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Original article

Sinonasal pathology in nonallergic asthma and COPD: 'united airway disease' beyond the scope of allergy

Background: In contrast to the epidemiological and clinical association between allergic rhinitis and asthma, upper airway inflammation is less characterized in patients with nonatopic asthma and virtually unexplored in chronic obstructive pulmonary disease (COPD). Here, sinonasal pathology is studied in patients with allergic asthma, nonallergic asthma and COPD.
Methods: Ninety patients with stable bronchial disease were included in the study, of which 35 were diagnosed with allergic asthma, 24 with nonallergic asthma and 31 with COPD. Concurrently, 61 control subjects without pulmonary disease were included and matched for age and smoking habits respectively with the asthma and the COPD group. Sinonasal symptoms were evaluated on a visual analogue scale and rhinosinusitis-related impairment of quality of life was assessed with the sino-nasal outcome test-22 (SNOT-22) questionnaire. Nasal mucosal abnormalities were quantified with nasal endoscopy and nasal secretions collected for measuring inflammatory mediators.
Results: Allergic asthmatics, nonallergic asthmatics and COPD patients reported more nasal symptoms than their respective control subjects, had a higher SNOT-22 score and presented more mucosal abnormalities in the nose. Nasal secretions of both allergic and nonallergic asthmatics contained higher levels of eotaxin, G-CSF, IFN-γ and MCP-1 than controls. Allergic asthmatics had higher nasal IP-10 levels as well. COPD-patients had higher nasal levels of eotaxin, G-CSF and IFN-γ than controls.
Conclusion: Patients with allergic and nonallergic asthma and COPD show increased nasal symptoms and more nasal inflammation. Hence, our data confirm the 'united airways' concept to be beyond the scope of allergic asthma.

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The relationship between allergic rhinitis and asthma is well studied, and a convincing body of epidemiological and clinical evidence suggests that both entities are manifestations of the same 'global airway disease' (1). It is generally accepted that up to 90% of allergic asthmatics have rhinitis, and one-third of allergic rhinitis patients suffer from asthma (2). Moreover, rhinitis patients have a threefold higher risk to develop asthma later in life (3). While it was first believed that the common atopic background accounts for the increased risk of developing asthma in rhinitis patients, more recent studies demonstrate that rhinitis is also a risk factor for asthma in nonatopic patients (3–5).

Of note, nasal involvement in bronchial disease may not be restricted to asthma alone, as suggested by a limited number of studies that found more sinonasal symptoms in patients with chronic obstructive pulmonary disease (COPD). In a survey performed in a random sample of 8469 adult inhabitants of southern Sweden, 33% of the total population reported nasal symptoms, as compared with 40% of patients with self-reported chronic bronchitis or emphysema and 46% of self-reported asthmatics (6). More recent studies report an even higher prevalence of sinonasal symptoms in COPD, ranging from 75% (7) to 88% (8). However, these results are limited by the uncontrolled design of the studies and the consideration that increasing age is accompanied with more nasal symptoms, mainly rhinorrhea (9).

Few studies have compared the type of sinonasal symptoms and signs in patients with different types of bronchial disease. It is known that nonatopic asthmatics have a higher incidence of nasal polyps (with or without aspirin intolerance) and rhinosinusitis (10, 11), while it seems evident that atopic asthmatics suffer more from allergic rhinitis. However, in the single study that compared nasal symptoms between allergic and nonallergic asthmatics, the prevalence of nasal symptoms was surprisingly similar in allergic and nonallergic asthmatics even for a symptom typically associated with allergy, namely sneezing (10). In COPD patients, the most

reported nasal symptoms are rhinorrhea, nasal obstruction and sneezing (6–8).

The upper airway inflammatory profile is well studied in allergic asthma, where the nasal inflammation resembles lower airway inflammation with an overt Th2 cytokine profile and influx of eosinophils (12, 13). No data on inflammation in the upper airways of nonatopic asthmatics are available at present, whereas upper airway inflammation in COPD is characterized by neutrophil infiltration and increased IL-8 (14, 15), hence resembling lower airway inflammation. Here, we performed a cross-sectional study at the outpatient Pulmonology/Allergology clinic of the University Hospital Leuven to characterize sinonasal pathology in patients with stable allergic asthma, nonallergic asthma and COPD, both at the clinical as well as at the immunopathological level.

