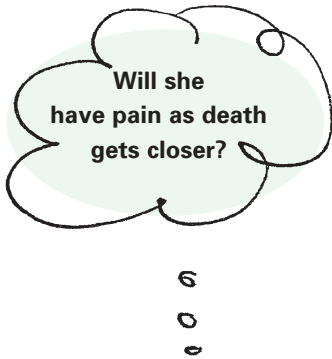**Will she have pain as death gets closer?**

To achieve optimal quality of life, an understanding of the underlying disease process and anticipated symptoms is required, as well as an understanding of the family dynamics and likely needs of the child and family. How we approach the care of a dying child and the family will greatly influence the quality of the child's remaining life and the ability of the parents, siblings and friends to cope after the child's death.

Symptom Management is the care given to improve the quality of life of patients who have a serious or life-threatening illness. The goal of symptom management is to prevent or treat as early as possible the symptoms of an illness, side effects caused by treatment of an illness, and psychological, social, and spiritual problems related to an illness or its treatment.[43]

The approach must be individualised, taking into account an often complex set of circumstances unique to each child's clinical situation. Hunt et. al.[44] analysed the most common symptoms experienced by children dying from numerous conditions within a children's hospice. More than 80% of patients had pain recorded as a symptom in the last month of life. Over one third of children also experienced constipation[44].

A more recent study found lethargy and drowsiness were the most common symptom, and were more commonly experienced on the hospital ward compared to the intensive care unit. Other symptoms dying children experience include dyspnoea, nausea and vomiting, excess airway secretions, dysphagia, anorexia, agitation and irritability, psychological distress, skin changes, seizures and peripheral oedema.[44, 45] Figure 6 shows the presence of the five most common symptoms based on a review of 170 child deaths in Queensland.

FIGURE 6 Symptoms experienced by dying Queensland children (n=170)
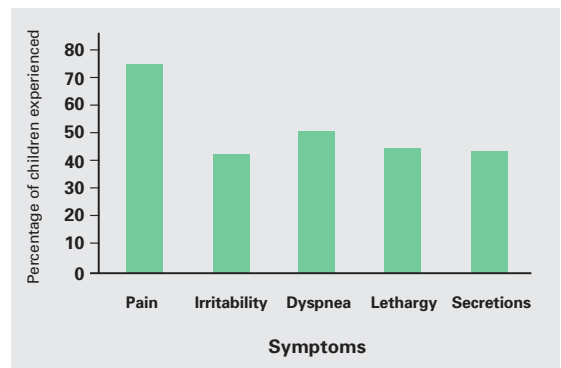
Pain is a commonly experienced symptom in children with life-limiting illnesses. Opioids are the cornerstone of pain management in this context, particularly during end-of-life care. Many children require opioid analgesia throughout the palliative phase of their illness.[3] One single institution found that of 105 children who died in the hospital over a 12 month period, 90% received analgesics in the 72 hours before death.[46] Of 44 patients with Cystic Fibrosis at another institution, 38 patients (86%) received opioids for severe dyspnoea and pain at the end of life.[47] The duration of treatment, in this study, varied from one month to one hour before death.

The fear of uncontrolled pain is also recognised as a source of anxiety for both children and their families.[48] Anxiety and other psychosocial factors will contribute to the total pain that is experienced by the child and family and this must be acknowledged and managed. The approach to such management of the child and family involves knowledge of the underlying disease, an understanding of the prior treatment or management, and of the child and family's responses to treatment and their transition from a curative to palliative focus.

This section is aimed at providing an overview of the more common symptoms experienced by children with life-limiting illnesses, and a guide to the possible approaches to management.

Symptom management can be broadly divided into five stages:

1. Obtaining of an accurate history and assessment
2. Identification of the cause (if possible)
3. Ongoing communication with the child and family
   - Explanation of symptoms and treatment options
   - Establishment of goals of therapy
4. Implementation of therapy
   - Treatment of underlying cause
   - Pharmacological, physical, psychological and complementary
5. Regular review and modification of treatment/management.

Won't using morphine make her die sooner?
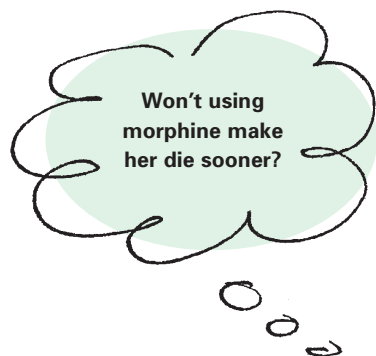
Dispelling the myths

Myth: *Young children and infants, experience less pain than adults.*

Truth: Similar myths suggest children tolerate pain better and there is rarely a requirement for opioid analgesia. Many clinical studies have now challenged these "beliefs" and have demonstrated that neonates, infants and children experience similar degrees of pain to adults.

Myth: *The child will become addicted to opioids.*

Truth: One of the major concerns of both family and health professionals is that of addiction to opioids. It is important to dispel this fear early in the treatment course. Addiction is predominantly a psychological dependence and patients with a life-threatening or life-limiting illness (such as cancer or severe cerebral palsy) who require titrated doses of morphine do not become addicted to opioids.[32] Tolerance to the analgesic effect of morphine is not a problem and psychological dependence in palliative patients is extremely rare. Parents should be reassured in this regard.

Myth: *Only the medical team can control the child's pain medications.*

Truth: If pain is poorly controlled or escalating, patients will ask for further doses of morphine to bring about relief from pain. The opioid doses can safely be increased by parents at home after discussion with the clinical team. This parental ownership of pain control is important. Adolescent patients also benefit when given some control and choice with how their pain is managed.

Myth: *It is not appropriate to use opioids with non-cancer conditions.*

Truth: Many patients with non-cancer life limiting conditions benefit from a trial of carefully titrated opioid analgesia. However, patients with a non-cancer diagnosis often do not require the rapid dose escalation that a child with a rapidly progressive solid tumour requires.

Myth: *Sedation will affect the quality of the child's life.*

Truth: Sedation from opioids will usually improve within a few days of commencement. This is because the child will develop tolerance to the central nervous system (CNS) depressant effects of morphine over time.

Myth: *Using morphine will result in respiratory depression.*

Truth: Respiratory depression can be avoided by gradual and steady increases in the dose. Like the CNS depressant effects, children will develop tolerance to the respiratory depressant effects of morphine. The use of morphine in adult patients with advanced chronic obstructive pulmonary disease (COPD) was found to relieve dyspnoea and improve sleep. It did not worsen respiratory failure.[49]

Myth: *Using morphine will shorten the child's life.*

Truth: Pain control does not shorten a child's life.

Rather it improves the child's quality of life and brings comfort to a child's death. It can even extend a child's life because they are not exhausted from fighting pain. The dosage can also be reduced or increased depending upon how the child and their disease responds to treatment. A study of adult patients found the use of opioids and sedatives did not have an association with shortened survival. [50]

Assessment of pain

The evaluation of pain in the child is significantly different from that in the adult, and is dependent upon the age, developmental stage, cognition and previous life experiences. As the child's vocabulary and past life experiences are often limited, it is difficult to obtain qualitative and quantitative descriptions of their pain. The use of a number of different parameters is often helpful in determining position, nature and severity of pain. Simple observation of the child's level of activity and behaviour is useful.

Any change in behaviour, such as irritability, fractiousness or withdrawal may indicate discomfort. The FLACC scale allows observation of such parameters and has been validated as a means of measuring pain in infants and children younger than four years of age.[51] Assessment in older children can be enhanced with the use of visual analogue tools, including the Faces pain scale-revised (Figure 7).[52] These scales share a common metric (generally 0–10). Pain scores fall into three ranges:

- mild (0–3)
- moderate (4–6)
- severe (7 or more).

The Non Communicating Children's Pain Checklist can be used for children with cognitive impairment, and the CRIES pain rating scale can be used for neonates.[53, 54]

The use of a body outline completed with the child and parent may also aid in determining the position of the pain and intensity can be highlighted by different shades of colours. Importantly, remember *"pain is where the hurt is".*
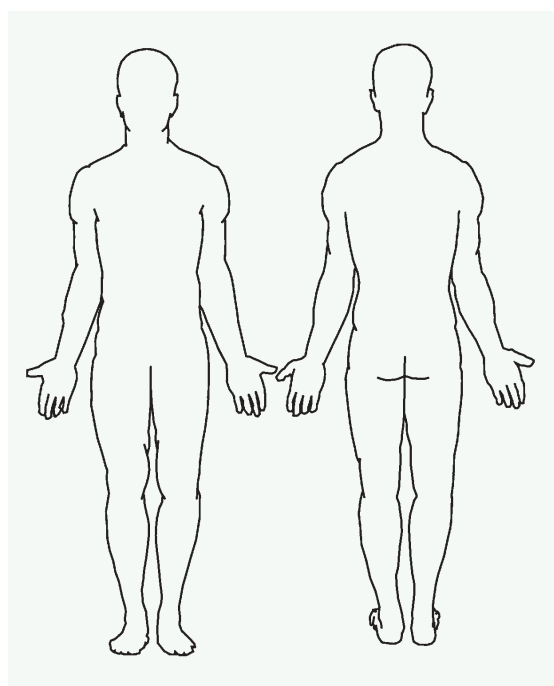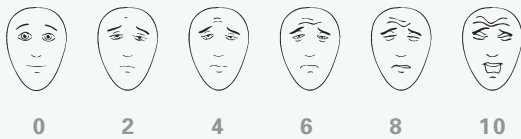
FIGURE 7 Faces Pain Scale

Faces Pain Scale – Revised (FPS-R)

The full-size version of the Faces Pain Scale (FPS-R), together with instructions for administration, are freely available for non-commercial clinical and research use from www.painsourcebook.ca.

| 0 | 2 | 4 | 6 | 8 | 10 |

Note: Numbers are not shown to the child

Instructions to the child are: These faces show how much something can hurt. This face (point to the left-most face) shows no pain or hurt. The faces show more and more pain (point to each from left to right) up to this one (point to the right-most face) – it shows very much pain. Point to the face that shows how much you hurt right now.

Do not use words like 'happy' or 'sad'. This scale is intended to measure how children feel inside, not how their face looks. Numbers are not shown to children; they are only shown here for reference. The instructions for administration are currently available in 12 languages from www.painsourcebook.ca.

FIGURE 8 Visual Analogue Scales

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

No pain   Worst pain
                                      imaginable

Aetiology of pain

Invasion of bone and bone marrow is the most common cause of pain in the child with cancer and is typical of somatic nociceptive pain.[55] Other causes of pain in the child with cancer are shown in Table 3.

In children with non-cancer diagnoses, pain is often multi-factorial. Musculoskeletal causes are common in this group of patients (e.g. scoliosis, dislocated hips, osteoporosis, and fractures). Pain due to dystonia/muscle spasm or gastrointestinal dysmotility is also common. Pain may also be associated with orthotic devices and can increase around the time of orthopaedic and other surgeries. Differentiating between cerebral irritability and pain can be challenging in the child with developmental disability.

TABLE 3 Aetiology of cancer pain

Tumour involvement
Direct tissue/nerve damage
Bone marrow infiltration
Infiltration of tissues
Compression of tissues
Nerve compression
Raised intracranial pressure

Treatment related
Infection due to immunosuppression
Mucositis related to chemotherapy and radiotherapy
Inflammation after surgery

Procedure related
Venepuncture
Surgical interventions
Investigations (e.g. lumbar puncture, bone marrow aspirate)

Pain can be classified by its origins and pathway of transmission to the brain into two broad categories, nociceptive (somatic and visceral) and neuropathic.[55] Details of these categories and the pathways are beyond the scope of this guide, but different mechanisms and pain characteristics occur.

Principles of pain management

The aims of pain management are to relieve pain at rest and during activity, and to ensure comfort during sleep with minimal side effects. To achieve this, the same general principles of symptom management are applied.

The World Health Organisation (WHO) published a guide, "Cancer Pain Relief and Palliative Care in Children" in 1998. Drug therapy is the mainstay of treatment and given the correct drug, dose and interval, pain relief is possible for most patients.[56] More recently, the WHO has published guidelines on the pharmacological treatment of persisting pain in children with medical illnesses.[57]

The general strategy for treatment is to keep it simple and to administer the drug(s):

- **By the mouth** – the oral route is convenient, non-invasive and cost effective.
- **By the clock** – regular scheduling ensures a steady blood level, reducing the peaks and troughs associated with "as required" or "pro re nata" (prn) dosing.
- **By the ladder** – enabling a stepwise approach to treatment commencing at an appropriate symptom level with non-opioid analgesia and progressing to opioids (Figure 9).

