Chapter 23

Therapy-related issues: malignant disease and immunosuppression

Policy for the administration and handling of cytotoxic drugs

Cytotoxic drugs are used in the treatment of cancers and certain other disorders. They act by killing dividing cells, by preventing their division. In addition to malignant cells, they also act on normal cells. Therefore their use poses certain risks to those who handle them. It is important to ensure the safety of staff and patients who come in contact with these drugs.

- Cytotoxic drugs may only be reconstituted in facilities specifically approved for the purpose.
- Staff who prescribe, clinically screen, reconstitute, label, administer, and dispose of cytotoxic drugs must be appropriately trained and assessed as competent and must follow the local approved procedures.
- In areas where cytotoxic drug use is infrequent, a risk assessment must be carried out before a cytotoxic drug is requested. This should assess the availability of appropriate equipment and evidence of training, and demonstrate competence in safe administration of the drugs.
- Oral anticancer medicines must be prescribed, dispensed, administered, and monitored using the same standards as for injectable chemotherapy.

Cytotoxic drug procedures

- Any area in the hospital (including the wards, out-patient or day-case areas, and pharmacy) using cytotoxic drugs should have available current information on the type of agents used. This information should include relevant health and safety information (Control of Substances Hazardous to Health).
- Cytotoxic drugs are occasionally used to treat clinical disorders other than cancer. In such instances, the patient should be referred to a clinical area where cytotoxic drugs are used routinely. Alternatively, a competent practitioner from such an area can administer the drug in the patient's own ward. A trained member of staff must undertake a risk assessment to determine by whom and in what circumstances the drug can be administered.

Prescription, preparation, and reconstitution

- Ideally, all chemotherapy prescriptions are prescribed on an electronic chemotherapy prescribing system. In non-cancer areas, prescriptions may be handwritten on standard prescription charts, and they must be written legibly and signed in indelible black ink. In some cases, prescriptions might be computer-generated, either on an approved chemotherapy chart or on a standard prescription chart.
- Chemotherapy should be prescribed by prescribers experienced in the treatment of neoplastic disorders. Be aware of local policies stipulating who can prescribe chemotherapy.

- The chief pharmacist is responsible for ensuring that cytotoxic drug reconstitution services are provided in appropriate facilities. In exceptional circumstances, they can designate other areas for reconstitution.

Labelling and transportation

- Syringes, infusion devices, and infusion fluids containing cytotoxic drugs must be clearly labelled, to identify the potential cytotoxic hazard, and placed inside a sealed plastic bag,
- Cytotoxic drugs must be packaged and transported in sealed containers identified as containing cytotoxic drugs. The designated cytotoxic drugs reconstitution services must be notified at once if the integrity of a container received is suspect.
- Oral cytotoxic drugs should be transported in the same way as non-cytotoxic medication. In-patient supplies should be labelled as 'cytotoxic' on the normal prescription label.

Administration

- Relevant clinical laboratory results, as defined by chemotherapy protocols, must be reviewed before administration, and appropriate action taken.
- The following checks are advised to be made by two qualified staff members, one of whom must be registered as competent in cytotoxic drug administration, depending on local policy.
  - Visual check of the product (to include signs of leakage, contamination, or breakdown products).
  - The drug has been appropriately stored and is within its expiry date.
  - Patients must be identified positively using three patient identifiers, as defined in the locally approved policy.
  - The following prescription details must be checked:
    - protocol
    - dose
    - diluent (if relevant)
    - route of administration
    - frequency.
  - Staff should use personal protective equipment and clothing if handling and administering cytotoxic drugs. This includes gloves, an apron, and in some cases protection for the face (either goggles or a mask.).

Accidental spillage

- All areas in which cytotoxic agents are stored, prepared, and administered should have a spill kit available for use at all times. These kits are usually obtained from the pharmacy department. The kit includes instructions on how to proceed safely. Staff should be familiar with the instructions before dealing with a spill.
- A trained healthcare professional should deal with the spill immediately. After use, the spillage kit should be replaced.
- Be familiar with your local policy and location of spillage kits in areas using cytotoxic drugs.

Disposal of product waste

- Cytotoxic waste should be disposed of separately to normal clinical waste and marked as being cytotoxic, according to local policy. The incorrect disposal of cytotoxic waste can result in prosecution under the Special Waste Regulations 1996.
- Cytotoxic waste includes vials that have contained cytotoxic drugs, syringes, needles, IV bags, infusion sets used to administer cytotoxic drugs, gowns, and gloves, and urinary catheters and drainage bags from patients undergoing cytotoxic therapy.
- Cytotoxic waste should be disposed of according to local policy and clearly marked with cytotoxic residue tape.
- Hospitals have specific policies on the storage and collection of cytotoxic waste to ensure that it does not enter the normal clinical waste stream.

Disposal of excreta and blood

- Precautions should be taken to prevent occupational skin contact.
- Because cytotoxic drugs have varying half-lives, specific information about them will be found on safety datasheets. If the information is not specified, it is deemed GCP to apply universal precautions for 48h after administration.
- Patients and relatives (particularly pregnant mothers) who handle body fluids at home should be given appropriate advice.
- Gloves must be worn when handling all body fluids (e.g. blood, urine, faeces, colostomy and urostomy bags, nappies) during and after the administration of cytotoxic drugs.
- Linen contaminated with body fluids and cytotoxic drugs must be handled according to the local policy for handling cytotoxic contaminated waste.
- If contamination of the skin, eyes, or mucous membranes is suspected, the area should be rinsed thoroughly with large amounts of water and then washed with soap and water.

Incidents arising from handling and administration of cytotoxic drugs

- Any incident involving prescribing, administration, and disposal of cytotoxic drugs must be reported according to the local incident reporting system.
- The most probable incident for staff is accidental exposure to the drug during the set-up and administration of the drug. This might result from a bag leaking or bursting, or problems with the line *in situ*.
- If there is eye and skin contamination, rinse the affected area with copious amounts of tapwater and seek further treatment, if needed. The occupational health department should be notified of all cases of staff exposure to organize risk assessment and follow-up care plans.
- For patients, the most probable incidents arising are extravasation during treatment (see 📖 p.486).

Handling cytotoxics during pregnancy

Pregnant staff should refer to their local policy with regard to handling cytotoxic drugs, because this group of drugs is potentially mutagenic, teratogenic, and carcinogenic. A risk assessment must be undertaken for each local area.

See 🕮 pp. 190–3 for recommendations on handling potentially teratogenic drugs in pregnancy.

Intrathecal chemotherapy

See 🕮 p. 494, 'Intrathecal administration of chemotherapy'.

Further reading

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March guidelines: 🖱 http://www.marchguidelines.com

Clinical screening of chemotherapy prescriptions

All chemotherapy prescriptions must be checked and authorized by an oncology pharmacist who has undertaken the appropriate specialist training and local accreditation. Where possible, chemotherapy should be prescribed using an electronic chemotherapy prescribing system.

Validating prescription details

- Check that doses have been correctly calculated and prescribed.
- Ensure that generic drug names have been used and the dosage form is specified.
- Check maximum doses according to the protocol.
- Check patient weight, height, and body surface area (BSA). Ensure that weight has been taken within time frames specified in local protocols—e.g. if it is more than 2 months since a patient has been weighed and no new weight is recorded, ask for the patient to be weighed.
- BSAs are often rounded. Do not query a discrepancy unless it is >0.1m^2 for adults.
- Oncology patients might have their BSA capped at 2m^2 or 2.2m^2,or calculated using ideal body weight. Check the local policy. For example, obese patients—confirm with the prescriber that BSA has not been capped if >2m^2 or >2.2m^2.
- Haematology patients may not have their BSA capped—check the local policy.
- Drug dosages should be expressed in metric notation. The word *units* should never be abbreviated.
- For rounding doses, be aware that the exact dose might have to be rounded to account for tablet or vial size, or dose banded according to local policy.
- Check cumulative doses—e.g. anthracyclines (doxorubicin has a maximum cumulative dose of 450mg/m^2) and bleomycin (maximum cumulative dose of 400,000 IU).
- Check local policy for variation in the dispensed dose compared with the prescribed dose that has been agreed (often 5% variation is agreed).
- Administration rate and route should be specified.
- Administration schedule and duration of treatment should be included.
- For oral anticancer agents, calculate the exact number of tablets or capsules to be supplied and annotate the prescription accordingly.
- Ensure that the appropriate prescriber has signed and dated the prescription.
- Ensure that the infusion fluid and volume are stated and appropriate.
- For routes other than IV, ensure that the route is prescribed in full (e.g. *intrathecal*, not *IT*).

Verification of cycle 1 prescriptions

- Check patient's name, date of birth and hospital/NHS number.
- Check the date the order was generated, and time and date treatments are to be administered.
- Check that the BSA has been calculated correctly:

$$\text{Surface area} = \sqrt{\left(\text{Height}\,[\text{cm}] \times \text{weight}\,[\text{kg}] / 3600\right)}$$

- BSA is often capped at $2m^2$ or $2.2m^2$. Check your local policy.
- Check the patient's ideal body weight (IBW). If the patient is significantly more or less than their IBW, discuss with their doctor. An example of an IBW formula is as follows:
  IBW (kg) men = [(height (cm) − 154) x 0.9] + 50
  IBW (kg) women = [(height (cm) − 154) x 0.9] + 45.5
  IBW calculators are available on the intranet (e.g. www.halls.md/ideal-weight/body.htm).
- Check the patient's treatment against the established protocol.
- Check the frequency of intended cycles and appropriate interval since any previous chemotherapy.
- Ensure that the protocol is the one intended to be prescribed by checking the patient's medical record.
- Check the patient's age, because some doses/protocols are age related.
- Check for verification of dose modification or variance from the protocol and identification of the factors on which treatment modifications are based.
- Confirm the dose per day versus the dose per cycle with the protocol.
- Interpret critical laboratory values to see if a dose modification is required—e.g. impaired renal function, clotting disorders and LFTs (if appropriate for drug).
- Check that the correct drugs have been prescribed and that all calculations have been performed correctly.
- Check if there are any drug interactions between the chemotherapy and the patient's regular medication.
- Check patient's allergies and medication sensitivities.
- Check if there are any drugs contraindicated with the chemotherapy.
- Check for authorized prescriber's name and signature.

Second and subsequent cycles

- Check that the chemotherapy cycle is correct for the protocol.
- Check that the correct cycle was ordered.
- Check that the drugs were prescribed on the correct days and start dates.
- Check that there has been no significant change in the patient's weight that might significantly change the calculated BSA.
- Check response to previous treatment:
  - blood indices—haematology/biochemical
  - tolerability and adverse reactions.
- Check to see if any appropriate modifications have been made in relation to a previous response or critical laboratory values (normally in the protocol).

Clinical check

- What type of malignancy does the patient have? Is the chemotherapy appropriate for the malignancy?
- What is the patient's renal and hepatic function? Do any of the doses need adjusting to take this into account?
- Has the patient had any chemotherapy before? Do any of the drugs have a maximum cumulative lifetime dose (e.g. anthracyclines)?
- Other checks include allergies/reactions to previous chemotherapy and the extent of disease (need for prehydration or allopurinol).
- Check critical laboratory values—if white cell count, neutrophils or Hb are above or below a predefined limit, refer to individual protocols.
- Check to see if any appropriate modifications have been made in relation to previous response or critical tests (normally in protocol).
- Check if any supportive care has been prescribed—e.g. antiemetics.

Endorsing prescriptions

- Amend any abbreviations.
- Annotate generic names.
- Ensure infusion fluid, volume, and rate of administration are stated and appropriate.
- Check that the appropriate route is prescribed.
- For routes other than IV, ensure that the route is prescribed in full—e.g. intrathecal not IT.
- Check that oral doses are rounded up or down to account for tablet size.

Annotations

- Sign and date the prescription to confirm that it is correct, safe, and appropriate.
- The following annotations should be made in the medical record.
  - Date.
  - 'Chemo ordered'—'confirmed' or 'awaiting confirmation (TBC)'.
  - Cycle number and date the cycle is due.
  - Any dose reductions.
  - Other relevant notes.
    - With the first cycle, annotate the drugs, doses, and frequency in the medical record, including reasons for alterations, so that it is clear exactly what the patient has received. Include the BSA, height, and weight that were used to calculate the doses and relevant biochemistry.
    - On the last cycle, record the cumulative dose of anthracyclines or bleomycin received.
  - Clinical pharmacist's signature and contact details.

Further reading

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Chemotherapy dosing

Cancer chemotherapy drugs often have a narrow therapeutic window between the dose that is effective and the dose that can be toxic. Inappropriate dose reduction reduces chemotherapy efficacy. However, if doses are not ↓ in patients with organ dysfunction, this can lead to serious or life-threatening toxicity. It is essential that cytotoxic drugs are dosed correctly and adapted to individual patients to enable the maximum probability of a desired therapeutic outcome, with minimum toxicity.

Before administration of chemotherapy, each patient should be assessed for performance status, renal function, liver biochemistry tests, serum albumin level, and prognosis. Myelosuppression is the most common and dangerous toxicity of cytotoxics, so all patients must have a blood count before each cycle of chemotherapy. Patients should only be administered chemotherapy if their white blood cell count is $>3.0 \times 10^9$/L (or neutrophil count is $>1.5 \times 10^9$/L) and platelet count is $>150 \times 10^9$/L. There can be exceptions to this in some local policies or for patients with haematological malignancies and those undergoing intensive treatment with specialized support.

Doses of cytotoxics are usually calculated on the basis of BSA, which is measured in square metres (m^2). The dose is quoted as units (e.g. milligrams, grams, or international units) per square metre. The patient's BSA is calculated using a nomogram from patient height and weight measurements or using the following calculation:

$$\text{Surface area} = \sqrt{\left(\text{Height}\,[\text{cm}] \times \text{weight}\,[\text{kg}] / 3600\right)}$$

This practice is derived from the relationship between body size and physiological parameters (e.g. renal function). The performance status of the patient and their renal and liver functions are also taken into account. Prior to each cycle of treatment, toxicities must be recorded using common toxicity criteria. Doses are modified if the patient experiences toxicity to treatment or changes in body weight occur. The size of the reduction depends on the nature and severity of the toxicity, taking into account whether the chemotherapy is palliative or curative in intent.

Obese patients have physiological changes that affect drug disposition, including ↑ blood volume, organ size, and adipose tissue mass. BSA is often 'capped' at 2.0–2.2m^2 in obese patients. The use of ideal body weight can be considered in these settings. However, the possibility of under-dosing needs to be considered in curative patients.

Although it is conventional to prescribe chemotherapy according to BSA, it is acceptable to use pre-prepared standard doses for commonly used drugs to facilitate bulk preparation and rapid dispensing. This is known as 'dose banding'. The rounded dose must be within agreed limits—e.g. within 5% of the calculated dose.

However, there are some exceptions to calculation of doses on the basis of BSA. Drugs whose doses can be calculated using other parameters include the following.

