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Research

Amoxicillin oral provocation challenge in a primary care clinic: a descriptive analysis

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Abstract

Background: Penicillin is the most frequently reported drug allergen; however, most of these allergies are not true allergies and do not justify the prescription of alternative, less effective and more expensive antibiotic drugs. We aimed to show that patients at low risk of amoxicillin allergy can safely and efficiently undergo oral provocation challenge (OPC) by their primary care physician.

Methods: In this descriptive analysis, we conducted a retrospective chart review of all primary care patients who had undergone OPC from November 2017 to October 2019 in the Amoxicillin Allergy Clinic at the North Perth Family Health Team, Listowel, Ontario. Eligibility for OPC among patients 18 months and older was determined through review of a self-reported patient intake form asking about symptoms, onset, duration, history and family history of allergic reactions, as well as the patient's electronic medical record. Patients were considered to be at low risk of true penicillin allergy if there was no history of anaphylaxis or severe cutaneous reactions. Those with low-risk allergic reactions returned for testing with an OPC to amoxicillin. We collected data on clinical characteristics, antibiotic exposure, parental drug allergy, response to OPC and wait time from referral. We used *t* tests to describe and compare these variables. Our primary outcome was reaction to OPC by severity as categorized by the World Allergy Organization grading system. Our secondary outcome was the time from referral to completed testing.

Results: In total, we included 99 patients (mean age 28.3, standard deviation [SD] 21.2 yr); 72 (73%) were female. Of those tested, 97% (n = 96) completed the OPC with no reaction, 3% (n = 3) had mild immediate reactions, and no serious immediate reactions developed. Mean wait time to testing was 59.0 (SD 69.8) days, with a median (interquartile range) of 39.5 (13.5–70.0) days.

Interpretation: Oral provocation challenge presents a safe and accessible opportunity for primary care providers to address erroneous allergy labels to penicillin and related drugs within the primary care office setting. There could be positive public health implications if OPC to penicillin drugs is implemented in primary care.

Affecting about 10% of patients, penicillin drug allergy is the most frequently reported drug allergy.[1] Penicillin drug allergy is commonly diagnosed after a childhood rash is assumed to be caused by recent penicillin administration but which is not investigated further.[2] T-lymphocyte–mediated nonimmediate reactions typically present with maculopapular rashes days after ingestion.[3] In contrast, immunoglobulin E (IgE)-mediated immediate reactions occur within the first hour and appear as urticaria, angioedema, rhinitis, bronchospasm or, rarely, as anaphylaxis.[2,4]

Despite their clinical use for over 70 years, penicillin and penicillin-related antibiotics continue to be recommended for first-line therapy in numerous respiratory tract, skin, joint and cardiovascular infections.[5,6] Although most reactions following use of penicillin and related antibiotics are not true drug allergies, medical practitioners often prescribe less effective or more expensive alternatives.[7–9] This leads to an increased risk of adverse events, more drug-resistant organisms and more *Clostridium difficile* infections.[10,11]

Presently, primary care providers struggle to rule out penicillin drug allergies.[12] A referral to an allergist for all patients with suspected penicillin drug allergy is impractical, as there are millions of patients with presumed penicillin allergy.[13] In Canada, there is less than 1 allergist per 100 000 people. Not surprisingly, this translates to long wait times, with an estimated wait time for penicillin drug allergy consultation of 12–18 months in rural southwestern Ontario (H.K., unpublished observations, 2019).

Primary care providers have limited experience and training in performing skin testing for drug allergy or measurement of specific IgE levels. Skin testing can be inconvenient and time

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consuming, and offers a poor clinical predictive value for nonimmediate reactions.[2] However, oral provocation challenge (OPC) testing presents an alternative that has been shown to be safe in both pediatric and adult populations without the need for allergy skin testing.[2,14] Oral provocation challenge is the definitive test for penicillin allergy.[2] When a patient with possible allergy can tolerate a reasonable dose of the presumed allergen in an OPC, allergy is essentially ruled out.[2] Thus, we aimed to show that patients with a low risk of amoxicillin allergy can safely and efficiently undergo OPC by their primary care providers.

Methods

Study design and setting

We conducted a descriptive analysis of cross-sectional data for patients who underwent consultation and OPC for presumed allergy to penicillin or related antibiotics between November 2017 to October 2019, in the primary care Amoxicillin Allergy Clinic at the rural North Perth Family Health Team in Listowel, Ontario (Appendix 1, available at www.cmajopen.ca/content/9/2/E394/suppl/DC1). The clinic is typically held monthly.

Initially, consultations and OPC were performed in the Listowel Memorial Hospital outpatient department from November 2017 to January 2018, before moving to the family medicine office at the North Perth Family Health Team in February 2018.

Participants

Patients who were allergic to amoxicillin or penicillin were recruited for the Amoxicillin Allergy Clinic after they returned a patient intake form that had been distributed through the North Perth Family Health Team office, the Listowel Memorial Hospital emergency department and preoperative clinic, and a local dentist's office. The form included the patient's history of anaphylaxis; allergic reaction symptoms, onset and duration; and personal and first-degree relatives' medical histories (Appendix 2, available at www.cmajopen.ca/content/9/2/E394/suppl/DC1). We determined eligibility of patients who had returned the form to undergo OPC through review of their electronic medical record from their family physician and patient consultation. At the consultation appointment, we interviewed the patient to clarify their reaction type as immediate or nonimmediate, determine reaction symptoms and their severity, and review their medical history.

Patients were eligible for OPC if they were 18 months of age or older, and if they were considered to be at low risk of true penicillin allergy (i.e., no history of anaphylaxis or severe cutaneous reactions). Patients were not eligible for OPC if they had previously received penicillin without any reaction. They were also not eligible if their reaction was IgE-mediated (e.g., angioedema, bronchospasm or anaphylaxis), if they had a previous severe reaction (e.g., Stevens–Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis or a drug reaction with eosinophilia and systemic symptoms), or if their clinical notes or history were substantially inconsistent or incomplete (Figure 1). Patients taking concurrent medications were not excluded.

Oral provocation challenge protocol

If patients were deemed low risk of true penicillin allergy after consultation and clinical history review, they were offered graded OPC immediately in either the Listowel Memorial Hospital outpatient clinic (November 2017 to January 2018) or the North Perth Family Health Team office (from February 2018). Patient consent was obtained before the procedure. Both settings were equipped with diphenhydramine elixir to manage mild reactions and epinephrine to manage anaphylactic reactions, as well as standard resuscitation medications and equipment.[15]

A 2-step graded OPC to amoxicillin was performed by a family physician and nurse practitioner. Amoxicillin was supplied as an oral suspension (250 mg/5 mL), with a total challenge dose of 500 mg for patients weighing more than 10 kg, or 45 mg/kg for pediatric patients weighing less than 10 kg.[2,16] The challenge dose was expected to be equivalent to that of a single therapeutic dose.

Patients were first administered 10% of the challenge dose (50 mg or 4.5 mg/kg if the patient weighed < 10 kg) and were observed for 20 minutes. If there was no reaction, patients received 90% of the therapeutic dose (450 mg or 40.5 mg/kg if the patient weighed < 10 kg) and were observed for 1 hour. If patients did not react to the therapeutic dose, this allergy was removed from the patient's chart, and the patient was advised to inform their pharmacist. This protocol was developed based on methods reported in publications by Mill and colleagues,[2] Hjortlund and colleagues[17] and Labrosse and colleagues.[18]

We considered the reaction to be positive on the development of objective findings (e.g., urticaria, wheeze, swelling); we did not consider subjective symptoms (e.g., pruritus without skin changes, dizziness) alone to be sufficient to diagnose an immune reaction.

We provided patients with follow-up instructions in writing that were adapted from the American College of Allergy, Asthma and Immunology.[19] Patients were instructed to report any delayed symptoms of rash, hives, wheezing or swelling in the same day or week, or during any subsequent treatments. Patients were advised about the safety of future prescription of penicillin, if clinically indicated.

Data sources

We retrospectively reviewed patient charts from the Amoxicillin Allergy Clinic for patients seen in the clinic from November 2017 to October 2019. The review included patient intake forms, consultation notes and clinic notes related to OPC. Data abstraction was performed by a single assessor (D.P.G) using a predefined abstraction form.

