Therapy-related issues: palliative care

Anorexia and cachexia

The dictionary definition of anorexia is a lack of appetite (for food). Cachexia is involuntary weight loss which can progress to an emaciated state. The majority of palliative care patients experience cachexia at some stage, and this difficult condition requires determination of the cause, if possible, and development of careful management. A number of Cochrane reviews have been published which summarize a fairly large volume of literature. The following interventions may be considered.

- Megestrol—evidence for effectiveness in stimulating appetite at doses ranging from 160 to 1600mg daily.
- Medroxyprogesterone acetate—evidence of greater weight gain and appetite than placebo at doses of 300—800mg daily.
- Corticosteroids—some evidence for improvement in appetite but not weight gain.
- Eicosapentanoic acid—somewhat heterogeneous literature with an unclear picture for benefit. Possibly worth trying if other treatments fail.

Constipation

Constipation is a common symptom in palliative care patients. It is related to opioid analgesic use, reduced food intake, and reduced activity. A patient diary can be helpful in determining the severity of the condition.

There is a lack of good-quality evidence for the effectiveness of laxatives, so a pragmatic approach is required. In general, it is necessary to combine an increase in fibre with a stool softener and probably a stimulant in order to maintain good bowel function. Choices can be based on local formularies. Rectal laxatives may be necessary for hard impacted faeces. This is not a pleasant option for either patient or care staff, but may be the only option for some cases.

A more recent and more expensive option is the use of peripheral opioid receptor antagonists. At the time of writing, only methylnaltrexone was licensed for use in the UK, administered by injection. The license is for opioid constipation in palliative care patients where other laxatives have failed. Methylnaltrexone is added to other laxative treatment. Doses should be reduced in renal failure.

Other drugs such as Alvimopan are under development and may prove useful. A Cochrane review of these agents suggested that there is currently insufficient evidence for the use of naloxone or nalbuphine.

Fatigue

- Fatigue is among the most common symptoms in palliative care patients. It is not easily defined, but is commonly described by words such as lethargy, muscle weakness, tiredness, and mood disturbance.
- A number of assessment tools exist and these are useful to monitor both decline and improvement.
- A number of Cochrane reviews and other systematic reviews show benefit from a range of interventions. These include cognitive behavioural therapy (CBT), erythropoietin and similar agents, and exercise.
- A systematic review has shown that Chinese herbal medicine is not effective.
- Patients who are able to undertake therapeutic exercise regimes may find these to be helpful.

Hypercalcaemia of malignancy

- This is a common complication, especially in breast and lung cancer and in myeloma, and often occurs with bone metastases.
- Mild hypercalcaemia—corrected serum calcium 2.7–3.0mmol/L.
- Moderate to severe hypercalcaemia—corrected calcium ≥3.0mmol/L.

Signs and symptoms

- Nausea
- Vomiting
- Thirst
- Polyuria
- Constipation
- Headache
- Impaired consciousness.

The patient may be severely dehydrated and in renal failure.

Management[1]

- Mild, asymptomatic—rehydrate and observation. Recheck calcium after 24h.
- Symptomatic—ensure hydration. Treat with bisphosphonates.
- Moderate to severe—urgent rehydration up to 3–6L in 24h and bisphosphonates.
- Stop any drugs that increase calcium levels—e.g. thiazide diuretics, lithium, calcium, and vitamin D supplements.

Bisphosphonates inhibit osteoclastic bone resorption. A significant decrease in serum calcium is generally observed 24–48h after IV administration and normalization is usually achieved within 3–7 days. If the patient is not normocalcaemic within this time a further dose can be given. Pamidronate should be infused at a concentration ≤60mg/250mL and a rate ≤60mg/h. Renal failure is a relative contraindication to the use of bisphosphonates and the dose should be administered at ≤20mg/h. The patient may be maintained on 4-weekly infusions or, for example, sodium clodronate orally 1.6–3.2g daily in divided doses.

Resisitant hypercalcaemia not responding to pamidronate or recurring frequently can be treated with zolendronic acid 4mg IV depending on renal function. With repeated use of bisphosphonates, be aware of the rare possibility of osteonecrosis of the jaw.

In severe hypercalcamia or with severe symptoms, calcitonin rapidly lowers serum calcium within hours, but the effect only lasts for hours and wears off altogether after a few days. Calcitonin 4–8IU/kg SC or IM every 6–12h for 2 days can be given along with bisphosphonate.

1 Twycross R (2007). *Palliative Care Formulary* (3rd edn): http://palliativedrugs.com

Mouth care

Patients find mouth problems very distressing, and careful attention should be paid to dental hygiene and risk factors for dry mouth.

Dry mouth

- Check for candidiasis.
- Ice-chips, fresh pineapple, sugar-free gum. Rinse with 0.9% saline.
- Artificial saliva and topical saliva stimulants, preferably with neutral pH.
- Review medicines as some (e.g. hyoscine and tricyclic antidepressants) exacerbate dry mouth.

Sore mouth

- Candidiasis—fluconazole 50mg orally once daily or nystatin 100 000IU four times daily for 7 days.
- Soak dentures overnight and ensure that they are thoroughly cleaned.
- A coated tongue can be cleaned by allowing a quarter of a 1g effervescent ascorbic acid tablet to dissolve on the tongue up to four times daily for a week.
- Mucositis—chlorhexidine or benzydamine mouthwashes.
- Stomatitis—choline salicylate gel or hydrocortisone 2.5mg pellets.
- Systemic analgesia may be needed if severe.

Noisy breathing

Noisy breathing (sometimes called death rattle) occurs in significant numbers of people who are dying. The cause of noisy breathing remains unproven, but it is presumed to be due to an accumulation of secretions in the airways. It is managed either physically (repositioning and clearing the upper airways of fluid with a mechanical sucker) or pharmacologically. There are a number of treatment options (mainly anticholinergic drugs with some trials of atropine, hyoscine butylbromide, hyoscine hydrobromide, and glycopyrronium) but studies have found no difference in efficacy between these. A Cochrane review was unable to demonstrate any real effectiveness, and these treatments remain time-honoured rather than evidence-based.

Insomnia

Insomnia is a common problem in palliative care. Daytime sleepiness can lead to nighttime wakefulness therefore so called 'sleep hygiene' is an important consideration. A sleep log may be useful to assess how much sleep is actually achieved. There are many contributing factors to insomnia including anxiety, pain, medications, or limb movements. Pharmacists can help by reviewing those medicines that can induce sleep during the daytime e.g tricyclic antidepressants for neuropathic pain and shifting the dose to later in the day. Ensure adequate pain relief is provided at night. Discourage the use of stimulants including caffeine in the evening. Consider sleep medication only after other issues have been considered and dealt with. There is no evidence that palliative care patients benefit from any different hypnotics that other patients so a general approach to use what is familiar is suggested.

Spinal cord compression

This is a complication of advanced cancer with tumour mass or bone compressing the dural sac and contents. This is a poor prognostic sign, with average survival of 4–6 months. 90% of patients present with back pain and 50% also have some neurological deficit—usually leg weakness with possible bowel or bladder involvement. Investigate with MRI of the whole spine or CT. Speed is of the essence to preserve mobility if the patient is ambulant at diagnosis.

Management

- Dexamethasone 16mg stat, then 8mg twice daily to reduce pain and spinal oedema. First 48h are crucial for the majority of clinical benefit. Taper steroids as appropriate thereafter.
- Radiotherapy within 24h if possible.
- Surgery if single site and patient has good performance status.

Malignant bowel obstruction

This is a complex problem which occurs mainly in patients with advanced gynaecological and gastrointestinal cancers. The condition can range from a partial to a complete obstruction. Symptoms can include nausea and vomiting as well as abdominal distension and pain. In complete obstruction no faeces or flatus are passed. Surgery is usually the first option, but many patients may not be fit for such an intervention and other interventions such as stents may be tried.

Drug therapy includes antiemetics, usually parenteral metoclopramide, anticholinergics such as hyoscine, or other drugs to reduce the persistent nausea that can accompany this condition.

Other interventions include the use of octreotide which may prevent damage to the intestine such as oedema or necrosis and may improve intestinal transit. The beneficial effects seem to be seen in the early stages of obstruction.

Syringe drivers and compatibility of medicines

The syringe driver is a simple and cost-effective method of delivering a continuous subcutaneous infusion (CSCI), which can be used to maintain symptom control in patients who are no longer able to take oral medication because of persistent nausea and vomiting, dysphagia, or bowel obstruction, or are in end-of-life care. Commonly used medicines in syringe drivers are opioid analgesics, antiemetics, antisecretories, and anxiolytics. In addition to the CSCI, each of the medicines should be prescribed prn for breakthrough symptoms and used to calculate the doses for the next driver. The prescription should be reviewed every 24h. Literature sources for compatible combinations of medicines are limited and the following is a guide for combinations known to be compatible when made up to 21mL with water for injection over 24h.