- Asparaginase—the dosage is IU/kg body weight or IU/BSA.
- Bleomycin—IU, either per patient surface area or as a fixed dose.
- Carboplatin—the Calvert equation[1] can be used to calculate the dose of carboplatin in patients with or without renal impairment:

$$\text{dose (mg)} = \text{AUC} \times (\text{GFR} + 25)$$

  where AUC is the target area under the plasma concentration curve (AUC is usually in the range 4–7) and GFR is the glomerular filtration rate. For example, the dose of carboplatin for a patient with a GFR of 75mL/min, using an AUC of 5, would be:

$$5 \times (75 + 25) = 500\text{mg carboplatin.}$$

- Cytarabine—dosage in mg/kg for certain indications.
- Floxuridine—dosage in mg/kg.
- Mitomycin—dosage in mg/kg for certain indications.

Some chemotherapy drugs (e.g. anthracyclines) have a maximum recommended cumulative lifetime dose. For example, doxorubicin has a maximum cumulative lifetime dose of 450mg/m^2 and bleomycin has a maximum cumulative lifetime dose of 400,000 IU. If patients receive more than the maximum cumulative lifetime dose, they are at increased risk of potentially life-threatening toxicity.

Frequency of chemotherapy administration

Chemotherapy is administered in various treatment cycles ranging from 1 to 6wks. Cycle frequency is based on cancer type and treatment choice. Frequency and duration of treatment cycles continue to evolve and are not absolute. It is important to always verify treatment selection, frequency, and duration with established protocols. For example, a lot of chemotherapy is administered at 3-week intervals, with up to 8–12 cycles of treatment being administered.

Some examples of exceptions to 3-week administration intervals are as follows:

- Carboplatin—can be administered every 3 or 4 weeks.
- Irinotecan—administered every 2 weeks.
- 5-fluorouracil—can be administered once weekly every 2, 3, or 4 weeks, depending on dosage schedule.
- Mitomycin—administered every 6 weeks.
- Paclitaxel—can be administered once weekly (unlicensed).
- Docetaxel—can be administered once weekly (unlicensed).

1 Calvert AH *et al.* (1989). Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *Journal of Clinical Oncology* **7**: 1748–56.

Critical tests for chemotherapy to proceed on time

Chemotherapy should only be administered at the full protocol dose if the haematological and biochemical parameters are within the normal range. Biochemical parameters depend on the excreted route of the drug. Creatinine clearance should be monitored for renally cleared drugs and LFTs should be monitored for those drugs metabolized hepatically. Haematological parameters include the white cell count (WCC), absolute neutrophil count (>1.5), and platelet count (>100).

If the biochemical or haematological parameters are not within the normal range, dose reduction or delaying subsequent doses must be considered. Doses are usually reduced by 20–25% initially. Chemotherapy is usually delayed by a week at a time.

Treatment guidelines

Oncology is an evolving field of practice. Treatments are becoming more individualized and targeted on the basis of genetics, tumour markers, and staging of disease. Check your local network protocols for information on cancer treatments locally.

For more detailed information on the management of oncological disorders, refer to the *Oxford Handbook of Oncology*.

Further reading

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Antiemetics for the prophylaxis of chemotherapy-induced nausea and vomiting

- Nausea and vomiting remain two of the most feared side effects of chemotherapy in cancer patients.
- The goal of antiemetic therapy is to prevent nausea and vomiting completely.
- Antiemetics should be given regularly and prophylactically.
- Combinations of antiemetics are significantly more effective than single agents.
- Clinical practice guidelines ensure appropriate and cost-effective antiemetic use.
- Factors that need to be considered when choosing an antiemetic regimen include the following:
  - The chemotherapy emetic risk (Table 23.1), dose, and schedule.
  - The type of nausea and vomiting being treated—anticipatory, acute, or delayed (Table 23.2).
  - The patient risk of nausea and vomiting (Table 23.3).
  - Other underlying causes of nausea and vomiting (Table 23.4).
  - The mechanism of action and routes of administration of the antiemetic (Tables 23.5–23.10).
  - The adverse effects of the drugs.
  - The cost-effectiveness of the drugs.
  - Whether patients can self-administer the antiemetic.

Chemotherapy drug combinations have an additive emetic effect. If chemotherapy drugs from the same category are combined, the regimen is classified as a higher emetic risk. If drugs are from different categories, the emetic risk is determined according to the most emetic drug in the combination.

Table 23.1 Emetic risk of chemotherapy

High emetic risk	Moderate emetic risk	Low emetic risk	Minimal emetic risk
Altretamine	Actinomycin-D	Bexarotene	Alemtuzumab
Carmustine >250mg/m^2	Amifostine	Capecitabine	Asparaginase
Cisplatin ≥50mg/m^2	Amsacrine	Cyclophosphamide (oral)	Bevacizumab
Cyclophosphamide >1500mg/m^2	Arsenic	Cytarabine	Bleomycin
Dacarbazine	Azacitidine	Docetaxel	Bortezomib
Doxorubicin/epirubicin + cyclophosphamide combination	Busulfan >4mg/day	Doxorubicin 20–59mg/m^2	Busulfan (low dose)
Mustine	Carboplatin	Etoposide	Chlorambucil (oral)
Procarbazine	Carmustine ≤250mg/m^2	Fludarabine	Chlorodeoxyadenosine
Streptozocin	Cisplatin <50mg/m^2	5-Fluorouracil	Cetuximab
	Cyclophosphamide ≤1500mg/m^2	Gemcitabine	Dasatinib
	Cytarabine >1000mg/m^2	Imatinib	Dexrazoxane
	Daunorubicin	Methotrexate 50–250mg/m^2	Erlotinib
	Doxorubicin	Mitomycin	Fludarabine
	Doxorubicin (liposomal)	Mitoxantrone	Gefitinib
	Epirubicin	Paclitaxel	Gemtuzumab
	Idarubicin	Pemetrexed	Hydroxycarbamide
		Teniposide	

(continued)

Table 23.1 (*Contd.*)

High emetic risk	Moderate emetic risk	Low emetic risk	Minimal emetic risk
	Ifosfamide	Topotecan	Lapatinib
	Irinotecan	Treosulphan	Lenalidomide
	Lomustine	Vorinostat	Melphalan (low dose)
	Melphalan >50mg/m^2		Mercaptopurine
	Methotrexate 250–1000mg/m^2		Methotrexate ≤50mg/m^2
	Oxaliplatin		Rituximab
	Temozolomide		Temsirolimus
	Topotecan		Thalidomide
	Treosulfan		Tioguanine
			Vinblastine
			Vincristine
			Vindesine

Table 23.2 Definitions of chemotherapy-induced nausea and vomiting

Acute nausea and vomiting	Initial 24h after chemotherapy
Delayed nausea and vomiting	>24h after chemotherapy
Anticipatory nausea and anticipatory nausea/vomiting	Days to hours before chemotherapy

Table 23.3 Patient risk factors which predict poor antiemetic control

Patients with more than three or four risk factors should be considered to receive additional antiemetics at the outset.

- Female
- <30 years old
- History of sickness—in pregnancy/travel sickness/with surgery
- Poor control with prior chemotherapy
- Underlying nausea and vomiting
- Anxiety

Note: high alcohol intake can have a protective effect and ↓ risk of emesis.

Table 23.4 Other causes of nausea and vomiting to be considered

- Radiotherapy
- Radiosensitizers
- Infection
- Metabolic disorders
- Electrolyte disturbances
- Constipation
- GI obstruction
- Cachexia syndrome
- Metastases (brain, liver or bone)
- Paraneoplasia
- Emetic medication (e.g. opioids, antibiotics, antifungals, or amifostine)

Table 23.5 Notes on appropriate antiemetic prescribing with chemotherapy

- Antiemetics should be administered regularly, prophylactically, and orally.
- (Serotonin) 5HT-3 receptor antagonists are equally efficacious and should be administered orally, and only for acute nausea and vomiting.
- There is only evidence for the use of 5HT-3 receptor antagonists for an additional day in the delayed phase for cyclophosphamide and carboplatin.
- Neurokinin receptor antagonists (e.g. aprepitant) can be considered as an adjunct to dexamethasone and a 5HT-3 receptor antagonist to prevent acute and delayed nausea and vomiting with cisplatin-based chemotherapy.
- Optimal emetic control in the acute phase is essential to prevent nausea and vomiting in the delayed phase.
- Dexamethasone is not required when steroids are included in chemotherapy regimen and for some haematology regimens.
- Consider administering antiemetics by IV infusion, subcutaneously, rectally, or sublingually (if available in those formulations) if the patient is unable to take oral antiemetics.
- Metoclopramide can be replaced with domperidone if the patient has extra-pyramidal side effects.
- If a patient is already taking antiemetics (e.g. cyclizine or prochlorperazine) for underlying nausea and vomiting before starting on chemotherapy, these drugs could be continued as a substitute for metoclopramide.

Table 23.6 Combinations of oral antiemetics to prevent chemotherapy-induced nausea and vomiting

High emetic risk	
Acutely	Serotonin receptor antagonist oral start 1h before chemotherapy (Table 23.1) on days of chemotherapy
	Dexamethasone 12mg oral once daily, starting on the morning of chemotherapy until 24h after highly emetic chemotherapy
	Continue for the duration of highly emetic chemotherapy administration
	Neurokinin receptor antagonist (e.g. aprepitant 125mg 1h before chemotherapy)
Delayed phase	Dexamethasone 8mg orally daily (single or divided doses) for 3–4 days, which can be reduced to 4mg daily for 1–2 additional days
	Neurokinin receptor antagonist (e.g. aprepitant 80mg daily for 2 days) given in addition to dexamethasone
	Metoclopramide 10–20mg orally four times daily for 3–4 days regularly, then if required
Moderate emetic risk	
Acutely	Serotonin receptor antagonist oral start 1h before chemotherapy (Table 23.1) on days of chemotherapy
	Dexamethasone 12mg oral daily, starting on the morning of chemotherapy until 24h after chemotherapy.
Delayed phase	Dexamethasone 8mg oral daily for 3 days
	Metoclopramide 10–20mg oral four times daily for 3–4 days, if required

Table 23.6 (*Contd.*)

Low emetic risk	
Acutely	Dexamethasone 12mg oral daily for days of chemotherapy
	Metoclopramide 10–20mg oral four times daily for 3–4 days
Minimal emetic risk	
No routine prophylaxis required	
Metoclopramide 10–20mg oral four times daily, if required.	

Note: for patients <30 years old, consider domperidone instead of metoclopramide if the patient experiences extrapyramidal side effects.

Table 23.7 Recommended oral daily doses of serotonin 5-HT_3 receptor antagonists to be administered 1h before chemotherapy

- Granisetron 2mg daily
- Ondansetron 8mg 1h before chemotherapy and another dose 12h later
- Tropisetron 5mg daily
- Dolasetron 200mg daily

Table 23.8 Recommended IV doses of 5-HT_3 receptor antagonists to be administered if patients are unable to tolerate medicines by the oral route

- Granisetron 1mg daily
- Ondansetron 8mg daily
- Tropisetron 5mg daily
- Dolasetron 100mg daily

Table 23.9 Antiemetics for failure of control

- Aprepitant and dexamethasone are the most useful agents for delayed nausea and vomiting
- To ensure absorption of antiemetics administered, consider subcutaneous, IV, or rectal administration if available (e.g. prochlorperazine 25mg rectally 2–4 times daily, or domperidone 30–60mg rectally 4 times daily
- Ensure antiemetics cover full period of nausea and vomiting

Table 23.10 Suggested antiemetics for patients refractory to first-line antiemetics

Acutely

1. Use antiemetics recommended for more emetic chemotherapy (for low or moderate emetic risk regimens)

2. If highly emetic chemotherapy, consider **one** of the following options.

   Add **lorazepam 1mg orally/sublingual/IV every 8h** if anxious (sedative and amnesic)

   Consider **levomepromazine 6.25–12.5mg orally as a single daily dose** instead of metoclopramide

   Replace lorazepam and metoclopramide with **levomepromazine 6.25–12.5mg oral or subcutaneous (in the evening) as a single daily dose (Note: 12.5mg oral = 6.25mg subcutaneous)**

   Prescribe regular lorazepam with prochlorperazine 10mg oral four times daily instead of metoclopramide

3. For cisplatin-containing regimens, consider adding a neurokinin receptor antagonist to dexamethasone and a 5HT-3 receptor antagonist on subsequent cycles of chemotherapy (e.g. aprepitant 125mg 1h before chemotherapy, then 80mg daily for 2 days)

Delayed

Dexamethasone 4mg twice daily for up to 1 week after chemotherapy

Consider **levomepromazine 6.25–12.5mg oral as a single daily dose** instead of metoclopramide

Anticipatory

Consider **lorazepam** 1mg oral at night (or dose up to 1mg three times daily) orally if anxious or anticipatory nausea and vomiting.

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Principles of extravasation

- Extravasation is the inadvertent administration of IV administered vesicants into the tissue instead of into the intended IV compartment. A number of agents used in cancer chemotherapy are extremely damaging if they extravasate or infiltrate into the tissues rather than remaining within the vasculature.
- If left undiagnosed or inappropriately treated, extravasation of chemotherapy can cause necrosis and functional loss of the tissue and limb concerned.
- Extravasation can occur with any IV injection. However, it is only considered to be a problem with compounds that are known to be vesicant or irritant.
- Appropriate treatment of extravasation within 24h should ensure that the patient has no further problems.

Signs and symptoms

- Pain, burning, swelling, erythema, loss of blood return, skin necrosis, inflammation, and discomfort.

Risk factors

Risk factors associated with extravasation include the following.

- Administration technique—↑ risk if staff are inadequately trained.
- Administration device—use of unsuitable cannulae (e.g. cannulae 24h old), large-gauge catheters, unsecured IV devices.
- Location of cannulation site—the forearm is the favoured site.
- Distractions during IV infusion.
- Patient factors:
  - underlying conditions, such as lymphoedema, diabetes, and peripheral circulatory diseases.
  - Patient age—additional precaution required for paediatric and elderly patients.
- Concurrent medication—e.g. steroids and anticoagulants.
- Physical properties of the administered drug–e.g. high vesicant potential of medication infused.

Prevention

- Extravasation is best prevented using one or more of the following techniques.
  - Avoid areas of joint flexion for IV sites.
  - Use smallest gauge catheter possible.
  - Use of central line for slow infusions of high-risk drugs.
  - Administer cytotoxic drugs through a recently sited cannula.
  - Ensure cannula cannot be dislodged during drug administration.
  - Ensure that the cannula is patent before administration by confirming positive blood return through the catheter.
  - Administer vesicants by slow IV push into the side arm of a fast-running IV infusion of a compatible solution.
  - Administer the most vesicant drug first.
  - Assess the site continuously for any signs of redness or swelling.

  - Ensure that the patient is aware of extravasation risks and reports any burning or pain on administration of the drug.
  - Take time—do not rush.
- Stop the infusion or injection immediately if an extravasation is thought to have occurred and follow the local extravasation policy.
- An extravasation policy and kit must be available in all areas where chemotherapy is administered.
- Check your local extravasation policy, and be aware of the location of extravasation kits.

