HYPEREMESIS GRAVIDARUM (HG) AND WERNICKE'S ENCEPHALOPATHY

1 MOM is 2 Many

amplify, educate, advocate

WHAT IS WE

Wernicke's encephalopathy (WE) is a potentially life-threatening neurological condition primarily caused by severe thiamin (vitamin B1) deficiency (TD). WE is characterized by confusion, change in level of consciousness, aphasia, vision or oculomotor changes, ataxia, dysarthria, and hyperreflexia. Fetal loss rates and maternal morbidity are high without early and adequate intervention (MacGibbon, 2015; Vasan, 2020).

HG AND WE

Hyperemesis Gravidarum (HG) is a potentially life-threatening pregnancy disease that may cause weight loss, malnutrition, dehydration, and debility due to severe nausea and/or vomiting and may cause long-term health issues for mother and baby(ies).

» Due to malnutrition, vomiting and resulting gastrointestinal damage, a 45% increase in B1 requirement in pregnancy (Oudman, 2019), and medications, HG patients are at very high risk for WE, especially if prolonged or severe symptoms.

» **Supplementation** of thiamin (B1) in all HG patients regardless of body mass index should be implemented before/at the onset of nausea and vomiting, and women should be screened for WE at every visit.
  - Women with HG rarely tolerate prenatal vitamins throughout pregnancy and not all prenatal vitamins have B1; none have adequate doses (≥ 50 mg minimum) for patients with HG.
  - Obese patients and those with poor nutrition may have preexisting B1 deficiency and may develop WE rapidly.
  - Due to intermittent IV/PO vitamins, and extreme irregularity in diet often high in carbohydrates, symptoms of TD may persist at varying levels chronically without B1 supplementation and a consistent, healthy diet for 3+ months.

» MRI can be diagnostic but findings may be lacking in early WE. Location of lesions in HG patients may differ than alcoholics. (Ashraf, 2016; Galvin et al., 2010).

➡ Because thiamin deficiency mimics and exacerbates HG, all women with HG should be prescribed oral thiamin, as well as IV thiamin when symptomatic and proactively with every bag of IV fluid.

INITIAL SIGNS/SYMPTOMS

The classic triad of signs includes oculomotor signs, cerebellar dysfunction and confusion but these are not always present, esp in those with HG where vision changes, apathy, muscle weakness, neuropathy and weight loss are common (Lonsdale, 2017; Nhari, 2018; Oudman, 2019).

» Ocular signs (double vision, palsies)
» Altered mental status (dizziness, drowsiness, apathy, confusion)
» Pain sensitivity
» Cerebellar dysfunction (ataxia)
» Anorexia or inadequate diet
» Weight loss
» Pain (head, abdomen, muscles)
» Nausea/vomiting
» Peripheral neuropathy
» Muscle weakness
» Mood changes (depression, irritability)
» Cognitive changes

RISK FACTORS FOR WE

(Galvin, 2010; Oudman et al., 2019; Sechi and Serra, 2007)

- Malnutrition/high carbohydrate diet
- Gastrointestinal symptoms (vomiting, diarrhea)
- Medications (antibiotics, antiacids, diuretics, IV dextrose/parenteral nutrition)
- Malabsorption syndromes
- Refeeding syndrome
- Thyroid disease
- Poor intake/weight loss
- Infection
- Peptic ulcers
- Atrophy/reduced muscle mass
- Persistent/prolonged NVP
- Multiple gestation with NVP
- Anemia
- Electrolyte/nutrient deficiencies
- History of bariatric surgery, anorexia nervosa, inflammatory bowel disease

IMPACT/INCIDENCE

The incidence of WE due to HG is unknown but reports have increased with over 177 cases published (Oudman et al., 2019).

