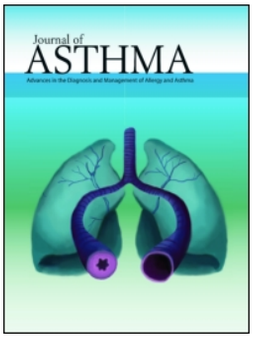

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Manifesto on united airways diseases (UAD): an Interasma (global asthma association – GAA) document

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ABSTRACT

Objective: The large amount of evidence and the renewed interest in upper and lower airways involvement in infectious and inflammatory diseases has led Interasma (Global Asthma Association) to take a position on United Airways Diseases (UAD).

Methods: Starting from an extensive literature review, Interasma executive committee discussed and approved this Manifesto developed by Interasma scientific network (INES) members.

Results: The manifesto describes the evidence gathered to date and defines, states, advocates, and proposes issues on UAD (rhinitis, rhinosinusitis and nasal polyposis), and concomitant/comorbid lower airways disorders (asthma, chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, obstructive sleep apnoea) with the aim of challenging assumptions, fostering commitment, and bringing about change. UAD refers to clinical pictures characterized by the coexistence of upper and lower airways involvement, driven by a common pathophysiological mechanism, leading to a greater burden on patient's health status and requiring an integrated diagnostic and therapeutic plan. The high prevalence of UAD must be taken into account. Upper and lower airways diseases influence disease control and patient's quality of life.

Conclusions: Patients with UAD need to have a timely and adequate diagnosis, treatment, and, when recommended, referral for management in a specialized center. Diagnostic testing including skin prick or serum specific IgE, lung function, fractional exhaled nitric oxide (FeNO), polysomnography, allergen-specific immunotherapies, biological therapies and home based continuous positive airway pressure (CPAP) whenever these are recommended, should be part of the management plan for UAD. Education of medical students, physicians, health professionals, patients and caregivers on the UAD is needed.

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Background

A manifesto, from the Latin "*manifestum*" (meaning clear or evident), is a declaration of the beliefs, opinions, motives, and intentions of the issuer. It is based on published opinion or public consensus and attempts to promote new ideas with prescriptive notions. In the context of health care, a manifesto describes confirmed evidence, actions required, and investigations necessary; it is issued by a group of experts or a scientific organization on a specific topic. By leading people to evaluate the gap between these principles and their current reality, the manifesto challenges assumptions, fosters commitment, and provokes change.

United airway diseases (UAD) is the concept that upper and lower airways form a single organ, with upper and lower airway diseases co-occurring frequently because they reflect different epidemiological, pathophysiological, and clinical manifestations of a single underlying disease process. UAD refers to rhinitis, chronic rhinosinusitis (CSR) and nasal polyposis (NP), and concomitant/comorbid lower airways disorders refers to asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis (CF), obstructive sleep apnea (OSA). The UAD are currently object of research and debate, and the ability to identify, assess, and access the UAD allowed us to take a position on this timely issue in light of available evidence.

Methods

We performed systematic research of the existing literature, focusing on meta-analysis, systematic review, randomized controlled trials, cohort studies, and laboratory studies for mechanisms, molecules and cells involved in the inflammation. We searched using the MeSH terms rhinitis, rhinosinusitis and polyposis each matched with "asthma", "chronic obstructive pulmonary disease", "bronchiectasis", "obstructive sleep apnea", and "cystic fibrosis". Since the term united airways disease is not very suitable for this type of analysis, we included in the general research "Upper and lower airways", for every specific common condition affecting this area. We looked for published papers identified by a computerized literature search of electronic databases including PubMed, ScienceDirect, Scirus, ISI Web of Knowledge, Google Scholar, and Cochrane Central Register of Controlled Trials. The first article with the term "United Airways Disease" was published in 2000.

All selected papers were initially evaluated by a panel of experts in 6 working groups to assess their eligibility in contributing to the statements of the manifesto. The most relevant papers were selected by each group based on their expertise. In October 2020, the draft of the Manifesto was circulated among the Board of Officers of Interasma (Global Asthma Association) who appraised, discussed, modified and approved the final version.

We define

Despite the artificial distinction of the respiratory tract into the upper and lower airways, they are anatomically contiguous and immunologically related.

