Sample Collaborative Practice Agreement

MultiCare Health System	*Medication Guideline*
	Title: MANAGEMENT OF CANCER-RELATED AND CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (ADULT)
	Scope/Patient Population: Adult oncology patients 18 years of age or older being treated with emetogenic chemotherapy or with cancer-related nausea/vomiting.
	Policy Statement/Background: Nausea and vomiting are some of the most feared side effects of cancer treatment and can significantly impact the patient's quality of life and adherence with treatment. As many as 80% of patients receiving chemotherapy experience nausea and/or vomiting. However, the severity of these symptoms can often be minimized or prevented with an effective anti-emetic plan. A variety of risk factors need to be considered when formulating an anti-emetic plan in addition to the emetogenic potential of the ordered chemotherapy treatment. These include age, gender, co-morbidities, radiation treatment, and personal history of nausea. Other potential causes of nausea and vomiting in cancer patients should be considered as well. This guideline will provide a general standard of practice to ensure the appropriate management of cancer and chemotherapy-related nausea/vomiting in adult oncology patients. This guideline also serves as a collaborative practice agreement between providers and MHS pharmacists for pharmacy-managed antiemetic therapy as delegated by a privileged provider.
	Special Instructions: **1.** Inclusion Criteria: a) Adult patients with a cancer diagnosis under the care of an MRCC provider during an outpatient clinic visit or inpatient admission. b) Adult patients under the care of any oncologist receiving inpatient chemotherapy. **2.** Pharmacists will assess all adult patients receiving chemotherapy for initial anti-emetic management, and provide ongoing assessment and anti-emetic adjustments as needed. **3.** Patients presenting with nausea and/or vomiting as a result of cancer, radiation or chemotherapy treatment may be assessed and treated for nausea or vomiting within the scope of this guideline.
	Procedure: I. Physician A. Authorizes pharmacists to perform anti-emetic assessment and management within the scope of this agreement.

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B. Provides direction and consultation for anti-emetic therapy or supportive care as needed.

II. Pharmacist:

A. Reviews patient medication allergies, current medications and past medical history in medical record

B. Reviews cancer diagnosis and chemotherapy treatment plan in patient medical record.

C. Performs full assessment of the individual patient, with consideration given to each of the following:

1. Emetogenic potential of the ordered chemotherapy regimen and dosage
2. Patient's prior experience with anti-emetics
3. Patient risk factors for acute nausea and vomiting:
   - Age (<50 have increased risk)
   - Gender (female gender has increased risk),
   - History of motion sickness
   - History of morning sickness with pregnancy,
   - History of chronic alcohol exposure (negative risk factor)
   - Previous chemotherapy exposure
   - Efficacy of antiemetic regimen
4. Potential additive toxicity of antiemetic agent(s) including increased risk of QT prolongation in patients with underlying cardiac disease, congestive heart failure, bradycardia, patients with electrolyte abnormalities, or treatment with chemotherapy agents (arsenic trioxide, etc) that could increase their risk for PR or QT prolongation with use of serotonin (5-HT3) receptor antagonists
5. Other potential causes of nausea/vomiting should be considered, including:
   - Radiation therapy
   - Partial or complete bowel obstruction
   - Vestibular dysfunction
   - Brain metastases
   - Electrolyte imbalances (hypercalcemia, hyperglycemia, hyponatremia)
   - Uremia
   - Gastroparesis
   - Psychophysiologic (anxiety, anticipatory nausea and vomiting)

D. Document all activities in progress notes.

III. Formulation of antiemetic plan:

A. Basic principles

1. Identify emetogenicity of chemotherapy regimen; IV chemotherapy agents are classified into 4 categories of emetic risk: (see Appendix A)
   - High emetic risk- 90% or more of patients experience acute nausea
   - Moderate emetic risk- 30-90% or patients experience acute

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nausea
- Low emetic risk- 10-30% of patients experience acute nausea
- Minimal emetic risk- less than 10% of patients experience acute nausea

