# Nausea and Vomiting Management for Patients Receiving Chemotherapy or Radiotherapy

| | |
|---|---|
| Reference: | CG900 |
| Written by: | Karen Whitehouse |
| Peer reviewer | Jeanette Payne |
| Approved by RRGM: | 8th February 2023 |
| Approved by D&TC: | 21st October 2022 |
| Review Due: | February 2028 |

**Single use printed copies are valid on date of printing from SCH Intranet and for 30 days following printing. If document is still required after 30 days it MUST be reprinted. Date and time of printing 22/02/2023 13:24**

## Intended Audience

This document contains information regarding the management of chemotherapy and radiotherapy induced nausea and vomiting within Sheffield Children's NHS Foundation Trust (SCFT). It is to be used by staff within the Trust whenever they are dealing with patients receiving chemotherapy or radiotherapy.

## Purpose

The purpose of this guideline is to provide information on the most appropriate choice of antiemetics for patients receiving chemotherapy and or radiotherapy. It also provides appropriate doses, and cautions and contraindications for each antiemetic in the guideline. To allow the most appropriate antiemetic to be prescribed to prevent nausea and vomiting associated with chemotherapy or radiotherapy and to also give advice on how to treat breakthrough nausea and vomiting.

## Table of contents

**Nausea and Vomiting Management**

## 1. Introduction

Chemotherapy induced nausea and vomiting (CINV) are considered one of the most distressing side effects of chemotherapy treatment, potentially influencing compliance with future treatments if not managed appropriately. Therefore it is vital that it is prevented and treated with appropriate levels of antiemetics.

Nausea and vomiting are reflexes initiated by the body to expel toxic substances from the stomach and intestine. Vomiting is mediated by the vomiting centre located in the medullary reticular formation. Chemotherapeutic agents induce vomiting either by stimulation of the vomiting centre or via direct or indirect stimulation of the chemoreceptor trigger zone (CTZ). The CTZ possess many $5HT_3$ receptors, NK1 receptors and Dopamine (D2) receptors. The vomiting centre is stimulated by drugs, smells, sights, emotions as well as GI input. Radiation-induced nausea and vomiting may be mediated through the CTZ and also via peripheral mechanisms.

Most cytotoxic drugs cause nausea and vomiting of varying degree. Total body, cranial and abdominal irradiation are all emetogenic (particularly the latter). Nausea and vomiting are thus a significant management challenge in the treatment of children with malignant disease. There is considerable variation in the severity of nausea and vomiting caused depending on the chemotherapeutic agent administered (see Table I).

Acute symptoms are those occurring during the first 24 hours after chemotherapy administration. Delayed nausea and vomiting occur 24-120 hours after emetogenic treatment. Anticipatory vomiting is the onset of nausea and/or vomiting before the administration of chemotherapy. It is particularly difficult to treat because it is a conditioned response and may be related to anxiety. It is important to bear in mind that vomiting following chemotherapy may be due to other causes, e.g. constipation, gastritis, ileus, mucositis. Appropriate history, examination and investigations may be required in order that such underlying causes can be treated.

In most reported studies poor control of acute vomiting is associated with a higher incidence of delayed nausea and vomiting. It follows that good control in the first 24 hours of chemotherapy, even with apparent "over treatment", may avoid the need for additional and prolonged "rescue" therapy and subsequent problems with anticipatory vomiting.

Because nausea and vomiting are predictable, a planned approach to prophylactic treatment is indicated and scheduled doses should be administered in a timely way, regardless of whether symptoms appear. The duration of follow-up therapy should be determined by the expected duration of emetic activity of the administered chemotherapy, and also by the previous pattern of symptoms experienced by the patient.

Chemotherapy should be assessed for emetogenicity and antiemetics prescribed prior to starting chemotherapy. Table I includes cytotoxic drugs in use on The Haematology & Oncology Unit, and the likelihood of the drug to cause vomiting. Cytotoxic drugs are classified into emetic risk categories. Some drugs may be in more than one category depending on the dose used (cyclophosphamide, cytarabine, melphalan, methotrexate).

