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OCCUPATIONAL ASTHMA DIAGNOSIS IN WORKERS EXPOSED TO ORGANIC DUST

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Abstract: The clinical evaluation of newly developed asthma in an adult should always include consideration of his occupational environment, since an abundance of different exposures, which are known causes of asthma, occur in workplaces. Two types of occupational asthma (OA) are distinguished, by whether they appear after a latency period: 1) Immunological OA, characterised by a latency period, caused by high and low-molecular-weight agents, with or without an IgE mechanism 2) Non-immunological, i.e. irritant induced asthma. The first step of the clinical evaluation is to confirm a diagnosis of asthma. Second step is to find out if there is a temporo-spatial distribution of symptoms and lung function that are indicative of OA. Third step is to determine if the disease at hand is an IgE or a non-IgE mediated disease. Last step is a challenge test that can be either unspecific, in order to assess the responsiveness of the lung, or specific challenge test, especially for the non-IgE mediated OA. The depth of clinical evaluation may vary from a situation in which a classical history confirms the clinical symptoms in e.g. a baker with confirmed allergy towards well-known allergens and a characteristic pattern in serial measurements of lung function, to more elaborate investigations in a situation with no or unknown allergen. In the latter situation, a specific challenge test might be necessary in order to find the offending agent. Finally, challenge tests are important in order to distinguish a causal relation from unspecific hyperresponsiveness in persons with pre-existing asthma. In these situations, extended sick leave and challenge tests can be the only way to find the answer.

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INTRODUCTION

Asthma is a problem worldwide, and the disease's social burden and costs to health care systems are substantial [18]. There is good evidence that the prevalence of asthma is increasing in many countries, and a large international population survey (ECRHS) is currently being conducted in order to explore prevalence and incidence of adult asthma [10, 29].

Work related asthma includes occupational asthma (OA) and work-aggravated asthma. A significant proportion of asthma in adults is related to agents encountered in the workplace. In a review from 1999, Blanc and Torén [3] arrived at a median overall estimate of the attributable risk of work related asthma of 9% (range 5–25%). In a population-based cohort study including the entire employed Finnish population aged 25-59 years, the fraction of work related asthma was 29% for males and 17% for females [12]. In another Finnish study, the incidence of OA by occupation and industry was estimated based on data from the Finnish registry of occupational disease [13]. The annual incidence rate was

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17.4 cases/100,000 employed workers or approximately 400 new cases of OA each year.

As summarised by Vandenplas and Malo [30] several definitions of OA has been proposed. Pepys, who made an important contribution to the field of OA with his pioneered work in the 1960s and 1970s suggested the following definition: Having made a diagnosis of asthma, it is then necessary in OA to establish a relationship to the work as recommended by Ramazzini [21]. At the first international Jack Pepys occupational asthma symposium in 2002, one agreed on an OA definition including cases without a latency period: OA is a disease characterised by variable airway limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace [2, 8]. Two types of occupational asthma are distinguished, by whether they appear after a latency period:

1) Immunological OA, characterised by a latency period, caused by a) high and low-molecular-weight agents for which an IgE mechanism has been proven (e.g. flour, animal dander) and b) agents for which a specific immune mechanism has not been identified (e.g. Western red cedar).

2) Non-immunological, i.e. irritant induced asthma, which may occur after a single or multiple exposures to non-specific irritants in high concentrations.

According to the revised nomenclature of Allergy and Clinical immunology [11], OA mediated by immunological mechanisms should be termed “allergic OA”. When there is evidence of IgE-mediated mechanisms, the term should be “IgE mediated allergic OA”. Other non-immunological types of asthma causally related to the workplace should be labelled “non-allergic OA”.

Work-aggravated asthma is defined as pre-existing or concurrent asthma that is exacerbated by workplace exposure.

Organic dust is usually defined as aerosols or particulate matter of microbial, plant or animal origin. Organic dust may consist of live or dead bacteria, viruses, allergens, bacterial endotoxins, mycotoxins, glucans, pollen, plant fibres etc. Occupational exposure to organic dust is very common and is a causal as well as aggravating factor for asthma. In the Finnish study mentioned above [13], OA caused by organic dust (animals, flour, grain, fodder) accounts for 60% of the total amount of OA in Finland.

