THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Hyperemesis Gravidarum (HG)

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Objectives

1. Introduce both definitions/diagnostic criteria for HG
2. Discuss both initial and more advanced methods of treatment
3. Discuss treatment alternatives for more resistant causes of HG
4. Introduce novel new scoring system and standardized care plan for HG

Hyperemesis Gravidarum(HG)

- Most severe end of N/V of pregnancy spectrum
- Affects up to 3% of pregnancies
- Most common cause for hospitalization of pregnancy overall

Complications of HG

- Dehydration
- Esophageal trauma
- Electrolyte abnormalities
- Cardia arrhythmias
- Rhabdomyolysis
- Nutritional deficiencies
- Wernicke's Encephalopathy

Complications of HG (continued)

- Negative psychosocial effects
- Depression / anxiety
- PTSD
- Pregnancy termination of otherwise desired pregnancies
- Adverse pregnancy outcome
  - SGA
  - Preeclampsia
  - Placental abruption (excessive retching)

Risk Factors for Development of HG

- Personal Hx (history) of HG
- Family Hx (mother or sisters)
- Young maternal age (<18yo)
- Female fetus
- Multiple gestation
- Personal Hx motion sickness

Co-morbid medical conditions

- Parathyroid dysfunction
- Thyroid disorder
- T1DM (Type 1 diabetes)
- Helicobacter pylori infection (Hx of peptic ulcer diseases)
- Hyperestrogenism (PCOS)
- Migraine headache with nausea
- Assisted Reproductive Technology (ART)
- BMI
  - Underweight
  - Overweight

Genetic Associations

- Recent Genome-Wide association studies identified 2 genes
  - GDF15 (Growth differentiation factor)
  - IGFBP7 (Insulin-like growth factor-binding protein 7)
- Both play important roles with:
  1. Placentation
  2. Appetite
  3. Cachexia
- Family history increases risk….suggests genetic component

Diagnosis of HG

- Intractable N/V with symptoms as early as 6 weeks
- Weight loss (5% pre-pregnancy weight)
- **Clinical signs of dehydration:**
  - Ketonuria
  - Maternal tachycardia
  - Orthostatic hypotension
- **Lab Abnormalities**:
  1. Electrolytes
  2. Thyroid tests
  3. LFTs (liver function test)

Indications of Hospitalization

- No standardized criteria
- Roughly 5-8% weight loss of pregnancy weight
- Unresponsive to oral antiemetics
  - Failed outpatient management
- Unable to tolerate oral intake
- Marked lab abnormalities
- Co-morbid conditions needing attention

Inpatient Management Goals

- Stabilization with rehydration and electrolyte replacement
- Resume oral intake
- Tolerate oral antiemetics
- Maintain nutrition

Inpatient Fluid Management

Aggressive rehydration

- 2 L IV crystalloid
- Fluids
  - D5NS vs NS
    - No difference in time to oral intake
  - LR as alternative

Maintenance

- IV fluids tolerating oral intake
  - 125-150 cc/hr

Wernicke's Encephalopathy

Acute Neuropsychiatric Disorder

Clinical triad:

- Ophthalmoplegia
- Ataxia
- Confusion

Other symptoms:

- Double vision
- Nystagmus
- Delirium/Memory loss

Treatment:

- Thiamine (Vitamin B1) should be added
- 200-500 mg IV
- Multivitamin (banana bag)

Pharmacotherapeutic Management (Hyperemesis Gravidarum - HG)

If inpatient for HG:

- Patients typically cannot tolerate oral medications

Alternative routes:

- Intravenous (V)
- Intermuscular (M)
- Rectal
- Transdermal

Continue until oral intake can be restored

First Line Considerations (IV Meds)

