Clinical Policy Title: Treatments of hyperemesis gravidarum

Clinical Policy Number: 12.02.02

Effective Date: January 1, 2016
Initial Review Date: February 19, 2014
Most Recent Review Date: September 21, 2016
Next Review Date: September 2017

Related policies:
None

ABOUT THIS POLICY: Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First’s clinical policies are not guarantees of payment.

Coverage policy

A. Keystone First considers the use of Zofran via subcutaneous (s.c.) microinfusion pump to be clinically proven for the treatment of hyperemesis gravidarum (HG) during pregnancy and, therefore, medically necessary when all of the following criteria are met:

- HG is diagnosed after nine weeks of gestation.
- All other causes of nausea and vomiting have been ruled out.
- Evidence of persistent vomiting, weight loss of more than five percent.
- Documentation of one of the following: ketouria, hypokalemia or high urine specific gravity (dehydration).

- A step trial in the following order is conducted unless contraindicated:
  - Step #1. A trial of at least one of the following five drugs has been attempted and failed:
    - Prochlorperazine (Compazine IM/PO).
- Trimethobenzamide (Tigan PR).
- Promethazine (Phenergan IM/PO/PR).
- Metoclopramide (Reglan PO).
- Ondansetron (Zofran PO).

  o Step #2. If control not achieved with drugs in step #1, then a trial of doxylamine and pyridoxine (Diclegis® PO) has been attempted.

  o Step #3. If drugs in steps #1 and #2 have been tried without success, then either intravenous (IV) metoclopramide (Reglan) or IV ondansetron (Zofran) has been attempted and failed.

  o Step #4. Upon failure of drugs in steps #1, #2 and #3, the continuous infusion of ondansetron (Zofran).

B. Keystone First considers the use of IV hydration (CPT codes 96360, 96361) for HG to be clinically proven and, therefore, medically necessary if either clinical signs of dehydration (e.g., high urine specific gravity, ketonuria or hypokalemia) or the inability to tolerate oral liquids without vomiting for more than three weeks is present.

- IV hydration should be continued until ketosis and vitamin deficiency have been corrected and until the patient can tolerate oral fluids.
- At any step consider parenteral nutrition if dehydration persists or persistent weight loss is noted.
- Alternative therapies may be added any time depending on patient acceptance and clinician familiarity.
- Thiamine, 100 mg daily, IV for two to three days (followed by IV multivitamins) is recommended for every woman who requires IV hydration and has vomiting for more than three weeks.

**Limitations of coverage:**

- All other uses of Zofran s.c. microinfusion pumps are not medically necessary.
- All other uses of IV hydration for hyperemesis during pregnancy (e.g., prevention of dehydration) are not medically necessary.
- In general, an imbalance of less than 500 ml of volume is not likely to require IV rehydration. Therefore, rehydration with the administration of an amount of fluid equal to or less than 500 ml is not medically necessary.

**Alternative covered services:**

- Nutritional counseling, physician office visits.

**Background**

Nausea and vomiting of pregnancy (NVP) affects approximately 80 percent of pregnant women (Einarson 2013). Uncomplicated NVP, commonly known as “morning sickness,” is generally a mild, self-limited condition that may be controlled with conservative measures. A small percentage of pregnant women have a more profound course, with the most severe form being HG. Severe hyperemesis requiring hospital admission occurs in 0.3 percent to two percent of pregnancies (Einarson 2013, Piwko 2013).
Unlike morning sickness, HG may have negative implications for maternal and fetal health (Vandraas 2013, Veenendaal 2011).

There is no one accepted definition of HG. According to the American College of Obstetricians and Gynecologists (ACOG), the most commonly cited criteria for HG include persistent vomiting not related to other causes, a measure of acute starvation (usually large ketonuria), and some discrete measure of weight loss, most often at least five percent of pre-pregnancy weight. Electrolyte, thyroid, and liver abnormalities may be present (ACOG 2014). The International Statistical Classification of Disease and Related Health Problems, Ninth Revision (ICD-9-CM) defines HG as persistent and excessive vomiting starting before the end of the 22nd week of gestation; HG is further subdivided into mild and severe, with severe being associated with metabolic disturbances, such as carbohydrate depletion, dehydration, or electrolyte imbalance (AMA 2014).

