Current Treatment of Childhood Bronchial Asthma Based on the Guidelines

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Abstract: According to “Guidelines for Treatment and Control of Childhood Bronchial Asthma 2000,” guidance on daily living combined with pharmacotherapy is important in the treatment of bronchial asthma. Since atopic asthma is common in childhood, environmental control may be effective if the antigens responsible are identified. In the event of acute attacks, therapeutic drugs should be selected according to the severity of the attack. For symptomatic relief, inhaled bronchodilators should be administered repeatedly for mild attacks, followed by intravenous injection of aminophylline for moderate attacks. In the case of severe attacks, intravenous injection of steroids should be added to the above-described treatment. For long-term control (controllers), anti-inflammatory drugs, such as oral anti-allergic drugs and inhaled steroids, as well as drugs providing symptomatic relief (relievers), such as long-acting bronchodilators, should be administered according to the severity of the disease. Patient education should aim at promotion of self care. The patients should be encouraged to objectively monitor their condition by maintaining diaries and regularly monitoring their peak expiratory flows. It is also important to promote patients’ understanding of the content of the treatment, and to gain their cooperation. Group therapy by admission to camps or facilities may also be effective. At school, where asthmatic children spend a large part of their daily lives, cooperation between the medical staff and educational staff is important.

Key words: Children; Bronchial asthma; Guidelines; Controllers; Relievers

Introduction

In this article, I shall discuss, in brief, the treatment of childhood bronchial asthma (hereinafter referred to as asthma), mainly based on “Guidelines for Treatment and Control of Childhood Bronchial Asthma 2000,” published by the Japanese Society of Pediatric Allergy &
Characteristics of Childhood Asthma

Since atopic asthma, in which past and family history reveal a history of allergy, is common in childhood, the antigens responsible can be identified, based on information collected from detailed history taking as well as the results of specific IgE antibody testing and skin tests. Elimination of the environmental antigens thus identified often leads to symptomatic improvement. In this respect, childhood asthma differs significantly from adult asthma, which is of the non-atopic type in most cases.

The severity of asthmatic attacks is evaluated by the degree of disturbance of daily living and the pulmonary function status, and is classified as mild, moderate or severe (Table 1). When the severity of childhood asthma is compared with that of adult asthma based on the degree of disturbance of daily living, mild attacks in adults are equated to moderate attacks in children.

In childhood asthma, reversibility of airway obstruction is preserved relatively well, and pulmonary functions are almost normal during the intervals between attacks. In contrast, in adults, pulmonary functions are often impaired even in between the attacks, the airway obstruction is less reversible, and bronchodilators tend to be relatively less effective.

Measures against Acute Asthmatic Attacks

It is necessary to explain the measures taken to handle acute asthmatic attacks, as described below, to children who have the ability to understand, as well as to guardians, such as parents, under whose direct care they are placed.

Clinical Immunology in April 2000.

### Table 1 Criteria for Evaluation of the Severity of Attacks

<table>
<thead>
<tr>
<th>Pulmonary function status</th>
<th>Activities of daily life</th>
<th>Matters for reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Play</td>
<td>Sleep</td>
</tr>
<tr>
<td>Mild attack</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Obvious stridor, intercostal retraction and dyspnea are noted.</td>
<td>Rather difficult</td>
<td>Occasionally wake up</td>
</tr>
<tr>
<td>Severe attack</td>
<td>Marked stridor, dyspnea and orthopnea are noted.</td>
<td>Impossible or almost impossible</td>
</tr>
</tbody>
</table>

Note) Signs of respiratory failure (marked dyspnea, cyanosis, diminished breath sounds, and neurological disorder, including diminished reaction to pain, irritability or consciousness disturbance) should be watched for.

Note 2) PEF is expressed as a percentage of the predicted value before inhalation of β₂-agonist, or against the self-best value.

Additional note) The severity of attacks is determined based on the above-described clinical symptoms. In children, the pulmonary function status does not always corroborate the severity of the clinical symptoms. Nonetheless, pulmonary functions are also determined to help in guiding the treatment in the “Guidelines”. At present, standard values for the pulmonary functions are not specified. Therefore, the values presented here are just for the sake of reference. Re-examination of this subject is necessary in the near future. It goes without saying that priority should be accorded to clinical symptoms when judging the severity of the attacks for the purpose of treatment.
1. Measures at home

When mild attacks occur at home, the patient should be advised to relax and practice abdominal breathing, and simple physical therapy, such as encouraging water intake to facilitate expectoration of sputum, should be instituted, before pharmacotherapy is started. Such a calm approach to assess the severity of attacks can help avoid overuse of $\beta_2$-agonists by metered dose inhalers (MDI). However, it should be ensured that there is no delay in the start of appropriate treatment. If oral bronchodilators and inhaled $\beta_2$-agonists as prescribed by the physician do not work, local medical facilities must be consulted.

