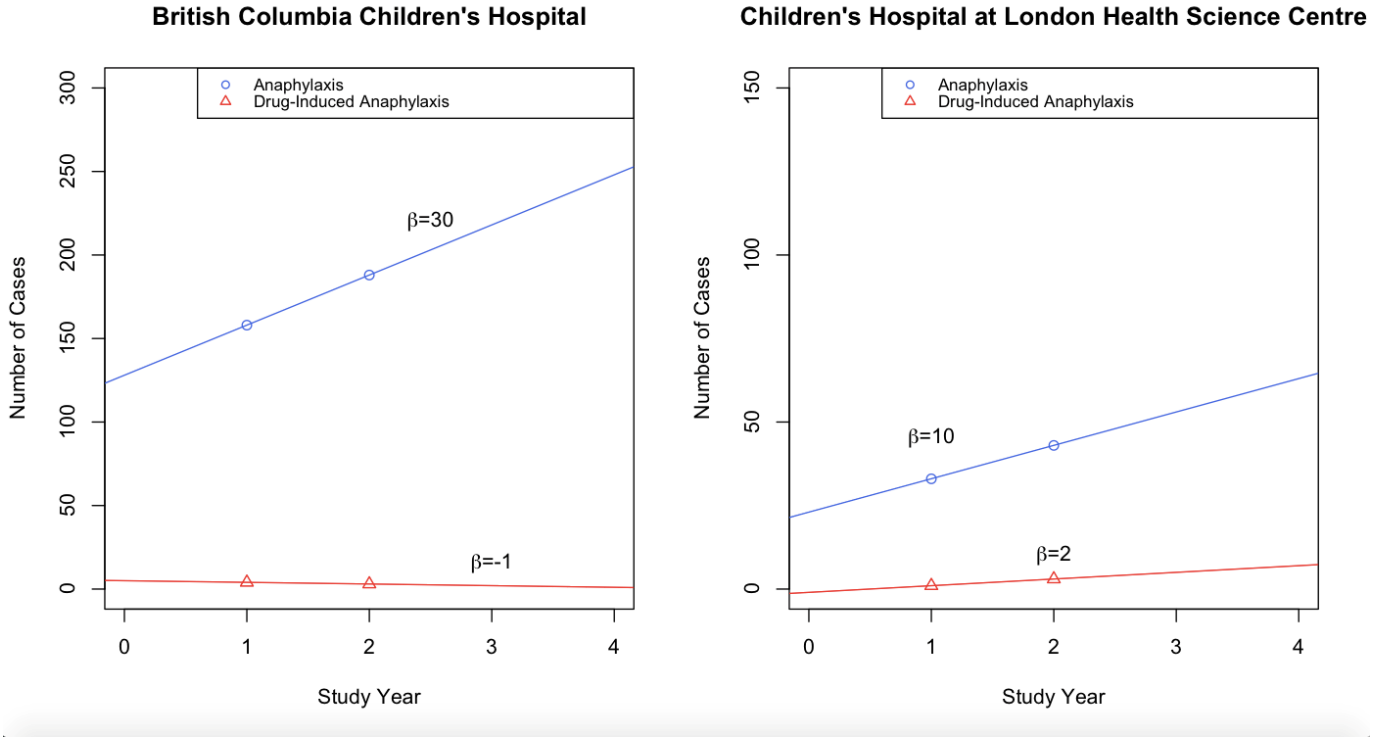


Figure 2. Rate of Anaphylaxis and Drug-Induced Anaphylaxis at British Columbia Children's Hospital and Children's Hospital at London Health Science Centre over 2 years



5.2 Demographics and Clinical Characteristics

From June 2012 to May 2016, 40 pediatric patients presented to the MCH with DIA. Half of the children were recruited prospectively, of which the mean follow-up time to determine if the patients had been assessed by an allergist was 1.36 years (Table IV). The majority of the reactions were triggered by non-antibiotic drugs, of which the main culprit was non-steroidal anti-inflammatory drugs (NSAIDs) (Table III). The rest of the reactions were triggered by antibiotics, mainly β-lactams, with a smaller percentage reacting to macrolides and fluoroquinolones (Table III). Only 3 children reported having a history of drug allergy, with 1 child reacting to the known drug culprit.

From June 2014 to May 2016, 7 pediatric patients presented with DIA to the BCCH of which 57.1% were recruited prospectively with a mean follow-up time of 1 year (Table V). The

majority of the reactions were triggered by non-antibiotic drugs, with NSAIDs accounting for 14.3% (95%CI, 0%, 53.0%) of reactions. There were two reactions triggered by antibiotics, specifically to β-lactams (Table III). Only one child reported a history of drug allergy, which was different than the culprit drug.

During the same 2-year period, 4 pediatric patients presented to the LHSC with DIA, of which only one patient was recruited prospectively with a follow-up time of 1.08 years (Table V). Of these reactions, three patients reacted to non-antibiotic drugs, of which the majority were NSAIDs. The other patient reacted to a β-lactam antibiotic (Table III). No patients reported history of a known drug allergy.

From June 2012 to May 2016, 64 adults presented with DIA at HSC of which 81.3% were recruited prospectively, with a mean follow-up of 1.33 years (Table IV). The majority reacted to antibiotics, mainly β-lactams, fluoroquinolones, and macrolides. In cases of DIA not triggered by antibiotics, the main culprit was NSAIDS (Table III). Seventeen adults reported having a history of drug allergy, of which 3 reacted to the known drug culprit.

Differences in clinical characteristics between prospectively recruited and retrospectively recruited patients were conducted. At the MCH, the percentage of prospective patients with known food allergy and known asthma were significantly higher than in retrospective patients (Table IV). At the BCCH, the percentage of prospective patients which received the drug culprit parenterally was significantly higher than in retrospective patients (Table V).

5.3 Management in the ED

At the 3 pediatric centres across Canada, epinephrine was used to treat over half of the reactions (Table III). Antihistamines were used in about 50% of cases at the MCH and LHSC, however, their use was over 80% at the BCCH (Table III). Steroids were used the least at the

MCH ED compared to the BCCH and LSHC (Table III). About half of the adults were treated with epinephrine, while over 80% were treated with antihistamines and/or steroids at HSC (Table III). At the MCH, there was a significantly larger percentage of prospective patients who received epinephrine treatment compared to retrospective patients (Table IV).

Table III. Characteristics of Patients Presenting to the Emergency Department with Drug-Induced Anaphylaxis

