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REVIEW

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Pediatric asthma comorbidities: Global impact and unmet needs

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ABSTRACT

Real-world data on the range and impact of comorbid health conditions that affect pediatric asthma are scant, especially from developing countries. Lack of data hinders effective diagnosis, treatment, and overall management of these complex cases. We, hereby, describe the common pediatric asthma comorbid conditions in terms of evidence for association, potential mechanisms of impact on asthma control, and treatment benefit. Obesity, upper airway allergies, dysfunctional breathing, multiple sensitizations, depressive disorders, food allergy, and gastro-esophageal reflux are common associations with difficult-to-treat asthma. On the other hand, asthma symptoms and/or management may negatively impact the well-being of children through drug adverse effects, worsening of anaphylaxis symptoms, and disturbing mental health.

Awareness of these ailments may be crucial for designing the optimum care for each asthmatic child individually and may ultimately improve the quality of life of patients and their families. A multidisciplinary team of physicians is required to identify and manage such comorbidities aiming to mitigate the over-use of asthma pharmacotherapy. Asthma research should target relevant real-world difficulties encountered at clinical practice and focus on interventions that would mitigate the impact of such comorbidities. Finally, policymakers and global healthcare organizations are urged to recognize pediatric asthma control as a healthcare priority and allocate resources for research and clinical interventions. In other words, global asthma control needs support by compassionate scientific partnership.

Keywords: Asthma, Children, Comorbid conditions, Asthma control, Obesity, Upper airway, Allergy

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INTRODUCTION

Asthma is one of the most common chronic non-communicable diseases in children and its proper control involves consideration of risk factors, comorbidities, medication adverse effects, and quality of life.[1] Difficult-to-treat asthma could be a consequence of a wide variety of comorbidities and asthma mimickers. Potential allergic and non-allergic comorbidities in the pediatric age group are plentiful, including obesity, vocal cord dysfunction (VCD), obstructive sleep apnea, gastroesophageal reflux disease (GERD), rhinosinusitis with nasal polyps, and anxiety.[2,3] Comorbid conditions can impede asthma management in several ways. For instance, they may share the same pathophysiological process (eg, allergic rhinitis (AR)), mimic and/or exacerbate asthma flares (eg, GERD and VCD), or affect asthma control (eg, obesity). Some medications given for some comorbid conditions may negatively impact asthma control (eg, β-blockers and non-steroidal anti-inflammatory drugs (NSAIDs)).[4]

Recognition of such comorbidities is important because they are treatable or modifiable and their proper management can improve asthma outcome and/or morbidity.[5,6] Also, identifying comorbid T2 inflammatory disorders such as AR and atopic dermatitis may aid optimal selection of biologic therapies.[7,8]

While a reasonable volume of information on asthma comorbidities is available in adults,[9] published data on the magnitude of pediatric asthma comorbidities are scant. This article is aimed to raise awareness of their characteristics, impact, and management. It addresses some global challenges and unmet needs in controlling these treatable causes of poor asthma control.

Mainly IgE-mediated comorbidities

Allergic rhinitis

According to the International Study of Asthma and Allergies in Childhood (ISAAC) phase I, the prevalence of allergic rhinitis (AR) worldwide ranged from 0.8% to 14.9% in 6–7 years old and 1.4%–39.7% in 13–14 years old children worldwide.[10] AR commonly coexists with asthma since the upper and lower airways share anatomical, functional, pathogenic, and immunological patterns.[11] Up to 80% of children with asthma have AR, whereas approximately 30% of children with AR have asthma.[10,12] A recent review and meta-analysis revealed a 10.48% overall prevalence of physician-diagnosed AR in children. Self-reported current AR prevalence was 18.12%, and lifetime prevalence was 19.93%. The incidence could not be determined.[13]

As the nasal passages play a key role in conditioning the breathed air (filtering, warming, and moisturizing), the presence of rhinitis can have a deleterious effect on the lower airways.[14] There is evidence that concomitant AR has a negative impact on asthma control, such as quality of life,[15] asthma medication use, physician visits, emergency department visits, and hospitalization rate.[16] Furthermore, asthma and AR in childhood are early-life predictors of lung function decline in adulthood, and there is a synergistic effect between childhood asthma and AR on the lung function trajectory.[17]

Epidemiologic data suggest a strong impact of AR on asthma control and/or severity. The Allergic Rhinitis and its Impact on Asthma (ARIA) guideline highlights the relationship between AR and asthma and recommends a simultaneous assessment of both conditions in order to optimize symptom management.[18] Nasal corticosteroid treatment might improve disease control level[13] and the extent of exercise-induced bronchoconstriction in asthmatic children with AR.[19] Both subcutaneous and sublingual immunotherapy (SCIT and SLIT) were reported to reduce the risk of developing asthma in children with isolated allergic rhinitis and rhinoconjunctivitis.[20–22]

