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DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

Current opinions for the management of asthma associated with ear, nose and throat comorbidities

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ENT comorbidities contribute to poor asthma control. These comorbidities are "treatable traits", adding impetus to their evaluation and management to improve asthma outcomes.
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ABSTRACT Ear, nose and throat (ENT) comorbidities are common in patients with asthma and are frequently associated with poorer asthma outcomes. All these comorbidities are "treatable traits" in asthma. Identification and management of these disorders may spare medication usage and contribute to improved asthma control and quality of life, and a decrease in exacerbation rates.

This review summarises recent data about the prevalence, clinical impact and treatment effects of ENT comorbidities in asthma including allergic rhinitis, chronic rhinosinusitis with and without nasal polyposis, aspirin-exacerbated respiratory disease, obstructive sleep apnoea and vocal cord dysfunction.

Many of these comorbidities are possible to be managed by the pulmonologist, but the collaboration with the ENT specialist is essential for patients with chronic rhinosinusitis or vocal cord dysfunction. Further rigorous research is needed to study the efficacy of comorbidity treatment to improve asthma outcomes, in particular with the development of biotherapies in severe asthma that can also be beneficial in some ENT diseases.

Introduction

The concept of unified airways was observed by Claudius Galenus [1], and it was extensively researched during the 1970s and 1980s [2–4]. A scientific and clinical revival was made during the last 20 years [5–8]. Both the upper and lower airway act as one system of conductive airways, presenting anatomical and functional similarities including conditioning, cleaning and conduction of the inspired air to the periphery of the lungs. Scientific research in the field of upper and lower airways has brought up significant epidemiologic, pathophysiologic, and clinical evidence supporting an integrated view of upper airways disorders and asthma. The unified airway disease can be presented in different phenotypes, including both allergic and nonallergic hypersensitivity reactions.

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TABLE 1 Prevalence, diagnosis and management of ear, nose and throat comorbidities in asthma

Comorbidity	Prevalence	Test	Management
Allergic rhinitis	80% [6]	History Sinonasal questionnaire [9] Skin-prick test/specific IgE	Nasal steroids Antihistamines Anti-leukotrienes Allergen immunotherapy
Chronic rhinosinusitis	22–42% [9]	History Sinonasal questionnaire [9] CT of sinuses Endoscopy of nasal cavity	Nasal steroids Surgery Anti-leukotrienes Macrolides Biologics
Aspirin-exacerbated respiratory disease	7.2% [9]	History Sinonasal questionnaire [9] CT of sinuses Endoscopy of nasal cavity Provocative challenge with aspirin/NSAIDs	Avoidance of aspirin/COX1 inhibitors Aspirin desensitisation Low salicylate diet Nasal steroids Surgery Anti-leukotrienes Biologics
Obstructive sleep apnoea	20–40% [10, 11]	History Berlin questionnaire [9] Polysomnography	Continuous positive airway pressure
VCD	19% [12]	History Pittsburgh VCD index [9] Laryngoscopy	Speech therapy Psychotherapy Injection with botulinic toxin in laryngeal muscles Inhaled ipratropium

VCD: vocal cord dysfunction; Ig: immunoglobulin; CT: computed tomography; NSAID: nonsteroidal anti-inflammatory drug.

Epidemiological evidence supports the coexistence of asthma and upper airway disorders, including allergic rhinitis, chronic rhinosinusitis (CRS) with or without nasal polyposis, obstructive sleep apnoea (OSA) and vocal cord dysfunction (VCD) (table 1). It was found that approximately 80% of asthmatics have rhinitis, and roughly 30% of patients with rhinitis have asthma, with rhinitis symptoms reported in 98.9% of allergic asthmatics and in 78.4% of nonallergic asthmatics [6]. Patients with perennial allergic rhinitis have a greater bronchial reactivity than those with seasonal allergic rhinitis [13], and patients with only allergic rhinitis and no asthma have lower bronchial hyperresponsiveness (BHR) [14] outside of and during the pollination season (11% *versus* 48%) [15]. Previous studies suggested that rhinitis and nonallergic rhinitis represent a significant risk factor for the development of asthma [16–18]. The adjusted relative risk for asthma in the study by Shaaban *et al.* [16] was 1.63 for the atopy only group, 2.71 for the group with non-allergic rhinitis, and 3.53 for the allergic rhinitis group.