Variable (%, 95%CI)	Montreal Children's Hospital (N=40)	Hôpital Sacré-Coeur (N=64)	British Columbia Children's Hospital (N=7)	Children's Hospital at London Health Science Centre (N=4)
Age at Reaction (median, IQR)	8.4 (3.8, 15.6)	49.4 (40.1, 62.9)	9.3 (6.5, 14.85)	4.7 (1.2, 8.0)
Age at Reaction (mean, standard deviation)	9.2 (6.1)	48.9 (14.8)	10.2 (5.3)	4.6 (4.0)
Sex (% males)	50.0% (35.2%, 64.8%)	28.1% (17.9%, 41.0%)	71.4% (30.3%, 94.9%)	50.0% (15.0%, 85.0%)
Medication type				
Antibiotics	40.0%(28.1%, 58.9%)	57.8% (44.8%, 69.8%)	28.6% (5.1%, 69.7%)	25.0% (1.3%, 78.1%)
Beta-Lactams	32.5% (17.5%, 48.8%)	28.1% (17.2%, 41.3%)	28.6% (0%, 67.3%)	25.0% (0%, 85.8%)
Macrolides	5.0% (0%, 21.3%)	3.1% (0%, 16.3%)	0% (0%, 38.7%)	0% (0%, 60.8%)
Quinolones	2.5% (0%, 18.8%)	20.3% (9.4%, 33.5%)	0% (0%, 38.7%)	0% (0%, 60.8%)
Other Antibiotics	0% (0%, 16.3%)	6.3% (0%, 19.4%)	0% (0%, 38.7%)	0% (0%, 60.8%)
Non-Antibiotic Drugs	60.0% (43.4%, 74.7%)	42.2% (30.2%, 55.2%)	71.4% (30.3%, 94.9%)	75.0% (21.9%, 98.7%)
NSAIDs	20.0% (5.0%, 36.3%)	20.3% (9.4%, 33.5%)	14.3% (0%, 53.0%)	50.0% (25.0%, 100%)
Contrast Agents	2.5% (0%, 18.8%)	3.1% (0%, 16.3%)	14.3% (0%, 53.0%)	0% (0%, 60.8%)
Other Non-Antibiotic Drugs[a]	37.5 %(22.5%, 53.8%)	18.8% (7.8%, 31.9%)	42.8% (14.3%, 81.6%)	25.0% (0%, 85.8%)
Known Drug Allergy	7.5% (2.0%, 21.5%)	26.6% (16.7%, 39.3%)	14.3% (0.8%, 58.0%)	0% (0%, 60.4%)
Known Food Allergy	25.0% (13.2%, 41.5%)	12.5% (5.9%, 23.7%)	28.6% (5.1%, 69.7%)	0% (0%, 60.4%)
Known Asthma	25.0% (13.2%, 41.5%)	9.4% (3.9%, 19.9%)	0% (0%, 43.9%)	0% (0%, 60.4%)
Reaction type				
Mild[b]	20.0% (10.0%, 34.5%)	0% (0%, 9.7%)	42.9% (14.3%, 76.4%)	50.0% (25.0%, 100%)
Moderate[c]	75.0% (65.0%, 89.5%)	82.8% (75.0%, 92.1%)	57.1% (28.6%, 90.7%)	50.0% (25.0%, 100%)
Severe[d]	5.0% (0%, 19.5%)	17.2% (9.4%, 26.5%)	0% (0%, 33.6%)	0% (0%, 57.1%)
Exposure Route				
Ingestion	75.0% (65.0%, 89.2%)	93.8% (89.1%, 98.7%)	57.1% (28.6%, 90.7%)	100% (100%, 100%)
Contact[e]	7.5% (0%, 21.7%)	0% (0%, 4.9%)	0% (0%, 33.6%)	0% (0%, 41.6%)
Inhaled	2.5% (0%, 16.7%)	1.6% (0%, 6.5%)	0% (0%, 33.6%)	0% (0%, 41.6%)
Parenteral	15.0% (5.0%, 29.2%)	4.9% (0%, 9.6%)	42.9% (14.3%, 76.4%)	0% (0%, 41.6%)
Treatment in ED				
Epinephrine	57.5% (41.0%, 72.6%)	51.6% (38.8%, 64.1%)	57.1% (20.2%, 88.2%)	75.0% (21.9%, 98.7%)
Antihistamines	45.0% (29.6%, 61.3%)	82.8% (70.9%, 90.7%)	85.7% (42.0%, 99.2%)	50.0% (15.0%, 85.0%)
Steroids	20.0% (9.6%, 36.1%)	82.8% (70.9%, 90.7%)	57.1% (20.2%, 88.2%)	100% (39.6%, 100%)

[a]Other Non-Antibiotics Drugs:
Children: Marijuana, Local anesthetic (Prilocaine), Antihistamine (Claritin), Corticosteroids (Dexamethasone and Prednisone), N-acetyl cysteine, Zantac, Oralair, Triptan, Cyclopentolate eye drops, Wilate (Factor 8), Morphine, Vicks VapoDrops, Granulocyte-macrophage colony-stimulating factor (GM-CSF), Atypical Antipsychotic (Risperdal)
Adults: Tylenol, Codeine, Cocaine, Alpha1-Adrenergic Receptor Antagonist (Terazosin), Antifungal Medication (Fluconazole), Lactase (Lacteeze), Benylin cough syrup, Angiotensin-converting Enzyme (ACE) Inhibitor (Ramipril), Protein Pump Inhibitor (Pantoprazole), Anticonvulsant (Lyrica)

[b]Symptoms include urticaria, erythema, angioedema, oral pruritus, nausea, nasal congestion, sneezing, rhinorrhea or throat tightness[16]
[c]Symptoms include crampy abdominal pain, diarrhea, recurrent vomiting, dyspnea, stridor, cough, wheeze, or "light-headedness"[16]
[d]Symptoms include cyanosis, hypoxia, respiratory arrest, hypotension, dysrhythmia, confusion, or loss of consciousness.[16]
[e]Cyclopentolate eye drops

Table IV. Characteristics of Prospective versus Retrospective Patients Presenting to the Emergency Department with Drug-Induced Anaphylaxis at Montreal Children's Hospital and Hôpital Sacré-Coeur

Variable (%, 95%CI)	Montreal Children's Hospital			Hôpital Sacré-Coeur		
	Prospective (N=20)	Retrospective (N=20)	Difference	Prospective (N=52)	Retrospective (N=12)	Difference
Age at Reaction (median, IQR)	6.5 (3.5, 15.5)	9.5 (5.6, 15.6)		49.4 (41.0, 62.3)	50.3 (34.5, 64.3)	
Age at Reaction (mean, standard deviation)	8.7 (6.3)	9.6 (6.0)	-0.9 (-4.9, 3.0)	49.3 (14.0)	47.1 (18.3)	2.2 (-9.9, 14.3)
Length of follow-up in years (mean, standard deviation)	1.36 (0.52)			1.33 (0.40)		
Sex (% males)	65.0% (40.9%, 83.7%)	35.0% (16.3%, 59.1%)	30.0% (-4.6%, 64.6%)	30.8% (19.1%, 45.3%)	16.7% (2.9%, 49.1%)	14.1% (-15.6%, 43.8%)
Known Drug Allergy	5.0% (0.3%, 26.9%)	10.0% (1.8%, 33.1%)	-5.0% (-26.3%, 16.3%)	26.9% (16.0%, 41.3%)	25.0% (6.7%, 57.2%)	1.9% (-27.3%, 31.2%)
Known Food Allergy	40.0% (20.0%, 63.6%)	10.0% (1.8%, 33.1%)	30.0% (0.2%, 60.2%)	13.5% (6.0%, 26.4%)	8.3% (0.4%, 40.2%)	5.1% (-18.2%, 28.4%)
Known Asthma	38.1% (20.0%, 63.6%)	10.0% (1.8%, 33.1%)	30.0% (0.2%, 60.2%)	7.7% (2.5%, 19.4%)	16.7%(2.9%, 49.1%)	-9.0% (-36.4%, 18.4%)
Reaction type						
Mild[a]	15.0% (0%, 33.3%)	25.0% (10.0%, 44.2%)	-10.0% (-39.6%, 19.6%)	0% (0%, 11.0%)	0% (0%, 24.2%)	0% (0%, 0%)
Moderate[b]	75.0% (60.0%, 93.3%)	75.0% (60.0%, 94.2%)	0% (-26.8%, 26.8%)	82.7% (75.0%, 93.7%)	83.3% (75.0%, 100%)	-0.6% (-24.7%, 23.5%)
Severe[c]	10.0% (0%, 28.3%)	0% (0%, 19.2%)	10.0% (-8.1, 28.1%)	17.3% (9.6%, 28.3%)	16.7% (8.3%, 40.9%)	-0.6% (-23.5%, 24.7%)
Exposure Route						
Ingestion	75.0% (60.0%, 92.8%)	75.0% (60.0%, 93.3%)	0% (-26.8%, 26.8%)	91.8% (85.7%, 98.2%)	100% (100%, 100%)	-8.2% (-21.0%, 4.7%)
Contact[d]	5.0% (0%, 22.8%)	10.0% (0%, 28.3%)	-5.0% (-26.3%, 16.3%)	0% (0%, 6.3%)	0% (0%, 13.5%)	0% (0%, 0%)
Inhaled	5.0% (0%, 22.8%)	0% (0%, 18.3%)	5.0% (-9.6%, 19.6%)	2.0% (0%, 8.4%)	0% (0%, 13.5%)	2.0% (-4.0%, 8.0%)
Parenteral	15.0% (0%, 32.8%)	15.0% (0%, 33.3%)	0% (-22.1%, 22.1%)	6.1% (0%, 12.4%)	0% (0%, 13.5%)	6.1% (-5.8%, 18.0%)
Treatment in ED						
Epinephrine	80.0% (55.7%, 93.4%)	35.0% (16.3%, 59.1%)	45.0% (12.7%, 77.3%)	55.8% (41.4%, 69.3%)	33.3% (11.3%, 64.6%)	22.4% (-12.6%, 57.5%)
Antihistamines	40.0% (20.0%, 63.6%)	50.0% (29.9%, 70.1%)	-10.0% (-45.7%, 25.7%)	86.5% (73.6%, 94.0%)	66.7% (35.4%, 88.7%)	19.9% (-13.5%, 53.2%)
Steroids	25.0% (9.6%, 49.4%)	15.0% (4.0%, 38.9%)	10.0% (-19.6%, 39.6%)	80.8% (67.0%, 89.9%)	91.7% (59.8%, 99.6%)	-10.9% (-35.0%, 13.2%)