Methods

Study subjects

Ninety adult patients (≥18 years) with either asthma or COPD were studied during routine follow-up clinical visits at the outpatient clinic of either the Department of Respiratory Medicine or Allergology of a tertiary referral centre (University Hospital Leuven, Belgium). This study was conducted between March 2006 and January 2007. Thirty-five patients were previously diagnosed with allergic asthma, 24 with nonallergic asthma and 31 with COPD. Asthma diagnosis was made according to American Thoracic Society (ATS) criteria and was based on the presence of typical asthmatic symptoms, with either an improvement of the forced expiratory volume in the first second (FEV_1) with >12% of baseline and 200 ml after inhalation of salbutamol or a positive histamine bronchial provocation test (PC_{20} < 8 mg/dl). Chronic obstructive pulmonary disease diagnosis was made according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and was based on the presence of typical symptoms, a history of cigarette smoke exposure and a FEV_1 < 80% of the predicted value without significant reversibility (<8% improvement of the FEV1 after inhalation of salbutamol). All asthmatic patients had recent records of either skin prick tests or radioallergosorbent test for the most prevalent aero-allergens, and those with a positive test for at least one allergen were classified as being allergic. Patients with significant lower respiratory disease other than COPD or asthma were excluded. Asthmatics with a smoking history of more than 15 packyears were excluded. Patients with a common cold at the time of the study or during the last 2 weeks prior to their visit, were also excluded. Other upper respiratory diseases, and previous or current treatment for rhinosinusitis were not considered an inclusion or exclusion criteria.

Sixty control subjects, without known disease of the lower airways, were recruited among persons who accompanied patients at the outpatient clinic. To prevent any selection bias of control subjects, no exclusion was made on the basis of upper respiratory tract disease or treatment, except for subjects with a current or recent (<2 weeks prior to their visit) common cold. Control subjects were divided into two groups, one for the asthma group (n = 37) and one for the COPD group (n = 23), so that there were no significant differences in age or smoking habits between patient groups and their respective control groups. No matching was performed for gender. This study was approved by the local ethical committee, and all patients and control subjects gave written informed consent.

Nasal symptoms and signs

All patients and control subjects were asked to mark their momentary nasal symptoms on a visual analogue scale (0–10). Five symptoms were assessed: nasal obstruction, nasal discharge, headache, sneezing and itchy nose or eyes. Patients and controls also filled in the sino-nasal outcome test-22 (SNOT-22) questionnaire, a validated disease-specific quality-of-life questionnaire for rhinosinusitis (16), in which patients have to score a total of 22 items on a scale of 0 (no problem) to 5 (problem as severe as can be). The total SNOT-22 score was divided by 22. Nasal endoscopy was performed in all individuals by an otorhinolaryngologist, who was not blinded to the underlying diagnosis. Nasal congestion and the presence of nasal secretions were scored on a scale from 0–3 on both sides (0: none; 1: mild; 2: moderate or 3: severe). Nasal polyps were scored on both sides as follows: 0: none; 1: cobblestone; 2: nasal polyps not reaching below the upper border of the inferior nasal turbinate; 3: nasal polyps reaching below the upper border of the inferior nasal turbinate; 4: nasal polyps reaching below the inferior border of the inferior nasal turbinate; 5: nasal polyps reaching the floor of the nasal cavity. Scores for all signs were added to obtain a global endoscopic score of maximum 22.

Nasal inflammatory mediators

To collect nasal secretions, a nasal tampon was weighed and inserted in the right nostril (Ivalon Surgical products, San Diego, CA, USA: Post-Op Sinus Pack, K9). After 5 min, the tampon was removed and weighed again. Approximately 1.5 ml saline was added, the tampon was squeezed and centrifuged at 1500 ***g*** at 4°C over 5 min. The supernatants was stored at −20°C until analysis.