Acid-reducing Agents	Antihistamines	Dopamine Antagonists

• H2 Blockers
  • Pepcid (famotidine)
• PPI's (proton pump inhibitors)
  • Protonix (pantoprazole)
  • Prilosec (omeprazole)
	• Benadryl (Diphenhydramine)
	• Dramamine (Dimenhydrinate)
		• Reglan (metoclopramide)
		• Phenergan (promethazine)
		• Compazine (prochlorperazine)

Serotonin Antagonists

- **Zofran** (Ondansetron)

Alternative Therapies for Refractory Cases

Remeron (Mirtazapine)

- Antidepressant/ anxiolytic
- Antiemetic
- Appetite stimulant

Zyprexa (Olanzapine)

- Antipsychotic
- Off-label use:
  - Chemotherapy-induced nausea
  - Post-surgical nausea/vomiting

Continued Alternatives for Refractory Cases

Corticosteroids

- Commonly used for chemotherapy-induced nausea
- Work by altering brainstem chemoreceptors
- Several RCTs show positive results

Concerns

- Older animal studies
  - Increased risk of orofacial clefts
- Some human studies
  - Possible association with first trimester cleft palate

Continued Alternatives for Refractory Cases

Key Points:

- Limited recent evidence
- Use shared decision-making regarding fetal effects
- Avoid at 6-9 weeks if possible
- Reserve for refractory cases after 10 weeks

Gabapentin

Originally for:

- Seizures
- Neuropathic pain
- Restless leg syndrome

Also helps:

- Chemotherapy-induced nausea
- Postoperative pain
- Mechanism unclear
  - Early studies suggest it may be more effective in reducing nausea/vomiting in resistant cases than standard care in patients admitted for HG

Nutritional Support (Inpatient Management)

Recommendations:

Consult dietitian or nutrition services

- Indications
  - When IV therapy fails to allow oral intake
  - Weight loss reaches 8-10%

Enteral Nutrition

- Nasogastric (NG) tube
- Naso jejunal or nasoduodenal tube (Dobhoff tube)
- Percutaneous tubes

Evidence regarding their overall success in fetal benefits:

- Mixed results on improvement in birthweight and outcomes

Parenteral Nutrition (PN)

Only if enteral feeding fails

Types:

- **Peripheral (PICC line)**
  - Limited by osmolarity
  - Requires larger volumes
  - Can be used 2-12 weeks
- **Central catheters**
  - Provide full nutritional needs
  - Require smaller volume

Parenteral Nutrition (PN)

Risk

~25% complication rate (catheter-related)

- Can lead to ICU admission
- Central line sepsis and septic valve vegetations leading to valvular damage
  - Use only as a last resort

Pitfalls in HG Management

- Frequent breakdowns in initial management
- Symptoms often underestimated by providers-patient mistrust
- No universal management algorithm
- Fragmented care / “doctor shopping”
- High relapse and readmission rates

HER Foundation (2019)

Hyperemesis Gravidarum Research

- Developed standardized approach for HG
- Introduced **HELP Score (Hyperemesis Level Prediction)**
  - Quantifies symptoms over time
  - Monitors response to treatment
- Scoring:
  - 20 Mild (morning sickness or mild HG)
  - 20-32 Moderate
  - 33-60 Severe (requires aggressive care)

HELP (HyperEmesis Level Prediction) SCORE

Name: _____ Date: _____ Gestational Age: _____ SCORE: _____

TODAY'S Weight: _____ LAST WEEK'S Weight: _____ Change: _____% PREVIOUS SCORE: _____

Meds: ☐ Ondansetron ☐ Granisetron ☐ Diclegis ☐ Promethazine ☐ Metoclopramide ☐_____

Mark ONE box in EACH ROW that describes symptoms over the last 24 hours unless specified otherwise.