Treatment should be individualised according to the child's pain, response to treatment, and frequently reassessed and modified as required.

A multimodal approach to pain management has recently been advocated.[58] This approach advocates the early introduction of adjuvant therapies when appropriate.

ANALGESIC AGENTS

The analgesics can be broadly classified into two groups:

1. **Primary analgesics.**
   - Non-opioid and non-steroidal anti-inflammatory drugs.
   - Weak opioids.
   - Strong opioids.

2. **Secondary analgesics/Adjuvant drugs.**
   - Antidepressants.
   - Anticonvulsants.
   - Corticosteroids.

Which drug to prescribe is dependent upon the nature and severity of pain. A step-wise approach to drug administration is recommended as shown with the WHO ladder commencing with simple non-opioid drugs and progressing to opioids at appropriate doses to control increasing pain (Figure 9).

FIGURE 9 WHO 2 Step analgesic ladder
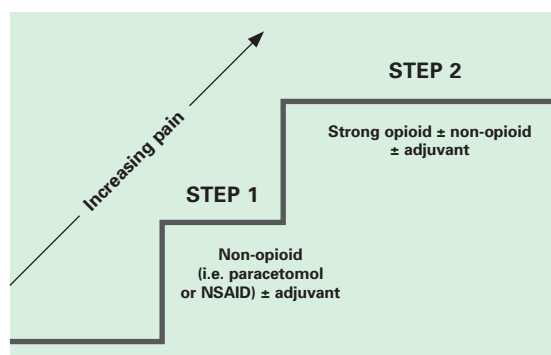
PRIMARY ANALGESICS

Non-opioids

The non-steroidal anti-inflammatory drugs (NSAID) are weak primary analgesic agents whose main action is to suppress inflammation by their anti-prostaglandin activity. Examples include naproxen, ibuprofen and diclofenac. They are effective at reducing fever and bone pain. They have significant side effects, however, including gastric irritation and ulceration. They also interfere with platelet function and should be used cautiously in children who are thrombocytopaenic, as risk of bleeding may be increased. Caution should also be used when prescribing these medications to children who are dehydrated, have renal impairment or gastric irritation. Aspirin is not prescribed to children because of the association with Reye's Syndrome.

Sensory input of pain can also be reduced by the administration of regular paracetamol. This drug has a mild anti-inflammatory effect and is very useful for musculo-skeletal pain. It is also an effective antipyretic. Paracetamol is generally well tolerated by children and is available in oral (tablet/capsule/ syrup – various concentrations available), rectal and parenteral formulations, and is the preferred non-opioid analgesic for children (15mg/kg/dose q4h orally, maximum 4g/day). There are some families that are already familiar with preparations combining paracetamol with codeine e.g. Painstop®. Careful explanation regarding the use of regular paracetamol with combined agents is required to ensure recommended daily limits are adhered to. It is preferred that the combined agents are avoided. It may be preferable to use low dose morphine syrup and regular paracetamol instead.

Paracetamol used in conjunction with an opioid is a simple example of the multimodal approach.

Care should be taken when prescribing paracetamol for extended periods of time. Hepatic toxicity has been reported in children following chronic therapeutic dosing.

Oral opioids

The opioids are the mainstay of treatment for the majority of patients with severe pain associated with cancer and other life-limiting illnesses. If pain is not controlled with paracetamol, a weak opioid such as codeine phosphate (0.5mg/kg/dose q4h) could be commenced. However, the WHO guidelines now suggest low dose morphine is preferable in children, as codeine has a ceiling analgesic effect, causes significant constipation, and a small percentage of the population does not metabolise codeine adequately.

Morphine

Morphine remains the standard against which other opioid analgesics are compared. Morphine is available in oral (mixture/ syrup – in various concentrations, tablets, and immediate and slow release formulations), parenteral, spinal and rectal preparations. The oral route is the preferred route of administration as it is readily absorbed and tolerated by most children. Liquid / syrup morphine, in the appropriate dose, provides 4–6 hours of pain relief and it should be prescribed as a regular dose every four hours.

There is no role for *prn* dosing in the palliative patient. End of dose breakthrough pain is distressing and more difficult to control as the plasma drug level falls.

Severe pain that is not adequately controlled with the commencing dose of morphine orally (0.2mg/kg/dose q4h) is an indication to increase the dose. Incremental increases of 30–50% per dose may be required within 24 hours. Once the appropriate 24 hour dose of morphine is determined, transfer to sustained release morphine preparations is possible.

The slow release preparations, MS Contin® (available in tablets and dispersible sachets) and Kapanol® (capsule), have a slower onset of action than immediate release morphine, but have a longer duration of action.

The dose is determined by calculating the total daily amount of morphine (six x regular dose). For example 5mg of morphine mixture every four hours is a total daily dose of 30mg, which is converted to 15mg of MS Contin® twice daily. Immediate release morphine should be available for "breakthrough pain" which may occur. The "breakthrough" dose is equivalent to one-sixth of the total daily dose. Using the same example, this would equal 5mg (see Table 4). The breakthrough dose of morphine should be increased enough to alleviate any breakthrough pain. Breakthrough pain is covered in more detail in the following pages.

If repeated doses of breakthrough morphine are required, this is an indication to increase the total daily dose of sustained release morphine to the equivalent total dose of morphine required in the preceding 24 hours. For example if two doses of 5mg were required it would be appropriate to

increase the dose of MS Contin® to 20mg bd. With an increase in MS Contin® the breakthrough dose of morphine will also need adjustment. For 40mg/day the appropriate breakthrough dose of immediate release morphine is approximately 6.5mg. If greater than six breakthrough doses of opioids are required in a 24 hour period, it is an indication to increase the background opioid dose by 50%.

Oxycodone

Oxycodone is a useful alternative to morphine and is available as tablets, capsules and syrup. It has an increased potency compared to morphine in children (morphine: oxycodone = 1.5:1). It may also have kappa-receptor agonist activity, which relieves neuropathic pain. Its oral bioavailability is higher than morphine (50–60%). The oral dose is 0.1–0.2mg every 4 hours. It is available as a tablet (scored), capsules and syrup (concentration 1mg/ml only). Onset of action is 20–30 minutes making it a good option for breakthrough pain. It is a good alternative to morphine especially when morphine contributes to vomiting, pruritus or delirium. Slow release preparations are available in tablet form only and cannot be crushed.

Oxycodone-with-naloxone controlled-release (CR) tablets (Targin®) are also available and provide equivalent analgesia to that of oxycodone CR tablets of the same oxycodone dose. The addition of the naloxone component reduces, but does not eliminate, constipation. (There is no literature available on the use of Targin® in children and it

TABLE 4 Example of daily morphine equivalent dosing and conversion from immediate release morphine to sustained release morphine, for a 15kg child receiving an initial dose of ~ 0.3mg/kg.

q4h dose	Total 24h dose	MS Contin dose	Breakthrough dose
5mg	30mg	15mg q12h	5mg

can initially provoke withdrawal symptoms or diarrhoea in children who are opioid tolerant).

Tramadol

Although not a pure opioid, tramadol can be effective for moderate to severe pain in older children. It is a weak mu-receptor agonist and a serotonin and norepinephrine reuptake inhibitor. The dose is 1mg/kg every 4 hours. While not a first line agent, it can have a role in certain situations. Care should be taken to avoid drug interactions especially with selective serotonin-reuptake inhibitors and tricyclic antidepressants. It can also lower the seizure threshold.

Hydromorphone

Hydromorphone is a derivative of morphine with a higher potency. The parenteral formulation is up to five times as potent as the oral formulation. It is available as a syrup (concentration 1mg/ml and in tablet form). There is also a slow release preparation available in tablet form (Jurnista®) which is taken once daily.

Buprenorphine

Buprenorphine is a synthetic lipophilic opioid with 30–50 times the analgesic potency of morphine. This molecule has been available for parenteral and sublingual administration for more than 25 years. Currently its use in paediatrics is expanding due to the introduction of a transdermal matrix patch. Sublingual tablets (200 micrograms) have a duration of action of 6–8 hours. The lowest dose patch (5 microgram/hour) has the benefit of having a much lower morphine equivalent dose than the lowest dose fentanyl patch (12 micrograms/hour) and is applied every seven days. The patches are an easily administered option for low dose

background opioid analgesia in a stable situation e.g. in severe neurological impairment.[59]

In clinical practice, buprenorphine does not have a ceiling effect. A ceiling effect has however, been demonstrated for respiratory depression resulting in an improved safety profile compared to other opioids, such as fentanyl. Its pharmacokinetic properties, such as faecal elimination, allow its use in patients with renal impairment. It has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms in children dependent on other opioids.[60, 61]

In Table 5, the available preparations and dose for oral morphine, oxycodone and hydromorphone are presented.

Methadone

Methadone is a synthetic, lipid soluble opioid and has a chemical structure very different to morphine. It acts on the μ-opioid receptor and antagonises the N-methyl D-aspartate (NMDA) receptor. Consequently, it is very effective at treating somatic, visceral and neuropathic pain. Methadone has a long half-life with large inter-individual variability in its half-life (3.8 to 62 hours). It can accumulate in the plasma causing severe somnolence which is slow to reverse. Patients need to be observed closely when commencing methadone or switching from another opioid.

Methadone also prolongs the QT interval through its effect on cardiac potassium channels. This may predispose patients to arrhythmias, particularly when the parenteral formulation is used. Consequently, it is often reserved for patients receiving palliative care where other methods of pain management have failed. The goals of care, including the risk of arrhythmia, need to be discussed with the family.

TABLE 5 Oral Morphine, Oxycodone and Hydromorphone Preparations

Drug	Release	Form	Dose
Morphine	Immediate Q4 hr	Liquid	1, 2, 5 and 10mg per ml (Ordine®) (40mg/ml on request)
	Immediate Q4 hr	Tablet	10 and 20mg (Sevredol®)
	Controlled Q12 hr	Suspension (granules dispersed in water)	20, 30, 60, 100 and 200mg (MS Contin® Sachets)
	Controlled Q12 hr	Tablets	5, 10, 30, 60, 100 and 200mg (MS Contin®)
	Controlled Q12–24 hr	Capsule	10, 20, 50 and 100mg (Kapanol®)
Oxycodone	Immediate	Liquid	1mg/ml (Oxynorm®)
	Immediate	Tablets	5, 10mg (Endone®)
	Immediate	Capsule	5, 10, 20mg (Oxynorm®)
	Controlled	Tablets	5, 10, 20, 40, 80mg (Oxycontin®) (Targin® – Oxycodone-with-naloxone)
Hydromorphone	Immediate	Liquid	1mg/ml (Dilaudid ®)
	Immediate	Tablets	2, 4, 8mg (Dilaudid ®)
	Controlled Q24 hr	Tablets	4, 8, 16, 32, 64mg (Jurnistor ®)

Methadone is available in tablet and liquid formulation and has very good bioavailability (almost 100%). The dose should be doubled when converting from parenteral to oral methadone. The starting dose for an opioid naïve patient is similar to that of morphine (0.1mg/kg every 6–8 hours).[62] This frequency of dose can be continued until the patient becomes pain free or drowsy. At this point the dosing frequency should be reduced to two to three times daily.

Calculating the dose of methadone in patients already established on another opioid is more complex. This is because cross-tolerance with methadone will be low. The starting dose is usually one tenth of the morphine equivalent dose. Because it is infrequently used in paediatric pain management and it has complex pharmacokinetics, methadone should only be prescribed by experienced practitioners. Its use needs further evaluation in a clinical research setting.

