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REVIEW

# Treatment of cluster headache in pregnancy and lactation

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Cluster headache is a rare disorder in women, but has a serious impact on the affected woman's life, especially on family planning. Women with cluster headache who are pregnant need special support, including the expertise of an experienced headache centre, an experienced gynaecologist and possibly a teratology information centre. The patient should be seen through all stages of the pregnancy. A detailed briefing about the risks and safety of various treatment options is mandatory. In general, both the number of medications and the dosage should be kept as low as possible. Preferred treatments include oxygen, subcutaneous or intranasal sumatriptan for acute pain and verapamil and prednisone/prednisolone as preventatives. If there is a compelling reason to treat the patient with another preventative, gabapentin is the drug of choice. While breastfeeding, oxygen, sumatriptan and lidocaine for acute pain and prednisone/prednisolone, verapamil, and lithium as preventatives are the drugs of choice. As the individual pharmacokinetics differ substantially, adverse drug effects should be considered if unexplained symptoms occur in the newborn. □*Cluster headache, pregnancy, lactation, triptan, treatment*

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## Introduction: cluster headache in pregnancy and lactation

The role of hormones in primary headache has been examined extensively in migraine. Two subtypes of migraine associated with the menstrual cycle have been included in the ICHD-II diagnostic criteria: pure menstrual migraine without aura (A1.1.1) and menstrually related migraine without aura (A1.1.2). However, as cluster headache (CH) is, at least in comparison with migraine, a relatively rare disorder that mainly affects males, little is known about the epidemiology of cluster headache during pregnancy and breastfeeding.

Ekbom and Waldenlind (1) found that significantly fewer women than men suffered from CH. Interestingly, women who developed cluster headache before having children had fewer children than those women who developed cluster headache after having a child or after menopause. While the vast majority of patients did not describe any correlation between menstruation and headache attacks, six out of eight patients who became pregnant after the onset of the disease reported a remission during pregnancy. In contrast to these findings, Manzoni and co-workers (2) found that CH remained unaffected by menstruation, pregnancy and puerperium in 82 cases.

Recently, a questionnaire-based retrospective controlled survey was performed in 196 women with cluster headache compared with subjects with migraine and healthy controls (3). The majority of women with CH and at least one pregnancy ($n = 143$) experienced their first cluster headache attacks after their pregnancy (62%), while 37% experienced it before. Only in 1% did the CH

manifest itself during pregnancy. Thirteen per cent of the patients recalled the occurrence of attacks during pregnancy, with the majority not noticing any change in either frequency or intensity. Again, the number of pregnancies in patients who had their first attack before their first pregnancy was lower than in patients who had their first attack after their first pregnancy. One-third of the CH patients who intentionally did not have any children reported that this decision was due to their CH.

Bahra et al. (4) found that only 5% of female CH patients suffered from attacks during pregnancy and that their seasonal pattern changed when they became pregnant (i.e. although they were due for a bout, it did not start). The majority of these studies underline that CH during pregnancy is a relatively rare condition, albeit with potentially severe implications, as the attacks remained unchanged in the majority of patients, unlike in migraine, where most patients report an improvement in the third trimester (5). Unfortunately, little is known about the course of CH in breastfeeding women. Manzoni (2) reported that the course of cluster headache did not seem to be influenced by puerperium.

## Guidelines for the treatment of cluster headache

Based on the recently published European guidelines (6) and others (7, 8), the treatment of cluster headache can be subdivided into acute treatment aimed at aborting attacks and preventive treatment. Acute treatment comprises subcutaneously or intranasal administered triptans (sumatriptan and zolmitriptan), inhalation of 100% oxygen, ipsilateral nasal instillation of lidocain and various applications (mainly intravenous and oral) of ergotamines. Short-term preventive treatment is recommended in the following cases:

- short bouts (up to 4–6 weeks) with few attacks (up to 1–2 per day);
- to bridge the interval in cases that require a slow dose escalation of another preventive drug (like verapamil) for long-term use; and
- in exacerbations of chronic cluster headache.

