National Institute for Health and Clinical Excellence

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Sickle cell acute painful episode

Management of an acute painful sickle cell episode in hospital

NICE clinical guideline 143
Developed by the Centre for Clinical Practice at NICE

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Sickle cell acute painful episode

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- The NICE guideline – all the recommendations.
- The NICE pathway – a set of online diagrams that brings together all NICE guidance and support tools.
- 'Understanding NICE guidance' – a summary for patients and carers.
- The full guideline (this document) – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

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This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

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Appendices C, D, E and F are in separate files.

NHS Evidence has accredited the process used by the Centre for Clinical Practice at NICE to produce guidelines. Accreditation is valid for 3 years from April 2010 and is applicable to guidance produced using the processes described in NICE's 'The guidelines manual' (2009). More information on accreditation can be viewed at www.evidence.nhs.uk

Introduction

Acute painful sickle cell episodes

Sickle cell disease is the name given to a group of lifelong inherited conditions of haemoglobin formation. Most people affected are of African or African-Caribbean origin, although the sickle gene is found in all ethnic groups. Sickle cell disease can have a significant impact on morbidity and mortality.

It is estimated that there are between 12,500 and 15,000 people with sickle cell disease in the UK. The prevalence of the disease is increasing because of immigration into the UK and new births. The NHS Sickle Cell and Thalassaemia Screening Programme also means that more cases are being diagnosed.

Acute painful sickle cell episodes (also known as painful crises) are caused by blockage of the small blood vessels. The red blood cells in people with sickle cell disease behave differently under a variety of conditions, including dehydration, low oxygen levels and elevated temperature. Changes in any of these conditions may cause the cells to block small blood vessels and cause tissue infarction. Repeated episodes may result in organ damage.

Acute painful sickle cell episodes occur unpredictably, often without clear precipitating factors. Their frequency may vary from less than one episode a year to severe pain at least once a week. Pain can fluctuate in both intensity and duration, and may be excruciating. The majority of painful episodes are managed at home, with patients usually seeking hospital care only if the pain is uncontrolled or they have no access to analgesia. Patients who require admission may remain in hospital for several days. The primary goal in the management of an acute painful sickle cell episode is to achieve effective pain control both promptly and safely.

The management of acute painful sickle cell episodes for patients presenting at hospital is variable throughout the UK, and this is a frequent source of complaints from patients. Common problems include unacceptable delays in

receiving analgesia, insufficient or excessive doses, inappropriate analgesia, and stigmatising the patient as drug seeking.

This guideline addresses the management of an acute painful sickle cell episode in patients presenting to hospital until discharge. This includes the use of pharmacological and non-pharmacological interventions, identifying the signs and symptoms of acute complications, skills and settings for managing an acute painful episode, and the information and support needs of patients.

This is an overarching guideline covering the principles of how to manage an acute painful sickle cell episode in hospital. Local protocols should be referred to for specific management plans, including drug choice and dosages. This guideline includes the management of acute painful sickle cell episodes in children and young people and in pregnant women. The guideline recommendations apply to all patients presenting with an acute painful sickle episode unless there are differences in management for these groups, in which case these are clearly outlined.

Drug recommendations

The guideline does not make recommendations on drug dosage; prescribers should refer to the ‘British national formulary (BNF)’ and ‘BNF for children’ for this information. The guideline also assumes that prescribers will use a drug’s summary of product characteristics to inform decisions made with individual patients.

Who this guideline is for

This document is for healthcare professionals and other staff who care for people with an acute painful sickle cell episode in hospital. People with sickle cell disease and their family members and carers may also find it useful.

Patient-centred care

This guideline offers best practice advice on the care of adults, young people and children presenting at hospital with an acute painful sickle cell episode.

Treatment and care should take into account patients' needs and preferences. People with an acute painful sickle cell episode should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent and the code of practice that accompanies the Mental Capacity Act. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

If the patient is under 16, healthcare professionals should follow the guidelines in 'Seeking consent: working with children'.

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people'.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with an acute painful sickle cell episode. Diagnosis and management should be reviewed throughout the

transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1 Recommendations

1.1 List of all recommendations

Individualised assessment at presentation

1.1.1 Treat an acute painful sickle cell episode as an acute medical emergency. Follow locally agreed protocols for managing acute painful sickle cell episodes and/or acute medical emergencies that are consistent with this guideline.

1.1.2 Throughout an acute painful sickle cell episode, regard the patient (and/or their carer) as an expert in their condition, listen to their views and discuss with them:

- the planned treatment regimen for the episode
- treatment received during previous episodes
- any concerns they may have about the current episode
- any psychological and/or social support they may need.

1.1.3 Assess pain and use an age-appropriate pain scoring tool for all patients presenting at hospital with an acute painful sickle cell episode.

1.1.4 Offer analgesia within 30 minutes of presentation to all patients presenting at hospital with an acute painful sickle cell episode (see also recommendations 1.1.7 to 1.1.11).

1.1.5 Clinically assess all patients presenting at hospital with an acute painful sickle cell episode, including monitoring of:

- blood pressure
- oxygen saturation on air (if oxygen saturation is 95% or below, offer oxygen therapy)
- pulse rate

- respiratory rate
- temperature.

1.1.6 Assess all patients with sickle cell disease who present with acute pain to determine whether their pain is being caused by an acute painful sickle cell episode or whether an alternative diagnosis is possible, particularly if pain is reported as atypical by the patient.

Primary analgesia

1.1.7 When offering analgesia for an acute painful sickle cell episode:

- ask about and take into account any analgesia taken by the patient for the current episode before presentation
- ensure that the drug, dose and administration route are suitable for the severity of the pain and the age of the patient
- refer to the patient's individual care plan if available.

1.1.8 Offer a bolus dose of a strong opioid by a suitable administration route, in accordance with locally agreed protocols for managing acute painful sickle cell episodes, to:

- all patients presenting with severe pain
- all patients presenting with moderate pain who have already had some analgesia before presentation.

1.1.9 Consider a weak opioid as an alternative to a strong opioid for patients presenting with moderate pain who have not yet had any analgesia.

1.1.10 Offer all patients regular paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) by a suitable administration route, in addition to an opioid, unless contraindicated[1].

[1] The use of NSAIDs should be avoided during pregnancy, unless the potential benefits outweigh the risks. NSAIDs should be avoided for treating an acute painful sickle cell episode in women in the third trimester. See the 'British National Formulary' for details of contraindications.

1.1.11 Do not offer pethidine for treating pain in an acute painful sickle cell episode.

Reassessment and ongoing management

1.1.12 Assess the effectiveness of pain relief:

- every 30 minutes until satisfactory pain relief has been achieved, and at least every 4 hours thereafter
- using an age-appropriate pain scoring tool
- by asking questions, such as:
  - How well did that last painkiller work?
  - Do you feel that you need more pain relief?

1.1.13 If the patient has severe pain on reassessment, offer a second bolus dose of a strong opioid (or a first bolus dose if they have not yet received a strong opioid).

1.1.14 Consider patient-controlled analgesia if repeated bolus doses of a strong opioid are needed within 2 hours. Ensure that patient-controlled analgesia is used in accordance with locally agreed protocols for managing acute painful sickle cell episodes and/or acute medical emergencies.

1.1.15 Offer all patients who are taking an opioid:

- laxatives on a regular basis
- anti-emetics as needed
- antipruritics as needed.

1.1.16 Monitor patients taking strong opioids for adverse events, and perform a clinical assessment (including sedation score):

- every 1 hour for the first 6 hours
- at least every 4 hours thereafter.

1.1.17 If the patient does not respond to standard treatment for an acute painful sickle cell episode, reassess them for the possibility of an alternative diagnosis.

1.1.18 As the acute painful sickle cell episode resolves, follow locally agreed protocols for managing acute painful sickle cell episodes to step down pharmacological treatment, in consultation with the patient.

Possible acute complications

1.1.19 Be aware of the possibility of acute chest syndrome in patients with an acute painful sickle cell episode if any of the following are present at any time from presentation to discharge:

- abnormal respiratory signs and/or symptoms
- chest pain
- fever
- signs and symptoms of hypoxia:
  - oxygen saturation of 95% or below **or**
  - an escalating oxygen requirement.

1.1.20 Be aware of other possible complications seen with an acute painful sickle cell episode, at any time from presentation to discharge, including:

- acute stroke
- aplastic crisis
- infections
- osteomyelitis
- splenic sequestration.

Management of underlying pathology

1.1.21 Do not use corticosteroids in the management of an uncomplicated acute painful sickle cell episode.

Non-pharmacological interventions

1.1.22 Encourage the patient to use their own coping mechanisms (for example, relaxation techniques) for dealing with acute pain.

Settings and training

1.1.23 All healthcare professionals who care for patients with an acute painful sickle cell episode should receive regular training, with topics including:

- pain monitoring and relief
- the ability to identify potential acute complications
- attitudes towards and preconceptions about patients presenting with an acute painful sickle cell episode.

1.1.24 Where available, use daycare settings in which staff have specialist knowledge and training for the initial assessment and treatment of patients presenting with an acute painful sickle cell episode.

1.1.25 All healthcare professionals in emergency departments who care for patients with an acute painful sickle cell episode should have access to locally agreed protocols and specialist support from designated centres.

1.1.26 Patients with an acute painful sickle cell episode should be cared for in an age-appropriate setting.

1.1.27 For pregnant women with an acute painful sickle cell episode, seek advice from the obstetrics team and refer when indicated.

Discharge information

1.1.28 Before discharge, provide the patient (and/or their carer) with information on how to continue to manage the current episode, including:

- how to obtain specialist support
- how to obtain additional medication

- how to manage any potential side effects of the treatment they have received in hospital.

2 Evidence review and recommendations

This guideline was developed in accordance with the process for short clinical guidelines set out in ‘The guidelines manual' (2009). Where non-standard methods were used or there were deviations from the manual, details are provided under the specific review question. For details of how this guideline was developed see appendix D.

2.1 Pharmacological management

2.1.1 Review question

How should an acute painful sickle cell episode be managed using pharmacological interventions?

2.1.2 Evidence review

This review question focused on the use of pharmacological interventions to manage an acute painful sickle cell episode. This includes the timing, choice and route of administration of drugs, the use of patient-controlled analgesia (PCA), and the timing and frequency of monitoring of pain and physiological measures. Pharmacological interventions include primary analgesic treatments that are used to manage pain, such as non-steroidal anti-inflammatory drugs (NSAIDs), non-opioids, strong opioids (such as morphine, which is used to treat severe pain) and weak opioids (such as codeine, which is used to treat mild to moderate pain). The use of other pharmacological interventions to manage the underlying sickling process was also assessed: these included corticosteroids, low-molecular-weight heparin (LMWH) and oxygen, all of which are provided in addition to analgesia. This review question also assessed the use of different modes of delivery, including PCA, intramuscular injection, and intravenous (including intermittent intravenous injection and continuous infusion) and oral routes of administration.

For all review questions, papers were identified from one database using a broad search strategy and included all papers relating to acute pain in sickle cell disease. Only randomised controlled trials (RCTs) that compared a pharmacological intervention with either a placebo or another comparator in

patients having an acute painful sickle cell episode were considered for inclusion. From a database of 5534 abstracts, 232 full-text articles were ordered and 20 papers describing 19 primary studies were selected (Adams-Graves et al. 1997; Adawy et al. 2005; Al-Jam'a et al. 1999; Bartolucci et al. 2009; Gladwin et al. 2011; Gonzalez et al. 1991; Griffin et al. 1994; Grisham and Vichinsky 1996; Hardwick, Jr. et al. 1999; Head et al. 2010; Jacobson et al. 1997; Orringer et al. 2001; Perlin et al. 1994; Qari et al. 2007; Robieux et al. 1992; Teuscher et al. 1989; van Beers et al. 2007; Weiner et al. 2003; Wright et al. 1992; Zipursky et al. 1992). Table 1 lists the details of the included studies.

Trials were excluded if they:

- focused on reducing the incidence of acute painful sickle cell episodes **or**
- used unlicensed drugs **or**
- used unclear measurements of pain **or**
- were carried out in settings other than hospital, for example in the community.

(For a full list of excluded papers for this review question, see appendix D).

For this review question, the GDG selected outcomes as 'critical' or 'important' after evidence synthesis. At the GDG meeting, the outcomes and their relative importance were discussed. It was agreed that pain rating, amount of analgesia used, use of additional or rescue doses of analgesia, length of stay in hospital and adverse events were considered 'critical' to decision making, while the duration of the acute painful sickle cell episode and readmission were outcomes that were 'important' to decision making.

There was limited pooling of studies, because a number of different interventions were being assessed and there was heterogeneity across the included studies. Where meta-analysis was possible, a forest plot is also presented (see appendix E). Where sufficient data were available, mean differences (MDs) were calculated for continuous outcomes and relative risks (RRs) for binary outcomes. Results from other categorical outcomes were summarised from the papers.

Two full GRADE tables are presented for this review question: one for primary analgesia and one for treatments managing the underlying pathology of the sickling process (see appendix E). Summary GRADE tables divided by intervention are presented below.

Table 1 Summary of included studies for pharmacological management

Author (year)	Participants	Drug comparison	Baseline pain	Intervention	Control	Monitoring	Location
Pharmacological treatments aimed at managing the underlying sickling process							
Griffin et al. (1994)	56 episodes of severe pain in 36 children (age range 2–19 years)	Corticosteroid compared with placebo	VAS score on admission not reported	IV methylprednisolone (15 mg/kg) + IV fluids (5% dextrose and 0.45% saline) + IV bolus injection of morphine sulphate (0.1 mg/kg/dose) or continuous infusion of morphine (if ≥8 boluses given and severe pain after 24 hours of hospitalisation)at the discretion of the treating physician	IV saline + IV fluids (5% dextrose and 0.45% saline) + IV bolus injection of morphine sulphate (0.1 mg/kg/dose)	Not reported	USA
Adam-Graves et al. (1997)	50 adults (age range 15–55 years)	Non-ionic surfactant compared with placebo	39% of patients had severe pain at baseline in the intervention group; 64% had severe pain in the placebo group	IV poloxamer 188 + analgesia (at discretion of investigator)	Placebo (the vehicle for poloxamer injection) + analgesia (at discretion of investigator)	No details reported	USA
Orringer et al. (2001)	255 patients (mixed adults and children); subgroup analyses for children 15 years or younger	Non-ionic surfactant compared with placebo	Mean VAS score at baseline was 7.3 in the intervention group and 7.4 in the control group	IV purified poloxamer 188 + IM, IV or oral analgesia (from limited choice)	Saline solution + IM, IV or oral analgesia (from limited choice)	VAS pain assessments were obtained every 4 hours	USA
Al-Jama et al. (1999)	43 patients (older than 12 years)	Vasodilator compared with opioid	Visual pain score at baseline was 10 in both groups (visual pain scale 0–10)	5 or 10 mg isoxsuprine (IM) + IV fluids (5% dextrose alternating with normal saline) + need for extra analgesics was assessed and recorded	50 or 100 mg pethidine (meperidine) (IM) + IV fluids (5% dextrose alternating with normal saline) + need for extra analgesics was assessed and recorded	Assessment was carried out at 30 and 60 minutes and 2, 6 and 24 hours after treatment	Saudi Arabia

Author (year)	Participants	Drug comparison	Baseline pain	Intervention	Control	Monitoring	Location
Teuscher et al. (1989)	37 children and adolescents	Xanthine derivative compared with placebo	VAS score on admission not reported	Pentoxifylline (pentoxiphyllin) + standardised analgesic + chloroquine	Placebo (saline) + standardised analgesic + chloroquine	Vital sign were recorded twice daily	West Africa
Qari et al. (2007)	253 patients (adults and children older than 12 years)	Tinzaparin compared with placebo	Pain score at baseline appeared to be 10 on numerical pain scale (0–10) in both intervention and control groups	Tinzaparin + IV morphine + saline	Placebo + IV morphine + saline	Details not reported	Saudi Arabia
Robieux et al. (1992) and Zipursky et al. (1992)	25 children	Oxygen compared with air	All children recorded initial scores >6 on behavioural pain score (a score of 6 or more was considered to represent moderate to severe pain)	50% oxygen (Venturi mask) + continuous IV infusion (CIV) morphine (loading dose 0.15 mg/kg morphine sulphate then CIV 40 µg/kg/hour; max. rate 100 µg/kg/hour) + IV fluids + continued penicillin prophylaxis + docusate	Room air (Venturi mask) + CIV morphine (loading dose 0.15 mg/kg morphine sulphate then CIV 40 µg/kg/hour; max rate 100 µg/kg/hour) + IV fluids + continued penicillin prophylaxis + docusate	Severity of pain assessed every 8 hours by behavioural observation; vital signs recorded every 2 hours. In phase B, oxygen saturation was measured on admission, every 8 hours for the first 24 hours and then daily.	Canada
Head et al. (2010)	18 adults (no details about characteristics reported)	Nitric oxide compared with placebo	Mean VAS scores appeared to be >8 in both groups[1]	Nitric oxide (80 ppm. with 21% inspired oxygen) + IV morphine sulphate + fluids	21% inspired oxygen + IV morphine sulphate + fluids	Vital signs monitored continuously and recorded hourly	USA
Gladwin et al. (2011)	150 patients (adults and children older than 10 years)	Nitric oxide compared with placebo	Median VAS score 7.7 in intervention group and 7.6 in placebo group	Nitric oxide (face mask; 80 ppm for 4 hours then 40 ppm for 4 hours; 24% inspired oxygen) (opioid use also assessed as outcome but no details)	Placebo gas (100% grade 5 nitrogen gas by face mask; 24% inspired oxygen) (opioid use also assessed as outcome	Pain assessed at 2, 4, 6 and 8 hours after the start of the study drug and then at 4-hour intervals	USA

Author (year)	Participants	Drug comparison	Baseline pain	Intervention	Control	Monitoring	Location
					but no details)		
Weiner et al. (2003)	20 patients (mostly children: age range 10–21 years)	Nitric oxide compared with placebo	Mean VAS scores at ED arrival appeared to be >8 in both groups[1]	Inhaled NO (80 ppm with 21% final concentration of inspired oxygen by face mask) + PCA morphine (0.1 mg/kg, max. dose 6 mg) + fluids (isotonic sodium chloride, 10 ml/kg)	Placebo (21% inspired oxygen by face mask) + PCA morphine (0.1 mg/kg, max. dose 6 mg) + fluids (isotonic sodium chloride, 10 ml/kg)	Pain assessment, physiological and laboratory studies performed immediately before inhalation, each hour during the 4 hours of inhalation and for 2 hours after inhalation	USA
Primary analgesia							
Gonzalez et al. (1991)	Phase 1: 30 cases (15 in intermittent IV group and 15 in PCA group) in 20 randomised adults Phase 2: 40 cases (23 in intermittent IV group and 17 in PCA group) in 25 randomised adults	PCA morphine compared with intermittent IV injection morphine	Mean initial linear pain score in phase 1 (0–10) was 9.1 and 9.2 in intermittent IV and PCA groups respectively. Mean scores in phase 2 were 9.1 and 8.7 in intermittent IV and PCA groups respectively.	Phase 1: PCA morphine sulphate (2 mg then 1 mg) + IV 5% dextrose and 0.45% saline Phase 2: higher doses (5 mg then 2.7 mg)	Phase 1: IV morphine sulphate (4 mg) + IV 5% dextrose and 0.45% saline Phase 2: higher dose (8 mg)	Pain ratings and physiological assessments were carried out before analgesic administration, every 60 minutes thereafter, and at the time of discharge from the ED	USA
Van Beers et al. (2007)	25 episodes in 19 patients	PCA morphine compared with IV morphine	Median baseline VAS score was 5.9 in the continuous infusion group and 7.2 in the PCA group	PCA morphine (5 mg bolus injection then 0.01 mg/kg by PCA) + oral acetaminophen (500 mg six times daily) + 50 mg diclofenac (or tramadol)	IV morphine (5 mg bolus injection then 0.03 mg/kg/hour by continuous infusion) + oral acetaminophen (500 mg six times daily) + 50 mg diclofenac (or tramadol)	Pain intensity was assessed and recorded four times a day with a verbal response scale	The Netherlands

Author (year)	Participants	Drug comparison	Baseline pain	Intervention	Control	Monitoring	Location
Jacobson et al. (1997)	50 children (analysed)	Oral morphine compared with IV morphine	Mean pain scores at baseline not reported	IV morphine (up to 0.15 mg/kg) + oral morphine (1.9mg/kg every 12 hours) + IV placebo (saline) + rescue analgesia (immediate-release oral morphine 0.4 mg/kg or IV morphine bolus 0.1 mg/kg)	IV morphine (up to 0.15 mg/kg) + oral placebo tablets + IV morphine (0.04 mg/kg/hour)	Pain was assessed four times a day and physiological measures were measured every 4 hours	Canada
Wright et al. (1992)	18 adults	IM ketorolac compared with IM saline	Mean baseline VAS score 7.0 in intervention group and 7.9 in control group	IM ketorolac (60 mg) + IV pethidine (meperidine) (50 mg) + IV promethazine (12.5 mg) + IV fluids ($D_5$1/2 normal saline) + oxygen (2 litres per minute by nasal cannula)	IM saline + IV pethidine (50 mg) + IV promethazine (12.5 mg) + IV fluids (D51/2 normal saline) + oxygen (2 litres per minute by nasal cannula)	Vital signs were measured at least every hour	USA
Bartolucci et al. (2009)	54 adults (older than15 years)	IV ketoprofen compared with saline (syringe pump)	At inclusion, mean VAS score was 7.3 in the intervention group and 7.1 in the control group	IV ketoprofen (300 mg/day) then 100 mg oral ketoprofen (every 8 hours) + IV fluid (5% glucose) + oral alkali water + folic acid + analgesia (morphine 0.1mg/kg every 5 minutes until pain relief was achieved, followed by continuous morphine infusion at an initial dose of 2 mg/hour with repeated pulses until pain was well controlled; and IV proparacetamol)	IV saline + IV fluid (5% glucose) + oral alkali water + folic acid + analgesia (morphine 0.1mg/kg every 5 minutes until pain relief was achieved, followed by continuous morphine infusion at an initial dose of 2 mg/hour with repeated pulses until pain was well controlled; and IV proparacetamol)	VAS was recorded every 4 hours and a Categorical Pain Score every 12 hours	France
Perlin et al. (1994)	21 adults	IV ketorolac compared with IV saline	Mean baseline VAS score was 7.6 in the intervention group and 7.9 in the control group	IV ketorolac (30 mg then 120 mg at 5 mg/hour) + IM pethidine (meperidine) (100 mg if needed) + oral hydroxyzine + oral or IV hydration	IV saline + IM pethidine (100 mg if needed) + oral hydroxyzine + oral or IV hydration	Not reported	USA

Author (year)	Participants	Drug comparison	Baseline pain	Intervention	Control	Monitoring	Location
Hardwick et al. (1999)	29 children	IV ketorolac compared with IV saline	Mean initial VAS score was 5.9 in intervention group and 5.4 in control group	IV ketorolac (0.9 mg/kg) + D5 1/2 normal saline + IV morphine sulphate (0.1 mg/kg)	IV saline + D5 1/2 normal saline + IV morphine sulphate (0.1 mg/kg)	Vital signs including pulse, respirations, and blood pressure were taken at least every 60 minutes throughout the 6-hour observation period	USA
Adawy et al. (2005)	45 children	Three-arm trial (IV ketorolac compared with IV methylpred-nisolone compared with IV placebo)	Median pain score at baseline was 8 in all three groups (measured using nine faces pain score, where 9 represents severe pain)	Group K: IV ketorolac (1.0 mg/kg) + IV fluids (D5W in 0.45% saline at 1.5 times the normal requirement) + oxygen (2 litres/minute via nasal cannula) + morphine sulphate (0.5 mg via PCA) Group M: IV methylprednisolone (15 mg/kg) + IV fluids (D5W in 0.45% saline at 1.5 times the normal requirement) + oxygen (2 litres/minute via nasal cannula) + morphine sulphate (0.5 mg via PCA)	Group P: IV saline (50 ml of 0.9% saline) + IV fluids (D5W in 0.45% saline at 1.5 times the normal requirement) + oxygen (2 litres/minute via nasal cannula) + morphine sulphate (0.5 mg via PCA)	Pain assessment was started at time of ED admission and then carried out every 15 minutes in the first hour and then hourly until the end of the 6-hour observation period	Egypt

Author (year)	Participants	Drug comparison	Baseline pain	Intervention	Control	Monitoring	Location
Grisham and Vichinsky (1996)	20 children (range 11–19 years)	Pethidine (meperidine) compared with ketorolac (crossover trial; after 2.5 hours of assessment, patients with persistent pain received the other drug)	Mean baseline VAS score in phase 1 was 7.3. In phase 2 mean baseline VAS score was 5.3 for those who received ketorolac first and 6.5 for those who received pethidine first	Parenteral (IM for first 8 patients and IV for all subsequent patients) pethidine (1.5 mg/kg) + IV hydration (minimum 1.5 times maintenance)	Parenteral (IM for first 8 patients and IV for all subsequent patients) ketorolac (1.0 mg/kg) + IV hydration (minimum 1.5 times maintenance)	Pain and sedation scales were recorded at 30-minute intervals	USA

Abbreviations: D51/2 normal saline, 5% dextrose in ½ normal saline; D5W, 5% dextrose in water; ED, emergency department; IM, intramuscular; IV, intravenous; PCA, patient-controlled analgesia; VAS, visual analogue scale.

[1] From graph.

Table 2 Summary GRADE table for pharmacological management of the underlying sickling process: isoxsuprine compared with pethidine (meperidine)

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating up to 24 hours (assessed with: Visual Analogue Scale [VAS], 0–10, with 0 indicating no pain) in adults					
1 (Al-Jama et al. 1999)	isoxsuprine	pethidine	Mean change from baseline −5 in both isoxsuprine and meperidine groups (from 10 at baseline in both groups) MD* (30 minutes) = 2.00 (CI 0.82, 3.18) MD (1 hour) = 1.60 (CI 0.25, 2.95) MD (2 hours) = 0.70 (CI −0.89, 2.29) MD (6 hours) = 1.00 (CI −0.77, 2.77) MD (24 hours) = 0.00 (SE 0.91, 95% CI −1.77 to 1.77)	Low	Critical

Duration of the painful episode in adults					
1 (Al-Jama et al. 1999)	isoxsuprine	pethidine	The median duration of the painful episode did not differ significantly between the isoxsuprine group (24 hours, range 8–120) compared with the opioid group (48 hours, range 24–168, p =0.44)	Low	Important
Length of stay (LOS) in adults					
1 (Al-Jama et al. 1999)	isoxsuprine	pethidine	There was no significant difference in the median duration of hospitalisation in the isoxsuprine group (72 hours, range 24–288) compared with the meperidine group (72 hours, range 24–216, p = 0.7)	Low	Critical
Abbreviations: CI, confidence interval; MD, mean difference.					

Table 3 Summary GRADE table for pharmacological management of the underlying sickling process: intravenous purified poloxamer 188 compared with placebo

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating at 7 days (assessed with Visual Analogue Scale [VAS]) in adults					
1 (Orringer et al. 2001)	IV PP188	saline	MD = 8.70 units/hour (95% CI −94.52 to 111.92)	Low	Critical
Pain intensity at 7 days (assessed with 5-point pain intensity scale, 0–3, with 0 indicating no pain) in adults					
1 (Adam-Graves et al. 1997)	IV PP188	saline	Median pain intensity ratings did not differ significantly between PP188 group (median = 0.8) and placebo group (median = 1.4, p=0.07†)	Very low	Critical
Amount of analgesia used in adults					
1 (Adam-Graves et al. 1997)	IV PP188	saline	The PP188 group used less parenteral analgesics (MEU) compared with the placebo group (median 47 vs 149 mg, p = 0.2)	Very low	Critical
2 (Orringer et al. 2003, Adam-Graves et al. 1997)	IV PP188	saline	MD (total analgesic use) = −0.11 MEU/kg (CI −0.61, 0.39) and median MEU 57 mg in intervention group and 159 mg in placebo group (adjusted p = 0.2)	Very low	Critical

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Duration of the painful episode in adults					
1 (Adam-Graves et al. 1997)	IV PP188	saline	The median duration of painful episodes did not differ significantly between the PP188 group (67, range 12–178) and the placebo group (80 hours, range 12–315 hours, p = 0.182)	Very low	Important
1 (Orringer et al. 2003)	IV PP188	saline	MD = −4.81 hours (CI −15.03, 5.41)	Low	Important
Adverse events in adults					
1 (Adam-Graves et al. 1997)	IV PP188	saline	Adverse events were similar in the PP188 group (28 events in at least 2 patients) and the placebo group (16 events in at least 2 patients); most of these were mild or moderate in intensity. One serious adverse event (transient increase in serum creatinine) was attributable to the study medication but no treatment was required.	Very low	Critical
1 (Orringer et al. 2003)	IV PP188	saline	There were no differences between the two groups in the overall incidence of adverse events, for adverse events defined as serious or for adverse events involving any body system for the groups as a whole. There was no evidence of increased risk of bleeding during PP188 treatment. There was one death in the PP188 group because of pulmonary fat embolism but the patient had not received the study drug infusion for 3 days prior to death.	Low	Critical
Length of stay (LOS) in adults					
1 (Adam-Graves et al. 1997)	IV PP188	saline	There were no significant differences in the median duration of hospitalisation between the PP188 group (5 days) and the placebo group (6 days, p = 0.258)	Very low	Critical
1 (Orringer et al. 2003)	IV PP188	saline	MD = −4.00 hours (CI −25.23, 17.23)	Low	Critical
Pain rating at 7 days (assessed with Visual Analogue Scale [VAS]) in children					
1 (Orringer et al. 2003)	IV PP188	saline	MD = -132.90 units/hour (95% CI −345.83, 80.03)	Moderate	Critical
Amount of analgesia used in children					
1 (Orringer et al. 2003)	IV PP188	saline	MD (total analgesic use) = −0.19 MEU/kg (CI −0.47, 0.09)	Moderate	Critical

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Duration of painful episode in children					
1 (Orringer et al. 2003)	IV PP188	saline	MD = −21.51 hours (CI −39.71, −3.31)	Moderate	Important
Length of stay (LOS) in children					
1 (Orringer et al. 2003)	IV PP188	saline	MD = −3.98 hours (CI −43.22, 35.26)	Moderate	Critical
Abbreviations: CI, confidence interval; IV, intravenous; MD, mean difference; MEU, morphine-equivalent units; PP188, purified poloxamer 188. † linear model adjusted for baseline pain score.					

