# Effects of Immunotherapy on Thai Asthmatic Children*

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**SUMMARY** **Presented in this report are the retrospective evaluations of 72 Thai asthmatic children who received immunotherapy. The subjects were classified into three therapeutic groups, viz: 1) children receiving bacterial vaccine injections, who had a history of recurrent asthmatic attacks associated with respiratory infection (n=25); 2) children receiving allergen injections, who manifested distinctive evidence of atopy (n=35); and 3) children receiving bacterial vaccine and allergen treatments, who displayed symptoms of atopy and had a history of asthmatic attacks provoked by respiratory infection as well as allergen exposure (n=12). After long-term immunotherapy the rate of effective response was as follows: group 1=88.00 per cent, group 2=82.86 per cent and group 3=58.33 per cent. Based on this preliminary study, we tentatively concluded that the efficacy of immunotherapy with bacterial vaccine or with relevant allergens in treating Thai asthmatic children was satisfactory.**

ASIAN PACIFIC J ALLERG IMMUN 1984; 2 : 32-36.

Bronchial asthma is a common disease characterized by recurrent attacks of paroxysmal dyspnoea. It is the result of an increased responsiveness of the airway to various stimuli and is manifested by a slowing of forced expiration which changes in severity either spontaneously or as a result of therapy.[1] Bronchial asthma may be classified as allergic (extrinsic) and non-allergic (intrinsic) depending on the provocative factors in the particular areas.[2] Allergic asthma is triggered by allergens, whereas non-allergic asthma is provoked by non-specific agents such as infections, psychogenic factors, irritants etc. There is also a group of patients who may be classified as having "mixed asthma". These patients are definitely sensitive to environmental allergens; at the same time, however, infection of the respiratory system also plays an important role in provoking their asthmatic attacks.[2]

Current knowledge of pathophysiological and immunological relationships leads to the possibility of applying various prophylactic and therapeutic measures in systemic, well-directed regimens for asthmatics. Because of the complicated nature of bronchial asthma, monotherapy is inadequate to control the symptoms.[3] At our allergy clinic, we administer immunotherapy as part of the total management of asthmatic patients who have been referred to us for long-term treatment.

Immunotherapy (hyposensitisation) involves the injection at regular intervals of allergenic extracts. We had earlier reported that about 60 per cent of the asthmatic adults treated at our clinic with aeroallergenic extracts showed satisfactory results.[4] However, the efficacy of immunotherapy for asthmatic children hitherto had not been evaluated in this region. This paper presents a retrospective analysis of the efficacy of long-term immunotherapy involving injections of bacterial vaccine, allergenic extract of common inhalants, or both. The study was conducted on Thai asthmatic children who reside in the city of Bangkok.

## MATERIALS AND METHODS

### Subjects

Medical records of children under 15 years of age, who had received immunotherapy at the allergy clinic of the Police General Hospital during the period 1976 to 1980 were analysed. The total number of children was 107. Ninety-four children (87.85% of the total) received immunotherapy uninterruptedly at the clinic for more than 12 months. Of the 94, 72 (76.60%) were asthmatic and 22 (23.40%) rhinitic. Only the records of the asthmatic children were analysed. The methods of immunotherapy which they received were divided into three groups:

Group 1: Bacterial vaccine injection.

Group 2: Allergenic extract injection.

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*Table 1.* Basic data on subjects studied

| Type of treatment | Number of cases | Age* (yrs) | M:F | Duration of illness (yrs) | Duration of observation (months) | Family history (%+ ve) | Skin test (% +ve) |
|---|---|---|---|---|---|---|---|
| Bacterial vaccine | 25 | 4.28±2.55 | 1.5:1 | 1.96±1.61 | 41.28±22.42 | 40 | 42.25 |
| Allergens | 35 | 7.85±2.88 | 2.2:1 | 3.8 ±2.7 | 39.71±20.68 | 60 | 100 |
| Bacterial vaccine + allergens | 12 | 6.66±2.64 | 5:1 | 2.83±2.24 | 59.41±31.88 | 33.33 | 100 |

*mean ± SEM

Group 3: Bacterial vaccine and allergenic extract injection.

The basic data on each therapeutic group are tabulated in Table 1.

