

- [10] Richardson KL, Driedger MS, Pizzi NJ, Wu J, Moghadas SM. Indigenous populations health protection: a Canadian perspective. *BMC Public Health*. 2012; 12:1098.
- [11] National Center for Health Statistics. *Health, United States, 2012: With Special Feature on Emergency Care*. Hyattsville, MD: National Center for Health Statistics; 2013.
- [12] Lasser KE, Himmelstein DU, Woolhandler S. Access to care, health status, and health disparities in the United States and Canada: results of a cross-national population-based survey. *Am J Public Health*. 2006;96:1300–1307.
- [13] Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. *CMAJ*. 2012;184: 297–302.

Risk of allergic reaction and sensitization to antibiotics in foods



The use of antibiotics in the agro-food industry is globally widespread not only as growth promoters in livestock, poultry, and aquaculture but also as pesticides in fruits, with a clear effect on the human microbiome. Although a common concern is the emergence of antibiotic multiresistant bacterial strains,¹ allergic reaction to antibiotic residues in foods is an underrecognized risk that has been described, with reports of anaphylaxis to antibiotics contained in milk and meats.² We investigated a 10-year-old girl who presented with anaphylaxis after the ingestion of a blueberry pie, likely caused by the ingestion of antibiotic-contaminated fruit. The patient had a medical history of asthma and allergic rhinitis. She had known anaphylaxis to penicillin and IgE-mediated cow's milk allergy.

The patient presented with facial flushing, generalized urticaria, and stridor 10 minutes after the consumption of a slice of blueberry pie. No milk had been ingested in the hours before the reaction. She was taken to the emergency department of a community hospital and was treated with epinephrine, methylprednisolone, and diphenhydramine. She was kept overnight for observation with subsequent improvement of symptoms.

She was referred to our allergy department because of an anaphylactic reaction of unknown origin. Skin tests for tart ingredients were performed 5 weeks after the initial reaction: fresh blueberries and peels, eggs, soya, peanuts, nuts, and cereal. All the test results were negative. Skin tests to milk elicited 13-mm-diameter wheals.

In the context of an important allergic reaction with no clear trigger and positive skin test results to milk, the blueberry tart in question was sent for analysis to the Quebec Ministry of Agriculture, Fisheries, and Food for detection of milk. Bacterial growth inhibition testing was also performed on the pie samples for detection of antibiotics. Pie sample analyses using enzyme-linked immunosorbent assay and the modified Monier-Williams method revealed milk below the detection limit. However, the samples were found to contain a non- β -lactam antibiotic after bacterial growth inhibition testing. The laboratory was not able to confirm the identity of the antibiotic because of an insufficient amount of the original sample.

Because streptomycin is commonly used in orchards to treat bacterial infections of fruit, we decided to perform skin testing with dilutions of streptomycin. The results of skin prick tests to streptomycin (400 mg/mL) were negative. We then performed intradermal skin tests with a dilution of 1:100 (4 mg/mL). This dilution was reported as a nonirritating concentration for aminoglycoside antibiotics.² This test elicited an 8-mm-diameter wheal with a 20-mm-diameter flare. We repeated the test with a 1:10,000 dilution (0.04 mg/mL) to ensure that we did not have an irritative effect. The skin test elicited a 7-mm-diameter wheal with a 16-mm-diameter flare. Normal saline control test results were negative. Five controls had negative intradermal streptomycin test results with 1:100 dilutions. Within minutes after the intradermal testing to streptomycin, the patient developed neck urticaria, was kept under observation for 4 hours, and given 10 mg of cetirizine with resolution of symptoms. She was discharged but was admitted

3 hours later for a late-phase reaction with inspiratory stridor and generalized urticaria. She had never been treated with streptomycin in the past.

Although we did not have enough of the original blueberry pie sample to perform streptomycin detection assays, the positive intradermal skin test results, the systemic reaction after the cutaneous tests to streptomycin, and the presence of a non- β -lactam antibiotic in the analyzed sample suggested that a streptomycin-contaminated blueberry was responsible for the anaphylactic reaction. Systemic reactions to food contaminants, although rare, have been reported. One case report linked the consumption of streptomycin-contaminated beef to 4 episodes of severe anaphylaxis in a 14-year-old child.³ Others reported anaphylaxis after the consumption of milk and meats that contained penicillin residues.⁴ The link between antimicrobial residues in foods and anaphylaxis is often difficult to establish because of numerous confounding factors and limited access of clinicians to analytical methods that enable the correct identification of antibiotic residues.

