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REVIEW ARTICLE

Environmental Risk Factors for Asthma: A Review of Literature

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ABSTRACT

Asthma is a severe respiratory illness affecting all age groups globally. It is estimated that 18% of the population, which is around 262 million people, are affected, experiencing recurrent episodes of wheezing, chest tightness, and shortness of breath. It is the main cause of morbidity and mortality in children, measured by school absenteeism, emergency visits, and hospital admissions. For patients with asthma, exacerbations and poor control can result from a complex interplay between genetic predisposition and environmental immunity modifiers that can be grouped as biological and physical factors that include (genetics, endotoxin, pollutants, microbes, and aeroallergens). The psychological environmental factors like stress, neighborhood safety, discrimination, and housing have been noted to influence asthma. The objective of this review is to make a summary of various international literature written on aspects of both home and school environments and their effects on asthma prevalence, and to determine whether the environment plays a great role in achieving control. Literatures from 1995 to 2019 in the area of environment in relation to childhood asthma were identified by use of PubMed and Google Scholar, using the key terms: childhood asthma, asthma, and environmental effects. A reference list of all retrieved articles, related articles, and author names were used to expand the search that was used for this review. A conclusion was made that, despite the various treatment guidelines and medications available, the kind of environment children are exposed to plays a very significant role in attaining control and reducing exacerbations.

Keywords: *Asthma, Environment, Childhood asthma, Allergens*

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INTRODUCTION

Asthma is the most frequent chronic disease of childhood, affecting one out of seven 13-14 year-olds, resulting in significant of morbidity and disability. However, the predominance of asthma is expanding in many areas of the planet by as much as 50% consistently. The Global Initiative for Asthma defines asthma as a 'heterogeneous disease, usually characterized by chronic airway inflammation and defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation'(Anon 2014). It is momentous that asthma has been characterized differently since the beginning of time, including as a 'neurotic affection' by Sir William Osler, the father of modern medicine.

In 2019, asthma affected around 262 million or 18% of the total population and caused 455,000 deaths (Song et al. 2022). Asthma prevalence has been increasing across Africa because in 1990, about 11.7% (74 million including 34.1 million children) of the population had asthma and by 2010, this had increased to 12.8% (119 million including 49.7 million children) (Adeloye et al. 2013).

In sub-Saharan Africa, asthma is underdiagnosed and undertreated leading to a high burden of severe asthma symptoms and mortality rates. For instance, in Uganda, a low-income sub-Sahara African country, only 33% of people with asthma have controlled asthma by use of inhaled controller medications and 60% had ≥1 exacerbations a year (Kirenga et al. 2018). Over 90% of under 5-year-old children exhibiting asthma symptoms, were diagnosed with pneumonia and treated with antibiotics and hence missing opportunities to address the true underlying issues (Nantanda et al. 2013). This overall has led to a mortality rate of 19 deaths per 1000 person-yearly which is 90 times that of the UK.

The rising prevalence of childhood asthma in many countries in the developing world is a reason for concern. In developing countries such as Kenya by contrast, asthma prevalence was recently viewed to be low, but studies have shown that childhood asthma is on the rise, especially in urban areas and that a significant difference exists in the prevalence of childhood asthma when urban and rural centres are compared. Until fairly recently, children in many African nations lived mainly in rural areas and were not exposed to the impacts of urbanization accompanied by several risk factors for asthma such as pollution asthma (Adeloye et al. 2013).

Childhood asthma prevalence studies, particularly from Kenya and Ghana, have affirmed the urban-rural differences but with a narrower gap. This might be the after effect of exposure of rural children to environments that would typically be viewed as potentially highly allergenic. They may include, floors made of a combination of mud and compost, indoor wood fires, domestic animals that share the same room as the owner, to agricultural pesticides and irritants as well as of the high inclination to embrace a more Westernized life such as the use of beds with mattresses, pillows, carpets, and blankets and also air pollution from industries being set up in those areas (Adeloye et al. 2013). These conditions in Africa provide a natural research facility in the mission to understand the factors that impact the development of asthma in susceptible children.

