MANAGEMENT OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

1. INTRODUCTION

Chemotherapy induced nausea and vomiting (CINV) is one of the most distressing side effects of childhood cancer treatment, and if not managed appropriately can affect compliance with future treatment. If not controlled, CINV can also lead to complications such as malnutrition, dehydration, electrolyte imbalances, prolonged hospitalisation and psychological issues including anticipatory nausea and vomiting.

CINV can be:

- acute (0–24 hours after first dose),
- delayed (24 hours–5 days post chemotherapy)
- anticipatory (prior to the start of chemotherapy)

Physiological differences exist between the acute and delayed CINV, therefore optimal management may require different therapeutic approaches to gain adequate control.

The Children's Cancer and Leukaemia Group (CCLG) have produced a national framework document to guide local implementation, which has been used to guide the content of this Trust guideline.

2. PURPOSE/SCOPE

The following guidelines are for the management of CINV in paediatric oncology/haematology patients. The guideline should be used in conjunction with the patient's individual anti-emetic history.

3. RECOMMENDATIONS

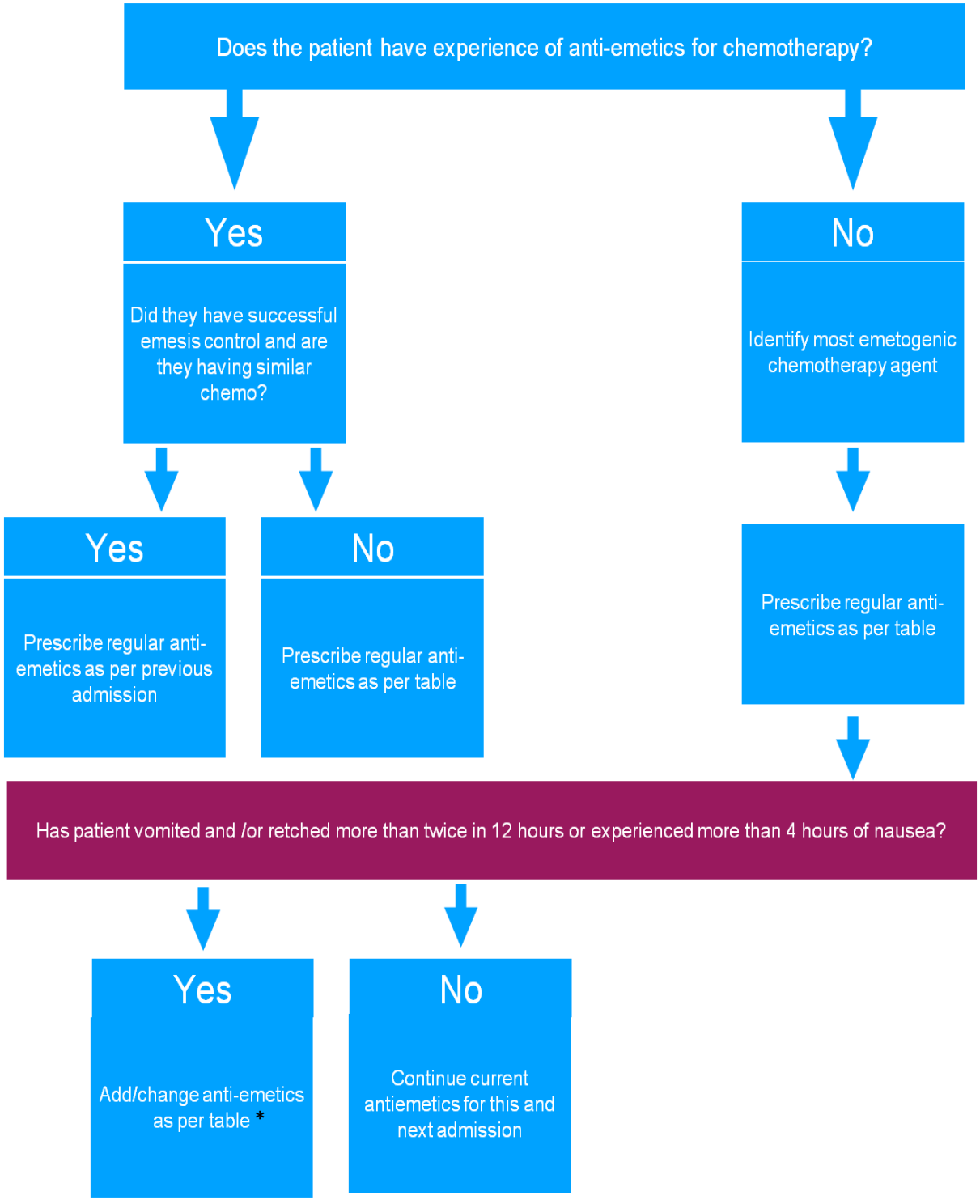
Children and young people about to receive chemotherapy should have their chemotherapy assessed for emetogenicity. The CCLG have recommended chemotherapy be divided into four strata:

