Guideline

GUIDELINES FOR THE MANAGEMENT OF THE ACUTE PAINFUL CRISIS IN SICKLE CELL DISEASE

Severe acute pain is the commonest manifestation of sickle cell disease (SCD) requiring hospital admission in Europe and the USA. Although the pain itself is not directly life-threatening, inappropriate treatment leads to unnecessary suffering and potentially fatal complications, related both to the disease and the treatment, and repeated admissions with pain are associated with a higher mortality rate (Platt *et al*, 1994). There are thought to be more than 10 000 patients with SCD in the UK (Streetly *et al*, 1997), the majority of these live in London. Whereas some hospitals see large numbers of patients with SCD and have established protocols and experienced staff, most hospitals will see only a few patients each year. These guidelines aim to provide advice on a basic, minimum standard of care for patients with acute painful crises and SCD, and pay particular attention to adequate analgesia and monitoring for life-threatening complications.

CONDITIONS COVERED BY THESE GUIDELINES

Homozygous sickle cell anaemia (HbSS) is the most common and most severe form of sickle disease in the UK, accounting for about 70% of patients. Compound heterozygotes for HbS and HbC (HbSC) account for the majority of the remainder. Other compound heterozygous states can also produce SCD, most notably HbS/β°thalassaemia, HbS/β^{+}thalassaemia (including HbS/HbLepore), HbS/D^{Punjab}, HbS/O^{Arab}. Sickle cell trait (HbAS) and HbS/(hereditary persistence of fetal haemoglobin) cause symptoms only in very extreme circumstances, and should not be considered as the cause of pain.

METHODS

Medline was searched via PubMed from 1965 to 2001. A number of terms were used in the search including 'sickle' and 'pain'. Haematologists with a known interest in SCD were contacted and asked to submit any hospital guidelines they used for the management of sickle cell pain. Six haematologists with knowledge of SCD prepared an initial draft, based on the literature and available protocols. The draft guideline was submitted to interested parties for comment (see *Acknowledgments*).

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PAIN IN SICKLE CELL DISEASE

Recurrent episodes of acute, severe pain are the hallmark of SCD. The pain is highly variable both within and among patients, and is the result of complex and poorly understood interactions between biological and psychosocial factors. Vaso-occlusion within the bone marrow vasculature leads to bone infarction, which in turn results in the release of inflammatory mediators that activate afferent nerve fibres and cause pain. Although the basic mechanism is simple, the precise details of the vaso-occlusion are poorly understood, involving complex interactions between red cells, endothelium, white cells and platelets. The unpredictability of the pain is a major factor in undermining the patient's ability to cope (Ballas, 1998). Acute pain frequently occurs spontaneously, but may be precipitated by infections, skin cooling, dehydration or stress. Acute pain in SCD is described as throbbing, sharp or gnawing, and patients can usually recognize whether it is typical of their SCD. If the patient thinks the pain is atypical, then other causes of pain should be sought. Acute painful episodes may occur on top of chronic pain, or be precipitated by other painful events, such as cholecystitis. Hospital admissions for acute pain in SCD typically last 4–10 d, but this varies widely.

ARRANGEMENTS FOR ADMISSION TO HOSPITAL

It is thought that the majority of painful episodes are managed at home. Patients and parents should be educated as to when to seek medical help, and their general practitioners (GPs), health visitors and haemoglobinopathy counsellors can play a vital role in this. Many patients present to hospital only when oral analgesia is insufficient or symptoms suggest a serious complication.

Patients should be given clear instructions on how to arrange rapid admission to hospital, either via direct access to a haematology or day ward, through the Accident and Emergency Department, or via the GP. Fast-track admission may be possible in units with larger number of patients, and is generally preferred by patients (Fertleman *et al*, 1997). All units receiving people with acute sickle crises should have a written protocol for fast assessment of pain and rapid safe administration of analgesia. This protocol should state who is responsible for the initial assessment of the patient, e.g. triage nurse, Accident and Emergency doctor, general physician, haematologist. Patients who are admitted frequently should have personalized care plans made available to on-call medical staff. Patients should be given

haemoglobinopathy cards to carry with them, stating their diagnosis and baseline haematological data. Analgesia should be started within 30 min of arrival in hospital after a rapid initial assessment and the pain should be controlled within 60 min of starting analgesia. Nitrous oxide (50%) and oxygen (50%) (Entonox, Equanox) can be used in the ambulance and for the first 30–60 min in hospital, but should not be continued long-term because of the risk of megaloblastic anaemia and neuropathy (Ogundipe *et al*, 1999). Individual patients may find it particularly useful and its short-term use can be included in personalized care plans.

RAPID ASSESSMENT OF A PAINFUL EPISODE

Initial medical assessment does not need to be extensive and should focus on detection of the following medical complications requiring specific therapy: infection, dehydration, acute chest syndrome (fever, tachypnoea, chest pain, hypoxia, chest signs), severe anaemia, cholecystitis, splenic enlargement, abdominal crisis, neurological events (cerebral infarct, cerebral haemorrhage, transient ischaemic attack, seizure) and priapism.

