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REVIEW ARTICLE

The 2002 Japanese Pediatric Guideline for the Treatment and Management of Asthma

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ABSTRACT

The Japanese Pediatric Asthma Guideline was revised in November of 2002. The guideline, the JPGL2002, has several characteristics different from other asthma guidelines. One of the important differences is the classification of asthma severity ; the frequencies of asthma symptoms in Steps 2, 3 and 4 of the JPGL2002 are similar to those of Steps 1, 2 and 3, respectively, of the Global Initiative for Asthma (GINA). In the JPGL2002, infantile asthma is classified separately, considering the necessity of special concern due to the characteristic features, and three different protocols for long-term management are provided according to the patients' ages : younger than 2 years, 2 to 5 years, and older than 5 years. For patients older than 5 years, inhaled glucocorticosteroid (ICS) is recommended for asthma with symptoms more than once a month but less than once a week (Step 2). The GINA classifies this as Step 1 and does not recommend the use of ICS. The recommended dosages of ICS for Steps 3 and 4 of the JPGL2002 are, however, smaller than those for Steps 2 and 3, respectively, of the GINA. It should be clarified in future studies whether or not such a use of ICS can lead to earlier and more frequent remission of asthma, hopefully resulting in the asthma being outgrown.

KEY WORDS

asthma, children, guideline, Japan

INTRODUCTION

The Japanese Pediatric Guideline for the Treatment and Management of Asthma was revised in November of 2002 by the 2002 Asthma Guideline Committee of the Japanese Society of Pediatric Allergy and Clinical Immunology. This revised guideline[1] (JPGL2002) shares the same concept with other asthma guidelines such as the Global Initiative for Asthma 2002[2] and 2003[3] (GINA) in the definition of asthma, the airway pathology in and mechanisms of asthma, and the diagnosis of asthma, but has several important differences from other guidelines, especially in the classification of the severity of and medications for asthma. In this review, mainly these characteristic features of the JPGL2002 will be discussed.

CLASSIFICATION OF ASTHMA SEVERITY IN THE JPGL2002

The JPGL2002 provides criteria for classification of asthma severity different from those of the GINA. As shown in Figure 1, the JPGL2002 classifies asthma severity into 4 steps according to the clinical features before treatment : intermittent asthma (Step 1), mild persistent asthma (Step 2), moderate persistent asthma (Step 3) and severe persistent asthma (Step 4). This classification is similar to that of the GINA, but the JPGL2002 divides Step 4 into Step 4−1 and Step 4−2, the latter including severe persistent asthma which is resistant to appropriate medications for Step 4−1.

However, the frequency of asthma symptoms and other features of each step of the JPGL2002 are quite different from those of the GINA ; those of each step of the JPGL2002 are milder than those of the GINA. Step 2 is included in Step 1 in the GINA ; Steps 3 and 4 are very similar to Steps 2 and 3, respectively, of the GINA. The 2002 Japanese Pediatric Asthma Guideline Committee has adopted the JPGL2002 classification because it seems more suitable for the classifica-

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JPGL2002	GINA
STEP 1: Intermittent	
Seasonal cough and slight wheeze several times a year Exacerbations with dyspnea with good response to β_2-agonist may occur	Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month Normal lung function between episodes
STEP 2: Mild Persistent	
Cough and slight wheeze more than once a month but less than once a week Brief exacerbation	Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month Normal lung function between episodes
STEP 3: Moderate Persistent	
Cough and slight wheeze more than once a week but less than once a day Exacerbations may affect activity and sleep	Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting β_2-agonist Slightly decreased lung function*
STEP 4: Severe Persistent	
<STEP 4-1> Cough and wheeze daily Moderate to severe exacerbations affecting activity and sleep once to twice a week <STEP 4-2> Same as STEP 4-1 in spite of receiving appropriate medications against STEP 4-1	Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities Decreased lung function**

Fig. 1 Classification of asthma severity by clinical features before treatment in the JPGL2002 and GINA2002.
*60% < FEV_1 < 80% predicted or 60% < PEF < 80% of personal best
**FEV_1 ≦ 60% predicted or PEF ≦ 60% of personal best

tion of asthma severity in childhood ; the clinical features of each step of the GINA seem too severe for the clinical features of childhood asthma. Asthmatic children who have symptoms more than once a month but less than once a week might be better considered as having mild persistent asthma (Step 2), and asthmatic children with frequent symptoms such as daily symptoms and nocturnal symptoms more than once a week (Step 3 of the GINA) are rare in Japan and thus might be better considered as severe persistent asthma (Step 4).

The JPGL2002 also provides the classification of asthma severity defined by daily medication regimen and response to the treatmen(Fig. 2), which is similar to that of the GINA.

MEDICATIONS

Another important characteristic of the JPGL2002 is the medication protocol for each step of asthma, especially for long-term management. The JPGL2002 provides three different recommendations for long-term asthma management according to the patients' ages : for patients younger than 2 years, 2 to 5 years, and older than 5 years(Figs. 3–5). A separate chapter for infantile asthma is provided because it has many characteristics different from those of older children and needs special consideration. In each age group, the recommended medications are defined according to the levels of asthma severity.

