

Exposure to Cypress Pollens and Subsequent Symptoms: A Panel Study

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Keywords

Environment · Pollen · Cypress · Allergy · Rhinitis · Conjunctivitis

Abstract

Objective: The objective of this panel study was to document the relationship between exposure to cypress pollen and allergic symptoms. **Methods:** The study group included 47 patients with allergy to cypress pollen who completed a daily diary and a weekly evaluation of quality of life (QoL) during the cypress pollen season. Different patients were included in three consecutive pollen seasons: 2014–2015, 2015–2016, and 2016–2017. Daily cypress pollen counts were obtained from the National Aerobiological Network. Air pollution and meteorological data were recorded on a daily basis. The pollen-symptoms relationship was quantified by calculating odds ratios for an increase of 1 log of grains of pollen/m³, taking into account potential confounding factors. The QoL score was expressed with a beta coefficient that increased with 1 grain of pollen/m³. **Results:** There was a marked increase in rhinitis and ocular symptoms during the pollen season, with a plateau effect at high levels of exposure, but no relationship with bronchial symptoms. The

QoL score had a linear and significant relationship with the cypress pollen count. We did not detect any threshold level.

Conclusion: This panel study demonstrated a significant association between exposure to cypress pollens and allergic symptoms, with a plateau effect for high exposures.

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Introduction

Cypress pollen is thought to be one of the most frequent causes of allergy in adults living in the Mediterranean area [1]. Allergy to cypress pollen also appears to be the most impairing pollen allergy [2]. Although the health effects are assumed to be due to exposure to pollen, the relationships between cypress pollen exposure and symptoms, over the course of the pollen seasons, have not been described to date. We therefore performed a panel study on a group of individuals with allergy to cypress pollen in the Mediterranean part of France.

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Materials and Methods

Study Population and Allergy Testing

The panel study took place over 3 consecutive years in Marseille, France. Adult patients sensitized to cypress pollen were recruited from the active file of the pulmonology outpatient clinic of Marseille North Hospital. Sensitization was defined as a positive skin prick test (wheal diameter $\geq 50\%$ of a positive control) to cypress pollen extracts (Stallergenes Laboratory, Antony, France). Conventional skin prick tests using samples of common aero-allergens were carried out using the Stallerpoint lancet according to international recommendations. A test was considered to be positive when the wheal diameter to the allergenic extract was at least 3 mm greater than that of the negative control. The following eligibility criteria for the study were used: occurrence of winter rhinitis/rhino-conjunctivitis in the past 2 years or longer, at least 18 years of age, sensitization to cypress pollen, and residing within 30 km of the Marseille pollen trap. The following exclusion criteria were applied: perennial rhinitis, current asthma with daily treatment, sensitization to cat and/or mites with perennial symptoms, and long-term oral corticosteroid treatment.

On inclusion, a physician completed a questionnaire to collect data on demographics, rhinoconjunctivitis history, medical history, and medication use. They also provided the participants with detailed instructions on how to make entries in a symptom diary.

Symptom Diary

All of the participants were asked to use a paper symptom diary from either December 15, 2014 to May 3, 2015, from December 14, 2015 to May 8, 2016, or from December 12, 2016 to April 23, 2017. They were asked to record their daily nasal, ocular, and bronchial symptoms, respiratory infections, and medication use (antihistamines, local treatment for conjunctivitis and/or rhinitis, and asthma) every evening. The severity of eye (itching and/or tear flow and/or conjunctival redness), nose (sneezing and/or runny nose and/or blocked nose), and bronchial (cough and/or wheezing and/or asthma) symptoms were recorded on a 4-point scale (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms). The completed diaries had to be sent to the hospital every Monday and they were checked at the reception. When an entry was missing, the patient was contacted by phone in an effort to obtain the missing information. Furthermore, the participants also filled out a standardized questionnaire on quality of life (QoL) every week during the pollen season [3].