Several terms, definition and acronyms such as UAD (1–6), unified airways disease (7,8), one airway one disease (9,10), rhino–bronchial syndrome (11), combined airways diseases (12) have been proposed for its identification.

We define UAD as the clinical picture characterized by the coexistence of upper and lower airways involvement, driven or not by a common pathophysiological mechanism, leading to a greater burden on patient's health status and requiring an integrated diagnostic and therapeutic plan.

Rhinitis and lower airway diseases

We know

Allergic rhinitis (AR) and asthma

Epidemiological evidence supports that approximately 80% of asthmatics have rhinitis, and roughly 30% of patients with rhinitis have asthma (13).

AR represents a significant risk factor for asthma (odds ratio, OR 3.5) (13).

The risk of asthma in AR is more evident in European population than in the non-European (OR 4.4 vs. 2.8), and in children than in adults (OR 4.1 vs. 3.4) (14).

AR and asthma are complex multifactorial disorders with both genetic and environmental components determining disease expression (15–23).

The role of inhalant allergens (16–21) in inducing immunopathological features based on allergen-specific T-helper (Th-2) cell response with eosinophils and T-lymphocytes predominant airway inflammation, thickening of the basement membrane and goblet–cell hyperplasia has been established both in asthma and AR (22,24).

Usually, early onset allergic asthma is associated with allergic sensitization and AR (13).

Patients with AR have poorer asthma control, frequent exacerbations and emergency visits, higher healthcare costs and lower Health Related Quality of Life (HRQoL) (25–32).

Perennial AR and its severity were identified as risk factors for uncontrolled asthma among patients with asthma and associated AR (28).

A progression from mild to moderate/severe asthma has been identified in 8% of patients observed for 10 years. While inappropriate use of medication and older age were the most important determinants for progression, AR had not significant effect (33).

The presence of AR is a significant early-life predictor for an accelerated decline in lung function from the first to the sixth decade of life (34).

A relevant proportion of patients with AR without symptoms of asthma had airway hyperresponsiveness (AHR) with a positive histamine challenge or airflow obstruction evident on lung function (35–37). Nonasthmatic patients with AR also showed the presence of lower airway inflammation and some degree of airway remodeling.

Young people with asthma and AR have higher severity in AHR compared to subjects who suffered only asthma or AR (38).

Patients with AR have higher nasal nitric oxide (nNO) levels than healthy volunteers and show a significant decrease upon treatment by nasal corticosteroids (CSs) (39,40).n NO levels are positively correlated with nasal symptoms and with FeNO (fractional exhaled nitric oxide) in patients with AR irrespective of concomitant asthma (41,42).

FeNO is a quantitative, noninvasive and simple method of measuring type 2 airway inflammation. Increased FeNO is associated with a significantly longer AR duration, impaired lung function, more severe symptoms, and more frequent AHR. In addition, more than one quarter of the patients with a FeNO >50 parts per billion (ppb) developed asthma at 2-year follow-up (43).

An electronic nose can discriminate exhaled volatile compounds of patients with asthma from healthy individuals. Electronic nose could be an interesting tool in the future to discriminate subjects with AR from those with AR and asthma (44).

Sensitization to dust mite, pet dander, pollen, fungi and cockroaches has been associated with AR and asthma development or symptoms exacerbation in patients who suffer these conditions. Reduction of allergen exposure decreased symptoms in patients with dust mite driven AR and asthma (45–51). Most of the preventive measures of allergens exposure alone are not effective in obtaining a relevant clinical improvement in asthma and AR (46).

Specific allergen immunotherapy (AIT) has shown to be effective in respiratory allergies and several routes of its administration have been developed (47–50).

Inhaled corticosteroids (ICS) are considered the most effective treatment for AR and asthma (51). They are highly efficient anti-inflammatory therapy for allergy because they interfere with many of the inflammatory pathways involved in the pathogenesis of AR and asthma (52,53).

Antihistamines are the cornerstone of the treatment of AR. The use of the first-generation antihistamines (e.g. brompheniramine, chlorpheniramine, cyproheptadine, diphenhydramine, deschlorpheniramine, doxylamine, hydroxyzine, ketotifen, oxatomide, promethazine, tripelennamine) is considerably limited by side effects (i.e. drowsiness, dry mouth, nose, and throat, headache) (54).