In Kenya, about 4 million people have asthma accounting for 10% of the population with 3.1% from Nakuru County. The prevalence ranges from 1-18%. The higher prevalence is found in urban areas as compared to rural areas due to increased urbanization and industrialization in the country (Cecilia and Pharm 2014). In the 'Help Me Breath' campaign launched by KAPTLD in 2013, it was estimated that more than 1.3 million school going children are forced to skip school as a result of poor diagnosis and management.

Kenya developed the 'The Kenya National Asthma Guidelines' so as to increase awareness among the health workers and so improve the asthma management and outcome. Despite the presence of the guidelines and availability of the drugs, hospitalization and emergency visits due to asthma attacks have not reduced (Cloutier et al. 2005). This shows that there are other factors in play that influence asthma control. Some of these factors are related to health workers, guideline underutilization, caregivers' knowledge and perception of asthma and the kind of environment the children are exposed to (Capanoglu et al., 2015).

This review will go a long way in providing researchers a foundation of study and broaden the line of thought in the medical world when it comes to asthma management.

Biological Environment

Over the past two decades, there has been increased attention to the role of the indoor environment (e.g. work, home, school) in asthma management. Exposure to multiple indoor allergens in U.S. homes is common in a cross-sectional study more than half of surveyed homes

had detectable levels of all allergens (dust mite, dog, cat, cockroach, mouse, and Alternaria alternata), and most homes had at least 3 allergens at increased levels (Salo et al. 2008). Multiple studies have shown that indoor allergens, biological matter, and pollutants including mouse, cockroach, pets, dust mite, mold, endotoxin and nitrogen dioxide are important asthma symptom risk factors in homes and schools' (Kanchongkittiphon et al. n.d.). In 2007, Simons demonstrated in a study of 120 inner-city homes of children with asthma that the high airborne pollutant levels and inner-city home characteristics predisposed them to greater asthma morbidity (Simons et al. 2007). In addition to home, children with asthma will have exposures in other environments where they spend time, e.g. school (Kanchongkittiphon et al. n.d.). The indoor school environment is a reservoir of allergens, molds, pollutants, and endotoxin, and recent studies suggest a significant relationship between school allergen exposure and paediatric asthma morbidity (Esty and Phipatanakul 2018). Additionally, there is a paucity of high-quality evidence regarding single component interventions and indoor allergen exposure reduction and asthma outcomes (Leas et al. 2018).

1. Allergens

Dust mites

Dust mites are one of the most prevalent sources of indoor allergens and the most studied allergen in asthma development (Gaffin and Phipatanakul 2009). The most common dust mite species are Der f 1 (Dermatophagoides farinae) and Der p 2 (Dermatophagoides pteronyssinus). Dust mite allergens activate the adaptive and innate immune systems (Calderón et al. 2015), and Der f 1 induces inflammatory cell death in bronchial epithelial cells (Tsai et al. 2018). Almost 85% of allergic asthmatic children are sensitized to either or both dust mite species. In children who are sensitized to dust mite, dust mite exposure is associated with increased bronchial-hyper responsiveness, impaired respiratory function, and increased inflammation (Tsai et al. 2018).

Strategies to reduce dust mite include: frequent washing of all bed linens in hot water, use of allergen-impermeable mattresses and pillow encasements and dust mite reservoirs removal measures such as vacuuming, removal of carpet and stuffed toys and use of dust mite acaricides. Maintaining indoor humidity at 35–50% can reduce dust mite proliferation and survival but can be difficult to sustain. Moreover, HEPA filtration has not been shown to have a great effect on lessening dust mite exposure (Portnoy et al. 2013).