## Immunotherapy

### *1. Bacterial vaccine*

Commercially available stock bacterial vaccines (Broncasma Berna®) were used for injection. The products were manufactured by the Swiss Serum and Vaccine Institute, Berne. Data on the contents of vaccine in ampoule are contained in Table 2.

*Table 2.* Bacterial vaccine (bacterial contents = 1,000 million/ml)

| Organisms | million/ml |
|---|---|
| *Staphylococcus* | 500 |
| *Pseudomonas aeruginosa* | 250 |
| *Neisseria catarrhalis* | 60 |
| *Streptococcus pneumoniae* I, II, III | 50 |
| *Streptococcus* | 40 |
| *Klebsiella pneumoniae* | 40 |
| *Haemophilus influenzae* | 40 |
| *Micrococcus tetragenes* | 20 |

### *2. Mite extract*

Bulk extract of cultured *Dermatophagoides farinae* in aqueous form, 1:100 (weight/volume) was purchased from Hollister-Stier Laboratory, U.S.A.

### *3. Other extracts*

Bulk extracts of common inhalant allergens in concentrated aqueous solution, 1:10 (weight/volume) were also purchased from Hollister-Stier Laboratory.

Graduated dilutions of the mite and other extracts were prepared for immunotherapy purposes using a buffered saline solution. The dosage schedules for administering the bacterial vaccine, mite extract and other allergens are shown in Tables 3, 4 and 5, respectively.

## Clinical assessments

To evaluate the efficacy of immunotherapy, we employed the criteria for therapeutic response as proposed by Phanuphak.[5] In order to simplify expression, the degrees of response were also graded according to a 4-point scale varying from 4+ (very effective), 3+ (effective), 2+ (slightly effective) to 1+ (ineffective). Subjects who had scores of 3+ or 4+ were considered to have had an "effective response", whereas those with scores from 1+ to 2+ were considered to have experienced "therapeutic failure" (Table 6).

*Table 3.* Schedule of immunotherapy with bacterial vaccine

| Injection No. | ml | Frequency (weeks) |
|---|---|---|
| 1 | 0.2 | 1 |
| 2 | 0.3 | 1 |
| 3 | 0.4 | 1 |
| 4 | 0.5 | 1 |
| 5 | 0.6 | 1 |
| 6 | 0.7 | 1 |
| 7 | 0.8 | 1 |
| 8 | 0.9 | 1 |
| 9 | 1.0 | 1 |
| 10 | 1.0 | 1 |
| Maintenance | 1.0 | 2 to 4 |

## RESULTS

The medical records of the 72 asthmatic children who fulfilled the criteria were analysed. Twenty-five children received bacterial vaccine: 35, allergenic extract; and 12, both bacterial vaccine and allergenic extract (Table 1).

### Group 1. Bacterial vaccine treatment (Table 7)

All 25 children in this group had a history of previous hospitalisation (in paediatric wards) with the chief complaint being respiratory distress. Their wheezing episodes were always related to fever and respiratory infection. Positive skin test to at least one common inhalant allergen was detected among 42.25 per cent of the 25 patients. However, none of them had any relevant history of asthmatic attack precipitated by allergen exposure. Both the mean age of the patients and the duration of their asthmatic symptoms prior to bacterial vaccine injection were lower in this group than in those of Groups 2 and 3. The mean number of bacterial vaccine injections for this group was

*Table 4.* Schedule of immunotherapy with allergenic extracts (except mite antigen)

| Injection No. | Concentration (w/v) | ml | Frequency (wk) |
|---|---|---|---|
| 1 | 1:1,000 | 0.1 | 1 |
| 2 | | 0.2 | 1 |
| 3 | | 0.4 | 1 |
| 4 | | 0.7 | 1 |
| 5 | 1:100 | 0.1 | 1 |
| 6 | | 0.2 | 1 |
| 7 | | 0.4 | 1 |
| 8 | | 0.7 | 1 |
| 9 | 1:10 | 0.1 | 1 |
| 10 | | 0.2 | 1 |
| Maintenance | | 0.3 | 2 to 4 |

*Table 5.* Schedule of immunotherapy with mite antigen

| Injection No. | Concentration (w/v) | ml | Frequency (wk) |
|---|---|---|---|
| 1 | 1:10,000 | 0.1 | 1 |
| 2 | | 0.2 | 1 |
| 3 | | 0.3 | 1 |
| 4 | | 0.4 | 1 |
| 5 | | 0.5 | 1 |
| 6 | | 0.6 | 1 |
| 7 | | 0.7 | 1 |
| 8 | | 0.8 | 1 |
| 9 | 1: 1,000 | 0.1 | 1 |
| 10 | | 0.2 | 1 |
| Maintenance | | 0.3 | 2 to 4 |

35.92 ± 4.09 (SEM). Evaluation revealed that 88 per cent of the children treated with bacterial vaccine had effective response (3+ to 4+).