The important systemic reaction of the patient after skin testing supported a severe allergy to streptomycin. Romano et al⁵ similarly reported a systemic reaction after skin prick testing with streptomycin in a patient sensitized to streptomycin via cutaneous absorption while administering antibiotics to cows. Because our patient had never been treated with streptomycin in the past, we speculate that she could have been sensitized to this drug via consumption of residues in food products. Although the Food and Drug Administration (FDA) has established maximum residue limits (MRLs) in foods, antibiotic residues in foods may still be present (Table 1).^{6,7} As an example, the daily consumption of streptomycin via food and water sources for a 60-kg adult was estimated to be 120 μ g,⁸ approximately 40 times higher than the 3- μ g threshold for oral antibiotic reaction in presensitized individuals.⁹ A previous study¹⁰ found that the consumption of inadvertent antibiotics via meat and dairy products was correlated with urinary excretion of antibiotics. Finally, food exportation from countries with less stringent policies regulating the veterinary use of antibiotics may have higher antibiotic residues than the MRLs tolerated by the FDA.

Although streptomycin sprays are commonly used in plant agriculture, this is the first report, to our knowledge, that links an allergic reaction to fruits treated with antibiotic pesticides. Streptomycin sprays are reportedly used in orchards and nurseries to treat fire blight of apples and pears, a bacterial disease caused by *Erwinia amylovora*, which causes devastation in fruit harvests.¹¹ Streptomycin is also used in nurseries in combination with copper oxychloride to control infections by another frequently encountered bacterium, *Pseudomonas syringae*. Alarmingly, a European study¹² found that significant residues of streptomycin were detected in apples 3 months after the application of streptomycin pesticide.

Antibiotic allergies are self-reported in up to 15.3% of the general population,¹³ but on workup most are not confirmed to be IgE mediated. Rarely allergic reactions to foods could be potentially linked to antibiotic contamination. Further research will be necessary to quantitate the risk of allergic sensitization from or

Table 1Selected MRLs in food products based on data from the WHO⁶ and the FDA⁷

Food product	MRL, µg/kg					
	Streptomycin		Oxytetracycline		Neomycin	
	WHO	FDA	WHO	FDA	WHO	FDA
Cattle*	600	500	200	2,000	500	1,200
Poultry*	600	500	200	2,000	500	1,200
Pig*	600	500	200	2,000	500	1,200
Milk	200	NA	100	300	1,500	150
Fish	NA	NA	200	2,000	NA	NA
Fruits and vegetables	NA	250	NA	350	NA	NA

Abbreviations: FDA, Food and Drug Administration; MRL, maximum residue limit; NA, not available; WHO, World Health Organization.

*MRL in muscle tissues: tolerance for residues in liver and kidney tissues up to 20 times higher.

reactions to intermittent low-concentration antibiotic exposures in foods. Certain countries, including Europe, have banned the use of antibiotics for growth promotion since 2006. However, regulations in the United States and Canada are less stringent and still allow antibiotic use in agriculture for nontherapeutic purposes, although new regulations from the FDA may be finally helping to reduce this. Stricter policies to reduce antibiotic contaminants in foods will help reduce antibiotic resistance and may also help reduce this type of rare event.

François Graham, MD, MSc*
 Louis Paradis, MD, FRCP, FAAAAI†
 Philippe Bégin, MD, MSc, FRCP*
 Jean Paradis, MD, FRCP*
 Yves Babin, PhD‡
 Anne Des Roches, MD, FRCP, FAAAAI†
 *CHUM, Hôpital Notre-Dame
 †CHU Sainte-Justine
 Montreal, Quebec, Canada

‡Ministère de l'Agriculture des Pêcheries et de l'Alimentation
 du Québec, Quebec, Quebec, Canada
 a.des.roches@umontreal.ca

References

- [1] Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. *Clin Microbiol Rev*. 2011;24:718–733.
- [2] Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol*. 2003;112:629–630.
- [3] Tinkelman DG, Bock A. Anaphylaxis presumed to be caused by beef containing streptomycin. *Ann Allergy*. 1984;53:243–244.
- [4] Dayan AD. Allergy to antimicrobial residues in food: assessment of the risk to man. *Vet Microbiol*. 1993;35:213–226.
- [5] Romano A, Viola M, Di Fonso M, Perrone MR, Gaeta F, Andriolo M. Anaphylaxis to streptomycin. *Allergy*. 2002;57:1080–1092.
- [6] Maximum Residue Limits for Veterinary Drugs in Foods. Codex Alimentarius Commission. 35th Session, Food and Agriculture Organization (FAO) Headquarters, Rome, Italy, July 2–7, 2012. http://ftp.fao.org/codex/weblinks/MRL2_e_2012.pdf. Accessed June 13, 2013.
- [7] US Environmental Protection Agency. Electronic code of federal regulations (eCFR). Title 21: Food and Drugs. PART 556—Tolerances for residues of new animal drugs in food. Subpart B—Specific Tolerances for Residues of New Animal Drugs. <http://www.ecfr.gov/>. Accessed April 7, 2014.
- [8] US Environmental Protection Agency. Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Streptomycin. July 2006:738–R-06–012.
- [9] Dewdney JM, Maes L, Raynaud JP, et al. Risk assessment of antibiotic residues of beta-lactams and macrolides in food products with regard to their immuno-allergic potential. *Food Chem Toxicol*. 1991;29:477–483.
- [10] Ji K, Kho Y, Park C, et al. Influence of water and food consumption on inadvertent antibiotics intake among general population. *Environ Res*. 2010;110:641–649.
- [11] McManus PS, Stockwell VO, Sundin GV, Jones AL. Antibiotic use in plant agriculture. *Annu Rev Phytopathol*. 2002;40:443–465.
- [12] Mayerhofer G, Schwaiger-Nemirova I, Kuhn T, Girsch L, Allerberger F. Detecting streptomycin in apples from orchards treated for fire blight. *J Antimicrob Chemother*. 2010;63:1076–1077.
- [13] Macy E, Poon KWT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009;122:778e1–778e7.

Evaluation of a skin testing protocol for diagnosing perioperative anaphylaxis due to isosulfan blue allergy



Perioperative anaphylaxis presents a diagnostic challenge for allergists because surgical patients often have been exposed to several agents during a short period. One particularly complex scenario is anaphylaxis during procedures involving sentinel lymph node biopsies. Isosulfan blue is a triphenylmethane dye routinely used in sentinel lymph node biopsy procedures during breast cancer and melanoma surgeries.¹ Anaphylaxis to isosulfan blue is estimated to complicate 1% to 3% of sentinel lymph node biopsy procedures, making it an uncommon but clinically significant adverse event.² The mechanism for isosulfan blue allergy is believed to be a type I hypersensitivity reaction mediated by IgE.^{1,3} Given the low molecular weight of isosulfan blue, this likely involves its acting as a hapten. Sensitization is thought to occur from exposure to isosulfan blue and its cross-reactants in textiles, cosmetics, detergents, ink, paper, paint, leather, and medications.^{2,4,5} Previous studies have reported diagnoses of isosulfan blue allergy based on skin testing results,^{3,6–9} but no standardized skin testing protocol exists. As such, we report on a validated skin testing protocol for diagnosing isosulfan blue allergy based on our

experience with 3 patients allergic to this dye and 5 control subjects tested at our institution and a review of the literature.

Three patients who developed perioperative anaphylaxis during sentinel lymph node biopsy with positive isosulfan blue exposure were identified in our clinical practice. All 3 patients were women 45 to 64 years old who underwent sentinel lymph node biopsy for breast cancer at our institution from October 2012 through August 2013. The diagnosis of perioperative anaphylaxis was established based on the development of symptoms of anaphylaxis, including hypotension, angioedema, laryngeal edema, urticaria, and wheezing 10 to 30 minutes after peritumoral injection of isosulfan blue. Tryptase levels were drawn from 2 of the patients and were elevated from baseline. One patient was managed with diphenhydramine, permitting the completion of the procedure, whereas the other 2 patients required treatment with epinephrine, prolonged intubation, and procedure delay.

Allergy testing in the outpatient setting was performed 3 to 4 weeks after anaphylaxis and was conducted in a stepwise fashion consisting of the following tests (Table 1): skin prick test (SPT) with a 1:10 dilution of isosulfan blue and with full strength isosulfan blue and intradermal test (IDT) with a 1:1,000 dilution of isosulfan blue, a 1:100 dilution of isosulfan blue, and a 1:10 dilution of isosulfan blue. If a positive result to isosulfan blue was obtained, no

Disclosure: Dr Baker owns stock in Pfizer, which does not manufacture isosulfan blue. Dr Lawrence has consulted for Regado Biosciences.

Funding: National Institutes of Health grants RO1 AI1057438 and UO1 AI100799.