TABLE 6 Parenteral and Transdermal Opioid Preparations

Drug	*Parenteral Preparations*	*Transdermal Preparations*
Morphine sulphate	5mg/ml, 10mg/ml,15mg/ml, 30mg/ml	
Morphine tartrate	120mg/1.5ml, 400mg/5ml	
Hydromorphone	2mg/ml, 10mg /ml, 50mg/5ml, 500mg/50ml	
Methadone	10mg/ml	
Fentanyl	100mcg/2ml, 500 mcg/10ml	12 mcg/hr, 25mcg/hr, 50mcg/hr, 75mcg/hr, 100 mcg/hr.
Buprenorphine	300mcg/ml	5mcg/hour, 10mcg/hour, 20mcg/hour

Parenteral opioids

If the child is unable to take drugs orally, alternative routes of drug delivery are available. MS Contin tablets can be given rectally and morphine suppositories can be obtained. In the acute situation, a subcutaneous injection of morphine (0.1–0.2mg/kg) is easily administered and has a rapid onset of action.

There is no role for intramuscular pethidine (or other drugs) in the management of pain related to progressive illness.

If the oral route remains problematic, a subcutaneous infusion of morphine is a simple and effective mode of drug delivery. Some children will still have a central venous access device (central line or port-a-cath) and morphine can then be delivered intravenously. Insertion of a central venous access device for pain management in certain situations is appropriate.

The 24 hour dose of parenteral morphine is equivalent to one third (1/3) of the total oral dose. For example, a child receiving 150mg of oral morphine per day would require 50mg of morphine delivered as a continuous subcutaneous infusion per 24 hours.

Fentanyl, hydromorphone and methadone can also be administered parenterally (see Table 6).

Fentanyl

Fentanyl is a lipophilic synthetic opioid and is approximately 10–40 times more potent than morphine. It is less potent in neonates and smaller children. Like morphine, it has an affinity for the mu-opioid receptor and acts as a pure agonist. It is available in a transdermal formulation. Clinical studies in children have shown that transdermal fentanyl is an effective alternative to oral opioids with studies suggesting fewer side effects (particularly constipation and nausea) and improved quality of life.[63–65] Its topical route of absorption removes the need for oral or parenteral administration. Recently developed matrix patches can be cut, allowing smaller doses to be administered.

Fentanyl is well absorbed via the oral mucosal route providing prompt pain relief. Oral transmucosal fentanyl citrate (OTFC) lozenges and buccal tablets offer promise in providing non-invasive means of treating breakthrough pain. The use of intra-nasal fentanyl (dose 1–2 mcg/kg using mucosal atomiser devices) for breakthrough pain relief has been described in emergency departments, cancer pain relief, and in neonates and infants.[66-68]

Refer to Appendix 2 for guidelines on commencing a subcutaneous infusion.

BREAKTHROUGH PAIN

When exacerbations of medium to severe pain occur on the background of otherwise controlled pain, it is commonly described as breakthrough pain. There is a high incidence of breakthrough pain in paediatric oncology patients with one study finding at least one episode of such pain per day in 57% of patients.[69] This pain can last from seconds to minutes and is frequently described as "sharp" or "shooting". The pain may be incidental (related to movement, breathing, coughing or eating) or spontaneous with no obvious cause.

Management of breakthrough pain

Breakthrough pain usually requires the administration of rescue doses in addition to medications used to control baseline pain as outlined above. If the child experiences breakthrough pain, morphine can be administered as a bolus. This is usually one sixth (1/6) of the total daily dose; the equivalent of 8mg for a 50mg 24hr dose). This can be administered through the sidearm of the subcutaneous cannula.

The following pharmacological approaches can help in the management of breakthrough pain:

• Increasing the quantity of long-acting opioid.
• Increasing the frequency of a short-acting opioid.
• Replacing a short-acting opioid with a long-acting opioid.
• Adding a rapid-onset opioid to around-the-clock medication.[70]

Non-pharmacological management strategies may also be appropriate and may be combined with the use of medications. This may include heat, ice and some of the complementary therapies outlined below.

Paediatric pain crisis

A pain crisis in a child is an emergency and requires treatment beyond conventional means. If a child has persistent and severe pain (and with close medical supervision and instructions) the dosing frequency of oral opioid can be reduced to 1–2 hours. At the same time a specific diagnosis of the underlying cause should be attempted to allow more effective therapies to be implemented.

The intravenous route of administration provides rapid onset of analgesia. On occasion, the clinician may need to remain by the child's bedside to titrate incremental intravenous doses every 10–15 minutes until effective analgesia has been achieved. The analgesic effects of opioids increase in a log-linear function, with incremental opioid dosing required until either analgesia is achieved or somnolence occurs. The total amount of opioid administered to require this reduction in pain intensity is considered the opioid loading dose. A continuous infusion of opioid may need to be commenced to maintain this level of analgesia. An alternative to a continuous infusion of opioid is intermittent parenteral opioid, especially in the setting of an unpredictable pain syndrome.

Patient Controlled Analgesia (PCA)

A PCA is an infusion device which can be activated by the patient to self-administer a set bolus dose of analgesia. Children as young as seven years of age are able to use a PCA.[71] Nurse controlled analgesia (NCA) is appropriate for the control of pain in infants, pre-verbal children and children with severe developmental delay who cannot use a PCA. Some hospitals allow parent controlled analgesia in younger children. Parent controlled analgesia can also be provided in the home. Two modes can be used, bolus only or bolus plus a continuous background continuous infusion.

Additional doses of pain relief can be administered for breakthrough and incident pain in addition to a background infusion. The prompt and safe delivery of analgesia associated with this modality allows control over the wide and unexpected analgesic requirements of children. There is good evidence to support the use of PCAs in patients with mucositis undergoing bone marrow transplantation.[72, 73] Adolescents have reduced sedation and morphine intake with similar pain relief when using PCAs compared to infusions.[72] Both modes (PCA and NCA) are suited to provide analgesia where there is a large component of "incident pain" e.g. pain on movement or with coughing.[69] There is also evidence to support this modality of pain management in the palliative care context.[74]

TABLE 7 Patient Controlled Analgesia and Nurse Controlled Analgesia

Mode	Concentration	Continuous infusion	Patient bolus	Lock out interval	Hourly dose limit
Morphine PCA	0.5–1mg/kg in 50mls (max 50mg)	0–1ml/hr	1ml	5 min	150mcg/kg/hr
Morphine NCA		0–0.5ml/hr	1ml	10–30 min	120mcg/kg/hr
Morphine Infusion		0–2.5ml/hr	N/A	N/A	N/A
Fentanyl PCA	25–50mcg/kg in 50mls (max 2.5mgs)	0–1ml/hr	0.5ml	5 min	5mcg/kg/hr
Fentanyl NCA		0–0.5ml/hr	0.5ml	10–30 min	3mcg//kg/hr
Hydromorphone PCA	150mcg/kg in 50mls (max 7mg)	0–1ml/hr	1ml	5 min	20mcg/kg/hr
Hydromorphone NCA		0–0.5ml/hr	1ml	10–30 min	15mcg//kg/hr
Adding ketamine to morphine OR	Add 1mg/kg ketamine to the 50ml opioid syringe. Use parameters as given above. (Ketamine may be added to the opioid-containing syringe)				
Run a separate ketamine infusion	Add 5mg/kg ketamine to 50mls. Run at 1ml/hr to deliver 100mcg/kg/hr				

The PCA device must be programmed to deliver an opioid dose at a predetermined frequency, with a maximum total dose allowed per hour. Table 7 outlines guidelines for the initial prescription of a PCA in an opioid naïve patient. Rescue doses are kept as a proportion of the baseline opioid infusion rate and re-calculated as between 50% and 200% of the hourly basal infusion rate. Bolus attempts and successes should be documented as part of the observations.

A PCA (or NCA) can be used to safely titrate analgesia during a pain crisis. It is possible to transition a patient back onto long acting opioid preparations after the child's pain has stabilised and the total daily opioid requirement has become clear. A PCA can be continued at home using a computerised ambulatory delivery device (CADD) pump. Parent controlled analgesia is also possible in younger children in the home setting.[75] Methadone can be administered in a PCA if the lockout interval is increased to 30–60 minutes given its long half-life.

SIDE EFFECTS AND PRECAUTIONS OF OPIOIDS

All preparations of opioids have side effects. Constipation can be a major problem and consideration should always be given to prescribing laxatives whenever opioids are used. Unlike many of the other side effects, in particular nausea and drowsiness, tolerance to constipation does not occur. Methylnaltrexone (sub-cutaneous) is a competitive antagonist for the µ-receptor. It works at the level of the gastro-intestinal tract and does not cross the blood brain barrier. Its use has been described in case studies and a dose of 0.15mg/kg administered subcutaneously has been recommended.[76, 77] It has a role when children cannot tolerate or respond to enteral or rectal laxatives.

Nausea and vomiting can occur upon initiation of treatment with an opioid and an antiemetic will be required. After administration of breakthrough doses of morphine it is not unusual for drowsiness to occur, but once a stable dose of morphine is achieved this becomes less problematic and children are likely to be more active and alert with good analgesia. Pruritus is not uncommon and can be relieved with the concomitant use of an antihistamine. Low dose naloxone infusions have also been used to prevent itch associated with opioid infusions (dose 0.5microgram/kg/hr).[78]

Opioids will cause respiratory depression only if given in an inappropriate dose, which is usually above that required for analgesia. This is particularly the case for opioid naïve patients. Extreme caution should be used in giving naloxone at a treatment dose to patients who have been receiving chronic opioid therapy, since severe pain and symptoms of opioid withdrawal may ensue.

Patients with significant renal impairment will accumulate metabolites of morphine. In this context, drowsiness and respiratory depression can occur after 24 hours. Careful supervision of dosing is required and a lower initial dose should be prescribed and titrated according to response. Similarly, a lower initial dose should be used for children with liver failure as bioavailability of morphine is increased.

Opioid rotation

It is possible to improve pain management by changing to a different opioid medication. This process is called opioid rotation.

The usual indications for switching to an alternative opioid are:

• Excessive side effects (e.g. itch, nausea, delirium) with adequate analgesia (70%).
• Side effects with inadequate analgesia (17%).
• Tolerance (7%).[79]

Alternatives to morphine include fentanyl, hydromorphone and sometimes methadone. A switch from one opioid to another is often accompanied by change in the balance between analgesia and side-effects.

Table 8 assists with conversion of morphine to fentanyl and hydromorphone. Both background and bolus doses should be taken into account when switching opioids. Switching to methadone is more complex as discussed above.

Opioid resistant pain

While opioids are the gold standard for treatment of cancer pain, not all pain is opioid sensitive (see Table 9).

Relative resistance can be overcome by increasing the dose, improving support of the child and family, or using an alternative route of drug delivery. The addition of a non-steroidal anti-inflammatory drug or paracetamol may alleviate pain related to soft tissue or bony metastases. Pelvic pain is also potentially difficult to control and consideration of nerve blocks or palliative radiotherapy may be required.

Neuropathic pain tends to be relatively resistant to the above approaches and is due to the compression or infiltration of nerves, or to neuropathy, which may be disease or treatment related. For example, medications used in cancer (e.g. vincristine) and HIV therapy (e.g. didanosine, zalcitabine) can cause neuropathy. The nature of neuropathic pain has different characteristics and tends to be either spasmodic/shooting or continuous burning/piercing. Abnormal sensation, either increased with or without tingling, may co-exist. Younger children often cannot differentiate between or precisely describe the different qualities of pain.

TABLE 9 Causes of opioid resistant pain

Relative resistance
Under-dosing
Poor absorption orally
Lack of emotional support
Semi-resistant pain
Soft tissue/muscle infiltration
Bony metastases
Raised intracranial pressure
Neuropathic pain
Resistant pain
Neuropathic pain
Muscle pain

TABLE 8 Conversion of morphine to fentanyl and hydromorphone

Drug	*Morphine*	*Fentanyl*	*Hydromorphone*
Relative Potency	1	40[119]	5–7[120]
Example Dose Comparisons	4mg	100 micrograms (i.e. 0.1mg)	570 micrograms

SECONDARY ANALGESICS

Antidepressants in low dose are useful for neuropathic pain, particularly painful paraesthesia and peripheral neuropathy. As well as having a direct analgesic effect, they potentiate opioid analgesia via adrenergic or serotinergic mechanisms. A low dose of amitriptyline (starting dose 0.2mg/kg) at night usually has an effect within 48–72 hours.

Anticonvulsants, such as gabapentin, pregabalin, carbamazepine or sodium valproate are useful for pain related to nerve infiltration/compression, which is often periodic or spasmodic. The anticonvulsants have a stabilising effect on excitable cell membranes and prevent the spread of neuronal excitation.[32]

Clonidine and ketamine can be useful for patients with refractory neuropathic pain. They are, however, rarely required in children receiving palliative care.