**Nausea and Vomiting Management**

| Category | Risk of emesis |
|---|---|
| High/very high | > 90% |
| Moderate | 30% - 90% |
| Low | 10% - 30% |
| Minimal | < 10% |

Most children receive combination treatment with more than one drug, so the anti-emetic prescription should be based on the drug with highest emetogenic potential. However, if two or more **moderately** emetogenic drugs are prescribed together:

e.g. anthracycline with methotrexate >5g/$m^2$ or cyclophosphamide

e.g cyclophosphamide with etoposide

e.g cytarabine >300mg/$m^2$ with etoposide

then the emetogenicity of the course is increased and patients should be treated as if receiving highly/very highly emetogenic chemotherapy.

During chemotherapy, the symptoms of nausea and vomiting should be assessed and treatment stepped up if required.

## 2. Table I - Emetic Potential of Cytotoxic Drugs in Use on The Haematology and Oncology Unit
**(Adapted from CCLG guideline on management of chemotherapy induced nausea and vomiting: March 2018)**

| High/Very High* (> 90%) | Moderate (30% - 90%) | Low (10% - 30%) | Minimal (< 10%) |
|---|---|---|---|
| Asparaginase (Erwinia) IV | Aldesleukin | Amsacrine | Alemtuzumab |
| Carboplatin | | | |
| Carmustine >250mg/m$^2$ | Arsenic Trioxide (caution with IV ondansetron) | ATG | Asparaginase IM |
| Cisplatin | Azacitidine | Bortezomib | Bevacizumab |
| Cyclophosphamide (> 1g/m$^2$) | Cladribine | Busulfan(antiemetics not usually required – discuss with consultant) | Bleomycin |
| Cytarabine (≥ 3000mg/m$^2$) | Clofarabine | | Chlorambucil |
| Dacarbazine | Cyclophosphamide (<1g/ m$^2$) | Cyclophosphamide <300mg/m$^2$ | Dasatinib |
| Dactinomycin | Cytarabine (< 3000mg/m$^2$) | Dinutuximab Beta | Mercaptopurine |
| Doxorubicin >30mg/m2/dose | | Everolimus | |
| Ifosfamide | Daunorubicin | Fludarabine | Methotrexate <1g/m$^2$ |
| Melphalan | Docetaxel | 5-Fluorouracil | Nelarabine |
| Methotrexate ≥12g/m$^2$ | Doxorubicin <30mg/m2/dose | Gemcitabine | Rituximab |
| Thiotepa >/= 300mg/m2 (10mg/kg) | | | |
| | Epirubicin | | Sorafenib |
| | Etoposide | Hydroxyurea | Sunitinib |
| | Gemtuzumab | | |
| | Idarubicin | Intrathecals | Thioguanine |
| | Imatinib | Nilotinib | |
| | Inotuzumab | Thiotepa <300mg/m2 | |
| | Irinotecan | Topotecan | |
| | Lomustine | Vincristine | |
| | Methotrexate ≥1g/m$^2$ to <12g/m$^2$ | Vindesine | |
| | Mitoxantrone | Vinorelbine | |
| | Oxaliplatin >75mg/m$^2$2 | Vinblastine | |
| | Procarbazine | | |
| | Temozolamide | | |
| | Treosulfan | | |

## 3. Anti-Emetic Therapy

Drugs used in the prevention of nausea and vomiting include both specific anti-emetics and adjuvant agents. The latter are used to potentiate the effects of the true anti-emetics, to treat anxiety or to induce sleep.

Substantial progress has been made in improving the control of chemotherapy induced nausea and vomiting, due mainly to the introduction of selective type-three-5-hydroxytryptamine ($5\text{-}HT_3$) receptor antagonists. More recently antagonists of the neurokinin -1 receptor ($NK_1$), which mediates the actions of Substance P (a regulatory peptide found in areas of the CNS and the gastro-intestinal tract believed to be essential components of the emetic reflex), have shown promise in particular at controlling delayed vomiting. Aprepitant is one of this category of drugs. It is licensed for use in children aged >6 months of age. Children receiving any cisplatin based regimens aged >6months should receive aprepitant, as long as there are no other drug interactions.