Table 4 Summary GRADE table for pharmacological management of the underlying sickling process: tinzaparin compared with placebo

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Duration of the painful episode in adults					
Qari et al. (2007)	tinzaparin	saline	MD = −1.78 days (CI −1.94, −1.62)	Low	Important
Adverse events in adults					
Qari et al. (2007)	tinzaparin	saline	Tinzaparin treatment was associated with two minor bleeding events that were reported and treated by cessation of treatment	Low	Critical
Length of stay (LOS) in adults					
Qari et al. (2007)	tinzaparin	saline	MD = −4.98 days (CI −5.48, −4.48)	Low	Critical
Abbreviations: CI, confidence interval; MD, mean difference.					

Table 5 Summary GRADE table for pharmacological management of the underlying sickling process: intravenous methylprednisolone compared with intravenous placebo

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Amount of analgesia used in children					
1 (Griffin et al. 1994)	IV methylprednisolone	IV saline	There were no significant differences between the number of doses of morphine per episode (6.5 vs 8.7) or the amount of morphine received (0.82 vs 0.97 mg/kg) in the methylprednisolone group compared with the placebo group	Low	Critical
1 (Adawy et al. 2005)	IV methylprednisolone	IV saline	MD (1 hour) = −0.30 cumulative morphine requirements (CI −1.11, 0.51) MD (2 hours) = −1.11 (CI −2.32, 0.10) MD (3 hours) = −2.00 (CI −3.57, −0.43) MD (4 hours) = −2.27 (CI −4.24, −0.30) MD (5 hours) = −2.70 (CI −5.07, −0.33) MD (6 hours) = −2.95 (CI −5.51, −0.39)	Moderate	Critical
Use of additional/rescue doses of analgesia in children					
1 (Griffin et al. 1994)	IV methylprednisolone	IV saline	RR 0.49 (CI 0.14, 1.72)	Low	Critical
1 (Adawy et al. 2005)	IV methylprednisolone	IV saline	MD (mean rescue doses) = −0.95 mg (CI −1.70 to −0.20)	Moderate	Critical
Adverse events in children					
1 (Griffin et al. 1994)	IV methylprednisolone	IV saline	No complications were observed during the study period related to corticosteroid use.	Low	Critical
1 (Adawy et al. 2005)	IV methylprednisolone	IV saline	There were significantly fewer events of nausea (2 vs 9) and vomiting (0 vs 7, $p < 0.05$) in the methylprednisolone group compared with the placebo group. There were no significant differences in the number of pruritus events (0 vs 2).	Moderate	Critical

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Readmission within 48 hours in children					
1 (Adawy et al. 2005)	IV methylprednisolone	IV saline	No patients returned to emergency department within 48 hours	Moderate	Important
Readmission within 2 weeks in children					
1 (Griffin et al. 1994)	IV methylprednisolone	IV saline	RR 4.62 (CI 0.55, 38.74)	Low	Important
Abbreviations: CI, confidence interval; IV, intravenous; MD, mean difference; RR, relative risk.					

Table 6 Summary GRADE table for pharmacological management of the underlying sickling process: pentoxifylline (pentoxiphyllin) compared with placebo

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Duration of painful episode in children					
Teuscher et al. 1989	Pentoxifylline	saline	MD = −24.80 hours (CI −46.74, −2.86)	Low	Important
Adverse events in children					
Teuscher et al. 1989	Pentoxifylline	saline	RR 2.00 (CI 0.59, 6.79). Adverse events were fever, shivering and pruritus.	Low	Critical
Abbreviations: CI, confidence interval; MD, mean difference; RR, relative risk.					

Table 7 Summary GRADE table for pharmacological management of the underlying sickling process: oxygen compared with air

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Amount of analgesia used in children					
1(Zipursky et al. 1992)	50% oxygen (Venturi mask)	Room air	MD (mean hourly morphine dose) = 8.00 µg/kg/hour (CI −9.37, 25.37)	Moderate	Critical
Duration of painful episode in children					
1(Zipursky et al. 1992)	50% oxygen (Venturi mask)	Room air	MD = 0.01 days (CI −0.89, 0.91)	Moderate	Important
Length of stay (LOS) in children					
1(Zipursky et al. 1992)	50% oxygen (Venturi mask)	Room air	MD = 1.30 days (CI −1.13, 3.73)	Moderate	Critical
Abbreviations: CI, confidence interval; MD, mean difference.					

Table 8 Summary GRADE table for pharmacological management of the underlying sickling process: nitric oxide compared with placebo

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating at 4 hours (assessed with Visual Analogue Scale [VAS]) in adults					
1 (Head et al. 2010)	Nitric oxide (NO, 80 ppm with 21% inspired oxygen)	21% inspired oxygen	The mean total reduction was 6.3 (SD 2.2) in the nitric oxide group vs2.97 (SD 2.1) in the placebo group (p = 0.02)	Very low	Critical
Pain ratings up to 24 hours (assessed with: Visual Analogue Scale [VAS]) in adults					

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
1 (Gladwin et al. 2011)	Nitric oxide (face mask, 80 ppm for 4 hours then 40 ppm for 4 hours, 24% inspired oxygen	Placebo gas (100% grade 5 nitrogen gas by face mask, 24% inspired oxygen)	Baseline VAS score 7.7 in nitric oxide group and 7.6 in placebo MD (mean VAS score at 24 hours) = 0.10 cm (95% CI −0.86, 1.06)	Low	Critical
Amount of analgesia used in adults					
1 (Gladwin et al. 2011)	Nitric oxide (face mask, 80 ppm for 4 hours then 40 ppm for 4 hours, 24% inspired oxygen	Placebo gas (100% grade 5 nitrogen gas by face mask, 24% inspired oxygen)	There were no significant differences between the median amount of opioids used in the first 8 hours in the nitric oxide group (0.28 mg/kg, IQR 0.09–0.54) compared with the placebo group (0.23 mg/kg, IQR 0.07–0.70, p = 0.74). There was also no difference in the total median opioid use between the groups (2.8 mg/kg, IQR 1.4–6.1 vs 2.9 mg/kg, IQR 1.1–9.9, p = 0.73)	Low	Critical
Duration of the painful episode in adults					
1 (Gladwin et al. 2011)	Nitric oxide (face mask, 80 ppm for 4 hours then 40 ppm for 4 hours, 24% inspired oxygen	Placebo gas (100% grade 5 nitrogen gas by face mask, 24% inspired oxygen)	Median time to vaso-occlusive crisis resolution did not differ significantly in the nitric oxide group (73 hours, CI 46.0, 91.0) compared with the placebo group (65.5 hours, CI 48.1, 84.0, p = 0.87)	Low	Important
Adverse events in adults					
1 (Gladwin et al. 2011)	Nitric oxide (face mask, 80 ppm for 4 hours then 40 ppm for 4 hours, 24% inspired oxygen	Placebo gas (100% grade 5 nitrogen gas by face mask, 24% inspired oxygen)	RR 1.33 (CI 0.49, 3.66) for any serious adverse event including acute chest syndrome, dysphagia, pyrexia and sensation of foreign body	Low	Critical
Length of stay in adults					
1 (Gladwin et al. 2011)	Nitric oxide (face mask, 80 ppm for 4 hours then 40 ppm for 4 hours, 24% inspired oxygen	Placebo gas (100% grade 5 nitrogen gas by face mask, 24% inspired oxygen)	There was no significant difference in the median length of hospitalisation between the nitric oxide group (4.1 days, IQR 2.0–6.0) and the placebo group (3.1 days, IQR 1.7–6.4, p = 0.30)	Low	Critical
Readmission within 30 days in adults					

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
1 (Gladwin et al. 2011)	Nitric oxide (face mask, 80 ppm for 4 hours then 40 ppm for 4 hours, 24% inspired oxygen	Placebo gas (100% grade 5 nitrogen gas by face mask, 24% inspired oxygen)	RR 0.53 (CI 0.25, 1.11)	Low	Important
Pain rating at 4 hours (assessed with Visual Analogue Scale [VAS]) in children					
1 (Weiner et al. 2003)	iNO (80 ppm with 21% final concentration of inspired oxygen by face mask	21% inspired oxygen	Overall mean change from baseline was −2.0 cm in the nitric oxide group and −1.2 cm in the placebo group, but this was not statistically significant (p = 0.37)	Very low	Critical
Amount of analgesia used in children					
1 (Weiner et al. 2003)	iNO (80 ppm with 21% final concentration of inspired oxygen by face mask	21% inspired oxygen	At 4 hours, there were no significant differences between the nitric oxide group (0.26 mg/kg) and the placebo group (0.32 mg/kg, p = 0.21) At 6 hours the nitric oxide group used significantly less parenteral morphine (0.29 vs 0.44 mg/kg, p = 0.03) At 24 hours, there were no significant differences (0.63 vs 0.91 mg/kg, p = 0.15)	Very low	Critical
Adverse events in children					
1 (Weiner et al. 2003)	iNO (80 ppm with 21% final concentration of inspired oxygen by face mask	21% inspired oxygen	There were no episodes of hypotension, clinically significant SPO_2 (oxygen saturation), toxic concentrations of NO_2 or clinically significant increases in met-haemoglobin	Very low	Critical
Length of stay in children					
1 (Weiner et al. 2003)	iNO (80 ppm with 21% final concentration of inspired oxygen by face mask	21% inspired oxygen	There were no significant differences in the median length of hospitalisation between the nitric oxide group (78 hours) and the placebo group (100 hours, p = 0.19)	Very low	Critical
Abbreviations: CI, confidence interval; iNO, inhaled nitric oxide; IQR, interquartile range; MD, mean difference; RR, relative risk.					

Table 9 Summary GRADE table for primary analgesia: patient-controlled analgesia (PCA) morphine compared with intravenous morphine

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating 2 days after treatment (assessed with 11-point verbal response scale, 0–10, with 0 indicating no pain) in adults					
Van Beers et al. 2007	PCA Morphine (5 mg bolus injection then 0.01 mg/kg by PCA)	IV morphine (5 mg bolus injection then 0.03 mg/kg/hour by continuous infusion)	Mean verbal response pain score did not differ significantly in the PCA group (5.3, CI 4.5–6.9) compared with the IV group (4.9, CI 3.9–5.8, p = 0.09)	Moderate	Critical
Pain rating up to 5 days after treatment (assessed with Visual Analogue Scale [VAS]) in adults					
Van Beers et al. 2007	PCA Morphine (5 mg bolus injection then 0.01 mg/kg by PCA)	IV morphine (5 mg bolus injection then 0.03 mg/kg/hour by continuous infusion)	Median change from baseline was −3.8 (IQR −5.2 to 4) in the PCA group and −2.4 (−5.7 to −1.1) in the continuous infusion group; not significantly different (p = 1.00)	Moderate	Critical
Amount of analgesia used in adults					
Van Beers et al. 2007	PCA Morphine (5 mg bolus injection then 0.01 mg/kg by PCA)	IV morphine (5 mg bolus injection then 0.03 mg/kg/hour by continuous infusion)	The median morphine dose was significantly lower in the PCA group (0.5 mg/hour, IQR 0.3–0.6) compared with the IV group (2.4 mg/hour, IQR 1.4–4.2, p = 0.001). The median total morphine dose was also significantly lower in the PCA group (33 mg, IQR 10–68) compared with the IV group (260 mg, IQR 204–529)	Moderate	Critical
Use of additional/rescue doses of analgesia in adults					
Van Beers et al. 2007	PCA Morphine (5 mg bolus injection then 0.01 mg/kg by PCA)	IV morphine (5 mg bolus injection then 0.03 mg/kg/hour by continuous infusion)	RR 1.30 (CI 0.53, 3.17) for requiring an increased dose if there is no adequate pain relief	Moderate	Critical
Adverse events in adults					
Van Beers et al. 2007	PCA Morphine (5 mg bolus injection then 0.01 mg/kg by PCA)	IV morphine (5 mg bolus injection then 0.03 mg/kg/hour by continuous infusion)	The area under the curve of experienced nausea (median 11, IQR 3–21, vs 18, IQR 3–55, p = 0.045) and constipation (30, IQR 10–40, vs 45, IQR 36–59, p = 0.02) side-effect scores were significantly lower in the PCA group compared with the IV group. No significant differences were found for pruritus and sedation.	Moderate	Critical

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Length of stay in adults					
Van Beers et al. 2007	PCA Morphine (5 mg bolus injection then 0.01 mg/kg by PCA)	IV morphine (5 mg bolus injection then 0.03 mg/kg/hour by continuous infusion)	There were no significant differences in the median admission duration in the PCA group (6.0 days, IQR 4.3–9.3) compared with the IV group (9.0 days, IQR 6.0–12.0, p = 0.15)	Moderate	Critical
Abbreviations: CI, confidence interval; IQR, interquartile range; IV, intravenous; MD, mean difference; PCA, patient-controlled analgesia; RR, relative risk.					

Table 10 Summary GRADE table for primary analgesia: patient-controlled analgesia (PCA) morphine compared with intermittent intravenous morphine

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating at 8 hours (assessed with Visual Analogue Scale [VAS]) in adults					
1 (Gonzalez et al. 1991)	PCA morphine sulphate (2 mg then 1 mg)	IV morphine sulphate (4 mg)	Mean changes from baseline in phase 1 and 2 were −5.99 and −5.61 in PCA group and −5.85 and −5.18 in the IV group respectively MD (phase 1) = 0.01 (CI −2.19, 2.21) MD (phase 2) = −0.90 (CI −3.09, 1.29)	Low	Critical
Amount of analgesia used in adults					

1 (Gonzalez et al. 1991)	PCA morphine sulphate (2 mg then 1 mg)	IV morphine sulphate (4 mg)	PHASE 1 The total number of doses was significantly higher in the PCA group (35.5 ± 23.5 mg) compared with the IV group (6.5 ± 2.6 mg, p = 0.0006). However, the total amount of morphine administered did not differ significantly between the PCA group (35.5 ± 23.5 mg) and the IV group (28.8 ± 13 mg, p = 0.269) PHASE 2 The total number of doses was significantly higher in the PCA group (11.6 ± 6.3 vs 4.9 ± 2.0, p = 0.0002). The total amount of morphine administered did not differ significantly between the IV and PCA groups (41.0 ± 17.6 vs 34.6 ± 20.9 mg, p = 0.945)	Low	Critical
Use of additional/rescue doses of analgesia in adults					
1 (Gonzalez et al. 1991)	PCA morphine sulphate (2 mg then 1 mg)	IV morphine sulphate (4 mg)	PHASE 1: RR 0.63 (CI 0.26, 1.47) for requiring an increased dose of analgesia PHASE 2: RR 0.68 (CI 0.24, 1.88)	Low	Critical
Adverse events in adults					
1 (Gonzalez et al. 1991)	PCA morphine sulphate (2 mg then 1 mg)	IV morphine sulphate (4 mg)	PHASE 1: RR 0.88 (CI 0.43, 1.80)	Low	Critical
Length of stay in adults					
1 (Gonzalez et al. 1991)	PCA morphine sulphate (2 mg then 1 mg)	IV morphine sulphate (4 mg)	PHASE 1: MD = 0.60 hours (CI −1.65, 2.85) PHASE 2: MD = 0.20 hours (CI −0.92, 1.32)	Very low	Critical
Abbreviations: CI, confidence interval; IV, intravenous; MD, mean difference; PCA, patient-controlled analgesia; RR, relative risk.					

Table 11 Summary GRADE table for primary analgesia: oral morphine compared with intravenous morphine

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating (assessed with various scales: OUCHER on a 0–100 scale, CHEOPS, Faces and clinical assessment) in children					
1 (Jacobson et al. 1997)	oral morphine (1.9 mg/kg every 12 hours) + IV placebo (saline)	oral placebo tablets + IV morphine (0.04 mg/kg/hour)	The mean differences between the oral group and the IV group were not significant for any of the pain assessments ($p > 0.05$)	Moderate	Critical
Amount of analgesia used in children					
1 (Jacobson et al. 1997)	oral morphine (1.9 mg/kg every 12 hours) + IV placebo (saline)	oral placebo tablets + IV morphine (0.04 mg/kg/hour)	MD = 2.18 mg/kg (CI 1.86, 2.50) mean oral to parenteral dose ratio was 3.7 (consistent with target dose ratio of 4.0).	Moderate	Critical
Use of additional/rescue doses of analgesia in children					
1 (Jacobson et al. 1997)	oral morphine (1.9 mg/kg every 12 hours) + IV placebo (saline)	oral placebo tablets + IV morphine (0.04 mg/kg/hour)	MD (mean rescue doses/day) = −0.20 (CI −0.62, 0.22)	Moderate	Critical
Adverse events in children					
1 (Jacobson et al. 1997)	oral morphine (1.9 mg/kg every 12 hours) + IV placebo (saline)	oral placebo tablets + IV morphine (0.04 mg/kg/hour)	The frequency and severity of adverse events did not differ significantly between the two groups (62 vs 52 reports, 16 vs 19 severe intensity events). Common events included fever, pruritus, nausea and vomiting and constipation	Moderate	Critical
Abbreviations: CI, confidence interval; IV, intravenous; MD, mean difference.					

Table 12 Summary GRADE table for primary analgesia: ketorolac compared with placebo

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating at 4 hours (assessed with Visual Analogue Scale [VAS]) in adults					
1 (Wright et al. 1992)	IM ketorolac (60 mg)	IM saline	Overall mean change from baseline was −2.63 in the ketorolac group and−-4.23 in the placebo group MD = 0.70 (95% CI −1.90 to 3.30)	Moderate	Critical
Pain rating up to 5 days after treatment (assessed with Visual Analogue Scale [VAS]) in adults					
1 (Perlin et al. 1994)	IV ketorolac (30 mg then 120 mg at 5 mg/hour)	IV saline	MD (day 1) = −1.40 (CI −2.63, −0.17) MD (day 2) = −1.59 (CI −3.23, 0.05) MD (day 3) = −2.38 (CI −4.41, −0.35) MD (day 4) = −2.27 (CI −4.26, −0.28) MD (day 5) = −2.08 (CI −4.28, 0.12)	Moderate	Critical
Pain rating 5 days and after (assessed with Verbal Categorical Score [VPS], 0–3, with 0 indicating no pain) in adults					
1(Perlin et al. 1994)	IV ketorolac (30 mg then 120 mg at 5 mg/hour)	IV saline	Mean VPS score was significantly lower in the ketorolac group (1.1) compared with the placebo group (1.7, $p < 0.05$)	Moderate	Critical
Pain relief 5 days and after (assessed with: pain relief score, 0–4, with 4 indicating complete relief) in adults					
1 (Perlin et al. 1994)	IV ketorolac (30 mg then 120 mg at 5 mg/hour)	IV saline	Mean pain relief score did not differ significantly between the ketorolac (2.7) and placebo groups (2.4, $p > 0.05$)	Moderate	Critical
Amount of analgesia used in adults					
1 (Wright et al. 1992)	IM ketorolac (60 mg)	IM saline	At 4 hours the mean amount of meperidine (pethidine) used in the ketorolac group (231 mg, SD 92) did not significantly differ compared with the placebo group (250 mg, SD 85, $p = 0.61$)	Moderate	Critical
1 (Perlin et al. 1994)	IV ketorolac (30 mg then 120 mg at 5 mg/hour)	IV saline	MD (total dose meperidine required) = −937.30 (CI −1802.72, −71.88) MD (mean daily dose meperidine) = −138.80 (CI −289.46, 11.86)	Moderate	Critical

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Length of stay in adults					
1 (Perlin et al. 1994)	IV ketorolac (30 mg then 120 mg at 5 mg/hour)	IV saline	The median duration of hospitalisation was significantly lower in the ketorolac group compared with the placebo group (3.3. vs 7.2 days, $p < 0.05$)	Moderate	Critical
Pain rating at 6 hours (assessed with Visual Analogue Scale [VAS]) in children					
1 (Hardwick et al. 1999)	IV ketorolac (0.9 mg/kg)	IV saline	Overall mean change from baseline was −2.26 in the ketorolac group and −0.42 in the placebo group MD (1 hour) = −0.09 (CI −1.71, 1.53) MD (2 hours) = −0.59 (CI −2.25, 1.07) MD (3 hours) = −1.06 (CI −3.17, 1.05) MD (4 hours) = −1.20 (CI −2.95, 0.55) MD (5 hours) = −1.41 (CI −3.07, 0.25) MD (6 hours) = 0.70 (CI −1.90, 3.30)	Moderate	Critical
Pain rating at 6 hours (assessed with: Nine Faces Pain Scale [NFPS], 0–9, with 0 indicating no pain) in children					
1 (Adawy et al. 2005)	IV ketorolac (1.0 mg/kg)	IV saline	Median NFPS scores were significantly lower in the ketorolac group (2, range 1–2) compared with the placebo group (3, range 2-3, $p < 0.05$)	Moderate	Critical
Amount of analgesia used in children					
2 (Hardwick et al. 1999, Adawy et al. 2005)	IV ketorolac	IV saline	Pooled MD = −0.01 mg/kg/hour (95% CI −0.03, 0.00), $p = 0.07$ (see forest plot).	Very low	Critical
Use of additional/rescue doses of analgesia in children					
1 (Adawy et al. 2005)	IV ketorolac (1.0 mg/kg)	IV saline	MD (mean rescue doses) = −1.10 mg (CI −1.84, −0.36)	Moderate	Critical
Adverse events in children					
1(Hardwick et al. 1999)	IV ketorolac (0.9 mg/kg)	IV saline	One patient experienced a local histamine reaction to morphine and no other adverse events were noted	Moderate	Critical

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
1 (Adawy et al. 2005)	IV ketorolac (1.0 mg/kg)	IV saline	There were significantly fewer events of nausea (2 vs 9, $p < 0.05$) and vomiting (1 vs 7, $p < 0.05$) in the ketorolac group compared with the placebo group. There were no significant differences in the number of pruritus events (2 vs 2).	Moderate	Critical
Readmission within 48 hours in children					
1(Hardwick et al. 1999)	IV ketorolac (0.9 mg/kg)	IV saline	RR 5.00 (CI 0.29, 86.43)	Moderate	Important
1 (Adawy et al. 2005)	IV ketorolac (1.0 mg/kg)	IV saline	No patients returned to the emergency department within 48 hours	Moderate	Important
Abbreviations: CI, confidence interval; IM, intramuscular; IV, intravenous; MD, mean difference; RR, relative risk.					

Table 13 Summary GRADE table for primary analgesia: ketoprofen compared with placebo

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating up to 5 days after treatment (assessed with Visual Analogue Scale [VAS]) in adults					
1 (Bartolucci et al. 2009)	IV ketoprofen (300 mg/day) then 100 mg oral ketoprofen (every 8 hours)	IV saline	Median change from baseline was −6.04 in the ketoprofen group and −6.14 in the placebo group. Median VAS score in the ketoprofen (1.26, IQR 0.48 to 2.32) and placebo (0.96, IQR 0.58 to 3.32) groups did not differ significantly ($p = 0.5$)	Moderate	Critical
Pain rating 5 days and after (assessed with Categorical Pain Score [CPS], 0–3, Verbal Categorical Score [VPS], 0–3, with 0 indicating no pain) in adults					
1 (Bartolucci et al. 2009)	IV ketoprofen (300 mg/day) then 100 mg oral ketoprofen (every 8 hours)	IV saline	Median CPS did not significantly differ between the ketoprofen (0.4, IQR 0.2 to 0.7) and placebo (0.4, IQR 0.2 to 0.7, $p = 0.46$) groups	Moderate	Critical
Amount of analgesia used in adults					

1 (Bartolucci et al. 2009)	IV ketoprofen (300 mg/day) then 100 mg oral ketoprofen (every 8 hours)	IV saline	There were no significant differences in the median morphine dose used in the ketoprofen group (110 mg, IQR 46–195) and the placebo group (88 mg, IQR 52.5–262.5)	Moderate	Critical
Duration of the painful episode in adults					
1 (Bartolucci et al. 2009)	IV ketoprofen (300 mg/day) then 100 mg oral ketoprofen (every 8 hours)	IV saline	Median duration of vaso-occlusive crisis did not differ significantly in the ketoprofen group (51 hours, IQR 35.5–87) compared with the placebo group (50 hours, IQR 36–103)	Moderate	Important
Adverse events in adults					
1 (Bartolucci et al. 2009)	IV ketoprofen (300 mg/day) then 100 mg oral ketoprofen (every 8 hours)	IV saline	The types and frequencies of adverse events were similar for the two groups (events include nausea, vomiting, pruritus, constipation and epigastralgia)	Moderate	Critical
Abbreviations: IV, intravenous; IQR, interquartile range.					

Table 14 Summary GRADE table for primary analgesia: pethidine (meperidine) compared with ketorolac

Number of studies	Treatment	Placebo	Measure of effect	Quality	Importance
Pain rating at 2 hours (assessed with Visual Analogue Scale [VAS], 0–10, with 0 indicating no pain) in children					
1 (Grisham & Vichinsky 1996)	Parenteral (IM for first 8 and IV for others) meperidine (1.5 mg/kg)	Parenteral (IM for first 8 and IV for others) ketorolac (1.0 mg/kg)	Patients receiving ketorolac had significantly larger decreases in VAS scores over 150 minutes compared with the meperidine group ($p < 0.001$). The greatest decrease in pain scores occurred in first 30 minutes for both drugs (ketorolac = 3.9, meperidine = 5.4, $p < 0.001$)	Low	Critical
1 (Grisham & Vichinsky 1996)	Parenteral (IM for first 8 and IV for others) meperidine (1.5 mg/kg)	Parenteral (IM for first 8 and IV for others) ketorolac (1.0 mg/kg)	There was no significant difference in VAS scores of either group (meperidine then ketorolac or ketorolac then meperidine) after 150 minutes (mean VAS ketorolac/meperidine = 3.8, meperidine/ketorolac = 5.1)	Low	Critical
Abbreviations: IM, intramuscular; IV, intravenous.					

See appendix E for the evidence tables in full.

2.1.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Pharmacological treatments aimed at managing the underlying sickling process

Isoxsuprine compared with pethidine

Critical outcomes

2.1.3.1 *Low-quality evidence from one RCT of a total of 43 patients showed that mean VAS (visual analogue scale) pain ratings were significantly higher in the isoxsuprine group compared with the pethidine group at 30 minutes (mean difference [MD] 2.00; 95% confidence interval [CI] 0.82 to 3.18) and 1 hour (MD 1.60, CI 0.25 to 2.95) after treatment. However, this difference did not persist at 2, 6 or 24 hours (MD 0.00, CI −1.77 to 1.77) after treatment.*

2.1.3.2 *Low-quality evidence from one RCT of a total of 43 patients showed that the length of stay in hospital did not differ significantly between the isoxsuprine group and the pethidine group.*

Important outcomes

2.1.3.3 *Low-quality evidence from one RCT of a total of 43 patients showed that the duration of the painful episode did not differ significantly between the isoxsuprine group and the pethidine group.*

Purified poloxamer 188 (PP188) compared with placebo

Critical outcomes

2.1.3.4 *Low-quality to very-low-quality evidence from two RCTs of a total of 280 patients showed that mean VAS pain ratings and median pain intensity ratings did not differ significantly between the PP188 group and the placebo group.*

2.1.3.5 Very-low-quality evidence from one RCT of a total of 31 patients showed that the use of parenteral analgesics did not differ significantly between the PP188 group and the placebo group (median 47 mg compared with 149 mg, p = 0.22) when an intention-to-treat analysis was adjusted for baseline pain.

2.1.3.6 Very low-quality evidence from two RCTs with a total of 280 patients showed that total analgesic use did not differ significantly between the PP188 group and the placebo group.

2.1.3.7 Low-quality to very-low-quality evidence from two RCTs with a total of 280 patients showed that the numbers of adverse events were similar in the PP188 group and the placebo group.

2.1.3.8 Low-quality to very-low-quality evidence from two RCTs with a total of 280 patients showed that, overall, rates of adverse events were similar in the intervention and control groups. Each study reported one case of a serious adverse event (one death and one transient increase in serum creatinine levels) in patients who had been randomised to the PP188 group.

2.1.3.9 Low-quality to very-low-quality evidence from two RCTs with a total of 280 patients showed that the length of stay in hospital did not differ significantly between the PP188 group and the placebo group.

2.1.3.10 Moderate-quality evidence from one RCT of a total of 73 children showed that mean VAS pain ratings at 7 days did not differ significantly between the PP188 group and the placebo group.

2.1.3.11 Moderate-quality evidence from one RCT of a total of 73 children showed that total analgesic use did not differ significantly between the PP188 group and the placebo group (MD −0.19 MEU (morphine-equivalent units)/kg, CI −0.47 to 0.09 MEU/kg).

2.1.3.12 Moderate-quality evidence from one RCT of a total of 73 children showed that the length of stay in hospital did not differ significantly between the PP188 group and the placebo group.

Important outcomes

2.1.3.13 Low-quality to very-low-quality evidence from two RCTs with a total of 280 patients showed that the duration of the painful episode did not differ significantly between the PP188 group and the placebo group.

2.1.3.14 Moderate-quality evidence from one RCT of a total of 73 children showed that the duration of the painful episode was significantly shorter in the PP188 group compared with the placebo group (MD −21.51 hours, CI −39.71 to −3.31 hours).

Tinzaparin (low-molecular-weight heparin) compared with placebo

Critical outcomes

2.1.3.15 Low-quality evidence from one RCT of a total of 253 patients (12 years and over) showed that treatment with tinzaparin was associated with two minor bleeding events

This study (Quari et al. 2007) did not report the number of adverse events, if any, in the control group. The minor bleeding events in the intervention group were treated by stopping tinzaparin.

2.1.3.16 Low-quality evidence from one RCT of a total of 253 patients showed that the length of stay in hospital was significantly shorter in the group receiving tinzaparin at therapeutic dose as an adjunct treatment compared with the placebo group (MD = −4.98 days, CI −5.48 to −4.48 days).