Further reading

Allwood M *et al.* (2002). *The Cytotoxics Handbook*. (4th edn). Abingdon: Radcliffe Medical Press.
National Extravasation Information Service: http://www.extravasation.org.uk/home.html

Extravasation of chemotherapy in adult patients

A number of agents used in cancer chemotherapy are extremely damaging if they extravasate or infiltrate into the tissues, rather than remaining within the vasculature (Table 23.11). Extravasation might have occurred if there is evidence of the following.

- Any pain or burning on administration, either at the cannulation site or in the surrounding area.
- Swelling, inflammation, redness, or erythema around or above the cannulation site.
- Redness or heat at or around the area.

If the patient makes any complaint, stop the administration and check the site. If extravasation is suspected, the nursing/medical staff should follow the directions:

- The administration of the infusion/injection must be stopped and the cannula left in place.
- The healthcare professional administering the treatment should remain with the patient and ask a colleague to collect the extravasation kit and summon a doctor to examine and prescribe the appropriate treatment, according to the local extravasation policy.
- If a vesicant or exfoliant drug (Table 23.11) has been extravasated, the plastic surgical specialist registrar on-call 24h should be contacted according to the local policy. An emergency intervention/antidote might be required, according to the local policy.
- Disconnect the infusion and aspirate as much of the fluid from the extravasation site, through the cannula if possible, with a 10mL syringe.
- Mark the affected area. If possible take digital images of the site.
- The cannula can then be removed.
- Hydrocortisone 1% cream should be applied topically to the extravasated site twice daily, as long as redness persists, according to local policy.
- The extravasated area should be covered with a sterile gauze dressing. Depending on the drug extravasated and the local policy, heat can be applied to disperse the extravasated drug or the area can be cooled to localize the extravasation. Check the local policy to see whether a heat or cold pack should be used for the extravasated drug. For example:
  - vinca alkaloids—warm pack
  - oxaliplatin—heat pack
  - other vesicant drugs—cold pack
  - non-vesicant drugs—cold pack.
- The site should be elevated while swelling persists.
- Analgesia should be provided, if required.
- For the management of each individual drug, refer to the management plans in the local policy.

Table 23.11 Extravasation classification of anticancer drugs

Vesicants	**Exfoliants**
Amsacrine	Aclarubicin
Carmustine	Cisplatin
Dacarbazine	Daunorubicin (liposomal)
Dactinomycin	Docetaxel
Daunorubicin	Doxorubicin (liposomal)
Doxorubicin	Floxuridine
Epirubicin	Oxaliplatin
Idarubicin	Topotecan
Mitomycin	**Irritants**
Mitoxantrone	Bortezomib
Chlormethine (mustine)	Carboplatin
Paclitaxel*	Etoposide
Streptozocin	Irinotecan
Treosulfan	Mesna (undiluted)
Vinblastine	Teniposide
Vincristine	**Neutrals**
Vindesine	Asparaginase
Vinorelbine	Bleomycin
Inflammatory agents	Cladribine
Aldesleukin	Cyclophosphamide
Etoposide phosphate	Cytarabine
Fluorouracil	Fludarabine
Methotrexate	Gemcitabine
Pemetrexed	Ifosfamide
Raltitrexed	Interferons
Mesna (diluted)	Interleukin 2
	Melphalan
	Pentostatin
	Rituximab
	Thiotepa
	Trastuzumab

*Classification as vesicant or irritant.

- The following documents should be completed, according to local policy.
  - Standard local documentation for extravasation—file in patient's notes.
  - Record in patient's notes.
  - Local incident form.
- The patient's consultant should be informed within 24h (at the discretion of the specialist registrar on-call).

Follow-up care

- If IV chemotherapy is to be continued on the same day as an extravasation incident, if possible avoid using the limb where the extravasation has occurred.
- Review the extravasation site (suggested at ~24h and at 7 days). If not ulcerated, advise gradual return to normal use. For subsequent cycles of chemotherapy, consider surgical opinion if persistent pain, swelling, or delayed ulceration occurs.
- Inform risk management of the outcome.

Extravasation risk for chemotherapy products

There is no standard test to determine a drug's extravasation risk. The absolute risk is determined by extravasation reports originating from clinical practice and therefore controversy will exist for certain drugs.

Definitions of cytotoxic drug classification

- Vesicants—capable of causing pain, inflammation, and blistering of the local skin, underlying flesh, and structures, leading to tissue death and necrosis. This can result in loss of limb function and mobility.
- Exfoliants—capable of causing inflammation and shedding of skin, but less likely to cause tissue death.
- Irritants—capable of causing pain, inflammation, and irritation, rarely proceeding to breakdown of the tissue. This usually occurs at the administration site and/or along the vein.
- Inflammatory agents—capable of causing mild to moderate inflammation and flare in local tissues.
- Neutral—ostensibly inert or neutral compounds that do not cause inflammation or damage.

Guidelines for the use of hyaluronidase for an extravasated vinca alkaloids

Hyaluronidase may be indicated for a suspected or known extravasation of vinca alkaloids. It should be administered within 1h of the extravasation, before applying hydrocortisone cream. 1500IU of hyaluronidase is diluted in 1mL of water for injection. A 25 or 27 gauge needle is used to administer the dose intradermally or subcutaneously around the peripheral extravasation at approximately five separate sites. Clean the skin and change the needle after each injection. Consider infusing 0.4mL of the dose directly through the affected IV catheter if there is no blood return, prior to removing the catheter.

Guidelines for the use of dexamethasone for an extravasated vesicant drug

Dexamethasone may be indicated for a suspected or known extravasation of a vesicant drug. It should be administered within 1h of the extra-vasation, before applying hydrocortisone cream. 4mg dexamethasone injection is diluted in 1mL of water for injection. After cleaning the skin, a 25 or 27 gauge needle is used to administer the dexamethasone intra-dermally or subcutaneously around the peripheral extravasation. Administer 0.2mL at each site, changing the needle after each injection.

Guidelines for the use of dexrazoxane for an extravasated anthracycline

Dexrazoxane is a DNA topoisomerase II inhibitor licensed for administration after an anthracycline (doxorubicin, epirubicin, daunorubicin, idarubicin) extravasation of ≥3mL. The dose should be administered in the opposite limb over 1–2h within 6h of the extravasation:

- day 1: 1000mg/m^2
- day 2: 1000mg/m^2
- day 3: 500mg/m^2

The dose should be capped at a BSA of 2m^2, with a single dose not exceeding 2000mg.

Suggested contents of an extravasation kit

- Cold/hot packs × 2 (one to be stored in the freezer and one to be microwaved for a hot pack)
- Hydrocortisone 1% cream × 1
- Dexamethasone injection 8mg/2mL
- Hyaluronidase 1500IU injection
- 10mL water for injection x 2
- 2mL syringes
- 10mL syringes
- 25G needles
- Copy of local extravasation policy
- Extravasation incident forms
- Patient extravasation information leaflet
- Consent form for photographs
- Gloves and apron
- Gauze swab and tape
- Alcohol swabs
- Drug chart and pen

Further reading

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National Extravasation Information Service: http://www.extravasation.org.uk/home.html

Extravasation of chemotherapy in paediatric patients

Central venous catheters

- The majority of chemotherapy administered to children is given through indwelling central venous catheters.
- It is very unusual for administration of chemotherapy through indwelling central venous catheters to result in any problems with extravasation.
- The very occasional problems that occur with leakage or rupture of indwelling lines must be dealt with on their individual merits, taking account of such factors as site of the leak, type of drug being administered, and volume of drug thought to have been extravasated.

Peripheral catheters

- The same principles regarding extravasation apply to paediatric patients as for adult patients. However, treatment will differ and should be according to a local policy.
- The cannula should be sited on the dorsum of the hand or foot, and NEVER sited at the antecubital fossa or any other deep vein that cannot be carefully monitored.
- During the administration of bolus chemotherapy, very careful attention must be paid to ensure that there is no evidence of extravasation at the time of the injection, with intermittent careful aspiration throughout to demonstrate patency and correct positioning.
- Administration must be stopped immediately if there is swelling around the site of the cannula. Some patients can experience discomfort during IV injection and therefore pain is a less reliable sign of extra-vasation. Some drugs can induce marked amounts of flare, even when being delivered safely into the vein, and therefore the presence of flare is not an indication that extravasation is occurring.
- Infusion chemotherapy should be administered using a pressure-monitoring pump, with the pressure limit set as low as possible.
- Antidotes are usually avoided in paediatric extravasations because some antidotes can cause more damage than the extravasation itself.
- Suggested contents for a paediatric extravasation kit:
  - hot pack
  - cold pack
  - copy of local extravasation policy
  - extravasation documentation forms.
- Problems of extravasation are most likely to occur with the administration of vincristine or vinblastine. Extravasations with vincristine or vinblastine should be regarded as an emergency. If there is an extra-vasation of either of these two drugs, it is appropriate to call the plastic surgeons so that the site of the extravasation can be extensively irrigated. Arrangements should be made quickly for the patient to be taken to theatre and anaesthetized and the area irrigated.
- Lead consultant for the patient or the haematology/oncology consultant in charge at the time should be notified of the event immediately.

Further reading

Allwood M *et al.* (2002). *The Cytotoxics Handbook* (4th edn). Abingdon: Radcliffe Medical Press.

Common Terminology Criteria for Adverse Events (CTCAE)

The CTCAE are a standardized classification developed by the National Cancer Institute (NCI) used for the side effects of chemotherapy drugs. The adverse events are graded from 0 (none) to 5 (death) for all possible side effects. The CTCAE are used in cancer clinical trials, adverse drug reporting, and publications to ensure uniform capture of toxicity data.The full CTCAE table is available from the website http://ctep.cancer.gov/forms; select link 'CTCAE v.3'.

Intrathecal administration of chemotherapy

Background

- Intrathecal chemotherapy is mainly used to treat CNS complications of haematological malignancy.
- Only three chemotherapy drugs are licensed to be given intrathecally: cytarabine, methotrexate, and hydrocortisone.
- However, other non-cytotoxic drugs can be administered by this route and include bupivicaine, opioids, baclofen, clonidine, gentamicin, hydrocortisone, and vancomycin.

Safe practice

- In the UK, there is a national policy that encompasses a range of standards that hospitals must comply with to enable staff to administer intrathecal chemotherapy.[1]
- To prevent inadvertent mix-up with other drugs, intrathecal chemotherapy is segregated from IV chemotherapy. The separate delivery and locations for these drugs help to ensure that IV drugs are never present in the same location as intrathecal medications.
- To facilitate this, intrathecal medications should only be administered in a designated location, such as an anaesthetic room, at a standard time by competent registered staff. In this way, the pharmacy can release intrathecal medications to the doctor immediately before they are needed.
- Also, at least two health professionals should independently verify the accuracy of all intrathecal doses before administration.

Frequently asked questions

Which drugs are contraindicated for use through the intrathecal route?

Vinca alkaloids (e.g. vincristine, vinblastine, vinorelbine, and vindesine) must never be given by this route. Vincristine is the most commonly used drug of this group.

Neurotoxicity of vincristine

Vincristine and the other vinca alkaloids do not pass through the blood–brain barrier. They are always used intravenously. Peripheral neurotoxicity is one of the main side effects, which ↑ in a cumulative fashion with the total dose of treatment. Hence, when vinca alkaloids are inadvertently injected into the cerebrospinal fluid (CSF) the outcome is normally fatal. Since 1975, 14 people have died in the UK because vincristine was mistakenly given intrathecally—i.e. as a spinal injection.

How should vincristine to be labelled?

The label will state 'For IV use only—fatal if given by other routes'. The dose is be diluted to a fixed volume of 50mL for all adults and to a fixed concentration of 0.1mL/mL for paediatric patients.

1 http://www.dh.gov.uk

Explain the intrathecal route of administration?

Chemotherapy is injected into the area of the lower spine into the CSF. This injection is also termed 'spinal' or subarachnoid. It is mainly indicated when patients show clinical signs that their disease has spread into the CNS. Drugs can also be administered through an Ommaya reservoir, discussed later in this section.

Why have people been given the wrong drug intrathecally?

The main problem occurs as a result of inexperienced health professionals becoming involved in the process with the result that the drug vincristine (intended solely for the IV route) is administered in error using the intrathecal route. This results in immediate neural damage that normally results in death.

How are intrathecal products labelled?

The label on the product states that the drug is intended for intrathecal use only. The product is packaged and transported in a separate container from other IV chemotherapy products and collected by the person who is going to give the drug.

What range of volumes is administered intrathecally?

Generally, the volume administered varies with the dose, but the typical volume tends to be 5mL.

Who is allowed to administer intrathecal products?

Until 2008, only doctors who were registered were allowed to administer chemotherapy products intrathecally. However, staff must be appropriately trained, deemed competent by a designated lead trainer, and registered for the administration task . Obviously, anaethetists also administer intrathecal products, but are not allowed to administer cytotoxic chemotherapy intrathecally unless they are deemed competent and are authorized on the trust's register. Senior hospital officers can only be involved in administration if a risk assessment has been undertaken and a waiver that endorses their involvement has been signed by the chief executive.

What is an Ommaya reservoir?

It is a small plastic dome-like device with a small tube. The reservoir is placed under the scalp and the tube is placed into the ventricles so that it connects with the CSF. The Ommaya reservoir is permanent, unless there are complications. This device allows certain drugs to be administered into the CSF and allows CSF sampling without repeated need for lumbar puncture.

How are intrathecal products administered?

A spinal needle is inserted past the epidural space until the dura is pierced and enters the CSF, which should flow from the needle. When CSF appears, care is needed not to alter the position of the spinal needle while the syringe for chemotherapy is being attached. The syringe is attached firmly to the hub of the needle and then injected slowly. When the injection is complete, the needle is removed.

Collecting

The staff member who is to administer the intrathecal chemotherapy should collect the drug in person by presenting the intrathecal prescription and any other chemotherapy prescriptions for that patient. The person must check the drug against the prescription before accepting the drug. It must be released only by a pharmacist authorized to do so. The drug should be carried to the patient from pharmacy in a dedicated container.

Administering

Frequently asked questions about administering include the following.

Where can intrathecal chemotherapy be administered?

This must be done only in designated areas.

When can intrathecal chemotherapy be administered?

This can only be done at designated times that have been approved locally, and must be undertaken within normal working hours.

Who checks the intrathecal chemotherapy at the bedside?

This should be done by a staff nurse authorized to perform this task. A final check must always be done by the administering doctor just before injection.

How should intrathecal chemotherapy be administered?

Access to the CSF should be obtained by a standard lumbar puncture procedure to obtain free flow of CSF. Injection of the chemotherapy must only be performed when the physician is confident that the spinal needle is in the intrathecal space. If assistance from an anaesthetist is required to perform the lumbar puncture, the chemotherapy must only be injected intrathecally by an authorized doctor, as outlined.

Pertinent points for nursing staff

For nurses to be able to check intrathecal drugs, they have to have received specific training related to these drugs and must be registered locally after competency assessment.

