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Asthma Frequently Asked Questions

Question 1: Why do children still die from asthma?

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Educational aims

The reader will come to appreciate that:

- Many but not all asthma deaths in children are preventable.
- Vulnerable children are at an increased risk of dying from asthma.
- Facilitating access and better adherence to inhaled corticosteroids for children with persistent asthma is the cornerstone of management.

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ABSTRACT

Asthma is one of the commonest chronic conditions in children and can occasionally be fatal. Little has changed regarding the risk factors for children dying from asthma in the last 30 years. The majority of deaths from asthma occur in children from socio-economically disadvantaged backgrounds. These should be preventable with better education of families, oversight of medication adherence and improved communication between health care professionals and families. More needs to be done to deliver basic messages more effectively about asthma management to the most vulnerable in communities around the world.

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INTRODUCTION

Death from asthma is tragic. Fatal asthma in children is fortunately relatively uncommon, but the majority of cases are probably preventable, with failure to recognize and treat poor asthma control being the most commonly identified avoidable factors. While life-threatening asthma attacks are more frequently recognized in the hospital setting, reliable and consistent data collection on prevalence of asthma deaths are lacking. This inhibits our ability to truly establish accurate risks of dying from asthma in childhood and adolescence. Asthma deaths are the “tip of the iceberg” of under-appreciated and undertreated asthma in our communities. So, in trying to establish why children still die from asthma it is appropriate to consider the epidemiology and pathophysiology of

asthma deaths before considering the clinical profiles of victims of fatal asthma and ways of mitigating the risks in vulnerable children.

ASTHMA MORTALITY RATES AROUND THE GLOBE AND REGIONAL DIFFERENCES

Asthma is one of the most frequent chronic diseases in childhood. In 2013, the International Study of Asthma and Allergies in Childhood (ISAAC) reported on a survey of almost 1200000 children in 233 centers in 98 countries, finding a current asthma prevalence in the 13–14-year age group of 14.1% and 11.7% in the 6–7-year range, with high variability in the prevalence and severity of asthma around the globe [1,2]. Asthma mortality rates also differ between countries, ranging from less than 0.1 per 100000 inhabitants in countries such as Greece, Sweden and Finland, to more than 1.5 per 100000 inhabitants in countries like South Africa, Turkmenistan and Kazakhstan [3]. Asthma mortality rates also present variations depending on age, sex and race. It is

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three times higher for black people compared with white people, and it is almost seven times higher in adults compared to children [4,5]. Asthma mortality rates among adults are higher in females than in males with a ratio of 4:1. However, in children the rate for males is greater than or equal to that for females. Deaths from asthma in children are rare, ranging from 0.0 to 0.7/100,000 in different parts of the world [1]. A decrease in asthma mortality rates in all age groups around the world has been observed, but recent data from the World Health Organization, including data from 46 different countries, showed that despite the apparent decrease in some countries and regions, there was no significant change in global asthma mortality rates from 2006 to 2012 [4,6–8].