Corticosteroids and methysergide are particularly helpful in these cases, although various oral triptans and ergotamine derivates can be used as well. For longer bouts and in chronic cases verapamil remains the standard therapy, although lithium carbonate and topiramate are recommended as drugs of first choice as well. Drugs of second or third line therapy comprise pizotifen, gabapentin, valproate, intranasal application of capsaicin, and oral intake of melatonin. Especially in chronic cluster headache, monotherapy can be futile, leaving up to 15% of the patients refractory (7). In these patients, combinations of up to three or four drugs may be necessary, whereas verapamil should always be part of the combination. If the headache remains intractable despite combination therapy, deep brain stimulation of the posterior hypothalamus can be effective in chronic CH (9–11). Recently, stimulation of the greater occipital nerve has also been shown to provide some relief (12, 13).

## Drugs in pregnancy: both a blessing and a curse?

It can be assumed that a certain proportion of female CH patients voluntarily avoid pregnancy for fear of having to discontinue acute and preventative medication therapies. As most physicians are not well acquainted with detailed information on the embryotoxic and teratogenic properties of drugs used in the preventive treatment of cluster headache, a possible withholding of an effective and indicated drug therapy can be assumed (14). Due to the fact that most drugs are used off-label, legal concerns of the prescribing physician can also be a factor. As controlled prospective studies in pregnant women are not available for most drugs, their use is generally not recommended during pregnancy according to the package insert. However, CH is an excruciating headache with significant impairment of the patient's quality of life (15). Unfortunately, even today cases of suicide occur in patients with intractable or untreated CH. As the clinical presentation can vary, the decision for drug therapy and the extent (acute medication alone or an additional prophylactic medication) has to be made on an individual basis guided by clinical severity. If a drug therapy is necessary, it is always an off-label use. Thus, the patient has to be informed thoroughly about potential risks and side-effects. The drug of choice should be efficient and of low embryotoxic and fetotoxic potential. Prenatal toxicity may result in spontaneous abortion or fetal death, birth defects (structural abnormality and/or impaired function), intrauterine growth restriction, prematurity and functional abnormalities (e.g. behavioural or cognitive disorders). However, with respect to birth defects, only 2–4% are exclusively caused by chemical and physical factors, including

pharmaceuticals and social drugs. Within this percentage, alcohol is by far the most common teratogenic agent.

## Drugs in lactation: choice between breastfeeding and sufficient pain control?

Drug therapy during this period should be regarded with caution as transmission of the drug to the infant through breast milk is possible. The extent of transmission is influenced by various factors, including lipophilia, protein binding, molecular mass and acidity of the compound, as well as the time interval between maternal drug intake and the following breast meal (14).

## Risks of drugs administered in pregnancy and lactation for the treatment of cluster headache

Safety warnings on package leaflets or in pharmacopoeias such as the Physicians' Desk Reference are so general, out-dated and in some cases even misleading, that the prescribing physician is unable to make a rational or even 'tailor-made' choice for a patient (16). These texts are intended primarily to protect the drug producer from litigation cases. The label 'contraindication in pregnancy' is in some cases correctly applied to an embryo- or foetotoxic product, but it can also mean that experience with this drug in pregnancy has not been sufficiently documented or is limited to animal data. The latter still holds true for the majority of agents (17).

Classification systems on drug risks during pregnancy have been introduced in Sweden, Australia, the USA, and other European countries since 1984. They are general and do not permit quantifying a risk and drawing conclusions for any intervention like change of therapy, additional prenatal diagnostics or decision-making on continuing a pregnancy (18).

The current recommendations on the treatment of primary headache during pregnancy and lactation (14, 19) mainly rely on the FDA (Food and Drug Administration) and TERIS (Teratogenity Information System) assessment. Regarding breastfeeding, many recommendations are based on the American Academy of Pediatrics (AAP) classification. In this article, we review the relevant literature on developmental toxicity of the recommended drugs in CH and present primary data from the Berlin Institute for Clinical Teratology and Drug Risk Assessment During Pregnancy (German pharmacovigilance centre), which is a member of the European Network of Teratology Information Services (ENTIS). Using these sources, recommendations on the preferred drugs for acute and prophylactic treatment of cluster headache are given.

## Acute treatment

### *Sumatriptan*

*Pregnancy*

More than 700 pregnancies have been studied prospectively by the manufacturer in a registry and in some other prospective studies (20–24). Another 700 pregnancies have been studied in retrospective studies (25), the majority of them being exposed during the first trimester. These data do not indicate a teratogenic potential in human beings. One small study found a slight trend for preterm delivery (26); however, this finding has not been confirmed by other studies.