My nausea level most of the time:	0	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
I average __ vomiting episodes/day:	0	1-2	3-5	6-8	9-12	13 or more
I retch/dry heave __ episodes daily:	0	1-2	3-5	6-8	9-12	13 or more
I am urinating/voiding:	Same	More often due to IV fluids; or light color	Slightly less often, and normal color	Once every 8 hours; or slightly dark yellow	Less than every 8 hours or darker	Rarely; dark or bloody; or foul smell
Nausea/vomiting severity 1 hour after meds OR after food/drink if no meds:	0 or No Meds	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
Average number of hours I'm unable to work adequately at my job and/or at home due to being sick has been:	0	1-2 (hours are slightly less)	3-4 (can work part time)	5-7 (can only do a little work)	8-10 (can't care for family)	11+ (can't care for myself)
I have been coping with the nausea, vomiting and retching:	Nor-mal	Tired but mood is ok	Slightly less than normal	It's tolerable but difficult	Struggling: moody, emotional	Poorly: irritable depressed

Total amount I have been able to eat/ drink AND keep it down: Medium water bottle/large cup = 2 cups/500mL.	Same; no weight loss	Total of about 3 meals & 6+ cups fluid	Total of about 2 meals & some fluid	1 meal & few cups fluid; or only fluid or only food	Very little, <1 meal/minimal fluids; or frequent IV	Nothing goes or stays down, or daily **IV/TPN/NG**
My anti-nausea/vomiting meds stay down or are tolerated:	No meds	Always	Nearly always	Sometimes	Rarely	Never/**IV/SQ** (SubQ pump)
My symptoms compared to last week:	Great	Better	About Same	Worse	Much Worse	So Much Worse!!!
Weight loss over last 7 days: ___%	0%	1%	2%	3%	4%	5%
Number of Rx's for nausea/vomiting*	0	1	2	3	4	5+
	0 pts	**1 pt/answer**	**2 pts/answer**	**3 pts/answer**	**4 pts/answer**	**5 pts/answer**
TOTAL each column = (#answers in column) x (# points for each answer)	0	_____	_____	_____	_____	_____
TOTAL for ALL columns: _____	**None/Mild ≤ 19**		**Moderate 20-32**		**Severe 33-60**	

Weight Loss % = (Amount lost + Pre-pregnancy weight) x 100
(Weight loss calculation optional for home use)
* Number of Rx's = Number of Rx medications for HG (not doses)

HER Foundation

info@hyperemesis.org
www.hyperemesis.org
www.HelpHER.org

Support:
help@hyperemesis.org

HER Foundation
10117 SE Sunnyside Road F8
Clackamas, OR 97015 USA

Reprints:
www.hyperemesis.org/tools

Validation Study (2021)
Compare HELP Score to PUQE Score

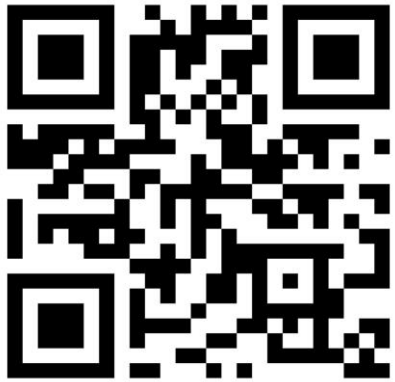
Findings

- Help score performs better in:
  - Assessing quality of life
  - Identifying severe cases needing intervention
- PUQE Limitations
  - Does not assess quality of life
  - Less effective in severe HG

Use of HER Algorithm & Help Score (Regional One)

- Used in clinic, triage and ER
- Inpatients managed by attending physicians using standardized plan
- Discharged patients followed closely in clinic
- Knowledge of HELP Score is in the EMR
- Can tailor treatment responses along algorithm

HER HG Treatment Algorithm



NAUSEA/VOMITING OF PREGNANCY ALGORITHM

(HELP Score <20)

1. B6/Pyridoxine 10–25 mg PO with or without Doxylamine 10-25 mg q 6-8 h (Either separately or as delayed release combination)
2. Thiamin/Benfotiamine 100 mg PO 1-3 times per day (250 mg daily PO minimum after 20 weeks)
3. Continue prenatal vitamin if tolerated or change to single vitamins (B1, B9, D with K, Ca, Mg).
4. Add gastric/esophageal protection at bedtime with onset of vomiting or poor intake. (See shaded box below.)