Pathophysiological analysis proved a continuum of shared properties along upper and lower airways, including the ciliary epithelium, basement membrane, lamina propria, glands and goblet cells [19]. United airway disease can present as two phenotypes: allergic and nonallergic. The allergic phenotype is well characterised as allergic rhinitis and asthma share the same immunopathological features based on allergen-specific T-helper (Th)2 cell response, an immunoglobulin (Ig)E-mediated reaction associated with airway inflammation, thickening of the basement membrane and goblet-cell hyperplasia [20]. However, the aetiology and mechanisms involved in nonallergic united airway disease needs clarification. The importance of the mucosal epithelium of the upper and lower airways in the pathogenesis of CRS and asthma has been recently recognised, but not all implicated mechanisms have been identified [21, 22]. It is known that, in response to pathogenic triggers and allergens, human airway epithelial cells produced thymic stromal lymphopoietin, interleukin (IL)-25 and IL-33 which are recognised as important mediators of innate type-2 immune reactions implicated in the pathogenesis of eosinophilic asthma and CRS with nasal polyposis [21, 22]. The role of air pollution, occupational and other environmental exposures, second-hand smoke, microbiome, infectious agents (viruses and bacteria), epigenetics in the pathogenesis of asthma and CRS is not very well understood at the moment. In addition, similar pathological features can be seen in both asthma and CRS including remodelling and thickening mucosa due to oedema, submucosal gland and smooth muscle hypertrophy, collagen deposition, basement membrane thickening, and subepithelial fibrosis in the lamina reticularis [23].

The main pathophysiological concept of the united airway disease is the influence of the upper airway on the function of the lower airway or *vice versa*, with interactions *via* air conditioning, inflammation and/or neural reflexes [24]. Influence of air conditioning is evident from the defence ability of the nose for the lower airways through preparation of the air and the innate and adaptive immune defence (*i.e.* release of antibacterial proteins, chemical defences, antioxidants, secretory IgA, *etc.*). Therefore, with the loss of nasal functions the lower airways are "opened" to extrinsic influence.

There are two main mechanisms of how propagation of inflammation from the upper airway to lower airway may occur: post-nasal drip and systemic circulation, with the first one being quite speculative [24]. In a series of experiments Braunstahl *et al.* [25] found that allergens placed in the nose resulted in upregulation of inflammatory mediators in the distal bronchi. Similarly, segmental bronchial challenge with allergen induced an upregulation of inflammatory mediators in the nose and peripheral blood eosinophilia [26–28]. Yan *et al.* [3] suggest this "nasobronchial" reflex originates from the sensory nerves in the nose, through the trigeminal nerve to the central nervous system, with an efferent vagal nerve pathway which may produce airway smooth muscle contractions. In this study [3], nasal histamine provocation induced bronchoconstriction in six out of 12 patients with perennial allergic rhinitis and stable asthma. Similarly, nasal inhalation of dust, polluants and irritants can induce immediate bronchoconstriction with cessation of respiration in the expiratory phase, due to relaxation of inspiratory muscles [29]. Interactions between the nose and lung, including neurogenic and nasobronchial reflexes and neural plasticity, are implicated in allergic rhinitis and non-allergic rhinitis and asthma, explaining the worsening of asthma symptoms after nasal injury [13].

Severe uncontrolled allergic rhinitis, non-allergic rhinitis, CRS and aspirin-exacerbated respiratory disease (AERD) are defined as severe chronic upper airway diseases [30–32] and impact on the lower airway disease. It has been demonstrated that more severe rhinitis is associated with an increased risk of asthma [33], with less favourable outcomes in patients with asthma [34–36]. It has also been shown that the treatment of rhinitis can be beneficial for many of the asthma outcomes (less symptoms, emergency room visits, and hospitalisations) [37–39]. In difficult-to-treat and severe asthma, rhinitis is proposed as one of the main comorbidities to be assessed and treated [40]. Treatment of upper airways diseases is important in asthma, leading to a better control of both disorders, but further studies are needed to completely understand the interactions between the upper and lower airways.

Allergic rhinitis and asthma

As already mentioned in the introduction, allergic rhinitis and asthma often coexist, sharing many common disease characteristics such as chronic airway inflammation, common genetic backgrounds, similar triggers including allergen exposure, viral infections, cold air, and air pollution [5]. A strong set of epidemiologic evidence confirms this notion [16, 18, 33, 41–45]. Results from 8329 randomised adults from the SAPALDIA study [45] showed similarities in the inflammatory pattern of asthma and allergic rhinitis, in which eosinophils and T-lymphocytes are the predominant cells.

Typically, early onset allergic asthma is associated with allergic sensitisation and allergic rhinitis. These patients tend to have a clear association between allergen exposure and symptoms, as well as between upper and lower airway symptoms [46]. Patients with allergic rhinitis report poorer asthma control, more exacerbations and emergency visits and have more difficulty achieving symptom control [6, 47]. The presence of allergic rhinitis is a significant early-life predictor for an accelerated decline in lung function from the first to sixth decade of life [48].