Corticosteroids either alone or in combination with an anticonvulsant is effective to reduce swelling associated with nerve compression/infiltration. They can also alleviate some of the symptoms related to raised intracranial pressure. Low-dose steroids act as anti-inflammatory drugs and can reduce bone pain. Dosing should be restricted, however, as significant side effects occur, including excessive weight gain, gastric irritation and susceptibility to infection. Acid suppressing agents (e.g. omeprazole or ranitidine) are usually given concurrently with corticosteroids.

Other drugs recognised as secondary analgesics include: antispasmodics, anxiolytics and bisphosphonates. Hyoscine N-Butylbromide (Buscopan®) is useful for bladder or bowel spasm and low dose diazepam is effective treatment for muscle spasms and myoclonus. Regular review, reassessment and an individualised approach are essential for successful treatment of pain.

OTHER THERAPIES FOR PAIN

Antibiotics or antifungal agents will improve pain control when there is an underlying infection such as cellulitis or mucositis. Consideration should be given to practical, oral anti-infective therapy in these situations. Bisphosphonates such as pamidronate and zoledronate inhibit bone reabsorption and are useful for the treatment of pain secondary to hypercalcaemia, disseminated bone metastases, avascular necrosis and pathological fractures related to osteoporosis.

Both chemotherapy and radiotherapy can be used as palliative treatment, and radiotherapy particularly, can have a potent analgesic effect in patients with cancer. One or two fractions are often all that are required, and the effect can be quite rapid. Consequently the opioid requirement is likely to lessen and drowsiness may occur.[80] During radiotherapy it is often useful to revert from sustained release preparations of morphine to immediate release morphine.

Pain from bone metastases can also be relieved with injectable radiopharmaceuticals. Samarium has an affinity for skeletal tissue and concentrates in areas of bone turnover.

Meta-iodobenzylguanidine (MIBG) is taken up by neuroblastoma cells. Treatment with these agents can allow the reduction of opioid use and can provide several weeks of pain relief.[81] Eventually treatment with radiotherapy and chemotherapy will not be a viable option, as the child will continue to have progressive disease, and the journey from home to treatment centre will become too exhausting for child and family.

Nerve blocks are occasionally used for children with well-defined somatic or visceral pain.[82] Spinal opioid therapy and epidural anaesthetics are very effective for pelvic pain and often allow the reduction of sedation doses of oral or subcutaneous opioids. Blocks can be temporary, prophylactic or permanent and should be placed by anaesthetists experienced in such pain management techniques.

Sedation as a therapeutic modality for intractable pain

The use of sedation is reserved for select situations of refractory pain where conventional therapies have been unsuccessful.[83] All acceptable means of providing timely analgesia without compromising consciousness should be exhausted. This trade-off between sedation and inadequate pain relief requires the consideration of the wishes of the child and his or her family. Sedation should be prescribed by an experienced practitioner with the primary aim of relieving suffering. Ethical principles including the principle of double effect are important in this context. The continuation of high-dose opioid infusions in these circumstances is recommended to avoid situations in which a patient may have unrelieved pain but inadequate clarity to report pain perception. A variety of drugs have been used in this setting, including barbiturates, benzodiazepines, and phenothiazines.[84]

NON-PHARMACOLOGICAL THERAPIES FOR PAIN MANAGEMENT

A range of physical therapies such as warmth, cold, touch and electrical therapy are used in the management of various types and locations of pain. Touch and massage can produce relaxation as well as stimulating afferent pathways. Transcutaneous electrical nerve stimulation (TENS) is useful in treating musculoskeletal and neuralgic pain. It acts by inducing electrical activity in larger afferent fibres thereby reducing the nociceptive pain signals in the dorsal horn of the spinal cord, inducing paraesthesia over the painful area. Involvement of a physiotherapist may helpful with education for the family on how to use a TENS and in the provision of massage therapy.

Acupuncture is another modality which offers promise as a potential source of assistance for children with unrelenting pain, nausea, or other unpleasant symptoms due to disease or treatment.[85] Some families explore numerous other complementary therapies in order to help their child with pain and other symptoms. It is important to encourage open conversation regarding these therapies.

Fear and anxiety will aggravate pain, and communication with the child and family about symptoms and their treatment can assist in management. Simple measures of distraction, play, and music therapy, may be helpful. Touch and massage will facilitate relaxation in many children. Parents and siblings often like to perform the massage, and particularly for siblings, this enables them to be actively involved in their brother or sister's care. Older children and adolescents are also able to learn different relaxation techniques which may be as simple as listening to music. Cognitive-behavioural techniques of pain control such as breathing exercises, guided imagery and hypnosis are also important to consider.[86] These non-invasive measures allow control to be regained and will often aid in total pain relief for the child.

ORAL PROBLEMS

Mouth care

Mouth care at the end of life is essential, as children who are debilitated have poor oral intake and/or poor oral hygiene, and are susceptible to mouth problems. A reduction in a child's immune system as a result of prior radiotherapy, chemotherapy and progressive malignancy also increases their susceptibility to mouth problems.

Regular mouth care can prevent many oral problems. Cleaning teeth twice daily with a soft tooth brush or swab, and mouth washes with chlorhexidine or chlorhexidine gel are beneficial. Gentle irrigation of the mouth with warm salt water (0.9% saline solution) will help remove debris and soothes the mouth. Lips can be kept moist with lip balm or paraffin. The mouth can be kept fresh by sucking ice chips.

Xerostomia

Xerostomia or dry mouth is a common problem. This can result from mouth breathing, dehydration, anxiety, drugs and infection. Simple measures such as sucking ice cream, ice cubes, frozen juices and drinks will moisten the mouth and relieve thirst, while chewing or sucking unsweetened pineapple pieces increases salivary flow and can also help clean the mouth as it contains ananase, an enzyme which breaks down protein.

Mucositis

Mucositis or mouth ulcers are a well-known side effect of chemotherapy and after head and neck radiotherapy. Mucositis can also arise as a consequence of poor oral hygiene, neutropenia (low white blood cell levels) and infection.

Apthous ulcers are small, shallow, painful ulcers that can be relieved with simple analgesic mouth wash, such as benzydamine hydrochloride (Difflam®). Lignocaine (Xylocaine®) viscous (local anaesthetic gel) may also be used.

Herpetic ulcers are painful, larger ulcers and can also cause significant oesophagitis. Oral acyclovir in addition to an analgesic mouthwash should be used. The pain of severe ulceration may require oral or parenteral morphine in combination with parenteral acyclovir to ensure absorption.

Children who are immunosuppressed are at risk of fungal infection. Candidiasis may present as stomatitis (inflammation of the mouth) when the obvious white plaques may not be evident. Oral nystatin (Nilstat®) (100,000 U/ml) 1–2mls, or amphotericin (Fungilin®) lozenges, or miconazole (Daktarin® gel) every 4–6h should be used. In children where there is clear localised candida infection, or where topical treatments have been ineffective, once daily oral fluconazole (Diflucan®) may be indicated.

Mucosal bleeding can be reduced by improving mouth care, and treating or preventing infection. Thrombocytopaenia (low platelet levels) will aggravate bleeding and a platelet transfusion should be considered. This will depend on the child's stage of disease. Oral tranexamic acid (Cyklokapron®) and topical sucralfate suspension (1g tablet dissolved in 10ml) may be beneficial.[87]

NAUSEA AND VOMITING

There are many reasons why a child can become nauseated or vomit. Common causes in palliative care include:

- Opioids and other drugs.
- Upper gastro-intestinal inflammation.
- Raised intracranial pressure.
- Metabolic disturbances.
- Constipation.
- Infection.

TABLE 10 Choice of antiemetic therapy

Site	Aetiology	Antiemetic
CTZ	Drugs (opioids) Metabolic (hypercalcaemia)	Ondansetron/Zofran® (0.1–0.2mg/kg q8–12h; Max 8mg/Dose)
		Metoclopramide/Maxolon®* (0.15mg/kg q6–8h; Max 10mg/Dose)
		Prochlorperazine/Stemetil®* (0.1–0.2mg/kg q8h)
		Haloperidol/Serenace®* (0.01mg–0.1mg/kg q12–24h)
Vomiting centre	Direct stimulation (pain, fear) Viscera (gut obstruction) Raised intracranial pressure	Anti-anxiety medication
		Promethazine/Phenergan ® (0.2–0.5mg/kg q8h)
		Hyoscine N-Butylbromide/Buscopan® (0.3–0.5mg/kg q6–8h; Max 20mg/Dose)
		Hyoscine hydrobromide (6–10 µg/kg q6h; Max 400 µg/Dose)
		Cyclizine/Valoid® (0.5–1mg/kg q8h; Max 50mg/Dose)
Gastric outlet	Opioids Stasis /compression	Metoclopramide – see above
		Domperidone/Motilium® (0.2–0.4mg/kg q4–8h; Max 10mg/Dose)
GI Inflammation	Gastritis (secondary to NSAIDs, steroids)	Mylanta 10–20mls qid
		Omeprazole/Losec ® (0.5–1mg/kg q12–24h; Max 20mg/Dose)
		Ranitidine/Zantac® (2–4mg/kg q12h; Max 150mg/Dose)
		Sucralfate (dose depends on age)

*The phenothiazines, (Maxolon® and Stemetil®) can cause dystonic reactions more commonly in children compared to in adults. These reactions are usually easily recognised and families should be informed of such a possibility. Benztropine/Cogentin® (0.02mg/kg SC) rapidly reverses this effect and should be available.

Vomiting is initiated by the vomiting centre when it is stimulated directly or through the chemoreceptor trigger zone (CTZ), autonomic afferents from the viscera (gut organs) and higher brain centres. Antiemetic drugs have different effects upon these sites and the agent chosen should depend upon the most likely reason for the nausea or vomiting (Table 10). For example, drugs and metabolic disturbances act on the CTZ and antiemetics affecting this site are indicated while disturbances of gastric (stomach) emptying can be helped with agents that increase gastric emptying such as metoclopramide (Maxolon®) and domperidone (Motilium®).[87] It is important to note that children with a possible gut obstruction should avoid stimulant agents such as metoclopramide as they can aggravate the obstruction resulting in increased pain. Octreotide, administered intravenously or subcutaneously as a bolus or infusion, may relieve vomiting associated with bowel obstruction.[88]

Other causes of vomiting include severe constipation which should be relieved with adequate treatment. Raised intracranial pressure which causes vomiting is usually, but not always, associated with headache. Steroids can alleviate these symptoms, but long term steroid use is associated with excessive weight gain with a change in appearance, behavioural changes, fragile skin and ultimately resistance. Drugs acting on the vomiting centre can be beneficial and used instead of steroids (e.g. cyclizine).

If possible, the preferred route for medication is by mouth. It may be necessary to give initial doses of medication by the intravenous, subcutaneous or, very occasionally by the rectal route. Many agents which can be administered subcutaneously are compatible with morphine and therefore, can be used in combination in infusion pumps.

Further details regarding drug compatibilities are outlined in Appendix 3.

Non-pharmacological management strategies to consider include:

- Chewing ginger pieces or taking ginger tablets.
- Sipping water, juice or flat soft drinks.
- Eat foods with a lot of water in them. Try clear soups, ice blocks and jelly.
- Offering bland foods or salty foods and snacks.
- Altering feed regimes if the child is receiving enteral nutrition (e.g. giving continuous instead of bolus feeds).
- Trial of hydrolyte or similar in replacement of milk based feeds.
- Aromatherapy.

CONSTIPATION

Normal bowel function ranges from three motions a day to one motion passed every three days, or up to two weeks in a breast feed infant. Constipation refers to a significant variation from the normal bowel habit. It refers to difficulty, discomfort or delay in passing a bowel motion.

Constipation is an extremely common symptom and can contribute to abdominal pain, anorexia, nausea and vomiting as well as overflow diarrhoea. Factors known to make constipation more likely are outlined in Table 11.

The assessment of constipation is based upon:

- The underlying condition (including any neurological problem).
- Food and fluid intake.
- Medication.
- Previous laxative use.
- Previous and current pattern of bowel habit, including frequency and consistency of stool.

Chronic constipation is common in children with an underlying neurologic impairment, usually as a result of poor tone and reduced mobility.