The $5\text{-}HT_3$ receptor antagonists (ondansetron, granisetron etc) are potent anti-emetics. Studies have shown that there is relevant equivalence of oral and parenteral routes. Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. It is recommended to infuse IV ondansetron over at least 15 minutes to reduce the risk of QT interval prolongation. Aim to correct $Mg^{2+}$ and $K^+$ electrolyte abnormalities before administering intravenous ondansetron.

Children receiving moderate or highly emetogenic chemotherapy (please note this includes **any** drug in the high or moderate category in the preceding table) should be given ondansetron in doses described in table IV. These are higher doses than in the BNFc to take into account the variation of pharmacokinetics in children.

Dexamethasone should also be given before chemotherapy if not contraindicated (see below) to children receiving very high/highly emetogenic or more than 1 moderately emetogenic chemotherapy drug.

Dexamethasone should **not** be prescribed as an anti-emetic for patients with leukaemia, or patients receiving steroids as part of their chemotherapy course (some lymphoma courses). This does not apply to these patients who are receiving highly emetogenic conditioning for a SCT. Dexamethasone should also not be prescribed with mifamurtide.

Dexamethasone may be contra-indicated **during** chemotherapy for patients with CNS tumours. However, dexamethasone may be prescribed **following** chemotherapy to reduce delayed vomiting in children with CNS tumours receiving highly emetogenic chemotherapy, such as cisplatin. Always discuss with consultant before prescribing dexamethasone as anti-emetic for a child with a CNS tumour.

Children receiving low emetogenic category chemotherapy should be given prn ondansetron. If breakthrough nausea occurs then give regularly with next cycle of chemotherapy. Children receiving chemotherapy with minimal emetogenic risk do not require anti-emetic treatment (unless they have had previous problems with these drugs).

Ondansetron may be required before intrathecal chemotherapy if nausea is a problem.

**Nausea and Vomiting Management**

Most chemotherapy courses will have anti-emetics prescribed on Chemocare as part of the course. Additions/changes for individual patients can be made in advance electronically, following a course, or during a course by adding to the inpatient/outpatient drug card or TTO. The registrar should review emesis on discharge and make a note of any required changes for future courses in EDMS. The antiemetics can then be tailored to the previous experience, and add in further drugs if not controlled.

## Table II Also refer to Table IV for further drug and dosage information

| Clinical Situation | Anti-emetic regimen |
|---|---|
| Very High emetogenic chemotherapy<br>(mainly cisplatin regimens or combinations of highly emetogenic drugs) | **Step 1:** Combination of regular:<br>**Ondansetron** – Optimal dose based on age, pre chemotherapy, for duration of chemotherapy, and for 3 days after<br>**Dexamethasone** – unless contraindicated, pre chemotherapy and for duration of chemotherapy, for a maximum 5 days.<br>**Aprepitant –** (age > 6months) and no drug interactions, daily for 3 days.<br>**In addition:** prescribe prn antiemetics for breakthrough CINV, eg metoclopramide, and ensure supplied for home for delayed nausea.<br>**Step 2:** If cannot have aprepitant or dexamethasone, add another regular antiemetic such as metoclopramide or levomepromazine.<br>If breakthrough occurs, switch prn choice to regular. |
| Highly emetogenic chemotherapy | **Step 1:** Combination of regular:<br>**Ondansetron** – Optimal dose based on age, pre chemotherapy, for duration of chemotherapy, and for 3 days after.<br>**Dexamethasone** – unless contraindicated, pre chemotherapy and for duration of chemotherapy, for a maximum 5 days.<br>**In addition:** prescribe prn antiemetics for breakthrough CINV, eg metoclopramide, and ensure supply for home for delayed nausea.<br>**Step 2: next page** |