Pertinent points for pharmacists

Clinically screening prescriptions

Pharmacists must have been assessed as competent and registered to screen intrathecal chemotherapy. Follow the chemotherapy screening protocol.

Releasing the product to medical staff

Only pharmacists who have been authorized and registered are involved in this process. The staff member who is due to administer the intrathecal product presents the correct prescriptions to an authorized pharmacist who releases the product provided that there is documented evidence that any IV chemotherapy intended on the same day has already been administered.

Chapter 24

Therapy-related issues: nutrition and blood

Administration sets

A standard administration set, which does not have a filter chamber, is suitable for most IV infusions except the following.

- Blood and blood products—a blood administration set has an integral filter chamber.
- Platelets—a special administration set is usually supplied with platelets.
- Neonates and paediatrics—a burette should be used.

Rates

These sets deliver different number of drops/mL:

- Standard administration set—20 drops/mL.
- Blood administration set—15 drops/mL.
- Burette—60 drops/mL.

Note: an amiodarone infusion alters the surface tension of the infusion, resulting in a different number of drops/mL.

Changing administration sets

Administration sets should normally be changed every 24h as a precaution on microbiological grounds, although a number of studies have shown that, during administration of crystalloid infusions, there is not an ↑ in infection rates if administration sets are left unchanged for up to 72h. Contamination of infusion fluid during manufacture is extremely rare. However, if drugs are added to infusion fluids at ward level, the risk of microbial contamination is high and sets must be changed every 24h.

Administration sets should be changed every 24h for the following:

- parenteral nutrition
- blood and blood products
- infusions to which drugs have been added.

Calculating flow rates

If an infusion depends on gravity for its flow, there will be a limitation to its rate and accuracy of delivery. The rate of administration also needs to be calculated, using the following formula:

$$\text{no of drops/min} = \frac{\text{quantity to be infused (mL)} \times \text{no of drops/mL}}{\text{no of hours over which infusion is to be delivered} \times 60\,\text{min}}$$

The number of drops/mL depends on the administration set and the viscosity of the fluid. If greater safety is required, a burette administration set can be used, particularly if large bolus volumes could be harmful (e.g. in children or in patients with cardiac failure).

The burette set has a discreet 150–200mL chamber that can be filled from the infusion bag, as necessary, depending on the flow rate. This enables the nurse to ensure that the patient receives no more than the prescribed hourly rate.

Peripheral venous access devices

- Provides a relatively easy method for obtaining immediate IV access.
- Used for short-term drug and/or fluid administration and blood transfusion. Principal problems associated with peripheral cannulae are infection, occlusion, phlebitis, and extravasation.

For central venous access see 🕮 p.540.

Size of cannula

The size of cannula is relevant to the potential trauma it may cause to the vein in which it rests. Cannula size relates to the diameter and is stated in gauge size, where the increase in gauge number is inversely proportional to the diameter of the cannula (Table 24.1).

The cannula should be considered as a wound with direct entry to the vascular system and must be treated as any other wound using an aseptic technique.

Dressings should be changed only if they are bloodstained or have become wet or stained, or when fluid has collected at the insertion point. If they are dry and intact it is preferable to leave them alone to minimize exogenous infection or dislodgement of the cannula at the site.

If there are any signs of inflammation or pain, the cannula should be removed. If it is not in regular use, removal should also be considered. Most institutions recommend that peripheral cannulae should not remain in place for longer than a specified period (e.g. 48h).

Table 24.1 Cannula sizes

Size (gauge)/actual diameter (mm)	Colour	Use	Flow rate (mL/min)
22G/0.8mm	Blue	For small fragile veins	35
20G/1mm	Pink	For IV drug and fluid administration in patients who have fragile veins	60
18G/1.2mm	Green	Standard size for IV drug and fluid administration	100
16G/1.7mm	Grey	For patients requiring rapid IV fluid replacement	200
14G/2mm	Brown	Used in theatre for rapid transfusion	350

Intravenous (IV) administration pumps and other devices

Classification

The Medical Devices Agency (MDA) has developed a classification for pumps according to the perceived risk and suitability of a device for a specific clinical purpose.

- Neonatal—the highest risk category.
- High-risk infusions—infusion of fluids in children, where fluid balance is critical, or the infusion of drugs (e.g. cardiac inotropes) or cytotoxic drugs where consistency of flow and accuracy are important.
- Lower-risk infusions—delivery of simple electrolytes, parenteral nutrition, and infusional antibiotics.

Neonatal

The required characteristics of neonatal devices are as follows.

- High accuracy.
- Consistency of flow delivery, with very low flow rates.
- Flow rate increments in mL/h.
- Very short occlusion and low-pressure alarm times.
- Very low bolus volume on release of occlusion.

High-risk infusion pumps

The required characteristics of high-risk infusion pumps are as follows.

- High accuracy.
- Consistency of flow delivery.
- Short occlusion and low-pressure alarm times.
- Low bolus volume on release of occlusion.

Lower-risk infusion pumps

The characteristics of lower-risk infusion pumps are as follows.

- Lower accuracy over the long and short terms.
- Less consistent flow.
- Rudimentary alarm and safety features.
- Higher occlusion alarm pressure.
- Poorer overall occlusion alarm response.

IV pumps and syringe drivers are increasingly being used to control infusions in general wards, in addition to specialist clinical areas. Operators have a responsibility to ensure that they are fully conversant with any device being used. Training is provided initially by company representatives, although long-term local on-the-job competency training is the usual method employed.

There is a continuingly expanding range of infusion devices, which vary slightly in design. However, there are normally a number of common features that operators need to be familiar with to understand the appropriate clinical use of each device.

Most devices require a specific administration set, cassette, or syringe. The use of the incorrect type can have a detrimental effect on patient care. If a pump is designed to use a variety of sets or syringes, it normally must be programmed with information regarding the type and size being used.

Devices can be grouped into four main types.

- Infusion devices using a syringe:
  - syringe infusion pumps
  - syringe drivers
  - anaesthetic pumps
  - patient-controlled analgesia pumps.
- Infusion devices using gravity controllers:
  - drip-rate controllers
  - volumetric controllers.
- Infusion pumps:
  - drip-rate pumps
  - volumetric pumps
  - patient-controlled analgesia pumps.
- Ambulatory pumps:
  - continuous infusion
  - multimodality pumps
  - patient-controlled analgesia pumps.

Syringe infusion pumps

These are devices in which a syringe containing fluid or a drug in solution is fitted into the pump and the plunger of the syringe is driven forwards at a predetermined rate. These pumps are usually set to run at mL/h.

Application

Designed for the accurate delivery of fluids at low flow rates. Therefore syringe pumps are ideally selected for the safe infusion of fluids and drugs to neonates or children and drugs to adults. Often used in anaesthesia and critical care areas. Commonly used for the administration of patient-controlled analgesia.

Gravity controllers

Electronic devices that achieve the desired infusion rate on the principle of restricting flow through the administration set by an infusion force that depends on gravity (drip-rate control) or via a dedicated rate-controlling administration set.

Application

Suitable for most low-risk infusions such as IV fluids (e.g. sodium chloride or glucose 5% solutions). Not recommended for total parenteral nutrition (TPN).

Volumetric pumps

Application

Preferred for larger flow rates. They usually weigh between 3 and 5kg, and are designed to be 'stationary'. Volumetric pumps have the facility to work off mains power or a battery. The infusion rate is set using mL/h and most devices can be programmed to between 1 and 1000mL/h, although if used at rates <5mL/h, accuracy might ↓. Most pumps use a linear peristaltic pumping action.

The pump can often be programmed to stop infusing after a set volume, which useful if it is necessary to give a proportion of an infusion bottle or bag.

Ambulatory pumps

Small portable devices

They can use a small syringe but most use a reservoir bag of volume 100–250mL. Pumps are preprogrammable.

Implanted pumps

Implanted pumps have been developed for those ambulatory patients who need long-term low-volume therapy. These pumps are small and are implanted subcutaneously. The drug is then infused through an internal catheter into a vein, an artery, or an area of dedicated tissue.

Disposable pumps

These are non-electronic devices, which are generally very lightweight and small. Usually very 'user-friendly', requiring the minimum of input from the patient. They do not require a battery.

Disposable pumps work on a variety of principles.

- An elastomeric balloon, which is situated inside a plastic cylinder. When the balloon is filled with the infusion fluid, the resulting hydrostatic pressure inside the balloon is enough to power the infusion. The drug is infused through a small-bore administration set, which usually has a rate restrictor at the patient end.
- SideKick® exerts mechanical pressure from a spring-loaded device.
- SmartDose® works by generation of CO_2 in the space between a rigid plastic outer cylinder and the infusion bag.

Management of flow control devices

Any technical equipment will only function optimally if maintained appropriately and standardized, because devices are often moved with patients through various wards and departments. Care should be taken to comply with the manufacturer's instructions regarding storage of their product.

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Management of magnesium imbalance

- The normal range of magnesium is 0.7–1.0mmol/L.

Hypomagnesaemia

Causes of hypomagnesaemia

- Malnutrition
- Burns
- Trauma
- Alcoholism
- Medications—e.g. amphotericin B, cisplatin, cyclosporin, loop diuretics

Complications of hypomagnesaemia

- Hypokalaemia
- Hypocalcaemia
- Tetany
- Seizure
- Arrhythmias
- Cardiac arrest

Preparations for replacement

- Magnesium glycerophosphate tablets (4mmol)
- Magnesium hydroxide mixture (14mmol/10mL)
- Magnesium sulphate 50% solution 5g in 10mL (20mmol/10mL)

Mild hypomagnesaemia (0.5–0.7mmol/L) or asymptomatic patients

- Magnesium glycerophosphate tablets (4mmol): one or two tablets three to four times daily. Unlicensed, but shows greatest absorption and least side effects (diarrhoea).
- Magnesium hydroxide mixture (14mmol/10mL): 5–10mL three to four times daily. Dosing can be increased up to 50mmol orally, but can be limited by side effects.

Moderate to severe hypomagnesaemia (<0.5mmol/L) or symptomatic patients

- Magnesium sulphate injection of 10–20mmol (2.5–5g) in 1L infusion fluid over 12h daily until serum magnesium is within the normal range.
- The volume of fluid is not critical but consider the following.
  - The maximum peripheral concentration is 20% (20mmol in 25mL) because the injection has a very high osmolality.
  - The maximum rate is 150mg/min (20mmol over a period of 40min).
- Magnesium sulphate is compatible with sodium chloride 0.9% solution, glucose 5% solution, and sodium chloride/glucose solution.

Monitoring

Magnesium levels for symptomatic patients should be checked daily until corrected. Note that plasma levels might be artificially high while magnesium equilibrates with the intracellular compartment. However, if toxicity is suspected, treatment should be discontinued.

Hypermagnesaemia

Causes of hypermagnesaemia

- Renal insufficiency
- Hypothyroidism
- Medications (lithium)

Complicaitons of hypermagnesaemia

- Hypotension
- Bradycardia
- Confusion
- Respiratory depression
- Coma

Non-pharmacological treatment

- Treat underlying disorder
- External cardiac pacing (symptomatic)
- Mechanical ventilation (symptomatic)
- Dialysis (use only in emergency situations unless patient is already on dialysis)

Pharmacological treatment

- 1000mg calcium gluconate: slow IV push over 10min
- Hydration with sodium chloride 0.9% solution (200mL/h)
- Add calcium gluconate 1000mg to each litre of fluid
- Loop diuretics (e.g. furosemide 40mg IV push) to maintain urine output

Monitoring

- Serum magnesium every 2h until normalized and patient is asymptomatic

Management of phosphate imbalance

- The normal range of phosphate is 0.8–1.45mmol/L.

Hypophosphataemia

Causes of hypophosphataemia

- Malnutrition
- Increased urine excretion of phosphorus
- Hyperparathyroidism
- Refeeding syndrome
- Medications

Complications of hypophosphataemia

- Myalgias
- Peripheral neuropathy
- Paralysis
- Rhabdomyolysis
- Seizures
- Acute respiratory failure

Tratment of hypophosphataemia (Table 24.2)

- Mild hypophosphataemia: 0.61–0.79mmol/L
- Moderate hypophosphataemia: 0.41–0.60mmol/L
- Severe hypophosphataemia: <0.40mmol/L

Table 24.2 Treatment of hypophosphataemia

	Moderate (0.4–0.6mmol/L) Asymptomatic	**Moderate (0.4–0.6mmol/L) Symptomatic**	**Severe (<0.4mmol/L)**
Patient able to tolerate oral or enteral therapy	Phosphate-Sandoz® effervescent tablets: 2 tabs twice daily (16mmol phosphate/tab)	Oral therapy not appropriate	
Patient on IV therapy only	20mmol phosphate as sodium glycerophosphate in 0.9% sodium chloride or 5% glucose over 12h. Dilution volume ≤50mL must be administered via central access	20mmol phosphate as sodium glycerophosphate in 0.9% sodium chloride or 5% glucose over 6h. Dilution volume ≤50mL must be administered via central access.	

- Oral supplementation should be considered as first line in all patients who can tolerate oral therapy and who do not have a sodium restriction.
- Check plasma calcium. If high, seek specialist advice prior to supplementation.
- Half the dose in renal impairment and in patients <40kg.

Monitoring

Serum levels need to be checked 6h after the end of the infusion to enable time for distribution.

Hyperphosphataemia

Causes of hyperphosphataemia

- Renal insufficiency
- Acidosis
- Hypoparathryoidism
- Tumour lysis syndrome
- Medications—e.g. phosphate supplements, bisphosphonates

Complications of hyperphosphataemia

- Calcium–phosphate complex formation and deposit in muscle
- Tetany
- Mortality

Non-pharmacological treatment

- Treat underlying condition
- Dialysis—use only in emergency situations, unless patient is already on dialysis

Pharmacological treatment

- Phosphate binders.
  - Calcium carbonate 1250mg oral three times daily with each meal.
  - Calcium acetate 1000mg oral three times daily with each meal (adjusted to requirements).
  - Sevelamer 800–1600 mg oral three times daily with each meal.
  - Aluminium-based products are not usually recommended because of aluminium toxicity.

Seek specialist information for dosing schedule.

Monitoring

- Serum phosphorus levels until normal.
- Serum calcium levels.

Management of hypokalaemia

Causes of hypokalaemia

- Excessive loss through GI tract or kidney
- Hypomagnesaemia
- Intracellular shift
- Medications—e.g. diuretics

Complications of hypokalaemia

- Nausea/vomiting
- Weakness/fatigue
- Constipation
- Paralysis
- Respiratory failure
- Arrhythmias
- Sudden death

Treatment of hypokalaemia

Treatment is summarized in Table 24.3.

Risks associated with IV potassium

- Rapid administration of IV potassium or administration of concentrated IV potassium can result in hyperkalaemia paralysis, respiratory failure, arrhythmias, and asystole
- Potassium should NOT be administered undiluted or by IV push
- Peripheral administration of potassium may lead to burning, phlebitis, and necrosis, less concentrated solutions should be used peripherally.

