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Review article

Preschool wheeze: the gaps and the prospects?

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Introduction

Wheezing in preschool children is one of the most commonly presented symptoms in everyday pediatric practice [1] occurring in a third of children by their third birthday and half of children by 6 years. The prevalence of parent reported wheeze in 2-year-old children was 2–17% in the European EuroPrevall birth cohort study. Preschool wheeze (PSW) is associated with significant healthcare resource utilization, accounting for approximately 75% of all childhood hospital admissions for acute wheeze and associated with significant impact on family quality of life. [2]

PSW has been classified in several different ways, based on time of appearance, natural history, comorbidities, and triggers. Some of these children with different phenotypes of wheezing will develop asthma later in life. However, until the diagnosis is confirmed, decision making regarding the proper treatment is uncertain and challenging. [1]

PSW can be described as a multifactorial disease influenced by various genetic and environmental factors. Early viral infections, bacterial colonization and allergen sensitization are among the most important in causing wheeze and the subsequent development of asthma. These early life exposures, together with genetically determined susceptibility, can affect the immune system early in life with a major impact on the natural history of the disease. [3]

This review aims to discuss different phenotypes of preschool wheeze, underlying mechanisms, natural history and possible risk factors.

Definition of Preschool wheeze (PSW)

Wheezing is described by the European Respiratory Society (ERS) as "a soft polyphonic noise or whistling sound heard mainly expiratory, caused by turbulent airflow occurring simultaneously in airways of different caliber**.** [4]

The term PSW has not been appropriately defined, and it varies significantly among countries regarding the age of diagnosis; for example, a 2-5 years gap according to the Centers for Disease Control and Prevention (CDC), less than 4 years in the United Kingdom (UK), and less than 7 years in Scandinavian countries and Poland.[1]

Prevalence and importance of PSW

PSW is common: Wheezing has tripled in prevalence over the past 30 years. Wheezing affects one in three children during the first 3 yrs of life and almost 50% of all preschool children suffer at least one episode of wheezing before 6 years of age; of these, nearly 40% have recurrent wheezing episodes during early life.[5] In a retrospective cohort study conducted on 1209 Egyptian children aged 6-10, prevalence of recurrent PSW was found to be 24.6% with 10.3% of the whole cohort progressing to childhood asthma. [6]

PSW is troublesome: It is true that not all preschool wheezers will go on to become asthmatic and 60% will end up being asymptomatic by 6 yrs, yet the course of PSW is not without hardships**.** Compared with older children with persistent asthma, preschool children with recurrent wheezing have nearly twice the rate of outpatient physician visits and emergency department (ED) visits and more than 5 times the rate of hospitalization because of the wheeze flare ups. Missed days from work and impaired caregiver functional status are also significant concerns that drive the growing economic burden of wheezing in preschool children.[5]

PSW is not without morbidity: Although wheezing pathobiology and the severity, frequency, and persistence of wheezing in later childhood vary among affected children, those with recurrent wheezing experience obvious morbidity. Early life, whether in utero or in the first few years of life, presents a window of vulnerability during which airway injury results in persistent airway dysfunction. [7] At the age of 5 yrs, airway resistance was observed to be higher in children with early or recurrent wheeze compared to never wheezers. Also, persistence of PSW to school age, even if it subsequently remits, was linked to lower pulmonary function and chronic lung disease; the magnitude of

the reduction was approximately a 10% lower predicted forced expiratory volume in 1 s (FEV_1), compared with healthy peers. Airway remodeling was documented in toddlers.[8]

In a study to determine the prognosis for never, transient wheezers, persistent and late-onset wheezers., with reference to lung function and symptoms, through adolescence, Morgan et al reported that persistent wheezers had forced expiratory flows that were slightly lower but not significantly different from those of never wheezers at age 2.4 months, whereas transient early wheezers had significantly diminished flows at that age. at age 6 years, both these groups had significantly lower flows than never wheezers. Diminished flows were still present at ages 11 and 16 years for persistent wheezers; however, there did not appear to be any further decline with age relative to their peers. Transient early wheezers did not change their position, relative to their peers, from age 6 to 16 years (**figure 1**). [9]

Natural Course of preschool wheezing: The need for timely and stronger predictors of outcome

From epidemiologic data, several early childhood wheezing phenotypes were described based on the natural history and risk factors associated with each.[10]