A pain chart should be started, using a pain scale appropriate to the patient's age and cognitive abilities (American Pain Society, 1993). Initially, the patient should be monitored at 20 min intervals for pain, respiratory rate and sedation, until the patient is stable with adequate pain control. Discharge may be possible after a few hours if the pain has settled and there are no complications. Many patients who require repeat doses of opiate analgesia will require hospital admission, although this is not inevitable if day-care facilities are available (Ware *et al*, 1999; Benjamin *et al*, 2000). Ideally, beds should be available on a designated ward with nursing staff trained and experienced in the management of patients with SCD, although this may not be possible in hospitals with very few sickle cell patients. Doctors with a designated interest in SCD should care for the patients. Depending on local circumstances, further multidisciplinary involvement may be appropriate, including pain teams, palliative care, anaesthetists and psychologists.

Recommendations upon admission and for assessment
Sickle cell trait should not be considered as a likely cause of pain (B).

Patients should be issued with cards showing their diagnosis, baseline haematological data and usual analgesic requirements (C).

Nitrous oxide/oxygen (50/50) can be used for pain control in the ambulance but should not be used frequently or for more than 60 min (C).

Analgesia should be given within 30 min of entering the hospital and effective analgesia achieved by 60 min(C).

Pain, respiratory rate and sedation should be assessed every 20 min until pain is controlled (C).

A multidisciplinary approach should be used, involving haematologists, paediatricians, pain teams, anaesthetists, psychologists, physiotherapists and counsellors (C).

PHARMACOLOGICAL MANAGEMENT OF SICKLE PAIN

General approach to pain control

There are no objective measurements of pain severity, and analgesia should be titrated against the patient's reported pain, as recorded on a pain chart. The severity of pain in SCD can vary enormously, requiring a number of different approaches. It is also necessary to try and distinguish between acute and chronic pain. Ideally the choice of drug should be influenced by an individual's analgesic history, and some patients may carry cards with details of their ideal analgesic regimen; often patients will be seen for the first time in a particular hospital and an empirical approach will be necessary.

Initial management should be aimed at providing rapid pain control. Analgesia should then be maintained with long-acting oral or parenteral analgesia, with provision for bolus analgesia if breakthrough pain occurs. The choice of analgesia will depend on how far along the 'analgesic ladder' the patient has already progressed and treatment should generally start with the next 'step-up' (Table I). Once pain is controlled, the underlying cause should be assessed more comprehensively. Further investigations should be undertaken for atypical pain. The patient should be monitored regularly for effectiveness of analgesia, complications of SCD and hypoxia (Table II). There are no large controlled trials of analgesic regimens in SCD; a number of smaller trials have generally failed to produce any optimal regimen (Ballas, 1998)

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)

These drugs are appropriate for mild to moderate pain. The only trials of their use in SCD involve ketorolac, the most potent NSAID. This has been shown to have an equivalent analgesic action to pethidine and morphine in the postoperative setting (Gillis & Brogden, 1997), but there are few studies in SCD. One small randomized controlled trial showed a reduction in pethidine use in children who were also given ketorolac compared with those given pethidine alone (Perlin *et al*, 1994), while a second small randomized controlled trial showed no additional benefit of ketorolac over intravenous morphine (Hardwick *et al*, 1999). Paracetamol is contraindicated in patients with liver failure, and NSAIDs should be used with caution in patients with a history of peptic ulcer, asthma, renal failure or bleeding tendencies. NSAIDs can be used to control mild to moderate

Table I. Pharmacological management of pain using the World Health Organization three-step ladder.

Step 1: mild pain
  Non-opioid ± adjuvant
Step 2: moderate pain
  Weak opioid (or low dose of strong opioid) ± non-opioid ± adjuvant
Step 3: severe pain
  Strong opioid ± non-opioid ± adjuvant

Table II.

(A) Outline of management of acute pain in opioid-naive adults.

1 Rapid clinical assessment
2 If pain severe and oral analgesia not effective, give strong opioids:
  morphine
  0·1 mg/kg i.v./s.c. repeated every 20 min until pain controlled
  Then 0·05–0·1 mg/kg every 2–4 h i.v./s.c./p.o. – consider PCA
  or
  diamorphine
  0·1 mg/kg i.v./s.c. repeated every 20 min until pain controlled
  Then 0·05–0·1 mg/kg every 2–4 h i.v./s.c. – consider PCA
3 Give adjuvant non-opioid analgesia: paracetamol, ibuprofen, diclofenac, ketorolac
4 Prescribe laxatives routinely and other adjuvants as necessary:
  laxatives: lactulose 10 ml/b.i.d., senna 2–4 tablets o.d., docusate 100 mg b.i.d.
  antipruritics: hydroxyzine 25 mg b.i.d.
  antiemetics: prochlorperazine 5–10 mg tds, cyclizine 50 mg tds
  anxiolytic: haloperidol 1–3 mg p.o./i.m. b.i.d.
5 Monitor pain, sedation, vital signs, respiratory rate and oxygen saturations every 30 min until pain controlled and stable, and then every 2 h
6 Give rescue doses of analgesia every 30 min for breakthrough pains: 50% of maintenance dose
7 If respiratory rate less than 10/min, omit maintenance analgesia. If severe respiratory depression/sedation, give 100 μg naloxone i.v., repeating every 2 min as necessary
8 Consider reducing analgesia after 2–3 d and replacing injections with equivalent dose of oral opiate
9 Discharge patient when pain controlled and improving without analgesia or on acceptable doses of oral analgesia
10 Arrange any necessary home care and an outpatient follow-up appointment

(B) Outline of management of acute pain in opioid-naive children.