We selected variables based on a previously published study from a specialist clinic.[2] These included data on demographic and clinical characteristics, previous antibiotic exposure, personal and first-degree relatives' medical histories, reaction management and response to OPC.

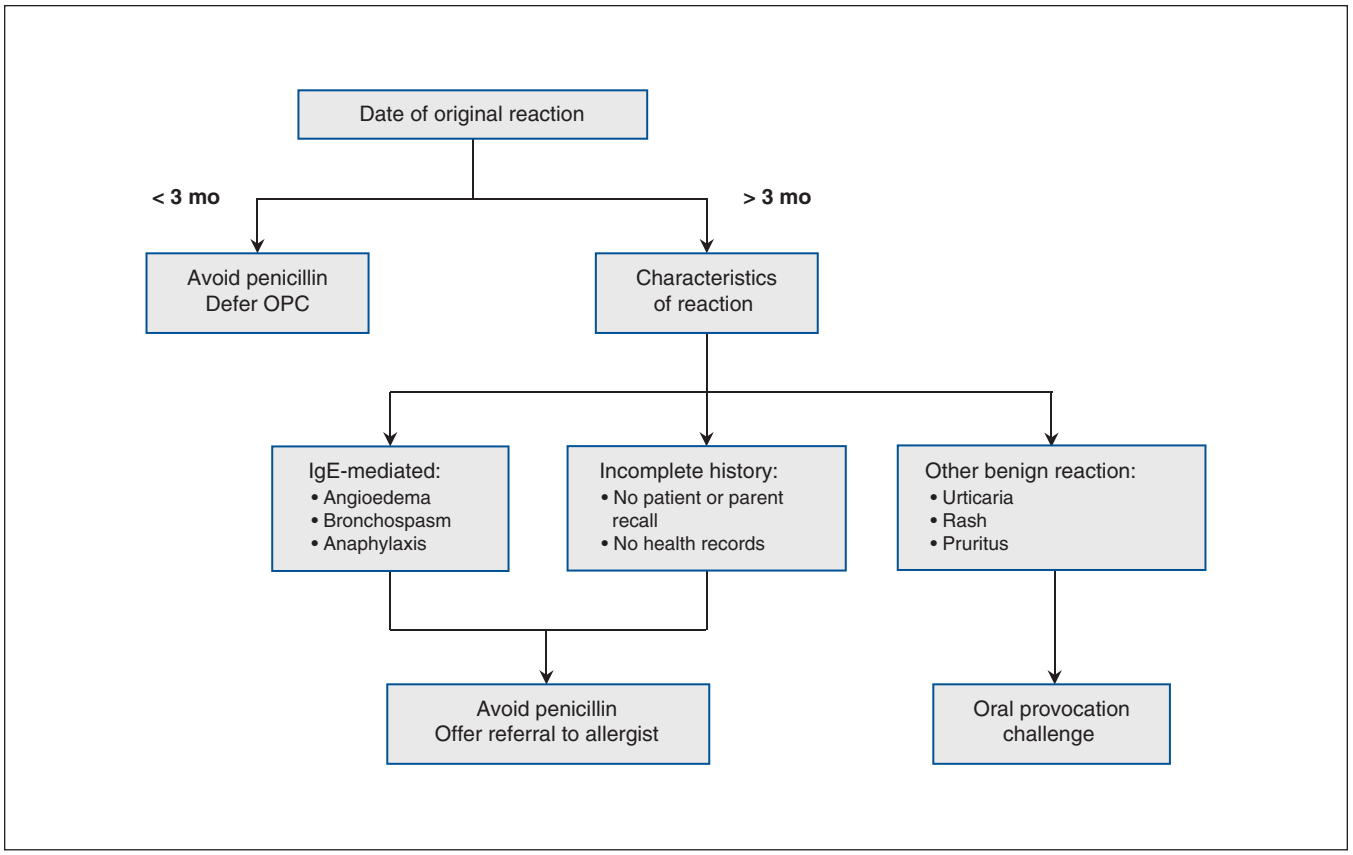

Figure 1: Protocol for eligibility for oral provocation challenge, using the self-reported results from the patient intake form (Appendix 2, available at www.cmajopen.ca/content/9/2/E394/suppl/DC1).

Outcomes

Our primary outcome of interest was the frequency and type of reaction to OPC. We classified the OPC reactions using the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System, which comprises 5 grades ranging from 1 (cutaneous, upper respiratory, conjunctival or other symptoms) to 5 (death; Table 1).[20] For patients with reaction to OPC, demographic information and reaction were described narratively. Our secondary outcome was the wait time to complete OPC.

Variables included sex (binary, male or female), age (continuous, yr) and wait times (continuous, from day of review of the patient intake form to the date of testing). We gave additional consideration to pediatric patients by stratifying age into less than 18 years and 18 years and older.

Wait times were stratified into 2 groups: less than 45 days and more than 45 days. We thought that a wait time of more than 6 weeks would be perceived by patients as a subjectively long wait versus a short wait in the context of elective allergy testing. To clarify the timing, the wait time began with receipt of the completed intake survey and ended with the consultation and provision of OPC (simultaneous) in the clinic.

Additional variables included history of immediate allergy and family history of penicillin allergy. We considered reactions within 1 hour of drug exposure to be immediate.[2] We defined a family history of penicillin allergy as any report of a known parental allergy, regardless of severity. For patients with reaction to OPC, demographic information and reaction were described narratively.

Statistical methods

We used sample size, percentages and means with standard deviations (SDs) to describe data (e.g., sex, age, average wait

Table 1: World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System[20]

Grade	Symptoms or signs
1	Cutaneous, upper respiratory (rhinitis, throat clearing, cough), conjunctival or other (nausea, metallic taste or headache)
2	More than 1 organ system, lower respiratory, gastrointestinal, or uterine cramps
3	Lower respiratory or upper respiratory (laryngeal, uvula or tongue edema)
4	Respiratory failure or cardiovascular (hypotension)
5	Death

times and family and personal history of penicillin allergy, including reaction and reaction grade). We compared differences in average wait times between pediatric and adult patients using *t* tests. We also calculated medians with interquartile ranges (IQRs) and maximums wait times. We used the Wilson method to calculate 95% confidence intervals (CIs) for the proportion of patients with a reaction. Observations with missing information on variables were excluded from the relevant analyses. Statistical significance was set at $p < 0.05$. Data were analyzed using Stata 15.1.

Ethics approval

We obtained approval for this study from the Hamilton Integrated Research Ethics Board, affiliated with McMaster University (Project No. 7414-C).

Results

Between Nov. 20, 2017, and Oct. 1, 2019, we offered OPC to 103 patients. Of the 99 (97%) who completed OPC, 72 were female (73%), with a mean age of 28.3 (SD 21.1) years. In total, 41.8% (41/98) were pediatric patients (mean age 8.0 [SD 4.0] yr) (Table 2). Mean age for adult patients was 42.9 (SD 15.5) years. Although the sex distribution was nearly even in the pediatric sample (19 male, 22 female), the adult sample population was disproportionately female (50/58).

The mean wait time was about 2 months (59.0 [SD 69.8] d), with median and maximum wait times of 39.5 (IQR 13.5–70.0) and 420 days, respectively. Mean wait times were significantly longer for pediatric patients compared with those for adult patients (77.3 [SD 90.2] v. 45.3 [SD 45.6] d; $p < 0.02$). Corresponding median and maximum wait times were, for pediatrics, 47 (IQR 18–94) and 420 days, respectively, and for adults, 39 (IQR 12–59) and 201 days, respectively.

When known, most patients had neither a family history of penicillin allergy (82.5%, 80/97) nor a personal history of immediate reaction to penicillin (90.0%, 81/90).

Reactions to OPC were uncommon (3/99, 3.0%, 95% CI 3%–9%). The patients who had an immediate reaction were pediatric and had a World Allergy Organization reaction grade of 1. All 3 patients who reacted had a personal history of immediate reaction, out of the 9 patients with a similar history (reaction rate of 33%). Diphenhydramine was used to treat symptoms; epinephrine was not administered in any cases. There were no reported delayed reactions to OPC. The demographic characteristics of the patients who reacted to the challenge and our narrative descriptions of their reactions to amoxicillin are provided in Appendix 3, available at www.cmajopen.ca/content/9/2/E394/suppl/DC1.