Pollen Data

Daily cypress pollen counts were obtained from the National Aerobiological Network (RNSA). Measurements were made using a Hirst-type volumetric sampler (Lanzoni VPPS2000) on the roof of the Air Quality Monitoring Network building (Air PACA) that since the beginning of 2015 has been located in the city center of Marseille. It was previously located on the roof of the North Hospital in the northern outskirts of Marseille. This method involves continuously passing 10 L of air per minute over a tape coated with adhesive. Particles in the air adhere to the tape, which moves past the inlet at a speed of 2 mm per hour, thereby providing a time-

dependent sample. The pollen was then identified and quantified by a trained palynologist and related to the volume of air averaged over 24 h.

Air Pollution and Meteorological Data

The average daily concentrations of nitrogen dioxide (NO_2) and particles with a median diameter of 10μ or less (PM_{10}) as well as daily maximum 8-h average ozone (O_3) concentrations were obtained in Marseille from Air PACA. The meteorological data (daily maximum temperature, average relative humidity, wind speed, rainfall, and atmospheric pressure) were measured by the national meteorology service (Météo-France). For the QoL score analysis, the weekly means of every indicator were used, instead of the daily means.

Statistical Methods

The percentage of days with “moderate or severe symptoms” was first described for each year and for four time periods: the entire study period, the study period excluding “the cypress pollen and high cypress pollen seasons,” “the cypress pollen season excluding the high cypress pollen season,” and “the high cypress pollen season,” the last two as defined in Pfaar et al. [4]. The definition of the time periods by Pfaar et al. [4] allows the year to year variability of pollen seasons to be shown in terms of the starting date, the duration, and the concentration of pollens.

For modelling, each daily nasal, ocular, and respiratory symptom was transformed into a dichotomous response variable: “no symptoms” for mild or no symptoms and “symptoms” for moderate or severe symptoms. Weekly QoL scores were used as a continuous variable.

An appropriate model for repeated data, GEE, was applied using an autoregressive correlation matrix, with the GENMOD procedure in SAS [5]. First, the linearity of the pollen-symptom relationship was checked graphically by using Generalized Additive Mixed Models (GAMM) with introduction of splines in the models [6]. As the relationships with the symptoms were not linear, the logarithm of pollen counts was used in the models.

The pollen-symptom relationship was quantified by calculating odds ratios (ORs) for an increase of 1 log of grains of pollen/ m^3 , while the QoL score was expressed with a beta coefficient increasing with 1 grain of pollen/ m^3 . Confounding variables were chosen to avoid highly correlated variables. The maximum daily temperature, atmospheric pressure, mean relative humidity, wind speed, O_3 (8-h maximum average concentration), and PM_{10} were selected together with the participant's age and gender. Three time-trend variables were introduced: year (“1” for the first winter, “2” for the second winter, and “3” for the third winter) to take into account variations between the pollen seasons, months, and days of the week (“1” for Saturday and Sunday vs. “0” for weekdays) to account for the fact that people perform different activities (e.g., more outdoor activities) on weekends. Three different lags for weather, pollution, and pollen variables were tested: “0” (same day pollen), “1” (previous day pollen), and “01” (the average for these two days), and the model with the smallest QIC (Quasi-Information Criterion to evaluate goodness of fit for GEE models) was retained. Interactions between pollen and age, gender, weekend, or year were tested. As none of these interactions were found to be significant, none were retained.

Table 1. Characteristics of the study population

	2015 (<i>n</i> = 20)	2016 (<i>n</i> = 11)	2017 (<i>n</i> = 16)	Total (<i>n</i> = 47)
Gender				
Female	15 (75)	5 (45.4)	11 (68.8)	31 (66)
Male	5 (25)	6 (54.6)	5 (31.2)	16 (34)
Active smoker				
Non-smoker	14 (70)	9 (81.8)	14 (87.5)	37 (78.7)
Former smoker	3 (15)	1 (9.1)	2 (12.5)	6 (12.8)
Smoker	3 (15)	1 (9.1)	0	4 (8.5)
Previous or current desensitization				
Yes	3 (15)	6 (55)	6 (37.5)	15 (32)
No	6 (30)	0	10 (62.5)	16 (34)
NA	11 (55)	5 (45.5)	0	16 (34)
Mean age (SD), years	43.2 (13.5)	43.3 (16.8)	38.9 (9.4)	41.7 (13.0)
Mean time residing in the area (SD), years	11.4 (9.5)	34 (15.5)	25.1 (16)	21.2 (16.1)

Data are presented as *n* (%) of patients, unless otherwise specified. NA, data not available.