1 Rapid clinical assessment
2 If pain severe and non-opioids not effective, give opioids:
  Oral regime: oral morphine 0·4 mg/kg p.o., or diamorphine 0·1 mg/kg i.v./i.m./s.c. stat, slow release morphine
  1 mg/kg (rounded up to nearest 5 mg) every 12 h, with oral morphine 0·3 mg/kg every 3 h as necessary.
  If more than three doses oral morphine needed in first 24 h, increase slow release morphine to 1·5 mg/kg every 12 h or consider parenteral opiates
  Parenteral opiates: diamorphine 0·1 mg/kg repeated every 20 min until pain controlled, then diamorphine 0·05–0·1 mg/kg every 2–4 h i.v./s.c. – consider PCA
3 Give adjuvant non-opioid analgesia: paracetamol 20 mg/kg every 6 h, ibuprofen 10 mg/kg tds
4 Prescribe laxatives routinely and other adjuvants as necessary:
  laxatives: lactulose 2·5–10 ml/b.i.d., senna 2–4 tablets o.d.
  antipruritics: hydroxyzine 5–50 mg b.i.d.
  antiemetics: prochlorperazine 250 μg/kg tds, cyclizine 12·5–25 mg tds
5 Monitor pain, sedation, vital signs, respiratory rate, oxygen saturations: every 30 min until pain controlled and stable, and then every 2 h
6 Give rescue doses of analgesia every 30 min for breakthrough pains: 50% of maintenance dose
7 If respiratory rate less than 10/min, omit maintenance analgesia. If severe respiratory depression/sedation, give 10 μg/kg naloxone i.v., followed by 100 μg/kg if no response
8 Consider reducing analgesia after 2–3 d and replacing injections with equivalent dose of oral opiate
9 Discharge patient when pain controlled and improving without analgesia or on acceptable doses of oral analgesia
10 Arrange any necessary home care and outpatient follow-up appointment

pain and may have an additive role in combination with opioids for severe pain. Ketorolac can be given by intramuscular injection, but intramuscular diclofenac should be avoided, as the larger volumes and alkaline pH of this drug can lead to the development of sterile abscesses. The role of cyclo-oxygenase-2 (Cox-2) inhibitors is yet to be established, but they are as effective as other NSAIDs and should be considered in patients with a definite history of peptic ulceration or those who develop gastrointestinal symptoms on conventional NSAIDs.

Opioid analgesia
Opioids are used for severe pain in SCD. Ideally each admission should be treated with an individualized analgesic regimen, accounting for the site and duration of the pain and the patient's history. In practice, this is often not possible, because it is difficult for any one hospital to safely administer a large number of different opioid protocols and detailed information on a patient's analgesic history may not be readily available. All patients on regular opioids should routinely be given laxatives.

Co-proxamol, co-codamol and dihydrocodeine. Co-proxamol and cocodamol are strong, oral, compound analgesics containing paracetamol with dextropropoxyphene and codeine respectively. These can be useful if the pain is moderate and the patient has not already tried them. They are not recommended for use in children and should be used with caution if the patient may have already taken paracetamol. Dihydrocodeine can be used similarly, but contains no paracetamol and can be used in children.

Pethidine. The use of pethidine (meperidine) in SCD is a cause of much conflict in the UK. Pethidine has been used for many years in SCD and continues to be widely prescribed, particularly in the USA (Pegelow, 1992). However, there is increasing concern regarding problems directly related to the use of pethidine. Pethidine is short acting with poor bioavailability and is metabolized to norpethidine, which is a renally excreted cerebral irritant, causing dysphoria, clonus and seizures. It is usually given by repeated, high-dose intramuscular injections and anecdotally this has resulted in severe muscle damage. Pethidine should only be used in exceptional circumstances, when there is a severe allergy to morphine and diamorphine (see later), and no other analgesic regimen is acceptable to the patient. Continuous infusions of pethidine should be avoided and it should not be used for more than 48 h or at doses greater than 600 mg/24 h (American Pain Society, 1999a). After 48 h, the pethidine should be stopped and an alternative opiate used if necessary. It is absolutely contraindicated in certain circumstances (Table III).

Morphine and diamorphine. Morphine and its acetylated derivative diamorphine are the most widely used drugs for severe pain from SCD in the UK. Diamorphine (heroin) has the advantage of being more water and lipid soluble, making it faster acting and easier to inject in small volumes of water. Some patients dislike it because of its association with drug abuse (Clare, 1998) and, for this reason, it is not prescribable in some countries. Although itching commonly occurs with morphine and diamorphine, this is effectively treated by hydroxyzine and is not a reason for using pethidine. Severe allergy includes hypotension, bronchospasm and laryngeal oedema, and is very rare. Morphine can be used similarly to diamorphine parenterally and is the drug of choice for oral administration. Appropriate regimens are given in Table II.