PSW can be categorized in four different ways: based on timing, triggers, severity of wheeze, or presence of allergy. [11] The Tucson Children Respiratory Study (TCRS) presented the first longitudinal classification of children into four distinct wheeze phenotypes:, children who never wheezed (51%), transient early wheezers: children presented with recurring wheeze until age of three years, but grew out of wheeze by age of six years (20%), late-onset wheezers: these children did not wheeze in the first three years of life but had wheeze at age six years (15%), persistent wheezers: these children had an onset of wheeze in early life which persisted to age of six years (14%). [12] Two wheezing phenotypes were recognized to be associated with increased risk of persistent wheezing at 16 years : the persistent and the late-onset wheezing phenotypes**.** [13]

Subsequent prospective studies based on Tucson cohort led to revised definitions of the three groups of wheezers. The transient wheeze in infancy begins in infancy and resolves by age of 3 years; it is associated with decreased lung function, [14] maternal tobacco smoking during pregnancy, having siblings, and daycare attendance. [15] The non-atopic persistent wheezing begins in infancy and resolves in early school years; it is associated with positive peak flow variability [14] and represents nearly 40% of patients with persistent wheeze. This group usually presents as episodic attacks of wheeze triggered mainly by viral illness; thus, often referred to as a virus-induced wheeze (VIW).[12] The IgE-associated and/or atopic persistent wheezing accounts for 60% of persistent wheezing cases and usually begins in the second year of life and persists into late childhood. The risk factors in this subgroup include male sex, a family history of asthma [12] or atopic dermatitis (AD), house dust mites (HDM), eosinophilia in the first year of life, and early sensitization to food and aeroallergens.[16]

The ALSPAC (formerly the Avon Longitudinal Study of Pregnancy and Childhood) prospective longitudinal cohort study conducted on 6265 children to evaluate wheezing from birth to 7 years added two additional phenotypes to those of the Tucson study: the prolonged early wheeze (9%), in which wheezing is common from 6 to 54 months but rare to never after 69 months; and the intermediate-onset wheeze (3%), in which wheezing is rare to never from 6 to 18 months but common thereafter. [17] They were described with the continued longitudinal follow-up and incorporation of objective measures (e.g., lung function and allergen sensitization). A parental history of asthma, mainly maternal, and a personal history of atopic disease were among the risk factors for developing wheezes. [18] Early infancy wheezing was associated with other factors, such as maternal smoking during pregnancy and the presence of older siblings. [10]

PSW phenotypes in low to middle income versus high income countries

There are few birth cohorts from low- and middle-income countries, in the face of around 18 from high-income countries. The Drakenstein Child Health Study, a South African birth cohort, described 3 phenotypes, the early transient, the late onset, and the recurrent phenotype. Differences from cohorts in high-income countries were earlier age of onset (median 8·3 mo (IQR 3·3–16·8)), respiratory syncytial virus (RSV) was most strongly associated, and absence of a persistent phenotype. The late onset phenotype was observed in one fifth of wheezers. [19]

It is to be noted that the phenotypes used in epidemiological studies (transient versus persistent wheeze) are longitudinal definitions, and an important drawback is that these can only be established retrospectively. Therefore, this phenotype categorization had little to no value for treatment decisions early on in life and for planning

measures for prevention; not to mention. deciding about the prognosis of asthma.

Phenotypes based on triggering factors

The European Respiratory Study (ERS) symptom-based classification recognized episodic (viral) wheeze (VIW) described as wheeze with viral infections only, with absence of wheeze in between episodes, and multiple-trigger wheeze (MTW), which is wheeze on exposure to a variety of triggers, rather than solely with viral infections with wheezing continuous between exacerbations. The most important triggers were tobacco smoke and allergen exposure, but some children may also wheeze in response to mist, crying, laughter or exercise. Airway function was observed to be lower in MTW than in episodic phenotype, which suggested that these are distinct phenotypes. [20] However, multiple studies pointed out that wheeze patterns varied over time and could sometimes overlap in young children. This made it difficult to distinguish between EVW and MTW.