**Group 2. Allergenic extract treatment** (Table 8)

All 35 children in this group had a positive skin test to at least one common inhalant allergen. Both their mean age and their history of symptoms prior to immunotherapy were higher than those of Groups 1 and 3. The mean number of injections in this group was 44.51 ± 3.81 (SEM); the rate of effective response, 82.86 per cent. The incidence of allergic diseases among immediate family members was highest in this therapeutic group.

**Group 3. Bacterial vaccine and allergenic extract treatment** (Table 9)

All 12 children in this group had a positive skin test to at least one common aero-allergen; they also had a history of recurrent asthmatic attack related to respiratory tract infection as well as allergen exposure. These children were given both bacterial vaccine and allergenic extract injections simultaneously. The mean number of injections (bacterial vaccine and allergenic extract) for this group was 22.80±3.53 (SEM); the rate of effective response following immunotherapy, 58.33 per cent.

*Table 6.* Criteria for classifying therapeutic response

| Degree of response (score) | Reduction of symptoms | Reduction of medication | Descriptive terms |
|---|---|---|---|
| Very effective (4 +) | >75% | >50% | Attacks either absent or mild; medication can be reduced by more than half. |
| Effective (3 +) | 50 – 74% | 25 – 49% | Attacks clearly reduced (definite subjective improvement) & medication can be reduced by ¼ to ½. |
| Slightly effective (2 +) | 25 – 49% | <25% | Slight or questionable subjective improvement with only a small reduction in medication. |
| Ineffective (1 +) | <25% | 0% | No subjective improvement and no reduction in medication. |

When data on the effectiveness of immunotherapy for the three therapeutic groups were compiled for analysis, the overall rate of effective response was 80.56 per cent (Table 10).

*Table 7.* Therapeutic response: injections of bacterial vaccine (N = 25)

| Score of improvement | No. | % | Effective vs failure (%) |
|---|---|---|---|
| 4+ | 2 | 8 | 88 |
| 3+ | 20 | 80 | |
| 2+ | 3 | 12 | 12 |
| 1+ | 0 | 0 | |

*Table 8.* Therapeutic response: injections of allergen extracts (N = 35)

| Score of improvement | No. | % | Effective vs failure (%) |
|---|---|---|---|
| 4+ | 14 | 40.00 | 82.86 |
| 3+ | 15 | 42.86 | |
| 2+ | 1 | 2.86 | 17.14 |
| 1+ | 5 | 14.28 | |

*Table 9.* Therapeutic response: injections of allergen extracts and bacterial vaccine (N = 12)

| Score of improvement | No. | % | Effective vs failure (%) |
|---|---|---|---|
| 4+ | 0 | 0 | 58.33 |
| 3+ | 7 | 58.33 | |
| 2+ | 3 | 25.00 | 41.67 |
| 1+ | 2 | 16.67 | |

The allergen extracts employed for Groups 2 and 3 are listed in Table 11. Each subject was injected with from one to four different kinds of extract based on the skin test results and the pertinent history of symptoms. The majority of children in this series received housedust and housedust-mite immunotherapy.

## DISCUSSION

Immunotherapy is only a component of allergic treatment but not a substitute for environmental control, appropriate symptomatic medication and clinical supervision.[3]

In reviewing the literature, evidence has been presented that immunotherapy benefits some asthmatic children known to be sensitive to specific allergens. A 20-year follow-up study by Rackemann and Edwards[6] revealed that 75 per cent of asthmatic children given a course of immunotherapy were free of asthma, whereas 75 per cent of untreated children continued to have symptoms that continued into adolescence. A prospective study by Johnstone and Dutton[7] demonstrates the efficacy of immunotherapy versus placebo injection. Seventy per cent of the children receiving immunotherapy compared with only 20 per cent of those receiving placebo injections were free of asthmatic symptoms by the age of 16 years. There are three series of long-term studies on the follow-up of untreated asthmatic children, at least 75 per cent of the children studied continued to have asthmatic symptoms into adolescence.[8-10] In Thailand, data on the long-term prognosis of asthmatic children, whether receiving immunotherapy or not, are currently not available for comparison.

