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# A retrospective analysis of allergic reaction severities and minimal eliciting doses for peanut, milk, egg, and soy oral food challenges

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ABSTRACT

Food allergy is a public health concern, affecting up to 6% of children and 2% of adults. The severity of allergic reactions can range from mild to potentially life-threatening. In addition, the minimum amount of protein needed to provoke an allergic reaction in an individual patient (the minimal eliciting dose (MED)) ranges from a few micrograms to several grams. To determine whether a retrospective analysis of published data from oral food challenges could be used to assess the potential relationship between MEDs and reaction severities at the MEDs, a three class (mild, moderate, severe) reaction grading system was developed by integrating previously published reaction grading systems. MEDs and symptoms were collected from food challenge studies and each reaction was graded using the integrated grading system. Peanut allergic patients who experienced severe reactions had significantly higher MEDs and threshold distribution doses than those who experienced mild and moderate reactions. No significant differences in threshold distributions according to the severity grading were found for milk, egg and soy. The relationship between threshold dose distribution and reaction severity based on these grading criteria differed between peanut and other allergens, and severe reactions were found to occur in some patients at low MEDs for all of these food allergens.

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## 1. Introduction

Food allergy is a growing public health concern in industrialized countries, affecting up to 6% of children and 2% of adults (Baral and Hourihane, 2005; Liu et al., 2010; Sicherer and Sampson, 2010). Many affected children will "outgrow" their allergy with age (Sampson and Scanlon, 1989). However, food allergy can be a lifelong concern especially for peanut-allergic patients (Busse et al., 2002; Fleischer et al., 2004). There is some evidence that the incidence of food allergy may have increased since 1997 in the United States and in other countries (Branum and Lukacs, 2008; Grundy et al., 2002).

Food allergy is usually diagnosed based on a combination of history, clinical examination, measurement of allergen-specific IgE levels and skin prick tests (SPTs) (Sampson and Albergo, 1984). However, the double-blind, placebo-controlled oral food challenge (DBPCFC) is considered to be the "gold standard" for diagnosing food allergy because it removes patient and observer bias (May, 1976; Sampson and Albergo, 1984). Open or single-blind oral food challenges are considered useful when the challenge outcome is negative or when obvious objective symptoms are elicited, especially in young children (Boyce et al., 2010). In addition, oral food challenges (OFCs) may be used to determine whether a food allergy has resolved and to characterize an individual patient's sensitivity to an allergen (Taylor et al., 2004).

The minimum amount of food that elicits an allergic reaction in a sensitized individual in an OFC is often referred to as the "minimum eliciting dose" (MED) (Flinterman et al., 2006b; Peeters et al., 2007). It is well established that there is a wide range in MEDs among individuals with IgE-mediated food allergies (Crevel et al., 2007). However, limited data are available on the correlation between the MED and reaction severity at the MED for individual patients. Anecdotal clinical observations suggest that reactions occurring at low allergen doses during challenge are relatively mild. However, DBPCFC studies have shown that allergenic food doses as low as 0.3 to 1 mg of protein can cause serious reactions of laryngeal edema or throat closing (Anagnostou et al., 2011; Wensing et al., 2002b). In some studies serious reactions occurred at the lowest challenge dose used (Knight et al., 2006; Nicolaou et al., 2010; Sicherer et al., 2000). Thus, it remains possible that serious reactions could have occurred at even lower doses in those patients. Several studies found no correlation between MED and reaction severity during the challenge (Flinterman et al., 2006b; Glaumann et al., 2012; Lam et al., 2008; Sicherer et al., 2000). One study found that patients with a history

*Abbreviations:* AIC, Akaike information criterion; AP, abdominal pain; CI, confidence interval; DBPCFC, double-blind placebo-controlled food challenge; ED, eliciting dose; GI, gastrointestinal; OAS, oral allergy syndrome; LOAEL, the lowest observed adverse effect level; NOAEL, the no observed adverse effect level; OFC, oral food challenges; RC, rhinoconjunctivitis; SPTs, skin prick tests.

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of severe reactions or patients with moderate-to-severe reactions during challenge had significantly lower MEDs than patients with milder reactions (Wensing et al., 2002b), while another study found no significant difference between the threshold distributions of patients with histories of more severe or less severe reactions (Taylor et al., 2010). All of these studies had confounding factors such as testing of a small number of individuals, differences in geographic location, use of different test material, use of different dosing protocol, etc., that create uncertainty as to how the results apply to the general food allergic population. In addition, standards for classifying the severity of allergic reactions varied among the studies, leading to difficulties in evaluating and comparing results.

The aim of our study was to determine whether a retrospective analysis of published data from OFCs with peanut, milk, egg and soy allergic individuals could be used to assess the potential relationship between MEDs and reaction severities at the MEDs. Because there is no generally accepted system for evaluating allergic reaction severity, and because the terminology used to describe the observed reactions differed between studies, we developed an integrated reaction severity grading system based on eight previously published grading systems. The observed reactions from published OFC studies were then graded based on this integrated grading system and the relationships between MEDs or threshold distributions and reaction severities at the MEDs for the four allergens were analyzed by statistical modeling.