Trajectories of PSW exacerbations

The PSW phenotypes, or the courses of symptom development, appear to be heterogeneous and are poor prognosticators. Rather, it is the severity and frequency of wheezing episodes which are the stronger predictors of long-term outcome. [11]

Longitudinal trajectories of severe wheeze exacerbations were studied from infancy to school age; 498/887 children (56%) had physician-confirmed wheeze by age 8 years, of whom 160 had at least one severe exacerbation. Two distinct trajectories of severe exacerbations were identified: Infrequent exacerbations (IE) (93.7%) and early-onset frequent exacerbations (FE) (6.3%). Shorter duration of breastfeeding was the strongest early-life risk factor for FE. Specific airway resistance (sR_{aw}) was significantly higher in FE compared with IE trajectory throughout childhood. At age 8 years, FEV_1 /FVC was significantly lower and FeNO significantly higher among FE group with higher probability to develop asthma and use inhaled corticosteroids (ICS) by adolescence. [21]

Risk factors of asthma development

Genetic, environmental, developmental, and host factors may contribute solely or combined to the development, severity, and persistence of the asthma over time. [22] Early viral infections, bacterial colonization and allergen sensitization are among the most important risk factors in causing wheeze and the subsequent development of asthma. These early life exposures, coupled with genetically determined susceptibility, can affect the immune system in its early stages of development and have a major impact on the natural history of the disease. Persistent wheezing was also related to preterm delivery and lower socioeconomic status.[10] Identifying risk factors may allow the identification of measures and interventions to prevent the development of preschool wheezing and its evolution into childhood asthma. [3]

Genetic factors:

Genetic studies on asthma revealed a large number of candidate genes associated with immune system modulations that are potentially involved in the pathogenesis of early life wheeze. [23] Genome-wide association studies (GWAS) identified several associated single nucleotide polymorphisms (SNPs), including the 17q12–21 region, which increased the risk of wheeze persistence, [2] and was found to be associated with rhinovirus wheezing in childhood. [11] Moreover, GWAS identified IL33 and IL-1 receptor-like 1 (IL1RL1)/IL18R1 as asthma susceptibility loci. IL33 and IL1RL1 were highly associated with intermediate onset wheeze, late onset wheeze and persistent wheeze phenotypes. [24] This pathway is under clinical evaluation for potential biological therapy for childhood asthma. Interleukin-33 (IL33) blockade with monoclonal antibody itepekimab led to better asthma control than placebo, and improved lung function and quality of life in adult patients with moderate-to-severe asthma. [25]

Viral Infections:

Viral wheezing illnesses during childhood are widespread. Using sensitive molecular viral diagnostics, viral pathogens have been demonstrated in up to 90% of acute wheezing episodes in the first 3 years of life. The types of viruses detected during that period included human rhinovirus (HRV), respiratory syncytial virus (RSV), parainfluenza (PIV), human metapneumovirus (MPV), coronavirus (CoV), adenovirus (AdV), influenza viruses (IFV), and bocavirus, with RV and RSV being the most important. [26]

HRV. HRVs are detected in 60%–90% of asthma exacerbations in different populations. Three distinct species, HRV-A, HRV-B, and HRV-C have been characterized; the C and the A were found to prevail in asthma exacerbations. [26] In a metanalysis, HRV wheezing illness in the first 3 years of life was associated with an increased risk of wheezing/asthma in later life (relative risk (RR)=2.00, 95% CI 1.62 to 2.49, $p<0.001$).[27]

Wheezing with HRV infection was a strong predictor of future wheezing episodes, and this prediction was higher in atopic individuals. [28] HRV wheezing illness in the first year of life was associated with increased asthma risk at 5 and 10 years only in those with aeroallergen sensitization at 2 years of age. HRV infections may increase airway sensitization and inflammation through altering the epithelial barrier, inducing the release of epithelial cytokines (i.e., IL-25 and IL-33) through T-helper 2 (Th2) stimulation and production of IL-4, IL-5 and IL-13, stimulating the production of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, IL-1α, IL-1β and eventually contributing to airway remodeling by stimulating angiogenesis and differentiation of myofibroblasts with the release of extracellular matrix proteins. [3]

In the meantime, allergic inflammation impairs antiviral responses. through bias toward Th2 rather than effective anti-viral Th1 responses. [2] The Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) trial showed that omalizumab treated children had a restored anti-viral IFN-α response to rhinovirus. This suggested that omalizumab may prevent IgE driven responses to offending allergens and attenuate viral infections in those with Type 2 asthma. [29]