Constipation should be expected in all children receiving opioid analgesia. Opioid receptors in the gut increase the tone and non-propulsive motility in the ileum and colon.[89] Laxatives should **always** be prescribed with opioid medication.

The effect of laxatives is dose related and there is large variation between individuals. If diarrhoea occurs, and overflow incontinence has been excluded, the laxative treatment should be modified according to the child's needs.

TABLE 11 Exacerbating factors for constipation

Exacerbating factors
Poor dietary intake
Poor fluid intake
Immobility
Medication
• Opioids
• Anticholinergics
• Antidepressants
• Anticonvulsants
• Antiemetics
Local factors
• Anal fissures/infection
Previous constipation
Electrolyte disturbance
(e.g. hypercalcaemia, hypokalaemia)

Treatment and general measures

- Predict and prevent.
- Encourage fluid and fibre intake.
- Encourage movement.
- Stop or reduce unnecessary drugs .
- Laxative treatment.

The laxative used should be based upon patient preference of formulation and the degree of constipation (see Table 12). Parachoc® is well tolerated by children. Lactulose is often used as the laxative of first choice and can be mixed with juice, cordial or milk. However, the sweet taste can deter some children, and it can cause bloating and cramping – particularly for children with slowed bowel activity from medications such as opioids. Coloxyl®, as tablets, is favoured in older children and adolescents.

Treatment for opioid induced constipation should be directed at the large bowel to stimulate and soften the stool. For example the combination of coloxyl with senna promotes secretion of fluid thereby softening the stool through the coloxyl component while senna stimulates peristalsis. Care must be taken when using senna as it may cause excessive bowel spasm. Macrogol 3350 (e.g. Movicol ® sachets given up to three or four times a day) can also be very effective. An alternative to Movicol® is OsmoLax® (polyethyleneglycol laxative) which does not have the salty background taste of Movicol®.

If the stool volume or frequency remains inadequate, and constipation is well established, suppositories or a small enema will be required to clear the lower bowel before a normal pattern can be established. Enemas or suppositories are best avoided in neutropenic patients. Durolax® or glycerin suppositories are generally effective.

Small volume enemas such as Microlax® are easy to use and usually not too distressing for the child. Larger volume enemas can lead to fluid and electrolyte disturbances particularly in the debilitated or dehydrated child. For refractory constipation an oil retention enema can be useful. Once the constipation is relieved, prophylaxis should continue.

During the terminal phase, significant discomfort related to constipation is uncommon. As fluid and oral intake are generally decreased, oral laxatives can be discontinued. A suppository or Microlax® enema may help reduce rectal discomfort arising from the urge to defecate or if there is overflow incontinence from faecal impaction.

TABLE 12 Action of laxatives

Lubricants and stool softeners
Parachoc® (Paraffin liquid)   Coloxyl ® (Docusate Sodium) – softener and promotes secretion of fluid
Stimulants/contact laxatives – promote secretion of fluid into bowel to stimulate peristalsis
Senokot® (Senna), cascara   Durolax® (Bisacodyl) – primary effect on colon within 24h
Osmotic – draws fluid into bowel to soften the stool & stimulates peristalsis
Duphalac® (Lactulose)   Sorbitol   Movicol ® (Macrogol 3350 with electrolytes)   ClearLax ® (Macrogol 3350)   OsmoLax ® (Macrogol 3350)   Golytely® – effective within 6 hours but may cause significant fluid shift; should be used with caution
Suppositories and enemas – often a combination of softener and stimulant (rectal administration)
Glycerin suppository – softener   Durolax® (Bisacodyl) – contact/stimulant

Non-pharmacological management strategies to consider include:

• Pear or prune juice.
• Liquorice.
• Adding fibre to feeds.
• Sugar free gum or lollies in generous amounts have a laxative effect.

DIARRHOEA

Diarrhoea is characterised by an increase in frequency and wateriness of the stool. The cause is usually evident from the history and the underlying condition. Simple measures such as discontinuing laxatives, high fibre foods and enteric supplements will often aid management. Consideration should be given to possibility of infectious causes of diarrhoea (e.g. rotavirus).

Medication is frequently required and loperamide (Imodium®) is generally well tolerated and effective. If severe watery/osmotic diarrhoea is suspected, such as can occur with severe graft versus host disease of the gut and in children with HIV infection, then octreotide can be helpful. Octreotide may also reduce diarrhoea refractory to other treatments. It can be administered intravenously or subcutaneously, and given as a bolus or infusion.[103]

In the terminal stage, loperamide (a potent μ-receptor antagonist at 0.2mg/kg qid, increasing to 2mg/kg/day if required) will usually be sufficient. Loperamide capsules can be dispersed in water to make a 0.2–1mg/ml solution allowing for easier administration to children who prefer liquid formulations. Likewise, morphine either orally or subcutaneously can also alleviate diarrhoea.

Non-pharmacological management strategies may include provision of oral rehydration solutions (e.g. gastrolyte or hydrolyte) instead of feeds for 24–48 hours. Sometimes changing feed regimes from bolus to continuous feeds, or to an elemental feed may reduce the volume of diarrhoea. Collaboration with the paediatric team and dietician is often required in this context.

Extra care and attention is recommended with hygiene and skin care to the peri-anal area in the presence of ongoing diarrhoea. There is also an increased risk of electrolyte disturbance.

ANOREXIA AND CACHEXIA

He hasn't eaten for days, shouldn't we do something?

Anorexia or loss of appetite is common in the later stage of the child's illness and can be associated with cachexia (loss of muscle and fat). There are often multiple causes in addition to the underlying disease including pain, nausea, constipation, drugs, anxiety, depression, oesophagitis and gastritis; addressing these is an important step in treatment.

A pre-emptive explanation of what can occur is essential and providing simple advice in regards to dietary habits such as offering the child small, simple meals can be very effective.

Medical devices for feeding

A large number of children, particularly those with non-cancer life-limiting diseases, receive part or all their nutrition by medical devices. Such devices include NG (nasogastric), NJ (nasojejunal), PEG (percutaneous enteral gastrostomy) tubes, and intravenous fluids including total parenteral nutrition (TPN). Providing food and fluids to a child through a medical device may be the only way a child can receive nutrition, or may be a comfort measure, but in some situations, particularly at the end of a child's life, can increase or prolong suffering.

In a child with a relatively prolonged palliative period who is having swallowing difficulties or difficulty maintaining their weight because of insufficient caloric intake, it may be considered beneficial.

Use of devices to provide food and fluids at the end of life should be considered on the basis of whether it will have more benefits than burdens for the child to allow the child's interests to be advanced.

FEEDING INTOLERANCE

A small group of children who receive nutrition through medical devices can develop a progressive intolerance often seen as worsening abdominal symptoms such as reflux, vomiting, abdominal bloating, irritability, and pain, which can be severe. If feed intolerance does not respond to the usual dietary modifications, (e.g. changing the formula type or route, decrease in feed volume, or usual anti-reflux medications) then visceral hyperalgesia should be considered.

Visceral hyperalgesia seems to result from an alteration in response to normal bowel sensations which are perceived as pain. Successful treatment often requires analgesic medication including strong opioids or agents such as tricyclic antidepressants (amitriptyline) or anticonvulsants (gabapentin).

FORGOING NUTRITION AND HYDRATION

It is ethically permissible to stop, or not start, medically provided food and fluids when the hope of recovery for the child is low or non-existent. However, families often find this thought distressing as it raises fears of their child suffering and "starving to death".

Clinical experience would suggest this is not the case. Children with progressive disease can survive for significant periods of time with little oral intake and have minimal complaints during their last days or weeks of life. Comfort medications, such as morphine or benzodiazepines, are infrequently needed because of limited nutritional intake.

A reduced fluid intake can lessen distressing symptoms such as nausea, vomiting, cerebral oedema, excessive secretions and urinary incontinence while maintaining artificial hydration can aggravate such symptoms.[31, 90]

The family require a careful and sensitive discussion on the reasons for considering limiting or withdrawing food and fluids, with the focus being the goal of improving distressing symptoms. It can be helpful to work with a dietician who has experience with paediatric palliative care to help the family understand the changing goals. If the family remain resistant to the idea then a three–day trial reduction in feed volume of 25 percent to 50 percent may provide objective evidence to gain their confidence and improve rapport.

Consideration should be given to cultural influences where provision of nutrition and food has significant meaning and where limiting nutritional intake can be a challenging concept to understand and adhere to.

Goals of care

In patients with non-cancer life-limiting illnesses, the occurrence of episodes of severe respiratory symptoms is often the point at which issues around resuscitation come sharply into focus. However, it is important to recognise that for many children, there may have been numerous previous episodes of severe respiratory symptoms from which the child has recovered well despite predictions otherwise from treating health care professionals. Severe respiratory symptoms are also relatively common in children dying from cancer.

Whether severe respiratory symptoms occur at home or in the hospital, a common question to be addressed is whether the patient is to be 'resuscitated'. These discussions will require the parents or care-givers to indicate whether the child is to be intubated, ventilated (via tube or via non-invasive ventilation – see below). There will also need to be discussion about location of care at these times and whether care in an Intensive Care Unit or retrieval to another hospital is to be considered.

Another aspect of these discussions relates to the risks and benefits of investigations, interventions and symptom management as part of the treatment plan for the respiratory symptoms. There is often discussion around the extent of monitoring and what is to be done if the child's vital observations fall outside normal parameters. Many parents will also wish to monitor their child's oxygen saturations and other vital signs at home (especially at night). Monitoring equipment is not routinely provided for this and the discussions in relation to these requests can be quite challenging. The key is to validate parental concerns and re-affirm their skills at detecting or observing deterioration in their child without the presence of technology.

DYSPNOEA

Dyspnoea (breathlessness or shortness of breath) is relatively common in children with life limiting illnesses. Dyspnoea may reflect deterioration or may be intermittent and/or reversible. At times dyspnoea may be so severe as to constitute a palliative care emergency. It frequently occurs in conjunction with other symptoms and is almost always associated with anxiety, for both child and family. Causes of breathlessness include respiratory and non-respiratory system related conditions. The types of conditions which affect the respiratory system include infection, inflammation, fluid accumulation and problems with the muscles for breathing or the structure of the chest wall (see Table 13).

Emergency management of severe dyspnoea

- Determine resuscitation status and underlying disease status.
- Correct easily reversible causes.
- Position patient sitting up if possible.
- Oxygen if tolerated.
- Suction secretions if indicated (and used with care).
- Morphine 0.05mg/kg parenterally, repeat in 15minutes (if given iv) or 30 minutes (if given subcutaneously) if dyspnoea not settling.
- Midazolam 0.05mg/kg parenterally or clonazepam drops (2.5mg/mL) 0.01mg/kg buccally for anxiety/distress – repeat if necessary.

Specific treatment

Some causes are reversible with relatively simple measures. For example, a short course of antibiotics may be appropriate for the management of infection, and analgesia will alleviate dyspnoea related to pain. Packed cell transfusion may be considered in individual situations when anaemia may be contributing to dyspnoea.

A course of intravenous antibiotics may be appropriate for pneumonia but this will depend upon a number of factors including parental wishes, prior performance status and disease trajectory, and ease of obtaining intravenous access. Parents will often opt for enteral antibiotics for pneumonia if they have adopted a more palliative approach for their child.

Pleural effusions in children with non-cancer conditions are less common than in the setting of a cancer diagnosis. Management should be discussed with a respiratory paediatrician.

TABLE 13 Causes of breathlessness

Respiratory	*Non-Respiratory*
Airway obstruction – lower or upper	Mediastinal disease
Chest wall deformity such as severe scoliosis	SVC obstruction
Rib fractures (with or without pneumothorax)	Cardiac disease/congenital heart disease
Respiratory muscle dysfunction including generalised muscle weakness (e.g. Spinal Muscular Atrophy) or phrenic nerve palsy	Metabolic causes including metabolic acidosis
Pleural effusion – inflammatory, cardiac, hypoalbuminaemia, malignant	Cerebral causes including raised intracranial pressure
Atelectasis and mucous plugging	Elevated diaphragm:
Asthma	- Ascites
Bronchiectasis	- Abdominal distension
Infection (viral pneumonitis/pneumonia)	Anaemia
Pneumothorax	Anxiety
Pulmonary oedema	Pain
Interstitial lung disease (idiopathic, chemotherapy, radiation)	
Pulmonary embolism	
Pulmonary hypertension	

In a child with a known cardiac condition, respiratory symptoms can sometimes be eased with titration of medications including diuretics. This should be done in consultation with the child's cardiologist.