*Lactation*

Sumatriptan has a milk to plasma concentration ratio (M/P ratio) of about five, which suggests a relevant shift of sumatriptan from the plasma into the milk compartment. Following subcutaneous injection of 6 mg (in five women studied), exclusively breastfed infants were exposed to 3.5% of the maternal sumatriptan dose after adjustment for weight. Considering an oral bioavailability of 14% and limited clearance in infancy, the effective sumatriptan dosage lies between 0.7% of the maternal dose in a 30-week-old baby and 4.9% of the maternal dose in a very premature neonate (27). There is no information yet on any side effects of sumatriptan in the breastfed child, but due to its common short-term (single-dose) use, they would scarcely be expected.

### *Zolmitriptan*

*Pregnancy*

Among 28 pregnancies exposed to zolmitriptan during the first trimester, there were two major birth defects: microphthalmia plus cataract and a small ventricular septal defect (28). These data are insufficient for risk assessment.

*Lactation*

There is insufficient experience with zolmitriptan.

 

### *Other triptans*

*Pregnancy*
Based on about 50 documented pregnancies exposed to naratriptan during the first trimester (unpublished experience TIS Berlin and 21), there is yet no indication of teratogenicity. However, animal experiments have shown skeletal and vascular anomalies associated with plasma concentrations only 2.5 times greater than the human therapeutic level (product prescribing information; for detailed review including all available triptans see (29)).

There are almost 100 prospective and retrospective case reports on rizatriptan collected by the Swedish medical birth registry and the manufacturer, and these do not indicate teratogenicity (30). An additional 27 exposed pregnancies without indication for teratogenicity were ascertained by one of the authors (CS, TIS Berlin).

No clinical data are available for eletriptan, frovatriptan and almotriptan.

*Lactation*
There is insufficient experience with almotriptan, eletriptan, frovatriptan, naratriptan and rizatriptan. However, due to their common short-term (single-dose) use, substantial adverse effects in the breastfed infant would scarcely be expected.

### *Oxygen*

*Pregnancy*
No adverse effects of oxygen are known in pregnancy.

*Lactation*
No adverse effects of oxygen are known in lactation.

### *Lidocain*

*Pregnancy*
This widely used local anaesthetic is able to cross the placenta, but it does not seem to have any adverse effect on pregnancy outcome. In prospective studies of more than 1200 pregnant women, there was no increase in major or minor anomalies (31). Lidocaine is also used for epidural analgesia in labour to alleviate the pain without affecting uterine contractions. Although epidural anaesthesia has been associated in some studies with abnormalities of neurobehavioural testing in the neonate, more recent studies have shown that such abnormalities are rare and, if occurring, they are mild or transient (32).

*Lactation*
Lidocaine, even in intravenous treatment of cardiac arrhythmia, passes into the mother's milk only in limited amounts. Based on data from 27 patients (33) who received epidural anaesthesia for a Caesarean section and had, on average, 183 mg of lidocaine, the expected percentage of the weight adjusted maternal daily dose transferred to a fully breastfed child in 24 h (defined as relative dose) was no more than 1% to, at maximum, 4% of the active agent, which has in any case a limited oral availability. The children observed were unremarkable. Comparable low weight-related dosages were found after local lidocaine anaesthesia (without adrenaline) during dental procedures (34).

### *Ergotamine (ergotamine, dihydroergotamine)*

*Pregnancy*
Ergot alkaloids are problematic during pregnancy because of their ability to disrupt fetal blood supply, which can lead to fetal damage or death. They can also produce uterine contractions and perfusion disturbances in the placenta (35, 36). Individual cases of birth defects due to vascular disruption and stillbirths have been observed (37, 38), although epidemiological studies have not, as yet, documented a clear increase in the rate of birth defects (39). In conclusion, on the basis of current data all ergotamines are contraindicated in pregnancy which is also stated in the FDA guidelines (category X).

*Lactation*
Ergotamine (tartrate) may be more likely than the less fat-soluble dihydroergotamine to cause symptoms of ergotism by passing into the milk. Milk production may decrease in the presence of ergotamine derivatives as a result of the antiprolactinergic action. There are, as yet, no sufficient data on the passage of ergotamine alkaloids into the mother's milk.