Schedules and routes of administration. Opioids can be given orally, intravenously, by intramuscular injection or subcutaneous injection. Oral analgesia can be used to treat moderate pain prior to deciding on hospital admission and

has been shown to be effective in children after initial intravenous treatment with a single injection (Jacobson *et al*, 1997). Increasingly children are managed solely with oral analgesia and, as these children grow-up, it is likely that oral analgesia will be used to manage the majority of painful episodes in all ages. Intramuscular injections have been widely used in SCD, particularly for giving pethidine. Repeated intramuscular injections can be associated with unpredictable absorption and potentially serious muscle fibrosis, contra-indicating this route of administration. Intravenous analgesia is rapid and avoids absorption problems but repeated venous cannulation can lead to a loss of peripheral venous access. Subcutaneous injection is probably the route of choice in SCD, although again absorption can be unpredictable and injection sites should be rotated.

Analgesia may be given continuously, intermittently or a combination of both. It can be administered by medical/nursing staff or be based around a patient-controlled analgesia system (PCA). Continuous infusions should not be used unless there are established protocols for monitoring respiratory rate, hypoxia and sedation, and an established number of nurses trained in their use to ensure that this monitoring occurs effectively. Intermittent injections may provide less consistent pain relief and make considerable demands on nursing time, but are safer. PCA has been developed for the management of postoperative pain and its use has not been systematically studied in SCD, but a number of small studies in the early 1990s suggested that it could be effective for acute sickle pain, in both adults and older children (Holbrook, 1990; McPherson *et al*, 1990; Gonzalez *et al*, 1991; Shapiro *et al*, 1993). However, some patients seem unable to achieve adequate pain relief from PCA, and PCA should not be started until the acute pain is under control from bolus opioids (American Pain Society, 1999a). PCA should also not be used unless relevant protocols are in place, and the nursing and medical staff are familiar with its use. A small retrospective chart review of children with sickle cell pain treated with PCA suggested that high-dose PCA with low basal infusion rate was more effective than low PCA with high basal infusion, resulting in fewer days in hospital and more rapid pain control (Trentadue *et al*, 1998). At its simplest, PCA can be used to enable the patient to administer intermittent injections, without a basal infusion (Table IV).

Adjuvant medications

Sedatives and anxiolytics are sometimes used in agitated or frightened patients, although they should not be used as a

Table III. Absolute contraindications to pethidine in SCD.

Impaired renal function
Taking monoamine oxidase inhibitors
History of fits
History of mood swings/dysphoria on pethidine
Evidence of infection or muscle damage at injection sites
(Doses should not exceed 600 mg/24 h and the duration of use should be less than 48 h)

Table IV. Example of a PCA diamorphine regimen for an adult ≥ 50 kg.

To be started once pain is controlled
Continuous infusion 0–10 mg/h
PCA bolus dose 2–10 mg
Dose duration 1 min
Lockout time 20–30 min

Monitoring should proceed as listed in Table II.

substitute for adequate analgesia. Laxatives should be routinely prescribed for people receiving regular opioids, and regular antiemetics and antipruritics will frequently be necessary (Table II). SCD is believed to be a prothrombotic state (Wright *et al*, 1997) and painful crises can result in prolonged periods of relative immobility in bed. Prophylactic anticoagulation should, therefore, be considered for all patients who are confined to bed for more than 16 h/d, particularly if there are additional risk factors for venous thrombosis, such as previous history of venous thrombosis, increasing age, or insertion of a femoral line.

NON-PHARMACOLOGICAL PAIN MANAGEMENT

Psychological and behavioural approaches

A number of strategies are potentially of benefit but, as with most aspects of management, there is little objective evidence to support one approach over another. Both adults and children are often very frightened during admission for a painful crisis, and will benefit from simple reassurance. Distraction and entertainment may be of some benefit, and include television, video games, repeating inspirational phrases and mental calculations. In general, it is difficult to provide therapies specific to sickle cell pain except in centres with large numbers of patients, although attempts should be made to provide a pleasant, distracting environment and integrate care with what is used for other patients experiencing acute and chronic pain. Studies have suggested that cognitive behavioural therapy for chronic pain can teach patients coping strategies that are also useful for acute pain (Thomas *et al*, 2001). Community nurses may play an important role in educating patients and parents at home, such that they fully understand their disease and can act as 'expert patients' on admission to hospital.

A number of small studies have shown beneficial effects of patient education, behavioural and cognitive strategies, biofeedback techniques, and hypnosis, but no clear picture emerges as to how to harness these possible benefits in routine care of sickle cell pain (Anie & Green, 2002).

Physical approaches

There are theoretical and intuitive reasons why local application of heat pads and massage might be useful, but little evidence of direct benefit. Heat pads should be used with caution in patients on opioids as the associated sedation may allow skin burns to occur. Transcutaneous electrical nerve stimulation, acupuncture and acupressure may again be beneficial when practised appropriately, but there is little evidence to support their generalized use.

Recommendations on the management of pain

Paracetamol and NSAID's should be used with opioids to control severe pain (C).

Laxatives should be prescribed routinely with opioids (C).