DEHYDRATION? NO / YES

(HELP Score <32)

Add up to 1 from each class:

1. Antihistamine (discontinue doxylamine)
   - *Dimenhydrinate* 25-50 mg q 4–6 h PO or PR (limit to 200 mg per day if taking doxylamine)
   - *Diphenhydramine* 25–50 mg PO q 4–6 h
   - *Meclizine* or *Cyclizine* 25 mg PO q 6-8 h
2. Dopamine Antagonist (Use only 1 at a time or alternate.)
   - *Metoclopramide* 2.5-10 mg q 6-8 h PO or ODT
   - *Promethazine* 25 mg q 4-6 h PO or PR (avoid IM/IV)
   - *Prochlorperazine* 5-10 mg q 6-8 h PO or 25 mg PR q 12 h
   - *Domperidone* 10-20 mg PO q 6-8 h

Add DAILY bowel care + serotonin antagonists (5-HT3) (prescribe on a strict schedule, NOT prn):

1. Bowel Care: Daily stool softener, magnesium (citrate, oxide), polyethylene glycol + stimulant laxative or enema up to 3x per week prn
2. *Ondansetron* 4-8 mg q 3-6 h PO or ODT, or ODT given vaginally (max 32 mg per day) ***OR***
3. *Granisetron* 1 mg q 12 h PO or 3 mg TD patch (give 1 mg oral/IV dose on days 1 and 2 until steady state)
   NOTE: Monitor EKG if risk of QT prolongation.

Consider NUTRITION (see box on right) + FLUIDS + 1+ of the following:

1. *Mirtazapine* 15 mg q 8 h PO or ODT (d/c other 5HT-3)
2. *Methylprednisolone* (if 9+ weeks) 16 mg q 8 h PO or IV for 3 days. Taper over 2 weeks. Maintain on lowest effective dose if needed. Avoid administration exceeding 6 weeks.
3. *Chlorpromazine* 25–50 mg IV or 10–25 mg PO q 4-6 h
4. Olanzapine 5 mg PO q 8-12 h
5. Gabapentin 300-800 mg PO q 8 h

GERD or gastric/esophageal protection options:

1. Calcium antacid (avoid Aluminum, Bismuth or Bicarbonate)
2. H2 antagonist BID: *famotidine* 20-40 mg PO/IV
3. Proton Pump Inhibitor (PPI) q 24 h at bedtime
   - *Esomeprazole or pantoprazole* 40 mg PO or IV q HS
   - *Lansoprazole* 15-30 mg PO or ODT q HS

(HELP Score ≥32)

IV fluids and dilute vitamins; infuse slowly:

1. NS or LR + MVI + B1 + B6 + B Complex (w/B2, B3, B9)
   - Add prn: KCl, Na, vit D, Zn, Se, Fe, Mg & Ca
   - Always give 200 mg B1 IV w/dextrose (prevent WE).
   - Slowly replace low/marginal electrolytes (prevent ODS).
   - Consider restricted PO intake for 24-72 h (gut rest).
   - Consider midline or central line for frequent IVs.
2. **Always include Thiamin/B1 100-500 mg IV q 8 h daily.**
3. Choose MVI containing vitamin K or add vitamin K prn.