- Very highly emetogenic chemotherapy
- Highly emetogenic chemotherapy
- Moderately emetogenic chemotherapy
- Low emetogenic chemotherapy

Children and young people should have their symptoms of nausea and vomiting assessed.

Children and young people about to undertake chemotherapy should have antiemetics prescribed prior to chemotherapy, adapted to their own personal experience.
While the evidence underpinning personalisation of therapy is weak, it is common practice to use higher-level antiemetics when a child or young person has experienced problems with nausea and/or vomiting previously. Good control is thought to reduce the chances of anticipatory, and breakthrough/refractory, nausea and vomiting in subsequent courses.

4. **FLOWCHART – OVERALL APPROACH TO SELECTING ANTI-EMETICS**



*** Using table 1:** move to the next step within the antiemetic intensity level. For subsequent cycles where the same drug/drug combinations or drug-combinations of similar emetogenic potential are given consider starting prophylaxis at the increased intensity level.

Table 1: MANAGEMENT OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)	
Using table: move to the next step within the antiemetic intensity level. For subsequent cycles where the same drug/drug combinations or drug-combinations of similar emetogenic potential are given consider starting prophylaxis at the increased intensity level. ***Avoid dexamethasone in the following groups:** 1. Brain tumour patients (cyclizine may be helpful) 2. Leukaemia patients 3. Any treatment cycles which include steroids as anti-cancer therapy 4. Post BMT and SCT patients 5. Patients receiving immunotherapy (e.g. mifamurtide) Reduce dexamethasone dose to 50% when given with aprepitant.	
Very Highly Emetogenic Chemotherapy (1)	
Cisplatin **Melphalan**	**Step 1:** Aprepitant + ondansetron + dexamethasone50% dose) **Step 2:** Add regular levomepromazine If fails step 1: For subsequent cycles (if ≥ 6 months old) : Aprepitant + ondansetron + dexamethasone* (50% dose) + levomepromazine For patients < 6 months old do not give aprepitant: **Step 1:** Ondansetron + levomepromazine **Step 2:** Add regular dexamethasone* If fails step 1: For subsequent cycles (if < 6 months old): Ondansetron + levomepromazine + dexamethasone
Very Highly Emetogenic Chemotherapy (2)	
Thiotepa **Cyclophosphamide >2g/m2** **Cyclophosphamide + anthracycline** **Cyclophosphamide + etoposide** **Doxorubicin + Ifosfamide** **Cytarabine 300mg/m^2 + etoposide** **Doxorubicin + methotrexate 5g/m^2**	**Step 1:** Ondansetron + levomepromazine + PRN dexamethasone dose) **Step 2:** Add regular dexamethasone* If fails step 2: For subsequent cycles escalate to treatments from the "very highly emetogenic chemotherapy regimens (1 i.e. (if ≥ 6 months old) aprepitant + ondansetron + dexamethasone* (50% dose)

