Oral Immunotherapy Using an Automated Volumetric-Based Dosing Protocol for Food Flours

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Abstract: Oral immunotherapy is an emerging treatment option for anaphylactic food allergies. It can be difficult to accurately measure the low starting doses required for the safety of the patient and success of the treatment. We attempt to automate the creation of oral immunotherapy dosing schedules using an MS Excel worksheet of protein densities and corresponding measurable teaspoon fractions. Due to varying flour protein densities and the varying degree of patient sensitivity, we felt it was necessary to create a tool that allows the allergist to more easily customize a schedule for any given situation. However, there remains considerable concern for dosing errors, especially when these protocols use complex combinations of multiple teaspoon fractions to achieve target protein densities. Constant monitoring or staff measurement of doses will be necessary to ensure dose accuracy. While imperfect, this method may represent a step forward in economizing the delivery of oral immunotherapy within allergy clinics.

Keywords: Food hypersensitivity, Desensitization, Pediatric dosing, Pharmacoeconomics, Patient safety.

1. INTRODUCTION

Anaphylactic food allergy has a prevalence of 2-10% [1]. The standard of care treatment is complete avoidance. Accidental ingestion of the allergic food can lead to fatal anaphylaxis which has a death incidence rate of 1.81 per million person-years and has generated interest in oral immunotherapy (OIT) [2]. OIT consists of daily ingestion of the allergenic food with a gradual dose escalation until a target daily dose is reached. Due to protein allergenic protein content variation, changes in source foods should be made carefully [3]. Whether oral immunotherapy should be offered outside a clinical research center setting is controversial. OIT is a treatment that requires a high level of compliance and has an increased side effect profile compared to avoidance. Anaphylaxis, eosinophilic esophagitis, eczema, and asthma are all potential side effects. In a recent meta-analysis of 12 peanut OIT trials, patients on OIT were at higher risk for anaphylaxis than were controls (due to intentional exposure) with no significant improvement in quality of life [4, 5]. Alternatives to OIT include home-based reintroduction of foods that are lower in dose and modified to reduce allergenicity [6-11]. Peptide vaccine www.aravax.com.au, oral mucosal www.intrommune.com, and epicutaneous www.dbv-technologies.com immunotherapies are in development.

Patients and families are still interested in having access to OIT and various clinics and companies are meeting this need. OIT is safe in experienced centers and offers rapid desensitization within months [12]. Informing patients that symptoms during OIT can signal desensitization improves the experience [13]. Clinics that offer OIT have logistic difficulties in providing accurate doses of food, particularly in the early stages when low doses are administered. The private company Aimmune plans to provide FDA-approved premeasured doses of peanut flour at a cost of $5,000 to $10,000. Allergy Partners Clinic (Dallas, Texas) provides a protocol to board-certified allergists which utilizes a liquid based dosing system using many available foods. Another method involves measurement of small weights of flour by clinic staff, which is laborious and is a rate-limiting step in expanding an OIT program. There are some studies that have shown that absolute precise dosing of food for OIT may not be necessary for all patients [14, 15]. We wanted to determine if it would be possible to create OIT dose schedules using Excel to accommodate differing flour densities and protein contents. The novelty of our Excel worksheet is that it can dynamically produce any dosing schedule in response to chosen starting doses, dose growth multipliers, protein densities that can be variably adjusted by the clinician on-demand. In comparison, existing methods only offer static schedules. However, again, even with this level of flexibility and accuracy, the underlying point remains: the safety of precisely volumetrically measuring these doses is questionable.