## Preventive treatment

### *Verapamil*

*Pregnancy*
No congenital anomalies were reported among about 25 infants whose mothers took verapamil during the first trimester of pregnancy (40). No

adverse drug-related effects were observed among the infants of 137 hypertensive women treated with verapamil in late pregnancy in two therapeutic trials (41, 42). There was no increased incidence of fetal or neonatal toxicity among 76 newborns exposed to verapamil during the first trimester (43). Another multicenter study on first-trimester exposure to calcium blockers analysed 61 prospectively ascertained pregnancies and did not find an increased rate of all major malformations or of digital defects. However, reduced birth weight among term newborns and a more than three-fold increase in the rate of preterm births were found in the exposed group. Reduced birth weight was probably due to placental perfusion problems caused by hypertension, and not by the drugs themselves. There is a case report of a pregnant woman who was treated with verapamil for supra-ventricular tachycardia twice during the third trimester, and subsequently had an infant with severe congenital hypertrophic cardiomyopathy despite the fact that a fetal echocardiogram at 31 weeks' gestation was normal (44). This finding has not been confirmed by other investigators.

*Lactation*

With ongoing treatment using 240–360 mg verapamil daily, up to 0.3 mg/L was measured in the milk. The M/P ratio lies between 0.2 and 0.9. The amount taken in by the infant was calculated at a maximum of 0.05 mg/kg daily. This represents about 1% of the maternal dosage per kg of body weight. A concentration of 2.1 μg/L was found in the plasma of one of the breastfed infants. No side effects were described (45). It has to be pointed out that in cluster headache much higher dosages of verapamil may be required. However, no data regarding pregnancy or lactation exist.

## *Lithium carbonate*

*Pregnancy*

In the 1970s, lithium treatment during pregnancy was strongly associated with congenital heart malformations, especially Ebstein's anomaly. Other defects ascribed to lithium were anomalies of the external ear, CNS, ureter and the endocrine system (46). The teratogenic risk of first-trimester lithium use now appears to be lower than previously suggested (47–49). If a causal association does exist, it is probably weak (i.e. only 1 in 1000 fetuses exposed during the first trimester is affected) (50). Other adverse effects that have been reported occasionally are polyhydramnios after fetal polyuria, stillbirth, fetal and neonatal arrhythmia, neonatal jaundice, and maternal and neonatal goiter (51).

*Lactation*

The M/P ratio varies with the dosage, ranging between 0.3 and (for high doses) 1.7. Based on 11 mother–child pairs, the relative dose for the breastfed child is up to 30%, but in half of the cases it was less than 10% (52). Older publications report that a relative dose of up to 80% can be transmitted to the baby via the mother's milk. After the very high immediate postpartum levels have dropped, significantly lower concentrations are found in the infant's serum. Seldom do they exceed a third of the maternal levels, and frequently they are even lower. None of the 11 infants observed by Moretti (52) were symptomatic. However, one publication reported a 2-month-old infant with a tremor and abnormal pattern of movement. The lithium levels in his serum were twice as high as those in his mother (53).

## *Methysergide*

*Pregnancy*

The ergotamine derivative methysergide is not well studied for its tolerability during pregnancy, and, given the data on ergotamine, must therefore be avoided (35, 36).

*Lactation*

Ergotamine derivatives like methysergide may cause symptoms of ergotism by passing into the milk. Milk production may decrease in the presence of ergotamine derivatives as a result of the antiprolactinergic action. There are, as yet, no sufficient data on the passage of ergotamine alkaloids into the mother's milk.

## *Corticosteroids*

*Pregnancy*

Some prospective epidemiological studies have been published in which there was no evidence to suggest a significantly increased risk of congenital malformations (54, 55). Other studies have found associations with an increased risk of oral clefts (56–59), which is consistent with animal studies. Taking the published data into consideration, it is reasonable to conclude that there is no evidence of a significant increase in the basal risk for congenital anomalies, although a possible association with clefts cannot be excluded.

