

Challenges in Paediatric Asthma Today

Lynette PC Shek,¹*MRCP*, Daniel YT Goh,¹*MMed (Paeds), FRCPC*, Hugo Van Bever,¹*PhD*, Bee-Wah Lee,¹*MMed (Paeds), MD, FRCPC*

Asthma today affects more than 300 million people worldwide and its prevalence is increasing, particularly among children. The rise in asthma prevalence has been likened to an epidemic, and is expected to afflict up to 400 million people by 2025.¹ In Singapore, it is estimated that 1 in 5 children suffer from it. It is a chronic condition with considerable morbidity and mortality, with many asthma patients having a self-perception of poor health.² The cost of asthma is also high, and is conservatively thought to exceed US\$33.93 million per annum in Singapore.³

Over the past few decades, significant improvement in treatment options available and in our understanding of its pathogenesis have revolutionised the way we manage this condition. However, there are still significant challenges to reducing the global burden of asthma, and in preventing its onset in the first place. These include a lack of education on the disease, a lack of infrastructure to manage the condition on a wide scale, underdiagnosis because of misconceptions and fear of long-term effects of asthma medication.

In view of the pressing need to improve asthma awareness and education, the Global Initiative for Asthma (GINA) inaugurated the first World Asthma Day in 1998. Since then, it has been observed every first Tuesday in May and celebrated its 10th anniversary on May 1st this year. The primary goal of this day is to improve awareness about the disease among healthcare professionals, the general public and patients affected by it. In Singapore, this event has been marked by public talks, road shows and media activities. Still, more needs to be done to achieve control of asthma so as to enable every child with it to lead a normal, unrestricted life. Some of the challenges faced by doctors will be discussed here.

The New Goal in Asthma Care is Control

Previous asthma guidelines emphasised treatment based on disease severity. However, asthma severity involves both the severity of disease at diagnosis and response to treatment. Also, it is well known that asthma is a dynamic disease and severity changes with time. Despite the presence of guidelines stressing treatment based on disease severity, studies have demonstrated a lack of control of asthma in countries that have adopted them.⁴

In view of these, updated guidelines have recently been published by GINA that emphasise control as the goal in asthma care, de-emphasising the previously held central role of severity.⁵ These new guidelines still rely on a step-up and step-down approach based on the presence or absence of 7 parameters that are key to control (symptoms, exacerbations, use of rescue bronchodilator, physical activity, peak flow variability, emergency visits and adverse events from treatment). This allows the clinician to focus on level of control during *each* clinic visit instead of theoretical severity classifications. Treatment can then be tailored accordingly for the individual patient.

Asthma, Whatever its Form and Severity, is an Inflammatory Disorder

Asthma has long been recognised as a chronic inflammatory disorder of the airways in which eosinophils, mast cells and other cellular elements play a major role.⁶ The evidence that inflammation plays a significant role is multiple. Examination of bronchial biopsy specimens in asthmatics consistently demonstrates inflammation, even in patients with mild disease.⁷ Inflammatory cytokines contribute to airway oedema, mucus plug formation, airflow limitation and airway hyper-responsiveness. Inflammatory markers, such as serum and sputum eosinophilic cationic protein, have been shown to be reliable surrogate markers of airway hyperresponsiveness.⁸ Treatment strategies aimed at reducing airway inflammation have been found to reduce exacerbations, admissions and the need for more anti-inflammatory treatment.⁹

The inflammation in asthma is driven by a variety of factors including exposure to environmental tobacco smoke.¹⁰ Cigarette smoke enhances airway inflammation by recruiting neutrophils, increasing the release of cytokines including TNF- α and interleukin-8. Allergen exposure is another key trigger in initiating and maintaining the inflammation in asthmatic airways. There is good evidence that chronic exposure to allergens such as house dust mite, pollen or animal dander can increase airway inflammation and precipitate exacerbations.^{11,12} Finally, viral respiratory infections are also common causes of airway hyper-responsiveness and loss of asthma control.

1 Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, and The Children's Medical Institute, National University Hospital, Singapore

Address for Correspondence: Dr Lynette Shek, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, 5 Lower Kent Ridge Road, Singapore 119074.