2. When combination chemotherapy is administered, the antiemetic regimen should be chosen according to the chemotherapy agent with the highest emetogenic potential.
3. Acute nausea/vomiting usually occurs within a few minutes to several hours after drug administration, generally peaks within 5-6 hours and commonly resolves within the first 24 hours.
   - Delayed nausea/vomiting occur commonly after administration of cisplatin, carboplatin, cyclophosphamide and/or doxorubicin. Cisplatin-associated nausea/vomiting peaks 48-72 hours following chemotherapy and can last 6-7 days.
   - Delayed nausea/vomiting is more common than acute nausea/vomiting, is often more severe, and tends to be resistant to treatment
4. Other anti-emetic agents may be included in national guidelines and may be included in anti-emetic regimens as appropriate.

B. Multiple-Day Chemotherapy Regimens
1. Evaluate emetogenic potential of chemotherapy agents for each day individually. Consider need for prophylaxis of delayed nausea/vomiting.
2. A 5-HT3 receptor antagonist should be administered prior to each day of moderately- or highly-emetogenic chemotherapy.
3. Dexamethasone should be administered once daily for each day of moderately- or highly-emetogenic chemotherapy AND for 2-3 days after regimens that is likely to cause significant delayed nausea/vomiting. (Dexamethasone may be omitted if chemotherapy regimen includes a corticosteroid)
4. Consider adding a Neurokinin-1- (NK1) receptor antagonist to regimens with high emetogenic potential that also have risk of delayed nausea/vomiting.

C. General Principles for Prevention of Nausea/Vomiting (see Appendix B)
1. Treatment goal is to prevent nausea and vomiting throughout the entire period of emetic risk.
2. Oral (PO) and intravenous (IV) formulations have equivalent efficacy.
3. Use of lowest, maximally effective antiemetic dose is recommended.
4. Potential toxicities of antiemetic agent(s) should be considered.

D. Special Considerations
1. Medication administration
2. Antiemetic pre-medications should be given 15-30 minutes prior to chemotherapy administration.
3. Drug interactions
   - Aprepitant is a substrate, moderate inducer and moderate inhibitor of CYP3A4, and also induces CYP2C9.

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	• The entire patient medication profile should be reviewed for potential drug-drug interactions. • NK1 antagonists have been shown to interact with dexamethasone, resulting in approximately two-fold higher concentrations of dexamethasone. The maximum dose of dexamethasone when given with an NK1 antagonist is 12 mg. 4. Dietician consult may be necessary to help patients with diet plan E. Breakthrough Nausea/Vomiting (see Appendix B) 1. The general principle of treating breakthrough nausea/vomiting is to give an additional agent from a different drug class to be used on an as-needed basis. • May advance level of coverage (i.e. addition of an NK1 antagonist) if other therapies optimized. • Multiple concurrent agents in alternating schedules or alternating routes may be necessary 2. If nausea/vomiting controlled with added agent, continue it on a scheduled basis for subsequent cycles. 3. Consider use of antacid therapy (H2RA or PPI) to manage dyspepsia, which can mimic nausea. F. Anticipatory emesis prevention/treatment 1. Use optimal antiemetic therapy during every cycle of treatment to prevent anticipatory nausea/vomiting. 2. Consider using a benzodiazepine such as lorazepam ~~or alprazolam~~ the night before and/or morning of treatment. 3. Alternative therapies may be helpful including: • Acupuncture/acupressure • Behavioral therapy such as relaxation, systematic desensitization techniques, hypnosis/guided imagery, or music therapy IV. Definitions: A. Acute-onset nausea and/or vomiting: occurs within minutes to hours after drug administration, generally peaks after 5-6 hours and resolves within 24 hours. B. Delayed-onset nausea and/or vomiting: develops more than 24 hours after chemotherapy administration and can last 6-7 days. C. Anticipatory nausea and/or vomiting: occurs prior to receiving chemotherapy, and occurs in response to a past negative experience with chemotherapy. D. Breakthrough emesis: occurs despite prophylactic treatment and/or requires "rescue" with antiemetic agents. E. Refractory emesis: occurs when antiemetic prophylaxis and/or rescue treatment fail.
	Related Policies: Oncology Supportive Care Management (Adult)
	Related Forms:
	Attachments: Appendix A: Emetogenicity of Chemotherapy Agents

