Birmingham Children's Hospital NHS
NHS Foundation Trust

GUIDELINE FOR THE MANAGEMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING.

Version:	2.1.0
Ratified by:	Drug & Therapeutics Committee
Date ratified:	Feb 2016
Name of originator/author:	Eloise Neumann and Jason Patel
Name of responsible committee/individual:	Chemotherapy Working Group (CWG)
Date issued:	Feb 2016
Review date:	Document to be reviewed not less than every two years –Dec 2018
Target audience:	Medical, nursing and pharmacy staff within the Haematology Oncology Specialty

Contents

1 Introduction

This guideline has been developed in order to ensure that the prophylaxis and treatment of chemotherapy-induced nausea and vomiting is provided in a manner which aims to take account of the emetogenic stimulus provided by the chemotherapy and the known actions of the individual anti-emetic drugs.

2 Purpose

This guideline aims to provide a logically consistent framework within which prescribing will be done, and other support to the patient provided.

It also addresses the issue of costs. Expenditure on 5-HT_3 blockers such as ondansetron, is still considerable and requires appropriate management.

3 Duties

3.1 Duties within the Organization

The lead officer for this document is identified on the title page.

3.2 Identification of Stakeholders

The following stakeholders have been identified within BCH: The Chemotherapy Working Group (CWG); the Cancer Locality Group; the Haematology Oncology Program meeting; nursing and support staff within the Haematology Oncology specialty.

Outside BCH: The West Midlands Children's Cancer Network Group; Pan Birmingham Cancer Network Drug & Therapeutics Committee.

4 Method for development

4.1 Consultation and Communication with Stakeholders

The policy was originally drafted by Nigel Ballantine (previous Chair, CWG) and reviewed by the stakeholders previously identified. It has been updated by Eloise Neumann (ANP) and Jason Patel (Lead cancer pharmacist). Comments and suggestions were incorporated until a final version was agreed by the CWG and ratified by the Head of Chemotherapy (HoC) and Lead Cancer Clinician (LCC).

5 Content

5.1 Background

It is unlikely that a single agent, or combination of drugs will totally abolish chemotherapy- induced nausea and vomiting in all patients.

All children should receive anti-emetic therapy which, as far as can be predicted, is appropriate to the emetic potential of the prescribed chemotherapy and their previous experience of receiving chemotherapy.

Definition: There are three types of CINV

Acute: begins with the first dose of antineoplastic or radiotherapy therapy, continues during each consecutive day that antineoplastic therapy is given and for 24 hours following the last dose of antineoplastic therapy.

Delayed: begins 24 hours after the last dose of antineoplastic or radiotherapy and may persist for up to 7days.

Anticipatory: is a learned response that is best prevented by use of an adequate antiemetic regimen during the patients' first experience with chemotherapy. It is more common in teenagers, children who suffer with motion sickness, or previous negative post chemotherapy nausea or vomiting experience.

Breakthrough: occurs when a patient experiences vomiting, retching or significant nausea despite appropriate antiemetic prophylaxis.

The designation of acute and delayed CINV as distinct is more than mere timing; physiologic differences exist in the pathways involved in these two forms of CINV (Jordan et al., 2007). Acute CINV appears to be mediated primarily by serotonin pathways and delayed CINV is more substance P mediated (Jordan et al. 2007). Therefore a combination of anti-emetic medication is beneficial.

It is recognised that control of nausea and vomiting declines during a multi-day treatment block, despite appropriate and effective anti-emetic treatment on Day 1. Once control of nausea and vomiting is reduced or lost it is highly unlikely that additional interventions will be successful in regaining control within an individual treatment block.

Anticipatory nausea and vomiting may adversely affect the efficacy of anti-emetic treatment given with chemotherapy, perhaps because the anti-emetic treatment itself provides a further anticipatory stimulus. Adolescent patients, in particular, may benefit from pre-medication with benzodiazepines, e.g. lorazepam, to reduce the anticipatory aspect of their nausea and vomiting and maximise the efficacy of anti-emetic treatment.

