Systemic effects of terminal diseases

Paraneoplastic syndromes
The remote effects of cancer can be classified as paraneoplastic syndromes. They are thought to be rare, affecting perhaps only 1% of people with cancer. These syndromes may be identified before the diagnosis of cancer is made.

Dermatological syndromes
There are a number of skin disorders that herald the presence of underlying malignant disease. Consultation with a specialist dermatologist is advised.

- acanthosis nigricans (treatment generally ineffective)
- dermatomyositis (treatment requires removal of the cause but symptoms may be managed with corticosteroids)
  - associated with lung, breast, ovarian, pancreatic, stomach, colorectal cancers and non-Hodgkin’s lymphoma
- acquired ichthyosis (treat the underlying cause)
- paraneoplastic pemphigus (use steroids and ciclosporin)

Metabolic syndromes

- hypercalcaemia - see ‘Hypercalcaemia section’ p. 60
- Cushing’s syndrome (ectopic secretion of ACTH)
- SIADH - syndrome of inappropriate antidiuretic hormone secretion
  - results in hyponatraemia which is common near the end-of-life
  - symptoms appear at plasma sodium concentrations <125 mmol/L and include stupor, coma and seizures

Neurological/psychiatric syndromes

- Lambert-Eaton myasthenic syndrome (LEMS)
  - associated with small-cell lung cancer
  - manifests as muscle weakness and fatigue
  - may respond to immunosuppression, plasmapheresis and 3,4 diaminopyridine (3,4 DAP)
- sub-acute cerebellar degeneration
  - associated with ovarian and lung cancer
- polymyositis
  - associated with non-Hodgkin lymphoma, lung cancers, bladder cancers
- motor neuropathy
  - associated with lymphoma
- peripheral neuropathy
  - associated with small-cell lung cancer
- limbic encephalitis
  - changes in mood, personality
– memory impairment (recent more than remote)
– seizures

**Management**
All of these syndromes are usually irreversible and treatment is largely symptomatic.

**Venous thromboembolism** ...........................................................
Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a lethal disorder that is common in people with cancer and to a lesser extent in other advanced diseases.

**Diagnosis/symptoms**
- PE - episodic and otherwise unexplained breathlessness or confusion, tachypnoea, and pleuritic chest pain - may be difficult to interpret in the presence of other pulmonary pathology
- DVT - pain or tenderness and swelling, increased warmth, oedema and redness
- tests such as D-Dimers are generally unhelpful in advanced cancer but Doppler scans may reveal DVTs in large veins.

**Causes and risk factors**
- malignant disease
- recent chemotherapy or surgery
- immobility
- malignant pelvic disease
- familial (hereditary factors)
- age (over 40)
- obesity

**Management**
If the patient is at risk of VTE
- take into account any risk of bleeding and expected prognosis
- discuss with the patient and family (an important proxy for those with advanced dementia) whether they want to have active prophylaxis with anti-embolism stockings and low molecular weight (LMW) heparin as appropriate, balancing risks and benefits to optimise quality of life
- if the patient is in the last few days or weeks of life then thromboprophylaxis is often not appropriate, and is not routine - the best evidence in favour of thromboprophylaxis is in potentially reversible co-existing acute conditions

Treatment for VTE (DVT- includes prevention of PE and/or recurrent thrombosis)
- anticoagulation with a LMW heparin e.g. enoxaparin should be started immediately unless there is a contraindication - the preferred option because it is more effective in VTE associated with malignancy, and if dosed properly is less likely to cause bleeding
• LMW heparin followed by warfarin or dabigatran is cheaper and perhaps more convenient, but warfarin requires blood tests (INR may be very difficult to keep stable in those with advanced disease and variable nutritional intake)
• re-assess the patient regularly to confirm the management plan is appropriate to the stage of their illness and their wishes
• if warfarin is used start at the same time as LMW heparin and continue the LMW heparin for 2 days after achieving therapeutic INR
• haemorrhagic complications occur in almost 50% of people with advanced cancer (due to drug interactions or hepatic dysfunction)

**Weakness/fatigue**

Weakness and fatigue are amongst the most common and debilitating symptoms at or near the end-of-life.