Reported cases to the occupational safety and health agency in Denmark during the period 1989–1991 showed that the occupational group with the highest number of reports of asthmatic diseases was agriculture with 30 new reports per 10^5 person years (py), followed by 25×10^{-5}py in the metal industry and 23×10^{-5}py in “other industry”. Hence in countries with a substantial number of agricultural workplaces farming is a major source of OA in the society [26].

In the following, an approach to diagnosis and management of OA will be described, and furthermore we present 4 cases of OA causally related to organic dust exposure.

Table 1. Common occupations and types of organic dust causally related to OA.

Occupations	Agents	IgE mediated	non-IgE mediated
Farmers, veterinarians, animal handlers	Animal urine or dander:	++	++
	Grain dust:	++	++
	Endotoxin:		++
	Storage mite:	++	
	Fungi, moulds:	+	++
Swine breeding	Swine dander:	+	++
	Endotoxin:		++
Wood workers, carpenters, saw mill workers	Western red cedar:	+	++
	Other wood dust:	+	++
	(pine, iroko, oak, etc.)		
	Endotoxin:		++
	Fungi, moulds:	+	++
Bakers, food workers	Flour:	++	++
	Amylase:	++	
	Storage mite, cockroach:	++	
Waste handlers	Endotoxin:		++
	Fungi, moulds:	+	++
Sewage workers	Endotoxin:		++
	Fungi, moulds:	+	++
Health care workers	Latex:	++	
Cotton workers	Endotoxin:		++

++: A common mechanism, +: A rare mechanism.

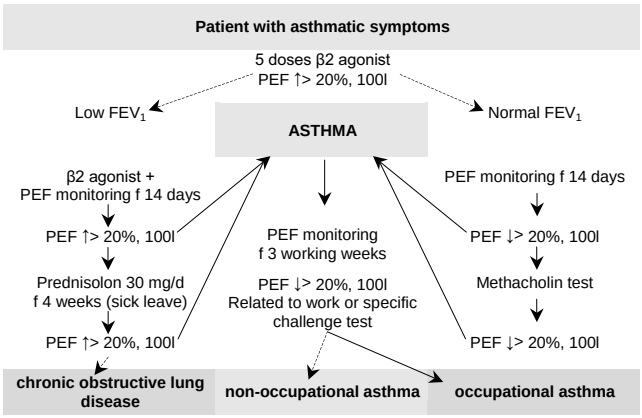

Figure 1. Diagnostic flow sheet for occupational asthma. Full lines indicate a positive test-result, dotted lines indicate a negative test-result.

THE DIAGNOSTIC STEPS

The clinical evaluation of a newly developed asthma in an adult should always include consideration of the occupational environment, since an abundancy of different exposures, which are known causes of asthma occur in workplaces. A comprehensive and updated list of verified causes of OA is found on the internet [15].

The steps are outlined in Figure 1. For most patients the diagnose of asthma is already known when the question of occupational association is raised. However in some instances as e.g. surveys of a workplace, this first step has to be accomplished first. For this discussion we refer to recent recommendations from NHLBI and others that deal with the clinical diagnose of asthma [18].

Second step is to find out if there is a temporo-spatial distribution of symptoms and lung function that are indicative of an occupational origin of the disease.

Third step is to determine if the disease at hand is an IgE or a non-IgE mediated disease.

Fourth step is a challenge test that can be either unspecific, in order to assess the responsiveness of the lung or a specific challenge test, especially for the non-IgE mediated OA there is a need for challenge-testing with the suspected agent/environment in order to secure a proper diagnosis.

The depth of the clinical evaluation may vary from a situation in which a classical history confirms the clinical symptoms in a baker with confirmed allergy towards well known allergen and a characteristic pattern in serial measurements of lung function to more elaborate investigations in a situation with no or unknown allergens as e.g. in swine breeding. In the latter situation a specific challenge test might be necessary, in order to find the offending agent. Finally challenge tests are important in order to distinguish a causal relation from unspecific hyperresponsiveness in persons with preexisting asthma. In these situations extended sick leave and challenge tests can be the only way to find the answer.