Rodents (Mice)

The major mouse allergen, Mus m 1, is excreted in mouse urine and found in dander and hair follicles. It is carried in the air in small particles and remains airborne for prolonged periods of time. It is found in house dust particles mostly in kitchens and bedrooms (Kopel, Phipatanakul, and Gaffin 2014), Recent studies demonstrate a high prevalence of mouse allergen in domestic households, where urban homes have higher mouse allergen levels compared to suburban and rural homes. Patient reports of rodent infestation have a high positive predictive value for high home mouse allergen levels (Loo et al. 2010).

Mouse allergen had the highest rate of detection than cockroaches in homes and schools but was significantly higher in schools in the School Inner-City Asthma Study. Mouse allergen exposure, independent of sensitization and home allergen exposure, was significantly associated with more asthma symptoms days and decreased FEV1 % predicted, suggesting the school environment's importance in urban asthma (Esty and Phipatanakul 2018).

Cockroach

Cockroach allergy has been established as an important cause of asthma exacerbations for the past few decades. The German cockroach (Blattella germanica) and American cockroach (Periplaneta americana) are the most medically important species. Cockroach allergens Bla g 1 and Bla g 2 are mostly evaluated in exposure assessment studies (Phipatanakul 2006).

Recent evidence based on skin prick testing, found that 60–80% of inner-city children with asthma are sensitized to cockroach. A study in 61 homes of low-income Chicago children also found that cockroach allergen exposure in bedrooms was associated with increased asthma symptoms (Turyk et al. 2006). Although less investigated, cockroach allergen is also detectable in suburban and rural homes, at lower concentrations.

Two components to cockroach allergen remediation are suppression of cockroach populations and removal of the residual cockroach allergen (Coleman et al. 2014). The New Orleans Roach Elimination Study was a randomized trial examining the effect of cockroach insecticidal bait on asthma symptom days. Interestingly, the intervention effect was associated with cockroach sensitization. Cockroach sensitized children in the control group had a significantly higher number of missed school days, symptom days and healthcare utilization. Notably cockroach numbers significantly reduced and stayed low for 6 to 12

months, but symptoms gradually improved over 6 to 12 months. This lag in symptom improvement has been attributed to the cockroach allergen in cracks, crevices and walls – suggesting professional cleaning and abatement is critical to comprehensive cockroach management (Portnoy et al. 2013).

Cat and Dog

Cat and dog are the most common indoor furry pets and sensitization is known to be associated with severe asthma in childhood. Allergic sensitization to cat and dog is quite common; approximately 12% of the general population and 25% to 65% of children with persistent asthma are sensitized to cat or dog allergens (Gergen et al. 2018). Fel d 1 and Can f 1 are the major allergens for cat and dog, respectively, and are present in saliva, hair follicles, and skin. Pet allergens are predominantly carried on small particles (<10–20 mm), allowing them to remain airborne for long periods of time and adhere to clothing and surfaces. Therefore, pet allergens are carried long distances, and are passively transferred to environments where no pets are present, leading to indirect exposure (Gergen et al. 2018). Children in classes with > 18% cat owners had a 9-fold increased risk of exacerbated asthma after school started compared with children in classes with ≤18% cat owners (Almqvist et al. 2001).

The ideal approach to furry pet allergen exposure reduction is to remove the pet from the home. The only study examining pet removal demonstrated that by 20 to 24 weeks after cat removal, most homes with pet cats had cat allergen levels similar to control homes without cats. Control of cat allergen exposure is needed by: pet removal from the home/bedroom; regular cleaning allergen reservoirs (upholstered furniture, walls, and carpet), encase the mattress and pillows with bed encasing (pore diameter <6 μm), regular pet washing and HEPA filtration (Gergen et al. 2018).