Adding further drugs to anti-emetic regimes which are appropriate to the emetogenicity (potential to produce nausea and vomiting) of the chemotherapy being administered is unlikely to provide more than marginal additional benefit.

Other modes of treatment, such as play therapy, should not be overlooked.

Treatment failure:

Treatment is considered to have failed if:

- The patient vomits twice in an eight hour period.
- The patient experiences nausea which is prolonged, continuous and interferes with or prevents normal activities.

Consider other causes:

- Increased intracranial pressure,
- GI obstruction or ileus
- Signs of dehydration,
- Opioid- induced vomiting.

Specific recommendations are as follows:

- Anticipatory nausea, emesis, or both: Add lorazepam (0.02-0.05 mg/kg/dose intravenously every 6 h as needed) to the regimen.
- Breakthrough and refractory emesis: If nausea and vomiting is controlled, continue breakthrough medication on a scheduled regimen (ie, not PRN or "as needed").

5.2 Policy:

It should be recognised by all those treating patients receiving cytotoxic chemotherapy that effective anti-emetic treatment is available.

However, it must also be understood, and older patients and parents counseled in this regard, that no anti-emetic regime can be relied upon to abolish nausea and vomiting completely.

Anti-emetic treatment appropriate to the emetogenicity of the chemotherapy is set out in the table which follows (see Standard Anti-emetic Regimes for Haematology Oncology). Ranking of the emetogenicity of drug treatment is based on single agent treatment. The emetogenic potential of the whole treatment block should be assessed, along with the response of the individual patient. Anti-emetic treatment should then be prescribed accordingly.

The anti-emetic regime should only be escalated when treatment on the existing regime has failed according to the criteria defined above.

In general, no patient should receive more than three anti-emetic drugs concurrently, unless they have a history of antiemetic failure.

5-HT_3 antagonists, e.g. ondansetron, should be given to cover the acute emetic stimulus of chemotherapy administration **ONLY**. Whilst it is well recognised that nausea, in particular, continues after chemotherapy has finished, there is good evidence that 5-HT_3 antagonists are less effective against delayed nausea and vomiting than against the acute stimulus of chemotherapy administration.

For delayed nausea, dopamine antagonists, e.g. metoclopramide, are more effective, with or without concurrent dexamethasone. Administration of aprepitant as a first-line anti-emetic can have a positive effect on delayed nausea and vomiting.

Anticipatory nausea and vomiting, and its effect on subsequent control during chemotherapy treatment, may be helped by the administration of lorazepam or other anxiolytic treatment, for 48 hours prior to a treatment block, particularly in adolescent patients.

5.3 Drugs available:

For drug doses please refer to Appendix D.

Ondansetron:

Mechanism of action: 5-HT_3 (serotonin) antagonist.

Notes on use:

This group of drugs has become the 'gold standard' in the treatment of chemotherapy-induced nausea and vomiting.

They are expensive and are not needed if patients are receiving only weakly emetic treatment.

Ondansetron is not effective against delayed nausea and vomiting, metoclopramide is preferred (see below).

On Day 1 of any in-patient chemotherapy ondansetron should be administered parenterally where possible.

On Day 2, and any subsequent days of a single treatment block, ondansetron should be administered orally as tablets, films, or syrup according to the child's preference.

Ondansetron should be stopped on the last day of chemotherapy, unless the patient is receiving highly emetogenic chemotherapy, in which case it can be continued for a maximum of three days after the last dose of chemotherapy. As for in-patients, it can be prescribed on a TTO for **3 days only** following highly emetogenic chemotherapy, if needed.

Out-patients and day-case patients, receiving weakly to moderately emetogenic chemotherapy should receive a single dose of ondansetron parenterally or orally, prior to treatment. Subsequent doses should continue to be given orally as above.

