

## **Protocol: Water Deprivation Test**

*Approved by the Scientific Advisory Committee  
of the Diabetes Insipidus Foundation, Inc.*

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### **Preamble**

This document is directed primarily to physicians who may wish to conduct a water deprivation test on their own. The reader will soon sense that a complete, properly performed test is a complicated procedure that requires specially trained personnel. Therefore, we recommend that when a water deprivation test is needed—i.e., when the patient's basal plasma sodium concentration is within the normal range while the concurrent urine osmolality is below 300 mOsm/kg H<sub>2</sub>O—the patient be referred to a specialist.

Still, for those physicians who prefer to run the test on their own, an abbreviated test comprising only *Phase I* (i.e., Steps 1 through 6 under Procedure) may suffice to diagnose either complete (severe) neurogenic or complete (severe) nephrogenic DI. We stress that even an abbreviated water deprivation test must be started in the morning and must be conducted in a controlled setting where the patient is observed constantly throughout the entire test.

If, however, the patient concentrates the urine in response to fluid deprivation before the plasma sodium concentration rises out of the normal range [i.e., if Step (b) under Procedure 5 occurs before Step (a)], then *Phase II* (Step 7) will be required in order to make the difficult differential diagnosis among primary polydipsia, partial neurogenic DI, and partial nephrogenic DI. Inasmuch as Step 7 entails the measurement of plasma vasopressin (AVP) concentration (which is performed with the required accuracy in only a few select laboratories), and often entails as well the monitored infusion of hypertonic saline, *Phase II* should be performed only in specialized centers.

### **Purpose of Test**

To distinguish among the major forms of Diabetes Insipidus (DI):

- (a) *neurogenic* (or central or pituitary), where the water diuresis results from a deficiency of the antidiuretic hormone, arginine vasopressin (AVP);
- (b) *nephrogenic*, where the water diuresis results from an inability of the kidneys to respond to AVP;
- (c) *polydipsic* (also known as primary polydipsia), where the water diuresis results from the suppression of AVP release by excessive fluid intake.

A modified version of the test may be used to verify

(d) *gestagenic*, where the water diuresis results from destruction of AVP by the placental enzyme, vasopressinase.

## Notes of Caution

1. Although the measurement of plasma osmolality is widely available, relatively few laboratories carry out this measurement with the degree of accuracy required for the water deprivation test (see *Potential Problems and Pitfalls*). Plasma sodium concentration can substitute for plasma osmolality in this test, and the sodium concentration is measured with the required accuracy in virtually all laboratories. We therefore advise the substitution of plasma sodium for plasma osmolality in most instances. (These cautionary notes do not apply to the measurement of urine osmolality.)

Furthermore, both osmolality and AVP concentration must be determined on plasma obtained from heparinized blood rather than on serum or plasma obtained from EDTA-treated blood. Throughout this protocol, we will specify "plasma sodium concentration" since then all three measurements—osmolality, AVP concentration, and sodium concentration—can be obtained from the same heparinized blood sample.

2. The water deprivation test should be performed only if the patient's basal plasma sodium concentration is within the normal range (and while the concurrent urine osmolality is below 300 mOsm/kg H<sub>2</sub>O) during ad libitum fluid and food intake.

If basal plasma sodium concentration is above normal while the urine osmolality is below 300 mOsm/kg H<sub>2</sub>O, the water deprivation test is unnecessary and potentially harmful. In this case, skip to the dDAVP challenge test (see below, under Procedure, Phase I, Step 6).

3. Do not perform the water deprivation test in patients with: (a) renal insufficiency; (b) uncontrolled diabetes mellitus; (c) hypovolemia of any cause; or (d) uncorrected deficiency of adrenal or thyroid hormone.

4. While the test is in progress, carefully monitor water balance of the patient through hourly determinations of body weight and plasma sodium concentration (and plasma osmolality where that variable can be measured with the required accuracy). Dehydration may develop rapidly if the patient has severe neurogenic or nephrogenic DI.

5. Observe the patient for the entire duration of the test, not only to prevent surreptitious drinking but also to be certain that the results are not confused by non-osmotic stimulants of AVP secretion—e.g., smoking, postural hypotension, vaso-vagal reactions, or other episodes of nausea or hypotension.