Diagnosis of AR is clinically based on its typical symptoms along with supportive physical findings and evidence of sensitization to aeroallergen(s) by skin prick testing (SPT) or serum allergen specific IgE assay. AR shares similar symptoms with other nasal conditions such as rhinosinusitis and non-allergic rhinitis, making the diagnosis sometimes difficult especially in young children. Moreover, a substantial number of children with non-allergic rhinitis showed positive response to nasal challenge test (NCT) with aeroallergen(s), which was considered local allergic rhinitis (LAR) and asthma symptoms were observed in 20%–47% of patients with LAR.[23] It was reported that 37.6% of children with chronic rhinitis

symptoms showed a mismatch between SPT and NCT results.[24] Therefore, achieving better management of asthma in children with comorbid AR and preventing the development of asthma in children with AR alone requires making an accurate and early diagnosis of AR.

Food allergy

The frequency of food allergy (FA) in asthma is usually underestimated; however, food allergy has been shown to trigger or exacerbate symptoms in 2–8.5% of children with asthma.[25] This association is more intense when the food hypersensitivity is persistent or starts in the early years of life especially for milk and egg, and FA may be a relevant clinical marker for severe atopic asthma.[26] The prevalence of other comorbidities (atopic dermatitis, urticaria, rhinitis), serum IgE level, and the positive family history of atopy were found significantly higher in asthmatic children with as compared to those without FA. Moreover, FA was associated with worse morbidity, greater severity, and poorer asthma control.[27] Several publications have shown that FA can be a risk factor for life-threatening asthma,[28] and asthma also seems to be a risk factor for severe anaphylaxis in children with food allergy.[29]

Given such link between asthma and food allergy, it is important to look for food allergy in patients with asthma and to look for asthma in patients with food allergy. A detailed clinical history should be taken to identify potential triggers and asthmatic patients with FA should be offered careful monitoring and access to self-injectable adrenaline.[28]

Anaphylaxis

Anaphylaxis is a severe and potentially life-threatening acute allergic reaction that is increasing in incidence in several parts of the world. For instance, the incidence of anaphylaxis in Taiwan has been increasing at an average rate of 5% per year.[30] Global anaphylaxis guidelines agree that severe/uncontrolled asthma is a risk factor for severe anaphylactic reactions and a criterion to be considered for the hospitalization of these children. Asthma has been considered a significant risk factor for fatal anaphylactic reactions in children. First-line clinicians should consider a history of asthma when assessing the risk of anaphylaxis/severe allergic reactions during initial evaluation.[31] Patients with food-induced anaphylaxis are at higher risk of wheezing (OR, 2.2; 95% CI, 1.1–4.5) and respiratory arrest (OR, 6.9; 95% CI, 1.4–34.2).[32]

On the other hand, a retrospective cohort study of 603 children hospitalized with anaphylaxis revealed that asthmatic children were less likely to develop serious allergic reactions compared to children who did not have asthma. (OR, 0.97; 95% CI, 0.67–1.39). The authors concluded that children with anaphylaxis should be managed according to symptom severity and that asthma comorbidity should not be considered a stand-alone criterion for hospitalization.[33]

Anaphylaxis is a significant comorbidity, and among the most important unmet needs is the suboptimal use of intramuscular epinephrine.[34]

Mixed IgE-non-IgE immune comorbidities

Atopic Dermatitis

Atopic Dermatitis (AD) usually marks the initial stage of allergic diseases. The sequential development of respiratory allergies such as asthma and rhinitis was described in the past era as "the atopic march".[35] Nowadays, considering that fewer than 7% of children with AD will follow this pathway and the heterogeneity of these diseases that exist in time, it is debatable whether this represents a causal relationship, or a multimorbidity concept.[35–37]

Severity is an important risk factor. In children, severe versus mild-moderate AD was associated with a higher lifetime prevalence of asthma (36.9% vs 24.3) and a prevalence of severe asthma (36.1% vs 5.5%).[38]

Longitudinal birth cohort studies over the last decade identified different phenotypes of AD linked to asthma were identified.[39] The presence of filaggrin mutations is associated with an increased risk of asthma development and persistency.[40] Children with concomitant allergic sensitization (food and/aeroallergen) and parental asthma history have greater risk for asthma expression.[41,42]

Although current treatment options with monoclonal antibodies (ie, dupilumab)/biologics are

useful in targeting both diseases, future research should be directed to develop approaches and initiate strategies for mechanism-based treatment and personalized strategies for prevention.