Pethidine should not be used for routine analgesia (C).

Morphine or diamorphine should be used as first choice opiate analgesics (C).

In children, oral analgesia should be used preferentially, although very severe pain may require initial control with parenteral analgesia (C).

PCA may be helpful, if the appropriate protocols and expertise are available. The majority of the drug should be given as boluses, with a low rate of basal infusion (C).

FURTHER INVESTIGATIONS AND MONITORING

The patient should be monitored throughout their admission for pain, complications of SCD and complications of treatment. Once the patient's pain is controlled on a stable analgesic regimen, they should be monitored every 2 h for pain control (using a pain chart), sedation, respiratory rate and oxygen saturation, and every 4 h for temperature and pulse.

Full blood count, urea, creatinine and electrolytes should be performed on all patients requiring admission. Further investigations should be directed towards specific clinical problems. The following investigations may be useful but should not be performed routinely, without specific indication:

- chest radiograph (febrile, breathless, tachypnoea, chest pain, chest signs, reduced oxygen saturations);
- arterial blood gases (oxygen saturations < 95%, unexplained drowsiness);
- liver function tests (LFT's), (amylase, increased jaundice, abdominal pain);
- reticulocytes (haemoglobin lower than normal or falling);
- blood and urine cultures (febrile, rigors, hypotensive);
- ultrasound abdomen (abnormal LFT's, abdominal pain, splenomegaly);
- parvovirus B19 serology (reticulocytopenia);
- computerized tomography/magnetic resonance imaging (MRI) scans of brain (if seizure, transient ishaemic attack, stroke, severe headache).

Limb radiographs should not be performed unless there are other worrying features, such as a history of trauma or persistent, unexplained swelling. Sickling may cause localized, painful swelling, and differentiation from osteomyelitis is difficult. High fevers, positive blood cultures and high C-reactive protein (CRP) level should increase the suspicion of osteomyelitis. Bone scans are generally unhelpful and MRI scanning may help to make the diagnosis.

FURTHER MANAGEMENT

Fluid replacement therapy

Altered renal function characterized by hyposthenuria is present from early infancy (Keitel *et al*, 1956). Fluid balance should be monitored in all patients. The patient should be encouraged to take oral fluids (60 ml/kg/24 h in adults). If the patient is unable to drink sufficient amounts or is vomiting, intravenous or nasogastric fluids are necessary at a similar rate. Cannulation of veins in the legs, ankles and feet should be avoided because of the risk of venous thrombosis and leg ulceration. Central lines, including femoral lines, should be avoided unless needed for life-saving

blood transfusions, because of the high rate of complications (Mehta *et al*, 2002). Although adequate hydration is important, there is little evidence to direct the choice of intravenous fluid. Dextrose (5%) can induce hyponatraemia, which may be of marginal benefit during painful crises (Rosa *et al*, 1980, 1982), although significant hyponatraemia should be avoided.

Oxygen
There have been no large trials of oxygen therapy for acute pain in SCD. Two small, randomized control trials showed no clinical benefit for routine oxygen administration (Robieux *et al*, 1992; Zipursky *et al*, 1992). Oxygen should be given if pulse oximetry shows the oxygen saturation is below the patient's known steady-state level. Some patients have low steady-state oxygen saturations, which appear to be well tolerated without oxygen. (Homi *et al*, 1997); if a patient's steady-state oxygen saturation is not known, then oxygen should be given when the pulse oximetry shows oxygen saturation is below 95%.

Antibiotics
There are no trials assessing the use of antibiotics in painful sickle cell crises. It is established that SCD patients are more susceptible to serious infection, particularly from *Streptococcus pneumoniae*, *Haemophilus influenzae B*, meningococcus and *Salmonella* species, related to hyposplenism and more subtle alterations in immunity (Leikin *et al*, 1989). All children should be taking penicillin prophylaxis and this should be continued. Older patients should continue with whatever prophylactic regime they are taking. Broad-spectrum antibiotics should be started if the patient is febrile (temperature > 38°C), generally unwell, has chest symptoms or signs, or infection is suspected for some other reason. White cell counts are routinely elevated in SCD and leucocytosis does not always equate with infection. Antibiotic choice will depend on local policies but should cover likely pathogens, e.g. ceftriaxone in children, amoxicillin or cefuroxime in adults. If chest signs are present, a macrolide should also be given, e.g. erythromycin (Vichinsky *et al*, 1997; Anonymous, 2001). If a patient is receiving iron chelation with desferrioxamine or deferiprone and has abdominal pain or diarrhoea, the chelation should be stopped, blood and stool cultures sent, and ciprofloxacin given to treat possible *Yersinia* infections.

Blood transfusions
Haemoglobin may fall 1–2 g/dl in an uncomplicated painful crisis, but blood transfusion is not routinely indicated. Blood transfusions should be used if the patient develops signs or symptoms which may be due to anaemia, including unexplained tachycardia, tachypnoea, dyspnoea and fatigue. A low reticulocyte count ($< 100 \times 10^9$/l) and a falling haemoglobin make transfusion more appropriate. Typically, blood transfusion will not be necessary unless the haemoglobin has fallen more than 2 g/dl and is below 5 g/dl, and should aim to return the haemoglobin to the steady-state level. Blood should be leucocyte depleted and matched for Rh (C, D and E) and Kell antigens (Vichinsky *et al*, 1990). If blood transfusion becomes necessary, the

possibility of splenic or hepatic sequestration, or parvovirus infection should be considered. Exchange transfusions are indicated for severe chest crises, suspected cerebrovascular events and multiorgan failure.

