

Current Opinions for the Management of Asthma Associated with ear, Nose and Throat Comorbidities

Tiotiu, Angelica; Plavec, Davor; Novakova, Silviya; Mihaicuta, Stefan;
Novakova, Plamena; Labor, Marina; Bikov, Andras

Source / Izvornik: **European Respiratory Review, 2018, 27, 1 - 14**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1183/16000617.0056-2018>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:239:480191>

Rights / Prava: [Attribution 4.0 International](#)/[Imenovanje 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2024-12-23**




Repository / Repozitorij:

[Repository UHC Osijek - Repository University
Hospital Centre Osijek](#)




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

Angelica Tiotiu ^{1,2}, Davor Plavec³, Silviya Novakova⁴, Stefan Mihaicuta⁵, Plamena Novakova⁶, Marina Labor⁷ and Andras Bikov⁸

Affiliations: ¹Pulmonology Dept, University Hospital, Nancy, France. ²EA 3450 DevAH, Development, Adaptation, Cardio-Respiratory Regulations and Motor Control, University of Lorraine, Nancy, France. ³Srebrnjak Children's Hospital, Zagreb, Croatia. ⁴Allergy Unit, University Hospital "St. George", Plovdiv, Bulgaria. ⁵Pulmonology Dept, University Hospital, Timisoara, Romania. ⁶Dept of Allergology and Asthma, Aleksandrovska Hospital, Sofia, Bulgaria. ⁷Pulmonology Dept, University Hospital Centre Osijek, Osijek, Croatia. ⁸NIHR Clinical Research Facility, Manchester University NHS Foundation Trust, Manchester, UK.

Correspondence: Angelica Tiotiu, Pulmonology Dept, University Hospital of Nancy, 9, Rue du Morvan, 54511 Vandoeuvre-lès-Nancy, France. E-mail: a.tiotiu@chru-nancy.fr

 @ERSpublications
ENT comorbidities contribute to poor asthma control. These comorbidities are “treatable traits”, adding impetus to their evaluation and management to improve asthma outcomes.
<http://ow.ly/zLuQ30mcVwD>

Cite this article as: Tiotiu A, Plavec D, Novakova S, *et al.* Current opinions for the management of asthma associated with ear, nose and throat comorbidities. *Eur Respir Rev* 2018; 27: 180056 [<https://doi.org/10.1183/16000617.0056-2018>].

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.

Provenance: Submitted article, peer reviewed.

Received: June 12 2018 | Accepted after revision: Oct 03 2018

Copyright ©ERS 2018. ERR articles are open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

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, pollutants 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 bronchodilator 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) administered 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 (FEV₁)) 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 FEV₁ of at 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 FEV₁ declines $\geq 20\%$ 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 FEV₁, 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-4 α 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 ≥ 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.

Acknowledgements: The authors would like to thank the Interasma European Scientific network (INES).

Conflict of interest: A. Tiotiu has nothing to disclose. D. Plavec reports grants and personal fees from GlaxoSmithKline, personal fees from Menarini, Pliva, Belupo, AbbVie, Novartis, MSD, Chiesi and Revenio, personal fees and non-financial support from Boehringer Ingelheim, and non-financial support from Philips, outside the submitted work. S. Novakova has nothing to disclose. S. Mihaicuta has nothing to disclose. P. Novakova has nothing to disclose. M. Labor has nothing to disclose. A. Bikov has nothing to disclose.