Allergic bronchopulmonary aspergillosis and other fungal sensitizations

Exposure and sensitization to fungal allergens have been suggested as risk factors for the development and worsening of asthma. Around 80 taxa of fungi have been implicated; of particular importance are Alternaria, Cladosporium, Penicillium, Aspergillus, Malassezia, and Candida.[43] Data concerning fungal sensitization among asthmatic children are limited but rates are reported to range from 12 to 50%.[44,45] Previous work suggested a close association of fungal sensitization – particularly Alternaria and Aspergillus – with impaired lower lung functions and increased airway hyperresponsiveness.[46]

Aspergillus sensitization (AS) is considered the first step in the development of allergic bronchopulmonary aspergillosis (ABPA). ABPA represents a complex immunological disorder caused by increased type-2 immune responses against *Aspergillus fumigatus* colonizing the tracheobronchial tree. In a systematic review and metanalysis, the observed pooled prevalence rates of AS and ABPA among asthmatic children were 16.1% and 9.9%, respectively, with the possibility of underestimation owing to the lack of routine screening.[47]

Children with ABPA usually manifest with difficult-to-treat asthma, migrating pulmonary shadows, and expectoration of brownish-black mucus plugs. Undiagnosed/untreated cases may progress to bronchiectasis, pulmonary fibrosis, or lung collapse. Several diagnostic criteria have been proposed and updated for the diagnosis of ABPA, but they are not specific for children.[47,48]

Systemic corticosteroids and itraconazole are the mainstays of therapy for ABPA, although there is lack of randomized clinical trials regarding their usefulness in children. Monoclonal antibodies, such as omalizumab and mepolizumab, may be potential therapies for refractory cases; however, further data are needed to clarify their optimal use.[49]

Multiple sensitizations

Sensitization to aeroallergens, although different than other comorbidities, seems to be a major risk factor for childhood asthma.[50] Early life and multiple sensitizations in particular might significantly increase the risk of asthma development in school age and are more strongly predictive of persistence throughout childhood and into adulthood.[51,52] However, although the majority of patients with asthma are sensitized, many individuals with allergic sensitization do not have symptoms of allergic disease, and in a proportion of patients with asthma, sensitization is a chance finding. Within the sensitized group, some have multiple sensitizations which may have further significant clinical implications. In a cross-sectional study, children sensitized to >2 allergens were 12.8 times more likely to have physician-diagnosed asthma than those without allergies.[53] This finding is also supported by the results of the Manchester Allergy and Asthma Study (MAAS)[54] which showed that the risk of asthma was increased more than twenty-fold among children sensitized to multiple allergens in early life, but not among those in other classes. In addition, the risk of hospital admission was significantly greater (HR 9.2; 95% CI, 3.5–24) in the same group compared to others. This association of severe asthma with multiple allergen sensitizations is also supported by the finding that most children (>85%) with severe asthma show a certain degree of eosinophilic inflammation with multiple aero-allergen sensitization. This observation has also implications regarding the treatment of disease using biologicals such as omalizumab as at least one-third of children with severe asthma have an IgE greater than 1500 IU/ml because of severe and multiple allergies.[55] Another study that aimed to define distinct allergic phenotypes by unsupervised cluster analysis found that out of 125 children, 20 had multiple allergies and severe asthma phenotype. They displayed significantly decreased lung functions, had higher values of IgE (1123 kU/L) and all had eczema.[56] Taken together, these data suggest that sensitization to multiple aeroallergens is important not only in the inception of asthma but also as a determinant of disease severity.

It is well known that allergen exposure may exacerbate asthma symptoms and efforts to reduce the allergen concentration in the environment may be a useful adjunct in the treatment of asthma. However, successful environmental control may be difficult to achieve because patients often react to a variety of allergens. Therefore, identifying patients with multiple allergies becomes important as a single intervention is unlikely to provide clinical benefit.[57] In fact, studies have shown that environmental control measures targeting sensitizations profiles have resulted in greater clinical benefit than mono allergen approach which failed to produce consistent results.[57,58] A meta-analysis investigating the effect of multifaceted versus mono-faceted intervention in children has found that multifaceted intervention studies had an odds ratio (OR) of 0.73 (95% CI, 0.55–0.97), whereas the mono-intervention studies had an OR of 1.22 (95% CI, 0.83–1.78) in patients younger than 5 years and an OR of 0.52 (95% CI, 0.32–0.84) versus 0.93 (95% CI, 0.66–1.31) in patients older than 5 years.[59]

Practicing physicians face a problem that confirmation of sensitization using standard allergy tests does not prove that the patient's symptoms are caused by allergy. We thus need to develop better ways of differentiating sensitization, which is clinically important, from sensitization which is not. Using specific IgE titre and the size of SPT wheal can increase the specificity.[60] We can now assess sensitization in much greater detail using component-resolved diagnostics (CRD) which may be more informative than standard tests in the assessment of respiratory allergy.[61,62]

Eosinophilic esophagitis

Initially undistinguished from gastroesophageal reflux disease (GERD) associated esophageal eosinophilia, eosinophilic esophagitis (EoE) is now recognized as a distinct entity exhibiting inflammatory features of other allergic conditions.[63] EoE is the most common cause of chronic dysphagia in children. A systematic review of 21 studies including 53,592 adult and pediatric EoE patients found that asthma was significantly more common among EoE patients compared to controls (OR 3.06; 95% CI 2.01–4.66).[64] EoE was detected in 62/3071 subjects with asthma (2%), and active EoE was associated with more severe asthma ($p = 0.002$), lower FEV1 ($p = 0.014$) and FEV1/FVC ratio ($p = 0.0208$).[65] EoE outcomes may vary with other comorbidities such as eczema.[66]