Physiotherapy
Incentive spirometry, performed regularly every 2 h, has been shown to be beneficial in patients with chest pain, back pain, chest infection or hypoxia, reducing the risk of acute chest syndrome and atelectasis (Bellet *et al*, 1995). Physiotherapy may have a role in aiding mobilization as acute pain is settling and in chest infections.

Other drugs
There is no evidence that any drug is effective at altering the natural history of an acute painful crisis. Hydroxyurea has been shown to significantly reduce the frequency of painful crises (Charache *et al*, 1995), but its role during acute pain is unclear. Hydroxyurea should be stopped during an acute crisis if there is neutropenia ($< 1 \times 10^9$/l), thrombocytopenia ($< 100 \times 10^9$/l) or reticulocytopenia ($< 100 \times 10^9$/l). High-dose intravenous methylprednisolone has been used in children, with possible benefit but a high 'relapse' rate, making it of little overall benefit (Griffin *et al*, 1994).

NURSING CARE

There has been research that indicates the complex issues surrounding the nursing of a patient during a painful crisis (Alleyne & Thomas, 1994; Oni, 1998). There is general agreement that appropriate nursing is very important and the need for further research in this area was identified several years ago (Anionwu, 1996). It is recommended that nurses caring for sickle cell patients should have an interest in the condition and be provided with continuing education and support (Streetly *et al*, 1997). In particular, training may be necessary to avoid negative attitudes from staff, and to address the issues of perceived racism and possible cultural differences in expressing feelings (Anionwu & Atkin, 2001). Nurses should be able to recognize and assess pain, help the individual cope, cannulate veins and undertake phlebotomy, recognize signs of complications, identify psychosocial problems, and involve appropriate support agencies. Nurse practitioners with an interest in SCD may play an important role in more specialized procedures, nurse education and maintaining nursing standards.

Recommendations on further investigation, management and nursing

Full blood count should be performed on all admissions and other investigations dictated by the clinical situation (C).

Intravenous fluids should not be used routinely, but should be given if the patient is unable to drink, is vomiting or has diarrhoea. Nasogastric fluids should be considered as an alternative to intravenous fluids (C).

Oxygen should not be used routinely, but is appropriate if oxygen saturation is less than 95% (C).

> Cannulation of feet and legs should be avoided, and central lines only used if necessary for life-saving blood transfusion (C).
>
> Broad-spectrum antibiotics should be used if the patient is febrile (T > 38°C), systemically unwell, or has chest symptoms (C).
>
> Blood transfusions should not be used as a treatment for pain, but are important for symptomatic anaemia (C).
>
> Blood for transfusion should be leucodepleted and matched for Rh (C, D and E) and Kell antigens (B).
>
> Incentive spirometry should be used for patients with chest or back pain (A).
>
> Patients should be monitored every 2 h for pain control (using a pain chart), sedation, respiratory rate and oxygen saturation, and every 4 h for temperature and pulse.

ACUTE COMPLICATIONS

It is beyond the scope of these guidelines to give recommendations on the management of all the complications of SCD. It is important to monitor for the following problems during an apparently uncomplicated painful crisis:

- acute chest syndrome or chest crisis;
- abdominal crisis;
- priapism;
- stroke;
- sequestration crises.

PAEDIATRIC ISSUES

As for adults, children should ideally be assessed and nursed on a ward where staff are familiar with SCD. Care should be multidisciplinary, and include paediatricians, haematologists, nurses and pain control specialists. GP's should be involved and informed when the patient is discharged to allow early home visiting. Parents may not yet be familiar with the spectrum of the severity of sickle crises and will require support and education. Dactylitis is more common in young children and may be managed at home with good hydration and analgesia (paracetamol, ibuprofen). Many episodes of pain may be managed at home with oral analgesia. Severe pain may require admission and the majority of episodes can be managed with oral analgesia, following rapid control with parenteral morphine (Jacobson *et al*, 1997) (Table IIB). In a minority of cases, it may be necessary to use parenteral analgesia, either by continuous infusion or a patient/nurse-controlled pump. Methods of pain assessment depend critically on the age and cognitive abilities of the child (American Pain Society, 1999b).

SPECIAL CIRCUMSTANCES

Pregnancy

Pregnancy can exacerbate the frequency of painful crises, particularly in the third trimester and postpartum period (Adams, 1996). Painful crises should be managed as for the non-pregnant patient, and opiate analgesia should be given as necessary. Painful crises in the last trimester may follow a prolonged course and not fully resolve until delivery occurs. Many maternal and fetal complications of pregnancy are more common in SCD, including pre-eclampsia, premature labour and intrauterine growth retardation. Regular blood transfusions are sometimes used to try and improve pregnancy outcome, although their exact role is not defined. If a woman has severe problems in pregnancy related to SCD, then regular blood transfusions during the third trimester may be appropriate. Close involvement of midwifery, obstetric and haematology teams is important during the admission and throughout the pregnancy. If opiates have been used in the days and hours leading up to labour, neonatologists should be alerted and be present at delivery in case of fetal sedation or dependence.