References

- 1 Yusuf O. *Streptococcus pyogenes* upper respiratory infections and their effect on atopic conditions. *Prim Care Respir J* 2012; 21: 126–127.
- 2 Kaufman J, Wright GW. The effect of nasal and nasopharyngeal irritation on airway resistance in man. *Am Rev Respir Dis* 1969; 100: 626–630.
- 3 Yan K, Salome C. The response of the airways to nasal stimulation in asthmatics with rhinitis. *Eur J Respir Dis Suppl* 1983; 128: 105–109.
- 4 Schumacher MJ, Cota KA, Taussig LM. Pulmonary response to nasal-challenge testing of atopic subjects with stable asthma. *J Allergy Clin Immunol* 1986; 78: 30–35.
- 5 Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108: Suppl. 5, S147–S334.
- 6 Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63: Suppl. 86, 8–160.
- 7 Cingi C, Muluk NB, Cobanoglu B, et al. Nasobronchial interaction. *World J Clin Cases* 2015; 3: 499–503.
- 8 Ciprandi G, Caimmi D, Miraglia Del Giudice M, et al. Recent developments in United airways disease. *Allergy Asthma Immunol Res* 2012; 4: 171–177.
- 9 Tay TR, Hew M. Comorbid “treatable traits” in difficult asthma: current evidence and clinical evaluation. *Allergy* 2018; 73: 1369–1382.
- 10 Auckley D, Moallem M, Shaman Z, et al. Findings of a Berlin Questionnaire survey: comparison between patients seen in an asthma clinic versus internal medicine clinic. *Sleep Med* 2008; 9: 494–499.
- 11 Ginis T, Akcan FA, Capanoglu M, et al. The frequency of sleep-disordered breathing in children with asthma and its effects on asthma control. *J Asthma* 2017; 54: 403–410.