CLINICAL HISTORY

When taking a history of a possible case of OA the type of work is of importance, since some types of occupations like e.g. bakery are known to cause primarily IgE mediated asthma whereas swine breeding work mostly causes non-IgE dependent asthma among workers. In Table 1 a list of organic dust exposures and the type of asthma associated to these is presented.

If the type of asthma is IgE mediated people with atopy will be more prone to be afflicted by allergic symptoms and therefore the patient will often have accompanying allergic symptoms from eyes and nose. In these instances an allergy towards other non-occupational allergens is a strong predictor of work related reactions. It is typical for the IgE mediated type of OA, that there is a latency period from start of exposure to the symptom debut. This period can be anywhere between a few weeks and several years, and the reason for this latency period is the time needed to initiate the induction of allergy towards the offending agent. If the latency period is very long it is often of great value to investigate changes in production prior to the first symptom that could explain the occurrence of a new disease or symptoms. Often the patient improves away from work on weekends and holidays, and therefore has

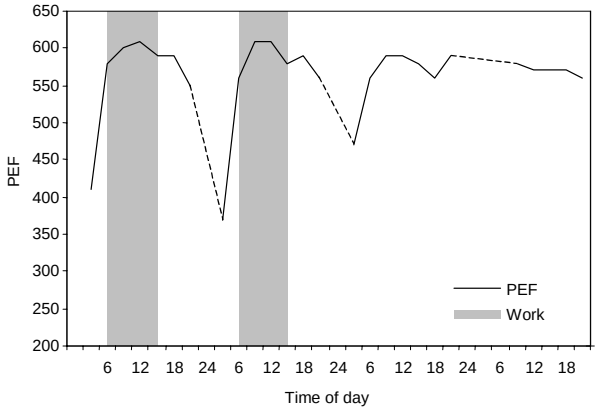

Figure 2. Late phase reaction in a garbage worker with non-IgE dependent asthma. The only symptoms were nocturnal asthma with wheeze and exercise induced asthma with cough.

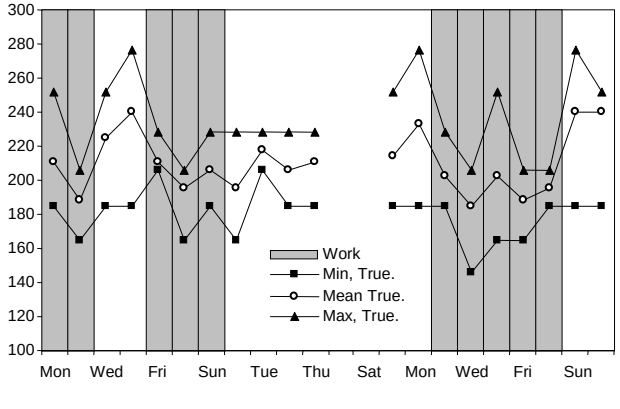

Figure 3. Female cotton worker with byssinosis grade 1 having chest tightness only first day of the working week. Notice that PEF decreases on every workday.