Two medicine combinations

Up to **50mg morphine sulphate** may be combined with **one** of the following medicines.

- Cyclizine up to a maximum dose of 150mg.
- Haloperidol up to a maximum dose of 10mg.
- Metoclopramide up to a maximum dose of 75mg.
- Midazolam up to a maximum dose of 30mg.
- Hyoscine butylbromide up to a maximum dose of 120mg.

Three medicine combinations

Up to **30mg of morphine sulphate** may be combined with the following medicines.

- Cyclizine (up to150mg) and haloperidol (up to 2.5mg).
- Cyclizine (up to 150mg) and midazolam (up to 20mg).
- Midazolam (up to 30mg)and metoclopramide (up to 40mg).
- Midazolam (up to 30mg) and haloperidol (up to 5mg).
- Midazolam (up to 30mg) and hyoscine butylbromide (up to 80mg).
- Haloperidol (up to 5mg) and hyoscine butylbromide (up to 80mg).

Any other combinations or diluents should be confirmed against the references in the 'Further reading' listing in this section or referred for specialist advice.

Further reading

Dickman A *et al.* (2005). *The Syringe Driver* (2nd edn). Oxford: Oxford University Press.
Trissel LA (2009). *Handbook on Injectable Drugs* (15th edn). Bethesda, MD: American Society of Health System Pharmacists.

End-of-life pathways

- Pharmacists need to be aware of the existence of these pathways which have been pioneered by clinicians in Liverpool.
- The Liverpool Care Pathway is an integrated care pathway that is used at the bedside to improve quality of the dying in the last hours and days of life in any setting.
- It is a means of transferring the lessons learnt in the care of the dying from hospices to other clinical areas.
- It is recommended as a best practice model by the UK Department of Health.

Anaemia

Anaemia is a decrease in red blood cells (RBC), haematocrit, or haemoglobin (Hb) because of:

- blood loss—e.g. GI bleed.
- deficient RBC production (erythropoesis)—e.g. iron deficiency, vitamin B_{12} deficiency.
- excessive RBC destruction (haemolysis)—e.g. G6PD deficiency (see 📖 p.200, 'G6PD deficiency', Chapter 10.

Anaemia is not a diagnosis in its own right but a manifestation of an underlying disorder (e.g. NSAID-induced GI bleed), and so should be investigated to determine the cause. A low Hb is defined as <13.5g/dL in ♂ and <11.5g/dL in ♀ but symptoms are uncommon until Hb <7g/dL, although they may occur at higher Hb if there is an acute ↓ or limited cardiopulmonary reserve.

Signs and symptoms

- Fatigue
- Dyspnoea
- Faintness
- Headache
- Pallor (including conjunctival pallor)

Haematological investigations

- Mean cell volume (MCV) – a measure of RBC size.
- Mean corpuscular haemoglobin (MCH)—a measure of the amount of Hb in RBCs
- Mean corpuscular haemoglobin concentration (MCHC)—a measure of the concentration of Hb in RBCs
- Haematocrit—a measure of the percentage of blood that is RBCs.

These investigations can help to indicate the mechanism of anaemia and thus help determine the cause (Table 27.1).

- Microcytic anaemia (i.e. MCV is low) indicates altered haem or globin synthesis.
- Macrocytic anaemia (i.e. MCV is high) indicates impaired DNA synthesis.
- Normocytic anaemia results from insufficient or inadequate response to erythropoietin.
- Hypochromic anaemia (i.e. MCH and MCHC are low).

Table 27.1 Some causes of anaemia based on the MCV

Microcytic/ hypochromic	↓MCV, ↓ MCHC (e.g. Fe deficiency) Thalassaemia Anaemia of chronic disease
Macrocytic	↑ MCV Reticulocytis (polychromasia on blood film) B_{12} or folate deficiency Chronic liver disease Hypothyroidism Alcohol Myelodysplasia
Normocytic/ normochromic	↔ MCV, MCHC Anaemia of chronic disease (e.g. chronic infection, inflammation) Inflammatory disease or malignancy Acute blood loss Renal failure Myeloma

Iron-deficiency anaemia

Iron is present in the body at ~ 50mg/kg of which ~60% is in RBCs, 30% in body stores (as ferritin and haemosiderin), 5% in muscle cell myoglobin and 5% in various enzymes or bound to transferring. Dietary intake is needed to replace normal losses:

- 0.5–1mg/day in faeces, urine, sweat
- 0.5–0.7mg/day (averaged over the month) in menstruating women.

Pregnant women need an additional 1–2mg/day.

Dietary intake comes from haem iron (in meat and fish) and non-haem iron (in grains, fruit, and vegetables). Haem iron is better absorbed than non-haem iron but the absorption of the latter may be ↑ by ascorbic acid or citric acid. Iron is mostly absorbed in the duodenum and jejunum, and the excess is excreted in the faeces.

A low Hb does not necessarily mean low iron and a full blood count as well as iron studies should be conducted to determine whether it is iron-deficiency anaemia and so iron supplements are required (Table 27.2).

Treatment

Treatment includes finding and treating the underlying cause (e.g. GI bleed, menorrhagia) as well as correcting the deficiency. Hb should be ↑ by 1–2g/L every day and continued for 3 months after normalization of Hb to replenish iron stores. Different iron salts contain different amounts of elemental iron (Table 27.3), but the aim is to give 100–200mg elemental iron per day (e.g. as ferrous sulphate 200mg three times daily). Other salts are sometimes better tolerated but may be more expensive. Modified release or enteric-coated preparations supposedly improve tolerability, but may not be released until after the duodenum where absorption is poor.

Parenteral iron (as iron dextran or iron sucrose complex) has no advantage over oral iron as it replenishes Hb, at the same rate although

iron stores are replenished more quickly, and it has been associated with hypersensitivity reactions. It is used in specific situations:
- haemodialysis patients
- intolerance to oral iron
- poor compliance
- continuing blood loss
- documented malabsorption (e.g. IBD).

Prophylaxis with oral or parenteral (if fits listed criteria) iron may be given if there are risk factors for iron deficiency—e.g. pregnancy, malabsorption conditions (e.g. gastrectomy), haemodialysis.

Blood transfusion is not usually necessary in most patients unless Hb <7g/dl. It is potentially hazardous with a risk of transfusion reactions (hypersensitivity type symptoms), fluid overload potentially leading to heart failure, and haemolytic reactions due to blood group or Rhesus factor incompatibility. Fevers and mild allergic reactions are also fairly common, although rarely serious. Therefore transfusion should only be carried out in the following situations:
- acute situation (e.g. haemorrhage)
- comorbidity (e.g. IHD, heart failure, COPD)
- patient symptomatic.

Vitamin B_{12} deficiency/pernicious anaemia

Vitamin B_{12} is found in meat and dairy products but not in plants. Signs and symptoms include:
- general symptoms of anaemia
- glossitis
- angular cheilosis
- peripheral neuropathy.

Causes include dietary (e.g. vegans), malabsorption (e.g. gastrectomy, Crohn's disease), lack of intrinsic factor (necessary for absorption). ↑Hb, ↑MCV, and ↓B_{12}. Treatment is with parenteral vitamin B_{12} (hydroxocobalamin)—initially alternate day injections for 2wks to replenish stores and then every 3 months. Pharmacists need to be aware of the need for continuing maintenance injections in long-stay patients. Oral maintenance with cyanocobalamin is an option only if the deficiency is due to diet alone.

Folate deficiency

Folate is found in most foods, especially green vegetables, but it can be destroyed by cooking. Causes of folate deficiency include:
- dietary deficiency
- malabsorption
- increased requirements (e.g. pregnancy)
- increased losses (e.g. malignancy)
- other causes (e.g. prematurity, folate antagonist drugs)

Folate deficiency is relatively common in patients with grossly deficient diets as stores are only sufficient for 3–4 months. Clinical presentation is similar to vitamin B_{12} deficiency but:
- there is a more rapid onset of symptoms
- neuropsychiatric disorders are rare.

Table 27.2 Interpreting plasma iron studies

	Iron	TIBC	Ferritin
Iron deficiency	↓	↑	↓
Anaemia of chronic disease	↓	↓	↑
Chronic haemolysis	↑	↓	↑
Haemochromatosis	↑	↓ (or ↔)	↑
Pregnancy	↑	↑	↔
Sideroblastic anaemia	↑	↔	↑

TIBC, total iron-binding capacity.