Besides food allergens, other inhaled and subsequently swallowed environmental allergens may contribute to EoE through triggering mucosal histologic changes. Another possible mechanism is that a local airway or a more systemic response, is followed by trafficking of eosinophils into the esophagus.[67] An interesting link between EoE and asthma is that, often the only way to deliver systemic corticosteroids to the esophagus, is using asthma medications. Both oral viscous budesonide and fluticasone administered by metered-dose inhaler (MDI) induce and maintain remission in EoE in children.[68] More recently, it has been shown that dupilumab can be used in patients with multiple atopic diseases and it effectively induces symptomatic and histologic remission of EoE.[69]

Chronic rhinosinusitis

Chronic rhinosinusitis has an estimated prevalence around 5%, and is less frequent in children than adults.[70] Chronic rhinosinusitis diagnosis in children requires at least 2 out of 4 cardinal symptoms: nasal obstruction, nasal congestion or discharge, facial pain, and cough, which must be present for at least 12 weeks.[71] An important feature in children is the presence of coughing more frequently than seen in adults, as well as less clinical signs of T2-type inflammation before reaching 12 years of age.[72]

In recent years, the common airway concept has emerged, which suggests that upper and lower airways share close characteristics, and that the presence of varied diseases affects the entire airway,[73] as seen in patients with asthma and chronic rhinosinusitis. Studies have shown the association between patients with severe or difficult-to-control asthma and chronic rhinosinusitis as comorbidity. Furthermore, it has been observed that the treatment of chronic rhinosinusitis has led to a better pediatric asthma control, as well as a decrease in the number of exacerbations and an improvement in the quality of life.[74]

Mechanical comorbidities

Vocal cord dysfunction

Vocal cord dysfunction (VCD), included in the inducible laryngeal obstruction disorders (ILO), refers to unsynchronized, transient, and reversible vocal cord movement due to partial or complete adduction during inspiration, resulting in varying degrees of stridor, cough, and difficulty in breathing.[75] ILO is often misdiagnosed as asthma or exercise induced bronchoconstriction.[76,77]

The main elicitors for ILO are exercise, exposure to irritants and emotional stress, while one third of asthmatic patients with concomitant ILO present mental health disorders.[78] The prevalence of ILO ranges from 3 to 7% in the general adolescent population, with an estimated 70% female predominance, with an average age at diagnosis of 14 years. Noteworthy, almost one third of the pediatric referrals for exercise induced asthma were diagnosed as ILO,[79] while data from adults show that up to 50% of difficult to treat asthmatic patients had concurrent ILO.[80] Comorbid ILO in pediatric asthmatic patients is associated with increased number of exacerbations, higher healthcare utilization, β2 agonist and corticosteroid overuse and worse quality of life outcomes.[81]

Regarding diagnosis, symptom questionnaire lack validation, while in the absence of symptoms, physical examination and spirometry are not discriminative between ILO and asthma. Currently, video-recorded endoscopic verification of ILO is the gold standard for ILO diagnosis.[77] Management of ILO includes removal of suspected irritants, combined speech therapy, inspiratory muscle training and psychological support, while effectiveness of low-dose tricyclic antidepressants and botulin toxin injection has been shown in case reports. Supraglottoplasty is reserved for adolescent patients with clinically severe breathing problems.[5] Future management should include validated non-invasive diagnostic tools and standardized treatment algorithms, to optimize ILO treatment in asthmatic children.

Obstructive sleep apnea and dysfunctional breathing

Dysfunctional breathing is a term describing changes in breathing pattern that result most commonly in chronic dyspnea, sharing symptoms with other respiratory disorders that can co-exist, such as asthma, obstructive sleep apnea and ILO.[82]

Obstructive sleep apnea (OSA) is present in up to 2/3 of asthmatic children (with a higher prevalence in severe asthmatics), being 20-fold higher than in the general pediatric population.[83] Adenoids and tonsils hypertrophy and nasal obstruction due to allergic rhinitis, were identified as primary reasons of OSA in children, but anatomical variations and obesity must also be considered.[83,84] OSA is associated with poorer asthma control and increased exacerbation rates and was identified as an independent risk factor for increased utilization of mechanical ventilation, increased total length of hospital stay and hospitalization cost.[84–86] OSA may impact asthma through increasing airway neutrophilic inflammation and/or leading to a higher vagal tone due to upper airway collapse, increasing bronchial hyperresponsiveness.[87]

OSA is characterized by total or partial repetitive obstruction of the upper airway during sleep, leading to poor quality of sleep, nocturnal awakenings, dyspnea and cough, daytime sleepiness and fatigue, and mood and memory disturbances. It may negatively influence the attention deficit and hyperactivity disorder and decrease lung function in children.[84,88] OSA may also aggravate or mimic asthma symptoms, and both can simultaneously cause airway obstruction.[84,87,89]

