

Pediatric Asthma Management in China: Current and Future Challenges

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Abstract The purpose of this report was to review the state of asthma diagnosis and treatment in China and to examine challenges in achieving earlier diagnosis and treatment. The prevalence of asthma in children in China has increased over past decades, and data published in 2013 indicated a prevalence of 3.0% in children aged 0–14 years. Although this prevalence has increased, the percentage of children with acute asthma attacks decreased from 86% in 2000 to 77% in 2010, and the frequency of hospitalizations for asthma attacks decreased from 54.0 to 47%. These decreases are attributed to aggressive promotion of the Global Initiative for Asthma (GINA) protocol and updated Chinese guidelines for the prevention and treatment of asthma in children. The use of inhaled corticosteroids increased and that of systemic corticosteroids decreased between 2000 and 2010. Despite these advances, a number of issues remain to be addressed. Parents lack basic knowledge of asthma and fear the use of corticosteroids. Physician education regarding the diagnosis of asthma in children aged <6 years is lacking. Patients require training in the administration of inhaled corticosteroids and control of environmental triggers. The Chinese national guidelines for childhood asthma have been updated, but implementation remains a real challenge.

Key Points

Although the prevalence of childhood asthma has increased in China, both the percentage of children with acute asthma attacks and the frequency of hospitalizations for asthma attacks have decreased, as has the use of systemic corticosteroids.

Decreases in acute asthma exacerbations and hospitalizations can in part be attributed to aggressive promotion of the Global Initiative for Asthma (GINA) protocol and updated Chinese guidelines for the prevention and treatment of asthma in children.

Areas needing improvement are parents' lack of basic knowledge about asthma and fear of corticosteroid use, physician education about the diagnosis of asthma in children aged <6 years, and the training of patients on the correct administration of inhaled corticosteroids and control of environmental triggers.

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1 Introduction

Asthma is a common chronic inflammatory disorder in children and one of the greatest burdens on healthcare resources in China. The prevalence of asthma among children in China has increased significantly in past decades. Since 1990, we have conducted three national epidemiological surveys of childhood asthma in urban areas of China at 10-year intervals. Data from the surveys indicate

that the prevalence of asthma in children increased by almost 50% every 10 years [1–3]. The latest data, published in 2013, indicated a total prevalence of asthma in children aged 0–14 years in Chinese cities of 3.0% [3]. The rates were highest in eastern China (4.2%) and lowest in northeast China (2.0%) [3]. The city with the highest rate was Shanghai (7.6%) [3].

Despite the increase in prevalence, data from the 2000–2010 survey datasets indicated that the percentage of children with acute asthma attacks in the previous year of the last survey decreased from 86 to 77%, and the frequency of hospitalizations for asthma attacks decreased from 54.0 to 47% [4]. These findings suggest that clinician's knowledge about asthma and its early diagnosis improved with the long-term use of the Global Initiative for Asthma (GINA) protocol [5] and the updated 2016 Chinese *Guideline for the Diagnosis and Prevention of Bronchial Asthma in Children* [6], both of which have been aggressively promoted in China.

Thus, the purpose of this report was to review the state of asthma diagnosis and treatment in China and to examine the challenges in achieving earlier diagnosis and treatment.

2 Asthma in China

2.1 Asthma Control Rates

Asthma control remains a significant challenge in the pediatric age range, as seen in numerous recent studies, and this can have important consequences for health and education. For example, Wong et al. [7] found the disease was poorly controlled in 53% of children. On the other hand, a cross-sectional survey by Xiang et al. [8] evaluated asthma control among Chinese pediatric patients and found that asthma was uncontrolled in 20% of subjects, and that treatment adherence (44%) and allergic rhinitis (23%) were the most significant risk factors for uncontrolled asthma. These studies used the Chinese guideline [6] definitions of “controlled,” “partially controlled,” and “uncontrolled,” as follows. Controlled asthma was defined as (1) daytime symptoms two or fewer times per week, (2) no nocturnal symptoms, (3) no activity limitations, and (4) requiring a relief agent two or fewer times per week. Partially controlled asthma was defined as one of the following: (1) daytime symptoms more than twice a week, (2) at least one episode of activity limitation per week, (3) nocturnal symptoms, or (4) requirement of a relief agent more than twice a week. Uncontrolled asthma was defined as the existence of at least three or more features of partially controlled asthma in a week. Xiang et al. [8] also reported that disease duration ≥ 1.5 years and having first-degree relatives with allergic rhinitis were risk factors