• it is often assumed that weakness is an inevitable consequence of approaching death BUT there are many factors that may exacerbate or precipitate weakness
• careful assessment may result in interventions that can improve quality of life
• there are often two main contributing factors
  – cachexia
  – asthenia

  > a debilitating state of involuntary weight loss complicating chronic malignant, infectious and inflammatory diseases that contributes to mortality
  > fatigue or lassitude
  ~ easily tired and a decreased capacity to maintain adequate performance
  > generalised weakness
  ~ anticipatory subjective sensation of difficulty in initiating a certain activity

**Causes**

*Cancer related*

• cachexia (see cachexia section)
• decreased food intake
  – nausea, vomiting, constipation, intestinal obstruction, diarrhoea, malabsorption, 'squashed stomach syndrome' in hepatomegaly, tumours, ascites, mouth and throat problems including infection, poor teeth, thrush, taste alteration
• metabolic problems
  – hyponatraemia, uraemia, liver failure, hypercalcaemia, anaemia from any cause
• emotional causes
  – anxiety, depression, fear, isolation, apathy, stress
• neuromuscular damage by tumour
  – to brain, spinal cord, peripheral nerves
• paraneoplastic syndromes e.g. Lambert-Eaton myasthenic syndrome, motor neuropathy
• radiotherapy and chemotherapy
• insomnia
• depression

Non-cancer related
• drugs
  – long-term steroids
  – some psychotropics
  – diuretics
  – antihypertensives
  – oral hypoglycaemics
  – statins
• neurovascular problems
  – transient ischaemic attacks, motor neurone disease, myasthenia gravis, Parkinson’s disease, peripheral neuropathies
• metabolic diseases
  – diabetes mellitus, Addison’s, hyper/hypothyroidism, tuberculosis, subacute bacterial endocarditis, connective tissue disorders

Management
• establish and, where possible, treat or remove cause
  – review the drug regimen
  – correct metabolic abnormalities
• give dietary advice/support
  – increase calorific intake if possible and appropriate
• exercise
  – exercise may be effective particularly in fatigue caused by radiotherapy
  – limited exercise programmes have been shown to be beneficial even in those close to the end-of-life
• drug therapy
  – hormones e.g. megestrol acetate, medroxyprogesterone
    > mechanism of action is unclear but dose related weight gain, improved calorie intake and improved sense of well-being have been reported
    > effect on fatigue is thought to be minimal
  – prokinetic antiemetics e.g. metoclopramide
    > decrease nausea and vomiting, increase food intake and appetite
    > no evidence of weight gain has been reported
  – steroids e.g. dexamethasone
    > weight gain and fat deposition has been documented but with no increase in lean body mass
    > benefit may be transient
eicosapentaenoic acid (EPA) and nutritional support in combination with anti-inflammatory agents (COX2 inhibitors) have been used

stimulants e.g. methylphenidate, modafinil

Although these drugs may be effective in some patients with fatigue potential benefit should be weighed against adverse effects e.g. long-term steroids causing muscle weakness.

**Cachexia**

Cachexia can be distressing for both the patient and their family and carers. It is difficult to watch a person ‘waste away’ and is often perceived as a sign of impending death.

- cachexia is derived from the Greek kakos (bad) and hexis (condition)
- defined as a multifactorial syndrome with ongoing loss of skeletal muscle mass that cannot be fully reversed leading to progressive functional impairment
- diagnosis - weight loss greater than 5%, or 2% in individuals already showing depletion
- develops progressively through various stages - precachexia, cachexia, and refractory cachexia
- refractory cachexia or cancer anorexia cachexia syndrome - very advanced cancer (preterminal), active catabolism low performance status (WHO score 3 or 4), and life expectancy less than 3 months
- may complicate many chronic or end-stage diseases in addition to cancer
- not starvation, which can be reversed with nutrition
- distinct from age-related loss of muscle mass, primary depression, malabsorption syndromes and hyperthyroidism
- in the setting of advanced dementia, the presence of cachexia will often reflect a deteriorating oral intake over the preceding weeks/month rather than a more traditional ‘ominous’ cause. Declining oral intake leading to significant weight loss is a poor prognostic sign in this group, however, and its presence may be a marker that the person with dementia is entering a palliative stage of management

**Causes**

The metabolic mechanism of the progressive wasting is uncertain.