## Procedure

### *Phase I—Abbreviated Form: through Step 6 but not beyond*

1. Start the test between 7 and 9 am, and have someone with the patient throughout the test. The patient should not eat or use tobacco for at least 2 hours before and during the test.
2. Allow continued drinking *ad libitum* while completing the following five preparations in the order given.
  - (i) place patient recumbent for 30 minutes, during which steps ii - v can be carried out (patient may sit or stand during voiding of urine and determination of weight)
  - (ii) insert and firmly anchor a heparin lock in an arm vein
  - (iii) collect 7 - 10 ml of heparinized blood into an iced tube and send it to the lab for immediate processing (results available within 20 to 30 minutes) and measurement of sodium concentration (and osmolality if it can be measured accurately). Freeze 2 ml of plasma for later assay of AVP
  - (iv) ask patient to empty her/his bladder, record the urine volume, and send the sample to lab for stat measurement of osmolality. Patient may stand briefly to void
  - (v) weigh patient to nearest 0.1 kg and record the value as well as the blood pressure and pulse
3. Start complete fluid restriction and keep patient in semi-recumbent position, except for short periods of standing if that is necessary to void urine.
4. Every hour, repeat steps iii, iv, and v above, and record patient's symptoms, if there are any.
5. Continue these steps until one of the following occurs:
  - (a) plasma sodium concentration or osmolality rise above upper limit of normal **or**
  - (b) urine osmolality rises above 300 mOsm/kg H<sub>2</sub>O

Subsequent steps will vary depending on which event occurs first.

6. ***IF*** (a) ***OCCURS BEFORE*** (b), then **primary polydipsia, partial neurogenic, and partial nephrogenic** DI are excluded, and a challenge test with dDAVP (desamino-d-arginine vasopressin, also called desmopressin) should be done to determine whether the patient has complete (severe) neurogenic or complete (severe) nephrogenic DI.

#### dDAVP Challenge Test

- a. inject 2 micrograms ( $\mu\text{g}$  or mcg) of dDAVP subcutaneously
- b. ask patient to empty bladder at 1 and 2 hours after the injection and measure the osmolality of these samples

- c. if either sample has an osmolality more than 50% higher than the value immediately before dDAVP was given, the patient probably has **complete (severe) neurogenic DI**
- d. if the rise in urine osmolality after dDAVP is less than 50%, then **complete (severe) nephrogenic DI** is very likely

***Phase II – Requires Trained Personnel and Specialized Measurements***

7. ***IF (b) IN STEP 5 OCCURS BEFORE (a), complete (severe) neurogenic and complete (severe) nephrogenic DI are excluded, and the procedures outlined in Step 6 cannot be used to further differentiate among partial nephrogenic DI, partial neurogenic DI, and primary polydipsia. In this situation, several other approaches should be used.***

The preferred method is to measure plasma AVP on samples collected before and during water deprivation (Steps 2, 3, and 4 under *Procedure*) and interpret the results in relation to the *concurrent* plasma sodium concentration (or plasma osmolality, if sufficiently accurate) as well as against the *concurrent* urine osmolality (Figs. 1 and 2). [NOTE: Interpretation of the results is always clear when plasma sodium and plasma osmolality are above the normal range. If this does not occur through water deprivation alone, infuse hypertonic (3%) saline at 0.1 ml per kg body weight per minute and measure plasma sodium (and osmolality if sufficiently accurate) stat every 30 minutes until they rise above the normal range; measure plasma AVP concentration in the same samples.] These results can be interpreted as follows:

- If *under basal conditions*, plasma AVP is higher than 2 pg/ml, while *during fluid deprivation* it is normal or high in relation to the concurrent plasma osmolality (Fig. 1b) or plasma sodium concentration (Fig. 2) -- and falls to the right of the normal (shaded) area in relation to the urine osmolality (Fig. 1a) -- the patient has **partial nephrogenic DI**
- If *under basal conditions*, plasma AVP is less than 1 pg/ml, while *during fluid deprivation and/or hypertonic saline infusion* it is below normal in relation to the concurrent plasma osmolality (Fig. 1b) or plasma sodium concentration (Fig. 2) -- and is normal or lower than normal in relation to the urine osmolality (Fig. 1a) —the patient has **partial neurogenic DI**
- If *under basal conditions*, plasma AVP is less than 1 pg/ml, while *during fluid deprivation and/or hypertonic saline infusion* it is normal in relation to the concurrent plasma osmolality (Fig. 1b) or plasma sodium concentration (Fig. 2) – and falls within the normal (shaded) area in relation to the urine osmolality (Fig. 1a)—the patient has **primary polydipsia**.