2. MATERIALS AND METHODS

Our dose schedule generation worksheet was implemented using Microsoft Excel (Redmond, WA). As stated, this worksheet can generate a dosing

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schedule using any input variables for starting dose, dose multiplier, and protein density. To verify the method using realistic values for these input variables, we purchased dose escalation protocols offered by a private allergy clinic and used their starting dose values. This existing OIT dosing schedule was used to verify the method of our worksheet. Densities of food flour were either obtained from the United States Department of Agriculture Food Composition Databases (https://ndb.nal.usda.gov/ndb/), the Aqua-calc online reference for food characteristics (https://www.aqua-calc.com) or calculated by weighing a tablespoon of food flour using a food scale calibrated to measure in 0.001mg increments. Some of the food flours did not have enough volume to work with the initial doses of schedules produced. For these doses, the allergenic food flour was diluted with oat flour to produce a diluted flour mixture of enough measurable volume given our available scoops. Later doses in the schedule utilize the undiluted protein flours. These flours and flour mixtures were then measured using volume increments of 1/128 tsp, 1/64 tsp, 1/32 tsp, 1/16 tsp, 1/8 tsp and ¼ tsp. We aimed for a 50% dose increase for each subsequent dose. The following dose schedules were created: almond, walnut, peanut, egg, milk and cashew, which exemplifies a range of flour densities and protein content.

3. RESULTS

Schedules were easily generated using a range of flour densities and protein contents allowing the allergist to create a dosing schedule. This method met the objectives of providing schedules that had an average dose increases of 50-60%. Figures **1** through **4** show generated schedules for almond, peanut, walnut and egg. These flours differ in density and protein content and were accommodated by the dosing program.

4. DISCUSSION AND CONCLUSIONS

We were able to quickly generate convenient, customized dosing schedules for allergists and patients. Customization is necessary to accommodate variable flours densities and patient allergy severities. However, dosing errors are more common when using scoops compared to syringes delivering liquids [16-25], but can be reduced with continuous patient education [26] particularly in situations when flours are oily or sticky. Vigilance is therefore required. A balance scale

Patient:	The King Arthur Flour Company		Scoop A is 1/128 tsp
Food:	Almond		Scoop B is 1/64tsp
Density of flour mg/ml:	473		Scoop C is 1/32 tsp
Protein content ratio:	0.21	DOSE	Scoop D is 1/16 tsp
Starting dose in mg	0.4		Scoop E is 1/8 tsp
Vial 2 flour mixture	0.1		Scoop F is 1/4 tsp
Dose Multiplier:	1.6		
Suggested Dose schedule			mg protein
Step 1	Vial 2: Administer Scoop A		0.381799688
Step 2	Vial 2: Administer Scoop B		0.763599375
Step 3	Vial 2: Administer Scoops A + B		1.145399063
Step 4	Vial 2: Administer Scoop C		1.52719875
Step 5	Vial 2: Administer Scoop D		3.0543975
Step 6	Vial 2: Administer Scoops C+D		4.58159625
Step 7	Vial 2: Administer Scoops B+E		6.872394375
Step 8	Vial 1: Administer Scoops A + B		11.45399063
Step 9	Vial 1: Administer Scoops A + C		19.08998438
Step 10	Vial 1: Administer Scoop D		30.543975
Step 11	Vial 1: Administer Scoops C+D		45.8159625
Step 12	Vial 1: Administer Scoops B+E		68.72394375
Step 13	Vial 1: Administer Scoop F		122.1759
Step 14	Vial 1: Administer Scoops E + F		183.26385

Figure 1: Suggested Almond Flour (King Arthur) Schedule (MS Excel).

Patient:	Defatted Flour		Scoop A is 1/128 tsp
Food:	Peanut www.aqua-calc.com		Scoop B is 1/64tsp
Density of flour mg/ml:	254		Scoop C is 1/32 tsp
Protein content ratio:	0.52	DOSE	Scoop D is 1/16 tsp
Starting dose in mg	0.3		Scoop E is 1/8 tsp
Vial 2 flour mixture	0.05		Scoop F is 1/4 tsp
Dose Multiplier:	1.6		
Suggested Dose schedule			mg protein
Step 1	Vial 2: Administer Scoop A		0.25384125
Step 2	Vial 2: Administer Scoop B		0.5076825
Step 3	Vial 2: Administer Scoops A + B		0.76152375
Step 4	Vial 2: Administer Scoops A + C		1.26920625
Step 5	Vial 2: Administer Scoop D		2.03073
Step 6	Vial 2: Administer Scoops C+D		3.046095
Step 7	Vial 1: Administer Scoop A		5.076825
Step 8	Vial 1: Administer Scoop B		10.15365
Step 9	Vial 1: Administer Scoops A + B		15.230475
Step 10	Vial 1: Administer Scoop C		20.3073
Step 11	Vial 1: Administer Scoops B+C		30.46095
Step 12	Vial 1: Administer Scoops B+ D		50.76825
Step 13	Vial 1: Administer Scoops A + E		86.306025
Step 14	Vial 1: Administer Scoops D+E		121.8438
Step 15	Vial 1: Administer Scoops D+F		203.073

Figure 2: Suggested Peanut OIT Schedule (MS Excel).