Renal failure

Renal impairment increases in frequency with age in sickle cell patients, particularly after the age of 40 years. In people with known renal impairment, the doses of renally excreted drugs should be adjusted and pethidine, in particular, should be avoided, as its toxic metabolite norpethidine is renally excreted. Care should also be taken with long-acting opiates. NSAID's can worsen renal function; if they are used, the dose should be adjusted and limited to 5 d (Allon *et al*, 1988).

Long-term opiate use

Some patients with severe chronic pain may be admitted with acute pain while still taking regular oral opiates. The regular opiate should be continued at its normal dose and additional analgesia given to treat acute pain in the normal way. When the pain has improved sufficiently, the patient should be discharged on his/her normal opiate dose. It should be made explicit whether the hospital or GP prescribes the long-term opiates, and the GP should be kept informed of the clinical situation.

Prepared on behalf of the British Committee for Standards in Haematology General Haematology Task Force by the Sickle Cell Working Party

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REFERENCES

Adams, S. (1996) Caring for the pregnant woman with sickle cell crisis. *Professional Care of Mother and Child*, 6, 34–36.

Alleyne, J. & Thomas, V.J. (1994) The management of sickle cell crisis pain as experienced by patients and their carers. *Journal of Advanced Nursing*, 19, 500–506.

Allon, M., Lawson, L., Eckman, J.R., Delaney, V. & Bourke, E. (1988) Effects of nonsteroidal drugs on renal function in sickle cell anaemia. *Kidney International*, 34, 500–506.

American Pain Society (1993) *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*, 3rd edn. American Pain Society, Stokie, IL.

American Pain Society (1999a) *Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease*. American Pain Society, Glenview, IL.

American Pain Society (1999b) *Principles of Analgesic Use in the Management of Acute Pain and Cancer Pain*. American Pain Society, Evanston, IL.

Anie, K.A. & Green, J. (2002) Psychological therapies for sickle cell disease and pain (Cochrane Review). *The Cochrane Library*, Issue 4. Update Software, Oxford.

Anionwu, E.N. (1996) Sickle cell and thalassaemia: some priorities for nursing research. *Journal of Advanced Nursing*, 6, 853–856.

Anionwu, E.N. & Atkin, K. (2001) *The Politics of Sickle Cell and Thalassaemia*. Open University Press, Buckinghamshire, UK.

Anonymous (2001) Acute complications of sickle cell disease in children. *Drug and Therapeutics Bulletin*, 39, 33–37.

Ballas, S.K. (1998) *Sickle Cell Pain*. IASP Press, Seattle.

Bellet, P.S., Kalinyak, K.A., Shukla, R., Gelfand, M.J. & Rucknagel, D.L. (1995) Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. *New England Journal of Medicine*, 333, 699–703.

Benjamin, L.J., Swinson, G.I. & Nagel, R.L. (2000) Sickle cell anemia day hospital: an approach for the management of uncomplicated painful crises. *Blood*, 95, 1130–1136.

Charache, S., Terrin, M.L., Moore, R.D., Dover, G.J., Barton, F.B., Eckert, S.V., McMahon, R.P. & Bonds, D.R. (1995) Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *New England Journal of Medicine*, 332, 1317–1322.

Clare, N. (1998) Management would improve if doctors listened more to patients. *Lancet*, 316, 935.

Fertleman, C.R., Gallagher, A. & Rossiter, M.A. (1997) Evaluation of fast track admission policy for children with sickle cell crises: questionnaire survey of parents' preferences. *British Medical Journal*, 315, 650.

Gillis, J. & Brogden, R. (1997) Ketorolac. A reappraisal of its pharmacodynamic properties and therapeutic use in pain management. *Drugs*, 53, 139–188.

Gonzalez, E.R., Bahal, N., Hansen, L.A., Ware, D., Bull, D.S., Ornato, J.P. & Lehman, M.E. (1991) Intermittent injection vs patient-controlled analgesia for sickle cell crisis pain. Comparisons in patients in the emergency department. *Archives of Internal Medicine*, 151, 1373–1378.

Griffin, T.C., McIntire, D. & Buchanan, G.R. (1994) High dose intravenous methylprednisolone for pain in children and adolescents with sickle cell disease. *New England Journal of Medicine*, 330, 733–737.

Hardwick, Jr, W., Givens, T., Monroe, K., King, W. & Lawley, D. (1999) Effect of ketorolac in pediatric sickle cell vaso-occlusive pain. *Pediatric Emergency Care*, 15, 179–182.

Holbrook, C.T. (1990) Patient-controlled analgesia pain management for children with sickle cell disease. *Journal of the Association of Academic Minor Physicians*, 1, 93–96.

Homi, J., Levee, L., Higgs, D., Thomas, P. & Serjeant, G. (1997) Pulse oximetry in a cohort study of sickle cell disease. *Clinical Laboratory Haematology*, 19, 17–22.