## Water Deprivation Test in Patients with Diabetes Insipidus

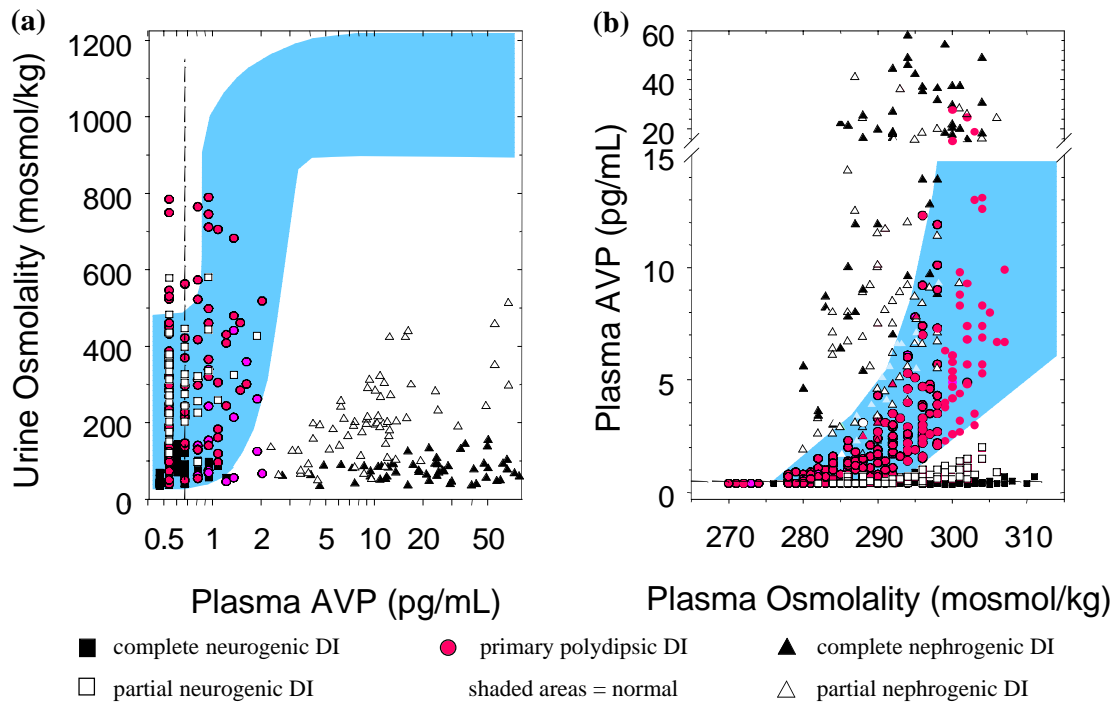
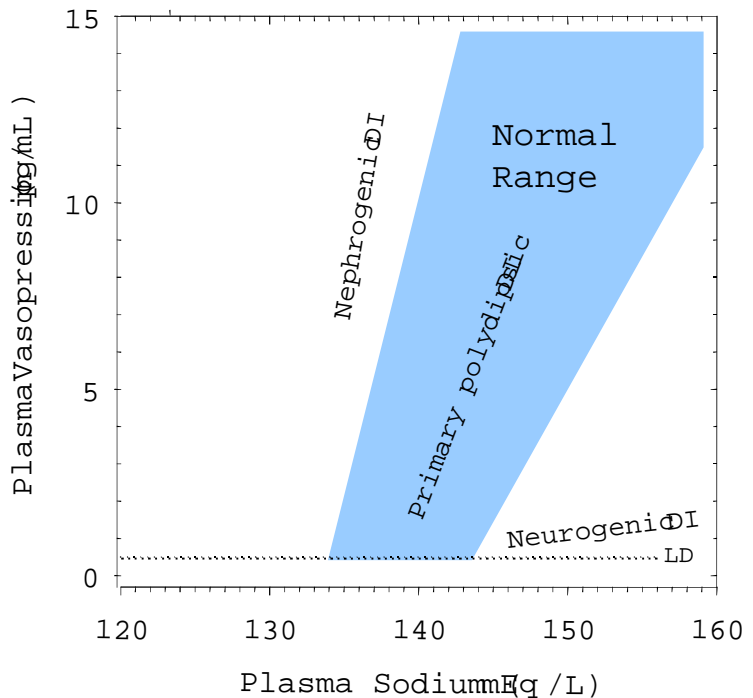