Email: paeshekl@nus.edu.sg

In view of the central role of inflammation in asthma pathogenesis, one of the most important management goals in asthma treatment is the reduction of airway inflammation and its long-term sequelae. All international guidelines state that inhaled corticosteroids (ICS), powerful suppressors of airway inflammation, are the cornerstone of treatment for uncontrolled asthma. ICS monotherapy achieves control of asthma in the vast majority of patients, resulting in improved clinical symptoms and lung function. It also results in decreased airway hyperresponsiveness, frequency of exacerbations and reduced mortality.^{13,14} Patients with poor control of asthma on ICS alone have the option of stepping-up therapy with other “add-on” medicines such as long-acting β_2 -agonist (LABA) or leukotriene receptor antagonists. However, this should be done only if ICS monotherapy has proved to be insufficient. This is an important point to note as we often see inappropriate treatment of patients, even the very young, with combination therapy when ICS monotherapy would probably suffice for these children. LABAs have not been well studied in children, and there are no published, systematic studies in children less than 6 years of age. Its efficacy and safety in paediatric patients is therefore unclear, and care needs to be taken if these medicines are prescribed for young children.

Early Treatment May Not Make a Difference

It is well known that the highest incidence of wheezing disease occurs in the preschool years. Many of these children continue to have asthma symptoms and airway inflammation for many years after. Childhood is therefore potentially an important window of opportunity for early therapeutic intervention with the objective of halting the decline in lung function. The hope was that asthma would be more amenable to therapy if treatment was initiated soon after onset of disease to offer a greater chance of preserving lung function and normalising airways.

There was initially some evidence for this as seen in the Childhood Asthma Management Program (CAMP) study.¹⁵ In that study, the longer the duration of asthma, the worse the decline in pulmonary function. Delay in onset of therapy resulted in blunting of lung function improvement, greater methacholine responsiveness, more asthma symptoms and greater use of as-needed rescue therapy. In another study, children who started budesonide more than 5 years after asthma diagnosis had poorer lung function compared to those who started ICS within 2 years of diagnosis.¹⁶

However, 2 recent studies have challenged this assumption. Martinez’s group in Arizona recruited children aged 2 to 3 years at high risk for development of asthma and randomised them into treatment with fluticasone propionate or placebo for 2 years, followed by a 1-year period without

study medication. Children on ICS did better during the treatment period. However, no significant differences were seen between the 2 groups in episode-free days, the number of exacerbations, or lung function during the observation period. This suggests that there is no long-term disease-modifying effect of ICS after treatment is discontinued.¹⁷

In the Manchester study, children were also randomised to treatment with fluticasone propionate or to placebo. The authors found no difference in lung function or airway reactivity between both arms during follow-up. They concluded that the early use of ICS for wheezing in preschool children had no effect on the natural history of asthma or wheeze later in childhood, and did not prevent lung function decline or reduce airway reactivity.¹⁸ Based on these 2 well-designed, randomised, controlled studies, it is currently not possible to recommend early treatment of asthma with ICS as a means to preserve lung function in asthmatic children.

Achieving Optimal Outcomes – A Multifaceted Approach

Many factors influence outcome in the successful management of asthma. Treatment has to be tailored to the patient’s age, concomitant medical conditions, lifestyle, patient’s preferences and caregivers’ expectations. Previous reviews have demonstrated that relying on medication alone is not enough.¹⁹ Many patients underuse controller medicine and over-rely on relievers. Also, the repertoire of medicines available to children is limited compared to adults. Many medications are used “off-label”, having little age-specific data, particularly in young children. This is not unexpected because ethically, it is difficult to perform clinical studies in the paediatric population. Doctors must therefore exercise caution when using these medicines in children as one cannot always extrapolate adult data to the treatment of children.²⁰

Treating asthma in children is more than just prescribing medication. It is offering a whole individualised package (holistic approach) to the parent that includes education, which improves compliance. It is about monitoring of asthma, assessment of severity (lung function testing) and assessment of allergic triggers. It is about treating concomitant allergic disease (rhinitis and eczema) and instituting appropriate immunomodulatory treatment (immunotherapy, probiotics) as necessary. As asthma patients are on long-term medications, monitoring is important to assess the continued efficacy, safety and need for such treatment. The medication regimen should be reviewed for compliance, appropriate technique of administration and possible drug interactions. In all this, it is important to involve the parents, as the biggest advocate a child can have in gaining control of his disease is his parent or caregiver. Parental involvement and guidance is

vital to keep a child actively taking medication and following prescribed control measures. Asthma disease management programmes implementing these have been shown to be cost-effective and to reduce morbidity.²¹