- HG is a major risk factor for WE with up to 86.2% of multigravida with WE having HG in a previous pregnancy. (Di Gangi, 2012)
- Diagnosis and management of WE has advanced (Sechi, 2007; Sutaamnartpong, 2013), but prevention is rare.
- Half of HG patients lack Wernicke's classic triad (confusion, oculomotor abnormalities, and ataxia), especially with gradual or episodic symptoms (Di Gangi, 2012; Garla, 2017; Nhari, 2018).
- Complete remission of WE occurs in only <32% of cases, with recovery requiring months to years and permanent impairments are common (Di Gangi, 2012; Oudman, 2019; Scalzo, 2015).
- Korsakoff Syndrome develops in those with inadequate or delayed B1 replenishment, and results in permanent amnesia, memory loss, impairments in acquiring new information, behavioral dysfunction, apathy, affective disorders, and changes in emotions and social cognition (Pacei, 2020; Thomson, 2002).
- About 20% of those with WE do not survive, and 68% develop severe cognitive problems. Neurological damage or death may occur in the children as well (Oudman et al., 2019).

RED FLAGS FOR ADVANCED WE

Any of these signs necessitate immediate and aggressive IV thiamin administration with B complex and methodical correction of electrolytes to avoid death or serious long-term injury (Sechi and Serra, 2007).

- Oculomotor palsy
- Dysarthria
- Confabulation
- Hallucinations
- Akinetic mutism
- Hearing loss
- Spastic paresis
- Amnesia
- Aphasia
- Hypo/hyperthermia
- Epileptic seizures
- Mental status changes (memory loss, cognitive impairment)
- Gait abnormalities
- Respiratory difficulty/failure
- Aphonia
- Myoclonus with nuchal rigidity
- Absent/hyper-reflexes
- Comatose state
- Cardiac Symptoms
  - Pulmonary and peripheral edema
  - Heart failure
  - Orthopnea
  - Cardiomyopathy
  - Hypotension
  - Tachycardia
  - Arrythmias

RECOMMENDATIONS/ TREATMENT

Royal College of Physicians (Thomson, 2002) & The European Federation of Neurological Societies (Galvin et al., 2010) recommendations for malnourished, non-alcoholic patients:

- **WE Prevention:** B1 250-500 mg IV daily for 3-5 Days for malnourished patients.
- **WE Treatment:** B1 250-500 mg IV 3 times per day for 3 days, then 250 mg daily until clinical improvement ceases.
- Parenteral B vitamins should be given in 100 ml normal saline over 30 min.
- IV dextrose should include 200 mg B1.
- Per 250 mg B1: 4 mg B2, 50 mg B6, 160 mg B3, 500 mg vit C, 60–180 mEq K, 10–40 mmoL/L Phos and 10–30 mEq Mg.

HER Recommendations

In the absence of a universal standard for prevention and treatment of WE during HG, the HER Foundation proposes the following based on the scientific literature and medical society guidelines. Given most recommendations are for non-pregnant patients without HG, higher doses for a longer time may be needed.

- **Prevention during pregnancy:** Patients with a history of NVP/HG should take a high-quality prenatal multivitamin and a B complex vitamin prior to conception, and as tolerated during pregnancy. Add B1 50-100 mg orally when NVP starts.
- **Prevention of WE during NVP/HG:** Give B1 100 mg 1-3 times daily PO/IV.
- Order a dietary consult to increase thiamin intake and screen for excessive carbohydrate intake.
- **Screen** patients at every visit for signs of B1 deficiency and WE.
- **Infuse** B1 over 30 minutes or longer to increase absorption.
- **Treatment of WE+HG:** B1 500 mg IV 3 times per day for 1 week or until symptoms subside or no further benefit is seen. (** MUST GIVE THIAMIN IV **)
- Methodical replacement of electrolytes, especially Mg & Phos, and vitamins (B2, B3, B6, B9, C, D, K) is important during treatment and recovery from HG and WE.
- Before or simultaneous to administration of IV dextrose and enteral or parenteral nutrition, give B1 200 mg IV.
- IV B1 supplementation should continue daily in symptomatic patients and those unable to consistently tolerate daily oral dosing.
- After IV B1 replenishment, B1 100 mg orally 3 times per day is needed for at least 3 months, longer if breastfeeding, inadequate nutrition, and/or ongoing HG.
- See HER Foundation treatment algorithm and protocol: hyperemesis.org/tools.