Figure 1. Results of the water deprivation test on normal subjects (shaded areas) and patients with the three major forms of diabetes insipidus. Each plotted symbol represents a simultaneous sampling for two variables: plasma AVP (the antidiuretic hormone, arginine vasopressin) and urine osmolality (Fig. 1a); and plasma osmolality and plasma AVP (Fig. 1b). The interrupted lines denote the limit of the assay for plasma AVP; below the limiting value, no AVP can be detected in the plasma. The data come from patients seen by Dr. Gary L. Robertson.

Figure 2. Range for plasma AVP concentrations in normal subjects at various plasma sodium concentrations. For instances where plasma sodium concentration—but not plasma osmolality—was measured during the water deprivation test, this graph can be used to apply the reasoning listed as the 7th step under *Procedure*. The interrupted line has the same meaning as explained in the legend for Fig. 1; LD = limit of detection. Graph from Dr. Gary L. Robertson.



## *Other Approaches to Differential Diagnosis*

Two further, ancillary measures can help in the often difficult differential diagnosis among the above three entities:

One is to examine the T-1 weighted images on an MRI of the brain and look for the hyperintense signal normally emitted by the posterior pituitary gland (the "bright spot"). If the bright spot is present, the patient probably has primary polydipsia, whereas if the bright spot is small or absent, the patient likely has either neurogenic or nephrogenic DI. It is important for the *clinician to alert the neuroradiologist* to this test, in order to avoid confounding factors, such as the use of gadillinium.

The other is to administer therapeutic doses of dDAVP (2 µg per day subcutaneously in adults) for one or two days and closely monitor the effect on the patient's thirst, ad libitum fluid intake, urine output and osmolality, body weight, and plasma sodium (and plasma osmolality, if accurate). (*CAUTION: Because patients with primary polydipsia may develop severe water intoxication within 24 hours of starting dDAVP, the therapeutic trial with dDAVP should be conducted in a hospital.*)

- If the treatment has no significant effect on any variable within 48 hours, the patient has **nephrogenic DI**.
- If the treatment promptly and completely abolishes the thirst, polydipsia and polyuria, and concentrates the urine without producing hyponatremia, the patient has **neurogenic DI**.
- If the treatment abolishes the polyuria and concentrates the urine, but has no or a delayed effect on thirst and polydipsia—and leads to hyponatremia—the patient probably has **primary polydipsia** or a **combination of primary polydipsia and neurogenic DI**. As outlined above, the distinction between primary polydipsia and neurogenic DI can be achieved by means of an MRI or a water deprivation test that includes measurement of the plasma AVP concentration.

## **Potential Problems and Pitfalls**

Several details are particularly important for correct performance and interpretation of the water deprivation test.

1. Monitor carefully for signs of surreptitious drinking or adding water to urine samples. These interferences should be suspected if body weight does not decrease by an amount equal to or greater than the weight of urine excreted (assume 1 ml = 1 g). For example, if the total volume of urine produced over a 3-hour period is 600 ml (~600 g), body weight should fall by at least 0.6 kg during the same period. If it does not, either the measurement of weight was inaccurate or the patient compromised the test by drinking or adding water to the urine.

2. Monitor closely for non-osmotic stimuli that can increase AVP release. Such stimuli include smoking, hypotension, and nausea. The latter two can occur as a result of a vaso-vagal reaction produced in some patients by the simple act of drawing blood. If a transient episode of hypotension and nausea occurred, the entire test is invalid, and it will need to be repeated on another day.
3. Complete emptying of the bladder during each collection is important. If complete emptying is not achieved, the residual volume left in the bladder may dilute the urine of the next collection, causing a spuriously low osmolality that can mislead interpretation. If incomplete emptying is suspected, creatinine concentration should be measured on each urine sample, for the excretion rate of creatinine in mg/min (urine creatinine concentration multiplied by the urine volume) should be quite constant.
4. Measure urine osmolality rather than urine specific gravity. The latter, though simpler, is more susceptible to gross error.
5. Determine osmolality on plasma obtained from heparinized blood. Plasma or serum obtained from blood processed with EDTA should not be used because such samples contain variable artifacts that raise osmolality by 3 to 10%. An error of this magnitude is unacceptable since the increases in plasma osmolality induced by dehydration should not exceed 3 to 7%.