While the etiology of HG is unknown, it is most likely a multifactorial condition and has been associated with largely non-modifiable risk factors such as family history (genetics) or a history of HG in a previous pregnancy (ACOG 2004). Hyperemesis is also associated with female gestation, multiple gestation, triploidy, trisomy 21, current or prior molar pregnancy, and hydrops fetalis. Women with a history of motion sickness, migraine headaches, psychiatric illness, pre-gestational diabetes, pre-gestational underweight, hyperthyroidism, pyridoxine deficiency, and gastrointestinal disorders are at an increased risk of HG. Women with HG are more likely to be younger, pregnant for the first time, persons of color, and less likely to drink alcohol (ACOG 2004, McCarthy 2014a).

Diagnosing HG is determined primarily by ruling out other underlying complications associated with persistent vomiting (Niebyl 2010, Niemeijer 2014). The management of HG is based on correcting electrolyte imbalance and dehydration, prophylaxis against recognized complications, and providing symptomatic relief (McCarthy 2014a, Bottomley 2009). Treatment may be administered singularly or in combination in inpatient and outpatient settings.

Guidelines encourage early, safe and effective treatment with vitamins and non-pharmacologic alternatives that may prevent complications or reduce the need for pharmacologics or IV hydration and hospitalization (ACOG 2004, Arsenault 2002). Non-pharmacologic options such as ginger, acupressure, acupuncture and chiropractic may offer symptomatic relief. Pharmacological treatments include antihistamines, anticholinergics, dopamine antagonists, 5-HT3 antagonists, corticosteroids, cisapride, and cannabinoids (Niebyl 2010).

If oral and IV administrations prove inadequate, subcutaneous drug infusion may be necessary. Drug delivery via microinfusion devices may reduce the plasma drug concentration fluctuation associated with oral delivery and the slow onset and long depot effect associated with transdermal patch delivery. This type of device can be worn on the skin in a discrete and convenient manner, deliver drug from a pressure-driven reservoir through the needle into the skin, and serve as a potential replacement for conventional hypodermic needles and infusion sets.

Searches

Keystone First searched PubMed and the databases of:

- UK National Health Services Center for Reviews and Dissemination.
We conducted searches on August 15, 2016. Searched terms were: "hyperemesis gravidarum" (MeSH) and "morning sickness" (MeSH).

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Limited high-quality research is available to inform clinical practice on advanced treatment of HG. The ACOG summarized the evidence for guidance on treatment of nausea and vomiting during pregnancy and serves as the basis of this policy (ACOG 2004). The ACOG guidance focuses on treatment for all stages of nausea and vomiting of pregnancy, as failure to treat early manifestations of NVP increases the likelihood of hospital admission for HG. ACOG presents an algorithm of treatment options according to the strength of evidence for fetal safety and efficacy of treatments available in the U.S.

A Cochrane review of interventions for NVP (excluding HG) determined there was insufficient strong evidence of safety and effectiveness to support any one intervention over another (Matthews 2014). In the absence of one pharmacologic regimen clearly demonstrating benefit over any other, a decision algorithm that begins with the most cost-effective and readily accessible treatment options, as depicted in the ACOG treatment hierarchy, is a reasonable approach to managing HG. A summary of these guidelines are as follows:

- ACOG recommends treatments with the strongest safety-efficacy profile as first-line treatments. These include dietary changes, emotional support, vitamin B6 and doxylamine (ACOG 2004).
- Pharmacologic management is indicated for relatively mild cases and patients who cannot tolerate oral treatment or are dehydrated, or both. Sufficient data on the safety of antihistamines, phenothiazines and metoclopramide in early pregnancy show no teratogenicity with any of these agents. Therefore, antiemetic treatment should not be withheld on the basis of teratogenicity concerns.
- For use of continuous s.c. anti-emetic therapy, the entire body of evidence consists of five industry-sponsored and authored nonrandomized reports. These therapies do not appear, based on published payment levels, to be cost-effective when compared to conventional treatment alternatives, including episodic hospitalization (Reichmann 2012). Therefore, it is reasonable to design evidence-based clinical coverage guidance to limit their use to extremely
recalcitrant cases of HG until sufficiently powered, independent, randomized controlled trials (RCTs) demonstrate clinical efficacy and cost-effectiveness.

