The purpose of these dosing protocols is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The protocols attempt to define principles of practice, which should produce quality patient care.

The dosing protocols should not be considered inclusive of all appropriate processes of care. The clinician, in light of individual patient situations, must make the ultimate judgment regarding the propriety of any course of treatment.

PROTOCOL FOR THE USE OF ANTIEMETICS TO PREVENT CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

BACKGROUND

The impact of uncontrolled nausea and vomiting may be significant. Patients can develop dehydration, electrolyte imbalances, aspiration pneumonia, and malnutrition and may discontinue therapy due to a negative impact on quality of life. Many clinical trials have addressed the use of numerous antiemetic agents in this area; however, no consistent management plan has arisen from the investigations.

Several agents are available to prophylaxis against and to treat nausea and vomiting. **Table 1** provides a discussion of the various classes and their mechanisms of action. Preventive use of these agents is often more successful than treating an event once it develops. Further episodes of nausea and vomiting can often be prevented with early intervention.

Table 1: Antiemetic Agents

Class of Drug	Example	Receptor	Site of action
Phenothiazines	Prochlorperazine	Dopamine	GI, CNS
Butyrophenones	Haloperidol	Dopamine	GI, CNS
Benzamides	Metoclopramide	Dopamine Serotonin	GI, CNS
Antihistamine	Diphenhydramine	Histamine	CNS
Anticholinergic	Scopolamine	Acetylcholines	CNS
Cannabinoids	Dronabinol	Unknown	CNS
Serotonin antagonist	Ondansetron	Serotonin	GI, CNS
Corticosteroids	Dexamethasone	Unknown	GI

The decision to institute prophylaxis with an antiemetic agent must be based on patient specific factors. The type, dose, route, and schedule of chemotherapy must be considered. Prior history of nausea and vomiting, anticipated adverse effects, and previous antiemetic success must also be evaluated. **Table 2** provides a listing of emetogenicity potential for chemotherapy agents. The use of this information in the following algorithim can predict emetogenicity of combination regimens

Algorithim for predicting the acute emetogenicity of combination chemotherapy regimens:

1. Identify the most emetogenic agent in the combination
2. Assess the relative contribution of other agents to the emetogenicity of the combination. When considering other agents the following rules apply:
    - Level 1 agents do not contribute to the emetogenicity of a given regimen
    - Adding one or more level 2 agents increases the emetogenicity of the combination by 1 level greater then the most emetogenic agent in the combination
    - Adding level 3 or 4 agents increases the emetogenicity of the combination by 1 level per agent

Combination algorithm examples:

Level 2 + Level 2 = 3

Level 2 + Level 2 + Level 2 = 3

Level 3 + level 2 = 4

Level 3 + level 2 + level 2 = 4

Level 3 + Level 3+ Level 3 = 5

Moderately to highly emetogenic regimens (level 3-5)

Ondansetron 16 mg PO or 8 mg IV
Plus
Dexamethasone 20 mg IV/PO
Prochlorperazine 10 mg IV/PO Q6H prn breakthrough N/V

- Use oral regimens whenever possible.
- Concurrent use of corticosteroids provides synergy with 5-HT3 receptor antagonists. Patients receiving a combination regimen containing a steroid do not require additional dexamethasone.
- Lorazepam is a weak antiemetic and should be reserved for patients with significant anxiety or anticipatory N/V. The sedative and amnestic effects of benzodiazepines may be beneficial in this setting. Outpatients given lorazepam must have someone drive them home.
- Ondansetron doses may need to be increased to 24 mg PO with some level 5 regimens.