Treating coexisting allergic rhinitis improves asthma control and decreases healthcare resource utilisation [6]. Several early studies provided evidence that appropriate treatment of allergic rhinitis results in the improvement of asthma.

H1-antihistamines, the first-line treatment in controlling the classic symptoms of allergic rhinitis, is not recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [6] for treating asthma. However, evidence suggests that this treatment appears to delay asthma development in high-risk atopic infants [49, 50] and has beneficial effects on asthma outcomes when it is used to treat allergic rhinitis [39, 51, 52]. H1-antihistamine administration in an ordinary dose for allergic rhinitis is associated with a significant improvement in allergic rhinitis and asthma symptoms [51, 53–55] and quality of life [56] without a significant impact on the lung function [53, 57, 58] probably related to the fact that more elevated doses are needed to obtain a bronchodilatator effect. In a 6-week randomised, double-blind study enrolling patients with seasonal allergic rhinitis and mild-to-moderate asthma [59], the association between 5 mg loratadine and 120 mg pseudoephedrine twice daily significantly improved nasal and asthma symptoms, pulmonary function and quality of life compared to placebo. Similarly, the association of 20 mg loratadine and 10 mg montelukast daily seems to be more effective in asthma control than

montelukast alone in patients with asthma and rhinitis [60]. To the best of our knowledge, no data about the impact of the intranasal association between azelastine and fluticasone on asthma outcomes are available.

Intranasal corticosteroid therapy in patients with both allergic rhinitis and asthma significantly decreased asthma symptom scores, disease severity and rescue medication use, could prevent the increase in BHR associated with seasonal pollen exposure and exercise-induced asthma, and improved lung function [38, 61, 62]. A pivotal study by Dahl *et al.* [63] using fluticasone propionate as intranasal and inhaled corticosteroid treatment showed that topical treatment of both diseases is needed to control clinical manifestations and inflammation of coexisting seasonal allergic rhinitis and asthma.

Available data suggest that anti-leukotrienes should be considered as a beneficial anti-asthma treatment targeting both upper and lower airways in asthma and allergic rhinitis [6, 64]. Biologic therapies such as omalizumab, an anti-IgE therapy, and, more recently, dupilumab, an anti-IL-4 receptor-α antibody, could be a therapeutic option in patients with both severe allergic asthma and allergic rhinitis. Omalizumab is effective in preventing asthma exacerbations and in improving asthma/rhinitis symptoms and quality of life in this population [65, 66]. A recent study proves that 300 mg dupilumab every 2 weeks significantly improves allergic rhinitis-associated nasal symptoms in patients with uncontrolled persistent asthma [67].

The benefit of allergen immunotherapy has been proven in allergic rhinitis (improvement of symptom score and quality of life with decrease in medication use) [68] and asthma (increase in time to first asthma exacerbation following weaning of inhaled corticosteroids) [69]. A Cochrane analysis [70] showed that immunotherapy improves asthma symptoms and BHR in patients with allergic rhinitis.

These data prompted both the introduction of an evidence-based document from ARIA to provide a guide for the diagnosis and management of allergic rhinitis and asthma multimorbidity, and its updates but also significant research regarding both underlying mechanisms and treatment options [5, 6, 71, 72]. In the 2010 ARIA revision the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach was adopted [73]. For the latest revision ARIA introduced integrated care pathways for the management of allergic rhinitis and asthma by a multidisciplinary group centred around the patients using shared decision making with interventional therapy evidence-based tools, thus empowering the patient to make treatment decisions focused on disease control, by using the guided self-management plan proposed by their healthcare professionals [73, 74]. Thus, ARIA is unique as it includes the multimorbid component of the airway diseases currently being accepted worldwide [75–77]. The multimorbid concept has a direct benefit for the patient whose nasal symptoms are often more bothersome than asthma.

Asthma and CRS with and without nasal polyposis

CRS affects about 10.9% of the population in Europe and 13% in the USA. CRS and asthma are closely related to each other in many aspects. It is therefore no surprise that not only pathomechanisms but also therapeutic principles are similar in both sections of the airways [78, 79].

A strong association between CRS and asthma has been recognised (OR 3.47). This association is stronger in patients reporting both CRS and allergic rhinitis (OR 11.85) [80]. Most patients with CRS without clinical asthma show BHR [81]. A clinical history of nasal polyposis usually precedes asthma, and up to 45% of patients with nasal polyposis will develop asthma. The prevalence of CRS with nasal polyposis is higher in asthmatics (7%) compared to the general population (4%) [82].