RSV. Several epidemiological studies demonstrated that a history of severe RSV bronchiolitis is associated with subsequent persistent wheezing, childhood asthma or both. [30] RSV is the most common viral pathogen causing bronchiolitis in infancy. In children less than 5 years of age, it has been estimated that more than 3 million hospitalizations can be attributable to RSV infection globally, leading to approximately 60,000 deaths each year.[28] In 2021–2022 and 2022–2023, multiple countries experienced RSV epidemics with both altered seasonality and increased case counts relative to former RSV seasons.[31] This surge came 2 years after a season with no cases detected as a result of coronavirus disease 2019 nonpharmaceutical interventions (social distancing and masking) reduced RSV transmission, resulting in an increase in the pediatric population naïve to RSV. [32] Post pandemic RSV season showed surges in hospitalization for all ages, and severity and a shift of age distribution toward the 2- to 5-year age group, [33] the long-term health consequences of which remain to be determined.

In as much as HRV is closely linked to wheezing in high income countries, RSV seems to be the major player in less developed ones. The South African birth cohort showed that RSV infections were associated with all three wheezing phenotypes, the early, the late and the recurrent, whereas other respiratory viruses (rhinovirus, adenovirus, influenza, parainfluenza-virus) were observed at an older age and were not associated with any wheeze phenotype.[19] RSV infection causes necrosis of the bronchiolar epithelium with subsequent submucosal oedema, recruitment of polymorphonuclear leukocytes and massive release of pro-inflammatory mediators, increased mucus secretion and bronchoconstriction,[3] with a profound imbalance in type 1/type 2 cytokines with deficient type 1 and excess type 2 responses.

Hence, RSV seems to act as an "inducer" rather than a "trigger", it mainly affects infants and young children during a short epidemic season. Prematurity and young age are strong risk factors to developing severe lower respiratory tract symptoms. HRVs seem to act as a "trigger" rather than an "inducer", affecting all age groups including adults (figure 2). [30]

The risk of recurrent wheezing during preschool years may be significantly decreased by prophylaxis with RSV vaccines. RSV vaccine development began in the 1960s with an unsuccessful formalin-inactivated vaccine that induced a severe – and in two cases lethal – lung inflammatory response during the first natural RSV infection after vaccination of RSV-naive infants. Currently, there are available options for preventing (nirsevimab) and treating RSV in high-resource settings.

Airway bacterial pathogens

Airway bacteria can also trigger the development of asthma.**[28]** The most common bacterium found in upper airways in childhood include Staphylococcus, Streptococcus, Moraxella, Haemophilus, Dolosigranulum, and Corynebacterium.[35] In children aged 0 to 3 years, pathogenic bacteria have been identified in 86% of wheezing episodes of which 31% were exclusively bacterial. [28] In the prospective cohort Childhood Asthma Study (CAS), asymptomatic colonization with Streptococcus at the age of 2 months was associated with earlier respiratory tract infections and persistent wheeze at 5 years.[36] Viral respiratory tract infections were found to induce microbiome instability with shifts to a Moraxella, Streptococcus, or Hemophilus dominant state.[36] Cross-sectional cohort studies have demonstrated increased Moraxella and Hemophilus with rhinovirus bronchiolitis, whereas RSV bronchiolitis

had increased Streptococcus and Hemophilus species. [35]

Gut microbiome and mycobiome

Infants' acquisition of intestinal microbiome starts at the time of delivery, and an adult-like state is achieved by 12–36 months, paralleling the period of immune system. [37] It is hypothesized that colonization with protective gut microbiota has a direct anti-inflammatory effect on the respiratory tract, decreasing airway hyperreactivity.[10] Microbial metabolites might play a crucial role in maintaining an adequate immune balance and preventing asthma through its influence on regulatory T-cells (Tregs) and the Foxp3 gene. during pregnancy, caesarean delivery, prematurity An alteration in the gut microbiome (dysbiosis) may often occur during the initial gut colonization of the newborn, as a consequence of maternal dysbiosis or the excessive use of antibiotics perinatally.[38] Dysbiosis is associated with both the development of atopic diseases and increased susceptibility to viral infections. Gut microbial dysbiosis in the first year of life was associated with asthma in multiple birth cohort studies (**figure 3**). [39]