Validated questionnaires are available for screening of OSA, but polysomnography is the gold standard for its diagnosis.[87,90] The latter must be performed at a sleep center, but due to difficulties, it is possible to use home portable polygraphy as an optional tool.[84,91]

Leukotriene receptor antagonists, intranasal steroids, reduced exposure to allergens and pollutants, and weight loss in obesity, can significantly help in OSA control. Adenotonsillectomy, results in improved asthma control in patients suffering from OSA. Continuous positive airway pressure (CPAP) may be indicated, but larger observational studies are required to evaluate the impact of non-invasive ventilation on pediatric asthma outcomes.[92]

Gastroesophageal reflux disease (GERD)

Epidemiological studies have highlighted the close bidirectional relation between

gastroesophageal reflux disease (GERD) and asthma in children. Compared to controls, asthmatics demonstrated a 1.36 times higher rate for GERD ($P < 0.001$) and the GERD group showed a 1.62-fold higher rate for asthma ($P < 0.001$).[93] In one study, GER was present in 69.6% of asthmatic children.[94] Obese asthmatic children had seven times higher odds of reporting multiple GER symptoms.[95]

Asthma and GERD may have similar symptoms in childhood, such as nocturnal cough, chest tightness and exercise-induced discomfort, thus making it difficult to determine which children actually have GERD.[96] Besides, there is not enough evidence to support causality.

A metanalysis showed that GERD was associated, albeit weakly, with asthma exacerbations, especially with frequent and oral corticosteroid-requiring exacerbations and more so in pediatric than adult patients.[97] On the other hand, a recent study involving 127 children with severe asthma found no significant differences in asthma control, airway inflammation, or remodeling between those with acid gastroesophageal reflux and those without.[98] Further research on this relation is an unmet need.

Treatment of GERD with proton pump inhibitors (PPIs) in children with uncontrolled asthma does not substantively improve asthma outcomes. Furthermore, a cohort study showed that PPI use was associated with an increased risk of asthma in infants and children,[99] not to mention the safety concerns of the long-term use.

Metabolic comorbidities

Obesity and metabolic/hormonal disturbances

Obesity and asthma in children are 2 epidemics running in parallel with their relationship being weight-dependent, causal, and partly genetic. Although the exact prevalence of children with asthma and obesity is not known,[100] a recent meta-analysis, found a 20% increase in asthma incidence in overweight children and a 40% risk increase for obese children.[101] Furthermore, epidemiologic studies showed that obesity may precede asthma from the prenatal/early postnatal period.[102]

These 2 complex disorders are characterized by chronic inflammation. The underlying mechanism has not yet been fully elucidated; although mechanical, inflammatory, genetic, hormonal, and immune factors have been described. The role the hormonal changes (testosterone and estradiol) during puberty are debatable, mostly due to the wide variability of age range in different epidemiological studies and the inconclusive results.[103] In peripubertal age an increased free testosterone to estradiol ratio over time was associated with an increased lung function and, among girls with asthma, also with a decrease in eosinophil counts.[104] Moreover, insulin resistance, dyslipidemia and glucose intolerance play a major role in bronchial hyperreactivity in obese children through the induction of pro-inflammatory molecules (i.e., IL-6, TNF-α) and through inhibition of presynaptic M2 muscarinic receptors.[105]

In children, 2 obese-asthma phenotypes have been reported; the T2-high early-onset endotype, with predominantly eosinophilic inflammation, affecting equally both sexes of asthmatic children under 12 years of age, in which obesity worsens pre-existing asthma. The second, T2-low late-onset endotype, with predominantly neutrophilic inflammation, presents in non-atopic children with obesity.[106] Obese asthmatic children show higher morbidity, worse quality of life outcomes, increased and more severe exacerbations. Additionally, obese-asthmatic children are resistant to inhaled corticosteroids and bronchodilators, while the use of leukotriene receptor inhibitors may be beneficial.[107]

Recent retrospective studies conclude that overweight and obesity were underdiagnosed and undertreated in children hospitalized for asthma.[108] Pediatricians and general practitioners should be vigilant for obesity signs. Therapeutic strategies, such as family-based interventions for lifestyle approaches, aiming at prevention of obesity and are recommended in countries with increased prevalence.

Cardiovascular disease

Evidence suggests a complex interplay between asthma and cardiovascular disease (CVD), indicating a comorbid relationship. However, several

epidemiologic studies came out with conflicting results.