CRS comprises a spectrum of conditions with distinct clinical presentations and pathogenic mechanisms. Similar processes of inflammation have been noted in the functional units of the lung forming the basis of the unified airway theory. Up to 85% of cases of CRS with nasal polyposis are associated with the eosinophil-mediated T2-high (IL-4 high/IL-5 high/IL-13 high) cytokine profile, typical for Western populations. Upregulation of the Th2 system with predominantly eosinophilic inflammation and elevated levels of IL-5 and IgE are found. The release of toxic products by eosinophils leads to further inflammation and subsequent polyp formation. However, in an Asian population, inflammation is dominated by neutrophils with a Th1/Th17-type response [83, 84]. CRS without nasal polyposis is characterised by an increased production of Th1/Th0-associated cytokines (interferon-γ) and an upregulation of the transforming growth factor-β pathways [85]. However, cases of CRS without nasal polyposis are also fully capable of expressing profiles associated with Th1, Th2 and Th17 signatures alone or in combination [83].

Clinical phenotypes of patients with CRS with nasal polyposis and asthma have been characterised by older age, longer duration of nasal symptoms, higher incidence of allergic rhinitis, bronchial obstruction, higher computed tomography and endoscopy scores, a higher number of sinonasal surgeries and poorer quality of life. Asthmatics with comorbid CRS with nasal polyposis have late-onset, poorly controlled

asthma, increased airway obstruction and more severe asthma. These patients may have a more intense lower airway inflammation in relation to the presence of CRS with nasal polyposis [86]. Patients with nasal polyposis and comorbid asthma present different clinical phenotypes, inflammatory status and disease severity [87].

The impact of CRS treatment on asthma is controversial. For patients with CRS, it has been suggested that treatment of the nose may reduce nasal symptoms, but does not generally improve asthma outcomes [71, 88]. Both oral and topical intranasal corticosteroids are first-line treatment in patients with CRS. A placebo-controlled trial of nasal mometasone in adults and children with CRS and poorly controlled asthma showed an improvement of asthma symptoms in treated patients without benefit for asthma quality of life or lung function, suggesting that, while CRS can contribute to respiratory symptoms, its treatment in patients with asthma should be determined by the need to treat sinonasal disease rather than to improve asthma control [89].

Treatment of CRS with nasal polyposis plus asthma with montelukast was studied in two trials [90, 91]. Significant improvements in nasal and asthma symptoms, results of endoscopy and computed tomography scanning of the paranasal sinuses, and asthma medication intake were reported in both trials. No significant improvements were found either in nasal or pulmonary function tests. However, Schäper *et al*. [91] found that montelukast significantly increased the peak expiratory flow.

Erythromycin is believed to have an immunomodulatory effect and improves nasal symptoms, but despite routine administration of oral antibiotics in the treatment of CRS, a Cochrane review noted little evidence of benefit in the literature for their use [92].

When medical therapies of CRS with nasal polyposis have failed, surgical treatment is recommended. A meta-analysis involving a total of 891 patients [93] showed that endoscopic sinus surgery improves clinical asthma outcome measures: improved overall asthma control in 76.1% of patients, decreased the frequency of asthma attacks in 84.8% of patients, decreased the number of hospitalisations in 64.4%, decreased the use of oral corticosteroids in 72.8% of patients, decreased inhaled corticosteroid use in 28.5% and decreased bronchodilator use in 36.3% of patients. A recent study [94] confirmed that nasal surgery significantly improved asthma control and reduced lung function decline in severe asthma and CRS.

A systematic review analysed the effect of endoscopic sinus surgery *versus* medical treatment (montelukast, omalizumab or erythromycin) in patients with asthma plus CRS with nasal polyposis and did not find marked differences between asthma outcomes after medical or surgical treatment [95].

The expression of elevated levels of IgE, IL-5 and eosinophils in tissue samples of CRS with nasal polyposis patients implicate novel and potentially advantageous uses of biologics. For omalizumab, which has been on the market for the treatment of severe asthma for over 10 years, more data are available. In a previous study, including allergic and nonallergic asthma patients with nasal polyposis, after 16 weeks of omalizumab therapy significantly decreased endoscopic nasal polyposis scores, improved, nasal symptoms (congestion and anterior rhinorrhoea) and asthma symptoms (wheeze and dyspnoea), as well the quality of life were reported [96]. A recent real-life study [97] including patients with both CRS with nasal polyposis and severe refractory allergic asthma confirmed the effectiveness of omalizumab (16 weeks of treatment) in this association with a significant sinonasal improvement (measured by Sino-Nasal Outcome Test-22 score) in parallel to the improved asthma control questionnaire (ACQ7), comparable to endoscopic sinus surgery.