In 1980, we reported that 61.40 per cent of Thai asthmatic adults showed satisfactory beneficial response to aero-allergen immunotherapy.[4] The effective result of allergenic extract immunotherapy in asthmatic children (Group 2) as unveiled in the present series was 82.86 per cent which is a higher effective rate than that of the adults.

Since infection is a non-specific provocative factor in bronchial asthma, opinions are confused about the efficacy of using bacterial vaccine for treatment because of its failure to demonstrate specific circulatory antibodies to bacterial proteins and because of the concomitant inability of using bacterial skin tests for diagnosis. So-called "infectious asthma" is common among children. Some series[11,12] have shown bacterial involvement in about 20 per cent of children first diagnosed as having "asthmatic bronchitis" It has been common practice at various institutes to include bacterial vaccine injections in the treatment of childhood asthma.

The reports of Frankland and Hughes,[13] Helander[14] and Johnstone[15] revealed that bacterial vaccine as compared with placebo injection had not increased the rate of improvement in asthmatic subjects. The study by Mueller and Lanz[16] gave the opposite impression indicating that bacterial vaccine may

*Table 10.* Therapeutic response

| Result | Bact. vaccines | Allergens | Bact. vac. + Allergens | All groups |
|---|---|---|---|---|
| Effective* | 22 (88%) | 29 (82.86%) | 7 (58.33%) | 58 (80.56%) |
| Failure** | 3 (12%) | 6 (17.14%) | 5 (41.67%) | 14 (19.44%) |
| Total | 25 (100%) | 35 (100%) | 12 (100%) | 72 (100%) |

*Effective = 3+ to 4+ improvement scores
**Failure = 1+ to 2+ improvement scores

*Table 11.* Immunotherapy with allergen extracts (N = 47)

| Allergen | No. | % |
|---|---|---|
| Housedust | 44 | 93.62 |
| Housedust-mite | 43 | 91.49 |
| Moulds | 7 | 14.89 |
| Cockroach | 10 | 21.28 |
| Grass pollens | 12 | 25.53 |
| Kapok | 2 | 4.26 |
| Cat epithelium | 1 | 2.13 |

be of value in treating childhood infectious asthma if one properly selects the patients for treatment. They also showed that the largest tolerable dose of antigen is a critical factor in determining the success of therapy. In our series, all children in the bacterial vaccine treatment group had a definite history of repeated episodes of wheezing associated with fever and respiratory tract infection. Despite the fact that 42.25 per cent of the children in this group had positive skin tests to common aero-allergens, they had no record of asthmatic symptoms related to allergen exposure. Treatment with bacterial vaccine injections resulted in a reduction in the number of episodes of respiratory infection as well as a drop in the frequency of wheezy attacks. Stock bacterial vaccines were used empirically at our clinic. There was little justifaction for the use of autogenous vaccines because reported data show that bacterial flora in the respiratory tract of individuals vary markedly from day to day.[17]

The children who received both bacterial vaccine and allergen extract (Group 3) showed definite evidence of atopy as verified by positive skin tests to relevant allergens, but their asthmatic attacks were frequently provoked by allergen exposure as well as respiratory tract infection. This group of patients had a higher rate of "therapeutic failure" than the other groups. However, the duration of immunotherapy was shorter for this group compared with the other two groups; also, the number of subjects was small, so the significance of therapeutic effectiveness is questionable.

The procedure of investigation in our study was a drawback because it involved a retrospective analysis of medical records. We did not have access to a control group of asthmatic children because parents would not give their consent for placebo injections. Also, the duration of immunotherapy and the period of clinical assessment were not particularly defined for each group. A prospective controlled study of the efficacy of immunotherapy would be ideal for future investigation. Data derived from the present study may provide preliminary information on this aspect of treatment. Despite a wide divergence of opinion about the use of bacterial vaccine for treating childhood asthma and the fact that these vaccines have been used in general practice[18] more often than is necessary, they may be effective when used for treating properly selected children.

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