Ondansetron should **not** be provided to take home **UNLESS** the patient is returning on consecutive days to receive chemotherapy. Parents/patients should be advised not to take ondansetron at home on the morning of their chemotherapy, wait until they arrive in clinic to optimize the effect.

Only those patients for whom parenteral treatment is the preferred option on the following **clinical** grounds should continue to receive intravenous ondansetron:

- The child vomits back oral medicines.
- Sore mouth and/or unable to swallow

It should be noted that 5-HT_3 antagonists may cause **constipation**, as may levomepromazine. Patients and parents should be questioned about bowel habit, and encouraged to push oral fluids. Movicol, lactulose or another suitable laxatives should be considered as necessary.

Note on the administration of Ondansetron Melt® or Film preparations:
These are formulated to melt rapidly when placed on or under the tongue. This takes literally only a couple of seconds**. However, it is important to understand that the small volume of liquid which results must be swallowed for the ondansetron to be absorbed.** It is **not** absorbed from the buccal cavity.

Normally the melt tablets are quite palatable, having a strawberry taste and leaving a slight bitter taste in the mouth, **but** patients may not have normal taste sensation in consequence of their chemotherapy. Ondansetron films have a bitter taste.

Melt tablets are available in 4mg. and 8mg. strengths and may be halved in a tablet cutter, although they will start to melt if handled for other than a short period of time.

Aprepitant:

Mechanism of Action: Neurokinin-1 (Substance P) receptor antagonist.

Notes on Use:

- Must be given 1 hour prior to the first dose of chemotherapy
- Given with highly emotegenic (Group A) chemotherapy, in conjunction with ondansetron and dexamethasone (if appropriate).
- Dose of dexamethasone must be reduced by 50% in patients receiving aprepitant

Dexamethasone:

Mechanism of action: Corticosteroid with predominantly glucocorticoid (anti-inflammatory) effects.

Notes on use:

- An effective anti-emetic most commonly combined with other specific therapy, e.g. 5-HT_3 or D_2 receptor antagonists.
- Particularly helpful in the treatment of delayed nausea and vomiting.
- Dexamethasone should be given for a maximum of **FIVE** days whilst chemotherapy is being administered. It should only be started with the dose of anti-emetic immediately preceding the start of chemotherapy and should be stopped within 24 hours of the completion of chemotherapy.
- Dose must be reduced by 50% in patients receiving aprepitant.

It should not be given to patients:

- Concurrently receiving high-dose steroid therapy as part of their chemotherapy, or for other reasons,
- Receiving BMT, from the start of conditioning until at least two weeks post-transplant.
- With brain tumours unless it has been demonstrated that their nausea and vomiting cannot be controlled using alternative treatment.

Metoclopramide:

Mechanism of action:
Antagonist of central dopamine (D_2) receptors and, probably, 5-HT_3 receptors in the G.I. tract.

Notes on use:

- Effective anti-emetic.
- Useful for delayed nausea and vomiting.
- Extrapyramidal reactions may be treated with procyclidine
- Not routinely given with aprepitant, dexamethasone and ondansetron as patients will not generally require four anti-emetics as first line treatment. There are no known drug interactions between metoclopramide and these three drugs but prescribers should consider leaving metoclopramide as a breakthrough drug if the patient has received aprepitant.
- Metoclopramide is the first line drug for TTOs due to its efficacy for delayed nausea and vomiting.

Levomepromazine:

Mechanism of action: A phenothiazine with effects at dopamine (D_2), histamine (H_1), muscarinic and 5-HT_2 receptors.

Notes on use:

- An effective anti-emetic, particularly by the parenteral route.
- Sedation is commonly significant
- Patients receiving ifosfamide should be carefully monitored since sedation may mask signs of encephalopathy.

Lorazepam:

Mechanism of action: A benzodiazepine anxiolytic.

