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# Allergen immunotherapy–induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study

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**Background:** An anaphylactic reaction is one of the alarming adverse effects of allergen immunotherapy. Although a systemic reaction can follow a biphasic course, its incidence, its outcome, and the risk factors for its development are unknown in patients treated with immunotherapy.

**Objective:** To record the incidence, characteristics, and outcome of immunotherapy-inflicted biphasic reactions (BRs).

**Methods:** All patients attending large in-hospital allergy clinics for immunotherapy were followed up prospectively. Recorded patient data included the following: demographics, diagnosis, type and phase of immunotherapy, and peak expiratory flow (PEF) before each administration of the injections. If an anaphylactic reaction occurred, medical treatment was recorded and the patient was asked to complete a 3-day diary that included symptoms and periodic measurements of PEF. A BR was defined as a late decrease in PEF of more than 20%, with or without accompanying symptoms.

**Results:** During 10,040 visits, 453 patients received 21,022 immunotherapy injections and 131 anaphylactic reactions occurred. Of these reactions, 11 (10%) were biphasic. Most uniphasic reactions (URs) and all BRs occurred in patients who were being treated for allergic rhinitis. A low baseline PEF or concomitant asthma was more common in patients with BRs. Other parameters were comparable between patients with URs and BRs. All BRs were mild and resolved either spontaneously or with oral antihistamines.

**Conclusions:** Immunotherapy-induced BRs are uncommon. They tend to be mild and might be more common in patients with a low baseline PEF or concomitant asthma. Therefore, a long observation after the initial reaction is not required.

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## INTRODUCTION

Anaphylaxis is an allergic emergency that has a potentially fatal outcome.<sup>1</sup> An anaphylactic reaction can be classified as either uniphasic or biphasic. In a uniphasic reaction (UR), symptoms usually begin within 5 to 30 minutes after exposure to the allergen and disappear gradually. In biphasic systemic reactions, symptoms of the initial episode disappear and then re-emerge, usually within several hours after they have completely subsided.

According to previous reports,<sup>2–5</sup> the overall incidence of biphasic reactions (BRs) varies from 3% to 23%. The number of cases in these reports ranged from 13 to 113. In a recent 14-year retrospective review<sup>6</sup> of 180 anaphylactic episodes in 106 pediatric patients, a biphasic event occurred in 6%; in another recent study by Ellis et al,<sup>7</sup> a BR incidence of 19.4% was reported in a mixed adult and pediatric population.

The initial description of biphasic anaphylaxis<sup>4</sup> was defined as an asymptomatic period, lasting from 1 to 8 hours,

between the 2 phases. However, subsequent publications<sup>8</sup> also documented a latent period of 28 and 72 hours. Symptoms of the late response may be milder, similar, or more severe than those of the initial event.

To our knowledge, there are no consistently reported risk factors for the development of a BR. However, several factors associated with the initial reaction have been mentioned: oral administration of the allergen, concomitant treatment with  $\beta$ -blockers, hypotension or laryngeal edema, an elderly patient with cardiovascular disease, and a delay of more than 30 minutes in the appearance of the first symptoms.<sup>9</sup> Some researchers suggest that a delayed or an inadequate dose of epinephrine during the initial episode creates a risk factor for the development of a late reaction.<sup>6</sup>

Although an anaphylactic reaction after the administration of allergen immunotherapy is the most serious adverse event associated with this treatment, until recently only a single retrospective study by Douglas et al<sup>3</sup> addressed this population specifically. In this study, 800 outpatients being treated with immunotherapy were observed. Forty-four episodes of anaphylaxis were identified in 35 patients (incidence, 0.06%). Two (5%) of them had a BR pattern. At the time of submission of the present study, Scranton et al<sup>10</sup> published a study addressing the same topic. In their prospective study, all patients treated with epinephrine for a systemic reaction after immunotherapy received a follow-up telephone call 24 hours after the reaction. According to this article, the incidence of

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BR after immunotherapy is 23%. Biphasic reactions were significantly less severe and tended to occur in female patients. In the present study, patients treated with immunotherapy in a large, university-affiliated, in-hospital allergy clinic were prospectively followed up for a 2-year period. Symptoms and peak expiratory flow (PEF) measurements were observed for 3 days in all patients who experienced a systemic reaction to allergen injections. We aimed to prospectively determine the incidence, predicting factors, and characteristics of immunotherapy-induced BRs in many patients.