A cohort study on 4430 school children showed that childhood asthma was not significantly associated with the subsequent development of CVD events in adulthood, including coronary heart disease events, heart failure events, or risk of CVD mortality.[109]

However, several population-based cohort studies in adults showed that asthma was associated with an increased risk of coronary heart disease (CHD) and cerebrovascular stroke. For instance, asthma was associated with an increased risk of CHD in a US cohort (hazard ratio [HR] = 1.47, 95% CI = 1.05–2.06).[110] In another study on US adults, asthma was associated with a 1.40-fold increased risk of coronary heart disease (95% CI 1.35–1.45).[111] Similarly, a study in Taiwan, utilizing data from the National Health Insurance Database, revealed that an asthma cohort had a 1.37-fold higher risk of stroke (95% CI 1.27–1.48) compared to a non-asthmatic cohort.[112] Using data from the Korean Genome and Epidemiology Study-Health Examinees, Wee et al reported that asthma was associated with ischemic heart disease, mainly in older and untreated asthma patients.[113]

However, contrasting findings have also been reported. A US population-based prospective cohort study found no increased risk of myocardial infarction associated with asthma (adjusted odds ratio [OR] = 1.34, 95% CI 0.84–2.15) after accounting for chronic obstructive pulmonary disease.[114] In a study using data from the Korean National Health Insurance Service-National Cohort, asthma did not increase the risk of either hemorrhagic stroke (HR = 0.86, 95 CI 0.78–0.94) or ischemic stroke (HR = 0.91, 95% CI 0.86–0.95).[115]

At least 2 recent meta-analyses have confirmed the increased risk of CVD in patients with asthma.[116,117] Although the outcomes refer to adult age, this increased risk supports the need for early prevention and control efforts.

Other comorbidities

Psychiatric problems

Psychiatric disorders have been documented to be more common in patients with asthma. A recent systematic review of 21 studies revealed an increased risk of schizophrenia in adult patients with asthma with an odds ratio of 1.7 when compared with healthy controls.[118] Asthmatic children were reported to have more anxiety problems than a matched healthy group. They were not significantly more depressed, but some had affective and disruptive behavior disorders.[119] Furthermore, mental health problems such as anxiety or depressive symptoms were associated with poorer asthma self-management in adolescent asthmatics.[120] A recent study that involved 87 asthmatic adolescents (60 males and 27 females; median age 14.2 years) revealed anxious symptoms in 16.1%, and depressive symptoms in 11.5%. Both were significantly associated with uncontrolled asthma ($p = 0.013$ and 0.043, respectively). Incorporating psychological assessment into adolescent asthma care could be beneficial in addressing the co-existing anxiety and depression they may experience.[121] This could involve among other interventions, counseling, and support groups to help manage these issues and improve overall well-being.

Asthmatic children with symptoms of attention deficit and hyperactivity were found to have reduced controller medication adherence and increased emergency room visits.[122] Not surprisingly, parents of children with poorly controlled asthma reported significantly greater level of anxiety.[123] Given the interaction between asthma control and mental health problems, careful assessment of mental health comorbidities in asthma patients is extremely important especially in patients with poorly controlled asthma. Timely referral to psychological or psychiatric assessment is needed to minimize the complications associated with poorly controlled asthma.

Drug adverse effects

The main drugs used in pediatric asthma have been around for over 50 years and have an excellent safety record with a low risk of inducing adverse events or representing comorbidities.

Inhaled corticosteroids (ICS) are by far the most used drugs for asthma prophylaxis. Side-effects are uncommon, but potentially important.[124,125] High doses may cause growth deficits, albeit small.[126] High doses can also cause adrenal

suppression.[127] The delivery system is crucial in determining lung/systemic dose[128] and therefore side-effects, but often overlooked in systematic reviews.[126,127] Static-reduced plastic spacers greatly increase lung delivery,[129] and therefore require a lower prescribed dose, reducing the risk for systemic side-effects. The risk of oral candidiasis with dry powder devices[125] can be reduced by mouth washing. Oral corticosteroids should be used sparingly to avoid systemic side-effects.[130]

Short-acting beta-2 agonists are generally safe, although adrenergic symptoms are common. Current guidelines suggest that beta-2 agonists should always be given together with an anti-inflammatory medication ie, ICS.[131] Long-acting beta2-agonists have been implicated but not proven to cause increases in hospital admissions and deaths.[132] As above they are only prescribed in combination with an ICS.

Leukotriene receptor antagonists have a good safety record with few side-effects,[133] although behavioural changes may occur. A black box warning for suicidality has been issued by the FDA for montelukast.[134]

Monoclonal antibodies are generally safe with severe adverse effects being rare (eg, anaphylaxis in omalizumab).[135]

The coexistence of asthma medication adverse effects could pose an impact on the wellbeing of the asthmatic child. As safer medications are being developed, the harm-benefit ratio and consequent adverse event thresholds will change in favour of the patients.