[a]Symptoms include urticaria, erythema, angioedema, oral pruritus, nausea, nasal congestion, sneezing, rhinorrhea or throat tightness[16]
[b]Symptoms include crampy abdominal pain, diarrhea, recurrent vomiting, dyspnea, stridor, cough, wheeze, or "light-headedness"[16]
[c]Symptoms include cyanosis, hypoxia, respiratory arrest, hypotension, dysrhythmia, confusion, or loss of consciousness.[16]
[d]Cyclopentolate eye drops

Table V. Characteristics of Prospective versus Retrospective Patients Presenting to the Emergency Department with Drug-Induced Anaphylaxis at British Columbia Children's Hospital and London Health Science Centre Children's Hospital

Variable (%, 95%CI)	British Columbia Children's Hospital			Children's Hospital at London Health Science Centre		
	Prospective (N=4)	Retrospective (N=3)	Difference	Prospective (N=1)	Retrospective (N=3)	Difference
Age at Reaction (median, IQR)	11.8 (7.0, 15.5)	9.3 (7.0, 11.9)		1.3 (1.3, 1.3)	8.0 (4.5, 8.0)	
Age at Reaction (mean, standard deviation)	10.8 (6.3)	9.5 (4.9)	1.3 (-9.7, 12.2)	1.3[e]	5.7 (4.0)	-4.4[e]
Length of follow-up in years (mean, standard deviation)	1			1.08		
Sex (% males)	50.0% (15.0%, 85.0%)	100% (31.0%, 100%)	-50.0% (-100%, 28.2%)	100% (5.5%, 100%)	33.3% (1.8%, 87.5%)	66.7% (-53.3%, 100%)
Known Drug Allergy	0% (0%, 60.4%)	33.3% (1.8%, 87.5%)	-33.3% (-100%, 49.2%)	0% (0%, 94.5%)	0% (0%, 69.0%)	0% (0%, 0%)
Known Food Allergy	50.0% (15.0%, 85.0%)	0% (0%, 69.0%)	50.0% (-28.2%, 100%)	0% (0%, 94.5%)	0% (0%, 69.0%)	0% (0%, 0%)
Known Asthma	0% (0%, 60.4%)	0% (0%, 69.0%)	0% (0%, 0%)	0% (0%, 94.5%)	0% (0%, 69.0%)	0% (0%, 0%)
Reaction type						
Mild[a]	50.0% (25.0%, 100%)	33.3% (0%, 68.7%)	16.7% (-72.4%, 100%)	100% (100%, 100%)	33.3% (0%, 68.7%)	66.7% (-53.3%, 100%)
Moderate[b]	50.0% (25.0%, 100%)	66.7% (33.3%, 100%)	-16.7% (-100%, 28.2%)	0% (0%, 100%)	66.7% (33.3%, 100%)	-66.7% (-100%, 53.3%)
Severe[c]	0% (0%, 57.1%)	0% (0%, 35.3%)	0% (0%, 0%)	0% (0%, 100%)	0% (0%, 35.3%)	0% (0%, 0%)
Exposure Route						
Ingestion	25.0% (0%, 60.1%)	100% (100%, 100%)	-75.0% (-100%, -3.4%)	100% (100%, 100%)	100% (100%, 100%)	0% (0%, 0%)
Contact[d]	0% (0%, 35.1%)	0% (0%, 56.1%)	0% (0%, 0%)	0% (0%, 100%)	0% (0%, 56.1%)	0% (0%, 0%)
Inhaled	0% (0%, 35.1%)	0% (0%, 56.1%)	0% (0%, 0%)	0% (0%, 100%)	0% (0%, 56.1%)	0% (0%,.0%)
Parenteral	75.0% (50.0%, 100%)	0% (0%, 56.1%)	75.0% (3.4%, 100%)	0% (0%, 100%)	0% (0%, 56.1%)	0% (0%, 0%)
Treatment in ED						
Epinephrine	75.0% (21.9%, 98.7%)	33.3% (1.8%, 87.5%)	41.7% (-55.7%, 100%)	100% (5.5%, 100%)	66.7% (12.5%, 98.2%)	33.3% (-53.3%, 100%)
Antihistamines	75.0% (21.9%, 98.7%)	100% (31.0%, 100%)	-25.0% (-92.4%, 42.4%)	100% (5.5%, 100%)	33.3% (1.8%, 87.5%)	66.7% (-53.3%, 100%)
Steroids	50.0% (15.0%, 85.0%)	66.7% (12.5%, 98.2%)	-16.7% (-100%, 72.4%)	100% (5.5%, 100%)	100% (31.0%, 100%)	0% (0%, 0%)

[a]Symptoms include urticaria, erythema, angioedema, oral pruritus, nausea, nasal congestion, sneezing, rhinorrhea or throat tightness[16]
[b]Symptoms include crampy abdominal pain, diarrhea, recurrent vomiting, dyspnea, stridor, cough, wheeze, or "light-headedness"[16]
[c]Symptoms include cyanosis, hypoxia, respiratory arrest, hypotension, dysrhythmia, confusion, or loss of consciousness[16]
[d]Cyclopentolate eye drops
[e]One patient therefore CI cannot be computed

5.4 Allergy Assessment

Consent for follow up was provided for 20 pediatric cases of suspected DIA at the MCH. Data for 20 retrospective cases was collected by chart review of the allergy visits. After the ED visit, 72.5% (95%CI, 55.9%, 84.9%) of children had seen an allergist for assessment and medical records were obtained for all children (Table VI). Of the 29 children who saw an allergist, 13 underwent skin testing of which 2 cases were positive. Of the 11 with a negative skin test, 5 underwent a graded oral challenge, which was positive in one case. Among the other children seeing the allergist, 4 underwent an oral challenge without prior skin testing, while 12 did not undergo any testing (Figure 3A).