2. Measures at medical institutions

When mild attacks occurring at home do not respond to the usual treatment, or progress to moderately severe attacks, treatment should be sought at a medical institution. If the condition does not respond to the treatment instituted according to the severity of the attack, treatment recommended for the next higher grade of severity should be commenced. If adequate response is observed, the treatment may be downgraded again.

3. Drugs for treating acute attacks (drugs providing symptomatic relief: relievers)

(Table 2)

Bronchodilators that help in remitting or eliminating the symptoms of acute attacks are called relievers. Differences in the measures adopted to treat acute attacks in children and adults are summarized by Hosoi as follows.2)

1) The severity of attacks in children is equated to the next higher grade of severity in adults.

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Table 2  Treatment of Acute Attacks of Childhood Asthma at Medical Institutions\(^1\)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>$\text{Sp}_{\text{O}_2}$</th>
<th>PEF (School children or older)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild attack</td>
<td>96% or more</td>
<td>Often 60% or more</td>
<td>(Step 1) $\beta_2$-agonists</td>
</tr>
<tr>
<td>Moderate attack</td>
<td>92–95%</td>
<td>Often between 30% and 60%</td>
<td>(Step 1) $\beta_2$-agonist inhalation</td>
</tr>
<tr>
<td>Severe attack</td>
<td>91% or less</td>
<td>Often 30% or less</td>
<td>(Step 1) Intravenous infusion or bolus injection of aminophylline</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>90% or less (With supplemental $\text{O}_2$)</td>
<td>Impossible to determine</td>
<td>Continuation of above-described treatment</td>
</tr>
</tbody>
</table>

Note) PEF is expressed as a percentage of the predicted value before inhalation of $\beta_2$-agonists, or against the self-best value.
2) Oral $\beta_2$-agonists play a greater role in mild cases of childhood asthma (mild intermittent and mild persistent cases), while MDIs are indicated carefully.

3) Oral steroids are used with prudence.

4) Aminophylline infusion and fluid replacement are commonly adopted for the treatment of moderate to severe attacks (Step 2).

5) Subcutaneous injection of Bosmin® (epinephrine) is not adopted as standard therapy.

6) Continuous inhalation of isoproterenol is used in the treatment of very severe attacks.

In the treatment of acute attacks in children, $\beta_2$-agonists are administered orally or by inhalation, and epinephrine is injected subcutaneously in emergent situations. Theophylline is administered orally or aminophylline by intravenous injection, and in some rare cases, inhaled anticholinergic drugs are used.

4. Treatment of acute attacks (Fig. 1)

(1) Treatment of mild attacks

$\beta_2$-agonists are administered by inhalation, and after monitoring the clinical course for 15 minutes, the severity of the attack is evaluated again. If there is some improvement, but the response is still inadequate, the inhalation should be repeated. If the response is not satisfactory, the treatment should be upgraded to that recommended for moderate attacks.

(2) Treatment of moderate attacks

$\beta_2$-agonists are administered first by inhalation. A venous line is secured, and an intravenous injection or drip infusion of 4 to 6 mg/kg body weight of aminophylline, added to maintenance fluid or 20% glucose solution, is administered over 20 minutes or longer. If the response observed is not satisfactory, the $\beta_2$-agonist inhalation should be repeated, and continuous aminophylline infusion must be started. If the latter becomes necessary, the patient should be hospitalized first.

(3) Treatment of severe attacks

In children, great individual differences are noted in the response to treatment, and effective treatment often varies among individuals. $\beta_2$-agonists are administered by inhalation while supplemental oxygen is started, and amino-
Phylline is administered by continuous intravenous infusion. Hydrocortisone at the dose of 5 to 7 mg/kg body weight is administered by slow intravenous injection at intervals of 4 to 6 hours, or prednisolone injection is started at the dose of 1 to 1.5 mg/kg body weight. If no adequate response is noted, continuous isoproterenol inhalation in an oxygen tent is employed. The heart rate, respiratory rate, and oxygen saturation should be closely monitored.