| | |
|---|---|
| | **<u>Step 2:</u>**<br>If dexamethasone is contraindicated, consider adding aprepitant if no drug interactions/age >6months.<br><br>If cannot have aprepitant or dexamethasone, add another regular antiemetic such as metoclopramide, levomepromazine.<br>If breakthrough occurs, switch prn choice to regular. |
| Moderately emetogenic chemotherapy<br>**N.B. If ≥ 2 moderately emetogenic drugs given together treat as per highly emetogenic chemotherapy** | **<u>Step 1</u>:**<br>**Ondansetron** - dose based on age, regularly for duration of chemotherapy Optimise dose for age if nausea occurs.<br>**Metoclopramide–** prescribed prn, and for delayed nausea. Switch to regular if CINV occurs.<br><br>**<u>Step 2</u>:**<br>**Dexamethasone** – consider adding to subsequent courses if no contraindications if had problems with nausea.<br>**Levomepromazine** – add if required for breakthrough nausea, or if metoclopramide contraindicated. |
| Low emetogenic chemotherapy | **Ondansetron** - dose based on age prescribed prn. If nausea is a problem, then switch to regular. |
| Minimal emetogenic chemotherapy | No anti-emetic required unless known to have vomited with previous treatment with the cytotoxic. If previous history, use ondansetron. |
| Intrathecal drugs | May require **Ondansetron** - single dose before LP. |
| Anticipatory nausea and vomiting | Oral lorazepam may be useful if there is significant nausea or vomiting prior to delivery of chemotherapy. It can be given the evening before the planned chemotherapy, and then again 1 hour before starting chemotherapy. |

## Treatment to reduce delayed emesis

Children should be discharged with appropriate medication as necessary to continue at home to prevent delayed emesis. A short (2-3 days) course of metoclopramide +/- dexamethasone appears to be the most effective combination based on the available evidence. Ondansetron is less effective than metoclopramide for delayed emesis.

Children receiving highly/very highly emetogenic chemotherapy should be given up to 3 days of ondansetron and metoclopramide (unless the latter contraindicated) post chemotherapy.

Children receiving moderately emetogenic chemotherapy should be given a three day course of metoclopramide (unless contraindicated) post chemotherapy. Metoclopramide can cause extra-pyramidal symptoms, so parents should be advised about discontinuing the drug and seeking advice if these occur. An alternative anti-emetic should be used in the future, such as levomepromazine. Discuss with the registrar or consultant as to what is most appropriate. Levomepromazine covers the antiemetic actions of metoclopramide, cyclizine and hyoscine but has a greater number of side effects.

Procyclidine can be used to treat acute dystonic reactions which may be caused by some antiemetics (eg metoclopramide). This can be given i.v or orally, as per the doses in the BNFc, and is kept as stock on the Haematology and Oncology ward.

Children receiving low emetogenic chemotherapy do not require further anti-emetic medication, unless they have experienced previous problems with delayed vomiting.

**Treatment during radiotherapy**

Anti-emetics for children receiving radiotherapy should be prescribed as below.

## Table III Anti-emetic regimens for the prevention of radiation induced emesis

| Radiation Emetic Risk | Irradiated area | Recommended Anti-emetics |
|---|---|---|
| High (> 90%) | Total Body (TBI) | Regular ondansetron (age based dose) and dexamethasone (unless contraindicated), for duration of radiation therapy and for at least 24 hours afterwards |
| Moderate (60 – 90%) | Upper Abdomen, upper body | Regular ondansetron (age based dose) until end of radiation therapy. |
| Low (30 – 60%) | Lower thorax Cranium, head and neck, cranio-spinal and pelvis. | Prophylaxis (or rescue) with ondansetron (age based dose). If rescue required, then administer regularly until end of radiation therapy. |
| Minimal (< 30%) | Extremities | Rescue with ondansetron (age based dose). If required continue for each remaining radiation treatment day. |

**Rescue treatment – breakthrough and refractory nausea or vomiting**

Breakthrough refers to the re-occurrence of significant nausea or vomiting after a period of acceptable control. Refractory refers to the continuation of significant nausea or vomiting without a period of acceptable control.