2. Molds

There is a wide variety of indoor and outdoor molds and their allergenic proteins vary by mold species. The most common species to which children are sensitized and exposed are Alternaria and Cladosporium (outdoor), Aspergillus and Penicillium (indoor). The prevalence of mold sensitization in children with persistent asthma is variable in the literature ranging from 12% to 66% (Byeon et al. 2017). Qualitative assessments of fungal exposure in the form of mildew odour or visible mold have been linked to increased risk of allergic rhinitis and asthma (Fukutomi and Taniguchi 2015). Furthermore, in 2019, Baxi SN conducted a study that demonstrated that the school/classroom environment can be a source of mold exposure both in quantity of spores and variety of mold types, and the presence of visible mold may be a predictor of high mold spore counts (Baxi et al. 2019).

Mold exposure can contribute to severe asthma and to asthma development. Mold sensitized children have significantly lower lung function and increased airway hyper-responsiveness compared to children not sensitized to mold (Byeon et al. 2017). Birth cohorts have demonstrated a relationship between mold sensitization and recurrent wheezing and asthma and a recent birth cohort study in Boston revealed a significant relationship between indoor dust-borne Alternaria at the age of 2 – 3 months and the frequency of wheeze, by one-year-old even after adjustment for outdoor airborne Alternaria concentrations (Behbod et al. 2013).

There are no solitary or randomized controlled trials of mold remediation. Mold remediation has only been included in multicomponent strategies (e.g. interventions also targeting dust mites or furry pet allergens), which have all showed improved asthma symptoms (Leas et al. 2018). Mold remediation includes: mold removal from surfaces (using cleaner and fungicide), repair of leaky water sources, dehumidification, and ventilator system installation. Mold remediation can be costly and burdensome. In 2016, Barnes et al., proposed a 2-part interview to guide clinicians on how to decide which patients would warrant in-home assessments for mold exposure with an indoor environment profession (IEP) (Barnes, Phipatanakul, and Larenas-linnemann 2017). Presently the literature insufficiently explains which children would be at-risk for developing asthma from mold exposure or if there is a dose-threshold of mold exposure that will exacerbate asthma.

3. Endotoxin

Endotoxin is part of the gram-negative bacteria's outer membrane and is shed after bacteria die. In 2012, Thorne conducted a study that established household endotoxin exposure as an important asthma risk factor that induces airway inflammation via Toll-like receptor (TLR) (Rennie et al. n.d.). Higher domestic endotoxin levels are linked to increased asthma prevalence, severity, and exacerbations. Endotoxin in homes has been demonstrated to increase wheeze and can potentiate the airway response to allergens in people with asthma. A cross-sectional study found: poverty, Mexican ethnicity, younger age, carpeting, furry pet, cockroaches, and/or a household smoker predicted higher endotoxin levels (Thorne et al. 2015). Endotoxin in other indoor areas such as the school also has an impact

on asthma morbidity. Sheehan et al identified higher settled-dust endotoxin levels in inner-city schools compared to students' homes. In this same cohort, classroom-specific airborne endotoxin levels were found to be independently associated with increased asthma symptoms in children with non-atopic asthma, after adjusting for home exposures (Lai et al. 2015).

Conversely, there is also literature supporting the contrary. Early endotoxin exposure is protective of childhood asthma (Karvonen et al. 2012). Endotoxin's protective qualities were recently highlighted by Stein et al, 2016 in their investigations of environmental exposures, ancestry and immune profiles of Amish and Hutterite children. None of the Amish children and 20% of the Hutterite children had asthma. The Amish homes had significantly higher median levels of endotoxin in airborne dust compared to the Hutterite homes, respectively. Endotoxin's protective and exacerbative roles in asthma underscores that the timing of exposures plays a critical role in asthma (Saranz 2017).

4. Genetics

Genetic variants and epigenetic changes are likely contributors to the origins of asthma, source of phenotypic variability, and response to therapy. Evidence of complex gene–environment interactions as seen in the increased risk of asthma in offspring of mothers who smoked during pregnancy and 17q21 variants are strongly associated with childhood asthma (Ramadas et al. 2008). Despite the progress in genetic research, our understanding is still limited as these genetic factors explain small proportion of total phenotypic variability, and the functional relationships between epigenetic processes, environmental stimuli and developmental programs (DeVries and Vercelli 2015). In 2018, Farzan et al examined the association of the rs7216389 (17q21 single SNP) with health care utilization and oral steroid bursts - from the pharmacogenetics in Childhood Asthma consortium. The rs7216389 SNP was significantly associated with asthma emergency room visits and admissions and use of oral steroid bursts (Farzan et al. 2018).