No associations were identified for family history of penicillin allergy when we compared pediatric with adult patients. Similarly, we did not find associations between family history and an interaction between sex and age. There was no difference in wait times whether patients had or did not have a family history of penicillin allergy. We could not determine associations between demographic characteristics and a personal history of immediate penicillin reaction.

Table 2: Demographic characteristics of patients who were included in the study

Characteristic	No. (%) of included patients*† *n* = 99
Sex	
Male	27 (27)
Female	72 (73)
Age, yr; mean ± SD (*n* = 98)	28.3 ± 21.1
Age < 18 yr	41 (42)
Mean	8.0 ± 4.1
Age ≥ 18 yr	57 (58)
Mean	42.9 ± 15.5
Wait time, d; mean ± SD (*n* = 97)	59.0 ± 69.8
Wait time < 45 d	53 (54)
Mean	18.0 ± 13.8
Wait time ≥ 45 d	46 (44)
Mean	108.4 ± 78.0
Family history of penicillin allergy (*n* = 97)	
No	80 (83)
Yes	17 (17)
Personal history of immediate reaction to penicillin (*n* = 90)	
No	81 (90)
Yes	9 (10)

Note: SD = standard deviation.
*Unless specified otherwise.
†Observations with missing information on a characteristic were excluded from the relevant analysis.

Interpretation

In our study, only 3 patients with a history of mild reactions had reactions to OPC, which were minor. Each of the 3 reactions were grade 1, meaning limited to just 1 sign or symptom (cutaneous, upper respiratory, conjunctival or other). Diphenhydramine was used to treat symptoms; epinephrine was not administered in any cases. There were no reported delayed reactions to OPC in our study.

Anaphylaxis with penicillin OPC in patients at low risk is uncommon and rarely fatal.[2,19–21] By comparison, subcutaneous immunotherapy, which is commonly performed in primary care, has a similar risk of systemic adverse events.[22,23] The training, equipment and skills to manage these complications would be directly relatable to OPC reactions. Given the high prevalence of low-risk penicillin allergy in Canada and long wait times for access to specialist testing, primary care providers may benefit from having a safe and accessible testing option.

This study adds to the body of evidence evaluating the safety of OPC for low-risk penicillin and amoxicillin allergy. Immediate mild allergic reactions occurred in 3% of patients in our study, which is similar to that reported by Labrosse and

colleagues.[18] Notably, that study reported an immediate allergic reaction rate of 2.3% during 5-day OPC in a pediatric population with mean age of 5.1 years.[20] In another study in a younger population (median age 1.7 [IQR 1.0–3.9] yr), reaction rates were higher (5.9%).[2] Although the methodology was different (patients were tested in an allergy clinic and had preceding intracutaneous testing), Hjortlund and colleagues[17] found a reaction rate of 4.5% (15/335) to OPC with penicillin V.[19] Sundquist and colleagues[12] also performed skin testing in an allergy clinic before OPC, and none of the 36 adult participants had an immediate reaction. Iammatteo and colleagues[14] conducted a single blind placebo-controlled direct amoxicillin challenge with 155 adults (mean age 51 yr), among whom the reaction rate was 2.6%. In a small study of 20 adult outpatients, the OPC reaction rate was 0%, and none had immediate or delayed hypersensitivity reactions.[24] Our study supports current evidence for conducting OPC without skin testing and extends this to the primary care office setting.

There were 3 immediate allergic reactions among those 9 patients with a history of immediate reaction (reaction rate of 33%). This represents a 10-fold increase over the reaction rate among all patients in our study who underwent OPC. Although history of immediate reaction is a risk factor for allergic reaction, most patients with a history of immediate reaction did not react to OPC, and were de-labelled as allergic to penicillin and related drugs.

In rural southwestern Ontario, a patient referred for penicillin drug allergy to an allergist commonly waits at least 12 months for assessment and testing. Patients in our sample population waited 59.0 days on average to be assessed, and 54% of patients were seen in less than 45 days. The allergy clinic was held once monthly; patients waited an average of 2 clinic cycles. There was a significantly longer wait in the pediatric population compared with that in adults, the reasons for which are unclear but may, in part, be due to school attendance or need for caregiver accompaniment. A study of physician barriers to patient recruitment noted that patients' unwillingness to take time to be tested was ranked most important.[12]

To add to the body of evidence evaluating the safety of OPC in primary care, our methodology could be replicated by primary care providers in different settings. A larger sample size would allow for the study of the effects of demographic characteristics, such as age, which may drive the study of specific mechanisms in reaction to OPC. Preoperative patients present another potential area of study. Although rapid access to OPC to de-label patients as allergic to penicillin drugs can be integrated into the surgical pathway, OPC by primary care providers may provide a cheaper or more convenient option.[25] We also propose to reassess the patients included in our study in the future to report which of these patients later received and tolerated penicillin for a clinical indication.

As the prevalence of inappropriate penicillin allergy labelling decreases, the prescribing of penicillin alternatives may decrease. We suggest that changing trends in antibiotic prescription may affect bacterial resistance patterns that could be studied. Subsequently, there may be both reductions in cost to the health care system and improvements in patient outcomes.[9,26]

In addition to the potential medical and public health benefits we have outlined, the clinical approach used at the primary care Amoxicillin Allergy Clinic was straightforward and not costly. Most primary care practitioners should be able to implement penicillin OPC in their clinics quite easily at minimal or no extra cost to the health care system.

Limitations

The study sample was dependent on referral from local primary care providers, so we are unaware if patients with greater or lesser risk of low-risk reactions were included in the study. The intake form responses were patient-reported, introducing possible recall bias. The form was available only in English. The total number of intake forms distributed and number of excluded patients were not measured.

Chart review was conducted by a single abstractor; therefore, it is possible that errors may have occurred during data abstraction. The definition for wait times was based on the opinions of the authors, and not formally tested. The low reaction rate for OPC precluded investigation of underlying demographic characteristics. Furthermore, only 10% of patients reported a personal history of immediate penicillin reaction; therefore, we could not calculate associations with sex, age and wait times. Our sample population was not large enough to consider factors that would have predicted an OPC reaction. Although patients were instructed to follow up with the clinic, delayed reactions may have been missed.

Importantly, the study was set at a single centre with 1 physician assessing patient eligibility and administering the OPC protocol; errors may have occurred at various points in clinic processes, protocol administration and clinical documentation. While we believe that the eligibility criteria for OPC and the clinical approach used at the Amoxicillin Allergy Clinic should be able to be implemented in other settings, we recognize that expertise and comfort level in performing OPC may differ among other primary care physicians.

Conclusion

We found OPC in the primary care setting within the primary care office setting to be a safe and accessible option for primary care providers to address erroneous penicillin allergy labels. Widespread implementation of penicillin OPC by primary care providers could have major health implications, particularly in sparsely populated regions.

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Contributors: Derek Gateman contributed to the conception and design of the study, collection of data, drafting and editing of the work. Jessie Rumble contributed to the collection of data, as well as drafting and editing of the work. Jennifer Protudjer contributed to the analysis of the data for the work and drafted the results section. Harold Kim contributed to the conception and design of the study and edited the final manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Data sharing: Individual participant data that underlie the results reports, once de-identified, may be requested beginning 3 months and ending 5 years following article publication by researchers who provide a methodologically sound proposal to meet the aims in the approved proposal. Proposals should be directed to derek.gateman@medportal.ca. To gain access, data requestors will be required to sign a data access agreement.

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/9/2/E394/suppl/DC1.