Supportive measures

Simple measures are often helpful at reducing the sensation of breathlessness. The child and family should be managed in calm and reassuring manner, as anxiety will contribute to the degree of dyspnoea. Breathing exercises and relaxation techniques may be beneficial to the older child. Increasing air movement with a portable fan and improving ventilation in the room by opening windows are simple, often helpful steps. Positioning the child in a comfortable and upright position in bed or chair will also aid breathlessness. Breathlessness is often accompanied by tachypnoea and mouth breathing which can lead to a dry and painful mouth. Simple measures directed toward keeping the mouth and lips moist will help. Humidification of room air may also be beneficial.

Drug therapy

Bronchodilators

If bronchospasm is present, or if there is a history of asthma, a trial of bronchodilators is indicated. Salbutamol (Ventolin®) via a spacer or nebuliser is simple to deliver and will aid in reversible airways disease.

Corticosteroids

Corticosteroids (either inhaled or systemic) are also effective and can be used in addition to bronchodilators in children who have a component of bronchial hyper-reactivity.

Prolonged therapy with steroids is not generally indicated, as their effect is not sustained and the side effects can be significant.

Opioids

Opioids moderate the reflexive drive to breathe and decrease patient awareness of dyspnoea. They may also improve the efficiency of breathing and exercise endurance.[32] Opioids, commenced at low dose and increased as required, may be given as required to children with intermittent dyspnoea or regularly for those with persistent breathlessness.

The best evidence is for morphine for the management of breathlessness. It is unclear whether other opioids are as effective as morphine and therefore morphine should be used as first line agent in this setting unless there is a compelling medical reason to the contrary. Oral/enteral, subcutaneous or nebulised morphine can be used. There is no proven advantage in administration of nebulised morphine over other routes of administration. However, some children do find this route of delivery beneficial.

The dose of morphine required for relief of dyspnoea is usually lower than that required for analgesia. In opioid naïve patients, a suggested starting dose would be 0.1mg/kg/dose orally/via PEG or 0.05mg/kg/dose subcutaneously or intravenously. Dosing intervals need to be determined on the basis of severity of dyspnoea, renal function and other clinical considerations. Morphine can be combined with midazolam (see below) in a subcutaneous infusion to relieve respiratory symptoms, particularly in the terminal phase.

Anxiolytics

The sensation of breathlessness can be very frightening and a small dose of oral diazepam (0.04–0.2mg/kg q8h) is often helpful to reduce associated anxiety. Optimising general symptom control, particularly pain, will also reduce the level of anxiety. Midazolam (0.1mg/kg intravenously or sub-cutaneously OR 0.3mg/kg buccally) decreases anxiety, agitation and distress in the child with dyspnoea.

Oxygen therapy

Many children with non-cancer diagnoses will have long-term respiratory issues where supplemental oxygen may be required either continuously or at times of respiratory illness. Many have chronically low oxygen saturations which they tolerate with no respiratory distress. The decision to administer oxygen on increased oxygen flow rates should be made in consultation with the child's parents.

Some children have chronic Type 2 respiratory failure and oxygen flow rates will have to be carefully considered to avoid hypercarbia. The decision to initiate and continue oxygen therapy in hospital should not be made based only on oxygen saturation readings but with consideration of level of dyspnoea, tolerability of oxygen mask or nasal cannula and child and parental wishes.

Home oxygen

Administration of supplemental oxygen in the home setting has additional complexities. The first issue is to determine whether supplemental oxygen will be required for a short period only (usually for end-of-life care) or whether it is likely provision will need to be long term.

Different funding pathways and equipment provision entities will be required for each child. Oxygen should be discontinued if there is no definite benefit noted.

Oxygen concentrators are useful for home use and are connected to a domestic power supply (rebates may be available from electricity suppliers for these). It is advisable to notify the electricity provider that the patient is receiving home oxygen to ensure their power is prioritised in the event of a power outage.

The use of oxygen prior to walking to the toilet or bathing may be all that is required. The maximum flow is 5L/min via mask or nasal prongs. This flow is sufficient for the majority of children but if a greater flow is needed an oxymiser nasal cannula can be obtained for use and allow a greater concentration of oxygen to be delivered. Portable oxygen concentrators are available but usually must be privately purchased.

Portable oxygen cylinders are also available and allow the child and family to leave the house. Care is needed when travelling with cylinders in the car as they need to be securely transported. A "C" size cylinder lasts for 2–3 hours at 2L/min. Reservoir cannulas or pendants conserve oxygen use such that oxygen is only used on inspiration however these are not routinely used for children as the child's inspiratory effort may be insufficient to trigger oxygen flow.

It is important to advise parents to ensure that no-one smokes close to the patient, near the source of the oxygen or anywhere inside as there is a significant explosion risk associated with oxygen concentrators and cylinders within the home.

COUGH

Many of the conditions causing dyspnoea will also produce cough. Cough results from irritation to the receptors in the upper or lower respiratory tract, the pleura, pericardium or diaphragm. Avoidance of irritants, the use of antihistamine or anticholinergic agents for post-nasal drip and antibiotics may provide symptomatic relief. Simple linctus will soothe the throat and reduce dry cough. For children with persistent dry cough, suppression is indicated. Opioids, due to their central action, are the treatment of choice. If a child is already receiving morphine for pain relief, increasing the total dose may be effective.

Bronchospasm can also contribute to cough and should be treated with nebulised or inhaled Salbutamol (Ventolin®). Nebulised saline is an effective mucolytic agent while nebulised local anaesthetic agents may be of benefit for intractable cough. Lignocaine 2% or bupivicaine 0.25%, 5ml via nebuliser every 4–6 hours can be used. **It is important to recognise that the gag reflex will also be impaired after this treatment. It is advisable not to eat or drink for 1–2 hours after.**

Non-pharmacological management strategies include humidification or use of a vaporiser in the child's bedroom. Cough related to pulmonary congestion can be eased with more upright positioning. Cold drinks should be avoided as these can trigger a coughing spasm.

Heart failure and pulmonary oedema

It is rare for a child who does not have known congenital heart disease to develop left sided heart failure or congestive cardiac failure.

If this is clinically thought to be occurring then frusemide (Lasix®) 0.5mg/kg sub-cutaneously can be given and repeated 4–6th hourly if necessary.

Acute pulmonary oedema is an emergency and should be treated with frusemide, morphine, oxygen, and positioning. Non-invasive ventilation may be helpful if available and indicated depending upon the stage of the child's illness.

In the case of a child with known congenital heart disease and deteriorating cardiac function, advice of the treating cardiologist should be obtained.

Home ventilation and tracheostomies

It is exceptionally rare for children to have home invasive ventilation and this topic is not covered further here. It is increasingly common that children with tracheostomies are referred to Palliative Care Services. Tracheostomy issues are best guided by Ear Nose and Throat (ENT) Surgeons and nursing staff, and are beyond the scope of this document.

Children with non-cancer life-threatening illnesses may have been commenced on home non-invasive ventilation (Continuous positive airway pressure [CPAP]/Bi-Level Positive Airway Pressure [BiPAP]/ Variable positive airway pressure [vPAP]) for sleep-disordered breathing or other indications, which may be used continuously, nocturnally or only when unwell.

Common issues arising from this intervention include:

- Navigating goals of care and escalation of intervention issues.
- Tolerability of non-invasive ventilation.
- Risk of aspiration.
- Equipment related issues including ill-fitting mask with leaks and/or pressure areas.
- Expert advice should be sought from a Respiratory Paediatrician for issues related to home ventilation.

Careful discussion with the respiratory team and family is required if decreasing the settings or cessation of ventilatory support seems appropriate due to disease progression.

EXCESS SECRETIONS

Gentle suction and physiotherapy can also have a role in managing secretions for patients at all stages of palliative care. Other non-pharmacological management strategies include regular positioning to allow secretions to drain, in combination with meticulous mouth care.

Hyoscine hydrobromide can be administered subcutaneously as a bolus (0.2–0.4mg every 4 hours) or by infusion (0.6–1.2mg over 24 hours). Glycopyrrolate (Robinul®) (4–10µg/kg q6h; max 0.4mg) also has anticholinergic properties and has a selective and prolonged effect on salivary and sweat gland secretions. Glycopyrrolate can be administered subcutaneously or intravenously, and is also compatible with morphine and midazolam. Consideration of the use of glycopyrrolate should be given if there is an inadequate response from hyoscine. Atropine (1% or 10mg/ml) drops are also an option as they are readily available in community pharmacies and can be administered sublingually (commencing with one drop every four hours). Atropine can cause bradycardia with repeated dosing.

ANAEMIA

Children with incurable leukaemia almost always develop significant anaemia. One of the most common sites of metastatic disease in children with cancer is the bone marrow. Consequently, anaemia is frequently seen as a complication in children receiving palliative care for cancer diagnoses. Children with non-cancer conditions can have anaemia due to chronic disease, nutritional deficiency, or blood loss due to various causes.

Decisions regarding red cell transfusion should be made on an individual basis and will depend upon the stage, life expectancy and symptoms of the child. If anaemia is interfering with the child's activity level causing tiredness, headache or irritability, whilst they otherwise are experiencing a reasonable quality of life, transfusion of packed cells may be appropriate. Packed cell transfusions can also be beneficial if the child has a special planned outing or activity arranged. However, as the disease progresses and the general activity level of the child is reduced, anaemia will be less symptomatic and any potential benefit of transfusion should be re-evaluated, especially with regards to the travel required to the hospital facility for transfusions. Discussion with the family regarding the value of ongoing transfusion should take place as it becomes evident that further transfusions are not appropriate.

BLEEDING

Thrombocytopaenia can be due to primary bone marrow infiltration or failure, hypersplenism or medications. Significant thrombocytopaenia may lead to spontaneous or easy bleeding. Bleeding can also occur due to coagulopathy secondary to liver disease, nutritional deficiencies, disseminated intravascular coagulation or drugs – especially NSAIDs and steroids.

During curative treatment platelet transfusions are given to children when the platelet count drops below a defined level. As disease progresses, platelet transfusions are reserved for cases of significant bleeding such as epistaxis, bleeding gums or gastrointestinal bleeding. The decision to transfuse with platelets should be based on each individual patient, discussed with the family and reviewed regularly.

Generally children and parents are prepared to come to hospital for platelet transfusions. However, as the child's disease progresses trips to hospital can be a major ordeal, both physically and psychologically. It is in these circumstances that the feasibility of delivering platelets at home could be considered. There are blood and blood product standards developed by the Australian Commission on Safety and Quality in Health Care. These standards must be adhered to within the palliative care context. Therefore, there may be some limitations on availability of blood and blood products for transfusion in regional, rural and home settings. These practical issues need exploring prior to incorporating transfusions into the child's management plan.

However, it is possible to administer platelets at home, if suitable experienced support is available. Transfusion reactions including anaphylaxis are the main side effects of platelet transfusions.

To minimise transfusion reactions at home, all children receiving platelets should receive pre-medications (e.g. promethazine and hydrocortisone) and have platelets infused via a platelet leucocyte filter. Medications should also be available to treat anaphylaxis.

Bruising and petechiae are common with thrombocytopaenia and coagulopathy. Catastrophic bleeding is unusual, but active bleeding is a very distressing event for the child and family, and prevention of major bleeding episodes should be attempted. Subconjunctival haemorrhages are obvious and frightening, but the child and family should be reassured that these bleeds are not life or vision threatening and do not require treatment. In the case of epistaxis, application of gentle pressure to the bridge of the nose, or icepacks on the back of the neck, will stem most episodes. Oozing from mucosal surfaces can lead to bleeding gums, dark stools, haematuria and rectal bleeding. Tranexamic acid (Cyklocapron® 20mg/kg q8h) may be given to help stabilise clots that form over the bleeding area. This can be given orally or as a mouth wash for mouth bleeds (500mg tablet dissolved in 5ml). Bleeding from ulcerated areas on the skin or peri-anally can usually be settled with topical 1:1000 adrenaline. Sucralfate dispersed in water-soluble gel can also be used topically to control local bleeding or oozing.