Important outcomes

2.1.3.17 Low-quality evidence from one RCT of a total of 253 patients (12 years and over) showed that the duration of the painful episode

was significantly shorter in the group receiving tinzaparin (a low-molecular-weight heparin) at therapeutic dose as an adjunct treatment compared with the placebo group (MD −1.78 day, CI −1.94 to −1.62 days)

Methylprednisolone compared with placebo

Critical outcomes

2.1.3.18 *Low-quality evidence from one RCT of a total of 46 children showed no significant differences between the methylprednisolone group and the placebo group in the number of doses of morphine per episode (6.5 compared with 8.7; no p-value reported) or the amount of morphine received (0.82 compared with 0.97 mg/kg; no p-value reported).*

2.1.3.19 *Moderate-quality evidence from one RCT of a total of 30 children showed that cumulative morphine requirements were significantly lower in the methylprednisolone group compared with the placebo group at 3 hours (MD −2.00 CI −3.57 to −0.43), 4 hours (MD −2.27, CI −4.24 to −0.30), 5 hours (MD −2.70, CI −5.07 to −0.33) and 6 hours (MD −2.95, CI −5.51 to −0.39) after the start of treatment.*

2.1.3.20 *Low-quality evidence from one RCT of a total of 56 children showed no significant difference in the risk of using rescue doses between the methylprednisolone group and the placebo group (RR 0.49, CI 0.14 to 1.72).*

2.1.3.21 *Moderate-quality evidence from one RCT of a total of 30 children showed that mean rescue doses were significantly lower in the methylprednisolone group compared with the placebo group, although this difference was small (MD −0.95 mg, CI −1.70 to −0.20 mg).*

2.1.3.22 *Moderate-quality to low-quality evidence from two RCTs with a total of 86 children showed that there were significantly fewer events of nausea (2 compared with 9 events) and vomiting (0 compared with*

7 events, p < 0.05) in the methylprednisolone group compared with the placebo group, or that no complications were observed in either group.

Important outcomes

2.1.3.23 *Moderate-quality evidence from one RCT of a total of 30 children showed that no patients in either group returned to the emergency department within 48 hours.*

2.1.3.24 *Low-quality evidence from one RCT of a total of 56 children showed no significant difference in the risk of readmission within 2 weeks between the methylprednisolone group and the placebo group.*

Pentoxifylline (pentoxiphyllin) compared with placebo

Critical outcomes

2.1.3.25 *Low-quality evidence from one RCT of a total of 36 children showed no significant difference in the risk of adverse events between the pentoxifylline group and the placebo group.*

Important outcomes

2.1.3.26 *Low-quality evidence from one RCT of a total of 36 children showed that the duration of the painful episode was significantly shorter in the pentoxifylline group compared with the placebo group (MD −24.80 hours, CI −46.74 to −2.86 hours).*

Oxygen compared with air

Critical outcomes

2.1.3.27 *Moderate-quality evidence from one RCT of a total of 25 children showed that the mean hourly morphine dose did not differ significantly between a group treated with 50% oxygen through a Venturi mask and a group treated with room air through a Venturi mask.*

2.1.3.28 Moderate-quality evidence from one RCT of a total of 25 children showed that the mean length of stay in hospital did not differ significantly between a group treated with 50% oxygen through a Venturi mask and a group treated with room air through a Venturi mask.

Important outcomes

2.1.3.29 Moderate-quality evidence from one RCT of a total of 25 children showed that the duration of the painful episode did not differ significantly between a group treated with 50% oxygen through a Venturi mask and a group treated with room air through a Venturi mask.

Nitric oxide compared with placebo

Critical outcomes

2.1.3.30 Very-low-quality evidence from one RCT of a total of 18 patients showed a significantly larger mean total reduction in VAS ratings at 4 hours in the nitric oxide group compared with the placebo group (reduction of 6.3 [SD 2.2] compared with 2.97 [SD 2.1]; p = 0.02) .

2.1.3.31 Low-quality evidence from one RCT of a total of 150 patients showed no significant difference in mean VAS pain ratings at 24 hours between the nitric oxide group and the placebo group.

2.1.3.32 Low-quality evidence from one RCT of a total of 150 patients showed no significant difference in the median amount of opioids used in the first 8 hours between the nitric oxide group (0.28 mg/kg; interquartile range [IQR] 0.09–0.54 mg/kg) and the placebo group (0.23 mg/kg; IQR 0.07–0.70 mg/kg) (p = 0.74).

2.1.3.33 Low-quality evidence from one RCT of a total of 150 patients showed no significant difference in the risk of adverse events between the nitric oxide group and the placebo group.

2.1.3.34 Low-quality evidence from one RCT of a total of 150 patients showed no significant difference in the median length of stay in hospital between the nitric oxide group (4.1 days, IQR 2.0–6.0 days) and the placebo group (3.1 days, IQR 1.7–6.4) (p = 0.30).

2.1.3.35 Very-low-quality evidence from one RCT of a total of 170 children showed no significant difference in the mean VAS pain rating between the nitric oxide group and the placebo group.

2.1.3.36 Very-low-quality evidence from one RCT of 20 children showed that the use of analgesia was significantly reduced at 6 hours in the nitric oxide group compared with the placebo group (0.29 compared with 0.44mg/kg, p = 0.03). Differences were not significant at 4 and 24 hours.

2.1.3.37 Very-low-quality evidence from one RCT of 20 children showed that there were no adverse events in either the nitric oxide group or the placebo group.

2.1.3.38 Very-low-quality evidence from one RCT of 20 children showed no significant difference in the length of stay in hospital between the nitric oxide group and the placebo group.

Important outcomes

2.1.3.39 Low-quality evidence from one RCT of a total of 150 patients showed no significant difference in the median time to resolution of vaso-occlusive crisis between the nitric oxide group (73 hours, CI 46.0–91.0 hours) and the placebo group (65.5 hours, CI 48.1–84.0 hours) (p = 0.87).

2.1.3.40 Low-quality evidence from one RCT of a total of 150 patients showed no significant difference in the risk of readmission within 30 days between the nitric oxide group and the placebo group.

Primary analgesia

PCA morphine compared with dose-adjusted continuous intravenous morphine

Critical outcomes

2.1.3.41 *Moderate-quality evidence from one RCT of a total of 25 episodes showed no significant differences in mean VAS or verbal response pain ratings 2 days and 5 days after treatment between the PCA morphine group and the continuous intravenous morphine group.*

2.1.3.42 *Moderate-quality evidence from one RCT of a total of 25 episodes showed that the median morphine hourly dose (0.5 compared with 2.4 mg/hour, p = 0.0001) and total dose (33 compared with 260 mg, p = 0.02) were significantly lower in the PCA group compared with the continuous intravenous morphine group.*

2.1.3.43 *Moderate-quality evidence from one RCT of a total of 25 episodes showed no significant difference in the risk of using additional or rescue analgesia if there was no adequate pain relief between the PCA morphine group and the continuous intravenous morphine group.*

2.1.3.44 *Moderate-quality evidence from one RCT of a total of 25 episodes showed that median side-effect scores for nausea (median 11, IQR 3 to 21, compared with median 18, IQR 3 to 55, p = 0.045) and constipation (median 30, IQR 10 to 40, compared with median 45, IQR 36 to 59, p = 0.02) were significantly lower in the PCA morphine group compared with the continuous intravenous morphine group.*

2.1.3.45 *Moderate-quality evidence from one RCT of a total of 25 episodes showed that the length of stay in hospital did not differ significantly between the PCA morphine group and the continuous intravenous morphine group.*

PCA morphine compared with intermittent intravenous morphine

Critical outcomes

2.1.3.46 *Low-quality evidence from one RCT of a total of 45 patients showed no significant differences in VAS pain ratings at 8 hours between the PCA morphine group and the intermittent intravenous morphine group.*

This study (Gonzalez et al. 1991) assessed outcomes during two phases. The second phase involved the use of higher doses of morphine in both groups compared with the first phase.

2.1.3.47 *Low-quality evidence from one RCT of a total of 45 patients showed that the total number of doses was significantly higher in the PCA morphine group compared with the intermittent intravenous morphine group in both phase 1 (6.5 compared with 35.5 mg, $p < 0.001$) and phase 2 (4.9 compared with 11.6 mg, $p < 0.001$). There were no significant differences between the groups in terms of the total amount of morphine administered in both phases.*

2.1.3.48 *Low-quality evidence from one RCT of a total of 45 patients showed no significant differences in the risk of requiring an increased dose of analgesia between the PCA morphine group and the intermittent intravenous morphine group during both phases.*

In this study (Gonzalez et al. 1991), if the initial phase 1 regimes failed to provide adequate pain relief (measured as visual linear analogue pain intensity score < 50 mm) within a minimum of 3 hours, the dose of morphine was increased to 6 mg in the intermittent intravenous group and to 1.5 mg with a 6-minute lock-out in the PCA group. During phase 2, doses were increased to 3.3 mg in the PCA group and to 10 mg in the intermittent group every 30 to 60 minutes as needed.

2.1.3.49 Low-quality evidence from one RCT of a total of 45 patients showed no significant difference in the risk of adverse events between the PCA morphine group and the intermittent intravenous morphine group during both phases.

2.1.3.50 Very-low-quality evidence from one RCT of a total of 45 patients showed no significant difference in the mean length of stay in hospital between the PCA morphine group and the intermittent intravenous morphine group during both phases.

Oral morphine compared with intravenous morphine

Critical outcomes

2.1.3.51 Moderate-quality evidence from one RCT of a total of 50 children showed no significant differences in pain ratings between the oral morphine group and the intravenous morphine group.

2.1.3.52 Moderate-quality evidence from one RCT of a total of 50 children showed that the daily morphine dose was significantly higher in the oral morphine group compared with the intravenous morphine group (MD 2.18 mg/kg, CI 1.86 to 2.50 mg/kg).

2.1.3.53 Moderate-quality evidence from one RCT of a total of 50 children showed that the mean rescue dose per day did not differ significantly between the oral morphine group and the intravenous morphine group.

2.1.3.54 Moderate-quality evidence from one RCT of a total of 50 children showed that the frequency and severity of adverse events did not differ significantly between the oral morphine group and the intravenous morphine group.

Ketorolac compared with placebo

Critical outcomes

2.1.3.55 Moderate-quality evidence from one RCT of a total of 18 patients showed no significant difference in mean VAS pain ratings at

4 hours between the intramuscular ketorolac group and the placebo group.

2.1.3.56 *Moderate-quality evidence from one RCT of a total of 20 patients showed significant reductions in VAS score in the intravenous ketorolac group on day 1 (MD −1.40, CI −2.63 to −0.17), day 3 (MD −2.38, CI −4.41 to −0.35) and day 4 (MD −2.27, CI −4.26 to −0.28) compared with the placebo group. The mean verbal categorical score was also significantly lower in the ketorolac group (1.1 compared with 1.7, $p < 0.05$), but the mean pain relief score did not differ significantly between the two groups.*

2.1.3.57 *Moderate-quality evidence from one RCT of a total of 18 patients showed that the mean amount of pethidine (meperidine) used at 4 hours did not differ significantly between the intramuscular ketorolac group and the placebo group.*

In this study (Wright et al. 1992), patients were given further intravenous doses of pethidine every 30 minutes during the study period as needed, based on their pain intensity rated on a categorical scale. Patients with ‘mild’ or ‘moderate’ pain were given 25 mg pethidine and those with ‘severe’ pain were given 50 mg. Patients without pain were not given further doses of pethidine unless pain recurred.

2.1.3.58 *Moderate-quality evidence from one RCT of a total of 20 patients showed that the mean total dose of pethidine was significantly lower in the intravenous ketorolac group compared with the placebo group (MD −937.30 mg, CI −1802.7 to −71.9 mg). There was no significant difference between groups in the mean daily dose of pethidine.*

In this study (Perlin et al. 1994), 100 mg pethidine was administered every 3 hours if the patient reported moderate pain to the staff nurse and requested pain relief.

2.1.3.59 Moderate-quality evidence from one RCT of a total of 20 patients showed that the median length of stay in hospital was significantly lower in the intravenous ketorolac group compared with the placebo group (3.3 compared with 7.2 days, p < 0.05).

2.1.3.60 Moderate-quality evidence from one RCT of 41 visits by a total of 29 children showed that mean VAS pain ratings did not differ significantly between the intravenous ketorolac group and the placebo group up to 6 hours after treatment.

2.1.3.61 Moderate-quality evidence from one three-arm trial of a total of 45 children showed that median pain ratings at 6 hours (assessed using the nine faces pain scale) were significantly lower in the intravenous ketorolac group compared with the placebo group (2 compared with 3, p < 0.05).

In this study (Adawy et al. 2005), pain was assessed using the nine faces pain scale, which ranges from 0 to 9 (with 0 indicating no pain).

2.1.3.62 Very-low-quality evidence from two RCTs of 71 episodes in children showed that the use of analgesia was reduced in the intravenous ketorolac group compared with the placebo group, but this difference was not significant (pooled MD = −0.01 mg/kg/hour, 95% CI −0.03 to 0.00 mg/kg/hour, p = 0.07).

2.1.3.63 Moderate-quality evidence from one RCT of 30 children showed that mean rescue doses were significantly lower in the intravenous ketorolac group compared with the placebo group (MD −1.10 mg, CI −1.84 to −0.36 mg).

2.1.3.64 Moderate-quality evidence from one RCT of 41 visits by a total of 29 children showed that one patient experienced a local histamine reaction to morphine, but no other adverse events were noted.

2.1.3.65 Moderate-quality evidence from one RCT of a total of 30 children showed that there were significantly fewer events of nausea (2 compared with 9, $p < 0.05$) and vomiting (1 compared with 7, $p < 0.05$) in the intravenous ketorolac group compared with the placebo group.

Important outcomes

2.1.3.66 Moderate-quality evidence from two RCTs of 52 children showed no significant difference in the risk of readmission in the intravenous ketorolac group compared with the placebo group.

Ketoprofen compared with placebo

Critical outcomes

2.1.3.67 Moderate-quality evidence from one RCT of a total of 52 patients showed no significant differences in VAS and categorical pain ratings up to 5 days after treatment between the intravenous ketoprofen group and the placebo group.

2.1.3.68 Moderate-quality evidence from one RCT of a total of 52 patients showed no significant differences in median morphine dose between the intravenous ketoprofen group and the placebo group.

2.1.3.69 Moderate-quality evidence from one RCT of a total of 52 patients showed that the types and frequencies of adverse events were similar for the two groups.

Important outcomes

2.1.3.70 Moderate-quality evidence from one RCT of 52 patients showed no significant difference in the duration of the painful episode between the intravenous ketoprofen group and the placebo group.

Pethidine (meperidine) compared with ketorolac

Critical outcomes

2.1.3.71 Low-quality evidence from one crossover trial of a total of 20 children showed that the ketorolac group had significantly larger decreases in VAS score over 150 minutes compared with the pethidine group ($p < 0.001$), with the greatest decrease in pain scores occurring in first 30 minutes (score of 3.9 for the ketorolac group compared with 5.4 for the pethidine group, $p < 0.001$). There was no significant difference in VAS scores between the crossover groups (pethidine then ketorolac or ketorolac then pethidine) after 150 minutes.

In this study (Grisham and Vichinsky 1996), patients received a parenteral dose of either pethidine (1.5 mg/kg) or ketorolac (1.0 mg/kg) as the first drug. After a 2.5-hour assessment, patients who experienced complete relief were sent home and did not participate in the second phase. Patients with persistent pain received the other drug (that is, those who received pethidine first were given ketorolac and those who received ketorolac first were given pethidine). Each phase lasted for 150 minutes.

2.1.4 Health economic modelling

This is a summary of the modelling carried out for this review question. See appendix F for full details of the modelling carried out for the guideline.

A search for published health economic analyses addressing the questions of interest yielded a total of 1189 unique citations. However, none of these studies analysed both the costs and health consequences of the alternative modes of managing an acute painful sickle cell episode (for details, please see appendix F). In the absence of relevant published literature, an original health economic model was constructed.

Decision problems

Two questions were addressed, based on the literature that had been identified in the review of clinical effectiveness evidence:

- What is the cost effectiveness of administering morphine via patient-controlled analgesia (PCA), compared with continuous intravenous infusion of morphine (C-IV)?
- What is the cost effectiveness of low-molecular-weight heparin (LMWH) as an adjunct to standard care, when compared with standard care alone?

Both questions were explored using the same model structure and, as far as the underlying simulation of an acute painful sickle cell episode was concerned, the same model parameters.

Methods and parameters

The model used a Markov structure, capturing costs and effects associated with a series of discrete health states. Figure 1 presents a simplified representation of the model structure, which was based on the natural history of an acute painful sickle cell episode and inputs from the GDG.

Patients can remain in the 'uncomplicated' state during which their pain is expected to subside progressively until discharge, or they can have a complication which results in a longer duration of hospital stay and/or ongoing morbidity from the complication. Simulated patients entering the 'acute complications' state are also subject to a risk of death. In the model's base case, there is no possibility of death from an uncomplicated episode, as it is assumed that the risk of mortality in acute painful sickle cell episodes arises as a result of acute complications. A proportion of patients are expected to experience adverse effects of treatment while in hospital. The death state and the two discharge states – 'with morbidity' and 'without morbidity' – are absorbing states.

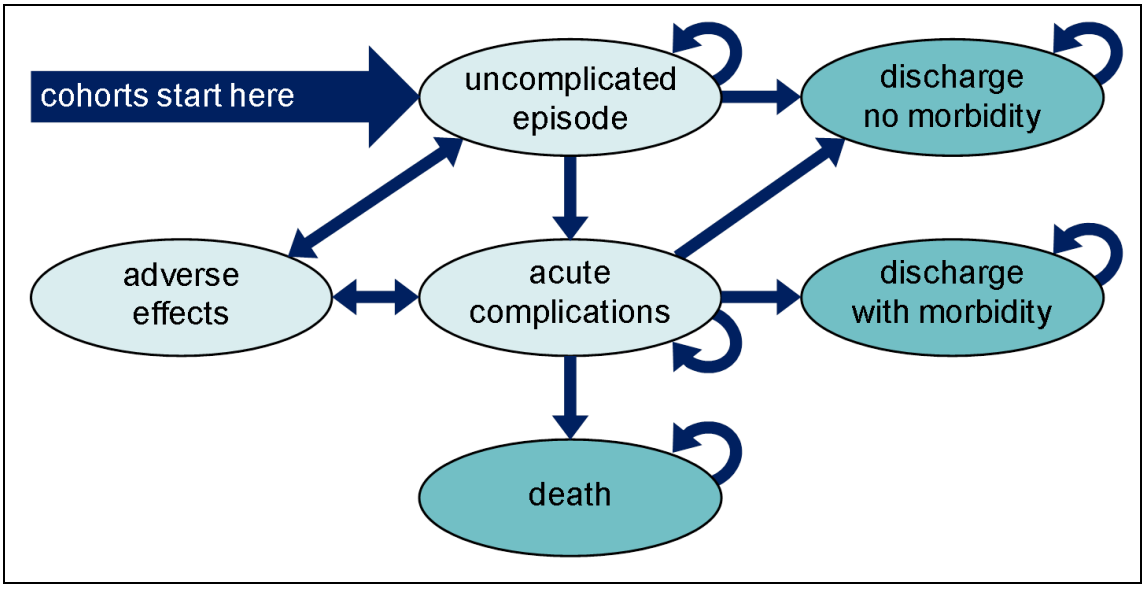

Figure 1 Model structure

In simulating the course of a single acute painful sickle cell episode, the model uses hourly cycles and a time horizon of 28 days. However, the model also calculates the long-term consequences of the episode – such as morbidity and mortality impacts and their associated costs – for the full lifetime of patients.

The model was constructed in Microsoft Excel 2010. Costs and benefits were discounted at 3.5% per annum each.

Modelling pain over time

Because pain (measured by visual analogue scale [VAS]) is the one outcome that is reported with some consistency in effectiveness studies, the model was configured to simulate patient experience as a function of pain level. For this reason, the model assumes a relationship between pain (VAS score) and all of the following:

- health-related quality of life (utility)
- likelihood of complications
- requirement for analgesia
- length of hospital stay (in some scenarios; see below)
- resource use.

Modelling length of hospital stay and likelihood of complications

Average length of stay (LOS) in hospital is a reported outcome in some effectiveness studies (see sections 2.1.2 and 2.1.3). However, none of this evidence originates in the UK and much of it suggests that average LOS is rather longer than would be expected in UK practice, in the opinion of the GDG. Moreover, LOS is likely to be dependent on the severity of the episode (as reflected in assumed baseline VAS score). Therefore, as an alternative to relying on empirical data, the model explored scenarios in which LOS was calculated as a function of pain (VAS score). In these scenarios, simulated patients were assumed to be discharged when their VAS score had fallen to a certain level. In the base case, a VAS score of 3 was selected as an average score at discharge, on the basis of GDG advice. In order to estimate the proportion of each cohort below the score of interest (given a mean and SD VAS score predicted by the model), a beta distribution of pain scores was assumed. This distribution was selected as it is constrained at both ends, enabling the straightforward simulation of scores between 0 and 10 (for full details of technical implementation, see appendix F).

Similarly, there was uncertainty over the best approach to modelling the likelihood of acute complications. There is good evidence that the incidence of acute chest syndrome is related to VAS score (Buchanan et al. 2005). However, the temporal and causal relationship between pain and acute chest syndrome is unclear. Incipient acute chest syndrome could be a cause of pain, in which case pain management can have no impact on the incidence of acute chest syndrome. Alternatively, pain could be a predisposing factor for acute chest syndrome (perhaps mediated via shallow breathing), in which case better management of pain would lead to fewer episodes of acute chest syndrome. Because of this uncertainty, separate scenarios were modelled, in which the likelihood of complications was related either to baseline VAS score alone or to ongoing VAS score (as affected by treatment).

In combination, these two pairs of different assumptions lead to a total of four separate scenarios that were explored in the model:

- **1A:** Independent LOS (empirical, treatment-specific data drawn from effectiveness studies) with a fixed complication rate (based on assumed VAS score at baseline, and therefore unrelated to treatment allocation).
- **1B:** Independent LOS with a dynamic complication rate (based on progress of VAS score over time throughout the model).
- **2A:** Pain-dependent LOS (the average patient is discharged when their VAS score falls to 3 or lower) with a fixed complication rate.
- **2B:** Pain-dependent LOS with a dynamic complication rate.

Relationship between pain and health-related quality of life

No published evidence reporting health-related quality of life (HRQoL) during an acute painful sickle cell episode was identified. However, a member of the GDG was able to provide EQ-5D and VAS data (Anie et al. 2012). The dataset comprised 510 adult UK patients (mean age 29; 62% female) with sickle cell disease who presented with an acute painful episode. Utility weights were calculated for each set of EQ-5D measurements, using UK population tariffs (Kind et al. 1999), and the resulting scores were regressed against VAS score. A random-effects time-series regression model accounting for within-person correlation was used (`xtreg` command in Stata 8.0).

The best fit to the data was achieved using a polynomial function:

$$\text{Utility} = 0.887 - (0.124 \times \text{VAS}) + (0.014 \times \text{VAS}^2) - (0.001 \times \text{VAS}^3)$$

$$R^2 = 0.445$$

This function was used to estimate the baseline utility of people in all states throughout the 28-day acute phase of the model.

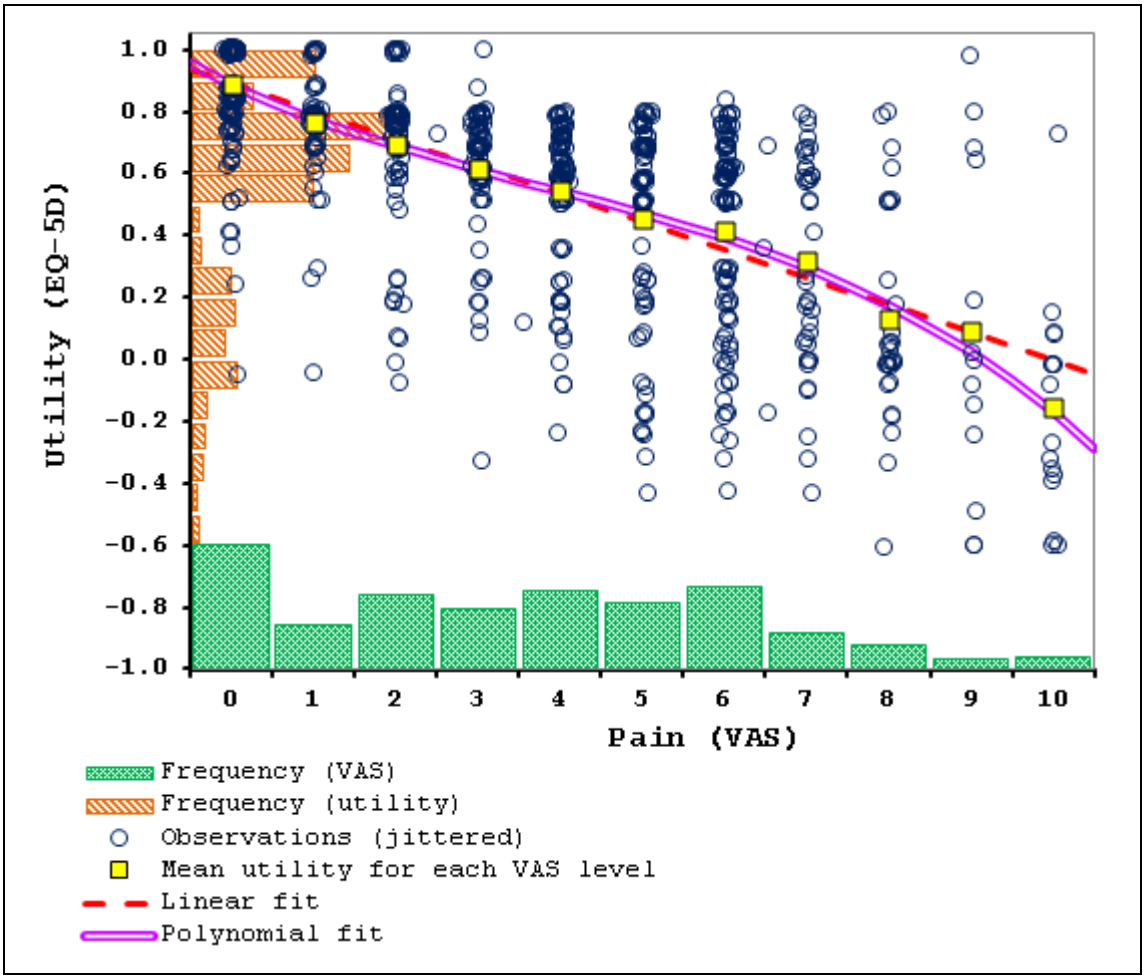

Figure 2 Relationship between pain and utility, with frequency distributions and fitted linear and polynomial models

Costs

The daily cost of hospital admission for an acute painful sickle cell episode was derived from the NHS Reference Cost Guide (2011), using weighted averages of costs recorded in four 'department' categories and three 'currency' codes. The resulting estimates were £589 per day for children and £456 per day for adults.

The cost of ongoing care for patients with sickle cell disease after recovery from an acute painful episode was not included, as the clinical course of the disease is chronic and not directly influenced by management of an acute painful episode. Costs associated with care after stroke events were included, comprising a one-off cost to reflect immediate rehabilitation and an annual cost to reflect ongoing care and support. Additional costs were included to reflect the maintenance transfusion that is routinely performed in people with

sickle cell disease who have had a stroke, including iron chelation therapy for a proportion of people.

Parameters particular to the PCA model

The clinical effectiveness parameters for the PCA model were based on the RCT reported by van Beers et al. (2007), in which 25 episodes of acute painful sickle cell episode were randomly assigned to morphine administration via PCA or via continuous intravenous infusion (C-IV).

Pain (VAS score) over time

Because van Beers et al. (2007) report only a single data point for reduction in VAS score after 2 days of treatment, a simple exponential decline was assumed. To enable the exploration of different starting values for VAS score, it was assumed that the reported relative reduction in pain for each trial arm could be applied. The impact of using an absolute reduction instead was tested in sensitivity analysis.

Length of hospital stay

For LOS, van Beers et al. (2007) report a median and interquartile range for each arm. Weibull functions were fitted to these three data points and used in model scenarios 1A and 1B.

Parameters particular to the LMWH model

The clinical effectiveness parameters for the LMWH model were based on the Saudi Arabian RCT reported by Qari et al. (2007). Investigators randomly assigned 253 adult participants with an acute painful sickle cell episode to a therapeutic dose of LMWH (tinzaparin at 175 units/kg/day) or placebo, in addition to standard care that included intravenous morphine (1 mg per hour) for all participants.

Pain (VAS score) over time

Qari et al. (2007) provide longitudinal data on the pain (VAS) scores of their cohorts over a 7-day period in a graph. These data were extracted and parametric (scaled Weibull) curves were fitted. Although there was a clear, statistically significant difference in VAS score in favour of LMWH in the first 3 days' follow-up, the curves converged and then crossed as follow-up

extended, with a small, non-statistically-significant benefit for the placebo arm on days 6 and 7. Because the model curves were fitted to extracted aggregate data rather than the underlying individual patient data, there was a danger of placing undue emphasis on this feature in the model, and this would be exaggerated as follow-up was extrapolated beyond the observed 7 days. For this reason, a separate curve was fitted to the average experience of the LMWH and placebo cohorts, and both arms were assumed to follow this course from halfway through day 5 onwards. The impact of varying this assumption was tested in sensitivity analysis.

Length of hospital stay

Qari et al. (2007) report mean LOS only, from which it is not possible to infer the shape of the LOS function. Therefore, a Weibull curve was used with a shape parameter imputed from another data source (Orringer et al. 2001).

Types of analysis

Both deterministic analysis (using only point estimates) and probabilistic analysis were conducted to examine cost effectiveness. In the latter, 10,000 Monte-Carlo simulations per scenario – a total of 40,000 iterations overall – were performed, with parameter values randomly sampled from distributions reflecting uncertainty around their true values. Deterministic one-way sensitivity analyses were also conducted to illustrate which model inputs have the greatest impact on the cost–utility results.