ADDITIONAL DESCRIPTION OF CLINICAL SETTING

North Perth Family Health Team

The North Perth Family Health Team (NPFHT) is a comprehensive primary health care centre located in the rural Southwestern Ontario community of Listowel, Ontario. Listowel is the main community in the Municipality of North Perth which has a population of 13,130. It is located about 1 hour from Kitchener and 1 hour from London, which are the closest referral centres for allergist consultation. The team includes 12 physicians and multiple interprofessional team members including 17 nurses, 2 nurse practitioners, 1 dietician, 1 pharmacist, 2 counsellors, 1 addictions youth worker and 18 administrative professionals. Based on a recent review of the electronic medication record (Accuro©), the NPFHT provides care to 14,698 rostered patients, 1,208 (8.22%) of which have a penicillin or amoxicillin allergy documented in their chart. The NPFHT operates during the hours of 09:00 to 17:00 and after-hours urgent care is available through the 24-hour emergency department at the Listowel Memorial Hospital, which is located directly across the street. In addition to primary care, the physicians also provide hospitalist services on the medicine and complex continuing care wards, emergency department, anaesthesia, surgical unit, and obstetrics. Physicians also act as medical directors for numerous local long-term care homes.

Amoxicillin Allergy Clinic

The Amoxicillin Allergy Clinic is held on a continuous monthly basis and is staffed by a family physician and nurse practitioner. Reception and nursing staff support appointment scheduling. Patients are scheduled in 15-minute increments and up to 10 patients can be tested in an afternoon. The initial assessment, review of completed survey, and consultation is completed by the family physician. If considered eligible for testing, patients are directed to see the nurse practitioner who administers the amoxicillin as per the testing protocol and observes for reactions in the waiting area. In total, patients are typically in the clinic for 90 minutes. Emergency anaphylaxis medications (epinephrine and oral diphenhydramine) are readily accessible in the testing exam room. Additional emergency equipment and medications, including a resuscitation cart, are located in the clinic. The resuscitation cart contains: standard resuscitation medications per ACLS (epinephrine, diphenhydramine, aspirin, nitroglycerine, benzodiazepines, atropine, salbutamol, glucagon, 50% dextrose, and naloxone), an oxygen tank, adult and paediatric bag valve masks, non-rebreather masks, oral and nasopharyngeal airways, peripheral intravenous supplies,

Appendix 1, as supplied by the authors. Appendix to: Gateman DP, Rumble JE, Protudjer J LP, et al. Amoxicillin oral provocation challenge in a primary care clinic: a descriptive analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200077. Copyright © 2021 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.

and a defibrillator. In the case of an immediate anaphylaxis reaction, patients could be easily transported by wheelchair to the hospital, over a distance of approximately 90 meters.

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Amoxicillin Allergy Survey

Name:
Date of Birth: PATIENT STICKER Date of Allergic Reaction: _____
Health Card Number:
Family Physician:

Background:
Amoxicillin is a penicillin-based antibiotic used to treat many common infections. Adverse reactions to penicillins are reported in as many as 5 to 10% of patients. Often a reaction will lead patients and physicians to avoid prescribing amoxicillin, but many of these are not true allergic reactions. Patients who have experienced serious, or anaphylactic, reactions should not use amoxicillin. There is growing research to show that amoxicillin can be used safely when there has previously been a mild, moderate, or delayed reaction. The following survey will help your physician to understand your reaction, and determine the future risks associated with amoxicillin.

Symptoms:
Please indicate if any of the following symptoms were part of your allergic reaction:

- ❑ Loss of consciousness, fainting, or near fainting
- ❑ Difficulty breathing, wheezing
- ❑ Swelling of the lips, tongue, or face
- ❑ Vomiting
- ❑ Abdominal pain
- ❑ Anaphylaxis

If you selected one of the above answers, please STOP HERE. If you did not, then continue below:

What kind of symptoms did you have:

- ❑ Rash
- ❑ Itching
- ❑ Blistering
- ❑ Other _____

When did the symptoms start:

- ❑ Within minutes or hours
- ❑ Within 24hrs
- ❑ After 24hrs

How long did the symptoms last:

- ❑ Hours
- ❑ Days
- ❑ Weeks

Other reactions or allergies:
Have you had an allergic reaction to another medication(s)?

Has one of your parents had an allergic reaction to amoxicillin?

Assurance of Accuracy:
By signing below, you certify that the information provided in this survey is accurate and complete to best of knowledge. Withholding or providing misinformation will affect your physician's ability to treat you safely, and could lead to very dangerous medical complications.

Patient/Parent Name:

Patient/Parent Signature:

Office Use Only: □ *Immediate* □ *Ig-E* □ *Severe* □ *Challenge*

Appendix 2, as supplied by the authors. Appendix to: Gateman DP, Rumble JE, Protudjer J LP, et al. Amoxicillin oral provocation challenge in a primary care clinic: a descriptive analysis. CMAJ Open 2021. DOI:10.9778/cmajo.20200077. Copyright © 2021 The Author(s) or their employ-er(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.

NARRATIVE DESCRIPTION OF REACTIONS TO OPC

Reaction #1

Patient A was a 3 year-old male who presented with history of maculopapular rash that onset 3 days after starting amoxicillin for acute otitis media at age 16 months. He had neither a personal history of immediate reaction nor parental history of amoxicillin allergy. There were no other documented allergies.

During the challenge, he developed urticaria on the face and the trunk 20 minutes following exposure to the initial amoxicillin dose of 50mg. He was treated with diphenhydramine 18mg, and the urticaria resolved within 20 minutes.

Reaction #2

Patient B was an 8 year-old female who presented with a history of maculopapular rash that worsened 2 days after starting amoxicillin for acute otitis media and pharyngitis at age 14 months. Clinicians suspected roseola vs. drug allergy. She had no personal history of immediate reaction. She also had an allergy to clarithromycin. Both of her parents had documented history of amoxicillin allergy.

During the challenge, she developed a sensation of swollen and sore throat 45 minutes following exposure to the second amoxicillin dose of 450mg, and then sensation of itching of the lips at 75 minutes. She was treated with diphenhydramine 12.5mg, and symptoms improved within 25 minutes.

Reaction #3

Patient C was a 9 year-old female who presented with history of maculopapular rash and sore throat that onset after the third dose of amoxicillin for pharyngitis at age 6 years. She had neither a personal history of immediate reaction nor parental history of amoxicillin allergy. There were no other documented allergies.

Appendix 3, as supplied by the authors. Appendix to: Gateman DP, Rumble JE, Protudjer J LP, et al. Amoxicillin oral provocation challenge in a primary care clinic: a descriptive analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200077. Copyright © 2021 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.

During the challenge, she developed urticaria on the neck and right flank and pruritus 27 minutes following exposure to the initial amoxicillin dose of 50mg. She was treated with diphenhydramine 25mg, and the pruritus resolved within 30 minutes.

Appendix 3, as supplied by the authors. Appendix to: Gateman DP, Rumble JE, Protudjer J LP, et al. Amoxicillin oral provocation challenge in a primary care clinic: a descriptive analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200077. Copyright © 2021 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.

Article details: 2020-0077	
Title	Amoxicillin oral provocation challenge in primary care: an observational cohort study
Authors	Derek Gateman XX XX, Jessie Rumble XX XX, Jennifer Protudjer XX XX, Harold Kim XX XX
Reviewer 1	Alexandros Grammatikos
Institution	Alexandros, Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece
General comments (author response in bold)	This manuscript addresses an important topic; whether patients with reported penicillin allergy can be investigated in a primary care setting, by oral provocation. However, there are several issues that need to be addressed in order for this study to answer this question reliably. **Thank you for your positive comments!** Major issues This study investigates the immediate outcome of penicillin oral provocation testing, but only few of the patients tested (11%) had a previous immediate reaction. In patients with a previous history of a delayed reaction an extended home provocation challenge is advised – which was not performed. **Thank you for your comments. We agree that a prolonged oral challenge at home is reasonable. But previously published data (Mills et al., 2016) suggests that the majority of patients who tolerated the initial oral challenge tolerated a full course of penicillin later. We did not feel a longer oral challenge was indicated and may have led to other side effects such as C. difficile.** All patients were challenged with amoxicillin but no information is provided on the type of penicillin that patients reacted to in the first place. Reactions to penicillin antibiotics are commonly due to side chains, so the index antibiotic needs to be tested in order to safely exclude hypersensitivity. **Thank you for your comments. In Canada, the vast majority of outpatient penicillin prescriptions are for amoxicillin. So most patients had original reactions to amoxicillin. We understand that European studies have used other penicillin products. The side chain issue may be important clinically. As noted the vast majority of patients in Canada has amoxicillin as the penicillin of record. So if the patient tolerates amoxicillin, we presume no other penicillin allergy.** According to figure 1 part of the exclusion criteria for this study was IgE-mediated symptoms. This contradicts the fact that 11% of included patients had an immediate reaction to penicillin. **Thank you. We agree. The paper has been modified.** Only a very low incidence of reactions was seen by oral provocation testing, which was likely due to the stringent exclusion criteria applied. Patients with severe/ moderate reactions and even those with reactions of unknown severity or a complex reaction history were excluded. This is not clear from the text. **Thank you. We have modified the paper to clarify these issues. We excluded high risk patients. This should lead to more wide spread and safe OPCs being performed in private practice.**

