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Editorial

Bird's eye overview of asthma in children

Asthma is a major chronic disease estimated to affect more than 339 million people globally[1]. It imposes a substantial burden to the affected individuals and their families, being the most common non-communicable disease in children. It affects the quality of life (QoL) of affected children and their parents/caregivers, impacting on activity levels, daily functioning, school and work productivity and absenteeism[2,3]. With an increasing prevalence in many regions, the health and economic burden remain substantial.

Asthma is a condition that affects both children and adults. In young children, viral infections particularly rhinovirus infection, can cause recurrent acute asthma exacerbations and/or recurrent wheezing[4]. For many of these children, the recurrent wheezing episodes cease in later childhood but in some, asthma persists. In older children, recurrent asthma exacerbations with chronic interval symptoms on a background of atopy are common. The 'atopic march' starts in infancy as eczema, subsequently as allergic rhinitis and then in later childhood, as asthma[5]. There is a male predominance in childhood asthma. After puberty, females have a higher risk of asthma[6]. In contrast, adults have a more diverse pattern and many have co-existing comorbidities and associations *e.g.*, obesity, gastroesophageal reflux, rhinosinusitis and nasal polyposis and tobacco smoking. Steroid-resistant asthma is more commonly seen in adults than in children[7]. Adult-onset asthma with nasal polyps (eosinophilic type) without atopy is uncommon in children[7]. Severe asthma is rare in preschool children, in contrast to adults, whereby the majority of deaths due to asthma occur in adult-onset asthma.

In the management of childhood asthma, concepts are generally categorized into acute and non-acute asthma. In the non-acute phase, a regular controller/preventer *e.g.*, a low dose inhaled corticosteroid (ICS) or montelukast should be considered to manage symptoms and reduce the risk of serious exacerbations[8]. Parents or caregivers should be cautioned about the potential adverse neuropsychiatric effects of montelukast. Stepping up treatment in those with persistent symptoms should be considered, after checking inhaler technique, adherence, persistent allergen exposure and addressing comorbidities. Stepping down treatment to the minimum effective dose to maintain good asthma control should subsequently be considered. Suboptimal adherence to controller/preventer medication such as ICS is associated with morbidity and mortality. It can lead to poor clinical outcomes, increased hospitalizations and health care utilization. Poor treatment adherence is thought to be multifactorial. Some of the factors leading to poor treatment adherence are potentially modifiable including access to health care, follow up and medications. Effective monitoring and education can promote treatment adherence. A written personalized asthma action plan should routinely form part of the management plan. Parental/caregivers' beliefs/misconceptions about medication can potentially be modified with ongoing education. Interventions targeting contributing factors may help improve treatment adherence.

The main goal of asthma management should be to achieve and maintain control, *i.e.* to minimize and prevent acute asthma exacerbations, hence reducing the risk of morbidity. Controller/preventer medications include ICS, long-acting $beta_2$-agonists with ICS, leukotriene-receptor antagonists, long-acting muscarinic receptor antagonists and in highly selected individuals, monoclonal antibody (biological) agents[9]. The primary goal of asthma control is to use the minimum doses of medications to achieve control of symptoms. Ongoing follow up and monitoring are crucial and treatment may need to be adjusted from time to time. Improved follow up and access to

a physician as well as comprehensive education will likely reduce asthma readmission rates, which will, in turn, reduce the burden on affected individuals, the healthcare system and the economy.

Though asthma is known as a chronic airway problem, the large burden in children with asthma relates to acute/recurrent exacerbations of flare-ups. Acute asthma is one of the most common causes of children presenting to emergency departments[10]. In the USA, 17.2 per cent of children with asthma reported an emergency department or urgent care visit within the past 12 months[11]. Despite the burden of asthma exacerbations, there are relatively little data on the determinants affecting the severity of acute asthma. This is a clinical research gap. Current likely factors include extrinsic determinants (*e.g.,* access to health care and socio-economic influences)[12] and biological factors. Atopy[13,14] and viral infections[4] are likely contributing factors. Up to 80 per cent of children with asthma exacerbations have viral infections detected[4]. Asthma studies in children have described allergic sensitization and risk of hospitalization for acute asthma[15,16]. Viruses together with allergen exposure likely increase the risk of hospitalization with asthma[13,17]. We have shown that the presence of viruses does not appear to impact on asthma recovery but children with atopy appear to be more likely to represent for asthma relapse within 14 days[18].