The fungal microbiome, known as the mycobiome, a small but crucial component of the gut microbiome, has gained attention as a role player in human health and disease.[40] Gut mycobiome studies in infant populations referred to significant associations between mycobiome alterations and subsequent asthma and atopy susceptibility.[41] A study conducted on 200 Egyptian wheezy infants aged 2-36 months, showed increased risk of PSW in association with treatment with antibiotics during the first week of life among other risk factors. Therefore, alteration of the microbiota map through early exposure to antibiotics, can deviate the immune responses and modify the immune tolerance, which in turn would augment the risk of wheezes and atopy.[42]

Allergen sensitization and Atopy

Multiple aeroallergen sensitization are associated with persistent wheezing and development of asthma. Atopy and allergy have a pivotal role as risk factors in preschool wheezing, as shown by many studies conducted over the past years. [3] In the Multicenter Allergy Study (MAS), high exposure to indoor allergens (mites, and cat and dog epithelia) was found to be a risk for specific sensitization, which was linked to the development of asthma at 11-13 years and impaired lung function at early school age. [43] Prenatal and postnatal tobacco smoke exposure, parental atopy, co-existence with eczema or allergic rhinitis increased the development of specific allergic sensitization and asthma.[44]

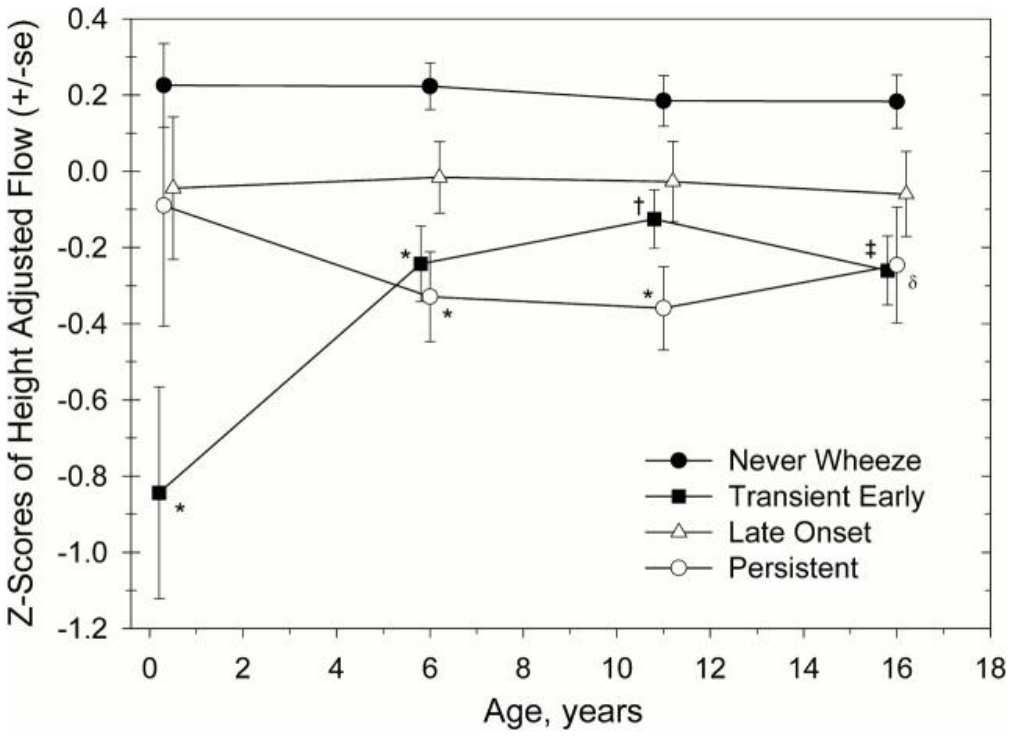

Figure 1. Cross-sectional *z* scores of height-adjusted maximal expiratory flows at ages 24 mo and 6, 11, and 16 yr for the preschool wheeze phenotypes.[9]