More recently, biologics targeting IL-5 and IL-4/IL-13 cytokine pathways have been studied in CRS with nasal polyposis and asthma, but at the moment available data are limited. Anti-IL-5 therapy (mepolizumab/reslizumab) administrated in patients with CRS with nasal polyposis demonstrated a significant improvement of nasal symptoms, endoscopic nasal polyposis score, computed tomography scan score, Sino-Nasal Outcome Test score [82, 98, 99] and reduction in the need for surgery [100] but, unfortunately, the direct impact on asthma was not analysed in these populations. In a recent study [101] including patients with CRS with nasal polyposis which compared the effectiveness of the association of dupilumab/intranasal mometasone *versus* intranasal mometasone in the subgroup with asthma, the addition of dupilumab significantly decreased the nasal polyposis score, and improved nasal congestion, smell and Sino-Nasal Outcome Test-22 score, as well lung function (forced expiratory volume in 1 s (FEV_1)) and ACQ5.

The potential to treat the one airway with one drug (biotherapy) is on the horizon, but large studies using broad biomarker groups assessing the upper and lower outcomes together are needed to realise the next step in personalised medicine in the association of asthma with CRS with nasal polyposis. Currently, the use of biologic therapies should be reserved for select patients with refractory CRS with nasal polyposis and severe asthma with evidence of atopy or eosinophil-driven diseases which can't be controlled by the other medical therapies [80, 99].

Aspirin-exacerbated respiratory disease

AERD is a major clinical phenotype of nonsteroidal anti-inflammatory drugs (NSAIDs) hypersensitivity that affects 0.3–2.5% of the general population [102] and 7.2% of patients with asthma [103]. It includes asthma and CRS with nasal polyposis, with exacerbated symptoms upon ingestion of cyclooxygenase (COX)-1 inhibitors (aspirin and nonselective NSAIDs). Patients with AERD have a higher prevalence of severe asthma (14.9%) and a need for high-dose corticosteroids compared to aspirin-tolerant asthma [9, 103]. 7% of the asthmatics are aspirin sensitive and the prevalence doubles in severe asthmatics. AERD mostly affects women without any AERD family history [104].

Symptoms of AERD usually follow a certain pattern: the first clinical manifestation is rhinitis, which progresses into chronic hyperplastic eosinophilic sinusitis. Asthma appears approximately 2 years after the onset of rhinitis, and the aspirin/NSAID intolerance at any time (usually 4 years later) [102].

The exact pathomechanism of AERD is not fully understood. A hallmark in the pathogenesis is the dysregulated metabolism of the arachidonic acid [105]. This induces an imbalance between pro-inflammatory and anti-inflammatory substances, an overproduction of cysteinyl leukotrienes (CysLTs) and an underproduction of prostaglandin-E2. CysLTs lead to bronchoconstriction, mucus secretion, eosinophilic inflammation and vascular leak through the interaction with their specific receptors. The expression of CysLTs receptors (CysLTR1 and CysLTR2) in mucosal tissue in AERD is elevated compared to aspirin tolerant patients [102]. COX inhibitors shift arachidonic acid metabolism from COX to 5-lipoxygenase (5-LO) and increase the production of CysLTs [100]. AERD patients also have elevated prostaglandin-D2 which induces bronchoconstriction, vasodilation and recruitment of eosinophils, basophils and TH cells. IL-5 and thymic stromal lymphopoietin are increased in nasal polyposis tissue of AERD patients [106].

The diagnosis of AERD is confirmed only after a positive provocative challenge with aspirin/NSAIDs. The oral challenge is the most commonly performed. It has the best predictive value and should be performed in the cases of a negative nasal or bronchial provocation challenge test if clinical suspicion remains. The test must be performed in patients in a stable condition with an FEV_1 of least 70% of the predicted value, under the direct supervision of a physician in a laboratory with emergency resuscitative equipment and highly trained personnel for the management of potential anaphylactic reactions [107]. The test is considered positive if the FEV_1 declines $\geqslant$20% from the baseline value after aspirin administration according to a certain protocol [102]. 14–16% of patients with a positive history for AERD have a negative oral challenge [108]. Negative results do not exclude AERD, since they could be a result of other medications used to control chronic inflammatory diseases. Other diagnostic tests such as basophil activation test or exhaled nitric oxide fraction after aspirin ingestion, and measurement of eosinophil levels in blood, sputum and nasal mucus can also be performed. They are still of low sensitivity and/or require validation [102].