(4) Treatment of respiratory failure

If the pulmonary functions do not improve despite the above measures, endotracheal intubation, assisted ventilation, and artificial ventilation may become necessary.

(5) Indications for hospitalization

Children with acute asthma are hospitalized more frequently than adult patients with acute asthma, so as to ensure that they are treated as quickly and as safely as possible. The indications for hospitalization can be summarized as follows.
1) Severe attacks
2) Moderate attacks that do not respond even after 2 hours of appropriate treatment at the outpatient clinic
3) Moderate attacks lasting more than 24 hours
4) Acute asthma in infants
5) Complications, such as pneumonia, atelectasis, and pneumothorax
6) Inadequate response despite upgradation of long-term control

Measures for Long-term Control of Asthma

1. Drugs used for long-term control (controllers)

The drugs used for long-term control of bronchial asthma are called controllers, because they stabilize respiratory functions and improve the quality of life (QOL) of the subjects. The pharmacotherapy for long-term control of childhood asthma differs from that for adult-onset asthma in the following ways.2)

1) Even if the same terms are used for classification of the severity of symptoms, the same clinical condition is assigned a higher level of severity in children.
2) The intermittent type of adult asthma encompasses the mild intermittent type, mild persistent type, and moderate persistent type of childhood asthma.
3) Basically, the timing of initiation of inhaled steroids is the same in both groups.
4) Treatment from Step 1 to Step 3 is carried out before starting inhaled steroids.
5) Specialist guidance is required for long-term administration of oral steroids.
6) In the treatment of the severe persistent type of asthma, psychosocial factors and long-term hospitalization (institutionalization) should be considered.

(1) Anti-inflammatory drugs

1) Inhaled steroids

Beclomethasone dipropionate is available in two formulations, which deliver 50μg and 100μg per inhaled dose. Fluticasone propionate, which is commonly used in adults, has begun to be used in some older children, but the drug should be administered with caution in children.

2) Sodium cromoglycate (DSCG)

DSCG is available in capsule, liquid, and aerosol formulations. Inhaled DSCG in combination with β2-agonists has been reported to be effective in the treatment of moderate or severe asthma in children.

3) Oral anti-allergic drugs

Oral anti-allergic drugs include inhibitors of the release of chemical mediators, histamine H1-receptor antagonists, and leukotriene antagonists. When administered systemically, they are known to exert effects against allergic diseases in general.

(2) Long-acting bronchodilators

1) Long-acting β2-agonists

In Japan, only short-acting β2-agonists are commercially available, and sufficient information regarding long-acting β2-agonists is lacking.

2) Sustained-release theophylline

The rate of metabolism of theophylline in the liver differs among different individuals,
Moreover, the influences of complications, such as infection, contents of meals, and concomitantly administered drugs should also be taken into consideration. When adequate effects are not obtained after administration of the usual dose, or adverse drug reactions are suspected, the blood concentration of the drug should be determined. Since the drug is known to induce convulsions even at low concentrations in patients with a past history of central nervous system disorder, caution must be exercised during administration of the drug.

Fig. 2 Pharmacotherapy plan for long-term control of childhood asthma

<table>
<thead>
<tr>
<th>Step</th>
<th>Type</th>
<th>Intermittent type</th>
<th>Moderate persistent type</th>
<th>Severe persistent type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Xanthine preparation (RTC)</td>
<td>DSCG + salbutamol, twice daily</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>BDP inhalation, 100 µg to up to 600 µg/day</td>
</tr>
<tr>
<td>Step 2</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>Xanthine preparation (RTC)</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>DSCG + salbutamol, twice daily</td>
</tr>
<tr>
<td>Step 3</td>
<td>Therapeutic blood concentration of aminophylline, 5 to 15 µg/ml</td>
<td>Xanthine preparation (RTC)</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>BDP inhalation, 200 µg to up to 1,200 µg/day</td>
</tr>
<tr>
<td>Step 4</td>
<td>Therapeutic blood concentration of aminophylline, 5 to 15 µg/ml</td>
<td>Xanthine preparation (RTC)</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>DSCG + salbutamol, twice to four times daily</td>
</tr>
<tr>
<td>Step 5</td>
<td>Therapeutic blood concentration of aminophylline, 5 to 15 µg/ml</td>
<td>Xanthine preparation (RTC)</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>BDP inhalation, 200 µg to up to 1,200 µg/day</td>
</tr>
<tr>
<td>Step 6</td>
<td>Therapeutic blood concentration of aminophylline, 5 to 15 µg/ml</td>
<td>Xanthine preparation (RTC)</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>DSCG + salbutamol, four times daily</td>
</tr>
<tr>
<td>Step 7</td>
<td>Therapeutic blood concentration of aminophylline, 5 to 15 µg/ml</td>
<td>Xanthine preparation (RTC)</td>
<td>Anti-allergic drugs, oral/DSCG</td>
<td>BDP inhalation, 200 µg to up to 1,200 µg/day</td>
</tr>
</tbody>
</table>