	Minor issues Introduction/ Line 36: Skin testing for penicillin does not offer a poor clinical predictive value. **Thank you. We will reference the data supporting this comment from Mills et al. (2016).** Methods /Setting and Participants: Were patients with acute generalised exanthematous pustulosis, or drug reaction with eosinophilia and systemic symptoms also excluded? **Yes they were excluded. This part of the text has been modified.** Methods: According to the study questionnaire, patients reporting difficulty breathing, wheezing, swelling of the lips, tongue, face, vomiting, loss of consciousness, fainting, near fainting, or abdominal pain were excluded from the study. Not all these symptoms translate into anaphylaxis, which needs to be clarified in the text. **Thank you. We have clarified this in our inclusion criteria in our Methods.** Methods /Line 34: Were patients with a suspected reaction to multiple concurrent medications (including penicillin) also excluded? **They were not excluded. The Methods text has been modified.** Results section: the type of reaction that patients had needs to be clarified. Was it a remote history of a reaction, e.g. in childhood? What were the symptoms? What was the time-interval for symptoms onset? Did these factors play any role in the outcomes? **Thank you for this comment. We agree that this information would be interesting to add to our paper, but the majority of patients did not recall the specific dates or ages of the original reactions. Therefore, we would prefer to leave this information out of the paper. Given the low reaction rates, we do not believe we could comment on these as factors associated with the OPC outcome.** Results section/ Reaction 2: this patient developed a sensation of swollen /sore throat and itching of her lips. No objective signs so should have been classified as negative according to the study protocol ("subjective symptoms alone not sufficient to diagnose a reaction"). **We included this patient. We felt this was most conservative approach.** Table 1: 10% of patients had a personal history of an immediate reaction to penicillin- this contradicts the text, where it is mentioned as 11%. **Thank you for this comment and the text has been corrected. See Table 2 now.**
Reviewer 2	Philip Lam
Institution	Infectious Diseases, Sunnybrook Health Sciences Centre, Toronto, Ont.
General comments (author response in bold)	In this manuscript, Dr. Gateman and colleagues describe their experiences with oral amoxicillin provocation challenge in patients with a low-risk amoxicillin allergy history. This report contributes to the literature by demonstrating the feasibility of carrying out oral provocation challenges in the primary care setting. Given the relatively low resource requirements needed for oral provocation challenges, this

	intervention has significant potential to be adapted to other primary care settings. The authors should consider the following suggestions to further improve the quality of their manuscript: **Thank you very much for the kind comments. We agree with the comments as the implementation of this low risk procedure in primary care may lead to improvements in public health and individual's health.** 1) In the Introductory paragraph, the author compares and contrasts T-cell versus Ig-E mediated reactions. T-cell lymphocyte mediated reactions typically occur on the time course of days, whereas IgE-mediated reactions can occur within minutes to hours (Shenoy ES, JAMA 2019). The authors should consider adjusting their descriptions of these reactions. **Thank you. We have corrected the text and incorporated this reference.** 2) At the end of the first paragraph of the Introduction, the authors should also highlight the risk of increased adverse events (MacFadden DR, Clin Infect Dis 2016), drug-resistant organisms, and C. difficile (Macy E, J Allergy Clin Immunol 2014) in addition to decreased efficacy and increased cost with alternative antibiotic therapies. **Thank you. We have modified the text using these two references.** 3) The title of the manuscript "Oral provocation challenge for low risk amoxicillin allergy in primary care" suggests that the patient population were only those with a history of allergy to amoxicillin specifically. However, in the "Settings and Participants" section, the authors state "Patients were recruited after returning a self-reported allergic reaction intake survey, and excluded if found to have received penicillin recently…". The authors should clarify whether reported amoxicillin allergy, penicillin allergy (or both) were included in the study. If both were included, the breakdown of antibiotic type would be useful to include in Table 1. **Most patients had amoxicillin allergy reported. Although not confirmed in large studies, most patients who tolerate amoxicillin will tolerate other penicillins, but both were included. The oral challenge was given with amoxicillin. Table 1 has been retitled Table 2.** 4) If the authors only included patients with amoxicillin allergy, what was the rationale for excluding those with penicillin allergy? If the authors only included patients with amoxicillin allergy only, then the manuscript should be updated to replace any mention of penicillin with amoxicillin. **The majority of patients in Canada receive amoxicillin as "penicillin". We did not exclude patients with penicillin allergy.** 5) In the Setting and Participants section, the authors state that patients were "excluded if found to have received penicillin recently without any reaction or had a prior reaction consistent with anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis". However, in Figure 1 it appears that patients with urticaria, angioedema or bronchospasm were also excluded. The authors should clarify whether these patients were indeed excluded. **Thank you. Patients with urticaria, angioedema were not excluded. Patients with more significant systemic reactions were excluded. The Methods section and Figure 1 have both been modified.**

	6) The authors state that "Patients were recruited after returning a self-reported allergic reaction intake survey". Were these patients identified by primary care physicians within the NPFHT roster, or were outside referrals also accepted? How were patients approached? Were the primary care physicians asked to only refer low-risk patients based on Figure 1 protocol? What was the response rate for the survey? If the study was limited to patients served by the NPFHT, are the authors able to provide an estimate of how large the NPFHT practice is, and how many patients in the NPFHT have a reported penicillin/amoxicillin allergy? This information would help provide perspective for other primary care teams who are thinking of implementing something similar in terms of expected volume of patients. **Thank you. The patients were from our primary care practice or referred by other family physicians. We have added further information to the Methods describing our inclusion criteria, and now attach Appendix 1 to provide more background information about the NPFHT and Allergy Clinic in specific.** 7) Please share with the reader a bit more about the Primary Care Amoxicillin Allergy Clinic. How many days per week did this clinic run? Did the primary care physician complete any additional training with regards to allergy/immunology or oral provocation challenges? Was the clinic staffed by only one physician? Was nursing support also available? Please also provide some information on what medications were available in the event of an allergic reaction (e.g. epinephrine, dimenhydrinate, salbutamol, corticosteroids?) **Thank you for this comment. Again, we have modified the Methods section and added Appendix 1 to provide more background information about the NPFHT and Allergy Clinic in specific.** 8) In the Measurements section, the author states "The primary outcome of interest was the frequency and type of reaction to OPC". The primary outcome is appropriately addressed in the Abstract "A total of 103 patients were studied… Of the 99 patients, 97% completed with OPC with no reaction". However, this important piece of information is not clearly stated in the Results section. This should be one of the most important points to convey to the reader. **Thank you. We have revised the wording of the first two sentences of the Results section as follows:** **Between November 20, 2017 and October 1, 2019, a total of 103 patients were studied, including 97% (n=99) who completed the OPC with no reaction. Of these 99 (n=72 (72.7%) females), the average age was 28.3±21.1 years. In total, 42.3% (41/97) were paediatric patients (mean age 8.0±4.0) years (Table 2).** 9) In the Oral Provocation Challenge Protocol section, the authors state "Patients were informed it was safe to receive future prescription of penicillin if clinically indicated". Were patients also informed that they could take other beta-lactams (amoxicillin, cephalosporins, etc)? Was the medical chart and pharmacy records updated with their allergy test result? De-labeling of a previously reported allergy is an equally important aspect to consider. If this was not done, the authors should acknowledge this as a potential area for improvement. **Thank you for this comment. We have updated the text regarding the Challenge Protocol to clarify our de-labeling actions and patient information.**