Careful avoidance of aspirin and other NSAIDs, which are strong COX- 1 inhibitors, is necessary to prevent severe asthma attacks. Acetaminophen or selective COX-2 inhibitors are recommended. Asthma treatment in AERD should be performed according to the current asthma management guidelines [102]. Addition of a leukotriene receptor antagonist (*e.g.* montelukast) and 5-LO inhibitors (*e.g.* zileuton) to standard anti-inflammatory therapy of asthma have been shown to be effective in improving FEV_1, quality of life and decreasing the use of rescue medication in some patients with AERD, but the degree of improvement is similar to aspirin tolerant asthmatics [109]. There is a slight superiority of zileuton since it prevents leukotriene production. Montelukast selectively targets the CysLT1 receptor. Nevertheless, montelukast is used more often because it is less expensive and has fewer side-effects [110].

Aspirin desensitisation can be a treatment option in these patients. It decreases AERD activity, improves upper and lower airway symptoms, reduces hospitalisation and emergency room visits, and decreases the need for surgery. However, only a very small percentage of patients with AERD will benefit from aspirin desensitisation [111]. At present, standardised desensitisation protocols are still lacking and it is not possible to predict the responders.

Biologic therapies such as anti-IgE, anti-IL-5 monoclonal antibodies (mepolizumab, reslizumab and benralizumab), the IL-4α receptor antagonist (dupilumab) and anti-thymic stromal lymphopoietin seem to be promising therapeutic options for AERD patients given their effectiveness in nasal polyposis and asthma [9, 98]. Omalizumab improves upper and lower airway symptoms, quality of life and nasal polyposis score similarly in asthma patients with and without aspirin hypersensitivity [9, 96]. A recent study showed that omalizumab therapy (16 weeks) in atopic AERD patients could increase the tolerability to aspirin desensitisation [78, 112]. However, data about the place of biologics in the AERD population are still lacking.

Despite advances in the knowledge of AERD, more data are needed to improve the diagnostic and therapeutic options as well as patients' quality of life.

OSA and asthma

OSA affects around 5% of children [113] and 10% of adults [114]. This disease is characterised by the total or partial repetitive obstruction of the pharyngeal airways during sleep. OSA is diagnosed on the basis of the frequency of sleep-disordered breathing events during overnight polysomnography, but this approach is poorly suited to the clinical evaluation of large at-risk populations [115]. In children, OSA is primarily caused by enlarged adenoids and tonsils and nasal obstruction, while in adulthood it is caused by a mixture of aetiological factors which lead to increased collapse potential of the pharyngeal muscles. These factors traditionally include anatomical variations, age, male sex, ethnic difference and obesity [114]. Phenomena leading to pharyngeal neuropathy (*i.e.* smoking, diabetes, hypothyroidism), mucosal swelling (*i.e.* cardiac failure) and impaired ventilatory control (*i.e.* alcohol consumption, medication usage) may also contribute to OSA [116]. Irrespective from age and the underlying cause, OSA triggers snoring-related vibration trauma and intermittent hypoxia. Both of these enhance inflammation in the upper and lower airways [117]. Lower airway inflammation is characterised by neutrophilia and a cascade of pro- and type-I inflammatory mediators [117].

The prevalence of OSA among asthmatic subjects seems to be higher than in the general population and is estimated to be 20–40% [10, 118]. In paediatric OSA, the corresponding numbers are even higher (30–60%) [11, 119]. However, the prevalence of asthma in OSA seems to be similar to the general population [120]. However, many of these studies used questionnaires and symptoms to evaluate OSA, while objective polysomnographic studies have only been conducted in smaller cohorts [121, 122]. Still, the data are similar to the epidemiological studies [10, 118]. Interestingly, OSA is more prevalent in severe asthma than in moderate disease in adults [122], and OSA is associated with more severe exacerbations in adults [123] and poorer asthma control in children [120, 121]. Analysing the data of Wisconsin Sleep Cohort, self-reported asthma was associated with an increased risk for the development of objectively diagnosed OSA, with a direct relationship between asthma duration and risk for OSA development [124]. However, in well-defined asthmatic participants of the Severe Asthma Research Program II, more frequent symptoms, worse lung function, poorer quality of life, greater BHR and sputum neutrophilia were associated with increased OSA risk [125]. Theoretically, obesity, rhinitis and nasal polyposis, as well as myopathy of the upper airway muscles induced by oral and inhaled steroids, are factors which may link asthma to OSA [126]. In a recent pilot study, inhaled fluticasone significantly reduced upper airway collapsibility in asthmatic subjects, suggesting that treatment of asthma may blunt the development of OSA and may decrease disease severity in asthmatic patients with obstructive sleep apnoea [127].

