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The Role of Comorbidities in Difficult-to-Control Asthma in Adults and Children

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Abstract

Assessment of asthma comorbidities, conditions that adversely affect the pathobiology of asthma or impair its response to therapies, is a fundamental step in the evaluation and management of patients with difficult-to-treat asthma. Identifying and effectively treating asthma comorbidities, such as obesity, obstructive sleep apnea, and chronic sinusitis with nasal polyps may improve asthma control and reduce exacerbations. Additionally, identifying comorbid T2 inflammatory conditions may help guide optimal selection of biologic therapies. Here, we describe common comorbid conditions found in adult and pediatric difficult-to-control asthma, discuss evidence for the association with asthma morbidity and treatment benefit, and provide information on how and when to assess comorbidities.

Introduction

Asthma comorbidities augment the symptoms of asthma, worsen the intrinsic disease, or provide additional limitations to asthma management. Assessing and treating comorbidities is a fundamental step in evaluating patients with difficult-to-treat asthma. In many cases, appropriate management of the comorbid condition(s) may improve asthma symptoms or morbidity. Additionally, comorbid conditions that share Type 2 inflammatory pathways may inform optimal choice of biologic asthma therapy.

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We review the evidence for comorbidities in pediatric and adult patients with difficult-to-control asthma (Table 1), highlighting the domains of asthma control affected, evaluation, and, where available, anticipated asthma outcomes with treatment of the comorbidity (Table 2). We present a clinical pathway for evaluating asthma comorbidities (Figure 2).

Comorbidities

Allergic Rhinitis

Epidemiological evidence supports the coexistence of asthma and upper airway disorders, including allergic rhinitis and chronic rhinosinusitis (CRS) with or without nasal polyposis[1–4]. The upper and lower airways are linked by shared exposure to air pollutants and aeroallergens and respond via similar pathophysiologic mechanisms[5].

Allergic rhinitis is characterized as nasal congestion, rhinorrhea, and sneezing, often associated with itchiness of the eyes, nose and palate, post-nasal drip, throat clearing, and cough, in response to an allergen exposure in a sensitized individual. The diagnosis is typically made on clinical grounds based on presence of these symptoms, evidence on nasal mucosal edema, rhinorrhea, and facial features such as infraorbital edema and darkening ("allergic shiners"), Dennie-Morgan lines, and transverse nasal crease. Many patients are treated empirically, but allergen diagnostic testing by skin prick with allergen extracts or specific IgE serum antibodies, can differentiate allergic from non-allergic rhinitis and lead to allergen-specific therapies, such as environmental controls or allergen immunotherapy.

Asthma and allergic rhinitis share type 2 inflammatory pathways. The Asthma Phenotypes in the Inner City (APIC) study reported rhinitis in 93.5% of 619 inner-city children with asthma and was more severe in those with difficult-to-control asthma[6], consistent with other cohorts[7, 8]. In adults, allergic rhinitis severity correlates with asthma morbidity. Patients with persistent asthma and seasonal rhinitis have significantly greater asthma symptoms, hospitalizations, and cost of medical care than those without[9–11].

Highly effective management strategies are available for allergic rhinitis, with intranasal corticosteroids (INCS) being the preferred monotherapy[12] with adjunctive approaches including the addition of intranasal antihistamines, oral antihistamines, montelukast, and nasal saline irrigation[12]. The effect of rhinitis management on asthma control is less clear. A meta-analysis including 2162 patients found no significant change in asthma outcomes with the addition of INCS to orally inhaled corticosteroids[13]. A subsequent randomized controlled trial including 151 children with inadequately controlled asthma and chronic sinonasal disease found no differences in measures of impairment, FeNO, or methacholine reactivity with intranasal mometasone, but treatment did result in 36% fewer episodes of poor asthma control defined by 30% drops in peak expiratory flows for 2 consecutive days[14].

Chronic Rhinosinusitis (with and without Nasal Polyps)

CRS can be present with (CRSwNP) and without nasal polyps (CRSsNP). CRSsNP is primarily a Th1/neutrophilic process whereas CRSwNP is a TH2/eosinophilic process[11]. Infection may play a role in the initiation or sustenance of inflammation in CRS[15]

and impact the lower airway by seeding chronic bronchitis, bronchiectasis, or inducing mucociliary dysfunction.

The cardinal symptoms of CRS include mucopurulent nasal discharge, nasal congestion or blockage, facial pain/pressure, and reduction or loss of sense of smell, as well as chronic cough[16]. Differentiating CRS from allergic and non-allergic rhinitis can be difficult[16]. Rhinoscopy is limited to visualization of the anterior structures of the nose whereas nasal endoscopy can identify purulent drainage from the inferior and middle meatus and sphenoethmoidal drainage, and polypoid tissue, but requires specific training and equipment not common to general clinical practice. Non-contrast sinus CT scan remains the preferred modality to image mucosal disease and occlusion of the sinus ostia[17].