Innate immunity genes (CD14, TLR4 and TLR2, the critical mediators of responses to bacteria in the extracellular space) also play a prominent role among gene-environment interaction studies of asthma-related phenotypes (Vercelli 2010).

Physical Factors

Air pollution is a ubiquitous combination of pollutants including, particulate matter (PM), chemical and biological materials like carbon monoxide (CO), nitrogen dioxide (NO2), black carbon (CO), and sulphur dioxide (SO2). There is a multitude of evidence that ambient air pollution can exacerbate pre-existing asthma. Exposure to high levels of NO2, PM2.5 (aerodynamic diameter of 2.5 microns or less) and CO are associated with increased differentially methylated regions of the Foxp3 gene promoter region which was shown to be significantly associated with asthma (Prunicki et al. 2018).

A 2017 meta-analysis investigated the association between outdoor air pollution and asthma exacerbations, taking into consideration lag times between air pollution increase and asthma exacerbations. In the subgroup analysis of children, asthma exacerbations were significantly associated with higher concentration of NO2, SO2, and PM2.5. Even short term exposure to ozone, NO2, SO2 can increase children's asthma symptoms (Orellano et al. 2017).

Another study revealed a significant association between traffic-related air pollution exposure and higher hospital readmission rates. Such findings are critical for inner-city schools because of their close proximity to highways, heavy traffic, and industrial buildings. These establishments tend to be located centrally, among condensed traffic, with sites of idling cars increasing air pollution within and around the school (Pollock, Shi, and Gimbel 2017).

NO2, is generated from fossil fuel combustion in homes and outdoors but can be found in other settings. In 2018, Gaffin et al, showed a non-significant temporally distinct association of NO2 levels measured in inner-city school classrooms with airflow obstruction in children with asthma. This concordance was attributed to NO2 having adverse effects on health outcomes at levels undetected by the existing standards, in a susceptible population (Gaffin et al. 2018).

PM are airborne particles expressed as either PM2.5 or PM10–2.5 (aerodynamic diameter more than 2.5 microns to 10 microns). PM2.5 is associated with worsening asthma symptoms and increased oxidative stress based on inflammation biomarkers (Pollock et al. 2017).

In 2018, Bouazza et al found an association between PM2.5 and ED paediatric visits. There is less data on the long-term consequences of PM10–2.5 due to the lack of monitoring locations for both PM10 and PM2.5. Additionally, PM10–2.5 is thought to be less harmful than PM2.5, as its size may limit its lung penetration (Bouazza et al. 2018) but Keet et al., found that PM10–2.5 was associated with increased asthma prevalence and healthcare utilization (Keet, Keller, and Peng 2018).

Psychosocial Factors

The psychosocial environment is becoming increasingly recognized as a significant contributor to asthma morbidity. It includes a person's neighbourhood, caregiver stress, socioeconomic status, family relationships and social networks (Chen and Schreier 2008).

Kopel et al., 2015, demonstrated that the primary caregiver's perception of neighbourhood safety is associated with childhood asthma morbidity among inner city schoolchildren with asthma; and caregiver stress is related to asthma morbidity among children (Kopel et al. 2015).

Chen et al., 2017, investigated whether living in areas high in greenspace would help balance the effects of difficult family relationship for children with asthma. A synergistic effect of positive family relationships across the physical and social domains was seen, and children with asthma benefited the most when they lived in high greenspace areas and had positive family relationships (Chen et al. 2017).