## METHODS

### *Patient Data Collection*

Each patient attending the Meir Hospital Allergy Clinic, Kfar-Saba, Israel, for conventional allergen immunotherapy was required to record the best of 3 PEF measurements before receiving his or her immunotherapy injections. (This PEF measurement technique applies to all PEF measurements mentioned.) The nurses inquired about the patient's general well-being and then specifically about whether any adverse event had occurred during or after the last immunotherapy visit. The extracts used for immunotherapy for inhaled allergen were all glycerinated. The extracts used for venom immunotherapy were reconstituted with albumin saline diluent. A constant number of injections were given to each patient, disregarding the phase of immunotherapy (buildup or maintenance phase). After the injections were administered, the patient remained in the clinic for 30 minutes; patients with accompanying asthma remained in the clinic for 45 minutes. If an anaphylactic reaction occurred, PEF was remeasured, the patient was examined by the allergist, and medical treatment was applied. After the resolution of all signs and symptoms of the systemic reaction, including the return of PEF to at least 90% of the prereaction value, the patient was discharged with specific instructions to return to the clinic or to the emergency department if symptoms recurred. All patients were equipped with antihistamines, and those with asthma also had a  $\beta$ -agonist inhaler. Instructions on how to use these drugs were repeated before discharge. Each patient was also given a diary and a peak flow meter and instructed to measure and record the PEF and any other symptoms and medication use for 72 hours. The PEF was measured every 3 hours during the first 12 hours after the reaction, and morning and evening measurements were recorded for the following 2 days. The allergist obtained a repeat medical history and reviewed the diary 3 to 7 days after the reaction.

All participants signed an informed consent form, and the study was approved by the Meir Hospital Human Research Ethics Committee.

### *Definition of Anaphylaxis*

Anaphylaxis was identified by the known symptoms and signs of generalized mast cell mediator release, involving the skin or respiratory tract, the gastrointestinal tract, or the cardiovascular system.<sup>1</sup> All patients defined as having anaphylaxis had at least 2 of the following signs and symptoms:

(1) skin and/or mucosal involvement (generalized hives, pruritus, flushing, or facial or tongue swelling), (2) respiratory compromise (dyspnea, wheezing, stridor, or hypoxemia), (3) reduced blood pressure, or (4) gastrointestinal symptoms (cramps, abdominal pain, or vomiting). The severity of anaphylaxis was graded as follows: 1, mild; 2, moderate; or 3, severe (as suggested by Brown).<sup>11</sup> The severity grading did not include the reduction in PEF.

In an attempt to have an objective evaluation of the reactions, we compared the prereaction PEF value with the values obtained during the postreaction 3-day follow-up period. An objective BR was defined as a decrease of more than 20% in the PEF value in at least 1 PEF measurement performed 3 hours or more after resolution of the initial anaphylactic reaction. A subjective BR was defined as the reoccurrence of the signs and symptoms previously mentioned after resolution of the initial reaction.

### *Data Collection*

Data regarding adverse reactions were collected on the visit after the index reaction. Information included demographics, patient diagnosis, type of allergens administered for immunotherapy (house dust mites, pollens, or venom), phase of immunotherapy (buildup or maintenance phase), number of injections per visit (each allergen indicates 1 injection), and a thorough history of the period after the adverse reaction, including medications. The PEF records of the follow-up diary and 5 PEF measurements from adjacent, consecutive, and uneventful visits were also recorded.

### *Statistical Analysis*

The  $\chi^2$  test was used to compare categorical variables and *t* test results for continuous variables between the 2 types of reactions. Repeated measures were used to compare differences between groups and within each group.