CRS is associated with impaired asthma control[18] and increased exacerbation frequency[19], and is an independent risk factor for difficult asthma[20]. Among the 709 Severe Asthma Research Program-3 (SARP-3) participants (including 187 children), the presence of chronic or recurrent sinusitis was associated with the exacerbation-prone (3+ exacerbations in the prior year) phenotype[19].

Nasal polyposis is rare in children, regardless of underlying asthma, and should prompt a careful evaluation for other conditions, such as cystic fibrosis, ciliary dyskinesia, and aspirin exacerbated respiratory disease (AERD). Among the pediatric SARP-3 participants, fewer than 10% reported nasal polyposis and prevalence did not differ by asthma exacerbation frequency[19]. Data to support management of CRS in children with difficult-to-control asthma is very limited.

In adults, CRSwNP frequently indicates AERD. Histopathology demonstrates mast cell activation, marked eosinophilia, epithelial disruption, and pro-inflammatory cytokine production of both the upper and lower airways[21]. In such patients, aspirin desensitization has been shown to provide additional clinical benefit[22].

Treatment of CRS includes oral and intranasal corticosteroids, antihistamines, nasal saline irrigation, and when associated with nasal polyposis, biologic therapies may be considered. Dupilumab, omalizumab, and mepolizumab are FDA approved therapies for CRSwNP and have been shown to lead to decreased polyp burden and improvement in quality of life[23, 24]. Reslizumab and benralizumab have also been studied but have not yet received FDA approval for CRSwNP. Preclinical data indicates that thymic stromal lymphopoietin (TSLP) may be upregulated in nasal polyp tissue in patients with CRSwNP[25] suggesting tezepelumab, which binds TSLP, may be another potentially beneficial therapeutic in the pipeline[26]. Guidelines support consideration of biologic therapy in patients CRSwNP, with or without asthma[27].

Retrospective analyses of patients undergoing endoscopic sinus surgery (ESS)/polypectomy have found ESS to improve asthma symptoms, improve FEV1, and decreased use of inhaled corticosteroids in both aspirin-sensitive and aspirin-tolerant patients[28]. Two recent meta-analyses of ESS in adults with asthma and chronic rhinosinusitis suggest modest benefits in clinical[29] and pulmonary function[30] outcomes, but the lack of high quality randomized controlled trials is limiting. Cost analysis, comparing ESS to treatment with dupilumab for

CRSwNP, has demonstrated both produced quality adjusted life years (QALYs), but sinus surgery produced more QALYs and is less expensive than dupilumab[31]. However, in persons with comorbid difficult-to-control asthma, a biologic agent may improve both CRSwNP and asthma morbidity.

Obesity

Obesity, referring to excess body fat, is indirectly measured in clinical practice by body mass index (BMI), the anthropometric relationship between weight and height. In children, standard references are available from age 2 years[32]. The definition of overweight (BMI ≥ 85 percentile) and obese (BMI≥ 95 percentile) approach adult thresholds of BMI ≥ 25 and 30 kg/m^2, respectively, in late adolescence.

Obesity and asthma have a bidirectional relationship[33]. Among children with asthma, obesity is associated with greater exacerbation frequency and severity, including need for mechanical ventilation[34], greater symptom frequency, worse control[35], poor quality of life[36], impaired response to ICS therapy[37], and worse parent-perceived overall child health[38]. Despite this, the vast majority of obese children hospitalized for asthma exacerbations lack a discharge diagnosis or treatment plans for obesity[39].

Relatively small, randomized controlled trials have demonstrated beneficial effects of weight loss on asthma control and quality of life in children[40–42]. An 18-month multifactorial weight loss intervention demonstrated improvements in weight and asthma measures in both treatment and control groups, although lung function, asthma control and quality of life improved more in the intervention group[42].

In adults, asthma and obesity are frequently comorbid[43–49]. Early onset allergic asthma (EOAA) develops in childhood, independent of obesity, and obesity can worsen asthma symptoms. Alternatively, late onset non-atopic asthma (LONA) may develop as a consequence of obesity, with the risk of asthma increasing by 50%[50]. LONA, characterized by a non–T2 phenotype, obesity, and female sex has been consistently identified in cluster analyses[51–53].

Weight loss improves asthma-related quality of life, asthma control and lung function[40], and in patients with LONA, asthma may resolve with weight loss[54]. A recent randomized trial of either dietary, exercise, or a combination of both interventions in overweight/obese adults with asthma found 5–10% weight loss resulted in clinically important improvements to asthma control in 58%, and quality of life in 83% of subjects[55]. Similarly, adding exercise to a short-term weight-loss program improved asthma control while achieving greater weight loss and aerobic capacity compared with weight loss alone[56, 57]. Bariatric surgery also improves asthma symptoms and exacerbation rates[58–60], however, one study suggested improvements may be limited to those without metabolic syndrome[61].