Of the 16 patients that presented to the MCH ED with anaphylaxis to antibiotics, only 10 patients had seen an allergist for assessment. Of the 10 children, 7 underwent skin testing, of which 1 was positive to ceftriaxone by intradermal skin testing. Among the 6 with a negative skin test, 2 proceeded to a graded oral challenge, which was positive in one case to amoxicillin. Among the other children seeing an allergist, 2 underwent an oral challenge without prior skin testing, of which one patient had a positive challenge to clarithromycin. One patient did not undergo any testing despite having seen an allergist (Figure 3B).

Among the 24 patients from the MCH ED who reacted to non-antibiotic drugs, 19 had been assessed by an allergist. Six patients underwent skin testing of which 5 were negative. The positive skin test was to cyclopentolate. Of the 5 patients with negative skin tests, 3 proceeded with a graded oral challenge which were all negative. Two patients underwent a graded oral challenge without prior skin testing, which were both negative (Figure 3C).

Among the 8 patients from the MCH ED who reacted to NSAIDs, 7 had been assessed by an allergist. One patient underwent skin testing which was negative. Two patients underwent a

graded oral challenge to the same drug suspected of causing the DIA, which were both negative. Four patients did not undergo any testing (Figure 3D).

Consent for follow-up was provided in 4 of the 7 cases of reported DIA at BCCH. Of the 4 patients, only 1 patient was assessed by an allergist. The patient underwent skin testing which was negative, but had no challenge. Therefore, drug allergy was not established (Table VI).

Of the 4 pediatric patients with DIA from LHSC, only 1 patient provided consent for follow-up, however, the patient had not been assessed by an allergist.

Among the 64 adult patients from HSC with DIA, 52 patients were prospective and eligible for follow-up. Of the 37 patients reached, less than a third had been assessed by an allergist after the ED visit. Medical charts were obtained for over 50.0% of adults who had seen an allergist (Table VI). Of the 6 adult patients who were assessed by an allergist and provided consent to provide medical records, only 2 underwent skin testing of which 1 was reported by the patient as positive to a contrast agent. The patient with the negative skin test had a graded oral challenge which was positive to an antibiotic. Therefore, drug allergy was confirmed by skin test in one patient and an oral challenge in another patient (Figure 4A).

Of the 29 adults with anaphylaxis to antibiotics, 21 consented to follow-up, of which only 7 had been assessed by an allergist. Of these 7 patients, 4 provided consent to provide medical records. One patient underwent skin testing which was negative and that same patient underwent a graded oral challenge which was positive to cefadroxil (Figure 4B).

Of the 22 adult prospective patients who reacted to non-antibiotic drugs, 16 consented to follow-up, of which only 3 had been assessed by an allergist. Of these patients, 2 consented to provide medical records. One patient underwent skin testing which was positive to a contrast agent. The second patients did not undergo any testing (Figure 4C).

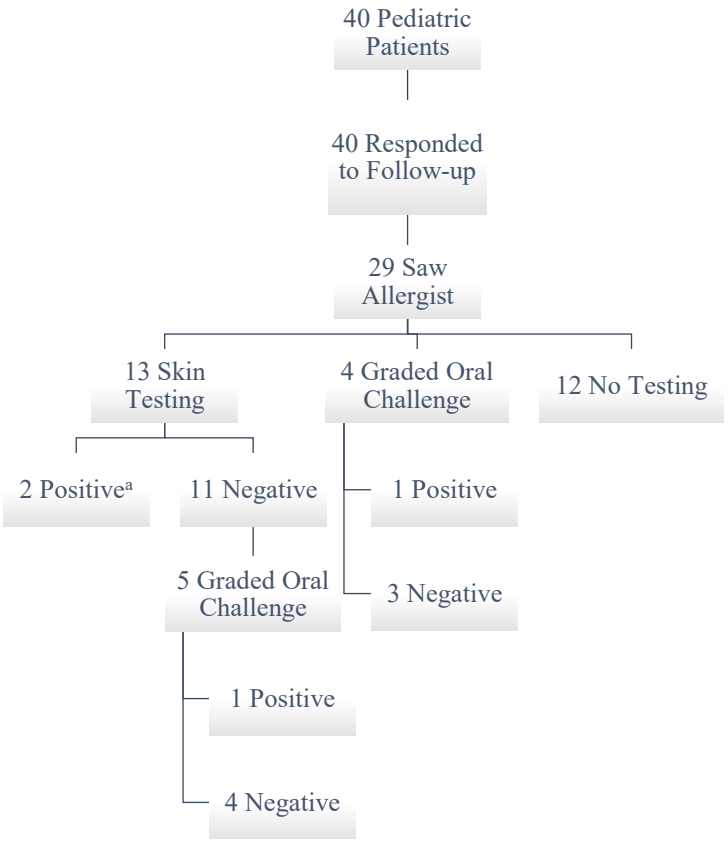
Of the 10 adult patients who reacted to NSAIDs, 7 consented to the follow-up and none were assessed by an allergist (Figure 4D).

The characteristics of patients assessed and allergy tested versus patients not assessed or not tested were compared at the MCH and HSC, finding no significant differences (Tables VII and VIII).

Figure 3. Flow Diagram of Montreal Children's Hospital Pediatric Patients Assessed by an Allergist

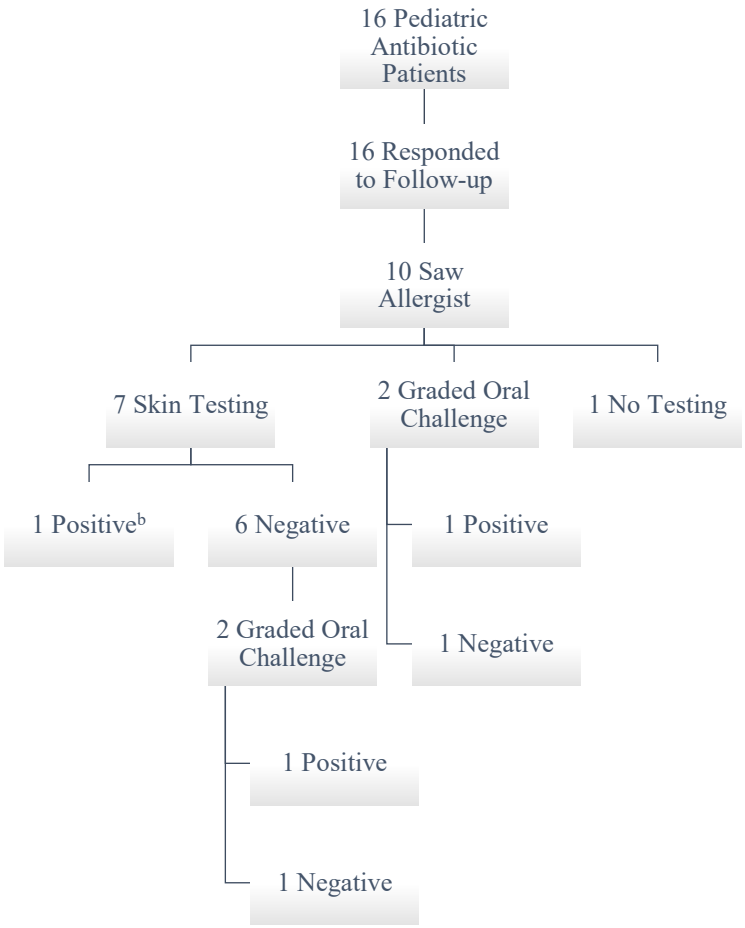
A. Flow diagram of all children who reacted to drugs.
B. Flow diagram of children who reacted to antibiotics.
C. Flow diagram of children who reacted to non-antibiotic drugs.
D. Flow diagram of children who reacted to NSAIDs.