associated with uncontrolled asthma. The difference in the rate of uncontrolled asthma between the two studies is likely due to the different study locations and durations. The study by Wong et al. [7] was a cross-sectional community-based survey conducted between September and December 2006 in 12 geographic areas: two major urban areas in mainland China, Hong Kong, India, Indonesia, Malaysia, the Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam. The study by Xiang et al. [8] was conducted between October 2012 and June 2013 and included patients from 42 tertiary hospitals across all regions of mainland China except Tibet.

The most recent survey found that 53% of children had uncontrolled asthma and 44% had partially controlled asthma and that asthma symptoms were controlled in only 2.5% of children [3]. The study also found that demand for urgent healthcare services (52%) and use of short-acting beta-agonists (55%) was high. A study of asthma control among almost 3000 children aged 0–14 years in 29 Chinese cities found that 66% had experienced an asthma attack within the 12 months before the study. Of these children, only 27% had visited the emergency department and 16% had been hospitalized for treatment [9].

2.2 Factors Affecting Asthma Control

A number of factors have been identified that affect the control of asthma in Chinese children. Zhao et al. [10] examined the knowledge, attitudes, and practices of parents of children with asthma to analyze how knowledge and attitudes related to practices. The authors found that 64% of parents knew asthma was a chronic allergen-induced inflammatory airway disease, 85% believed their children could participate in sports if their asthma was under control, and—of these parents—60% believed children with asthma could exercise as much as children without asthma. However, 34% of parents would only allow their children to participate in minor sports. Interestingly, 81% of parents consulted with physicians for minor symptoms, suggesting a poor basic knowledge of asthma among parents. Knowledge and attitudes were positively associated with pulmonary function testing, regular physician visits, monitoring with a peak flow meter and the Childhood Asthma Control Test (C-ACT), avoidance of asthma triggers, using an inhaled β_2 receptor agonist, and adherence to a medication regimen. Attitudes were also associated with allergen testing. These findings indicated that improved asthma knowledge and attitudes can result in better monitoring of a child's asthma symptoms and adherence to their medication regimen. Therefore, we suggest that the most important component of childhood asthma treatment is parent education to improve their asthma management practices.

Overall, treatment adherence and the diagnosis and treatment of allergic rhinitis should be improved to increase the level of asthma control in Chinese children, and practical tools such as the ACT or C-ACT may help clinicians assess asthma control and facilitate adjustment of asthma medications [7, 8].

3 Diagnosis of Asthma in China

The updated Chinese *Guidelines for the Diagnosis and Prevention of Bronchial Asthma in Children* provide practical and reliable recommendations for Chinese clinicians [6]. In China, a suspected diagnosis of asthma is typically confirmed via physical examination and review of history, records and test results [6]. Although approximately one-third of children with asthma are either not diagnosed at an early disease stage or are misdiagnosed, the frequency of a correct asthma diagnosis prior to the 2010 survey was 65%. In 2010, it had significantly increased to 71%, which was attributed to adherence to recommendations from GINA and the Chinese guidelines [4]. In addition, as mentioned, the rate of early diagnosis (within 1 year of symptom onset) was 51% in 2000 and 79% in 2010 [4].