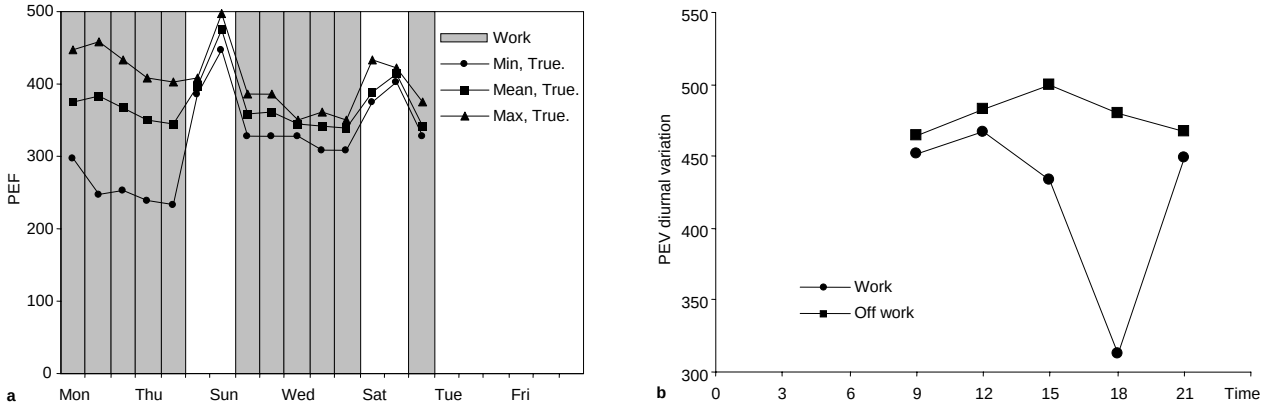

Figure 4. a: An example of a 2 week PEF recording of a kindergarten teacher exposed to indoor moulds. In week 1 he was working inside, in week 2 he worked outside in the playground; b: The diurnal variation shows a typical late phase reaction occurring 10 hrs after beginning of work.

the feeling of work relation. However for many organic exposures occurring in farming there are only very few periods away from work, and therefore the patient will not himself consider the disease to be related to his work. This feeling of work relatedness can be accentuated by the fact that symptoms often also occur as late phase reactions at night leading to the false understanding that there is something outside work triggering symptoms. If the disease is severe, secondary intolerance to irritants triggers symptoms distracting the patient's attention from the causative agent and directing attention to e.g. perfumes, tobacco smoke, cold air etc.

The non-IgE dependent asthma can occur after a very short exposure to very high concentrations of some type of organic dust, like garbage dust [24].

Often, the late phase reaction is dominating with a weak or absent acute phase reaction leading to a perception of a non-occupational problem, since the symptoms only occur at home (Fig. 2). Persons with non-IgE mediated asthma often have a "Monday feeling", that is, symptoms are worse on a Monday after a week-end or after a holiday. For occupations with high LPS exposure this has been shown to be caused by a down regulation of Anti LPS during a pause in exposure leading to an increased susceptibility upon return to work [22].

Byssinosis has been considered a special entity since the features were outlined by Schilling [23]. These features are now known not to be confined to cotton exposure, but is also seen in garbage workers, farmers and others exposed to organic dust. Therefore, byssinosis can be classified as another type of non-IgE dependent asthma. Another feature of byssinosis worth noting is the PEF-variability which is not only seen on the first day of the working week when the patient is having symptoms, but also on subsequent days (Fig. 3).

LUNG FUNCTION

Lung function, especially serial measurements of FEV_1 or PEF, is a central part of the diagnosis of OA, since it is possible to investigate the differences between exposed and unexposed periods. As the diagnosis of OA has the variability of lung function as a pre-requisite, it may be necessary to treat the patient for a period of time before it is possible to show any variability in e.g. PEF (Fig. 1).

When lung function is performed at the workplace, a portable device is advisable. Serial measurements are preferred in order to pick up the work relation during the day. Although different protocols are recommended, there is a consensus that at least 3 full weeks of monitoring, including 3 periods away from work, are needed. Each day should have at least 5 measurements and these should be at fixed time points [7]. The patient is instructed to skip a measurement if the time is passed by more than 30 minutes. A special field is allocated to occasions when the patient awakes during night with dyspnoea or wheezing. Before the start of the monitoring period the person is thoroughly instructed in the technique and the performance is checked by the physician. To eliminate learning effects, the first 2 days can be omitted from the readings. Presentation of the data (Fig. 4), are for each day, the Mean, Max, Mean range in %. The working hours are also represented in order to facilitate interpretation of the work association. It is often also of great value to plot the mean of the individual time points for work days and off-work days separately, in order to study the diurnal variation. The late phase reactions are especially obvious in this type of plot. The standard instrument for these investigations are a portable Peak Flow Meter (PEF meter). Many of these devices are prone to a non-linear error causing overreading in the middle area, and underreading in the 2 extremes. This will lead to overestimation of differences in the low PEF and an underestimation of the PEF variation at the high end; the readings therefore have to be corrected to true flow before interpretation of the data are performed [16, 17].

Interpretation of the work association can be performed by eye-balling, and although there is no perfect correlation for the interpretation, a fair proportion of tests will be quite straight forward (e.g. in Fig. 3 and Fig. 4) where there is only a change in PEF when the person is working, and the validity of these readings are high [20].