Inducible Laryngeal Obstruction

Inducible laryngeal obstruction (ILO), also called vocal cord dysfunction (VCD)[62], paradoxical vocal fold movement disorder (PVFMD), or exercise-induced laryngeal obstruction (EILO)[63], describes an episodic upper airway obstruction secondary to

inappropriate narrowing of the true vocal fold and/or the supraglottic structures in response to external trigger. Exercise, irritants, and emotional stress are the primary inducers of ILO. ILO is associated with current or historical psychosocial disorders, particularly anxiety and stress[64, 65], but also depression, post-traumatic stress disorder, and personality disorders, and others[66]. It can result in severe obstruction leading to intubation.

The prevalence of ILO among children with severe or difficult-to-control asthma is not well documented, but among adults with severe asthma, may be as high as 19–32%[20, 67–69].Patients generally describe distinct episodes of dyspnea with an identifiable start and end, may have stridor as a prominent sign, and that are typically not prevented or resolved with beta-agonists. In the absence of symptoms, physical examination and spirometry are usually normal. Symptom questionnaires to detect ILO lack comprehensive validation[70–72]; while flattening of inspiratory flow-volume loop can be helpful but is neither sensitive nor specific[73]. The gold standard for diagnosis of ILO/EILO is continuous laryngoscopy during evoked challenge[62].

Management of ILO and EILO involves speech-language therapy to allow patients to identify early symptoms and to employ controlled breathing techniques[74]. Behavioral interventions focus on avoidance of exposure to presumed triggers, visual biofeedback during episodes, and behavioral health/psychology[62]. Small prospective observational studies have reported reductions in asthma medication use and symptoms following these treatment strategies[75, 76]. Limited case series have reported inhaled anticholinergics may prevent symptoms[77]. Case reports have suggested benefit from tricyclic antidepressants, allergy or GERD therapies, inspiratory muscle training, botulinum toxin injections in the vocal folds[78, 79], and in refractory cases, supraglottoplasty[80].

Dysfunctional Breathing

Dysfunctional breathing describes disruption to the normal biomechanics of breathing and may present as hyperventilation, sighing, thoracic-dominant or thoraco-abdominal asynchronous patterns, among others, that leads to dyspnea and can mimic or be comorbid with difficult-to-control asthma in almost 50% of adults[81, 82]. It is associated with concurrent anxiety, depression and, to a lesser extent, sinonasal symptoms[82]. Instruments have been developed to accurately identify dysfunctional breathing[83, 84] and retraining is associated with improved asthma control and quality of life[85].

Obstructive Sleep Apnea (OSA)

Symptoms suggestive of obstructive sleep apnea (OSA) include snoring, gasping, choking, snorting during sleep, daytime hypersomnolence, morning headaches, and particularly in children, behavioral disturbances and inattentiveness. Physical examination may identify obesity and/or anatomically narrowed oropharyngeal airway. The gold standard for diagnosis in both adults and children is polysomnography.

In children, asthma is a risk factor for more severe OSA and OSA is associated with more severe asthma[86]. Abnormal scores on the Pediatric Sleep Questionnaire (PSQ), a validated screening tool for OSA, are associated with poor asthma control[87, 88]. Adenotonsillectomy is

the first line treatment for OSA in children, which can result in significant improvements in asthma exacerbations[89] and symptom control[86].

In adults, obesity is the major risk factor linking asthma and OSA, and this can be augmented by frequent oral corticosteroid use resulting in myopathy, weight gain, and fat redistribution to the neck area. Independent of OCS, inhaled corticosteroids (ICS) are associated with habitual snoring and OSA in a dose-dependent manner[90]. Prospective studies demonstrate an increased risk of incident OSA among patients with asthma[91–94], however, the relationship to asthma severity is inconsistent. Some studies report increased OSA in severe compared to moderate asthma[90, 95–97] while others find no difference[98, 99]. Similarly, OSA is associated with increased asthma exacerbations, decreased quality of life and asthma control in some studies[100, 101], while others report no relationship to asthma morbidity[20, 96].

Continuous positive airway pressure (CPAP), the primary intervention for adult OSA, has been associated with improved quality of life[102], improved asthma control[102, 103] and decreased decline in FEV_1[95]. However, a recent meta-analysis found CPAP improved quality of life but has an inconsistent impact on asthma control and lung function[104].

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) typically presents with heartburn and food regurgitation, but chest pain, odynophagia, and dysphagia may also occur.