Results

Study Population, Symptoms, and Quality-of-Life Data

Fifty adults with allergy to cypress pollen were included in the panel: 20 in 2014–2015, 13 in 2015–2016, and 17 in 2016–2017. None of the patients participated in the panel more than once. Three participants were excluded because they only provided the requested daily health records for the time prior to the presence of cypress pollen. Thus, our analyses were based on data from 47 participants.

Table 1 shows the general social, demographic, and clinical characteristics of the population collected at inclusion. The mean (SD) age of the study population was 41.7 (13) years, and 66% of the patients were females. One-third of the patients had previously undergone hyposensitization treatment for cypress pollens, one-third had not undergone hyposensitization treatment, and this information was lacking for the remaining third.

During the pollen season, missing symptom data occurred on 229 person-days (4.5% of the total expected follow-up of 5,106 person-days) because some of the subjects had left the study area for an entire day or were ill, thus resulting in 4,877 person-days of observations. Table 2 shows the percentage of days that the participants had moderate or severe allergy symptoms. Figure 1 shows the daily variation in nasal and ocular symptoms during the 3-year study period. The most frequent symptoms were nasal and ocular symptoms, with ocular symptoms being almost as frequent as nasal symptoms. Respiratory symptoms were notably less common. There were fewer symp-

toms in 2016 than in the other 2 years that were investigated.

The number of QoL questionnaires received by the hospital reception ranged from 4 to 20, with a mean of 15 during the study. The mean QoL score was 1.29 (SD 1.37).

Environmental Data

Table 3 lists the cypress pollen counts in Marseille during the 3 years in question and the changes in daily pollen levels are shown in Figure 1. The 2016 “cypress pollen season” differed from the two other seasons, with a longer duration (86 vs. 56 and 54 days, respectively) but a lower amount of pollen grains (maximal value: 1,708 vs. 2,365 and 2,192 grains/m³, respectively). The “high cypress pollen season” was also twice as long in 2016 compared with 2015 and 2017 (62 vs. 30 and 34 days, respectively). However, the 2015 cypress pollen season started later (February 10 vs. the January 27 and 28 for the 2 other years, respectively).

Comparison of Symptoms for the 3 Years of the Study

The results for the comparison of the percentage of symptoms between the different study periods are shown in Table 2 and Figure 1 (nasal and ocular symptoms only). Although some symptoms were present before the start of the “cypress pollen season,” as defined by Pfaar et al. [4], there was a marked increase in symptoms during the “cypress pollen season” and even more so during the “high cypress pollen season” for 2015 and 2017. In 2016, there was only an increase during the “high cypress pollen season,” and this increase was less pronounced than for the other 2 years. Table 4 provides the QoL scores according to different periods.

