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Causes of Chronic Cough in Non-smoking Patients

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Abstract

Chronic cough is a common medical problem. The aim of the study was to analyze chronic cough causes in non-smoking patients and to search for demographic factors associated with different cough reasons. The etiology of cough was determined by medical history, diagnostic tests and response to specific treatment. Patients with significant abnormalities in the chest radiograph or spirometry were not included. The study included 131 non-smoking patients; median age 54 years, 77 % female. The most frequent causes of cough were gastroesophageal reflux disease (GERD) (62 %) and upper airway cough syndrome (UACS) (46 %). Cough variant asthma and non-asthmatic eosinophilic bronchitis (NAEB) were diagnosed in 32 (25 %) and 19 (15 %) patients, respectively. Other cough causes were found in 27 patients (21 %). Asthma was a significantly more common cause of chronic cough in women than in men (31 % *vs.* 3 %, $p = 0.005$). A reverse relationship was demonstrated for UACS (39 % *vs.* 67 %, $p = 0.01$). Patients with chronic cough aged >50 yrs were more likely to be diagnosed with less common cough causes. In conclusion, the most common chronic cough reasons are GERD and UACS. Asthma-related cough is diagnosed more frequently in females, while UACS-related cough is more frequent in males.

Keywords

Asthma • Chronic cough • Gastroesophageal reflux disease • Non-asthmatic eosinophilic bronchitis • Upper airway cough syndrome

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1 Introduction

Chronic cough (lasting over 8 weeks) is a common medical problem with a prevalence ranging from 10 to 20 % in the adult population (Morice et al. 2006). There is a wide variety of chronic cough causes including different pulmonary and extrapulmonary disorders. Some of these entities are relatively easy to diagnose while the others might be a considerable diagnostic challenge. The first include smoking associated chronic bronchitis, which is the most common cause of chronic cough, and some other conditions that can be easily diagnosed by a plain chest radiograph, e.g., lung tumors, tuberculosis, or interstitial lung diseases. Therefore, the chest radiograph plays a pivotal role in the diagnosis of chronic cough. On the other hand, a significant proportion of patients with chronic cough do not have any abnormality in the chest X-ray. In these patients additional diagnostic procedures are usually necessary to identify the underlying cause of cough. The most common causes of chronic cough in adult non-smokers with a normal chest radiograph are: upper airway cough syndrome (UACS), i.e., chronic rhinitis, rhinosinusitis, gastroesophageal reflux disease (GERD), asthma and non-asthmatic eosinophilic bronchitis (NAEB). The prevalence of these conditions shows slight differences related to specific features of the studied population, spectrum of the available diagnostic methods, and interpretation of the diagnostic test results (Levine 2008; Morice et al. 2004, 2006; Irwin et al. 2006; Palombini et al. 1999).

Since there are very few reports concerning the etiology of chronic cough in Polish patients, we undertook a study aimed to define the prevalence of chronic cough causes in a population of adult non-smokers with a normal chest radiograph. The second goal of the study was to search for any demographic factors associated with different cough causes.

2 Methods

2.1 Material

The protocol of the study was approved by the Institutional Review Board of the Medical University of Warsaw, Poland (KB/101/2009). The study was performed in patients with chronic cough, who were referred to the out-patient clinic in the Department of Internal Medicine, Pneumonology and Allergology, Medical University of Warsaw, Poland between 2009 and 2011. Non-smoking (at least for 1 year, with smoking history less than 10 pack-years) adult patients with cough lasting more than 8 weeks were regarded as potential candidates for the study. One hundred forty patients were included in the study. Nine patients had not completed the pre-planned diagnostic procedures and the cause of cough could not be determined. Those patients were excluded from analysis. Finally, the study included 131 non-smoking patients; median age 54 years, range 18–81 years, F/M – 101/30. All patients signed an informed consent.

2.2 Study Design

Pre-enrollment assessment included: chest radiograph (postero-anterior view) and spirometry with reversibility testing when applicable. Patients who were active smokers, patients with significant abnormalities in the chest radiograph (e.g., lung tumor or masses, lung opacities, interstitial changes, or heart failure), and patients with an abnormal ventilatory pattern were excluded from further analysis. The patients with chronic cough who had been previously unsuccessfully treated were included.