ULTRA-STRUCTURAL CHANGES AND INFLAMMATORY PATTERNS

Children with asthma have remodeling and eosinophilic inflammation of the airways like adults. Remodeling is characterized by epithelial injury, thickening of the reticular basement membrane (RBM), airway smooth muscle hypertrophy and hyperplasia and angiogenesis [9]. The increase in RBM thickness and eosinophilic inflammation can be observed in preschool wheezers at a median age of 29 months [10]. In a Finnish study, the histopathology of fatal pediatric asthma was evaluated in 12 fatal asthma cases and 8 non-asthmatic control subjects [9]. They found significantly increased RBM thickness in large airways in most fatal asthma cases compared to the control group. Airway smooth muscle (ASM) was increased in large airways in one third of asthmatics but in small airways ASM was found equally in both groups. Mucous plugs were found in large and small airways significantly more prominently in fatal asthma than in control cases, especially in large airways. Based on the time from the onset of symptoms to death, some studies have divided patients into two distinct groups: short (<3 h) and long course (>8 h) [11,12]. It has been reported that the type of inflammation present in the airways in these two groups of patients could be different. In the short course group the predominant cells found were neutrophils whereas in long duration group the predominant cells were eosinophils. In an Australian study, which included 18 asthmatic adults who died, it was shown that in cases with fatal exacerbations of short duration, the numbers of neutrophils and the mucous gland area were increased and the numbers of eosinophils were reduced compared to cases with fatal exacerbations of long duration. Lymphocyte numbers, airway wall thickness, areas of smooth muscle and cartilage and the amount of smooth muscle shortening were similar in both groups [11]. This study hypothesizes that the increased mucous gland area observed in short duration cases could have contributed to a rapid fatal exacerbation of asthma. Another Australian study including 19 asthmatic adults who died of an asthma exacerbation also found that short course cases had a higher ratio of neutrophils to eosinophils in the airway wall [12]. This study also showed that short-duration cases had an increase in airway smooth muscle shortening whereas in long-duration cases there tended to be increased mucus secretion. The reasons for this reproducible dichotomy in the inflammatory pattern are not clear. It seems that the predominance of neutrophils or eosinophils is a function of time rather than being a characteristic of the different groups. Nevertheless, the other possibility is that different nature of the stimulus that caused the exacerbation may determine the type of the predominant inflammatory response in the airways [11]. There are also other cells that could play a role in fatal asthma, such as mast cells and cytotoxic CD8 T-cells. Mast cells are responsible for smooth muscle contraction and mucous gland secretion during an asthma exacerbation. In 29 cases of fatal asthma, the ratio of degranulated to intact mast cells was significantly increased in the smooth muscle and the outer airway wall in short duration

cases [13]. Cytotoxic CD8 cells and natural killer cells have granules that contain a family of serine proteases called granzymes (Gzm). They cleave extracellular matrix components, contributing to remodeling in chronic inflammation and can activate macrophages to secrete cytokines. In a Brazilian study which included post mortem lung tissues from 21 subjects with fatal asthma and 14 non-asthmatic controls, a significantly higher number of Gzm + cells in the inner and outer layers of the airways and in the peribronchiolar septa was found in the fatal asthma cases, showing that granzymes may be involved in the mechanisms preceding asthma deaths [14].

DEMOGRAPHICS OF CHILDREN DYING FROM ASTHMA

In a series of 20 childhood deaths from asthma [aged 4–17 years] in Australia between 2004 and 2013, 90% were atopic, 70% had a family history of allergy or atopy in a first-degree relative, 70% were male and 55% occurred in those aged 10–14 years [15]. A close relative or carer smoked in 35% of cases. Psychosocial issues were identified in 55% of cases, which included 25% of patients who had had notification to child protection services within the three years preceding the fatal attack of asthma. Another 15% had a sibling notified to child protection services previously. One child was in out of home care at the time of death. There was an overrepresentation of families from low socio-economic status (35% came from the lowest quintile). Similarly, overrepresentation of asthma deaths in vulnerable families from minorities and socio-economically disadvantaged backgrounds has been reported in adults and children from other western countries including England, Canada and the United States [16–19].

HISTORY OF SEVERITY OF ASTHMA IN FATAL CASES

The majority of children who have fatal asthma attacks have been prescribed inhaled corticosteroids and/or long acting beta-agonists [17]. Typically, adherence with preventative treatment was suboptimal and recent interval reviews of asthma were often absent or perfunctory [15,17]. A history of a previous admission to hospital or an intensive care unit admission has long been regarded as a risk factor for a more severe, or life-threatening asthma attack [20,21]. Follow-up after discharge is often inconsistent and a significant proportion of fatal asthma cases in children have had a hospitalization within the preceding 12 months [15,17,18,20–22]. On representation with the fatal exacerbation of asthma it may be demonstrated that the parent/primary carer has not consistently obtained, administered or overseen the delivery of prescribed preventive medications in the months preceding the fatal attack [15,22]. Over-reliance on the very frequent use of high doses of short acting beta agonists for symptom relief as the fatal episode develops is a consistent finding, usually in the home setting [15,17,23]. Interestingly, about 50% of cases are acute in onset with rapid progression of symptoms and death within hours [15]. Other presentations, in this series 25%, are slower in onset, with children described as active and “normal” in the weeks leading up to the fatal episode and some having a grumbling onset over days with more cough and wheeze, sleep disruption and declining response to escalating doses of short acting beta-agonists. In an Australian report, most patients [85%] reached hospital by ambulance but were neurologically non-responsive on arrival at the Emergency Department [15].