- 12 Li R-C, Singh U, Windom HP, *et al.* Clinical associations in the diagnosis of vocal cord dysfunction. *Ann Allergy Asthma Immunol* 2016; 117: 354–358.
- 13 Giavina-Bianchi P, Aun MV, Takejima P, *et al.* United airway disease: current perspectives. *J Asthma Allergy* 2016; 9: 93–100.
- 14 Crapo RO, Casaburi R, Coates AL, *et al.* Guidelines for methacholine and exercise challenge testing – 1999. *Am J Respir Crit Care Med* 2000; 161: 309–329.
- 15 Madonini E, Briatico-Vangosa G, Pappacoda A, *et al.* Seasonal increase of bronchial reactivity in allergic rhinitis. *J Allergy Clin Immunol* 1987; 79: 358–363.
- 16 Shaaban R, Zureik M, Soussan D, *et al.* Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet Lond Engl* 2008; 372: 1049–1057.
- 17 Rochat MK, Illi S, Ege MJ, *et al.* Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol* 2010; 126: 1170–1175.
- 18 Leynaert B, Bousquet J, Neukirch C, *et al.* Perennial rhinitis: a independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; 104: 301–304.
- 19 Feng CH, Miller MD, Simon RA. The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis. *Am J Rhinol Allergy* 2012; 26: 187–190.
- 20 Okano M, Kariya S, Ohta N, *et al.* Association and management of eosinophilic inflammation in upper and lower airways. *Allergol Int* 2015; 64: 131–138.
- 21 Bachert C, Gevaert E. Advances in rhinitis and rhinosinusitis in 2015. *J Allergy Clin Immunol* 2016; 138: 1277–1283.
- 22 Edwards MR, Saglani S, Schwarze J, *et al.* Addressing unmet needs in understanding asthma mechanisms: From the European Asthma Research and Innovation Partnership (EARIP) Work Package (WP)2 collaborators. *Eur Respir J* 2017; 49: 1602448.
- 23 Ponikau JU, Sherris DA, Kephart GM, *et al.* Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? *J Allergy Clin Immunol* 2003; 112: 877–882.
- 24 Togias A. Mechanisms of nose-lung interaction. *Allergy* 1999; 54: Suppl. 57, 94–105.
- 25 Braunstahl GJ, Overbeek SE, Kleinjan A, *et al.* Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001; 107: 469–476.
- 26 Braunstahl GJ, Kleinjan A, Overbeek SE, *et al.* Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000; 161: 2051–2057.
- 27 Braunstahl GJ, Overbeek SE, Fokkens WJ, *et al.* Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 2001; 164: 858–865.
- 28 Georgopoulos R, Krouse JH, Toskala E. Why otolaryngologists and asthma are a good match: the allergic rhinitis-asthma connection. *Otolaryngol Clin North Am* 2014; 47: 1–12.
- 29 Baraniuk JN, Merck SJ. Nasal reflexes: implications for exercise, breathing, and sex. *Curr Allergy Asthma Rep* 2008; 8: 147–153.
- 30 Bousquet J, Bachert C, Canonica GW, *et al.* Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol* 2009; 124: 428–433.
- 31 Hellings PW, Hens G. Rhinosinusitis and the lower airways. *Immunol Allergy Clin North Am* 2009; 29: 733–740.
- 32 Prokopakis EP, Vlastos IM, Ferguson BJ, *et al.* SCUAD and chronic rhinosinusitis. Reinforcing hypothesis driven research in difficult cases. *Rhinology* 2014; 52: 3–8.
- 33 Guerra S, Sherrill DL, Martinez FD, *et al.* Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; 109: 419–425.
- 34 Antonicelli L, Micucci C, Voltolini S, *et al.* Relationship between ARIA classification and drug treatment in allergic rhinitis and asthma. *Allergy* 2007; 62: 1064–1070.
- 35 Halpern MT, Schmier JK, Richner R, *et al.* Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 2004; 41: 117–126.
- 36 Ponte EV, Franco R, Nascimento HF, *et al.* Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. *Allergy* 2008; 63: 564–569.
- 37 Agondi RC, Machado ML, Kalil J, *et al.* Intranasal corticosteroid administration reduces nonspecific bronchial hyperresponsiveness and improves asthma symptoms. *J Asthma* 2008; 45: 754–757.
- 38 Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. *Allergy* 2013; 68: 569–579.
- 39 Crystal-Peters J, Neslusan C, Crown WH, *et al.* Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002; 109: 57–62.
- 40 Giavina-Bianchi P, Aun MV, Bisaccioni C, *et al.* Difficult-to-control asthma management through the use of a specific protocol. *Clin Sao Paulo Braz* 2010; 65: 905–918.
- 41 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998; 351: 1225–1232.
- 42 Braun-Fahrländer C, Gassner M, Grize L, *et al.* No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J* 2004; 23: 407–413.
- 43 Burgess JA, Walters EH, Byrnes GB, *et al.* Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol* 2007; 120: 863–869.
- 44 Huovinen E, Kaprio J, Laitinen LA, *et al.* Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest* 1999; 115: 928–936.
- 45 Tschopp JM, Sistek D, Schindler C, *et al.* Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the SAPALDIA Study. Swiss Study on Air Pollution and Lung Diseases in Adults. *Allergy* 1998; 53: 608–613.
- 46 Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. *Respirology* 2017; 22: 651–661.