Among the second-generation of antihistamines (e.g. desloratadine, fexofenadine, levocetirizine, bilastine, rupatadine), nonbrain penetrating agents (i.e. bilastine, fexofenadine) have been demonstrated to effectively decrease allergy symptoms without causing nighttime sleep disturbances and related adverse events (54).

Bilastine showed the fastest onset of action (55,56), a good safety and tolerability profile and it especially does not impair performance of tasks requiring attention (57–59).

Local administration of antihistamines has the advantage of avoiding hepatic first-pass metabolism. The direct nasal drug application is able to provide a potent local effect with a fast action onset and minimal systemic side effects (60).

The leukotriene antagonists have been used extensively in the treatment of AR and asthma, but some concern have been raised due to the potential relationship with neuropsychiatric events (anxiety, abnormal behavior, aggression, fear, suicidal ideation) (61,62).

Biological molecules, developed for severe asthma treatment, showed efficacy in improving concomitant rhinitis (63–65).

Digital solution to care and to manage AR and asthma multimorbidity promotes evidence-based information and enables patients to provide their doctors with feedback and data on their health (66–71). There are online virtual community platforms to support people remotely, some new smart inhalers, and mobile healthcare system for asthma (66–71).

Non allergic rhinitis (NAR) and asthma

Epidemiologic data on NAR are scarce and difficult to interpret as a result of the lack of consensus on both definition and diagnostic criteria. However, its prevalence has been estimated between 6.3% and 24.9% within the pediatric population and at 9.6% in a population of subjects of 15 years or older (72). NAR represent a relative risk factor (RR 2.7) for asthma (13).

Occupational rhinitis is 2 to 3 times more frequent than occupational asthma and most of patients with occupational asthma have occupational rhinitis as well (73). This association is more evident for high molecular weight agents (OR 4.79) (74).

Occupational rhinitis often precedes the development of occupational asthma (75) and longitudinal cohort studies identified occupational rhinitis as risk factor for the development of occupational asthma (72,73). Patients with occupational rhinitis and prolonged exposure could progress to asthma (72). The recognition of occupational rhinitis (73) is considered to be crucial in the prevention of occupational asthma (72).

Moderate to severe persistent occupational rhinitis is a predictor for the presence of nocturnal respiratory

symptoms (OR 9.3) and moderate–severe persistent occupational asthma (OR 19.0) (75).

Hormonal changes during puberty, menstrual cycle, pregnancy, menopause, but also in hypothyroidism and acromegaly were identified as possible etiological factors for NAR (72).

NAR in pregnant women with asthma is associated with poorer asthma control, sinonasal and asthma-related QoL, and increased anxiety symptoms, lower lung function and higher FeNO compared to those with NAR alone. More than half of patients had moderate to severe rhinitis, but symptom severity improved significantly during gestation with adequate treatments for asthma/rhinitis and monthly monitoring (76,77).

Rhinitis and COPD

Patients with history of childhood asthma eczema, and AR had an increased risk (34) for chronic airways obstruction.

About 30% of COPD patients suffer from AR whose prevalence is higher in patients with asthma–COPD pattern (78).

COPD has been identified as a risk factor for developing noninfectious rhinitis. An incidence of 10.8% of new-onset noninfectious rhinitis has been reported in a COPD and was higher (12.1%) among subjects aged ≥40 years (79).

Chronic rhinitis is a risk factor for 30-day COPD-related hospital readmission (hazard ratio, HR 2.4 for AR, and 2.6 for NAR compared to patients without rhinitis) (80). In contrast with these results, a smaller Korean study failed to find an association between the presence of AR and the risk of exacerbations in mild-moderate COPD patients (81).

COPD patients with AR have more frequent ICSs prescription in primary care than those without this diagnosis (82).

Intranasal administration of ICS improves nasal symptoms score but also the COPD assessment test score and decreases dyspnea, quantified according to the modified Medical Research Council (mMRC) scale (83).

Rhinitis and bronchiectasis

The prevalence of AR in patients with noncystic fibrosis (non-CF) bronchiectasis was estimated at 31.7% (84).

Patients with non-CF bronchiectasis and AR more frequently have dyspnea, have lower lung function and greater number of emergency department admission in the previous year than those without AR (3.2 vs. 1.9) (84).