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	Appendix B: Chemotherapy Anti-Emetic Management Guidelines
	References: Basch, E. et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 29 (31):4189-4198. Nov 1, 2011. National Comprehensive Cancer Network®: Antiemesis V.2.2015. National Comprehensive Cancer Network. Fort Washington, PA. Available at http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Report on Medicare Compliance. Volume 20, Number 41; November 14, 2011 Ondansetron (Zofran) IV: Drug Safety Communication – QT prolongation; posted June 29, 2012. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm310219.htm (Accessed 8/16/12). Decision Memo for Aprepitant for Chemotherapy-Induced Emesis (CAG-00248R). Published May 29, 2013. Available at www.cms.gov. (Accessed on 10/31/13.)
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Appendix A: Emetogenicity of Chemotherapy Agents

Emetogenic Potential	Intravenous Chemotherapy Agents	
High (>90%)	AC combination (either doxorubicin or epirubicin with cyclophosphamide)	
	Carmustine (>250 mg/m2)	Epirubicin (>90 mg/m2)
	Cisplatin	Ifosfamide (≥2 g/m2 per dose)
	Cyclophosphamide >1500 mg/m2	Mechlorethamine
	Dacarbazine	Steptozocin
	Doxorubicin (≥60 mg/m2)	
Moderate (30-90%)	Aldeslukin (>12-15 IU/m2)	Dactinomycin
	Amifostine (>300 mg/m2)	Daunorubicin
	Arsenic trioxide	Doxorubicin (<60mg/m2)
	Azacitidine	Epirubicin (≤90mg/m2)
	Bendamustine	Idarubicin
	Busulfan	Ifosfamide (<2 g/m2 per dose)
	Carboplatin	Interferon α (≥10 million IU/m2)
	Carmustine (≤250 mg/m2)	Irinotecan
	Clofarabine	Melphalan
	Cyclophosphamide (≤1500 mg/m2)	Methotrexate (≥250 mg/m2)
	Cytarabine (>200 mg/m2	Oxaliplatin
		Temozolamide
Low (10-30%)	Ado-trastuzumab emtansine	Interferon α (5-10 million IU/m2)
	Aldeslukin (≤12 million IU/m2)	Ixabepilone
	Amifostine ≤300 mg/m2	Methotrexate 50-250 mg/m2
	Belinostat	Mitomycin
	Blinatumomab	Mitoxantrone
	Brentuximab vedotin	Omacetaxine
	Cabazitaxel	Paclitaxel

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	Cytarabine (100-200 mg/m2) Docetaxel Doxorubicin (liposomal) Eribulin Etoposide Floxuridine Fluorouracil Gemcitabine	Paclitaxel-albumin (Abraxane) Pemetrexed Pentostatin Pralatrexate Romidepsin Thiotepa Topotecan Ziv-aflibercept
Minimal (<10%)	Alemtuzumab Asparaginase Bevacizumab Bleomycin Bortezomib Cetuximab Cladribine Cytarabine (<100 mg/m2) Decitabine Denileukin diftitox Dexrazoxane Fludarabine Interferon α (<5 million IU/m2) Ipilimumab	Methotrexate (≤50 mg/m2) Nelarabine Nivolumab Ofatumumab Obinutuzumab Panitumumab Pegasparagase Peginterferon Pembrolizumab Pertuzumab Ramucirumab Rituximab Siltuximab Temsirolimus Trastuzumab Valrubicin Vinblastine Vincristine Vincristine (liposomal) Vinorelbine

Adapted from: National Comprehensive Cancer Network®: Antiemesis V.2.2015.
List not all inclusive. Refer to package insert, clinical trials, etc. for additional info.