Table 27.3 Ferrous iron content of different iron tablets

Iron salt	Tablet strength	Ferrous iron content
Ferrous fumarate	200mg	65mg
Ferrous gluconate	300mg	35mg
Ferrous sulphate	300mg	60mg
Ferrous sulphate, dried	200mg	65mg

Treatment

Treatment is with folic acid 5mg daily and patients should be encouraged to increase dietary intake. Coexisting vitamin B_{12} deficiency should be corrected.

Folate deficiency in pregnancy can lead to neural tube defects. Women who are pregnant or planning a pregnancy should be advised to take folate supplements:

- 400micrograms daily before conception and for the first 12 weeks gestation.
- 5mg daily in women with diabetes or sickle cell disease, or on anti-convulsants.

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Chapter 28

Therapy-related issues: miscellaneous

Introduction to critical care

For the purposes of critical care in the UK, patients are grouped into one of four levels of care, an allocation that changes according to severity of illness and degree of actual or potential organ support required by the patient.

- Level 0 patients have needs that can be met by normal ward care.
- Level 1 patients have needs that can be met on an acute ward with additional advice and support from the critical care team. They are at risk of their condition deteriorating, or have recently been relocated from higher levels of care.
- Level 2 patients require more detailed observation or intervention, including support for a single failing organ system or postoperative care, and include patients stepping down from higher levels of care (formerly known as high dependency unit (HDU) patients).
- Level 3 patients require advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multi-organ failure (formerly known as intensive care unit (ICU) patients).

This classification has meant that critical care has come to define a type of therapy, rather than a specific place where such therapy is administered. Critical care teams work in ICUs, HDUs, specialist surgical units, recovery areas, and perioperative care, and on general wards with outreach teams. Therefore critical care encompasses a diverse area for pharmacists to work within, and pharmacists working on general wards are increasingly coming into contact with critically ill patients. For the pharmacist who commits to a career in critical care, a competency framework describing various levels of specialist pharmacist practice has been drawn up and is published on the Department of Health's website.[1]

Tips, hints, and things you should bear in mind

Critical care can at first be a daunting area within which to work. Patients are on the extremes of the physiological spectra, often accompanied by a frightening array of equipment that bristles with buttons and gaudy displays, issuing all manner of warning squeaks, pips, and beeps. The patient is cared for by experienced efficient nurses and calm intelligent doctors, and can be surrounded by teams of personnel attending to various functions of care. An enormous variety and quantity of data are generated, with the patient's notes quickly expanding in size. All this activity is being watched by tense, tired, and often tearful relatives or carers, who are constantly looking for the slightest sign that their loved one's condition is getting either better or worse.

1 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_084011

Put the patient first

In all your endeavours and work, you must put the patient first. If there are limited resources and you have several patient care responsibilities, then you must do the best you can for the patients who need you the most.

Not all patients are model citizens. They may have led very colourful lives, and this can complicate their medical management and their dealings with relatives, or affect your own personal feelings for them. You must put these aspects aside in order to do your best for them.

You will have to come to terms with the fact that a significant proportion of patients will die despite your best efforts. This of course reflects the severity of their illness, not your performance, and you will need to remind yourself of this from time to time.

Remember the relatives, carers, and friends

The patient is not always alone. Loved ones visit and stay by the bedside without restrictions on visiting hours. As a member of the team, you will be asked about various aspects of the patient's care. As a junior pharmacist, you should refer requests for information about progress or planning to a member of the medical team. This ensures that visitors receive consistent information. You may still need to talk to relatives to obtain information about medications, or possibly because you are asked to discuss a specific aspect of care with them by the medical team. When you do so, employ great sensitivity. Loved ones have a lot of time to think and dwell on the consequences of the illness that brings the patient to critical care, and as such can be extremely fragile. Remember that certain aspects of the patient may not be known to them and should not be divulged, sometimes at the specific request of the patient. This can give rise to some extraordinary circumstances, yet you must still employ strict patient confidentiality. Because of the situation they find themselves in, visitors may not take in everything you are saying. They may also make their own interpretation of any information you are giving them or asking of them. Be as clear and concise as you can. Note the key points of conversation in the patient's notes and, if possible, ensure that the patient's nurse is party to the conversation. As well as acting as a witness, they can dig you out of a hole.

Do not worry

You may not know the nuances and subtleties of various standard critical care interventions such as the use of vasopressors or sedation and analgesia. In fact you are unlikely to, unless you have committed to a career in critical care pharmacy. Fortunately, intensivists tend to know a fair bit about these agents and so you should be assured that, at more junior levels of practice, such in-depth knowledge is not necessary in order to contribute meaningfully to the team.

Nor will you be expected to know the function of every piece of kit available at the bedside, and no one will expect you to be able to interpret pressure waveforms or scan results. Your role is not the same as everyone else's. In time, you may understand the intricacies of the available monitoring and supporting equipment, but for now, concentrate on the area that you know best—basic clinical pharmacy.

Develop a methodical approach

Every critical care patient requires a high degree of pharmaceutical care/medicines management. You must know the patient's medical history, drug history, allergy history, admitting complaint, progress, pharmacokinetic reserve, and prescription as a minimum dataset from which to work. Making professional notes is important in order to record all pertinent information and to aid in planning the patient care (including follow-up).

Do not become overloaded with the huge amount of information available. Always summarize trends and interpret where possible. It is usual to think in terms of individual body systems in order to avoid missing anything out, but of course these are interrelated and so you must always step back and consider the patient as a whole. Remember that medicines are only one of the tools that can be utilized in the care of a patient. Try to think beyond just drugs (e.g. there are mechanical methods for venous thrombus prophylaxis, as well as anticoagulants).

Draw on what you know . . .

Your broad generalist knowledge of medicine is a bonus. Critical care teams are highly specialist, and despite the broad case mix, many of the patients present to intensive care for the same sorts of reasons and require the same sorts of treatments. The fact that you know a bit about other medications found outside critical care is very useful to the team.

Despite the fact that the majority of critically ill patients have disturbances of organ function that necessitate adjustments of dose, route, or choice of agent, this area is often not consistently tackled by medical staff and is one area where you can make a major contribution. Examples include dose adjustment in renal dysfunction or changes in route of administration because of surgery.

Looking out for, or avoiding, adverse drug reactions/interactions is very important. This can sometimes be more about refuting that such a reaction has taken place rather than the more usual situation of avoiding problems that may arise.

. . . and say when you don't know

Knowing your limitations is something to be respected. Do not bluff your way through an issue—it is obvious when you do and nobody likes it. It can result in inappropriate interventions in the short term and appropriate advice or interventions being ignored or treated as suspect in the future.

Recognize others' expertise

Everyone has expertise: medics, surgeons, nurses, physiotherapists, dieticians, relatives, and loved ones—everyone. There will be overlaps as well as gaps in knowledge and differences in opinion. Learn to live with it and collaborate. Do not create conflict. This will not help the patient.

Be aware and utilize other resources

Liaise with pharmacists from the service that the patient came from. Critical care is a support service, treating the sickest patients from many other services. Obtaining valuable advice from pharmacists who routinely work in those services will greatly aid in the provision of appropriate care for the patient.

Critical care units do not work in isolation from each other. Each unit is part of a larger network or group of units that covers a distinct geographical location. This means that, within each network or group, there will be other critical care pharmacists whom you can talk to or draw support from. Find out who they are and introduce yourself to them (face to face, by telephone, or by email), before you need their advice in a crisis. Each network or group will have standards of practice and therapeutic protocols (often called care bundles). Obtain copies and be familiar with them.

Delirium/acute confusional state

Large numbers of patients become delirious in critical care. Some studies put the incidence as high as 80%, although it is probably nearer to 50% in a general ICU population in the UK. Delirium is important—it is associated with excess mortality, increased length of stay, new admissions to care home after leaving hospital, and increased likelihood of a long-term cognitive dysfunction (i.e. dementia).

Historically, delirium has been poorly recognized and treated. In particular, agitated delirium has been treated with sedation, which masks the condition without treating it, whilst non-agitated delirium goes unrecognized.

Detection

Detection should be through the routine use of a screening tool such as the Confusion Assessment Method modified for critically ill patients (CAM-ICU). Other tools also exist, such as the Intensive Care Delirium Screening Checklist (ISDSC) which some find easier to use. Routine screening increases recognition.

Prevention

Preventative measures are simple interventions such as avoiding dehydration, ensuring good sleep patterns and good nutrition, and normalizing the environment as much as possible. Humane attention to detail such as use of glasses and hearing aids make a difference, as well as interacting with the patient as much as possible.

Many medications may cause delirium. Good pharmaceutical care (reducing doses in renal failure and hepatic failure) and avoidance of precipitants such as drugs with anticholinergic activity, daily sedation breaks, and good sedative management all help.