Cough etiology was diagnosed based on the detailed medical history, physical examination, and additional investigations. The algorithm of the applied diagnostic work-up (Fig. 1) was based

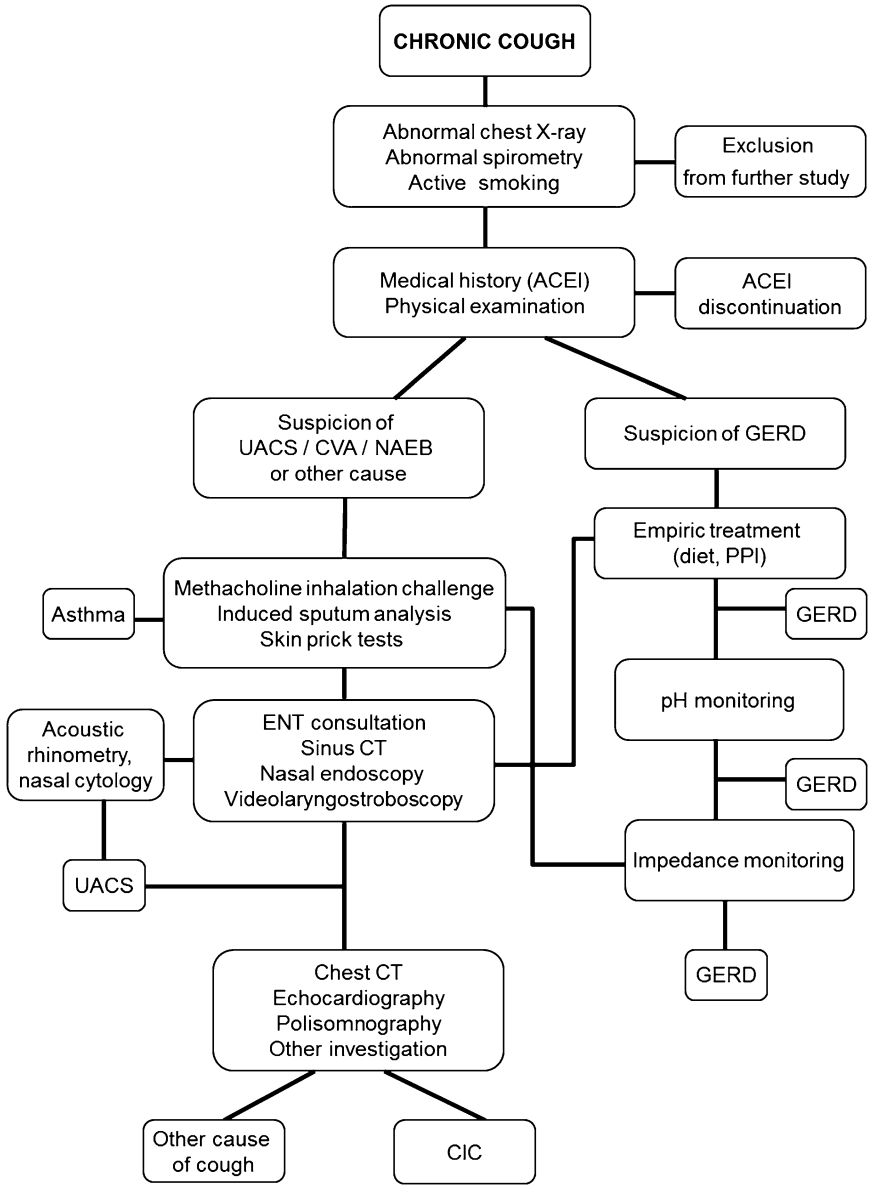

Fig. 1 Flow chart presenting the diagnostic workup designed to diagnose the cause of chronic cough. *ACEI* angiotensin-converting-enzyme inhibitor, *CIC* chronic idiopathic cough, *CVA* cough variant asthma, *GERD* gastroesophageal reflux disease, *PPI* proton pump inhibitor, *NAEB* non-asthmatic eosinophilic bronchitis, *UACS* upper airway cough syndrome

on the international guidelines (Morice et al. 2006; Irwin et al. 2006). Cough etiology was considered as proved when medical history, physical examination, or results of additional tests suggested a specific etiology, and a partial or complete response to specific treatment was confirmed by the patient him- or herself. If specific treatment was unsuccessful, further diagnostic tests were recommended.

2.3 Definitions of the Main Cough Etiologies

The diagnosis of asthma was based on the GINA guidelines (GINA 2014). Cough variant asthma was presumed if spirometry was normal and bronchial hyperresponsiveness was documented in a methacholine inhalation challenge with a provocative concentration of methacholine causing a 20 % drop in FEV_1 (PC_{20}) of less than 4 mg/ml (Lougheed et al. 2012). In case of the negative methacholine challenge, induced sputum eosinophil count was evaluated in order to confirm or exclude NAEB. NAEB was diagnosed when sputum eosinophilia exceeded 3 % of nonsquamous cells (Brightling 2006).

UACS includes chronic rhinitis and rhinosinusitis. The diagnosis of chronic rhinosinusitis required the presence of clinical symptoms defined in the EPOS document and changes in computer tomography sinus scan evaluated according to the Lund and Mackay score (Fokkens et al. 2012). Chronic rhinitis and its etiology were diagnosed on the basis of clinical signs and symptoms and, if suspected by an ear-nose-throat specialist, based on additional examination including nasal endoscopy, acoustic rhinometry or nasal cytology (Pratter 2006).

GERD was diagnosed when improvement after anti-reflux treatment (diet and proton pump inhibitors for 10 weeks) was observed or by results of 24-h esophageal pH or multichannel intraluminal impedance monitoring. The measurements of esophageal pH were performed using two-antimony-pH-electrodes esophageal catheter connected with Digitrapper pH 400 recorder (Synectics Medical; Enfield, UK). A rapid drop of pH below the value of 4 for at least 12 s was necessary to diagnose an acid reflux episode. The diagnosis of GERD-associated cough was made if cough, registered by the patient on the recorder, appeared within 2 min after the reflux episode (Tutuian 2008). Combined multichannel intraluminal impedance–pH monitoring (MII/pH) was performed in patients suspected of weakly acidic or non-acidic reflux. Pathological weakly acidic or non-acidic reflux was diagnosed based on bolus exposure, total reflux percentage time, or median bolus clearance time (Tutuian 2008).

In several patients, other than the above mentioned cough reasons were found. Finally, if none of the known causes of chronic cough could have been diagnosed and no improvement was noted after empiric treatment, chronic idiopathic cough (CIC) was recognized.

2.4 Data Presentation and Statistical Analysis

Data on patient characteristics are shown as median and ranges. Relative contribution of different cough causes was presented in two different ways: as percentage of patients with a particular cough cause and as percentage of all diagnosed causes of cough. The Chi-squared test was used to compare the proportions of patients with various cough etiologies in different groups. A p-value lower than 0.05 was regarded significant.

3 Results

Of the 131 patients, the cause of cough was established in 127 cases (97 %). In four patients the cause of chronic cough was not identified, despite completion of the full diagnostic pathway. Most of the patients (76/131, 58 %) had been unsuccessfully diagnosed or treated because of cough previously.

The median duration of cough was 24 (2.5–360) months. Ninety two patients (70 %) were never smokers, the remaining were ex-smokers (less than 10 pack-years). The median body mass index (BMI) of the whole group was 27.6 kg/m^2. A single cough cause was found in 54 patients (54/127, 42.5 %), two and three coexisting cough causes were diagnosed in 57 (57/127, 45 %) and 16 (16/127, 12.5 %) patients, respectively.

Data on the distribution of specific cough etiologies are presented in Table 1. GERD was

Table 1 Etiology of chronic cough

	Total number (%) of patients with cough etiology	Percentage of all (216) diagnosed causes of cough
GERD	79/127 (62 %)	79/216 (37 %)
UACS	59/127 (46 %)	59/216 (27 %)
Asthma	32/127 (25 %)	32/216 (15 %)
NAEB	19/127 (15 %)	19/216 (9 %)
CIC	4/131 (3 %)	4/216 (2 %)
Other	27/127 (21 %)	27/216 (13 %)

GERD gastroesophageal reflux disease, *UACS* upper airway cough syndrome, *NAEB* non-asthmatic eosinophilic bronchitis, *CIC* chronic idiopathic cough

the most common cough reason and was diagnosed in 79 patients (79/127, 62 % of patients and 37 % of all cough causes). GERD was diagnosed most frequently by cough amelioration after empiric treatment (45 patients). In 28 patients, the diagnosis of GERD was based on the result of pH monitoring and in 6 patients on MII monitoring.