Jacobson, S.J., Kopecky, B.A., Joshi, P. & Babul, N. (1997) Randomized trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet*, 350, 1358–1361.

Keitel, H.G., Thompson, D. & Itano, H.A. (1956) Hyposthenuria in sickle cell anaemia: a reversible renal defect. *Journal of Clinical Investigation*, 39, 998–1007.

Leikin, S.L., Gallagher, D., Kinney, T.R., Sloane, D., Klug, P. & Rida, W. (1989) Mortality in children and adolescents with sickle cell disease. *Pediatrics*, 84, 500–508.

McPherson, E., Perlin, E., Finke, H., Castro, O. & Pittman, J. (1990) Patient-controlled analgesia in patients with sickle cell vaso-occlusive crisis. *American Journal of Medical Science*, 299, 10–12.

Mehta, P., Bareford, D., Wright, C. & Wright, J. (2002) High complication rate of central lines in SCD. *British Journal of Haematology*, 117, 9a.

Ogundipe, O., Pearson, M.W., Slater, N.G., Adepegba, T. & Westerdale, N. (1999) Sickle cell disease and nitrous-oxide induced neuropathy. *Clinical and Laboratory Haematology*, 21, 409–412.

Oni, L. (1998) Sickle cell disease and the carer–client relationship. *Nursing Times*, 94, 64–65.

Pegelow, C.H. (1992) Survey of pain management therapy provided for children with sickle cell disease. *Clinical Pediatrics*, 31, 211–214.

Perlin, E., Finke, H., Castro, O., Rana, S., Pittman, J., Burt, R., Ruff, C. & McHugh, D. (1994) Enhancement of pain control with ketorolac in patients with occlusive crisis. *American Journal of Hematology*, 46, 43–47.

Platt, O., Brambilla, D., Rosse, W., Milner, P., Castro, O., Steinberg, M. & Klug, P. (1994) Mortality in sickle cell disease: life expectancy and risk factors for early death. *New England Journal of Medicine*, 330, 1639–1644.

Robieux, I.C., Kellner, J.D. & Coppes, M.J. (1992) Analgesia in children with sickle cell crisis: comparison of intermittent opioids vs. continuous infusion of morphine and placebo controlled study of oxygen inhalation. *Paediatric Haematology and Oncology*, 9, 317–326.

Rosa, R.M., Bierer, B.E., Thomas, R., Stoff, J.S., Kruskall, M., Robinson, J., Bunn, H.F. & Epstein, F.H. (1980) A study of induced hyponatraemia in the prevention and treatment of sickle cell crisis. *New England Journal of Medicine*, 303, 1138–1143.

Rosa, R.M., Bierer, B.E., Bunn, H.F. & Epstein, F.H. (1982) The treatment of sickle cell anemia with induced hyponatremia. *Blood Cells*, 8, 329–335.

Shapiro, B.S., Cohen, D.E. & Howe, C.J. (1993) Patient-controlled analgesia for sickle-cell-related pain. *Journal of Pain and Symptom Management*, 8, 22–28.

Streetly, A., Maxwell, K. & Mejia, A. (1997) Sickle cell disorders in Greater London: a needs assessment of screening and care services. *The Fair Shares for London Report* Department of Public Health Medicine, UMDS and St Thomas' Hospital, London.

Thomas, V.J., Gruen, R. & Shu, S. (2001) Cognitive-behavioural therapy for the management of sickle cell disease pain: identification and assessment of costs. *Ethnicity and Health*, 6, 59–67.

Trentadue, N.O., Kachoyeanos, M.K. & Lea, G. (1998) A comparison of two regimens of patient-controlled analgesia for children with sickle cell disease. *Journal of Pediatric Nursing*, **13**, 15–19.

Vichinsky, E.P., Earles, A., Johnson, R.A., Hoag, M.S., Williams, A. & Lubin, B. (1990) Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *New England Journal of Medicine*, **322**, 1617–1621.

Vichinsky, E.P., Styles, L.A., Colangelo, L.H., Wright, E.C., Castro, O. & Nickerson, B. (1997) Acute chest syndrome in sickle cell disease: clinical presentation and course. *Blood*, **89**, 1787–1792.

Ware, M.A., Hambleton, I., Ochaya, I. & Serjeant, G.R. (1999) Day care management of sickle cell painful crisis in Jamaica: a model applicable elsewhere? *British Journal of Haematology*, **104**, 93–96.

Wright, J.G., Malia, R., Cooper, P., Thomas, P., Preston, F.E. & Serjeant, G.R. (1997) Protein C and protein S in homozygous sickle cell disease: does hepatic dysfunction contribute to low levels? *British Journal of Haematology*, **98**, 627–631.

Zipursky, A., Robieux, I.C., Brown, E.J., Shaw, D., O'Brodovich, H., Kellner, J.D., Coppes, M.J., Koren, G. & Olivieri, N.F. (1992) Oxygen therapy in sickle cell disease. *American Journal of Pediatric Hematology and Oncology*, **14**, 222–228.

APPENDIX

Classification of grades of recommendations

A	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation
B	Requires the availability of well-conducted clinical studies, but no randomized clinical trials on the topic of recommendation
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality