Rescuing CINV, Moving beyond the Guidelines

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Oncology Clinical Pharmacist
Assistant Professor of Medicine
Nausea and Vomiting

- Retching
- Expulsion
- Hurl
- Puke
- Spew
- Emesis
- Upset Stomach
- Barf
- Spit Up
- Retching
- Honk
- Gag
- Vomito
- Sick
- Ow
- Technicolor
- Yawn
- Upchuck
- Heave
- Blow Chunks
- Spit Up
- Regurgitation
- Emesis
- Upset Stomach
- Hyperemesis
- Disgorgement
- OH
- Throw up

Worshipping the Porcelain Goddess
### CINV Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute N/V</strong></td>
<td>Occurs within 24 hours of antineoplastic administration</td>
</tr>
<tr>
<td><strong>Delayed N/V</strong></td>
<td>Onset occurs &gt; 24 hours after antineoplastic administration</td>
</tr>
<tr>
<td><strong>Anticipatory N/V</strong></td>
<td>Occurs prior to or at other times without agent being administered</td>
</tr>
<tr>
<td><strong>Breakthrough N/V</strong></td>
<td>Occurs despite prophylaxis and requires rescue</td>
</tr>
<tr>
<td><strong>Refractory N/V</strong></td>
<td>Occurs despite prophylaxis and rescue therapy</td>
</tr>
</tbody>
</table>

Conceptual Model of Acute & Delayed CINV

Pattern of Emesis Induced by Cisplatin Compared to Cyclophosphamide and Carboplatin

Intensity of emesis

Days

Cisplatin
Cyclophosphamide/Carboplatin

Martin M. *Oncology*. 1996;53 (suppl 1):26
• 91/111 (82%) in Groups III/IV w/emesis had it in the 1st 8 hrs

• Groups I/II had minimal emesis in the 1st 8 hrs

• Study of +/- granisetron, dexamethasone, +/- aprepitant

Hesketh PJ et al European Jnl of Cancer 2003;39:1074-80
• $5HT_3$ mediated emesis predominates in the $1^{st}$ 12 hours

• After 12 hours $Nk_1$ dependent mechanisms appear to dominate

• $Nk_1$ activity becomes clearly different at $\sim$16 hours post dose

Hesketh PJ et al European Jnl of Cancer 2003;39:1074-80
Risk Factors for Nausea and Vomiting

Therapy Related Factors
- Intrinsic emetogenicity of antineoplastic agent
- Dose, route, and administration rate of antineoplastic agent
- Multiple Chemotherapy cycles
- Concomitant Radiation

Patient Factors
- Poor control with prior therapy
- Age < 50
- Alcohol use history (< 10 drinks/wk or 1-1/2 oz/day)
- Female
- History of motion sickness or morning sickness
Neurotransmitter Roles in N & V

• Histamine/muscarinic – role in vestibular etiology
• Dopamine (D$_2$) – Clearly additive factor in acute and delayed types
  – No longer considered a major component of CINV
• Serotonin (5HT$_3$) – The most important in acute CINV, but minimal serotonin release seen in delayed CINV phase
• Substance P (SP) – Additive to modulate acute and most significant in delayed CINV
Antiemetic Guidelines

• Evidence based – ASCO (2020), MASCC (2016)
• Practice based – NCCN (quarterly update)
• All based on 4 levels of risk
• General consensus with some areas of controversy/unmet need
• Separate pediatric guidelines
Prevention of Acute CINV

• High emetogenic risk regimens
  – $5HT_3a + NK1a + \text{steroids} + Oz \pm BZ$

• Moderate emetogenic risk regimens
  – Carboplatin AUC $\geq 4$
    • $5HT_3a + NK1a + \text{steroids} \pm BZ$
  – Other Moderate risk regimens
    • $5HT_3a + \text{steroids} \pm BZ$

• Low emetogenic risk regimens
  – $5HT_3a$
    – Dexamethasone 8 mg PO

• Minimal risk - none required

Agent-Based Emetogenic Risk

- Based upon highest risk agent
- Additional agents may contribute but are considered regimen by regimen
## Emetogenicity Examples

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate Risk</th>
<th>Low</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Azacitidine</td>
<td>Epirubicin</td>
<td>Cytarabine &lt;1000 mg/m2</td>
</tr>
<tr>
<td>Cyclophosphamide &gt; 1.5 gm/m2</td>
<td>Carboplatin</td>
<td>Idarubicin</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Cyclophosphamide ≤ 1500 mg/m2</td>
<td>Ifosfamide</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>Cytarabine &gt; 1000 mg/m2</td>
<td>Irinotecan</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Streptozocin</td>
<td>Doxorubicin*</td>
<td>Oxaliplatin</td>
<td>Paclitaxel</td>
</tr>
</tbody>
</table>

* When combined with cyclophosphamide is classified as high risk

Adapted from Hesketh PJ et al. J CO 2017;35(28):3240-3261
Case 1

• Ms B comes in for her first cycle of AC chemotherapy.
• Cyclophosphamide 600mg/m² Day 1
• Doxorubicin 60 mg/m² Day 1

What antiemetic prophylaxis should Ms B receive?
AC

- Cyclophosphamide 750 mg/m² = Moderate
- Doxorubicin 50 mg/m² = Moderate
- *Combination however is classified as high risk
- Should receive quadruple therapy
  - NKIα, 5HT3α, corticosteroid, olanzapine
- How is this different from R-CHOP?
N & V Risk Summary

• Intrinsic Chemotherapy emetogenicity most important
• Most important risk factor for delayed n/v is acute control
• Control in 1st cycle influences other cycles
• Patient risk factors affect the other therapy related factors

Gralla RJ et al JCO 1999;17:2971-94
Hesketh PJ Oncologist 1999;4:191-6
Evolution of Antiemetic Agents Reflects Advances in Neuropharmacology of Emesis

1960s
- Phenothiazines (dopamine)

1970s
- High-dose metoclopramide (serotonin)
- Combination regimens
- Predictive variables identified

1980s
- First 5-HT \textsubscript{3} receptor antagonist
- Further understanding of delayed emesis
- Combination of Dex and 5-HT \textsubscript{3} receptor antagonist

1990s
- NK\textsubscript{1} receptor antagonists (substance P)
- Second generation 5-HT\textsubscript{3} antagonist
- Olanzapine

2000s
- Combination of Dex and 5-HT\textsubscript{3} receptor antagonist

5-HT\textsubscript{3} = serotonin receptor type 3; Dex = dexamethasone; NK\textsubscript{1} = neurokinin-1.
Antiemetic Drug Classes

- Serotonin (5-HT$_3$) receptor antagonists
- Neurokinin 1 antagonists (NK$_{1a}$)
- Dopamine (D$_2$) receptor antagonists
  - Phenothiazines
  - Substituted benzamides
  - Butyrophenones
  - Olanzapine
- Steroids
- Benzodiazepines (BZ)
- Cannabinoids
- Histamine (H$_1$) receptor antagonists
- Muscarinic receptor antagonists
How do you define breakthrough N/V?

• What is your “go to: rescue agent?"
## NCI CTCAE Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting (3.0) 2006</td>
<td>1 episode per 24 hrs</td>
<td>2-5 episodes in 24 hrs, hydration indicated &lt; 24 hrs</td>
<td>6 or &gt; episodes in 24 hrs, TPN or IV hydration indicated &gt; 24 hrs</td>
<td>Life threatening</td>
<td>Death</td>
</tr>
<tr>
<td>Vomiting (4.0) 2009</td>
<td>1-2 episodes in 24 hrs</td>
<td>3-5 episodes in 24 hrs</td>
<td>6 or &gt; episodes in 24 hrs, tube feeding, TPN, hospitalization indicated</td>
<td>Life threatening urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Vomiting (5.0) 2017</td>
<td>Intervention not indicated</td>
<td>Outpatient IV hydration Medical intervention indicated</td>
<td>Tube feeding, TPN, or hospitalization indicated</td>
<td>Life threatening consequences</td>
<td>Death</td>
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# NCI CTCAE Definitions

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<tr>
<td>Nausea (3.0) 2006</td>
<td>Appetite loss no change in eating</td>
<td>Oral intake decreased without significant weight loss, dehydration,</td>
<td>Inadequate oral caloric or fluid intake, TPN, tube feeding or iv</td>
<td>Life threatening</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>malnutrition, &lt; 24 hrs</td>
<td>hydration &gt; 24 hrs</td>
<td></td>
<td></td>
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MASCC: Antiemetics in Advanced Cancer Guideline