The diagnosis of UACS was established in 59 patients (59/127, 46 %). In this group, rhinosinusitis was found in 9 subjects (9/127, 7 %) while chronic rhinitis in 50 (50/127, 39 %). The most common etiology of UACS was persistent allergic rhinitis (30/127, 24 %). The subgroup of patients with persistent allergic rhinitis included 19 patients allergic to house dust mites, 7 to mold, and 4 to animal dander. In 20 patients non-allergic rhinitis was diagnosed.

Asthma and NAEB were diagnosed in 32 (25 %) and 19 (15 %) patients, respectively. Other cough reasons were found in 27 patients (27/127, 21 %), with the most common being an angiotensin converting enzyme inhibitor (ACEI) treatment (14/127, 11 %). Cough due to bronchiectases was diagnosed in 3 patients, prolonged post-infectious cough in 1 female, airway colonization with *Mycobacterium xenopi* (without radiological signs of pulmonary involvement) in 2 patients, heart failure in 2 patients, mitral valve stenosis in 1, obstructive sleep apnea (OSA) in 3 patients, and pulmonary embolism in 1 patient. Chronic idiopathic cough was diagnosed in 4 (3 %) patients, all of them being never smoking women.

Table 2 Differences in cough etiology in relation to gender

	Female	Male
	n = 101	n = 30
Age (median, range) (years)	59 (18–81)	51 (24–73)
GERD	59 (58 %)	20 (67 %)
UACS	39 (39 %)*	20 (67 %) *
Asthma	31 (31 %)*	1 (3 %) *
NAEB	16 (16 %)	3 (10 %)
CIC	4 (4 %)	0
Other	19 (19 %)	8 (27 %)
Single cough etiology	36 (36 %)	14 (47 %)
Multiple cough etiology	61 (60 %)	16 (53 %)

GERD gastroesophageal reflux disease, *UACS* upper airway cough syndrome, *NAEB* non-asthmatic eosinophilic bronchitis, *CIC* chronic idiopathic cough
*$p < 0.05$

Table 3 Cough etiology in relation to smoking history

	Never smokers	Ex-smokers
	n = 92	n = 39
Age (median, range) (years)	57 (18–81)	53 (19–77)
Female/Male	76/16	25/14
GERD	54 (59 %)	25 (64 %)
UACS	39 (42 %)	20 (51 %)
Asthma	21 (23 %)	11 (28 %)
NAEB	15 (16 %)	4 (10 %)
CIC	4 (4 %)	0
Other	16 (17 %)	11 (28 %)
Single cough etiology	41 (45 %)	13 (33 %)
Multiple cough etiology	47 (51 %)	26 (67 %)

GERD gastroesophageal reflux disease, *UACS* upper airway cough syndrome, *NAEB* non-asthmatic eosinophilic bronchitis, *CIC* chronic idiopathic cough

Asthma was a significantly more common cause of chronic cough in women than in men (31 % *vs*. 3 %, $p = 0.005$). A reverse relationship was demonstrated for UACS (39 % *vs*. 67 %, $p = 0.01$) (Table 2). There were no differences in the proportion of patients with GERD and NAEB-related cough in men and women. Similar results were found for never smokers *vs*. ex-smokers and for patients younger than 50 *vs*. older than 50 years (Tables 3 and 4). The patients with chronic cough aged over 50 were more likely to be diagnosed with less common cough

Table 4 Cough etiology in patients younger and older than 50 years of age

	Age ≤50 years n = 52	Age >50 years n = 79
Age (median, range) (years)	32 (18–50)	63 (51–81)
Female/Male	38/14	63/16
GERD	30 (58 %)	52 (66 %)
UACS	28 (54 %)	32 (40 %)
Asthma	16 (31 %)	19 (24 %)
NAEB	7 (13 %)	12 (15 %)
CIC	1 (2 %)	3 (4 %)
Other	2 (4 %)*	24 (30 %)*
Single cough etiology	24 (46 %)	30 (38 %)
Multiple cough etiology	27 (52 %)	46 (58 %)

GERD gastroesophageal reflux disease, *UACS* upper airway cough syndrome, *NAEB* non-asthmatic eosinophilic bronchitis, *CIC* chronic idiopathic cough
*$p < 0.05$

causes (other than GERD, UACS, asthma, and NEAB, $p = 0.005$) (Table 4).