## RESULTS

During the 2-year study period, 453 patients (263 men [58.1%] and 190 women [41.9%]) with a mean (range) age of 31 (4–81) years received immunotherapy at the allergy unit. Most patients (302 [66.7%]) were treated for allergic rhinitis; 133 patients (29.4%) also had asthma. Other treatment indications included 144 patients (31.8%) with venom allergy and 7 patients (1.5%) with both allergic rhinitis and venom allergy. During 10,040 visits, patients received a total of 21,022 immunotherapy injections (11,117 buildup and 9,905 maintenance injections). A total of 131 anaphylactic reactions were recorded in 76 patients. The incidence of anaphylactic reactions per visit was 1.3%. Table 1 summarizes the characteristics of the reactions. The mean (range) observation period after the reaction was 1.7 (1.3–3.2) hours. Complete follow-up diaries were obtained from 112 of 131 reactions (response rate, 85.5%), and only these diaries were included in the study. One hundred one patients had a UR (50 [49.5%] were men and 51 [50.5%] were women); their mean (range) age was 29.1 (11–56) years. Ten patients (3 men and 7 women), with a mean (range) age of 29.6 (14–48) years, had

Table 1. Characteristics of the 131 Systemic Reactions

| Characteristic                          | Type of reaction <sup>a</sup> |                       | Total No. |
|-----------------------------------------|-------------------------------|-----------------------|-----------|
|                                         | Uniphasic                     | Biphasic              |           |
| Total <sup>a</sup>                      | 120 (91.6)                    | 11 (8.4)              | 131       |
| Complete records <sup>a</sup>           | 101 (90.2)                    | 11 (9.8)              | 112       |
| Severity of first reaction <sup>b</sup> |                               |                       |           |
| 1                                       | 12 (10.9)                     | 0 (0)                 | 11        |
| 2                                       | 79 (78.2)                     | 11 (100.0)            | 90        |
| 3                                       | 11 (10.9)                     | 0 (0)                 | 11        |
| Treatment of first reaction             |                               |                       |           |
| Epinephrine                             | 59 (58.4)                     | 6 (54.5)              | 65        |
| Inhalation                              | 80 (79.2)                     | 10 (90.9)             | 90        |
| Antihistamines                          | 70 (69.3)                     | 9 (81.8)              | 79        |
| Indication for immunotherapy            |                               |                       |           |
| Allergic rhinitis                       | 91 (90.1)                     | 11 (100.0)            | 102       |
| Venom allergy                           | 10 (9.9)                      | 0 (0)                 | 10        |
| Concomitant asthma                      | 54 (53.5)                     | 9 (81.8) <sup>c</sup> | 63        |
| Pretreatment with antihistamines        | 57 (56.4)                     | 7 (63.6)              | 64        |
| Phase on immunotherapy                  |                               |                       |           |
| Buildup                                 | 67 (66.3)                     | 5 (45.5)              | 72        |
| Maintenance                             | 34 (33.7)                     | 6 (54.5)              | 40        |
| Late subjective symptoms                | 0 (0)                         | 4 (36.4)              | 4         |
| Mean PEF in 5 uneventful visits, L/min  | 464                           | 394 <sup>d</sup>      | NA        |

Abbreviations: NA, not applicable; PEF, peak expiratory flow.

<sup>a</sup> Data are given as number (percentage) of the total number.

<sup>b</sup> Data are given as number (percentage) of the complete records for each type of reaction (n=101 for uniphasic and n=11 for biphasic).

<sup>c</sup>  $P = .07$ .

<sup>d</sup>  $P = .03$ .

11 (10.9%) objective BRs. Thus, in addition to the decline in PEF by more than 20%, subjective symptoms were reported in 4 (36.4%) of 11 objective BRs. The symptoms included nasal congestion, rhinitis, itchy eyes, cough, and mild shortness of breath. Ten (9%) of 112 patients had subjective BR. Four of them had a decrease in PEF by more than 20% in addition to the subjective symptoms. Their symptoms included 1 or more of the following: cough, shortness of breath, rhinitis, itchy eyes, and chest tightness. In all patients with a BR, defined by either PEF or symptoms, the symptoms subsided spontaneously or with antihistamines.

The severity of both BR and UR was similar, with grade 2 reactions in 11 (100.0%) and 79 (78.2%) of patients, respectively ( $P = .22$ ). All BRs occurred in patients with allergic rhinitis who were receiving immunotherapy with inhaled allergens. Most of them (9 patients [81.8%]) also had asthma. In the UR group, 91 patients (90.1%) had allergic rhinitis treated by immunotherapy to inhaled allergens. Although there were fewer patients with asthma in this group (54 [53.4%]), the difference did not reach significance ( $P = .07$ ). Systemic reactions during the maintenance dose phase of immunotherapy occurred in 6 patients with BR (54.5%) and in 34 patients with UR (33.7%) ( $P = .17$ ). Most patients (77.2%) who experienced a UR or a BR received 2 or more injections per visit, as opposed to 58.1% of the nonreacting patients ( $P = .001$ ). However, there was no difference in the number of injections per visit between the patients in the UR

and BR groups. No difference was found between the 2 groups in regard to the various types of injected allergens. Of the 101 patients with a UR, 57 (56.4%) regularly used antihistamines as premedication before immunotherapy, compared with 7 (63.6%) of the 11 patients with a BR ( $P = .64$ ).