Patients with bronchiectasis have higher frequency of sensitization to multiple allergens than patients with AR (57.6% vs. 26.9%) (85).

Sensitization to ≥3 allergens in non-CF bronchiectasis was associated with poor clinical outcomes, including decreased pulmonary function and more severe disease (85).

The sensitization to Aspergillus fumigatus has been identified as risk factor for progression to bronchiectasis in COPD patients (86).

AR has been detected as a risk factor for chronic rhinosinusitis on sinus CT scan in patients with bronchiectasis (87).

Rhinitis and cystic fibrosis (CF)

The prevalence of AR in patients with CF was estimated at 48%, greater than in patients with non-CF bronchiectasis (88).

No significant effects of AR on sinopulmonary exacerbations or respiratory symptoms severity were found in adults with CF despite the worse endoscopic appearance compared to those without this comorbidity (88,89).

The presence of allergy symptoms has a negative impact on the sinus and nasal QoL (quality of life) scores in children with CF >12 years of age (90).

The use of nasal corticosteroids improves nasal endoscopic appearance over time (85), but the benefit from this treatment in individuals with CF and AR remains to be elucidated.

Rhinitis and OSA

OSA and rhinitis often co-exist. AR has been considered a risk factor for OSA. The prevalence of AR in OSA/sleep-related breathing disorder (SBD) is higher and children with SBD suffer from AR more often than non-SBD (91).

AR itself is connected to sleep disturbances. Patients with AR have significantly worse sleep disturbances scores, and prolonged sleep latency than the general population (92).

Adverse effects of CPAP (continuous positive airway pressure) such as rhinitis, dry/congested nose, and mouth/throat dryness are common and could lead to poor adherence to therapy. Heated humidification with CPAP decreases nose/throat discomfort and could be a successful solution to overcome these problems and improve compliance with therapy (93).

CPAP leads to a neutrophil inflammation in both AR and non-AR patients. However, in patients with AR an improvement of nasal symptoms and HRQoL has been demonstrated, whereas in patients with non-AR, a relevant worsening of nasal dryness and mucociliary transport has been observed (94).

Rhinitis and lower airways diseases: the Interasma perspective

We state

Rhinitis is a risk factor for asthma onset.

Symptomatic rhinitis makes the control of concomitant asthma more difficult.

A combined management approach of rhinitis and asthma is always needed.

The management of AR and asthma is based on allergen avoidance and environmental control measures, allergen-specific immunotherapy and, pharmacologic/biological treatments.

Digital solutions to care and to manage rhinitis and asthma are indispensable tools for the management of rhinitis and concomitant asthma.

The prevalence of rhinitis in COPD and bronchiectasis is relevant and a mutual influence is shown.

Rhinitis is a risk factor for chronic rhinosinusitis in patients with bronchiectasis.

The sleep impairment due to rhinitis, OSA and drugs (e.g. 1st generation antihistamine) is relevant.

We advocate

The development of exhaled biomarkers to be able to discriminate each disease - rhinitis or asthma – from the combination of the two diseases, asthma and rhinitis, in a single patient.

Research to assess the influence of rhinitis in the progression of asthma and other lower airways diseases.

Studies aimed to assess the overall efficacy of chemical, biological treatments and nonpharmacological treatments, from the patient point of view, on UAD.

There should be better education of medical students, physicians, health professionals, patients and caregivers on rhinitis and concomitant/comorbid lower airways involvement.

We propose

In each country, health authorities and professional organizations should agree on the development and implementation of evidence-based guidelines and clinical pathways to ensure that all patients with AR and NAR have access to the right diagnosis and care.

Patients who have AR and NAR should be screened for common comorbidities such as asthma, COPD, bronchiectasis, cystic fibrosis or OSA.

Patients with suboptimal disease control despite optimized treatment should be referred to specialized care in a multidisciplinary center.

Chronic rhinosinusitis (CRS) and lower airways diseases

We know

CRS and asthma

CRS is frequently encountered in patients with asthma (92). A bidirectional impact on the occurrence of asthma and CRS has been demonstrated. Patients with asthma have an increased risk for developing CRS (adjusted HR = 1.74) and patients with CRS have an increased risk for developing asthma (HR 1.85) with similar results for those with and without polyps (95).

The presence of CRS adversely affects the course of asthma leading to more severe disease with more frequent and severe exacerbations as well as worse HRQoL and other comorbidities (96–99).