	10) In the Abstract, the author states, "A total of 103 patients were studied… Of the 99 patients, 97% completed with OPC with no reaction". What happened to the 4 patients who were not tested? Were these patients excluded based on the Figure 1 protocol, or did they refuse testing? The authors should clarify this point. **Thank you for this question. We have clarified our inclusion criteria in our Methods section. Those 4 patients attended the clinic for assessment, but were not eligible for OPC (did not truly have a penicillin allergy, or had recently been exposed to and tolerated a full course of penicillin). We will include only the patients who were tested as we intend to study that group specifically.** 11) The authors reported an average wait time of about 2 months, which is significantly shorter compared to allergy clinic assessment wait times. Nonetheless, the authors should comment on why there was a 2 month delay from review of intake to date of testing. Was it related to the limited number of appointment slots in each clinic? Was it because the clinic was only staffed by one physician? I think the readers would find it interesting to know what the "bottlenecks" were in triaging and running the Primary Care Amoxicillin Allergy Clinic. **Thank you for this comment. While we did not measure factors that would influence delay to testing, the authors could certainly speculate. We would be very keen to share these sorts of experiences and challenges; however, we believe this cannot be adequately discussed within the word limit of this publication. We have added some clarification regarding the frequency of the clinic to help add context to the wait time (once monthly clinic, 2 month wait represents 1 or 2 missed clinics)** 12) In the Results section (paragraph 2), the authors perform a logistic regression looking at the impact of gender on family history of penicillin allergy. The main focus of this paper is describing the outcome of oral provocation challenges, so these results feel out of place. Knowing that females had a lower odds of a family history of penicillin allergy does not significantly change the interpretation of the study results or how these patients should be approached. Similarly in paragraph 3 of the Results section, the authors comment on the association between demographic characteristics and personal history of immediate penicillin reaction. I am not sure what the utility of this analysis is. I would consider removing both of these paragraphs. The one analysis that I would be interested to know is whether there were any factors that would have predicted a positive OPC reaction, but I suspect the sample size is too small to draw any conclusions. **At the request of Reviewer 2, we have removed the logistic regression analyses, and the corresponding table (Table 2) from the revised version. Regrettably, the sample size was too small to rigorously consider any factors that would have predicted an OPC reaction. We have added a sentence to this effect in the limitation.** 13) In the Results section, the authors report the average wait time for the 3 individuals who had a reaction to the OPC. Why was this specific analysis completed? I am unclear as to how this adds to the interpretation of the study. I would consider removing the statement.

	Thank you for this suggestion. At Reviewer 2's request, we have removed this statement. 14) The authors should consider including a paragraph in the Interpretation section on their overall experiences with the Primary Care Amoxicillin Allergy Clinic. What were the challenges and lessons learned? What was the overall cost and time commitment to this program? Is the program sustainable? **Thank you. As we mention in Comment 11 above, we agree with the reviewer, but due to our paper approaching the maximum word count, we prefer to leave this point out of the paper.** 15) Since the ultimate goal of OPC is to improve the use of beta-lactam antibiotics as 1st line therapy, I think it would be very impactful to demonstrate whether the 96 patients who passed their OPC went on to actually receive beta-lactam antibiotics. Something to consider once more time has elapsed from the study period. **Thank you for this suggestion. We agree that this should be addressed. We will consider another analysis of these patients later to see if they did receive beta lactams. We have added this follow-up idea to our Interpretation and Limitations section.** 16) The authors state that there may be potential application for OPC in pre-operative patients. Cefazolin (the surgical prophylaxis antibiotic of choice in most surgeries) can be safely given in patients with true penicillin allergy due to lack of cross reactivity (it possesses a structurally different R1 side chain) without the need for skin testing or OPC. (Lam PW, Clin Infect Dis 2020). **We agree. This protocol is in use in some centers in Canada.** 17) I would suggest removing "Reaction" and "Reaction grade" from Table 1, since these are not technically demographic features of the study population. This data relates to the primary outcome, and can be explained in the text alone in the Results section (see point #8) **At Reviewer 2's request, we have removed "Reaction" and "Reaction grade" from Table 1, but retained this information in the text alone.** 18) It would be interesting to provide a breakdown of the reported allergic history in Table 1 (i.e. how many had rash, or other benign reactions, like headache, dizziness, etc). **Thank you for this comment. We agree that this information would be interesting to add to our paper, but the majority of patients did not recall the specific dates or ages of the original reactions. Therefore, we would prefer to leave this information out of the paper. More than 50% of patients reported some type of rash. Our data extraction tool did not include these different symptoms. Given the low reaction rates, we do not believe we could comment on these as factors associated with the OPC outcome.** 19) The authors should consider removal of Table 2, as it does not significantly contribute to the interpretation of the study (see point #12). **At the request of Reviewer 2, we have removed the logistic regression analyses, and the corresponding table (Table 2) from the revised version.**

	20) In Figure #1 protocol, there is a clear distinction between the triage pathway for urticaria (Avoid penicillin, offer referral to allergist) and rash (Oral provocation challenge). However, in the Amoxicillin Allergy Survey, there is no section for the patient to report “hives” or “urticaria” – only “Rash”. How was the physician able to discern urticaria from rash based on the allergy survey? Patients will often not know the difference between the two and will report their reaction as a rash. **Thank you for this comment. We have modified the Methods section as well as Figure 1 to clarify this. The difference was not evident by our survey, but clarified during the clinical interview, and recorded in the consultation note when possible to distinguish.**

INTRODUCTION

Penicillin drug allergy presents a challenge to primary care providers and allergists alike. It is the most frequently reported drug allergy, affecting about 10% of patients. (1) Many of these allergies are diagnosed after a childhood rash that is assumed to be caused by recent penicillin administration, and not investigated further. (2) T-lymphocyte mediated non-immediate reactions typically present with maculopapular rashes after the first hour of ingestion. In contrast, Immunoglobulin E (IgE)-mediated immediate reactions occur within the first hour, and appear as urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis. (2) Life-threatening anaphylactic reactions are reported in only 0.02-0.04% of cases. (3) Despite its clinical use for over 70 years, penicillin and penicillin-related antibiotics continue to be recommended for first line therapy in numerous respiratory tract, skin, joint, and cardiovascular infections. (4) (5) Although the majority of reactions are not true drug allergies, medical practitioners will usually prescribe less effective and more expensive alternatives. (6) (7) (8)

Presently, primary care practitioners struggle to rule out penicillin drug allergies. (9) A referral to an allergist for all of these patients is impractical. Yet, there are millions of patients with presumed penicillin allergy. (10) In Canada, there are less than 1 allergists per 100,000 people. Not surprisingly, this translates to long wait times, with an estimated wait time for penicillin drug allergy consultation of 12-18 months based on a conversation with H. L. Kim, MD (December 2019). Primary care providers have limited experience and training in performing skin testing for drug allergy or measurement of specific IgE levels. Skin testing can be inconvenient and time consuming, while still offering a poor clinical predictive value. Oral provocation challenge (OPC) testing presents an alternative, which has demonstrated safety in both pediatric and adult populations without the need for allergy skin testing. (2) (11) Thus, we aimed to demonstrate that patients with low risk amoxicillin allergy can safely and efficiently undergo OPC by their primary care physician.

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METHODS

Study Design

This was an observational cohort study. All patient charts from the Primary Care Amoxicillin Allergy Clinic were reviewed retrospectively. Ethics approval was obtained from the Hamilton Integrated Research Ethics Board affiliated with McMaster University (Project Number 7414-C).

Setting and Participants

We collected cross-sectional data from 103 patients assessed in the Primary Care Amoxicillin Allergy Clinic at the rural North Perth Family Health Team (NPFHT) in Listowel, Ontario, Canada. Consultations and OPC were performed initially in the outpatient hospital department from November 2017 to January 2018, before moving to the family medicine office at the NPFHT from February 2018 to October 2019. Patients were recruited after returning a self-reported allergic reaction intake survey, and excluded if found to have received penicillin recently without any reaction or had a prior reaction consistent with anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Patients were also excluded if their clinical notes or history were significantly inconsistent or incomplete (Figure 1).