A confident diagnosis of asthma in children aged ≤ 5 years can be difficult because episodic respiratory symptoms such as wheezing and cough are also common in children without asthma in this age group. Pediatric asthma usually starts before the age of 3 years, and—among children with persistent asthma—lung function damage often occurs before they reach school age. “Pre-school wheeze” can affect around one-third of children between the ages of 1 and 6 years, and—although asthma is a frequent cause—other factors may be involved. Therefore, identifying children who have the potential to develop persistent asthma and initiating treatment early is a priority. However, no specific testing or indicators are available to confirm a diagnosis of pediatric asthma in pre-school children. For children without typical clinical features, the frequency and severity of symptoms and exacerbations and the existence of asthma risk factors are the main considerations when determining the likelihood of persistent asthma developing and whether long-term controller treatment is necessary. The Chinese guidelines [6] provide recommendations for the diagnosis of asthma in young children. The following features are highly suggestive of an asthma diagnosis in wheezing children: (1) wheezing that occurs more frequently than once a month, (2) exercise-induced cough or wheeze, (3) an intermittent nocturnal cough that is not caused by viral infection, (4) continued wheezing after the age of 3 years, (5) anti-asthmatic treatment is effective and symptoms recur after treatment discontinuation [6].

A prospective multicenter study was recently initiated in China to establish a diagnostic system for asthma in children aged < 6 years; it will be completed in the fourth quarter of 2018 [11]. This national study considered the widely used diagnostic criteria for asthma in young children and babies and developed a new scoring system. In the pilot study, the following variables were used in the diagnostic criteria for asthma in young children and babies: accumulative frequency of asthma ≥ 4 times per year, reversible airflow limitation, definite wheezing during inspiration, allergic rhinitis or allergic dermatitis, a history of allergy in first-degree relatives, testing for in vivo or in vitro antigens, and proportion of blood eosinophils $\geq 3\%$. Further studies, especially multicenter clinical studies, are needed to confirm the clinical value of these variables in the diagnosis of asthma in young children.

If asthma is suspected, tentative treatment can be initiated according to the protocol for asthma treatment, and response to therapy should be assessed regularly. If the child responds well to treatment, a diagnosis of asthma can be established. On the other hand, if there is no obvious improvement after 4–8 weeks of therapy, treatment should be discontinued and the child’s symptoms re-evaluated. Ultimately, most preschool children with asthma have a good prognosis and outgrow their symptoms. Children should be regularly (every 3–6 months) re-evaluated to determine whether treatment should be continued.

4 Management of Asthma in Chinese Children

4.1 General Guidelines and Environmental Triggers

The updated Chinese guidelines with respect to pharmacological management are similar to those of GINA. However, the updated Chinese guidelines do not include detailed descriptions of asthma pathophysiology. Instead, they focus on the two clinical features required for diagnosis: respiratory symptoms and variable expiratory airflow limitation. They also emphasize the heterogeneity of asthma and multiple clinical phenotypes, which can help establish an individualized management approach.

The most common triggers for asthma exacerbations were respiratory tract infections (87.9%) and changes in weather/inhaling cold air (5.5%) [3]. Another study revealed a high prevalence of human rhinoviruses (HRVs) in children with asthma in China, regardless of clinical status [12]. HRV-C was the dominant species and may be one of the key factors in the association of HRVs with asthma. A recent study indicated that rhinovirus-triggered asthma exacerbations became more severe as the degree of sensitization to dust mite allergens increased [13]. Further studies are needed to understand the relationship between

HRV serotype and the severity of illness or specific disease, especially with asthma.

Non-pharmacological interventions, such as patient education and avoiding allergens and triggers, remain important tools in the long-term management of pediatric asthma. Many triggers can influence asthma control, including respiratory tract infection, allergens, food, and changes in climate. Xu et al. [14] reported that respiratory tract infection was the most common trigger of asthma attacks (85%), with other common causes including cold air, house dust, exercise, fish and shrimp, and pollen. The study also found that some triggers were more common in children aged ≥ 6 years than in those aged ≤ 5 years, including exercise, emotional changes, house dust, pollen, renovation work in the home, mosquito repellent, and pets.