OSA may also interfere with various measures of asthma. OSA is associated with sputum neutrophilia [117] and slightly elevated levels of exhaled nitric oxide fraction [128] confounding the clinical interpretation of these parameters in asthma. Studies reported both direct [129, 130] and no association between OSA and BHR [131, 132]; however, those showing no relationship included higher numbers of subjects. The severity of OSA is linearly related to the decreased lung volumes [117] and is associated with overnight variation of lung function [133], a phenomenon known for asthma. More importantly, OSA is also associated with accelerated lung function decline in asthma [134]. Asthma may also interact with measures of OSA by contributing to fragmented sleep architecture and deepened nocturnal hypoxaemia [135].

Diagnosis of OSA is not different in asthma than in the general population and is based on the combination of night- and daytime symptoms, suggestive comorbidities and objective sleep studies. However, the differential diagnosis may be challenging as night time symptoms are frequent in both diseases. Asthmatic children with coexisting allergic rhinitis require special attention, as OSA is associated with allergic rhinitis childhood [136].

Contrary to the diagnosis, treatment of OSA has some special aspects in asthma. In children with allergic rhinitis, nasal corticosteroids may decrease OSA severity [137, 138]. Continuous positive airway pressure (CPAP), the gold standard therapy for severe OSA, may worsen BHR, as reported by some [132, 139, 140] but not all studies [141], possibly due to drying airway mucosa. Interestingly, in asthmatic patients with OSA, CPAP therapy did not change [142] or even improve BHR [141]. One explanation for the discrepancies between asthmatic and non-asthmatic subjects could be the fact that patients with asthma were on inhaled corticosteroid treatment which might have prevented worsening of BHR. Using heated humidification with CPAP could be a possible solution, as this was more effective in reducing airway [142] and nasal inflammation [143]. Recent data showed an improvement of asthma control, quality of life and lung function after starting CPAP in asthmatics with moderate-to-severe OSA [144].

VCD and asthma

VCD is characterised by episodes of involuntary paradoxical movements of vocal folds in adduction during inspiration that results in extrathoracic airway obstruction inducing dyspnoea and wheezing, principally in the cervical region, as well as stridor in certain cases [145, 146].

The prevalence of VCD in the general population has not been adequately estimated [147]. In a pilot study in adults based on a questionnaire, 4% reported either of VCD-like symptoms (dyspnoea and wheezing) [148]. First described in 1983, VCD was considered to mimic asthma [149] but further studies have revealed that asthma and VCD frequently coexist [150–153]. In a retrospective study including 95 patients with laryngoscopically proved VCD, 56% of patients had asthma [152]. More than three-quarters of VCD patients without asthma were treated by unnecessary systemic corticosteroids for their symptoms (mean dose 29.2 mg prednisolone daily). These patients had a high healthcare utilisation (9.7 emergency visits, 5.9 hospital admissions in the year prior to evaluation), and 28% of them were previously intubated during severe dyspnoea attacks [152]. In a case–control study, Yelken *et al.* [154] found a significantly higher prevalence of VCD in asthmatic adults (19%) *versus* controls (5%; $p<0.001$). The prevalence of VCD is up to 40% in patients with difficult-to-control asthma [136] and is associated with a poorer quality of life [103], but little is known about the true prevalence of VCD in severe asthma because most studies have examined selected patient groups [46]. VCD is often misdiagnosed as asthma, which leads to an inappropriate choice of treatment options for subjects with this condition and inappropriate stepping up of medications to generate a better therapeutic response for "unresponsive" asthma, which places the patient at risk for more potential adverse effects and greater medical costs [12, 155]. In the study of Traister *et al.* [156], 42.4% of patients with VCD were misdiagnosed as asthma for an average 9 years. When the VCD is not recognised, patients frequently return to the emergency department, leading to delays in diagnosis and potentially unnecessary intensive care unit admissions, intubations and tracheostomies [157]. The time from symptom onset to diagnosis of VCD is >4 years [158].

The exact pathophysiology of VCD remains unknown [145, 155]. Proposed theories include altered autonomic input from central brain regions polysynaptically linked to the larynx resulting in hyperkinetic laryngeal dysfunction [155]. A classification was proposed by Forrest *et al.* [159] into primary VCD (75%), which is psychological, and secondary VCD (25%) to medical disorders divided into irritable larynx syndrome and neurological disorder. The triggers that induce an episode of VCD are frequently similar to those that exacerbate asthma, including emotional stress, airway irritants, changes in humidity or extreme temperatures, respiratory infections and physical exercise [12, 46, 145]. Asthma and VCD have several common comorbidities, including chronic allergic and non-allergic rhinitis with post-nasal drip, gastro-oesophageal reflux disease, untreated sleep apnoea, smoking, anxiety and hyperventilation [12, 145, 155].