Concentrations of pro-inflammatory mediators (IFN-γ, TNF, IL-1β, IL-8, IL-5, eotaxin, MIG, IP-10, MCP-1, VEGF and G-CSF) were measured in 50 μl of the supernatants of nasal secretions by means of cytometric bead array Flex (BD Biosciences, Erembodegem, Belgium) according to the manufacturers' instructions. Samples were acquired with the FACSArray (BD Biosciences) and acquisition software capable of saving data in a Flow Cytometry Standard (FCS) 2.0 file format. FCAP ARRAY software analyses the FCS2.0 files.

As the volume of collected secretions differed between subjects, a correction for dilution differences was made by dividing the concentration of each mediator through the total protein concentration of the sample, as measured with the BCA Protein Assay Kit (Pierce, Rockford, IL, USA).

Data analyses

Comparisons between the patient groups and their respective control group were made using a Mann–Whitney U-test. A difference was considered to be significant when $P < 0.05$ (one-tailed P-values). Data are represented as mean ± SEM.

Results

Patient characteristics

Patient characteristics are described in Table 1. Most allergic asthmatics were polysensitized and sensitization

Table 1. Patient characteristics

	Asthma			COPD	
	Allergic patients	Nonallergic patients	Controls	Patients	Controls
Number	34	25	37	31	24
Age*	42.7 ± 3.0	54.2 ± 3.0	47.5 ± 2.5	65.7 ± 1.7	61.3 ± 2.3
Gender					
Male (%)	14 (41)	14 (56)	15 (41)	27 (87)	10 (42)
Female (%)	20 (59)	11 (44)	22 (59)	4 (13)	14 (58)
Current smokers (%)	2 (6)	2 (8)	4 (11)	9 (29)	7 (29)
No. patients treated with inhaled corticosteroids/long acting β-agonists/anticholinergica (%)	31 (91)/9 (26)/7 (21)	24 (96)/3 (12)/8 (32)	NA	23 (74)/5 (16)/23 (74)	NA
FEV_1 (% predicted)*	88.2 ± 4.1	84.8 ± 3.4	NA	59.1 ± 4.6	NA
FEV_1/FVC*	74.1 ± 2.6	68.0 ± 2.1	NA	50.5 ± 2.5	NA

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FVC, force vital capacity; NA, not applicable.
*Mean ± SEM.

Table 2. History of nasal disease

	Asthma			COPD	
	Allergic patients (%)	Nonallergic patients (%)	Controls (%)	Patients (%)	Controls (%)
History of ENT consultation for sinonasal complaints	12 (35)	12 (48)	0 (0)	6 (19)	5 (20)
History of sinus surgery	5 (14)	2 (8)	0 (0)	1 (3)	0 (0)
History of nasal septum surgery	3 (8)	1 (4)	0 (0)	1 (3)	0 (0)
Current nasal treatment					
Nasal corticosteroids	10 (29)	11 (44)	1 (2)	5 (16)	0 (0)
Antihistamines	17 (50)	3 (12)	1 (2)	0 (0)	0 (0)
Decongestants	5 (14)	2 (8)	1 (2)	2 (6)	1 (4)

COPD, chronic obstructive pulmonary disease.

for house dust mite was present in 32/35 patients. All patients received inhaled therapy for their asthma or COPD, as listed in Table 1. The relevant medical rhinologic history of patients and control subjects is depicted in Table 2.

Sinonasal symptoms, signs and rhinosinusitis-related quality of life

Both allergic and nonallergic asthmatic patients reported significantly more nasal obstruction, nasal discharge, headache, sneezing and itchy nose or eyes than the control subjects (Table 3). Strikingly, the mean severity reported for each nasal symptom was comparable with the allergic and nonallergic patients, even for symptoms typically associated with allergy like sneezing and itching. Nasal obstruction and itching were considered most bothersome in both patient groups. Chronic obstructive pulmonary disease patients (Table 3) also reported significantly more nasal symptoms than their control group, in particular nasal obstruction, nasal discharge and headache. In COPD patients, nasal discharge was considered most bothersome.