Low emetogenic potential regimens (level 2)

Prochlorperazine 10 mg IV/PO X1 pre-chemotherapy
Prochlorperazine 10 mg IV/PO Q6H prn breakthrough N/V

- Patients who fail or who do not tolerate prochlorperazine should be changed to dexamethasone 10-20 mg IV/PO X1 pre-chemotherapy

Very Low emetogenic potential regimens (level 1)

No pre-medications routinely needed
Prochlorperazine 10 mg IV/PO Q6H prn breakthrough N/V

Delayed Emesis Regimen for Cisplatin and High Dose Cyclophosphamide (> 2gm/m^2)

Prochlorperazine 10 mg PO Q6H X 3 days
Dexamethasone 4-8 mg PO BID on day 2 and day 3

- Ondansetron 8 mg PO BID or haloperidol 2 mg PO BID may be substituted for prochlorperazine resistant or intolerant patients.
- High-dose metoclopramide 1-2mg/kg IV Q2-4H may be useful in limited patients. Due to the increased risk of adverse effects with this dose (i.e., dystonia) the dose needs to be preceded with diphenhydramine.

Table 2:Acute Emetogenicity Potential of Chemotherapy Agents

Level	Classification	Frequency of emesis	Agent	Combination regimens
5	High	>90%	Carmustine > 250 mg/m^2 Cisplatin ≥ 50 mg/m^2 Cyclophosphamide > 1500 mg/m^2 Dacarbazine Lomustine ≥ 100 mg/m^2 Mechlorethamine Melphalan ≥ 100 mg/m^2 Nitrogen mustard Pentostatin Steptozocin Thiotepa ≥ 100 mg/m^2	Amifostine containing regimens ABVD Cisplatin+BCNU+DTIC Cisplatin+cyclophosphamide Cisplatin+5-FU day 1 only Cisplatin+VP-16 day 1 only Cisplatin+vinorelbine day 1 only MOPP MOPP-ABV day 1 only MVAC Day 2 only PEB VIP
4	Moderately high	60-90%	Carboplatin Carmustine ≤ 250 mg/m^2 Cisplatin < 50 mg/m^2 Cyclophosphamide > 750 mg/m^2 ≤ 1500 mg/m^2 Cytarabine > 1000 mg/m^2 Dactinomycin Doxorubicin > 60 mg/m^2 Methotrexate >1000 mg/m^2 Mitoxantrone < 15 mg/m^2 Procarbazine (oral)	AC CAF Carboplatin+5-FU day 1 only Carboplatin+ Cyclophosphamide Carboplatin+ paclitaxel Carboplatin+ VP-16 day 1 only DHAP 2 day regimen ESHAP day 5 FAM MAID MINE
3	Moderate	30-60%	aldesleukin Cyclophosphamide ≤ 750 mg/m^2 Cyclophosphamide (oral) Doxorubicin 20-60 mg/m^2 Epirubicin ≤ 90 mg/m^2 Idarubicin Ifosfamide Irinotecan Methenamine (oral) Methotrexate 250-1000 mg/m^2	CHOP CMF CNF Daunorubicin+ARA-C (7+3) day1-3 Mitomycin C+vinblastine Mitoxantrone+VP-16 MOPP-ABV day 8 only PFL
2	Moderately low	10-30%	Asparaginase Cytarabine < 1g/ m^2 Docetaxel Etoposide 5-Flurouracil <1000 mg/m^2 gemcitabine methotrexate >50 mg/m^2 <250 mg/m^2 mitomycin paclitaxel teniposide thiotepa topotecan	ESHAP days 1-4 Leucovorin+ 5-FU levamisole+ 5-FU MVAC days 1, 15, 22 VAD
1	Low	< 10%	Androgens bleomycin Busulfan Chlorambucil (oral) cladribine fludarabine hydroxyurea interferon melphalan (oral) mercaptopurine methotrexate ≤ 50 mg/m^2 thioguanine (oral) tretinoin vinblastine vincristine vinorelbine	

PROTOCOL FOR THE USE OF ANTIEMETICS TO PREVENT RADIATION THERAPY-INDUCED NAUSEA AND VOMITING

BACKGROUND

Many patients who receive radiation therapy do not develop nausea and vomiting. However, if it does develop the course is usually not as predictable or as severe as that associated with chemotherapy-induced nausea and vomiting. Factors which predispose patients include; site and dose of radiation, dose rate, field size and patient variables such as age, sex, and prior chemotherapy. The majority of patients who receive total body radiation will develop nausea and vomiting. Approximately 83% of those receiving mid and upper-hemi body irradiation will experience this problem. Single high dose radiation induces more nausea and vomiting than the same dose given in a fractionated manner.