Emetogenic Potential	Oral Chemotherapy Agents	
Moderate to High (>30%)	Altretamine Busulfan (≥4 mg/d) Ceritinib Crizotinimb Cyclophosphamide (≥100 mg/m2/d) Estramustine Etoposide	Levantinib Lomustine Mitotane Olaparib Panobinostat Procarbazine Temozolomide (>75 mg/m2/d) Vismodegib
Low to Minimal (<30%)	Afatinib Axitinib Bexarotene Bosutinib Busulfan (<4 mg/day) Cabozantinib Capecitabine Chlorambucil Cyclophosphamide (<100 mg/m2/d) Dabrafenib Dasatinib Erlotinib Everolimus	Melphalan Mercaptopurine Methotrexate Nilotinib Palbociclib Pazopanib Pomalidomide Ponatinib Regorafenib Ruxolitinib Sorafenib Sunitinib Temozolamide (≤75 mg/m2/d)

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	Fludarabine	Thalidomide
	Gefitinib	Thioguanine
	Hydroxyurea	Topotecan
	Ibrutinib	Trametinib
	Idelalisib	Tretinoin
	Imatinib	Vandetanib
	Lapatinib	Vemurafenib
	Lenalidomide	Vorinostat

Adapted from: National Comprehensive Cancer Network®: Antiemesis V.2.2015
List not all inclusive. Refer to package insert, clinical trials, etc. for additional info.

Appendix B: Chemotherapy Anti-Emetic Management Guidelines

NOTE: Evaluate use of dexamethasone if patient is already receiving corticosteroids as part of treatment plan. Corticosteroids should be used with caution in patients with diabetes. If steroids are given for more than 5 days, consider tapering off.

Fosaprepitant (Emend IV) 150mg is the preferred NK-1 antagonist for extended coverage with highly antiemetic chemotherapy. Fosaprepitant 150mg should be infused over at least 20 minutes. Other NK-1 antagonists are available including oral agents and may be substituted for IV formulations when appropriate. Oral aprepitant* (125mg on day 1 + 80 mg on days 2-3) may be substituted for IV fosaprepitant therapy in patients receiving multi-day chemotherapy regimens or who are not able to tolerate the IV infusion.
Aprepitant capsules may be opened and given via G- or J-tube and flushed with 20-30mL of water before and after administration.

Acute Emesis Prevention:

High Emetogenic Potential (>90% emetic incidence)

- NK-1 receptor antagonist (Fosaprepitant (Emend) 150 mg IV day 1preferred) **AND**
- Dexamethasone (Decadron) 12 mg IV/PO day 1 and 8 mg IV/PO daily on days 2-4 (may give bid days 3-4 per fosaprepitant package insert) **AND**
- 5-HT_3 antagonist
  - palonosetron (Aloxi) 0.25 mg IV day 1 ***(outpatient only)*** **OR**
  - ondansetron (Zofran) 8-16 mg IV or 8-24mg PO
- +/- lorazepam (Ativan) 0.5-2 mg IV/PO q4-6h prn days 1-4
- +/- H2 blocker or proton pump inhibitor

Olanzapine based regimen is option in patients for nausea/vomiting not controlled by NK-1 based regimens.