*Lactation*
An average of 1–2% of the maternal weight-related dosage can be expected for the infant (45, 60). In the case of a 1-g intravenous dose, the infant received 0.2 mg of prednisolone per kg bodyweight with the first breastfeed an hour after the injection. Over 24 h, it was 0.32 mg/kg. Even the highest maternal dosage provides only about a sixth of a therapeutic child's dosage (2 mg/kg per day), which is usually well tolerated (38). There are only insufficient data on transfer with the other corticoids and toxicity in breastfed infants has not been reported.

## *Topiramate*

*Pregnancy*
Hoyme et al. (61) reported on a growth-retarded girl with hirsutism and dysmorphic features of the nose and distal phalanges, whose mother took 700 mg topiramate twice daily throughout the pregnancy. In the post-marketing surveillance system of the company, 38 exposed pregnancies (17 of them under monotherapy) were registered; three of the polytherapy-exposed infants had congenital anomalies. Yerby (62) mentioned five cases of hypospadias among 110 pregnancies reported to the drug company without details. Additional case reports with normal outcomes were reported by Ohman et al. (63) and Vajda et al. (64). The UK Epilepsy and Pregnancy Register (65) includes 28 pregnancy outcomes with exposure to topiramate monotherapy, and two major congenital malformations (cleft lip and palate, hypospadias) were observed. In summary, about 150 exposed pregnancies so far have a documented outcome, but these data are insufficient for ruling out a moderate risk, given the fact that topiramate is teratogenic in animal experiments, sometimes with an equivalence of only 20% of the human dosage (per surface area).

*Lactation*
No topiramate or only low concentrations (at maximum, 20% of the maternal serum concentration) were detected in the serum of three unremarkable infants aged 2–3 weeks. The M/P ratio was 0.7–0.9, the relative dosage 3–23% (63).

## *Gabapentin*

*Pregnancy*
Morrow (65) reported 31 informative pregnancy outcomes with exposure to gabapentin monotherapy, and observed one congenital malformation (ventriculoseptal defect). Moreover, 51 pregnancies were reported to the company (66), and a similar number of cases was gathered in a prescription study (67) performed within the Australian Epilepsy Register. Four different birth defects were observed among these prospective and retrospective studies, all with polytherapy including gabapentin. Chambers (68) reported one newborn with facial dysmorphy after monotherapy. Although there is no evidence yet for human teratogenicity, the evidence is insufficient to rule out a moderate risk.

*Lactation*
For gabapentin, there is published experience with more than 10 lactating mothers (69, 70). The average M/P ratio is 1. Based on five mothers, Ohman et al. (70) calculated a relative dosage of 1.3–3.8% for the fully breastfed child. As the milk specimens were taken before drug administration, these relative dosages do not represent the maximum values. Concentrations in the infant's serum were around 12% of maternal values; no adverse effects were reported.

## *Valproate*

*Pregnancy*
With valproic acid (VPA) monotherapy, the overall risk of birth defects is two to three times higher than the basic risk of untreated pregnant women, and also higher than with other antiepileptic drugs in monotherapy (38).

Malformations associated with valproic acid are spina bifida, cardiac malformations, hypospadias and limb-reduction defects (38). A dose–response relationship was found in some recent studies. Women receiving daily doses of 1000 mg VPA or more, or having plasma levels exceeding 70 μg/mL, were at a significantly increased risk for having a child with a major malformation (71). Valproic acid should not be prescribed to potentially pregnant women if not compellingly indicated for otherwise intractable epilepsy.

*Lactation*
Based on data from more than 40 mothers (69), valproic acid passes into the milk with an M/P ratio of about 0.05 and a relative dosage of around 1% on average (maximum value 7%). Even so, as a result of the decidedly longer half-life of around 47 h, a 'steady state' can develop in the breastfed infant with a serum concentration of 7% (or even more) of the maternal value. However, a more

recent study of six children found 0.7–1.5 μg/mL, or only 0.9–2.3% of the maternal concentrations, which were between 39 and 79 μg/mL (72). No symptoms have been reported.

### *Pizotifen*

*Pregnancy*
Pizotifen has not been adequately evaluated for reproductive effects. It has similarities to the antihistamine cyproheptadine. In mice, there was a decrease in fetal weight observed with no increase in congenital malformations (73).

*Lactation*
We could not find any published data on the amount of pizotifen transfer into human milk.