- IV hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Signs of dehydration may include:
  - Decreased skin turgor.
  - Postural changes in blood pressure and pulse.
  - Abnormal electrolyte, BUN, creatinine, and serum ketone levels.
  - Abnormal urine specific gravity and ketone levels.

- IV hydration should be continued until ketosis and vitamin deficiency have been corrected and until the patient can tolerate oral fluids. IV thiamine 100 mg daily for two to three days (followed by IV multivitamins) is recommended for every woman who requires IV hydration and has vomited for more than three weeks.

- The evidence for any clinical benefit of using a compound solution over normal saline 0.9% is unclear. One RCT comparing IV 5% dextrose and saline vs. normal saline for rehydration found women treated with 5% dextrose experienced short-term (< 24 hours) improvement in vomiting, but the effects had dissipated by 24 hours (Tan 2014). All participants received IV thiamine and an antiemetic, and other outcomes were similar between groups. Administering dextrose may stop the breakdown of fat, but it may also precipitate Wernicke encephalopathy in the presence of a thiamine deficiency. For any patient in whom vitamin deficiency is a concern, thiamine 100 mg should be given before initiating dextrose-containing fluids.

- Other interventions such as enteral tube feeding may be needed to serve as either as a supplemental or primary source of nutrition.

- Hospitalization is recommended when a woman cannot tolerate liquids without vomiting and has not responded to outpatient management. No controlled trials have compared hospitalization with outpatient management of HG. The option of hospitalization for observation and further assessment should be preserved for patients who experience a change in vital signs or a change in affect or who continue to lose weight. After the patient has been hospitalized on one occasion and a workup for other causes of severe vomiting has been undertaken, IV hydration, nutritional support, and modification of antiemetic therapy often can be accomplished at home.

Results of two surveys found a growing awareness, yet continued under-prescribing and use, of early effective treatments (e.g., vitamins, antihistamines and bed rest) in favor or more expensive antiemetics, suggesting that greater adherence to these guidelines may be needed (Power 2007, Goodwin 2008). Greater awareness of evidence-based guidance, particularly for safe and effective early prevention strategies using vitamins/B6 therapy, is needed as are high-quality studies that focus on safe non-pharmacologic treatments, preventive measures in high-risk women, new biomarkers underlying the etiology of HG, and interventions that may reduce adverse pregnancy outcomes (McCarthy 2014a).

Policy updates:

For the 2015 update, a recently completed RCT comparing the effect of day care services versus standard inpatient management on duration of hospitalization and patient satisfaction for the initial treatment of nausea and vomiting of pregnancy, including HG, will soon publish its findings (Clinicaltrials.gov NLM identifier: NCT00795561). A systematic review and economic evaluation underway in the United Kingdom to assess the relative clinical- and cost-effectiveness of interventions for HG has not yet been published (Vale 2015, updated 2016).
For the 2016 update, we included one new Cochrane review (Boelig 2016), one practice guideline update (ACOG 2015) and the results of the above RCT (Murphy 2016, McCarthy 2014b). The RCT was carried out at a tertiary referral maternity hospital in Ireland and included women seeking treatment for nausea and vomiting of pregnancy. Ninety-eight women were randomized to initial day care treatment (n=42) or inpatient management (n=56). Compared to initial inpatient care, women randomized to day care treatment had shorter inpatient stays (median [interquartile range]: 2 [1-4] days vs. 0 [0-2], P<.001) and fewer hospital admissions (one [1-2] vs. zero [0-1] admissions, P<.001); both inpatient care and day care were equally acceptable to patients (McCarthy 2014b). A cost-utility analysis found day care management of NVP remained less costly (mean [95% confidence interval]: €985 [705-1,456] vs. €3837 [2,124-8,466]) and at least as effective (mean 9.42 quality-adjusted life years [4.19-12.25] vs. 9.49 [4.32-12.39]) than inpatient management from both the healthcare provider and patient's perspectives (Murphy 2016).