Day 1:

- Olanzapine 10mg po Day 1
- Palonosetron 0.25mg IV Day 1
- Dexamethasone 20mg IV Day 1

Days 2, 3, 4:

- Olanzapine 10mg

Moderate Emetogenic Potential (30-90% emetic incidence)

Day 1:

- Dexamethasone (Decadron) 12 mg IV/PO day 1 **AND**
- 5-HT_3 antagonist day 1

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- palonosetron (Aloxi) 0.25 mg IV preferred ***(outpatient only)*** **OR**
- ondansetron (Zofran) 8-16 mg IV or 8-16mg PO

Days 2-3:

- Dexamethasone (Decadron) 8 mg IV/PO days 2-3 **OR**
- 5-HT_3 antagonist days 2-3 *if not given Aloxi on day 1*
  - ondansetron (Zofran) 8 mg IV/PO BID or 16mg PO QD
- +/- lorazepam (Ativan) 0.5-2 mg IV/PO q4-6h prn days 1-4
- +/- H2 blocker or proton pump inhibitor
- Add NK-1 antagonist aprepitant ~~(Emend) IV or PO day 1~~ (as guidelines above) ***in select patients*** receiving agents with moderately-high emetogenic potential (including carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate).

Olanzapine based regimen is option in patients for nausea/vomiting not controlled by NK-1 based regimens:

Day 1:

- Olanzapine 10mg
- Palonosetron 0.25mg IV
- Dexamethasone 20mg IV

Days 2, 3, 4:

- Olanzapine 10mg

Low Emetogenic Potential (10-30% emetic incidence)

- Dexamethasone (Decadron) 12 mg IV/PO day 1 **OR**
- Prochlorperazine (Compazine) 10 mg IV/PO q6h PRN **OR**
- Metoclopramide (Reglan) 10-40 mg IV/PO q4-6h PRN
- +/- lorazepam (Ativan) 0.5-2 mg IV/PO q4-6h prn days 1-4
- +/- H2 blocker or proton pump inhibitor

Minimal Emetogenic Potential (<10% emetic incidence)

- No scheduled pre-medication required.
- May provide breakthrough anti-emetic medications according to provider discretion.
- If acute nausea/emesis occurs with chemotherapy, follow recommendations for prophylaxis with low emetogenic potential agents.

Breakthrough nausea/emesis treatment:

General practice is to add one agent from a different drug class to the current regimen

- Atypical antipsychotic:
  - Olanzapine 10mg po daily for 3 days
- Benzodiazepine:
  - Lorazepam 0.5-2mg po/sl/IV every 6 hours
- Cannabinoid:
  - Dronabinol 5-10mg po every 3-6 hours
  - Nabilone 1-2mg po BID
- Phenothiazine:

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- Prochlorperazine 10mg po/iv every 6 hours
- Promethazine (Phenergan) 12.5-25 mg IV/PO/PR q4-6h prn (IV use central line only)

- Serotonin 5-HT3 antagonist:
  - Ondansetron *16mg PO/IV daily (preferred formulary agent)*
  - Dolasetron 100mg po daily
  - Granisetron 1mg IV daily or 1-2mg po daily
- Steroid:
  - Dexamethasone 12mg po/IV daily
- Other:
  - Scopolamine transdermal patch every 72 hours
  - Haloperidol 0.5-2mg po/IV every 4-6 hours (IV use restricted to inpatient)
  - Metoclopramide 10-40mg po/IV every 4-6 hours (IV use restricted to inpatient)

Prevention of Emesis Due to Radiation Therapy:

Total body irradiation:

- Pretreat for each day of radiation therapy with 5-HT_3 antagonist PO (ondansetron 8mg po BID) ± dexamethasone 4 mg PO daily

Radiation to upper abdomen:

- Pretreat for each day of radiation therapy with 5-HT_3 antagonist PO (ondansetron 8mg po BID)± dexamethasone 4 mg PO daily

Radiation to other sites:

- No pretreatment required, follow protocol for breakthrough emesis

Prevention of Nausea/vomiting Due to Oral chemotherapy:

- High-moderate emetic risk (appendix A)
  - 1. 5-HT3 antagonist
    - Ondansetron 16-24mg po daily
    - Dolasetron 100mg po daily
    - Granistron 1-2mg po daily
- Low-minimal emetic risk:
  - 1. 5-HT3 antagonist as needed
- Refer to breakthrough nausea/vomiting appendix

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