Miscellaneous comorbidities

The association of asthma and several other conditions has been explored in numerous studies. Observed associations entail both direct and indirect linking mechanisms. An increased risk for attention deficit hyperactivity disorder (ADHD) has been reported in children, whereas the evidence is inconclusive regarding autism spectrum disorders.[136,137] Sleep disorders are frequently reported by parents of asthmatic children, especially those with severe or poorly controlled disease.[138] Although an association of asthma and inflammatory bowel disease (IBD) has been reported in adults, there is a paucity of studies in pediatric-onset IBD to draw firm conclusions.[139] In addition, only a few studies have investigated possible associations of asthma with other chronic inflammatory diseases, such as celiac disease and juvenile idiopathic arthritis, reporting mixed results.[136] Finally, an increased risk of immunodeficiencies and alpha 1-antitrypsin deficiency have been reported in patients with asthma compared with controls.[140]

Recurrent and/or emerging infections (eg, SARS-CoV-2) represented a source of concern for being a risk factor for worsening pediatric asthma course and control.[141] However, this was not evident from published data. According to a PeARL (Pediatric Asthma in Real Life) Group multinational cohort that included 1054 asthmatic and 505 non-asthmatic children, aged between 4 and 18 years, from 15 countries globally, childhood asthma outcomes, including control, were improved during the first wave of the COVID-19 pandemic, probably because of reduced exposure to asthma triggers and increased treatment adherence.[142] Asthma exacerbations that required treatment with systemic steroids were less reported during the first 12 months of the pandemic; probably social distancing reduced asthma trigger exposure.[143] The decreased frequency of acute episodes thus does not support the notion that childhood asthma is a risk factor for acquiring COVID-19.[142] Also, the lockdown had a significant impact on asthma control in children and on their attitude toward maintenance therapy.[144]

The relation in terms of severity is somewhat different. A study that included 1492 children without asthma and 93 asthmatics reported that the latter were less likely to be seen in the ED for COVID-19-related disease, but if they did, they were significantly more likely to be hospitalized, require oxygen, and have more severe forms of COVID-19 ($p < 0.0001$).[145] Adjusted for obesity and poor physical function, asthma was shown to significantly enhance the length of stay and days on maximum respiratory support in a pediatric ICU setting.[146]

Asthma medications did not pose any negative impact on COVID-19 course or severity and whatever the controller medication used, it should not be reduced or discontinued. Moreover, patients treated with biologics were not more prone to get

Comorbidity	Key points	Ref
Allergic rhinitis (AR) ± conjunctivitis	AR commonly coexists with asthma and can negatively impact asthma control. Allergen immunotherapy may reduce the risk of asthma in children with AR and rhinoconjunctivitis.	**12-22**
Food allergy (FA)	The association is more intense when the food hypersensitivity is persistent or starts early in life. FA was linked to greater severity, and poorer asthma control and FA can be a risk factor for severe anaphylaxis in FA.	**25-29**
Anaphylaxis	Childhood asthma has been considered a significant risk factor for fatal anaphylaxis and the global suboptimal use of intramuscular epinephrine is an unmet need.	**30-33**
Atopic dermatitis (AD)	Early-onset AD is associated with asthma and allergic multimorbidity; however, most children with AD will not develop asthma. AD severity is an important risk factor.	**35-38**
ABPA and fungal sensitizations	Rates of fungal sensitization in pediatric asthma range from 12 to 50%. ABPA may manifest as difficult-to-treat asthma and may progress to bronchiectasis, pulmonary fibrosis, or lung collapse.	**43-48**
Multiple sensitizations	Sensitization to multiple aeroallergens, especially in early life, is important not only in the inception of asthma but also as determinant of disease severity. Specific IgE titre values and SPT wheal size can increase the specificity of sensitization tests.	**50-57**
Eosinophilic esophagitis (EoE)	Active EoE was found associated with severe asthma and deterioration of pulmonary function tests.	**61-63**
Chronic Rhinosinusitis (CRS)	CRS was linked to difficult-to-treat asthma and its management led to a better pediatric asthma control.	**71,72**
VCD and inducible laryngeal obstruction disorders (ILO)	ILO may be misdiagnosed as asthma or exercise induced bronchoconstriction and their coexistence is associated with increased number of exacerbations.	**74,75,78,79**
Obstructive sleep apnea (OSA)	OSA is 20-fold higher in asthmatic versus general pediatric population and may aggravate airway neutrophilic inflammation and/or lead to high vagal tone enhancing bronchial hyperresponsiveness.	**81-87**
Gastroesophageal reflux disease (GERD)	Epidemiological studies have shown bidirectional relation between GERD and asthma in children and their symptoms hold some similarity. However, there is not enough evidence to support causality.	**91-96**

(continued)

Comorbidity	Key points	Ref
Obesity	Obesity is a modifiable risk factor for pediatric asthma that is associated with higher asthma morbidity, worse quality of life, more exacerbations, and pharmacotherapy resistance.	99,104,105
Cardiovascular disease (CVD)	Evidence suggests a complex interplay between asthma and CVD, but a cohort study showed that childhood asthma was not associated with the subsequent development of CVD in adulthood. Further studies are needed.	107
Psychiatric comorbidities	Asthmatic children were reported to have more anxiety problems, and some had affective and disruptive behavior disorders. This was associated with poorer asthma self-management in adolescent asthmatics. Also, parents of children with poorly controlled asthma reported greater levels of anxiety.	117-119,121
Drug adverse effects	The main drugs used in pediatric asthma have a good safety record, but the greatest pharmacological unmet need is to prevent asthma exacerbations ever developing.	123-133