It has also been recently evaluated as a contributor to poor outcomes in medical conditions. Thakur et al, 2017, investigated the association between perceived discrimination and asthma status and morbidity in Black and Latino youth with asthma. Blacks reporting any severity of discrimination had a 78% increased odds of having asthma and 97% increased odds of poor asthma control (Thakur et al. 2017).

Structural discrimination can impact asthma as it can manifest as unequal access to high-quality medical resources, sub-standard housing and lack of home ownership and living in neighbourhoods with higher levels of pollution (e.g. closer proximity to highways, pollutant producing factories). The 2011 American Housing Survey was analysed by Hughes et al, who found that poor housing quality was significantly associated with asthma diagnosis and Emergency Department visits. Home ownership was associated with lower odds of asthma emergency department visits (Shamasunder et al. 2018).

Diagnosis of asthma

The diagnosis of asthma involves a thorough medical history, physical examination, and assessments of lung function (spirometry) to confirm the diagnosis. Challenge testing and markers assessment of airway inflammation may also be used in diagnosing asthma especially when lung functions are normal in the presence of asthma symptoms (Anon 2014).

Patients with a medical history of recurrent cough, wheeze, chest tightness and shortness of breath that occur on exposure to allergens or irritants, that worsen at night, and that respond to appropriate asthma therapy are strongly suggestive of asthma (Kaplan et al. 2009). It is also important to examine for possible triggers such as dust mites, cockroaches, animal dander, molds, pollens, exercise, and exposure to tobacco smoke or cold air.

A positive family history of asthma or other atopic diseases and/or a personal history of atopic disorders, particularly allergic rhinitis, can be used to identify patients with asthma. Exposure to agents encountered in the work environment can also cause asthma. It is also important to assess for comorbidities that can aggravate asthma symptoms, such as allergic rhinitis, sinusitis, obstructive sleep apnea and gastroesophageal reflux disease (Kaplan et al. 2009).

The diagnosis of asthma in young children is more difficult since episodic wheezing and cough are relatively common in this population and spirometry is unreliable in patients under 6 years of age. A useful method of confirming the diagnosis in young children is a trial of treatment with short-acting bronchodilators and inhaled corticosteroids (ICSs). A great clinical improvement during treatment and deterioration upon cessation of therapy supports a diagnosis of asthma (Kovesi et al. 2010).

Physical findings are only evident if the patient is symptomatic and so the absence of physical findings does not rule out a diagnosis of asthma. The most common physical finding is wheezing on auscultation, which confirms the presence of airflow obstruction (Anon 2014). Healthcare providers should also examine the upper respiratory tract and skin for signs of other atopic conditions such as allergic rhinitis or dermatitis (Kaplan et al. 2009).

Spirometry is mostly used to assess for reversible airway obstruction (i.e., rapid improvement in lung function after inhalation of a rapid-acting bronchodilator) and to confirm a diagnosis of asthma. It is recommended for all patients over 6

years of age who are able to undergo lung function testing (Anon 2014). During spirometry, the patient is instructed to take the deepest breath possible and then to exhale as hard and as fully as possible into the mouthpiece of the spirometer. The instrument measures the forced vital capacity (the maximum volume of air that can be exhaled) and the forced expiratory volume in 1 second (FEV1). The ratio of FEV1 to FVC provides a measure of airflow obstruction. A diagnosis of asthma is confirmed when there is an improvement in FEV1 of at least 12% and at least 200 mL 15–20 minutes after administration of an inhaled rapid-acting bronchodilator or an improvement in FEV1 of at least 20% and at least 200 mL after 2 weeks of treatment with an anti-inflammatory agent (Anon 2014; Kaplan et al. 2009).