Medications used to treat the initial reaction were similar in the 2 groups: 54% of the patients with BR and 58% of those with UR were initially treated with epinephrine (all patients with a grade 3 reaction and 48 patients with a grade 2 reaction) ( $P = .90$ ). Antihistamines were administered in 81% of the BR and in 69% of the UR groups ( $P = .38$ ), and  $\beta$ -agonist inhalation was used in 90% of the BR and in 79% of the UR groups ( $P = .35$ ).

As can be seen in Figure 1, no difference was found in PEF measurements between the 2 groups before injection, during the initial reaction, and 3 hours after the reaction. However, a significant decrease in PEF values was noted at 6, 12, 24, 48, and 60 hours in the BR group compared with the UR group. The mean (variability) value of PEF measurements performed in 5 consecutive uneventful visits adjacent to the systemic reaction was  $394 \pm (92)$  L/min in the BR group and  $464 \pm (103)$  L/min in the UR group ( $P = .03$ , with more variability in the UR group). The mean PEF value was similar in the 54 patients with UR who had concomitant asthma compared with the 47 patients with only allergic rhinitis (440 and 474 L/min, respectively;  $P = .15$ ). The mean PEF value of patients with concomitant asthma was 440 L/min in the UR

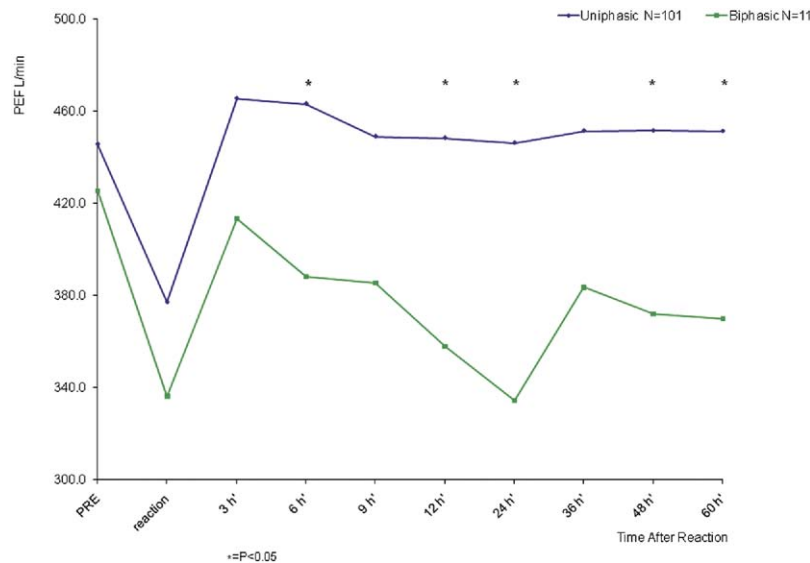


Figure 1. Mean peak expiratory flow (PEF) during the follow-up period comparing uniphasic reactions with biphasic reactions.

group (n = 54) and 388 L/min in the BR group (n = 9) ( $P = .19$ ).

A BR defined by subjective symptoms was observed in 10 patients. As can be seen in Table 2, the indication for immunotherapy, the severity of the initial reaction, medications used to treat the reaction, and the mean value of PEF measurements performed in 5 consecutive uneventful visits adjacent to the index reaction were comparable to those of patients with a BR identified by PEF measurements. However, concomitant asthma was found in only 4 patients (40.0%) in the subjective BR group, similar to the patients in the UR group.

## DISCUSSION

The term *anaphylaxis* refers to an acute, immediate, and systemic hypersensitivity reaction. Symptoms and signs of anaphylaxis usually begin within minutes after exposure to the allergen. When the reaction abates and reappears several hours later, it is termed a *BR*. Conflicting reports exist regarding the incidence, characteristics, predicting factors, and management of a BR. Allergen immunotherapy is an effective treatment for allergic rhinitis, asthma, and venom allergy. Although an anaphylactic reaction is not an unusual adverse effect of this treatment, allergists still lack reliable information regarding immunotherapy-induced BRs.