At the National University Hospital, we have adopted a comprehensive approach through an asthma and allergy management programme known as the Children's Asthma and Allergy Network (also known as "I CAN!"). This programme utilises a tailored strategy to address all the needs of the child to optimise asthma control and improve quality of life. Patients with asthma seen by our paediatricians are automatically enrolled in the programme, while children not under our care are enrolled as associate members. All patients in the programme receive counselling by a trained nurse, have access to her through the "I CAN!" hotline, have a written asthma action plan and have their drug delivery technique reviewed regularly. The programme also provides printed educational material and management aids, regular newsletters for the public and doctors, information through our website (www.ican.com.sg), workshops for medical professionals and outdoor activities for our patients. This is done in partnership with primary healthcare providers. Since the implementation of this programme, there have been improvements in the quality of life for the children and the parents, with less loss of schooldays and workdays respectively.

Conclusion: The Way Ahead

Even though many advances have been made in the understanding of asthma and in asthma research, our knowledge and understanding of this common disease remains incomplete. Deficiencies include understanding the role of genes versus environment²² (including the prenatal environment), the role of infectious agents and allergens, and the inability to prevent or cure it. The Holy Grail for all of us involved in asthma care would be to prevent its onset, but as of today, we can only attempt to prevent the development of allergy, which is an important, but not the only, risk factor for the development of asthma. Much more research needs to be done in this field. At the same time, all stakeholders (doctors, parents and patients) need to remember that with vigilance and better understanding of the disease, we can minimise the morbidity of asthmatic children and improve the long-term course of asthma.

REFERENCES

1. A plea to abandon asthma as a disease concept. *Lancet* 2006;368:705.
2. Wang JJ, Smith W, Cumming RG, Mitchell P. Variables determining perceived global health ranks: findings from a population-based study. *Ann Acad Med Singapore* 2006;35:190-7.
3. Chew FT, Goh DY, Lee BW. The economic cost of asthma in Singapore. *Aust N Z J Med* 1999;29:228-33.
4. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;16:802-7.
5. Bousquet J, Clark TJ, Hurd S, Khaltayev N, Lenfant C, O'byrne P, et al. GINA guidelines on asthma and beyond. *Allergy* 2007;62:102-12.
6. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000;161:1720-45.
7. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med* 1998;157(3 Pt 2):S1-53.
8. Koh GC, Shek LP, Goh DY, Van Bever H, Koh DS. Eosinophil cationic protein: Is it useful in asthma? A systematic review. *Respir Med* 2007;101:696-705.
9. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
10. Bousquet J, Vignola AM. Exposure to environmental tobacco smoke and adult asthma. *Allergy* 2001;56:466-9.
11. de Kluijver J, Evertse CE, Schruppf JA, van der Veen H, Zwinderman AH, Hiemstra PS, et al. Asymptomatic worsening of airway inflammation during low-dose allergen exposure in asthma: protection by inhaled steroids. *Am J Respir Crit Care Med* 2002;166:294-300.
12. Chew FT, Teo J, Quak SH, Connett GJ, Lee BW. Presence of domestic pets and respiratory symptoms in asthmatic children. *Ann Acad Med Singapore* 1997;26:294-8.
13. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;343:1054-63.
14. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
15. Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin Immunol* 1999;103(3 Pt 1):376-87.
16. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
17. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
18. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006;368:754-62.
19. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40-7.
20. Custovic A, Simons FER. Drugs used in paediatric allergy: should we conduct studies in children or extrapolate from adults? *Clin Exp Allergy Rev* 2006;6:1-5.
21. Abisheganaden J. Asthma disease management: a provider's perspective. *Ann Acad Med Singapore* 2002;31:467-73.
22. Shek LP, Tay AH, Goh DL, Lee BW. Ethnic differences in genetic susceptibility to atopy and asthma in Singapore. *Ann Acad Med Singapore* 2000;29:346-50.