4.2 Pharmacological Treatment

The main pathological feature of bronchial asthma is chronic inflammation of the airway. In China [6], treatment goals include symptom control, improving lung function, and minimizing future risks (acute exacerbation and death) and treatment-related adverse effects. Individualized pharmacological management based on symptom control should be started as early as possible after diagnosis.

To prevent the progression of irreversible airway remodeling, inflammation needs to be controlled early. Although the proportion of children with asthma receiving long-term medical control has increased over the last 10 years [4], both under- and over-treatment still occur [15]. Inhaled corticosteroids (ICS) currently represent the most effective method for controlling inflammation, and the Chinese guidelines recommend them as the primary therapeutic agents for asthma [6]. Early initial treatment with low-dose ICS more effectively improved lung function than ICS started 2–4 years after asthma diagnosis [16]. A recent study [14] found that about 61% of patients received combination therapies, with ICS plus a long-acting β -adrenoceptor agonist (LABA) the most common combination, followed by ICS plus a leukotriene receptor antagonist (LTRA) [14]. About one-third of the patients used monotherapies; ICS was the most frequently used, and other medical treatments included antibiotics and traditional Chinese medicine. Another study reported that 46% of patients used an ICS plus a LABA, and 44% used some type of traditional Chinese medicine [14]. Traditional Chinese medical treatments for asthma include moxibustion, acupuncture, and a number of herbal medications such as Mai Men Dong Tang and Ding Chuan Tang [17]. There is also evidence that massage therapy can improve the symptoms of children with asthma [18]. Interestingly, the third epidemiological survey on asthma in children revealed that the number of children with asthma using an

ICS had increased from 36.3% in 2000 to 61.7% in 2010 [4]. Furthermore, the proportion of children with asthma using systemic corticosteroids had decreased from 74% to 39% over the same period [4].

4.3 Barriers to Medical Treatment

More children than adults have poor inhaler technique. The need for proper training and devices to use ICS/ICS plus LABA, especially in small children, may contribute to their lack of use in some children. The available tools for corticosteroid inhalation include pressurized metered dose inhalers (pMDIs), breath-activated aerosol inhaler, dry powder inhaler, and oxygen/air-driven aerosol inhalers. Children have difficulty learning to use a pMDI, and an additional storage tank is needed because it may increase the deposition of the drug in the lung and reduce the residual drug in the mouth. A dry powder inhaler requires a high inhalation rate and is only used in children aged >5 years and after extensive training. An aerosol inhaler can be used by children of any age, but the amount of drug deposited in the lung is difficult to determine. Thus, the selection of inhaler should be based on age, asthma severity, and technical proficiency, and detailed guidance should be provided.

A study conducted in 220 children with asthma found that only 74 used ICS correctly [19]. Although age, sex, years using ICS, and mother's education level did not influence the correct use of ICS, guidance from medical staff significantly affected correct use [19]. Many parents refuse to use corticosteroids, even ICS, for fear of potential adverse effects. A study of ICS use in children found that 67% of parents worried about negative effects on their child's growth, 41% worried about drug dependence, and 24% worried about potential harm to their child's intelligence [20]. Xiang et al. [8] reported that 11% of children with asthma were not taking any medication for asthma control, indicating insufficient treatment was the most significant factor for uncontrolled asthma. Most of the patients who had not used medical therapy for asthma control during the previous 4 weeks stopped taking the medication on their own because they thought their asthma symptoms had been sufficiently treated. This finding suggests that the children and their parents may overestimate the level of asthma control they had achieved.