- complex metabolic and catabolic processes occur with cytokines playing a major role
- tumour initiates an inflammatory response probably mediated by tumour-derived proinflammatory cytokines (interleukin-1, interleukin-6, interferon-gamma, tumour necrosis factor-alpha)
- cancer cachexia involves inflammation, hypermetabolism, neuro-hormonal changes, and the proteolytic and lipolytic factors
- enhanced substrate cycling (fat, carbohydrate and protein) occurs which is associated with metabolic inefficiency, weight loss and a suboptimal response to nutritional support (‘anabolic blockade’)
- neural pathways controlling energy homeostasis are disturbed (particularly the hypothalamic melanocortin system), promoting catabolic activity

**Assessment**
Cachexia should be considered if the patient has lost $\geq 5\%$ of their body weight and/or has a BMI $< 20$ kg/m$^2$ and 3 out of the following are present

- decreased muscle strength
- fatigue or reduced physical activity
- anorexia
- low fat-free mass index (low muscle mass)
- abnormal biochemistry
  - CRP $> 5$ mg/L
  - IL-6 $> 4$ pg/ml
  - Hb $< 12$ g/dL
  - serum albumin $< 32$ g/L

**Treatments**

- favourite foods
- un-pressured eating
- referral to a dietician
- drugs (efficacy is minimal for most)
  - dexamethasone 4 mg/day for 5 days
  - medroxyprogesterone
  - megestrol
  - EPA (up to 2 g per day)
  - cannabinoids
  - prokinetics e.g. metoclopramide
  - antidepressants e.g. mirtazapine
  - thalidomide
  - olanzapine

**Anaemia**

A significant proportion of people with advanced or chronic disease are anaemic. Symptomatic anaemia usually presents when the haemoglobin is below 80 g/L although, if chronic, patients may adapt to this concentration

**Symptoms**

- fatigue
- delirium
- dyspnoea
- dizziness (postural hypotension)
- exacerbations of angina/heart failure

**Causes (often multiple)**

- chronic disease (normocytic)
- haemorrhage (microcytic, low iron levels)
- bone marrow failure (pancytopenic)
- malnutrition (macrocytic, folate and iron deficiencies)
• chronic renal failure (reduced erythropoietin production)

**Management**

• blood transfusion
  – rarely improves symptoms significantly for any length of time BUT may be considered, prior to further active treatment or a significant family event
  – it is often easier to give a transfusion rather than deal with the negotiation involved in not treating although the latter may be more appropriate
  – time, attention to detail and information for the patient and the family are all essential in the decision making and consent process
• erythropoietin
  – expensive, not readily available and response can be slow and limited

**Hypercalcaemia of malignant disease** ..................................................  
The symptoms and signs of hypercalcaemia are often insidious in their onset. It can be classified as a paraneoplastic syndrome.

• should be considered in patients who have vague symptoms
• consider appropriateness of treatment BEFORE a calcium concentration
• if the patient has a serum calcium > 2.6 mmol/L consider treatment

**Symptoms**

• thirst and dehydration
• increased urinary output
• constipation
• loss of appetite
• nausea and or vomiting
• fatigue
• pain - usually back and abdominal
• confusion, depression

**Causes**

• bone metastases
• increased bone metabolism
• decreased renal clearance of calcium
• dehydration
• enhanced absorption from the gut

**Management**

• make the diagnosis
• decide about the most appropriate course of action together with the patient, family and team
• consider stopping diuretics, vitamin D and calcium
• the aim is to provide symptom relief and reduce serum calcium to an acceptable level using minimal intervention
- mild to moderate (serum calcium 2.6 to 3 mmol/L)
  > initially oral then, if necessary, iv rehydration
  > consider steroids
- moderate to severe (serum calcium 3 to 3.5 mmol/L)
  > initially iv or subcut rehydration
    - 2 to 3 L normal saline/24 hours
  > then iv/subcut bisphosphonate (may take 72 hours to work)
    - pamidronate 90mg iv infusion (can be given as a subcutaneous infusion)
    - zoledronic acid 4mg iv infusion can be used but is significantly more expensive
    - calcitonin may be useful when bisphosphonates begin to fail

Nutrition in palliative care

Good nutritional advice from a dietician improves patients’ quality of life.