Extraesophageal symptoms of chronic cough, hoarseness and wheezing[105–108] may be due to neuronally-mediated bronchial hyperresponsiveness, airway edema, mucus secretion[105], alterations of mucosal immunity[109], and micro-aspiration. Diagnosis is often based on the presence of classic symptoms of heartburn. A trial of lifestyle and diet modification, and acid suppression therapy may be pursued prior to invasive testing. Additional evaluation may include upper gastrointestinal endoscopy which can help differentiate GERD from eosinophilic esophagitis and alternative diagnoses, and assess complications, such as strictures mucosal metaplasia, dysplasia and malignancy in adults. Ambulatory pH or impedance monitoring of the esophagus in concert with symptom recording can identify frequency of reflux events and correlate with symptoms to aid in diagnosis[110, 111].

In children, GERD is associated with 36% increased odds of uncontrolled asthma. The SARP-3 cohort found GERD was associated with exacerbation prone asthma in both children and adults[19]. Despite these associations, a randomized double blind placebo control study evaluating the effect of lansoprazole in children with poorly controlled asthma and asymptomatic GERD failed to show a change in asthma control, lung function, quality of life or acute exacerbations. The treatment group reported more upper respiratory infections, sore throat, and bronchitis, raising potential safety concerns[112].

GERD is present in 60–80% of adults with asthma. However, clinical trials of anti-reflux therapy have demonstrated no significant effect on asthma control or exacerbations[113, 114], even among those with positive esophageal pH probe studies[115]. A recent Cochrane review of adult and pediatric studies concluded there was uncertain evidence that medical treatment

of GERD improved exacerbations though reported moderate evidence for slightly improved FEV1 (O.1 L, 95% CI 0.05 to 0.15) and β-agonist use (−0.7 puffs/day, 95% CI −1.20 to −0.22)[116]. For both pediatric and adult patients with difficult-to-treat asthma, a trial of anti-reflux therapy should be reserved only for patients with symptomatic reflux[117, 118]. Surgical therapy has insufficient evidence for recommendation, though one randomized trial of fundoplication reported improvement in asthma symptoms[119].

Anxiety/depression

Pateraki, Vance and Morris describe three potential mechanisms for comorbid anxiety and asthma: asthma triggering unhelpful thinking and behavior that raises anxiety; anxiety impairing self-care and triggering hyperventilation; and both leading to self-perpetuating feedback cycles and symptom confusion[38]. Anxiety is also associated with altered perception of dyspnea and greater symptom reporting[36]. Physiologic responses to psychological distress include decreased expression of beta-2-adrenergic receptor (*ADRB2*) and glucocorticoid receptor *NR3C1*[120, 121], enhanced generation of pro-inflammatory cytokines[122], and stress-induced changes in gene expression that regulate immunological responses[118, 121, 123].

Children with asthma have a higher prevalence of anxiety and depression which correlates with asthma severity[124–127]; up to 60% of children with severe asthma express anxious symptomatology[128, 129]. Children with anxiety report more asthma symptoms[130], have lower ACT scores, more frequent exacerbations[35], longer length of hospital stay for asthma[131], and greater use of rescue medications. In a large pediatric claims-based study, Bardach et al. found an increased rate of emergency department (ED) visits for asthma in patients with anxiety or depression, and greatest for those with both conditions[132]. Additionally, psychological stress of the child's *caregiver* is associated with greater asthma symptoms[133] and ED utilization[134–136]. Depressed mothers are more likely to report medication non-adherence, lack of understanding of the medications' functions, and inability to manage episodes at home[137].

In adults, epidemiologic evidence suggests a relationship between anxiety and depression with asthma and allergic diseases[138]. Anxiety and depression are related to worse asthma control, exacerbations, and healthcare utilization. Up to 24% of asthma patients report anxiety and 12% report depression, and these patients have a significant increase in exacerbations and use of health care resources, with a four-fold greater impact of anxiety on asthma control than depression[139].

Most evidence supports cognitive behavioral therapy can improve anxiety in children and adults with asthma, but few data support improved asthma outcomes[140–143]. A trial of antidepressive medication may improve symptoms and exacerbations in adults with high levels of asthma morbidity and major depressive symptoms[144].

Vitamin D deficiency

Hypovitaminosis D leading to osteomalacia or rickets in children is rare in developed parts of the world, but prevalence of vitamin D <20 ng/ml [50 nmol/L] is approximately 15% for

children[145] and 18% in US adults[146]. It is typically assessed by serum 25-hydroxyvitamin D (25[OH]D).