Another underappreciated issue in asthma is the morbidity after an acute exacerbation *i.e.*, in the asthma recovery phase where many experience ongoing morbidity[19,20]. Despite significant advances in asthma therapies, research gaps exist and need to be addressed as a priority. There is little research in the recovery phase following asthma exacerbations despite the importance of asthma exacerbations and its burden on affected children and their families[21,22]. In our asthma studies[18,23,24], we have shown that the morbidity of asthma extends well beyond the immediate acute phase. We used several patient-oriented and validated outcomes in children including the Asthma Diary Scale (ADS)[25] and the Paediatric Asthma Quality of Life Questionnaire[26], which measure the impairments due to limitations of daily activities and the anxieties/fears of parents/carers due to their child's illness. Other tools available which we used included the validated cough diary scale[27] to measure prolonged cough in the recovery phase in children with asthma exacerbations[23]. The Canadian Acute Respiratory Illness and Flu Scale (CARIFS)[28] is another validated tool that can be used as a measure of disease severity and burden of illness to the parent/carer in children with acute respiratory infections. We have utilized the CARIFS instrument in asthma studies and found that the CARIFS and ADS scores correlated well as a disease severity measure during the post-asthma exacerbation recovery phase in children[24].

Much progress has been made in the field of asthma, ranging from mechanisms, treatments and measurement outcomes, but many clinical research gaps remain. There is substantial research into the genetics of asthma susceptibility, severity and response to treatment (pharmacogenetics). Novel molecular targets in the pathogenesis of asthma with the genome-wide association studies have significantly improved our understanding but only a small proportion of the heritability of asthma can be accounted for[29]. Many biomarkers in asthma have been investigated and researched, however, only a few so far are practical and used in clinical practice. Using a panel of biomarkers could improve the identification of asthma phenotypes and endotypes which in turn may predict therapeutic response to biologic treatments[30]. Biomarkers include blood eosinophils, serum IgE, serum periostin, sputum eosinophils and fractional nitric oxide in the exhaled breath (FeNO) but all these have limitations in clinical practice. Unfortunately, an ideal biomarker does not exist currently. In addition, there is research into newer imaging modalities using quantitative computed tomography, which can estimate airway wall thickness and wall area percentages, thereby estimating airway wall remodelling. Air-trapping can also be calculated and together with remodelling, can be correlated with lung function and asthma severity[31]. Biologics for the management of severe asthma such as anti-IgE (omalizumab), anti-interleukin (IL)-5 (mepolizumab, reslizumab and benralizumab), anti-IL-4/IL-13 (dupilumab) and anti-thymic stromal lymphopoietin (tezepelumab) have been shown to reduce asthma exacerbations[32]. These biologics can reduce steroid-associated adverse events in the management of severe asthma.

Current treatments available are highly effective and significant advances have been made in understanding the underlying mechanisms causing asthma. In spite of this, considerable morbidity and mortality exist. Most asthma-related mortality occurs in lower-income countries, and most asthma deaths are preventable[33]. Improving access to health care and medications and education regarding potential exposure to risk factors

would likely reduce morbidity and mortality related to asthma. There is currently no cure for asthma but reducing or preventing asthma exacerbations and optimizing management should be aimed for.

In summary, despite substantial advances in asthma research, considerable clinical research gaps exist. The goals of asthma research should be prevention of its onset, optimization of management including education of risk factors and correct use of delivery devices, treatment adherence, reduction in ongoing morbidity and improvement in the QoL of individuals and their families and ultimately cure of the disease. Governments should concentrate on research, intervention and monitoring with the aim of reducing the burden of asthma globally.

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Laurel Teoh[1,2,3] & Anne B Chang[1,4,5,*]
[1]Child Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, [2]Faculty of Medicine, The University of Queensland, [3]Department of Paediatrics, Caboolture Hospital, Caboolture, Queensland 4510, [4]Department of Respiratory & Sleep Medicine, Queensland Children's Hospital, [5]Australian Centre for Health Services Innovation, Queensland University of Technology, Brisbane, Australia
[*]*For correspondence*: anne.chang@menzies.edu.au

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