Safety measures for IV potassium

- In July 2002, the National Patient Safety Agency (NPSA) in the UK issued a patient safety alert to prevent further fatalities following accidental overdose with IV potassium chloride concentrate that had been misidentified for sodium chloride 0.9% solution and water for injections.
- The risks associated with IV potassium chloride are well known. Potassium chloride, if injected too rapidly or in too high a dose, can cause cardiac arrest within minutes. The effect of hyperkalaemia on the heart is complex—virtually any arrhythmia could be observed.
- The true incidence of potassium-related fatalities and incidents is unknown.
- The alert identified safe medication practice recommendations concerning the prescribing, distribution, storage, and preparation of potassium chloride solutions in hospitals.
- The NPSA recommended withdrawal of concentrated potassium solutions from ward stock to be replaced by ready-to-use infusion products.
- The NPSA recommended that new control arrangements be introduced in critical care areas continuing to use potassium chloride concentrate ampoules and development of the use of pre-filled potassium syringes.

- Although recommendations have ↓ the risk to patients, staff still need to be vigilant to minimize and prevent harm to patients from incompetent/dangerous practice.

Minimizing risk: points pharmacists should encourage

- Labelling: the labelling format used differs between different manufacturers. The font size of K^+ details should be ↑ to improve identification. Historically, there has been a reliance on specifying the K^+ concentration as a percentage rather than mmol/volume on products as the primary focus. The latter should become main emphasis in future.
- Storage: decanting from boxes should be discouraged. Although most ward areas have limited storage space, it is GCP to segregate K^+-containing bags from other infusion fluids.
- Develop and publish a local range of infusions (e.g. Table 24.4)
- Staff competency needs to be established for IV fluid administration.

Concentrated K^+-containing products

Critical areas, high-dependency areas, and cardiac theatres that are allowed to store ampoules of potassium chloride locally should have a risk assessment performed periodically to overview the prescribing, ordering, storage, and administration processes. Other areas, such as general theatres, should not have access to concentrated ampoules of K^+.

Training development

The process from prescribing through to administration needs to be mapped and used as a backbone to develop multidisciplinary training.

Table 24.3 Treatment and monitoring of hypokalaemia

Serum potassium level (mmol/L)	Degree of hypokalaemia	Treatment
3.0–3.4	Mild or asymptomatic hypokalaemia	Oral potassium replacement is preferred for patients who are asymptomatic IV replacement: 40mmol in 1L of sodium chloride 0.9% solution or glucose 5% solution administered peripherally (or centrally) over at least 6h
<3.0	Severe or symptomatic hypokalaemia	IV replacement with 40mmol in 500mL sodium chloride 0.9% solution or glucose 5% solution administered peripherally (or centrally) over at least 4h or over at least 2h through a central line with continuous ECG monitoring of heart rate and rhythm; repeat according to serum potassium levels
Monitoring	Serum potassium level every 1–6h if severe or symptomatic or if IV treatment ongoing	Testing serum magnesium may be indicated if hypokalaemia is resistant to treatment, and magnesium correction warranted if low

Table 24.4 Suggested example of formulary for K^+-containing IV fluids

Approved name	Manufacturer	Bag price*	Notes
Potassium chloride 20mmol in 50mL sodium chloride 0.9% in pre-filled syringe	NHS manufacturer	£6	20mmol in 50mL (critical care only)
Potassium chloride 0.15%, glucose 10% (500mL)	Baxter	£6	10mmol in 500mL
Potassium chloride 0.15%, glucose 10% sodium chloride 0.18% (500mL)	IVEX	£5	10mmol in 500mL
Potassium chloride 0.15%, glucose 2.5%, sodium chloride 0.45% (1000mL)	Fresenius Kabi	£5	20mmol in 1L
Potassium chloride 0.15%, glucose 4% sodium chloride 0.18% (1000mL)	Fresenius Kabi	£1	20mmol in 1L
Potassium chloride 0.15%, glucose 5% (1000mL)	Fresenius Kabi	£1	20mmol in 1L
Potassium chloride 0.15%, sodium chloride 0.9% (1000mL)	TPS	£1	20mmol in 1L
Potassium chloride 0.15%, sodium chloride 0.9% (500mL)	TPS	£1	10mmol in 500mL
Potassium chloride 0.3%, glucose 4%, sodium chloride 0.18% (1000mL)	Fresenius Kabi	£1	40mmol in 1L
Potassium chloride 0.3%, glucose 5%, sodium chloride 0.18% (500mL)	Fresenius Kabi	£1	20mmol in 500mL
Potassium chloride 0.3%, glucose 5% (1000mL)	Fresenius Kabi	£1	40mmol in 1L

Table 24.4 (*Contd.*)

Approved name	Manufacturer	Bag price*	Notes
Potassium chloride 0.3%, sodium chloride 0.9% (1000mL)	Fresenius Kabi	£1	40mmol in 1L
Potassium chloride 0.3%, sodium chloride 0.9% (500mL)	Fresenius Kabi	£1	20mmol in 500mL
Potassium chloride 0.6% sodium chloride 0.9% (500mL)	Baxter	£5	40mmol in 500mL
Potassium chloride 0.6%, sodium chloride 0.9% (1000mL)	Baxter	£5	80mmol in 1L
Potassium chloride 3%, sodium chloride 0.9% (100mL)	Baxter	£4	40mmol in 100mL

*Prices listed as guide only. Cost will vary locally.

Guidelines for the treatment of hypocalcaemia

- The normal range of total calcium is 2.15–2.60mmol/L.
- The normal range of ionized calcium is 1.1–1.4mmol/L.

Causes of hypocalcaemia

- Malabsorption, inadequate intake, vitamin D deficency
- Hypoalbuminaemia
- Hyperphosphataemia
- Hypomagnesaemia
- Pancreatitis
- Hypoparathryroidism

Complications of hypocalcaemia

- Dysrhythmias
- Muscle cramping
- Paresthesiae
- Seizures
- Stridor
- Tetany

Non-pharmacological treatment

Treat the underlying disorder. The most common cause of low total serum calcium is hypo-albuminaemia. Therefore it is important to measure ionized calcium or correct the total serum calcium using the formula

$$Ca_{corrected} = [(40 - Alb_{measured}) \times (0.02)] + Ca_{measured.}$$

Preparations for replacement

- Calcium gluconate 10% (0.1g/mL)—injection contains 0.22mmol/mL of calcium.
- Calcium chloride 14.7% (0.147g/mL)—injection contains 1mmol/mL of calcium.
- Calcium solutions (especially calcium chloride) are irritants and care should be taken to prevent extravasation.

Dilution

- A calcium gluconate 10% injection can be given undiluted, or diluted in glucose 5% solution or sodium chloride 0.9% solution.
- A calcium chloride 14.7% solution should ideally be diluted in at least twice its volume of glucose 5% solution or sodium chloride 0.9% solution for peripheral administration. Calcium chloride can be given un-diluted by central line administration only.

Emergency elevation of serum calcium in symptomatic patients

- Give 2.25mmol IV stat over 10min.
- This is equal to either of the following:
  - 10mL of calcium gluconate 10% solution
  - 2.25mL of calcium chloride 14.7% solution.

Hyperkalaemia and disturbance of ECG function

- 2.25–4.5mmol of calcium over 10–20min, depending on dose (up to a maximum rate of 0.2mmol/min).
- This is equal to either of the following:
  - 2–4mL of calcium chloride 14.7% injection
  - 10–20mL of calcium gluconate 10% injection.
- Titrate dose according to ECG.

Monitoring

For symptomatic patients calcium and albumin levels should be checked every 4h until corrected. Serum phosphate and magnesium levels should be monitored periodically.

Suggested dosing in asymptomatic hypocalcaemic patients

IV infusion to give 9mmol daily, which might need to be repeated at intervals of 1–3 days, as follows.

- 40mL of calcium gluconate 10% injection over 4h can be given neat or diluted in glucose 5% solution or sodium chloride 0.9% solution.
- 9mL of calcium chloride 14.7% injection over 4h diluted in 100mL of glucose 5% solution or sodium chloride 0.9% solution.

If the patient is absorbing oral medication, consider the use of soluble calcium tablets in divided doses.

Prescribing IV fluids

The aim of fluid therapy is to facilitate the patient's recovery by maintaining the following:

- blood volume
- fluid and electrolyte balance
- renal function.

Three phases need to be considered when planning a suitable fluid regimen:

- maintenance
- correction of pre-existing dehydration
- abnormal losses—e.g. fluid management of the surgical patient.

Fluids for maintenance

- A patient who is unable to take fluid by mouth needs a basic IV regimen. In temperate climates, this is 1.5L/m^2 surface area of fluid or 30–40mL/kg body in 24h.
- Basic electrolyte requirements are sodium (1mmol/kg body weight daily) and potassium (1mmol/kg body weight daily).
- The patient can manage with lower sodium intakes because of efficient conservation processes. However, if there are obligatory losses of K^+ and insufficient replacement, patients become K^+ depleted.
- Remember that febrile patients will have ↑ insensible losses.

Correction of existing dehydration

- Identify the compartment(s) from which the fluid has been lost and the extent of the losses.
- Check fluid charts, and note any loss from drains or catheters.
- Most body fluids contain salt (Table 24.5), but at lower levels than plasma. Thus replacement requires a mixture of sodium chloride and glucose.
- Clinical history and examination are vital but can be assisted by the measurement of changes in electrolytes, packed cell volume (PCV), and plasma proteins.
- Patients with heart failure are at greater risk of pulmonary oedema if over-hydrated. They also are unable to tolerate ↑ salt load because sodium retention accompanies heart failure.
- Patients with liver failure, despite being oedematous and often hypo-natraemic, have ↑ total body sodium. Therefore sodium chloride is best avoided in fluid regimens.

Abnormal losses: fluid management of the surgical patient

Planning an IV fluid therapy regimen

- Ensure adequate preoperative hydration.
- Minimize insensible losses during surgery:
  - humidify inspired gases, minimize sweating by ensuring adequate anaesthesia, and, where possible, cover the patient to ensure adequate ambient temperature.
- Replace losses, such as blood loss.

Preoperative considerations

For routine elective surgery, the patient is kept NBM for 6–12h and takes little oral fluid for 6h postoperatively. A fluid deficit of 1000–1500mL arises, but this will be quickly corrected when the patient is drinking normally. IV fluid therapy is not required for many routine operations in adults, provided that the patient is not dehydrated. IV therapy is indicated preoperatively if the patient is likely to be NBM for >8h. Anaesthetists might set up an IV infusion of Hartmann's solution just before induction. On return to the surgical ward, this should be switched to sodium chloride or glucose as required, because there is no evidence that further treatment with Hartmann's solution has a clinical benefit compared with other crystalloids.

Perioperative considerations and blood loss

Operative blood loss of up to 500mL can be replaced with crystalloid solution (remembering that four times as much crystalloid solution will be needed). Use the following replacement fluids for blood loss:

- <500mL—use crystalloid solution
- 500–1000mL—use colloid solution
- >1000mL or Hb <10gdL—use whole blood.

Other replacement fluid is more appropriate if there is excess fluid loss from a specific compartment.

Hartmann's solution causes the least disturbance to plasma electrolyte concentrations and avoids postoperative fluid depletion. An allowance of 1mL/kg body weight/h should be begun at the start of anaesthesia to replace essential losses intraoperatively.

Table 24.5 Composition of gastrointestinal body fluid

	Volume (L/24h)	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)	pH
Saliva	0.5–1.5	20–80	10–20	20–40	20–60	7–8
Gastric juice	1.0–2.0	20–100	5–10	120–160	0	1–7
Bile	0.5–1.0	150–250	5–10	40–120	20–40	7–8
Pancreatic juice	1.0–2.0	120–250	5–10	10–60	80–120	7–8

Postoperative considerations

- Normal fluid requirement is 2–3L/24h.
- Electrolyte requirements: Na^+, 2mmol/kg body weight; K^+, 1mmol/kg body weight.
- Low urine output (night after surgery) almost always results from inadequate fluid replacement, but might be a consequence of the anaesthetic technique. (K^+ is not normally administered during the first24h in such patients.) Check JVP/CVP for signs of cardiac failure and consider fluid challenge, if appropriate.
- Check operation notes for extent of bleeding in theatre.
- Losses from gut—replace NGT; aspirate volume with sodium chloride 0.9% solution.

- Losses from surgical drains—replace significant losses. However, calculate total fluid loss (24h) as follows:
  - estimate skin and lung loss = (10 × body weight)mL.
  - estimation of stool losses = 50mL.
  - estimation of urine losses, normally measured directly.
  - drain loss/NGT loss.

Design a fluid regimen

- Calculate fluid losses and replace them (as outlined).
- Calculate Na^+ and K^+ requirements.
- Measure plasma U&Es if patient is ill.
- Start oral fluids as soon as possible.

For example, a fluid regimen for a 60kg patient would be calculated as follows.

- Fluid losses:
  - patient urine output 1500mL
  - fluid losses = (10 × 60) + 1500 + 50mL = 2150mL
  - NGT loss = 1000mL.
- Na^+ requirement = 2 × 60 = 120mmol.
- K^+ requirement = 1 × 60 = 60mmol.
- Volume of sodium chloride 0.9% solution that will provide sodium requirement = 1000mL (154mmol Na^+).
- Amount of K^+ required = 60mmoL
- Remember that glucose 5% solution can be considered as isotonic water and will be used to make up the difference for the patient's fluid requirement.
- NGT replacement = 1000mL sodium chloride 0.9% solution.

Hence, a suitable 24h regimen for a 60kg patient with 1.5L urinary output and 1L NGT losses would be as follows:

- 2 × 1000mL sodium chloride 0.9% solution + 20mmol potassium chloride.
- 1000mL glucose 5% solution + 20mmoL potassium chloride.
- Each bag runs for a period of 8h.
- Start oral fluids as soon as reasonable, depending on the patient's condition/indication for surgery.

Special conditions that need more specialist fluid knowledge

- Haemorrhagic/hypovolaemic shock
- Septic shock
- Heart or liver impairment
- Excessive vomiting

Fluid balance

During a lifetime, the water content and fluid compartments within the body alter. In infants, fluid content is 70–80% of body weight. This progressively ↓, reaching 60% of body weight at age 2 years. In adults, the fluid content accounts for 60% of body weight in ♂ and 55% in ♀, and the ratio of extracellular fluid (ECF) to intracellular fluid (ICF) is 1:3.

For example, the fluid content of a 70kg ♂ is as follows:

- total fluid = 42L
- ICF – 67% of body water = 28L
- ECF – 33% of body water = 14. (25% of intravascular space = 3.5L; 75% of interstitium = 10.5L).

Compartment barriers

- The fluid compartments are separated from one another by semi-permeable membranes through which water and solutes can pass. The composition of each fluid compartment is maintained by the selectivity of its membrane.
- The barrier between plasma and the interstitium is the capillary endo-thelium, which allows free passage of water and electrolytes but not large molecules such as proteins.
- The barrier between the ECF and the ICF is the cell membrane.