Notes on use:

- Has minimal anti-emetic properties, but is considered useful for its amnesic and anxiolytic properties.
- Administration during chemotherapy may attenuate the memory of an unpleasant experience and administration immediately prior to a block of treatment (1-3 days) may be beneficial in reducing the anticipatory aspect of nausea and vomiting.

Nabilone:

Mechanism of action: A cannabinoid drug with central actions at the level of the cerebral cortex.

Notes on use:

- Use is limited by the non-availability of formulations other than a capsule.
- Evidence suggests that the effect on vomiting may be greater than that on nausea.
- May be helpful in managing intractable vomiting and nausea uncontrolled by other treatment.

- Many patients find the adverse effects on mood and behaviour unacceptable.

5.4 Education and training

All staff prescribing anti-emetics for haematology / oncology patients will be expected to familiarize themselves and comply with these guidelines. Anti-emetic prescribing will be included in induction for new doctors and supplementary prescribers joining the specialty.

6.0 Monitoring Compliance With and the Effectiveness of the policy

Routine audit of clinical areas.

References:

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Jordan, K., Sippel, C., & Schmoll, H.J. (2007). Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: Past, present, and future recommendations. *Oncologist, 12*(9), 1143–1150.

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Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol*. Jan 1997;15(1):103-9

Appendix A: summary of anti-emetic prescribing (normal renal & hepatic function)

GROUP A—HIGHLY EMETOGENIC REGIMENS: >90% CINV

Cisplatin
Carmustine
Cyclophosphamide >1.5g/m^2
Dacarbazine (DTIC)
Ifosfamide

DAY 1 ONLY:
> 40KG/ >12 yrs
Aprepitant PO OD
< 40KG Metoclopramide IV/PO TDS
PLUS
Ondansetron IV TDS
Dexamethasone IV TDS

→

DAY 2 & 3:
> 40KG/ >12 yrs Aprepitant PO OD
< 40KG Metoclopramide IV/PO TDS
PLUS
Ondansetron PO TDS
Dexamethasone IV TDS

→

DAY 4 +:
Ondansetron PO TDS for up to 72 hours after last dose of chemotherapy, if required.
Metoclopramide PO TDS.

→

BREAKTHROUGH N&V:
Add Levomepromazine OR Metoclopramide if not given previously

TTO:
Ondansetron 3 days
Metoclopramide 5 days

GROUP B– MODERATELY EMETOGENIC REGIMENS: 30-90% CINV

Dactinomycin
Daunorubicin
Doxorubicin
Cyclophosphamide <1500mg/m^2
Irinotecan
Carboplatin
Cytarabine ≥ 1g/m^2
Idarubicin
Mitozantrone
Oxaliplatin,
Topotecan

DAY 1 ONLY:

Ondansetron IV TDS
PLUS
Dexamethasone IV TDS
OR
Metoclopramide IV/PO TDS

→

DAY 2 to end of chemo and up to 48hrs if needed:

Ondansetron PO TDS

Dexamethasone IV/PO TDS /Metoclopramide IV/PO TDS

→

BREAKTHROUGH N&V:
Add Levomepromazine OR Metoclopramide if not given previously

TTO:
Metoclopramide 5 days

GROUP C– WEAKLY TO MODERATELY EMETOGENIC REGIMENS 10- 30% CINV

Bortezomib, Cytarabine < 1g/m^2, Docetaxel, Fluoruracil, Gemcitabine, Methotrexate

DAY 1 ONLY:

Ondansetron PO TDS

Metoclopramide PO/IV TDS (if needed previously)

→

DAY 2 to end of chemo:

Ondansetron PO TDS

Metoclopramide IV/PO TDS

→

BREAKTHROUGH N&V:
Add Levomepromazine OR Dexamethasone

TTO:
Metoclopramide 5 days

GROUP D– WEAKLY EMETOGENIC CHEMOTHERAPY REGIMENS: <10% CINV

Aspariginase, Bevacizumab, Bleomycin, Busulfan, Cladribine, Etoposide, Fludarabine, Rituximab, Vinblastine, Vincristine, Vinorelbine