Clinical trials investigating antiemetic prophylaxis and treatment for radiation therapy have failed to define an optimum regimen for management. Variability in radiation type, concurrent chemotherapy, population size, and dosage regimen has made results hard to interpret.

Total or Hemi-body Irradiation, Single-exposure high-dose irradiation to the upper abdomen

Ondansetron 16 mg PO 1 hr prior to therapy every day of therapy

- An oral route is preferred but IV may be used in patients unable to tolerate oral medication
- There is no evidence to support use of a 5HT3 receptor antagonist 24 hours beyond the last radiation dose
- To treat established or breakthrough nausea and vomiting- Prochlorperazine 10 mg PO Q6H may be used

PROTOCOL FOR THE USE OF ANTIEMETICS TO PREVENT POSTOPERATIVIE NAUSEA AND VOMITING

BACKGROUND

Approximately 20-40% of patients will develop postoperative nausea and vomiting (PONV). In outpatient surgery this figure can increase to as high as 80% and is one of the primary reasons for unexpected admission following outpatient surgery. Many factors impact the incidence of PONV. Patient specific factors, operative procedures, and anesthetic agents all contribute to the development of this adverse event. There are a wide variety of medications to choose from in the prevention and treatment of PONV. The choice of an agent should take into consideration the likelihood of a patient developing PONV. **Table 1** lists factors that are associated with an increased risk of PONV.

Table 1: Risk Factors for Postoperative Nausea and Vomiting

Patient Specific Factors
- Female (especially premenopausal)
- Age
- Adults
- Obesity
- Anxiety
- Gastroparesis
- GERD
- Prior history of PONV or motion sickness
- Gastric volume

Operative Procedure
- Gynecologic
- Intraabdominal
- ENT
- Ophthalmologic
- Laparoscopic
- Testicular
- Plastic and reconstructive
- Prolonged procedures

Anesthetic Agents
- Narcotics
- Anticholinesterases
- Induction agent: etomidate, thiopental, ketamine
- Nitrous oxide

Postoperative Factors
- Uncontrolled pain
- Premature oral intake
- Sudden motion changes
- Opioid use
- Swallowed blood
- Hypotension
- Hypoglycemia

Prophylaxis of Postoperative Nausea and Vomiting in the High Risk Patient

Patients have an increased risk for developing PONV if conditions presented in Table 1 exist. A patient is considered "high-risk" if they have a history of intractable PONV or if the patient may develop life - threatening sequalae from vomiting, i.e.: wound dehiscence, aspiration, head and neck surgery. These patients should receive prophylaxis to prevent PONV.

Droperidol 0.625-1.25 mg IV given with in 30-60 minutes before the end of the procedure
Or
Metoclopramide 10 mg IV given approximately 30 minutes before the end of the procedure

These agents should be used initially. If patients have failed prior prophylactic therapy with the above agents or are at risk for side effects (extrapyramidal symptoms, dystonia, akathisia, or neuroleptic malignant syndrome) with these agents, the following may be used:

Ondansetron 4 mg IV during induction or if surgical procedure exceeds one hour, 30 minutes before the end of the procedure.

Treatment of Postoperative Nausea and Vomiting

Treatment of established PONV should be instituted as rapidly as possible. The choice of agent should be based on patient specific factors as discussed previously. If droperidol 0.625mg was used as prophylaxis, this dose may be repeated to total 1.25 mg. Doses greater than 1.25 mg have a negligible increase in effectiveness but a great increase in adverse effects (i.e. sedation, hypotension, tachycardia) If the maximal dose of droperidol or metoclopramide has been reached, ondansetron may be used for refractory patients.