

Table 1
Samples and distribution

Medication type	Average wholesale price, \$			
	1998	2005	2009	2012
Antibiotics	26,000	40,000	11,000	1,400
Nasal antihistamines	52,000	50,000	33,000	10,000
Nasal steroids	85,000	78,000	35,000	39,000
Inhaled corticosteroids with or without LABA (Advair)	70,000	164,000	171,000	122,000
Miscellaneous	125,000	88,000	76,000	
	29,000	68,000	90,000	45,000
Total	262,000	400,000	335,000	217,000
Practice type				
No. of physicians	1	2	1	1
No. of nurse practitioners	2	1	1	1
No. of offices	2	3	2	2

Abbreviation: LABA, Long-acting beta₂-adrenergic agonist.

January through June of 2012 was catalogued and its value determined (average wholesale price).

This calendar year, we extrapolate that the pharmaceutical industry will contribute \$217,000 worth of samples to our practice (Table 1). This represents roughly a 50% decrease in the amount of samples given to us in 2005. As recently as 2007, in better economic times, in excess of \$8 billion of sample medication may have been distributed nationally.³

A decrease in the dollar amount of sample medication available to patients and clinicians reflects multiple factors, including a reduction in the pharmaceutical sales force and a diminution in sample size (decreased number of days of medication supplied per sample). Paradoxically, the total number of samples may increase over time for some drugs. As busy asthma specialists, an inordinate supply of 1 drug, Advair, has continued to be given to our practice. At the beginning of 2009, an Advair sample went from providing 2 weeks of medication to 1 week of medication. Therefore, the \$76,000 of Advair this year is representative of actually a greater number of Advair samples given to our practice than in 2005 (\$125,000) but 14% less than 2009 (\$88,000).

As branded drugs come off patent, samples of those drugs cease. Thus, antibiotic samples have almost disappeared. Drugs accounting for \$250 billion in sales are losing their patents by 2015, including Advair in 2012, further threatening the flow of samples.⁴ However, in a given class, other new drugs often replenish the stream of sample medication. As an example, we are on pace this year to receive 4,500 pills of a certain proton pump inhibitor.

Some clinicians or practices are reliant on sample medications (and vouchers) to provide short-term medication need, enable their patients to try new medication, and help bridge patients when applicable to fulfillment of a 3-month medication supply. Others use sample medication, in part, to assist poor and financially challenged patients. Naysayers cite the potential evils of sampling, specifically the potential to influence the prescribing patterns of clinicians.^{5,6} However, samples remain important to many, including the marketing strategy of pharmaceutical companies. With health care costs rising, the importance of samples and their trend is impactful and noteworthy.

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Acquired angioedema with raised serum tryptase

In a patient presenting with acute angioedema, a raised serum mast-cell tryptase level may at first suggest an allergic cause. Persistent tryptase elevation may indicate a mast cell disorder. In this case, the raised tryptase turned out to be incidental to the final diagnosis, which was acquired C1 inhibitor deficiency caused by a B-cell lymphoma. We believe this is the first report of elevated tryptase in association with B-cell lymphoid malignancy and acquired angioedema.

A 54-year-old woman presented to the emergency department (ED) with sudden onset of sore throat and dysphonia. There was no history of dyspnea or dysphagia, she had no stridor, and the oropharynx appeared normal. She was evaluated by the otolaryngology team; at flexible nasendoscopy the epiglottis, arytenoids, and aryepiglottic folds were edematous. The initial diagnosis was infective supraglottitis, and she was treated with intravenous ceftriaxone and dexamethasone, followed by oral amoxicillin/clavulanate and prednisolone. She recovered and was discharged the following day. Two months later, a similar presentation was managed in the same way.

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Six weeks later she presented with facial swelling. This commenced on the right side of the lip but over the course of a day the whole face, including the eyelids, became swollen. The swelling had the characteristics of angioedema; the tongue was not swollen, and there was no urticaria. There was no airway compromise, and results of flexible laryngoscopy were normal. At this time she was evaluated by the immunology team. There were no allergic triggers such as stings or new medications, in particular no antibiotics or nonsteroidal anti-inflammatory drugs, and she did not take angiotensin converting enzyme inhibitors. She was treated with adrenaline, hydrocortisone, and promethazine, with gradual recovery. Moderate splenomegaly without lymphadenopathy was found on examination.

The serum tryptase had been ordered by the ED physician at the time of her first presentation with laryngeal edema and was elevated at 23 µg/L (reference, <12 µg/L), but this result had not been followed up; during the episode of facial edema, the tryptase was 24 µg/L. However, subsequent tryptase levels at times when no angioedema was present varied between 17 and 23 µg/L. Additional testing indicated reduced C4 < 0.02 g/L (reference, >0.16), functional C1 inhibitor 30% (reference, >85%), and C1 inhibitor

immunoassay < 0.05 g/L (reference, >0.15 g/L). Normal studies included C3, extensive autoimmune serology, serum electrophoresis, and basic hematology and biochemistry. The C1q level was reduced at 22 mg/L (reference, >118 mg/L), and a diagnosis of acquired C1 inhibitor deficiency was made. Peripheral blood immunophenotyping showed B-cell monoclonality. Bone marrow biopsy confirmed the diagnosis of non-Hodgkin's lymphoma; on the basis of splenomegaly and CD5/CD10 negative B-cells, the final diagnosis was probable marginal zone lymphoma. There was no excess of CD117+ mast cells in the marrow, and the c-kit D816V mutation was not detected.

The patient subsequently experienced episodes of vulval edema and edema of the hands and feet. Two subsequent episodes of facial and incipient airway angioedema were treated with subcutaneous icatibant 30 mg, with rapid resolution. Treatment was commenced with cyclophosphamide, vincristine, and prednisolone with rituximab; after 3 cycles the C1 inhibitor and C4 had nearly normalized (C4 0.11 g/L, functional C1 inhibitor 68%, C1 inhibitor immunoassay 0.31 g/L). The patient has had no further episodes of angioedema, and a recent serum tryptase level was normal at 12 µg/L.

Acquired angioedema (AAE) due to C1 inhibitor (C1-INH) deficiency is rare, and most cases are linked to underlying B-cell lymphoproliferative diseases.¹ AAE is characterized by activation of the classical complement pathway, presumably on the surface of the abnormal B-cells, with depletion of C1q and C4 associated with consumption of C1-INH. Reduction of C1-INH leads to increased activity of plasma factor XII and kallikrein, leading to increased formation of bradykinin and angioedema.

Tryptase-positive mast cells are present in B-cell non-Hodgkin's lymphomas and correlate with tumor grade and angiogenesis² and tumor fibrosis,³ but elevation of serum tryptase has not to our knowledge been reported in lymphoma. Mastocytosis with elevated serum tryptase may be associated with myeloid (not lymphoid) hematological malignancies,⁴ and tryptase is elevated in a significant proportion of patients with myelodysplastic

syndromes.⁵ This is the first report of elevated serum tryptase in B-cell non-Hodgkin's lymphoma, with apparent correlation with tumor activity. There was no evidence of coexisting mastocytosis or monoclonal mast cell disorder. Elevation of serum tryptase in the context of an acute allergic-type reaction suggests anaphylaxis, but the test should be repeated to confirm normalization⁶; persistent elevation suggests mastocytosis or mast cell activation syndrome. However, if the presentation is recurrent isolated angioedema, it is appropriate to measure serum C4 and, if low, C1-INH activity. This case shows that elevated serum tryptase may coexist with AAE caused by lymphoma.

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Anaphylaxis to quinoa

Quinoa, *Chenopodium quinoa* Willd., is a plant that originated in the Andean region of Bolivia and Peru.¹ It is often eaten in the United States as a supplement for other grains. However, quinoa is actually a fruit and has been called a pseudo-cereal.¹ The most common use of quinoa is the consumption of its seeds. The protein content in quinoa ranges from 13.8% to 16.5%.¹

We present a case of quinoa allergy diagnosed in our clinic. A 29-year-old woman presented for evaluation of food allergy after developing lip angioedema, pruritis of her palms and soles, “choking” sensation, and urticaria on her arms and chest, within 5 minutes of eating a quinoa salad. The salad included quinoa, red and green pepper, pineapple, orange, sweet and sour sauce, thai chili sauce, and plum sauce. The patient's medical history included lip angioedema after ingesting poultry on 2 separate occasions, once in 2009 and again in 2010, intermittent asthma, and allergic rhinitis elicited by dogs and cats. During the initial visit the patient underwent skin prick testing (SPT) to common St. Louis inhalant allergens, corn, ginger, orange, green pepper, black pepper, pineapple, soybean, and wheat. The SPT was positive to pineapple with a wheal diameter of 6 mm, to soy with a wheal diameter of 5 mm, and to cat and dog with a wheal diameter of 8 mm.

Given these results, our patient was advised to strictly avoid pineapple, soy, and poultry. Approximately 1 month after the visit, the patient called to inform us that she developed a feeling of “throat fullness,” lip angioedema, and nausea within several minutes of eating plain quinoa. Symptoms resolved with an oral antihistamine. The patient was instructed to avoid quinoa and return to clinic for SPT.

We prepared the quinoa extract used for skin prick testing in our laboratory. We first ground the quinoa seeds with a mortar and pestle to increase the surface area of the quinoa grain and break up the cell membrane. We then mixed 1 g quinoa with acetone to defat the product. This step was repeated twice. Once the acetone was decanted, we allowed the quinoa to dry for 24 hours. We then started the extraction process to remove the active allergenic components from the quinoa and suspend them in a solvent. The quinoa was soaked in Coca's Solution, prepared in our laboratory, for 48 hours at 4°C on a shaker at low speed.² We filtered the solution, using a Whatman 0.2 µm PSU Media filter, and then diluted the solution with glycerin to a final concentration of 1:20.

The patient returned for skin prick testing and was found to be skin test positive to quinoa with a wheal diameter of 7 mm and to chicken with a wheal diameter of 5 mm. We also tested the quinoa extract on 3 control subjects. All 3 subjects had a negative response to quinoa and a positive histamine control. To the best of our