For major bleeding when death is imminent, treatment should be directed at calming the family and simple supportive measures. Bleeding generally lessens as the blood pressure and cardiac output drops. The use of dark coloured bedding and towels to disguise the extent of bleeding and the use of disposable pads and nappies can be helpful. If the child is aware, appropriate analgesia and sedation should be administered to relieve distress. It is helpful to have medications such as morphine, midazolam and adrenaline soaked dressings available in the home. If major bleeding is anticipated, it can be helpful to have a sensitive conversation with the family about how this distressing symptom can best be managed.

ANXIETY

All children will experience anxiety during the treatment of their life-threatening or life-limiting condition and when deterioration occurs this may be significantly exacerbated. Fear of the unknown, or of potential symptoms and suffering, will cause agitation in both the child and family. Anxiety is a normal response to these issues. Communicating with the child and family will help allay some fears, but occasionally anxiolytics may be of benefit. The use of a hypnotic such as temazepam (Normison®/Temaze®) at night will be helpful for some children and adolescents. Lorazepam (Ativan®) (0.02–0.06mg/kg q8–24h) is an intermediate acting benzodiazepine, can reduce anxiety and may be helpful in addition to being a hypnotic. Antidepressant medications can be helpful and are usually prescribed after liaison with the psychiatry team. Relaxation techniques, distraction, music and meditation for older children will reduce levels of anxiety. Members of the allied health team can assist with the provision of some of these strategies.

What do we do if he has a fit?
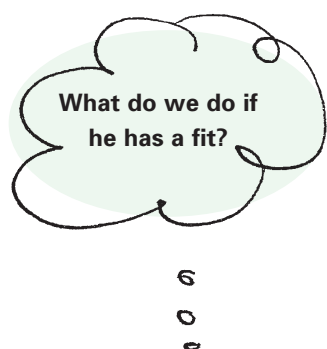
SEIZURES

Even brief generalised seizures can be very distressing for parents to witness, and the family should be prepared for such a possibility.

As with other symptoms, knowledge of the patient's past history and an understanding of the natural history of the underlying disease will suggest which children may be at risk (Table 14).

TABLE 14 Causes of seizures

Brain tumours – primary, metastatic or meningeal lesions
Raised intracranial pressure
Intracranial haemorrhage
Metabolic disturbances
- hypoglycaemia
- hyponatraemia
- hypocalcaemia
- hepatic encephalopathy
Infection and fever
Pre-existing epilepsy

Treatment

Children who have a history of epilepsy or previous seizures will usually be on anticonvulsants and these should be continued. However, control of seizures may be lost if the child becomes unable to tolerate medication. Phenytoin (Dilantin®), however, has a relatively long half-life and levels may not fall until several doses have been missed (Table 15).[59]

Buccal or intranasal Midazolam is a good first line agent for breakthrough seizure management where seizures are not controlled by prescribed anticonvulsants. It has been shown to be at least as effective as rectal diazepam in the acute treatment of seizures.[59, 91] Administration via the mouth is more acceptable and convenient and may become the preferred treatment for prolonged seizures that occur outside hospital.[92]

TABLE 15 Treatment of seizures

Emergency treatment
Diazepam 0.2–0.4mg/kg IV or PR or
Clonazepam PO drops 0.5mg <10y 1mg >10y IV, SC or PR or
Midazolam 0.1–0.2mg/kg IV or SC
< 20 kg: 0.3–0.5mg/kg buccal or intranasal
> 20 kg: 5–10mg/dose buccal or intranasal

Maintenance treatment – oral
Phenytoin 2mg/kg q6–12h or
Phenobarbitone 2.5mg/kg q12h
Carbamazepine 2mg/kg q8h

Continuous treatment when oral route not possible
Diazepam PR (5mg 1–5yrs, 10mg >5yrs) as required Midazolam 50–150micrograms/kg/h (1mg/kg–4mg/kg 24h). A starting dose is often 10–30mg/24 hours by SC infusion, increasing as required

The buccal or intranasal dose is the same as the oral dose of midazolam used for sedation (0.3–0.5mg/kg per dose, maximum dose 10mg). It is helpful to have a supply of oral midazolam or rectal diazepam in the home for emergency use for fitting or agitation, as they are safe and easily administered by carers. A seizure management plan with clear guidelines of when to call for further assistance or medication advice is necessary. When prescribing midazolam, specify plastic vials if available, as these will be easier to manage in this situation. Subcutaneous or intramuscular diazepam should be avoided because of local irritation and poor drug availability.

Oral clonazepam drops can be administered sublingually and may be useful for diazepam resistant seizures. Clonazepam may increase oral secretions and thus this needs to be taken into account especially when given regularly. If further seizures are likely, regular oral or subcutaneous anticonvulsants should be commenced. Oral phenytoin (Dilantin®) or phenobarbitone can be given as maintenance therapy.

If the child is unable to tolerate oral drugs, alternative routes and drugs will be required if seizures are a possibility. Midazolam is easily prepared and can be administered subcutaneously. It is compatible with morphine and also has an anxiolytic and sedating effect. If seizures occur despite a continuous infusion, boluses of midazolam can be given followed by an increase in the dose of infused midazolam. Increasing doses will generally obtain control over seizures. Phenobarbitone and clonazepam are also effective anticonvulsants, and can be administered subcutaneously if necessary. It is recommended these medications are titrated by a specialist team.

MUSCLE SPASM AND MYOCLONUS

Muscle spasm can occur as a result of immobility, pain, neuropathic spasm or cramp. Appropriate analgesia will reduce the protective muscle spasm effect. Low dose diazepam (Valium®) (0.1mg/kg/dose) can also be considered if muscle spasm is causing pain. Encouraging mobility or changing position regularly in children with little energy will also reduce spasm and the development of painful contractures.

For long term treatment of spasm, baclofen can be considered. The main concerns with baclofen are a possible reduction in seizure threshold and

potential adverse effects on swallow and airway protection. Involvement of a paediatric rehabilitation specialist or neurologist is helpful in this context. Localised spasticity can sometimes be managed with Botulinum toxin (Botox®) injections. For patients with severe spasticity, an intrathecal baclofen pump can considered.

Myoclonus is involuntary twitching involving single muscles or groups of muscles. It is a recognised toxic effect of opioids, occurring more frequently if pethidine is used.[90] It is more common in the terminal phase of illnesses and in those with underlying renal impairment especially with morphine use due to the build-up of secondary toxic metabolites. Treatment includes reduction of the dose of opioid, if possible, or change to an alternative drug. Midazolam as a bolus or infusion is usually effective in controlling myoclonus.

IRRITABILITY AND AGITATION

There are many causes of irritability and agitation, many of which may be treatable (see Table 16). Reversible conditions can be managed appropriately but cerebral irritability can be difficult to manage with distress and inconsolability lasting for hours.

Gabapentin (Neurontin®) can be considered to manage distress, anxiety and pain. It is effective for cerebral irritability, visceral hyperalgesia and autonomic dysfunction.[93] It comes only as an oral preparation (capsules) but these can be split and the contents administered via NGT/PEG tubes. There are minimal-to-no interactions with other medications. It is renally excreted and the dose should to be adjusted in renal impairment.

Gabapentin Dosing

Day 1:   5–10/mg/kg (maximum dose 300mg).

Day 2:   5–10mg/kg twice daily.

Day 3 onwards: 5–10mg/kg three times daily.

For marked distress, levopromazine, clonidine or chloral hydrate can be used.

Buccal midazolam (0.3–0.5mg/kg) can be used in a crisis situation to break the cycle of distress. This should not be considered for ongoing treatment of distress, but an option for crisis management.

In cases where irritability and behaviour disturbance are causing significant burden to the family, it can be helpful to consult with a psychiatrist for evaluation and guidance on whether psychotropic medications may be of assistance.

Non-pharmacological management strategies may include:

- A calm and quiet environment.
- Reassurance by touch and the voice of familiar people.
- Use of senses that are intact e.g. reading a story or music (auditory).
- Assess and manage a full bladder.
- Assess and manage pain.

ACUTE DYSTONIC CRISIS

An acute dystonic crisis is characterised by facial and skeletal muscle spasms and oculogyric crises. Acute dystonic reactions are usually a consequence of antiemetics which block central dopamine receptors. These reactions are commoner in children, especially girls and, generally occur within a few days of starting treatment and may take 24hrs to subside after stopping the drug.

TABLE 16 Sources of pain/irritability in children with neurologic impairment

Somatic pain	
Head, eyes, ears, nose, throat	Headaches, VP shunt malfunction, otitis, corneal abrasion, sinusitis, pharyngitis, corneal abrasion, glaucoma, dental pain
Musculoskeletal	Chronic/acute musculoskeletal pain, spasticity, hip dislocation, fracture, osteomyelitis
Gastrointestinal	Gastro-esophageal reflux, esophagitis, pancreatitis (associated with hypothermia and valproate), ulcer, gallstones, cholecystitis, constipation, rectal fissure, food allergy, retching and vomiting
Renal	Urinary tract infection/pyelonephritis, neuropathic bladder, obstructive uropathy, renal stones (associated with ketogenic diet and topiramate)
Respiratory	Aspiration, reactive airway, costochondritis
Genito-urinary	Testicular/ovarian torsion, inguinal hernia, menstrual cramps
Skin	Pressure sore
General	Medication toxicity, sleep disturbance, obstructive apnoea
Neuropathic pain	
General neuropathic pain	Suggested by pain that appears out of proportion to an identified source or pain behaviours that develop weeks to months following surgery
Visceral hyperalgesia and Central pain	Suggested by pain and/or retching associated with gastric and intestinal feedings, intestinal gas, flatus, and bowel movements
Autonomic dysfunction	Suggested by sweating, increased salivation, flushing or pallor of skin, retching, vomiting, pain localized to the abdomen, agitation, arching, stiffening
Cerebral irritability	Diagnosis of exclusion. May be a feature of severe birth asphyxia and neurodegenerative conditions

Drugs that may cause Acute Dystonic Crisis:

- Metoclopramide (Maxolon®)
- Haloperidol (Seranace®)
- Levomepromazine (Nozinan®)
- Risperidone (Risperdal®)
- Prochlorperazine (Stemetil®)

Acute treatment for symptom relief can be achieved with IV diazepam. For specific treatment, IV/IM benztropine (Cogentin®) 0.02mg/kg (max 1mg) either intramuscularly or intravenously is recommended. This can be repeated once, but if the intramuscular route is used, allow 30 minutes to elapse before repeating. The same dose should be given orally, twice daily for the next 24–48 hours to prevent recurrence.[94]

Dystonia as a chronic symptom is treated with various drugs and is mainly dealt with in conjunction with neurologists.

INSOMNIA

Sleep disturbance is common in children with life-threatening illness. The aetiology of insomnia is multi-factorial and is often a combination of physical, psychological and perhaps environmental factors. When depression or anxiety is a factor, consideration should be given to psychotherapy and pharmacologic treatment.

Lifestyle changes, including improved sleep hygiene and exercise may be helpful to improve sleep. Staff caring for patients in the hospital and hospice settings should reduce interruptions, noise and light as much as possible.

Low dose amitriptyline (Endep®) can be helpful as a pharmacologic agent for the management of insomnia in terminally ill children, particularly if neuropathic pain is also present. When clinically indicated, management of persistent pain with a background infusion of opioid or oral controlled release opioid preparation will enhance sleep and minimise the need for breakthrough analgesia. Melatonin can also be considered, particularly in children with neurological conditions and those with an altered circadian rhythm. Stronger sedative medications or psychotherapeutic agents may be required in very severe cases.[21]

The care of a child or young person with End Stage Renal Disease (ESRD) can be challenging and complex. This may include managing co-morbidities, ESRD-related symptoms, renal replacement therapy (RRT) or conservative supportive care. Supportive care needs to be offered to all patients with progressive end stage renal disease and those with a poor prognosis. An integrated early palliative approach may improve the symptom burden for patients pursing active dialysis.[95]

ESRD is the state in which a patient's renal dysfunction has progressed to the point at which homeostasis and survival can no longer be sustained by the native kidney and maximum medical management. RRT or pre-emptive transplantation may be required. Continual dialysis is based on a combination of biochemical abnormalities and clinical factors which include refractory fluid overload, electrolyte imbalance, acidosis, growth failure, uraemic symptoms and impaired school performance.[96]

Palliative care in ESRD can be initiated whilst the patient requires RRT, such as dialysis or transplantation, and withdrawn if the child or young person improves. RRT may be necessary not only to prolong life, but to maintain a patient's quality of life at an acceptable level. In patients still receiving RRT, palliative care plays a supportive role.