Results: PCA compared with C-IV

The deterministic base-case results (Table 15) suggested that PCA is likely to be preferred to C-IV for managing pain during an acute painful sickle cell episode. PCA was associated with modest additional health gains of between 0.002 and 0.003 quality-adjusted life-years (QALYs) per person, depending on the assumptions adopted. The model also predicted average cost savings of £170 to £1329 per person for PCA compared with C-IV. These cost savings were primarily as a result of reduction in length of hospital stay in all four scenarios and also a reduction in complication rates in scenarios 1B and 2B. As a result, PCA dominated C-IV (that is, it was less expensive and more effective) in all four scenarios.

Table 15 Deterministic base-case cost–utility results: PCA compared with C-IV

	Independent LOS						VAS-dependent LOS					
	Single complication rate (Scenario 1A)			Dynamic complications (Scenario 1B)			Single complication rate (Scenario 2A)			Dynamic complications (Scenario 2B)		
	C-IV	PCA	Difference	C-IV	PCA	Difference	C-IV	PCA	Difference	C-IV	PCA	Difference
Costs												
Acute episode:												
Inpatient care	£4301	£3043	−£1258	£4270	£2974	−£1296	£1106	£929	−£178	£909	£712	−£197
PCA consumables	£0.00	£32.14	£32.14	£0.00	£31.54	£31.54	£0.00	£15.78	£15.78	£0.00	£13.87	£13.87
Morphine	£26.00	£3.30	−£22.70	£26.00	£3.30	−£22.70	£27.00	£18.84	−£8.16	£27.00	£18.84	−£8.16
Subtotal	£4,327	£3078	−£1249	£4296	£3009	−£1287	£1133	£963	−£170	£936	£745	−£191
Long-term costs:												
Stroke rehabilitation	£532.69	£532.69	£0.00	£134.29	£92.52	−£41.76	£532.69	£532.69	£0.00	£58.46	£44.63	−£13.83
Total	£4860	£3611	−£1249	£4431	£3102	−£1329	£1666	£1,496	−£170	£994	£789	−£205
Effects												
Episodes of ACS	6.26%	6.26%		1.58%	1.09%		6.26%	6.26%		0.69%	0.52%	
Strokes	0.23%	0.23%		0.06%	0.04%		0.23%	0.23%		0.03%	0.02%	
Deaths	0.18%	0.18%		0.05%	0.03%		0.18%	0.18%		0.02%	0.02%	
Mean LOS (days)	9.440	6.678		9.372	6.528		2.428	2.038		1.994	1.562	
QALYs:												
Acute episode	0.062	0.063	0.002	0.062	0.064	0.002	0.062	0.063	0.002	0.063	0.064	0.002
Subsequent LE (discounted)	13.029	13.029	0.000	13.040	13.042	0.001	13.029	13.029	0.000	13.043	13.043	0.000
Total	**13.090**	**13.092**	**0.002**	**13.103**	**13.106**	**0.003**	**13.090**	**13.092**	**0.002**	**13.105**	**13.107**	**0.002**
ICER	**PCA dominates**			**PCA dominates**			**PCA dominates**			**PCA dominates**		
Incremental NMB:												
MAICER = £20, 000 / QALY	£1282.04			£1388.03			£202.27			£245.81		
MAICER = £30, 000 / QALY	£1298.60			£1417.62			£218.43			£266.28		

ACS, acute chest syndrome; C-IV, continuous intravenous infusion; ICER, incremental cost-effectiveness ratio; LE, life expectancy; LOS, length of (hospital) stay; MAICER, maximum acceptable ICER;NMB, net monetary benefit; PCA, patient-controlled analgesia; QALY, quality-adjusted life-year; VAS, visual analogue scale.

One-way deterministic sensitivity analysis

In scenarios 1A and 1B, the model was sensitive to changes in median LOS and, to a lesser extent, relative reduction in VAS score, the daily cost of inpatient care and the mean VAS score at baseline. However, changes to these parameters were not, in themselves, sufficient to affect cost–utility conclusions (that is, PCA remained cost effective with all values tested).

In scenarios 2A and 2B, the model was most sensitive to the relative reduction in VAS score and, to a lesser extent, the mean VAS score at baseline and VAS score threshold for discharge. The analysis suggested that cost–utility conclusions could potentially be altered when parameters for the relative reduction in VAS score were varied. Therefore, threshold analyses were conducted to identify the point at which those conclusions would be altered. These analyses suggest that providing PCA remains the most cost-effective option unless the relative reduction in VAS score for people on C-IV exceeds 51.7% (base case: 40.7%), or the relative reduction in VAS score for people on PCA drops below 41.5% (base case: 52.8%). This is closely equivalent to saying that the comparator with the superior VAS score reduction will be the option with a favourable cost–utility profile. This is unsurprising since, in scenarios 2A and 2B, all critical cost and QALY outputs are dependent on modelled VAS score.

Probabilistic sensitivity analysis

Table 16 summarises mean values from 40,000 Monte-Carlo simulations.

In scenarios 1A and 1B, PCA was associated with greater QALY gains than C-IV in around 72% of simulations and lower costs than C-IV in over 95% of simulations. Results are unrelated to the assumed maximum acceptable ICER. PCA would have more than a 9-in-10 chance of being cost effective irrespective of the value that society is assumed to place on each QALY gained.

Table 16 PCA compared with C-IV: summary of cost–utility results (mean estimates) from probabilistic sensitivity analysis

	Independent LOS		VAS-dependent LOS		All four scenarios combined
	Single complication rate (Scenario 1A)	Dynamic complications (Scenario 1B)	Single complication rate (Scenario 2A)	Dynamic complications (Scenario 2B)	
C-IV					
Costs	£4515	£4367	£1511	£1167	£2890
QALYs	12.986	13.027	13.010	12.990	13.003
PCA					
Costs	£3261	£3065	£1233	£860	£2105
QALYs	12.989	13.030	13.012	12.992	13.006
Incremental					
Costs	−£1254	−£1302	−£278	−£308	−£786
QALYs	0.002	0.003	0.002	0.002	0.002
ICER	**PCA dominates**	**PCA dominates**	**PCA dominates**	**PCA dominates**	**PCA dominates**
Incremental NMB:					
at £20,000 / QALY	£1299	£1358	£322	£355	£833
at £30,000 / QALY	£1322	£1386	£344	£378	£857
Probability cost effective:					
at £20,000 / QALY	0.961	0.956	0.690	0.686	0.823
at £30,000 / QALY	0.962	0.957	0.691	0.686	0.824

C-IV, continuous intravenous infusion; ICER, incremental cost-effectiveness ratio; LOS, length of (hospital) stay; NMB, net monetary benefit; PCA, patient-controlled analgesia; QALY, quality-adjusted life-year; VAS, visual analogue scale.

In scenarios 2A and 2B, there was an obvious correlation between costs and QALYs. In simulations in which PCA was estimated to provide less health gain than C-IV (negative incremental QALYs), it was also highly likely to be associated with increased costs. Conversely, those simulations in which PCA appeared more effective were also those in which it appeared less expensive. This is a predictable finding: as demonstrated in one-way sensitivity analysis, the model is almost entirely driven by VAS score in scenarios 2A and 2B. Accordingly, it is to be expected that probabilistic results are very heavily dependent on randomly assigned VAS values: when decline in VAS score is sampled to be superior in PCA than C-IV, PCA will dominate C-IV, and vice versa. However, because the distributions from which the model samples favour PCA in the majority of cases, there is a preponderance of data points in the South-East (dominant) quadrant of the cost–utility plane (see appendix F). According to this analysis, PCA has a little less than a 7-in-10 chance of

being cost effective irrespective of the value that society is assumed to place on each QALY gained.

Overall, the results substantiate those produced in the deterministic analysis. Considering all four scenarios combined, PCA appears cost effective with about 82% certainty when compared with C-IV, irrespective of the value that society is assumed to place on each QALY gained

Discussion: PCA compared with C-IV

Deterministic and probabilistic analyses strongly suggest that, when compared with morphine delivered by C-IV, morphine delivered by PCA is likely to be the cheaper and most effective (dominant) approach.

However, GDG opinion suggests that C-IV administration of morphine is not very common in UK practice, and that a more realistic comparator for PCA would be the intermittent injection of morphine via an intramuscular or subcutaneous route. However, there are no data on the effectiveness of an intermittent regimen, so we could not incorporate this comparator in our cost–utility model. For this reason, we performed an additional cost-minimisation analysis exploring differences in resource-use between PCA and intermittent approaches (see below).

The analysis did not account for the purchase price of PCA pumps, as prices are variable, and many hospital units already have access to pumps that have been acquired for other indications. However, it was calculated that the expected cost savings would offset an average purchase price of around £2500 (personal communication from manufacturer of one type of PCA pump), if it was assumed that each pump would be used for a minimum of between two and nine acute painful sickle cell episodes (depending on the scenario adopted in the analyses).

Results: LMWH

In its deterministic base case (Table 17), the economic model suggested that LMWH – when used as an adjunct to standard care – is likely to be preferred to standard care alone for managing pain during an acute painful sickle cell episode. On average, LMWH was associated with modest health gains of

between 0.001 and 0.004 QALYs (depending on the assumption adopted). Treatment was also associated with cost savings ranging from £373 to £2218 per person when compared with standard care. These cost savings were primarily as a result of reduction in LOS in all four scenarios, and also because of a reduction in complication rates in scenarios 1B and 2B. As a result, standard care was dominated by (that is, was more expensive and less effective than) LMWH in all four scenarios.

One-way deterministic sensitivity analysis

In scenarios 1A and 1B, the model was most sensitive to changes in the parameters influencing modelled LOS (particularly the shape parameter applied to both arms, as well as the mean LOS used for each arm). However, none of the changes in these parameters had sufficient impact to affect the cost–utility conclusions (that is, LMWH remained cost effective with all values tested).

In scenarios 2A and 2B, the model was sensitive to all VAS parameters and, in particular, the threshold for shared VAS scores (that is, the point in the model at which separate VAS profiles for each arm were discontinued and a common distribution assumed). This was the only parameter which might, on its own, have an important influence on cost–utility conclusions. Therefore, a threshold analysis was conducted to identify the point at which those conclusions would be altered. This analysis suggested that LMWH would remain cost effective unless the threshold for shared VAS scores was set at zero. In other words, LMWH appeared to provide slightly worse value for money than standard care alone when its effectiveness profile was set to be identical to that of the placebo arm. However, LMWH remained cost effective even when its benefits were assumed to accrue over 1 day only.

Table 17 Deterministic base-case cost–utility results: LMWH

	Independent LOS						VAS-dependent LOS					
	Single complication rate (Scenario 1A)			Dynamic complications (Scenario 1B)			Single complication rate (Scenario 2A)			Dynamic complications (Scenario 2B)		
	Placebo	LMWH	Difference	Placebo	LMWH	Difference	Placebo	LMWH	Difference	Placebo	LMWH	Difference
Costs												
Acute episode:												
Inpatient care	£5524	£3355	−£2169	£5507	£3245	−£2262	£1067	£686	−£381	£853	£451	−£402
LMWH	£0.00	£68.27	£68.27	£0.00	£66.21	£66.21	£0.00	£17.05	£17.05	£0.00	£12.57	£12.57
Morphine	£26.00	£3.30	−£22.70	£26.00	£3.30	−£22.70	£23.16	£14.53	−£8.63	£23.16	£14.53	−£8.63
Subtotal	£5550	£3427	−£2124	£5533	£3314	−£2218	£1090	£717	−£373	£876	£478	−£398
Long-term costs:												
Stroke rehabilitation	£532.69	£532.69	£0.00	£158.47	£72.15	−£86.31	£532.69	£532.69	£0.00	£72.96	£22.72	−£50.24
Total	£6083	£3959	−£2124	£5691	£3386	−£2305	£1623	£1250	−£373	£949	£500	−£448
Effects												
Episodes of ACS	6.26%	6.26%		1.86%	0.85%		6.26%	6.26%		0.86%	0.27%	
Strokes	0.23%	0.23%		0.07%	0.03%		0.23%	0.23%		0.03%	0.01%	
Deaths	0.18%	0.18%		0.06%	0.03%		0.18%	0.18%		0.03%	0.01%	
Mean LOS (days)	12.125	7.363		12.086	7.122		2.342	1.505		1.871	0.989	
QALYs:												
Acute episode	0.063	0.064	0.001	0.063	0.065	0.001	0.063	0.064	0.001	0.064	0.065	0.001
Subsequent LE (discounted)	13.029	13.029	0.000	13.040	13.042	0.003	13.029	13.029	0.000	13.042	13.044	0.001
Total	13.091	13.093	0.001	13.103	13.107	0.004	13.091	13.093	0.001	13.106	13.108	0.003
ICER	**LMWH dominates**			**LMWH dominates**			**LMWH dominates**			**LMWH dominates**		
Incremental NMB:												
MAICER = £20,000 / QALY	£2148.15			£2382.79			£396.66			£503.71		
MAICER = £30,000 / QALY	£2160.27			£2421.84			£408.58			£531.35		

ACS, acute chest syndrome; ICER, incremental cost-effectiveness ratio; LE, life expectancy; LMWH, low-molecular-weight heparin; LOS, length of (hospital) stay; MAICER, maximum acceptable ICER; NMB, net monetary benefit; QALY, quality-adjusted life-year; VAS, visual analogue scale.

Probabilistic sensitivity analysis

Table 18 summarises mean values from 40,000 Monte-Carlo simulations.

Table 18 LMWH: summary of cost–utility results (mean estimates) from probabilistic sensitivity analysis

	Independent LOS		VAS-dependent LOS		
	Single complication rate (Scenario 1A)	**Dynamic complications (Scenario 1B)**	**Single complication rate (Scenario 2A)**	**Dynamic complications (Scenario 2B)**	**All four scenarios combined**
C−IV					
Costs	£5733	£5610	£1283	£917	£3386
QALYs	12.998	13.019	13.007	13.018	13.010
PCA					
Costs	£3614	£3361	£946	£539	£2115
QALYs	13.000	13.020	13.008	13.019	13.012
Incremental					
Costs	−£2120	−£2249	−£337	−£378	−£1271
QALYs	0.001	0.002	0.001	0.001	0.001
ICER	**LMWH dominates**	**LMWH dominates**	**LMWH dominates**	**LMWH dominates**	**LMWH dominates**
Incremental NMB:					
at £20,000 / QALY	£2140	£2289	£357	£355	£833
at £30,000 / QALY	£2151	£2308	£367	£378	£857
Probability cost effective:					
at £20,000 / QALY	1.000	1.000	0.989	0.993	0.995
at £30,000 / QALY	1.000	1.000	0.989	0.993	0.996

ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin; LOS, length of (hospital) stay; NMB, net monetary benefit; QALY, quality-adjusted life-year; VAS, visual analogue scale.

In scenarios 1A and 1B, LMWH produced more QALYs and was cheaper than standard care alone in almost all cases. It would be highly unlikely, given the specified uncertainty across all parameters in the model, for people who receive adjunctive LMWH therapy to experience a net disadvantage in QALYs gained (across 20,000 simulations for these scenarios, only 9 resulted in higher QALYs for standard care alone). As a consequence, LMWH is very nearly certain to be considered cost effective, regardless of the value that society is assumed to place on QALY gains.

Results in scenarios 2A and 2B were similar to those in scenarios 1A and 1B, with the exception that there were smaller cost savings, although QALY gains were not much reduced. As above, in these two scenarios it appears highly

unlikely that people who receive adjunctive LMWH therapy experience a net disadvantage in QALYs. Again, LMWH would almost certainly be considered cost effective regardless of what the ceiling value per QALY gained is.

Overall, the results substantiate those produced in the deterministic analysis. Considering all four scenarios combined, LMWH can be concluded as being cost effective with greater than 99.5% certainty when compared with standard care alone, irrespective of the value that society is assumed to place on each QALY gained.

Discussion: LMWH

Deterministic and probabilistic analyses strongly suggest that, if the evidence from the Saudi Arabian RCT reported by Qari et al. (2007) can be assumed to generalise to the UK setting, the use of LMWH would both reduce costs and improve outcomes, making it excellent value for money. However, these results should be treated with substantial caution. The provision of healthcare in Saudi Arabia and the characteristics of the trial participants are likely to be very different from those encountered in the UK.

Moreover, in the UK, adult patients who are admitted for an acute painful sickle cell episode routinely receive a low dose of LMWH as prophylaxis against venous thromboembolism. Therefore a placebo-controlled RCT does not provide applicable evidence for the UK decision-making context: prophylactic-dose LMWH would be the relevant comparator against which to assess the clinical and cost effectiveness of therapeutic-dose LMWH in UK practice.

For this reason, the effectiveness of therapeutic-dose LMWH in this analysis may have been substantially overestimated. However, the model shows that, even if relatively modest health gains could be achieved by therapeutic-dose LMWH in comparison with prophylactic-dose LMWH, the routine use of the higher dose could be expected to represent an effective use of NHS resources.

Although prophylactic-dose LMWH is not routinely given to children in the UK, the effectiveness – and, hence, cost effectiveness – of therapeutic-dose LMWH in this population is unknown.

Additional cost-minimisation analysis: PCA compared with intermittent administration of morphine

As noted above, the GDG expressed concern that, in assessing the cost effectiveness of PCA, the C-IV regimen for which comparative effectiveness data were available did not represent an ideal comparator. This is because a more common approach in UK practice (in cases in which PCA is not currently used) is to administer morphine using a regimen of intermittent injections. However, no data on the effectiveness of this approach were available. Therefore, a cost-minimisation analysis comparing PCA with intermittent administration of morphine was undertaken, in which the two approaches were assumed to be identically effective (in terms of patient outcomes) and associated with identical consumption of morphine (both dose and duration or requirement).

Particular attention was focused on the amount of nursing time required, as the GDG identified this as the primary difference in resource use between the two approaches. The GDG provided estimates of the typical nursing time needed to set up and then administer morphine in the two regimens. Separate estimates were obtained from GDG members whose primary experience was of adult and paediatric clinical environments. It was assumed that the choice of administration regimen would have no impact on the time of other healthcare professionals, including doctors. The costs of necessary consumables (syringes and PCA administration sets) were also included in the analysis.

Parameters and results of the analysis for adults are shown in tables 19 and 20 respectively. The same data for children appear in tables 21 and 22.

Table 19 Cost-minimisation analysis of PCA compared with intermittent administration of morphine: parameters (adults)

Parameter	Intermittent		PCA		Source
	n[1]	Mean[2]	n[1]	Mean[2]	
No. of doses/changes per day	4	10	4	1.75	GDG
Administration time:					
initial set-up (minutes)	4	10	4	21.25	GDG
time per subsequent dose/change (minutes)	4	7.5	4	10	GDG
nurses per set-up/dose/change	4	2	4	2	GDG
Observations:					
no. of observations required/day	4	11.5	4	11	GDG
nurses per observation	4	1	4	1	GDG
length of time per observation (minutes)	4	4.25	4	5.75	GDG
Resource use:					
no. of syringes (per day)	4	10	4	1.75	GDG
no. of PCA administration sets (per day)	4	0	2	0.33	GDG
average length of stay (days)	Mean = 3.7				HES 2010/11
Costs:					
PCA administration set (£)	9.25				NHS tariff
PCA pump (£)	2495				Manufacturer
5 ml syringe hypodermic (£)	0.11				NHS catalogue 2011
nursing time per hour (£)	52				PSSRU 2011

[1] Number of GDG members providing estimates; [2] mean of values provided by GDG members .

Table 20 Cost-minimisation analysis of PCA compared with intermittent administration of morphine: results (adults)

	Intermittent	PCA
Nursing time:		
initial set-up time (hours)	0.33	0.71
total time for subsequent doses/changes (hours/episode)	9.00	1.82
total observation time (hours/episode)	3.01	3.90
total nursing time (hours/episode)	12.35	6.43
difference in total nursing time (hours/episode)	5.91	
nursing costs per episode (£)	642.06	334.55
Cost of consumables per episode (£)	4.07	19.27
Cost savings per episode for PCA compared with intermittent (£)	292.30	

Table 21 Cost-minimisation analysis of PCA compared with intermittent administration of morphine: parameters (children)

Parameter	Intermittent		PCA		Source
	n[1]	Mean[2]	n[1]	Mean[2]	
No. of doses/changes per day	1	6	1	1	GDG
Administration time:					
initial set-up (minutes)	1	10	2	31.25	GDG
time per subsequent dose/change (minutes)	1	10	2	16.25	GDG
nurses per set-up/dose/change	1	2	2	2	GDG
Observations:					
no. of observations required/day	1	10	2	15	GDG
nurses per observation	1	1	2	1	GDG
length of time per observation (minutes)	1	5	2	5.271	GDG
Resource use:					
syringes (per day)	1	12	2	1	GDG
PCA administration sets (per day)	1	0	2	0.33	GDG
average length of stay (days)	Mean = 3.7				HES 2010/11
Costs:					
PCA administration set (£)	9.25				NHS tariff
PCA pump (£)	2495				Manufacturer
5 ml syringe hypodermic (£)	0.11				NHS catalogue 2011
nursing time per hour (£)	52				PSSRU 2011

[1] Number of GDG members providing estimates; [2] mean of values provided by GDG members.

Table 22 Cost-minimisation analysis of PCA compared with intermittent administration of morphine: results (children)

	Intermittent	PCA
Nursing time:		
initial set-up time (hours)	0.33	1.04
total time for subsequent doses/changes (hours/episode)	7.07	1.46
total observation time (hours/episode)	3.08	4.88
total nursing time (hours/episode)	10.48	7.38
difference in total nursing time (hours/episode)	3.10	
nursing costs per episode (£)	545.13	383.74
Cost of consumables per episode (£)	4.95	18.94
Cost savings per episode for PCA compared with intermittent (£)	147.40	

Discussion: cost-minimisation analysis of PCA compared with intermittent administration of morphine

These analyses suggest that, in both adults and children, PCA is likely to be a cost-saving method of administering morphine compared with intermittent injections, if it can be assumed that it is no less effective an approach. However, for the same reasons as for the cost–utility model described above,

these analyses do not account for the purchase price of PCA pumps. It is calculated that the expected cost savings would offset an average purchase price of around £2500 (personal communication from manufacturer of one type of PCA pump) if each pump is used for a minimum of nine episodes (adults) or 17 episodes (children). It is possible that these results are conservative, because GDG opinion and evidence comparing PCA with other modes of administration suggests that PCA may be associated with lower doses of morphine, shorter length of hospital stay and higher levels of patient satisfaction, none of which are reflected in this analysis.

2.1.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes after evidence synthesis and agreed that pain rating, amount of analgesia used, use of additional or rescue doses of analgesia, length of stay in hospital and adverse events were critical to decision making. The GDG agreed that although the amount of analgesia used was a critical outcome, it may not always be useful for making a recommendation. This is because it does not provide detailed information on how much analgesia was used initially to control severe pain and how much analgesia was used to maintain pain relief. The relative importance of the timing of pain ratings was also discussed, and early ratings (at 2 hours) were considered to be a critical outcome for patients, because they reflect the initial control of pain. The GDG considered mean differences of 3 cm in visual analogue scale (VAS) scores (scale of 1–10 cm) and 2 days in length of stay as representing minimal important differences. It was also discussed that, at longer follow-up times, adverse events may be more important and ongoing pain may indicate complicated episodes.
Trade-off between benefits and harms	**Primary analgesia** The GDG discussed the range of opioids and NSAIDs used in the included papers. It concluded that many of these are not used in the UK and it would be difficult to generalise the findings to the UK population with sickle cell disease. Specifically, it was agreed that the use of pethidine (meperidine) is associated with a high risk of fits in patients with sickle cell disease. Pethidine also has a limited effective dose which may not provide sufficient analgesia, and may lead to pseudo-drug-seeking behaviour. The BNF also states that pethidine is not indicated for continuous or ongoing pain, which is a characteristic of an acute painful sickle cell episode. As a result the GDG felt that it was important to make a recommendation to ensure that this drug is not used to treat an acute painful sickle cell episode. It was also agreed that tramadol and ketorolac are not widely used for treating acute painful sickle cell episodes in the UK, and that ketorolac has been linked with renal side effects.

	Pharmacological treatments aimed at managing the underlying pathology of sickle cell disease The GDG discussed the use of other treatments to manage the underlying pathophysiology of sickle cell disease, and agreed that many of the treatments used in the included papers are not used in UK clinical practice. It was also agreed that some treatments had been used off-label, and that it would be difficult to make positive recommendations for these drugs on the basis of low-quality evidence from a small number of trials. Although the evidence reviewed suggested that there were some beneficial effects associated with the use of methylprednisolone, the GDG discussed the risk of long-term toxicity with corticosteroids. It was agreed that this adverse event would not be apparent in the results of the RCT but would be evident in clinical practice and in trials with a longer follow-up period. Specifically, the GDG agreed that the risk of harm outweighs the potential benefits of using corticosteroids, and felt that a 'do not do' recommendation was necessary to reduce the risk of harm to patients. The evidence reviewed did not show any risk of harm associated with the use of oxygen, and the GDG agreed that although oxygen should not be used directly to manage pain, it is used routinely to treat hypoxia. The GDG discussed the treatment of hypoxia and agreed that this was part of good clinical practice. A clinical threshold of 95% oxygen saturation for starting oxygen therapy was agreed, based on consensus and the expertise of the GDG members. The group also noted that baseline levels of oxygen saturation may not be available when the patient presents to hospital and agreed that this should not delay treatment. Therefore baseline levels are not specifically referred to in the final recommendations. The GDG also discussed the evidence relating to nitric oxide, but did not feel that there was enough strong evidence of a beneficial effect to support a recommendation. In addition, no evidence was identified on the use of prescribed fluids for the management of an acute painful sickle cell episode, and therefore no specific recommendations were made.
Economic considerations	**Patient-controlled analgesia** An original cost–utility model was based on effectiveness data from a small Dutch RCT comparing morphine delivered by patient-controlled analgesia with morphine delivered by continuous intravenous infusion (van Beers et al. 2007). This suggested that patient-controlled analgesia was likely to be the cheapest and most effective (dominant) approach. However, the GDG noted that continuous intravenous morphine infusion is not commonly used in UK clinical practice, and that a more realistic comparator for patient-controlled analgesia would be the intermittent injection of morphine via an intramuscular or subcutaneous route. In the absence of effectiveness data comparing these approaches, a simple cost-minimisation analysis – assuming equivalent effectiveness – was undertaken. This analysis suggested that patient-controlled analgesia may represent a cost-saving approach, largely because of an expected net reduction in nursing time. Neither of these analyses accounted for the purchase price of patient-controlled analgesia pumps. However, it was calculated that the

	expected cost savings would offset an average purchase price if it was assumed that each pump would be used for a minimum of between two and 17 acute painful sickle cell episodes (depending on the analysis preferred and the assumptions adopted). The GDG agreed that it was very likely that a patient-controlled analgesia pump would be used for more than this number of episodes in its lifetime. Therefore it was safe to conclude that delivery of morphine by patient-controlled analgesia represents an effective use of NHS resources. **Therapeutic-dose low-molecular-weight heparin** An additional health economic model explored the cost effectiveness of adding therapeutic-dose low-molecular-weight heparin (LMWH) to standard care, on the basis of evidence from the Saudi Arabian placebo-controlled RCT of tinzaparin (Qari et al. 2007; see 'Quality of evidence', below). This analysis showed that, if the Saudi Arabian evidence could be assumed to generalise to the UK setting, the use of LMWH would both reduce costs and improve outcomes, making it excellent value for money. However, the GDG had little confidence in the applicability of the Saudi Arabian evidence. In the UK, adult patients who are admitted for an acute painful sickle cell episode routinely receive a lower dose of LMWH as prophylaxis against venous thromboembolism. Therefore a placebo-controlled RCT does not provide applicable evidence for the UK decision-making context: prophylactic-dose LMWH would be the relevant comparator against which to assess the clinical and cost effectiveness of therapeutic-dose LMWH in UK practice. In the absence of such evidence, the GDG could not recommend the use of therapeutic-dose LMWH; however, it recommended that research should be undertaken to generate the relevant information. Prophylactic-dose LMWH is not routinely given to children in the UK; however, the effectiveness and cost effectiveness of therapeutic-dose LMWH in this population is unknown.
Quality of evidence	The GDG agreed that overall there was a lack of evidence, and that the evidence reviewed was of low quality and sample sizes tended to be small. It also agreed that the evidence was neutral, often showing no significant effect and either no or mild adverse events. The GDG concluded that although it may be useful to look at the studies that used pethidine in addition to NSAIDs, a study that compared different routes of pethidine (Perlin et al. 1993) should be excluded. It was agreed that papers comparing piroxicam with aspirin (Eke et al. 2000) and tramadol with pethidine (Uzan et al. 2010) should also be excluded. (See appendix D for details of excluded studies.) The GDG agreed that there were a number of gaps in the evidence relating to the pharmacological management of an acute painful sickle cell episode. These included the following: • Treatments such as paracetamol, oxycodone and other analgesics that are commonly used in clinical practice. • Studies of patients who are already on high doses of morphine (in whom pain management may be more complicated). • The use of alternative subcutaneous routes of delivery (which may be useful where there are problems gaining intravenous access). • The effective management of peaks of pain when there is no access to patient-controlled analgesia.