Food	Custom ▾
Name	Walnut-Holmquist Flour
Density (mg/mL)	367
Protein Ratio	0.17
Starting Dose (mg of protein)	0.4
Minimum Ending Dose (mg of protein)	120
Dilution	0.1
Growth Rate Range	1.5 to 2.2

Figure 3: Suggested Walnut (Holmquist farms) Flour OIT Schedule www.python.org.

is needed to measure flour densities, which can be refined using published protein allergen contents [3]. More conservative dose escalations can be used in situations when flours have unknown protein allergen contents.

A potential alternative to using flour and liquid mixtures and solutions which dilute the highly allergenic food protein at the beginning stages of OIT, is to modify the allergenicity of the food for the beginning stages. Using low doses of boiled walnuts [9], and peanuts [27], heated egg and milk [6-8, 10, 11], and heat/pressure treated cashews and pistachios [28], could possibly substitute for the initial stages of traditional OIT. This preliminary desensitization could allow transition to measuring pure flour using scoops [27].

The greater dose variation of scoops may not be clinically significant except in cases of extreme patient sensitivity or significant allergic comorbidity, like severe asthma and eczema. In such cases, liquid dosing using syringes, or concomitant treatment with omalizumab would be prudent [29]. Currently, there are several

Patient:	Honeyville Farms Egg Whites		Scoop A is 1/128 tsp
Food:	Egg		Scoop B is 1/64tsp
Density of flour mg/ml:	452		Scoop C is 1/32 tsp
Protein content ratio:	0.75	DOSE	Scoop D is 1/16 tsp
Starting dose in mg	0.75		Scoop E is 1/8 tsp
Vial 2 flour mixture	0.05		Scoop F is 1/4 tsp
Dose Multiplier:	1.5		
Suggested Dose schedule			mg protein
Step 1	Vial 2: Administer Scoop A		0.651515625
Step 2	Vial 2: Administer Scoop B		1.30303125
Step 3	Vial 2: Administer Scoops A + B		1.954546875
Step 4	Vial 2: Administer Scoop C		2.6060625
Step 5	Vial 2: Administer Scoops B+C		3.90909375
Step 6	Vial 2: Administer Scoops A + D		5.863640625
Step 7	Vial 2: Administer Scoops C+D		7.8181875
Step 8	Vial 2: Administer Scoops C+E		13.0303125
Step 9	Vial 2: Administer Scoop F		20.8485
Step 10	Vial 2: Administer Scoops E + F		31.27275
Step 11	Vial 1: Administer Scoops A + B		39.0909375
Step 12	Vial 1: Administer Scoops A + C		65.1515625
Step 13	Vial 1: Administer Scoop D		104.2425
Step 14	Vial 1: Administer Scoops C+D		156.36375
Step 15	Vial 1: Administer Scoops A + E		221.5153125

Figure 4: Suggested Egg (Honeyville Farms Egg Whites) OIT Schedule.

allergy groups in the US that successfully use dosing scoops. We hope that this dosing tool is useful for those who use this approach.

Conclusions: Dosing schedules using scoops and flour can be generated easily which allows for greater ease of administering OIT. Dose inaccuracies using scoops perhaps is not clinically significant except for those who are very sensitive and suffer from severe asthma and eczema. Liquid based dosing schedules, although perhaps more cumbersome, may be more accurate and allow for more precise administration of doses lower than 1milligram which can facilitate rapid desensitization and intuitive dose adjustments which may be necessary if excessive side effects occur. A trial is needed to compare liquid and solid volumetric dosing systems evaluating for dosing errors, time to maintenance, and efficiency.

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