Vitamin D deficiency is associated with impaired lung function[147], increased exacerbation frequency[148], severity[149], and reduced corticosteroid responsiveness[150, 151] in asthmatics. It has been associated with lower mean FEV_1 and increased odds of severe asthma exacerbations in the Childhood Asthma Management Program (CAMP) and other pediatric cohorts[151–153] and correlates with increased need for inhaled and oral corticosteroids to achieve asthma control[154].

Evidence that vitamin D supplementation leads to improvement in asthma control is inconsistent[117]. Recent systematic reviews have demonstrated that vitamin D supplementation in children and adults reduces the rate of asthma exacerbations and risk of ED visit or hospitalization in those with low vitamin D[155, 156]. However, the recent Vitamin D to Prevent Severe Asthma Exacerbations (VDKA) Study ended prior to full enrollment but found no benefit to supplemental vitamin D in children who were deficient[157]. The Vitamin D Add-On Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA) study determined that supplemental oral vitamin D3 added to inhaled corticosteroids did not alter the rate of first treatment failure or reduce exacerbations in adults with persistent asthma and vitamin D deficiency. Notably, the subset of patients that achieved vitamin D sufficiency (>30 ng/ml) had significant reduction in exacerbations[158].

Allergic bronchopulmonary aspergillosis/Severe Asthma with Fungal Sensitization

Allergic bronchopulmonary aspergillosis (ABPA) refers to a hypersensitivity reaction to *Aspergillus fumigatus*, though a similar syndrome exists for a variety of molds, termed allergic bronchopulmonary mycosis, ABPM. It is hypothesized that the presence of Aspergillus antigens from fungal spore inhalation leads to a hypersensitivity immune response associated with inflammation of the airways in susceptible hosts[159, 160].

ABPA typically presents as uncontrolled asthma or chronic bronchitis symptoms with or without the expectoration of mucus plugs. Diagnostic criteria include evidence of an immune reaction to aspergillus in patients with predisposing asthma or cystic fibrosis (see table 2)[161]. High resolution chest CT may identify central bronchiectasis.

The prevalence of ABPA in patients with asthma ranges from 2.5% to 22.3%, with a pooled prevalence of 8.4%[162, 163]. It is more common in adults[164]. A recent study at a single site in India found 11% of children with poorly controlled asthma had comorbid ABPA and 61% had aspergillus sensitivity. Fungal sensitization, alone, has been associated with severe asthma classification and lower lung function[165].

Management of ABPA includes systemic corticosteroids[166] and adjunctive antifungal therapy. Itraconazole is the only antifungal agent evaluated in randomized controlled trials[167] but small studies have used voriconazole and posaconazole. Experience with anti-IgE therapy, omalizumab, is growing in ABPA but few randomized controlled trials exist; a synthesis of the published data reported significant reductions in exacerbations, improved asthma control and lung function in patients with ABPA[168]. Anti-IL5/-IL5R[169–171] and

anti-IL4R[172] have been effective in cases refractory to corticosteroids, antifungals and omalizumab.

More recently, a phenotype of severe asthma with fungal sensitization (SAFS) has been defined as severe asthma and sensitization to a fungal species without evidence of ABPA or ABPM[160], likely part of a spectrum of fungal sensitization-induced airways reaction[159]. Randomized controlled trials of antifungal medications for SAFS have reported conflicting results. A randomized controlled trial of itraconazole in adults led to improved asthma quality of life and peak flow measurements[173]. However, a 3-month intervention with voriconazole failed to find improved exacerbation rates or quality of life[174]. The American Thoracic Society/European Respiratory Society Taskforce on Severe asthma discourage use antifungal agents for the treatment of severe asthma outside of ABPA[175].

Asthmatic smokers/ACO

Smoking in adolescence has been associated with asthma symptoms and airflow obstruction in general population studies[176]. Adolescents with asthma may have higher rates of nicotine dependence, are more likely to use E-cigarettes[177], and more difficulty achieving smoking cessation[178]. Secondhand smoke (SHS) exposure in children with asthma is associated with greater asthma symptoms[179], medication use[180], ED visits[181], and impaired lung function[182–184]. Interventions to decrease SHS improve asthma severity and lung function[185]. Asthma guidelines universally recommend smoking cessation and SHS avoidance[118, 186].

Adult asthmatics who smoke have worse asthma control, lung function decline, and response to asthma medications[187]. The mechanism is thought to be related to increased airway permeability and relative corticosteroid resistance[188, 189]. Price et al randomized 1,019 patients to montelukast 10mg/day, fluticasone propionate 250 mcg twice daily or placebo and found that both treatments significantly increased the mean days of asthma control with a greater benefit with fluticasone in those with ≤11 pack-year smoking history and greater benefit with montelukast in those with greater smoking history[190]. Therefore, in addition to smoking cessation interventions, clinicians should assess smoking history to decide whether to treat with inhaled corticosteroids or montelukast.