When lung function tests are normal, but there are symptoms suggestive of asthma, challenge tests can be done. They can include using direct airway challenges to inhaled bronchoconstriction stimuli (e.g., methacholine or histamine) or indirect challenges with mannitol or exercise may help confirm a diagnosis of asthma. Testing involves the patient inhaling increasing doses or concentrations of a stimulus until a given level of bronchoconstriction is achieved, typically a 20% fall in FEV1. An inhaled rapid-acting bronchodilator is then provided to reverse the obstruction. Test results are usually expressed by use of dose or concentration of the provoking agent that causes the FEV1 to drop by 20% (the PD20 or PC20, respectively). For methacholine, a PC20 value less than 8 mg/mL is considered a positive result indicative of airway hyper reactivity, and supports a diagnosis of asthma (Byeon et al. 2017).

The measurement of inflammatory markers such as sputum eosinophilia or levels of exhaled nitric oxide (produced by some cells on inflammation) can also be useful for asthma diagnosis. Evidence suggests that exhaled nitric oxide levels may be better able to identify asthmatic patients than basic lung function testing and in monitoring patient response to asthma therapy (Kaplan et al. 2009) .

Allergy skin testing is also recommended to determine the allergic status of the patient and to identify possible asthma triggers. Testing is typically performed using the allergens relevant to the patient's geographic region (Anon 2014; Byeon et al. 2017; Fukutomi and Taniguchi 2015).

Treatment of asthma

The primary goal of asthma management is to achieve and maintain control of the disease in order to prevent and reduce the risk of morbidity and mortality (Kim and Mazza 2011). In most asthma patients, control can be achieved through the use of both avoidance measures to relevant allergens/irritants and pharmacological interventions. The pharmacologic agents can be classified as controller and reliever medication (Anon 2014; Nantanda et al. 2013).

Controller medications

They are drugs taken daily for a long period of time so as to achieve control through anti-inflammatory effects. They include ICSs, leukotriene receptor antagonists (LTRAs), long-acting beta2-agonists (LABAs) in combination with an ICS, and anti-IgE therapy.

Inhaled corticosteroids (ICSs) - are the most effective anti-inflammatory medications available for the treatment of asthma. Low-dose ICS monotherapy is used as first-line maintenance therapy for most children and adults with asthma. Regular ICS use has been shown to reduce symptoms and exacerbations, and improve lung function and quality of life. For most children, ICS moderate dose is the preferred approach to achieve control, while the addition of another class of medications (LABA) is recommended for patients over 12 years of age (Lougheed et al. n.d.). The most common local adverse events associated with ICS therapy are oral thrush and dysphonia (difficulty speaking). Rinsing and expectorating (spitting) after each inhalation or the use of a spacer device can help reduce the risk of these side effects. Systemic adverse effects with ICS therapy are rare, but may include adrenal suppression, changes in bone density, cataracts, glaucoma and growth retardation (Anon 2014).

Leukotriene receptor antagonists (LTRAs) that include; Montelukast and Zafirlukast are generally considered to be safe and well tolerated. However, they are less effective than ICS treatment when used as monotherapy and therefore reserved for patients who are unwilling or unable to use ICSs. LTRAs can also be used as add-on therapy if asthma is uncontrolled despite the use of low-to-moderate dose ICS therapy (Anon 2014; Nakagome and Nagata 2021).In children, however, the data are less clear and, therefore, the child's symptoms and the presence of comorbidities may help direct treatment. For example, if a child with asthma also has allergic rhinitis, the addition of montelukast should be considered. The combination of a LABA and ICS has been shown to be highly effective in reducing asthma symptoms and exacerbations and is the preferred treatment option in adolescents or adults whose asthma is inadequately controlled on low-dose ICS therapy, or in children over 6 years of age who are uncontrolled on moderate ICS doses (Lougheed et al. n.d.).

Theophylline is an oral bronchodilator with modest anti-inflammatory effects with a narrow therapeutic window and frequent adverse events like; gastrointestinal symptoms, loose stools, seizures, cardiac arrhythmias, nausea and vomiting. It is therefore reserved for patients whose asthma is uncontrolled despite an adequate trial of ICS, LABAs and/or LTRAs (Anon 2014).