Because small changes in osmolality are involved in the water deprivation test, the osmometer needs to be calibrated frequently against standard solutions of 290, as well as 100 and 500 mOsm/kg H<sub>2</sub>O. Most hospital laboratories are unable to provide this degree of precision. Therefore—except in special circumstances—it is better to rely on measurements of plasma sodium concentration, which are determined with sufficient accuracy by most routine hospital laboratories.

6. Collect plasma for AVP determination without disturbing the buffy coat, so as to minimize contamination of the plasma with platelets (which "sop up" large amounts of AVP). Store and transport the plasma for AVP at -20° C to prevent degradation of AVP. Additional precautions during pregnancy are given below.
7. To measure AVP concentration in plasma, use only specialized laboratories. These laboratories provide not only their own normal values but—equally important—plot their values as a function of the concurrent plasma sodium concentration or plasma osmolality determined in the same laboratory. The importance of having plasma AVP measured in an experienced laboratory cannot be overemphasized.

### **Water Deprivation Test During Pregnancy**

The purpose, precautions, and procedure of the test during pregnancy are the same as those for non-pregnant patients, except that: (a) blood for AVP measurement must be collected in tubes containing 6 mg of 1, 10-phenanthroline to prevent degradation of AVP by placental vasopressinase (which is present in plasma); and (b) the results must be evaluated

in the context of an altered relationship between the plasma osmolality or sodium concentration and the plasma AVP concentration (Figs. 1b and 2, respectively; see Davison, J.M., E.A. Gilmore, J. Durr, G.L. Robertson, and M. Lindheimer. Altered osmotic thresholds for vasopressin secretion and thirst in human pregnancy. *Am J Physiol* 246:F105-F109, 1984).

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# Polyuria and Polydipsia

## *Think of Diabetes Insipidus (DI)*

### *not just Diabetes Mellitus*

#### Importance

Although diabetes mellitus is widely recognized as the commonest cause of polyuria and polydipsia, the possibility of diabetes insipidus (DI) is too often overlooked by physicians. It is very important to bear DI in mind because missing the diagnosis can lead to needless suffering by patients and their families; indeed, failure to make the diagnosis can result in severe dehydration with irreversible brain damage, even death. Moreover, DI can be an early sign of serious underlying disease, such as brain tumor.

Experiences by patients with DI have been gathered by three organizations: *The Diabetes Insipidus Foundation* (DiF), the *Nephrogenic Diabetes Insipidus Foundation* (NDIF), and the *NDI Network*. The histories attest to numerous instances where the diagnosis of DI was missed—sometimes for years—when ultimately the correct diagnosis led to effective treatment.

Beyond the need for correct diagnosis and treatment, it is important for physicians to be aware of DI because current research utilizing molecular and cell-biological techniques is providing new insights into DI that could soon lead to more specific and more effective treatment.

#### Forms of DI

The term *Diabetes Insipidus* refers to an abnormal state of water diuresis (as opposed to an abnormal state of osmotic diuresis, as in diabetes mellitus); DI is characterized by a large volume of dilute urine (hypotonic polyuria) associated with increased fluid intake (polydipsia). It is now known that there are four types of DI: (1) **neurogenic (or central) DI**, where the water diuresis results from a deficiency of the antidiuretic hormone (ADH), often referred to as AVP (arginine vasopressin); (2) **nephrogenic DI**, where the water diuresis results from an inability of the kidneys to respond to ADH; (3) **primary polydipsic DI** (or primary polydipsia) in which the water diuresis is due to suppression of ADH by excessive fluid intake [the high intake can result from abnormal thirst (*dipsogenic DI*), from psychological or emotional disturbances (*psychogenic DI*) or from fashionable—but scientifically unproven—beliefs in the benefits of a high fluid intake (*iatrogenic DI*)]; (4) **gestagenic DI**, which occurs only during pregnancy and is due to destruction of vasopressin by the placenta.