Treatment

Pharmacological treatment options are based on a small evidence base. Antipsychotics are used at the lowest effective dose and withdrawn as the delirium clears. Specialist advice should be sought if delirium fails to clear after a week of therapy to rule out a more permanent decline in cognitive function (dementia). The aim of therapy is not to sedate the patient, but to clear the cognitive deficit. A sedative may be required in addition to keep a severely disturbed patient safe.

Haloperidol

Haloperidol is flexible; it has a wide dosing range and can be administered via a variety of routes (PO, NG, IV, IM). Typical doses are 1–5mg, depending on the degree of illness and age of the patient, given regularly every 6–8h.

Olanzapine

Olanzapine can be administered NG and IM. Typical doses are 2.5–10mg/day. It may be more effective in certain types of delirium and has fewer side effects than haloperidol.

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Stress ulcer prophylaxis

Over three-quarters of ICU patients have endoscopic evidence of mucosal damage within 1–2 days of admission to intensive care, although in most cases the damage is superficial and will heal quickly. Clinical evidence for gastric bleeding occurs in up to a quarter of patients ('coffee grounds', malaena), and up to 6% of patients suffer clinically important bleeding that results in haemodynamic instability or a requirement for blood transfusions. The incidence of stress ulceration appears to be falling, probably because of general advances in the management of critically ill patients as well as specific prophylactic measures for stress ulceration.

Pathophysiology

It is thought that mucosal damage is brought about by a number of factors, such as disturbances in mucosal blood flow due to cardiovascular instability and hypoperfusion leading to a relative mucosal ischaemia, the presence of reduced gastric luminal pH, and altered mucosal protective mechanisms. At pH <4, the proteolytic enzyme pepsin destroys clots forming on damaged gastric mucosa, increasing the likelihood of bleeding and the extent of gastric damage.

Risk factors

A large number of risk factors have been identified for stress ulceration:

- >48 hours mechanical ventilation
- coagulopathy
- acute renal failure
- acute liver failure
- sepsis
- hypotension
- severe head injury
- history of GI bleeding
- burns covering >35% of body surface
- major surgery.

The two most important are mechanical ventilation for >48h and coagulopathy.

Aim of therapy

An increase in the gastric pH to >4 is thought to be sufficient to prevent superficial stress ulceration progressing to a more serious pathological state which is much more difficult to treat. Therefore the aim of therapy is to prevent further attack on already injured mucosa by reducing acidity and/or preventing proteolytic enzymes from attacking unprotected gastric mucosa. This can be differentiated from the aim of therapy for non-variceal upper GI bleeding where a higher pH is required (pH >6).

Methods of stress ulcer prophylaxis

Several large randomized placebo-controlled studies have been conducted, with conflicting results arising from each. The therapy of choice has changed a number of times over the years.

- H_2-receptor antagonists are usually used first line. Ranitidine 50mg given by bolus injection three times daily is common.
- PPI use is increasing, although there is at present no defining study that places this agent at the heart of stress ulcer prophylaxis therapy. Once-daily injections of omeprazole or pantoprazole have been used, and some centres use an extemporaneously prepared enteral formulation of omeprazole (simplified omeprazole suspension).
- The use of sucralfate has almost disappeared, and antacids are no longer used.

It is common practice to cease stress ulcer prophylaxis when NG feeding is established, although the limited evidence available suggests that feed is not an effective form of stress ulcer prophylaxis.

Some surgical procedures may result in a reduced acid secretory function through denervation of the stomach (e.g. oesophagectomy), but the effect this has on stress ulcer formation has not been studied.

Pharmacological stress ulcer prophylaxis is so routine in critical care that the prescribing of prophylaxis becomes an almost reflex response. Stopping acid suppression therapy in patients with a total gastrectomy can be a common pharmacist's intervention. Partial gastrectomy may still require stress ulcer prophylaxis if the acid secretory function remains intact (i.e. where the antrum of the stomach remains).

Unwanted effects of stress ulcer prophylaxis

- One large study found an increased incidence of nosocomial pneumonia in the ranitidine arm. This has largely been ignored since it was not found in subsequent studies, although an increased incidence of pneumonia in an ambulatory population taking acid suppressant therapy has also been reported.
- There is growing evidence that the use of acid suppressants increases *Clostridium difficile* acquisition rates. This effect may be greater with PPIs than with H_2 antagonists.
- The use of pH testing strips to confirm the correct placement of enteral tubes is unreliable where acid suppressant therapy is used.
- Ranitidine is associated with a number of side effects, including cardiac rhythm disturbance, but the evidence that it causes thrombocytopenia is very poor.

Motility stimulants

The provision of early enteral feed is an important goal in critically ill patients and has several advantages over parenteral feeding. Haemodynamic disturbance, pre-existing disease states, and drugs used in the critically ill patient (e.g. adrenergic agents, opiates) frequently result in failure of the patient to absorb enteral feed.

It is usual to use markers such as bowel sounds and gastric residue volume on aspiration to assess gut motility, although neither method is particularly reliable.

Metoclopramide

Metoclopramide is widely used to promote gut motility. However, the evidence base in the critically ill is very poor. This dopamine antagonist possibly works through blockade of dopaminergic neurons in the stomach and small bowel that would normally inhibit GI motility. It also increases lower oesophageal sphincter tone. A typical dose is 10mg three times daily.

Erythromycin

The evidence base for erythromycin is stronger than that for metoclopramide and comes from several small-scale studies, but it is often reserved for second-line therapy after metoclopramide because of concerns about promoting antimicrobial resistance. Erythromycin acts as a motilin receptor agonist. The addition of erythromycin to a metoclopramide regime is not evidence based, although simultaneously targeting different motility pathways may prove beneficial.

Typical doses range from 250mg twice daily to 200mg three times daily intravenously. Doses as small as 70mg have been shown to have an effect in adults. It is believed that smaller doses are more effective than larger doses, and this is consistent with the well-known upper GI effects of antibiotic doses.

Neostigmine

Neostigmine infusions have been used to promote normal bowel function in the critically ill. Neostigmine directly stimulates acetylcholine release from nerve plexi within the gut wall. A continuous infusion of 0.4–0.8mg/h has found to be an effective prokinetic based on frequency of stool production.

Domperidone

There is no evidence to support or refute the usefulness of domperidone for gut motility. Activation of dopaminergic fibres found in the smooth muscle of the GI tract inhibit smooth muscle contraction and so blockade of these fibres by dopamine antagonists may encourage smooth muscle contraction. Therefore it is possible that a role for domperidone and other dopamine antagonists may be found in the future.

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Mechanical ventilation

Mechanical respiratory support may be required in patients with a certain degree of respiratory failure. Typically such failure can be described in terms of a failure to oxygenate blood, such as during an acute asthma attack (type 1 respiratory failure), or a failure to ventilate the lungs resulting in carbon dioxide retention, such as in exacerbations of COPD (type 2 respiratory failure). Patients who do not protect their airway (e.g. through the consequences of acute head injury) may also require respiratory support.

Non-invasive ventilation

Selected patients may initially be managed using a form of tight-fitting facemask which acts as the interface between patient and ventilator. These come in a variety of shapes and sizes. An NG tube is usually *in situ* in order to decompress the stomach, which can frequently become inflated as a result of swallowing air.

Invasive ventilation

The more typical method for connecting a ventilator to a patient is through the insertion of a plastic pipe into the patient's trachea, placed either through the upper airways (nasal passages or mouth) or through a stoma in the patient's neck under the larynx. An inflatable cuff at the end of the tube secures it in the trachea. The ventilator is attached to the other end of the tube. The act of tube placement is known as intubation.

Drugs used to facilitate intubation

Feeding a large-diameter tube through the mouth or nose into the trachea generates all manner of physiological responses, none of which are described as 'pleasant'. Various agents are used to manage or attenuate such a noxious stimulus.

Rapid-sequence induction

This technique is used to secure the patient's airway rapidly whilst minimizing the risk of soiling the airways with stomach contents. A sedative agent such as thiopental 3–4mg/kg is used in combination with a muscle relaxant such as suxamethonium 1–1.5mg/kg to facilitate the technique. Other sedative agents used include propofol 2mg/kg, etomidate 0.1–0.4mg/kg, or occasionally ketamine 1–2mg/kg. Alternative muscle relaxants include rocuronium 1mg/kg or vecuronium 80–100micrograms/kg.

Awake intubation

This is used to secure an airway where a difficult intubation is anticipated e.g. due to previous history or airway obstruction, unstable cervical spine fracture, or when anaesthetic induction is dangerous for the patient. Comfort for the patient is provided using topical anaesthetics such as lidocaine 4%, possibly with light sedation with an agent such as midazolam 1–2mg. Atropine 400–600micrograms or glycopyrronium bromide 200–400micrograms is given to dry up secretions.