Table 2. Moderate or severe symptoms according to different periods

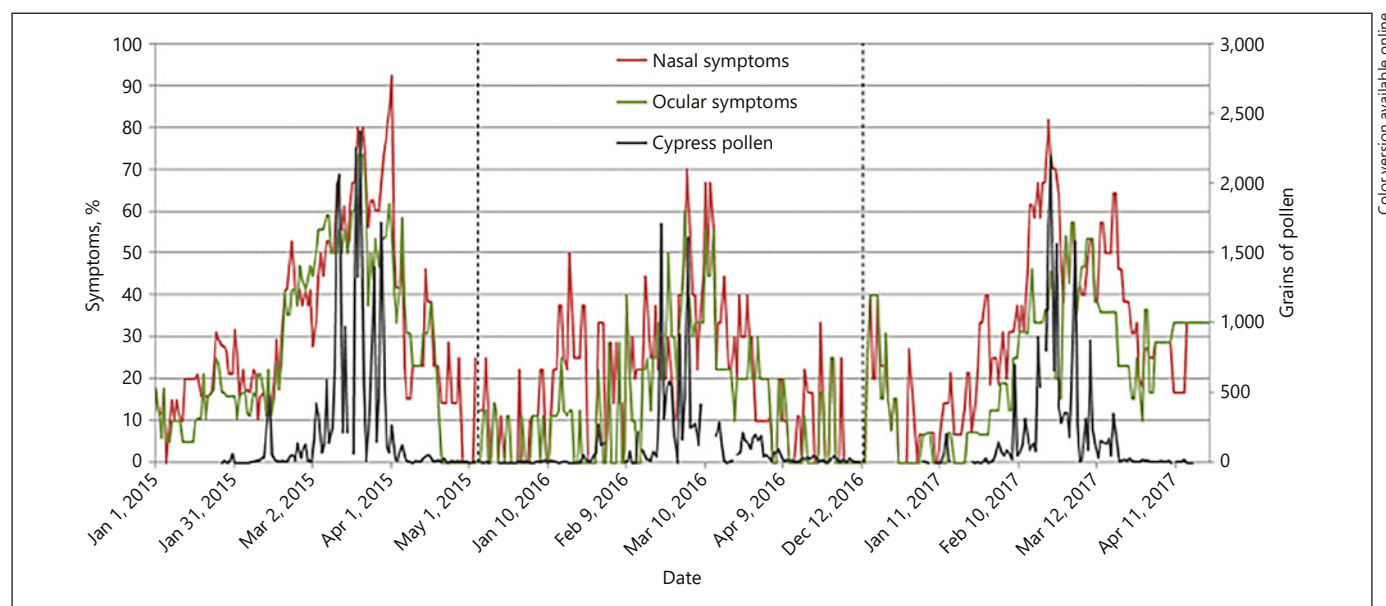
	2015 ^a	2016 ^b	2017 ^c	Total
Study period				
Nasal symptoms	31.1 (29.1–33.1)	20.7 (18.4–23.0)	30.8 (28.5–33.1)	28.4 (27.1–29.7)
Ocular symptoms	27.3 (25.4–29.2)	15.0 (13.0–17.0)	21.6 (19.6–23.6)	22.4 (21.2–23.6)
Bronchial symptoms	9.2 (8.0–10.4)	5.6 (4.3–6.9)	13.2 (11.5–14.9)	9.6 (8.8–10.4)
Study period excluding “cypress and high cypress pollen season”				
Nasal symptoms	18.3 (16.1–20.5)	13.5 (10.3–16.7)	17.4 (14.9–19.9)	17.1 (15.6–18.6)
Ocular symptoms	13.8 (11.8–15.8)	6.1 (3.8–8.4)	12.3 (10.1–14.5)	12.0 (10.7–13.3)
Bronchial symptoms	6.4 (5.0–7.8)	3.7 (1.9–5.5)	12.4 (10.2–14.6)	8.0 (6.9–9.1)
“Cypress pollen season” excluding “high cypress pollen season”				
Nasal symptoms	35.9 (31.4–40.4)	8.5 (4.7–12.3)	35.1 (29.7–40.5)	29.5 (26.6–32.4)
Ocular symptoms	33.8 (29.3–38.3)	7.5 (3.9–11.1)	19.8 (15.3–24.3)	23.4 (20.7–26.1)
Bronchial symptoms	9.9 (7.1–12.7)	7.8 (4.2–11.4)	12.9 (9.1–16.7)	10.4 (8.5–12.3)
“High cypress pollen season”				
Nasal symptoms	58.4 (54.0–62.8)	30.6 (26.8–34.4)	52.2 (47.4–57.0)	46.0 (43.4–48.6)
Ocular symptoms	54.6 (50.1–59.1)	24.5 (21.0–28.0)	39.7 (35.0–44.4)	38.7 (36.2–41.2)
Bronchial symptoms	15.8 (12.5–19.1)	6.2 (4.2–8.2)	14.7 (11.3–18.1)	11.8 (10.1–13.3)

Data are presented as % (SE).

^a “Cypress pollen season”: Feb 10 to Apr 6, 2015, “high cypress pollen season”: Mar 2 to Mar 30, 2015.

^b “Cypress pollen season”: Jan 27 to Apr 21, 2016, “high cypress pollen season”: Jan 29 to Mar 30, 2016.

^c “Cypress pollen season”: Jan 28 to Mar 22, 2017, “high cypress pollen season”: Feb 11 to Mar 16, 2017.