- 47 Valovirta E, Pawankar R. Survey on the impact of comorbid allergic rhinitis in patients with asthma. *BMC Pulm Med* 2006; 6: Suppl. 1, S3.
- 48 Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018; 6: 535–544.
- 49 Iikura Y, Naspitz CK, Mikawa H, et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992; 68: 233–236.
- 50 Bustos GJ, Bustos D, Bustos GJ, et al. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995; 25: 568–573.
- 51 Simons FE. Is antihistamine (H1-receptor antagonist) therapy useful in clinical asthma? *Clin Exp Allergy* 1999; 29: Suppl. 3, 98–104.
- 52 Grant JA, Nicodemus CF, Findlay SR, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995; 95: 923–932.
- 53 Baena-Cagnani CE, Berger WE, DuBuske LM, et al. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of β_2 -agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol* 2003; 130: 307–313.
- 54 Baena-Cagnani CE. Desloratadine activity in concurrent seasonal allergic rhinitis and asthma. *Allergy* 2001; 56: Suppl. 65, 21–27.
- 55 Berger WE, Schenkel EJ, Mansfield LE, et al. Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. *Ann Allergy Asthma Immunol* 2002; 89: 485–491.
- 56 Pasquali M, Baiardini I, Rogkakou A, et al. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters. *Clin Exp Allergy* 2006; 36: 1161–1167.
- 57 Wilson AM. The role of antihistamines in asthma management. *Treat Respir Med* 2006; 5: 149–158.
- 58 Bachert C, Maspero J. Efficacy of second-generation antihistamines in patients with allergic rhinitis and comorbid asthma. *J Asthma* 2011; 48: 965–973.
- 59 Corren J, Harris AG, Aaronson D, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997; 100: 781–788.
- 60 Reicin A, White R, Weinstein SF, et al. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 2000; 160: 2481–2488.
- 61 Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. *Am Rev Respir Dis* 1984; 130: 1014–1018.
- 62 Corren J, Adinoff AD, Buchmeier AD, et al. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992; 90: 250–256.
- 63 Dahl R, Nielsen LP, Kips J, et al. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. *Allergy* 2005; 60: 875–881.
- 64 Price DB, Swern A, Tozzi CA, et al. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy* 2006; 61: 737–742.
- 65 Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; 59: 709–717.
- 66 Humbert M, Boulet LP, Niven RM, et al. Omalizumab therapy: patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis. *Allergy* 2009; 64: 81–84.
- 67 Weinstein SF, Katial R, Jayawardena S, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. *J Allergy Clin Immunol* 2018; 142: 171–177.
- 68 Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2016; 137: 444–451.
- 69 Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA* 2016; 315: 1715–1725.
- 70 Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; 8: CD001186.
- 71 Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; 126: 466–476.
- 72 Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines –2016 revision. *J Allergy Clin Immunol* 2017; 140: 950–958.
- 73 Guadagnoli E, Ward P. Patient participation in decision-making. *Soc Sci Med* 1998; 47: 329–339.
- 74 Kew KM, Malik P, Aniruddhan K, et al. Shared decision-making for people with asthma. *Cochrane Database Syst Rev* 2017; 10: CD012330.
- 75 Wallace DV, Dykewicz MS, Oppenheimer J, et al. Pharmacologic treatment of seasonal allergic rhinitis: synopsis of guidance from the 2017 Joint Task Force on Practice Parameters. *Ann Intern Med* 2017; 167: 876–881.
- 76 Okubo K, Kurono Y, Ichimura K, et al. Japanese guidelines for allergic rhinitis 2017. *Allergol Int* 2017; 66: 205–219.
- 77 Navarro AM, Delgado J, Muñoz-Cano RM, et al. Allergic respiratory disease (ARD), setting forth the basics: proposals of an expert consensus report. *Clin Transl Allergy* 2017; 7: 16.
- 78 Bachert C, Gevaert P, Hellings P. Biotherapeutics in chronic rhinosinusitis with and without nasal polyps. *J Allergy Clin Immunol Pract* 2017; 5: 1512–1516.
- 79 Geramas I, Terzakis D, Hatzimanolis E, et al. Social factors in the development of chronic rhinosinusitis: a systematic review. *Curr Allergy Asthma Rep* 2018; 18: 7.
- 80 Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy* 2012; 67: 91–98.
- 81 Dixon AE, Kaminsky DA, Holbrook JT, et al. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. *Chest* 2006; 130: 429–435.
- 82 Langdon C, Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. *J Asthma Allergy* 2016; 9: 45–53.