- ensuring food choices that are
  - of good quality and attractively presented
  - appealing on multiple sensory levels (sight, taste, aroma, texture) to maximise cues to eating, particularly in those with impaired cognition
  - appropriate to the patients’ cognitive level (e.g. provision of finger foods where the ability to use cutlery has been lost)
  - appropriate to the maintenance of quality of life
  - not detrimental to the patient i.e. aggravate nausea, or be of a difficult texture/moisture content to swallow
  - preferred foods which may entail lifting dietary restrictions and discussing with the patient’s family that food intake is no longer for the purpose of sustaining life and fuelling bodily processes
- providing an environment that allows for social interaction around meal times i.e. central dining room, playing of music during meal times
- note that for people with advanced dementia, a quieter environment that minimises distractions during mealtimes may be more useful.
- maintaining comfort
- providing weight gain may be appropriate initially but during the terminal phase it is not an appropriate nutrition intervention goal

In some instances, it may become inappropriate to hydrate or feed a patient, these cases should be discussed by a multidisciplinary team on a case by case basis.

A dietitian can provide

- complete nutrition assessments
- nutritional care plans considering an individual’s life expectancy, treatment plan and overall functional status
- assessments of nutritional factors impairing the patient’s physical and psychological wellbeing
• patient-centred strategies such as food fortification, meal timing/frequency and oral nutrition support
• flexible menus by liaising with catering staff to enable inpatients to enjoy their preferred foods
• an advocate role for the patient (both for and against) regarding more aggressive forms of nutrition support on a case by case basis
• clarification for the team and the patient the place of artificial nutrition when the patient is approaching the terminal phase

Organ failure

Renal failure

The following does not apply to patients who are being dialysed. For information on drug dosing during dialysis consult a renal specialist or drug information service.

Symptoms
• oedema (from sodium and water retention)
• restless legs (may respond to clonazepam, very low dose gabapentin)
• itch (from raised urea or phosphate)
• nausea/vomiting (from increased toxins)
• fatigue (from anaemia)

Management
• the same as those outlined in the relevant sections e.g. nausea/vomiting
• when pain is an issue remember that
  – morphine’s metabolite is renally cleared so use fentanyl or methadone instead (or perhaps oxycodone)
  – NSAIDs increase sodium and water retention, are nephrotoxic and if urea is raised risk of GI bleed increases so avoid

Drug dosing
• as the kidneys fail creatinine plasma concentrations will rise
• many labs now report an estimated glomerular filtration rate (eGFR) - there is some debate as to whether this can be used to adjust the doses of renally cleared drugs
• to calculate how well the kidneys are functioning, calculate creatinine clearance in mLs/minute using the Cockcroft and Gault equation:

Creatinine clearance (CrCl)

\[
CrCl (\text{mLs/min}) = \frac{(140-\text{age}) \times \text{ideal body weight (kg)} \times 0.85 \text{ if female}}{\text{plasma creatinine (umol/L) x 0.8}}
\]

(ideal body weight = 50kg + 0.9kg for each cm above 150cm (replace 50kg with 45 kg if female)
• the creatinine clearance is important in the dosing of renally cleared drugs e.g. gabapentin or drugs whose metabolites are renally cleared e.g. morphine (see end section)
for drugs that are almost completely renally cleared the dose regimen is a proportion of the normal dose:

\[
\text{Adjusted dose} = \frac{\text{calculated creatinine clearance} \times \text{normal dose}}{100\text{mL/min}} \div 1
\]

**Hepatic failure**

End stage liver failure is usually seen with liver metastases, liver primary and/or past alcohol abuse/hepatitis.

**Symptoms**

- raised liver enzymes
- jaundice
- ascites
- itch
- encephalopathy
- low albumin and raised INR

**Drug dosing**

- there is no single marker for liver dysfunction but albumin concentrations and INR are a measure of how well the liver can clear drugs (its metabolic capacity)
- doses of metabolised drugs (drugs that are mainly cleared from the body by the liver rather than the kidneys i.e. approx 70% of drugs) should be adjusted in severe liver failure (albumin of < 30 g/L and an INR of > 1.2) by approximately 50% especially drugs with low therapeutic index e.g. antidepressants, antipsychotics, opioids, paracetamol, anticonvulsants, NSAIDs

Management is the same as that outlined in the relevant sections.

**Cardiac failure**

The treatment of patients with end stage cardiac failure centres around the relief of the accompanying symptoms:

- dyspnoea
- cough
- fatigue
- immobility
- oedema

Treatment of the symptoms is the same as for other causes in palliative care.