A.



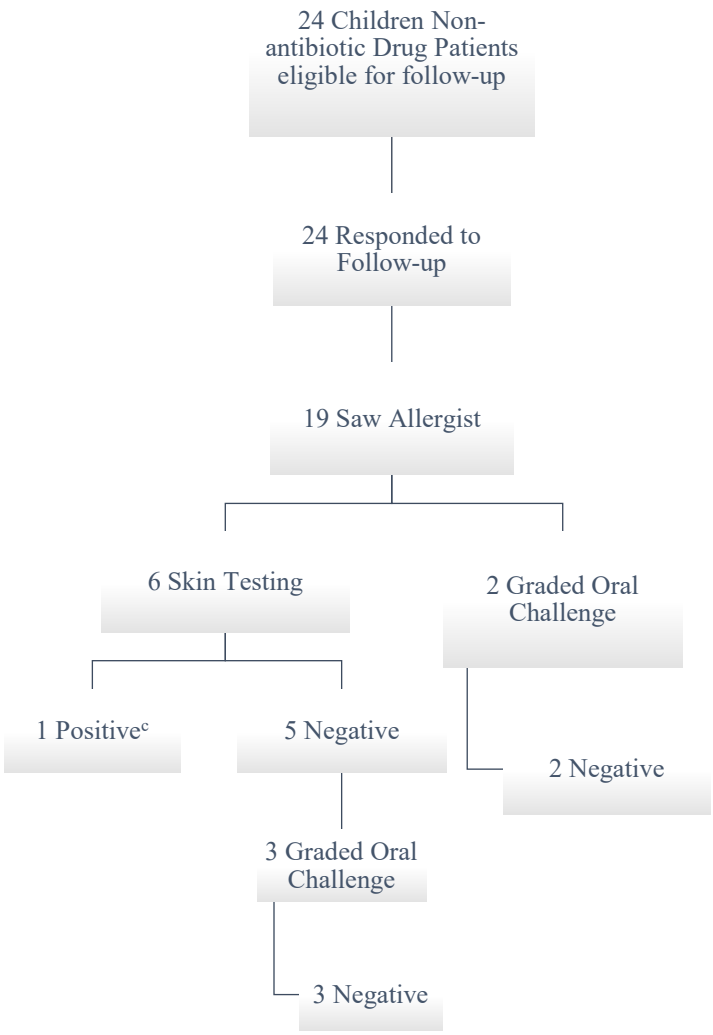
[a]Positive skin tests to Ceftriaxone by intradermal skin testing and Cyclopentolate by skin prick test.

B.



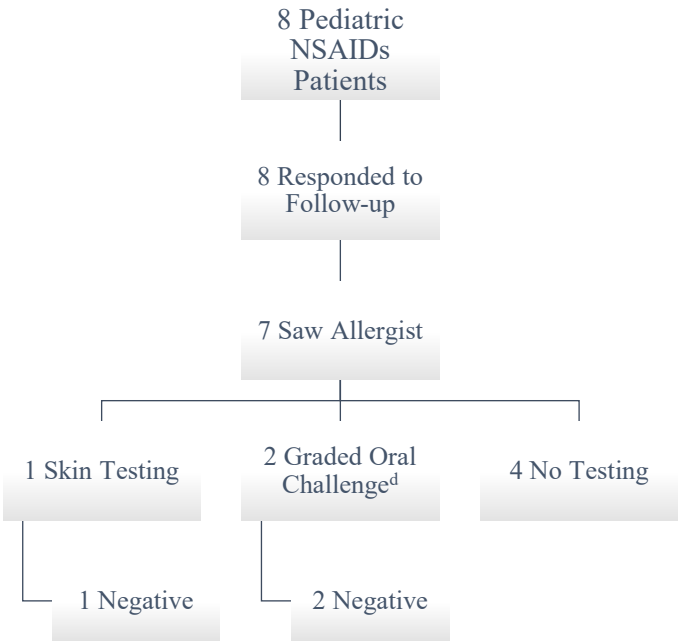
[b]Positive skin test to Ceftriaxone by intradermal skin testing.

C.



[c]Positive skin test to Cyclopentolate.

D.

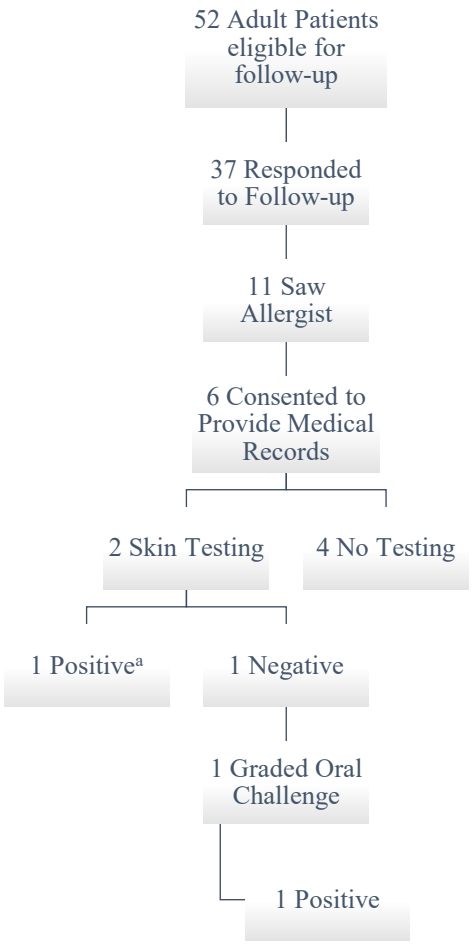


[d]Graded oral challenge was done with same drug (Advil) as previously reacted to.

Figure 4. Flow Diagram of HSC Adult Patients Assessed by an Allergist

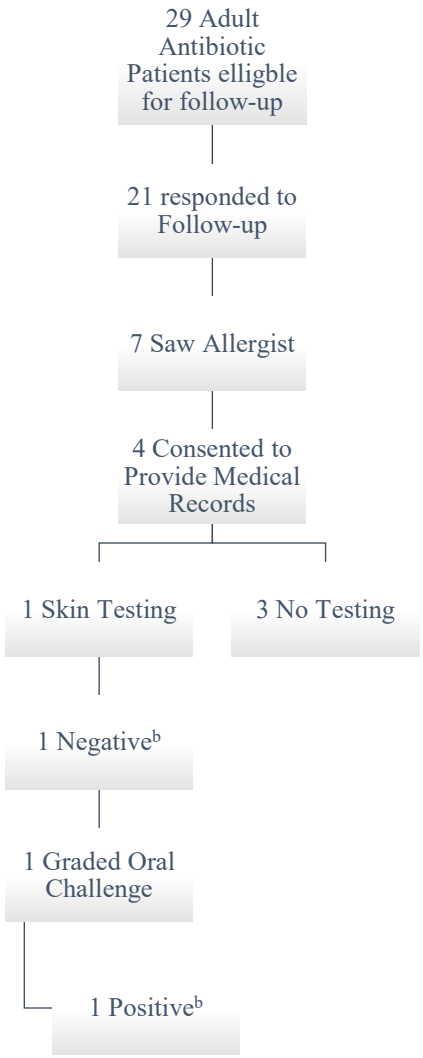
A. Flow diagram of all adults who reacted to drugs.
B. Flow diagram of adults who reacted to antibiotics.
C. Flow diagram of adults who reacted to non-antibiotic drugs.
D. Flow diagram of adults who reacted to NSAIDs.

A.