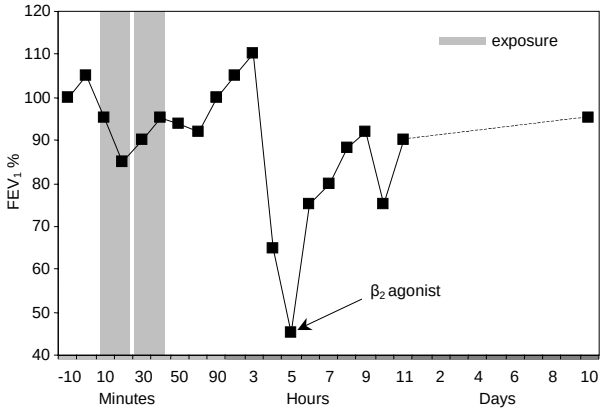

Figure 5. Specific challenge with Iroko (Yellow wood). After 3 hrs the patient suffered from runny eyes and runny nose. After 4 hrs the patient felt dyspnoeic. For further reference, see text.

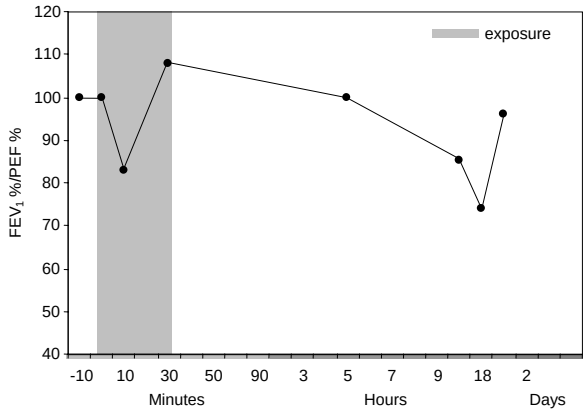

Figure 6. Specific challenge with Beech. For further reference see text. Note: After 30 minutes lung function was measured by PEF.

A programme that generates the PEF-figures based on true flow, as displayed in this article, is downloadable from the author's homepage [25]. Computer assisted interpretations have been recommended by some groups [1, 5, 6]. However, for all techniques, coaching and eliminating wrong technique remains an imperative in order to achieve successful performance.

During recent years, the development of portable devices enabling measurements of a flow volume curve have made the checking of timing and quality of single manoeuvres possible. This eliminates some of the uncertainties relating to the use of the traditional PEF-meters. However, it has not totally eliminated the possibilities for incorrect tests.

IMMUNOLOGICAL TESTING

During almost all investigations of OA, a standard prick test with common inhalant allergens will be of value, as this test will uncover the patients ability to react with IgE production towards allergens in the environment at large, and therefore also in the work environment.

If the patient is allergic to common inhalant allergens, the disease experienced as an OA might be an unspecific reaction towards irritants in the environment and therefore be the reason for work aggravated asthma. On the other hand, when a high molecular weight sensitiser is suspected, these atopic persons will be much more prone to develop a genuine occupational allergy and subsequent OA due to allergens in the work place.

For high molecular weight agents a specific skin prick test or a serological examination of IgE antibodies is of value, since it is possible to determine if there is a specific allergic reaction towards the work environment. One positive test is not a proof of causality; however, in many instances, for all practical purposes this is interpreted as a causal relationship. It should always be remembered, however, that there might be other allergens in the work environment that are important in the disease causation for the person. An example of this would be a baker sensitive to wheat flour cross-reacting with his grass-antibodies, who could also be sensitised to alpha-amylase, hemicellulase, cockroach, or one of the many other allergens commonly occurring in the bakery environment. It is therefore recommended that allergen panels relevant for the industry be used to evaluate the individual case. This will also attenuate the risk of false negative tests. Serological tests and skin prick tests supplement each other, and there is presently no consensus on what test should be the first choice. When using tests of IgE sensitisation it should always be remembered that when surveys are made in industrial cohorts there will be a proportion of sensitised workers without symptoms. It has been shown in animal laboratory workers that they run an increased risk of becoming symptomatic if they stay in the environment. However, some persons loose their sensitisation upon termination of exposure [28]. Hence, the specific sensitisation should be used as just another piece of the puzzle.