The combination of asthma and chronic obstructive pulmonary disease (COPD), referred to as ACO, is a distinct phenotype associated with more exacerbations, worse quality of life and increased healthcare costs[191]. Pharmacotherapy should be based on the clinical features favoring asthma or COPD along the spectrum of airway disease[186, 192]. For example, for features favoring asthma, low dose inhaled corticosteroids are indicated with addition of LABA or LAMA, as needed; if features favor COPD, then start with bronchodilators. Scant evidence exists for the use of a PDE inhibitor, such as roflumilast[193].

Hormonal fluctuation

Approximately one third of reproductive age women experience changes of ovarian hormones during the menstrual cycle that have been linked to increased symptoms and decreased peak flow rates[194, 195], correlating with increase sputum eosinophils and FeNO during the premenstrual phase[196]. Women with perimenstrual worsening of

asthma also report greater urgent health-care utilization for asthma[197], though emergency department-based studies have not found variation in menstrual phase among women presenting with asthma exacerbations[198, 199]. Animal models support the role of estrogen-dependent mechanisms that augment allergen-mediated airway inflammation and airway hyperreactivity[200]. Cross-sectional observational studies investigating oral contraceptive use on asthma morbidity have had mixed results[201, 202]. Randomized controlled interventional trials in patients with perimenstrual worsening of asthma are needed.

During pregnancy, about 1/3 of women have worsened asthma, with similar proportions having improvement and no change in asthma symptoms[203]. Increased asthma severity is associated with gestational asthma exacerbations[204]. However, adherence to asthma medication substantially improves the risk of worsened asthma symptoms during pregnancy[205, 206].

Addressing comorbidities in clinical practice

Evaluating adult and pediatric patients with difficult-to-treat asthma involves confirming the appropriate diagnosis, ensuring proper medication adherence and delivery, minimizing environmental triggers, and assessing and optimally managing comorbid conditions. It is important to consider comorbidities early in the evaluation and periodically reassess for their development and impact. A detailed history and physical examination provide the clinical clues to guide further evaluation for most of the comorbid conditions reviewed here (Figure 1). Testing for allergic sensitization can be helpful in assessing both asthma endotypes and atopic comorbidities. Laboratory evaluation including total IgE and vitamin D level may be used to assess biologic drug eligibility as well as screen for the possibility of ABPA, and vitamin D deficiency. Failure to improve nasal obstruction with appropriate therapy, or in the absence of atopy, should lead to further evaluation for CRS. A total serum IgE >1000 IU/ml raises suspicion for ABPA and should prompt further evaluation. As the timing and specific items evaluated will depend on individual patient characteristics, presenting signs and clinical course, there is no simple algorithm that can be utilized to systematically evaluate all of them. Table 2 details clinical clues and appropriate evaluation and management considerations for each asthma comorbidity.

Knowledge gaps

Further research is needed to understand the interaction of multiple comorbidities on asthma morbidity. For example, children who are overweight or obese have the greatest symptoms with smoke exposure[207]. Knowing the synergistic or effect-modifying effects of multi-comorbidity on asthma outcomes will help prioritize interventions. Broadening the evidentiary basis for treatment outcomes in asthma is greatly needed for most of the identified comorbidities. Large-scale randomized controlled clinical trials to test the effect of management of the comorbid condition(s) on asthma will enhance the personalized medicine approach to patient care. Moreover, further understanding how available and future therapies may differentially affect asthmatic populations with comorbidities will help clinicians select optimal treatments for their patients.

Conclusions

Identifying asthma comorbidities is an essential element of the evaluation of difficult-to-control asthma in children and adults. Targeted interventions to smoking cessation, obesity, OSA, ABPA and CRSwNP are likely to improve asthma morbidity. Treating allergic rhinitis, symptomatic GERD, vitamin D deficiency, and anxiety/depression should be considered to improve the comorbid condition but lack clear evidence for improving asthma. For patients in whom a monoclonal antibody-based therapy is considered, evaluation for concurrent chronic rhinosinusitis with nasal polyposis and allergic sensitization may inform a selection beneficial to both asthma and the comorbid condition.