Allergic asthmatics, nonallergic asthmatics and COPD patients all had significant impairment of their quality of

Table 3. Visual analogue scale scores

	Asthma			COPD	
	Allergic patients	Nonallergic patients	Controls	Patients	Controls
Nasal obstruction	3.77 ± 0.56***	3.47 ± 0.56***	0.52 ± 0.25	1.65 ± 0.47**	0.84 ± 0.43
Nasal discharge	2.23 ± 0.36***	2.54 ± 0.60**	0.60 ± 0.18	2.09 ± 0.49*	1.19 ± 0.47
Headache	2.32 ± 0.46***	2.35 ± 0.66**	0.97 ± 0.46	2.00 ± 0.52*	0.93 ± 0.38
Sneezing	2.83 ± 0.43***	3.26 ± 0.54***	0.87 ± 0.21	1.89 ± 0.43	1.23 ± 0.42
Itchy nose or eyes	3.65 ± 0.58***	3.68 ± 0.66***	0.74 ± 0.29	1.78 ± 0.45	1.16 ± 0.46

COPD, chronic obstructive pulmonary disease.
Mean visual analogue scale scores for the five investigated nasal symptoms. Data are expressed as mean ± SEM.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

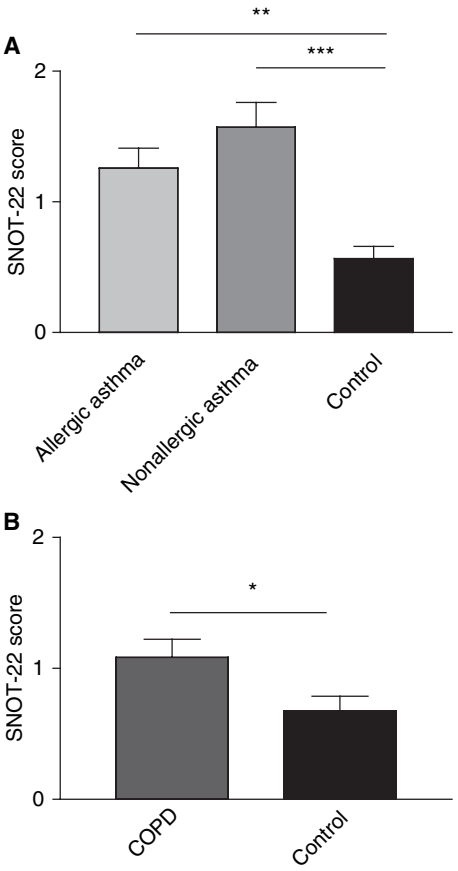

Figure 1. SNOT-22 score, mean scores on the SNOT-22 questionnaire. Data are presented as mean + SEM. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

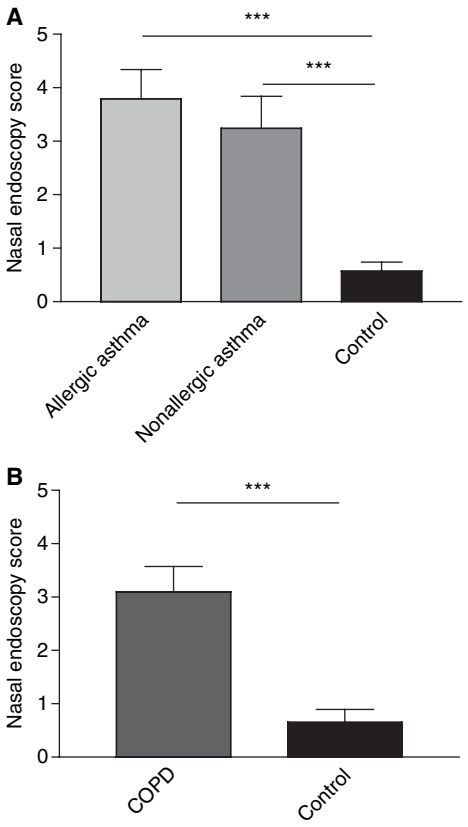

Figure 2. Nasal endoscopy score, mean nasal endoscopy score. Nasal congestion and the presence of nasal secretions were scored on a scale of 0–3 on both sides, nasal polyps were scored on a scale of 0–5. Data are presented as mean + SEM. $***P < 0.001$.

life related to rhinosinusitis (Fig. 1). The mean SNOT-22 score of allergic asthmatics was 1.26 ± 0.15, of nonallergic asthmatics 1.57 ± 0.19. The corresponding control group had a significantly lower score (0.57 ± 0.09). Chronic obstructive pulmonary disease patients had a mean SNOT-22 score of 1.08 ± 0.14, whereas the corresponding control subjects had a lower score (0.68 ± 0.11).