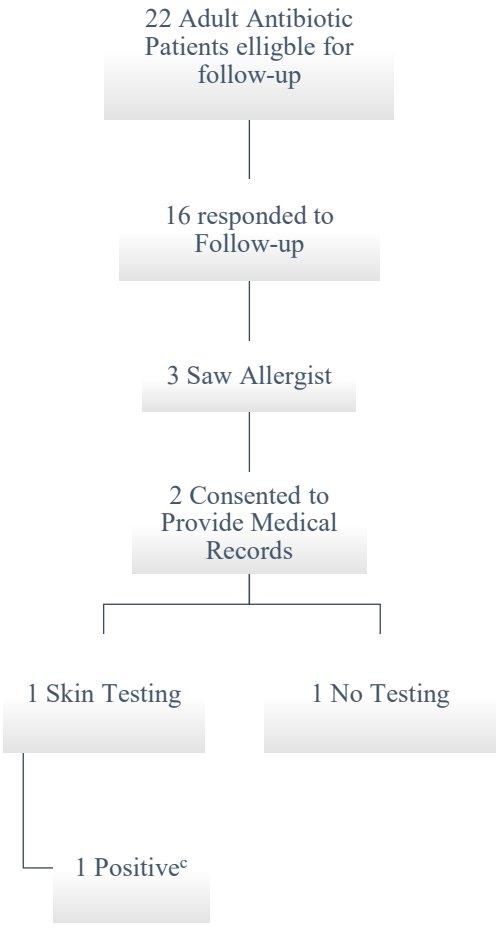
[a]Positive skin test to contrast agent.

B.



[b]Negative skin test and positive skin test to Cefadroxil.

C.



[c]Positive skin test to contrast agent.

D.

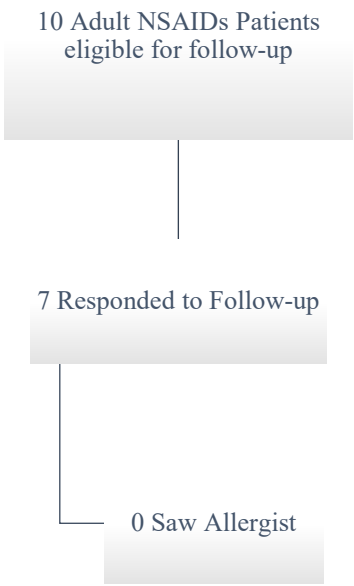

10 Adult NSAIDs Patients eligible for follow-up
7 Responded to Follow-up
0 Saw Allergist

Table VI. Follow-up for Diagnosis of Drug Trigger by Allergy Tests

Montreal Children's Hospital			Hôpital Sacré-Coeur			British Columbia Children's Hospital			Difference MCH and HSC	Difference MCH and BCCH	Difference HSC and BCCH
Variable	**No. (%)**	**95% CI**	**Variable**	**No. (%)**	**95% CI**	**Variable**	**No. (%)**	**95% CI**			
Responded to follow-up (N=40)	40 (100)		Responded to follow-up (N=52)	37 (71.2)		Responded to follow-up (N=4)	3 (75.0%)		3	37	34
Saw Allergist (N=40)	29 (73)	55.9%, 84.9%	Saw Allergist (N=37)	11 (30)	16.4%, 47.2%	Saw Allergist (N=3)	1 (33)	1.8%, 87.5%	42.8% (20.0%, 65.6%)	39.2% (-33.9%, 100%)	-3.6% (-62.5%, 55.3%)
Consented to Provide Medical Record (N=29)	29 (100)	84%, 100%	Consented to Provide Medical Records (N=11)	6 (55)	24.67%, 81.9%	Consented to Provide Medical Records (N=1)	1 (100)	5.5%, 100%	45.5% (9.8%, 81.1%)	0% (0%, 0%)	-45.5% (-100%, 29.4%)
Skin Test Only	8 (28)	10.3%, 46.3%	Skin Test Only (N=6)	1 (17)	0%, 62.0%	Skin Tests Only	1 (100)	100%, 100%	10.9% (-33.1%, 54.9%)	-72.4% (-100%, -4.4%)	-83.3% (-100%, 4.8%)
Oral Challenge Only	4 (14)	0%, 32.5%	Oral Challenge Only	0 (0)	0%, 45.3%	Oral Challenge Only	0 (0)	0%, 100%	13.8% (-8.8%, 36.4%)	13.8% (-12.6%, 40.1%)	0% (0%, 0%)
Skin Test and Oral Challenge	5 (17)	0%, 35.9%	Skin Test and Oral Challenge	1 (17)	0%, 62.0%	Skin Test and Oral Challenge	0 (0)	0%, 100%	0.6% (-32.8%, 34.0%)	17.2% (-13.7%, 48.2%)	16.7% (-29.8%, 63.2%)
No Tests	12 (41)	24.1%, 60.1%	No Tests	4 (67)	50.0%, 100%	No Tests	0 (0)	0%, 100%	-25.3% (-77.1%, 26.5%)	41.4% (-17.9%, 100%)	66.7% (-29.4%, 100%)
Diagnosed by Skin Test (N=13)	2 (15)	2.7%, 46.3%	Diagnosed by Skin Test (N=2)	1 (50)	9.5%, 90.5%	Diagnosed by Skin Test (N=1)	0 (0)	0%, 94.5%	-34.6% (-100%, 66.2%)	15.4% (-19.6%, 50.4%)	50.0% (-69.3%, 100%)
Diagnosed by Oral Challenge (N=9)	2 (22)	3.9%, 59.8%	Diagnosed by Oral Challenge (N=1)	1 (100)	5.5%, 100%	Diagnosed by Oral Challenge (N=0)[a]	0 (0)	NA[a]	-77.8% (-100%, 4.9%)	22.2%[a]	100%[a]
Established drug allergy by Skin test/Challenge in those assessed by allergist (N=29)	4 (14)	4.5%, 32.6%	Established drug allergy by Skin test/Challenge in those assessed by an allergist (N=6)	2 (33)	6.0%, 75.9%	Established drug allergy by Skin test/Challenge in those assessed by an allergist (N=1)	0 (0)	0%, 94.5%	-19.5% (-69.4%, 30.3%)	13.8% (-12.6%, 40.1%)	33.3% (-37.7%, 100%)

Positive tests among all those that underwent skin test/challenge (N=17)	4 (24)	7.8%, 50.2%	Positive tests among all those that underwent skin test/challenge (N=2)	2 (100)	19.8%, 100%	Positive tests among all those that underwent skin test/challenge (N=1)	0 (0)	0%, 94.5%	-76.5% (-100%, -28.4%)	23.5% (-20.2%, 67.2%)	100% (25.0%, 100%)
Percentage of DIA among anaphylaxis according to sensitivity analysis											
Year 1	0.66%		Year 1	20.0%					-19.34%		
Year 2	0.75%		Year 2	18.3%					-17.6%		
Year 3	0.83%		Year 3	21.1%		Year 1	0%		-20.3%	0.83%	21.1%
Year 4	0.85%		Year 4	22.1%		Year 2	0%		-21.3%	0.85%	22.1%

[a]One patient therefore CI cannot be computed

Table VII. Characteristics of Patients Assessed and Allergy Tested versus Patients Not Assessed or Not Tested at the Montreal Children's Hospital