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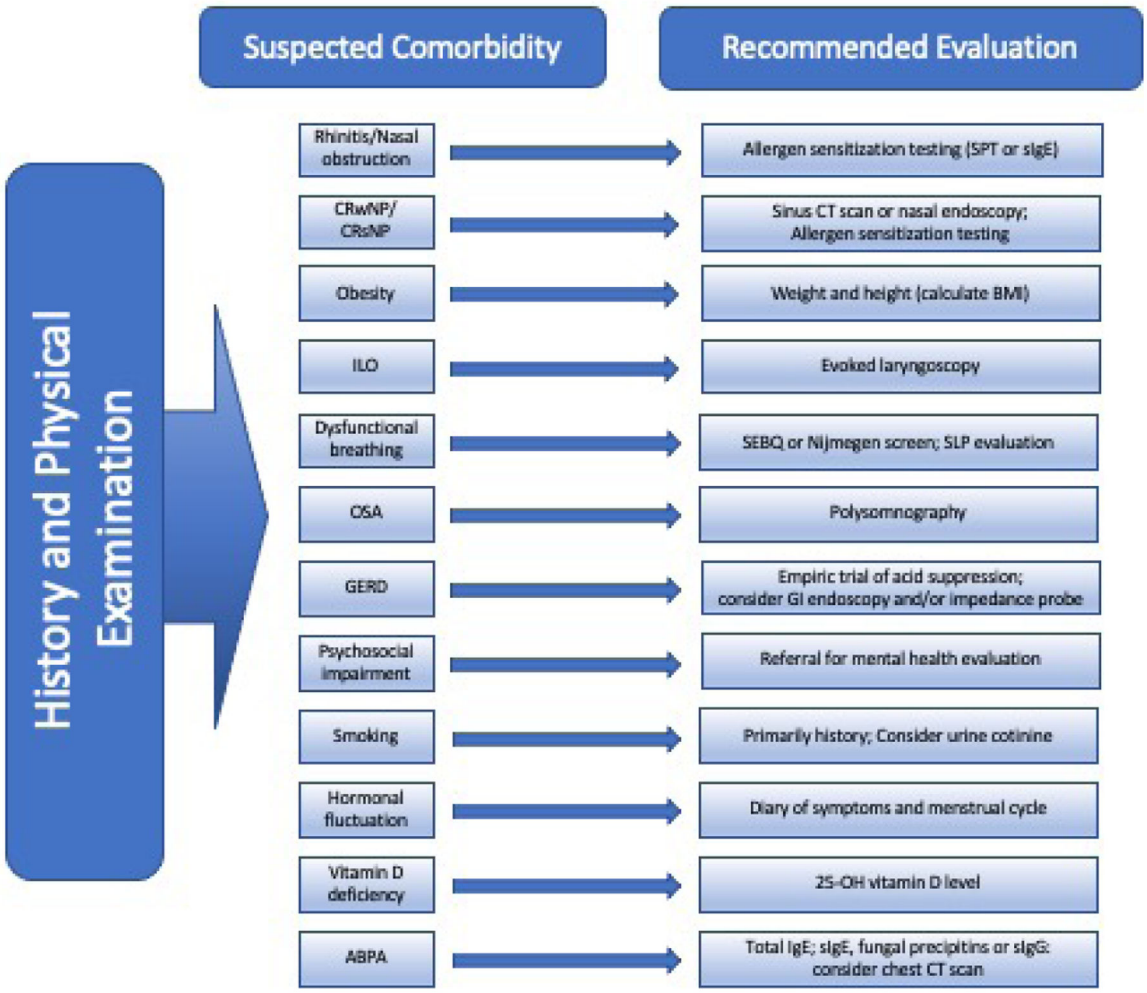

Figure 1. Flow diagram for recommended evaluation of comorbidities in patients with Difficult to Control asthma

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps;ILO, inducible laryngeal obstruction; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux; SPT, skin prick testing; sIgE, specific immunoglobulin E; CT, computed tomography; BMI, body mass index; SEBQ, Self-Evaluation of Breathing Questionnaire; GI, gastroenterology; PSG, polysomnography; ABPA, allergic bronchopulmonary aspergillosis; IgE, immunoglobulin E; sIgG, specific Immunoglobulin G.

Table 1.

Evidence of comorbidity effect on asthma control in adults and children

Comorbidity	Adult/pediatric	Level of evidence	Affected asthma domain		
			Patient reported outcomes (Sx/ QOL)	Exacerbation	Lung function
Allergic Rhinitis	Adult	Obs, RCT, Meta	x	x	-
	Pedi	Meta	x	x	-
CRSsNP	Adult	Obs, RCT	x	x	-
	Pedi	Obs	-	x	-
CRSwNP	Adult	Obs, RCT	x	x	x
	Pedi	Obs	-	-	-
Obesity	Adult	Obs, RCT	x	x	x
	Pedi	Obs, RCT	x	x	x
ILO	Adult	Obs	x	x	-
	Pedi	Obs	x	x	-
Dysfunctional breathing	Adult	Obs	x	x	
	Pedi	Obs	x	x	
OSA	Adult	Obs, RCT, Meta	x	x	x
	Pedi	Obs, RCT, Meta	x	x	-
GERD	Adult	Obs, RCT, Meta	x	x	x
	Pedi	Obs, RCT, Meta	x	x	-
Anxiety/depression	Adult	Obs	x	x	-
	Pedi	Obs	x	x	-
Vitamin D deficiency	Adult	Obs, RCT, Meta		x	
	Pedi	Obs, RCT, Meta	x	x	x
ABPA/M	Adult	Obs, RCT	x	x	x
	Pedi	Obs	x		x
Smoking/SHS	Adult	Obs, RCT	x		x
	Pedi	Obs	x	x	x