Significantly, more nasal endoscopic signs of inflammation (congestion, secretions and polyps) were found in allergic asthmatics, nonallergic asthmatics and COPD patients as compared with their respective control groups (Fig. 2). Allergic asthmatics had an endoscopy score of 3.79 ± 0.55, nonallergic asthmatics of 3.24 ± 0.60 and the corresponding control group of 0.57 ± 0.17. Chronic obstructive pulmonary disease patients had a score of 3.10 ± 0.47 and their control group of 0.65 ± 0.24. Nasal polyps were found in five patients, with four out of five being nonallergic asthmatic patients.

Nasal inflammatory mediators

Nasal secretions of both allergic and nonallergic asthmatics contained higher levels of eotaxin ($P = 0.005$ and $P = 0.005$), IFN-γ ($P = 0.012$ and $P = 0.031$), MCP-1 ($P = 0.047$ and $P = 0.008$) and G-CSF ($P = 0.001$ and $P = 0.095$, trend) than controls, whereas only allergic asthmatics had higher nasal IP-10 and G-CSF levels. Chronic obstructive pulmonary disease patients had elevated nasal levels of eotaxin ($P = 0.036$), G-CSF ($P = 0.005$) and IFN-γ ($P = 0.078$, trend) compared with the controls (Table 4).

Discussion

This is the first comparative study on nasal symptoms and clinical signs as well as nasal inflammatory mediators between patients with allergic asthma, nonallergic asthma and COPD. We have shown that both allergic and nonallergic asthmatic patients had more nasal symptoms, more nasal endoscopic signs of inflammation and elevated levels of inflammatory markers in nasal secretions, associated with a significant impairment of their quality of life. The similarity of nasal pathology in allergic *vs* nonallergic asthmatics was striking, with a similar symptom pattern, even for sneezing and itchy nose

Table 4. Inflammatory mediators in nasal secretions

	Asthma			COPD	
	Allergic patients	Nonallergic patients	Controls	Patients	Controls
Chemokines					
IL-8	70.58 ± 12.70	83.35 ± 20.78	61.72 ± 9.08	103.0 ± 24.83	79.94 ± 23.92
Eotaxin	2.09 ± 0.27**	2.33 ± 0.37**	1.11 ± 0.25	2.85 ± 0.48*	1.56 ± 0.37
IP10	57.33 ± 13.78*	60.73 ± 32.95	27.37 ± 5.70	40.85 ± 11.90	42.55 ± 17.19
MIG	71.93 ± 33.24	99.14 ± 69.44	10.91 ± 2.13	55.13 ± 24.73	39.59 ± 24.71
MCP-1	4.37 ± 0.78*	4.99 ± 0.86**	2.88 ± 0.59	5.34 ± 0.94	3.55 ± 0.85
Growth factors					
G-CSF	12.97 ± 3.90**	12.29 ± 6.72	3.56 ± 0.65	11.91 ± 4.98**	2.75 ± 0.40
VEGF	12.40 ± 0.82	15.36 ± 1.77	13.05 ± 1.45	15.58 ± 1.60	13.08 ± 1.19
Th2					
IL-5	Below detection limit in nearly all samples				
Th1					
IFN-γ	0.25 ± 0.05*	0.21 ± 0.05*	0.10 ± 0.03	0.38 ± 0.08	0.17 ± 0.04
Pro-inflammatory cytokines					
IL-1β	1.23 ± 0.34	3.27 ± 2.46	0.59 ± 0.08	1.74 ± 0.76	1.04 ± 0.40
TNF-α	Below detection limit in nearly all samples				

Inflammatory mediators in nasal secretions of patients with allergic asthma, nonallergic asthma and chronic obstructive pulmonary disease (COPD) and the respective control groups. Results are expressed as ratio of the measured concentrations over the total protein concentration of the sample. Data are expressed as mean ± SEM.
*$P < 0.05$; **$P < 0.01$.