	Assessment and Testing (N=17)		**No Assessment or Testing (N=23)**		**Difference**
Variable	**No. (%)**	**95%CI**	**No. (%)**	**95% CI**	
Sex (% males)	7 (41)	9.4%, 66.5%	13 (57)	34.9%, 76.1%	-15.3% (-51.4%, 20.7%)
Medication Type					
Antibiotics	9 (53)	28.5%, 76.1%	7 (30)	14.1%, 53.0%	22.5% (-12.9%, 57.9%)
Non-Antibiotic Drugs	8 (47)	23.9%, 71.5%	16 (70)	47.0%, 85.9%	-22.5% (-57.9%, 12.9%)
Known Drug Allergy	0 (0)	0%, 22.9%	3 (13)	3.4%, 34.7%	-13.0% (-31.9%, 5.8%)
Known Food Allergy	4 (24)	7.8%, 50.2%	6 (26)	11.1%, 48.7%	-2.6% (-32.1%, 27.0%)
Known Asthma	5 (29)	11.4%, 56.0%	5 (22)	8.3%, 44.2%	7.7% (-24.9%, 40.2%)
Reaction Type					
Mild Reaction	2 (12)	0%, 30.4%	6 (26)	13.0%, 47.1%	-14.3% (-43.0%, 14.4%)
Moderate Reaction	14 (82)	70.6%, 100%	16 (70)	56.5%, 90.6%	12.8% (-18.4%, 44.0%)
Severe Reaction	1 (6)	0%, 24.6%	1 (4)	0%, 25.4%	1.5% (-13.9%, 4.3%)

Table VIII. Characteristics of Patients Assessed and Allergy Tested versus Patients Not Assessed or Not Tested at the Hôpital du Sacré-Coeur

	Assessment and Testing (N=2)		No Assessment or No Testing (N=62)		Difference
Variable	**No. (%)**	**95%CI**	**No. (%)**	**95% CI**	
Sex (% males)	1 (50)	9.5%, 90.5%	17 (27)	17.2%, 40.4%	22.6% (-70.2%, 100%)
Medication Type					
Antibiotics	1 (50)	9.5%, 90.5%	36 (58)	44.9%, 70.3%	-8.1% (-86.5%, 70.4%)
Non-Antibiotic Drugs	1 (50)	9.5%, 90.5%	26 (42)	29.7%, 55.1%	8.1% (-70.4%, 86.5%)
Known Drug Allergy	1 (50)	9.5%, 90.5%	16 (26)	15.9%, 38.7%	24.2% (-70.1%, 100%)
Known Food Allergy	1 (50)	9.5%, 90.5%	7 (11)	5.0%, 22.5%	38.7% (-56.8%, 100%)
Known Asthma	0 (0)	0%, 80.2%	6 (10)	4.0%, 20.5%	-9.7% (-26.7%, 7.4%)
Reaction Type					
Mild Reaction	0 (0)	0%, 95.8%	0 (0)	0%, 8.7%	0% (0%, 0%)
Moderate Reaction	1 (50)	50%, 100%	52 (84)	75.8%, 92.5%	-33.9% (-100%, 61.8%)
Severe Reaction	1 (50)	50%, 100%	10 (16)	8.1%, 24.8%	33.9% (-61.8%, 100%)

5.5 Factors Associated with Severe DIA, Allergy Assessment, and Diagnosis of DIA

Among the patients at the 3 pediatric EDs, severe DIA was associated with parenteral exposure (OR 1.23 [95%CI, 1.07, 1.43]) while adjusting for age, sex, type of drug, history of asthma, history of known drug allergy, and history of known food allergy (Table IX).

Similarly, among adults at HSC, severe DIA was associated with parenteral exposure (OR 1.76 [95%CI, 1.10, 2.80]) when adjusting for age, sex, type of drug, history of asthma, history of known drug allergy, and history of known food allergy (Table X).

Among the patients at the 3 pediatric centres, assessment by an allergist was more likely in males and in patients presenting to the ED in Montreal versus the other EDs (OR 1.32 [95%CI, 1.01, 1.73] and OR 1.82 [95%CI, 1.10, 3.01], respectively) while adjusting for age, type of drug, exposure route, severity of reaction, and epinephrine treatment (Table XI). An established drug allergy by an allergist through a skin test/challenge was more likely in cases of antibiotic-induced reactions and less likely in younger children (OR 1.34 [95%CI, 1.05, 1.71] and OR 0.98 [95%CI, 0.96, 0.99], respectively) while adjusting for sex, centre location, exposure route, severity of reaction, and epinephrine treatment (Table XII).

Table IX. Factors Associated with Severe Reactions for All Drugs in Pediatric Patients

All Children from 3 Centres (N=51)		
	Univariate	**Multivariate[a]**
Characteristics	OR (95% CI)	OR (95% CI)
Age at reaction	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Sex (Males)	1.08 (0.97, 1.20)	1.09 (0.97, 1.22)
Antibiotics	1.02 (0.91, 1.14)	1.02 (0.91, 1.15)
Known Asthma	0.95 (0.82, 1.09)	0.97 (0.84, 1.13)
Known Drug Allergy	0.96 (0.78, 1.18)	0.94 (0.77, 1.15)
Known Food Allergy	0.95 (0.83, 1.08)	0.96 (0.84, 1.11)
Parenteral Exposure	1.25 (1.10, 1.42)	1.23 (1.07, 1.43)

[a]Adjusted Odds Ratio

Table X. Factors Associated with Severe Reactions for All Drugs in Adult Patients

Hôpital Sacré-Coeur (N=62)		
	Univariate	**Multivariate[a]**
Characteristics	OR (95% CI)	OR (95% CI)
Age at reaction	0.99 (0.99, 1.01)	0.99 (0.99, 1.00)
Sex (Males)	0.85 (0.69, 1.04)	0.83 (0.66, 1.03)
Antibiotic	0.92 (0.76, 1.11)	0.96 (0.78, 1.17)
Known Asthma	0.99 (0.72, 1.37)	1.03 (0.72, 1.47)
Known Drug Allergy	1.01 (0.81, 1.24)	0.93 (0.74, 1.17)
Known Food Allergy	1.09 (0.82, 1.45)	0.97 (0.71, 1.31)
Parenteral Exposure	1.67 (1.08, 2.58)	1.76 (1.10, 2.80)

[a]Adjusted Odds Ratio

Table XI. Factors Associated with Allergy Assessment by an Allergist in Pediatric Patients

All Children from 3 Centres (N=51)		
	Univariate	**Multivariate[a]**
Characteristics	OR (95% CI)	OR (95% CI)
Age at reaction	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Sex (Males)	1.13 (0.86, 1.47)	1.32 (1.01, 1.73)
Antibiotics	0.92 (0.69, 1.22)	1.11 (0.84, 1.46)
Quebec Centre	1.78 (1.19, 2.68)	1.82 (1.10, 3.01)
Parenteral Exposure	0.83 (0.60, 1.16)	0.98 (0.68, 1.42)
Severe Reaction	0.75 (0.41, 1.38)	0.57 (0.29, 1.11)
Epinephrine Treatment	1.06 (0.80, 1.40)	1.16 (0.89, 1.51)

[a]Adjusted Odds Ratio

Table XII. Factors Associated with an Established Allergy by an Allergist in Pediatric Patients

All Children from 3 Centres (N=51)		
	Univariate	**Multivariate[a]**
Characteristics	OR (95% CI)	OR (95% CI)
Age at reaction	0.98 (0.96, 1.00)	0.98 (0.96, 0.99)
Sex (Males)	0.77 (0.61, 0.97)	0.82 (0.66, 1.02)
Antibiotics	1.28 (0.99, 1.65)	1.34 (1.05, 1.71)
Quebec Centre	1.15 (0.57, 2.31)	0.97 (0.47, 2.04)
Parenteral Exposure	1.08 (0.77, 1.52)	1.12 (0.78, 1.62)
Severe Reaction	0.87 (0.43, 1.75)	0.76 (0.37, 1.56)
Epinephrine Treatment	1.23 (0.96, 1.58)	1.24 (0.99, 1.56)

[a]Adjusted Odds Ratio

6.0 Discussion

We have conducted the first prospective study assessing clinical characteristics and diagnosis of DIA in children and adults in 4 EDs across Canada. Our study reveals that while there was no conclusive change in the percentage of DIA over time in all 4 centres, the percentage of DIA among all cases of anaphylaxis is higher in adults than in children. Further, we report the disparities between reported DIA and established DIA in children. The main drug culprits in adults and children are antibiotics and non-antibiotic drugs, respectively, and, in both age groups, there is substantial underuse of epinephrine. Our findings show that the majority of pediatric and adult DIA cases are not appropriately assessed for the diagnosis of drug allergy.