## **Causes of DI**

Among some of the major causes are the following:

- (1) *Neurogenic*.   acquired: brain tumors; head trauma; granulomatous diseases; autoimmunity; idiopathic  
                          inherited: autosomal dominant or recessive mutation in the vasopressin gene; X-linked recessive mutation in an unknown gene
- (2) *Nephrogenic*: acquired: hypokalemia; hypercalcemia; lithium  
                          inherited: X-linked recessive mutation in vasopressin receptor; autosomal recessive or dominant mutation in water channel
- (3) *Polydipsic*    acquired: idiopathic (most); chronic meningitis; granulomatous diseases; multiple sclerosis or other diffuse pathology of brain; psychiatric illness
- (4) *Gestagenic*:   acquired: pregnancy

## **Guidelines for Diagnosis**

- Urinary frequency, nocturia, enuresis, and frequent or constant thirst should arouse suspicion of DI.  
*Caution.* Nephrogenic DI commonly occurs at birth, when thirst and polyuria will be signaled as unexplained fussiness or inconsolable crying, unusually wet diapers, frequent nursing—often accompanied by fever, dry skin with cool extremities, and failure to thrive. These signs and symptoms should arouse suspicion of polyuria/polydipsia in any infant or young child who cannot yet verbalize her/his complaints.
- On the basis of a good history and appropriate tests, rule out diabetes mellitus, the most common cause of polyuria/polydipsia. Usually, absence of glucose in the urine, as determined by Dipstick, will suffice.
- If possible, collect 24-hour urine into clean, 1-gallon, plastic milk containers during ad libitum fluid and food intake. A total volume of more than 3 quarts (40 ml/kg body weight per day or higher in adults and older children) with an osmolality below 300 mOsm/kg H<sub>2</sub>O (specific gravity <1.010) warrants further evaluation for DI. In infants or young children who are not yet toilet trained, it may be easier to measure fluid intake; an intake of approximately 1 1/2 to 2 quarts per day (100 ml/kg body weight per day or more) will be strongly suggestive of DI. An effort should then be made to differentiate among the forms of DI, as follows:
- Measure plasma sodium concentration during ad libitum fluid and food intake.
- If plasma sodium is above normal while urine osmolality is below 300 mOsm/kg H<sub>2</sub>O:  
Measure the urine osmolality of a spontaneously voided urine sample. Immediately thereafter, give an injection of desamino, d-arginine vasopressin (dDAVP) --1 to 3

micrograms subcutaneously (depending on age and body weight) and measure urine osmolality 1 to 2 hours later (or of the next spontaneously voided sample).

If the urine osmolality rises by 50% or more (e.g., from 280 mOsm/kg H<sub>2</sub>O before dDAVP to 420 mOsm/kg H<sub>2</sub>O or higher after dDAVP), then a diagnosis of **neurogenic DI** (pituitary or central DI) is likely.

If the urine osmolality after dDAVP rises by less than 50%, then **nephrogenic DI** may be present.

- If plasma sodium is normal while urine osmolality is below 300 mOsm/kg H<sub>2</sub>O, additional procedures, including a water deprivation test (sometimes with hypertonic saline infusion), will be needed for differential diagnosis. A protocol for this test can be found on the website of the DiF: <<http://diabetesinsipidus.maxinter.net/>>.

However, because this test can be difficult—it usually requires constant monitoring with serial, simultaneous measurement of plasma sodium and plasma osmolality, plasma vasopressin, body weight, and urine osmolality—we recommend that it be performed by an experienced specialist. Information about medical centers equipped to carry out and interpret the water-deprivation test can be obtained through the following websites, which also provide useful information and support for DI patients and their families:

DiF (<http://diabetesinsipidus.maxinter.net/>)

the NDIF (<http://www.ndif.org/>)

the NDI Network (<http://www.ndinetwork.org/>)

- It is also important to look for the cause of DI. If it is neurogenic or dipsogenic, an MRI of the brain and tests of anterior pituitary function are usually indicated. If the DI began during infancy or childhood or affects other family members, a genetic analysis should be performed.

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