- 83 Gurrola J, Borish L. Chronic rhinosinusitis: endotypes, biomarkers, and treatment response. *J Allergy Clin Immunol* 2017; 140: 1499–1508.
- 84 Hulse KE, Stevens WW, Tan BK, *et al.* Pathogenesis of nasal polyposis. *Clin Exp Allergy* 2015; 45: 328–346.
- 85 Stevens WW, Lee RJ, Schleimer RP, *et al.* Chronic rhinosinusitis pathogenesis. *J Allergy Clin Immunol* 2015; 136: 1442–1453.
- 86 Bilodeau L, Boulay M-E, Prince P, *et al.* Comparative clinical and airway inflammatory features of asthmatics with or without polyps. *Rhinology* 2010; 48: 420–425.
- 87 Wu D, Bleier BS, Li L, *et al.* Clinical phenotypes of nasal polyps and comorbid asthma based on cluster analysis of disease history. *J Allergy Clin Immunol Pract* 2018; 6: 1297–1305.
- 88 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available from www.ginasthma.org Date last accessed: May 23, 2018.
- 89 Dixon AE, Castro M, Cohen RI, *et al.* Efficacy of nasal mometasone for the treatment of chronic sinonasal disease in patients with inadequately controlled asthma. *J Allergy Clin Immunol* 2015; 135: 701–709.
- 90 Ragab S, Parikh A, Darby YC, *et al.* An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. *Clin Exp Allergy* 2001; 31: 1385–1391.
- 91 Schäper C, Noga O, Koch B, *et al.* Anti-inflammatory properties of montelukast, a leukotriene receptor antagonist in patients with asthma and nasal polyposis. *J Investig Allergol Clin Immunol* 2011; 21: 51–58.
- 92 Head K, Chong LY, Piromchai P, *et al.* Systemic and topical antibiotics for chronic rhinosinusitis. *Cochrane Database Syst Rev* 2016; 4: CD011994.
- 93 Vashishta R, Soler ZM, Nguyen SA, *et al.* A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2013; 3: 788–794.
- 94 Lee T-J, Fu C-H, Wang C-H, *et al.* Impact of chronic rhinosinusitis on severe asthma patients. *PLoS One* 2017; 12: e0171047.
- 95 Rix I, Håkansson K, Larsen CG, *et al.* Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: a systematic review. *Am J Rhinol Allergy* 2015; 29: 193–201.
- 96 Gevaert P, Calus L, Van Zele T, *et al.* Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2013; 131: 110–116.
- 97 Bidder T, Sahota J, Rennie C, *et al.* Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together—a real life study. *Rhinology* 2018; 56: 42–45.
- 98 Tsetsos N, Goudakos JK, Daskalakis D, *et al.* Monoclonal antibodies for the treatment of chronic rhinosinusitis with nasal polyposis: a systematic review. *Rhinology* 2018; 56: 11–21.
- 99 Rivero A, Liang J. Anti-IgE and anti-IL5 biologic therapy in the treatment of nasal polyposis: a systematic review and meta-analysis. *Ann Otol Rhinol Laryngol* 2017; 126: 739–747.
- 100 Bachert C, Sousa AR, Lund VJ, *et al.* Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol* 2017; 140: 1024–1031.
- 101 Bachert C, Mannent L, Naclerio RM, *et al.* Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 2016; 315: 469–479.
- 102 Rodríguez-Jiménez JC, Moreno-Paz FJ, Terán LM, *et al.* Aspirin exacerbated respiratory disease: current topics and trends. *Respir Med* 2018; 135: 62–75.
- 103 Le Pham D, Lee J-H, Park H-S. Aspirin-exacerbated respiratory disease: an update. *Curr Opin Pulm Med* 2017; 23: 89–96.
- 104 Rajan JP, Wineinger NE, Stevenson DD, *et al.* Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol* 2015; 135: 676–681.
- 105 Cahill KN, Boyce JA. Aspirin-exacerbated respiratory disease: mediators and mechanisms of a clinical disease. *J Allergy Clin Immunol* 2017; 139: 764–766.
- 106 De Schryver E, Devuyt L, Derycke L, *et al.* Local immunoglobulin E in the nasal mucosa: clinical implications. *Allergy Asthma Immunol Res* 2015; 7: 321–331.
- 107 Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, *et al.* EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007; 62: 1111–1118.
- 108 Dursun AB, Woessner KA, Simon RA, *et al.* Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 2008; 100: 420–425.
- 109 Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res* 2011; 3: 3–10.
- 110 Steinke JW, Wilson JM. Aspirin-exacerbated respiratory disease: pathophysiological insights and clinical advances. *J Asthma Allergy* 2016; 9: 37–43.
- 111 Cho K-S, Soudry E, Psaltis AJ, *et al.* Long-term sinonasal outcomes of aspirin desensitization in aspirin exacerbated respiratory disease. *Otolaryngol Head Neck Surg* 2014; 151: 575–581.
- 112 Lang DM, Aronica MA, Maierson ES, *et al.* Omalizumab can inhibit respiratory reaction during aspirin desensitization. *Ann Allergy Asthma Immunol* 2018; 121: 98–104.
- 113 Tan H-L, Gozal D, Kheirandish-Gozal L. Obstructive sleep apnea in children: a critical update. *Nat Sci Sleep* 2013; 5: 109–123.
- 114 Peppard PE, Young T, Barnet JH, *et al.* Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177: 1006–1014.
- 115 McNicholas WT, Bassetti CL, Ferini-Strambi L, *et al.* Challenges in obstructive sleep apnoea. *Lancet Respir Med* 2018; 6: 170–172.
- 116 Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014; 383: 736–747.
- 117 Bikov A, Losonczy G, Kunos L. Role of lung volume and airway inflammation in obstructive sleep apnea. *Respir Investig* 2017; 55: 326–333.
- 118 Larsson LG, Lindberg A, Franklin KA, *et al.* Symptoms related to obstructive sleep apnoea are common in subjects with asthma, chronic bronchitis and rhinitis in a general population. *Respir Med* 2001; 95: 423–429.
- 119 Nguyen-Hoang Y, Nguyen-Thi-Dieu T, Duong-Quy S. Study of the clinical and functional characteristics of asthmatic children with obstructive sleep apnea. *J Asthma Allergy* 2017; 10: 285–292.
- 120 Tveit RL, Lehmann S, Bjorvatn B. Prevalence of several somatic diseases depends on the presence and severity of obstructive sleep apnea. *PLoS One* 2018; 13: e0192671.