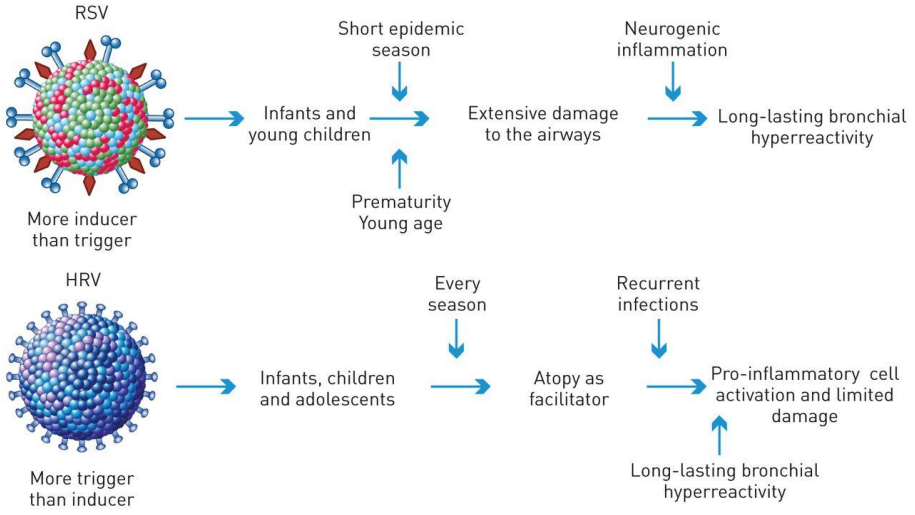

Figure 2. The two different prototypes of viral-induced respiratory infections[30]
RSV: Respiratory syncytial virus, HRV: Human rhinovirus

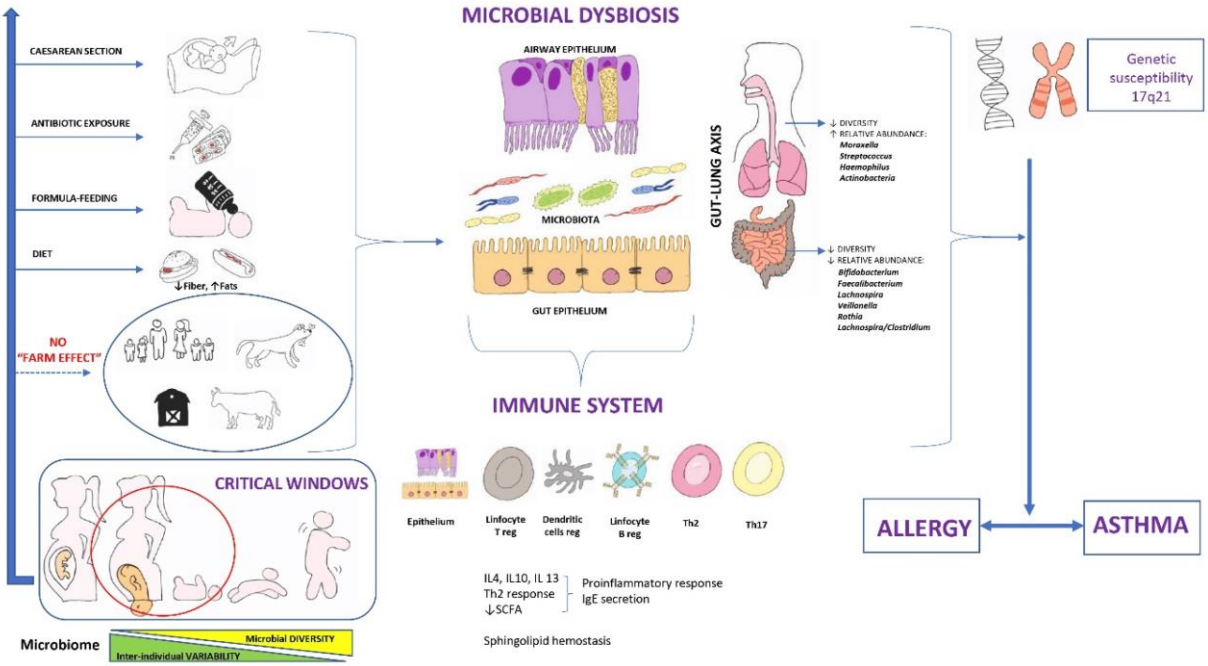

Figure (3): Microbial dysbiosis as an early origin of asthma [38]
Th: T helper, T reg: T regulatory, IL: Interleukin, SCFA: Short chain fatty acids