For both indications, then antiemetics need to be stepped up, and other agents added in.

In severe cases consider continuous infusions of cyclizine or levomepromazine. Hyoscine hydrobromide patches (doses as per BNFc) may be useful in refractory CINV, though cannot be used with cyclizine, metoclopramide and levomepromazine. Nabilone could also be considered for adolescents who are able to swallow capsules, Refer to Table IV for further information regarding drugs and dosage recommendations.

Avoid administering domperidone with drugs that are strong CYP3A4 inhibitors (systemic azoles, some macrolides, aprepitant), or any other drug known to prolong QT.

Avoid aprepitant in those age <6months, and be aware of any potential drug interactions.

If a child requires additional therapy, this should be recorded in the case notes and their antiemetic prescription changed for subsequent courses.

## 4. References

Paw Cho Sing E, Robinson PD, Flank J et al. Classification of the acute emetogenicity of chemotherapy in pediatric patients: A clinical practice guideline. Pedriatric Blood Cancer. 2019 Jan;66:e27646

Patel P, Robinson PD, Thackray J, Flank J et al. Guideline for the prevention of acute chemotherapy induced nausea and vomiting in pediatric cancer patient: a focused update. Pediatric Blood Cancer. 2017 Oct;64(10):e26542

Childrens Cancer and Leukaemia Group. CCLG guideline on the management of chemotherapy induced nausea and vomiting. Version 1. March 2018

Paediatric Formulary Committee. BNF for Children (online)London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. www.medicinescomplete.com [accessed on 26/05/2022]

Lexicomp Pediatric and Neonatal Dosage Handbook (online).Available https://online.lexi.com. [Accessed 26/05/2022]

## Table IV Anti-Emetic Drugs and Administration Give anti-emetic drugs IV only if cannot tolerate oral route

| Drug and formulation | Route | Regular Dose and frequency | | Comments |
|---|---|---|---|---|
| Ondansetron*<br>4mg + 8mg tablets<br>4mg + 8mg melts<br>4mg/5ml liquid<br>IV 2mg/ml | Oral/IV infusion | <5kg 1mg<br>< 1 year >5kg 2 mg<br>1 – 4 years 4 mg<br>4-11 years 4mg<br>≥ 12 years 8mg | **TWICE daily**<br>**TWICE daily**<br>**TWICE daily**<br>**TWICE/THREE times a day**<br>**TWICE/THREE times a day**<br><br>*doses differ than that in BNFc | During the days receiving chemotherapy. Ensure minimum of 4 hours between doses. For low/moderately emetogenic chemo, ondansetron would not usually be required beyond the end of chemotherapy. For highly/very high emetogenic chemotherapy, then up to 3 days regular ondansetron may be required once chemotherapy is complete. |
| Dexamethasone<br>2mg/5ml liquid<br>0.5mg and 2mg tablets.<br>IV injection | Oral/IV infusion | For highly emetogenic chemotherapy:10mg/$m^2$ (max 20mg) once daily on days of chemotherapy<br><br>For moderately emetogenic chemotherapy:<br>(if needing to step up antiemetics)<br>BSA ≤ 0.6$m^2$ : 2mg BD<br>BSA > 0.6$m^2$ - <1.2$m^2$: 4mg BD<br>BSA >1.2$m^2$ : 8mg BD | | For maximum 5 days.<br>Avoid with CNS tumours, and those already on steroids as part of chemotherapy (ALL, lymphoma). Avoid with mifamurtide.<br>**Reduce dose by 50% if administering with aprepitant**<br><br>If using BD dose – then give morning and afternoon to reduce insomnia. |
| Metoclopramide<br><br>10mg tablets<br>5mg/5ml liquid<br>10mg/2ml IV | Oral / IV | >1year: 150micrograms/kg (max dose 10mg)<br>8 hourly for up to 5 days<br><br>Not recommended in children <1 year. If using in children <1 year for an unlicensed indication, then max 100microgram/kg BD and a consultant decision. | | Used to prevent delayed nausea and vomiting. Effective for severe vomiting due to radiotherapy.<br>Use with caution with cyclizine and hyoscine – may reduce prokinetic effects. |
| Domperidone<br>10mg tablets<br>1mg/ml liquid | Oral | >1month & <35kg: 250 micrograms/kg TDS (max dose 10mg)<br>≥12 years and >35kg: 10mg TDS | | Not with metoclopramide<br>Contraindicated in patients with cardiac conductive disorders, or underlying cardiac disease. Avoid with concomitant administration of drugs that prolong the QT (eg Arsenic) or potent CYP3A4 inhibitors (eg azole antifungals). Avoid with aprepitant. |