INHALED GLUCOCORTICOSTEROID

Inhaled glucocorticosteroid (ICS) is defined as the fundamental medicine for persistent asthma patients in all three age groups, but the recommended dosages for patients are different according to their ages. ICS is recommended as the first-choice medicine for patients older than 5 years with mild persistent or severer asthma (Steps 2 to 4), whereas for patients at the younger ages, ICS is only recommended as the first-choice medicine for moderate and severe persistent asthma (Steps 3 and 4). This is because a suitable formulation of ICS for young children, such as the liquid type ICS, is not available in Japan and because Steps 2, 3, and 4 of the JPGL2002 are comparable to Steps 1, 2 and 3, respectively, of the GINA, as mentioned above.

Thus, in the JPGL2002, ICS is recommended for less severe asthma patients older than 5 years, whereas the recommendation for younger patients is very similar to the recommendation in the GINA. In

	Current Treatment Step			
	Step 1 Intermittent	Step 2 Mild persistent	Step 3 Moderate persistent	Step 4 Severe persistent
Severity on Current Therapy	Level of Severity			
Step 1 Intermittent	Intermittent (Step 1)	Mild persistent (Step 2)	Moderate persistent (Step 3)	Severe persistent (Step 4-1)
Step 2 Mild persistent	Mild persistent (Step 2)	Moderate persistent (Step 3)	Severe persistent (Step 4-1)	Severe persistent (Step 4-1)
Step 3 Moderate persistent	Moderate persistent (Step 3)	Severe persistent (Step 4-1)	Severe persistent (Step 4-1)	Severe persistent (Step 4-1)
Step 4-1 Severe persistent	Severe persistent (Step 4-1)	Severe persistent (Step 4-1)	Severe persistent (Step 4-1)	Severe persistent (Step 4-2)

Fig. 2 Classification of asthma severity by daily medication regimen and response to treatment

No daily controller medications necessary Anti-allergic drug might be considered if needed	Oral anti-allergic drug plus one or more of the following if needed: ・DSCG + β_2 agonist** inhalation (twice a day) ・Sustained-release theophylline# ICS (−100 μg/day)* if needed	ICS (−200 μg/day)* plus one or more of the following if needed: ・Oral anti-allergic drug ・DSCG + β_2 agonist** inhalation (twice a day) ・Sustained-release theophylline# ・Oral β_2 agonist or sustained-release terbutaline (tape) before sleep**	ICS (300−400 μg/day)* plus one or more of the following: ・Leukotriene modifier ・DSCG + β_2 agonist** inhalation (twice a day) ・Sustained-release theophylline# ・Oral β_2 agonist or sustained-release terbutaline (tape) before sleep**
Step 1 Intermittent	Step 2 Mild Persistent	Step 3 Moderate Persistent	Step 4-1## Severe Persistent

Fig. 3 Recommended medications by level of severity: <2 y.o.

*CFC-BDP or equivalent

** Regular administration of β_2 agonist should be ceased when asthma symptoms are controlled.

#serum concentration 5−10 μg/m

##If asthma is not controlled, more therapy including oral glucocorticosteroid administration should be considered as Step 4-2 by specialists for pediatric allergy.

more than 60% of Japanese children with asthma, the first symptoms are seen within the first 4 years of life, suggesting that many asthma patients older than 5 years have already been suffering from asthma for several years, and these patients categorized as having persistent asthma, even mild persistent asthma as defined by the JPGL 2002, need effective anti-inflammatory medicines in order to prevent further development of airway remodeling and to achieve earlier outgrowing of the asthma.

It should be mentioned that the JPGL2002 recommends smaller dosages of ICS for younger children. Although the GINA reduced the recommendation dosages of ICS in 2003 (GINA2003), the recommendation dosages of the JPGL2002 are still smaller than those of the GINA2003 for children at all ages. Other medicines such as leukotriene modifiers and sustained-release theophylline are recommended to be added instead of using increased dosages of ICS when the recommended dosage of ICS is insufficient to control asthma symptoms. Because Steps 2 to 4 of the JPGL2002 correspond more closely to milder asthma patients than those of the GINA, and because high dosages of ICS may show some systemic side effects, we think these smaller dosages may be better. However, there is no definitive evidence to show that the smaller dosages of ICS are sufficient to control the allergic inflammation of asthma of younger children, and therefore these recommended dosages of ICS in the JPGL2002 should be justified by further clinical study.

β_2-AGONISTS

In the JPGL2002, β_2-agonists are defined more clearly as relievers but not as controllers. For longer use, they should be used with ICS and/or other control-

No daily controller medications necessary Anti-allergic drugs might be considered if needed	One or more of the following: ・DSCG + β_2 agonist** inhalation (twice a day) ・Sustained-release theophylline# ICS (−200 μg/day)* if needed	ICS (200–300 μg/day)* plus one or more of the following if needed: ・Oral anti-allergic drug ・DSCG + β_2 agonist** inhalation (twice a day) ・Sustained-release theophylline# ・Oral β_2 agonist or sustained-release terbutaline (tape) before sleep**	ICS (300–600 μg/day)* plus one or more of the following: ・Leukotriene modifier ・DSCG + β_2 agonist** inhalation (twice a day) ・Sustained-release theophylline# ・Oral β_2 agonist or sustained-release terbutaline (tape) before sleep**
Step 1 Intermittent	Step 2 Mild Persistent	Step 3 Moderate Persistent	Step 4-1## Severe Persistent

Fig. 4 Recommended medications by level of severity: 2–5 y.o.
*CFC-BDP or equivalent
**Regular administration of β_2 agonist should be ceased when asthma symptoms are controlled.
#serum concentration 5–10 μg/ml
##If asthma is not controlled, more therapy including oral glucocorticosteroid administration should be considered as Step 4-2 by specialists for pediatric allergy.

No daily controller medications necessary Anti-allergic drugs might be considered if needed	ICS (−200 μg/day)* or One or more of the following: ・Oral anti-allergic drug ・DSCG inhalation** ・Sustained-release theophylline#	ICS (200–400 μg/day)* plus one or more of the following if needed: ・Oral anti-allergic drug ・DSCG inhalation** ・Sustained-release theophylline#	ICS (400–800 μg/day)* plus one or more of the following: ・Leukotriene modifier ・DSCG inhalation** ・Sustained-release theophylline# ・Long acting inhaled β_2 agonist or sustained-release terbutaline (tape)
Step 1 Intermittent	Step 2 Mild Persistent	Step 3 Moderate Persistent	Step 4-1## Severe Persistent

Fig. 5 Recommended medications by level of severity: >5 y.o.
*CFC-BDP or equivalent
**When β_2 agonist is inhaled in combination with DSCG, β_2 agonist should be deleted when asthma symptoms are controlled.
#serum concentration 5–10 μg/ml
##If asthma is not controlled, more therapy including oral glucocorticosteroid administration should be considered as Step 4-2 by specialists for pediatric allergy.

lers until asthma control is achieved, and after asthma is controlled, β_2-agonists should be ceased as early as possible. However, there might be cases when β_2-agonists are necessary for considerably long periods until asthma is controlled, especially in infants and young children, because we have no formulation of ICS suitable for the very young in Japan. In such cases, the use of sustained-release terbutaline (tape) before sleep might be valuable for preventing nocturnal symptoms. Because we did not have sufficient experience with long-acting β_2-agonists such as salmeterol for children in Japan in 2002, they would need to be described and evaluated more clearly in the next revision of the JPGL.

In the former JPGL (JPGL2000), regular inhalation of disodium cromoglycate (DSCG) with small amounts (0.05–0.1 ml) of salbutamol using a jet nebulizer was recommended for patients with moderate and severe persistent asthma. This medication has been shown to be very effective for controlling asthma symptoms of such patients[4] and has become very familiar in Japan. However, this medication may be insufficient to control allergic inflammations and remodeling of the lungs, at least in some cases. The good effectiveness of regular inhalation of DSCG + salbutamol for controlling asthma symptoms might

lead to the misunderstanding that allergic inflammation of the lungs is also well controlled in such patients. Therefore, in the JPGL2002, regular inhalation of DSCG + salbutamol is recommended until asthma symptoms are controlled. When control is achieved, inhalation of DSCG alone will be continued. If exacerbations then recur and asthma control cannot be achieved without the addition of salbutamol, ICS should be used instead of the extended regular use of DSCG + salbutamol.

THEOPHYLLINE

Sustained-release theophylline is listed as a controller in the JPGL2002 with a lower recommended serum concentration (5–10μg/ml), which hopefully reduces the possible side effects while keeping its anti-inflammatory effect. To help achieve the safe and desired effect of sustained-release theophylline, the administration dosages are listed very precisely.

Intravenous administration of theophylline is also listed in the JPGL2002 as a medication for acute exacerbation but with arguments against its effectiveness and warning of possible undesirable effects due to intoxication.

TOPICS FOR THE NEXT REVISION OF THE JPGL

The JPGL2002 first recommends ICS for asthmatic children older than 5 years with symptoms more than once a month but less than once a week (Step 2, which is included in Step 1 in the GINA). The JPGL 2002 also recommends smaller dosages of ICS with or without other controllers. It should be examined whether or not the medication protocols of the JPGL 2002 can lead to earlier and more frequent remission and outgrowing of asthma.

Another important point for revision might be the application of intravenously administered theophylline for acute exacerbation. The limited effectiveness and relatively high risk of intoxication may raise arguments against its being adopted for the asthma guideline used by all physicians.

Although the JPGL2002 does not mention much regarding long-acting β_2-agonists such as salmeterol, the GINA recommends it as a controller for moderate and severe persistent asthma when used in combination with ICS. In the next revision of the JPGL, the same evaluation may be adopted although there are only a few asthmatic children who need regular use of a long-acting β_2-agonist with ICS for a long period. It does seem possible to evaluate long-acting β_2-agonists, just as one would the sustained-release terbutaline, as a supplemental medicine to ICS until asthma symptoms are controlled.

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