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; ILO, inducible laryngeal obstruction; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux; ABPA/M. allergic bronchopulmonary aspergillosis/mycosis; SHS (secondhand smoke); Obs, observational; RCT, randomized control trial; Meta, metanalysis; Sx, symptoms; QOL, quality of life; “x” indicates supportive evidence of association with the outcome domain, “-“ indicates studies have not found significant associations, absence of rating indicates a lack of research studies related to the outcome domain.

Table 2.

Clinical evaluation and management of asthma comorbidities

Comorbidity	Clinical Clues	Suggested Evaluation	Recommended Intervention	Anticipated asthma benefit
Allergic Rhinitis	Nasal symptoms	SPT or sIgE	INCS ± oral/nasal antihistamines, montelukast, nasal saline	Uncertain, possible fewer exacerbations
CRSwNP	Chronic congestion, sinus pressure, cough	Nasal examination, sinus CT, rhinoscopy; Aspirin sensitivity In children: sweat test, ciliary bx/PCD genetics	Oral/intranasal steroids, antihistamines, nasal saline, antibiotics, sinus surgery; Aspirin desensitization; anti-IgE, anti-IL-5, IntiIL-4r therapy	Improved symptoms, FEV1, exacerbations
Obesity	Elevated BMI	BMI, Metabolic syndrome	Diet, exercise program; bariatric surgery (adult)	Improved QOL, asthma control, FEV1
ILO;	Stridor, discrete episodes, hyperventilation	Laryngoscopy with provocation;	Speech Pathology, stimulus avoidance, inhaled anticholinergics*; psychopharmacologic therapy, if indicated	Improved symptoms
Dysfunctional breathing	hyperventilation, sighing, asynchronous thoraco-abdominal breathing	SEBQ/Nijmegen Questionnaire	Breathing retraining	Improved symptoms, QOL
OSA	Snoring Daytime somnolence	PSG	Adenotonsillectomy (children) CPAP	Improved exacerbations, symptoms, QOL
GERD	Heartburn, regurgitation, chest pain, cough	GI endoscopy, impedence/pH probe	Gastric acid suppression, fundoplication	Slight improved FEV1 and rescue medication use
Anxiety/ depression	mood/behavioral cues	Screening tools (i.e., GAD7, PHQ9, HADS); psychology referral	CBT, psychopharmacologic therapy	Possible improved symptoms, QOL
Vitamin D deficiency		25 OH Vitamin D level (<30 ng/ml)	Vitamin D supplementation	Possible improved exacerbation rate in adults achieving normal Vitamin D levels
ABPA/M	Uncontrolled asthma, bronchitis, mucus plugs	Skin test/sIgE to fungus, total IgE, aspergillus precipitins or sIgG**; CXR; chest CT	Systemic corticosteroids + antifungal agent; alternative: omalizumab	Symptoms, lung function
Smoking/SHS	History, observed odor of smoke	History, urinary cotinine	Smoking cessation counseling, medical management	Symptoms, lung function, exacerbations
COPD	Dyspnea, chronic cough, sputum production	History, pre-and post spirometry	Smoking cessation; Asthma pharmacotherapy; LAMA-LABA-ICS therapy	Symptoms, lung function, exacerbations

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; ILO, inducible laryngeal obstruction; OSA, obstructive sleep apnea; GERD, gastroesophageal reflux; ABPA/M. allergic bronchopulmonary aspergillosis/mycosis; SHS (secondhand smoke); PSG, polysomnography; sIgE, specific Immunoglobulin E; CT, computed tomography; CPAP, continuous positive airway pressure; CBT, cognitive behavioral therapy; FEV1, forced exhalatory volume in one second; QOL, quality of life; GAD7, General Anxiety Disorder-7; PHQ9, Patient Health Questionnaire-9; HADS, Hospital Anxiety and Depression Scale; ICS, inhaled corticosteroids:*anecdotal evidence; ** ABPA diagnostic criteria: (1) predisposing asthma or CF, (2) Aspergillus skin test reactivity or detectable serum IgE to Aspergillus fumigatus, (3) total serum IgE >1000 IU/ml (lower levels acceptable if patient meets all other criteria), (4) at least two of the following: Precipitating antibodies or increased Aspergillus species IgG level; chest radiographic infiltrates; Total eosinophil count >500 cells/microL in glucocorticoid-naïve patients (may be historical).