There continues to be little high-quality and consistent evidence supporting the superiority of any one intervention over another for treating HG (Boelig 2016). Many studies combine interventions for NVP with the more severe condition of HG and fail to compare safety and efficacy data across interventions, making it difficult to determine optimal care. Current clinical practice guidelines continue to recommend a step-wise approach to care, beginning with interventions with the strongest safety-efficacy profiles and progressing to more advanced pharmacologic and hospitalization, when other approaches fail (ACOG 2015). These results do not change the previous findings. Therefore, no policy changes are warranted at this time.

**Summary of clinical evidence**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Boelig (2016)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>- Systematic review of 25 trials (2,052 total women) comparing various interventions (acupressure/acupuncture, outpatient care, IV fluids, and various pharmaceuticals).</td>
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<td>- Overall quality: very low to low. Mostly single, underpowered studies.</td>
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<td></td>
<td>- There is little high-quality and consistent evidence supporting any one intervention, and very limited reporting on the effect of treatment on adverse effects and maternal and fetal outcomes, or on the economic impact of HG.</td>
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<td></td>
<td>- The difficulties in interpreting and pooling the results of the studies of HG highlight the need for using validated outcome measures and larger placebo-controlled trials.</td>
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<tr>
<td>Reichmann (2012)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>- RCTs of sufficient power are necessary before long-term continuous s.c. metoclopramide or ondansetron can be used on a widespread basis to treat NVP.</td>
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<td></td>
<td>- Cost approximations in the case series are reported and, when compared to the cost of other methods of treatment previously published in the medical literature, the therapy appears to be cost-prohibitive. However, definitive statements cannot be made regarding cost- effectiveness until clinical efficacy is demonstrated through a sufficiently powered, well-designed, RCTs.</td>
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<tr>
<td></td>
<td>- Until then, the therapy should remain experimental and coverage is restricted to intractable HG that is unresponsive to more-conventional treatment options.</td>
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</table>
### Key points:
- Between January and December of 1997, 646 women with HG received continuous s.c. metoclopramide on an outpatient basis.
- A total of 413 patients (63.9%) had complete resolution of symptoms.
- Seventy-five percent of patients had received one or more antiemetic medications before initiation of s.c. metoclopramide.
- A total of 192 patients (30.5%) reported at least one side effect related to treatment.
- The majority of reported side effects was considered mild and did not require discontinuation of s.c. metoclopramide.

### Key points:
- Retrospective, matched control study comparing treatment at home (50 women) or in hospital (47 patients). Matched for gravidity, gestational age, and weight loss from pre-pregnancy weight.
- Similar mean percent of weight loss at initiation of therapy (home 4.6% +/- 5.7% vs. hospital 4.5% +/- 6.1%, not significant).
- Similar mean weight change during therapy (home +1.0 +/- 4.3 pounds vs. hospital +1.2 +/-8.6 pounds, not significant).
- At discontinuation of therapy 90% of the home patients no longer required any supportive therapy; 10% (n =5) required hospitalization because of relapse.
- The cost of therapy was significantly lower for patients in the home group ($708 +/- $533 vs. $2701 +/- $1717, p < 0.001).

### Glossary

**Antiemetic** — A drug used to treat nausea and vomiting.

**Dehydration** — A condition that occurs when the loss of body fluids, mostly water, exceeds the amount taken in.

**Emetogenic** — Having the capacity to induce emesis (vomiting), a common property of anticancer agents, narcotics and morphine.

**Hyperemesis gravidarum (HG)** — Severe nausea and vomiting during pregnancy not related to other causes that can lead to loss of weight (usually ≥ 5% of pre-pregnancy weight) and body fluids; HG is further subdivided into mild and severe, with severe being associated with metabolic disturbances, such as carbohydrate depletion, dehydration, or electrolyte imbalance.