4 Discussion

The cause of chronic cough depends mainly on the characteristics of studied population and methods used to diagnose different underlying conditions. The majority of authors apply different modifications of the anatomical diagnostic protocol proposed by Irwin (2006), which is based on limited diagnostic tests and empiric trails of treatment. The American College of Chest Physicians (ACCP) and the British Thoracic Society (BTS) recommend a similar diagnostic approach (Morice et al. 2006; Irwin et al. 2006). The value of such protocols is their simplicity and efficacy. The protocols allow recognizing and treating of the most important single cough reason. However, their application relatively often leads to the diagnosis of chronic idiopathic cough. On the other hand, protocols based on numerous diagnostic tests enable to recognize several coexisting cough causes and reduce the number of patients with idiopathic cough (Grabczak et al. 2008; Palombini et al. 1999). The present results are in concordance with those observations (Grabczak et al. 2008; Palombini et al. 1999) as the majority of our patients (57 %) had two or more cough reasons, while the percentage of patients with chronic idiopathic cough was relatively low (3 %).

The most frequent cough reason in the present study was GERD, but the proportion of patients with cough due to GERD in this study was higher than that in other studies; 62 % *vs*. 35–41 % reported by others (Kastelik et al. 2005; Palombini et al. 1999). This may have resulted from using several different diagnostic methods: empiric anti-reflux treatment, 24-h esophageal pH monitoring, and multichannel intraluminal impedance monitoring. Both 24-h esophageal pH and multichannel impedance monitoring are valuable methods in the diagnosis of GERD-related cough, although the interpretation of results is difficult and may vary depending on parameters applied (Kastelik et al. 2005). The sensitivity of pH monitoring in GERD diagnosis is estimated to reach 90 % (Irwin and Madison 2000). As multichannel intraluminal impedance combined with pH monitoring enables to diagnose all types of GERD (acid, weakly acid, and non-acid), it is a notably sensitive method for diagnosing GERD-related cough (Ang et al. 2011; Tutuian 2008).

The upper airway cough syndrome was the second most common cause of chronic cough in the present study (46 % of patients). This is consistent with the results of other authors (Palombini et al. 1999; McGarvey et al. 1998). In our group, chronic rhinitis was a more frequent cause of cough than rhinosinusitis. Persistent allergic rhinitis due to dust mite allergy was the most frequent, followed by allergy to animal coat and mold. It is noteworthy that a thorough ear-nose-throat examination and additional tests resulted in a relatively high recognition of non-allergic chronic rhinitis. Conditions leading to non-allergic rhinitis included structural rhinopathy due to deviation of the nasal septum or conchae hypertrophy. In six patients with chronic non-allergic rhinitis, we observed neutrophilia in nasal cytology (>10 %), despite no evident infection or structural abnormalities.

The significance of this observation is unclear. Rhinosinusitis was relatively rare in patients with upper airway cough syndrome, similarly to the observation of Watalet et al. (2010). Interestingly, in the present study cough related to this syndrome was significantly more common in men than in women. To our knowledge, such observation has not previously been reported. There have been reports that the frequency of allergic rhinitis is comparable in males and females, while chronic rhinosinusitis is slightly more frequent in females (Hastan et al. 2011; Bousquet et al. 2008).

Asthma is estimated to be the cause of chronic cough in 24–29 % of adult non-smokers (Dicpinigaitis 2006). The results of the present study correspond with these reports, as we recognized asthma in 25 % of the patients. Due to the inclusion criteria applied, only cough variant asthma was diagnosed in patients participating in this study. We might speculate, that had we not applied clinical and spirometric criteria excluding the majority of patients with asthma, the proportion of asthmatics in our study group would have been even higher. Cough variant asthma was diagnosed more often in females, what corresponds to a higher prevalence of asthma in adult women (GINA 2014).