- 2121 Yigla M, Tov N, Solomonov A, *et al.* Difficult-to-control asthma and obstructive sleep apnea. *J Asthma* 2003; 40: 865–871.
- 2122 Julien JY, Martin JG, Ernst P, *et al.* Prevalence of obstructive sleep apnea-hypopnea in severe *versus* moderate asthma. *J Allergy Clin Immunol* 2009; 124: 371–376.
- 2123 Wang Y, Liu K, Hu K, *et al.* Impact of obstructive sleep apnea on severe asthma exacerbations. *Sleep Med* 2016; 26: 1–5.
- 2124 Teodorescu M, Barnett JH, Hagen EW, *et al.* Association between asthma and risk of developing obstructive sleep apnea. *JAMA* 2015; 313: 156–164.
- 2125 Teodorescu M, Broymann O, Curran-Everett D, *et al.* Obstructive sleep apnea risk, asthma burden, and lower airway inflammation in adults in the Severe Asthma Research Program (SARP) II. *J Allergy Clin Immunol Pract* 2015; 3: 566–575.
- 2126 Alkhalil M, Schulman E, Getsy J. Obstructive sleep apnea syndrome and asthma: what are the links? *J Clin Sleep Med* 2009; 5: 71–78.
- 2127 Teodorescu M, Xie A, Sorkness CA, *et al.* Effects of inhaled fluticasone on upper airway during sleep and wakefulness in asthma: a pilot study. *J Clin Sleep Med* 2014; 10: 183–193.
- 2128 Bikov A, Hull JH, Kunos L. Exhaled breath analysis, a simple tool to study the pathophysiology of obstructive sleep apnoea. *Sleep Med Rev* 2016; 27: 1–8.
- 2129 Lin CC, Lin CY. Obstructive sleep apnea syndrome and bronchial hyperreactivity. *Lung* 1995; 173: 117–126.
- 2130 Sarman N, Levent E, Cubuk R, *et al.* Bronchial hyperreactivity and airway wall thickening in obstructive sleep apnea patients. *Sleep Breath* 2011; 15: 341–350.
- 2131 Lacedonia D, Salerno FG, Carpagnano GE, *et al.* Effect of CPAP-therapy on bronchial and nasal inflammation in patients affected by obstructive sleep apnea syndrome. *Rhinology* 2011; 49: 232–237.
- 2132 Devouassoux G, Lévy P, Rossini E, *et al.* Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure-induced airway hyperresponsiveness. *J Allergy Clin Immunol* 2007; 119: 597–603.
- 2133 Kunos L, Lazar Z, Martinovszky F, *et al.* Overnight changes in lung function of obese patients with obstructive sleep apnoea. *Lung* 2017; 195: 127–133.
- 2134 Wang T-Y, Lo Y-L, Lin S-M, *et al.* Obstructive sleep apnoea accelerates FEV1 decline in asthmatic patients. *BMC Pulm Med* 2017; 17: 55.
- 2135 Sundbom F, Janson C, Malinovschi A, *et al.* Effects of coexisting asthma and obstructive sleep apnea on sleep architecture, oxygen saturation, and systemic inflammation in women. *J Clin Sleep Med* 2018; 14: 253–259.
- 2136 Ng DK, Chan C, Hwang GY, *et al.* A review of the roles of allergic rhinitis in childhood obstructive sleep apnea syndrome. *Allergy Asthma Proc* 2006; 27: 240–242.
- 2137 Brouillette RT, Manoukian JJ, Ducharme FM, *et al.* Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J Pediatr* 2001; 138: 838–844.
- 2138 Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics* 2008; 122: e149–e155.