Transport mechanisms

- Simple diffusion: movement of solutes down concentration gradients.
- Facilitated diffusion: again depends on concentration gradient differences, but also relies on the availability of carrier substances.
- Osmosis: movement of solvent through semipermeable membranes.
- Active transport: e.g. Na^+/K^+ exchange pump.

Osmolality

- Osmotic pressure is generated by colloids impermeable to the membrane.
- Water distributes across in either direction if there is a difference in osmolality across the membrane.
- Osmolarity is the number of osmoles per litre of solution.
- Osmolality is the number of osmoles per kilogram of solvent or solution.
- The osmolality of blood is 285–295mOsm/L.

Tonicity

Molecules that affect the movement of water (e.g. sodium and glucose) are called 'effective osmoles' and contribute to compartment osmolality (sometimes termed 'tonicity'). The normal range of serum osmolality is 285–295mOsm/L. The measured osmolality should not exceed the predicted value by >10mOsm/L. A difference of >10mOsm/L is considered an osmolal gap. Causes of a serum osmolal gap include the presence of mannitol, ethanol, methanol, ethylene glycol, or other toxins (usually

small molecules) in very high concentrations. (The propylene glycol in lorazepam can cause hyperosmolarity and hyperosmolar coma in some patients, particularly when lorazepam is used as a continuous infusion.)

Serum osmolality is calculated as follows:

$$\text{serum osmolality} = [2 \times (Na^+ + K^+)] + (\text{glucose}/18) + (\text{BUN}/2.8)$$

where BUN is blood urea nitrogen. Na^+ and K^+ are in mmol/L, and glucose and BUN are in mg/dL. To convert glucose from mmol, divide by a factor of 0.05551. To convert BUN from mmol, divide by a factor of 0.3569.

Knowledge of fluid distribution

- Glucose 5% solution distributes through the ECF with a resultant fall in ECF osmolality, water distributes into the cells, and thus glucose 5% solution distributes throughout the body water.
- Conversely, a person marooned on a life raft with no water loses water from all compartments.
- Sodium chloride 0.9% solution contains 154mmol/L of sodium with an osmolality of 300mOmol/L. When infused, most of the solution stays in the ECF, which is of a similar osmolality.
- Conversely, if water and electrolytes are lost together (e.g. severe diarrhoea), fluid is mainly lost from the ECF.
- With ECF losses, sodium and water are lost together, so the sodium concentration in the remaining ECF does not change.
- However, protein and red cells are not lost so their concentration rises.
- If plasma alone is lost, only the PCV rises.
- Extra fluid for continuing losses should resemble as closely as possible the fluid that has been lost.

The body is normally in positive water balance (Table 24.6), with the kidney adjusting for varying intakes and losses by altering water clearance. The kidney requires 500mL of water to excrete the average daily load of osmotically active waste products at maximal urinary concentration.

Table 24.6 Fluid balance—average daily water balance

Input (mL of water)	Output (mL of water)
Drink: 1500	Urine: 1500
In food: 800	Insensible losses (lungs and skin): 800
Metabolism of food: 200	Stool: 200
Total: 2500	Total: 2500

Nutritional support in adults

Parenteral support

Poor nutritional status is a major determinant of a patient's morbidity (as a consequence of depressed cell-mediated immunity and wound healing) and mortality.

The decision to provide nutritional support must be as a result of a thorough clinical assessment of the patient's condition. Parenteral nutritional support should be for patients who are malnourished or likely to become so, and in whom the GI tract is not sufficiently functional to meet nutritional needs or is inaccessible.

Appropriate indications for parenteral nutrition

- Short bowel syndrome.
- GI fistulae.
- Prolonged paralytic ileus.
- Acute pancreatitis if jejunal feeding is contraindicated.
- Conditions severely affecting the GI tract, such as severe mucositis following systemic chemotherapy.

Guide to calculating parenteral nutritional requirements in adults

Nutritional assessment

Assessment is essential for the correct provision of nutritional support. A variety of techniques are available to assess nutritional status. Some of the common criteria used to define malnutrition are recent weight loss and changes in body mass index (BMI).

Identifying high-risk patients

- Unintentional weight loss—5–10% is clinically significant.
- ↓ oral intake—can result from vomiting, anorexia, or NBM.
- Weight loss—take oedema, ascites or dehydration into consideration.

Body mass index

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height}^2\,\text{(m)}}$$

Normal
♀ 20–25
♂ 22–27

BMI is useful for identifying malnourished underweight patients, but a normal BMI does not rule out malnutrition, especially in an increasingly obese population.

Normal nutritional requirements

The Schofield equation is used typically in the UK; the Harris–Benedict and Ireton–Jones equations are commonly referred to in US texts.

It is always best to be cautious and start low and titrate up, depending on tolerance and clinical response. Use actual bodyweight if BMI >30kg/m^2: A useful starting point in obese patients is to use 75% of body weight or alternatively feed to basal metabolic rate (BMR), without stress or activity factors added.

Macronutrients

- Calories
- Schofield equation
- Calculate BMR (*W* = weight in kilograms) (Table 24.7).

Add activity factor and stress factor as follows.

- Activity:
  - bedbound/immobile: +10%
  - bedbound mobile/sitting: +15–20%
  - mobile: +25% upwards.
- Stress: percentage added for stress varies widely depending on the clinical condition, but it is typically in the range 0–30%.

Harris–Benedict equation

♂: BMR = 66.473 + (13.751 × BW) + (5.0033 × HT) – (6.755 × age)
♀: BMR = 655.0955 + (9.463 × BW) + (1.8496 × HT) – (4.6756 × age)

where BW is body weight in kilograms, HT is height in centimetres, and age is in years.

Total caloric requirement is obtained by multiplying the BMR by the sum of the stress and activity factors. Stress conditions and activity factors need to be factored to calculate specific requirements).

Composition of parenteral nutrition regimens

- If possible, a balance of glucose and lipids should be used to provide total amount calories calculated.
- Glucose provision should be within the glucose oxidation rate (GOR) if possible.
- Normal GOR is 4–7mg/kg body weight/min.

Nitrogen

- Normal nitrogen requirements are 0.14–0.2g/kg body weight.
- Requirements in catabolic patients can be in the range of 0.2–0.3g/kg body weight.
- Non-renal nitrogen losses should be taken into consideration—e.g. wound, fistula, and burn losses.

Electrolytes

- Sodium (normal range 0.5–1.5mmol/kg body weight).
  - Sensitive to haemodilutional effects. Actual low sodium level is usually only as a result of excessive losses, and a moderately low level is unlikely to be clinically significant.
  - Renal excretion can be a useful indicator. Aim to keep urine sodium >20mmol/L.

- Potassium (normal range 0.3–1.0mmol/kg body weight).
  - Affected by renal function, drugs, or excessive losses.
- Calcium (normal range 0.1–0.15mmol/kg body weight).
  - Sensitive to haemoconcentration and haemodilution. Minimal supplementation generally adequate in short-term parenteral nutrition.
- Magnesium (normal range 0.1–0.2mmol/kg body weight).
  - Renally conserved. Minimal amounts generally suffice unless patient has excessive losses.
- Phosphate (normal range 0.5–1.0mmol/kg body weight).
  - Influenced by renal function, re-feeding syndrome, and onset of sepsis.

Trace elements and vitamins

Commercial multivitamin and mineral preparations (e.g. Solivito N®, Decan®, Additrace®, and Cernevit®) are suitable for most patients in the short to medium term. Requirements for long-term patients are dictated by monitoring.

Table 24.7 Calculation of BMR

♀ (kcal/day)		♂ (kcal/day)	
18–29yrs	(14.8W) + 692	18–29yrs	(15.1W) + 692
30–59yrs	(8.3W) + 846	30–59yrs	(11.5W) + 873
60–74yrs	(9.2W) + 687	60–74yrs	(11.9W) + 700
>75yrs	(9.8W) + 624	>75yrs	(8.3W) + 820

How specific clinical conditions can affect parenteral nutrition requirements and provision

Re-feeding syndrome

- Start with low calories/day (max 20kcal/kg body weight/day).
- Monitor and supplement potassium, magnesium, and phosphate as required.
- Ensure adequate vitamin supply, especially thiamine.

Acute renal failure

- Consider fluid, potassium, and phosphate restriction.
- Sodium restriction can also help to ↓ fluid retention.

Chronic renal failure

- Influenced by dialysis status.
- Consider need for nitrogen, potassium, and phosphate restriction.

Acute liver failure

- Use dry body weight to calculate requirements (especially if ascites is present).
- Patients might require sodium and fluid restriction. Protein restriction is not necessary.
- Provision of nutrition usually outweighs risks of abnormal LFTs.

Congestive cardiac failure

- Consider need for sodium and fluid restriction.

Practical issues concerning parenteral nutrition

The identification and selection of patients who require parenteral nutrition, and the subsequent provision and monitoring of this treatment, consist of a number of overlapping phases.

If there is concern with regard to a patient's nutrition they should be referred to the ward dietician for a full assessment.

Initiation of parenteral nutrition

Once referred to the nutrition support team, the patient will be formally assessed and, if it is felt appropriate, line access will be planned. For short-term parenteral nutrition (7–10 days), this will usually be a peripherally inserted venous catheter (PICC). A tunnelled central line will be used if the anticipated duration of parenteral nutrition is longer or peripheral access is limited.

Before initiating parenteral nutrition, baseline biochemistry should be checked (Table 24.8) and fluid and electrolyte abnormalities corrected. In those at risk of developing re-feeding syndrome. Additional IV vitamins might be required.

Early monitoring phase

During the first week of parenteral nutrition (and subsequently if the patient is 'unstable' with respect to fluid and electrolyte or metabolic issues) the patient is monitored intensively. This consists of a minimum set of mandatory ward observations, and appropriate blood and other laboratory tests. The aim is to optimize nutritional support, while remaining aware of the other therapeutic strategies in the patient's overall care plan.

It might be necessary to modify either nutritional support or the overall patient care plan to obtain the best patient outcomes.

Stable patient phase

After the patient is stabilized on parenteral nutrition a less intensive monitoring process is required.

Re-introduction of diet

At a certain point, diet or enteral feed is usually introduced in a transitional manner. Liaison with the ward dietician is essential and, if appropriate, reduction or cessation of parenteral nutrition is recommended.

Cessation of parenteral nutrition

Parenteral nutrition is usually stopped when oral nutritional intake is deemed adequate for the individual patient. As a general rule, cessation of parenteral nutrition is determined by a variety of factors and is a multidisciplinary decision.

Table 24.8 Suggested monitoring guide (please refer to local guidelines)

	Baseline	New patient or unstable	Stable patient
Blood biochemistry			
Urea and creatinine	Yes	Daily	Three times weekly
Sodium	Yes	Daily	Three times weekly
Potassium	Yes	Daily	Three times weekly
Bicarbonate	Yes	Daily	Three times weekly
Chloride	Yes	Daily	Three times weekly
LFTs: bilirubin	Yes	Daily	Three times weekly
ALP	Yes	Daily	Three times weekly
AST or ALT	Yes	Daily	Three times weekly
Albumin	Yes	Daily	Three times weekly
Calcium	Yes	Daily	Three times weekly
Magnesium	Yes	Daily	Three times weekly
Phosphate	Yes	Daily	Three times weekly
Zinc	Yes	Weekly	Every 2 weeks
Copper	Yes	Monthly	Every 3 months
CRP	Yes	Three times weekly	Three times weekly
Full blood count	Yes	Three times weekly	Weekly
Coagulation			
APTT	Yes	Weekly	Weekly
INR	Yes	Weekly	Weekly
Lipids			
Cholesterol	Yes	Weekly	Weekly
Triglycerides	Yes	Weekly	Weekly

LFT, liver function test; ALP, alkaline phosphatase; AST, aspartate amino-transferase; ALT, alanine aminotransferase; CRP, C-reactive protein; APTT, activated partial thromboplastin time.

IV access

Peripheral cannulae (Venflons®) should not be used routinely for the administration of parenteral nutrition. They should only be used in the short term for the administration of 'peripheral formulated' parenteral nutrition.

PICC lines are usually used for medium- to long-term venous access (2–6 months).

Tunnelled cuffed central venous catheters (CVs) are inserted via the subclavian (or jugular) vein for long-term feeding.

A dedicated single-lumen line is the safest route for parenteral nutrition administration. There is a greater risk of infection the more times a line is manipulated. Aseptic technique should be used. Nothing else should be given through this lumen, nor should blood be sampled from the line under normal circumstances (it might be appropriate for blood sampling in patients receiving parenteral nutrition at home).

If a multilumen line must be used for clinical reasons, one lumen should be dedicated for parenteral nutrition use only. Again, ideally, nothing else should be given through this lumen, nor should blood be sampled from it.

Prescribing parenteral nutrition

Patients' nutritional requirements are based on standard dietetic equations. A regimen close to a patient's requirements should be provided in a formulation prepared to minimize risk.

Nitrogen

Protein in parenteral nutrition is provided in the form of amino acids. Individual nitrogen requirements are calculated.

Carbohydrate and lipid

The energy in parenteral nutrition is generally described as non-protein calories (i.e. the figure excludes the energy provided from amino acids).

Total energy intake is best given as a mixture of glucose and lipid, usually in a ratio of 60:40. This might be varied if clinically important glucose intolerance develops or if there is a requirement for a lipid-free parenteral nutrition bag.

Volume

The overall aim is to provide all fluid volume requirements, including losses from wounds, drains, stomas, fistulae, etc., through parenteral nutrition. However, if these losses are large or highly variable, they should be managed separately.

Electrolytes

These are modified according to clinical requirements, with particular regard to extra-renal losses. Electrolytes should be reviewed daily initially and modified as necessary. Monitoring of urinary electrolyte losses is useful.

Vitamins, minerals, and trace elements

These are added routinely on a daily basis. Extra zinc or selenium might be required in patients with large GI losses. Patients on long-term parenteral nutrition will have routine micronutrient screening (Table 24.8).

Other medications

No drug additions should be made to parenteral nutrition on grounds of stability, unless stability work is undertaken. Additions of certain drugs (e.g. heparin) are known to lead to incompatibility.

Recommended monitoring/care (early monitoring phase)

- Daily weight (before starting parenteral nutrition and daily thereafter).
- Take temperature and BP reading every 4–6h. (Also observe for clinical evidence of infection and general well-being.)
- Accurate fluid-balance chart and summary (to maintain accurate fluid balance and homeostasis). Bag change should be undertaken at the same time of day.
- Capillary glucose monitoring (BMS) every 6h during the first 24h, and then twice or once daily until stable (generally, the glucose target should be 4–10mmol/L). Return to BMS every 6h when parenteral nutrition is being weaned off.
- Daily assessment for CVC/PICC site infection or leakage. Change dressing for CVCs at least every 72h and more frequently if loose, soiled, or wet. Change PICC dressings weekly.
- 24h urine collections for nitrogen balance and electrolytes should be undertaken according to local practice.

Storage of parenteral nutrition on ward

Bags not yet connected to the patient must be stored in a refrigerator (at 2–8°C). Bags stored in a drug refrigerator must be kept away from any freezer compartment to prevent ice crystal formation in the parenteral nutrition.