Note 1) BDP: beclomethasone dipropionate  RTC: round the clock  DSCG: disodium cromoglycate

Note 2) When multiple drugs are used concomitantly, it is important to ensure that ineffective drugs are eliminated in each patient, and that more than the required number of drugs are not administered.

Note 3) The efficacy of oral anti-allergic drugs in combination with leukotriene antagonists in severe persistent asthma is still unknown.
2. Pharmacotherapy for long-term control
(Fig. 2)

(1) Intermittent asthma
Drugs are administered according to the severity of the attacks. Administration of anti-allergic drugs should be started immediately, depending on the symptoms.

Inhaled DSCG or β₂-agonists should be used for the prevention of exercise-induced asthma.

(2) Mild persistent asthma
Round-the-clock (RTC) administration of theophylline is required. In addition, single use of oral or inhaled β₂-agonists is recommended.

(3) Moderate persistent asthma
Inhaled DSCG in combination with β₂-agonists is administered regularly. When oral or adhesive β₂-agonists are used regularly, they should be discontinued as the symptoms improve. If satisfactory response is obtained, combined inhalation of DSCG and β₂-agonists and RTC theophylline should be continued. When the treatment is ineffective, or only partially effective, inhaled beclomethasone should be used concomitantly. As to the standard dose, 100 to 150μg per dose should be administered two to four times a day using a spacer, and the patients should be advised to gargle after the inhalation.

(4) Severe persistent asthma
Beclomethasone dipropionate is administered at the dose of 100 to 300μg per dose two to four times a day, and the maximum daily dose should not exceed 1,200μg. Regular combined inhalation of a mixture of DSCG and β₂-agonists, oral β₂-agonists, and RTC theophylline is recommended.

When the condition does not respond to the above-described treatment and the patient’s daily life is disturbed, the patient is referred to a specialist, or on the basis of consultation with a specialist, the dose of inhaled beclomethasone is increased, or 5 to 10mg of prednisolone are administered once daily in the morning for up to one week.

If the condition still does not respond to these treatments, the patient should be admitted to a specialized medical institution for long-term hospitalization, while arranging for the children to receive education, possibly at a school for children with the disease.

Patient Education
Patient education regarding childhood asthma should be provided to both patients and their guardians, depending on the degree of understanding. In the case of infants, in particular, guardian education is essential. On the other hand, in the case of adolescents, the patients gradually come to play the main role in treatment, but often they are not sure at this age whether they should still be dependent on their parents or can act independently, and may become somewhat confused about their treatment. Since patients in their adolescence do not visit the hospital very often, the physicians should actively engage themselves in the task of educating this group of patients.

1. Promotion of self care
We have established the following goals to promote objective understanding by the patients of their condition.
1) Maintenance of an asthmatic diary.
2) Monitoring of peak flow rate.
3) Acquire knowledge and skills regarding how to use the drugs, the effects of the drugs, and adverse drug reactions.

2. Training
During the growing stage, physical training, while ensuring precautions to prevent exercise-induced asthma, is useful in improving the children’s QOL. Instructions are given so that children will be able to enjoy swimming, which is considered relatively less likely to induce attacks, as well as various other types of sports.

3. Group therapy
Group therapy plays an educational role by providing opportunities for developing interpersonal skills, and asthmatic children can learn to help each other through such activities as
summer camps.

4. Liaison between school and medical institution

The communication between the medical staff and educational staff to exchange information is expected to assume increasing importance, so that the children can play active roles in school, where they lead a large part of their daily lives.

Conclusion

Thus, as is evident from the above, “Guidelines for Treatment and Control of Childhood Bronchial Asthma 2000” comprehensively covers not only pharmacotherapy for the control of asthma, but also provides guidance on daily living. I would be greatly pleased if physicians found the “Guidelines” useful in their daily medical practice.

REFERENCES