## 2. Materials and methods

### 2.1. Development of the integrated grading system

Multiple published classification schemes or grading systems for allergic reaction severities were reviewed and compared (Table 1 and Supplementary Table S1) (Brockow and Ring, 2009; Brown, 2004; Cox et al., 2010; Ewan and Clark, 2001; Flinterman et al., 2007; Mueller, 1966; Rank et al., 2008; Sampson, 2003). These systems were developed independently, are widely recognized, and in some cases have been used by health agencies. Our system for classifying the severity of food allergic reactions was developed by integrating these eight schemes into a three class system (severity grades: mild, moderate or severe) as shown in Table 2.

Since these schemes varied in number of grades (3 to 5), purpose for the grading system (i.e., defining OFC responses vs classifying anaphylaxis or systemic reactions vs establishing priority allergens) and in the types of symptoms reported (Table 1 and Supplementary Table S1), the following criteria were used to integrate these different schemes into a unified three grade scoring system. First, because some of the published systems were developed to classify all types of allergic reactions, not just food allergies, only symptoms that were reported in the clinical studies we reviewed were included (Table 2). Second, for those published grading systems with 3 severity grades (Brown, 2004; Flinterman et al., 2007), their defined mild, moderate or severe reactions were considered as mild, moderate or severe in our systems; for the systems that defined 4 severity grades (Cox et al., 2010; Mueller, 1966; Rank et al., 2008) (Cox et al., 2010 defined 5 grades but the last grade is "death", so only the first 4 grades were considered), the first grade was considered as mild, the second grade was considered as moderate and the last two grades were considered as severe; for the systems that defined 5 grades (Ewan and Clark, 2001; Sampson, 2003), the first two grades were considered as mild, the third was considered as moderate, the fourth was either moderate or severe depending on the specific symptoms and the grading of those symptoms in the other published systems, and the fifth grade was considered as severe. Third, symptoms or reactions that were reported in the literature but not specifically listed in any of the schemes analyzed (e.g., asthenia, colic) were grouped with similar symptoms or assessed individually for severity by the authors and included in the final integrated scoring model. Other inconsistencies among the published systems were resolved by considering the most frequently used classifications in the eight published grading systems. Because most of the published grading systems and oral challenge studies lack detailed information on individual symptoms, we used broad descriptions in our integrated system.

### 2.2. Selection of allergic reaction data

Published OFC studies that included data on reaction severities were identified by searching the PubMed database using key words including specific allergen names (peanut, milk, egg or soy), and "oral food challenge", "threshold", or "double-blind

**Table 1**
Published allergic reaction grading systems.

| System | No. of grades | Purpose of grading system | Consideration of the number of organ systems involved? | Subjective symptoms included? |
|---|---|---|---|---|
| Sampson, 2003 | 5 | Grading of food-induced anaphylaxis | Yes | Yes (oral 'tingling') |
| Ewan and Clark, 2001 | 5 | Food allergic reaction severity | Yes | No |
| Cox et al., 2010[a] | 5 (5 = death) | Systemic reaction grading system for subcutaneous immunotherapy reactions | Yes | No |
| Rank et al., 2008[b] | 5 (0 = no symptoms or nonspecific symptoms) | Grading of severity for systemic side effects | No | No |
| Mueller, 1966 | 4 | Grading severity for systemic reactions to insect stings | Yes | Yes (malaise, anxiety) |
| Brockow and Ring, 2009 | 4 | Grading of anaphylactic/anaphylactoid reactions | Yes | No |
| Brown, 2004[c] | 3 | Grading system for generalized hypersensitivity reactions | Yes | No |
| Flinterman et al., 2007 | 3 | Food challenge severity | Yes | Yes (oral cavity) |

[a] World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System.
[b] 2006 EAACI (European Academy of Allergology and Clinical Immunology ) Grading of Severity for Systemic Side Effects.
[c] Used by Health Canada as part of their Criteria for the Establishment of New Priority Food Allergens.

**Table 2**
Integrated grading system for scoring reaction severity of oral food challenge (OFC) reactions.

| Grade | Symptoms/organ systems | Classification of combined organ systems |
|---|---|---|
| Mild | • OAS (Oral allergy syndrome)<br>• Skin: Eczema, erythema, flushing, pruritis, urticaria (not generalized), conjunctivitis, nonlaryngeal angioedema (e.g., lip swelling)<br>• Upper respiratory: rhinitis, rhinoconjunctivitis, nasal congestion, sneeze<br>• Gastrointestinal (GI) (mild): nausea alone, colic | All symptoms in any one system category (OAS, skin, upper respiratory, or nausea) alone |
| Moderate | • Skin (severe): generalized urticaria, facial swelling<br>• GI: abdominal pain, diarrhea, vomiting, cramps<br>• Mild lower respiratory : dyspnea, cough, chest or throat tightness<br>• Neurological: tiredness, agitated, asthenia, lethargy | All symptoms in GI or mild lower respiratory symptom alone; or combination of symptoms in any two systems of skin, GI, upper respiratory or mild lower respiratory |
| Severe | • Lower respiratory: asthma, bronchoconstriction (drop in peak flow), wheeze, stridor, hoarseness, laryngeal edema (or throat closing)<br>• Cardiovascular: tachycardia, shock, fall in blood pressure, hypotension, cyanosis<br>• Anaphylaxis, collapse<br>• Reaction requiring epinephrine treatment | Any symptom in lower respiratory and/or cardiovascular systems; or any combination of symptoms in three or more systems of mild/moderate grade (except OAS) |