5 Discussion and Conclusions

Although the rate of asthma detection in Chinese children has increased significantly in the last 10 years, about 30% of children with asthma are not diagnosed in a timely manner, suggesting that under-diagnosis remains an

important problem in the management of asthma in Chinese children. This lack is likely because asthma diagnosis is primarily based on clinical manifestations; although reliable quantitative indicators for the diagnosis of asthma, especially in young children, are available, physician knowledge of these is insufficient [15].

The Chinese guidelines for the diagnosis and management of asthma in children that were published in 2016 [6] provide recommendations using quantitative indicators for the diagnosis of asthma in children, especially young children, as well as clinical characteristics and symptoms. The guidelines emphasize that not all children with wheeze have asthma, and clinicians should pay attention to the frequency and severity of wheezing in the clinical assessment of wheezing in children aged <6 years, especially stressing the value of anti-asthma drugs in the diagnosis of asthma. The new guidelines also highlight that bronchial asthma is a heterogeneous disease characterized by chronic airway inflammation and airway hyper-responsiveness. The guidelines focus on the two clinical features required for diagnosis: respiratory symptoms and variable expiratory airflow limitation. Emphasis is placed on the heterogeneity of asthma and the multiple clinical phenotypes to establish an individualized management approach.

However, the relationship between pathophysiology, clinical phenotypes, and treatment response remains unclear. Since there is a large overlap between different phenotypes, and the rate of interchange between two different phenotypes within 1 year can be as high as 40%, current descriptions of clinical phenotypes are of limited use. The Chinese guideline avoids detailed descriptions of pathophysiology and phenotypes and recommends that physicians do not use them as a basis for diagnoses and treatment.

The new guideline for the diagnosis and treatment of asthma in children in China defines an asthma predictive index in children and provides several potential scales for the assessment of asthma in children. However, these scales are not included in the diagnostic criteria for asthma in children; they are only recommended for the assessment of asthma risk as their clinical significance requires further confirmation. We believe prospective studies are needed to more accurately classify asthma phenotype in Chinese children and determine a precise asthma predictive index. Although some problems with the diagnosis of asthma in children aged <6 years remain, the ongoing study by the Asthma Collaborative Group of the Respiratory Group of Pediatrics Branch of the Chinese Medical Association will hopefully provide some guidance when completed in late 2018.

The prevalence of childhood asthma varies significantly among regions in China, and the reasons for this are unclear. A recent study in Chongqing, China, found that short-term respiratory exposure to particulate <2.5 microns, particulate matter (PM) <2.5 microns, sulfur

dioxide, nitrogen dioxide, and carbon monoxide triggered hospital visits for asthma in children [21]. Interestingly, nitrogen dioxide was found to have an important role, whereas ozone had no effect. A study conducted in Shanghai showed that high dose-dependent concentrations of black carbon and PM_{2.5} were significantly correlated with an increased risk of hospitalization among children with asthma after adjusting for nitrogen dioxide and sulfur dioxide concentration [22]. These findings support the need for marked improvement in air quality.

Asthma in children requires long-term and continuous treatment and—while standardized—should be individualized to the unique needs of each child. Although Chinese epidemiological studies have shown that the number of children with asthma receiving long-term pharmacotherapy has increased compared with the 10 years prior, we should acknowledge that under- and overtreatment of asthma still takes place in China. From the viewpoint of standardized treatment and safe pharmacotherapy, overtreatment may be the major problem requiring attention. Although data are incomplete, some investigations have suggested that about 25% of children were treated for asthma with three or more drugs, and a treatment this aggressive is not consistent with the severity of asthma in Chinese children. The selection and adjustment of therapeutic protocols, and the assessment of therapeutic efficacy, are of great importance, continuous assessment of disease status is required, and new concepts such as intensified intervention and pre-intervention/intermittent treatment should be investigated. Unlike the three-stage management suggested in GINA (assess, adjust treatment, review response), the Chinese guideline promotes an open-ended management approach that includes intensified initial treatment, timely step-up and step-down, pre-emptive and intermittent interventions, and regular monitoring.

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Compliance with ethical standards

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