Similarly, in the Urban Environment and Childhood Asthma (URECA) study, cumulative exposure over the first 3 years of life to cockroach, mouse, and HDM allergens in the home was associated with sensitization to those allergens at age 3. Also, sensitization to any food or any aeroallergen was associated with recurrent wheeze at 3 years. [45] Six phenotypes, differentiated by patterns of wheezing and allergic sensitization were identified; low wheeze/low atopy (22%), low wheeze/high atopy (19%); transient wheeze/low atopy (17%), moderate wheeze/low atopy (12%), moderate wheeze/high atopy (17%), high wheeze/high atopy/low lung function (13%). [46,47] Environmental exposures early in life were found to differentiate these phenotypes. The high-wheeze/high-atopy/low lung function and high-wheeze/low-atopy phenotype groups were associated with low indoor allergen exposure and a high frequency of asthma by age of seven years. The high wheeze/high atopy/low lung function group also demonstrated the highest respiratory morbidity. [10]

Atopy was evaluated in a cohort of 298 Egyptian preschool wheezers by skin prick test (SPT). Eighty three percent (83.1%) showed positive result by SPT with the majority most sensitized to aspergillus fugimatus, HDM, pollen, cat epithelia and cockroach in a descending order. [6] Rhino-conjunctivitis and eczema increase the likelihood of persistent asthma, and persistent atopic asthma associated with concomitant childhood eczema or rhinitis predicted a nearly 12-fold increase in the risk of adult atopic asthma. [48] Through latent class analysis (LCA), Fitzpatrick and colleagues identified four latent classes of recurrent PSW on the basis of type-2 inflammatory features including blood eosinophils, atopic eczema, aeroallergen, and food sensitization and/or pet exposures. The probability of exacerbation was greater in children with sensitization and indoor pet exposure (latent class 2) and children with multiple sensitization and eczema (latent class 4). Overall, in children sensitized to aeroallergens, exacerbations were higher than in children with minimal sensitization (latent class 1- sporadic eczema, low blood eosinophils, low serum IgE levels, >90% with no sensitization to aeroallergen and food) or with sensitization plus tobacco smoke exposure (latent class 3) with no exposure to pet. [5] In a study on the effect of food allergy, asthma at age of 4 years was twice as common in those with challenge-proven food allergy at age of 1 year, irrespective of whether the food allergy subsequently resolved. Children with 2 or more food allergies and those with coexistent eczema were almost 3 times as likely to develop asthma compared with those with no food allergies. [49]

The Severe Asthma Molecular Phenotype cohort study described three clusters of severe recurrent wheeze and severe asthma during childhood in terms of triggers (allergic or not), involved cells (eosinophil or neutrophil), and response to ICS; cluster 1: Neutrophilic steroid-refractory recurrent wheeze phenotype, with children uncontrolled despite high-dose ICS, high incidence of pneumonia, more gastroesophageal reflux disease, and the highest blood neutrophil count; cluster 2: severe recurrent wheeze with sensitization to a single aeroallergen, with children controlled with high-dose ICS; cluster 3: eosinophilic steroid-refractory asthma phenotype, with children uncontrolled despite high-dose ICS with more allergic rhinitis, atopic dermatitis, and food allergies. They also had a higher blood eosinophil count and a higher percentage of BAL eosinophil. [50]

Recent studies have expanded the focus to include environmental influences and the impact of early life intervention. [51 52] In a secondary analysis of the data of the Canadian Asthma Primary Prevention Study (CAPPS), conducted on children at high risk of asthma, intervention measures implemented during the third trimester and first post-partum year including avoidance of house dust, pets, and environmental tobacco smoke and encouragement of exclusive breastfeeding with delayed introduction of solid foods and delayed daycare enrollment were effective in decreasing the risk of wheezing during mid-childhood in the early-persistent group. [53]

CONCLUSION

PSW and subsequent development of childhood asthma is a common public health problem that not only affects children's lung health and quality of life, but also burdens the healthcare system. Nation-focused studies should be done to identify and target risk factors and common exposures, specific to each country, that can lead to PSW and the evolution into asthma. Based on such good knowledge, new effective prophylactic measures and lines of treatment can be developed to prevent PSW or reduce its impact on child's health.

CONFLICTS OF INTEREST

Authors declare they have no conflicts of interest.

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