- 2139 Wenzel G, Schönhofer B, Wenzel M, *et al.* Bronchial hyperreactivity and nCPAP therapy. *Pneumologie* 1997; 51: Suppl. 3, 770–772.
- 2140 Korczynski P, Gorska K, Przybylowski T, *et al.* Continuous positive airway pressure treatment increases bronchial reactivity in obstructive sleep apnea patients. *Respir Int Rev Thorac Dis* 2009; 78: 404–410.
- 2141 Holbrook JT, Sugar EA, Brown RH, *et al.* Effect of continuous positive airway pressure on airway reactivity in asthma. a randomized, sham-controlled clinical trial. *Ann Am Thorac Soc* 2016; 13: 1940–1950.
- 2142 Lafond C, Sériès F, Lemièrre C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. *Eur Respir J* 2007; 29: 307–311.
- 2143 Koutsourelakis I, Vagiakis E, Perraki E, *et al.* Nasal inflammation in sleep apnoea patients using CPAP and effect of heated humidification. *Eur Respir J* 2011; 37: 587–594.
- 2144 Serrano-Pariente J, Plaza V, Soriano JB, *et al.* Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea. *Allergy* 2017; 72: 802–812.
- 2145 Pinto LHE, Aun MV, Cukier-Blaj S, *et al.* Vocal cord dysfunction diagnosis may be improved by a screening check list. *Allergol Int* 2016; 65: 180–185.
- 2146 Balkissoon R, Kenn K. Asthma: vocal cord dysfunction (VCD) and other dysfunctional breathing disorders. *Semin Respir Crit Care Med* 2012; 33: 595–605.
- 2147 Fretzayas A, Moustaki M, Loukou I, *et al.* Differentiating vocal cord dysfunction from asthma. *J Asthma Allergy* 2017; 10: 277–283.
- 2148 Bisdorff B, Kenn K, Nowak D, *et al.* Asthma and vocal cord dysfunction related symptoms in the general population – a pilot study. *Ann Allergy Asthma Immunol* 2014; 113: 576–577.
- 2149 Christopher KL, Wood RP, Eckert RC, *et al.* Vocal-cord dysfunction presenting as asthma. *N Engl J Med* 1983; 308: 1566–1570.
- 2150 Holmes PW, Lau KK, Crossett M, *et al.* Diagnosis of vocal cord dysfunction in asthma with high resolution dynamic volume computerized tomography of the larynx. *Respirol* 2009; 14: 1106–1113.
- 2151 Low K, Lau KK, Holmes P, *et al.* Abnormal vocal cord function in difficult-to-treat asthma. *Am J Respir Crit Care Med* 2011; 184: 50–56.
- 2152 Newman KB, Mason UG, Schmaling KB. Clinical features of vocal cord dysfunction. *Am J Respir Crit Care Med* 1995; 152: 1382–1386.
- 2153 Bardin PG, Johnston SL, Hamilton G. Middle airway obstruction – it may be happening under our noses. *Thorax* 2013; 68: 396–398.
- 2154 Yelken K, Yilmaz A, Guven M, *et al.* Paradoxical vocal fold motion dysfunction in asthma patients. *Respirol* 2009; 14: 729–733.
- 2155 Ng T-T. The forgotten cause of stridor in the emergency department. *Open Access Emerg Med* 2017; 9: 19–22.
- 2156 Traister RS, Fajt ML, Landsittel D, *et al.* A novel scoring system to distinguish vocal cord dysfunction from asthma. *J Allergy Clin Immunol Pract* 2014; 2: 65–69.
- 2157 Denipah N, Dominguez CM, Kraai EP, *et al.* Acute management of paradoxical vocal fold motion (vocal cord dysfunction). *Ann Emerg Med* 2017; 69: 18–23.