**Infusion pump** — A medical device that delivers fluids, such as nutrient, and medications, into a person’s a body in controlled amounts.

**Ketonuria** — A condition in which abnormally high amounts of ketones and ketone bodies are present in the urine.

**Ketosis** — A metabolic state that produces ketones, which are byproducts of burning fat for fuel when the diet does not provide sufficient carbohydrate to replenish glycogen stores. Excessive ketone levels can dull the appetite and cause nausea. Ketones that are not used for fuel are excreted the kidneys and the urine.
Microinfusion pump — Devices used to administer medications at low infusion rates and for chemotherapy and analgesia. Newer, compact, minimally invasive versions incorporate relatively short, 5-mm-long hypodermic microneedles coupled with a micropump for continuous, subcutaneous infusion.

Ondansetron (Zofran) — A selective 5-hydroxytryptamine (3) (5-HT (3)) receptor antagonist originally introduced as an antiemetic for cancer treatment-induced and anesthesia-related nausea and vomiting. Its use under these circumstances is both prophylactic and therapeutic.

Parenteral nutrition — Intravenous feeding.

Subcutaneous (s.c.) — Under the skin.

Wernicke encephalopathy — A serious neurologic disorder caused by thiamine (vitamin B-1) deficiency.

References

Professional society guidelines/others:


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on August 16, 2016 using terms hyperemesis gravidarum | Open Studies. Six studies found. Two relevant.


**CMS National Coverage Determination (NCDs):**

The NCD for infusion pumps at section 280.14 sets forth specific coverage criteria under sections A-D. Under section B.1.f other uses of external infusion pumps are covered if the contractor’s medical staff verifies the appropriateness of the therapy and the prescribed pump for the individual beneficiary.

**Local Coverage Determinations (LCDs):**


**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>99601</td>
<td>Home infusion/specialty drug administration, per visit (up to 2 hours) each additional hour.</td>
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<tr>
<td>99602</td>
<td>Each additional hour.</td>
<td>List separately in addition to code for primary procedure</td>
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<tr>
<td>96360</td>
<td>Intravenous infusion, hydration; initial, 31 minutes to 1 hour. (Do not report 96360 if performed as a concurrent infusion service.)</td>
<td>(Do not report intravenous infusion for hydration of 30 minutes or less.)</td>
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<tr>
<td>96361</td>
<td>Each additional hour. (List separately in addition to code for primary procedure.) (Use 96361 in conjunction with 96360.) Report 96361 to identify hydration if provided as a secondary or subsequent service after a different initial service (96360, 96365, 96374, 96409, 96413) is administered they the same IV access</td>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>O21.0</td>
<td>Mild hyperemesis gravidarum</td>
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<tr>
<td>O21.1</td>
<td>Hyperemesis gravidarum with metabolic disturbance</td>
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<td>O21.2</td>
<td>Late vomiting of pregnancy</td>
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<tr>
<td>O21.8</td>
<td>Other vomiting complicating pregnancy</td>
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<tr>
<td>O21.9</td>
<td>Vomiting of pregnancy, unspecified</td>
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<tr>
<th>HCPCS Level II</th>
<th>Description</th>
<th>Comment</th>
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<tr>
<td>J2405</td>
<td>Injection, Injection,(Zofran) ondansetron hydrochloride, per 1 mg.</td>
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<tr>
<td>J2765</td>
<td>Injection, Reglan (metoclopramide HCl), up to 10 mg.</td>
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<td>Code</td>
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<tr>
<td>E0779</td>
<td>Ambulatory infusion pump, mechanical, reusable, for infusion 8 hours or greater.</td>
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<tr>
<td>E0780</td>
<td>Ambulatory infusion pump, mechanical, reusable, for infusion less than 8 hours.</td>
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<tr>
<td>E0781</td>
<td>Ambulatory infusion pump, single or multiple channels, electric or battery operated, with administrative equipment, worn by patient.</td>
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<tr>
<td>S9351</td>
<td>Home infusion therapy, continuous or intermittent antiemetic infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem.</td>
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