The higher percentage of DIA in adults compared to children is consistent with previous retrospective reports suggesting that DIA occurs more frequently in adults[39]. The increased risk of DIA in adults could be due to greater exposure to antibiotics over the course of their life and in particular fluoroquinolones, that are relatively contraindicated in children[57]. Additionally, middle- and older-aged adults have a greater risk of drug reactions due to the simultaneous use of multiple drugs to treat co-morbidities and age-related changes in pharmacokinetics and pharmacodynamics[148]. While there was no sex dominance for children, fewer cases of DIA among adult males were found (Table III), which is in line with other studies[72, 76] and may be explained by the effects of estrogen on mediators of anaphylaxis during the reproductive years in females[72].

In our population, very few adult patients consulted an allergist after the initial ED visit. The low percentage of adults and children assessed for DIA may be due to patient-related factors or due to the factors related to the Canadian heath system. Studies suggest that young adults, between the ages of 17 to 44 years, are the least compliant with using referrals to be assessed by

medical specialists[149], which could be attributed to patients' other priorities and inability to take time off work[150, 151]. Health system-related factors that could contribute to underassessment of DIA include low number of allergists in Canada and long waiting time for specialist assessment[150]. Regardless of its cause, non-confirmed drug allergy may lead to mislabeling of patients[45]. Mislabeling of patients has been associated with increased use of alternative antibiotics[23, 135-137], increased risk of acquiring antibiotic-resistant infections[23, 45, 135-137], such as *C. difficile*, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA), significantly longer hospital stays[45, 137], increased healthcare costs[45], and increased mortality[133].

Our results indicate that majority of suspected DIA cases in adults and children are not assessed appropriately by allergists. Recent studies suggest that suspected cases of antibiotic allergy should be assessed with oral challenges[21]. Further, skin tests are not standardized for most antibiotics[21] and studies report poor predictive values for antibiotics[21] and NSAIDs[124] regarding skin tests. In the absence of sensitive and accurate skin tests, our results support the use of challenges only to establish the diagnosis of DIA. After conducting sensitivity analysis, it is likely that the percentage of DIA among anaphylaxis is overreported in children (Table VI).

In our study, the majority of children from 2 pediatric centres were assessed by an allergist after the initial reaction. Patients recruited from the Montreal pediatric centre and males were more likely to be assessed by an allergist. The presence of the large allergy division and a specific drug allergy clinic at the Montreal Children's Hospital allows for greater access to an allergy specialist compared to the other centres. In addition, given that a large antibiotic registry exists only in the Quebec centre and given numerous publications related to this specific registry, there may be higher awareness for referring to allergy specialists at this centre[21]. Our finding

that DIA is more likely established with a skin test and/or challenge in cases of antibiotic-induced reactions is not surprising given the availability of skin tests for antibiotics (mainly β-lactams) versus non-antibiotic drugs[152]. It is also possible that in younger children the diagnosis of DIA is less likely established because physicians will be more hesitant to conduct a drug challenge in young children who are less able to verbalize their complaints.

Our results reveal that fluoroquinolone antibiotics are a major trigger of DIA in adults. Recent studies have found that the number of immediate-type reactions to quinolones, especially moxifloxacin, have been increasing over the past few years[24, 29], which could be a result of the updated treatment guidelines recommending the use of moxifloxacin as first-line treatment in the management of bacterial respiratory infections, including sinusitis and pneumonia in adults[60]. Allergy to fluoroquinolone is rarely established likely due to the absence of standardized skin tests [29] and the risks related to conducting a drug challenge[153].

We demonstrate that NSAIDs are a common culprit of DIA in children and adults. NSAIDs were reported to be major triggers of DIA in other studies[30, 34, 65, 119], however none of these studies evaluated the long-term follow-up and assessment of those presenting with anaphylaxis to NSAIDs in the ED. The high percentage of reactions to NSAIDs could be explained by the increased consumption and high frequency of prescriptions to treat pain and fever[65, 154]. There are no standardized skin tests for the diagnosis of most NSAID-induced anaphylaxis[30]. Recent studies suggest that suspected cases of NSAID allergy should be assessed with oral challenges[20, 21, 124], however only a few challenges were conducted in our population. The underutilization of challenges in our population is likely attributable to the fact that such challenges are usually only performed in a hospital, under the supervision of an allergist[21] and there is limited access and long wait times for specialist assessment in some areas of Canada[150].

It is possible that in cases of DIA attributed to NSAIDS with negative challenges, NSAIDs may have acted as co-factors or augmenting factors rather than as a sole culprit for anaphylaxis[72]. It is also possible that cases reported as DIA, with a negative challenge, are likely attributable to the presence of unidentifiable factors or to conditions mimicking anaphylaxis, such as viral infections, food poisoning, or other toxic effects of medications[122].

Our study found that receiving parenteral drug treatment was associated with more severe reactions in both adults and children. It is reported that the vast majority of anaphylaxis fatalities have occurred in patients treated with intramuscular or intravenous antibiotic preparations, rather than oral[22, 42, 121]. This could be related to receiving a large amount of allergen into the body over a relatively short period of time, which reaches a high concentration in body organs[155]. Given the association of a severe reaction with parenteral administration of the drug in children and adults, caregivers should be made aware of the risk for severe anaphylaxis associated with those requiring IV treatment.

Our study has potential limitations. In the case of a negative skin test and negative oral graded challenge, it is possible that cases defined as DIA were actually idiopathic or caused by other unidentified factors. However, this limitation is shared with all studies assessing DIA. Given that the catchment population was based on only four sites across Canada, it is possible that our study cannot be generalized to the entire Canadian pediatric and adult populations. Our unique study design allowed for follow-up of prospective patients and the collection of data on established cases of DIA. Although we aimed to recruit all patients prospectively, almost 50% of the pediatric patients and 20% of the adult patients were identified retrospectively. Retrospective cases were identified by reviewing all cases presenting to the ED with ICD-10 codes for missed cases of anaphylaxis either due to misdiagnosis by an ED physician or the absence of a research

team member usually present to recruit patients. Given that we did not have permission to contact retrospective cases, data on assessment of these patients was only available via chart review of the allergy visit. However, demographic and clinical characteristics of DIA between retrospective and prospective patients were similar (Tables IV and V) and hence we believe that our findings are valid. Our study was limited as not all patients underwent allergy assessment and confirmatory testing, however comparisons revealed no substantial differences, therefore we do not expect our data to be biased (Table VI). Finally, our sample size prevented accurate estimation of the temporal change in percentage of DIA.

7.0 Conclusion

In conclusion, this is the first study to assess clinical characteristics and long-term assessment of DIA presenting in the EDs across Canada. In this cohort study, drug allergy was established by either skin test or oral challenge in less than a third of children at the Montreal Children's Hospital. The majority of adults are not appropriately assessed for the presence of drug allergy. Given our findings, policy changes, guidelines and educational programs prompting the use of confirmatory tests, mainly challenges, for the appropriate diagnosis of DIA should be developed. Future studies elucidating the pathogenesis of DIA and evaluating appropriate and efficient confirmatory tests will contribute to bridging the gaps related to the management of DIA.

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