Patients with asthma and CRS have greater airway remodeling (97,98).

The more severe the CRS is in patients with asthma, the greater the risk is for the loss of asthma control as reflected by the greater frequency of emergency department visits (99).

The alteration of the homeostasis in the upper airways is associated with an increased risk of asthma (100,101).

Inflammation in the upper airways of patients with CRS is associated with an impaired function of the lower airways (101). Enhanced nasal production of IL-25 in patients with CRS is associated with and can be considered as a biomarker of airway hyperresponsiveness (101).

Conversely, the presence of asthma adversely affects the course of CRS (102) and is associated with higher frequency of CRS exacerbations (103,104), reduced local response to CSs (105), prolonged systemic therapy (oral corticosteroid or biologics) after surgical treatment of patients with CRS (106), greater chance of recurrence of CRS after surgery (107), and increased risk of perioperative complications (108).

Among patients with CRS the presence of asthma is associated with enhanced inflammation and remodeling in the upper airways (109,110). Similar defects of epithelial tight junctions have been found in patients with asthma as well as CRS (111).

Co-occurrence of bronchial and nasal hyperresponsiveness to aspirin is associated with greater pro-inflammatory cytokine production (112).

Aspirin desensitization in patients with aspirin-exacerbated respiratory disease results in the improvement of both lower and upper respiratory symptoms (113).

A significant relationship between nasal Staphylococcus aureus colonization and asthma has been found in adult patients with asthma, supporting a potential role in the pathogenesis (100). However, also other pathogens and the specific microbiome composition induce pro-inflammatory responses and consequently alters the risk of asthma in patients with CRS, especially in children (114–116).

Aspergillus can cause both allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal rhinosinusitis (AFRS). AFRS is found in 80% of patients with ABPA. Most patients with AFRS + ABPA are sensitized to Aspergillus fumigatus and have more often complicated CRS with nasal polyposis and more severe forms of CRS (117).

Improved techniques (transnasal nebulization, bioabsorbable implants) designed for better corticosteroid delivery to the nasal cavities in patients with asthma and CRS improves both CRS and asthma outcomes (118,119).

Biologics used for asthma therapy, which target Th2 cytokines, such as IL-5 and IL4/IL13, or blocking IgE are also effective in patients with concomitant CRS (64,120–124).

Intranasal corticosteroids are the mainstay of the pharmacological therapy in patients with CRS (125–127). Efficacy of topical corticosteroids after endoscopic surgery has also been documented in patients with CRS (128).

Bioabsorbable steroid-releasing sinus implants that provide sustained release can improve endoscopic outcomes of frontal sinus surgery (129). Appropriate local delivery of CS into the sinonasal cavities is crucial for the beneficial effect (119). The efficacy of individual intranasal CS may differ (130).

In some patients, pharmacological treatment is insufficient and surgical management is necessary (131,132).

Surgically treated patients with CRS do not benefit from montelukast added to topical CSs (128).

Long term, low dose doxycycline in difficult-to-treat CRS results in improvement of clinical outcomes (133,134).

Expert panel recommendations for rhinosinusitis management during pregnancy included continuing nasal CS sprays for CRS maintenance, using pregnancy-safe antibiotics for acute rhinosinusitis and CRS exacerbations, and discontinuing aspirin desensitization for aspirin exacerbated respiratory disease (135).

CRS and COPD

Patients with COPD frequently suffer from CRS. In fact, 2.5–51% of patients with COPD patients have concomitant CRS (136,137) and the majority of them (82%) remain undiagnosed in routine clinical practice (136).

CRS and bronchiectasis

CRS is frequently seen in patients with bronchiectasis (138). Clinical and/or radiological features of CRS were found in 62% of patients with bronchiectasis (138). CRS was associated with a greater degree of bronchiectasis severity, poorer HRQoL, reduction in smell detection, elevated levels of inflammatory markers, and reduced time to first exacerbation (138). However, the association with airway obstruction was inconsistent (138). Surgical treatment of CRS beneficially affects the outcomes of lower airways in patients with concomitant bronchiectasis and CRS (139).