**Nausea and Vomiting Management**

| Drug and formulation | Route | Regular Dose and frequency | Comments |
|---|---|---|---|
| Lorazepam<br>1mg tablets<br>IV is available for intractable vomiting. | Oral/IV | <u>Breakthrough nausea and vomiting:</u><br>25 – 50micrograms/kg (max dose 1mg) 6 hourly<br><br>Anticipatory nausea and vomiting:<br>40-80micrograms/kg (max 2mg) as a single dose the evening before chemotherapy, and as a single dose one hour before chemotherapy. | There is no sublingual formulation, but if this route is required, the oral tablets can be used. |
| Cyclizine<br>50mg tablets<br>50mg/ml IV | Oral / IV | Age 1 month – 5 years: 0.5 - 1mg/kg (max 25mg) TDS<br>Age 6-11 years: 25 mg TDS<br>Age ≥ 12 years: 50 mg TDS | Can be given as continuous infusion – total daily dose infused over 24 hours<br>Tablets can disperse in water so round oral dose to be measurable increment of 50mg tablet. |
| Levomepromazine<br>6mg and 15mg tablets<br>IV 25mg/ml | Oral | Age 1 month – 11 years: 50-100 micrograms/kg once or twice daily. This may be increased as necessary and tolerated to max 1mg/kg (max 25mg) once or twice daily.<br>Age ≥12 years: 3mg once or twice daily. This may be increased as necessary and tolerated to a maximum of 25mg once or twice daily. | Higher doses are very sedative, so start at the lower end of the dose range.<br>Tablets can be dispersed in water, try to round where possible to a measurable tablet increment.<br>Avoid using with cyclizine, hyoscine and metoclopramide. |
| | IV | Slow infusion: 25-100microgram/kg once or twice daily.<br>Or as continuous infusion over 24 hours:<br>Age 1 month – 11 years: 100-400 micrograms/kg/24hours (max 25mg/24hour)<br>Age ≥12 years: 5-25mg over 24 hours. | |
| Aprepitant<br>125mg/5ml oral suspension<br>125mg + 80mg capsules | Oral | Age >6months (>6kg) to 11 years:<br>3mg/kg (max 125mg) on day 1, then 2mg/kg (max 80mg) daily on days 2 and 3.<br><br>Age ≥ 12 years: 125mg on day 1, then 80mg daily on days 2 and 3. | **Once Daily** for 3 days only<br>**Reduce antiemetic dose of dexamethasone to 50% due to drug interaction.**<br>Avoid with domperidone<br>Used only for highly/very high emetogenic chemo.<br>Use with caution or avoid in patients receiving drugs metabolised through CYP3A4 (eg ciclosporin, fentanyl, midazolam). Or inducers/inhibitors if CYP3A4 (eg azole antifungals). Avoid with ifosfamide and irinotecan. May alter the metabolism of cyclophosphamide and thiotepa. Contact the pharmacist for further information. |

| Drug and formulation | Route | Regular Dose and frequency | Comments |
|---|---|---|---|
| Nabilone 1mg capsule (controlled drug) | oral | Adolescents >30kg: 1mg TDS, reduce frequency if CNS side effects problematic | **Do not use with levomepromazine and lorazepam** |

References as above (section 4)