No Anti-emetic required

→

NAUSEA & VOMITING PRESENT:

Add Ondansetron or Metoclopramide

Appendix B – Anti-emetic dosing

DRUG	ROUTE	FREQUENCY	DOSE
Aprepitant	PO	OD (Max 3/7)	>40kg/>12 yrs: 1 hr prior to chemo on all 3 days: • 125mg Day 1, • 80mg Day 2 • 80mg Day 3. *Group A chemo ONLY*
Dexamethasone	IV/PO	TDS (Max 5/7)	• <=15kg : 1mg • 16-25kg: 2mg • 26-35kg: 3mg • 36-45kg: 4mg • 46-55kg: 5mg • >55kg : 6mg *Reduce Dex dose by 50% if patients are receiving aprepitant that day*
Levomepromazine	IV	BD	• 0.05mg/kg per dose
Lorazepam	PO	OD-BD	• >12 years: 1-2mg
Metoclopramide	IV/PO	TDS	• 0.2mg/kg *First line for TTOs*
Nabilone	PO	BD-TDS	• <18kg: 0.5mg • >18kg: 1mg
Ondansetron	IV/PO	TDS	• 5mg/m2 or • 0-2 yrs: 1-2mg • 2-12 yrs: 2-4mg • >12 yrs: 4-8mg *Avoid in TTOs if possible*

Appendix C – Policy Review Group Checklist for the Review and Approval of Procedural Document.

	Title of document being reviewed:	Yes/No/ Unsure	Comments
1.	**State Title:**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	
3.	**Development Process**		
	Is the method described in brief?	Yes	
	Are people involved in the development identified?	Yes	
	Do you feel a reasonable attempt has been made to ensure relevant expertise has been used?	Yes	
	Is there evidence of appropriate consultation with stakeholders and users?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
	Are the statements clear and unambiguous?	Yes	
5.	**Evidence Base**		
	Is the type of evidence to support the document identified explicitly?	Yes	
	Are key references cited?	Yes	
	Are the references cited in full?	Yes	
	Are supporting documents referenced?	Yes	

6.	**Approval**		
	If appropriate have the joint Human Resources/staff side committee (or equivalent) approved the document?	N/a	
7.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	Yes	
	Does the plan include the necessary training/support to ensure compliance?	N/a	
8.	**Document Control**		
	Does the document identify where it will be held?	Yes	
	Have archiving arrangements for superseded documents been addressed?	Yes	
9.	**Process to Monitor Compliance and Effectiveness**		
	Are there measurable standards or KPIs to support the monitoring of compliance with and effectiveness of the document?	No	
	Is there a plan to review or audit compliance with the document?	Yes	
10.	**Review Date**		
	Is the review date identified?	Yes	
	Is the frequency of review identified? If so is it acceptable?	Yes	
11.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?	Yes	

Policy Review Group Ratification
If you are happy to ratify this document, please sign and date.
Committee /Other Approval Name Signature

Appendix D - Equality Impact Assessment

To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval.

EQUALITY IMPACT ASSESSMENT FORM

SECTION 1:

Department: Haematology Oncology	**Assessor: Heather Petts**
Policy/ Service Title: Guideline for the management of chemotherapy-induced nausea and vomiting.	**Date of Assessment: 25.4.13**
1. Describe the purpose of this policy or Function	The Children's Cancer Measures 2009 requires the PTC (principal treatment centre) to have a range of policies in place to support the safe and effective delivery of chemotherapy from the perspective of patients, carers and staff. This policy has been in place for a number of years and is being reviewed as per Trust standard and as part of the peer view process for cancer services.
2. Who is affected by this policy?	Medical, nursing and pharmacy staff within the Haematology Oncology specialty at BCH.
3. What are the outcomes or intended outcomes of this policy/ function?	This policy will ensure that staff caring for patients with chemotherapy-induced nausea and/or vomiting have available a clinical guideline for effectively managing such patients. Secondarily, compliance with Children's Cancer Measures 2009.
4. What consultation has been undertaken during the development of this policy/function?	Stakeholders identified in the policy
5. What information or evidence has been used to assess the potential impact across the equality strands?	This policy will have no implications with respect to Equality Impact