Table 1. (Continued) Key points on pediatric asthma comorbidities

infected by SARS-CoV-2.[147] Several international allergy/pulmonology organizations including the American academy of allergy asthma and immunology (AAAAI), World allergy organization, British thoracic society (BTS), and Italian society of allergy, asthma and clinical immunology (SIAAIC), recommended continuation of biologic therapies in asthmatic patients during the pandemic.[148] It is not expected to worsen the clinical course or outcome of COVID-19 and may protect to some extent from developing severe forms.[147]

Finally, the interaction between asthma and COVID-19 seems to be bidirectional and needs to be more extensively studied.[149] This represents an unmet need in children as available data are scant and controversial.

UNMET NEEDS

Pediatricians and primary health care physicians should actively screen asthmatic children, especially those with difficult-to-control asthma, for

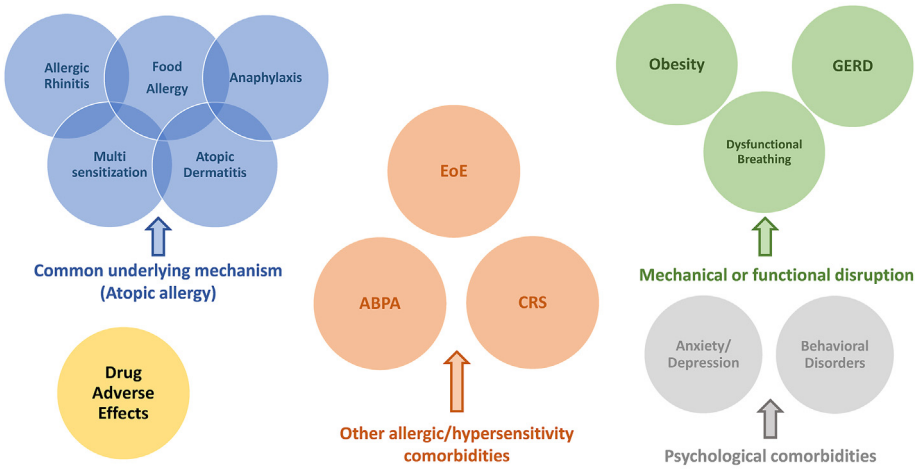

Fig. 1 Pediatric asthma multimorbidity universe.

the presence of obesity, upper airway allergies, dysfunctional breathing, multiple sensitizations, psychological disorders, food allergy and gastro-esophageal reflux. Pediatric asthma might affect the well-being of children through drug adverse effects, worsening of anaphylaxis symptoms, and disturbing mental health. Table 1 shows some key points about pediatric asthma comorbidities.

A multidisciplinary team of physicians is needed to identify and manage such comorbidities aiming to avoid the over-use of asthma pharmacotherapy. Asthma research should target relevant real-world difficulties at clinical practice, and address interventions to mitigate the impact of such comorbidities.

CONCLUSION

This review highlighted the burden of comorbidities among children with asthma (Fig. 1). It is crucial to identify and address these potentially modifiable conditions that impact asthma control, as well as overall well-being. This approach may eventually improve the quality of life of the patients and their families. Pediatric asthma should be regarded as a health care priority by policy makers and global organizations and its control should be supported by all possible means.

Abbreviations

ABPA, Allergic bronchopulmonary aspergillosis; AD, Atopic dermatitis; ADHD, Attention deficit hyperactivity disorder; AR, Allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; AS, Aspergillus sensitization; CHD, Coronary heart disease; COVID-19, Coronavirus Disease 2019; CPAP, Continuous positive airway pressure; CRD, Component-resolved diagnostics; CVD, Cardiovascular disease; EoE, Eosinophilic esophagitis; FA, Food allergy; FDA, Food and Drug Administration; FEV1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; GERD, Gastroesophageal reflux disease; IBD, Inflammatory bowel disease; ICS, Inhaled corticosteroids; IgE, Immunoglobulin E; ILO, Inducible laryngeal obstruction disorders; ISAAC, International Study of Asthma and Allergies in Childhood; LAR, Local allergic rhinitis; MAAS, Manchester Allergy and Asthma Study; MDI, Metered-dose inhaler; NCT, Nasal challenge test; NSAIDs, Nonsteroidal anti-inflammatory drugs; OR, Odds ratio; OSA, Obstructive sleep apnea; PeARL, Pediatric Asthma in Real Life; PPIs, Proton pump inhibitors; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SPT, Skin prick testing; T2, T helper 2; US, United States; VCD, Vocal cord dysfunction.

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Not applicable; the manuscript does not report on or involve the use of any animal or human data or tissue.

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