For non IgE mediated allergies there is no standardised clinical tools available for the diagnose of specific hyper-sensitivity, Although some tests [4, 14] are being tried for their ability to distinguish between cases and non-cases, none of these immunological tests can be diagnostic.

NON-SPECIFIC BRONCHIAL PROVOCATION

Non-specific bronchial hyperresponsiveness using different agents, such as metacholine, is a good measure of disease intensity. As a diagnostic tool this technique provides little help in itself, given the fact that a proportion of people loose their hyperresponsiveness when they avoid exposure, and some have only small changes in responsiveness during exposure. However, in some situations like Western red cedar [9], garbage exposure [24] and other non IgE mediated OA, it is a valuable tool since BHR is persistent in a high proportion of cases over longer periods of time.

It is also very useful to perform a non-specific bronchial challenge test in association with specific challenges because it shows unequivocally that the reaction seen in lung function is caused by an

inflammatory process, since a reaction persisting for more than 12 hours invariably involves the activation of inflammatory processess.

SPECIFIC BRONCHIAL CHALLENGE

The "Golden Standard" diagnostic tool for OA is the specific provocation test, and in some countries it is a mandatory test in evaluations of OA [19]. Other countries have a more stepwise approach, where this type of investigation is reserved for situations when other diagnostic tools have failed, or where a new agent or process is suspected.

The optimal procedure for the specific provocation test is a clinical trial with a double-blinded placebo controlled exposure. However, this is not always possible since the exposure may have characteristics revealing it to the patient, or the exposure has to be performed with the actual material because the offending agent is an unknown or complex mixture occurring only during a special work task. It can be very useful to titrate the exposure, especially in situations where a new allergen is suspected since there is always a risk of anaphylaxis. The dose of exposure should be controlled so that false positive (purely irritative) effects are avoided [27].

The pattern of response can be bipolar with an immediate reaction occurring within 10 minutes after the start of exposure and a late reaction starting 6–8 hours after exposure start, which is often seen with IgE mediated asthma. For non-IgE mediated asthma, the pattern tends to be dominated by the late phase reaction.

Figures 5 and 6 show examples of such provocations. Figure 5 illustrates an example of a work exposure where the patient under controlled circumstances performed the work task that was suspected of causing asthma attacks. The person was not atopic but had suffered from cough and dyspnoea since starting to use iroko in the production of window-frames in the small carpentry where he worked. He had been away from exposure 6 weeks before the challenge and had recovered from his dyspnoea. This case shows the dominating late phase reaction starting 5 hours after exposure.

As can be seen, after 10 days his lung function had not totally returned to normal. Interviewed 6 months later, he reported exercise-induced asthma during the 2 months following the exposure after which it finally ceased.

Figure 6 shows another example of controlled exposure to wood dust (beech). The patient was a non-atopic, formerly healthy 20-year-old female who developed wheezing in relation to beech exposure at a saw mill. The latency period was a few weeks. Peak flow confirmed the diagnosis of asthma, but was hard to interpret with respect to work relation, i.e. a specific provocation test was performed. A reaction was seen a few minutes and 18 hours after the provocation. Her asthma symptoms decreased after removal from beech exposure and after she began treatment with asthma medicine, but she continued to suffer from exercise-induced wheezing.

The above examples stress the fact that experimental exposure is to be performed by centres with expertise in the clinical treatment as well as in exposure control. Furthermore, even in the case of a negative acute reaction, the patient should be kept under surveillance for at least 24 hours before being allowed to return home.

CONCLUSIONS

Although there are some unsolved issues in the diagnosis of OA, most physicians rely on a combination of:

- Patient history including occupation.
- Knowledge of the causative agents in working environment.
- Serial measurements of lung function.
- Immunological tests.
- Specific and/or unspecific bronchial challenge tests.

The level of clinical depth of the clinical analysis may vary - from situations where a classic history with confirmed allergy towards well known allergens and a serial measurements of lung function confirms the clinical symptoms in a baker, to more elaborate investigations in situations with no or unknown allergens, e.g. in swine breeding, where a specific challenge test might be necessary in order to find the offending agent or to distinguish a causal relation from unspecific hyperresponsiveness in persons with pre-existing asthma. In these situations, extended sick leave and challenge tests can be the only way to find the answer.

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