If oral meds ineffective or not tolerated, change to *1 OF THE FOLLOWING with daily Bowel Care (see box on left):*

1. *Ondansetron*:
   - IV: 4-8 mg over 15 minutes q 3-6 h (up to 32 mg) or continuous infusion
   - Subcutaneous (SubQ) continuous infusion: 8 mg starting dose, then 12-40 mg/day; wean slowly to PO if stable
2. *Granisetron* 1mg q 12 h IV or continuous infusion or TD

If symptoms continue, add one or both of these meds:

1. *Dimenhydrinate* or *Diphenhydramine* 25-50 mg q 4–6 h IV
2. *Metoclopramide*:
   - IV: 2.5–10 mg q 8 h SLOW infusion
   - SubQ continuous infusion: 2.5-10 mg loading dose, then up to 60 mg/day

*** Wean IV/SubQ to PO very slowly when stable, then monitor for at least 24 hours before discharge to home.**
*** Consider enoxaparin for DVT prophylaxis**

NUTRITION - If weight loss ≥7% and/or persistent HG:

1. Consult with GI & Nutrition & IV access team.
2. Prevent Refeeding Syndrome: Very slowly restart nutrition & closely monitor weight, cardiac rhythm and electrolytes (especially phosphate) for 1+ week.
3. Consider EN/PN until gaining weight on PO intake.
   - *Enteral nutrition*: Gradually increase infusion (after resting GI tract) with or without additional parenteral/enteral fluids. (NJ or G/J-tube preferred). Insert SMALL bore nasal tube under sedation. Often poorly tolerated.
   - *Parenteral nutrition (partial peripheral or total central)*

IMPORTANT NOTES:

1. If symptoms persist, follow arrows to next level of care and consider non-oral forms of medications such as compounded, transdermal, IV, or SubQ. ALWAYS wean medications very slowly.
2. After IV therapy, use non-oral options or move slowly to oral medications as tolerated.
3. Most medications can cause QT prolongation, consider EKG or cardiac monitoring for high risk patients, high doses of medications, multiple medications, or electrolyte & vit B1 abnormalities.
4. Intramuscular injections (IM) not recommended due to muscle atrophy and pain sensitivity.
5. Dehydration and nutrient (e.g. electrolytes, B1) deficiencies decrease treatment response.
6. Start prophylactic anticoagulation for DVT if prolonged immobility/hospitalization over 72 hours.
7. Weaning too early or rapidly may result in worsening or refractory symptoms.
8. See less common medications on the HER Foundation website: www.hyperemesis.org/meds.
9. HELP = HyperEmesis Level Prediction Score. Learn more: www.hyperemesis.org/tools.

HER Foundation

www.hyperemesis.org/tools
Email: info@hyperemesis.org

Hyperemesis Gravidarum (HG) is diagnosed when a patient has nausea and vomiting that requires medication and/or intravenous therapy due to severe nausea and/or vomiting with poor intake, possible weight loss, and debility. Failure to adequately treat may result in refractory and prolonged symptoms, along with serious complications for both mother and child. HG is caused in part to genes (e.g. *GDF15*) that reduce appetite, alter taste, and cause nausea, vomiting and muscle wasting. Additionally, infections, stress, and nutrient deficiencies (e.g. B1, Mg, and K+) worsen symptoms and may increase GDF15 hormone levels. (hyperemesis.org/research/#cause)

ANTIEMETIC ESSENTIALS

1st Step: Δ dose/frequency
2nd Step: Δ route (SubQ, TD, rectal, IV, compounded)
3rd Step: Add/replace a medication

- Avoid abrupt Δ's in 1st trimester.
- Prevent/proactively treat side-effects.
- Give IV fluids SLOWLY and dilute irritating medications.
- Try continuous antiemetic infusions.
- **Cocktail:** Antihistamine + serontonin antagonist + acid reducer + promethazine OR metoclopramide + IV vitamins

Once stable for 2 weeks on IV or subcutaneous infusions, try transitioning to oral dosing, then if fails PO trial, return to IV/SubQ. Wait 2-4 weeks or until symptoms improve for 2 weeks before weaning again. Repeated failures to wean in later pregnancy suggest medications may be needed until delivery.