CLINICAL KEYS

- MVI has only 6 mg B1.
- IV dextrose can cause life-threatening complications in thiamin deficient patients.
- Always give 200 mg B1 IV with dextrose and 100 mg TID IV/PO with a high carbohydrate diet and/or severe HG.
- Methodically correct electrolytes.
- B1 serum testing is unreliable.
- Avoid IM B1 (atrophy, pain, hematoma).
- High doses of B1 TID increase absorption.
- Absorption less if vomiting/malnutrition.
- Replete for 3+ months to fully recover.

Health professionals play a crucial role in the prevention, recognition, and early treatment of WE in patients with HG so they and their children have a chance of survival and a healthy future.

Diagnosis can be challenging until severe WE and/or MRI positive. Assume WE and treat accordingly if there is improvement in symptoms with daily high dose intravenous B1. See HER WE algorithm.

THIAMIN DEFICIENCY COMPLICATIONS

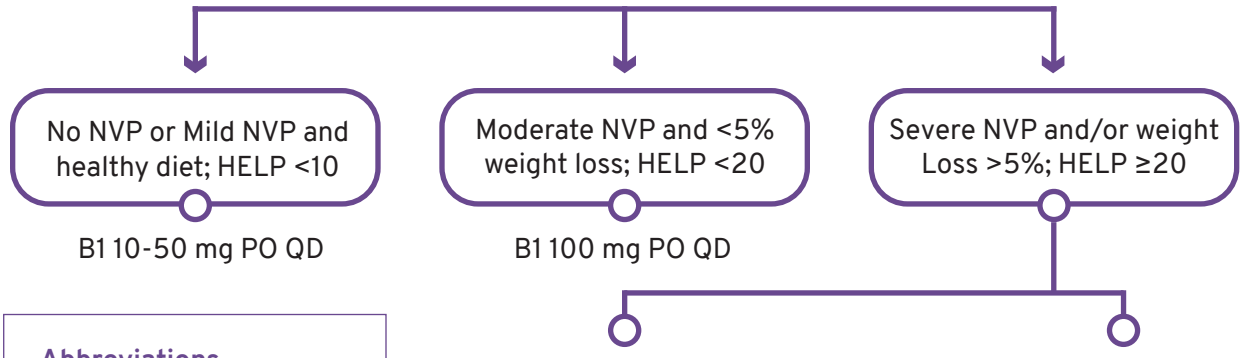
Maternal Complications:
- » Pre-eclampsia
- » Fetal loss
- » Cardiac failure
- » Cerebral edema
- » Korsakoff Syndrome: permanent cognitive impairment, memory loss
- » Death

Fetal/Child Complications:
- » Fetal demise
- » Impaired brain development
- » Neuromotor immaturity
- » Cranial malformations
- » Low birth weight or IUGR
- » Sudden Infant Death Syndrome
- » Behavioral changes
- » Autism Spectrum Disorder
- » Delayed language development
- » Decreased visual alertness

NOTE: Newborns breastfed from deficient mothers may develop dyspnea and cyanosis; diarrhea, vomiting, and aphonia may follow. Moderate deficiency can affect intellectual performance and well-being, despite a lack of apparent clinical symptoms. MAYO

Adequate Intake = Ideal macro and micronutrient levels + adequate hydration.

THIAMIN (B1) DEFICIENCY PREVENTION & TREATMENT



Asymptomatic:
- » B1 100-500 mg IV/PO 1-3 times per day until adequate intake or until 3+ months postpartum
- » MVI + B complex (B2, B3, B6, B9) with IV hydration

Symptomatic:
- » **Daily IV:** MVI + Vit C + B complex
- » **TID:** B1 250-500 mg IV TID for 3+ days
- » **PRN:** Electrolytes (esp Mg, Phos!)