Perhaps the most difficult part of the management of these patients is when and how to discontinue the many cardiac medications prescribed (See Deprescribing section following). As yet there is no clear evidence for the order or rate of discontinuation. Negotiation with patient, family and cardiologist may produce agreement on a process for this. Once swallowing becomes a problem consideration should be given to stopping medications.
Deprescribing in palliative care

Deprescribing is the process of ceasing inappropriate medications safely and effectively.

- an individualised process, focusing on the patient, and taking into account their physical function, comorbidities, preferences, and lifestyle
- an ongoing process as medicines that were initially appropriately prescribed may become inappropriate over time
- often not carried out in palliative care when it perhaps should be e.g. in cancer patients who are transitioning from curative to palliative treatment or in terminally ill patients on medications with long term benefits only e.g. statins
- important because polypharmacy may lead to an underuse of essential medications and a reluctance to start new medications and an increased risk of harm due to the ‘prescribing cascade’, where more medications are prescribed to treat the side effects of others
- always consider the time required to obtain the expected benefits from medications vs expected life expectancy

Benefits

- improved quality of life
- reduced pill burden
- reduced potential adverse drug reactions
- improved medication adherence

Triggers

- older patients presenting with falls, delirium, or cognitive impairment
- development of adverse drug reactions
- worsening physiological function (cardiac/hepatic/renal failure)
- transition of care moments (hospital <=> home <=> palliative care unit <=> nursing home/respite)
- end-of-life

Enablers for deprescribing

- fear of increased adverse effects, addiction or tolerance.
- inconvenience of medication taking

Barriers to deprescribing

- patient reluctance
- feelings of hopelessness (e.g. ‘not worth treating anymore’).
- family pressure to continue treatment, and concern from general practitioners about stopping medications first prescribed by medical specialists.
When deprescribing a medication remember that the pharmacodynamics and pharmacokinetics of other medications may be affected; use recognised tools as a starting point -

- Beers criteria
- STOPP (Screening Tool of Older Person’s Prescriptions)
- START (Screening Tool to Alert doctors to Right Treatment)
- anticholinergic risk scale

**The deprescribing process**

- take a comprehensive medication history
- ascertain indications, compliance, and potential adverse reactions
- use medication review/reconciliation services provided by pharmacists if available
- estimate life expectancy and identify any medications unlikely to provide meaningful benefit
- set goals and create a plan e.g.
  - reduced pill burden to the patient, adverse drug reactions
  - improved symptom relief and the quality of life
- emphasise that if medications are being ceased, it is not because the patient is not worth treating, but rather that the medications are causing harm or have no benefit
- relax targets of therapy e.g. levels for blood pressure, blood sugar levels, and whether blood tests should be performed
- deprescribe one or two medications at a time, not all at once
- consider a trial withdrawal to determine continuing efficacy
- provide education around what to do if symptoms return or withdrawal reactions occur
- a multidisciplinary approach should be used, with all involved and informed in the process

**Common deprescribing**

- anti-hypertensives
  - monitor blood pressure post cessation, as many patients remain normotensive
  - beta-blockers need to be weaned slowly to prevent rebound hypertension/tachycardia. NB use caution when ceasing in heart failure
- aspirin - time to benefit usually exceeds life expectancy
- diuretics - do not deprescribe if being used for symptomatic treatment or for heart failure
- statins - no evidence of benefit in shortened life expectancy or in older patients (when used for secondary prevention)
- oral hypoglycaemics (OHGs) - short term risks of continuing treatment outweigh benefits – see diabetes hyperglacaemia/hypoglycaemia page
- bisphosphonates - no evidence in shortened life expectancy, unless used for hypercalcaemia due to malignancy or for bone pain
- complementary alternative medicines (CAMs) - no evidence of benefit, unless treating a low blood plasma concentration, or to treat a symptom (zinc for taste disturbance)
- proton pump inhibitors (PPIs) - determine indication for use, as this is often not clear. Continue use if patient is on long term steroid treatment, has a history of peptic ulcer disease, active bleeding, or GORD
- cancer directed therapies - often continued in many palliative patients to improve symptoms and quality of life (e.g. preventing tumour flare at the end-of-life)