- Literature review and update from 2015 guideline (1/15-2/2021)
- 257 abstracts - used 1 review and 4 RCT to update guideline
- Evidence basis for treatment vs expert opinion which is included in current NCCN and ASCO palliative care guidelines

Davis M, et al Supportive Care in Cancer 2021;29:8097-8107
Results

- First line (II): metoclopramide, haloperidol
- Second line (II): methotrimeprazine, olanzapine
- Third line (III): tropisetron, levosulpride
- Doses were modest (haloperidol 1-2 mg 1-2 times daily), olanzapine 5 mg daily
- Metoclopramide was most common rescue for breakthrough
- Topical haloperidol no better than placebo due to poor absorption
Guideline Statements

• Little benefit for adding dexamethasone outside of brain metastases or bowel obstruction

• Antiemetics based upon etiology provides similar results as empiric haloperidol

• NEPA – despite a placebo run-in was no better than placebo in a small study

• Cyclizine, ondansetron, palonosetron, and scopolamine have no high quality evidence

• Topical haloperidol, diphenhydramine, lorazepam, and metoclopramide should not be used in advanced cancer

Davis M, et al Supportive Care in Cancer 2021;29:8097-8107
Fosaprepitant for Rescue of Breakthrough CINV

- Adults receiving MEC or HEC chemotherapy
- Standard antiemetic prophylaxis of 5HT3a and dexamethasone but no NK1a
- If emesis or nausea to the point the patient requested an antiemetic
  - Then patient given 150 mg IV fosaprepitant
- Primary endpoint: nausea/emesis at 2 hrs on VAS
- Secondary endpoints: VAS at 12 and 24 hours, #emesis, rescue meds, adverse events, nutritional intake

Bubalo J et al. Proceedings of ASCO 2013 e20627
Fosaprepitant Rescue: Results

• N=11 (6 M, 5 F)
• HiDAC, R-CHOP, Epirubicin/Ifosfamide, 7 + 3, R-EPOCH, HyperCVAD, VAC, R-ICE
• 3 treated for emesis, 8 for nausea
• 91% improved nausea at 2 hrs, 100% at 12 hrs, 64% at 24 hrs
• No additional emesis in 2/3 and no nauseated person had emesis
• 9/11 (82%) needed additional rescue for nausea

Bubalo J et al. Proceedings of ASCO 2013 e20627
Fosaprepitant Rescue: Results

• Appetite improved in 8/11, food intake improved in 5/11
• Adverse effects: headache 18%, dizziness 18%, hiccups 9%, indigestion 9%, 1 case ifosfamide encephalopathy
• May have helped decrease emesis but still significant nausea
• Study issue: Requires 10 consents per 2 study enrollees

Bubalo J et al. Proceedings of ASCO 2013 e20627
Benefits of Standard of Care (SOC) Antiemetics

- Adults receiving MEC or HEC chemotherapy
- Standard antiemetic prophylaxis of per guideline risk
- If emesis or nausea to the point the patient requested an antiemetic the patient received their rescue of choice and started their study diary
- Primary objective: time to recovery after significant nausea or an emetic event
SOC Antiemetics: Results

- Enrolled over 18 months - 174 screened, 56 enrolled, n = 50 with complete data
- 30 M, 20 F
- 60% prior chemo, 40% first cycle
- Average age 64 (18-74)
- 80% had CINV resolution within the study period
  - Average recovery time of 19 hours
SOC Results: Subset Analysis

Time to Resolution CINV

- Within 2 hour: 44%
- Within 6 hour: 7%
- Within 12 hour: 12%
- Within 24 hour: 2%
- Within 36 hour: 7%
- Within 72 hour: 7%
- No resolution: 20%
## Results

<table>
<thead>
<tr>
<th></th>
<th>Resolved (%)</th>
<th>Unresolved (%)</th>
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<tbody>
<tr>
<td>Prior chemo</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>HEC</td>
<td>24</td>
<td>25%</td>
</tr>
<tr>
<td>MEC</td>
<td>76</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiemetic used (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>Promethazine</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Multiple agents</td>
<td>39</td>
<td>50</td>
</tr>
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</table>
SOC Antiemetics: Analysis

- Resolution within 2 hours vs no resolution groups compared
- Demographics and outcomes comparable with a single significant difference
- Group without prior chemotherapy was significantly (p = 0.0036) more likely to not have CINV resolve
SOC Discussion Points

- ~34% needed rescue past 24 hours
- Rescue agents given at patient request, would scheduled be more effective?
- Results most applicable to prochlorperazine
- **Caveats**
  - Small N
  - Recall bias? Q 12 hr assessment up to 5 days
  - Time of emesis vs nausea unclear vs rescue
  - Patient (self-perceived) replies variable
Questions?
General Management of Nausea and Vomiting
Etiologies

• Acute or chronic event?
• Drug/treatment Induced
  – Opioids, supplements, antibiotics, cytotoxics, NSAIDs, SSRI, radiation (to GI, CNS)
• Disease related
  – Gastric irritation/obstruction, constipation, electrolyte/metabolic factors, increased intracranial pressure, vestibular disturbances
• Psychological Factors
  – Anxiety, fears, phobias, sights, odors
Therapy/Drug Selection Issues

- Drug affinity for probable cause (receptors, pharmacodynamics, etc)
- Available routes of administration
- Side effect profile
- Patient Contraindications
- Treat underlying condition if possible
Agents and Issues

- **Metoclopramide** – use if GI stasis or of need lower sedation level
- **Dexamethasone** – inflammatory component to nausea, cerebral edema, or additive effect desired
- **Octreotide** - Bowel obstruction in terminal disease or those who fail anticholinergics
- **Benzodiazepines, olanzapine** – anxiety, phobias, learned behaviors
Agents and Issues

- Phenothiazines – Broadly active, especially in combination
- Haloperidol, droperidol – similar to phenothiazines in spectrum of activity
- Meclizine, dimenhydrinate, scopolamine – for treatment of vestibular component
- Hyoscyamine, atropine – for nausea secondary to excess bronchial or gastric secretions
- Serotonin antagonists – Drug of last resort?, minimal effect for rescue. Possible exceptions pregnant patients, children, viral enteritis.
  – Correct dose?
Agents and Doses

- Metoclopramide 10-30 mg IM/IV/PO Q 4H PRN (60-100 mg/day on average)
- Droperidol 0.625 mg IV/IM Q 4H PRN
- Haloperidol 0.5-2 mg Q 6 H PRN
- Prochlorperazine 2.5-10 mg IV/IM/PO Q 4H PRN *
- Promethazine 6.25-25 mg IV/IM/PO/PR Q 4H PRN *
- Chlorpromazine 25-100 mg IV/PO Q 4H PRN

* Also have PR Option
Additional Agents

- Dexamethasone 4-8 mg IV/PO QD to QID
- Scopolamine patch 1.5 mg (up to 8 hours for effect) Q 3 days
- Dimenhydrinate 25-50 mg PO Q 4H PRN
- Meclizine 12.5-25 mg q 8 H PRN
Additional Routes

• Sub Q
  – Metoclopramide, octreotide, haloperidol, dexamethasone, scopolamine
• Don’t give Sub-Q (cause irritation and erosions)
  – Chlorpromazine, diazepam, prochlorperazine, promethazine, hydroxyzine
• Sublingual
  – Lorazepam, hyoscyamine, atropine, haloperidol
Combinations

- **D₂ Antagonist**
  - Metoclopramide
  - Prochlorperazine
  - Haloperidol
  - Droperidol
  - Promethazine

- **5HT₃ Antagonist**
  - Ondansetron
  - Granisetron
  - Dolasetron
  - Palonosetron – not for treatment

- **Other**
  - Dexamethasone
  - Dronabinol
  - Dimenhydrinate
  - Diphenhydramine
  - Hyoscyamine
  - Lorazepam
  - Meclizine
  - Nabilone
  - Olanzapine
  - Scopolamine
NonPharmacologic Approaches

- Decrease Milk products
- Clear liquid diet
- Bland diet
- Decrease sources of smell (cold and room temperature food)
- Manage anxiety
- Distraction techniques, guided imagery
- NG tube
Other Issues

- Multiple agents common
- Dosing and frequency?
- Gastric reflux issues
- Ginger, Peppermint oil (aromatherapy)
- Hydration
- Acupressure
- Marijuana
The Basics