**Fig. 1.** Nasal and ocular symptoms and cypress pollen rates over the 3 cypress pollen seasons.

Relationship between the Cypress Pollen Counts, Symptoms, and QoL Scores

The statistical analysis was only conducted for periods for which both the health and the pollen data were available; i.e., from January 26, 2015 to May 3, 2015, from

December 14, 2015 to May 5, 2016, and from January 4, 2017 to April 17, 2017 (Table 3). Table 5 shows the results for the GEE models. There were significant and positive relationships between nasal and ocular symptoms and the concentration of airborne cypress pollen, but not

Table 3. Cypress daily pollen counts (grains/m³) in Marseille (study period with both available health and pollen data)

Period	Town	Days, <i>n</i>	Mean	SD	Min.	Q1	Median	Q3	Max.
2015	Marseille	97	233.0	501.0	0	10.7	23.3	151.3	2,364.9
2016	Marseille	131	103.0	239.1	0	6.5	17.5	95.0	1,708.2
2017	Marseille	92	198.2	393.6	0	7.9	31.1	175.8	2,191.8

Table 4. QoL scores according to different periods

	2015 ^a	2016 ^b	2017 ^c	Total
Study period				
QoL score	1.29 (0.08)	1.03 (0.08)	1.49 (0.09)	1.29 (0.05)
Study period excluding “cypress and high cypress pollen season”				
QoL score	0.86 (0.09)	0.81 (0.11)	1.13 (0.10)	0.94 (0.06)
“Cypress pollen season” excluding “high cypress pollen season”				
QoL score	1.61 (0.20)	0.92 (0.20)	1.68 (0.22)	1.53 (0.13)
“High cypress pollen season”				
QoL score	2.03 (0.20)	1.26 (0.14)	2.14 (0.19)	1.76 (0.10)

Data are the mean (SE).

^a “Cypress pollen season”: Feb 10 to Apr 6, 2015, “high cypress pollen season”: Mar 2 to Mar 30, 2015.

^b “Cypress pollen season”: Jan 27 to Apr 21, 2016, “high cypress pollen season”: Jan 29 to Mar 30, 2016.

^c “Cypress pollen season”: Jan 28 to Mar 22, 2017, “high cypress pollen season”: Feb 11 to Mar 16, 2017.

Table 5. Relationship between the log of the cypress pollen counts and the allergic rhinoconjunctivitis symptoms

	Nasal symptoms		Ocular symptoms		Respiratory symptoms	
	OR	95% CI	OR	95% CI	OR	95% CI
Final model	1.25	1.17–1.34	1.16	1.08–1.24	1.00	0.98–1.05
For an increase between 0 and 500 grains	4.10	2.73–6.15	2.51	1.63–3.88	1.01	0.74–1.38
For an increase between 500 and 1,000 grains	1.17	1.12–1.22	1.11	1.06–1.16	1.00	0.97–1.04
For an increase between 1,000 and 1,500 grains	1.10	1.07–1.13	1.06	1.03–1.09	1.00	0.98–1.02
For an increase between 1,500 and 2,000 grains	1.07	1.05–1.09	1.04	1.02–1.06	1.00	0.99–1.01

with respiratory symptoms. The relationship between the symptoms and the cypress pollen counts has a logarithmic shape, with an attenuated increase in the OR when the pollen count increased. To help interpret our results, OR are provided for several increases of 500 grains. The OR was large for an increase between 0 and 500 grains, while it was greatly reduced with increasing numbers of grains. The lag for ear, nose, and throat (ENT) symptoms was 0–1 day, whereas it was 1 day for bronchial symptoms.

The QoL score had a linear and significant relationship with the cypress pollen counts. The QoL score increased

by 0.35 (95% CI 0.15–0.55) for each increase of 500 grains. There were too few medications recorded in the diaries to warrant a statistical analysis of this parameter.

Discussion

This study of a panel of patients who were allergic to cypress pollen has revealed a significant relationship between the concentration of cypress pollens and nasal and ocular symptoms, as well as with the QoL. The analysis was performed on all of the periods for which this infor-

mation and the symptoms and the pollen data were available, in order to increase the statistical power. There was a logarithmic-shaped relationship between the nasal and ocular symptoms and the level of airborne cypress pollen. While there was no apparent lower threshold for health effects, a plateau trend was observed at high levels of exposure. By contrast, there was a linear relationship between the QoL scores and the cypress pollen counts, based on the weekly analyses.