Ventilation modes

A bewildering array of ventilation modes are used. The following is intended to be a brief overview of those most commonly used.

Continuous mandatory ventilation (CMV)

The ventilator controls movement of gas through the patient's lungs according to set parameters and takes no account of any residual breathing effort the patient may make. Set parameters can be volume-based, pressure-based, or a mixture of both.

Assist control ventilation (ACV)

The ventilator controls movement of gas through the patient's lungs according to set parameters either when the patient triggers a breath (assisted breaths) or at the set respiratory rate if the patient fails to trigger a breath (controlled breaths).

Intermittent mandatory ventilation (IMV)

The ventilator controls movement of gas through the patient's lungs according to the parameters set at a mandatory respiratory rate, but allows spontaneous breathing to occur between mandatory breaths.

Synchronous intermittent mandatory ventilation (SIMV)

The ventilator controls movement of gas through the patient's lungs according to the parameters set at a mandatory respiratory rate, but allows spontaneous breathing to occur between mandatory breaths. Assisted breaths are synchronized with spontaneous breaths when their timing is sufficiently close.

Pressure support ventilation (PSV)

The ventilator augments the flow of gas moving into the patient's lungs in order to maintain a preset pressure in the ventilator circuit during inspiration. When the flow rate falls below a set value, the expiration cycle begins. PSV may be combined with other modes of ventilation to support spontaneous breaths.

Continuous positive airway pressure (CPAP)

The ventilator maintains the ventilator circuit pressure at a constant value above ambient pressure during spontaneous breaths.

Positive end-expiratory pressure (PEEP)

The ventilator maintains the ventilator circuit pressure at a constant value above ambient pressure during ventilator-generated breaths.

Bilevel positive airway pressure (BiPAP)

The ventilator maintains the ventilator circuit pressure at one value above ambient pressure during inspiration and at a lower value (still above ambient pressure) during expiration.

Vasoactive agents

A variety of agents can be used to manipulate the cardiovascular system in critical care. These agents should only be used after the patient has been adequately fluid resuscitated. Terminology is often used incorrectly and interchangeably.

- Inotropes—affect the force of contraction of the heart
- Chronotropes—affect the heart rate
- Vasopressors—increase blood pressure

Charts of receptor activity are widely available. However, they can be tricky to use as different activities predominate at different infusion rates.

Adrenaline (epinephrine) (α_1^{+++}, β_1^{+++}, β_2^{++}, D_1^0, D_2^0)

Dose range effects

- Low doses (<0.01micrograms/kg/min)—predominant β_2 stimulation leads to dilatation of skeletal vasculature resulting in a fall in blood pressure.
- Medium doses (0.04–0.1 micrograms/kg/min)—predominant β_1 stimulation leads to an increase in heart rate, stroke volume, and cardiac output.
- Large doses (0.1–0.3micrograms/kg/min)—α_1 stimulation predominates leading to vasoconstriction which increases systemic vascular resistance and therefore increases blood pressure.
- Larger doses (>0.3micrograms/kg/min)—increased α_1 stimulation causes reduced renal blood flow and reduced splanchnic vascular bed perfusion. GI motility and pyloric tone are also reduced.

Uses

Anaphylactic shock, severe congestive cardiac failure, septic shock, status asthmaticus.

Other effects

Infusions of adrenaline can lead to arrhythmias, hyperglycaemia, and metabolic acidosis.

Noradrenaline (norepinephrine) (α_1^{+++}, β_1^{+}, β_2^0, D_1^0, D_2^0)

Dose range effects

- Low doses (<2micrograms/min)—predominant β_1 stimulation leads to an increase in heart rate, stroke volume, and cardiac output.
- Higher doses (>4micrograms/min)—predominant α_1 stimulation leads to vasoconstriction. Baroreceptor-mediated bradycardia is possible.

Uses

Increase the mean arterial pressure e.g. in septic shock, in severe head injury.

Other effects

Infusions of noradrenaline can lead to arrhythmias, hyperglycaemia, and metabolic acidosis. Not useful for cardiogenic shock because of increased afterload.

Dopamine (α_1^{++}, β_1^{++}, β_2^{++}, D_1^{+++}, D_2^{+++})

Dose range effects

- Low doses (<2micrograms/kg/min)—predominant D_1 stimulation leads to increased renal, mesenteric, and coronary perfusion.
- Medium doses (2–5micrograms/kg/min)—predominant β_1 stimulation leads to an increase in heart rate, stroke volume, and cardiac output.
- Large doses (>6micrograms/kg/min)—predominant α_1 stimulation leads to vasoconstriction which increases systemic vascular resistance and therefore increases blood pressure.

Uses

Cardiogenic shock. Should not be used as a 'reno-protective' agent, except occasionally when used it is used as a vasopressor on general wards to support blood pressure (and hence improves renal perfusion).

Other effects

Infusions of dopamine can lead to arrhythmias, hyperglycaemia, and metabolic acidosis.

Dobutamine (α_1^{+}, β_1^{++}, β_2^{+}, D_1^{0}, D_2^{0})

Dose range effects

- Usual dose (2.5–10micrograms/kg/min)—predominant β_1 stimulation leads to increased cardiac output.

Uses

Cardiogenic shock.

Other effects

Blood pressure may fall in hypovolaemic patients.

Dopexamine (α_1^{0}, β_1^{+}, β_2^{+++}, D_1^{++}, D_2^{++})

Dose range effects

- Usual dose (0.5–6micrograms/kg/min)—strong β_2 stimulation leads to vaso-dilatation. D_1 leads to increased renal perfusion. Splanchnic perfusion may also be increased.

Uses

May be useful to improve splanchnic perfusion.

Other effects

Heart rate increases in a dose-dependent manner.

Phosphodiesterase inhibitors (non-receptor-mediated effect)

Pharmacology

Inhibits phosphodiesterase, causing an intracellular excess of cAMP which causes a calcium ion influx. This causes increased myocardial contractility and smooth muscle relaxation.

Uses

Cardiac failure.

Other effects

Hypotension due to vasodilatation.

Renal replacement therapy

Acute renal failure is a common feature of critical illness. Renal function will recover in the majority of patients, although a proportion will go on to require chronic renal support. During the period of time it takes for the kidneys to recover, renal replacement therapy will be required to undertake some of the functions that the healthy kidneys would perform.

Terminology

Confusion often arises over the various techniques used for renal replacement therapy. Abbreviations add to the confusion, but there are basically two main renal replacement modes (dialysis or filtration), with a hybrid of the two also being commonly employed (diafiltration). The process is usually continuous (C), but can be intermittent (I). Blood follows a pressure gradient that is generated either by taking blood from an artery and returning it to a vein (arteriovenous or AV) or by taking blood from a vein and using the machine to generate the pressure gradient required before returning the blood to a vein (venovenous or VV). Putting the various abbreviations together with the mode of renal replacement gives the appropriate abbreviation for the technique (e.g. CVVHDF = **C**ontinuous **V**eno**V**enous **H**aemo**D**ia**F**iltration).

Haemodialysis (HD)

Not normally used in critical care, but may be used in a stable or pre-existing chronic renal failure patient.

Blood is pushed through thousands of small tubes made of a semi-permeable membrane (Fig. 28.1) Clearance of small (<2000Da), water-soluble molecules occurs by diffusion through a semipermeable membrane into dialysis fluid that bathes the tubes. Water may also be drawn off by altering the concentration of glucose in the dialysis fluid.

Clean fluid can be infused back into the patient if required, although this is unusual for this form of renal replacement.

Haemofiltration (HF)

Blood passes through thousands of small tubes made of a membrane full of small holes (typically 20 000Da in diameter). A pressure gradient pushes the patient's plasma through the holes (filtration) and this eluent is discarded. (Fig. 28.2).

Clean fluid is infused back into the patient.

Haemodiafiltration (HDF)

This is a hybrid form which adds a dialysis element to haemofiltration by allowing dialysis fluid to be added to the eluent generated from the filter, thus diluting it and causing an additional diffusion process to occur.

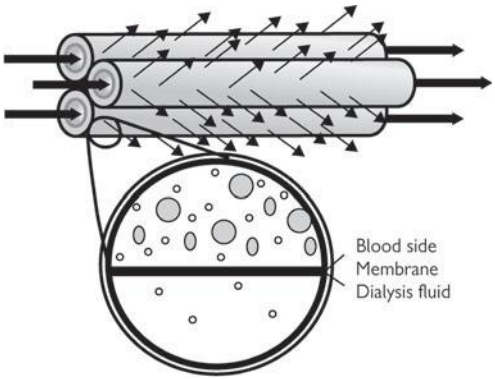

Fig. 28.1 Haemodialysis.