Highly Emetogenic Chemotherapy	
Carboplatin **Carmustine** **Cyclophosphamide >1g/m^2** **Cytarabine >1g/m^2** **Dacarbazine** **Ifosfamide** **Methotrexate >3g/m^2**	**Step 1:** Ondansetron +/- levomepromazine **Step 2:** Add regular levomepromazine if not given at step 1 **Step 3:** Add regular dexamethasone* for breakthrough If fails step 3: For subsequent cycles escalate to Very Highly Emetogenic Chemotherapy (1) (if ≥ 6 months old) i.e. aprepitant + ondansetron +/- dexamethasone* (50% dose)
Moderately Emetogenic Chemotherapy	
Amsacrine **Busulfan IV** **Cyclophosphamide <1g/m^2** **Cytarabine 500mg-1g/m^2** **Daunorubicin** **Doxorubicin** **Docetaxel** **Epirubicin** **Idarubicin** **Irinotecan** **Lomustine** **Mitoxantrone** **Temozolomide** **Actinomycin D**	**Step 1:** Ondansetron + PRN levomepromazine **Step 2:** Add regular levomepromazine **Step 3:** Add regular dexamethasone*) If fails step 3: For subsequent cycles escalate to Very Highly Emetogenic Chemotherapy (1) (if ≥ 6months old) : aprepitant + ondansetron +/- dexamethasone* (50% dose)
Arsenic trioxide	For arsenic give PRN Cyclizine ONLY (Arsenic prolongs QT interval).
Low Emetogenic Chemotherapy	
Asparaginase **Bleomycin** **Oral busulphan** **Cladribine** **Cytarabine <500mg/m^2** **Chlorambucil** **Etoposide** **Fludarabine** **Gemcitabine** **Mercaptopurine** **Procarbazine** **Thioguanine** **Topotecan** **Vinka Alkaloids**	**Step 1:** Ondansetron PRN **Step 2:** Regular ondansetron If fails step 2: For subsequent cycles escalate to Step 2 of Moderately Emetogenic Chemotherapy i.e. regular ondansetron and levomepromazine

IV fosaprepitant must only be prescribed when the oral route of aprepitant is not possible. The decision to use must be made by the consultant only, and should be documented clearly on Meditech.

5. REFRACTORY CINV

Following escalation through the intensity levels as detailed in table 1, consider alternate approaches e.g. switching levomepromazine from an IV bolus to IV infusion or adding lorazepam. Must be discussed with consultant and pharmacy.

6. ANTICIPATORY CINV

Consider home administration of ondansetron +/- levomepromazine up to 24 hours prior to administration of chemotherapy. Low dose lorazepam may be prescribed (must be discussed with a consultant). Offer psychological interventions.

7. DELAYED CINV:

To be discussed with consultant and pharmacy.

8. INFORMATION FOR SHARED CARE CENTRES

For nausea and/or vomiting that occurs > 5 days post chemotherapy, consider regular ondansetron or alternative antiemetics as directed by consultant locally. If vomiting persists discuss with oncology/haematology consultant at Alder Hey.

9. PREFERRED ROUTE OF ADMINISTRATION

Oral/Orodispersible administration is preferred wherever possible. Dual IV and oral routes can be prescribed for ondansetron, dexamethasone and levomepromazine ONLY.

For duplicate route prescribing the prescriber must add a free text note in the 'Dose Instruction' field indicating there is a duplicate route 'see IV/ Oral also'.

The nurse should choose the route at the point of administration and for the route not given: select 'not given' and add free text – 'duplicate route'. If the patient is an outlier only one route of prescribing is allowable.