The strengths of this study are as follows. There are no panel studies in the literature on patients with allergy to cypress pollen. The results were adjusted for temporal factors, meteorological conditions, and pollution. We found only one other study [7] which employed completion of the QoL questionnaire on a weekly basis. The variations in the QoL provide a more global view than the symptoms of the impact of the allergy on the daily life of afflicted individuals, and the QoL was evaluated in a relatively straightforward manner with a standardized tool. It should be pointed out that use of the weekly data resulted in a smoothing of both the environmental as well as the health data.

The weaknesses of this study are the following. It lacks power as there were few patients included each year. The diagnosis of pollen allergy relied on the questionnaire and skin-prick tests, but no serological tests were performed. The sets of individuals in the 3 consecutive years were different in terms of several characteristics. There were more females, more subjects with previous or current desensitization, and longer residence times for the set in 2016 compared with those for 2015 and 2017. The set of data was sufficient to show a pollen-symptoms link, although it was not sufficiently robust to define a trigger threshold and to perform sensitivity studies (treatments, desensitization). The patients may not represent the general population with hay fever induced by cypress pollen, but rather patients with severe symptoms and who are typically treated at a hospital [8]. In 2015 and 2016, for more than half of the individuals, it was not known whether they had been desensitized. There were quite a few missing questionnaires on QoL because some of the patients had left the area, were ill for part of the time, or lost their motivation to continue with the study. Pollen exposure was based on data from a single pollen sampler. A single collector can nevertheless reflect temporal variations in pollen concentrations for a given species within a 30-km radius [9], and although rooftop pollen counts do not fully reproduce human exposure at street level, individual exposure to pollen correlates well with stationary measurements used to report pollen counts [10].

Several results warrant further comment. Firstly, the demographic characteristics of the panel. There were more females, despite the fact that pollen allergies generally affect men more [11]. Comparison of a group of patients who were allergic to cypress pollen and a group of patients allergic to grass pollen has led to the conclusion that females and males are equally susceptible to cypress pollen allergy, whereas the sex ratio was equal to two for patients allergic to grass pollen. The mean age was 41.7 years, whereas it is much less with other pollen allergies [11]. Secondly, the type of symptoms. Ocular symptoms were almost as common as nasal symptoms, whereas nasal symptoms predominate with other pollen allergies. Conjunctivitis is, however, the most disabling symptom, occurring in 72% of patients allergic to cypress pollen versus 26% of patients allergic to grass pollen [11]. Only 9.6% of patients had moderate to severe bronchial symptoms. The percentage was twice as high in the survey by Caimmi et al. [12], where 18% of cypress pollen-allergic patients acknowledged worsening of symptoms and increased need for rescue medication during exposure to cypress pollens. Thirdly, the fact that the first symptoms occurred before pollen counts started to rise could be related to local pollination, and this provides support for programs based on phenological observation. It could also be related to non-pollenic allergens, as was suggested by Takahashi et al. [13, 14] in the field of Japanese cedar pollen and also in the field of birch allergens [15]. For better management of this pollen allergy, patients should be aware of the very beginning of the pollination period. Therefore, they should be alerted as soon as the pollen count reaches a threshold that can be assumed to elicit allergic symptoms. Fourthly, the logarithmic shape of the dose-response curve, including a plateau effect, has been observed previously in patients allergic to grass pollen [16] and other pollens such as *Parietaria* and ragweed [17]. Fifthly, the lack of an association between pollen exposure and bronchial symptoms is likely due to the small number of patients included, given that about one-third have associated bronchial symptoms. Lastly, the lag time identified in this study was in keeping with previous studies which found a lag phase of 1–5 days [18, 19].

Conclusions

There was a statistically significant relationship between cypress pollen counts and rhinoconjunctivitis symptoms, with a plateau effect. There was also a relationship with QoL, although we did not detect a threshold

for this or for symptom occurrence. It would be interesting to conduct a larger study capable of detecting a potential threshold.

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Statement of Ethics

The study was approved by the regional ethics committee (CPP Sud Méditerranée 1).

Disclosure Statement

The authors have no conflicts of interest to declare.

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