Abbreviations
B1 = Thiamin
BID = Twice a day
TID = Three times a day
QD = Every day
PO = Per oral
PRN = As needed
Vit = Vitamin
IV = Intravenous
IM = Intramuscular injection
LFT = Liver Function Tests
EKG = Electrocardiogram
NVP = Nausea & vomiting in pregnancy
MVI = Multivitamin Infusion
TD = Thiamin Deficiency
WE = Wernicke's encephalopathy
HELP = HyperEmesis Level Prediction Score (hyperemesis.org/tools)

WERNICKE'S ENCEPHALOPATHY

STEP 01

Day 1: B1 500 mg IV TID with multivitamin infusion (MVI) and B complex IV.

» Immediate bolus of 100 mg B1 IV push
» Dilute B1 in 100 mL NS and infuse over 30-60 minutes
» Baseline MRI (T2, FLAIR, DWI)
» Methodically correct electrolytes
» Administer cofactors IV: Niacin/B3, B6
» Consider parenteral nutrition and/or additional vitamins (C, D, K)
» Baseline thiamin whole blood testing (TDP) (Normal > 70 nmol/L)
» Reduce risk factors
» Neurology consult
» Assess cardiac, renal and hepatic function

STEP 02

Days 2-7+: B1 500 mg IV TID with MVI + B complex IV (including B3, B6) + electrolytes until asymptomatic.

» Diagnostics: electrolytes, LFT, EKG, MRI
» Monitor: refeeding syndrome (if initiating nutrition)

STEP 03

Continue B1 100 mg IV TID until no remaining symptoms of B1 deficiency and able to tolerate both B1 100 mg PO TID and >50% of adequate oral intake consistently.

» Continue B1 100 mg PO TID for 4 weeks or longer (until HG resolves) and patient is able to consistently achieve healthy weight gain for gestational age.
• Continue B1 100 mg PO BID or TID for 3 months or more. If 3rd trimester HG symptoms, continue B1 postpartum while breastfeeding.

The longer the delay in treatment, the poorer the outcome.

Oral Thiamin Derivatives:
(Lonsdale 2017 p203-204)

Thiamin hydrochloride is readily available but not as absorbable as derivatives such as TTFD which provides a higher blood concentration of B1.

1 Thiamine tetrahydrofurfuryl disulfide (TTFD), a synthetic derivative, is preferred because it penetrates into cells without a thiamin transporter and crosses the blood-brain barrier. (Fursultiamine, Lipothiamine)
2. S-Benzoylthiamine monophosphate (Benfotiamine) likely crosses the blood-brain barrier. It is easier to find/buy.

THIAMIN DEFICIENCY (TD) SYMPTOMS

- Depression/Irritability
- Weakness
- Headache
- Dizziness
- Insomnia
- Muscle pain/atrophy
- Weight loss
- Resting tachycardia
- Decreased reflexes
- Anorexia
- Nausea/vomiting
- Cognitive changes
- Pain sensitivity
- Constipation/diarrhea
- Abdominal pain
- Sleepiness
- Peripheral neuropathy
- Enlarged heart

WERNICKE'S ENCEPHALOPATHY SYMPTOMS

- Refractory/severe NVP
- Symptoms of TD
- **Mental status changes: drowsiness, apathy, confusion, and cognitive impairment**
- Dysarthria
- Severe weight loss
- Confabulation
- Akinetic mutism
- Aphasia
- Cardiac rate or rhythm changes or failure
- Seizures
- **Vision/eye movement changes**
- **Abnormal gait or uncoordinated movement**
- Spastic paresis
- Myoclonus with nuchal rigidity
- Abnormal diagnostics: liver function tests, CSF protein, MRI, EEG.

SOURCES

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