• Schedule the medications
  – Early vs later

• Consider combining multiple mechanisms of action based on patient’s symptoms/triggers

• Titrate to effect/side effects
  – Initial frequency based on side effect tolerance
  – Delirium and fall risk important factors

• Antihistamines in low doses for EPS

• Lorazepam is not an antiemetic!
Example: Emesis Rescue Algorithm

- **5HT3 antagonist on board?**
  - Yes
  - Dopamine antagonist (DA) on board?
    - Yes
    - △ to Haloperidol
    - No
    - Begin prochlorperazine
  - No
  - Schedule: ondansetron
    - 4 mg IV q 12 H x 48 hrs
    - Benefit? Yes, then Continue. If BT after 24 hrs then DC

- Selective NK1 addition to Chemo regimens

- Anxiety management – olanzapine first choice
- Scopolamine?
- Metoclopramide, if constipated
- Dietary review
- Antihistamine?
- Continue dexamethasone?
Example: Nausea Rescue Algorithm

5HT3 antagonist on board?

Yes

Dopamine antagonist (DA) on board?

Yes

Δ to Haloperidol

No

Begin prochlorperazine

No

Schedule: ondansetron 4 mg IV q 12 H x 48 hrs

• Scopolamine?
• Dronabinol - Second agent if DA antagonist fails them
• Anxiety management – olanzapine first choice
• Dietary review
• Antihistamine?
• Continue dexamethasone?
# Agents and Suggested Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt; 60 y/o, ≥ 50 kg, not sedation prone</th>
<th>≥ 60 y/o, &lt; 50 kg, sedation prone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>12.5 mg IV Q 6 H</td>
<td>6.25 mg IV Q 6-8 H</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>5-20 mg PO Q 4 H</td>
<td>2.5-10 mg PO Q 6 H</td>
</tr>
<tr>
<td>Droperidol</td>
<td>0.625 mg IV Q 4 H</td>
<td>0.625 mg IV Q 6 H</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5-2 mg IV Q 6 H</td>
<td>0.5-1 mg IV Q 6 H</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5 mg IV Q 4 H</td>
<td>0.5 mg IV Q 6 H</td>
</tr>
<tr>
<td>Meclizine</td>
<td>25 mg PO Q 8-12 H</td>
<td>12.5 mg PO Q 12 H</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10-30 mg IV Q 4 H</td>
<td>10-20 mg IV Q 4 H</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4 mg IV q 12 H</td>
<td>4 mg IV q 12 H</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5 mg Po Q HS</td>
<td>2.5-5 mg PO Q HS</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>5-10 mg IV Q 4 H</td>
<td>2.5-5 mg IV Q 6 H</td>
</tr>
<tr>
<td>Promethazine</td>
<td>6.25-25 mg IV Q 4 H</td>
<td>6.25-12.5 mg IV Q 6 H</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>1 patch Q 72 H</td>
<td>1 patch Q 72H</td>
</tr>
</tbody>
</table>
Summary

CINV

• Choose a guideline and stay with it
• Personalize for patient risks vs results
• Build from these basics based on evidence as it develops

General emesis issues

• Assessment is key
• What are the patient’s goals?
• From what agent can you get the most positive effect(s) with the least negative effects
• Consider non-pharmacologic interventions
## Antiemetics in Pregnancy

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Pregnancy Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>B</td>
<td>4-8 mg TID X 24 hrs then 4 TID maintenance</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Bm</td>
<td>Used safely in all trimesters</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>D 1&lt;sup&gt;st&lt;/sup&gt; trimester, then C</td>
<td>Rare adrenal suppression</td>
</tr>
<tr>
<td>Promethazine</td>
<td>C</td>
<td>Avoid in 1&lt;sup&gt;st&lt;/sup&gt; trimester, use lowest effective dose</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>D</td>
<td>All trimesters</td>
</tr>
<tr>
<td>Droperidol</td>
<td>C</td>
<td>Avoid in 1&lt;sup&gt;st&lt;/sup&gt; trimester</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Bm</td>
<td></td>
</tr>
<tr>
<td>Meclizine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginger</td>
<td>C</td>
<td>Purity and dose?</td>
</tr>
</tbody>
</table>
Thank you!