	• Exploration of the specific sequencing of drugs to manage an acute painful sickle cell episode. It was also noted that there are very few RCTs comparing different opioids, and the GDG agreed that it was not possible to recommend a specific opioid for treating acute painful sickle cell episodes. The GDG also agreed that although the evidence relating to the use of tinzaparin (a LMWH) at a therapeutic dose appears to show some beneficial effects, this was from a single study conducted in Saudi Arabia. It was noted that practice may differ from that in the UK and that this may have had an impact on outcomes such as length of stay in hospital. Although the GDG agreed that there was not enough evidence to support a recommendation for the use of therapeutic doses of LMWH, it felt that a research recommendation is appropriate.
Other considerations	**Basic principles of care and monitoring** The GDG considered and discussed the basic principles of care, and agreed that all patients presenting to hospital with an acute painful sickle cell episode should have an individualised assessment, reassessments, continued management and ongoing monitoring. It was agreed that the prompt availability of analgesia is very important to patients and that treatment should not be delayed when they present at hospital. The GDG agreed that 30 minutes should be the maximum length of time a patient should wait, as the episode should be treated as an acute medical emergency. The GDG also discussed that carrying out basic clinical assessments, including monitoring of blood pressure, oxygen saturation, pulse rate, respiration rate and temperature, in patients on presentation to hospital constitutes good clinical practice. The GDG agreed that these clinical assessments should be more frequent within the first 6 hours after presentation and less frequent thereafter. The GDG recommended hourly assessments for the first 6 hours in order to ensure patient safety, because the risk of adverse events is higher within this period. This rate of monitoring is also in keeping with the majority of studies included for the assessment of primary analgesia in the management of an acute painful sickle cell episode. The risk of sedation was specifically discussed in relation to the use of opioids, and the recommendation relating to timing of clinical assessments makes specific reference to this. The reassessment of pain was also considered very important, and it was agreed that the initial timing of this should be the same as for an acute medical emergency (every 30 minutes for the initial drug titration period), with subsequent timing depending on whether the patient feels that pain relief is adequate. The GDG agreed that pain should be assessed at least every 4 hours after satisfactory pain relief has been achieved. The GDG also agreed that it is good clinical practice to ensure that patients who are taking an opioid are offered treatments to manage well-known side effects (such as constipation, nausea, vomiting and itching). **Severity of pain** The GDG discussed that pain is a subjective judgement and the perception of pain differs between individuals. Therefore it is difficult to provide general numerical definitions of pain severity that would apply to all patients. It was agreed that levels of pain similar to those in the evidence review (baseline VAS scores ranged from 5.4 to 10, but were

	generally above 7) should be considered to be severe pain. However, the GDG also noted that there may be some patients who have lower VAS scores or moderate pain, but who may not have access to analgesia, and so will also present at hospital. The GDG agreed general definitions of severe pain as VAS (or equivalent) scores typically above 7, and of moderate pain as VAS (or equivalent) scores typically within the range of 4 to 7. However, it noted that these should not be interpreted as strict definitions and will not apply to all patients because pain is subjective. **Primary analgesia** The GDG agreed that the main aim of this guideline should be to provide guidance on how to manage pain safely and quickly. In particular, the group discussed how strong opioids should be used without delay when patients present to hospital. However, it was also agreed that analgesia may differ depending on the severity of pain on presentation. Specifically, a strong opioid should be offered to patients with severe pain and patients with moderate pain who have already had some analgesia before presentation. It was also noted that there is extensive clinical experience with the use of morphine, but in some situations (such as patients with morphine allergy or with specific individualised care plans) it may be appropriate to consider an alternative strong opioid, so a non-specific recommendation was made. Adverse events, including the risk of sedation with the use of strong opioids, were also discussed and were considered important issues to address in recommendations about monitoring. In situations where patients present with moderate pain and have not taken analgesia, the GDG agreed that healthcare professionals may consider a weak opioid as an alternative to a strong opioid. The GDG agreed that the use of NSAIDs has an opioid sparing effect. A separate recommendation was made to ensure that NSAIDs and paracetamol are offered to all patients in addition to an opioid and that this is not delayed. The GDG also discussed the importance of stepping down pharmacological treatments as the acute painful sickle cell episode resolves, and a specific recommendation was made to address this issue. It was assumed that healthcare professionals will use their clinical judgement as well as the patient's assessment and reassessment of their pain, and will refer to local protocols, to step down treatment as appropriate. **Route of administration of analgesia** The GDG specifically discussed the use of oral opioids in children. The study by Jacobson et al. (1997) showed that this route worked as well as opioids administered by intravenous routes in children. Although the GDG agreed that this route may be quicker in acute settings where there are often difficulties in gaining intravenous access, it felt that recommending a bolus dose of analgesia would allow healthcare practitioners to select the most appropriate route for each patient. There was no evidence on the use of oral opioids in adults; however, the GDG felt that they are likely to be as effective as in children, but agreed that generally intravenous routes are quicker. The GDG concluded that all patients should be offered bolus doses, whichever route was used, and that further boluses should be offered if the pain continues to be uncontrolled.

	Subgroups (children and young people, and pregnant women) The GDG discussed the pharmacological treatment of acute painful sickle cell episodes in children and young people, and agreed that it would only differ from that for adults in two areas: dosages (in which case healthcare professionals should refer to the BNF and the BNF for children for information) and the use of age-appropriate pain scoring tools for assessing pain. The GDG included these issues in the final recommendations. The GDG also agreed that the pharmacological management of an acute painful sickle cell episode would not differ in pregnant women compared with women who are not pregnant, with the exception of avoiding the use of NSAIDs, especially in the third trimester. In this situation healthcare professionals should refer to the BNF, and this is signposted in the final recommendations. **Patient-controlled analgesia** The use of patient-controlled analgesia was discussed. The GDG agreed that its use may not be appropriate in patients with uncontrolled pain, but that it should be offered once patients have been given adequate pain relief, as patient-controlled analgesia is useful in patients needing repeated doses of analgesia. The use of patient-controlled analgesia in children and young people was also discussed, and it was agreed that the decision to use patient-controlled analgesia would not differ for children and young people compared with adults. It was also discussed that although alternatives such as nurse-controlled analgesia may be used in children and young people, information about the practicalities and methods associated with its use would be included in local protocols.

2.1.6 Recommendations and research recommendations for how an acute painful sickle cell episode should be managed using pharmacological interventions

Recommendations

Individualised assessment at presentation

Recommendation 1.1.1

Treat an acute painful sickle cell episode as an acute medical emergency. Follow locally agreed protocols for managing acute painful sickle cell episodes and/or acute medical emergencies that are consistent with this guideline.

Recommendation 1.1.3

Assess pain and use an age-appropriate pain scoring tool for all patients presenting at hospital with an acute painful sickle cell episode.

Recommendation 1.1.4

Offer analgesia within 30 minutes of presentation to all patients presenting at hospital with an acute painful sickle cell episode (see also recommendations 1.1.7 to 1.1.11).

Recommendation 1.1.5

Clinically assess all patients presenting at hospital with an acute painful sickle cell episode, including monitoring of:

- blood pressure
- oxygen saturation on air (if oxygen saturation is 95% or below, offer oxygen therapy)
- pulse rate
- respiratory rate
- temperature.

Primary analgesia

Recommendation 1.1.7

When offering analgesia for an acute painful sickle cell episode:

- ask about and take into account any analgesia taken by the patient for the current episode before presentation
- ensure that the drug, dose and administration route are suitable for the severity of the pain and the age of the patient
- refer to the patient's individual care plan if available

Recommendation 1.1.8

Offer a bolus dose of a strong opioid by a suitable administration route, in accordance with locally agreed protocols for managing acute painful sickle cell episodes, to:

- all patients presenting with severe pain
- all patients presenting with moderate pain who have already had some analgesia before presentation.

Recommendation 1.1.9

Consider a weak opioid as an alternative to a strong opioid for patients presenting with moderate pain who have not yet had any analgesia.

Recommendation 1.1.10

Offer all patients regular paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) by a suitable administration route, in addition to an opioid, unless contraindicated[2].

[2] The use of NSAIDs should be avoided during pregnancy, unless the potential benefits outweigh the risks. NSAIDs should be avoided for treating an acute painful sickle cell episode in women in the third trimester. See the 'British National Formulary' for details of contraindications.

Recommendation 1.1.11

Do not offer pethidine for treating pain in an acute painful sickle cell episode.

Reassessment and ongoing management

Recommendation 1.1.12

Assess the effectiveness of pain relief:

- every 30 minutes until satisfactory pain relief has been achieved, and at least every 4 hours thereafter
- using an age-appropriate pain scoring tool
- by asking questions, such as:
  - How well did that last painkiller work?
  - Do you feel that you need more pain relief?

Recommendation 1.1.13

If the patient has severe pain on reassessment, offer a second bolus dose of a strong opioid (or a first bolus dose if they have not yet received a strong opioid).

Recommendation 1.1.14

Consider patient-controlled analgesia if repeated bolus doses of a strong opioid are needed within 2 hours. Ensure that patient-controlled analgesia is used in accordance with locally agreed protocols for managing acute painful sickle cell episodes and/or acute medical emergencies.

Recommendation 1.1.15

Offer all patients who are taking an opioid:

- laxatives on a regular basis
- anti-emetics as needed
- antipruritics as needed.

Recommendation 1.1.16

Monitor patients taking strong opioids for adverse events, and perform a

clinical assessment (including sedation score):

- every 1 hour for the first 6 hours
- at least every 4 hours thereafter.

Recommendation 1.1.18

As the acute painful sickle cell episode resolves, follow locally agreed protocols for managing acute painful sickle cell episodes to step down pharmacological treatment, in consultation with the patient.

Management of underlying pathology

Recommendation 1.1.21

Do not use corticosteroids in the management of an uncomplicated acute painful sickle cell episode.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B1

For patients with an acute painful sickle cell episode, what are the effects of different opioid formulations, adjunct pain therapies and routes of administration on pain relief and acute sickle cell complications?

Research recommendation B2

Are therapeutic doses of low-molecular-weight heparin (LMWH) effective, compared with prophylactic doses of LMWH, in reducing the length of stay in hospital of patients with an acute painful sickle cell episode?

2.2 Non-pharmacological management

2.2.1 Review question

Which non-pharmacological interventions should be used in the management of an acute painful sickle cell episode?

2.2.2 Evidence review

This review question focused on the use of non-pharmacological interventions such as distraction and relaxation techniques, acupuncture, TENS (transcutaneous electrical nerve stimulation) and heat therapy in the management of an acute painful sickle cell episode. Only RCTs that compared a non-pharmacological intervention with either a placebo or another comparator in patients having an acute painful sickle cell episode were considered for inclusion. From a database of 5534 abstracts, 232 full-text articles were ordered and one paper was selected (Wang et al. 1988). Trials were excluded if they:

- focused on reducing the incidence of acute painful sickle cell episodes **or**
- used unclear measurements of pain **or**
- were carried out in settings other than in hospital, for example in the community.

(For a full list of excluded papers for this review question, see appendix D.)

Only one paper was included for this review question (see table 23), so no meta-analysis was carried out and a single GRADE table is presented (table 24).

Table 23 Summary of included studies for non-pharmacological management of an acute painful sickle cell episode

Author (year)	Participants	Baseline pain	Intervention	Control	Monitoring	Location
Wang et al. (1988)	22 patients (adults and children; age range 12–27 years)	Mean baseline VAS score not reported	TENS + usual pain medication	Placebo + usual pain medication	Not recorded	USA
Abbreviations: TENS, transcutaneous electrical stimulation.						

Table 24 GRADE table for the use of non-pharmacological interventions for the management of an acute painful sickle cell episode

Quality assessment							No. of patients		Effect size	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control		
Pain rating (assessed using a scale from 0 to 10, with 0 indicating no pain)										
1 (Wang et al. 1988)	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	30 trials	30 trials	There were no significant differences in improvement in pain ratings between the TENS group and the placebo group at 1 hour (44% compared with 31% improvement, p = 0.30) and 4 hours (52% compared with 47% improvement, p = 0.69)	Low

Use of analgesia										
1 (Wang et al. 1988)	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	30 trials	30 trials	There were no significant differences in the requirement for narcotic analgesia between the TENS group and the placebo group at 1 hour (14% compared with 25%, p = 0.30) and 4 hours (61% compared with 66%, p = 0.69)	Low
Patient evaluation										
1 (Wang et al. 1988)	Randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	30 trials	30 trials	The proportion of patients rating the intervention as helpful was significantly higher in the TENS group compared with the placebo group (74% compared with 39%, p = 0.01)	Low

[a] Downgrade by one level: limited baseline information is provided about patient characteristics, and baseline pain ratings are not reported.

[b] Downgrade by one level: for continuous variables the imprecision criterion was downgraded if the 95% CI crosses the minimal important difference (the GDG agreed that this is 3 cm for pain ratings using a VAS scale (1–10 cm) and 2 days for length of stay) or if the total sample size is less than 400 (rule of thumb from GRADE).

2.2.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

2.2.3.1 Low-quality evidence from one RCT with 22 adults and children showed no significant differences between the TENS group and the placebo group in the proportion of patients reporting improved pain ratings at 1 hour ($\chi^2 = 1.09$, $p = 0.30$) and at 4 hours ($\chi^2 = 0.16$, $p = 0.69$).

2.2.3.2 Low-quality evidence from one RCT with 22 adults and children showed no significant differences between the TENS group and the placebo group in the proportion of patients requiring narcotic analgesia at 1 hour ($\chi^2 = 1.07$, $p = 0.30$) and at 4 hours ($\chi^2 = 0.16$, $p = 0.69$).

2.2.3.3 Low-quality evidence from one RCT with 22 adults and children showed that the proportion of patients rating the intervention as helpful was significantly higher in the TENS group compared with the placebo group ($\chi^2 = 6.11$, $p = 0.01$).

2.2.4 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that all three outcomes that were assessed (that is, pain rating, use of analgesia and patient evaluation) were important; however, it was acknowledged that baseline pain ratings and details of specific analgesia were not reported. Specifically, pain rating and use of analgesia were identified previously as being critical to decision making, and the included study did not report any clinical benefit in these outcomes. The group discussed how patients may often feel beneficial effects from non-pharmacological treatments, and agreed that those that are not likely to cause harm (such as relaxation techniques) should be encouraged so that patients are empowered to manage their own pain. The GDG discussed the harms associated with some patient coping strategies that may not be helpful, but agreed that behaviours that may be harmful to the patient or others will be addressed using general hospital policies. A recommendation was therefore made to ensure that patients are encouraged to use their own coping mechanisms.
Trade off between benefits and harms	The evidence reviewed did not show any risk of harm associated with the use of TENS.

Economic considerations	The GDG concluded that there was no evidence to support any positive recommendations that would have an impact on NHS resources.
Quality of evidence	The GDG discussed the evidence reviewed, and agreed that the use of non-pharmacological interventions within hospital settings had not been well researched. It also agreed that well-designed RCTs are needed in this area to assess the usefulness of such interventions. Specifically, it was noted that the included study assessing the use of TENS did not show any reductions in either pain rating or use of analgesia, although it was acknowledged that this was a small trial and underpowered. The GDG felt there was inadequate support for a clinical benefit, and therefore no recommendation was made about the use of TENS machines in hospital. The GDG also noted that although there are no studies assessing the use of cognitive behavioural therapy (CBT) in an inpatient setting, there is evidence of beneficial effects associated with its use in patients with sickle cell disease in outpatient settings. The GDG felt that although a recommendation supporting the provision of such interventions is not supported by the evidence, patients should be encouraged to use non-pharmacological interventions that they may have learnt in other settings. In addition, the GDG noted that there were also gaps in the evidence relating to the use of general supportive treatments such as heat therapy, which are valued by patients.
Other considerations	**Practical issues** The GDG discussed the practicalities associated with the use of a TENS machine, and agreed that it would be difficult to use in hospital settings for acute pain. However, it was recognised that it may be possible to use it in other settings (such as daycare units, wards and in the community). The group also discussed the additional training needs associated with the use of TENS machines. **Subgroups (children and young people, and pregnant women)** The GDG discussed the non-pharmacological management of acute painful sickle cell episodes in children and young people and in pregnant women, and agreed that this would not differ compared with adults and women who are not pregnant. Therefore general recommendations were made to apply to all patients.

2.2.5 Recommendations and research recommendations for which non-pharmacological interventions should be used in the management of an acute painful sickle cell episode

Recommendations

Non-pharmacological interventions

Recommendation 1.1.22

Encourage the patient to use their own coping mechanisms (for example, relaxation techniques) for dealing with acute pain.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B3

For patients with an acute painful sickle cell episode, are psychological interventions, in conjunction with standard care, effective in providing pain relief?

Research recommendation B4

For patients with an acute painful sickle cell episode, are non-pharmacological interventions, such as massage, effective in improving their recovery from the episode?

2.3 Clinical signs and symptoms of acute complications

2.3.1 Review question

What clinical signs and symptoms should be used to identify patients who are likely to have acute complications associated with an acute painful sickle cell episode?

2.3.2 Evidence review

This review question focused on the use of clinical signs and symptoms and laboratory markers to identify acute complications in patients who present to hospital with an acute painful sickle cell episode. This question did not aim to identify all risk factors for the development of acute complications, but was limited to clinical signs and symptoms and laboratory markers that may be present during hospitalisation. Studies assessing other risk factors such as demographic characteristics were not included. As this question was restricted to specific risk factors, studies assessing these factors using any comparative analyses were included. The formal diagnosis of acute complications was specifically excluded as this was outside the scope of the guideline.

From a database of 5534 abstracts, 140 full-text articles were ordered and 13 papers were selected for this review question (Ander and Vallee 1997; Audard et al. 2010; Baumgartner and Klein 1989; Berger et al. 2009; Bernard et al. 2008; Buchanan and Glader 1978; Buchanan et al. 2005; Chapman et al. 2004; Finkelstein et al. 2007; Kopecky et al. 2004; Lewing et al. 2011; Pollack, Jr. et al. 1991; Styles et al. 2000). Studies were excluded if they:

- focused on risk factors for acute complications in patients in the 'steady state' of sickle cell disease **or**
- focused on the prevention or management of acute complications **or**
- did not provide comparative analyses (that is, they were narrative reviews, case studies or case series).

(For a full list of excluded papers, see appendix D.)

No specific studies were identified that focused on the effect of identifying acute complications on subsequent survival rates.

Because GRADE has not been developed for use with prognostic studies, a modified approach was used based on the use of GRADE for diagnostic studies. The same criteria (risk of bias, inconsistency, imprecision and indirectness) were used to downgrade the quality of the evidence. In terms of study design, prospective studies were started with a high-quality rating,

whereas retrospective studies were started with a low-quality rating and downgraded as appropriate. This is because there is a higher risk of information bias associated with retrospective study designs. Quality ratings were downgraded further for risk of bias if there was evidence of selection bias. Inconsistency was assessed by examining unexplained differences in estimates of effect. In this case, a range of different estimates of effect were reported, including diagnostic accuracy statistics, statistical measures of association or adjusted odds ratios from multivariate regression analyses. Indirectness was assessed by examining any important differences in population, prognostic factor or outcome of the included evidence compared with those for whom the recommendation is intended. Imprecision was assessed by examining the sample size or the 95% confidence intervals around the estimate of effect. Although GRADE provides rules of thumb when assessing imprecision in intervention questions (that is, where the total sample size is less than 400, the event rate is less than 300 or the 95% confidence intervals cross the thresholds for appreciable benefit or harm or the minimal important difference), these may not be directly applicable to prognostic studies. For this review question the evidence was downgraded for imprecision where 95% confidence intervals (if reported or calculated) were wide. This criterion was met if the interval was not narrow enough to support a recommendation or the final recommendation would change if the effect estimate was equal to the lower 95% boundary. Where no confidence intervals were reported, small sample size was used as a criterion for downgrading. As sample sizes were small for all included studies (less than 400) the evidence was generally downgraded for imprecision even if confidence intervals were relatively narrow.

Six modified GRADE tables are presented below, one for each acute complication examined in the included studies.

Table 25 Summary of included studies for clinical signs and symptoms of acute complications

Author (year)	Patient details	Study design	Acute complication	Prognostic factors investigated	Location
Kopecky et al. (2004)	50 paediatric patients (age range 5–17 years) who took part in an RCT comparing continuous intravenous infusion of morphine with an oral sustained release formulation of the drug; all patients presented with VOC	Post-hoc analysis of RCT	Acute chest syndrome	Exposure to morphine (all patients received intravenous loading dose of 0.15 mg/kg then infusion of at least 0.04 mg/kg/hour) Oral: sustained-release tablets giving a dose of at least 1.9 mg/kg/hour and placebo infusion Continuous intravenous infusion: at least 0.04 mg/kg/hour and oral placebo	Canada
Finkelstein et al. (2007)	17 paediatric patients (mean age 8.9 years, inclusion <18 years) who presented to the emergency department for painful VOC and developed acute chest syndrome	Retrospective, self-matched, case crossover design	Acute chest syndrome	Exposure to morphine	Canada
Buchanan et al. (2005)	175 paediatric patients (mean age 11 years, inclusion 5–19 years) with VOC	Retrospective chart review	Acute chest syndrome	Opioid selection (morphine compared with nalbuphine by intermittent injection or continuous infusion accompanied by patient-controlled analgesia)	USA
Lewing et al. (2011)	796 paediatric admissions (age range 3–17 years) for acute painful episodes in two institutions	Retrospective chart review	Acute chest syndrome	Parenteral narcotic choice (nalbuphine compared with morphine and other opioids)	USA
Styles et al. (2000)	14 paediatric patients (mean age 12.6 years, range 1.5–20 years) during 21 admissions for VOC	Prospective cohort	Acute chest syndrome	Secretory phospholipase A2 (inflammatory mediator)	USA
Audard et al. (2010)	254 episodes of VOC complications in 161 adult patients (age range 22–34 years)	Retrospective cohort study	Acute kidney Injury	Laboratory values (for example WBC, haemoglobin, platelets), echocardiography data (for example left ventricular ejection fraction, cardiac index, stroke index) and pulmonary hypertension	France
Baum-gartner et al. (1989)	53 adult patients (mean age 24.4 years in VOC group and 23.2 years in acute surgical group) with abdominal pain	Retrospective chart review	Acute abdomen	Pain distribution, historical factors (including emesis, similarity to previous cases, precipitating event), physical findings (temperature, peritoneal signs) and laboratory evaluation (WBC, haematocrit, bilirubin)	USA
Berger et al. (2009)	124 paediatric patients (mean age 8.5 years, inclusion ≤ 18 years) with sickle cell disease and VOC	Case-control design	Osteomyelitis (acute presentation)	Clinical features (pain, fever, swelling and number of affected sites) and WBC	Canada

Author (year)	Patient details	Study design	Acute complication	Prognostic factors investigated	Location
Buchanan and Glader (1978)	51 episodes of VOC in 40 paediatric patients (age range 5 months to 21 years)	Retrospective design (unclear)	Bacterial infection (14 episodes of bacteraemia, five of which were associated with localised focus of infection, including pneumonia, gastroenteritis and pyelonephritis)	Total WBC, segmented polymorphonuclear leukocytes (PMN), non-segmented PMN	USA
Ander et al. (1997)	94 visits by 38 adult patients (mean age 30 and 33 years for males and females respectively) who presented to the ED with pain typical of a VOC	Retrospective cohort	Pneumonia and UTI	Signs and symptoms including fever, chills, cough, shortness of breath, sputum production, chest pain, haemoptysis, abnormal pulmonary examination and temperature above 37.8°C	USA
Pollack et al. (1991)	71 patients (>14 years of age) with 134 separate ED visits for acute painful episodes	Prospective clinical study (some retrospective data collection)	Pneumonia and UTI	Pulmonary symptoms (temperature, chest pain, cough, haemoptysis and shortness of breath), systemic symptoms (fever, chills, nausea, vomiting, diarrhoea, upper respiratory infection) and laboratory data (WBC, haematocrit, peripheral reticulocyte count, peripheral absolute neutrophil count, urine pH and urine specific gravity)	USA
Bernard et al. (2008)	884 ED visits by 125 adult patients (mean age 36.3 years, age range 19–66 years); 199 of 284 patients admitted were found to have one or more of the outcomes; majority of ED visits were for acute painful episodes	Outcome prediction study using a retrospective cohort	No specific complication; outcomes included acute chest syndrome, aplastic crisis, splenic sequestration and blood transfusion or antibiotic administration	These included type of sickle cell disease, clinical symptoms (for example, pain similar to previous, chills, abnormal temperature) and laboratory values (haemoglobin)	USA

Author (year)	Patient details	Study design	Acute complication	Prognostic factors investigated	Location
Chapman et al. (2004)	86 visits by 30 paediatric patients (age range 11 months to 18 years old, median age 9.5 years)	Retrospective chart review	No specific complication; complicated visits defined as admission to hospital, need for antibiotics or blood products within 48 hours, or development of acute chest syndrome or aplasia within 48 hours	Haemoglobin value, WBC and differential reticulocyte count	USA
Abbreviations: ED, emergency department; UTI, urinary tract infection; VOC, vaso-occlusive crisis; WBC, white blood cell count.					

Table 26 GRADE table for signs and symptoms of acute chest syndrome in patients with an acute painful sickle cell episode

Outcome[1].										
Quality assessment							Summary of findings			
							No of episodes (No of patients)		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
Incidence										
5 studies (Kopecky 2004, Finkelstein 2007, Buchanan 2005, Lewing 2011, Styles 2000)	Prospective and retrospective study designs	N	S[l]	N	N	N	2148	148	The incidence of acute chest syndrome in patients presenting to hospital with a painful sickle cell episode ranged from 2.3% to 28.6%	Very low[l]
Clinical signs and/or symptoms: continuous infusion accompanied by PCA										
1 study (Buchanan 2005)	Retrospective design	S[e]	N	S[f]	S[g]	N	175	37	From multivariate analysis[d]: Model 3*** OR 3.18 (1.11, 9.08) Model 2: OR 2.29 (0.68, 7.65) Model 4[†] OR 6.8 (1.86, 25.2)	Very low
Clinical signs and/or symptoms: oral morphine compared with continuous infusion										
1 study (Kopecky 2004)	Post-hoc analysis of RCT	N	N	N	S[g]	N	44	16	Unadjusted RR 3.29 (1.25, 8.62) Children who received oral morphine and in whom acute chest syndrome developed showed significantly lower oxygen saturation (p = 0.01) and significantly higher heart rate (p = 0.05) and respiration rate (p = 0.01) compared with children in whom acute chest syndrome did not develop or who received continuous	Moderate

Outcome[1].										
Quality assessment							Summary of findings			
							No of episodes (No of patients)		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
									infusion morphine.	
Clinical signs and/or symptoms: cumulative morphine dose (mg/kg)										
1 (Finkelstein 2007)	Retrospective crossover case control	N	N	N	S[g]	N	17	17	Cumulative morphine dose did not significantly differ for hospitalisations during which acute chest syndrome developed (1.24 mg/kg, SD 0.60) compared with hospitalisations during which acute chest syndrome did not develop (1.44 mg/kg, SD 0.84, p = 0.21)	Very low
Clinical signs and/or symptoms: Pain score (range 1-10)										
1 study (Buchanan 2005)	Retrospective design	S[e]	N	S[f]	S[g]	N	175	37	From multivariate analysis[d]: Model 2: OR 1.86 (1.26, 2.72)	Very low
Laboratory marker: haemoglobin (g/dl)										
1 study (Buchanan 2005)	Retrospective design	S[e]	N	S[f]	S[g]	N	175	37	From multivariate analysis[d]: Model 2: OR 0.65 (0.47, 0.89); there are no cases of acute chest syndrome at a cut-off of 10.5	Very low
Laboratory marker: white cell count (10^3/litre)										
1 study (Buchanan 2005)	Retrospective design	S[e]	N	S[f]	S[g]	N	175	37	From multivariate analysis[d]: Model 2: OR 1.22 (1.10, 1.34); there are no cases of acute chest syndrome at a cut-off of 9	Very low
Laboratory marker: secretory phospholipase A_2 24–48 hours before acute chest syndrome clinically diagnosed										

Outcome[1].										
Quality assessment							Summary of findings			
							No of episodes (No of patients)		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
1 study (Styles 2000)	Prospective design	S[h]	N	N	S[g]	N	21[b]	6	OR 24.8 (95% CI 1.17, 527.5, p = 0.02) for elevated secretory phospholipase A_2 Diagnostic statistics: Sensitivity 100%, specificity 67%, PPV 55%, NPV 100%	Low
Combination of laboratory marker and clinical sign/symptom: secretory phospholipase A_2 and fever										
1 study (Styles 2000)	Prospective design	S[h]	N	N	S[g]	N	21[b]	6	Sensitivity 100%, specificity 87%, PPV 75%, NPV 100%	Low
Combination of laboratory marker and clinical sign/symptom: secretory phospholipase A_2 and chest pain										
1 study (Styles 2000)	Prospective design	S[h]	N	N	S[g]	N	21[b]	6	Sensitivity 50%, specificity 80%, PPV 50%, NPV 80%	Low
Combination of laboratory marker and clinical sign/symptom: secretory phospholipase A_2 and respiratory symptoms										
1 study (Styles 2000)	Prospective design	S[h]	N	N	S[g]	N	21[b]	6	Sensitivity 67%, specificity 100%, PPV 100%, NPV 88%	Low
Combination of laboratory marker and clinical signs/symptoms: secretory phospholipase A_2 and auscultatory findings										
1 study (Styles 2000)	Prospective design	S[h]	N	N	S[g]	N	21[b]	6	Sensitivity 67%, specificity 100%, PPV 100%, NPV 88%	Low
NB: all outcomes were assessed during hospitalisation S: serious N: no serious *model 1: where only morphine (and not PCA) is input into model **model 2: where both morphine and PCA are input into model ***model 3: where only PCA (and not morphine) is input into the model										

Outcome[1].										
Quality assessment							Summary of findings			
							No of episodes (No of patients)		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
†model 4: exploratory analysis excluding subjects that indicated a change in medication during hospitalisation (n = 13; 3 morphine, 10 nalbuphine) [a] prospective studies started with a high quality rating and retrospective studies were started with a low quality rating and were downgraded as appropriate [b] number of episodes [c] threshold used 100 ng/ml [d] using imputed pain scores based on associated factors where there are unreported pain scores at admission [e] Downgrade by 1 level: no standardised treatment protocol [f] Downgrade by 1 level: patients treated with morphine or nalbuphine (not in BNF) [g] Downgrade by 1 level: imprecision was downgraded if there was a wide confidence interval or a small sample size (less than 400 in total) [h] Downgrade by 1 level: limited patient characteristics reported [i] Downgrade by 1 level: wide variation in incidence of acute chest syndrome [j] Downgrade by 1 level: mixed retrospective and prospective studies [1] Kopecky et al. (2004) defined acute chest syndrome as the presence of new chest radiograph changes, the need for supplemental oxygen therapy and the presence of clinical findings such as fever or cough. Finklestein et al. (2007) defined acute chest syndrome as the combination of new onset of typical respiratory signs and symptoms with fever accompanied by the appearance of a new pulmonary infiltrate on chest radiography. Buchanan et al. (2005) defined acute chest syndrome as a new pulmonary infiltrate on chest radiograph after admission and before discharge. Styles et al. (2000) defined acute chest syndrome as the presence of a new pulmonary infiltrate in combination with fever, chest pain or respiratory symptoms. Lewing et al. (2011) defined acute chest syndrome as chest pain, some evidence of respiratory compromise or distress and a new infiltrate lesion on the chest X-ray; fever was not a criterion. Abbreviations: OR, odds ratio; NPV, negative predictive value; PCA, patient-controlled analgesia; PPV, positive predictive value; RR, relative risk.										