The diagnosis of VCD may be difficult to confirm because physical examination and spirometry may be normal between episodes [146], and the morbidity induced by the undiagnosed disease is high. During a VCD attack, some patients have stridor and hoarseness, but the majority of them have asthma symptoms (wheezing and dyspnoea) [46]. Symptoms are often episodic and reversible, with or without therapy [160]. The Pittsburgh VCD Index is a simple four-question questionnaire with a good predictive value to diagnose VCD (cut-off score $\geqslant 4$) and to distinguish VCD from asthma [46, 145, 155]. Patients with poorer asthma control, frequent exacerbations and emergency visits, and minimal response to corticosteroids should be investigated for VCD [46, 145, 160], and VCD should be included in the differential diagnosis of asthma [145].

The gold standard for diagnosing VCD is the demonstration by laryngoscopy of paradoxical vocal cord movement caused by the adduction of the anterior two-thirds of the vocal cords during attack [46, 145]. Usually, the laryngeal examination is normal outside attacks, and asking the patient to do a variety of manoeuvres or performing provocation studies may help to identify VCD [46, 145, 157].

Spirometry appears to have a low predictive value for detecting VCD, but a truncated inspiratory loop may be helpful for the diagnosis in the presence of symptoms [46, 147, 157, 160]. If the spirometry is normal, a methacholine challenge test is needed to diagnose asthma. Two studies showed indirect evidence that the methacholine challenge test may elicit VCD symptoms, and 60–70% of patients with VCD had a positive methacholine challenge test, indicating that VCD and BHR coexist [161, 162]. Recent data have shown that in patients with exercise-related symptoms, bronchial provocation testing does not detect exercise-induced laryngeal obstruction and continuous laryngoscopy during exercise is the gold standard for diagnosis [163–165]. The prevalence of exercise-induced laryngeal obstruction in severe asthma is unknown at the moment [46]. A recent study by Low *et al.* [166] showed that VCD is more often associated with asthma symptoms accompanied by airflow limitation (FEV_1 <80%) and dysfunctional breathing (Nijmegen scores >20).

The treatment of VCD includes nonpharmacological and pharmacological therapies [103]. Laryngeal control therapy with a speech pathologist is the cornerstone of VCD treatment [146, 155, 157]. A recent study [167] showed that diagnosis and treatment of VCD led to a decline in asthma medication use (79% of patients) and to an improvement of reported symptoms (82% of patients). Psychotherapy may be

beneficial in some patients [168]. In patients with difficult-to-treat asthma and VCD, injection with *Clostridium botulinum* toxin into laryngeal muscles reduced VCD and improved asthma control scores in an uncontrolled case series [169]. Similarly, inhaled ipratropium reduced exercise-induced VCD in a small case series [170]. Access to speech therapists or physiotherapists with experience in VCD is an important part of severe asthma management [42].

Conclusions

ENT comorbidities are important in the management of asthma because of the higher prevalence, many anatomical and functional similarities, and the association with poorer asthma outcomes. Achieving disease control on a minimum anti-asthmatic medication is the goal in patients with asthma and that may be possible with a systematic assessment and treatment of comorbidities in these patients.

The ARIA initiative introduced evidence-based management of both diseases by a multidisciplinary group with a focus on the patient and it includes the multimorbid concept that has a direct benefit for the patient whose nasal symptoms are often more bothersome than asthma. Topical treatment with inhaled corticosteroids on both levels is needed to control clinical symptoms and inflammation of coexisting asthma and allergic rhinitis.

Asthmatics with comorbid CRS with nasal polyposis have late-onset, poorly controlled asthma and increased airway obstruction. Treatment of the nose may reduce nasal symptoms, with controversial results on asthma. Inhaled corticosteroids, montelukast, omalizumab, erythromycin, biotherapeutics and endoscopic surgery produce similar effects.

AERD is a major clinical phenotype of NSAIDs hypersensitivity that includes asthma and CRS with nasal polyposis, and is exacerbated upon ingestion of COX-1 inhibitors (aspirin and nonselective NSAIDs). Therapeutic options are the addition of an anti-leukotriene inhibitor to standard therapy of asthma, aspirin desensitisation and biologic therapies.

OSA is more prevalent in severe asthma, and is associated with more severe exacerbations in adults and poorer asthma control in children. CPAP improves asthma control, quality of life, and lung function in asthmatics with moderate-to-severe OSA.

VCD may mimic or associate asthma and the prevalence is up to 40% in patients with difficult-to-control asthma. Speech psychotherapy with limited available pharmacological treatment is mandatory in severe asthma.

All these comorbidities are “treatable traits” in asthma and their specific management could improve asthma outcomes.

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