Bags that have been refrigerated should be removed at least 1–2h before being hung and infused, to enable the solution to reach room temperature. Bags connected to the patient should be protected from light using protective covers.

Children's parenteral nutrition regimens

Parenteral nutrition in children

Infants and children are particularly susceptible to the effects of starvation. The small preterm infant (1kg) contains only 1% fat and 8% protein, and has a non-protein caloric reserve of only 110kcal/kg body weight With growth, the fat and protein content rises, so a 1-year-old child weighing 10kg will have a non-protein calorie reserve of 221kcal/kg body weight All non-protein content and one-third of the protein content of the body is available for calorific needs at a rate of 50kcal/kg body weight/day in infants and children.

A small preterm baby (<1.5kg) has sufficient reserve to survive only 4 days of starvation, and a large preterm baby (>3kg) has enough for ~10–12 days. With ↑ calorific requirements associated with disease this might be reduced dramatically to <2 days for small preterm infants and perhaps 1 week for a large preterm baby.

Indications for parenteral nutrition

Some children require short-term parenteral nutrition in the following clinical situations:

- major intestinal surgery
- chemotherapy
- severe acute pancreatitis
- multiorgan failure in extensive trauma, burns, or prematurity.

Others will need long-term parenteral nutrition if there are prolonged episodes of intestinal failure—e.g. in the following clinical situations:

- protracted diarrhoea of infancy
- short bowel syndrome
- gastroschisis
- chronic intestinal pseudo-obstruction.

Nutritional requirements (Table 24.9)

Fluid requirements also depend on the child's size, abnormal losses (e.g. diarrhoea, fever), surgical procedures, and disease state. The requirements for fluid to body weight are much greater in very small children than in older children and adults. Infants have a much larger body surface area relative to weight than older patients. Infants lose more fluid through evaporation and dissipate much more heat per kilogram. The use of radiant heaters and phototherapy further ↑ a neonate's fluid loss, resulting in ↑ fluid requirement. Children with high urinary outputs, ↑ ileostomy or gastrostomy tube outputs, diarrhoea, or vomiting should have replacement fluids for these excessive losses in addition to their maintenance fluid requirements.

The child's weight and assessment of intake and output can be used to estimate hydration status. It is important that children receiving parenteral nutrition are weighed regularly (initially daily, then twice or three times weekly with growth plotted when their condition stabilizes) and their fluid balance is monitored when parenteral nutrition is prescribed.

Energy sources

The body of a child requires energy for physical growth and neurological development.

Carbohydrate

Glucose is the carbohydrate source of choice in parenteral nutrition. To prevent hyperosmolality and hyperinsulinaemia, glucose infusions are introduced in a stepwise manner. In infants, glucose is introduced at 5–7.5% glucose and ↑ by 2.5% each day to an upper limit on glucose infusion rate of 4–7mg/kg body weight/min. In older children parenteral nutrition is started at 10–15% and ↑ daily to 20%, as tolerated.

The amount of glucose depends on the type of feeding line inserted. The glucose concentration in parenteral nutrition infused peripherally is limited to 12.5%. If central access is available, up to 20% glucose can be infused. Infusion of parenteral nutrition with glucose concentrations >20% has been associated with cardiac arrhythmias.

The infant with very low birthweight has low glycogen reserves in the liver and a diminished capacity for gluconeogenesis. Hepatic glycogen is depleted within hours of birth, depriving the brain of metabolic fuel. Thus providing exogenous glucose through parenteral nutrition is a priority. Preterm infants, especially those with birthweights <1000g, are relatively glucose intolerant because of insulin resistance. Infusion of glucose >6mg/kg body weight/min may lead to hyperglycaemia and serum hyperosmolality, resulting in osmotic diuresis. Tolerance to glucose improves on subsequent days. It is generally recommended that the glucose infusion rate does not exceed 9mg/kg body weight/min for premature infants after the first day of life and that ↑ is implemented gradually as the infant develops.

Table 24.9 Estimated average requirements for fluid, energy, protein, and nitrogen

Age (yrs)	Fluid (mL/kg/day)	Energy (kcal/kg /day)	Protein (g/kg/day)	Nitrogen (g/kg/day)
Preterm	150–200	130–150	3.0–4.0	0.5–0.65
0–1	110–150	110–130	2.0–3.0	0.34–0.46
1–6	80–100	70–100	1.5–2.5	0.22–0.38
6–12	75–80	50–70	1.5–2.0	0.2–0.33
12–18	50–75	40–50	1.0–1.3	0.16–0.2

Lipids

- Regimens require fat as a source of essential fatty acids. Fat is an important parenteral substrate because it is a concentrated source of calories in an isotonic medium, which makes it useful for peripheral administration.
- Fat is a useful substitute for carbohydrate if glucose calories are limited because of glucose intolerance. It is available as emulsions of soybean, soybean–safflower oil mixtures, or olive oil. The major differences are their fatty acid contents.
- Essential fatty acid deficiency can develop in the premature newborn during the first week of life on lipid-free regimens. There is a maximum lipid utilization rate of 3.3–3.6g/kg body weight/day. Above these values, there is ↑ risk of fat deposition 2° to the incomplete metabolic utilization of the infused lipid.
- IV fat should be commenced at a dose not exceeding 1g/kg body weight/day and ↑ gradually to a maximum of 3g/kg body weight/day, depending on age. Tolerance should be assessed by measuring serum triglyceride and free fatty acid concentrations.

Nitrogen

Nitrogen is needed for growth, the formation of new tissues (e.g. wound healing), and the synthesis of plasma proteins, enzymes, and blood cells.

Requirements vary according to age, nutritional status, and disease state. Infants and children experiencing periods of growth have higher nitrogen requirements than adults. Low-birthweight infants have relatively high total amino acid requirements to support maintenance, growth, and developmental needs.

Amino acid intakes of 2.0–2.5g/kg body weight/day result in nitrogen retention comparable to the healthy enteral-fed infant. Rates of up to 4g/kg body weight/day might be required. Because the amino acid profile varies between commercial brands, their nitrogen contents are not equivalent and protein requirements are calculated as grams of amino acids rather than grams of nitrogen in children.

Choice of amino acid solution

The proteins of the human body are manufactured from 20 different amino acids. There are eight essential amino acids. Premature infants and children are unable to synthesize/metabolize some of the amino acids that are 'non-essential' for adults. The use of amino acid solutions designed for adults have resulted in abnormal plasma amino acid profiles in infants. Infants fed with adult amino acid solutions have been shown to develop high concentrations of phenylalanine and tyrosine and low levels of taurine.

Paediatric amino acid solutions

Amino acid solutions specifically designed for neonates have been developed, as follows.

- Higher concentration of branch-chain amino acids (leucine, isoleucine and valine) and lower content of glycine, methionine and phenylalanine.
- Higher percentage of amino acids essential for preterm infants, with wider distribution of nonessential amino acids.
- Contain taurine.

The amino acid preparations available are based on either the amino acid profile of human milk (Vaminolact®) or placental cord blood (Primene®).

Electrolytes

Normal baseline electrolyte requirements are shown in Table 24.10.

Trace elements

Requirements for trace elements are shown in Table 24.11

Table 24.10 Normal baseline electrolyte requirements

Electrolytes	Requirements according to age (mmol/kg body weight/day)	
	Infants	Children
Sodium	2.0–3.5	1.0–2.0
Potassium	2.0–3.0	1.0–2.0
Calcium	1.0–1.5	0.5–1.0
Magnesium	0.15–0.3	0.1–0.15
Phosphate	0.5–1.5	0.12–0.4
Chloride	1.8–1.5	1.2–2

Table 24.11 Requirements for trace elements

Element	Requirements according to age (micrograms/kg body weight/day)		
	Preterm	Infants	Children
Zinc	100–500	50–100	50–80
Copper	30–60	20–50	20
Selenium	n/a	2–5	2
Manganese	n/a	1	1
Iron	100–200	20–100	100

Vitamins

Requirements for vitamins are shown in Tables 24.12 and 24.13.

Administration of nutrition

- The aqueous phase runs over a period of 24h and the solution is filtered using a 0.2μm filter.
- Lipid normally runs over a period of 20–24h and is filtered using a 1.2μm filter, although some centres prefer not to use filters.
- The weight used for calculation is usually the actual weight of the child.

Complications

Catheter-related

Complications could be due to catheter insertion (e.g. malposition, haemorrhage, pneumothorax, air embolism, or nerve injury) or might occur subsequently (e.g. infection, occlusion, or thromboembolism).

Metabolic-related

In stable patients with no abnormal fluid losses or major organ failure, severe biochemical disturbances are unusual.

Parenteral-nutrition-associated cholestasis

The aetiology seems to be multifactorial, including the absence of enteral feeding, overfeeding, prematurity, surgery, and sepsis. It might progress to cirrhosis. Excessive calories, particularly glucose overload, can lower serum glucagon concentrations, which ↓ bile flow. Early initiation of oral calorie intake is the single most important factor in preventing or reversing cholestasis. Small intestinal bacterial overgrowth, which often occurs in the presence of intestinal stasis, can impair bile flow, leading to cholestasis.

Monitoring children receiving parenteral nutrition in hospital

Requires clinical and laboratory monitoring, observations, and assessment of growth. Growth is conveniently assessed by accurate measurement of weight and height, and development assessment is plotted over time. Fluid balance, temperature, and basal metabolism need to be assessed daily.

Laboratory monitoring

- Initial assessment—daily for first 3–4 days, then twice weekly.
- Full blood count.
- Blood test: sodium, potassium, urea, glucose.
- Calcium, magnesium, phosphate, bilirubin, ALP, AST, ALT, blood glucose albumin, triglycerides, cholesterol.
- Copper, zinc, selenium, vitamins A and E: baseline measurement.
- Urine: sodium and potassium (baseline).
- Continued monitoring depends on the child's clinical condition.

Table 24.12 Requirements for water-soluble vitamins

Vitamin	Requirements according to age		
	Preterm	Infants	Children
B_1 (mg)	0.1–05	0.4–1.5	1.0–3.0
B_2 (mg)	0.1–0.3	0.4–1.5	1.0–3.0
B_6 (mg)	008–0.4	0.1–1.0	1.0–2.0
B_{12} (micrograms)	0.3–0.6	0.3–30	20–40
C (mg)	20–40	20–40	20–40
Biotin (micrograms)	5–30	35–50	150–300
Folate (micrograms)	50–200	100–200	100–200
Niacin (mg)	2–5	5–10	5–20

Table 24.13 Requirements for fat-soluble vitamins

Vitamin	Preterm	Infant	Children
A (micrograms)	75–300	300–600	500–800
D (micrograms)	5–10	10–20	10–20
E mg	3–8	3–10	10–15
K (micrograms)	5–80	100–200	N/a

Enteral feeding

Enteral feeding should be considered in patients with a functioning GI tract who are unable to meet requirements with ordinary diet, food fortification, and/or oral nutritional supplements.

Enteral nutrition is contraindicated in patients with intestinal obstruction, paralytic ileus, GI ischaemia, intractable diarrhoea, and diffuse peritonitis. Enteral access device selection is based on several patient-specific factors, including GI anatomy, gastric emptying, tube placement duration, and aspiration potential.

Post-pyloric feeding is indicated if there is gastric outflow obstruction or severe pancreatitis, or if the patient is at risk from aspiration with intragastric feeding.

Types of tube feeding

Intragastric feeding

- Nasogastric
- Percutaneous endoscopic gastroscopy (PEG)

Post-pyloric feeding

- Nasojejunal
- Nasoduodenal
- PEG
- Percutaneous endoscopic jejunostomy
- Surgically placed jejunostomy

Feeding tube specific issues

Site of delivery

- Gastric tubes end in the stomach, whereas jejunal tubes end in the jejunum.
- Sterile water must be used for jejunal tubes because of gastric acid barrier bypass.

Number of differences between tubes apart from site of feed delivery

- Bore size—fine-bore tube is designed for administration of feeds, and wide-bore tube is designed for aspiration
- Number of lumens
- Rate of flow
- Length

Complications of tubes

- Removal by patient
- Oesophageal ulceration or strictures
- Incorrect positioning of tube.
- Blockage

Categories of feed

Polymeric feeds

Contain whole protein, carbohydrate, and fat, and can be used as the sole source of nutrition for those patients without any special nutrient requirements. Standard concentration is 1kcal/mL with 40–50g/L protein, but they can vary in energy density (0.8–2kcal/mL) and can be supplemented with fibre, which can help improve bowel function if this is problematic.

Elemental feeds

Contain amino acid and glucose or maltodextrins; fat content is very low. Used in situations of malabsorption or pancreatic insufficiency. Because of their high osmolality, they should not be used in patients with short bowel syndrome.

Disease-specific feeds and modular supplements

Certain clinical conditions require adjustment in diets—e.g. high-energy low-electrolyte feeds for patients requiring dialysis, and low-carbohydrate and high-fat diets for patients with CO_2 retention (for certain patients on ventilators) as carbohydrate leads to more CO_2 production compared with calorific equivalent amounts of protein or fat.

Modular supplements are used for a variety of conditions—e.g. malabsorption and hypoprotein states. They are not nutritionally complete and hence are not suitable as the sole source of food. These feeds contain extra substrates that are claimed to alter the immune and inflammatory responses. These substrates include glutamine, arginine, RNA, omega-3 fatty acids, and antioxidants.

Administration of tube feeds

For intragastric feeds, diet can be delivered at a continuous rate over a period of 16–18h daily. Alternatively, intermittent boluses of 50–250mL can be administered by syringe over a period of 10–30min 4–8 times a day, although complications such as aspiration and delayed gastric transit times have been reported more frequently with this approach.

Post-pyloric feeding is generally performed by continuous infusion because it is deemed more physiological.

Complications from feeds

Diarrhoea

Diarrhoea is the most common complication associated with enteral nutrition, occurring in 21–72% of patients. Severe diarrhoea can cause life-threatening electrolyte changes and hypovolaemia. Management is by excluding other explanations (e.g. colitis, laxative use, antibiotics, and malabsorption).

Concomitant medications need to be rationalized. Antidiarrhoeal medications (codeine phosphate and/or loperamide) are often useful and fibre can help in some cases.

If diarrhoea persists after treatment, consider switching to the post-pyloric route.

Constipation

Usually a result of a combination of inadequate fluid, dehydration, immobility, and drugs. If functional pathology is excluded, management is by laxatives, suppositories, and fibre-containing feeds.

Vomiting, aspiration, or reflux

Both nasogastric and post-pyloric feeding can ↑ the risk of aspiration. Both can interfere with oesophageal sphincter function, and wide-bore tubes cause more problems than fine-bore tubes. Standard antiemetics and prokinetics are usually effective.

Metabolic complications

Re-feeding syndrome

Excess carbohydrate stimulates insulin release, which leads to intracellular shifts of phosphate, magnesium, and potassium that can lead to cardiac arrhythmias or neurological events. Emaciated patients must have their feed introduced gradually at a rate of 20kcal/kg body weight and electrolytes replaced in accordance with daily blood levels.