According to the literature, NAEB is diagnosed in 10–30 % of patients with chronic cough (Brightling 2006). In the present study, NAEB was diagnosed in 15 % of patients. NAEB is an entity described quite recently, with an unclear prognosis. Most authors agree that NAEB responds well to treatment with inhaled steroids (Brightling 2006). However, there are studies suggesting that NAEB may lead to COPD or asthma. In an observational study by Berry et al. (2005) induced sputum eosinophilia and cough persisted in some patients with NAEB despite treatment with inhaled corticosteroids. Moreover, 25 % of these patients eventually developed airway obstruction (COPD in 16 % and asthma in 9 %).

In the present study, the cause of cough other than GERD, UACS, asthma, or NAEB was diagnosed relatively often. Despite the fact that 60 % of our patients had already been diagnosed or treated because of chronic cough previously, in as many as 14 patients (11 %) cough due to ACEI was diagnosed. That indicates that physicians should verify the patients' medication not only at the beginning, but also in the course of the diagnostic work-up. It also is worth noting that in another five patients we found cardiovascular diseases such as heart failure, mitral stenosis, and pulmonary embolism responsible for chronic cough. Those findings may have resulted from including patients up to the age of 80 years (median age was 54 years), which would be consistent with the observation that cough causes other than the four main entities discussed above are found more often in older patients. Among other cough reasons, we found OSA as one of comorbidities inducing cough in three patients. Recently, OSA has been suggested to be a cause of chronic unexplained cough in certain patients and treatment with continuous positive airway pressure leads to a decrease in the severity of OSA-related cough (Lee and Birring 2010).

If the cause of cough could not have been determined despite a thorough diagnostic work-up and empiric treatment – chronic unexplained or idiopathic cough was diagnosed (McGarvey et al. 2008). In the present study, the percentage of patients with CIC was merely 3 %. It probably resulted from the numerous additional tests included in the study protocol. The incidence of CIC depends on the study population and protocol, but according to certain authors it may reach up to 42 % (Haque et al. 2005). The etiology of CIC is unknown. However, hyperreactivity of the cough reflex in these patients has been found (Birring 2011). In some patients with CIC, autoimmunological disease, predominantly of the thyroid gland, and lymphocytic airway inflammation have been observed, but the importance of this phenomenon is unclear (Birring et al. 2003). CIC is more likely to occur in women (Haque et al. 2005; Birring et al. 2003). Further studies on the pathomechanism and treatment of CIC are needed.

The diagnosis of the underlying reason of cough requires not only the identification of the underlying disease, but also obtaining a decrease

in cough after specific treatment (Irwin et al. 2006). A limitation of the present study is using only subjective methods of assessment of the response of cough to treatment, based solely on the patient's opinion. Recent recommendations concerning chronic cough suggest using not only subjective but also objective methods of measuring cough severity (provocation tests with capsaicin or citric acid or monitor the number of cough episodes by using cough monitors) (Birring 2011). Another limitation may be a potential selection bias. Since as much as 60 % of our patients had earlier been diagnosed or treated because of cough, we may suppose that the patients might have particularly 'difficult to treat' cough. Besides, we excluded smokers or patients with abnormalities in chest X-ray and abnormal ventilatory pattern in spirometry. Thus, we had no patients diagnosed with COPD.

The thorough approach to diagnosing the cough reason requires cooperation of different specialists, such as pulmonologists, ear-nose-throat specialist, gastroenterologist, and others. Therefore, cough clinics are set up in many countries, which assemble different specialists in order to better diagnose and treat patients with chronic cough (Dicipingaitis 2012; Dettmar et al. 2009).

5 Conclusions

In conclusion, the most common reasons of chronic cough found in the present study were GERD and UACS. There are some differences in cough etiology between men and women: underlying asthma is are more frequently diagnosed more frequently in females, while UACS in males. Cough causes other than GERD, UACS, asthma, and NAEB are more frequently diagnosable in patients above the age of 50 years. Using a protocol with numerous diagnostic tests enables to find several coexisting cough causes and to reduce the number of patients with unexplained or idiopathic cough.

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Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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