Kimber's RULE OF 2'S

Wean medications for HG:

Wean each medication in 2nd trimester or later | After 2 weeks with minimal symptoms | Over 2+ weeks

ADDITIONAL MEDICATION TIPS

- Serotonin Syndrome - avoid combining serotonin antagonists with SSRIs and SSNIs
- Headache - common with ondansetron; switch to another serotonin antagonist
- Ptyalism - use anticholinergic medication
- Anxiety/panic - common with metoclopramide (esp. IV push)
- EPS - commonly caused by phenothiazines and metoclopramide; switch medication/class at onset; limit duration

The Genes Have Spoken: not in her HEAD but in her GENES

PATIENT/FAMILY EDUCATION

- Symptom relief not 100%
- Most meds don't help nausea
- Multiple meds typical
- May need non-oral meds
- Dose changes common
- Dosing same in pregnancy
- Don't stop meds abruptly
- Meds possible until delivery

I's of IMMEDIATE INTERVENTION

- Inability to tolerate antiemetics
- Intake of ≤1.5 meal/day
- Inadequate UOP/ketonuria
- Increasing weight loss (>2 lbs (1 kg) per week)
- Inability to cope or function
- Increasing HELP Score (>20)

Δ = Change
GERD = gastroesophageal reflux disease
GI = gastrointestinal
IM = Intramuscular
IV = Intravenous
LR = Lactated Ringers
MFM = Maternal-Fetal Medicine
ODS = Osmotic Demyelination Syndrome - includes CPM = Central Pontine Myelinolysis
PMAD = Perinatal Mood/Anxiety Disorder
HELP = HyperEmesis Level Prediction Score
PO = Per oral
PTSD = Post Traumatic Stress Disorder
SubQ = Subcutaneous
h = hours
UOP = urine output
UTI = Urinary Tract Infection
WE = Wernicke's encephalopathy

WERNICKE'S ESSENTIALS **Screen each visit**

Causes: Thiamin/B1 and electrolyte deficiency/shifts
Risks: Infection, diuretic, malabsorption, atrophy, malnutrition
Signs: Change in vision or speech or gait or mental status, abdominal pain, headache, cardiac symptoms (tachy then brady), somnolence, dizziness, weakness, aphasia, tremor, irritability, spastic paresis, seizure, myalgia, myoclonus, anorexia, dysphagia, elevated transaminase, refractory HG
Diagnosis: MRI may be normal. Assume WE if B1 ↓ symptoms.
Prevention/Ongoing Recovery: Oral/IV thiamin 100-500 mg PO/IV 1-3x daily; continue until consistent, healthy diet for 3+ months. Take while breastfeeding for mother/baby.
Acute Care: Thiamin 500 mg IV TID until asymptomatic, 5+ days. (See WE & Thiamin Fact Sheets. hyperemesis.org/tools)

SUMMARY OF CLINICAL KEYS

1. Changing medications abruptly/frequently may cause severe/refractory symptoms. Combine different classes.
2. Increasing dose, increasing frequency, changing route and combining medications can improve treatment efficacy.
3. Scheduled dosing and non-oral medications are beneficial.
4. Lack of nutrition/hydration reduce medication response, worsen symptoms, and increase risks/complications.
5. Side-effects are better prevented than managed.
6. If a history of HG or severe symptoms, rapidly intervene and move to non-oral medications when orals not tolerated.
7. Wean each medication separately and slowly after 2+ weeks of minimal symptoms with adequate PO intake and hydration.
8. Medication and IV therapy may be needed until delivery.
9. Listen as patients can offer valuable insight into their care.
10. HG is traumatic so treat with compassion and refer to the HER Foundation for resources. hyperemesis.org/support

COMFORT MEASURES

- Private room (avoid triggers)
- Avoid IM injections (atrophy)
- Warm IV fluids/blankets
- Use anesthetic for IVs
- Offer preferred foods when feeling least ill

CONSULTS/ADJUNCTIVE CARE

Consults: GI, nutrition, home health, mental health, social work, perinatology/MFM, case management, physical therapy
Adjunctive care: hypnosis, acupuncture, homeopathy, osteopathic manipulation

SELECTED REFERENCES

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