Table 27 GRADE table for signs and symptoms of acute kidney injury in patients with an acute painful sickle cell episode

Outcome[1]										
Quality assessment							Summary of findings			
							No of episodes (no patients)		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
Incidence										
1 study (Audard 2010)	Retrospective design	N	N	N	S[c]	N	254[b]	11	The incidence of acute kidney injury in patients presenting to hospital with a painful sickle cell episode was 4.3%	Very low
Clinical sign/symptom: severity of episode (uncomplicated, moderate acute chest syndrome, severe acute chest syndrome)										
1 study (Audard 2010)	Retrospective design	N	N	N	S[c]	N	254[b]	11	The incidence of acute kidney injury was 2.3% (4 episodes) during uncomplicated pain crisis, 6.9% (4 episodes) during moderate acute chest syndrome and 13.6% (3 episodes) during severe acute chest syndrome (p = 0.03)	Very low
Laboratory marker: white blood cells (10^9/litre)										
1 study (Audard 2010)	Retrospective design	N	N	N	S[c]	N	161	11	White blood cell count was significantly higher in patients with acute kidney injury (median 11.9) compared with patients without acute kidney injury (median 9.8, p = 0.03)	Very low
Laboratory marker: total haemoglobin (g/dl)										
1 study (Audard 2010)	Retrospective design	N	N	N	S[c]	N	161	11	Total haemoglobin was significantly lower in patients with acute kidney injury (median 8.2) compared with patients without acute kidney injury (median 8.9, p = 0.04)	Very low
Laboratory marker: lactate dehydrogenase (IU/litre)										

Outcome[1]										
Quality assessment							Summary of findings			
							No of episodes (no patients)		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
1 study (Audard 2010)	Retrospective design	N	N	N	S[c]	N	161	11	Lactate dehydrogenase was significantly higher in patients with acute kidney injury (median 453) compared with patients without acute kidney injury (median 325, p = 0.02)	Very low
Combination of clinical sign/symptom and laboratory marker: severe acute chest syndrome and aminotransferases (IU/litre)										
1 study (Audard 2010)	Retrospective design	N	N	S[d]	S[c]	N	59[b]	6	Aspartate aminotransferase (median 275 vs 36) and alanine aminotransferase (median 223 vs 27) levels were significantly higher in patients with severe acute chest syndrome with acute kidney injury compared with patients without acute kidney injury (p < 0.01)	Very low
Combination of clinical sign/symptom and laboratory marker: severe acute chest syndrome and bilirubin (µmol/litre)										
1 study (Audard 2010)	Retrospective design	N	N	S[d]	S[c]	N	59[b]	6	Total bilirubin (median 173 vs 68, p = 0.04) and direct bilirubin (median 100 vs 18, p = 0.03) were significantly higher in patients with severe acute chest syndrome with acute kidney injury compared with patients without acute kidney injury	Very low
Combination of clinical sign/symptom and laboratory marker: severe acute chest syndrome and lactate dehydrogenase (IU/litre)										
1 study (Audard 2010)	Retrospective design	N	N	S[d]	S[c]	N	59[b]	6	Lactate dehydrogenase was significantly higher in patients with severe acute chest syndrome with acute kidney injury (median 980) compared with patients without acute kidney injury (median 443, p = 0.04)	Very low
Combination of clinical sign/symptom and laboratory marker: severe acute chest syndrome and echocardiographic features of pulmonary hypertension										
1 study (Audard 2010)	Retrospective design	N	N	S[d]	S[c]	N	59[b]	6	Tricuspid regurgitant jet velocity (median 3.6 vs 2.8 m/s) and systolic pulmonary artery pressure (median	Very low

Outcome[1]										
Quality assessment							Summary of findings			
							No of episodes (no patients)		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
									67 vs 46 mmHg) were significantly higher and IVC collapse (median 16 vs 0%) and cor pulmonale (5 vs 4) were significantly lower in patients with severe acute chest syndrome with acute kidney injury compared with patients without acute kidney injury	

NB: all outcomes were assessed during hospitalisation
S: serious
N: no serious
[a] prospective studies started with a high quality rating and retrospective studies were started with a low quality rating and were downgraded as appropriate
[b] number of episodes
[c] Downgrade by one level: imprecision was downgraded if there was a wide confidence interval or a small sample size (less than 400 in total)
[d] Downgrade by one level: population of patients with severe acute chest syndrome were considered sicker than patients who would generally present to hospital with an acute painful episode.
[1] Acute kidney injury in adults defined in three stages. Stage 1 is an increase of serum creatinine of ≥ 26.4 µmol/litre or increase to ≥ 150–200% from baseline (the lowest measurement during the 3 months preceding hospitalisation). Stage 2 is an increase of serum creatinine of >200–300% from baseline. Stage 3 is an increase of serum creatinine to >300% from baseline or ≥ 354 µmol/litre with an acute increase of at least 44 µmol/litre.

Table 28 GRADE table for signs and symptoms of acute abdomen in patients with an acute painful sickle cell episode

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication	Effect/outcome	Quality[a]
Incidence										
1 study (Baumgartner 1989)	Retrospective design	S[e]	N	S[c]	S[d]	N	53	12	The incidence of a surgical abdomen in patients presenting to hospital with abdominal pain was 4.3%	Very low
Clinical sign/symptom: coexistent abdominal and remote pain (pain involving another body part)										
1 study (Baumgartner 1989)	Retrospective design	S[e]	N	S[c]	S[d]	N	53	12	When the abdominal pain was secondary to a vaso-occlusive crisis, another body part was involved 77% of the time, compared with 0% in patients with a surgical abdomen ($p < 0.005$)	Very low
Clinical sign/symptom: similarity to prior crisis										
1 study (Baumgartner 1989)	Retrospective design	S[e]	N	S[c]	S[d]	N	53	12	The presenting vaso-occlusive crisis was found to be similar to prior crises in 70% of instances compared with 8% in patients with a surgical abdomen ($p < 0.001$)	Very low
Clinical sign/symptom: precipitating event (majority were upper respiratory infection)										
1 study (Baumgartner 1989)	Retrospective design	S[e]	N	S[c]	S[d]	N	53	12	Precipitating events were significantly more likely to be reported in patients with vaso-occlusive crisis (50%) compared with patient with a surgical abdomen (0%, $p < 0.01$)	Very low
Clinical sign/symptom: pain relief with hydration and oxygen ≤ 48 hours										

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication	Effect/outcome	Quality[a]
1 study (Baumgartner 1989)	Retrospective design	S[e]	N	S[c]	S[d]	N	53	12	The pain from a vaso-occlusive crisis was relieved significantly more often compared with the pain associated with a surgical abdomen (97% vs. 0%, p < 0.005)	Very low
Clinical sign/symptom: temperature (°F)										
1 study (Baumgartner 1989)	Retrospective design	S[e]	N	N	S[d]	N	53	3	Temperature was significantly higher in patients with acute appendicitis (101.2°F, SD 1.2) compared with patients with vaso-occlusive crisis (99.1°F, SD 1.00, p < 0.01)	Very low

NB: all outcomes were assessed during hospitalisation
[a] prospective studies started with a high quality rating and retrospective studies were started with a low quality rating and were downgraded as appropriate
[b] number of episodes
S: serious
N: no serious
[c] Downgrade by 1 level: 9/12 patients had chronic and/or acute cholecystitis
[d] Downgrade by 1 level: imprecision was downgraded if there was a wide confidence interval or a small sample size (less than 400 in total)
[e] Downgrade by 1 level: unclear definition of how surgical abdomen was diagnosed
[1] Acute abdomen as a result of surgical abdomen in adults. This includes chronic/ acute cholecystitis and acute appendicitis

Table 29 GRADE table for signs and symptoms of acute osteomyelitis in patients with an acute painful sickle cell episode

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients		Effect/outcome	Quality[a]
o. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Controls	Cases		
Clinical sign/symptom: duration of fever before admission (days)										
1 (Berger 2009)	Retrospective case–control	N	N	N	S[c]	N	93	31	From multivariate logistic regression OR 1.8 (95% CI 1.2, 2.6, p = 0.004)	Very low
Clinical sign/symptom: duration of pain before admission (days)										
1 (Berger 2009)	Retrospective case–control	N	N	N	S[c]	N	93	31	From multivariate logistic regression OR 1.2 (95% CI 1.0, 1.4, p = 0.02)	Very low
Clinical sign/symptom: swelling of affected limb on presentation										
1 (Berger 2009)	Retrospective case–control	N	N	N	S[c]	N	93	31	From multivariate logistic regression OR 8.4 (95% CI 3.5, 20.0, p < 0.001)	Very low
Clinical sign/symptom: number of painful sites										
1 (Berger 2009)	Retrospective case–control	N	N	N	S[c]	N	93	31	From multivariate logistic regression OR 0.7 (95% CI 0.5, 1.0, p = 0.03)	Very low

NB: all outcomes were assessed during hospitalisation
[a] prospective studies started with a high quality rating and retrospective studies were started with a low quality rating and were downgraded as appropriate
[b] number of episodes
S serious
N no serious
[C] Downgrade by 1 level: imprecision was downgraded if there was a wide confidence interval or a small sample size (less than 400 in total)
[1] Osteomyelitis in children. Defined as patients with a discharge diagnosis of osteomyelitis and one or more of the following criteria (a) positive blood culture, (b) positive culture of a bone or joint aspirate and/or (c) typical radiographic findings of osteomyelitis as reported by a staff radiologist
Abbreviations: CI, confidence interval; OR, odds ratio.

Table 30 GRADE table for signs and symptoms of infection in patients with an acute painful sickle cell episode

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
Incidence of pneumonia in adults										
2 (Ander 1997, Pollack 1991)	Retrospective & prospective design	N	N	N	S[e]	N	228[b]	14	The incidence of a pneumonia in patients presenting to hospital with a painful episode was 6.1%	Very low
Clinical sign/symptom of pneumonia: 4 out of the following 9 symptoms: fever, chills, nausea/vomiting, upper respiratory tract infection, cough, shortness of breath, sputum, chest pain, haemoptysis										
1 (Ander 1997)	Retrospective design	N	N	N	S[e]	N	94[b]	6	Sensitivity 100%, specificity 87.5%, positive predictive value 35.3%, negative predictive value 100%	Very low
Clinical sign/symptom of pneumonia in adults: shortness of breath										
1 (Pollack 1991)	Prospective design	N	N	S[f]	S[e]	N	134[b]	8	Pneumonia patients (37.5%) complained of shortness of breath significantly more frequently compared with patients overall (20.9%, $p < 0.05$)	Low
Laboratory marker of pneumonia in adults: peripheral reticulocyte count (RC)										
1 (Pollack 1991)	Prospective design	N	N	S[f]	S[e]	N	134[b]	8	The average RC was significantly higher in patients with pneumonia (18.6, SD 10.9%) compared with patients overall (13.7, SD 8.4%, $p < 0.05$†)	Low
Laboratory marker of bacterial infection in children: total white blood count (WBC, 10^3/litre)*										
1 (Buchanan & Glader 1978)	Retrospective design	N	N	S[d]	S[e]	N	27[c]	13	WBC was higher in patients with bacterial infection (22.0, SD 10.7) compared with patients with vaso-occlusive crisis (16.4, SD 5.5)	Very low
Laboratory marker of bacterial infection in children: band (non segmented) neutrophils*										

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients		Effect/outcome	Quality[a]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication		
1 (Buchanan & Glader 1978)	Retrospective design	N	N	S[d]	S[e]	N	27[c]	13	Non segmented neutrophil count was higher in patients with bacterial infection (4.58, SD 2.8) compared with patients with vaso-occlusive crisis (0.32, SD 0.45)	Very low

NB: all outcomes were assessed during hospitalisation
* statistical analyses were not reported in the paper
† this statistically significant result reported in the paper was not replicated when a t-test was carried out
[a] prospective studies started with a high quality rating and retrospective studies were started with a low quality rating and were downgraded as appropriate
[b] number of episodes
[c] patients with vaso-occlusive crisis.
S: serious
N: no serious
[d] Downgrade by 1 level: unclear if patients with bacterial infection were assessed during acute painful episode (or vaso-occlusive crisis)
[e] Downgrade by 1 level: imprecision was downgraded if there was a wide confidence interval or a small sample size (less than 400 in total)
[f] Downgrade by 1 level: may include some children (included patients over 14 years old)
[1] Pneumonia in adults: definition varied slightly across studies but included the presence of an infiltrate and a positive clinical response to a course of antibiotics.
Outcome: bacterial infection in children was assessed using urine and/or blood culture.

Table 31 GRADE table for signs and symptoms of complications in patients with an acute painful sickle cell episode

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication	Effect/outcome	Quality[a]
Clinical sign/symptom in adults: sickle genotype										
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284[b]	199	From multivariate analysis: OR 2.97 (95% CI 1.15, 7.65) for HbSC (compared with Hb-Thal) OR 1.95 (95% CI 0.83, 4.56) for HbSS OR 8.08 (95% CI 2.84, 23.08) for other/unknown	Very low
Clinical sign/symptom in adults: chest pain										
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284[b]	199	From multivariate analysis: OR 1.83 (95% CI 1.13, 2.97)	Very low
Clinical sign/symptom in adults: pain similar to previous										
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284[b]	199	From multivariate analysis: OR 0.54 (95% CI 0.34, 0.85)	Very low
Clinical sign/symptom in adults: abnormal temperature										
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284b	199	From multivariate analysis: OR 5.35 (95% CI 2.29, 12.49)	Very low
Clinical sign/symptom in adults: abnormal pulse oximetry										
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284b	199	From multivariate analysis: OR 3.56 (95% CI 1.85, 6.85)	Very low
Clinical sign/symptom in adults: abnormal chest X-ray										

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication	Effect/outcome	Quality[a]
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284b	199	From multivariate analysis: OR 1.82 (95% CI 1.01, 3.27) for chronic abnormality OR 5.75 (95% CI 2.69, 12.31) for acute abnormality	Very low
Clinical sign/symptom in children: pain in arms										
1 (Chapman 2004)	Retrospective design	N	N	N	S[e]		86[b]	38	OR 0.2 (95% CI 0.04, 0.9)	Very low
Laboratory marker in children: change in haemoglobin from baseline (g/dl)										
1 (Chapman 2004)	Retrospective design	N	N	N	S[e]	N	86[b]	38	MD −0.4 (CI −0.8 to −0.1); change from baseline was −0.2 in complicated and 0.2 in uncomplicated group. The changes in haemoglobin are close to the normal differences in laboratory values found on repeated measurements of blood values	Very low
Laboratory marker in adults: haemoglobin < 10 g/dl										
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284[b]	199	From multivariate analysis: OR 2.88 (95% CI 1.68, 4.94)	Very low
Laboratory marker in adults: positive urine nitrite										
1 (Bernard 2008)	Retrospective design	N	N	S[d]	S[e]	N	284[b]	199	From multivariate analysis: OR 4.11 (95% CI 1.35, 12.56)	Very low

NB: all outcomes were assessed during hospitalisation
[a] prospective studies started with a high quality rating and retrospective studies were started with a low quality rating and were downgraded as appropriate
[b] number of visits
[c] threshold used 100 ng/ml
S: serious
N: no serious

Outcome[1]										
Quality assessment							Summary of findings			
							No of patients			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Acute complication	Effect/outcome	Quality[a]
[d] Downgrade by 1 level: some patients may not have a painful sickle cell episode and may not have been assessed for all complications [e] Downgrade by 1 level: imprecision was downgraded if there was a wide confidence interval or a small sample size (less than 400 in total) [1] Definition of complication varied across studies, but included hospitalisation with acute chest syndrome, aplastic crisis, splenic sequestration and blood transfusion, antibiotic administration within 48 or 96 hours of ED visit or ED presentation. Abbreviations: ED, emergency department; MD, mean difference; OR, odds ratio.										

See appendix E for the evidence tables in full.

2.3.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Acute chest syndrome

2.3.3.1 *Very-low-quality evidence from five studies with 2148 children presenting to hospital with an acute painful sickle cell episode showed that the incidence of acute chest syndrome ranged from 23 to 286 cases per 1000 people*

Two institutions were included in the Lewing et al. (2011) study: one primarily used morphine and the other primarily used a continuous infusion of nalbuphine to treat acute painful sickle cell episodes in hospitalised patients. In the Buchanan et al. (2005) study, patients were assigned to a medication group (morphine or nalbuphine) based on the first medication delivered once hospitalised. There was no standardised protocol for the selection of medication.

2.3.3.2 *Very-low-quality evidence from one retrospective study with 158 children showed that the association between morphine and the development of acute chest syndrome was confounded by continuous infusion with PCA and this was observed in various models (for morphine, excluding patients that changed medication during hospitalisation: stratified odds ratio [OR] 5.9, CI 1.5 to 27.8; unstratified OR 3.0, CI 0.64 to 14.3).*

2.3.3.3 *Moderate-quality evidence from one post hoc analysis of an RCT with 44 children showed that children on oral morphine were at significantly higher risk of developing acute chest syndrome (unadjusted RR 3.29, CI 1.25 to 8.26) and that children who developed acute chest syndrome had significantly lower oxygen saturation ($p = 0.01$) and higher heart rate ($p = 0.05$) and respiration rate ($p = 0.01$) compared with children in whom acute chest syndrome did not develop or who received continuous infusion of morphine.*

In this study (Kopecky et al. 2004), analysis of pharmacokinetic data showed that the AUCs (area under concentration–time curve from 0 to 12 hours) for morphine were significantly higher in patients treated with oral morphine compared with patients treated with infusion, suggesting that morphine itself may have an effect on the development of acute chest syndrome. However, this was based on a small sample of 15 children

2.3.3.4 *Very-low-quality evidence from one retrospective study with 17 children showed that there was no significant association between cumulative morphine dose and the development of acute chest syndrome (mean cumulative morphine dose 1.24 mg/kg when acute chest syndrome developed, compared with 1.44 mg/kg when it did not develop, p = 0.21).*

This study (Finkelstein et al. 2007) used a weight-based, fixed-dose protocol which will have reduced the risk of underdosing or overdosing. Patients presenting with pneumonia or incipient acute chest syndrome were excluded from the study.

2.3.3.5 *Very-low-quality evidence from one retrospective study with 175 children showed that a higher pain score (OR 1.86, CI 1.26 to 2.72), low haemoglobin (OR 0.65, CI 0.47 to 0.89) and high white blood cell count (OR 1.22, CI 1.10 to 1.34) significantly predicted the development of acute chest syndrome.*

2.3.3.6 *Low-quality evidence from one prospective study with 14 children showed that elevated secretory phospholipase A2 (defined as 100 ng/mg) was significantly associated with the development of acute chest syndrome (OR 24.8, CI 1.17 to 527.5, p = 0.02).*

2.3.3.7 *Low-quality evidence from one prospective study with 14 children showed that the association between elevated secretory phospholipase A2 (defined as 100 ng/mg) plus fever and the development of acute chest syndrome showed high sensitivity (sensitivity 100%, specificity 87%), and the association between*

elevated secretory phospholipase A2 plus respiratory symptoms or auscultatory findings and the development of acute chest syndrome showed high specificity (sensitivity 67%, specificity 100%).

Acute kidney injury

2.3.3.8 *Very-low-quality evidence from one retrospective study with 254 episodes of vaso-occlusive crisis showed that the incidence of acute kidney injury in patients presenting to hospital with an acute painful sickle cell episode was 43 cases per 1000 people.*

2.3.3.9 *Very-low-quality evidence from one retrospective study with 161 adults showed that the incidence of acute kidney injury was significantly higher in patients with moderate or severe acute chest syndrome compared with patients with an uncomplicated acute painful sickle cell episode ($p = 0.03$).*

2.3.3.10 *Very-low-quality evidence from one retrospective study with 161 adults showed that the white blood cell count was significantly higher and haemoglobin and lactate dehydrogenase levels were significantly lower in patients with an acute painful sickle cell episode with acute kidney injury compared with those without acute kidney injury ($p < 0.05$).*

2.3.3.11 *Very-low-quality evidence from one retrospective study with 59 episodes of severe acute chest syndrome showed that aspartate aminotransferase and alanine aminotransferase levels were significantly higher in patients with acute kidney injury compared with patients without ($p < 0.01$).*

2.3.3.12 *Very-low-quality evidence from one retrospective study of 59 episodes of severe acute chest syndrome showed that levels of total bilirubin ($p = 0.04$) and direct bilirubin ($p = 0.03$) were significantly higher in patients with acute kidney injury compared with patients without.*

2.3.3.13 Very-low-quality evidence from one retrospective study of 59 episodes of severe acute chest syndrome showed that lactate dehydrogenase levels were significantly higher in patients with acute kidney injury compared with patients without ($p = 0.04$).

2.3.3.14 Very-low-quality evidence from one retrospective study of 59 episodes of severe acute chest syndrome showed that echocardiographic features of pulmonary hypertension differed significantly between patients with and without acute kidney injury (median systolic pulmonary artery pressure 67 mmHg in patients with acute kidney injury compared with 46 mmHg in patients without acute kidney injury).

Acute abdomen

2.3.3.15 Very-low-quality evidence from one retrospective study with 53 adults with sickle cell disease showed that the incidence of surgical abdomen in patients presenting to hospital with abdominal pain was 43 cases per 1000 people

2.3.3.16 Very-low-quality evidence from one retrospective study with 53 adults showed that coexisting abdominal and remote pain ($p < 0.005$), similarity to a previous episode ($p < 0.001$), precipitating events ($p < 0.01$) and pain relief with hydration and oxygen ($p < 0.005$) were significantly less likely in patients with surgical abdomen compared with patients with vaso-occlusive crisis.

2.3.3.17 Very-low-quality evidence from one retrospective study with 53 adults showed that temperature was significantly higher in patients with acute appendicitis compared with patients with vaso-occlusive crisis ($p < 0.01$).

Acute osteomyelitis

2.3.3.18 Very-low-quality evidence from one retrospective study with 124 children with sickle cell disease showed that longer duration of

fever before admission significantly predicted the development of osteomyelitis (OR 1.8, CI 1.2 to 2.6) in multivariate logistic regression analysis.

2.3.3.19 *Very-low-quality evidence from one retrospective study with 124 children showed that longer duration of pain before admission significantly predicted the development of osteomyelitis (OR 1.2, CI 1.0 to 1.4).*

2.3.3.20 *Very-low-quality evidence from one retrospective study with 124 children showed that swelling of the affected limb on presentation significantly predicted the development of osteomyelitis (OR 8.4, CI 3.5 to 20.0).*

2.3.3.21 *Very-low-quality evidence from one retrospective study with 124 children showed that an increased number of painful sites reduced the odds of developing osteomyelitis by 30% compared with controls (OR 0.7, CI 0.5 to 1.0, p = 0.03) in multivariate analysis.*

Infection

2.3.3.22 *Very-low-quality evidence from two studies with 109 adults showed that the incidence of pneumonia in patients presenting to hospital with an acute painful sickle cell episode was 61 cases per 1000 people.*

2.3.3.23 *Very-low-quality evidence from one retrospective study with 38 adults showed that the association between the presence of four out of nine symptoms (fever, chills, nausea/vomiting, upper respiratory infection, cough, shortness of breath, sputum, chest pain and haemoptysis) and the development of pneumonia had a sensitivity of 100%, a specificity of 87.5%, a positive predictive value of 35.3% and a negative predictive value of 100%.*

2.3.3.24 *Low-quality evidence from one prospective study with 71 adults showed that patients with pneumonia complained of shortness of*

breath significantly more frequently compared with patients overall (p < 0.05).

2.3.3.25 *Low-quality evidence from one prospective study with 71 adults showed that the average reticulocyte count was significantly higher in patients with pneumonia compared with patients overall (p < 0.05).*

2.3.3.26 *Very-low-quality evidence from one retrospective study with 40 children showed that counts of white blood cells and non-segmented polymorphonuclear leukocytes were higher in patients with bacterial infection compared with patients with vaso-occlusive crisis (p-value not reported).*

Complications

2.3.3.27 *Very-low-quality evidence from one retrospective study with 125 adults showed that the HbSC, SS and other/unknown sickle genotypes rather than thalassaemia (OR range from 1.95 to 8.08), chest pain (OR 1.83, CI 1.13 to 2.97), pain not similar to previous (OR 0.54, CI 0.34 to 0.85), temperature less than 36°C or more than 38°C (OR 5.35, CI 2.29 to 12.49), pulse oximetry < 95% (OR 3.56, CI 1.85 to 6.85) and chronic (OR 1.82, CI 1.01 to 3.27) or acute (OR 5.75, CI 2.69 to 12.31) abnormalities on chest X-ray predicted adverse patient outcomes in multivariate analysis.*

In this study (Bernard et al. 2008), the primary outcome measures were acute chest syndrome, aplastic crisis, splenic sequestration and blood transfusion or antibiotic administration within 96 hours of presentation at the emergency department.

2.3.3.28 *Very-low-quality evidence from one retrospective study with 125 adults showed that both a haemoglobin level of less than 10 g/dl (OR 2.88, CI 1.68 to 4.94) and a positive urine nitrite reading (OR 4.11, CI 1.35 to 12.56) predicted adverse patient outcomes.*

2.3.3.29 *Very-low-quality evidence from one retrospective study with 30 children showed that median age was significantly higher for patients with a complicated course of an acute painful episode compared with patients with an uncomplicated course (p = 0.04).*

In this study (Chapman et al. 2004), a complicated visit was defined as an acute painful sickle cell crisis followed by admission to hospital, the need for antibiotics or blood products either in the emergency department or within 48 hours of the visit, or the development of acute chest syndrome or aplasia within 48 hours of the visit.

2.3.3.30 *Very-low-quality evidence from one retrospective study with 30 children showed that the presence of pain in only the arms significantly reduced the odds of a complicated painful episode (OR 0.2, CI 0.04 to 0.9).*

2.3.3.31 *Very-low-quality evidence from one retrospective study with 30 children showed a significant difference in the change in haemoglobin levels from baseline in uncomplicated compared with complicated pain episodes (MD −0.4, CI −0.8 to −0.1).*

2.3.4 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative value of the outcomes, and agreed that the type of opioid (morphine or nalbuphine) should not be included as an outcome, because nalbuphine is not licensed for use in the UK. In addition, one of the studies included patients treated in two different centres: nalbuphine was primarily used to treat an acute painful sickle cell episode in one centre, whereas morphine was used in the other. The GDG agreed that the differences found in the evidence may have been the result of differences between the two centres rather than being related to the specific opioid used. The GDG discussed the incidence of acute chest syndrome in the included studies, which ranged from 23 to 286 cases per 1000 people, and felt that this wide variation may have been because of differing definitions of acute chest syndrome that were used. It was also agreed that prospective studies could lead to a higher incidence of acute chest syndrome because healthcare professionals may be more directed to this potential diagnosis. The GDG also noted that all the included studies were on children, who are at higher risk of infection compared with adults.

	In addition, the clinical indications for the use of chest X-rays have changed, and they are now used less regularly because of the risk of overexposure to radiation. Furthermore, changes seen on chest X-rays will differ according to age, with adults showing more diffuse changes and children showing more localised changes. While recognising these limitations, the GDG made a recommendation highlighting the increased risk of acute chest syndrome in patients with chest pain, hypoxia (low oxygen saturation), fever and respiratory symptoms. This was supported by evidence from the included studies of acute chest syndrome and of general acute complications, and was in agreement with clinical experience. The GDG also discussed laboratory markers, and noted that although some markers showed statistically significant differences, many of these did not reflect clinically important differences. Therefore the GDG decided not to make any recommendations on the use of specific laboratory markers.
Trade off between benefits and harms	The GDG discussed the specific signs and symptoms associated with the development of acute complications, and agreed that these were only markers of increased risk. It also noted that many of these signs and symptoms do not differ from markers identified in the general, non-sickle-cell, population. The GDG felt it was important to highlight that all patients with sickle cell disease presenting to hospital with an acute painful episode are at risk of developing an acute complication. In addition, the GDG discussed alternative diagnoses (these could be related to sickle cell disease or not), and felt that it was important to make a recommendation to ensure that healthcare professionals assess patients for alternative causes of pain when they present to hospital, particularly if pain is reported as atypical.
Economic considerations	Because the GDG did not feel that the available evidence supported the use of laboratory markers to predict acute complications, it was not necessary to assess the cost impact of the assays. The GDG noted that, in the health economic model for the pharmacological management of acute painful sickle cell episodes (see section 2.1.4), acute complications – especially stroke – were associated with very significant costs as well as having a substantial impact on quality of life. Therefore the prevention of such complications is important from an economic as well as a patient-care perspective.
Quality of evidence	The GDG agreed that the evidence for this review question was of low quality and often did not show any clinically important differences. Specifically, the study of Audard et al. (2010) was discussed in detail and it was agreed that patients with moderate or severe acute chest syndrome would form a sicker population compared with patients with uncomplicated painful episodes. Specifically, it was suggested that many of these patients may be experiencing multi-organ failure and would be more likely to have renal dysfunction. It was felt that this population differed from the population of patients with sickle cell disease who generally present to hospital with an acute painful episode, and so the

	findings of this paper could not be generalised to the target population. The GDG also discussed the study of Styles et al. (2000), which investigated the association between elevated levels of secretory phospholipase A2 and the development of acute chest syndrome in patients who were hospitalised with an acute painful sickle cell episode. Although the GDG agreed that this paper provided good preliminary data showing that elevated secretory phospholipase A2 levels were associated with high odds of developing acute chest syndrome, it was also noted that these results were observed in a small sample of 14 children. The GDG felt that this test may be a good indicator for acute chest syndrome, but at present it is available in the UK only as a research tool and therefore it would be impractical to make a recommendation for its use. The GDG also noted that further research is being carried out on the use of this test as a diagnostic tool, and so a specific research recommendation was not considered necessary. The GDG also considered the study of Bernard et al. (2008), which aimed to develop an emergency department risk score that predicts adverse outcomes for patients with sickle cell disease. The results of this study suggested that the sickle genotype may be predictive of adverse outcomes, including acute complications. However, the GDG felt that using patients with sickle cell beta thalassaemia disease as a reference group was inappropriate because this includes patients with mild cases of sickle cell disease, and these patients may be less likely to experience acute painful episodes.
Other considerations	**Monitoring** The GDG discussed the importance of ongoing monitoring, because some acute complications can develop at any time during an acute painful sickle cell episode. Therefore a general recommendation for healthcare professionals to be aware of other possible complications at any time during the episode was made. **Subgroups (children and young people, and pregnant women)** The GDG discussed the identification of acute complications in children and young people and in pregnant women. It was agreed that this would not differ compared with adults and women who are not pregnant, and so general recommendations were made to apply to all patients.