or eyes. Moreover, the nasal inflammatory profile was similar in nonallergic and allergic asthmatics. Whether bronchial inflammation in nonatopic asthmatics differs from the inflammation in atopic asthmatics remains unclear. Some authors have found differences in inflammatory profile, with the nonatopic asthma patients having more neutrophils, IL-8 and IFN-γ, and the atopic asthmatics having more eosinophils and Th2 cytokines and a better response to corticosteroid treatment. However, these differences seem quantitative rather than qualitative as both groups showed an increase of all markers of inflammation as compared with healthy controls (17–19). Other authors failed to demonstrate similar differences in inflammatory profile and showed an upregulation of Th2 cytokines and eosinophils in atopic as well as in nonatopic asthma, suggesting that both clinical entities share to a certain extent a similar immunopathology (20, 21). Indeed, IgE has recently been suggested to play a role not only in allergic but also in nonallergic asthma. As opposed to an increased systemic IgE production in atopy, there may be a local mucosal production of IgE in the airways of nonatopic asthmatics (22). Our data on nasal inflammation in atopic *vs* nonatopic asthmatics seem to support the hypothesis that both groups share the same immunopathology, with elevated nasal levels of eotaxin, MCP-1, IFN-γ and G-CSF in both patient groups. IP-10 was only significantly increased in atopic asthmatics, though this may be primarily because of the lower number of patients in the nonatopic patient group.

The present study also shows that COPD patients, although to a lesser extent than the asthmatic patients, had significantly more nasal symptoms, especially nasal discharge, nasal obstruction and headache, than the control group. An age-matched control group was used in this study, ruling out that the demonstrated differences were caused by age-related nasal symptoms in the elder patient group. Chronic obstructive pulmonary disease patients also showed an increased nasal inflammation, with elevated levels of eotaxin, G-CSF and a trend towards elevated levels of IFN-γ. Unlike previous studies (14, 15), we did not find significantly higher IL-8 levels in nasal secretions of COPD patients. Differences in the sampled COPD patients may account for the observed discrepancy: Vachier et al. (15) only included current smokers with COPD, while the COPD patients recruited by Hurst et al. (14) had a lower FEV_1 than the patients in our study. Moreover, some of the patients in the study by Hurst et al. (14) had nasal colonization with bacteria. In contrast, we did find significantly higher concentrations of the eosinophil chemokine eotaxin in the nasal secretions of COPD patients, confirming previous observations of bronchial eosinophilic influx and elevated eotaxin levels in the lower airways of patients with COPD (23). Barnes (24) reported that the levels of eosinophil basic proteins in induced sputum of COPD patients are comparable with those of asthmatics even in the absence of eosinophils, suggesting that eosinophils are degranulated in COPD.

In the present study, G-CSF was also significantly increased in nasal secretions of COPD. G-CSF is classically known as a growth factor promoting granulocyte production, maturation and activation (25) and this can be produced by airway epithelial cells and is associated with neutrophilic airway inflammation (26). Recently, a role in adaptive immune regulation has also been

attributed to G-CSF (25). We were unable to find any significant correlations between nasal symptom scores or specific nasal inflammatory mediators with lung function parameters in the three patient groups. To further explore the relevance of nasal inflammation in bronchial disease, a large-scale study systematically screening nasal inflammation in all patients presenting with bronchial disease is warranted.

The lack of stringent selection criteria for inclusion may be considered a limitation of this present study. Indeed, a heterogeneous patient population was recruited, containing patients with a variety of pulmonary disease severity, smoking status and different treatment modalities of both upper and lower airways. However, the heterogeneity of the patient population studied represents the everyday clinical practice at the outpatient clinic. Indeed, in a random patient population, sinonasal symptoms are present with impairment of quality of life, not only in asthmatics, but also in COPD patients. While the importance of treating the nose in asthmatics is generally accepted, COPD patients are likely to be undertreated for nasal pathology because of unawareness of upper airway inflammation and symptoms both by the patients as well as by the treating physician. Further research on nasal pathology in large groups of COPD patients is mandatory, as implicated by the findings in our study.

In conclusion, we have shown that both allergic and nonallergic asthma as well as COPD were associated with significant sinonasal inflammation and symptoms hampering the quality of life of these patients. This raises the important issue of taking into account nasal inflammation in the diagnostic and therapeutic approach of pneumological patients beyond the scope of allergic inflammation.

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