Oral Provocation Challenge Protocol

After reviewing the clinical history and obtaining consent, low risk patients were offered a two-step graded oral provocation challenge to amoxicillin. The challenge was performed in a primary care office setting by a family physician equipped to manage anaphylactic reactions. Amoxicillin was supplied as an oral suspension (250mg/5ml) with a total challenge dose of 500mg for patients weighing >10kg, or 45mg/kg for pediatric patients weighing < 10kg. (2) (12) The challenge dose was expected to be equivalent to that of a single therapeutic dose. Patients were first administered 10% of the challenge dose (50mg or 4.5mg/kg if < 10kg) then observed for 20 minutes in the waiting room. If there was no reaction, they were then given 90% of the therapeutic dose (450mg or 40.5mg/kg if <10kg) and observed in the waiting room for 1 hour. The reaction was considered positive on the development of objective symptoms; subjective symptoms alone were not considered sufficient to diagnose an immune reaction. Follow-up instructions were provided and patients were instructed to report any delayed symptoms of rash, hives, wheezing, or swelling in the same day/week or during any subsequent treatments. Patients were informed it was safe to receive future prescription of penicillin if clinically indicated.

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Measurements

The primary outcome of interest was the frequency and type of reaction to OPC. The reactions to the OPC were classified using the World Allergy Organization's reaction grading system. (13) A secondary outcome was the wait time to complete OPC. This interval was calculated as the time from the review of the intake survey to the date of testing. Exposure variables included gender (binary; male, female), age (continuous; years) and wait times (continuous; from day of recruitment to testing). Additional consideration was given to pediatric compared to adult patients, for which we stratified age into <18 years and 18+ years. Wait times were stratified into two groups: <45 days versus 45+ days. These variables were measured from the patient's electronic medical record and intake survey, while history of immediate allergy was determined from their pre-testing interview. Records for all patients referred for testing in the allergy clinic were assessed, so as to limit selection bias. The patient's original intake survey and consultation notes were both reviewed.

Statistical Methods

Descriptive statistics included sample size, percentage, mean ± standard deviation (SD) and t-tests. Analytic statistics included logistic regression analyses, reported as odds ratio (OR) and 95th percent confidence intervals (95%CI), with $p<0.05$. Regression models were adjusted for age, gender and wait times, unless the individual variable was used as the exposure. We also considered an interaction between gender and age group. As we had few missing data points (no more than 2 missing points for most variables), these data were removed from the analyses.

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RESULTS

Between November 20, 2017 and October 1, 2019, 99 (n=72 (72.7%) females) participants who were referred with a completed intake survey were seen for amoxicillin OPC (Table 1). The average age was 28.3±21.1 years. In total, 42.3% (41/97) were pediatric patients (mean age 8.0±4.0) years. Adult patients were, on average, 42.9±15.5 years old. Whereas the pediatric population was comparable in terms of gender distribution (19 males, 23 females), the adult population was disproportionately female (53/61; p<0.001). The average wait time was about 2 months (59.0±69.8 days). Wait times were significantly longer for pediatric patients compared to adult patients (77.3±90.2 vs. 45.3±45.6 days, respectively; p<0.02). Most patients had neither a family history of penicillin allergy (82.5%; 80/97), nor a personal history of immediate reaction to penicillin (90.0%; 81/90). Reactions were rare (3.0%; 3/99). Amongst those who did react, all had a WAO reaction grade of 1. The average wait time for these 3 individuals was similar to that for all patients (62.0±85.2 days).

Amongst those tested, females had a significantly lower odds of having a family history of penicillin allergy (OR 0.22; 95%CI 0.06; 0.83; p=0.03; Table 2). No significant associations were identified for paediatric compared to adult patients and family history of penicillin allergy. Similarly, no associations found between family history and an interaction between gender and age. Few patients with a family history of penicillin allergy had a reaction within 7 days after starting penicillin. Consideration to wait times in association with family history of penicillin allergy did not yield any statistically significant findings.

Associations between demographic characteristics and a personal history of immediate penicillin reaction could not be determined because only 1 female with a personal history of immediate reaction to penicillin was included, and only 1 person <18 years with a personal history of immediate reaction to penicillin was included.

Reactions to OPC were rare in the study population. All three cases are presented below including demographic characteristics and a narrative description of the reaction to amoxicillin:

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Reaction #1

JG was a 3 year-old male who presented with history of maculopapular rash that onset 3 days after starting amoxicillin for acute otitis media at age 16 months. He had neither a personal history of immediate reaction nor parental history of amoxicillin allergy. There were no other documented allergies.

During the challenge, he developed urticaria on the face and the trunk 20 minutes following exposure to the initial amoxicillin dose of 50mg. He was treated with diphenhydramine 18mg, and the urticaria resolved within 20 minutes.

Reaction #2

KG was an 8 year-old female who presented with a history of maculopapular rash that worsened 2 days after starting amoxicillin for acute otitis media and pharyngitis at age 14 months. Clinicians suspected roseola vs. drug allergy. She had no personal history of immediate reaction. She also had an allergy to clarithromycin. Both of her parents had documented history of amoxicillin allergy.

During the challenge, she developed a sensation of swollen and sore throat 45 minutes following exposure to the second amoxicillin dose of 450mg, and then sensation of itching of the lips at 75 minutes. She was treated with diphenhydramine 12.5mg, and symptoms improved within 25 minutes.

Reaction #3

SS was a 9 year-old female who presented with history of maculopapular rash and sore throat that onset after the third dose of amoxicillin for pharyngitis at age 6 years. She had neither a personal history of immediate reaction nor parental history of amoxicillin allergy. There were no other documented allergies.

During the challenge, she developed urticaria on the neck and right flank and pruritus 27 minutes following exposure to the initial amoxicillin dose of 50mg. She was treated with diphenhydramine 25mg, and the pruritus resolved within 30 minutes.

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INTERPRETATION

Our study is the first to assess the use of graded OPC in the office setting by primary care practitioners. The results demonstrate that reactions to OPC are both infrequent and minor in patients with a history of mild reactions. Each of the three reactions were Grade 1, meaning limited to just one sign or symptom present from cutaneous, upper respiratory, conjunctival, or other. Diphenhydramine was used to treat symptoms; epinephrine was not administered in any cases. As well, there were no reported delayed reactions to the OPC in our study. Further, in office testing was quite timely with a mean wait time of 58.5 days. Given the high prevalence of low risk penicillin allergy in Canada and long wait times for access to specialist testing, primary care providers may benefit from having a safe and accessible testing option.

This study adds to the growing body of evidence evaluating the safety of direct oral provocation challenge for low risk amoxicillin allergy. Immediate mild allergic reactions occurred in 3% of cases in our study, which is comparable to similar studies in the literature. (2) (14) Mills et al. (2016) however, studied a younger population, age interquartile range 1.0-3.9 years, and found a higher reaction rate of 5.9%. (2) Labrosse et al. (2018) found a similarly low immediate allergic reaction rate of 2.3% during 5-day oral provocation challenge in a pediatric population with mean age of 5.1 years. (14) Though methodologically different having been tested in an allergist clinic and with preceding intracutaneous testing, Hjortlund et al describe a reaction rate of 4.5% (15/335) to OPC with penicillin V. (15) Sundquist et al. also performed skin testing in an allergist clinic before OPC, and none of the 36 adult participants had an immediate reaction. (9) Iammatteo et al (2019) conducted a single blind placebo-controlled direct amoxicillin challenge with 155 adults (mean age of 51 years) and found a reaction rate of 2.6%. (11) A smaller study with 20 adult outpatients had a 0% reaction rate to oral provocation challenge; none developed immediate or delayed hypersensitivity reactions. (16) Whereas the reaction rate in our study is consistent with current literature, we present the first study of OPC conducted without skin testing, and in the primary care office setting.