Early integration of palliative care also facilitates discussions about transition to palliation in patients where renal replacement therapy is discontinued because it is thought not to be in the child's best interests. The palliative care team can help with discussions regarding discontinuation or abatement of dialysis, and end of life care.

The median survival time after stopping dialysis is variable and depends on co-morbidities and the rate of decline in renal function. Abatement of dialysis is a less common occurrence in paediatric palliative care compared to adult practice.

Decisions regarding whether to offer or continue dialysis should consider the following factors:

- Prognosis – which can be uncertain and unpredictable.
- Symptoms associated with ESRD.
- Reduction in dose or cessation of medication because of the diminished renal function to avoid accumulation of metabolites.
- Dietary and fluid restrictions.
- Place of end of life care and advanced care plans.
- The severity of other co-morbidities e.g. other organ failure.

In some circumstances, the decision to stop dialysis may not be elective due to contra-indications for continuing either peritoneal dialysis or haemo-dialysis (e.g. difficulty maintaining vascular access). Alternatively, a sudden deterioration (e.g. infection and sepsis resistant to antibiotic therapy) is also possible.

While renal transplantation can be offered to many children, it may not always be possible depending upon the size of the child, availability of donor kidneys and presence of other co-morbidities (e.g. liver or heart failure). Further, it is also possible that a renal transplant may fail or be rejected. Options at the time of renal transplant failure include re-commencement of RRT, consideration of a further transplant and sometimes supportive care only.

Symptom management in End Stage Renal Disease

Symptomatic management for patients with ESRD is usually managed by the nephrologists. Palliative care specialists help in the management of difficult symptoms which are also commonly encountered in other end-stage conditions. ESRD-related symptoms can include pain, dyspnoea, anorexia, nausea, pruritus, peripheral oedema or difficulty with sleep. Symptoms related to the CNS can include malaise, confusion, apathy, twitching, seizures, stupor and coma. Psychological symptoms can include depression and anxiety. Management and treatment of these symptoms are discussed elsewhere in this book.

It is hoped that both health professionals and parents can mutually agree upon various interventions that could or should be offered to the child. This involves balancing benefits and burdens of various interventions with a focus on the child's quality of life. This is often a process and requires multiple discussions. Not all families are able to make these difficult decisions and an approach that is flexible and patient and family centred should be taken. Discussions and decisions around management of issues such as fluid balance (including albumin infusions) and whether it is appropriate to continue performing blood tests (e.g. monitoring of electrolytes) are important to consider in light of the parent's preferences and child's quality of life.

The symptom management of children with ESRD who are dying will require reduced dosing and frequency of medications. Children with ESRD who are dying require half the recommended dose of glycopyrrolate to manage secretions. The presence of terminal agitation is usually managed by a reduced dose of midazolam with an increased dose interval to avoid excessive drowsiness.[95] Fentanyl is the opioid of choice for pain or dyspnoea. Other opioids such as oxycodone and hydromorphone can be used short term if fentanyl is not available. They should be used with caution starting at a low dose and reduced frequency.[97, 98] They should be given on an "as required" basis at the commencement of therapy, rather than regularly or as an infusion, particularly at the commencement of therapy.[95] Methadone and buprenorphine are opioids that are safe to use in renal failure. Methadone and fentanyl are not readily dialyzable.[98, 99]

Dermatologic conditions in paediatric palliative care

Dermatological conditions and symptoms in paediatric palliative care are common. Symptoms can be distressing for the child and parents. Children with life-limiting illnesses, like other children, are prone to skin conditions.[3, 21] Commonly occurring skin problems include itch, rashes, skin ulcers or skin infections. Dermatological symptoms are often attributed to the underlying medical condition, or complications related to treatment. Management may require a multidisciplinary approach especially in the presence of pain or itch which can be difficult to manage. Symptoms amenable to treatment may be relieved by collaboration with a dermatologist. Some symptom presentations may not be obvious and require a high index of suspicion, especially in the unsettled non-verbal child. Commonly occurring symptoms are discussed below.

PRURITUS

Pruritus or itch is an unpleasant cutaneous sensation that provokes the desire to scratch.[21] Its presence can be both distressing and difficult to manage. The pathophysiological mechanism of pruritus is complex and it involves activation of C-fibres in the skin through mechanical stimuli, or chemical substances such as histamine and several other substances. Neuronal mechanisms have also been identified in the pathophysiology of itch. Neuropathic analgesics, such as gabapentin and pregabalin, have been shown to be efficacious antipruritic therapeutic options. Although further research is required, gabapentin is safe and has been found to be effective in pruritus related to uraemia, cancer, opioid medication and burn injury.[100, 101]

There are numerous causes of pruritus which include dermatologic conditions, systemic disease, neurologic conditions, uraemia, biliary obstruction, medication side effects, dry skin and psychological factors. Management includes a through history to determine the cause, physical examination to evaluate the skin and appropriate investigations which may include a skin biopsy. Some causes of pruritus are discussed below.

Dry skin

Dry skin can cause or exacerbate pruritus. The commonest cause of dry skin in children is atopic dermatitis, also known as atopic eczema. The aetiology of atopic dermatitis includes a complex interplay of genetic and environmental factors and there is no single cause. Another cause of dry skin includes Ichthyosis, a genetic skin disorder, that presents at or shortly after birth and persists throughout life. This usually presents with a chronically dry, scaly skin. Dry skin can present in a spectrum of other medical conditions and can also be associated with dehydration.[21] The mainstay of dry skin treatment is keeping the skin moist with oil based emollients.

Opioid induced pruritus

The incidence of opioid induced pruritus is variable and commonly seen with the parenteral use of opioids.[21] The pruritus is mainly localised to the face and trunk. The exact mechanism by which opioids cause pruritus is not known. Treatment may require switching opioids.[45] Alternatively, a low dose opioid receptor antagonist, such as naloxone, can be trialled.[78] Other treatment alternatives are serotonin receptor antagonists (e.g. ondanestron)[102] and dopamine (D_2) receptor antagonists (e.g. droperidol).

Cholestasis

The mechanism of cholestasis induced pruritus is unclear. Circulating bile acids and endogenous opioids are thought to play a role. The main management of this pruritus involves decreasing the level of circulating bile acids.[102] Bile acids are reduced by using cholestyramine, rifampicin or phenobarbitone. Other therapies that have been shown to be effective include opioid antagonists such as naloxone and naltrexone.[21, 78] In some instances surgical interventions may be helpful. Interventions include partial external biliary diversion, stenting of the bile duct and terminal ileal exclusion in patients with intrahepatic cholestatsis.[21]

Uraemia

Uraemia induced pruritus is seen commonly in patients with chronic renal failure receiving dialysis.[21] Therapeutic measures include an enhanced dialysis regimen, correcting any electrolyte abnormalities, and treating hyperparathyroidism. Recent new therapies that have been successfully trialled include the use of gabapentin and UV- B therapy.

General measures for treating pruritus

- Treat the underlying medical conditions.
- Shorter bath times and the use of lukewarm water, with mild or low pH soaps, and the addition of sodium bicarbonate to the bath.
- Use of bath oil or soap substitute such as aqueous cream, bath washes, hydrating or moisturising lotions, and soap free cleansing bars.
- Use shampoo substitute (e.g. oatmeal shampoos).

- Keep the skin moist by regular use of emollients. There are a variety of emollients. Examples include Glycerol 10% in sorbolene cream and aqueous cream (aqueous cream strength can be varied by adding liquid paraffin, white soft paraffin, or olive oil). Urea based creams are useful for very dry skin or coexisting ichthyosis.
- Maintain a cool ambient temperature and avoid rapid temperature changes.
- Prevent the child scratching. Keep the fingernails short, use mittens to cover the hands.

Pharmacological treatment of pruritus

Topical corticosteroids are used for the treatment of atopic dermatitis. Ointment based creams are better at maintaining moisture and the use of wet dressings is recommended if there is severe inflammation and thickened skin. Resistant cases can be referred to a paediatric dermatologist and may require treatment with topical immunosuppressants such as Pimecrolimus.

Antipruritics include either sedating antihistamines (such as promethazine hydrochloride and trimeprazine), or non-sedating antihistamines (such as cetirizine or loratadine). The sedative effects can be helpful in calming any agitation associated with pruritus, particularly at night.

The use of some psychotropic medications has also been described in the alleviation of itch e.g.

- Doxepin – tricyclic anti-depressant.
- Paroxetine – selective serotonin uptake inhibitor.
- Mirtazapine – tetracyclic anti-depressant.

PRESSURE ULCERS

Children who are unable to reposition themselves, and who are bed or chair bound are at higher risk of developing pressure ulcers. Pressure ulcers or sores can develop quickly. Areas likely to develop pressure ulcers are the heels, neck, sacrum and scalp. Risk factors that lead to pressure ulcers are a poor nutritional status, conditions leading to moist skin like incontinence, and poor circulation.

Preventive measures include:

• Reposition patients by lifting to avoid shearing forces every two hours for patients that are bedbound, and hourly if chairbound.
• Use pressure reducing mattresses and gel pads.
• Use absorbent nappies for incontinent patients.
• Protect the skin by using barrier creams.
• Avoid letting the skin become dry – use regular moisturiser.
• Examine pressure areas regularly.

Pressure ulcers can be painful and require appropriate analgesia depending on the severity. Refer to the "Pain" section earlier in this book. Good wound care is essential for wound healing and pain control. Hydrocolloid dressings are used to dress shallow ulcers. Some ulcers can become infected and these require antimicrobial dressings, superficial debridement and wound cleansing.[21]

The management of pressure ulcers also depends on the patient's prognosis. In patients with a short life expectancy, managing accompanying symptoms of pain and odour may be more important than healing the ulcer. Odour is often well managed with topical metronidazole gel.[103] Silver sulfadiazine, iodine cleanser or charcoal dressings are other alternative therapies to manage odour. Environmental adjustments to control odours include placing activated charcoal in a container to absorb odour. Alternate smells that can be introduced to the room using aromatherapy include vanilla, citrus or vinegar.

OTHER SKIN CONDITIONS

Nappy rash

There are many factors that contribute to dermatitis confined to the nappy area. These include excessive skin hydration, friction trauma, irritants such as ammonia from urine, soaps and other creams and powders, and local fungal infection. Recommended treatments include frequent nappy changes, use of barrier creams, and treating any associated candida infections.

Skin infections

Skin infections can occur as a complication of wounds or trauma leading to localised infection such as cellulitis. A wound swab should be taken and appropriate antibiotic treatment instituted. Tinea is another common infection in children. Other uncommon skin infections are herpes zoster and herpes simplex.

Hyperhidrosis

There are several causes of hyperhidrosis (excessive sweating) that are seen in children with life-limiting conditions. Causes include psychological factors, familial dysautonomia, Epidermolysis Bullosa, heart failure, metabolic and endocrine conditions (such as hypoglycaemia and hyperthyroidism) and medication side effects.[96] Treating the underlying medical condition (if possible) is the preferred management strategy. Anticholinergics medications can also have a role in management.[96]

Epidermolysis Bullosa

Epidermolysis Bullosa (EB) is an inherited blistering condition with a wide spectrum of disease and prognosis. The skin and mucosa is extremely fragile. The most severe forms are junctional EB and recessive dystrophic EB. Complications (dependent on the type of EB) may include early death, formation of contractures, and increased risk of developing squamous cell carcinoma.

Symptoms of EB include varying severity of pain and gastrointestinal symptoms (including gastro oesophageal reflux) as well as bleeding from mucosal blistering.[3] Rare complications include the development of dilated cardiomyopathy and renal complications. Care of children with EB include gentle baths, use of lubrication to minimise trauma and avoiding heat and high humidity – which help prevent blister formation. Broken skin should be appropriately dressed and antibiotics should be commenced early to prevent infection.[3] Pharmacological and non-pharmacological management strategies should be used to lessen anxiety associated with dressings, and appropriate interventions to manage pain should be used.