2.3.5 Recommendations for what clinical signs and symptoms should be used to identify patients who are likely to have acute complications

Recommendations

Individualised assessment at presentation

Recommendation 1.1.6

Assess all patients with sickle cell disease who present with acute pain to determine whether their pain is being caused by an acute painful sickle cell episode or whether an alternative diagnosis is possible, particularly if pain is reported as atypical by the patient.

Reassessment and ongoing management

Recommendation 1.1.17

If the patient does not respond to standard treatment for an acute painful sickle cell episode, reassess them for the possibility of an alternative diagnosis.

Possible acute complications

Recommendation 1.1.19

Be aware of the possibility of acute chest syndrome in patients with an acute painful sickle cell episode if any of the following are present at any time from presentation to discharge:

- abnormal respiratory signs and/or symptoms
- chest pain
- fever
- signs and symptoms of hypoxia:
  - oxygen saturation of 95% or below **or**
  - an escalating oxygen requirement.

Recommendation 1.1.20

Be aware of other possible complications seen with an acute painful sickle cell episode, at any time from presentation to discharge, including:

- acute stroke
- aplastic crisis
- infections
- osteomyelitis
- splenic sequestration.

2.4 Settings and skills for managing an acute painful sickle cell episode

2.4.1 Review question

(a) Where should an acute painful sickle cell episode be managed?

(b) What skills and knowledge are required by healthcare professionals and teams providing care?

2.4.2 Evidence review

This review question focused on identifying the best setting in which to manage an acute painful sickle cell episode and the skills required by healthcare professionals. Any papers focusing on the organisation of care or the skills and/or knowledge of healthcare professionals were considered for inclusion for this review question. From a database of 5534 abstracts, 78 full-text articles were ordered and eight papers were selected (Adams-Graves et al. 2008; Benjamin et al. 2000; Frei-Jones et al. 2009; Jamison and Brown 2002; Mitchell et al. 2002; Montanez and Berland 2002; Raphael et al. 2008; Wright et al. 2004). Trials were excluded if they:

- focused on the use of a clinical pathway without reference to the organisation of care or the skills and knowledge of healthcare professionals **or**

- related to the management of an acute painful sickle cell episode in the community.

Several papers did not report any statistical analyses, but results are summarised in the GRADE profile for those that did. Mean differences were not calculated in papers where the standard deviation (SD) was not reported. There was limited pooling because there was heterogeneity across the included studies. Where meta-analysis was possible, a forest plot is also presented (see appendix E). A single GRADE table is presented for this review question.

Table 32 Summary of included studies for settings and skills for managing an acute painful sickle cell episode

Author (year)	Patients	Intervention	Comparator	Location	Follow-up
Day hospital compared with inpatient setting					
Raphael et al. (2008)	70 children with vaso-occlusive crisis	HCPs include haematology/oncology physician or nurse practitioner; pain management protocol used	HCPs include paediatric emergency medicine physicians, and general paediatricians once admitted; same pain management protocol as in day hospital group	USA	7 years (covers care from 2000 to 2006); only one admission per patient
Benjamin et al. (2000)	2554 adult visits to day hospital and 2612 ED visits	HCPs include day hospital physicians; treatment protocol used	Treated in ED and followed by physicians not associated with the day hospital	USA	5 years (1989–1993)
Wright et al. (2004)	440 episodes of severe pain in 89 adult patients over 5 years	Day unit staff (including nurse specialist, psychologist, nursing auxiliary, receptionist, social worker and consultant haematologist); protocol used	Pre-unit conditions not reported	UK	5 years (2 years pre-unit set up and 3 years post-unit set up)
Assessing outcomes before and after introducing a sickle cell intervention in hospital					
Frei-Jones et al. (2009)	124 children with SCD pain	Education for all hospital house staff physicians about pain management (provided by physician with expertise in SCD); education for patients/ caregivers; protocol used	Patients with SCD pain 1 year before the intervention; pain management protocol was used in only 32% of patients (51/159)	USA	Assessed during intervention (6 months), pre-intervention and after end of educational component
Adam-Graves et al. (2008)	Patient characteristics not reported	Dedicated inpatient SCD unit; education for staff; direct admissions from home; protocol used	Patients presented to either ED or the outpatient sickle cell centre	USA	9 years (1999 to 2007); specialised unit set up in 2004
Jamison and Brown (2008)	204 patients admitted with acute painful sickle cell episode	Admitted to oncology (dedicated area); education for staff; protocol used	Before establishing this programme, patients were placed on various departments of the hospital, but most often admitted through ED	USA	2 years (1 year pre-intervention and 1 year post-intervention)

Author (year)	Patients	Intervention	Comparator	Location	Follow-up
Mitchell et al. (2002)	122 admissions in 27 patients	Education for staff; HCPs included case manager to coordinate care for all sickle cell inpatients; protocol used	Care in ED and hospital setting	USA	1 year (6 months pre-intervention and 6 months post-intervention)
Montanez and Berland (2002)	110 adults admitted with an acute painful sickle cell episode	HCPs included multidisciplinary pain team (pain specialist, haematologist, clinical pharmacologist and two internists); pain team functioned as case management team; education for staff provided by the pain team; protocol used	Patients admitted to ED or inpatient medical services	USA	17 months (7 months pre-intervention, 7 months of intervention, 3 months post-intervention)
Abbreviations: ED, emergency department; HCP, healthcare professional; SCD, sickle cell disease.					

Table 33 GRADE table for settings and skills for managing an acute painful sickle cell episode

Quality assessment							No. of patients		Effect/outcome	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Day hospital/post-intervention setting	Inpatient/ pre-intervention setting		
Mean LOS (days) in children treated in day hospital compared with inpatient setting										
1 (Raphael et al. 2008)	observational study	no serious risk of bias**	no serious inconsistency	serious[1]	serious[2]	none	35 patients	35 patients	Multivariate analysis* showed a statistically significant 39% reduction in average LOS in day hospital admissions compared with inpatient admissions (RR 0.61, 95% CI 0.46 to 0.81, p = 0.0006).	Very low

Quality assessment							No. of patients		Effect/outcome	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Day hospital/post-intervention setting	Inpatient/ pre-intervention setting		
Mean LOS (hours) in adults treated in day hospital compared with ED										
1 (Benjamin et al. 2000)	observational study	serious[3]	no serious inconsistency	serious[1]	serious[4]	none	2554 visits	2612 visits	Mean LOS tended to be lower in the day hospital setting (4.5 hours, range 2 to 7 hours) compared with the ED (13 hours, range 11 minutes to 90 hours).	Very low
1 (Benjamin et al. 2000)	observational study	serious[3]	no serious inconsistency	serious[1]	NA	none	2554 visits	2612 visits	Regardless of whether patients were admitted through day hospital or ED, LOS in patients followed by day hospital physicians with the assistance of house staff was reduced from 9.3 days in the first year to an average of 7.3 days in the fifth year, while LOS in patients followed by non-day-hospital staff remained unchanged.	Very low
Mean LOS (days) in children treated during and after implementation of SCD programme										
1 (Frei-Jones et al. 2009)	observational study	no serious risk of bias	serious[5]	serious[1]	serious[2]	none	89 admissions	85 admissions	Mean LOS was significantly higher after the intervention compared with during the intervention (5 compared with 4 days, p = 0.03, 95% CI −1.8 to −0.1).	Very low

Quality assessment							No. of patients		Effect/outcome	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Day hospital/post-intervention setting	Inpatient/ pre-intervention setting		
Mean LOS (days) in adults treated before and after implementation of SCD programme										
2 (Jamison and Brown 2008, Mitchell et al. 2002)	observational study	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	156 admissions	170 admissions	Mean LOS tended to be lower in the post-intervention groups (3.8 and 6.3 days) compared with the pre-intervention groups (4.9 and 8.7 days).	Very low
1 (Montanez and Berland 2002)	observational study	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	13 patients admitted	57 patients admitted	Mean LOS was significantly lower in the post-intervention group (2.8 days, range 1–5 days) compared with during the intervention (4.7 days, range 1–14 days, p = 0.05). Mean LOS also tended to be lower in the post-intervention group compared with the pre-intervention group (5.5 days, range 1–17 days)***.	Very low
Mean pain score at discharge in children treated before and after implementation of SCD programme										
1 (Frei-Jones et al. 2009)	observational study	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	89 admissions	85 admissions	Mean pain score at discharge was significantly lower in the post-intervention group (1.9) compared with the pre-intervention group (3.3, p = 0.003, 95% CI 0.3 to 1.5).	Very low

Quality assessment							No. of patients		Effect/outcome	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Day hospital/post-intervention setting	Inpatient/ pre-intervention setting		
Average change in pain score at discharge in children treated before and after implementation of SCD programme										
1 (Frei-Jones et al. 2009)	observational study	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	89 admissions	85 admissions	Mean change in pain score at discharge was significantly higher in the post-intervention group (6.4) compared with the pre-intervention group (5.3, p = 0.02, 95% CI −2.1 to −0.15).	Very low
Severity of pain on day 2 (no pain, mild, moderate or severe) in adults treated before and after implementation of SCD programme										
1 (Montanez and Berland 2002)	observational study	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	13 patients admitted	57 patients admitted	The percentage of patients with severe pain (8% compared with 23%) and moderate pain (31% compared with 38%) tended to be lower in the post-intervention group. The percentage of patients with mild pain (54% compared with 33%) and no pain (7% compared with 5%) tended to be higher in the post-intervention group. However, these differences were not statistically significant (p > 0.05).	Very low
Mean time to pain relief (hours) in children treated before and after implementation of SCD programme										
1 (Montanez and Berland	observational study	serious[3]	no serious inconsistency	Serious[1, 6]	serious[2]	none	10 patients	29 patients during the intervention	Mean time to pain relief decreased from 27.4 hours during the intervention period	Very low

Quality assessment							No. of patients		Effect/outcome	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Day hospital/post-intervention setting	Inpatient/ pre-intervention setting		
2002)								period	to 7 hours during the post-intervention period (p < 0.08)***.	
Admission rates in adults treated in day hospital compared with ED										
Wright et al. (2004)	observational study	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	444 patients with SCD	280 patients with SCD	There was a significant reduction in the rate of admissions per patient in the day hospital compared with ED (rate ratio 0.35, 95% CI 0.3 to 0.4, p < 0.001)	Very low
1 (Benjamin et al. 2000)	observational study	serious[3]	no serious inconsistency	serious[1]	no serious imprecision	none	2033 visits	1818 visits	There was a significant 81% reduction in admissions in patients treated in the day hospital compared with the ED (RR 0.19, 95% CI 0.16 to 0.23)	Very low
Admission rates in adults treated before and after implementation of SCD programme										
2 (Mitchell et al. 2002; Montanez and Berland 2002)	observational studies	serious[3]	no serious inconsistency	serious[1]	serious[7]	none	59 admissions	132 admissions	The meta-analysis showed a significant 31% reduction in admission in the post-intervention group compared with the pre-intervention group (RR 0.69, 95% CI 0.54 to 0.88)	Very low

Quality assessment							No. of patients		Effect/outcome	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Day hospital/post-intervention setting	Inpatient/ pre-intervention setting		
Readmission at 48 hours in children treated in day hospital compared with inpatient setting										
1 (Raphael et al. 2008)	observational study	no serious risk of bias**	no serious inconsistency	serious[1]	serious[7]	none	35 patients	35 patients	Two patients were readmitted at 48 hours in the day hospital group compared with no patients in the inpatient group (RR 5.00, 95% CI 0.25 to 100.53)	Very low
Readmission within 30 days in children treated before and after implementation of SCD programme										
1 (Frei-Jones et al. 2009)	observational study	no serious risk of bias	no serious inconsistency	serious[1]	serious[7]	none	89 admissions	85 admissions	Readmission rate within 30 days was significantly lower for children admitted during the intervention period than during the control period (11% compared with 28%, p < 0.002, 95% CI 0.1 to 0.6)	Very low
Readmission rate within 30 days for admissions post-intervention (after end of educational intervention)										
1 (Frei-Jones et al. 2009)	observational study	no serious risk of bias	no serious inconsistency	serious[1]	serious[7]	none	89 admissions	85 admissions	The significant reduction in 30-day readmission rate for children admitted with SCD pain during the educational intervention disappeared, with overall 30-day readmission rate increasing from 11% to 19% (33/173), compared with a readmission rate of 28% (44/159) in the previous year (p = 0.06, 95% CI 0.4 to 1)	Very low

Quality assessment							No. of patients		Effect/outcome	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Day hospital/post-intervention setting	Inpatient/ pre-intervention setting		
Patient satisfaction in adults treated before and after implementation of intervention										
1 (Jamison and Brown 2008)	observational study	serious[3]	no serious inconsistency	serious[1]	serious[7]	none	18 patients who frequently sought treatment at the study hospital and/or attended support group meetings		Overall satisfaction tended to increase after the new programme was implemented (0% of patients provided 'good' and 'very good' ratings pre-intervention and this increased to 50% for each category post-intervention)	Very low

Abbreviations: SCD, sickle cell disease; LOS, length of stay; RR, relative risk; 95% CI, 95% confidence interval

* Adjusted for sickle cell type, pain score and age.

** Patients in the day hospital and those treated as inpatients received the same pain management protocol.

*** t-tests were only conducted to compare the mean length of stay and the mean number of hours to pain relief between patients admitted during pathway implementation and the post-intervention group.

NA: no CI is reported so imprecision cannot be assessed.

[1] Downgrade 1 level: all studies were carried out in the USA where treatment practices may differ.

[2] Downgrade 1 level: for continuous variables the imprecision criterion was downgraded if the 95% CI crosses the minimal important difference (the GDG agreed that this is 3 cm for pain ratings using a VAS scale (1–10cm) and 2 days for length of stay) or if the total sample size is less than 400 (rule of thumb from GRADE).

[3] Downgrade 1 level: studies did not report details of patient characteristics, which may have differed between the groups, and patients may have received different care.

[4] Downgrade 1 level: no statistical analyses were conducted to compare outcomes.

[5] Frei-Jones et al. (2009) found a significant increase in mean length of stay in the post-intervention group and no plausible explanation was reported.

[6] Downgrade 1 level: the non-specialist setting used for this outcome was assessed during the intervention period rather than a pre-intervention period.

[7] Downgrade 1 level: for binary variables the imprecision criterion was downgraded if the 95% CI crosses the threshold for 'appreciable benefit' or 'appreciable harm' (defined as a relative risk reduction or relative risk increase greater than 25%) or if the total number of events is less than 300 (rule of thumb from GRADE).

See appendix E for the evidence tables in full.

2.4.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Mean length of stay (LOS): day hospital compared with inpatient setting

2.4.3.1 *Very-low-quality evidence from one observational study with 70 children showed a statistically significant 39% reduction in average LOS for day hospital admissions compared with inpatient admissions (relative ratio of average length of stay 0.61, 95% CI 0.46 to 0.81, p = 0.0006).*

In this study (Raphael et al. 2008), both groups of children were treated using the same pain management protocol. The setting differed with respect to the type of healthcare professionals providing care and the procedures, facilities and environment associated with day hospitals and inpatient care. A multivariate logistic regression analysis was carried out, with hospital admission type as the predictor of interest. The ratios of average length of stay were calculated for each variable relative to the baseline group. For hospital admission type the baseline was inpatient admission.

2.4.3.2 *Very-low-quality evidence from one observational study with 5166 adult visits showed that mean LOS tended to be lower in the day hospital setting (4.5 hours, range 2 to 7 hours) compared with the ED (13 hours, range 11 minutes to 90 hours).*

2.4.3.3 *Very-low-quality evidence from one observational study with 5166 adult visits showed that, regardless of whether patients were admitted through the day hospital or ED, LOS in patients followed by day hospital physicians with the assistance of house staff was reduced from 9.3 days in the first year to an average of 7.3 days in the fifth year, while LOS in patients followed by non-day-hospital staff remained unchanged.*

In this study (Benjamin et al. 2000), the day hospital provided care for patients with uncomplicated painful episodes. Comparisons were made with the portion of the population admitted through the ED that was comparable with the population with uncomplicated painful episodes.

Mean length of stay (LOS) after implementation of a sickle cell disease intervention in a hospital setting

2.4.3.4 *Very-low-quality evidence from one observational study of 174 child admissions showed that mean LOS was significantly higher after the intervention compared with during the intervention (5 compared with 4 days, p = 0.03, 95% CI −1.8 to −0.1).*

2.4.3.5 *Very-low-quality evidence from two observational studies with 326 adult admissions showed that mean LOS tended to be lower in the post-intervention groups (3.8 and 6.29 days) compared with the pre-intervention groups (4.9 and 8.7 days).*

Both studies provided education for staff and a pain management protocol as part of the intervention. One study (Jamison and Brown 2008) also provided admission to the oncology department with nurses who have experience of pain management for haematologically similar conditions. The other study (Mitchell et al. 2002) included a case manager coordinating care for all patients with sickle cell disease.

2.4.3.6 *Very-low-quality evidence from one observational study of 70 adult patients admitted showed that mean LOS was significantly lower in the post-intervention group (2.8 days, range 1–5 days) compared with during the intervention (4.7 days, range 1–14 days, p = 0.05), and the mean LOS tended to be lower in the post-intervention group than in the pre-intervention group (5.5 days, range 1–17 days).*

In this study (Montanez and Berland 2002), as well as providing education for staff and a pain management protocol, the

intervention also involved a pain team (pain specialist, haematologist, clinical pharmacologist and internists) which functioned as a case management team and participated in care. The team members remained available for informal consultation and education after the intervention period

Pain after implementation of a sickle cell disease intervention in a hospital setting

2.4.3.7 *Very-low-quality evidence from one observational study of 174 child admissions showed that the mean pain score at discharge was significantly lower in the intervention group (1.9) compared with the control group (3.3) ($p = 0.003$, 95% CI 0.3 to 1.5)*

2.4.3.8 *Very-low-quality evidence from one observational study of 174 child admissions showed that mean change in pain score at discharge was significantly higher in the intervention group (6.4) compared with the control group (5.3) ($p = 0.02$, 95% CI −2.1 to −0.15)*

This study (Frei-Jones et al. 2009) used the 10-cm visual analogue scale, the Wong Baker FACES scale or the modified Children's Hospital of Eastern Ontario Pain Scale to assess pain in children.

2.4.3.9 *Very-low-quality evidence from one observational study of 70 adult patients admitted showed that the percentages of patients with severe pain (8% compared with 23%) and moderate pain (31% compared with 38%) tended to be lower in the post-intervention group compared with the pre-intervention group. The percentages of patients with mild pain (54% compared with 33%) and no pain (7% compared with 5%) tended to be higher in the post-intervention group. However, these differences were not statistically significant ($p > 0.05$).*

This study (Montanez and Berland 2002) used a standard questionnaire to assess pain.

2.4.3.10 *Very-low-quality evidence from one observational study with 39 children showed a reduction in mean time to pain relief in the post-intervention period compared with the intervention period, but this was not statistically significant ($p < 0.08$).*

Admission rates: day hospital compared with inpatient setting

2.4.3.11 *Very-low-quality evidence from one observational study of 440 episodes of severe pain showed that the rate of admission per patient in the day hospital was significantly lower compared with that in the ED (rate ratio 0.35, 95% CI 0.3 to 0.4, $p < 0.001$).*

This study (Wright et al. 2004) was conducted in the UK and compared the experience of the population of patients with sickle cell disease for 2 years before and for 2 years after the unit was set up.

2.4.3.12 *Very-low-quality evidence from one observational study of 3851 visits for uncomplicated pain episodes showed a significant 81% reduction in admission for patients treated in the day hospital compared with the ED (RR 0.19, 95% CI 0.16 to 0.23).*

Admission rates after implementation of a sickle cell disease intervention in a hospital setting

2.4.3.13 *Very-low-quality evidence from two observational studies with 191 admissions showed a significant 31% reduction in admissions in the post-intervention group compared with the pre-intervention group (RR 0.69, 95% CI 0.54 to 0.88).*

In these two studies (Mitchell et al. 2002; Montanez and Berland 2002), case management formed part of the intervention.

Readmission: day hospital compared with inpatient setting

2.4.3.14 *Very-low-quality evidence from one observational study of 70 children showed no statistical difference in readmission at 48 hours between the two groups (day hospital = 2 patients, inpatient = 0 patients; RR 5.00, 95% CI 0.25 to 100.53).*

Readmission after implementation of a sickle cell disease intervention in a hospital setting

2.4.3.15 *Very-low-quality evidence from one observational study with 174 child admissions showed that the readmission rate within 30 days was significantly lower for children admitted during the intervention period than for those admitted during the control period (11% compared with 28%, $p < 0.002$, 95% CI 0.1 to 0.6).*

2.4.3.16 *Very-low-quality evidence from one observational study with 174 child admissions showed that the significant reduction in the 30-day readmission rate for children admitted with an acute painful episode during the educational intervention disappeared once the intervention had stopped, with the overall 30-day readmission rate increasing from 11% to 19% (33/173), compared with 28% (44/159) in the previous year ($p = 0.06$, 95% CI 0.4 to 1.0). The effect was no longer statistically significant 6 months after removing the education component.*

In this study (Frei-Jones et al. 2009), the educational component of the intervention involved monthly education about sickle cell pain for hospital house staff, as well as patient and carer education.

Patient satisfaction in adults treated before and after implementation of an intervention

2.4.3.17 *Very-low-quality evidence from one observational study with 18 adult patients showed that overall satisfaction tended to increase after the new programme was implemented (0% of patients provided 'good' and 'very good' ratings pre-intervention, which increased to 50% for each category post-intervention).*

In this study (Jamison and Brown 2008), patient satisfaction was measured using a 5-point Likert scale. The survey tools were evaluated by five healthcare professionals involved directly in the programme development.

2.4.4 Health economics

This is a summary of the analysis carried out for this review question. See appendix F for full details of the economic analyses carried out for the guideline.

Methods

No data are available on health-related quality of life (HRQoL) and other patient benefits that may be provided by the daycare setting. Therefore, to explore the economic impact of dedicated sickle cell centres from an NHS perspective, an exploratory cost-minimisation analysis was conducted based on the data reported in the before-and-after study of Wright et al. (2004) (see section 2.4.2). To do this, equivalent effectiveness was assumed between a daycare-based strategy and one consisting of presentation at the emergency department and hospital ward admission.

Costs

The cost of hospital admission for an acute painful sickle cell episode was estimated using the same NHS Reference Cost 2010/11 values applied in our cost–utility model (see appendix F). Weighted averages of costs recorded in four 'department' categories and three 'currency' codes were used. The estimated daily cost of treating an episode in a daycare centre was multiplied by the average number of daycare centre visits per episode from Wright et al. (2004) to obtain the cost per episode of treatment in a daycare centre. Those who started treatment in a daycare centre but eventually required admission to hospital within 7 days – described as 'failure of daycare' by Wright et al. (2004) – incurred both the cost of daycare treatment and the cost of hospital admission (31% of hospital admissions were 'daycare failures').

To calculate the cost savings per episode of starting treatment at a daycare centre, the 'cost per episode treated in the daycare centre (including daycare failures)' was subtracted from the 'expected cost per episode of hospital admission (assuming no daycare failures)'. A detailed description of the calculations used to derive these estimates can be found in appendix F.

To provide validation for this calculation, current pay rates (PSSRU 2011) were applied to the annual staff input reported by Wright et al., in order to calculate the cost per case treated in a sickle cell daycare centre, assuming that the number of cases and staff requirement remained the same as that estimated in 2003.

Results

The results (Table 34) suggest that dedicated sickle cell daycare centres may provide cost savings of around £800 per episode for children and £1100 per episode for adults, primarily by reducing the need for hospital admission.

Table 34 Cost-minimisation analysis of a dedicated sickle cell daycare centre

	Derivation	Children	Adults
NHS Reference Costs Codes		PA47Z	SA10E & SA10F
Weighted average cost of combined day cases and short stay	a	£565	£430
Average day centre visits per episode	b	1.53	1.53
Observed mean cost per episode treated in daycare centre	c = a × b	£864	£658
Observed mean cost of long-stay admission	d	£2504	£2576
Proportion of patients on admission who are daycare failures	e	0.31	0.31
Expected cost per episode of long-stay admissions without daycare centres	f = d − (c × e)	£2236	£2372
Expected cost per episode for daycare failures	g = f + c	£3100	£3030
Proportion of daycare centre patients who become daycare failures	h	0.25	0.25
Total cost per patient treated in daycare centre (including daycare failures)	i =c + (f × h)	£1423	£1251
Cost saving per patient treated at daycare centre	f – i	£813	£1121

The updated annual staffing cost based on the structure reported by Wright et al. (2004) suggested that the cost per episode of treatment in a daycare centre is about £974. This is somewhat higher than the figure estimated in the analysis of the NHS Reference cost data.

Discussion

Overall, the analyses suggest that treating acute painful sickle episodes in dedicated sickle cell daycare centres would be associated with cost savings, primarily as result of a reduction in the need for hospital ward admission.

The updated staff costs based on the structure reported by Wright et al. (2004) suggest that daycare centres may be somewhat more expensive on a per-episode level than estimated in our analysis (£974 per episode, compared with £658–864). However, GDG opinion suggests that the staffing requirement set out by Wright et al. is a generous one: it is likely that most sickle cell daycare centres operating in the NHS and contributing data to the NHS Reference Costs have a lower full-time equivalent staffing level. Furthermore, it was reported in the study by Wright et al. – and substantiated by the GDG – that daycare centre staff were also engaged in other services (such as blood transfusion for people with thalassaemia), suggesting that costs solely attributable to the treatment of acute painful sickle cell episodes may have been overestimated. Therefore, it is to be expected that an estimate of costs derived from the Reference Costs will be somewhat lower. Moreover, even if the updated staffing costs were used in the cost-minimisation analysis as an estimate of the costs to the NHS of a daycare-centre episode, positive cost savings would still be associated with the use of daycare centres.

However, it should be noted that this analysis did not take into account the set-up costs of units, which will be extremely variable, depending on the extent and nature of current provision in each locality, as well as the size of the population that is expected to benefit from the facility.

2.4.5 Evidence to recommendations

Relative value of different outcomes	Admission rate and mean length of stay were considered to be important outcomes, and drove the GDG discussions and recommendations. The GDG agreed that where statistical testing was not reported, the overall direction of trends appeared to show a beneficial effect after a sickle cell intervention (this may involve education for staff, a pain protocol or other specialised input) that would be clinically important.
Trade off between benefits and harms	The GDG recognised that there are geographical areas where there is a high prevalence of sickle cell disease, and that the demand for treatment and management differs across England and Wales. The GDG agreed that daycare facilities are not necessarily already in place in low-prevalence areas, and models of care would need to reflect differing demands and potential changes in prevalence. The GDG discussed the structure and nature of a daycare setting and suggested that this may facilitate a high concentration of expertise and education. It was agreed that providing training and protocols to staff in emergency departments would increase the

	quality of care received by patients compared with current practice, and this is reflected in the evidence. It was also proposed that the quality of care may be increased further if these interventions are carried out in a daycare setting. The GDG agreed that education of healthcare professionals needs to be regular and ongoing, because the evidence shows that reductions in readmission rates were not significant when the educational component was removed.
Economic considerations	Very limited evidence was available to explore the economic impact of providing daycare facilities (see 'Quality of evidence', below). An exploratory cost-minimisation analysis based on the UK data reported by Wright et al. (2004) suggested that, by reducing the requirement for hospital inpatient care, daycare units may provide cost savings of up to £1000 per acute painful sickle cell episode. However, this analysis was unable to account for the set-up costs of units, which will be extremely variable, depending on the extent and nature of current provision in each locality, as well as the size of the population that is expected to benefit from the facility.
Quality of evidence	The GDG agreed that, overall, the evidence was of very low quality. However, it was also acknowledged that it would not be possible to conduct a blinded RCT for this question. The GDG discussed the value of a body of evidence in other areas that suggests that providing specialist care is in general beneficial compared with non-specialist care, and agreed that this could be applied to patients with sickle cell disease. The GDG noted that many of the studies were conducted in the USA, where facilities and clinical practice may differ from those in the UK. The GDG discussed the value of the UK-based study (Wright et al. 2004) and felt that evidence from that study was more generalisable than that from the other studies.
Other considerations	**Subgroups (children and young people, and pregnant women)** The GDG discussed the treatment of children and young people presenting to hospital with an acute painful sickle cell episode, and agreed that specialist healthcare professionals caring for adults and children would differ. For adults these would include haematologists, pain specialists and other healthcare professionals with expertise in sickle cell disease. For children these would include paediatricians who have haematology as a sub-speciality. Therefore a recommendation was made that patients should be cared for in an age-appropriate setting. The GDG also discussed the treatment of pregnant women, and agreed that there is generally little difference in the management of an acute painful sickle cell episode in women who are pregnant compared with those who are not pregnant. However, it was agreed that in all cases it will be necessary to seek advice from the obstetrics team.

2.4.6 Recommendations and research recommendations for settings and skills for managing an acute painful sickle cell episode

Recommendations

Settings and training

Recommendation 1.1.23

All healthcare professionals who care for patients with an acute painful sickle cell episode should receive regular training, with topics including:

- pain monitoring and relief
- the ability to identify potential acute complications
- attitudes towards and preconceptions about patients presenting with an acute painful sickle cell episode.

Recommendation 1.1.24

Where available, use daycare settings in which staff have specialist knowledge and training for the initial assessment and treatment of patients presenting with an acute painful sickle cell episode.

Recommendation 1.1.25

All healthcare professionals in emergency departments who care for patients with an acute painful sickle cell episode should have access to locally agreed protocols and specialist support from designated centres.