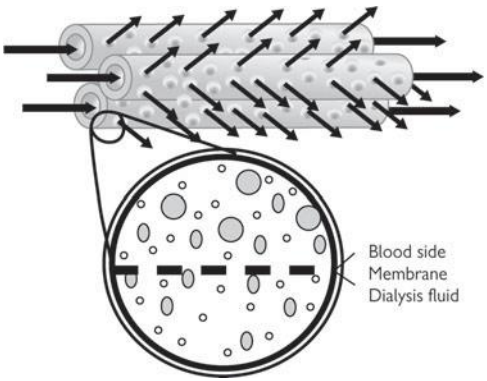

Fig 28.2 Haemofiltration.

Buffer

Whichever technique is employed, vast quantities of fluid are required for the process to take place. One of the many small molecules that are cleared is bicarbonate. Bicarbonate is central to the acid–base balance of the human body, and its steady removal in renal replacement therapy without replacement would lead to increasing acidosis and ultimately to the patient's death.

Initial stability difficulties precluded manufacturers from simply adding bicarbonate to the dialysis or replacement fluids (although this has now been overcome). Therefore a buffer was added to the fluids in the form of either lactate or acetate, both of which are converted to bicarbonate by the patient. This may become problematic if the patient cannot utilize the buffer.

Anticoagulation

The passage of blood through the extracorporeal circuit activates clotting pathways (Fig. 28.3). The resulting coagulation clogs the filter circuit, reducing its efficiency and ultimately destroying its patency.

Anticoagulants are employed to maintain circuit patency, unless the patient is particularly coagulopathic.

Heparin

Heparin has long been used to maintain filter patency through its inhibitory effects on the enzyme cascade. It can be infused into the circuit or the patient to maintain an APTT of 1.5–2 times normal. Heparin is poorly cleared by renal replacement therapy. Attempts have been made to neutralize heparin with protamine before it is returned to the patient, but the technique is tricky and not widely used.

Epoprostenol

Prostaglandins produced by the endothelial lining of the vasculature inhibit the effect of thromboxane on platelet activation. This activity is lost in the artificial environment of an extracorporeal circuit. Epoprostenol can be infused into the circuit as a substitute at 1–5ng/kg/min, and occasionally at even higher doses. Hypotension is a problematic side effect. The combination of heparin and epoprostenol has been shown to be synergistic.

Citrate

Citrate has been used to bind up ionized calcium in the circuit, thus inhibiting several calcium-dependent steps in the clotting cascade and inhibiting calcium influx into platelets, preventing platelet activation. Large quantities of citrate are needed, and this results in a large solute load and metabolic alkalosis. Specialized fluids are required and sourcing citrate can be problematic. This technique, whilst promising, is not widely used.

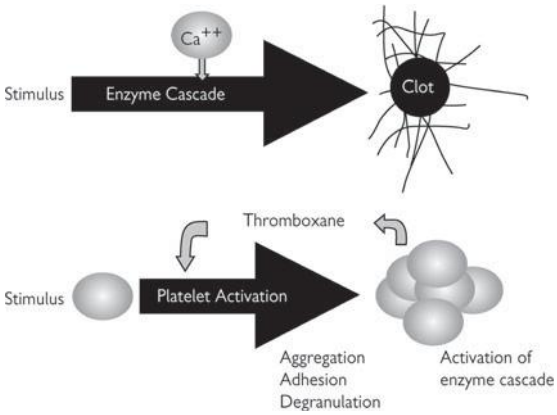

Fig. 28.3 Activation of the clotting cascade.

Treatment of alcohol withdrawal

Alcohol withdrawal syndrome is characterized by a range of symptoms including tremor, paroxysmal sweats, nausea and vomiting, anxiety, agitation, headache, and perceptual disturbances. Seizures are occasionally observed. Half of patients who experience a seizure only suffer a single fit. Some patients with severe withdrawal will progress to delirium tremens. Symptoms usually appear within 6–24h of the last consumption of alcohol and typically persist for 72h, but can last for several weeks.

Many alcohol-dependent people require no medication when withdrawing from alcohol. Supportive care, including information on the withdrawal syndrome, monitoring, reassurance, and a low-stimulus environment, are effective in ↓ withdrawal severity. Many alcohol-dependent patients might not be obvious 'alcoholics'.

If medication is required, a benzodiazepine loading dose technique is usually employed. The patient is given repeated doses until symptoms have diminished to an acceptable level. Chlordiazepoxide or diazepam are effective in the prevention and treatment of acute alcohol withdrawal seizures. Because of the relatively large doses usually given, and the long half-lives, it might not be necessary to give any further medication for withdrawal relief. However, if symptoms reappear, further doses should be administered, titrated according to symptom severity.

Suggested withdrawal regimen

Therapy should be started as soon as the patient can tolerate oral medication. Patients should be sedated on admission with chlordiazepoxide 20mg four times daily for 1–2 days, followed by rapid tailing-off over the subsequent 3–4 days.

- Day 1—20mg four times daily + 10mg when required up to a maximum of 200mg daily.
- Day 2—20mg four times daily + 10mg when required up to a maximum of 200mg daily.
- Day 3—20mg three times daily.
- Day 4—20mg twice daily.
- Day 5—10mg twice daily.
- Day 6—STOP.

Review dose daily and titrate on individual patient basis

There is a clinical opinion that patients given the recommended maximum dose and still suffering symptoms of withdrawal should be given further doses every 2h until symptoms are controlled or they are obviously too drowsy to swallow any more!

Cautions

- Patients might experience seizures as the dose of benzodiazepine is tailed off.
- Patients who are sedated for too long might develop a chest infection.
- The dose should be adjusted to provide effective sedative and anticonvulsant endpoints while preventing oversedation, respiratory depression, and hypotension.

- ❗ Benzodiazepines can cause temporary cognitive slowing and may interfere with learning and planning. This, and the need to avoid benzodiazepine dependence, are reasons for keeping the length of treatment to a maximum of 5 days.
- Doses of benzodiazepine should be reduced in severe liver dysfunction. Alternatively, a shorter-acting benzodiazepine (e.g. lorazepam) can be used (seek specialist advice). Patients with chronic liver disease should have their dose assessed twice daily to avoid oversedation.
- A maximum 24h dose (10mg twice daily) should only be prescribed on discharge from hospital if necessary.
- Clomethiazole, although historically used for the treatment in alcohol withdrawal of in-patients, has the potential for life-threatening respiratory depression if the patient continues to drink alcohol, which precludes its use.

Thiamine and vitamin supplements

Poor nutrition is common in patients who drink for the following reasons.

- Inadequate intake of food.
- Associated chronic liver disease.
- Chronic pancreatitis.
- Malabsorption (water-soluble and fat-soluble vitamins should be replaced and severely malnourished patients should be considered for enteral feeding).

Thiamine

Thiamine deficiency leads to polyneuritis with motor and sensory defects. Ophthalmoplegia (paralysis of the eye muscles), nystagmus, and ataxia are associated with Wernicke's encephalopathy, in which learning and memory are impaired; there is an estimated 10–20% mortality. Korsakoff's psychosis is characterized by confabulations (the patient invents material to fill memory blanks) and is less likely to be reversible once established.

IV thiamine replacement

There is no licensed IV thiamine preparation in the UK. One pair of Pabrinex® IV high-potency (vitamin B and C injection BPC) ampoules contain 250mg of thiamine. IV Pabrinex® should be given initially to those with severe withdrawal symptoms.

Dose

One pair of ampoules should be added to 100mL sodium chloride 0.9% solution or glucose 5% solution and administered intravenously over at least 10min once daily for 3 days or until the patient can take oral thiamine. In established Wernicke's encephalopathy higher doses are needed (consult product literature).

Oral thiamine replacement

If symptoms of withdrawal are not severe the following regimen is recommended.

- Oral thiamine 100mg should be given four times daily until withdrawal is complete. Then reduce the dose to 100mg twice daily.

Other vitamins

- Forceval® (or locally approved multivitamin product)—one capsule daily.
- Folic acid 5mg once daily (if folate deficient).

At discharge

Oral supplements should be continued at discharge in patients who are malnourished or have inadequate diets. Thiamine should be continued long term if there is cognitive impairment or peripheral neuropathy (100mg twice daily).

Consideration should also be given to the setting in which withdrawal occurs. Careful monitoring of withdrawal severity is essential in all cases, and more severe withdrawal requires in-patient care. Specialist alcohol treatment services and most hospitals can provide charts to be used in the monitoring of symptom severity.

Recommendations on the prevention of relapse in alcohol dependence

Acamprosate and supervised oral disulfiram are treatment options recommended as adjuncts to psychosocial interventions.