10. **ANTIEMETIC DRUG INFORMATION**

Drug	Dose	Additional information
Ondansetron ($5HT_3$ antagonist) **Preparations:** **IV:** 8mg/4mL **Oral Liquid:** 4mg/5mL **Tablets:** 4mg, 8mg **Sublingual melts:** 4mg, 8mg **Orodispersible films:** 4mg, 8mg	**IV infusion (over 15 minutes):** 5mg/m² three times daily (max single dose 8mg) **Oral:** every 8 or 12 hours <0.3m² 1mg 0.3-0.6m² 2mg 0.6-0.9m² 4mg 0.9-1.2m² 6mg >1.2m² 8mg (max single dose 8mg)	Reduce dose in moderate/severe hepatic impairment. Do not use with drugs that prolong QT interval. Dosing is for CINV only.
Dexamethasone **Preparations:** **IV:** 6.6mg/2ml **Oral Liquid:** 10mg/5mL **Tablets:** 500microgram, 2mg	**IV infusion (over 15 minutes)/oral LOADING DOSE:** 8mg/m² (max single dose 12mg) **then:** **IV infusion (over 15 minutes)/oral:** 5mg/m² three times daily (max single dose 8mg)	Dose of dexamethasone must be reduced by 50% when given with aprepitant. **Avoid dexamethasone in the following groups:** 1. Brain tumour patients (cyclizine may be helpful) 2. Leukaemia patients 3. Any treatment cycles which include steroids as anti-cancer therapy 4. Post BMT and SCT patients 5. Patients receiving immunotherapy (e.g. mifamurtide)
Levomepromazine **Preparations:** **IV:** 25mg/mL **Oral suspension:** 1mg/mL **Tablets:** 25mg scored	**IV infusion (over 30 minutes):** 0.1mg/kg twice daily (max single dose 6.25mg) **IV continuous infusion:** 0.25-0.5mg/kg/24 hours (max dose 25mg) **Oral:** 0.2 mg/kg twice daily (max single dose 12.5mg)	Monitor for drowsiness. Avoid using with cyclizine. Avoid use in hepatic impairment. Reduce dose in renal impairment. Can be useful in vomiting due to raised intracranial pressure. Care in patients receiving ifosfamide as sedation may mask signs of encephalopathy.

Aprepitant (oral) **Preparations:** **Capsules:** 80mg, 125mg	**6 months to <12 years old and ≥6kg:** Day 1: 3mg/kg once daily (max. dose 125mg) Day 2 & 3: 2mg/kg once daily (max. dose 80mg) **≥12 years old:** Day 1: 125mg once daily Day 2 & 3: 80mg once daily	NB. Can increase ifosfamide mediated neurotoxicity and irinotecan toxicity. Can increase exposure to vinca alkaloids. Can increase exposure to tyrosine kinase inhibitors. Monitor closely. Dose of dexamethasone must be reduced by 50% when given with aprepitant. Caution – check for drug interactions.
Fosaprepitant (IV) **Preparations:** **IV:** 150mg vial	**6 months to <12 years old and ≥6kg (IV infusion over 60 minutes):** Day 1: 3mg/kg once daily (max. dose 115mg) Day 2 & 3: 2mg/kg once daily (max. dose 80mg) **≥ 12 years old (IV infusion over 30 minutes):** Day 1: 115mg once daily Day 2 & 3: 80mg once daily	NB: Can increase ifosfamide mediated neurotoxicity and irinotecan toxicity. Can increase exposure to vinca alkaloids. Can increase exposure to tyrosine kinase inhibitors. Monitor closely. Dose of dexamethasone must be reduced by 50% when given with fosaprepitant. Caution – check for drug interactions.
Cyclizine **Preparations:** **IV:** 50mg/mL **Tablets:** 50mg scored **Oral solution:** 5mg/5mL	**IV bolus/oral:** up to three times daily 1 month-6 years: 0.5-1mg/kg (max 25mg) 6-12 years: 25mg 12-18 years: 50mg	Avoid using with levomepromazine.

References

1. Children's Cancer and Leukaemia Group (CCLG), "Guideline on the management of chemotherapy induced nausea and vomiting". CCLG Supportive Care Group, Version 1, 2018.
2. Alder Hey Children's NHS Foundation Trust. Management of Chemotherapy Induced Nausea and Vomiting. Jan 2016.
3. British National Formulary for Children 2019-2020.

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Section Number	Page Number	Revision(s) made	Reason for revision(s)
	2 & 3	Ondansetron IV 15 min infusion	SPC change
	2 & 3	Additional information on infusion times	For completeness
	3	Cyclizine added	In line with current usage
	3	Metoclopramide added	MHRA guidance
		Updated to reflect new national guidance on chemotherapy induced nausea and vomiting, produced by Children's Cancer and Leukaemia Group (CCLG)	CCLG guidance