- 158 Patel NJ, Jorgensen C, Kuhn J, *et al.* Concurrent laryngeal abnormalities in patients with paradoxical vocal fold dysfunction. *Otolaryngol Head Neck Surg* 2004; 130: 686–689.
- 159 Forrest LA, Husein T, Husein O. Paradoxical vocal cord motion: classification and treatment. *Laryngoscope* 2012; 122: 844–853.
- 160 Brussino L, Solidoro P, Rolla G. Is it severe asthma or asthma with severe comorbidities? *J Asthma Allergy* 2017; 10: 303–305.
- 161 Morris MJ, Deal LE, Bean DR, *et al.* Vocal cord dysfunction in patients with exertional dyspnea. *Chest* 1999; 116: 1676–1682.
- 162 Perkins PJ, Morris MJ. Vocal cord dysfunction induced by methacholine challenge testing. *Chest* 2002; 122: 1988–1993.
- 163 Liyanagedera S, McLeod R, Elhassan HA. Exercise induced laryngeal obstruction: a review of diagnosis and management. *Eur Arch Oto-Rhino-Laryngol* 2017; 274: 1781–1789.
- 164 Røksund OD, Heimdal J-H, Clemm H, *et al.* Exercise inducible laryngeal obstruction: diagnostics and management. *Paediatr Respir Rev* 2017; 21: 86–94.
- 165 Walsted ES, Hull JH, Sverrild A, *et al.* Bronchial provocation testing does not detect exercise-induced laryngeal obstruction. *J Asthma* 2017; 54: 77–83.
- 166 Low K, Ruane L, Uddin N, *et al.* Abnormal vocal cord movement in patients with and without airway obstruction and asthma symptoms. *Clin Exp Allergy* 2017; 47: 200–207.
- 167 Kramer S, de Silva B, Forrest LA, *et al.* Does treatment of paradoxical vocal fold movement disorder decrease asthma medication use? *Laryngoscope* 2017; 127: 1531–1537.
- 168 Husein OF, Husein TN, Gardner R, *et al.* Formal psychological testing in patients with paradoxical vocal fold dysfunction. *Laryngoscope* 2008; 118: 740–747.
- 169 Baxter M, Uddin N, Raghav S, *et al.* Abnormal vocal cord movement treated with botulinum toxin in patients with asthma resistant to optimised management. *Respirol* 2014; 19: 531–537.
- 170 Doshi DR, Weinberger MM. Long-term outcome of vocal cord dysfunction. *Ann Allergy Asthma Immunol* 2006; 96: 794–799.