Since BR was first described more than 80 years ago by Duke, a number of studies and case reports have addressed the subject.<sup>2-7</sup> The reported incidence of this reaction varies greatly. The study by Douglas et al<sup>3</sup> specifically addressing immunotherapy-induced BRs described an overall incidence of anaphylaxis of 0.06%, whereas the incidence of BR was 5% (2 episodes in 2 patients). In contrast to the data of Douglas et al, the recent study by Scranton et al<sup>10</sup> reported an incidence of 23%. The overall incidence of anaphylactic

reactions in our study was 1.3%, whereas 10% of the reactions were biphasic. This incidence is within the wide range reported by other studies but was not as low as that reported by Douglas et al and not as high as that reported by Scranton et al. The reason for this discrepancy is unknown. It may be

Table 2. Characteristics of Subjective and Objective BRs

| Characteristic                             | Type of biphasic reaction |           |
|--------------------------------------------|---------------------------|-----------|
|                                            | Subjective                | Objective |
| Total <sup>a</sup>                         | 10 (7.6)                  | 11 (8.3)  |
| Complete records                           | 10 (8.9)                  | 11 (9.8)  |
| Severity of first reaction <sup>b</sup>    |                           |           |
| 1                                          | 2 (20)                    | 0 (0)     |
| 2                                          | 8 (80)                    | 11 (100)  |
| 3                                          | 0 (0)                     | 0 (0)     |
| Treatment of first reaction <sup>b</sup>   |                           |           |
| Epinephrine                                | 8 (80)                    | 6 (55)    |
| $\beta$ -Agonist inhalation                | 8 (80)                    | 10 (91)   |
| Antihistamines                             | 9 (90)                    | 9 (82)    |
| Indication for immunotherapy <sup>b</sup>  |                           |           |
| Allergic rhinitis                          | 9 (90)                    | 11 (100)  |
| Venem allergy                              | 1 (10)                    | 0 (0)     |
| Concomitant asthma                         | 4 (40)                    | 9 (82)    |
| Pretreatment with antihistamines           | 6 (60)                    | 7 (64)    |
| Phase on immunotherapy <sup>b</sup>        |                           |           |
| Buildup                                    | 3 (30)                    | 5 (45)    |
| Maintenance                                | 7 (70)                    | 6 (55)    |
| Late subjective symptoms <sup>b</sup>      | 10 (100)                  | 4 (36)    |
| Late objective decline in PEF <sup>b</sup> | 4 (40)                    | 11 (100)  |
| Mean PEF in 5 uneventful visits, L/min     | 395                       | 394       |

Abbreviations: BR, biphasic reaction; PEF, peak expiratory flow.

<sup>a</sup> Data are given as number (percentage) of 112 complete records.

<sup>b</sup> Data are given as number (percentage) of the total in each column.

partially explained by methodological differences. In contrast to our prospective study, the report by Douglas et al was retrospective, based on symptoms only. The study by Scranton et al, although prospective, used a subjective symptom score and a limited follow-up of 24 hours. We used a significant decline of PEF as an objective parameter for defining BR and extended the follow-up to 72 hours. Despite the dissimilar methods, the discrepancy between the studies regarding the incidence of BR remained similar, even when we used symptoms rather than PEF measurements to define a BR. Although the incidence of BRs in our study was not minute, the patients had a favorable outcome and none required treatment other than oral antihistamines or inhaled  $\beta$ -agonists.

In addition to the prospective evaluation of the incidence and outcome of BRs, we attempted to identify risk factors for their development. In their comprehensive review, Tole and Lieberman<sup>9</sup> concluded that there were no consistent risk factors predictive of BRs. Scranton et al<sup>10</sup> found that patients experiencing BRs were more likely to be female. Our results, however, indicate 2 other possible risk factors for BRs.

The first is the relatively low PEF during uneventful visits. This finding was more common in patients with BRs than in those with URs ( $P = .03$ ) and remained consistent when BR was defined by either symptoms or a decrease in PEF. We found that the mean PEF value was similar in patients with UR regardless of concomitant asthma, thus ruling out the possibility that a low mean PEF could be attributed to concomitant asthma in most patients with BR. Although these results, which focus on the possible role of low PEF in BR, reached only modest statistical significance, they suggest a subgroup of patients who are prone to developing a BR.