IMPACT

1. What is the impact or likely impact, either positive or negative, of the initiative on individuals, staff, or the public at large? None		
2. Please complete the following list and identify if there is, or likely to be, an impact on a group		
a) Grounds of race, ethnicity, colour, nationality or national origins.	~~Yes~~ ☐ No ☐	Adverse? ☐ Provide further details:
b) Grounds of sexuality or marital status	~~Yes~~ ☐ No ☐	Adverse? ☐ Provide further details:
c) Grounds of Gender	~~Yes~~ ☐ No ☐	Adverse? ☐ Provide further details:
d) Grounds of religion or belief	~~Yes~~ ☐ No ☐	Adverse? ☐ Provide further details:
e) Grounds of Disability	~~Yes~~ ☐ No ☐	Adverse? ☐ Provide further details:
f) Grounds of age	~~Yes~~ ☐ No ☐	Adverse? ☐ Provide further details:
If you have stated that there is an adverse impact a Full Impact Assessment is Required. Complete Section 2.		

SECTION 2:

Modifications
1. If you stated that the policy/ function has or could have an adverse impact on any group, how could you modify it to reduce or eliminate any identified negative impacts?
2. If you make these modifications, would there be an impact on other groups, or on the ability of the policy to achieve its purpose?
Consultation **Under the Race Relations (Amendment) Act 2000 you are required to consult on the impact of new policies, functions and service change.**
3. How do you plan to consult on these modifications? Specify who would be involved, timescales and methods.

Decision Making
1. Who will make the decision? 2. What is the decision?
☐ Reject the policy/ function ☐ Introduce the policy/ function ☐ Amend the policy/ function ☐ Other (Please explain)

Monitoring and Review
1. How will the implementation of the policy/ function and its impact be monitored?
2. What are the overall learning points from this assessment? 3. What actions are recommended from this assessment?
4. When is the review date?

For advice in respect of answering the above questions, please contact the Equality and Diversity Officer on Ext: 8611. A completed form must be returned with your procedural document.

Appendix E – Plan for Dissemination of Procedural Documents

To be completed and attached to any document which guides practice when submitted to the Policy Review Group for consideration and approval.

Title of document:	Guideline for the management of chemotherapy-induced nausea and vomiting.		
Date finalised:	25.4.13	**Dissemination lead: Print name and contact details**	Heather Petts, Lead Cancer Nurse, 0121 333 8680
Previous document already being used?	**Yes / ~~No~~** (Please delete as appropriate)		
If yes, in what format and where?	Electronic on oncology p drive.		
Proposed action to retrieve out-of-date copies of the document:	Archive old versions		

To be disseminated to:	**How will it be disseminated, who will do it and when?**	**Paper or Electronic**	**Comments**
Medical Staff	Heather Petts to email staff signposting to computer drive April 2013	E	
Nursing staff	Dawn Forbes to email and provide teaching sessions	E	
POSCU's	Heather Petts to notify updates electronically via Lead Cancer Nurses and clinical oncology leads	E	

Dissemination Record – to be used once document is approved.

Date put on register / library of procedural documents		**Date due to be reviewed**	

Disseminated to: (either directly or via meetings, etc)	**Format (i.e. paper or electronic)**	**Date Disseminated**	**No. of Copies Sent**	**Contact Details / Comments**

Appendix F – Summary of Significant Changes to previous version of Policy

Policy Title			
Version	**Date**	**Author**	**Comment (Identify any significant changes to the procedural document)**
2.0	3/12/15	Eloise Neumann & Jason Patel	▪ Added information on aprepitant ▪ Updated prescribing flow chart and dosing table