CRS and CF

Among adult patients with CF, 84.6% had abnormal findings on paranasal CT scans (89) Despite high prevalence of abnormal CT findings, patients report mild intensity of sinonasal symptoms (89). The presence of CRS symptoms adversely affects the course of CF (89). Local administration of recombinant human deoxyribonuclease I (dornase alfa) to nasal cavity and paranasal sinuses in patients with CF and CRS results in significant improvement of nasal symptoms and lung function (140,141)

CRS and sleep obstructive-apnea syndrome (OSA)

The presence of CRS significantly affects sleep quality and it is associated with OSA (142). Surgical treatment of CRS leads also to improvement of sleep quality (143,144)

CRS and lower airways diseases: the Interasma perspective

We state

CRS is frequently found in patients with lower airway diseases including asthma, COPD bronchiectasis and CF.

Concomitant occurrence of lower airway diseases is associated with more severe CRS.

Similar pathological processes are found in upper and lower airways of patients with lower respiratory diseases and CRS.

CRS-comorbidity has a great impact on the clinical course of lower airway diseases. Medical and/or surgical treatment of CRS successfully improves lower respiratory disease outcomes.

In many patients with CRS application of topical CSs may lead to unsatisfactory effects due to their poor penetration into the sinonasal cavities.

Therapeutic modalities which improve the course of both CRS and asthma such as aspirin desensitization or biologics including anti-IgE, anti-IL5 or anti-IL-4/IL-13 are available.

We advocate

Patients with diseases affecting lower respiratory tract should be actively evaluated for the presence of CRS and vice versa.

Both medical and surgical approaches to the treatment of patients suffering from CRS is warranted.

We propose

A systematic assessment for lower airways diseases should be realized in practice for all patients with CRS.

Patients with suboptimal disease control despite optimized treatment should be referred to specialized care in a multidisciplinary center.

Strategies to improve the management of CRS should be developed by using a multidisciplinary approach and

taking into account the existence of effective therapies targeting both upper and lower airways diseases.

Nasal polyposis (NP) and lower airways disease

We know

NP and asthma

20–60% of patients with NP have asthma (145).

More than 40% of severe asthma patients suffer from NP (146).

A clinical history of NP usually precedes asthma, and up to 45% of patients with NP will develop adult-onset asthma (13).

NP contributes to disease severity and may lead to exacerbations in asthma (147).

Paranasal computed tomography in severe asthma patients showed that 46.7% presented NP (147).

The presence of NP accounted for a significant higher oral CS use (double days/year on oral CS) compared to severe asthma patients without NP (148).

Several clusters of asthmatics with NP were identified: predominantly atopic patients (with child-onset airway symptoms, intermediate disease duration, history of family asthma, better lung function, and less severe asthma); smokers (with short disease duration, adult-onset airway symptoms, less atopy, nonsteroidal anti-inflammatory drug sensitivity, prior sinus surgery history, eosinophilic airway phenotypes, worse lung function, and severe computed tomography appearance); older patients (with long disease duration, adult-onset airway symptoms, less atopy, more noneosinophilic airway phenotypes, and prior sinus surgery history) (147).

Patients may benefit from early anti-inflammatory treatment for NP (149).

Monoclonal antibodies available for treatment of severe asthma can reduce polyp size, sinus opacification, and severity of symptoms (64,120,121,150–153).

QoL outcomes are significantly improved after endoscopic sinus surgery among patients with NP (154).

NP and COPD

NP affects about 5% of patients with COPD (155) which is not different to the prevalence of NP in the adult population.

NP does not affect the COPD severity (155).

NP and bronchiectasis

The prevalence of NP in bronchiectasis is estimated at 29%. This association is linked to more severe bronchiectasis on imaging, poorer QoL, reduced ability to detect smells and a shorter time for the first exacerbation (138).

Bronchiectasis was identified in 60.4% of severe asthma patients with NP, who were older and had poorer lung function compared to those without bronchiectasis (156).

NP and CF

Around 50% of CF patients experience chronic rhinitis and 28% NP (89).

Despite high prevalence of abnormal tomographic findings, patients reported mild intensity of sinonasal symptoms (89).

NP can affect HRQoL and lead to pulmonary exacerbations, given that the paranasal sinuses can be colonized with pathogenic bacteria, especially *Pseudomonas aeruginosa* (157).

NP and OSA

The prevalence of NP (4%) is not different from the general adult population (158).