Further reading

SIGN (2003). *SIGN Guideline 74 The Management of Harmful Drinking and Alcohol Dependence in Primary Care*: http://www.sign.ac.uk/guidelines/fulltext/74/index.html

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Dealing with poisoning enquiries

Poisoning incidents can be caused by the following means.

- Accidental poisoning—e.g. small children eating tablets or berries.
- Non-accidental—e.g. Munchausen's syndrome by proxy (in this syndrome one person creates symptoms in another by, for example, administering drugs).
- Deliberate self-poisoning—e.g. tablets or chemicals are ingested intentionally, sometimes to manipulate family or friends and, rarely, with the intention of (successful) suicide.

Any enquiry regarding a possible acute poisoning incident should be treated as potentially serious and urgent. Questioning can quickly establish if there is little possibility of harm, but if there is any doubt the patient should be referred to the nearest A&E department and/or a poisons information centre should be contacted for advice.

Some misconceptions

Members of the public might not be aware of the following.

- Alcohol poisoning can be potentially fatal, especially in children and adolescents. In children, if there are any signs of intoxication the patient should be referred to an A&E department.
- Some forms of poisoning might not cause symptoms initially—e.g. paracetamol overdose, ingestion of sustained release tablets and capsules. This can create the impression that there is no intoxication. Referral to an A&E department should be made if sufficient tablets have been taken, even in the absence of symptoms.

Be aware that some over-the-counter preparations might have similar brand names, e.g. Piriton® and Piriteze® and, Anadin® and Anadin®-paracetamol. Ensure that you and other healthcare professionals are clear what product is involved.

Sources of information

TICTAC

TICTAC is a computerized tablet and capsule identification system used by medicines information and poisons information centres. Information required to identify a tablet or capsule using TICTAC includes the following.

- Shape—straight, rounded, or bevelled edge for tablets.
- Colour—cap, body, and contents for capsules.
- Markings—including whether half or quarter scored.
- Coating—film, sugar, or uncoated.
- Length and width (in millimetres)—at longest/widest point.
- Weight.

Toxbase[1]

Toxbase is an online poisons information database which covers drugs (including over-the-counter medication), plants, household, industrial and agricultural chemicals, and snake and insect bites. Details of probable toxic

1 http://www.toxbase.org

effects and appropriate management are provided. Toxbase is password-protected. Medicines information and poisons information centres have access to Toxbase, and NHS pharmacy departments can apply for a password through the website.

Poisons information centres

Poisons information centres provide 24h telephone advice. If there is any cause for concern in an acute poisoning incident, a poisons information centre should be contacted immediately. It is inappropriate to cause unnecessary delay in what might be a life-threatening situation by looking elsewhere for information. The doctor dealing with an acute incident should contact the poisons information centre direct so that first-hand information is given and received. Advise the doctor of the sort of information the poisons information centre might require. For a non-acute or general enquiry, it is appropriate for a pharmacist to contact the centre.

Information required to deal with a poisoning enquiry

Eliciting as much information as possible about a poisoning incident can facilitate speedy management. It is especially important to have the relevant information available when contacting a poisons information centre.

- Identity—brand name and active ingredients.
- Timing—when did the incident occur relative to the time of the enquiry.
- Quantity—number of tablets and volume of liquid. An estimate is better than no information. Checking the quantity left in a container versus its full contents at least gives an estimate of the maximum quantity ingested.
- If tablets or capsules—are these sustained release?
- Age and weight of the patient—especially if a child.
- Any relevant PMH—e.g. renal impairment.
- Any signs and symptoms observed.
- If the patient has vomited—any sign of the poison (e.g. coloured liquid, undigested plant material, tablet fragments).
- Any treatments or first aid already administered and the outcome.

If attendance at an A&E department is recommended, the enquirer should be advised to take any containers or plant material with them that could help with identification (taking suitable precautions to avoid contamination of skin or clothing with the poison).

First aid for poisoning incidents

- Do not induce vomiting.
- If fully conscious, give sips of water or milk.
- If unconscious, check ABC. As needed, perform the following.
  - Perform cardiopulmonary resuscitation, but not mouth-to-mouth except with a face shield (because of the risk of contaminating the first aider).
  - Place patient in the recovery position.
  - Call emergency services.
- Take the patient to an A&E department or phone the emergency services.

Further reading

Dines A *et al.* (2007) Poisoning: an overview of treatment. *Hospital Pharmacist* **14**: 7–9.
Dines A *et al.* (2007) Poisoning: antidotes and their use. *Hospital Pharmacist* **14**: 10–14.

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Drug desensitization

Patients with drug hypersensitivity can usually be treated with an alternative agent. However, on rare occasions if there is no suitable alternative, drug desensitization might be appropriate. Drug desensitization is potentially hazardous and should never be attempted in patients who have had a severe allergic reaction, such as bronchospasm, facial swelling, or anaphylaxis. However, it can be attempted in those who have had a rash provided that this was not a severe skin reaction, such as Stevens–Johnson syndrome.

Desensitization schedules using both oral and parenteral administration have been developed for a variety of drugs, but mostly for antibacterials (notably penicillins) and some chemotherapy drugs. Examples of these are listed at the end of this topic as further reading.

Drug desensitization is potentially hazardous because there is always a risk of anaphylaxis. Thus, when attempting the procedure, the following precautions should be observed.

- The patient is informed of the potential risks (it is advisable that they give written consent to the procedure).
- The patient must be reasonably well (i.e. no active disease other than the current infection).
- The patient's drug history should be reviewed and any drugs known to exacerbate allergic reactions stopped—notably β-blockers and NSAIDs.
- Desensitization should be carried out as an in-patient or closely monitored day-case procedure.
- A doctor or appropriately trained nurse with authority to administer emergency drugs should be present throughout.
- Drugs and equipment required for treatment of anaphylaxis should be available.
- The patient should have an IV cannula placed for administration of emergency drugs before starting the procedure.
- Prophylactic antihistamines, adrenaline, or steroids should not usually be given as these can mask a reaction:
- Patient monitoring should be carried out before each dose and every 30min (if the dose interval is longer), and should include:
  - temperature, pulse, and BP
  - respiratory signs, including peak flow measurement
  - observation and direct questioning of the patient for signs and symptoms of allergic reaction (e.g. skin flushing, rash, itching, wheeze, shortness of breath, and tingling lips or tongue).
- Patients should continue to be monitored for at least 1h after the final dose of the desensitization schedule.
- Observations and details of drug administration should be documented in the patient's medical notes.

It is important to ensure that the desensitization schedule is followed as rigorously as possible.

- Measure doses accurately—e.g. using an oral syringe.
- The patient should rinse their mouth with water and swallow after oral doses.
- Doses should be administered at exactly the specified time intervals.

Because of the requirement for direct medical observation throughout the procedure, most schedules involve rapid desensitization. However, some longer schedules have been used, in which case the procedure is carried out on an out-patient basis. The patient's GP should be informed that out-patient desensitization is planned.

It is important that patients performing drug desensitization at home are carefully selected and that the patient agrees to the following.

- Undertakes never to be on their own throughout the procedure.
- Understands the risks and what action to take if a reaction occurs. Ideally, another responsible person in the home should also be informed.
- Should have access to a telephone and contact numbers for the physician supervising the procedure.
- Has access to suitable transport so that they can attend the hospital in the event of a minor reaction (the patient should call emergency services if there is a major reaction).
- Lives reasonably close to the hospital, and certainly not in a remote area with difficult access.

After the schedule is complete and treatment doses of the drug are being administered without adverse effects, a treatment course of the drug can be given. Desensitization is usually lost within 1–2 days of stopping the drug. If it is probable that further courses of the drug will be needed, low doses should be administered until the next course is required. It is important that patients understand that drug desensitization is only temporary.

Further reading

Examples of drug desensitization schedules

Sullivan TJ *et al.* (1982). Desensitisation of patients allergic to penicillin using orally administered beta-lactam antibiotics. *Journal of Allergy and Immunology* **69**: 275–82.

Kalanadhabhatta V *et al.* (2004). Successful oral desensitisation to trimethoprimsulpha-methoxazole in acquired immune deficiency syndrome. *Annals of Allergy, Asthma and Immunology* **92**: 409–13.

Confino-Cohen R *et al.* (2005). Successful carboplatin desensitisation in patients with proven carboplatin allergy. *Cancer* **104**: 640–3.

Eapen SS *et al.* (2005). A successful rapid desensitisation protocol in a loop diuretic allergic patient. *Journal of Cardiac Failure* **11**: 481.

Drug interference with laboratory tests

Drugs can interfere with laboratory tests through a pharmacological, toxic effect or through actual chemical interference with the testing process.

A pharmacological or toxic effect on the laboratory value is often expected and reflects what is happening within the body—e.g. steroids causing hyperglycaemia or diuretics effecting electrolyte concentrations. An example of the toxic effect is elevated LFTs (e.g. elevated transaminase, bilirubin levels, and clotting factors) subsequent to paracetamol overdose.