In rural Southwestern Ontario, a patient referred for penicillin drug allergy to an allergist commonly would wait 12 months for assessment and testing based on a conversation with H. L. Kim, MD (December 2019). Our study population waited on average 58.5 days to be assessed, and 18.3% of patients were seen within 45 days. There was a significantly longer wait in the pediatric population compared to adults (77.3±14.1 vs. 45.3±5.9 days, respectively; $p<0.02$). The source of

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this difference is unclear, but may relate to the younger patient's school attendance or need for caregiver accompaniment. A study of physician barriers to patient recruitment noted that patients' not wanting to take time to be tested was ranked most important. (9)

In the future, we propose this study should be replicated with multiple centres and primary care providers. A larger sample size would allow for the study of the effects of demographic characteristics, which may drive further study of specific mechanisms in reaction to OPC. For example, we find here that both the reaction rate and wait time to testing was higher in the pediatric compared to adult group. The specific group of pre-operative patients present another potential area of study. While rapid access de-labelling can be integrated into the surgical pathway, OPC by primary care providers may provide a cheaper or more convenient option. (17) As the prevalence of inappropriate penicillin allergy label decreases, the prescribing of penicillin alternatives may decrease. We suggest that changing trends in antibiotic prescription may affect bacterial resistance patterns that could be studied. Subsequently, there may be both reductions in cost to the healthcare system, and improvements in patient outcomes. (8) (18)

Limitations

This single-centre study was conducted by a single primary care physician. The sample was dependent on the referral from local primary care providers, so it is unknown if certain patients with greater or lesser risk of low risk reactions were recruited, and therefore selection bias could exist. Additionally, the survey responses (e.g. reaction symptoms, family history) were patient-reported, which may result in recall bias. Though patients were instructed to follow up with the clinic, it is possible that delayed reactions were missed. The low reaction rate limited the authors from investigating the association with underlying demographic characteristics. Further, only 11% of patients reported a personal history of immediate penicillin reaction, so associations with gender, age, and wait times could not be calculated.

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Conclusion

To our knowledge, this was the first study to evaluate OPC for amoxicillin allergy without initial skin testing in a primary care setting. OPCs were found to be a safe and accessible option for primary care providers to address erroneous penicillin allergy labels within the primary care office setting. We believe that widespread implementation of penicillin OPC by primary care providers would have major public health implications. The impact may be greater in sparsely-populated rural Canada.

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DISCLOSURES

No funding or conflicts of interest.

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TABLES AND FIGURES

Table 1. Demographic characteristics of the study population (N=99)

Characteristic		N	%
Gender			
	Male	27	27.3
	Female	72	72.7
Age (years; N=98)			Mean ± SD
	Mean	98	28.3 ± 21.1
	<18 years	41	8.0 ± 4.1
	18+ years	57	42.9 ± 15.5
Average wait time (days; N=97)			
	Mean	97	59.0 ± 69.8
	<45 days	53	18.0 ± 13.8
	45+ days	44	108.4 ± 78.0
Family history of penicillin allergy (N=97)			
	No	80	82.5
	Yes	17	17.5
Personal history of immediate reaction to penicillin (N=90)			
	No	81	90.0
	Yes	9	10.0
Reaction			
	No	96	97.0
	Yes	3	3.0
Reaction grade (N=3)			
	1	3	100.0

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Table 2. Associations between demographic characteristics and a family history of penicillin allergy, amongst those tested

Characteristic	N	Unadjusted		Model 1*		Model 2†	
		OR	95%CI	OR	95%CI	OR	95%CI
Gender							
Male	27	1.00		1.00		1.00	
Female	70	0.35	0.12; 1.04	**0.25**	**0.07; 0.91‡**	**0.22**	**0.06; 0.83‡**
Age (years)							
<18	41	1.00		1.00		1.00	
18+	56	1.06	0.36; 3.06	1.69	0.51; 5.66	1.32	0.38; 4.61
Wait times (days)							
<45	51	1.00		1.00		1.00	
45+	46	1.31	0.45; 3.73	1.40	0.47; 4.22	-	-

*Adjusted for age and gender (unless the exposure variable)
†Adjusted for age, gender and wait time (unless the exposure variable)
‡p<0.05

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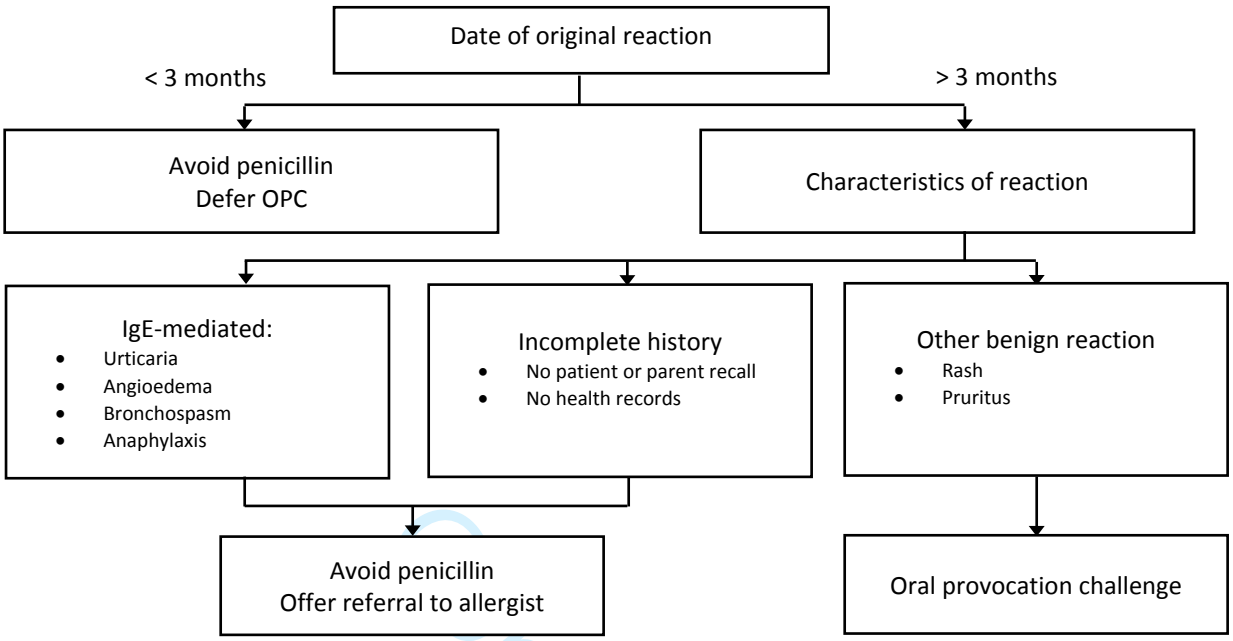
Figure 1. Protocol for evaluation of Amoxicillin Allergy Survey



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Amoxicillin Allergy Survey

Name:
Date of Birth: PATIENT STICKER Date of Allergic Reaction: _____
Health Card Number:
Family Physician:

Background:
Amoxicillin is a penicillin-based antibiotic used to treat many common infections. Adverse reactions to penicillins are reported in as many as 5 to 10% of patients. Often a reaction will lead patients and physicians to avoid prescribing amoxicillin, but many of these are not true allergic reactions. Patients who have experienced serious, or anaphylactic, reactions should not use amoxicillin. There is growing research to show that amoxicillin can be used safely when there has previously been a mild, moderate, or delayed reaction. The following survey will help your physician to understand your reaction, and determine the future risks associated with amoxicillin.

Symptoms:
Please indicate if any of the following symptoms were part of your allergic reaction:

- ❑ Loss of consciousness, fainting, or near fainting
- ❑ Difficulty breathing, wheezing
- ❑ Swelling of the lips, tongue, or face
- ❑ Vomiting
- ❑ Abdominal pain
- ❑ Anaphylaxis

If you selected one of the above answers, please STOP HERE. If you did not, then continue below:

What kind of symptoms did you have:

- ❑ Rash
- ❑ Itching
- ❑ Blistering
- ❑ Other _____

When did the symptoms start:

- ❑ Within minutes or hours
- ❑ Within 24hrs
- ❑ After 24hrs

How long did the symptoms last:

- ❑ Hours
- ❑ Days
- ❑ Weeks

Other reactions or allergies:
Have you had an allergic reaction to another medication(s)?

Has one of your parents had an allergic reaction to amoxicillin?

Assurance of Accuracy:
By signing below, you certify that the information provided in this survey is accurate and complete to best of knowledge. Withholding or providing misinformation will affect your physician's ability to treat you safely, and could lead to very dangerous medical complications.

Patient/Parent Name:

Patient/Parent Signature:

Office Use Only: □ *Immediate* □ *Ig-E* □ *Severe* □ *Challenge*

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	0
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	0
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	N/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5 5 n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.