### *Capsaicin*

*Pregnancy*
Chanda et al. (74) examined the embryotoxic and fetotoxic properties of trans-capsaicin in pregnant rats and rabbits and found no significant developmental irregularities apart from delays in skeletal ossification in rats at the highest dosage. There are no human data.

*Lactation*
There are no data.

### *Melatonin*

*Pregnancy*
Melatonin is present normally during pregnancy. Adverse effects of exogenous melatonin have not been shown. Some commentators advise against the agent in pregnancy because it may disturb the development of the postnatal circadian rhythm (75).

*Lactation*
Endogenous melatonin is excreted in human milk in a circadian cycle, with peak levels occurring at night (76). Some commentators have suggested that exogenous melatonin could interfere with the postnatal development of sleep patterns and other hormonal cycles, but no data are currently available to support these hypothetical concerns.

## Interventional treatments

Although various studies have been published on the efficacy of deep brain stimulation (DBS) of the posterior hypothalamus in intractable headache and it has been in clinical use since 2000, it still remains an experimental procedure. Detailed consensus criteria on patient selection have been published excluding pregnant patients (77). The relatively young and significantly less invasive technique of greater occipital nerve (GON) stimulation has yet to prove its efficacy and should likewise not be used in pregnancy. Other invasive techniques have shown less promising results and mostly imply destructive procedures. Therefore, no invasive technique can currently be recommended during pregnancy.

In breastfeeding women, DBS of the posterior hypothalamus as well as GON stimulation can be considered in cases refractory to medication, although it should only be placed in the hands of a specialized neurological and neurosurgical centre with special expertise in cluster headache and neurostimulation techniques.

## Recommendations for the acute and preventive treatment of cluster headache in pregnancy

An early and close collaboration between an experienced headache centre, an experienced gynaecologist and a teratology information centre through all stages of the pregnancy is mandatory. Prior to treatment, the patient should receive a detailed briefing about the risks and safety of various treatment options. For forensic reasons, this informed consent should be thoroughly documented, as most drugs in pregnancy are used off-label. The patient should receive regular pregnancy care, and a detailed fetal ultrasound around week 18 should be offered. In general, both the overall number of medications and the medication dosage should be kept as low as possible. Among treatments of first choice are oxygen, subcutaneous or intranasal sumatriptan for acute pain and verapamil and prednisone/prednisolone for preventative care. Lidocaine and lithium are drugs of second or third choice, respectively. All ergotamines are contraindicated in pregnancy and must be avoided. If there is a compelling reason to treat the patient with antiepileptics, gabapentin is the drug of choice. Valproic acid must be avoided when a pregnancy is planned and at the very least stopped during the 1st trimester. It is known that the clearance of antiepileptic drugs may change (increase) substantially during pregnancy (78, 79). Therefore, measurement of drug levels must be considered if an antiepileptic is essential. There is insufficient experience with pizotifen, melatonin and capsaicin.

 

## Recommendations for the acute and preventive treatment of cluster headache in breastfeeding women

Oxygen, sumatriptan and lidocaine for acute pain and prednisone/prednisolone, verapamil and lithium as prophylactics are the drugs of choice during lactation and do not require cessation of breastfeeding. In case of necessity another triptan is acceptable, too. Although valproate is considered reasonably safe during breastfeeding, it should be avoided if possible to prevent an unwanted exposure to a succeeding pregnancy. Because pharmacokinetics differ substantially among individuals, one should always consider adverse drug effects among young children of <2 months if unexplained symptoms occur. During the first 2 days after birth, symptoms due to contaminated breast milk are seldom because milk production is still limited. In the case of suspicious symptoms, a paediatrician and a teratology information service should be contacted immediately. If drug toxicity via breast milk is suspected, drug analysis of the infant's blood may be initiated.

In conclusion, cluster headache is a rare disorder in women and even more so in pregnant or breastfeeding women. Although low in number, the disease can have a serious impact on the affected women's lives and especially on family planning. As there is growing positive experience with sumatriptan, no concern against the use of oxygen, and reassuring experience with preventive drugs like verapamil, affected women need not abstain from getting pregnant. However, early and close collaboration between an experienced headache centre, the gynaecologist and a teratology information centre is recommended.

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