Recommendation 1.1.26

Patients with an acute painful sickle cell episode should be cared for in an age-appropriate setting.

Recommendation 1.1.27

For pregnant women with an acute painful sickle cell episode, seek advice from the obstetrics team and refer when indicated.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B5

Are daycare units cost effective compared with emergency settings for treating patients with an acute painful sickle cell episode?

2.5 Information and support needs of patients and their carers during an acute painful sickle cell episode

2.5.1 Review question

What information do people need during an acute painful sickle cell episode?

2.5.2 Evidence review

This review question considered the information and support needs of patients and their family members and/or carers during an acute painful sickle cell episode. From a database of 5534 studies, 69 articles were ordered. A further two articles (Shelley B 2011; Strickland et al. 2001) were identified from a systematic review, leaving a total of 71 papers for consideration.

Studies were considered for inclusion if they were related to an acute painful sickle cell episode within the hospital setting and covered education, patient experiences and/or information needs. As the scope of the guideline considered the management of sickle cell episodes in hospital, any paper that focused on management of an acute painful episode at home was excluded. There was no restriction on study design, although only full papers were eligible for inclusion. For a full list of excluded papers for this review question, see appendix D.

Ten full-text articles from nine primary studies met the eligibility criteria and were included in the final review (Alleyne and Thomas 1994; Booker et al. 2006; Harris et al. 1998; Johnson 2003; Lattimer et al. 2010; Maxwell et al. 1999a; Maxwell et al. 1999b; Mitchell et al. 2007; Murray and May 1988;

Waters and Thomas 1995). All of the included studies were qualitative in design (incorporating patient focus groups and/or interviews) or patient questionnaires, or a mix of the two designs.

The quality of all included studies was assessed using appropriate methodology checklists. The qualitative designs were assessed by using the relevant NICE methodology quality appraisal checklist. There is currently no checklist available for the assessment of survey or questionnaire designs. Therefore a checklist originally published in the British Medical Journal was modified to aid the quality assessment of these studies. (See appendix E for a copy of this checklist.)

Because GRADE methodology has not yet been adapted for use with qualitative studies, a thematic analysis was undertaken. All of the included studies were initially screened to identify common key themes and issues relating to patient experiences during admission for an acute painful sickle cell episode. The evidence was then further explored to identify common subthemes across all 10 papers. All papers were then re-examined to ensure that all relevant key themes and subthemes were extracted. These key themes and subthemes were then used to identify the information and support needs of patients and their carers during an acute painful sickle cell episode in hospital.

Quality assessment

Two studies were considered to provide a thorough reporting of the study design, data collection, validity and reliability of the research findings. The majority of the reviewed papers did, however, have some limitations. The main sources of bias were identified with study validity. Most papers did not adequately report the role of the researcher or consider the impact this could have upon participants' responses. Additionally, several papers did not describe the settings and context in which the research was undertaken in great detail. Any study-specific limitations identified by the quality assessment are included within the summary of included studies table (table 35).

The key themes and subthemes identified across all studies are shown within a key themes matrix, which provides a more detailed overview of the themes and issues identified within each study (table 36).

Table 35 Summary of all included studies for identifying information and support needs of patients and their carers during an acute painful sickle cell episode

Reference	Study design and aim	Loca-tion	Population	Recruitment/ sample collection	Limitations	Key themes			
						Pain management	Communi-cation	Information at discharge	Patient support needs
Qualitative designs									
Alleyne and Thomas (1994)	Design: qualitative study using semi-structured interviews Aim: To examine the patients' experience of pain management and the viewpoint of nurses providing care	UK	Adults 10 patients 8 female, 2 male All African-Caribbean ethnicity	Patients were recruited from adult sickle cell support groups held at the hospital All nurses were from the haematology ward	Lack of reflexivity in reporting the role of the researcher Unclear how reliable data assessment was Data analysis could have been more detailed	Pain monitoring Pain management methods Anxieties	Involvement and control Mutual exchange	No information related to this key theme was discussed in the study	No information related to this key theme was discussed in the study

Booker et al. (2006)	Design: qualitative study using focus groups Aim: to understand the barriers faced by patients in managing pain	UK	Adults 10 patients 4 female, 6 male; mean age 32.0 years, range 22–53 years; 8 African-Caribbean, 1 African, 1 Portuguese	Patients were randomly selected from a list of previous inpatients Purposive sampling by quota allocation ensured a balance of ages and genders	Full and clear reporting provides a thorough outline of context and findings of research	Pain management methods Anxieties	Conflict Mutual exchange	No information related to this key theme was discussed in the study	Psychosocial support
Mixed designs									
Johnson (2003)	Design: mixed design using focus group and questionnaire Aim: To collect data about patients' perceptions of using patient-controlled analgesia	UK	Adults 40 patients 22 female, 18 male (age range 18–49 years); ethnicity not reported	All adult patients with sickle cell disease admitted during the study period who were eligible to complete the questionnaire. Patients taking part in the focus group were identified through the modal age bracket.	Lack of reflexivity in reporting the role of the researcher Unclear how reliable data assessment was Considerations for context bias were not reported The paper could have provided excerpts from focus group	Pain management methods	Involvement and control Conflict Mutual exchange	No information related to this key theme was discussed in the study	No information related to this key theme was discussed in the study

Maxwell et al. (1999), Maxwell and Bevan (1998)	Design: mixed design using qualitative interview and questionnaire Aim: To examine patients' experiences of ward and services	UK	Adults 57 patients 32 female, 25 male; age range 20–60 years, mean age 34 years; 29 West African, 26 African-Caribbean, 2 other African	Theoretical sampling was used to recruit patients with sickle cell disease in the Greater London area	Full and clear reporting providing a thorough overview of context and findings	Pain monitoring Anxieties	Involvement and control Conflict Mutual exchange	Medication advice Personal needs	Psychosocial support
Harris et al. (2008)	Design: mixed design using qualitative interview, focus group and structured questionnaire Aim: to compare experiences of pain and pain management in patients with different frequencies of hospital admissions	UK	Adults 27 patients 12 female (mean age 30 years, range 18–60 years); 15 male (mean age 28 years, range 21–35 years); All patients were African or African-Caribbean	Patients were previous inpatients of the haematology ward Only patients admitted in the previous 12 months were eligible	Not sure how reliable the methods were: no triangulation Considerations for context bias were not reported Findings could have been more thorough Ethical considerations were not reported	Pain management methods Anxieties	Conflict Mutual exchange	No information related to this key theme was discussed in the study	Psychosocial support
Mitchell et al. (2007)	Design: mixed design using focus group and questionnaire Aim: to assess how healthcare services can be	USA	Parents or guardians (children) 53 participants representing 48 children with sickle cell	Participants were recruited via letters, telephone calls and clinic visits Only parents or guardians who	Findings could have been more thorough Ethical considerations were not reported in adequate detail	No information related to this key theme was discussed in the study	Involvement and control Mutual exchange	Medication advice	No information related to this key theme was discussed in the study

	optimised to improve utilisation by patients and their families		disease Parents and guardians: 46 female, 6 male Children: 24 female, 24 male; mean age 10.66 years All participants were African-American, except for one white adoptive parent	were living with the child and had been the primary caregiver for at least 12 months were eligible for inclusion					
Questionnaire/survey designs									
Waters and Thomas (1995)	Design: qualitative questionnaire Aim: to identify the perceptions and expectations of pain management in patients and nurses	UK	Adults 9 patients 3 female, 6 male; mean age 24.3 years; range 17–28 years) 17 nurses (12 qualified nurses , 5 student nurses); nurses' demographics were not reported	Patients with sickle cell disease admitted to a general medical ward All nurses were from the haematology ward	Lack of reflexivity in reporting the role of the researcher. Considerations for context bias were not reported Unclear about sampling strategy Data analysis methods were not reported Ethical considerations were not reported	Pain monitoring Pain management methods Anxieties	Involvement and control	No information related to this key theme was discussed in the study	Clinical support Psychosocial support

Lattimer et al. (2010)	Design: structured interviews presented in a survey design Aim: to measure the experience in hospital of patients compared with a national sample	USA	Adults 45 patients 25 female, 20 male; mean age 31.2 years, range 20–59 years	Patients were recruited from the emergency department and adult sickle cell and haematology outpatient clinics Participants from this cohort were interviewed each time they were admitted for a vaso-occlusive crisis	Lack of reflexivity in reporting the role of the researcher Considerations for context bias were not reported	Pain management methods	Involvement and control Mutual exchange	Personal needs	Psychosocial support
Murray and May (1988)	Design: structured questionnaire Aim: to collect information from patients on aspects of pain episodes	UK	Mixed population (adults and children) 102 patients 61 female, 41 male; age range 11–49 years)	All patients were attending haematology clinics 400 questionnaires were distributed to the clinics Response rate is unknown (number of questionnaires given to patients is unknown)	Methods of administration and distribution were inadequately reported Unclear if an existing tool was used or a new tool was developed Unclear how potential participants were identified Ethical considerations were not reported	Pain management methods Anxieties	Mutual exchange	No information related to this key theme was discussed in the study	No information related to this key theme was discussed in the study

Table 36 Key themes matrix showing common key themes and subthemes for identifying the information and support needs of patients and their carers during an acute painful sickle cell episode

	Key themes and subthemes			
	Pain management	**Communication**	**Information at discharge**	**Patients' support needs**
Alleyne and Thomas (1994)	**Pain monitoring** Patients perceived a lack of monitoring of their pain severity. Pain monitoring was carried out by the more inexperienced nurses. **Pain management methods** Pethidine was the most commonly used drug but patients reported difficulties in obtaining it. Patients' preferred route of administration was by continuous intravenous infusion because it was an effective way to control pain, but nurses thought it was an unsatisfactory route because patients were inclined to 'fiddle' with the drip and pump. Patients had to ask for painkillers and they perceived delays in their requests for pain relief being fulfilled. Patients thought that nurses were reluctant to supply adequate pain relief and deliberately delayed providing analgesia because they misinterpreted requests as 'drug-seeking' behaviour. **Anxieties** Nurses raised concerns about the prolonged use of pethidine. Nurses were anxious about their own ability to control patients' pain effectively and relied on 'trial and error' methods. Nurses worried about pethidine and were	**Involvement and control** Patients were not involved in decisions about their care. Patients thought they were not treated as individuals by nurses, but nurses were frustrated at being unable to individualise care. **Mutual exchange** Nurses tried to provide adequate explanations to patients about delays in their requests for analgesia. Patients thought nurses lacked sympathy and understanding of their needs.		

	reluctant to administer it because they doubted the genuine nature of patients' pain. Nurses worried that patients would become addicted to medication. Nurses were concerned about PCA and distrusted patients to be responsible enough to use it correctly.			
Booker et al. (2006)	**Pain management methods** Patients found that it was difficult to obtain painkillers from healthcare professionals. Patients were aware that some pain could be managed at home with non-prescription painkillers, whereas at other times medications were only available in hospital. **Anxieties** Patients worried about overdosing, high levels of analgesia and long-term effects of pain medication.	**Conflict** Patients likened the relationship with healthcare professionals to a battle. Patients would actively avoid consulting with healthcare professionals while they were having an acute painful sickle cell episode because of a fear of being perceived as opioid dependent. Patients' frustration at medication failure would be manifested in anger at others around them, anger at themselves and anger at healthcare professionals. **Mutual exchange** Some patients found that it was difficult to convince healthcare professionals that they were in pain. Many patients thought doctors had insufficient knowledge of sickle cell disease to be able to make suitable treatment decisions.		**Psychosocial support** Patient anxieties included fear of death because of complications associated with sickle cell disease.
Johnson (2003)	**Pain management methods** Patients perceived pethidine to be the most effective drug but some patients had had seizures while using it. Patients preferred diamorphine because of the more tolerable side effects. Patients perceived that the effectiveness of PCA was dependent on dosage and the administration frequency of the diamorphine	**Involvement and control** Patients favoured PCA because of its ability to provide more control of pain relief than other modalities. Most patients thought that PCA promoted timely pain relief. Patients thought that PCA provided freedom from staff, but the reduced staff involvement was thought to be		

	bolus. PCA was thought to have the potential to avert long delays for analgesia in emergency departments. Some patients thought that PCA improved pain tolerance because of the predictability of dose delivery. Patients identified problems with PCA functionality (for example, cumbersome and immobility of use) and issues associated with site infections from cannulae.	disadvantageous, leading to 'non-existent nursing care'. Patients did not feel involved in dosing decisions. Patients thought that PCA usage seemed to be dependent on nurses' choice. **Conflict** Some patients felt that they had been coerced by nurses to use PCA and that PCA was 'convenient for staff'. **Mutual exchange** Some patients thought that nurses were inclined to focus attention on the machine and not on the patient.		
Maxwell Streetly and Bevan (1999)	**Pain monitoring** Patients felt that a range of needs, including personal care and monitoring of vital signs, were neglected. **Anxieties** Patients reported that nurses deliberately avoided providing painkillers because they were scared that patients would become addicted.	**Involvement and control** Patients thought that nurses tried to control care regimes and would not involve patients in decisions. **Conflict** Some patients became frustrated and angry at the poor communication with care providers. Some patients who were admitted frequently to hospital became verbally or physical aggressive because of under-treatment of pain and poor communication with care providers. **Mutual exchange** There was a lack of communication in provision of tablets, and patients did not know they were taking painkillers. Patients rely on self-education to tell nurses what pain management they need, especially in situations where nurses had had no previous experience of treating		**Psychosocial support** Patients reported a failure to provide psychosocial support. They would have preferred to talk to somebody about their anxieties – but this was not always picked up by the healthcare professionals providing care.

		with patients with sickle cell disease.		
Maxwell and Streetly (1998) (supple-mentary to the above study)		**Involvement and control** Patients varied in the extent to which they were involved in decision-making about their care. Patients who were used to managing pain at home recognised their own ability to control their pain and demonstrated independence in pain management. Patients who were frequently admitted to hospital were less likely to be involved in their care. A small number of patients felt that they were unable to exert any control over their pain management and relied entirely on healthcare professionals to make decisions. Developing close relationships between patients and their healthcare providers was thought to contribute to positive experiences of care, because staff were able to individualise treatment decisions to specific patient needs. Some patients thought that healthcare professionals sometimes exerted control by involving family members in treatment decisions without the patient's consent.	**Medication advice** Patients reported experiencing withdrawal symptoms after coming off strong medications. Some patients identified the need for nursing support (for example, dispensation of appropriate medication and oxygen at home). Some patients sought primary care support after discharge (for example, prescribing of opioids, home visits and receiving injections and oxygen at home) **Personal needs** Physical weakness made it hard for patients to undertake daily tasks after discharge from hospital. Some patients found it difficult to readjust to independent care.	
Harris et al. (2008)	**Pain management methods** Most patients were satisfied with pain control in their last admission to hospital. The majority of patients received analgesia within 15 minutes of arrival at the emergency department. Some patients would have liked analgesia to be provided more promptly. Reported methods to cope with pain included	**Conflict** Some patients would only come to hospital when pain became too much to bear at home. Almost half of the patients thought that staff had negative attitudes to patients with sickle cell disease. Patients were afraid to go to hospital because of the attitudes of the nurses.		**Psychosocial support** Most patients were satisfied that they had received adequate opportunities to discuss their concerns and worries with a nurse or consultant, but some would have been interested in discussing their concerns further.

	staying in bed, rocking, positive thinking, distraction, rubbing the affected part and listening to music. Few patients found cognitive therapies to be useful. Some patients thought nurses were slow to provide analgesia. **Anxieties** The majority of patients were worried about becoming dependent on analgesia.	**Mutual exchange** A quarter of patients thought that staff lacked sufficient knowledge of sickle cell disease. Patients cited inadequate explanations for delays in receiving analgesia. Some patients thought the staff treated them as 'liars'.		
Mitchell et al. (2007)		**Involvement and control** Parents rely on children to monitor symptoms and tell them when they are experiencing pain. Children from aged 5 can be relied upon to be involved in their own care. Parents acknowledged limitations in their own ability to make decisions which were independent of their child. **Mutual exchange** Parents were frustrated that relatives of patients with sickle cell disease appeared to receive limited attention compared with relatives of children with other illnesses.	**Medication advice** Patients and parents would have liked to see more medication dispensing and options.	
Waters and Thomas (1995)	**Pain monitoring** Assessment of pain was unplanned and sporadic. Most nurses incorrectly estimated the severity and duration of pain. Half of the nurses mis-located the site of the patients' pain. **Pain management methods** There was inconsistency with pain control. Patients did not expect to receive full pain relief but the nurses were striving to achieve	**Involvement and control** Most patients felt less in control of their pain than they were at home and would have liked to have had more involvement in managing while on the ward.		**Clinical support** The majority of patients would have liked to have received more healthcare advice and information from nurses about self care and pain-relieving measures. **Psychosocial support** Most patients would have liked more emotional support to be provided by nurses.

	this. Less than half of the patients stated that their pain had been completely relieved at any one point. Some nurses were not aware of other forms of treatment for managing pain (for example, heat treatment). Most nurses stated that their ability to provide better pain relief using alternative methods was limited by other factors (these included limitations because of time or experience and lack of knowledge of the methods used) All nurses reported that their ability to reduce sickle-cell pain with analgesia was affected by other factors (for example, lack of time, lack of knowledge about narcotic analgesia, fears of patient overdosing and addiction, and lack of experience with patients with sickle cell disease). **Anxieties** Some nurses stated that worries about patient overdosing and addiction influenced their ability to provide effective pain relief.			
Lattimer et al. (2010)	**Pain management methods** Patients thought that staff did not do enough to control their pain. Patients were not always treated with respect and dignity.	**Involvement and control** Patients thought that they were insufficiently involved in decisions about their medical care. **Mutual exchange** Patients thought that family members were not given the opportunity to talk to a doctor. Patients thought that staff gave conflicting information, and that information given by both nurses and doctors was not always clear.	**Personal needs** Patients reported that their family members were not given enough information to help with their recovery.	**Psychosocial support** Patients thought that it was not always easy to find someone to talk to about their concerns. Patients thought that doctors and nurses did not always talk to patients about their fears and anxieties.
Murray	**Pain management methods**	**Mutual exchange**		

and May (1988)	Personal pain management was similar before and during periods of pain: methods included keeping warm, taking extra fluids, rest and taking painkilling drugs. Less frequently used pain-relief methods included taking extra vitamins, taking herbal remedies and talking about feelings and fears. Patients identified delays in receiving adequate pain relief. Some patients thought the delay in being seen was too long. **Anxieties** Patients who were using painkilling drugs described concerns about side effects, over-dosage and addiction.	Most patients thought that staff in emergency departments were the least able to understand problems associated with sickle cell disease, whereas staff on the ward would show a greater understanding.		
Abbreviations: PCA, patient-controlled analgesia.				

See appendix E for the evidence tables in full.

2.5.3 Evidence statements

Pain monitoring

2.5.3.1 Evidence from three studies showed that patients perceived a lack of monitoring of their pain and vital signs. When pain was assessed, this was usually carried out in an unplanned and sporadic manner by the more inexperienced nurses.

Pain management methods

2.5.3.2 Evidence from seven studies showed that patients had a comprehensive understanding of both analgesic and alternative pain management strategies, although patients and nurses had different expectations of pain control. Patients stated that it was difficult to obtain painkillers from healthcare professionals, and delays in receiving analgesia were put down to nurses misinterpreting their requests as 'drug seeking' behaviour.

Anxieties

2.5.3.3 Evidence from six studies showed that both patients and nurses worried about pain management. Patients raised concerns about their long-term dependence on painkillers. Nurses were anxious about their ability to control patients' pain effectively, and stated that their treatment decisions were influenced by worries about patients becoming addicted to analgesia.

Involvement and control

2.5.3.4 Evidence from five studies showed that patients are actively involved in making decisions about their own care from an early age, but feel less in control of their pain management in hospital than at home. Patients will use various approaches to become more involved in pain management decisions (ranging from passive to assertive approaches).

Conflict

2.5.3.5 *Evidence from four studies showed that patients' dissatisfaction with pain management decisions could be manifested in anger and frustration with others. This could lead to situations of conflict with healthcare professionals and for this reason some patients would actively avoid going to the hospital unless it was a last resort.*

Mutual exchange

2.5.3.6 *Evidence from eight studies showed that patients found it hard to convince staff that they were in pain, and this was because many healthcare professionals showed an inadequate knowledge and understanding of the needs of patients with sickle cell disease. When information was provided, it was often inconsistent and lacked clarity. Patients advocated the value of including family members in discussions with healthcare professionals and used self-education methods to deal with situations where staff had previously had limited experience of patients with sickle cell disease.*

Medication advice and personal needs

2.5.3.7 *Evidence from three studies showed that patients often experienced withdrawal symptoms after coming off strong medications. Some patients faced physical challenges adjusting to independent care and would have liked their family to receive more information to help with their recovery, while others would have liked to see more medication and dispensing options.*

Clinical and psychosocial support

2.5.3.8 *Evidence from five studies showed that patients had various support needs (including both clinical and psychosocial support), although some patients reported satisfaction in their ability to discuss concerns with a nurse or consultant.*

2.5.4 Health economic modelling

This was not considered to be a health economic question.

2.5.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relevance of the various themes and acknowledged that the evidence synthesis provided a comprehensive overview of patients' experiences. The GDG recognised that having previously experienced many acute painful episodes, patients with sickle cell disease are experts in their condition and should be involved in treatment decisions. Healthcare professionals should ask the patient about their previous treatment regimens, to help identify the patient's individual needs and assist in developing appropriate treatment plans for the current episode. The GDG appreciated that patients admitted during an acute painful episode can sometimes have worries or concerns about the care they will be receiving. It was thought that involving the patient in discussions would help to reassure them and provide an opportunity to discuss any concerns. The GDG acknowledged that some patient concerns may be related to factors beyond their current episode. Engaging in appropriate discussions could therefore help healthcare professionals to identify any need to refer a patient to appropriate support services during their admission. The GDG also discussed the relevance of providing information to patients at discharge. They acknowledged that some patients will be discharged from hospital while still continuing to experience the painful episode. These patients would therefore require appropriate information to help them to continue to manage their pain. Appropriate details should include information relating to medication dispensing, as well as information to assist with any side effects of the medication. It was noted that patients discharged during a painful episode may also have support needs, especially if they have been using psychological or support services during their admission. These patients would therefore need information about specialised support services.
Trade off between benefits and harms	The GDG recognised that there was a need to consider how information is provided to patients and carers. It was noted that there is a trade off regarding the need to provide information to patients and carers while at the same time making sure that the information is relevant and useful. Written information is useful as a reference point, but some patients may find written information difficult to understand. There is also the possibility of legal issues surrounding the provision of information to family members.
Economic considerations	Health economics were not considered for this review question.
Quality of evidence	The GDG agreed that the evidence statements were a true reflection of the literature. It was noted that the quality of evidence was based upon the methodology checklists and the limitations were described.

	Although some of the papers were over 18 years old and the issues raised were thought to be historical, the GDG acknowledged that the themes were representative of current factors. These issues were experienced across the board and were not limited to adult patients.
Other considerations	The GDG recognised that the evidence synthesis provided indirect evidence about issues relating to the training of healthcare professionals, which could support recommendations made in response to other review questions (see for example section 2.4). The GDG also acknowledged that evidence of the need for individualisation of care could support other recommendations.

2.5.6 Recommendations for identifying the information and support needs of patients and their carers during an acute painful sickle cell episode

Recommendations

Individualised assessment at presentation

Recommendation 1.1.2

Throughout an acute painful sickle cell episode, regard the patient (and/or their carer) as an expert in their condition, listen to their views and discuss with them:

- the planned treatment regimen for the episode
- treatment received during previous episodes
- any concerns they may have about the current episode
- any psychological and/or social support they may need.

Discharge information

Recommendation 1.1.28

Before discharge, provide the patient (and/or their carer) with information on how to continue to manage the current episode, including:

- how to obtain specialist support
- how to obtain additional medication
- how to manage any potential side effects of the treatment they have received in hospital.

3 Notes on the scope of the guideline

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is given in appendix C.

4 Implementation

NICE has developed tools to help organisations implement this guidance.

5 Other versions of this guideline

5.1 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway.

5.2 'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available.

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2749).

We encourage NHS and third sector, including voluntary, organisations to use text from this booklet in their own information about acute painful sickle cell episodes.

6 Related NICE guidance

Published

- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2009).
- Antenatal care. NICE clinical guideline 62 (2008).
- Intrapartum care. NICE clinical guideline 55 (2007).
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007).

7 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

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9 Glossary and abbreviations

Glossary

Acute painful sickle cell episode

An episode of pain that is caused by blockage of the small blood vessels in people with sickle cell disease. Also known as painful crisis.

Bolus dose

The administration of a medication, drug or other compound that is given to raise its concentration to an effective level. Administration can be intravenous, intramuscular, intrathecal or subcutaneous.

Hypoxia

A pathological condition in which a part of or the whole body is deprived of adequate oxygen supply.

Moderate pain

Pain with a VAS (or equivalent) score typically within the range of 4 to 7 (this description should not be interpreted as a strict definition and will not apply to all patients, as pain is subjective).

Patient-controlled analgesia (PCA)

A method of safely administering strong opioids which is controlled by the patient (or a nurse for nurse-controlled analgesia).

Severe pain

Pain with a VAS (or equivalent) score typically above 7 (this description should not be interpreted as a strict definition and will not apply to all patients, as pain is subjective).

VAS (visual analogue scale) score

Pain scoring tool measured on a linear scale from 0 to 10, with 0 indicating no pain.

Please see the NICE glossary for an explanation of terms not described above.

Abbreviations

Abbreviation	Term
ACS	Acute chest syndrome
C-IV	Continuous intravenous
DH	Day hospital
IM	Intramuscular
LMWH	Low-molecular-weight heparin
LOS	Length of stay
PCA	Patient-controlled analgesia
SCD	Sickle cell disease
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale

Appendix A Contributors and declarations of interests

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An internal clinical guidelines technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments.

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Declarations of interests

GDG member	Interest declared	Type of interest	Decisions taken
Hellen Adom	None		
Michelle Afif	None		
Kofi Anie	Research grant from Novartis Pharmaceuticals UK to North West London Hospitals NHS Trust as sponsor for the employment of research staff. This is unrelated to the matter under consideration.	Non-personal pecuniary – non-specific.	Declare and can participate in discussions on all topics.
Brigitta Brandner	None		
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Alexander McKnight	Acting as consultant to legal team preparing patent defence (on behalf on a commercial drug house) of opioid analgesic formulation, and recently as expert witness in court cases – patents expire during 2012/2013.		Stay for presentation and the discussion of the evidence, but to leave the room prior to any decisions and recommendations made.
Asa'ah Nkohkwo	Member of the expert working group working on a Department of Health-sponsored project under the British Committee for Standards in Haematology (British Society for Haematology)	Personal non-pecuniary.	Declare and can participate in discussions on all topics.

	which has recently (October 2011) resumed on the production/revision of ‘Guidelines for the management of sickle-cell pain’.		
Kate Ryan	None		
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Appendix B List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

B1 Pain management for patients with an acute painful sickle cell episode

For patients with an acute painful sickle cell episode, what are the effects of different opioid formulations, adjunct pain therapies and routes of administration on pain relief and acute sickle cell complications?

Why this is important

Limited evidence is available on the effectiveness of different opioid formulations, routes of administration and adjunct therapies in the treatment of an acute painful sickle cell episode. A series of RCTs should be conducted that compare the effects of different opioid formulations, adjunct pain therapies and routes of administration. These RCTs should be conducted separately in adults and children, and cover the duration of the acute painful episode. Outcomes should include pain and adverse events such as acute chest syndrome.

B2 Use of low-molecular-weight heparin to treat patients with an acute painful sickle cell episode

Are therapeutic doses of low-molecular-weight heparin (LMWH) effective, compared with prophylactic doses of LMWH, in reducing the length of stay in hospital of patients with an acute painful sickle cell episode?

Why this is important

Moderate-quality evidence from one RCT suggested a significant benefit of treating patients with an acute painful sickle cell episode with LMWH. This was supported by exploratory health economic analyses suggesting a large reduction in length of stay and associated costs. An RCT should be conducted that examines the effect of therapeutic doses of LMWH, compared with

prophylactic doses, on the length of stay in hospital of patients with an acute painful sickle cell episode. The RCT should be conducted separately in adults and children, and cover the duration of the painful episode.

B3 Psychological interventions for patients with an acute painful sickle cell episode

For patients with an acute painful sickle cell episode, are psychological interventions, in conjunction with standard care, effective in providing pain relief?

Why this is important

There was a lack of evidence on the benefits of psychological interventions for managing pain during an acute painful sickle cell episode. An RCT should be conducted in patients with an acute painful sickle cell episode that compares the effectiveness of psychological interventions plus standard care against standard care alone. The RCT should cover the duration of the painful episode, and should assess outcomes such as pain, mood and health status.

B4 Non-pharmacological interventions for patients with an acute painful sickle cell episode

For patients with an acute painful sickle cell episode, are non-pharmacological interventions, such as massage, effective in improving their recovery from the episode?

Why this is important

There was a lack of evidence on the potential benefits of supportive interventions for patients with an acute painful sickle cell episode. An RCT should be conducted that examines the effect of providing rehabilitation interventions that are aimed at improving a patient's recovery after an acute painful sickle cell episode. Such interventions could include massage and physical therapy. The intervention should be provided within the hospital setting, and patients should be followed up 7 days after the episode. Data should be collected to inform outcomes such as length of stay, health-related quality of life and coping strategies.

B5 Cost effectiveness of daycare units for treating patients with an acute painful sickle cell episode

Are daycare units cost effective compared with emergency settings for treating patients with an acute painful sickle cell episode?

Why this is important

There was a lack of evidence on the cost effectiveness of daycare units for treating patients with an acute painful sickle cell episode in the UK. A trial should be carried out that compares treating patients with an acute painful sickle cell episode in an emergency department setting and in a specialist sickle cell daycare unit. Outcomes should include health-related quality of life (HRQoL). Data should be collected using validated measure(s) of HRQoL, including EQ-5D.

Appendix C Guideline scope

See separate file.

Appendix D How this guideline was developed

See separate file.

Appendix E Evidence tables

See separate file.

Appendix F Full health economic report

See separate file.