Reliever medications

They are medications used on attack or whenever necessary for quick relief of symptoms. They include rapid-acting inhaled beta2-agonists and inhaled anticholinergics.

Inhaled rapid-acting beta2-agonists are the most preferred medications for the treatment of acute symptoms, and should be prescribed to all patients with asthma. In Canada, several short-acting beta2-agonists (SABAs; e.g., salbutamol, terbutaline) and one LABA (formoterol) are approved for this indication. SABAs should only be taken on an as needed basis for symptom relief. Increased use of 3 or more times per week, indicates worsening control and signals the need to reassess treatment to achieve control of symptoms. Unlike other LABAs, formoterol has a rapid onset of action and, therefore, can be used for acute symptom relief. However, given that LABA monotherapy has been associated with an increased risk of asthma-related morbidity and mortality, formoterol should only be used as a reliever in patients 12 years of age or older who are on regular controller therapy with an ICS (Anon 2014).

Short-acting anticholinergic bronchodilators, such as ipratropium bromide, may also be used as reliever. However, they appear to be less effective than inhaled rapid-acting beta2-agonists and are reserved as second-line therapy for patients who are unable to use SABAs. They may also be used in addition to SABAs in patients experiencing moderate to severe asthma exacerbations. Chronic SABA therapy is not recommended for use in children (Lougheed et al. n.d.).

Allergen-specific immunotherapy may also be considered in most patients with allergic asthma. It involves the subcutaneous administration of gradually increasing quantities of the patient's relevant allergens until a dose is reached that is effective in inducing immunologic tolerance to the allergen. Although it has been widely used to treat allergic asthma, it is not universally accepted by all clinical practice guideline committees due to the potential for serious anaphylactic reactions with this form of therapy (Frew 2010). A Cochrane review of 75 randomized controlled trials examining the use of allergen-specific immunotherapy in asthma management confirmed its efficacy in reducing asthma symptom scores and medication requirements, and improving airway hyper responsiveness (Abramson, Puy, and Weiner 2010).

At present, allergen-specific immunotherapy should be considered on a case-by-case basis. It can be used prior to a trial of ICS therapy in patients with very mild allergic asthma and concomitant allergic rhinitis and as add-on therapy in patients using ICSs alone (Zielen, Kardos, and Madonini 2010). Allergen-specific immunotherapy may also be considered in patients using combination inhalers, ICS/LTRAs and/or omalizumab if asthma symptoms are controlled. Since allergen-specific immunotherapy carries the risk of anaphylactic reactions, it should only be done by practitioners who have received enough training in treatment of allergy (Frew 2010).

Systemic corticosteroid therapy like with oral prednisone may also be required for the management of acute asthma exacerbations (Zielen et al. 2010).While chronic systemic corticosteroid therapy may also be effective for the management of difficult to control asthma, prolonged use of oral steroids are associated with serious adverse effects that may include: reversible abnormalities in glucose metabolism, increased appetite, oedema, weight gain, rounding of the face, mood alterations, hypertension, peptic ulcers and avascular necrosis. So long term use should be avoided at all cost (Lougheed et al. n.d.).

Conclusions

The literature cited in this review demonstrates clearly that the environment plays a very critical role in asthma control. This shows that even if caregivers are advised to keep their asthmatic children away from triggers known to them, there may be other factors in the real-world setting that may make it difficult for them to do this effectively. Mental illness has become a critical issue in present days as more and more people suffer in silence. This review has highlighted that this issue is part of the environment children are exposed to and it also affects asthma control. In this case, efforts to improve asthma outcomes should not only include avoiding physical allergens but also mental or psychosocial interventions. This review has also highlighted the fact that psychological environment has not been extensively explored as evidenced by the number of studies found. We are certain that this review forms a basis for researchers to further explore the psychosocial environment and generate more information that will help lower the prevalence of asthma.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

The first and the second author contributed equally to the conceptualization and writing of the article.

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