Vitamin/trace element deficiencies

Incidence is rare as commercially available feeds are nutritionally complete. Patients being fed over extended periods should be monitored appropriately.

Hyperglycaemia

Important in the critically ill. It is imperative that blood glucose is monitored and controlled because good glycaemic control reduces mortality rates in the critically ill.

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Drug administration in patients with feeding tubes

The administration of medication to patients with feeding tubes can be challenging, and a number of issues need to be considered in parallel with the patient's medical problems. These issues include the following:

- The continued need for the patient's regular medicines and the consequences of medication withdrawal or administration delay, both medically and legally.
- The intention to tube feed and subsequent compliance of the patient to retain the tube.
- Institutional ability to site percutaneous tubes.
- Availability and appropriateness of different formulations of medication.

Formulation difficulties

Pharmacists will be involved in influencing the choice of medication formulation on the basis of their training and experience.

Is there a formulation available for use by a licensed route? Use alternative routes of administration, if appropriate (i.e. buccal, intramuscular, intravenous, intraosseous, transdermal, topical, nebulized, rectal, subcutaneous, sublingual, etc.)

Pharmacists should also be able to calculate the cost implications of the different formulations and, importantly, should facilitate long-term choice, particularly if the parenteral route cannot be used in the long term.

- Is there a commercial oral solution, suspension, or soluble solid dose form?
- Oral liquid—dilute with 10–30mL sterile water or enteral formula if hyperosmolar.
- Oral immediate-release tablet—crush to fine powder and mix with 10–30mL water
- Oral immediate-release capsule—open capsule and crush contents to fine powder. Mix with 10–30mL sterile water.
- Oral soft gelatin capsule (e.g. acetazolamide, nifedipine)—remove liquid contents with a needle and syringe. Then mix with 10–30 mL of sterile water
- IV liquid preparation—draw dose into an amber oral syringe prior to administration
- Soluble tablets dissolved in 10mL of water are often the best option for tube-fed patients.
- Refer to specific manufacturer's advice for feed-tube administration.
- Remember to shake liquid preparations before administration.
- Viscous liquids might have to be diluted with water to ↓ tube blockage.
- Liquids with high osmolality or sorbitol content can lead to diarrhoea.
- Does the crushed tablet or capsule contents disperse fully or form a workable suspension that will not clog or block the feeding tube?
- Is the parenteral formulation of the product suitable for enteral use?
- Osmolality concerns for parenteral product.
- Additives in injections might make administration through a tube unsuitable.
- Is there a therapeutic substitute that can be administered via a tube?

Administration of medication through a tube

- Do not add medication directly to the feed.
- Only administer one medication at a time.
- Use an oral syringe if possible.
- Flush the tube with 50mL water immediately after stopping the feed.
- Add the volume of water used to fluid balance charts.
- Draw identified formulation into appropriate 50mL syringe.
- Attach the tube and apply gentle pressure.
- Flush with a minimum 15mL of water between different medicines.
- Flush with 50mL of water after the last medication.
- If drug is to be taken on an empty stomach, for gastric tubes, stop feed for 30min before the dose and resume feeding 30min afterwards. These measures are not relevant for jejunal tubes.
- Add the total volume of flushes and medicine to fluid balance chart.

Specific drug/tube feeding problems

Drug-specific issues

- Absorption could be unpredictable because the tube might be beyond the main site of absorption for the specific drug.
- Formulation issues of medication being administered through feeding tubes.
- Crushing destroys the formulation properties of tablets, altering peak and trough levels.
- Detrimental clinical effect for certain slow-release products (e.g. nifedipine LA), causing severe hypotension if inadvertently given crushed.

Adsorption onto feeding tubes

Examples are phenytoin, diazepam, and carbamazepine. Dilute with at least 50mL of water and flush the tube well.

Interactions causing blockage

Antacids and acidic formulations could cause precipitation because of an acid–base reaction.

Feed ↓ drug absorption

- Phenytoin—50–75% reduction in serum levels when given with enteral nutrition. Hold tube feeding for 2h before and after each dose as well as flushing the tube before and after each phenytoin dose.
- Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)—give enterally via large-bore feeding tube. Crush tablets and mix with 20–30mL of water prior to administration. Hold tube feeding for 2h before and 4h after administration. Ciprofloxacin suspension should not be administered via the feeding tube. It has a thick consistency that may clog the tube, and since it is an oil-based suspension it does not mix well with water.
- Warfarin—reductions in absorption may occur because enteral feeding solutions may bind warfarin.

Drug–feed interactions

If vitamin K is in present in the feed it means that doses of warfarin might need to be amended (monitor INR).

Bioequivalence

Different formulations might necessitate adjustment of dose (e.g. phenytoin tablets and liquid).

Further reading

Beckwith MC *et al.* (2004) A guide to drug therapy in patients with enteral feeding tubes: dosage form selection and administration methods. *Hospital Pharmacy* **39**: 225–37.

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IV therapy at home

Patients who are medically stable but require prolonged courses of IV drugs (usually antimicrobials) can benefit from IV therapy at home. Suitable indications or therapies are as follows:

- bone infections
- endocarditis
- cystic fibrosis
- cytomegalovirus infection
- total parenteral nutrition
- immunoglobulins.

The advantages of treating these patients at home are as follows:

- releases hospital beds for other patients
- avoids patient exposure to hospital-acquired infection
- ↑ patient autonomy
- improved patient comfort and convenience
- some patients can to return to work or study while therapy continues.

Despite the potential benefits, IV therapy at home should not be undertaken lightly. All IV therapy is potentially hazardous and complications, such as line sepsis or blockage, are potentially more probable and risky in the community.

It is recommended that a multidisciplinary home IV team is set up to oversee the process and that guidelines are drawn up to ensure that home IV therapy is done safely and effectively.[1]

Home IV therapy team

The following people should be included in the team. They may not have hands on involvement in every patient but should be available for advice and support.

- Clinician with an interest in home IV therapy (e.g. microbiologist, infectious diseases physician)
- Home IV therapy specialist nurse(s)/community liaison nurse(s).
- Pharmacist.
- Community representative (GP or community nurse).

24-hour access to key member(s) of the team (usually the specialist nurse and/or a clinician) is essential.

For individual patients, the medical and nursing team responsible for the patient's care should liaise with the home IV team and be involved in assessment, discharge planning, and follow-up.

IV access

Venous access through short peripheral lines (Venflons®) is unsuitable for home delivery because it is designed for short-term use and should be replaced every 48–72h. Peripheral access is also unsuitable for irritant or hyperosmolar infusions (e.g. TPN). Central venous access is preferred for the following reasons.

1 Nathwani D, Conlon C (1998). Outpatient and home parenteral antibiotic theraphy (OHPAT) in the UK: a consensus statement by a working party. *Clinical Microbiology and infection* **4**: 537–51.

- It can remain in place for prolonged periods.
- It can be used for irritant or hyperosmolar infusions.
- It is easier for patients to self-administer through a central line.

Three types of central IV access are used for home IV therapy.

- *Central line* (e.g. *Hickman® or Groshong®*)—the line is inserted, usually through the subclavian vein, and is threaded through a sub-cutaneous tunnel to exit on the chest wall. The tip lies in the superior vena cava or just inside the right atrium. Central lines are inserted under general or local anaesthetic. In some hospitals specialist nurses insert central lines. Central lines might have one or more lumens, but for IV therapy at home a single lumen line is recommended to ↓ complications. These lines can remain in place for many months.
- *Port-A-Cath®*—a central venous access device, consisting of a small reservoir (the port) attached to a catheter. The port is implanted into the chest wall, with the catheter inserted into the subclavian or internal jugular vein. The reservoir is covered with a thick rubber septum, which is accessed through the skin using a special needle known as a Huber® needle. Port-A-Caths® are inserted under general anaesthetic. They can remain in place for years. Because of the cost and complexity of insertion, Port-A-Caths® are only suitable for patients who require prolonged or repeated IV therapy (e.g. cystic fibrosis patients).
- *Peripherally inserted central catheters (PICCs)*—these are fine flexible catheters inserted into the basilic or cephalic vein at the ante-cubital fossa, in a similar manner to peripheral venous access. Using a guidewire, the catheter is threaded up the axillary vein and into a central vein. PICC lines are inserted under local anaesthetic and are the least complex of the three types to insert. They can remain in place for several weeks or months. PICC lines are the least costly and complex and therefore are usually the preferred type of access.

To preserve the patency of central lines and avoid septic complications, guidelines should give advice on handling the line, including the following.

- Aseptic technique for drug administration.
- Flushing the line between doses.
- Use of heparinized saline to avoid clot formation within the line.
- Dressing and cleaning the insertion site.
- Care of the line when not in use.
- Procedure if the line is blocked or damaged.
- Procedure if there are signs of infection/cellulitis around the insertion site or signs/symptoms of sepsis.

Assessment and discharge planning

The home IV team should take responsibility for assessing whether the patient is suitable for IV therapy at home and for planning the discharge jointly with other nursing/medical staff caring for the patient. It is important that sufficient time is allowed to ensure that assessment, training, and general

organization of the discharge are carried out adequately. Guidelines should advise a minimum of 48h notice, and ideally longer.

Patients should have the following characteristics:

- medically stable
- not likely to misuse the line
- psychologically able to cope with IV therapy at home
- willing to have IV therapy at home
- able to recognize problems and act accordingly.

The patient's home circumstances must also be taken into account.

- Is there another responsible adult who can support the patient and, if necessary, contact medical services themselves?
- Does the patient have a telephone?
- Are there reliable water and electricity supplies?
- Is there somewhere cool, dry, and safe to store drugs (out of reach of children)?
- Does the patient have a fridge, if needed, for drug storage (and do children have unsupervised access to this fridge)?
- Are there children or other people in the house who might be distressed by seeing drugs being administered IV?
- Does the patient have some means of transport to out-patient appointments?

Procedures for children receiving IV therapy at home are much the same as those for adults, but special attention must be paid to ensuring that home circumstances are suitable and that parents do not feel too pressured, especially if they are responsible for administering the drugs.

The discharge plan should be written in the patient's medical records (Table 24.14). A copy should be supplied to the GP, and patients should be provided with written information on the drugs, their administration, and their side effects, and given monitoring and emergency contact details.

Drug selection and administration

Drug selection primarily depends on the condition being treated. Ideally, drugs that are administered once daily should be used. In most UK schemes, IV infusions are avoided and wherever possible drugs are administered by slow IV push because this is a less complex and time-consuming method of drug administration. Where IV infusion cannot be avoided (e.g. vancomycin), the drug should be administered through a volumetric pump rather than a gravity drip. In some situations, it can be more appropriate to use an ambulatory infusion device such as an elastomeric pump (e.g. Homepump®) or other system (e.g. Sidekick®), rather than a volumetric pump. Discussion of these devices is beyond the scope of this chapter.

Guidelines should give advice on drug administration. Issues that must be considered are as follows.

- Who will administer the drug—e.g. patient, carer, community nurse?

- What training will they require?
- Who will do the training?

Many patients or their carers are capable of administering IV therapy provided that they receive suitable training and support. However, if therapy is only to continue for a week or less it is probably not worth the time taken to train a patient or carer. In some areas community nurses can administer the drugs, but they might also need additional training. Training is usually provided by a specialist nurse.

Training should include recognition of adverse effects and what action to take. This includes possible allergic or anaphylactic reactions. Protocols for administration of drugs by patients/carers or for community nurses to treat anaphylaxis should be in place and an 'anaphylaxis kit' kept in the patient's home. These protocols should follow UK Resuscitation Council guidelines.[1]

It is recommended that the first one or two doses of the drug should be administered in hospital so that the patient can be monitored for acute side effects.

Guidelines should include procedures for disposal of clinical waste (e.g. used dressings), sharps, and empty vials. These should follow local practice—e.g. some areas might accept sharps boxes for disposal in the community, whereas others might require them to be returned to the hospital.

Table 24.14 Checklist of information to be included in the discharge plan

Patient	Vascular access device	Treatment
Relevant past medical history	Type of device	Pathology and infecting organism
Problems/side effects experienced	When inserted or placed, and by whom	Details of antimicrobial regimen, drug, dose, etc
Frequency and timing of clinic visits during treatment	If centrally placed, where is the tip?	Administration details
Blood monitoring and frequency	Possible complications—signs, symptoms, prevention, and management	Side effects
Length of time on treatment	Day-to-day care of the line	Monitoring requirements and action required if results are abnormal
Finish/review date for treatment	Who to contact if there are any difficulties with the device	
How to access help	Who will remove the device and how	

1 *UK Resuscitation Council Guidelines*: http://www.resus.org.uk/pages/mediMain.htm

Community support

The patient's GP should be willing for the patient to go home with IV therapy. Even if they are not administering the drug, community nurses might be involved in other aspects of patient care and so should be kept informed. Good communication between the home IV therapy team and community healthcare workers is essential. Contact details for the hospital clinician and specialist home IV therapy nurse should be provided, including out-of-hours contact details.

Follow-up

Before discharge, follow-up arrangements should be planned. This should include the following.

- What to do if the patient has a significant ADR—who is responsible for managing this?
- Blood tests for monitoring ADR and TDM.
  - Who will take blood?
  - What tests are required?
  - Frequency.
  - How will the results be communicated and to whom?
  - Who will act on the results?
- The specialist home IV therapy nurse will usually be the main point of contact.
- The referring team should follow up the patient with respect to presenting indication, in addition to follow-up from the home IV therapy team.
- Duration of IV therapy is usually decided before discharge. It should be agreed which team is responsible for review of this and for provision of oral follow-on therapy.
- The home IV therapy team is usually responsible for line removal (as appropriate) at the end of the IV course.

The role of the pharmacist

The pharmacist is an important member of the home IV team. Their role includes the following responsibilities.

- Advice on drug stability and compatibility.
- Advice on drug administration, including infusion rates, and ambulatory infusion devices.
- Ensuring the supply of IV and ancillary drugs on discharge.
- Ensuring that follow-on oral therapy is prescribed.
- Provision of anaphylaxis kits.
- Liaison with homecare companies
- Supporting the training of patients, and community nurses.

The American Society of Health System Pharmacists has published guidelines on the pharmacist's role in home care which includes home IV therapy.[1] It should be borne in mind that these guidelines reflect the US system of healthcare and so some aspects might not be relevant to non-US pharmacists.

1 American Society of Health System Pharmacists (2000). ASHP guidelines on the pharmacist's role in home care. *Amercan Journal of Health Systems Pharmacy* **57**: 1252–7.

Drugs for home IV therapy at home fall into the 'hospital at home' category and, as such, all supplies should come from the hospital. Thus community pharmacists are rarely involved in IV therapy at home. However, it is important that hospital pharmacists liaise with their community colleagues as appropriate—e.g. where oral follow-on therapy might be prescribed by the GP.

Homecare companies

A number of companies provide support services for home IV therapy. The service may range from supply of drugs and ancillaries direct to the patient's home to provision of the IV drug in an ambulatory infusion device to full nursing support. Pharmacists should ensure that they are familiar with the services being provided by the homecare companies used and that local procedures are complied with.

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