An analytical interference differs in that the true laboratory value is not measured accurately. The result is inaccurate because of a problem with *in vitro* laboratory test procedure, or occurs when a substance or process falsely alters an assay result. This may lead to inappropriate further tests, incorrect diagnoses, and treatments with potentially unfavourable outcomes for the patient.

Drug interference may be (1) chemical where the parent drug, metabolites, or additives cross-react, (2) where drugs or additives act as accelerators or inhibitors of the assay, or (3) photometric where the parent drug, metabolites, or additives may have similar absorption peaks to that of the measured chromogen.

Table 28.1 is in no way intended to be comprehensive but to highlight to practitioners examples of analytical interference from drugs or their metabolites.

Table 28.1 Drug–laboratory interferences are usually overlooked

Laboratory test	Increased by	Decreased by
Blood, serum, plasma		
Creatinine	Ascorbic acid, flucytosine, furosemide, levodopa, nitrofurantoin	
Glucose	Cefotaxime, dextran, methyldopa	Isoniazid, levodopa
Iron	Citrate salts, ferrous salts, rifampicin	Heparin, desferrioxamine
Magnesium	Calcium salts, cefotaxime	Cefotaxime, phosphate salts.
Potassium	Iodine salts	
Thyroxine	Heparin	Danazol, heparin
Uric acid	Paracetamol, caffeine, hydralazine, isoniazid, theophylline	Levodopa, methyldopa, ascorbic acid, rasburicase
Drug assay		
Serum lithium levels	Inadvertent use of lithium–heparin collection tube leads to spuriously high serum lithium determination	
Digoxin assay	Spironolactone	Interferes with certain specific digoxin assays Refer to biochemistry department for type of assay used locally
Plasma cortisol levels (Synacthen® test)	Metabolites of spironolactone fluoresce, which interferes when fluorometric analysis is used for tests Erroneously ↑ cortisol levels	
Urine		
Ketones	Ifosfamide, levodopa, mesna, aspirin	
Protein test (bromophenol blue reagent, sulfosalicylic acid)	Carbonic anhydrase inhibitors (IV) False positive	

Therapeutic drug monitoring (TDM) in adults

Dosage requirements of certain drugs in individual patients can vary significantly, particularly if the drug has a narrow therapeutic window. Although an estimate of the apparent volume of distribution and clearance of a drug can be made from population values, these should only be used as a guide when commencing treatment. Measured plasma/blood levels will enable a more accurate idea of the pharmacokinetic values in specific patients. This will result in a reduction in the risk of toxicity and/or optimization of the effectiveness of the drug regimen.

Sample collection

Drug concentrations can be measured in blood, plasma, saliva, CNS fluid, and urine. The timing of the sample (relative to the previous dose and method of administration) influences the interpretation of a drug concentration measurement. For most drugs there is a relationship between response and concentration which is based on steady state samples taken at specific times after the dose.

Trough concentrations taken at the end of the dose interval are commonly used for anticonvulsant drugs. Peak concentration measurements are useful for some antimicrobials, although a relationship between concentration by time over a threshold value (e.g. MIC) is sometimes determined. Responses to some anticancer drugs and immunosuppressant's have been related to the overall exposure to a drug, as measured by the area under the concentration–time curve (AUC).

Patient/drug characteristics

The appropriate use of TDM requires more than simply measuring the concentration of a drug and comparing it with a target range. It starts at the point when the drug is first prescribed and involves determining an initial dosage regimen that is appropriate for the clinical condition being treated, the patient's clinical characteristics, and the drug's characteristics.

- Age, weight, gender, nicotine exposure, renal function, concomitant drug therapy.
- Clinical issues that might effect bioavailability of oral drug forms—e.g. diarrhoea, short gut anomalies.
- Dosage form, administration rate, first-pass metabolism, protein binding, volume of distribution, loading dose.

When interpreting concentration measurements, the following factors need consideration.

- The sampling time in relation to the dose.
- Dosage history (whether or not the result represents steady state).
- Patient's response and desired clinical targets.
- Missed doses.

This information is to provide an assessment of the drug concentration that will assist in achieving rapid, safe, and optimum treatment.

TDM is generally of value in the following situations.

- Good correlation between blood concentration and effect.
- Wide variations in metabolism.
- High risk of side effects.
- Narrow therapeutic index.

Routine measurements might be warranted, for example, in determining adequate concentrations post-organ transplantation or more commonly ordered to add evidence to a specific clinical problem—e.g. investigate handling a patient with concurrent disease or confirm excessive dosing correlating with signs of toxicity. Table 28.2 covers common drugs and Table 28.3 covers antibiotics. However, other drugs, such as those used to treat HIV., might also benefit from TDM.

- For antibiotic assays, doses should ideally be timed for convenience, e.g. 10.00am. For pre-dose levels, a sample should be taken and the dose administered.
- For dosage adjustment, sampling at steady state is essential, except for suspicion of toxic concentrations.
- Sampling is taken at an appropriate time during a dose interval. You must coordinate when, or if, your pathology department can undertake the test or coordinate with another centre.
- Concentrations can be affected by various factors, such as age, drug interactions, protein binding, metabolism, and organ dysfunction.
- The pharmacist has a very important role in interpreting results from TDM.
  - Advice on what to do if there is an unexpectedly high/low result—e.g. check that dose was given, timing of sample in relation to dose or sampling technique.
  - Advice on whether or not another dose should be given if awaiting result.
  - Dose adjustment—most drugs follow linear kinetics (i.e. doubling the dose will double the level), but certain drugs (e.g. phenytoin) exhibit non-linear kinetics and require small incremental dose adjustments.
  - Timing of sampling if there is a suspicion of drug interaction from the introduction of new therapies.

Table 28.2 Common drugs

Drug	Therapeutic range (standard units)	Ideal sampling time	Comments and SI units	Type of sample required
Carbamazepine	4–12mg/L	Trough measurement before dose	Therapeutic ranges: adults, 34–51 Units: mmol/L Ranges desired from pre-dose specimens	Serum or plasma—SST (orange) or PST heparin (green)
Ciclosporin	Varies with indication	Trough measurement before dose	Therapeutic range depends on disorder/clinical situation being treated	Whole blood—EDTA (lavender)
Digoxin	0.8–2micrograms/L Reference range is valid for specimens taken 6–8h post-dose.	Sampling 8–24h after last dose	Adults, 1.0–2.0 Units: nmol/L	Serum or plasma—SST (orange) or PST heparin (green)
Lithium	Minimum effective concentration in mania prophylaxis is 0.5–1.2mmol/L Toxic conc. >1.5mmol/L	12h post-dose	Therapeutic range: 0.5–0.8 Toxicity: >1.0 Units: mmol/L Not in lithium heparin tube Please measure maintenance range 12h after last dose.	Serum–SST (orange)

Phenytoin	10–20mg/L	Trough measurement before dose	Therapeutic levels (pre-dose specimen): 40–80 Units: mmol/L	Serum or plasma—SST (orange) or PST heparin (green)
Phenobarbital	15–40mg/L	Trough measurement before dose	Therapeutic range desired from pre-dose specimens: adults, 65–170 Units: μmol/L	Serum or plasma —SST (orange) or PST heparin (green)
Theophylline/ aminophylline	5–15mg/L	1) During a continuous infusion, preferably at 6h and 18h 2) SR preparation—pre-dose	28–85 Units: μmol/L.	Serum or plasma—SST (orange) or PST heparin (green)
Tacrolimus	5–15ng/mL	Trough measurement before dose	NA	Blood—EDTA (lavender)

Table 28.3 Antibiotics

Drug	Therapeutic range (mg/L)	Ideal sampling time	Comments	Type of sample required
Gentamicin, once daily	20	Trough level 18–24h after the first dose (ideal <1.0mg/L).	Not necessary to do a postdose level	Blood SST (orange)
Gentamicin, conventional dosing	Trough <2 Peak 5–10	Trough Peak—1h post-dose	Peak for endocarditis if having synergistic therapy 3–5mg/L	Blood SST (orange)
Amikacin	Trough <10 Peak 20–30	Trough Peak–1h post administration	Further usually twice weekly pre-dose levels if no dose changes and normal renal function	Blood SST
Vancomycin	Trough 5–10	Pre-dose before fourth dose	Further monitoring usually twice weekly	Blood SST (orange)
Teicoplanin	Trough 10–20	Trough	>20mg/L (<60mg/L) for deep seated infection	Blood SST (orange).
Tobramcyin	Trough <2 Peak 5–10	Trough 1h post-administration	Samples should to the fourth dose, depending on renal function	Blood SST