ARE ASTHMA DEATHS PREVENTABLE?

The short answer is probably yes: most cases of fatal asthma in children (approximately 60% to 70% in most studies), should be

preventable [15,17,24]. This has not changed over the last 25 years [20], and researchers invariably suggest the need to “reach the unreached” [24] or the most vulnerable in our communities [15]. During this time, there have been no significant changes in the classes of asthma preventative medications available for children with asthma in developed countries. In such countries, therefore, reduction of asthma mortality requires better communication between health care providers [hospitals and family practitioners], schools, community health care facilities and patients and families. The emphasis has always been on written communication with asthma management plans for patients and correspondence between health care professionals, with families excluded from receiving copies of the correspondence [16,23]. In the future more broadly, we can look toward electronic medical records and more secure email communication with personal devices as the mobile phone replaces the computer [25,26]. However, informed and appropriate information delivered during consultations remains the “gold standard” of asthma management [27]. Whether consciously delivered with motivational interviewing or simple and structured regular reviews designed to empower the patient and family to better manage a complex condition like asthma, more can be done to reduce fatal asthma attacks [28,29].

ADOLESCENTS

The over-representation of adolescent males in series of pediatric asthma deaths is a consistent finding and an area clinicians need to focus their attention when discussing medication use with patients and families [16,17]. Adolescence is a vulnerable period in life when there often exist excessive parental and societal expectations of independence and responsibility for a given age which do not align with the contrasting forces of peer pressure, risk taking behaviors and a feeling of invincibility which permeates through the adolescent psyche [28–30]. Clinicians must be aware of these unbalanced forces disrupting medication adherence and respond with patience, tolerance and realistic expectations of treatment compliance [30]. For the adolescent with persistent asthma, the need for ongoing review and repeated education for them and their families [healthcare provider – patient/parent collaboration] is vital to optimize understanding of the chronic nature of asthma, the importance of preventive treatment, the correct use of medication devices and the benefits of regular preventative therapy upon everyday activities [16,23,28,29].

BASIC MEDICATION AVAILABILITY AND ACCEPTANCE OF ASTHMA AS A CHRONIC CONDITION

Notwithstanding expensive biologicals introduced in wealthier countries, these treatments are not the solution to life threatening or severe asthma on a global scale.

Sadly, there are ongoing shortfalls in our ability to get inexpensive, generic inhaled corticosteroids, short acting beta agonists and cheap spacers to low-middle income countries where the burden of fatal asthma is less well documented. The situation is further complicated in some low- middle income countries by pervasive cultural reluctance to accept asthma as a diagnosis and fewer health care workers with sufficient expertise to address the problem of severe asthma disease in their communities [31].

THE SOLUTION IN A NUTSHELL?

Inhaled corticosteroids and targeted education are the answers to reducing asthma mortality across the globe [32]. In Finland, the beneficial effect of targeted medical education in the primary care setting which emphasized the use of inhaled corticosteroids to

treat persistent asthma has seen asthma morbidity, costs and mortality plummet from one of the highest to one of the lowest in Europe in less than 20 years [33]. Thus, with adequate resources, dramatic change is possible within a generation. The challenge for the rest of us is to translate the experience in Finland to models which will afford similar improvements in many varied settings around the world. This brings economic and political challenges which must be addressed as part of a global strategy.

DIRECTIONS FOR FUTURE RESEARCH

In the context of life threatening and fatal asthma, future research should involve:

- Facilitating a better understanding of the variable time-course of fatal asthma attacks in children so as to enable intervention earlier.
- Improving understanding of differing symptom perception in life threatening asthma exacerbations.
- Ways to enhance better co-ordination between child welfare agencies and medical care providers to improve the oversight and care of vulnerable children with asthma in differing cultural contexts.

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