Although NP may be the cause and could contribute to symptoms in some patients with OSA, in general it is not associated with increased daytime sleepiness or worse HRQoL (159).

NP and lower airways diseases: the Interasma perspective

We state

NP is frequent in patients with asthma and associated with a more severe disease, high number of exacerbations and increased oral CSs use.

NP has not demonstrated a significant impact on COPD and OSA outcomes.

NP is frequently found in patients with CF and non-CF bronchiectasis and linked to a more severe lower airway disease, poor lung function, high risk for exacerbations and worse HRQoL.

The management of NP could have a positive impact on lower disease outcomes.

Several biologics currently available to treat severe asthma demonstrated benefits on NP.

We advocate

Further studies are warranted to explore the burden and clinical as well as immunological impact of NP in bronchiectasis and COPD.

Future research is needed to compare the effectiveness of various biologic therapies between them and with the surgical treatment in patients with NP and lower airways diseases.

We propose

Nasal examination (e.g. CT imaging, endoscopy) should be systematically performed in patients with lower airways

diseases reporting nasal symptoms to screen for a possible NP.

All patients with NP with respiratory symptoms must be evaluated to detect the presence of a lower airway disease.

The development of multidisciplinary teams including ear, nose and throat specialists and pulmonologists is necessary in order to apply the personalized medicine to patients with NP and lower airways diseases.

Impact of COVID-19 on upper and lower airway diseases

By the tropism of the virus for the angiotensin-converting enzyme 2 (ACE2) receptors highly expressed in upper and lower airway epithelium and the major entrance door to the patient by the nose or nasopharynx, COVID-19 can induce symptoms such as nasal blockage, rhinorrhea, sneezing (common with AR), coughing, and dyspnea (common in asthma, COPD, bronchiectasis exacerbations) (160–162). However, the presence of other symptoms like fever, malaise, myalgia, anosmia (present in up to 60% of the patients), or diarrhea could differentiate COVID-19 from AR (160,161).

Current data suggests that type 2 immune conditions such as AR, CRS with NP, and asthma could have a protective effect against COVID-19 infection and its severity (160,162–166) Airway ACE-2 expression is reduced in patients with allergic asthma or in those treated by ICS, as well in NP versus control tissue (160,162). According to the limited evidence available to date, w, asthma is not associated with an increased risk of hospitalization in patients with COVID-19 (165–167). Patients with COVID-19 infection and asthma have a higher prevalence of comorbidities such as obesity, hypertension, OSA, COPD, coronary artery disease, gastroesophageal reflux disease, AR, NAR, and rhinosinusitis compared to those without asthma (165). The use of ICS as an asthma control treatment is not associated with COVID-19-related hospitalization (165). Some ICS (e.g. ciclesonide, mometasone) could suppress coronavirus replication (168). Biologic therapies targeting type 2 inflammation in severe asthma seem not associated with an increased risk for COVID-19 compared to the general population (168,169) although the upregulation of TMPRSS2 receptor for COVID-19 by type 2 inflammation, through the action of interleukin-13, reveals possible mechanisms influencing SARS-CoV-2 infectivity, COVID-19 clinical outcomes (170) and the opportunity to continue concomitant treatments with biologicals. Stopping biologics, however, may lead to higher risk of asthma exacerbation, often related to viral infections (171), and to increase in sputum production and cough, which could increase rates of transmission (172). Current recommendations are to continue the adapted treatment for chronic rhinitis and asthma by topical CS, biological therapies and AIT during COVID-19 pandemic (161,162,173).

OSA and COPD were identified as independent risk factors for severe COVID-19 and poor outcomes (174–178). The rate of COVID-19 in COPD patients is not different from the general population (176,179) but patients with COPD and COVID-19 infection are more likely to develop severe pneumonia and acute respiratory distress syndrome, bacterial or fungal coinfection and septic shock, have higher risk of healthcare utilization, hospitalization, admission to the intensive care unit, mechanical ventilation or death (175,176,178–182). In contrast with asthmatics, ACE-2 expression in bronchial epithelial cells from COPD patients is increased compared to controls (178).

Although people with CF are considered at high-risk for severe COVID-19 disease, currently the direct impact of pandemic on clinical outcomes in this population seems to be low (183,184). This could be the consequence of a greater respect of hygiene rules of prevention, shielding and lockdown.

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