The second possible risk factor detected is coexisting asthma in patients with allergic rhinitis. Asthma was more common in patients with BRs than in those with URs. This difference did not reach significance ( $P = .07$ ) and was totally abolished when a BR was defined by subjective symptoms. It is well established that patients with severe asthma are at greater relative risk of developing systemic reactions to allergen immunotherapy compared with patients with only rhinitis. Indeed, systemic reactions to immunotherapy are more common in patients with uncontrolled asthma, in patients treated with oral corticosteroids, and in patients with a forced expiratory volume in 1 second of less than 70% of the predicted value.<sup>12</sup> No data are available regarding BR in this subset of patients. In their study dedicated to immunotherapy in asthma, Bousquet et al<sup>13</sup> concluded that all adverse reactions to house dust mite injections occurred within 45 minutes and no late reactions were observed. Greenberg et al<sup>14</sup> reported a 4% incidence of late systemic reactions (30–360 minutes) after immunotherapy with inhaled allergens. Asthma was not specifically reported in this study, and BR was not specifically addressed. Recently, Winther et al<sup>15</sup> published a prospective study that monitored the adverse effects of allergen immunotherapy. As opposed to previous studies, they found that neither asthma nor other parameters

were predictive of adverse effects during immunotherapy. Nevertheless, the most recent guidelines from 2007<sup>16</sup> advocate immunotherapy administration only to patients with stable asthma. Nelson,<sup>12</sup> in Middleton's allergy textbook, specifies that asthmatic patients with a forced expiratory volume in 1 second of less than 70% of the predicted value are at risk. We comply with these guidelines. Furthermore, all of our patients recorded the PEF immediately before the injection, and treatment was withheld when there was a significant decrease. Therefore, unstable asthmatic patients were not included in our study. Consequently, it is difficult to compare our results with those of other previously mentioned reports. Whether asthma, stable or not, should be considered as a risk factor for BR is still unknown.

In addition to asthma as a possible risk factor for BR, 2 studies suggested an association with the medical treatment administered during the anaphylactic reactions. Delayed administration of epinephrine or undertreatment of the initial reaction with epinephrine has been associated with the occurrence of a BR.<sup>6,7</sup> Other previously mentioned predicting factors include oral administration of the allergen<sup>9</sup> and the presence of hypotension or laryngeal edema during the initial event.<sup>8</sup> We found no difference between UR and BR regarding all previously mentioned parameters (ie, none of our patients received oral allergen; in both groups epinephrine was administered as soon as indicated after the reaction was detected, which was always within the mandatory waiting period after immunotherapy). Other variables, such as being female, the phase of immunotherapy (buildup or maintenance phase), or administration of other medications to treat the initial reaction, were also comparable between a BR and a UR.

The current data do not support any definitive criteria to predict which patients are prone to developing a BR, as well as their outcome. As such, different researchers have suggested an observation period ranging from 8 to 24 hours after an anaphylactic reaction.<sup>6,9,17</sup> Despite the relatively short observation periods in our study population, all second-phase reactions were mild and did not require emergency intervention. This observation is in accordance with data published by Scranton et al. Their conclusion was that a BR after allergen immunotherapy was mild and self-limited.

Thus, our experience suggests that prolonged observation is not necessary when the initial reaction is properly treated and all signs resolve before discharge. Nevertheless, patients should be aware of the first signs of a recurrent reaction and should seek medical aid in case the symptoms worsen rapidly or do not respond to antihistamines.

In conclusion, this is the first prospective report investigating BR in patients treated with allergen immunotherapy. Its unique strength originates from the fact that BR was defined according to objective PEF measurements and patient symptoms, in a very large group of patients. We demonstrated that immunotherapy-induced BR occurred in 10% of patients with systemic reactions and that BR is probably more frequent in patients with a low baseline PEF or asthma.

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Measuring the PEF emerges as an instrument able to detect potential BRs, especially in asthmatic patients and in those patients who do not perceive their late-stage symptoms. The second-phase reactions are mild and can be easily controlled without emergency intervention. Therefore, a short observation period should suffice for most patients. An extended observation period should be reserved for those patients with concurrent serious medical problems, according to the physician's clinical judgment.

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